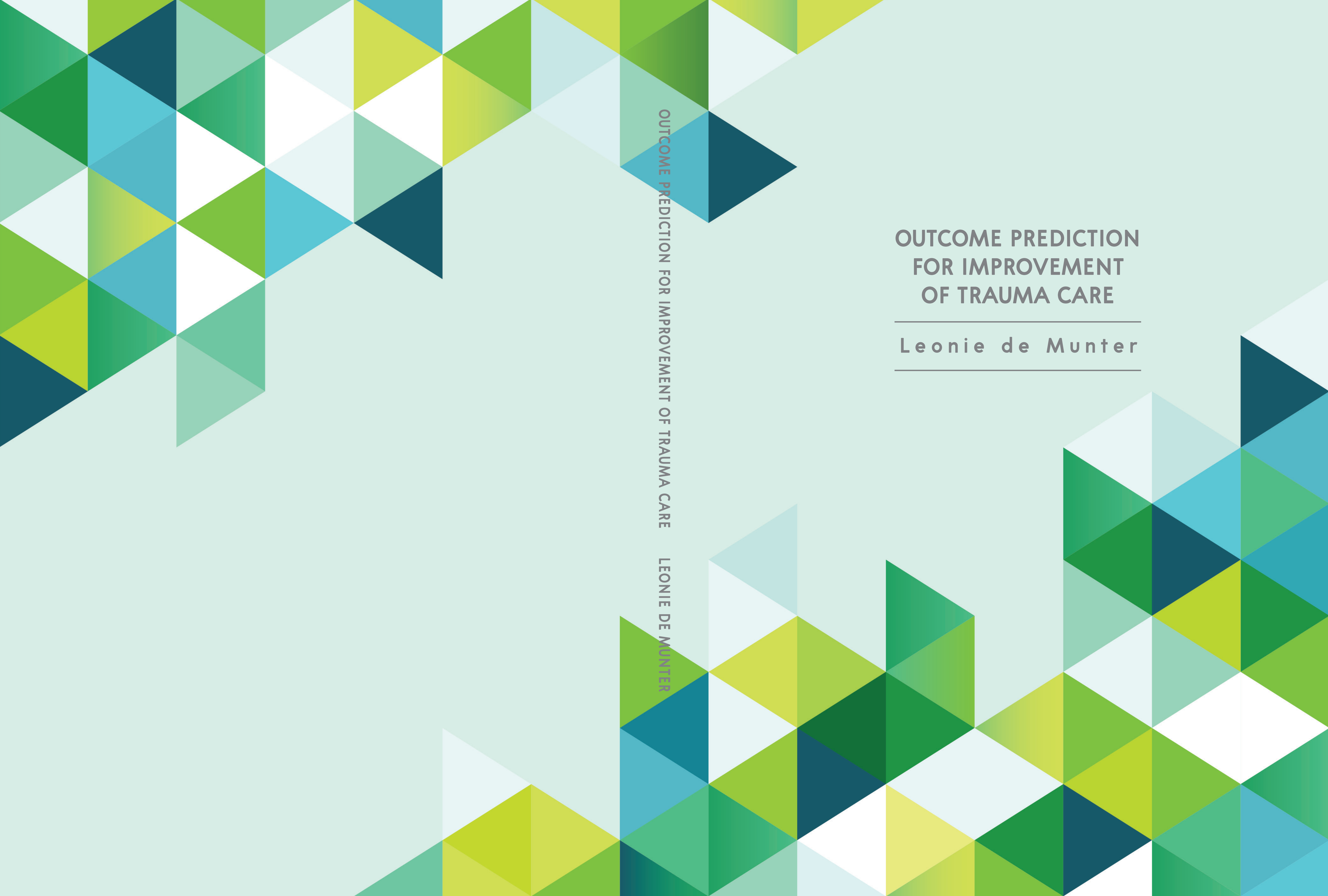

OUTCOME PREDICTION FOR IMPROVEMENT OF TRAUMA CARE

Leonie de Munter

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Voor mijn moeder

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I

GENERAL INTRODUCTION AND OUTLINE

Trauma, defined as a physical injury, is a global public health problem and is a leading cause of death among young adults[1-4]. It is estimated that trauma accounts for 9% of the world's deaths, of which road injury, self-harm, falls and interpersonal violence were the major causes[1,2]. This is only a small fraction of those suffering trauma, because the majority of trauma patients survives and often suffer temporary or permanent disabilities[2,5]. Besides, trauma is associated with high medical and societal costs[6,7]. In the Netherlands, the total costs of injuries were €3.5 billion annually[7].

The trauma population is a heterogeneous group of patients. Patients suffer from many different injury patterns, in both severity and body region, and are from various age groups. Besides, mechanism of injury (e.g. fracture or bleeding) or type of accident (e.g. road traffic accident, traffic, violence) can be divers.

Prediction models

Researchers have growing interest in predicting outcome after injury. The number of publications about outcome prediction in medicine to help care givers improve the quality of care increased the last decade[11]. Patient and injury characteristics can be combined in one model to predict outcome after trauma[12]. These prediction models can be valuable for medical research purposes and for medical practice, e.g. for health care providers, health insurers, researchers and policymakers[13]. The models can compare outcomes to support evaluation of quality of care between populations, hospitals, regions or countries and are often applied on population-based data. Besides, prediction models can target the individual patient who is in need for intervention. It can help with decision-making and could give information that can be useful for communication among physicians and patients.

Evaluation of trauma care

Trauma care has a long tradition of quality assessment, based on the comparison of mortality rates between institutions. It is meaningless to compare crude mortality rates between institutions without adjustment for its' patient population because it could influence the outcome after injury. For example, injury severity is a well-known risk factor of mortality after injury[14-16]. A hospital that mainly treats severely injured patients is expected to have a higher mortality rate compared to a hospital that only treats patients with minor injury. Patient and injury characteristics can be included in prediction models to account for these differences. A well-known instrument to compare patient outcomes among institutions is the Trauma Score and Injury Severity Score (TRISS) and was introduced in 1987[9,17]. The TRISS combines age, and anatomical and physiological variables to predict patient probabilities of survival (Ps)[18]. The sum of these probabilities for all patients admitted to the hospital is compared to the actual observed survival rate of those patients. A higher Ps compared with the actual observed survival indicates the number of excess survivors that would be achieved if the study center treated identically the same population as the reference population[19].

Medical practice in trauma care

In personalized medicine, prediction models could predict which patients are at high risk for poor outcome based on baseline characteristics[20]. These risk profiles could be the starting point for the development of specific clinical, psychological and functional programs for these high-risk patients to improve their outcome, reduce costs and to permit patients to return to society. The models aim to assist clinicians to provide the best medical care[21]. To be applicable, these models should have accurate outcome predictions and should be relatively easy to use in medical practice[20].

The Dutch Trauma Registry

As part of the inclusive trauma care system, the Dutch Trauma Registry (DTR) was introduced in 2007 to measure and improve the quality of trauma care in the Netherlands[8]. The DTR was based on the Major Trauma Outcome Study (MTOS) from the United States[8,9]. The DTR collects characteristics of the patient and the injury, admission related variables and outcome of all patients who are admitted to a hospital within 48 hours after trauma. Patients who were dead on arrival at the hospital were not registered in the DTR. Next to all variables from the MTOS, prehospital data was added to the registry and patients with short admissions or isolated hip fracture were included, creating a MTOS+ database[8]. In 2014, the database was extended with extra variables, e.g. pre-injury physical status, to comply with the Utstein template for international uniform reporting of data following trauma[10]. In 2017, approximately 79.000 patients were hospitalized and registered in the DTR due to trauma[8]. The mortality rate in the Netherlands is 2%, indicating that 98% of the trauma population survives.

Challenges in outcome prediction

The trauma registry provide a useful resource to study adverse effects and to predict outcome after injury. However, there are some challenges associated with outcome prediction after injury; i.e. case-mix differences, outcome measurement and data quality.

Case-mix differences

Many developed countries implemented nationwide trauma registries, but differences in trauma populations and injury characteristics between countries are distinct (i.e. case-mix). Differences in population, mechanism of trauma (blunt or penetrating), distance to the hospital, hospital treatment, inclusion criteria of the registry and health insurance status could all be reasons for differences in outcome. Those differences make outcome

comparison between countries ambiguous; are the differences in outcome explained by better quality of trauma care or by the differences in case-mix?
Another difference in case-mix is in the inclusion of patients with isolated hip fractures in the DTR. In 2017, more than 17,000 patients were admitted to a Dutch hospital due to an isolated hip fracture[8]. In line with Bergeron et al. (2005)[22], the DTR includes the extensive group of elderly patients with an isolated hip fracture. In contrast, others argue that elderly with an isolated hip fracture should be excluded or, at least, be analyzed separately because those elderly significantly influence the outcome[23,24]. To cover all trauma related injuries, it is preferable to include this subset if outcome predictions are accurate. Especially because it is expected that the number of elderly patients with a hip fracture will increase in the following years due to the ageing population.

Data quality

Trauma registries often have missing data, especially for physiological variables, i.e. in 2017 respiratory rate was missing in 41% of the cases and systolic blood pressure was missing in 23% of the cases[8]. Excluding cases with missing data can lead to biased results if those cases differ from the complete cases[31]. Although multiple imputation is a well-known strategy to deal with the problem of missing data, it is not yet fully established in trauma registries[32,33]. In addition, some well-known prognostic factors for poor non-fatal outcome after trauma (e.g. frailty and comorbidities[34-38]) are not readily available from the trauma registry or electronic medical files. These variables could not be incorporated in the prediction models or should manually be collected. Collection of those additional variables from all trauma patients is labor-intensive and could therefore be a costly procedure. Furthermore, uniform reporting of these additional variables should be established, to avoid methodological differences in grading between registries[10,39].

Outcome measurement

In countries with advanced health care, mortality rates after trauma decreased the past decades. The focus on trauma outcome has been, next to fatal outcome, complemented with non-fatal consequences, such as physical, psychological and social functioning after trauma[2,25,26]. For example, a young man with minor brain injury has a low risk of mortality, but has a high risk of short- and long-term impaired functional status, memory and concentration problems[27-30]. Quality of care assessment should be elaborated with innovative non-fatal prediction models to further evaluate and improve the quality of trauma care.

Non-fatal outcome measurement

Non-fatal outcome after injury can be measured with a prospective cohort design, in which outcome can be assessed with questionnaires at certain follow-up time points. Although several prospective cohort studies on non-fatal outcome after trauma were conducted, few of them were based on the total clinical trauma population, independent of severity or body region of injury, included both short- and long-term outcome and included a comprehensive outcome assessment[40-45].

The Brabant Injury Outcome Surveillance (BIOS) study[46] is a large prospective longitudinal cohort study. The BIOS-study included all adult trauma patients (≥18 years) who were admitted to the emergency department or ward in a hospital in Noord-Brabant, a region in the Netherlands, from August 2015 through November 2016. The BIOS-study assessed health related quality of life, psychological, social and functional outcome, and costs after injury. Data was collected by self-reported questionnaires at one week, and one, three, six, twelve and twenty-four months after injury. Injury characteristics were extracted from the DTR. Results from the BIOS-study are presented in Part II of this thesis.

Aim and outline of the thesis

The main aim of this thesis is to evaluate, develop and validate models for predicting fatal and non-fatal outcome after trauma in the Netherlands. The aim of this thesis is operationalized according to the following objectives, divided in two parts:

I. How can we improve and utilize prediction models for fatal outcome after trauma?
    a. Which outcome prediction models are available for the evaluation of trauma care?
    b. Are predictions from the TRISS model valid for the evaluation of quality of trauma care in the clinical Dutch trauma population?
    c. How could predictions from the TRISS model be improved for the evaluation of quality of trauma care?
II. To what extent can we predict non-fatal outcome after trauma?
    a. What are prognostic factors for health status after trauma?
    b. What are prognostic factors for psychological distress after trauma?
    c. What are prognostic factors for medical costs and return to work after trauma?

Part I (Chapter 2-5) describes the prediction of fatal outcome for the evaluation of quality of trauma care in the Netherlands (Figure 1). **Chapter 2** describes existing mortality prediction models for the general trauma population and the methodological quality of these models, and determined which variables are most relevant for the model prediction of mortality. The influence of simple imputation models on outcome comparison for the relatively high proportions of missing physiological values was demonstrated in **Chapter 3**. The prognostic ability of the current TRISS model was assessed in subsets of the clinical Dutch trauma population **(chapter 4)**. The subsets represent groups of patients that challenge trauma centers; e.g. elderly, children, traumatic brain injury, major trauma, longer length of stay in hospital and admission to a trauma center level I. In **chapter 5** a modified TRISS model was developed and validated for accurate survival prediction in the ageing trauma population.

Part II (Chapter 6-10) describes the prediction of non-fatal outcomes after trauma (Figure 1). **Chapter 6** assessed the predictive ability of the functional capacity index for health status and assessed the possibility to incorporate multiple injuries into one functional capacity score. Innovative prediction models for health status were developed for the evaluation of quality of trauma care **(Chapter 7)**. **Chapter 8** assessed prognostic factors for poor health status in the first year after trauma and identified high-risk groups for poor health status. **Chapter 9** describes prevalence and prognostic factors for psychological distress among the clinical trauma population in the first year after trauma. Prediction models for medical costs, productivity costs and return to work were assessed and described in **chapter 10**.

The general discussion (**Chapter 11**) provides answers to the research questions and summarizes the main findings of this thesis. Furthermore, recommendations for future research and practical implications are discussed.

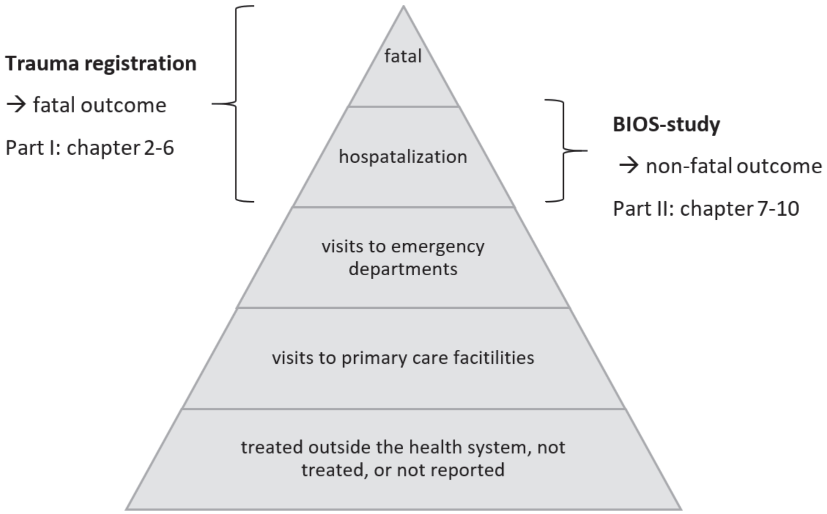

FIGURE 1. Outline of this thesis according to the injury pyramid; the relative numbers of fatal and non-fatal injuries[1].

REFERENCES

1. World Health Organization. Injuries and violence: The facts 2014. 2014;WO700(August).
2. Haagsma JA, Graetz N, Bolliger I, et al. The global burden of injury: Incidence, mortality, disability-adjusted life years and time trends from the global burden of disease study 2013. Inj Prev. 2016;22(1):3-18.
3. Abubakar I, Tillmann T, Banerjee A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the global burden of disease study 2013. Lancet. 2015;385(9963):117-171.
4. Rhee P, Joseph B, Pandit V, et al. Increasing trauma deaths in the united states. Ann Surg. 2014;260(1):13-21.
5. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. N Engl J Med. 2006;354(4):366-378.
6. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the united states: Stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. Arch Phys Med Rehabil. 2014;95(5):986-995. e1.
7. Polinder S, Haagsma J, Panneman M, Scholten A, Brugmans M, Van Beeck E. The economic burden of injury: Health care and productivity costs of injuries in the netherlands. Acc Anal Prev. 2016;93:92-100.
8. Landelijke Netwerk Acute Zorg (LNAZ). Annual report of the dutch trauma registry: Traumazorg in beeld 2013 - 2017. 2018.
9. Champion HR, Copes WS, Sacco WJ, Lawnick MM, Keast SL, Frey CF. The major trauma outcome study: Establishing national norms for trauma care. J Trauma. 1990;30(11):1356-1365.
10. Ringdal KG, Coats TJ, Lefering R, et al. The utstein template for uniform reporting of data following major trauma: A joint revision by SCANTEM, TARN, DGU-TR and RITG. Scand J Trauma Resusc Emerg Med. 2008;16(1):7.
11. Bernard A. Clinical prediction models: A fashion or a necessity in medicine? J Thorac Dis. 2017;9(10):3456-3457.
12. Steyerberg EW. Chapter 1: Introduction. In: Gail M, Tsiatis A, Krickeberg K, Wong W, Sarnet J, eds. Clinical prediction models: A practical approach to development, validation, and updating. Springer Science & Business Media; 2010:1-7.
13. Steyerberg EW. Chapter 2: Applications of prediction models. In: Clinical prediction models; A practical approach to development, validation, and updating. Springer Science & Business Media; 2009:11-31.
14. Bège T, Pauly V, Orleans V, Boyer L, Leone M. Epidemiology of trauma in france: Mortality and risk factors based on a national administrative health database. Available at SSRN 3263656. 2018.
15. Hashmi A, Ibrahim-Zada I, Rhee P, et al. Predictors of mortality in geriatric trauma patients: A systematic review and meta-analysis. J Trauma. 2014;76(3):894-901.
16. Palmer C. Major trauma and the injury severity score--where should we set the bar? Annu Proc Assoc Adv Automot Med. 2007;51:13-29.
17. Champion HR, Sacco WJ, Hunt TK. Trauma severity scoring to predict mortality. World J Surg. 1983;7(1):4-11.
18. Schluter PJ, Nathens A, Neal ML, et al. Trauma and injury severity score (TRISS) coefficients 2009 revision. J Trauma. 2010;68:761-770.
19. Younge P, Coats T, Gurney D, Kirk C. Interpretation of the ws statistic: Application to an integrated trauma system. J Trauma. 1997;43(3):511-515.
20. Lee Y, Bang H, Kim DJ. How to establish clinical prediction models. Endocrinol Metab (Seoul). 2016;31(1):38-44.
21. Steyerberg EW, Moons KG, van der Windt, Danielle A, et al. Prognosis research strategy (PROGRESS) 3: Prognostic model research. PLoS Med. 2013;10(2):e1001381.

22. Bergeron E, Lavoie A, Belcaid A, Ratte S, Clas D. Should patients with isolated hip fractures be included in trauma registries? J Trauma. 2005;58(4):793-797.
23. Gomez D, Haas B, Hemmila M, et al. Hips can lie: Impact of excluding isolated hip fractures on external benchmarking of trauma center performance. J Trauma. 2010;69(5):1037-1041.
24. American College of Surgeons. National trauma data bank: NTDB research data set admission year 2008. user manual. February 2010.
25. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. N Engl J Med. 2006;354(4):366-378.
26. Polinder S, Haagsma JA, Lyons RA, et al. Measuring the population burden of fatal and nonfatal injury. Epidemiol Rev. 2012;34:17-31.
27. McMahon PJ, Hricik A, Yue JK, et al. Symptomatology and functional outcome in mild traumatic brain injury: Results from the prospective TRACK-TBI study. J Neurotrauma. 2014;31(1):26-33.
28. Ponsford J, Cameron P, Fitzgerald M, Grant M, Mikocka-Walus A. Long-term outcomes after uncomplicated mild traumatic brain injury: A comparison with trauma controls. J Neurotrauma. 2011;28(6):937-946.
29. Ahman S, Saveman BI, Styrke J, Bjornstig U, Stalnacke BM. Long-term follow-up of patients with mild traumatic brain injury: A mixed-method study. J Rehabil Med. 2013;45(8):758-764.
30. Theadom A, Parag V, Dowell T, et al. Persistent problems 1 year after mild traumatic brain injury: A longitudinal population study in new zealand. Br J Gen Pract. 2016;66(642):e16-23.
31. Glance LG, Osler TM, Mukamel DB, Meredith W, Dick AW. Impact of statistical approaches for handling missing data on trauma center quality. Ann Surg. 2009;249(1):143-148.
32. Shivasabesan G, Mitra B, O'Reilly GM. Missing data in trauma registries: A systematic review. Injury. 2018;49(9):1641-1647.
33. Moore L, Hanley JA, Lavoie A, Turgeon A. Evaluating the validity of multiple imputation for missing physiological data in the national trauma data bank. J Emerg Trauma Shock. 2009;2(2):73-79.
34. Joseph B, Pandit V, Rhee P, et al. Predicting hospital discharge disposition in geriatric trauma patients: Is frailty the answer? J Trauma. 2014;76(1):196-200.
35. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210(6):901-908.
36. Gabbe BJ, Simpson PM, Sutherland AM, et al. Improved functional outcomes for major trauma patients in a regionalized, inclusive trauma system. Ann Surg. 2012;255(6):1009-1015.
37. Ringburg AN, Polinder S, van Ierland, Marie Catherine P, et al. Prevalence and prognostic factors of disability after major trauma. J Trauma. 2011;70(4):916-922.
38. Holtslag HR, van Beeck EF, Lindeman E, Leenen LP. Determinants of long-term functional consequences after major trauma. J Trauma. 2007;62(4):919-927.
39. Jones JM, Skaga NO, S SO, Lossius HM, Eken T. Norwegian survival prediction model in trauma: Modelling effects of anatomic injury, acute physiology, age, and co-morbidity. Acta Anaesthesiol Scand. 2014;58:303-315.
40. Polinder S, van Beeck EF, Essink-Bot ML, et al. Functional outcome at 2.5, 5, 9, and 24 months after injury in the netherlands. J Trauma. 2007;62(1):133-141.
41. Gabbe BJ, Braaf S, Fitzgerald M, et al. RESTORE: REcovery after serious trauma--outcomes, resource use and patient experiences study protocol. Inj Prev. 2015;21(5):348-354.
42. Kendrick D, Vinogradova Y, Coupland C, et al. Recovery from injury: The UK burden of injury multicentre longitudinal study. Inj Prev. 2013;19(6):370-381.
43. Langley J, Derrett S, Davie G, Ameratunga S, Wyeth E. A cohort study of short-term functional outcomes following injury: The role of pre-injury socio-demographic and health characteristics, injury and injury-related healthcare. Health Qual Life Outcomes. 2011;9(1):68.

44. Derrett S, Langley J, Hokowhitu B, et al. Prospective outcomes of injury study. Inj Prev. 2009;15(5):e3.
45. Edwards ER, Graves SE, McNeil JJ, et al. Orthopaedic trauma: Establishment of an outcomes registry to evaluate and monitor treatment effectiveness. Injury. 2006;37(2):95-96.
46. de Jongh MA, Kruithof N, Gosens T, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: The brabant injury outcome surveillance (BIOS) study. Inj Prev. 2017;23(1):59-2016-042032. Epub 2016 May 6.

PART I

PREDICTION OF FATAL OUTCOME AFTER TRAUMA

2

MORTALITY PREDICTION MODELS IN THE GENERAL TRAUMA POPULATION: A SYSTEMATIC REVIEW

L de Munter, S Polinder, KWW Lansink, MC Cnossen,
EW Steyerberg, MAC de Jongh

Injury. 2017;48(2):221-229.

ABSTRACT

Background Trauma is the leading cause of death in individuals younger than 40 years. There are many different models for predicting patient outcome following trauma. To our knowledge, no comprehensive review has been performed on prognostic models for the general trauma population. Therefore, this review aimed to describe (1) existing mortality prediction models for the general trauma population, (2) the methodological quality and (3) which variables are most relevant for the model prediction of mortality in the general trauma population.

Methods An online search was conducted in June 2015 using Embase, Medline, Web of Science, Cinahl, Cochrane, Google Scholar and PubMed. Relevant English peer-reviewed articles that developed, validated or updated mortality prediction models in a general trauma population were included.

Results A total of 90 articles were included. The cohort sizes ranged from 100 to 1,115,389 patients, with overall mortality rates that ranged from 0.6% to 35%. The Trauma and Injury Severity Score (TRISS) was the most commonly used model. A total of 258 models were described in the articles, of which only 103 models (40%) were externally validated. Cases with missing values were often excluded and discrimination of the different prediction models ranged widely (AUROC between 0.59 and 0.98). The predictors were often included as dichotomized or categorical variables, while continuous variables showed better performance.

Conclusion Researchers are still searching for a better mortality prediction model in the general trauma population. Models should 1) be developed and/or validated using an adequate sample size with sufficient events per predictor variable, 2) use multiple imputation models to address missing values, 3) use the continuous variant of the predictor if available and 4) incorporate all different types of readily available predictors (i.e., physiological variables, anatomical variables, injury cause/mechanism, and demographic variables). Furthermore, while mortality rates are decreasing, it is important to develop models that predict physical, cognitive status, or quality of life to measure quality of care.

BACKGROUND

Trauma is the leading cause of death in individuals younger than 40 years, resulting in more than 5 million deaths annually[1]. Survival status, which includes in-hospital mortality and 30-day mortality, is a commonly used outcome measure for evaluating the quality of trauma care. Outcome measurement can be performed using a comparison between observed and expected mortality rates. Expected mortality is measured by prediction modelling. However, it is meaningless to compare crude mortality rates without an adjustment for the differences in patient populations since outcome is largely dependent on patient characteristics, such as injury severity[2]. The heterogeneity of the trauma population makes it difficult to apply one accurate model for both minor and major injuries while also being applicable to all age groups.

Many different models were developed in previous decades to predict mortality or survival in trauma patients[3-6]. A frequently used and cited model is the Trauma and Injury Severity Score (TRISS)[3]. This prediction model is based on age, anatomical (Injury Severity Score [ISS]) and physiological (coded Revised Trauma Score [RTS]) variables and uses different coefficients for blunt and penetrating injuries. The ISS incorporates the sum of all squared Abbreviated Injury Scale (AIS) values of the three most severely injured areas. The coded RTS is the weighted sum of the Glasgow Coma Scale (GCS), the systolic blood pressure (SBP) and the respiratory rate (RR). The weights for the variables in the TRISS are derived from data based on trauma populations. Newly developed models incorporate other or revised predictors (e.g., comorbidities and different categories for age[4,6] or blood pressure[5]).

Systematic reviews have previously been conducted for prognostic models of trauma[7-11]. However, the reviews focused solely on specific predictive measures and traumatic injuries or excluded widely used models. To our knowledge, no comprehensive review has been performed on all prognostic models or incorporated all relevant predictive measures for both the general and heterogeneous trauma populations.

The aim of this review is to describe (1) the existing mortality prediction models for the general trauma population, (2) the methodological quality and (3) which variables are most relevant for the model prediction of mortality in the general trauma population.

METHODS

Search strategies

The databases Embase, Medline, Web of Science, Cinahl, Cochrane, Google Scholar and PubMed were searched for eligible articles in June 2015. With the assistance of a librarian, search strategies were developed using a combination of text words and subheadings that were matched to specific index terms of the database (Supplemental File 1). To identify other potentially relevant articles, references of the included articles were evaluated. Duplicates were removed by the reference management database RefWorks Write-N-Cite 4.2.

Inclusion and exclusion criteria

Articles that developed and/or validated a prediction model in the general clinical trauma population with mortality as an outcome measure were included. In this review, a prediction model was defined as a combination of at least two variables that predicted mortality. The general trauma population referred to all patients admitted to a hospital because of an injury due to an external cause. Last, included articles were required to have been published in scientific peer-reviewed English language journals up to June 2015. The exclusion of patients with low injury severity in the literature was not considered exclusionary criteria in this review because patient groups remained heterogeneous, with a large variety of injuries.

Articles that focused only on mortality within 24 hours after injury, those with specific age cohorts, or those with specific anatomical injuries were excluded.

Data screening and extraction

The first review investigator (LM) screened all titles and abstracts and excluded all articles that obviously met exclusionary criteria. After this selection, two reviewers (LM and MJ) independently screened the full text of the remaining manuscripts. Possible differences in opinion were resolved by discussion or consulting a third author (KL). The search process was documented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram[12] (Figure 1).

Data extraction was completed by one investigator (LM), and the data and decisions were verified by a second investigator (MJ). Any discrepancies were resolved by discussion with a senior member of the investigative team (KL). Information on the study population, outcome measures and modelling modalities was extracted (See Supplemental File 2).

Next, the performance of a prognostic model was assessed according to calibration (agreement between observed outcomes and predicted risks), discrimination (classification of patients with or without the outcome), and overall performance (distance between predicted and actual outcome)[13]. Common measures included the Hosmer-Lemeshow H or C goodness-of-fit statistics (H-L) for calibration and the area under the receiver operating characteristic curve (AUROC) for discrimination. If AUROC=1, the discrimination of the model was perfect, while an AUROC of 0.5 would indicate a chance occurrence.

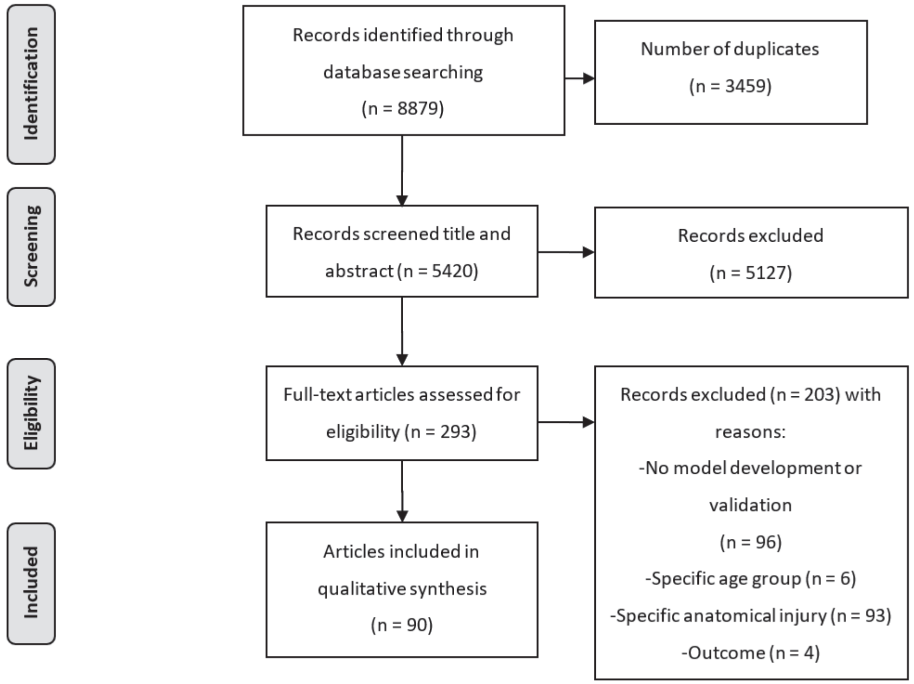

FIGURE 1. PRISMA Flow Diagram showing the selection of articles for mortality prediction models in a general trauma population.

Quality assessment

Hayden et al. (2006)[14] described six areas for potential bias for prognostic studies: study participation, study attrition (e.g., response rate, reasons for loss to follow-up), prognostic factor measurement, confounding measurement, outcome measurement, and analysis. In 2014, a Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) was proposed[15]. CHARMS captures ten areas of potential bias for prognostic studies: source of data, participants, outcome to be predicted, candidate predictors, sample size, missing data, model development, performance and evaluation, and results. Both assessment tools require further evaluation and improvement[14,15]. The two assessment frameworks were combined, and the issues that were considered essential to our review were extracted, including the size of the study, the rate of mortality, and the handling of missing values as well as whether the article described model development, validation or updating (See Supplemental File 2).

The quality assessment was primarily completed by the first investigator (LM) and secondarily examined by a second investigator (MJ).

Data analysis

All articles were included in the data analysis; when the same cohort was used in multiple articles, it was included in the analysis regardless of the methodological quality of both the article and the models. Due to substantial heterogeneity between study populations, it was not reasonable to perform a formal meta-analysis.

Predictors of the models were separated into four categories (i.e., anatomical, physiological, and demographic variables, and injury cause or mechanism). An additional category was created for predictors that could not be partitioned into these categories (Supplemental File 2).

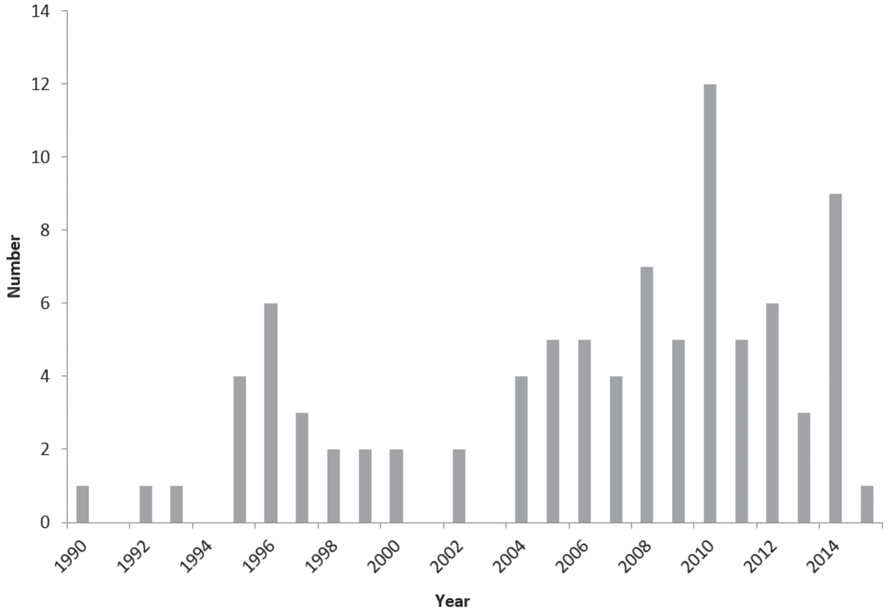

FIGURE 2. The number of included articles in this review according to the year the articles were published.

RESULTS

Search results

From the initial search, 8879 articles were identified. After the exclusion of duplicates and those articles that did not meet inclusionary criteria based on their titles and abstracts, 293 full text articles were assessed. A total of 96 articles were excluded because they lacked the development or validation of a mortality prediction model, 6 were excluded because they contained specific age-groups, 93 focused on a specific anatomical injury, 4 were excluded because they were limited to outcomes within a 24-hour period, and 4 were excluded because they were not written in English. Thus, 90 articles were included in the current review (Figure 1).

Study characteristics

The 90 included articles were conducted between 1990 and 2015 (Figure 2), with most of the articles published after the year 2000.

The majority of the articles were conducted in North America (N=42, 47%) and Europe (N=25, 28%) (Table 1). Three articles (3%)[16-18] did not mention the age boundaries of the included patients. Most articles (N=46, 51%) included patients of all ages in their study; however, 37 articles (41%) excluded patients younger than 18 years of age, and 4 articles (4%)[2,19-21] excluded patients <1 year of age.

Twenty-eight articles (31%) defined mortality as an outcome measurement without further specification of mortality. In-hospital mortality was studied in 51 articles (57%), while 10 articles (11%) studied 30-day mortality. Most articles included all trauma patients, independent of ISS or NISS (N=75, 83%), but 6 articles (7%) only included patients with an ISS>10 up to an ISS>16.

Models

The basic TRISS model was externally validated in 43 articles (Supplemental File 2). There were 112 TRISS-based models that were developed, validated or updated in 58 articles. The TRISS-model incorporated RTS, age as a dichotomous variable, ISS, and mechanism of injury. Variation in the traditional age identified in TRISS scoring that was included as either a continuous variable or anatomical variable was replaced with either the NISS or the International Classification of Disease-9 based ISS (ICISS). ICISS was used twelve times in 8 articles and often incorporated age as a continuous or categorical variable.

The Acute Physiology and Chronic Health Evaluation (APACHE) was used nine times (9 articles) and incorporated the Acute Physiological Score (APS), age, and the chronic health score. Age was most often included as a categorical variable, and ISS was added once as an additional variable to the APACHE model to predict mortality[22].

TABLE 1. Study characteristics of the included articles.

Study characteristics	N (%)	References
Country		
North-America	42 (46.7)	2,4,18,20-58
Europe	25 (27.8)	4,6,16,17,19,59-78
Asia	10 (11.1)	79-88
Oceania	7 (7.8)	89-95
Africa	4 (4.4)	96-99
Two or more countries	2 (2.2)	100,101
Age		
≥1 year	4 (4.4)	2,19-21
>12 to 18 years	37 (41.1)	4,23,24,26,32,34-36,40,41,48-52,61,62,66,67,69,71,73-77,82,87,88,91,92,95-97,99-101
All	46 (51.1)	6,22,25,27-31,33,37-39,42-47,53-60,63-65,68,70,72,78-81,83-86,89,90,93,94,98,102
Unknown	3 (3.3)	16-18
Patient Sample size		
<2500	35 (38.9)	16,17,25,27-37,59,60,63,65-72,82-84,89-92,96,98,102
2500-7500	18 (20.0)	4,6,19,38-42,61,73,79,85,86,93,95,97,99,101
>7500	29 (32.2)	2,18,20-24,26,43-57,62,74,75,87,88,94
Multiple sets with different sample sizes	8 (8.9)	58,64,76-78,80,81,100
Outcome		
In-hospital mortality	51 (56.7)	2,4,16,18-21,23-25,29,32-37,40,42,43,45-48,50-55,57,58,61,68-70,73,76,77,79,80,84,87,89,90,92-97
30-day mortality	10 (11.1)	6,17,30,62-64,74,75,82,101
4-week mortality	1 (1.1)	66
Unknown	28 (31.1)	22,26-28,31,38,39,41,44,49,55,59,60,65,67,71,72,78,81,83,85,86,88,91,98-100,102
Mortality rate		
<5%	15 (16.7)	2,20,21,30,42,46,62,74,76,78,85,90,92,96,98
5-10%	34 (37.8)	4,6,18,22-24,26,29,31,33,34,38-41,44,48-53,55-58,64,70,75,86,94,99-101
>10%	32 (35.6)	16,17,19,27,32,33,35-37,45,59-61,63,65-69,71,72,79,82-84,87,88,91,93,95,97,102
Combination (validation and development set)	6 (6.7)	28,43,77,80,81,89
Unknown	3 (3.3)	25,47,73
Model		
Development	15 (16.6)	18-21,27,29,40,41,46,51,52,54,58,88,94
Validation	25 (27.8)	32,33,37-39,44,48,53,55,63,66-68,70,72,75,77,82,84,91,96-99,102
Both	49 (54.4)	2,4,6,16,17,22-26,28,30,31,34-36,39,42,43,47,49,50,55,57,59-62,64,65,69,71,73,74,76,78-81,83,85,87,89,90,92,93,95,100,101
Update coefficients	19 (21.1)	4,16,22-24,39,40,48,55,60,70,79,81,86-88,91,93,100

TABLE 1. Continued.

Handling of missing values		
Complete case analysis	56 (62.2)	2,6,17,19,21,22,26-28,30-33,35,36,38,39,41-48,54,56,57,59,61,62,64,68,71,73,74,79-83,85-93,95,97-99,101,102
Multiple Imputation	10 (11.1)	18,20,23,24,51-53,63,76,77
Complete case analysis and Multiple imputation	4 (4.4)	55,60,75,100
Worst Case Scenario	1 (1.1)	4
Unknown	17 (18.9)	16,25,29,34,37,40,49,50,58,65,67,70,72,78,84,94,96
No missing values	2 (2.2)	66,69
ISS/NISS[1]		
All	75 (83.3)	2,4,16-18,20-33,35-38,40-44,46,47,49-58,60-62,64,66-82,84-86,88-90,92-94,96-100
>3 or >4	2 (2.2)	87,101
>8 to >12	7 (7.8)	6,34,39,45,48,59,83
>15 to > 18	6 (6.7)	19,63,65,91,95,102

[1] *List of abbreviations: ISS, Injury Severity Score; N, Number; NISS, New Injury Severity Score;*

A Severity Characterization of Trauma model (ASCOT) incorporated RTS, age as a categorical variable and the anatomic profile (AP; the square root of the sum of the squares of all the AIS scores in a region) and was used six times (6 articles). Mechanism of injury was also incorporated in 50% of the ASCOT models.

The Trauma Mortality Prediction Model (TMPM) was used six times (4 articles[2,19,21,23]). The TMPM and incorporated age and ICD-9-CM codes that were used as anatomical variables in which the five most severe injuries were coded and incorporated in the model. Mechanism of injury was included as a dichotomous or categorical variable.

Several new models were developed (and validated) that mostly incorporated the predictors of two or more models as mentioned above. These models showed variations in the anatomical variable, i.e., the Glasgow Coma Scale (GCS or only the motor component of the GCS) and specific blood values (e.g., base excess or base deficit). Many variations in measurement levels (e.g., continuous, dichotomous, and categorical) were used in the models (Figure 3).

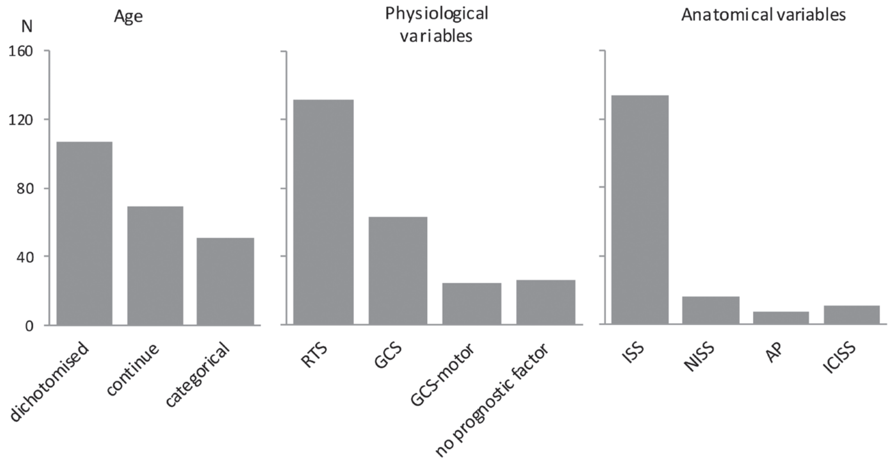

FIGURE 3. The number of models that used age (according to the measurement level) and physiological- or anatomical variables as predictor.
List of abbreviations: AP, Anatomic Profile; GCS, Glasgow Come Scale; ICISS, International classification of Disease-9 based Injury Severity Score model; ISS, Injury Severity Score; NISS, New Injury Severity Score; RTS, Revised Trauma Score.

Quality assessment

The cohort sizes ranged from 100[24] to 1,115,389[25] patients, with overall mortality rates that ranged from 0.6%[26] to 35.5%[27] (Supplemental File 2).

Fifteen articles (17%) developed a model, and twenty-five (28%) validated an existing model. Furthermore, 49 articles (56%) both developed and validated a prediction model. There were 19 articles (22%) that updated the coefficients of the original TRISS based on a previously developed goodness-of-fit model in their own study population.

Seventeen articles (20%) did not describe the handling of missing values. Missing values were mostly handled by complete case (CC) analysis (N=56, 62%), although the multiple imputation technique became more common in more recent studies (N=10, 12%).

A total of 258 models were developed, validated or updated in the 90 articles included in this analysis. There were 103 models (40%) that validated an external cohort, among which 24 were developed and validated in an external separate cohort in the same article. Nineteen models (8%) were validated in a random split sample, and ten articles (4%) used a temporal validation design with a split in calendar time. Two models[28] (0.8%) were validated using 3-fold validation.

Discrimination

Discrimination was mostly assessed with the AUROC and ranged between 0.59[29,30] and 0.98[31] (Supplemental File 2). Only three models had an AUROC<0.60. Nine models showed discrimination between 0.60 and 0.80. Most models showed an AUROC>0.80 (N=219, 86%). The highest AUROC was found for a TRISS-based model with updated coefficients based on goodness-of-fit for their own study population (AUROC: 0.981, 95% CI: unknown). The TRISS-based models in the same article with acute ethanol as an additional predictor showed discrimination values that were worse[31]. The lowest AUROCs were found in a model with age and comorbidities as predictors (AUROC: 0.59, 95% CI: 0.56, 0.62) and in the Kampala Trauma Score (KTS) (AUROC: 0.59, 95% CI: unknown). Models that included predictors from all categories (physiological, anatomical, and demographic variables, and injury cause/mechanism) showed better discrimination compared to models incorporating only one or two categories.

Calibration

Calibration was mostly assessed with the H-L statistics (N=149, 58%). Most models showed a non-significant miscalibration in model development (p>0.05), with small differences between models. Articles that compared the TRISS-based models with other models showed a worsening, but not significant, calibration for the TRISS[32-37]. Overall, calibration of the models was better when several categories of predictors were included in the model.

The inclusion of dichotomized, categorical or continuous predictors in the models resulted in differences in performance. Some articles compared the basic TRISS model with TRISS-based models that incorporated different measurement levels for age or ISS[4,28,38,39]. Models with categorical variables showed better calibration and discrimination compared with dichotomized variables, and models that included continuous variables showed even better calibration and discrimination[28,39-41].

Other measures of performance

Overall performance measures were not assessed in this review because Nagelkerke's R^2 and Brier Score were rarely measured in the included studies.

Predictors

Among 258 models, 132 (52%) incorporated the RTS (Additional File 2). The Glasgow Coma Scale (GCS) was the second most frequent variable and was used in 63 (24%) models. The motor component of the GCS was used in 24 (9%) models. Specific blood values (e.g., base excess or base deficit) were included in 18 models (7%), and the Acute Physiological Score (APS) was included in 17 (7%) models (Figure 3).

Injury Severity Score (ISS) was the most frequently used anatomical variable (N=133, 52%). Other anatomical variables that were used occasionally were the New ISS (NISS) (N=15, 6%) and the ICISS (N=9, 3%). Additionally, the ICD-9-CM (N=14, 5%) or ICD-10 (N=1, 0.4%) codes were used incorporated as anatomical variables in models where the five most severe injuries were coded. The anatomic profile (AP) score is the square root of the sum of the squares of all the AIS scores in a region and was used in 7 models (3%) (Figure 3).

Another important variable that was measured in many models was the mechanism or cause of injury. Mechanism of injury was dichotomized into blunt or penetrating injury in 84 models (33%). A few models (N=11, 4%) created a categorical variable for cause of injury (e.g., motor vehicle collision, pedestrian accident or fall), which replaced the mechanism of injury. Many variations in measurement levels (e.g., continuous, dichotomous, categorical) were used in the models (Figure 3). A total of 107 (41%) models incorporated age as a dichotomized variable. The dichotomous version of age frequently used the cut-off point of ≥55 years. Continuous and categorical variants of age were used in 69 (27%) and 51 (20%) models, respectively. Only 30 (12%) models did not incorporate age. Thirty models (12%) incorporated gender in the model. Comorbidity was included in 44 models (17%) mostly using the Charlson Comorbidity Index (CCI) or the chronic health score (11 (4%) and 9 (3%) models, respectively). Statistical interaction terms were included in 9 models (3%).

DISCUSSION

This systematic review assessed 90 articles reporting on mortality prediction models for the general trauma population. The study and model characteristics were heterogeneous, and methodological quality varied. TRISS was the most commonly used model. The predictors that were most often used were RTS, ISS, age and mechanism of injury. The predictors were mostly included as dichotomized or categorical variables, while continuous variables showed better performance, as might theoretically be expected[42-44].

Methodological quality

The methodological quality of the included articles varied widely. Key potential biases were addressed (Supplemental File 2) to allow for a detailed interpretation. For example, thresholds for continuous variables should have been avoided[42-45]. It is unlikely that a 55-year-old patient had a completely different prognosis than a 54-year-old patient. Additionally, neither of the previously mentioned patients would have the same prognosis as a patient who was 20 years old.

A sufficient sample size is important in model development and validation. A smaller sample size results in a low number of events per variable and a limited power in the analysis. Although Peduzzi et al. (1996)[46] introduced the general rule of a minimum of 10 outcome events per variable in logistic regression, other researchers suggest that this rule may be too conservative[47,48]. It could be argued that several studies included in this review did not have sufficient events for the amount of predictors included in the model for accurate validation or development[24,49-52]. Furthermore, mortality rates in countries with advanced health systems have rapidly decreased over recent decades[53]. Meanwhile, a growing number of patients are at risk of serious long-term disability[54]. Thus, it could be argued that the evaluation of trauma care should be extended to non-fatal outcomes.

The problem of missing data is common in trauma registries and in trauma mortality prediction research. CC analysis was mostly used in the articles for handling missing values. CC analysis excludes subjects with a missing value for any potential predictor. The missing values in trauma data are often associated with the outcome or with other covariables[55]. More recent research used multiple imputation (MI), which can be a valid and efficient solution to address the large amount of missing physiologic data[56,57]. The most common missing variable in trauma data is the RTS because it combines three physiological variables, including the respiratory rate. Therefore, RTS is often replaced by other variables with less missing values (e.g. GCS scores)[58,59]. However, these variables contain less information; thus, it can be argued that the priority should be on the improvement of data collection or data registration rather than on the adjustment of the models[60].

External validation is an essential key to determine the general applicability of a prediction model. Only relatively few models were validated in an external cohort. Additionally, few papers handled continuous variables or missing values adequately. This limited level of methodological quality was also reported in other reviews of prognostic models[7,11,61,62]. Bouwmeester et al. (2012)[63] stated that better quality models should be developed. A review for prognostic models in liver transplantation[62] recommended the development of disease-specific prediction models because the effect of some predictors depended on the underlying disease. Due to a high heterogeneity across trauma populations, it could be reasoned that researchers should not focus on the creation of a model for the general trauma population but should develop several models for subsets of patients to assess and compare the equitable quality of care., especially now as the number of patients increases in large registries[64]. Another possibility would be to create a single but more complex model that includes all important predictors for the different patient subsets.

Model performance and predictors

The performance of the same model differed widely between cohorts. This variation limited the validity of a quality of care comparison between the different cohorts. Calibration of a model depends on the setting while discrimination depends on the distribution of prognostic factors. Therefore, model performances were only compared within studies.

Models that incorporated several categories of predictors (e.g., anatomical, physiological, demographic) showed better calibration and discrimination compared to models that only included, for example, anatomical predictors. A hip fracture combined with old age and comorbidities may be fatal but may be less fatal in young and healthy patients. Anatomical measures should therefore be accompanied by physiological and demographic predictors. The TRISS model previously incorporated these parameters in 1984[3].

This systematic review showed that adding more predictors to the basic TRISS-model did not always result in higher performance[65-67]. Last, models should be practical. For example, the performance gained by incorporating comorbidity status may not outweigh the effort it takes to measure comorbidity status among all trauma patients adequately. Additionally, base deficit could be an important predictor for mortality in trauma care. However, base deficit is mostly assessed only in severely injured patients[68] and will often be recorded as a missing value in the general trauma population. Therefore, it is not feasible to incorporate this predictor in models that are designed to predict mortality for the general trauma population.

Limitations

There are some limitations to this review. A total of 27 articles did not provide a specific definition of the timing of mortality. Studies with only 24-hour mortality as an outcome were excluded, but it is possible that additional studies should have been excluded. Bias could have been introduced by excluding the non-English language articles (N=4). However, the number of articles identified through our systematic approach allowed the representation of the development in the field of trauma mortality prediction models. Last, publication bias could have been a threat to this review if studies with poor validation results were not published or if other non-English language articles were not found with our search strategy.

Conclusion

Researchers are still searching for a better mortality prediction model in the general trauma population. Every year, several articles are published that develop prediction models with small variations. This situation may indicate that the basic TRISS model is perceived as outdated although there is no current agreement on a better model to use in the quality assessment of trauma care in the general population. Most models are based on the TRISS variables and reach adequate performance with good discrimination and calibration. However, when testing TRISS on subsets of trauma patients, the results differ dramatically [69,70].

Future research on model development should focus on the methodological quality, on practically applicable models and on the performance in subsets of patient groups. Models should 1) be developed and/or validated using an adequate sample size with sufficient events per predictor variable, 2) use multiple imputation models to address missing values, 3) use the continuous variant of the predictor if available and 4) incorporate all different types of readily available predictors (i.e., physiological variables, anatomical variables, injury cause/mechanism, and demographic variables). The existing models did not meet all requirements for methodological accuracy; hence, further development of survival prediction models in trauma should not be based on previously built models but should be based on the literature and expert opinion. Furthermore, while mortality rates are decreasing, it is important to develop models that predict physical, cognitive status, or quality of life to measure quality of care.

REFERENCES

1. World Health Organization, Injuries and violence: the facts 2014. WO700.
2. Glance LG, Osler TM, Mukamel DB et al., TMPM-ICD9: A trauma mortality prediction model based on ICD-9-CM codes. *Ann Surg.* 2009;249(6):1032-9.
3. Champion H, Frey C, Sacco W, Determination of national normative outcomes for trauma. *J Trauma.* 1984;24:651.
4. Bergeron E, Rossignol M, Osler T et al., Improving the TRISS Methodology by Restructuring Age Categories and Adding Comorbidities. *J Trauma.* 2004;56(4):760-7.
5. Lefering R, Huber-Wagner S, Nienaber U et al., Update of the trauma risk adjustment model of the TraumaRegister DGU™: the Revised Injury Severity Classification, version II. *Crit Care*. 2014;18(5):476.
6. Jones JM, Skaga NO, S SO et al., Norwegian survival prediction model in trauma: Modelling effects of anatomic injury, acute physiology, age, and co-morbidity. *Acta Anaesthesiol Scand*. 2014;58(3):303-15.
7. Perel P, Edwards P, Wentz R, Roberts I, Systematic review of prognostic models in traumatic brain injury. *BMC Med Inform Decis Mak*. 2006;6:38.
8. Gagne M, Moore L, Beaudoin C et al., Performance of International Classification of Diseases-based injury severity measures used to predict in-hospital mortality: A systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2016;80(3):419-26.
9. Stoica B, Paun S, Tanase I et al., Probability of Survival Scores in Different Trauma Registries: A Systematic Review. *Chirurgia (Bucur).* 2016;111(2):115-9.
10. Deng Q, Tang B, Xue C et al., Comparison of the Ability to Predict Mortality between the Injury Severity Score and the New Injury Severity Score: A Meta-Analysis. *Int J Environ Res Public Health.* 2016;13(8):825.
11. Minne L, Ludikhuize J, De Jonge E et al., Prognostic models for predicting mortality in elderly ICU patients: a systematic review. *Intensive Care Med.* 2011;37(8):1258–68.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):264-9.
13. Steyerberg EW, Chapter 15: Evaluation of Performance. In: Gail M, Tsiatis A, Krickeberg K et al. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. Springer Science & Business Media; 2010:255-80.
14. Hayden JA, Côté P, Bombardier C, Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med.* 2006;144(6):427-37.
15. Moons KG, de Groot JA, Bouwmeester W et al., Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med.* 2014;11(10):e1001744
16. Kroezen F, Bijlsma TS, Liem MSL et al., Base deficit-based predictive modeling of outcome in trauma patients admitted to intensive care units in Dutch trauma centers. *J Trauma*. 2007;63(4):908-13.
17. Sartorius D, Le Manach Y, David JS et al., Mechanism, Glasgow Coma Scale, Age, and Arterial Pressure (MGAP): A new simple prehospital triage score to predict mortality in trauma patients. *Crit Care Med.* 2010;38(3):831-7.
18. Moore L, Hanley JA, Turgeon AF et al., A new method for evaluating trauma centre outcome performance: Tram-adjusted mortality estimates. *Ann Surg.* 2010;251(5):952-8.
19. Di Bartolomeo S, Ventura C, Marino M et al., Is the TMPM-ICD9 revolution in trauma risk-adjustment compatible with imperfect administrative coding? *Accid Anal Prev.* 2011;43(6):1955-9.
20. Glance LG, Osier TM, Mukamel DB et al., Expert consensus vs empirical estimation of injury severity effect on quality measurement in trauma. *Arch Surg.* 2009;144(4):326-32.
21. Osler T, Glance L, Buzas JS et al., A trauma mortality prediction model based on the anatomic injury scale. *Ann Surg*. 2008;247(6):1041-8.

22. Rutledge R, Fakhry S, Rutherford E et al., Comparison of APACHE II, trauma score, and injury severity score as predictors of outcome in critically injured trauma patients. *Am J Surg*. 1993;166(3):244-7.
23. Glance LG, Dick AW, Mukamel DB et al., The effect of preexisting conditions on hospital quality measurement for injured patients. *Ann Surg*. 2010;251(4):728-34.
24. Ahun E, Koksal O, Sigirli D et al., Value of the Glasgow coma scale, age, and arterial blood pressure score for predicting the mortality of major trauma patients presenting to the emergency department. *Ulusal Travma Acil Cerrahi Derg.* 2014;20(4):241-7.
25. Schluter PJ, Nathens A, Neal ML et al., Trauma and Injury Severity Score (TRISS) coefficients 2009 revision. *J Trauma*. 2010;68:761-70.
26. Weeks SR, Juillard CJ, Monono ME et al., Is the Kampala trauma score an effective predictor of mortality in low-resource settings? A comparison of multiple trauma severity scores. *World J Surg*. 2014;38:1905-11.
27. Batchinsky AI, Cancio LC, Salinas J et al., Prehospital loss of R-to-R interval complexity is associated with mortality in trauma patients. *J Trauma*. 2007;63(4):512-8.
28. Chan CKO, Yau KKW, Cheung MT, Trauma survival prediction in Asian population: A modification of TRISS to improve accuracy. *Emerg Med J*. 2014;31(2):126-33.
29. Thompson HJ, Rivara FP, Nathens A et al., Development and validation of the mortality risk for trauma comorbidity index. *Ann Surg.* 2010;252(2):370-5.
30. Haac B, Varela C, Geyer A et al., The utility of the Kampala trauma score as a triage tool in a sub-Saharan African trauma cohort. *World J Surg*. 2015;39(2):356-62.
31. Millham FH, LaMorte WW, Factors associated with mortality in trauma: Re-evaluation of the TRISS method using the National Trauma Data Bank. *J Trauma*. 2004;56(5):1090-6.
32. Lefering R, Development and Validation of the Revised Injury Severity Classification Score for Severely Injured Patients. *Eur J Trauma Emerg Surg*. 2009;35(5):437-47.
33. Reiter A, Mauritz W, Jordan B et al., Improving risk adjustment in critically ill trauma patients: The TRISS-SAPS score. *J Trauma.* 2004;57(2):375-80.
34. Huber-Wagner S, Qvick M, Mussack T et al., Massive blood transfusion and outcome in 1062 polytrauma patients: a prospective study based on the Trauma Registry of the German Trauma Society. *Vox Sang*. 2007;92(1):69-78.
35. Moore L, Lavoie A, Turgeon AF et al., The trauma risk adjustment model: A new model for evaluating trauma care. *Ann Surg.* 2009;249(6):1040-6.
36. Bouamra O, Wrotchford A, Hollis S et al., Outcome prediction in trauma. *Injury.* 2006;37(12):1092-7.
37. Brilej D, Vlaovic M, Komadina R, Improved prediction from revised injury severity classification (RISC) over trauma and injury severity score (TRISS) in an independent evaluation of major trauma patients. *J Int Med Res.* 2010;38(4):1530-8.
38. Moore L, Lavoie A, Turgeon AF et al., Improving Trauma mortality prediction modeling for blunt trauma. *J Trauma.* 2010;68(3):698-705.
39. Gabbe BJ, Magtengaard K, Hannaford AP, Cameron PA, Is the Charlson Comorbidity Index useful for predicting trauma outcomes? *Acad Emerg Med.* 2005;12(4):318-21.
40. Kimura A, Chadbunchachai W, Nakahara S, Modification of the Trauma and Injury Severity Score (TRISS) method provides better survival prediction in Asian blunt trauma victims. *World J Surg.* 2012;36(4):813-8.
41. Schluter PJ, Trauma and Injury Severity Score (TRISS): Is it time for variable re-categorisations and re-characterisations? *Injury.* 2011;42(1):83-9.
42. Harrell F, Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Springer; 2015.
43. Steyerberg EW, Chapter 9: Coding of Categorical and Continuous Predictors. In: Gail M, Tsiatis A, Krickeberg K et al. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating.* Springer Science & Business Media; 2010:159-173.
44. Royston P, Altman DG, Sauerbrei W, Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med.* 2006;25(1):127-41.

45. Wyatt JC, Altman DG, Commentary: Prognostic models: clinically useful or quickly forgotten? *BMJ*. 1995;311:1539-41.
46. Peduzzi P, Concato J, Kemper E et al., A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* 1996;49(12):1373-9.
47. Vittinghoff E, McCulloch CE, Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol.* 2007;165(5):710-8.
48. Austin PC, Steyerberg EW, Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. *Stat Methods Med Res.* 2017;26(2):796-808.
49. Cinelli SM, Brady P, Rennie CP et al., Comparative results of trauma scoring systems in fatal outcomes. *Conn Med.* 2009;73(5):261-5.
50. Hadzikadic M, Hakenewerth A, Bohren B et al., Concept formation vs. logistic regression: Predicting death in trauma patients. *Artif Intell Med.* 1996;8(5):493-504.
51. Corbanese U, Possamai C, Casagrande L, Bordino P, Evaluation of trauma care: Validation of the TRISS method in an Italian ICU. *Intensive Care Med.* 1996;22(9):941-6.
52. Thanapaisal C, Saksaen P, A comparison of the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Trauma-Injury Severity Score (TRISS) for outcome assessment in Srinagarind Intensive Care Unit trauma patients. *J Med Assoc Thai.* 2012;95 Suppl 11:S25-33.
53. MacKenzie EJ, Rivara FP, Jurkovich GJ et al., A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med*. 2006;354(4):366-78.
54. Polinder S, Haagsma JA, Lyons RA et al., Measuring the population burden of fatal and nonfatal injury. *Epidemiol Rev.* 2012;34:17-31.
55. Roudsari B, Field C, Caetano R, Clustered and missing data in the US National Trauma Data Bank: implications for analysis. *Inj Prev.* 2008;14(2):96-100.
56. Moore L, Lavoie A, LeSage N et al., Multiple imputation of the glasgow coma score. *J Trauma.* 2005;59(3):698-704.
57. Moore L, Hanley JA, Lavoie A, Turgeon A, Evaluating the validity of multiple imputation for missing physiological data in the national trauma data bank. *J Emerg Trauma Shock.* 2009;2(2):73-9.
58. Eftekhar B, Zarei MR, Ghodsi M et al., Comparing logistic models based on modified GCS motor component with other prognostic tools in prediction of mortality: Results of study in 7226 trauma patients. *Injury.* 2005;36(8):900-4.
59. Kuhls DA, Malone DL, McCarter RJ, Napolitano LM, Predictors of mortality in adult trauma patients: The physiologic trauma score is equivalent to the trauma and injury severity score. *J Am Coll Surg.* 2002;194(6):695-704.
60. Little RJ, D'Agostino R, Cohen ML et al., The prevention and treatment of missing data in clinical trials. *N Engl J Med.* 2012;367(14):1355-60.
61. Counsell C, Dennis M, Systematic review of prognostic models in patients with acute stroke. *Cerebrovasc Dis*. 2001;12(3):159-70.
62. Jacob M, Lewsey JD, Sharpin C et al., Systematic review and validation of prognostic models in liver transplantation. *Liver transpl.* 2005;11(7):814-25.
63. Bouwmeester W, Zuithoff NP, Mallett S et al., Reporting and methods in clinical prediction research: a systematic review. *PLoS Med.* 2012;9(5):1-12.
64. Iezzoni LI, Risk Adjustment for Measuring Healthcare Outcomes.: Health Administration Press 1997
65. Fueglistaler P, Amsler F, Schepp M et al., Prognostic value of sequential organ failure assessment and simplified acute physiology II score compared with trauma scores in the outcome of multiple-trauma patients. *Am J Surg*. 2010;200(2):204-14.
66. Gabbe BJ, Cameron PA, Wolfe R et al., Prehospital prediction of intensive care unit stay and mortality in blunt trauma patients. *J Trauma.* 2005;59(2):458-65.

67. Huber-Wagner S, Stegmaier J, Mathonia P et al., The sequential trauma score - A new instrument for the sequential mortality prediction in major trauma. *Eur J Med Res.* 2010;15(5):185-95.
68. Kroezen F, Bijlsma TS, Liem MS et al., Base deficit-based predictive modeling of outcome in trauma patients admitted to intensive care units in Dutch trauma centers. *J Trauma.* 2007;63(4):908-13.
69. De Jongh, M. A. C., Verhofstad MHJ, Leenen LPH, Accuracy of different survival prediction models in a trauma population. *Br J Surg*. 2010;97(12):1805-13.
70. Kennedy RL, Grant PT, Blackwell D, Low-impact falls: demands on a system of trauma management, prediction of outcome, and influence of comorbidities. *J Trauma.* 2001;51(5):717-24.
71. Kilgo PD, Meredith JW, Osler TM, Incorporating recent advances to make the TRISS approach universally available. *J Trauma.* 2006;60(5):1002-8.
72. Guzzo JL, Bochicchio GV, Napolitano LM et al., Prediction of outcomes in trauma: Anatomic or physiologic parameters? *J Am Coll Surg*. 2005;201(6):891-7.
73. Jones JM, Maryosh J, Johnstone S, Templeton J, A multivariate analysis of factors related to the mortality of blunt trauma admissions to the North Staffordshire Hospital Centre. *J Trauma.* 1995;38(1):118-22.
74. Millham FH, Malone M, Blansfield J et al., Predictive accuracy of the TRISS survival statistic is improved by a modification that includes admission pH. *Arch Surg.* 1995;130(3):307-11.
75. Rhee KJ, Baxt WG, Mackenzie JR et al., APACHE II scoring in the injured patient. *Crit Care Med.* 1990;18(8):827-30.
76. Vassar MJ, Wilkerson CL, Duran PJ et al., Comparison of Apache-II, Triss, and a Proposed 24-Hour Icu Point System for Prediction of Outcome in Icu Trauma Patients. *J Trauma.* 1992;32(4):490-500.
77. Vassar MJ, Lewis Jr FR, Chambers JA et al., Prediction of outcome in intensive care unit trauma patients: A multicenter study of acute physiology and chronic health evaluation (APACHE), trauma and injury severity score (TRISS), and a 24-hour intensive care unit (ICU) point system. *J Trauma*. 1999;47(2):324-9.
78. Wong DT, Barrow PM, Gomez M, McGuire GP, A comparison of the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Trauma-Injury Severity Score (TRISS) for outcome assessment in intensive care unit trauma patients. *Crit Care Med.* 1996;24(10):1642-8.
79. Demetriades D, Chan LS, Velmahos G et al., TRISS methodology in trauma: the need for alternatives. *Br J Surg.* 1998;85(3):379-84.
80. Garber BG, Hebert PC, Wells G, Yelle JD, Validation of trauma and injury severity score in blunt trauma patients by using a Canadian Trauma Registry. *J Trauma.* 1996;40(5):733-7.
81. Hannan EL, Mendeloff J, Farrell LS et al., Validation of TRISS and ASCOT using a non-MTOS trauma registry. *J Trauma.* 1995;38(1):83-8.
82. Imhoff BF, Thompson NJ, Hastings MA et al., Rapid Emergency Medicine Score (REMS) in the trauma population: A retrospective study. *BMJ Open.* 2014;4(5):e004738.
83. Rutledge R, Osler T, Emery S, Kromhout-Schiro S, The end of the Injury Severity Score (ISS) and the Trauma and Injury Severity Score (TRISS): ICISS, an international classification of diseases, ninth revision-based prediction tool, outperforms both ISS and TRISS as predictors of trauma patient survival, hospital charges, and hospital length of stay. *J Trauma.* 1998;44(1):41-9.
84. Burd RS, Ouyang M, Madigan D, Bayesian logistic injury severity score: A method for predicting mortality using international classification of disease-9 codes. *Acad Emerg Med.* 2008;15(5):466-75.
85. Champion HR, Copes WS, Sacco WJ et al., Improved predictions from A Severity Characterization of Trauma (ASCOT) over Trauma and Injury Severity Score (TRISS): Results of an independent evaluation. *J Trauma*. 1996;40(1):42-9.

86. Garber BG, Hebert PC, Wells G et al., Differential performance of TRISS-Like in early and late blunt trauma deaths. *J Trauma.* 1997;43(1):1-7.
87. Haider AH, Hashmi ZG, Zafar SN et al., Developing best practices to study trauma outcomes in large databases: An evidence-based approach to determine the best mortality risk adjustment model. *J Trauma Acute Care Surg*. 2014;76(4):1061-9.
88. Hannan EL, Farrell LS, Gorthy SFH et al., Predictors of mortality in adult patients with blunt injuries in New York State: A comparison of the Trauma and Injury Severity Score (TRISS) and the International Classification of Disease, Ninth Revision-based Injury Severity Score (ICISS). *J Trauma.* 1999;47(1):8-14.
89. Moore L, Lavoie A, Bergeron E, Modeling probability-based injury severity scores in logistic regression models: the logit transformation should be used. *J Trauma.* 2007;62(3):601-5.
90. Moore L, Lavoie A, Sage NL et al., Using Information on Preexisting Conditions to Predict Mortality From Traumatic Injury. *Ann Emerg Med.* 2008;52(4):356,364.e2.
91. Moore L, Lavoie A, Le Sage N et al., Consensus or data-derived anatomic injury severity scoring? *J Trauma.* 2008;64(2):420-6.
92. Moore L, Hanley JA, Turgeon AF, Lavoie A, Evaluating the performance of trauma centers: Hierarchical modeling should be used. *J Trauma.* 2010;69(5):1132-7.
93. Rutledge R, Hoyt DB, Eastman AB et al., Comparison of the Injury Severity Score and ICD-9 diagnosis codes as predictors of outcome in injury: analysis of 44,032 patients. *J Trauma.* 1997;42(3):487-479.
94. West TA, Rivara FP, Cummings P et al., Harborview assessment for risk of mortality: An improved measure of injury severity on the basis of ICD-9-CM. *J Trauma.* 2000;49(3):530-41.
95. Osler T, Rutledge R, Deis J, Bedrick E, ICISS: an international classification of disease-9 based injury severity score. *J Trauma.* 1996;41(3):386-388.
96. Belzunegui T, Gradin C, Fortun M et al., Major trauma registry of Navarre (Spain): The accuracy of different survival prediction models. *Am J Emerg Med.* 2013;31(9):1382-8.
97. Aydin SA, Bulut M, Ozguc H et al., Should the New Injury Severity Score replace the Injury Severity Score in the Trauma and Injury Severity Score? *Ulus Travma Acil Cerrahi Derg.* 2008;14(4):308-12.
98. Frankema SPG, Steyerberg EW, Edwards MJR, Van Vugt AB, Comparison of current injury scales for survival chance estimation: An evaluation comparing the predictive performance of the ISS, NISS, and AP scores in a Dutch local trauma registration. *J Trauma.* 2005;58(3):596-604.
99. Frankema SPG, Edwards MJR, Steyerberg EW, Van Vugt AB, Predicting survival after trauma: A comparison of TRISS and ASCOT in the Netherlands. *Eur J Trauma* 2002;28(6):355-64.
100. Sicignano A, Giudici D, Probability model of hospital death for severe trauma patients based on the simplified acute physiology score I: Development and validation. *J Trauma*. 1997;43(4):585-9.
101. Suarez-Alvarez J, Miquel J, Del Rio FJ, Ortega P, Epidemiologic aspects and results of applying the TRISS methodology in a Spanish trauma intensive care unit (TICU). *Intensive Care Med.* 1995;21(9):729-36.
102. Vivien B, Yeguiayan JM, Le Manach Y et al., The motor component does not convey all the mortality prediction capacity of the Glasgow Coma Scale in trauma patients. *Am J Emerg Med.* 2012;30(7):1032-41.
103. Bouamra O, Wrotchford A, Hollis S et al., A new approach to outcome prediction in trauma: A comparison with the triss model. *J Trauma.* 2006;61(3):701-10.
104. Hasler RM, Mealing N, Rothen HU et al., Validation and reclassification of MGAP and GAP in hospital settings using data from the Trauma Audit and Research Network. *J Trauma Acute Care Surg*. 2013;77(5):757-63.
105. Gunning AC, Leenen LPH, Applicability of the predictors of the historical trauma score in the present Dutch trauma population: Modelling the TRISS predictors. *J Trauma Acute Care Surg.* 2014;77(4):614-9.

106. Joosse P, De Jong, W. J. J., Reitsma JB et al., External validation of the emergency trauma score for early prediction of mortality in trauma patients. *Crit Care Med*. 2014;42(1):83-9.
107. Pearl A, Caspi R, Bar-Or D, Artificial neural network versus subjective scoring in predicting mortality in trauma patients. *Stud Health Technol Inform.* 2006;124:1019-24.
108. Kimura A, Nakahara S, Chadbunchachai W, The development of simple survival prediction models for blunt trauma victims treated at Asian emergency centers. *Scand J Trauma Resusc Emerg Med.* 2012;20:9.
109. Hwang SY, Lee JH, Lee YH et al., Comparison of the Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation II scoring system, and Trauma and Injury Severity Score method for predicting the outcomes of intensive care unit trauma patients. *Am J Emerg Med.* 2012;30(5):749-53.
110. Kim Y, Jung KY, Kim CY et al., Validation of the International Classification of Diseases 10th Edition-based Injury Severity Score (ICISS). *J Trauma*. 2000;48(2):280-5.
111. Rabbani A, Moini M, Application of "Trauma and Injury Severity Score" and "A Severity Characterization of Trauma" score to trauma patients in a setting different from "Major Trauma Outcome Study". *Arch Iran Med*. 2007;10(3):383-6.
112. Kondo Y, Abe T, Kohshi K et al., Revised trauma scoring system to predict in-hospital mortality in the emergency department: Glasgow Coma Scale, Age, and Systolic Blood Pressure score. *Crit Care*. 2011;15(4):R191.
113. Nakahara S, Ichikawa M, Kimura A, Simplified alternative to the TRISS method for resource-constrained settings. *World J Surg.* 2011;35(5):512-9.
114. Gabbe BJ, Cameron PA, Wolfe R et al., Predictors of mortality, length of stay and discharge destination in blunt trauma. *ANZ J Surg*. 2005;75(8):650-6.
115. Schluter PJ, Cameron CM, Davey TM et al., Contemporary New Zealand coefficients for the Trauma Injury Severity Score: TRISS(NZ). *New Zealand Med J*. 2009;122(1302):54-64
116. Wolfe R, McKenzie DP, Black J et al., Models developed by three techniques did not achieve acceptable prediction of binary trauma outcomes. *J Clin Epidemiol*. 2006;59(1):26-35.
117. Willis CD, Gabbe BJ, Jolley D et al., Predicting trauma patient mortality: ICD or ICD-10-AM] versus AIS based approaches. *ANZ J Surg*. 2010;80(11):802-6.
118. Davie G, Cryer C, Langley J, Improving the predictive ability of the ICD-based Injury Severity Score. *Inj Prev.* 2008;14(4):250-5.
119. Kahloul M, Bouida W, Boubaker H et al., Value of anatomic and physiologic scoring systems in outcome prediction of trauma patients. *Eur J Emerg Med.* 2014;21(2):125-9.
120. Mengistu Z, Azaj A, Trauma severities scores and their prediction of outcome among trauma patients in two hospitals of Addis Ababa, Ethiopia. *Ethiop Med J*. 2012;50(3):231-7.
121. Schluter PJ, The Trauma and Injury Severity Score (TRISS) revised. *Injury*. 2011;42(1):90-6.

SUPPLEMENTAL FILE 1

Search strategy

Database	*Search (N)*	*After removing duplicates (N)*
Embase.com	2449	2413
Medline (ovid)	2461	921
Web-of-science	2691	1457
Cinahl (ebsco)	785	278
PubMed publisher	194	171
Cochrane	49	11
Google scholar	250	171
Total	**8879**	**5422**

Embase.com (N=2449)

(injury/de OR 'accidental injury'/exp OR 'blunt trauma'/de OR 'crush trauma'/de OR 'injury scale'/exp OR 'injury severity'/exp OR 'penetrating trauma'/exp OR (injur* OR trauma* OR polytrauma* OR multitrauma*):ab,ti) AND (((model/de OR 'scoring system'/exp OR 'rating scale'/exp OR 'injury scale'/exp) AND ('validation study'/exp OR 'validation process'/exp OR 'instrument validation'/exp OR reliability/exp OR reproducibility/de OR 'sensitivity and specificity'/exp OR 'area under the curve'/exp OR accuracy/de)) OR (((model* OR instrument OR 'scoring system' OR 'scoring systems' OR 'trauma score' OR 'trauma scores') NEAR/6 (valid* OR develop* OR reliab* OR sensitiv* OR specificit* OR auc OR 'area under the curve' OR roc OR perform* OR compar* OR accura* OR value OR reproducib*))):ab,ti) AND (mortality/exp OR survival/exp OR death/de OR fatality/de OR (mortalit* OR surviv* OR death):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline (ovid) (N=2461)

("Wounds and Injuries"/ OR "Wounds, Nonpenetrating"/ OR exp "Trauma Severity Indices"/ OR "Wounds, Penetrating"/ OR (injur* OR trauma* OR polytrauma* OR multitrauma*).ab,ti.) AND (((Models, Theoretical/ OR exp "Models, Statistical"/ OR "Trauma Severity Indices"/) AND ("validation studies"/ OR "Validation Studies as Topic"/ OR "Reproducibility of Results"/ OR exp "Sensitivity and Specificity"/)) OR (((model* OR instrument OR "scoring system" OR "scoring systems" OR "trauma score" OR "trauma scores") ADJ6 (valid* OR develop* OR reliab* OR sensitiv* OR specificit* OR auc OR "area under the curve" OR roc OR perform* OR compar* OR accura* OR value OR reproducib*))).ab,ti.) AND (mortality/ OR mortality.xs. OR survival/ OR "Fatal Outcome"/ OR "Survival Rate"/ OR (mortalit* OR surviv* OR death).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane (N=49)

((injur* OR trauma* OR polytrauma* OR multitrauma*):ab,ti) AND ((((model* OR instrument OR 'scoring system' OR 'scoring systems' OR 'trauma score' OR 'trauma scores') NEAR/6 (valid* OR develop* OR reliab* OR sensitiv* OR specificit* OR auc OR 'area under the curve' OR roc OR perform* OR compar* OR accura* OR value OR reproducib*))):ab,ti) AND ((mortalit* OR surviv* OR death):ab,ti)

Web-of-science (N=2691)

TS=(((injur* OR trauma* OR polytrauma* OR multitrauma*)) AND ((((model* OR instrument OR "scoring system" OR "scoring systems" OR "trauma score" OR "trauma scores") NEAR/6 (valid* OR develop* OR reliab* OR sensitiv* OR specificit* OR auc OR "area under the curve" OR roc OR perform* OR compar* OR accura* OR value OR reproducib*)))) AND ((mortalit* OR surviv* OR death)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR pig OR pigs OR swine OR porcine OR rabbit* OR rodent* OR sheep OR ovine OR monkey*) NOT (human* OR patient*))) AND DT=(article)

Cinahl (ebsco) (N=785)

(MH "Wounds and Injuries" OR MH "Wounds, Nonpenetrating" OR MH "Trauma Severity Indices+" OR MH "Wounds, Penetrating+" OR (injur* OR trauma* OR polytrauma* OR multitrauma*)) AND (((MH "Models, Theoretical" OR MH "Models, Statistical+" OR MH "Trauma Severity Indices+") AND (MH "validation studies+" OR MH "Reproducibility of Results+" OR MH "Sensitivity and Specificity+")) OR (((model* OR instrument OR "scoring system" OR "scoring systems" OR "trauma score" OR "trauma scores") N6 (valid* OR develop* OR reliab* OR sensitiv* OR specificit* OR auc OR "area under the curve" OR roc OR perform* OR compar* OR accura* OR value OR reproducib*)))) AND (MH mortality OR MW mortality OR MH survival OR MH "Fatal Outcome" OR (mortalit* OR surviv* OR death)) NOT (MH animals+ NOT MH humans+) AND LA english NOT PT (letter OR news OR comment OR editorial OR congresses OR abstracts)

PubMed publisher (N=194)

("Wounds and Injuries"[mh] OR "Wounds, Nonpenetrating"[mh] OR "Trauma Severity Indices"[mh] OR "Wounds, Penetrating"[mh] OR (injur*[tiab] OR trauma*[tiab] OR polytrauma*[tiab] OR multitrauma*[tiab])) AND (((Models, Theoretical[mh] OR "Models, Statistical"[mh] OR "Trauma Severity Indices"[mh]) AND ("validation studies"[mh] OR "Validation Studies as Topic"[mh] OR "Reproducibility of Results"[mh] OR "Sensitivity and Specificity"[mh])) OR (((model*[tiab]) AND (validat*[tiab] OR develop*[tiab] OR reliabilit*[tiab] OR sensitiv*[tiab] OR specificit*[tiab] OR accura*[tiab] OR reproducib*[tiab])))) AND (mortality[mh] OR mortality[sh] OR survival[mh] OR "Fatal Outcome"[mh] OR "Survival

Rate"[mh] OR (mortalit*[tiab] OR surviv*[tiab] OR death)) NOT (animals[mh] NOT humans[mh]) AND english[la] NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR congresses[pt] OR abstracts[pt]) AND publisher[sb]

Google scholar (N=250)

injury|trauma|polytrauma|multitrauma "model|instrument validation|development|reliability|sensitivity|specificitity|performance|accuracy| reproducibility"|" validated|developed|performance * model|instrument " mortality|survival

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SUPPLEMENTAL FILE 2

Supplemental Table 2. Data extraction table of the 90 included articles in this review.

First author (year)	N	Outcome (%)	Population	Model						Performance		Purpose	Missing
				Name	Physiological	demographical	Anatomical	Injury cause/ mechanism	Additional	AUROC	H-L		
Ahun (2014)[24]	100	4-week mortality (12)	1) ≥ 18 years	TRISS[2a]	RTS	Age (dich)	ISS (con)			0.904		DM and T	No missings
			2) major trauma	GAP[2a]	SBP (cat), GCS (con)	Age (dich)				0.911			
			3) pregnant patients and those with psychiatric illnesses were excluded	MGAP[2a]	GCS (con), SBP (cat)	Age (dich)		dich		0.938			
Aydin (2008)[97]	550	mortality (21.6)	1) > 16 years 2) injuries in at least two organ systems	TRISS 1[2a]	RTS	Age (dich)	ISS (con)			0.934		QA	UK
				TRISS 2[2a]	RTS	Age (dich)	NISS (con)			0.935			
Bartolomeo (2011)[19]	3570	In-hospital mortality (12.11)	1) ≥ 1 year 2) ISS >15	ISS model[1]	GCS-motor, SBP (cat)	Age (con), gender	ISS (con)	dich		0.883 and 0.901		UK	CCA
				TMPM model[1]	GCS-motor, SBP (cat)	Age (con), gender	ICD-9-CM (5 worst injuries)	dich		0.870 and 0.898			
Batchinsky (2007)[27]	117	Mortality (35.5)	1) delivery via Life Flight helicopter to a regional Level I trauma center in Houston.	model 1[1]					approximate entropy, distribution of symbol 2	0.956 (0.86, 1,0)	p-value: >0.2	T	CCA
				model 2[1]	GCS-motor				approximate entropy,	0.886 (0.75, 1.0)	p-value: >0.2		

									distribution of symbol 2				
				model 3[1]	GCS-motor				approximate entropy	0.92 (0.80, 1.0)	p-value: >0.2		
				model 4[1]			ISS		approximate entropy	0.977 (0.91, 1.0)	p-value: >0.2		
Belzunegui (2013)[96]	378	Mortality (18.8)	1) NISS ≥ 15 2) burn patients, patients declared dead before arrival, admission more than 24 hours after injury or victim of asphyxia or drowning were excluded	TRISS[2a]	RTS	Age (dich)	ISS (con)			0.87 (0.83, 0.92)		QA	UK
				model 1[1]	RTS	Age (con)	NISS (con)		comorbidity (dich)	0.93 (0.91, 0.96)			
				model 2[1]	RTS (dich)	Age (dich)	NISS (dich)		comorbidity (dich)	0.88 (0.85, 0.92)			
Bergeron (2004)[4]	5672	In-hospital mortality (6.9)	1) blunt trauma patients 2) ≥ 15 years 3) admitted to a tertiary trauma center	TRISS[2a]	RTS	Age (dich)	ISS (con)			0.873 (0.850, 0.895)	144.7 (8)	QA	WCS
				TRISS[3]	RTS	Age (dich)	ISS (con)			0.878 (0.855, 0.900)	23.2 (7)		
				TRISS – 2[1]	RTS	Age (cat)	ISS (cat)			0.864 (0.839, 0.888)	9.8 (4)		
				TRISS – 3[1]	RTS	Age (cat)	ISS (cat)			0.903 (0.883, 0.923)	25.0 (4)		
				TRISSCOM[1]	RTS	Age (cat)	ISS (cat)		comorbidity (dich)	0.914 (0.896, 0.932)	10.2 (4)		
Bouamra (2006)[36]	development set: 48755 validation set: 20895	30-day mortality (4.4)	1) blunt trauma patients admitted to the hospital for 3 days or longer. 2) children, penetrating, transfers, burns, intubation/ventilation and patients with isolated hip fracture (>65 year) and with single uncomplicated limb injuries were excluded.	TRISS – new[1,2b]	RTS	Age (dich)	ISS (con)			0.941	64 (p-value: 0.000)	QA	CCA
				new model[1,2b]	GCS (cat)	Age (cat), gender	ISS (con)			0.942	15 (p-value: 0.113)		
Bouamra (2006)[103]	development set: 48755 validation set: 20895	30-day mortality (4.37)	1) blunt trauma patients admitted to the hospital for 3 days or longer. 2) children, penetrating, transfers, burns, intubation/ventilation and patients with isolated hip fracture (>65 year) and with single uncomplicated limb injuries were excluded.	TRISS[2a]	RTS	Age (dich)	ISS (con)			0.937 (0.932,0.943)		QA	CCA
				Model A[1,2b]	GCS (cat)	Age (cat), gender * age	ISS (con)			0.952 (0.946,0.957)			
Brilej (2010)[37]	148 (TRISS) and 149 (RISC)	Mortality (17)	1) ISS ≥ 18 2) isolated injuries and AIS of 5 in individual regions 3) AIS ≥ 4 and affected vital signs, and continuation of treatment in the ICU 4) at least two fractures of long tubular bones, pelvis or vertebrae and affected vital signs	TRISS[2a]	RTS	Age (dich)	ISS (con)	dich		0.89	21.1 (p-value=0.01)	QA	CCA
				RISC[2a]	Partial thromboplastin time (cat) & Base excess (cat) & bleeding signs (cat) & cardiac arrest (dich)	Age (cat)	NISS & AIS-head (cat) & AIS-extremities (cat)			0.94	3.5 (not significant)		

Brockamp (2013)[122]	4949	30-day mortality (9.10)	1) ≥ 18 years 2) ISS ≥ 4	BIG^{1}	base deficit, GCS				International Normalized Ratio (con)	0.849 (0.830 - 0.868)		QA	CCA
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.896 (0.882 - 0.909)			
				PS09 Score^{1}	GCS	Age (dich), gender, gender * age	ISS (con)		intubation (dich)	0.901 (0.887 - 0.914)			
Burd (2008)[84]	NTDB training: 447442 NTDB testing: 312592 NIS: 276366	In-hospital mortality (2.8, 4.8 and 5.1)	1) diagnosis of late effects of injury, foreign bodies entering through an orifice, and burns.	BLISS^{1,2c}	Injury codes, E-codes	Age (cat)		dich	two-way and three-way injury interaction, age*injury, injury type*injury, E-code*injury	~0.892	~1,347	QA	CCA
Champion (1996)[85]	14296	Mortality (9.7)	All clinical trauma patients	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		> 0.91	138.4	UK	CCA
				ASCOT^{2a}	RTS	Age (cat)	AP			> 0.91	20.3		
Chan (2014)[28]	5684	In-hospital mortality (11.9)	All clinical trauma patients	Model 1^{1,2d}	RTS	Age (con)	ISS	dich		0.932 (0.923 to 0.940)	p-value: 0.402	QA	CCA
				Model 2^{1,2d}	RTS	Age (dich)	ISS	dich		0.920 (0.910 to 0.930)	p-value: 0.038		
				Model 3^{1}	RTS	Age (cat)	ISS	dich		0.927 (0.917 to 0.936)	p-value: 0.050		
				Model 4^{1}	RTS	Age (dich)	ISS	dich		0.923 (0.913 to 0.933)	p-value: 0.070		
				MTOS TRISS^{2a}	RTS	Age (dich)	ISS	dich		0.886 (0.873 to 0.898)			
Cinelli (2009)[49]	34 (deaths)	In-hospital mortality (UK)	1) blunt trauma patients 2) patients with burns were excluded	TRISS^{2a}	RTS	Age (dich)	ISS	dich				QA	UK
				TRISSCOM^{1}	RTS	Age (dich)	ISS	dich	comorbidities (dich)				
				TRISSCOM – 2^{1}	RTS	Age (cat)	ISS	dich	comorbidities (dich)				
Corbanese (1996)[51]	162	In-hospital mortality (13)	1) trauma patients admitted to the ICU	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.963 (0.921, 0.986)	16.9 (p-value: 0.07)	QA	CCA
Davie (2008)[118]	186835	In-hospital mortality (5.3)	All clinical trauma patients	ICISS – 1^{1}			ICISS		HARM (ICD-codes)	0.874 (0.870 to 0.877)	1233	UK	UK
				ICISS – 2^{1}			ICISS		HARM (specific comorbidities)	0.866 (0.863 to 0.870)	1256		
				ICISS – 3^{1}			ICISS		CCI (ICD-codes)	0.891 (0.888 to 0.895)	926		
				ICISS – 4^{1}			ICISS		CCI (specific comorbidities)	0.885 (0.882 to 0.888)	910		
de Jongh (2010)[69]	Total: N=10777 subset: N=2720	30-day mortality (5.1)	All clinical trauma patients	MTOS^{2a}	RTS	Age (dich)	ISS (con)			0.905(0.892, 0.918)	figure	QA	CCA
				TARN Ps04/TARN Ps07^{2a}	GCS (cat)	Age (con), gender	ISS (con)			0.924 (0.913, 0.934)	figure		
				BISS^{2a}	delta base deficit	Age (con)	ISS (con)			0.875 (0.859, 0.892)	figure		
				BISSGCS^{1}	GCS (cat) & delta base deficit	Age (con)	ISS (con)			0.904 (0.890, 0.918)	figure		
Demetriades (1998)[79]	5445	Mortality (8.8)	1) Major trauma patients	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich				QA	CCA

Eftekhar (2005)[58]	7226	Mortality (3.8)	All clinical trauma patients	ISS / age^{1}	ISS	Age (dich)	ISS			0.948		UK	CCA
				TRISS^{2a}	RTS	Age (dich)	ISS	dich		0.969			
				RTS / age^{1}	RTS	Age (dich)				0.956			
				GCS / age^{1}	GCS	Age (dich)				0.955			
				GMR / age^{1}	GCS - Motor	Age (dich)				0.946			
				M / age^{1}	GCS - Motor (dich)	Age (dich)				0.942			
				MGMR / age^{1}	Modified GCS-motor (cat)	Age (dich)				0.947			
Frankema (2002)[99]	1024	In-hospital mortality (6.9)	1) exclusion of low-energy monotrauma 2) ≥ 15 year	TRISS^{2a,3}	RTS	Age (dich)	ISS (con)	dich		0.975	p-value: 0.02	QA	UK
				ASCOT^{2a,3}	RTS	Age (cat)	AP	dich		0.973	p-value: 0.28		
Frankema (2005)[98]	1102	In-hospital mortality (11)	1) exclusion of low-energy monotrauma 2) ≥ 15 year	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.940	22.32	UK	No missings
				ASCOT^{2a}	RTS	Age (cat)	AP	dich		0.956	13.90		
				ISS-model^{1}	RTS		ISS (con)	dich		0.953			
				NISS-model^{1}	weighted RTS		NISS	dich		0.966			
				AP-model^{1}	weighted RTS		AP	dich		0.959			
Fueglistaler (2010)[65]	237	30-day mortality (22.8)	1) ISS > 16 2) patients with mono trauma, ISS ≤ 16, or secondarily admitted from another hospital were excluded.	SOFA day 1^{2a}	PaO2/FIO2, GCS, arterial pressure, bilirubin, coagulation, creatinine (all cat)					0.79		QA	MI
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.83			
				PTS + SOFA^{2a}	PaO2/FIO2, GCS, arterial pressure, bilirubin, coagulation, creatinine (all cat)				site of injury (cat)	0.83			
				TRISS + SOFA^{2a}	PaO2/FIO2, GCS, arterial pressure, bilirubin, RTS, coagulation, creatinine (all cat)	Age (dich)	ISS (con)	dich		0.86			
				SAPS + SOFA^{2a}	PaO2/FIO2, GCS, arterial pressure, bilirubin, coagulation, creatinine (all cat), APS				chronic diseases & type of admission (both cat)	0.87			
Gabbe (2004)[39]	2819	In-hospital mortality (11.5)	1) only blunt trauma patients 2) ≥ 15 years 3) ISS > 15	TRISS^{2a}	RTS	Age (dich)	ISS (con)			0.83 (0.81, 0.86)	75.9 (p-value: < 0.001)	QA	CCA
				TRISS + CCI^{1}	RTS	Age (cat)	ISS (con)		CCI	0.86 (0.84, 0.88)	70.3 (p-value: < 0.001)		
				TRISSc^{1}	RTS	Age (con)	ISS (con)			0.91 (0.89, 0.92)	32.1 (p-value: < 0.001)		
				TRISSc + CCI^{1}	RTS	Age (con)	ISS (con)		CCI	0.91 (0.90, 0.92)	25.3 (p-value: < 0.001)		
Gabbe (2005)[114]	design set: 2059 validation set: 1387	In-hospital mortality (2.9 and 4.4)	1) Admission to an ICU for >24 h, requiring mechanical ventilation	new-model^{1,2a}	SBP (con), Pulse rate (con), GCS-motor (con), GCS-eye (con)	Age (con)	ISS (cat)		complications (dich), Triage (cat), patient funding (dich),	0.90		QA	CCA

			2) Significant injury to two or more ISS body regions or an ISS >15 3) Urgent surgery hospital admission for >3 days 4) Patients with penetrating, isolated hip fracture, an isolated soft tissue injury, or burns to <10% of the body were excluded						place of injury (cat)				
				TRISS[2a]	RTS	Age (dich)	ISS (con)			0.87			
				ASCOT[2a]	RTS	Age (cat)	AP			0.78			
Gabbe (2005)[66]	development set: 1330 validation set: 1312	In-hospital mortality (4.7 and 6.7)	1) Patients with isolated fractured neck of femur, an isolated closed limb fracture, an isolated injury distal to the wrist or ankle, an isolated soft tissue injury, or burns to <10% of the body were excluded 2) blunt trauma patients	Complex[1,2a]	GCS-motor, Pulse Rate (con), SBP (con), RR (con), GCS-verbal	Age (con)				0.86	35.4 (p-value: 0.001)	Triage	CCA
				Categorical[1,2a]	GCS-motor, Pulse Rate (cat), RR (cat), GCS-verbal	Age (cat)				0.86	28.7 (p-value: 0.001)		
				Simple[1,2a]	GCS-motor, Pulse Rate (con)	Age (con)				0.86	41.1 (p-value: 0.001)		
Garber (1996)[80]	5436	mortality (7)	1) ISS > 12 2) blunt trauma patients	TRISS[2a]	RTS	Age (dich)	ISS (con)				25.62 (p-value: >0.005)	QA	CCA
				OTRs-TRISS[3]	RTS	Age (dich)	ISS (con)				11.42 (p-value: 0.175)		
				OTRr-TRISS[3]	RTS	Age (dich)	ISS (con)				13.1 (p-value: 0.125)		
Garber (1997)[86]	7702	In-hospital mortality (12.3)	1) ISS > 12 2) admission to level 1 trauma hospitals in the province 3) blunt trauma patients	TRISS-like[1,2b]	SBP, GCS-motor	Age (con)	ISS			0.873		QA	CCA
Glance (2009)[2]	749374 (60% MARC development data set, 20% TMPM-ICD9 development data set and 20% validation data set)	In-hospital mortality (4.96)	1) hospitals admitting ≥ 500 patients per year 2) ≥ 1 year	ICISS[1,2b]		Age (con), gender	ICISS	6 categories		0.887 (0.884, 0.891)	44.7 (24.6–60.1)	QA	CCA
				Single Worst Injury[1,2b]		Age (con), gender	ICD-9-CM (most severe injury)	6 categories		0.892 (0.888, 0.895)	144 (101–185)		
				TMPM-ICD9[1,2b]		Age (con), gender	ICD-9-CM (5 worst injuries), 2 worst injuries (interaction), same region (dich)	6 categories		0.907 (0.903, 0.910)	16.9 (10.2–22.0)		
Glance (2009)[20]	66214	In-hospital mortality (4.22)	≥1 year	ISS – model[1]		Age (con), gender	ISS	dich		0.905	47.0	QA	MI
				ISS - model 2[1]	GCS-motor	Age (con), gender	ISS	dich		0.956	15.7		
				T-MPM – 1[1]		Age (con), gender	ICD-9-CM (5 worst injuries), 2 worst injuries (interaction), same region (dich)	dich		0.927	14.9		
				T-MPM – 2[1]	GCS-motor	Age (con), gender	ICD-9-CM (5 worst injuries), 2 worst injuries (interaction), same region (dich)	dich		0.962	25.2		

Glance (2010)[23]	474987	In-hospital mortality (2.51)	1) patients with burns, unspecified injuries, late effects, superficial or foreign bodies injuries were excluded	TMPM[1]		Age (con), gender	ICD-9-CM (5 worst injuries)	dich		0.882 (0.875–0.889)	12.72 (5.18–16.54)	QA	CCA
				TMPM-comorbidities[1]		Age (con), gender	ICD-9-CM (5 worst injuries)	dich	AHRQ-comorbidity	0.906 (0.901–0.913)	10.40 (5.85–12.47)		
Gunning (2014)[105]	Regional dataset: N=10235 Level I dataset: N= 4649	In-hospital mortality (3.3)	1) ≥ 18 years 2) limited to blunt trauma population	TRISS – 1[1,2a]	GCS & SBP	Age (dich)	ISS			0.939 (0.928,0.950)	13.25	QA	MI
				TRISS – 2[1]	GCS	Age (dich)	ISS			0.938 (0.927,0.949)	14.16		
Guzzo (2005)[72]	2412	mortality (4.5 and 15.1)	All clinical trauma patients	PTS[1]	GCS	Age (con)	SIRS			0.95 (0.93–0.96)	8.76	UK	CCA
				TRISS[2a]	RTS	Age (dich)	ISS (con)			0.97 (0.96–0.98)	93.63		
				mortality predictive equation[1]	GCS & base excess & transfusion requirement	Age (con)	ISS (con)			0.91 (0.89–0.93)	24.49		
Haac (2015)[30]	2884	Mortality (5)	1) All adult admitted trauma patients 2) Patients admitted through outpatient orthopedics and/or found on the surgical wards	KTS[2a]	SBP (cat), RR (cat), Neurological status (Cat)	Age (cat)		Number of serious injuries (cat)		0.593		T	CCA
Hadzikadic (1996)[50]	development: 1940 validation: 215	In-hospital mortality (7)	1) all trauma patients admitted to a level I trauma center	model 1[1]	TS, GCS-eye (cat)	Age (dich)			airway management, head CT scan (dich), cardiac complications (dich), ISS*TS			QA	UK
Haider (2014)[87]	2009(IM): 630307 2010(FM): 665138	In-hospital mortality (UK)	1) all clinical trauma patients. 2) patients who were dead on arrival or who experienced burns were excluded.	new-model[1,2c]	hypotension, pulse, RR, GCS (con)	Age (con), gender, race (cat)	ISS (cat), severe head injury (dich)	cat	ICU admission (dich), need for ventilator use (dich), insurance status (dich), level trauma center (cat), mode of transportation (cat)	0.9578 (0.9565-0.9590) and 0.9577 (0.9564-0.9589)		QA	CCA
Hannan (1995)[81]	4465	In-hospital mortality (6.8)	1) >13 years 2) blunt trauma patients	TRISS[3]	RTS, ISS (con)	Age (dich)	ISS (con)				6.3	QA	UK
				ASCOT[1]	RTS	Age (cat)	AP						
Hannan (1999)[88]	20883	In-hospital mortality (7.15)	1) >12 years 2) ISS ≥ 9	TRISS[2a]	RTS	Age (dich)	ISS (con)	dich			687.38	QA	CCA
				TRISS [3]	RTS	Age (dich)	ISS (con)	dich		0.96			
Hasler (2013)[104]	79807	30-day mortality (6.86)	1) >16 years 2) patients with nontraumatic brain injuries, simple skin lacerations, concussions or abrasions, minor penetrating injuries, singular uncomplicated limb injuries; and patients older than 65 years with isolated fractures of the femoral neck or pubic ramus are excluded.	GAP[2a]	SBP (cat), GCS (con)	Age (dich)				0.872 (0.867-0.877)		T	MI and CCA
				MGAP[2a]	SBP (cat), GCS (con)	Age (dich)		dich		0.868 (0.862-0.873)			
Hwang (2012)[109]	706	30-day mortality (20.8)	1) ≥ 15 year 2) patients with burns were excluded 3) trauma patients admitted to ICU	SOFA[2a]	PaO2/FIO2, GCS, arterial pressure, bilirubin, coagulation, creatinine (all cat)			dich		0.953 (0.937-0.969)	8.006	QA	CCA

				APACHE II[2a]	APS (con)	Age (cat)			chronic health score (cat)	0.950 (0.931-0.965)	9.521		
				TRISS[2a]	RTS	Age (dich)	ISS (con)			0.922 (0.900-0.941)	10.992		
Huber-Wagner (2010)[67]	development set: 1760 validation set: 594	mortality (16.5)	1) every injured patient admitted to one of the participating trauma hospitals 2) ISS ≥ 16 or ICU treatment is documented 3) ISS < 9 were excluded 4) patients who were transferred from other hospitals were excluded	model A[1]	SBP, pulse rate, GCS, anisocoria (all dich and prehospital)					0.75 (0.68, 0.81)	3.69 (p-value: 0.138)	DM	CCA
				model P+A[1]	SBP, pulse rate, GCS, anisocoria (all dich and prehospital)	Age (dich)				0.79 (0.73, 0.85)	4.68 (p-value: 0.322)		
				model B1[1]	O2 saturation, Base excess, Thromboplastin time, GCS, anisocoria (all dich and during trauma room phase)					0.77 (0.71, 0.83)	4.66 (p-value: 0.200)		
				model P+A+B1[1]	SBP, GCS, anisocoria (all dich and prehospital) and O2 saturation, Base excess, Thromboplastin time, anisocoria (all dich and during trauma room phase)	Age (dich)				0.82 (0.76, 0.88)	6.92 (p-value: 0.230)		
				Model B2[1]	CCCM, blood transfusion, massive transfusion		AIS-head (dich), AIS-max (cat)			0.82 (0.77, 0.87)	11.04 (p-value: 0.137)		
				Model p+A+B1+B2[1]	GCS, anisocoria (all dich and prehospital) and Base excess, Thromboplastin time, anisocoria, CCCM, massive tranfsusion (all dich and during trauma room phase)	Age (dich)	AIS-max (cat)			0.87 (0.82, 0.91)	6.01 (p-value: 0.420)		
				TRISS[2a]	RTS	Age (dich)	ISS (con)	dich		0.84 (0.79, 0.90)	35.60 (p-value < 0.001)		
				RISC[1]	Partial thromboplastin time (cat) & Base excess (cat) & bleeding signs (cat) & cardiac arrest (dich)	Age (cat)	NISS & AIS-head (cat) & AIS-extremities (cat)			0.89 (0.85, 0.93)	8.34 (p-value: 0.400)		
Imhoff (2014)[82]	3680	Mortality (5.20)	1) ≥ 14 year	REMS[1]	arterial pressure (cat), Heart rate (cat), RR (cat), O2-saturation (cat), GCS (cat)	Age (cat)				0.91		QA	CCA
Jones (1995)[73]	development sample: 2466 validation sample: 1334	30-day mortality (3.4)	1) blunt trauma patients	British model[1,2b]	RTS	Age (cat)	ISS (con)		place of injury (cat)			QA	CCA

Jones (2014)[6]	development set: 5363 validation set: 2517	30-day mortality (development set: 7.9% and 6.2% in validation set)	1) arrival within 24h after injury 2) ISS ≥ 10 3) AIS head ≥ 3, and/or with penetrating injuries towards the head, neck torso, and/or proximal to elbow or knee irrespective of ISS 4) Patients with isolated single extremity fracture were excluded unless the trauma team was activated.	NORMIT^{1,2c}	T-RTS (con)	Age (con)	NISS		ASA (cat)	0.946 (0.930, 0.962)		QA	CCA
Joosse (2014)[106]	4418 (cohort I: 3001, cohort II : 1417)	In-hospital mortality (6.7 and 14.3)	1) ≥ 16 years	EMTRAS^{2a}	GCS (cat) & base excess (cat) & prothrombin time (cat)	Age (cat)				Cohort I: 0.94(0.93, 0.96) & cohort II: 0.92 (0.90, 0.94)		DM	MI
Kahloul (2014)[119]	1136	In-hospital mortality (4.5)	1) ≥ 14 years	SAPS + NISS^{2a}	APS	Age (con)	NISS		chronic diseases & type of admission (both cat)	0.95 (0.92–0.98)	7.06	QA	UK
				SAPS + ISS^{2a}	APS	Age (con)	ISS		chronic diseases & type of admission (both cat)	0.95 (0.93–0.97)	9.73		
Kilgo (2006)[71]	310958	mortality (5.01)	1) ≥ 16 years	Model 1^{1}	GCS motor	Age (dich)	worst SRR			0.955	528	UK	CCA
				Model 2^{1}	GCS motor	Age (dich)	worst SRR	dich		0.953	344		
				Model 3^{1}	GCS motor	Age (con)	worst SRR			0.954	667		
				Model 4^{1}	GCS motor	Age (con)	worst SRR	dich		0.953	554		
				MTOS TRISS^{2a}	RTS	Age (con)	ISS	dich		0.939	2651		
				NTDB TRISS^{2a}	RTS	Age (con)	ISS	dich		0.950	380		
Kim (2000)[110]	367	mortality (21.3)	1) hospital A: severely injured patients who met the level I trauma center T criteria 2) hospital B: ISS > 10	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.958	3.4055 (p-value: 0.9064)	QA	CCA
				ICISS-9 full^{1}	RTS	Age (dich)	ICISS (ICD-9)			0.976	7.7377 (p-value: 0.4595)		
				ICISS-10 full^{1}	RTS	Age (dich)	ICISS (ICD-10)			0.956	7.2944 (p-value: 0.5052)		
Kimura (2012)[40]	JTDB: 15524 Khon Kaen: 6411	In-hospital mortality (15 and 4.1)	1) blunt trauma patients	TRISS^{2a}	RTS	Age (dich)	ISS (con)			0.9625 & 0.9628		QA	CCA
				ISS – 1^{1}	RTS	Age (dich)	ISS (con)			0.9598 & 0.9657			
				ISS – 2^{1}	RTS	Age (con)	ISS (con)			0.9624 & 0.9666			
				ISS – 3^{1}	SBP (cat), GCS (cat), RR (cat)	Age (con)	ISS (con)			0.9624 & 0.9667			
				ISS – 4^{1}	SBP (cat), GCS (cat)	Age (con)	ISS (con)			0.9617 & 0.9667			

Kimura (2012)[108]	Japan: 10210 Thailand: 6409	Mortality (4.1 and 16.9 and 17.9)	1) blunt trauma patients	TRISS^{1,2a}	RTS (con)	Age (dich)	ISS (con)			0.9627		QA	CCA
				TRISS -1^{3}	RTS(con)	Age (dich)	ISS (con)			0.9637			
				TRISS - 2 to 12^{1,2a}	SBP (cat) and/or GCS (cat) and/or RR(cat)	Age (dich)	ISS (con/cat)			range: 0.9433 - 0.9648			
Kondo (2011)[112]	derivation set: 13463 validation set: 13691	In-hospital mortality (15)	1) ≥ 16 years 2) ISS >3	TRISS^{3}	RTS	Age (dich)	ISS (con)	dich		0.948		CDM	CCA
				MGAP^{1,2b}	GCS & Arterial pressure	Age (dich)		dich		0.924			
				GAP^{1,2b}	GCS (at ED) & SBP (at ED)	Age (dich)				0.933			
Kroezen (2007)[16]	Tilburg: N=349 Utrecht: N=179	In-hospital mortality (14 and 22.3)	All clinical trauma patients	TRISS^{3}	RTS	Age (dich)	ISS (con)			0.891		QA	UK
				TRISS - 2^{1,2a}	RTS	Age (dich)	ISS (con)			0.811	0.53		
				BISS^{1,2a}	delta base deficit	Age (dich)	ISS (con)			0.793			
				BISS – 2^{1,2a}	delta base deficit	Age (con)	ISS (con)			0.803	0.33		
Kuhls (2002)[59]	9539	Mortality (7.15)	1) adult patients	SIRS^{1}	GCS	Age (con)	SIRS		SIRS * GCS	0.95	2.84	T	UK
				SIRS-2^{1}	GCS	Age (con)	SIRS			0.95	3.58		
				SIRS-3^{1}	RTS	Age (con)	SIRS			0.95	5.94		
				SIRS-4^{1}	RTS	Age (con)	SIRS		SIRS * RTS	0.95	6.25		
				SIRS-5^{1}		Age (con), gender	SIRS			0.84	10.18		
				TRISS^{2a}	RTS	Age (dich)	ISS	dich		0.96	44.39		
Lefering (2009)[32]	development: 1206 validation: 802	Mortality (16.2 and 16.6)	1) burns, poisoning, drowning and hip fractures in elderly were excluded	TRISS^{3}	RTS	Age (dich)	ISS (con)			0.860 (0.827–0.892)	101.0	QA	MI and CCA
				RISC^{1,2b}	Partial thromboplastin time (cat) & Base excess (cat) & bleeding signs (cat) & cardiac arrest (dich)	Age (cat)	NISS & AIS-head (cat) & AIS-extremities (cat)			0.909 (0.879–0.938)	6.7		
Mengistu (2012)[120]	3260	In-hospital mortality (18.3)	1) All admitted patients with age of 15 and above 2) Severely injured patients: AIS with or without altered level consciousness 3) Patients who died during transportation, did not receive trauma care, or referred or transferred to other hospital were excluded	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.97			CCA
Millham (1995)[74]	retrospective: 1708 prospective: 508	Mortality (5 and 6)	1) patients with burns were excluded	pH-TRISS^{1,2a}	RTS, pH, PCO2		HCAISS					QA	CCA
				CpH-A^{1,2a}	PCO2, pH								
Millham (2004)[31]	72517	Mortality (5.4)	All clinical trauma patients	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.981	312.87	QA	CCA
				TRISS ^{3}	RTS	Age (dich)	ISS (con)	dich		0.981	27.71		
				TRISS – 2^{1}	RTS	Age (dich)	ISS (con)	dich	acute ethanol (dich)	0.980	17.03		
				TRISS – 3^{1}	RTS	Age (dich)	ISS (con) + ISS^2	dich	acute ethanol (dich)	0.980	18.53		

Moore (2007)[89]	25111	In-hospital mortality (7.3)	1) ≥ 16 years 2) no hip fractures	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich			694 (541–743	QA	UK
				log-TRISS^{1}	RTS	Age (dich)	ISS (con)	dich			93 (76–143)		
Moore (2008)[35]	QTR: 72572 NTDB: 178377	In-hospital mortality (6.3)	1) QTR: >16 yrs and NTDB: >16 yrs 2) blunt trauma patients 3) no hip fractures	TRISS^{3}	RTS	Age (dich)	ISS (con)			0.924	256	QA	MI
				TRAM^{1,2a}	RTS	Age (con)	AIS (2 most severe injuries), place of worst injury		Number of comorbidities	0.941	127		
Moore (2008)[90]	20583	In-hospital mortality (6.0)	1) ≥ 16 years 2) no hip fractures	BRM^{1}	RTS	Age (con)	NISS			0.935 (0.929, 0.940)	17	UK	MI
				BRM + preexisting condition^{1}	RTS	Age (con)	NISS		preexisting condition	0.941 (0.936, 0.946)	23		
				BRM + at least 1 preexisting condition^{1}	RTS	Age (con)	NISS		preexisting condition (bin)	0.937 (0.932, 0.942)	21		
				BRM + number of preexisting conditions^{1}	RTS	Age (con)	NISS		preexisting condition	0.939 (0.934, 0.944)	22		
				BRM + CCI^{1}	RTS	Age (con)	NISS		CCI	0.938 (0.933, 0.944)	19		
Moore (2008)[91]	25111	In-hospital mortality (7.3)	1) ≥ 16 years 2) no hip fractures	AIS^{1}	GCS(con), RR(con), SBP (con)	Age (con)	AIS (2 worst injuries), body region (worst injury)			0.938	20 (-)	QA	MI
				ISS^{1}	GCS(con), RR(con), SBP (con)	Age (con)	ISS (con)			0.932	34 (14)		
				NISS^{1}	GCS(con), RR(con), SBP (con)	Age (con)	NISS			0.936	29 (18)		
				APS^{1}	GCS(con), RR(con), SBP (con), APS	Age (con)				0.934	22 (15)		
				ICISS^{1}	GCS(con), RR(con), SBP (con)	Age (con)	ICISS			0.939	12 (12)		
				TRAIS^{1}	GCS(con), RR(con), SBP (con)	Age (con)	TRAIS			0.940	20 (18)		
Moore (2010)[38]	QTR: 72572 NTDB: 178377	In-hospital mortality (6.3 and 6.2)	1) QTR: >16 yrs and NTDB: >16 yrs 2) blunt trauma patients 3) no hip fractures	TRISS – MTOS^{2a}	RTS	Age (dich)	ISS (con)			0.930 (0.929–0.933)	296	QA	MI
				TRISS ^{3}	RTS	Age (dich)	ISS (con)			0.931 (0.928–0.933)	308		
				TRISS – age^{1,2a}	RTS	Age (cat)	ISS (con)			0.935 (0.932–0.937)	295		
				TRISS – GCS^{1,2a}	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	ISS (con)			0.939 (0.937–0.942)	229		
				NISS^{1,2a}	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	NISS (con)			0.940 (0.938–0.942)	144		
				APS^{1,2a}	GCS (con) & SPB (cat) & RR (cat), APS (con)	Age (cat)				0.938 (0.936–0.941)	93		
				OC^{1,2a}	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	AIS (2 worst), AIS(body regions)			0.942 (0.940–0.944)	135		

				ICISS[1,2a]	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	ICISS (con)			0.939 (0.937–0.942)	157		
				TRAIS[1,2a]	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	TRAIS (con)			0.941 (0.939–0.943	160		
				NCOM[1,2a]	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	ISS (con		number of comorbidities (cat)	0.942 (0.938–0.946)	68		
				GAM[1,2a]	GCS (con) & SPB (cat) & RR (cat)	Age (cat)	ISS (con)			0.946 (0.944–0.948)	85		
Moore (2010)[18]	88235	In-hospital mortality (5.36)	1) no hip fractures	TRAM[1]	RTS	Age (con)	AIS (2 worst injuries), body region (worst injury)		number of comorbidities & transfer			QA	MI
Moore (2010)[92]	83504	In-hospital mortality (5.7)	All clinical trauma patients	TRAM[2]	RTS	Age (con)	AIS (2 most severe injuries), place of worst injury		Number of comorbidities,			QA	MI
Nakahara (2011)[113]	9840	Mortality (18)	1) ≥ 15 years 2) blunt trauma patients	TRISS[3]	RTS	Age (dich)	ISS (con)			0.962	61.2	QA	CCA
				TRISS - 2 to 21[1]	GCS / GCSm / SBP / RR / AVPU (all cat)	Age (dich)	Max AIS (cat/con)		Number of injuries (cat)	range: 0.861 - 0.949	range: 7.0 - 64.7		
Osler (1996)[95]	New Mexico: 3142 North Carolina: 314402	In-hospital mortality (9 and UK)	all clinical trauma patients	ISS – model[1]	RTS	Age (con), gender	ISS (con)	cat		penetrating 0.959 & blunt 0.934		UK	UK
				ICISS[1]	RTS	Age (dich)	ICISS	dich		penetrating 0.973 & blunt 0.950			
Osler (2008)[21]	702229 (60% MARC development data set, 20% development data set and 20% performance evaluation)	In-hospital mortality (4.1)	1) hospitals admitting ≥ 500 patients per year 2) ≥ 1 year	ISS – model[1]		Age (con), gender	ISS	6 categories		0.904 (0.900, 0.908)	54 (23–73)	QA	CCA
				SWI – model[1]		Age (con), gender	ICD-9-CM (worst injury)	6 categories		0.915 (0.911, 0.918)	128 (75.6–170)		
				All injury - model[1]		Age (con), gender	ICD-9-CM (all injuries)	6 categories		0.921 (0.918, 0.925)	159 (108–235)		
				TMPM[1]		Age (con), gender	ICD-9-CM (5 worst injuries) , 2 worst injuries (interaction), same region (dich)	6 categories		0.925 (0.922, 0.929)	19 (4–27)		
Pearl (2006)[107]	training set: 5881 test set: 1807	Mortality (3.4 and 3.6)	All clinical trauma patients	ANN – model[1,2c]	SBP (dich), RR (dich), GCS-motor (dich)	Age (cat)				Only in figure		QA	UK
Rabbani (2007)[111]	4096	Mortality (6)	All clinical trauma patients	TRISS[3]	RTS	Age (dich)	ISS	dich		>0.93		QA	CCA
				ASCOT[3]	RTS	Age (cat)	AP	dich		>0.93			
Reiter (2004)[33]	5538	In-hospital mortality (12.4)	1) ≥ 18 year 3) trauma patients admitted to ICU	SAPS II[1]	APS	Age (con)			chronic diseases & type of admission (both cat)	0.87 (0.86-0.89)	102.3	QA	CCA
				TRISS[2a]	RTS	Age (dich)	ISS (con)	dich		0.84 (0.82-0.85)	333.3		
				TRISS-SAPS[1]	RTS, APS	Age (con)	ISS (con)	dich	chronic diseases & type of admission (both cat)	0.89 (0.87-0.90)	10.44		

Rhee (1990)[75]	723	In-hospital mortality (15.4)	1) all injured patients > 10 years who were transported to the base hospital center	APACHE II^{2a}	APS (con)	Age (cat)			chronic health score (cat)	0.8515		UK	CCA
Rutledge (1993)[22]	428	In-hospital mortality (14)	1) admitted to the surgical ICU 2) ICD-9 CM code between 800 and 959.9 3) burn patients were excluded	APACHE II^{2a}	APS	Age (cat)			chronic health score (cat)			QA	CCA
				APACHE II + ISS^{2a}	APS	Age (cat)	ISS (con)		chronic health score (cat)				
				TS + ISS^{2a}	TS		ISS(con)						
Rutledge (1997)[93]	San Diego: 44032	In-hospital mortality (6.5)	All clinical trauma patients	ISS – model^{1}	RTS	Age (UK), gender	ISS & AIS-body					CDM	CCA
				SRR – model^{1}	RTS	Age (UK), gender	ICD-9-CM (SRR) & AIS-body, AIS max						
Rutledge (1998)[83]	7276	In-hospital mortality (3.7)	All clinical trauma patients	TRISS^{2a}	RTS	Age (dich)	ISS (con)					QA	CCA
				ICISS^{1}		Age (con), gender	ICISS	cat					
Sartorius (2010)[17]	Development: N=1360 Validation: N=1003	30-day mortality (18 and 16)	All clinical trauma patients	TRISS^{2a}	RTS	Age (dich)	ISS(con)	dich		0.974 (0.824, 0.992)		T	CCA
				MGAP^{2a}	GCS & systolic arterial blood (con)	Age (con)		dich		0.91 (0.88, 0.93)	3.56		
				MGAP – 2^{1,2c}	GCS & systolic arterial blood (cat)	Age (dich)		dich		0.90 (0.88, 0.92)	5.16		
Schluter (2009)[115]	1565	Mortality (13)	1) ≥ 15 years 2) ISS > 15 3) poisoning, burns, hangings, and simple fractured neck of femurs were excluded	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.890 (0.866, 0.913)		QA	CCA
				TRISS NZ^{3}	RTS	Age (dich)	ISS (con)	dich		0.901 (0.879, 0.923)			
Schluter (2011)[41]	NSP: 270081	In-hospital mortality (5.3)	all clinical trauma patients, except those with (I) late effects of injury; (II) blisters, contusions, abrasions, and insect bites; (III) foreign bodies.	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.911 (0.908, 0.914)		QA	CCA
				TRISS – 2^{1}	RTS	Age (dich)	ISS (con)	dich		0.919 (0.916, 0.922)			
				TRISS – 3^{1}	GCS (cat), RR (cat), SBP (cat)	Age (cat)	ISS (cat)	dich		0.930 (0.927, 0.933)			
				TRISS – 4^{1}	GCS (cat), RR (cat), SBP (cat)	Age (cat)	ISS (cat)	dich		0.933 (0.930, 0.935)			
Schluter (2010)[25]	NTDB: 1115389 NSP: 280129	Mortality (5.0 and 5.3)	1) late effects of injury, blisters, contusions, abrasions, and insect bites, foreign bodies, patients who died before receiving any evaluation or treatment or who were dead on arrival, and cases where the mechanism of injury was burns or UK were excluded.	TRISS – MTOS^{2a}	RTS	Age (dich)	ISS (con)	dich		range: 0.896 - 0.996		QA	MI and CCA
				TRISS - update NTDB^{3}	RTS	Age (dich)	ISS (con)	dich		range: 0.903 - 0.998			
				TRISS - update NSP^{3}	RTS	Age (dich)	ISS (con)	dich		range: 0.914 - 0.997			
Schluter (2011)[121]	NSP: 270081 NTDB: 806644 NZDB: 1441	Mortality (5.5)	1) ≥ 15 years 2) late effects of injury, blisters, contusions, abrasions, and insect bites, foreign bodies, patients who died before receiving any evaluation or treatment	TRISS^{3}	RTS	Age (dich)	ISS (con)	dich		range: 0.899 - 0.979		QA	MI and CCA
				TRISS ^{3}	RTS	Age (dich)	ISS (con)	dich		range: 0.894 - 0.980			
				main effect + interactions^{1,2a}	RTS	Age (dich)	ISS (con)	dich	AGE, RR, SBP, GCS, ISS (all	range: 0.916 - 0.982			

			or who were dead on arrival, and cases where the mechanism of injury was burns or UK were excluded.						combination interactions)				
Sicignano (1997)[100]	1156	Mortality (17.8)	1) ≥ 18 years 2) admitted to the ICU	SAPS-I^{1,2c}	APS	Age (con)				0.85 (0.83-0.87)	12.75	QA	CCA
Suarez-Alvarez (1995)[101]	404	Survival (19.6)	1) trauma patients admitted to ICU	TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.85		QA	UK
Thanapaisal (2012)[52]	132	In-hospital mortality (20)	1) trauma patients admitted to (neuro)surgical ICU or burn unit	APACHE II ^{2a}	APS (con)	Age (cat)			chronic health score (cat)	0.89		QA	UK
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.83			
Thompson (2010)[29]	validation set: 2322 development set: 2322 (both with weight factor)	In-hospital mortality (7.9)	1) between 18 and 84 years of age 2) at least 1 injury of 3 or higher on the AIS	CCI – 1^{1,2b}		Age (cat), gender			CCI	0.59 (0.56, 0.62)		UK	UK
				CCI – 2^{1,2b}		Age (con), gender	ISS		CCI	0.77 (0.75, 0.80)			
				MoRT – 1^{1,2b}		Age (cat), gender			MoRT (6 comorbidities)	0.59 (0.56, 0.62)			
				MoRT – 2^{1,2b}		Age (con), gender	ISS		MoRT (6 comorbidities)	0.77 (0.74, 0.79)			
Vassar (1992)[76]	design: 750 validation: 250	In-hospital mortality (14.5 and 11.2)	1) ≥ 16 year 2) patients with burns were excluded 3) trauma patients admitted to ICU	APACHE II ^{1}	APS (con)	Age (cat)			chronic health score (cat)		38.3 (p-value < 0.001)	QA	CCA
				24-hour ICU point system^{2c,3}	fluid balance, PaO2/FIO2, GCS						83.9 (p-value < 0.001)		
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich			5.4 (p-value > 0,75)		
Vassar (1999)[77]	2414	In-hospital mortality (12.3)	1) ≥ 16 year 2) patients with burns were excluded 3) trauma patients admitted to ICU	APACHE II^{2c,3}	APS (con)	Age (cat)			chronic health score (cat)	0.85		QA	CCA
				APACHE III^{2c,3}	APS (con)	Age (cat)			chronic health score (cat)	0.89			
				24-hour ICU point system^{2c,3}	fluid balance, PaO2/FIO2, GCS					0.89			
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.82			
Vivien (2012)[102]	2703	In-hospital mortality (UK)	1) >18 years 2) blunt trauma patients	T-RTS^{2a}	GCS (con), RR (con), SBP (con)					0.83	0.69	UK	CCA
				T-RTS-motor^{1}	GCS-motor (con), RR (con), SBP (con)					0.83	0.21		
				MGAP^{2a}	GCS (con), SBP (cat)			dich		0.86	0.30		
				MGAP-motor^{1}	GCS-motor (con), SBP (cat)			dich		0.86	0.83		
				TRISS^{2a}	RTS (con)		ISS (con)	dich		0.88	2.52		
				TRISS-motor^{1}	SPB (con), RR (con), GCS-motor (con)		ISS (con)	dich		0.88	2.16		
Weeks (2014)[26]	2472	Mortality (0.6)	All admitted trauma patients	KTS^{2a}	SBP (cat), RR (cat), Neurological status (Cat)	Age (cat)		Number of serious injuries (cat)		0.775 (0.629, 0.921)		QA and T	CCA
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.712 (0.535, 0.889)			

West (2000)[94]	Development: N=16185 Validation: N=16122	In-hospital mortality (6.7 and 6.9)	All clinical trauma patients	HARM^{1,2b}	injury (51 categories)	Age (con)		15 categories	Head*spinal cord, pelvis* age, chest*spinal cord	0.958	21.37	QA	CCA
				TRISS^{2a}	RTS	Age (dich)	ISS (con)	dich		0.947	59.54		
Willis (2010)[117]	training set: 5631 validation set: 5638 patients	In-hospital mortality (12)	1) Patients with isolated fractured neck of femur, an isolated closed limb fracture, an isolated injury distal to the wrist or ankle, an isolated soft tissue injury, or burns to <10% of the body were excluded 2) blunt trauma patients	TRISS^{3}	RTS	Age (dich)	ISS			0.80 (0.78, 0.81)	50.23 (p-value < 0.001)	QA and T	CCA
				ICISS^{2a}		Age (cat)	ICISS		CCI (cat)	0.84 (0.83, 0.86)	35.52 (p-value < 0.001)		
				new-model^{1,2b}		Age (cat)	ICD-10-AM (all injuries)		CCI (cat)	0.90 (0.88, 0.91)	7.65 (p-value: 0.468)		
				SRR-worst^{1,2b}		Age (cat)	SRR worst injury		CCI (cat)	0.87 (0.86, 0.88)	225.22 (p-value < 0.001)		
				Max AIS model^{1,2b}		Age (cat)	highest AIS score		CCI (cat)	0.84 (0.82, 0.86)	35.70 (p-value < 0.001)		
Wolfe (2006)[116]	2059	In-hospital mortality (2.9)	1) adult patients 2) blunt trauma patients	RMH^{1,2a}	GCS motor (cat), GCS eye (cat), SBP (con), pulse rate (con)	Age (con)	ISS (dich), place of injury (cat)		Funding status (dich), complications (dich), T category (cat)	0.96		UK	CCA
Wong (1996)[78]	470	In-hospital mortality (13)	1) trauma patients admitted to ICU	TRISS^{2a}	RTS	Age (dich)	ISS	dich		0.89		QA	UK
				APACHE II^{2a}	APS (con)	Age (cat)			chronic health score (cat)	0.92			

[a] List of abbreviations: AP, Anatomic Profile; APS, Acute Physiological Score; Cat, Categorical; CCA, Complete Case Analysis; CCI, Charlson Comorbidity Index; CDM, Clinical Decision Making; Con, Continue; Dich, Dichotomize; HARM, Harborview Assessment for Risk of Mortality; MCI, Missing Category Indicator; MI, Multiple Imputation; QA, Quality Assessment; T, Triage; UK, Unknown; WCS, Worst Case Scenario.

[b] ^{1}development; ^{2a}extern cohort validation; ^{2b}random split sample validation; ^{2c}temporal split sample validation; ^{2d}k-fold validation; ^{3}update coefficients

3

IMPUTATION STRATEGIES IN THE TRAUMA REGISTRATION

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ABSTRACT

Introduction Trauma databases often contain relatively high proportions of missing physiological values. Multiple Imputation (MI) could be a possible adequate solution for the missing values. This study aimed to demonstrate the influence of more simplified imputation models on Standardized W statistic (number of excess survivors per hundred patients that would be achieved if the study center treated identically the same case-mix as the reference population).

Methods Data from three trauma care networks in the Netherlands were used to investigate local differences in missing data. Five different imputation models (MI 1 to 5) were created, based on literature and expert opinion. A sixth database was created using maximal single imputation (MaxI) and a seventh database with only complete cases (CCA). The Ws values were calculated for the three regions separately.

Results A total of 8,853, 24,487 and 8,599 observations were examined in region 1, region 2 and region 3 respectively. The Ws in region 1 ranged from -0.48 (95% CI: -1.71, 0.80) for CCA to 0.53 (95% CI: -0.19, 1.26) for MI 4 and a range of 0.40 (95% CI -0.91, 0.10) for CCA to -0.32 (-0.69, 0.04) for MI 1 and MI 4 was found in region 2. The Ws for region 3 ranged from -0.19 (-0.83, 0.45) in all MI datasets to -0.12 (-0.76, 0.52) in the CCA dataset. Although there were no significant differences between the Ws of the imputation datasets and the CCA analysis, large differences were found in the region with the most missing values.

Conclusion Different imputation strategies did influence Ws values. Supplementary variables showed no additional value for the imputation process and a more simplified imputation model could be used to adequately impute missing data.

INTRODUCTION

The prevalence of missing data is a big challenge in trauma registries[1-3]. The prospective registration of admitted trauma patients allows us to compare populations and improve trauma care. The Dutch Trauma Registration (TR) included over 83,000 trauma patients in 2014 and is considered as an essential basis for evaluating the quality of trauma care[4]. Registrations are used to measure trauma care performance by calculating the Probability of Survival (Ps) for each patient and compare this with the observed survival proportions. The Trauma and Injury Severity Score (TRISS) is the most commonly used model to calculate the Ps and is based on the Major Trauma Outcome Study (MTOS)[5,6]. However, TRISS includes physiological values that are often missing in trauma registries, resulting in missing Ps calculations.

The comparison of trauma care performance can be complicated due to significant differences in trauma systems, data collection and populations. The standardized W-statistic (Ws) is developed to adjust for case mix and estimates the number of excess survivors per hundred patients that would be achieved if the study center treated identically the same case-mix of injury severity as the reference population[7].

Until now, Complete Case Analysis (CCA) is most often used for handling missing values in trauma registries[8]. CCA excludes subjects with a missing value for any potential predictor. However, the missing values in trauma registries are often associated with other covariables or with the outcome, and thus, CCA may give biased estimates. Furthermore, CCA leads to smaller samples, resulting in a decrease of statistical power.

Currently, the Dutch TR uses maximal single imputation (MaxI) as an incentive for a better registration; missing values in the physiologic data are considered as clinical normal[4]. Furthermore, unknown values of mechanism of injury are considered as blunt injury. These assumptions could lead to higher survival prediction and subsequently to a lower Ws. Multiple Imputation (MI) is a possible adequate solution for the high amount of missing values[9]. However, MI is a complicated method and differences in imputation models may influence outcome.

Moore et al. (2009)[1] proposed an imputation model and guidelines to the imputation process for trauma registries. Because not all variables (i.e. intubation scene/Emergency Department [ED], drugs and/or alcohol use, transfer, ED disposition, duration ventilator and discharge disposition) from the imputation model described by Moore et al. (2009)[1] were available or appropriately coded in the Dutch Trauma Registration, we aimed to demonstrate the influence of more simplified imputation models on the Ws. Data from three regional trauma care networks in the Netherlands were used to investigate local differences in missing data and the effect of MI, CCA and MaxI. We hypothesize that different imputation strategies result in different Ws values.

METHODS

Study population and data collection

The Netherlands consists of eleven trauma care networks. This research was conducted in three networks: Network Emergency Care Euregio (4 hospitals), Network Emergency Care Zwolle (7 hospitals) and Network Emergency Care Brabant (12 hospitals), all including one level I trauma center. The three trauma care networks represent 26% of the total Dutch trauma population.

Patients were registered in the TR if they have been admitted after visiting the Emergency Department (ED) within 48 hours after a trauma. Only patients that were transported to the ED by ambulance or trauma helicopter to one of the hospitals within the three trauma care networks between January 1, 2011 and December 31, 2014 were examined in this study.

The TR included physiological parameters which were assessed by Emergency Medical Services on time of arrival at the scene and recorded at presentation at the ED of the hospital. Physiological variables consists of the components of the Glasgow Coma Scale (GCS) (i.e. eye (E), motor (M) and verbal (V) component), systolic blood pressure (SBP) and respiratory rate (RR). Mechanism of injury (i.e. blunt or penetrating), total number of admission days, length of stay at the Intensive Care (IC), discharge disposition and Abbreviated Injury Scale (AIS, version 98) were collected in the hospital. The Injury Severity Score (ISS) was calculated using the AIS.

The calculation of survival probabilities

The Probability of survival (Ps) was calculated using the natural logarithm (Logit) of the TRISS[10,11]:

$$\text{Logit (Ps)} = \alpha_i + \beta_{RTS,i}*RTS + \beta_{ISS,i}*ISS + \beta_{age,i}*age$$

Age was equal to 0 if the patient is < 55 years and equal to 1 if the patient is ≥ 55 years of age. The coefficients were derived from Dutch Trauma Registration in 2015 with separate values for blunt and penetrating trauma (Supplemental File 1)[12].

Statistical analysis

Data preparation

Patients with unknown outcome (in-hospital mortality) or unknown injury severity were excluded from further analyses. Clinically relevant supplementary predictors for physiological variables were selected for the imputation models based on variables suggested by literature[1,13] and expert opinion. The following variables were considered relevant: age, ISS, prehospital E/M/V values, prehospital RR and prehospital SBP, mechanism of injury (blunt or penetrating), mortality, length of stay in hospital, length of stay at the ICU, head injury and maximal AIS score. Prehospital E/M/V and RR values were selected for survival prediction calculations in patients that were sedated and/or intubated, instead of the registered hospital values.

The associations between missing physiological values and supplementary variables were assessed with logistic regression, with α=0.05 and using a Bonferonni correction for multiple comparisons. The associations between supplementary variables and clinical abnormal physiological variables were assessed with logistic regression (also with Bonferonni correction). Due to different patterns of missing and clinical abnormal variables, the associations were assessed per region. Clinical abnormal values for the GCS were defined as: <4 for E, <6 for M and <5 for V. The clinically abnormal values for SBP and RR were <89, and <10 or >29 respectively.

Imputation process

Seven datasets were created. First, a dataset with only complete cases (CCA dataset) was created. Second, the MaxI dataset was created. MaxI coded missing physiological values as clinical normal (Supplemental file 1). Hence, missing SBP and RR values were coded as 4, missing E, M and V values were coded as 4, 6 and 5 respectively. Furthermore, all unknown mechanism of injuries were coded as blunt injury.

Next, three multiple imputation datasets were created based on different imputation models (MI 1 to MI 3, Table 1). The inclusion of highly correlated variables in the imputation model may cause problems in the imputation process[14]. Correlations were checked with Spearman's rho and Kendall's tau for categorical variables and Pearson correlations for continuous variables. Prehospital values were correlated with the hospital physiological values (data not shown), and were for that reason not included in the next imputation models. Furthermore, imputation models should include all variables (predictors and outcome) that are incorporated in the model[13]. Hence, MI 4 and MI 5 were created (Table 1). Assumptions for linear regression were checked; residuals should be normally distributed. SBP showed a normal distribution and RR was log transformed for normal residuals. E, M and V values were imputed using dummy variables with normal level of consciousness as reference category. The imputed E/M/V values were back-transformed using adaptive rounding[15]. Length of stay in hospital and length of stay at ICU were log-transformed, with deaths coded as missing value, to accomplish linearity between dependent and independent variables. The Markov Chain Monte Carlo (MCMC) was used to impute the missing physiological data. A total of 54, 40 and 5 imputations were used in region 1, region 2 and region 3 respectively (according to the maximal percentage of missing values for a physiological variable, and at least 5 imputations) with 10 iterations[16]. The imputation process was assessed by convergence plots. Logistic regression was performed to determine the area under the receiver operating characteristic curve (AUROC) of the five imputation models predicting the missing values and clinical abnormal values of hospital E, M, V, SBP

TABLE 1. The prediction variables and supplementary variables that are incorporated in the five multiple imputation models.

	Prediction variables									**Supplementary variables**									
	Hospital values					**mortality**	**Mechanism of injury**	**Age**	**ISS**	**Prehospital values**					**Gender**	**Hospital stay**	**ICU stay**	**Max AIS-head**	**Max AIS-score**
	E	**M**	**V**	**RR**	**SBP**					**E**	**M**	**V**	**RR**	**SBP**					
MI 1	X	X	X	X	X			X	X										
MI 2	X	X	X	X	X			X	X	X	X	X	X	X					
MI 3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MI 4	X	X	X	X	X	X	X	X	X										
MI 5	X	X	X	X	X	X	X	X	X						X	X	X	X	

List of abbreviations: E, Eye component of the Glasgow Coma Scale; ICU, Intensive Care Unit; ISS, Injury Severity Score; M, Motor component of the Glasgow Coma Scale; Max, Maximum; RR, Respiratory Rate; SBP, Systolic Blood Pressure; V, verbal component of the Glasgow Coma Scale

and RR, to determine the information content of selected imputation variables. Differences between AUROC values were considered significant if the 95% confidence interval did not overlap.

Ws calculation

Ws and the 95% CI were calculated for the three trauma regions separately according to the formulas of Younge et al. (1997)[7]. The dataset was split into Ps bins 0-0.25, 0.26-0.50, 0.51-0.75, 0.76-0.90, 0.91-0.95 and 0.96-1.00. Excess survivors were calculated and multiplied by the fraction of patients in the database. The Ws was calculated by adding the excess survivors of each bin. The Ws (95% CI) was calculated for the five MI datasets, for the MaxI dataset and for the dataset with only complete cases (CCA dataset). Differences between Ws values were considered significant if the 95% confidence interval did not overlap.

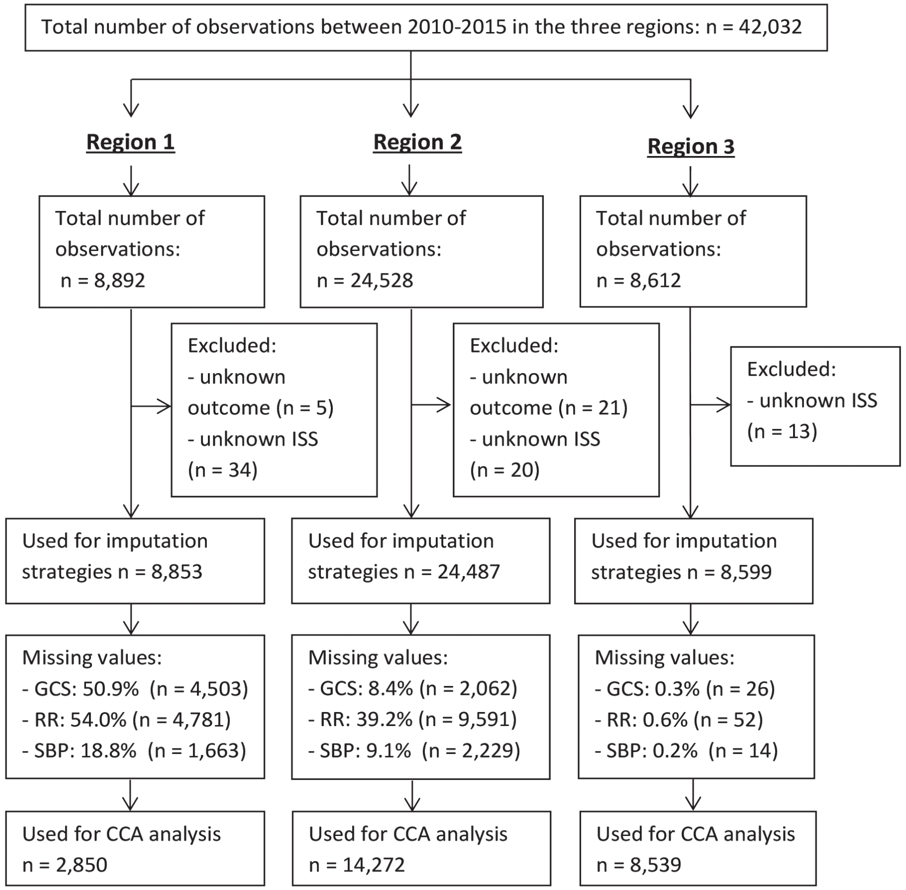

FIGURE 1. Summary of inclusion and exclusion of observations and missing values in the three regions.
Abbreviations: CCA, Complete Case Analysis; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; n, number; RR, Respiratory Rate; SBP, Systolic Blood Pressure.

RESULTS

Study characteristics

The three regions included 42,032 observations between 2011 and 2014 (Table 2, Figure 1). A total of 26 observations (0.1%) were excluded because the outcome was unknown and 67 (0.2%) observations were excluded due to an unknown ISS value, resulting in 41,939 observations for further analysis. The mean age (SD) of the total population was 59.3 (25.7) years and 51.6% of the population was male.

The median (Inter Quartile Range [IQR]) values for ISS were the same in all regions (9 [4-9]). A total of 7.7% of the total study population suffered multi trauma (ISS>15). The median (IQR) of GSC was 15 (15-15) in all regions, 11.4% of whom had a GCS lower than 15.

The median (IQR) of E, M and V of the GCS were 4 (4-4), 6 (6-6) and 5 (5-5), respectively. Respiratory Rate (median [IQR]) was 16 (15-20) for the total population and SBP (median [IQR]) ranged from 140 (120-157) in Region 3 to 145 (128-165) in Region 1. In-hospital mortality ranged from 2.8% in Region 1 to 3.1% in Region 3.

Missing data

The RR, SBP and GCS were missing in 34.3%, 9.3% and 15.5% of the observations, respectively (Table 2, Figure 1). The E, M and V components of the GCS were mainly missing in Region 1 (50.8%, 50.6% and 50.7%, respectively). Age, gender, ISS, in-hospital mortality and mechanism of injury were missing in only 0.0%, 0.0%, 0.2%, 0.1% and 0.4% of the observations, respectively. The CCA analysis was conducted in 2,850, 14,272 and 8,539 in region 1, region 2 and region 3 respectively, due to the missing data in the predictor variables of the TRISS.

Association supplementary variables and physiological values

Different patterns of missing physiological values were found between the regions (Table 3). There were significantly more missing physiological values in females and in patients with higher age in Region 1 and Region 2. Patients from region 1 and region 3 with a longer ICU stay had significantly more missing values for RR and SBP compared to patients without ICU stay. Region 2 showed less missing values for RR and SBP for an ICU stay of 1-3 days compared to no ICU stay. Patients with a higher ISS value had significantly more missing values in Region 3. Significant associations were most often found in Region 1, the region with the highest prevalence of missing values.

TABLE 2. Patient characteristics for the total study population and the three regions.

	Total	Region 1	Region 2	Region 3
N	42,032	8,892	24,528	8,612
N for CCA (%)	25,661 (61.1)	2,850 (32.1)	14,272 (58.2)	8,539 (99.2)
Age (mean, SD)	59.3 (25.7)	60.4 (25.7)	59.5 (25.4)	57.9 (26.4)
Missing (%)	0.0	0.0	0.0	0.0
Gender (% male)	51.6	51.2	51.7	51.6
Missing (%)	0.0	0.1	0.0	0.0
ISS (median, IQR)[a]	9 (4-9)	9 (4-9)	9 (4-9)	8 (4-9)
Missing (%)	0.2	0.4	0.1	0.2
ISS > 16 (%)	7.7	7.2	7.4	9.0
RR (median, IQR)[a]	16 (15-20)	17 (14-20)	15 (15-20)	17 (16-19)
Missing (%)	34.4	54.0	39.2	0.6
SBP (median, IQR)[a]	141 (125-160)	145 (128-165)	141 (125-160)	140 (120-157)
Missing (%)	9.3	18.8	9.1	0.2
GCS (median, IQR)[a]	15 (15-15)	15 (15-15)	15 (15-15)	15 (15-15)
Missing (%)	15.5	50.9	8.4	0.3
GCS < 15 (%)	11.4	19.5	10.5	9.9
E (median, IQR)[a]	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)
Missing (%)	15.4	50.6	8.0	0.3
E < 4 (%)	6.2	10.4	5.4	6.0
M (median, IQR)[a]	6 (6-6)	6 (6-6)	6 (6-6)	6 (6-6)
Missing (%)	15.4	50.7	8.0	0.3
M < 6 (%)	4.5	9.9	3.4	4.8
V (median, IQR)[a]	5 (5-5)	5 (5-5)	5 (5-5)	5 (5-5)
Missing (%)	15.6	50.6	8.3	0.3
V < 5 (%)	8.8	12.9	8.4	7.8
In-hospital mortality (%)	2.9	2.8	2.9	3.1
Missing (%)	0.1	0.1	0.1	0.0
Blunt injury (%)	97.5	97.5	97.8	96.4
Missing (%)	0.0	0.0	0.0	0.0

[a] Hospital values

List of abbreviations: N, Number; CCA, Complete Case Analysis; E, Eye component of the Glasgow Coma Scale; GCS, Glasgow Coma Scale; IQR, Inter Quartile Range; ISS, Injury Severity Score; M, Motor component of the Glasgow Coma Scale; RR, Respiratory Rate; SBP, Systolic Blood Pressure; SD, Standard Deviation; V, verbal component of the Glasgow Coma Scale

Patterns of clinical abnormal values were mostly the same between regions (Table 4). A higher age was associated with a lower risk of abnormal values for E in all regions. Clinical abnormal values for RR and SBP were more present in patients younger than 17 years. A higher AIS head score resulted in more clinical abnormal values for E, M and V, but for less clinical abnormal values for SBP. Death was positively associated with all clinical abnormal physiological values. Clinical abnormal values for SBP were most often found in patients with penetrating injury.

All supplementary variables were significantly associated with at least one missing or clinical abnormal physiological value.

Discriminative ability of supplementary variables

Discrimination of the logistic models predicting missing physiological values ranged from 0.519 (95% CI: 0.506, 0.532) for MI 1 predicting V in region 2 to 0.785 (95% CI: 0.686, 0.883) for MI 3 prediction SBP in region 1 (Table 5). The highest discrimination was found in MI 3, followed by MI 5. Nevertheless, discrimination for logistic models predicting missing physiological values was poor to fair.

Discrimination of the logistic models predicting clinical abnormal physiological values ranged from 0.582 (95% CI: 0.548, 0.616) for MI 1 predicting RR in region 2 to 0.948 (95% CI: 0.921, 0.976) for MI 3 predicting V in region 1 (Table 5). Overall, discrimination of MI 3 and MI 5 was excellent for predicting clinical abnormal physiological values.

Ws

The Ws (95% CI) in region 1 ranged from -0.48 (95% CI: -1.71, 0.80) for CCA to 0.53 (95% CI: -0.19, 1.26) for MI 4 (Figure 2). The Ws values were higher, although not significant, in the multiple imputation datasets than in the CCA or MaxI datasets. The Ws (95% CI) for region 2 ranged from -0.40 (95% CI -0.91, 0.10) for CCA to -0.32 (-0.69, 0.04) for MI 1 and MI 4. The Ws (95% CI) for region 3 ranged from -0.19 (-0.83, 0.45), in all multiple imputation datasets, to -0.12 (-0.76, 0.52) in the CCA dataset. No significant differences were found between the Ws values in region 2 and region 3. The Ws values did not differ between the five MI models in all three regions.

TABLE 3. Odds ratios from Logistic regression for missing physiological values, adjusted for all other supplementary variables.

	E^{a}			**M**^{a}			**V**^{a}			**RR**^{a}			**SBP**^{a}		
	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3
Gender															
female	1.160*	1.098	1.295	1.159*	1.099	1.295	1.159*	1.108	0.887	1.314*	1.182*	1.382	1.086	1.220*	1.855
Age															
<17	1.392*	1.007	2.275	1.467*	1.015	2.275	1.410*	1.006	1.806	1.574*	1.515*	2.379	2.802*	3.896*	3.542
17-54$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
55-64	1.017	1.103	1.465	1.017	1.103	1.465	1.017	1.101	1.854	1.259*	1.183*	0.449	1.116	1.206	0.641
65-74	1.339*	1.080	0.237	1.338*	1.065	0.237	1.350*	1.079	0.498	1.245*	1.201*	0.381	1.112	1.089	0.457
75-84	1.415*	1.142	0.639	1.413*	1.141	0.639	1.418*	1.126	0.754	1.491*	1.189*	0.835	1.101	0.927	0.263
>84	1.323*	1.227	0.451	1.323*	1.223	0.451	1.324*	1.201	0.920	1.438*	1.295*	0.526	1.071	0.928	1.038
Maximum AIS head															
Not coded$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1-2	0.367*	0.945	0.356	0.367*	0.947	0.356	0.366*	0.953	0.304	0.602*	0.912	0.467	0.477*	0.412*	2.306
3-4	0.293*	0.826	0.712	0.292*	0.800	0.712	0.298*	0.752	0.755	0.537*	0.709*	1.032	0.360*	0.366*	0.843
5-6	0.266*	1.581	0.571	0.266*	1.747	0.571	0.255*	1.924	0.933	0.810	2.309*	1.705	0.396*	0.616	0.999
Mechanism															
penetrating	1.516*	1.138	3.402	1.503*	1.169	3.402	1.538	1.133	2.447	1.123	1.135	0.943	1.247	1.592*	5.675
ISS															
1-3$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4-8	1.095	0.906	0.753	1.088	0.907	0.753	1.095	0.912	0.824	0.912	1.373*	3.366	1.103	1.862*	0.841
9-15	1.088	0.853	1.060	1.079	0.856	1.060	1.084	0.840	1.178	0.825*	1.331*	5.233	0.689*	1.357*	0.954
16-24	0.420*	0.800	1.602	0.416*	0.814	1.602	0.422*	0.829	2.615	0.312*	0.920	23.909*	0.378*	1.016	NA
25-75	0.591	0.742	3.357	0.586	0.679	3.357	0.647	0.634	5.548	0.526*	0.508*	42.978*	0.461	1.343	2.548
ICU stay (days)															
0$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1-3	1.704*	0.774	0.797	1.699*	0.778	0.797	1.702*	0.922	1.656	3.440*	0.650*	2.563	3.904*	0.551*	3.684
4-7	0.986	2.250*	6.282	0.982	2.283*	6.282	1.003	2.241*	4.480	2.686*	0.871	8.331*	2.863*	1.628	NA
>7	1.132	1.710	9.576	1.126	1.633	9.576	1.051	1.933*	6.945	2.026*	0.990	8.675*	3.339*	1.311	5.800

TABLE 3. Continued.

	E^{a}			**M**^{a}			**V**^{a}			**RR**^{a}			**SBP**^{a}		
	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3
Hospital stay (days)															
1-3$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4-7	0.915	0.952	2.536	0.919	0.954	2.536	0.912	0.954	1.309	0.787*	0.951	0.362	0.642*	0.862	1.843
>7	0.963	1.011	4.622	0.970	1.015	4.622	0.965	1.027	2.504	0.676*	0.993	0.577	0.576*	0.708*	4.783
Outcome															
In-hospital mortality	0.700	1.005	1.483	0.701	0.995	1.483	0.765	1.084	2.267	0.455*	0.901	2.232	0.463*	1.205	NA

^{a}Hospital values
*statistically significant ($p < 0.05/8$ i.e. $p < 0.00625$)
$^{\$}$ reference category
List of abbreviations: E, Eye component of the Glasgow Coma Scale; ICU, Intensive Care Unit; ISS, Injury Severity Score; M, Motor component of the Glasgow Coma Scale; RR, Respiratory Rate; SBP, Systolic Blood Pressure; V, verbal component of the Glasgow Coma Scale

TABLE 4. Odds ratio from logistic regression for the fact that the physiological variables are clinical abnormal, adjusting for all other variables.

	E^a			M^a			V^a			RR^a			SBP^a		
	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3
Gender															
female	1.240	0.952	0.855	1.026	0.878	0.841	0.901	0.832*	0.771	1.208	0.935	0.531	1.067	1.201	0.736
Age															
<17	0.996	0.841	0.646	1.315	1.001	0.771	0.611	0.520*	0.486*	4.696*	2.808*	1.744	4.651*	1.716	7.000*
17-54$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
55-64	0.820	0.656*	0.714	0.824	0.663	1.074	0.753	1.008	1.087	0.560	1.058	0.482	1.302	0.850	0.648
65-74	0.536*	0.529*	0.558*	0.628	0.709	0.865	0.660	0.961	0.894	1.019	0.837	0.386	1.857	1.031	0.649
75-84	0.403*	0.396*	0.449*	0.879	0.564*	0.523	0.668	0.973	0.839	0.610	0.956	0.484	1.222	0.866	0.853
>84	0.661	0.552*	0.254*	1.193	0.729	0.555	1.031	1.485*	1.256	0.716	1.372	0.403	1.224	0.845	0.757
Maximum AIS head															
Not coded$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1-2	5.671*	4.580*	3.710*	1.435	3.504*	2.874*	6.288*	5.330*	4.564*	1.217	1.150	2.391	1.131	0.920	2.658*
3-4	19.412*	11.486*	8.017*	4.095*	7.951*	5.270*	17.476*	11.848*	8.333*	0.934	0.683	3.468	0.532	0.304	0.487
5-6	25.138*	23.534*	62.212*	9.871*	15.296*	23.262*	39.577*	29.188*	42.256*	0.720	0.556	NA	0.616	0.152	1.082
Mechanism															
penetrating	0.904	1.281	0.563	0.542	1.375*	0.846	0.479	0.840	0.785	1.873	1.434	1.013	3.089	6.050*	3.363*
ISS															
1-3$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4-8	0.877	0.869	1.127	0.941	0.785	1.186	1.098	0.974	1.230	1.091	0.948	0.899	0.911	1.593	1.091
9-15	0.408*	0.659*	0.974	0.726	0.751	1.068	0.622	0.900	1.413	1.187	0.869	0.923	0.639	1.253	1.846
16-24	0.511	1.305	1.988	0.712	1.523	2.682*	0.679	1.034	1.808	1.275	1.979	0.740	1.292	3.688	6.999*
25-75	1.160	2.371*	2.016	1.299	3.025*	2.564	0.902	1.345	1.686	4.581*	2.694*	0.455	5.676*	14.529*	8.238*
ICU stay															
0$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1-3	3.172*	2.612*	3.440*	6.673*	2.943*	4.600*	2.756*	2.260*	2.996*	1.996	1.322	4.007	0.772	1.710	1.240
4-7	5.432*	2.973*	4.468*	7.945*	3.208*	6.319*	3.292*	2.813*	2.596	1.677	2.114	2.170	2.610	3.405*	2.385
>7	4.888*	4.214*	5.644*	11.412*	7.961*	9.906*	4.599*	3.463*	3.262*	1.335	2.317	2.412	1.047	2.265	2.665
Hospital stay															

TABLE 4. Continued.

	E^a			M^a			V^a			RR^a			SBP^a		
	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3	Region 1	Region 2	Region 3
1-3$^{\$}$	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4-7	1.259	0.869	0.870	0.856	0.733	0.779	1.091	0.907	0.815	0.648	0.951	1.261	0.534	0.749	0.482
>7	1.694*	1.027	1.217	0.557*	0.601*	0.774	1.688*	0.945	0.856	0.725	1.526	2.385	0.771	1.091	1.125
Missing	2.238	4.736*	NA	1.143	5.232*	NA	1.540	1.710	NA	2.029	4.152	NA	NA	3.755	NA
Outcome															
Mortality	4.921*	4.701*	4.275*	2.968*	6.440*	4.977*	4.140*	2.266*	2.201*	3.948*	2.123*	5.758*	5.888*	7.649*	5.241*

*statistically significant ($p < 0.05/8$ i.e. $p < 0.00625$)

$^{\$}$ reference category

List of abbreviations: E, Eye component of the Glasgow Coma Scale; ICU, Intensive Care Unit; ISS, Injury Severity Score; M, Motor component of the Glasgow Coma Scale; RR, Respiratory Rate; SBP, Systolic Blood Pressure; V, verbal component of the Glasgow Coma Scale

TABLE 5. AUROC (95% CI) of the logistic regression models for predicting the clinical abnormal value of physiologic variables and the missing values of physiologic variables in the total population.

Region	Imputation models		E[a]	M[a]	V[a]	RR[a]	SBP[a]
1	**MI 1**	Abnormal values[b]	0.729 (0.700, 0.758)	0.664 (0.632, 0.696)	0.668 (0.640, 0.696)	0.680 (0.629, 0.732)	0.619 (0.551, 0.687)
		Missing values	0.576 (0.564, 0.588)	0.575 (0.563, 0.587)	0.575 (0.564, 0.587)	0.554 (0.542, 0.566)	0.600 (0.585, 0.615)
	MI 2	Abnormal values[b]	0.918 (0.869, 0.966)	0.946 (0.902, 0.990)	0.951 (0.921, 0.980)	0.791 (0.669, 0.912)	0.863 (0.739, 0.986)
		Missing values	0.611 (0.557, 0.665)	0.612 (0.557, 0.666)	0.603 (0.548, 0.657)	0.580 (0.527, 0.632)	0.721 (0.641, 0.801)
	MI 3	Abnormal values[b]	0.919 (0.875, 0.963)	0.930 (0.878, 0.982)	0.948 (0.921, 0.976)	0.872 (0.768, 0.977)	0.821 (0.619, 1.000)
		Missing values	0.673 (0.619, 0.728)	0.672 (0.616, 0.728)	0.663 (0.606, 0.719)	0.602 (0.547, 0.658)	0.785 (0.686, 0.883)
	MI 4	Abnormal values[b]	0.748 (0.721, 0.776)	0.683 (0.652, 0.714)	0.690 (0.663, 0.717)	0.699 (0.648, 0.749)	0.689 (0.625, 0.752)
		Missing values	0.583 (0.571, 0.595)	0.581 (0.570, 0.593)	0.582 (0.570, 0.594)	0.561 (0.549, 0.573)	0.602 (0.587, 0.617)
	MI 5	Abnormal values[b]	0.826 (0.801, 0.851)	0.739 (0.710, 0.768)	0.814 (0.792, 0.836)	0.692 (0.641, 0.743)	0.668 (0.600, 0.737)
		Missing values	0.660 (0648, 0.672)	0.659 (0.647, 0.671)	0.659 (0.647, 0.671)	0.634 (0.621, 0.646)	0.713 (0.697, 0.729)
2	**MI 1**	Abnormal values[b]	0.746 (0.729,0.764)	0.780 (0.758, 0.801)	0.626 (0.611, 0.642)	0.582 (0.548, 0.616)	0.666 (0.624, 0.708)
		Missing values	0.521 (0.508, 0.535)	0.522 (0.509, 0.536)	0.519 (0.506, 0.532)	0.531 (0.524, 0.538)	0.584 (0.571, 0.596)
	MI 2	Abnormal values[b]	0.859 (0.841, 0.876)	0.916 (0.897, 0.934)	0.797 (0.780, 0.814)	0.637 (0.595, 0.680)	0.746 (0.697, 0.795)
		Missing values	0.595 (0.578, 0.611)	0.595 (0.578, 0.611)	0.595 (0.580, 0.611)	0.563 (0.553, 0.573)	0.571 (0.553, 0.590)
	MI 3	Abnormal values[b]	0.880 (0.862, 0.897)	0.914 (0.894, 0.933)	0.857 (0.843, 0.870)	0.661 (0.615, 0.706)	0.721 (0.662, 0.779)
		Missing values	0.591 (0.575, 0.608)	0.592 (0.575, 0.609)	0.589 (0.573, 0.606)	0.589 (0.578, 0.600)	0.650 (0.630, 0.670)
	MI 4	Abnormal values[b]	0.766 (0.750, 0.782)	0.804 (0.785, 0.824)	0.645 (0.631, 0.660)	0.603 (0.570, 0.636)	0.722 (0.681, 0.763)
		Missing values	0.525 (0.511, 0.538)	0.526 (0.512, 0.539)	0.525 (0.512, 0.539)	0.533 (0.526, 0.540)	0.584 (0.571, 0.596)
	MI 5	Abnormal values[b]	0.846 (0.832, 0.861)	0.857 (0.838, 0.876)	0.804 (0.791, 0.816)	0.642 (0.607, 0.677)	0.665 (0.614, 0.715)
		Missing values	0.530 (0.516, 0.544)	0.531 (0.517, 0.545)	0.530 (0.516, 0.544)	0.552 (0.545, 0.560)	0.630 (0.617, 0.643)

TABLE 5. Continued.

Region	Imputation models		E[a]	M[a]	V[a]	RR[a]	SBP[a]
3	**MI 1**	Abnormal values[b]	0.811 (0.788, 0.834)	0.815 (0.788, 0.842)	0.740 (0.717, 0.763)	0.653 (0.567, 0.738)	0.784 (0.731, 0.837)
		Missing values[c]	0.713 (0.586, 0.840)	0.713 (0.586, 0.840)	0.766 (0.656, 0.877)	0.865 (0.808, 0.923)	0.643 (0.462, 0.805)
	MI 2	Abnormal values[b]	0.918 (0.901, 0.935)	0.916 (0.896, 0.935)	0.881 (0.862, 0.900)	0.870 (0.764, 0.976)	0.836 (0.779, 0.893)
		Missing values[c]	No cases	No cases	No cases	No cases	No cases
	MI 3	Abnormal values[b]	0.925 (0.897, 0.952)	0.947 (0.923, 0.971)	0.937 (0.910, 0.963)	0.886 (0.720, 1.000)	0.889 (0.798, 0.980)
		Missing values[c]	No cases	No cases	No cases	No cases	No cases
	MI 4	Abnormal values[b]	0.822 (0.800, 0.844)	0.827 (0.802, 0.853)	0.743 (0.720, 0.767)	0.666 (0.578, 0.754)	0.810 (0.759, 0.861)
		Missing values[c]	0.725 (0.596, 0.853)	0.725 (0.596, 0.853)	0.770 (0.658, 0.882)	0.864 (0.805, 0.922)	0.651 (0.487, 0.816)
	MI 5	Abnormal values[b]	0.790 (0.745, 0.835)	0.771 (0.723, 0.818)	0.780 (0.735, 0.826)	0.770 (0.566, 0.973)	0.749 (0.636, 0.862)
		Missing values[c]	0.850 (0.705, 0.996)	0.850 (0.705, 0.996)	0.819 (0.667, 0.971)	0.802 (0.697, 0.907)	No cases

[a] Hospital values

[b] Clinical abnormal values were defined as: <4 for E, <6 for M and <5 for V. The clinical abnormal values for SBP and RR were <89, and <10 or >29 respectively.

[c] Region 3 has only few missing values for physiological variables. It was not always possible to perform logistic regression on the few missing cases.

List of abbreviations: AUROC, Area Under Receiver Operating Characteristic Curve; E, Eye component of the Glasgow Coma Scale; M, Motor component of the Glasgow Coma Scale; MI, Multiple Imputation model; RR, Respiratory Rate; SBP, Systolic Blood Pressure; SD, Standard Deviation; V, verbal component of the Glasgow Coma Scale

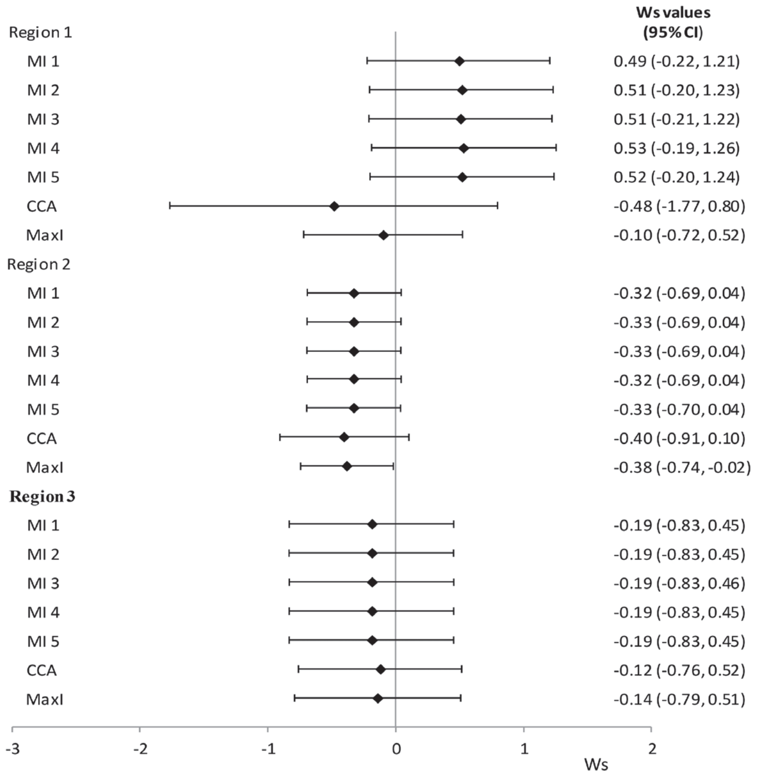

FIGURE 2. Ws values (95% CI) for the three different regions.
List of abbreviations: CCA, Complete Case Analysis; CI, Confidence Interval; MI, Multiple Imputation; MaxI, Maximal Imputation

DISCUSSION

It is a challenge to appropriate handle the high prevalence of missing data in trauma registries for the evaluation of trauma care. Data from three trauma care networks in the Netherlands were used to investigate local differences in missing data and the effect of the imputation methods on Ws. The missing values for physiological variables showed different distributions in the three regions. All supplementary variables were significant associated with at least one missing or clinical abnormal physiological variable. The best discriminative abilities for missing variables and for clinical abnormal values were found in the most comprehensive imputation models. Although there were no significant differences between the Ws of the imputation datasets and the CCA analysis, large differences were found in the region with the most missing values. Ws values for the imputation datasets were the same in all regions.

Missing values can be described by several mechanisms[17,18]. Values could be missing completely at random (MCAR); the subjects with missing values are representative and are a random sample from the complete population. In the case that missing values in trauma registries are MCAR, CCA will not lead to biased results. However, it will lead to a smaller sample size, a loss of statistical power, because all cases with missing data in the predictors and outcome are deleted. Previous research hypothesized that missing values in trauma registries are missing at random (MAR)[2,3,19,20]; the missing values are then related to known characteristics or the outcome. However, the discriminative abilities of the most imputation models for missing physiological values were close to 0.5. This could indicate that the supplementary variables do not contain information to explain the pattern of missing values. Hence, it is possible the missing values in our sample are not MAR.

Not all supplementary variables from the imputation model described by Moore et al. (2009)[1] were available in the Dutch Trauma Registration. The more variables included in the imputation model the better the discriminative ability[21,22]; as expected, the imputation model with most supplementary variables showed the highest AUROC for clinical abnormal values. Although discriminative ability between imputation models differed significantly, no differences were found in the Ws between the five multiple imputation models. O'Reilly (2010) et al.[23] suggested to include the physiological prehospital data, because it provides valuable information to the outcome analyses. However, the convergence plots showed a slight negative trend for the imputed variables in region 1 over the iterations, so it is possible that the correlated variables could have caused problems in the imputation process resulting in incorrect imputations.

The fraction of patients in the Ps bins showed large differences between imputation datasets and the CCA dataset among the regions. In region 1, 88% of the patients had an expected survival between 0.96 and 1.00 in the CCA dataset, and even more (93%) in the MaxI dataset.

However, after multiple imputation this fraction decreased (ranging from 77% to 80%). Based on the comparability of the regions, at least 90% of the patients should have an expected probability of survival between 0.96 and 1.00. This implies that patients with missing values were mostly distributed among the lower probability bins after multiple imputation. Although the correctness of imputed values could never be formally verified, the imputed values were probably lower than the actual physiological values. This phenomenon is especially seen in region 1, where the mortality rate in the CCA database is 4%, instead of the 2.8% in the total dataset. The imputation models compute values based on the available information. This information is mostly based on relatively badly injured patients, with more often a poor outcome and thus a lower observed survival rate. The missing variables might have clinical normal values, but were often imputed as clinical abnormal values. This results in a lower Ps and finally in higher, although probably incorrect, Ws values. A missing value rate of 50% is probably too high to impute missing data.

Multiple imputation increases precision and reduces bias compared with CCA and should be considered for studies when substantial portion (20-40% missing rate per hospital) of data are missing in trauma registries[3,19]. In contrast, Joseph et al. (2004)[20] and Rue et al. (2008)[24] concluded that great care is required with missing data, especially in trauma databases in which missing data may not be missing at random. The three trauma regions in this study have comparable patient compositions, but different missing values patterns. Due to the low prevalence of missing data, the Ws values in region 3 remained the same in all seven datasets, as expected. Also the Ws values in region 1 and 2 were constant in the different multiple imputation datasets. This implies that the supplementary variables do not add value to the imputation process and a more simplified model could be used for imputation of physiological variables.

MaxI will impute clinical normal values and will, therefore, lead to higher survival predictions and lower Ws values compared to the other datasets. However, the CCA dataset had a different patient composition due to the exclusion of the incomplete cases. This resulted in higher Ws values in the maximal imputation dataset compared to the CCA dataset in region 1 and region 2, which indicates that the pattern of missing data has big influence on the Ws values.

This study was conducted in three regions from the Dutch trauma population, which could indicate that the results may not be generalizable to other populations with different patient compositions. However, the three regions were representative for the total Dutch trauma population, including urban as well as rural populations. Therefore, the results could be extrapolated to the total Dutch trauma population and maybe also to other developed countries with similar trauma registries, missing value patterns and patients compositions.

Conclusions

Although much effort is put into the prevention of missing data, databases often contain relatively high proportions of missing physiological values. Missing data should be handled cautiously, based on the proportion of missing values and patterns of missing data in the dataset. This study showed that differences in strategies for handling missing data influence the Ws. However, there is no difference in Ws between comprehensive imputation models or more simplified models. Thus, supplementary variables showed no additional value for the imputation process and a more simplified imputation model could be used to adequately impute missing data.

REFERENCES

1. Moore L, Hanley JA, Turgeon AF, Lavoie A, Emond M. A Multiple Imputation Model for Imputing Missing Physiologic Data in the National Trauma Data Bank. *J Am Coll Surg.* 2009;209:572-579.
2. Moore L, Lavoie A, LeSage N, Liberman M, Sampalis JS, Bergeron E, Abdous B. Multiple imputation of the glasgow coma score. *J Trauma.* 2005;59(3):698-704.
3. Newgard CD. The Validity of Using Multiple Imputation for Missing Out-of-hospital Data in a State Trauma Registry. *Acad Emerg Med.* 2006;13(3):314-324.
4. Landelijke Netwerk Acute Zorg. Traumazorg in beeld: Landelijke Traumaregistratie 2010 - 2014, Rapportage Nederland. 2015.
5. Champion HR, Copes WS, Sacco WJ, Lawnick MM, Keast SL, Frey CF. The Major Trauma Outcome Study: establishing national norms for trauma care. *J Trauma.* 1990;30(11):1356-1365.
6. Champion H, Frey C, Sacco W. Determination of national normative outcomes for trauma. *J Trauma.* 1984;24(7):651-651.
7. Younge P, Coats T, Gurney D, Kirk C. Interpretation of the Ws statistic: application to an integrated trauma system. *J Trauma.* 1997;43(3):511-515.
8. de Munter L, Polinder S, Lansink K, Cnossen M, Steyerberg E, de Jongh M. Mortality prediction models in the general trauma population: A systematic review. *Injury.* 2017;48(2):221-229.
9. Moore L, Hanley JA, Lavoie A, Turgeon A. Evaluating the validity of multiple imputation for missing physiological data in the national trauma data bank. *J Emerg Trauma Shock.* 2009;2(2):73-79.
10. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. *J Trauma.* 1987;27(4):370-378.
11. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet.* 1974;304(7872):81-84.
12. WAR LTR. Landelijke Traumaregistratie - Toelichting uitkomstevaluatie 2015. TRISS model Nederlandse coëfficiënten en SMR. Resultaten 2015 regio: Netwerk Acute Zorg Brabant. 2016.
13. Steyerberg E. Chapter 7; Dealing with missing values. Clinical prediction models: a practical approach to development, validation, and updating: Springer Science & Business Media; 2008. p. 115-137.
14. Harrell F. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Springer; 2015.
15. Bernaards CA, Belin TR, Schafer JL. Robustness of a multivariate normal approximation for imputation of incomplete binary data. *Stat Med.* 2007;26(6):1368-1382.
16. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.
17. Little RJ, Rubin DB. Statistical analysis with missing data. John Wiley & Sons; 2014.
18. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581-592.
19. Glance LG, Osler TM, Mukamel DB, Meredith W, Dick AW. Impact of statistical approaches for handling missing data on trauma center quality. *Ann Surg.* 2009;249(1):143-148.
20. Joseph L, Bélisle P, Tamim H, Sampalis JS. Selection bias found in interpreting analyses with missing data for the prehospital index for trauma. *J Clin Epidemiol.* 2004;57(2):147-153.
21. Newgard CD, Haukoos JS. Advanced statistics: missing data in clinical research—part 2: multiple imputation. *Acad Emerg Med.* 2007;14(7):669-678.
22. Royston P. Multiple imputation of missing values. *Stata J.* 2004;4(3):227-241.
23. O'Reilly GM, Jolley DJ, Cameron PA, Gabbe B. Missing in action: a case study of the application of methods for dealing with missing data to trauma system benchmarking. *Acad Emerg Med.* 2010;17(10):1122-1129.
24. Rue T, Thompson HJ, Rivara FP, Mackenzie EJ, Jurkovich GJ. Managing the common problem of missing data in trauma studies. *J Nurs Scholarsh.* 2008;40(4):373-378.

SUPPLEMENTAL FILE I

GCS is calculated by adding the coded values for E, M and V[11]:

E	**(range: 1-4)**	**M**	**(range: 1-6)**	**V**	**(range: 1-5)**
4[a]	Eyes open spontaneously	6[a]	Obeys commands	5[a]	Oriented
3	Eyes open to verbal command	5	Localizes pain	4	Confused
2	Eyes open to pain	4	Withdrawal from pain	3	Inappropriate words
1	No eye opening	3	Flexion to pain	2	Incomprehensible sounds
		2	Extension to pain	1	No verbal response
		1	No motor response		

RR, SBP and GCS were coded as follow:

RR	**SBP**	**GCS**	**Coded value**
10-29[a]	>89[a]	13-15	4
>29	76-89	9-12	3
6-9	50-75	6-8	2
1-5	1-49	4-5	1
0	0	3	0

The estimated coefficients (b_n) of TRISS as used in this study[12]:

		Coefficients	
Variables		**Blunt Injury**	**Penetrating Injury**
Intercept	b_0	1.5090	0.6460
RR	b_1	0.2372	0.2114
SBP	b_2	0.6460	0.6806
GCS	b_3	0.4008	0.6333
ISS	b_4	-0.1087	-0.0922
Age Index	b_5	-2.2091	-1.5366

The probability of survival is calculated with the following equations:

$Ps = 1 / (1+e^{-b})$

With $b = b_0 + b_1 (RR) + b_2 (SBP) + b_3 (GCS) + b_4 (ISS) + b_5 (Age\ index)$

Age was equal to 0 if the patient is younger than 55 years and equal to 1 if the patient is equal to or older than 55 years.

[a] *Clinical normal physiological values*

List of abbreviations: E, Eye component of the Glasgow Coma Scale; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MTOS, Major Trauma Outcome Study; M, Motor component of the Glasgow Coma Scale; Ps, Probability of Survival; RR, Respiratory Rate; SBP, Systolic Blood Pressure; TRISS, Trauma Injury Severity Score; V, verbal component of the Glasgow Coma Scale;

4

PERFORMANCE OF THE MODIFIED TRISS FOR EVALUATING TRAUMA CARE IN SUBPOPULATIONS: A COHORT STUDY

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ABSTRACT

Introduction Previous research showed that there is no agreement on a practically applicable model to use in the evaluation of trauma care. A modification of the Trauma and Injury Severity Score (modified TRISS) is used to evaluate trauma care in the Netherlands. The aim of this study was to evaluate the prognostic ability of the modified TRISS and to determine where this model needs improvement for better survival predictions.

Methods Patients were included if they were registered in the Brabant Trauma Registry from 2010 through 2015. Missing values were imputed according to multiple imputation. Subsets were created based on age, length of stay, type of injury and injury severity. Probability of survival was calculated with the modified TRISS. Discrimination was assessed with the Area Under the Receiver Operating Curve (AUROC). Calibration was studied graphically.

Results The AUROC was 0.84 (95% CI: 0.83, 0.85) for the total cohort (N = 69 747) but only 0.53 (95% CI: 0.51, 0.56) for elderly patients with hip fracture. Overall, calibration of the modified TRISS was adequate for the total cohort, with an overestimation for elderly patients and an underestimation for patients without brain injury.

Conclusions Outcome comparison conducted with TRISS-based predictions should be interpreted with care. If possible, future research should develop a simple prediction model that has accurate survival prediction in the aging overall trauma population (preferable with patients with hip fracture), with readily available predictors.

INTRODUCTION

Prediction models that adequately predict survival are required to determine the quality of care in trauma patients. Trauma is a major cause of mortality in young adults worldwide[1]. In 2014, almost 84 000 patients were admitted due to injuries in the Netherlands and the 30-day mortality rate was 2.1%[2]. Scoring systems and prediction models are important tools to quantify the probability of survival and to evaluate and improve the quality of care for the large number of injured patients[3].

The Trauma and Injury Severity Score (TRISS) was developed from the Major Trauma Outcome Study (MTOS) in 1987 to evaluate the quality of trauma care by comparing outcomes with a norm score[4]. The TRISS is a weighted score based on the Injury Severity Score (ISS), age, and the coded Revised Trauma score (RTS). The RTS combines the Glasgow Coma Score (GCS), Systolic Blood Pressure (SBP) and Respiratory Rate (RR). The MTOS was a retrospective study conducted in North America from 1982 through 1987 and was of great value for the development of TRISS. It has been shown previously that the TRISS has several limitations[5,6]. The use of TRISS in an external population raises concerns, because differences between cohorts are distinct[7,8].

Previous research in the Dutch population demonstrated an adequate performance of the TRISS with coefficients from the MTOS or from the National Trauma Data Bank (NTDB) in the total population, but demonstrated a poor reflection of the mortality risk of elderly patients (with hip fractures)[9-12]. Furthermore, Frankema et al.[13] suggested developing and using a more accurate model for the evaluation of trauma care in the Dutch trauma population. A recent review showed that there is no agreement on a better and practically applicable model to use in the evaluation of trauma care[14].

In 2015 the Dutch Trauma Registry developed a new model based solely on the variables in the TRISS model according to their trauma population, including the elderly patients with hip fracture[15]. This model is used to compare quality of care between Dutch hospitals, but has never been validated in subsets. The aim of this study was to determine the performance of the modified TRISS in subpopulations and to determine where this model needs improvement for better survival predictions in the Dutch trauma population.

METHODS

Study population and data collection

At present, the Netherlands consists of eleven trauma regions, all including a coordinating trauma level I center. The region Noord-Brabant is representative of the total Dutch trauma population. It covers 16% of all admitted trauma patients in the Netherlands and includes urban as well as rural populations[2]. Eleven hospitals in the region Noord-Brabant contributed to the Brabant Trauma Registry (BTR), including one level I hospital and ten level II or III hospitals. The registry database contains data of all trauma patients in Noord-Brabant that were admitted after visiting the Emergency Department (ED) within 48 h after a trauma, independent of injury severity or injury type. Secondary referrals and patients who die in the ED were also registered. Patients who were dead on arrival were excluded from the registry. A total of 72411 patients were registered in the BTR from 2010 through 2015. Variables collected in this registry included demographics, SBP, RR, GCS, ISS, trauma mechanism (blunt vs. penetrating) and Abbreviated Injury Scale (AIS)-codes (version 1998)[16]. In-hospital mortality was considered as the primary outcome measure.

Model

The Probability of survival (Ps) was calculated using the natural logarithm (Logit) of the modified TRISS:

$\text{Logit (Ps)} = \alpha_i + \beta_{GCS,i}{*}GCS + \beta_{RR,i}{*}RR + \beta_{SBP,i}{*}SBP + \beta_{ISS,i}{*}ISS + \beta_{age,i}{*}age$

Age was equal to 0 if the patient was <55 years and equal to 1 if the patient was ≥55 years of age. The coefficients were derived from the Dutch Trauma Registry in 2015 (Table 1)[15].

TABLE 1. The estimated coefficients (b_n) of the modified TRISS as used in this study.

	Coefficients[a]
Mechanism of Injury	**Blunt**
Intercept	1.5090
RR	0.2372
SBP	0.6460
GCS	0.4008
ISS	-0.1087
Age	-2.2091

[a]All coefficients are for blunt injuries. Penetrating injuries have different coefficients (data not shown).

List of abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; RR, Respiratory Rate; SBP, Systolic Blood Pressure.

Subsets

Analyses were performed on the total cohort (with and without elderly patients with hip fractures) and on several subsets. Elderly patients with hip fractures (patients ≥65 years and an ISS ≤ 13, suffering an isolated fracture of the proximal femur [defined as: AIS 1998 codes 851808.3, 851810.3 and 851812.3]) were excluded in the subsets, because it was previously suggested that those patients should be excluded from prediction modeling[17,18]. Each subset represents different challenges to the trauma centers, and were based on:

- Age:
  - Elderly, including only patients >75 years
  - Children, including only patients ≤15 years
- Type of injury: Traumatic Brain Injury (TBI), defined as AIS-head ≥3
- Injury severity: Major trauma, defined as ISS > 15
- LOS > 2, including patients who die during the first 2 days of admission.
- Trauma center (including only patients admitted to a trauma center level I) and non-trauma center (including patients admitted to a trauma center level II or III).

Statistical analysis

Prehospital coded values for the V component of GCS and RR were selected in patients that were sedated and/or intubated, instead of the registered hospital values. Also, prehospital values for the E and M component of GCS were selected in patients that were sedated. Data were screened for missing values. ISS, RTS and age for patients with missing outcome values and with unknown mechanism of injury were compared to patients with known outcome values. Missing value patterns were analyzed for GCS, SBP, RR and ISS. The components of the GCS were transformed into dummy variables and RR was log-transformed in the imputation process. We assumed that missing values were Missing At Random (MAR)[19] and imputed missing values using the following variables: mortality, mechanism of injury, ISS, eye/motor/verbal (E, M and V) component of GCS, SBP, RR, age, with 45 imputations and 10 iterations. Sensitivity analysis was performed in which only complete cases were included. The performance measures that were used in this study were discrimination and calibration. Discrimination was calculated using the Area Under the Receiver Operating Curve (AUROC), including a 95% confidence interval (95% CI). Differences between AUROC were considered significant if the 95% CI did not overlap. Calibration was assessed graphically using calibration plots. In calibration plots the agreement between observed proportion of survival and the predicted probability is visualized using restricted cubic splines.

The performance of modified TRISS for the total group of patients was compared with the specific subsets, to determine the effect of inclusion and exclusion of the subsets. The statistical programs IBM SPSS version 24 (Chicago, USA) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for the analyses.

RESULTS

Baseline characteristics

A total of 72411 patients were included in the BTR. Patients with penetrating injury (N = 2539) were excluded because the number of non-survivors (N = 32) was too low to interpret the results of discrimination and calibration. Patients with unknown survival outcome (N = 125) were excluded from analysis. The excluded patients did not differ in age, RTS, or ISS from the total cohort (data not shown). There were 69747 patients used for further analysis, including 11 514 elderly patients with hip fracture. The eye component, motor component and verbal component of the Glasgow Coma Scale were missing in 5995 (8.6%), 6024 (8.6%) and 6162 (8.8%) observations, respectively. SBP was missing in 11 777 observations (16.9%), RR in 30 083 observations (43.1%) and ISS was missing in 158 patients (0.2%).

The mortality rate decreased (1.7% vs. 2.1%) in the total cohort after exclusion of elderly patients with hip fractures (Table 2). Next, the exclusion of children from the BTR resulted in an increase in mortality rate (2.1%). However, the ISS (median [IQR]) remained the same. Excluding the elderly from the BTR resulted in a higher percentage of men (60.7%) and a lower mortality rate (0.9%), compared to the total cohort.

The exclusion of non-TBI patients and minor injury resulted in older age (55.3 (SD:23.9) and 60.6 (SD:22.3) respectively) and higher mortality rates (12.1% and 12.8% respectively). Patients with LOS > 2 had a mean (SD) age of 60.6 (22.9) and a mortality rate of 3.4%.

Patients in the level I trauma center were younger (45.4 [SD: 27.6]), had a higher mortality rate (4.5%), and had a higher median ISS (9 [IQR: 4–11]) compared to the level II and III trauma centers (mortality rate: 1.2%, age: 47.9 [SD:27.9] and ISS [IQR]: 5 [4–9]).

Discrimination

No differences were found between complete case analysis and the imputed dataset for discrimination (data not shown). The AUROC of the total cohort was 0.84 (95% CI: 0.83, 0.85) and for the elderly patients with hip fracture 0.53 (95% CI: 0.51, 0.56) (Figure 1). After exclusion of the elderly patients with hip fracture the AUROC of the different subsets ranged from 0.72 (95% CI: 0.70, 0.74) for the subset older than 75 years to 0.93 (95% CI: 0.91, 0.94) for the subset level I trauma center. The subset with exclusion of children, the subset with elderly patients, the selections based on ISS, LOS > 2 days and the subset with only level II and III trauma centers decreased the discriminative ability significantly. Discrimination was significantly higher in the Level I trauma center than in the level II and III trauma centers.

TABLE 2. Study characteristics of the Brabant Trauma Registry with patient subsets from 2010 through 2015.

	Brabant Trauma Registry									
	Including elderly with hip fractures[a]		**Excluding elderly with hip fractures**[a]							
	Total cohort	**Hip fracture**[a]	**Total cohort**	**Age (years)**		**Trauma severity**			**Trauma center**	
				>15	**≤75**	**TBI**[b]	**Major trauma**[c]	**LOS > 2**	**Level I**	**Level II and III**
N	69 747	11 514	58 233	47 565	46 150	3 531	3 932	28 883	8 443	49 790
Age (mean, SD)	53.2 (28.6)	82.0 (7.7)	47.5 (27.8)	56.6 (22.2)	38.0 (23.0)	55.3 (23.9)	55.7 (22.3)	60.6 (22.9)	45.4 (27.6)	47.9 (27.9)
Male (%)	49.7	27.9	53.9	53.0	60.7	62.3	65.7	47.6	58.5	53.2
In-hospital mortality (%, N)	2.1 (1 490)	4.4 (502)	1.7 (988)	2.1 (982)	0.9 (406)	12.1 (428)	12.8 (503)	3.4 (975)	4.5 (381)	1.2 (605)
RTS (mean, SD)	7.7 (0.4)	7.8 (0.3)	7.7 (0.5)	7.7 (0.5)	7.7 (0.5)	7.1 (1.3)	7.2 (1.3)	7.7 (0.6)	7.5 (0.9)	7.7 (0.4)
ISS (median, IQR)	9 (4-9)	9 (9-9)	5 (4-9)	5 (4-9)	5 (4-9)	17 (11-25)	20 (17-26)	9 (4-9)	9 (4-11)	5 (4-9)
ISS (mean, SD)	7.5 (5.2)	9.0 (0.2)	7.2 (5.7)	7.4 (6.1)	7.2 (5.7)	19.2 (9.5)	22.9 (8.6)	8.7 (6.7)	10.2 (9.4)	6.7 (4.6)

List of abbreviations: AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; IQR, Interquartile range; LOS, Length of Stay; N, number; SD, Standard Deviation; RTS, Revised Trauma Score; TBI, Traumatic Brain Injury

[a] Patients with hip fracture were considered equal to or older than 65 years, ISS<13 and one of the following AIS 1998 codes 851808.3, 851810.3 or 851812.3

[b] Patients with TBI were defined as AIS-head ≥ 3

[c] Major trauma was defined as ISS > 15

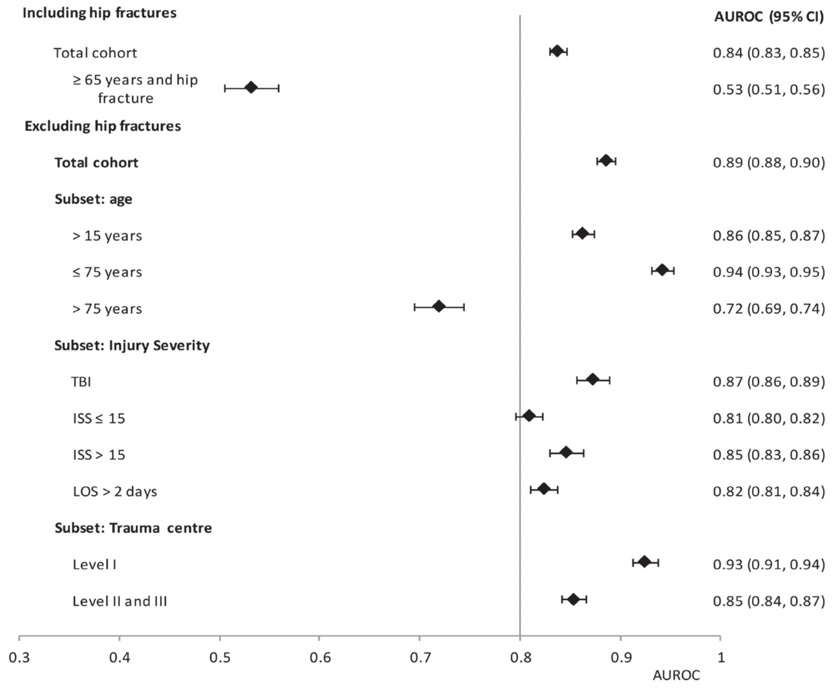

FIGURE 1. Discrimination of the modified TRISS for the total cohort and subpopulations.
List of abbreviations: AUROC, Area Under Receiver Operating Curve; CI, Confidence Interval; ISS, Injury Severity Score; LOS, Length of Stay; TBI, Traumatic Brain Injury.
*Patients with hip fracture were considered equal to or older than 65 years, ISS < 13 and one of the following AIS 1998 codes 851808.3, 851810.3 or 851812.3.

Calibration

Calibration curves for the modified TRISS were shown in Figure 2. There were no apparent differences between calibration of the total cohort and the complete cases. The total cohort showed predictions close to the identity line, thus equal observed proportion and predicted probabilities. After exclusion of the elderly patients with hip fracture, the cohort showed higher observed proportion of survival compared to the predicted probabilities in the highest Ps bins (0.8–1.0).

The subset ≤ 75 years old showed a higher observed proportion of survival compared to the total cohort, especially in the highest Ps bins (0.5–1.0). The subset of elderly showed a significant overestimation of the predicted survival rate.

The calibration curve of the TBI subset showed an underestimation of the predicted probabilities of the TRISS in the lower Ps bins (0.0–0.3) and an overestimation of the higher Ps bins (0.3–1.0). The non-TBI patients showed a significant underestimation of the predicted probability of survival in all probability bins. Calibration of the subset with an ISS > 15 showed a similar curve as the TBI subset. The subset LOS > 2 showed an calibration curve close

to the identity line. The level I trauma center had higher observed proportion survivors in the lower Ps bins (0.0–0.7) but lower observed proportion in the higher Ps bins (0.7–1.0) compared to the predicted probabilities. The calibration curve of the subset with only level II and level III trauma centers was close to the identity line.

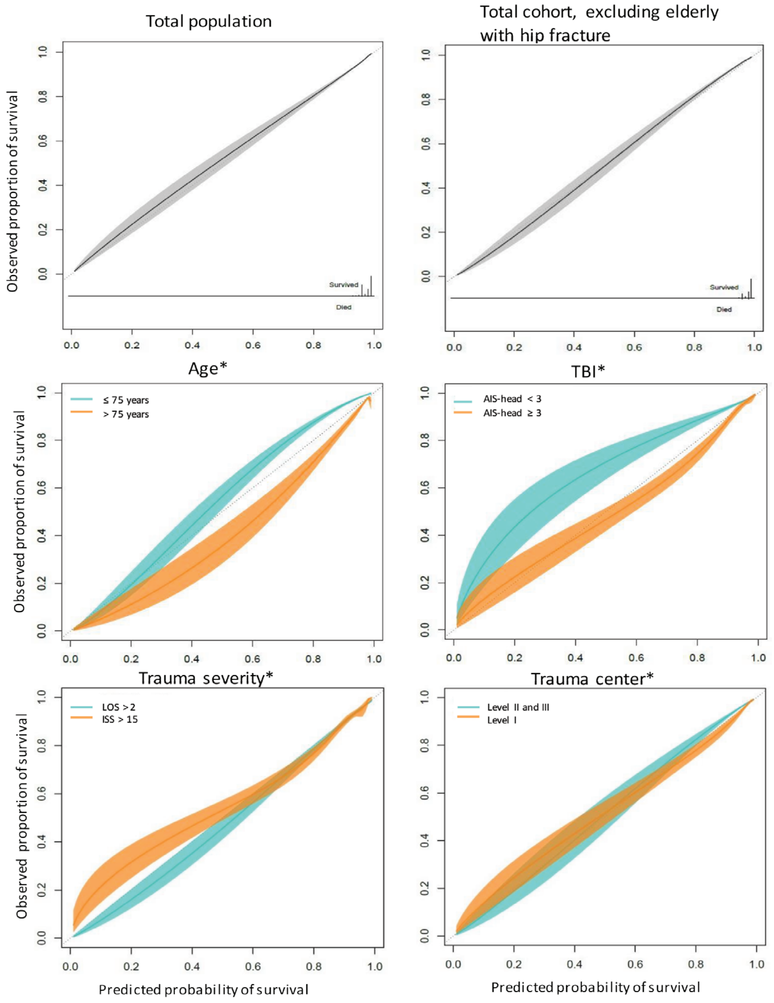

FIGURE 2. Calibration curves for the modified TRISS in the total cohort and in different subsets of patients.
List of abbreviations: ISS, Injury Severity Score; LOS, Length of Stay; TBI, Traumatic Brain Injury.
*Cohort, excluding patients with hip fracture (patients with hip fracture were considered equal to or older than 65 years, ISS < 13 and one of the following AIS 1998 codes 851808.3, 851810.3 or 851812.3).

DISCUSSION

Prediction models need to be reliable if used in evaluating the quality of trauma care. Although discrimination of the modified TRISS in the total trauma cohort was adequate, the model performed much better when excluding elderly, with or without hip fractures. Overall, calibration of the modified TRISS was adequate for the total cohort. However, the model overestimates the survival for the elderly and underestimates survival for patients without TBI.

Discrimination of a model is dependent on the distribution of prognostic factors. Discrimination in the elderly (with hip fractures) could be low because the heterogeneity of the case-mix decreased. In contrast to discrimination, calibration of the cohort excluding elderly with hip fractures showed no differences compared to calibration of the total cohort. The lack of differences in the calibration plot could be explained by the high number of patients remaining in the highest predicted probability group after excluding the relative low number of elderly with hip fractures. The NTDB encourages researchers to use inclusion and exclusion criteria in the data registry to create a more homogeneous group; for example, hip fractures should be excluded or analyzed separately, which is also confirmed by Gomez et al.[17,18]. In contrast, others argue that elderly with isolated hip fracture should be included in the trauma registry[20]. Elderly with hip fracture comprise currently 17% of the total Dutch trauma population[2]. Due to the aging population and the high incidence of falls within these often frail patients, the number of elderly in the trauma registries with hip fractures will increase the following decades. However, this study supports the fact that elderly with hip fracture should be excluded for general trauma center benchmarking when the modified TRISS is used and should be analyzed separately for benchmarking purposes using a more specific prediction model. Nevertheless, if it could be achieved to develop a model with accurate predictions in all subsets, it is preferable to include elderly with hip fractures for evaluation of quality care, to cover all trauma related injuries.

Another explanation of the moderate discrimination in elderly could be explained by the lack of measures for frailty in the model. Next to frailty, dichotomization of age leads to a loss of information, and could be one of the main reasons for the poor performance of the modified TRISS in the elderly[21,22]. Also, elderly often suffer from comorbidities, which could be important predictors of mortality in the aging population[17,23-25]. Some of these issues were already incorporated in previously developed models[26-28]. However, comorbidity measures and frailty are not incorporated in the Dutch Trauma Registry and could therefore not be used in benchmarking trauma care.

The TBI subset had accurate predictions among the lower survival probabilities intervals in the TBI subset. However, the higher intervals showed an overestimation of the survival predictions. Previous research suggested an inability of ISS to account enough for multiple injuries to the same body region[29]. While mortality is often attributed to TBI, severe TBI is often not entirely captured by a measure such as the ISS. Champion et al.[30] suggested to include all anatomic injuries for more accurate survival prediction in patients with TBI.

There are some limitations to this study. First, the modified TRISS is developed in the Dutch trauma population, including the BTR. Results could differ if this model is validated in an external cohort (i.e. a cohort that is not incorporated in the Dutch trauma registry). The study may not be generalizable to other settings with different patient composition. Second, missing values are a common problem in trauma registries. Ignoring them could influence the results and decrease the statistical power. Multiple imputation is an increasingly chosen solution to minimize bias and increase precision[31-33]. The imputation model applied in this study was based on literature[34]. Therefore, we assume that no major bias occurred, as confirmed by the similar results in a complete case analysis. However, it could also be argued to exclude predictors with a high proportion of missing values (e.g. RR in the modified TRISS) for more optimal predictions. Next, patients with unknown mechanism of injury (N = 1172) were included as patients with blunt injuries. It is unlikely this influenced the results, since most trauma patients have blunt injury[2]. In addition, the use of AIS98 is considered a shortcoming. The BTR included AIS08 codes from 2015 onwards, but conversion of AIS98 to AIS08 showed to be unreliable[35]. However, to obtain power to assess performances among subsets of the registry more years with old AIS98 codes were used, instead of two years with newer AIS08 codes. Last, we note that the outcome measure, in-hospital mortality, is a poor measure of outcome. A better outcome would be 30-day mortality. However, this outcome is not reported in the trauma registry.

The current overall mortality rate in the Netherlands of the acute hospitalized trauma population is only 2%. Therefore, it could be suggested that mortality is not the most important outcome to evaluate trauma care. With the decrease in mortality rates in the developed countries, trauma care could also be assessed with nonfatal outcome measures. Outcome comparison conducted with the modified TRISS should be interpreted with care, because the performance of the model is highly dependent on the case mix of the patients included in the registry. The quality of care in the elderly should not be evaluated when the modified TRISS is used. If it could be achieved in the future to develop a model with accurate predictions in all subsets, it is preferable to include elderly for evaluation of quality care to cover all trauma related injuries. Predictors should be readily available and easy to collect in the current trauma registry.

REFERENCES

1. World Health Organization. Injuries and violence: the facts. 2014 WO700 (August).
2. Landelijke Netwerk Acute Zorg. Traumazorg in beeld: Landelijke traumaregistratie 2012-2016. rapportage Nederland; 2017.
3. Rutledge R, Osler T, Emery S, Kromhout-Schiro S. The end of the injury severity score (ISS) and the trauma and injury severity score (TRISS): ICISS, an international classification of diseases, ninth revision-based prediction tool, outperforms both ISS and TRISS as predictors of trauma patient survival, hospital charges, and hospital length of stay. *J Trauma.* 1998;44(1):41–9.
4. Champion HR, Sacco WJ, Hunt TK. Trauma severity scoring to predict mortality. *World J Surg.* 1983;7(1):4–11.
5. Champion HR, Copes WS, Sacco WJ, Lawnick MM, Keast SL, Frey CF. The major trauma outcome study: establishing national norms for trauma care. *J Trauma.* 1990;30(11):1356–65.
6. Rogers FB, Osler T, Krasne M, Rogers A, Bradburn EH, Lee JC, et al. Has TRISS become an anachronism? A comparison of mortality between the national trauma data bank and major trauma outcome study databases. *J Trauma Acute Care Surg.* 2012;73(2):326–31.
7. Demetriades D, Chan LS, Velmahos G, Berne TV, Cornwell 3rd EE, Belzberg H, et al. TRISS methodology in trauma: the need for alternatives. *Br J Surg.* 1998;85 (3):379–84.
8. Cayten C, Stahl W, Murphy J, Agarwal N, Byrne D. Limitations of the TRISS method for interhospital comparisons: a multihospital study. *J Trauma.* 1991;31(4):471–82.
9. Champion H, Sacco W, Copes W. Injury severity scoring again. *J Trauma.* 1995;38(1):94–5.
10. Schluter PJ, Nathens A, Neal ML, Goble S, Cameron CM, Davey TM, et al. Trauma and injury severity score (TRISS) coefficients 2009 revision. *J Trauma.* 2010;68 (4):761–70.
11. De Jongh MAC, Verhofstad MHJ, Leenen LPH. Accuracy of different survival prediction models in a trauma population. *Br J Surg.* 2010;97(12):1805–13.
12. Joosse P, Schep NW, Goslings JC, Regional Trauma Network TraumaNet AMC Collaborators. Injury profiles related to mortality in patients with a low injury severity score: a case-mix issue? *J Trauma Acute Care Surg.* 2012;73(1):179–85.
13. Frankema SPG, Edwards MJR, Steyerberg EW, Van Vugt AB. Predicting survival after trauma: a comparison of TRISS and ASCOT in the netherlands. *Eur J Trauma.* 2002;28(6):355–64.
14. de Munter L, Polinder S, Lansink K, Cnossen M, Steyerberg E, de Jongh MAC. Mortality prediction models in the general trauma population: a systematic review. *Injury.* 2017;48(2):221–9.
15. WARLTR. Landelijke traumaregistratie–toelichting uitkomstevaluatie 2015. TRISS model Nederlandse coëfficiënten en SMR. resultaten 2015 regio: Netwerk Acute Zorg Brabant. 2016.
16. Association for the Advancement of Automotive Medicine. Abbreviated injury scale; 1990 revision: update 98. AAAM; 1998.
17. Gomez D, Haas B, Hemmila M, Pasquale M, Goble S, Neal M, et al. Hips can lie: impact of excluding isolated hip fractures on external benchmarking of trauma center performance. *J Trauma.* 2010;69(5):1037–41.
18. American College of Surgeons. National trauma data bank: NTDB research data set admission year 2008. User manual. 2010 February.
19. Little R, Rubin D. Statistical analysis with missing data. Wiley series in probability and mathematical statistics. John Wiley & Sons; 2014.
20. Bergeron E, Lavoie A, Belcaid A, Ratte S, Clas D. Should patients with isolated hip fractures be included in trauma registries? *J Trauma.* 2005;58(4):793–7.
21. Steyerberg EW. Chapter 9: coding of categorical and continuous predictors. *In: Clinical prediction models: a practical approach to development, validation, and updating.* Springer Science & Business Media; 2010. p. 159–73.

22. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med.* 2006;25(1):127–41.
23. Quail JM, Lix LM, Osman BA, Teare GF. Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. *BMC Health Serv Res.* 2011;11(1):1.
24. Glance LG, Dick AW, Mukamel DB, Meredith W, Osler TM. The effect of preexisting conditions on hospital quality measurement for injured patients. *Ann Surg.* 2010;251(4):728–34.
25. Thompson HJ, Rivara FP, Nathens A, Wang J, Jurkovich GJ, MacKenzie EJ. Development and validation of the mortality risk for trauma comorbidity index. *Ann Surg.* 2010;252(2):370–5.
26. Jones JM, Skaga NO, Søvik SO, Lossius HM, Eken T. Norwegian survival prediction model in trauma: modelling effects of anatomic injury, acute physiology, age, and co-morbidity. *Acta Anaesthesiol Scand.* 2014;58(3):303– 15.
27. Bouamra O, Wrotchford A, Hollis S, Vail A, Woodford M, Lecky F. A new approach to outcome prediction in trauma: a comparison with the triss model. *J Trauma.* 2006;61(3):701–10.
28. Bergeron E, Rossignol M, Osler T, Clas D. Improving the TRISS methodology by restructuring age categories and adding comorbidities. *J Trauma.* 2004;56 (4):760–7.
29. Moon J, Seo B, Jang J, Lee J, Moon H. Evaluation of probability of survival using trauma and injury severity score method in severe neurotrauma patients. *J Korean Neurosurg Soc.* 2013;54(1):42–6.
30. Champion HR, Copes WS, Sacco WJ, Frey CF, Holcroft JW, Hoyt DB, et al. Improved predictions from a severity characterization of trauma (ASCOT) over trauma and injury severity score (TRISS): results of an independent evaluation. *J Trauma.* 1996;40(1):42–9.
31. Moore L, Lavoie A, LeSage N, Liberman M, Sampalis JS, Bergeron E, et al. Multiple imputation of the glasgow coma score. *J Trauma.* 2005;59(3):698– 704.
32. O'Reilly GM, Jolley DJ, Cameron PA, Gabbe B. Missing in action: a case study of the application of methods for dealing with missing data to trauma system benchmarking. *Acad Emerg Med.* 2010;17(10):1122–9.
33. Newgard CD. The validity of using multiple imputation for missing out-of-hospital data in a state trauma registry. *Acad Emerg Med.* 2006;13(3):314–24.
34. de Munter L, ter Bogt NC, Hesselink DD, de Jongh MA. Imputation strategies in the trauma registration. *J Trauma Acute Care Surg.* 2017;83(5):828–36.
35. Palmer CS, Franklyn M. Assessment of the effects and limitations of the 1998 to 2008 abbreviated injury scale map using a large population-based dataset. *Scand J Trauma Resusc Emerg Med.* 2011;19(1):1.

5

IMPROVEMENT OF THE PERFORMANCE OF SURVIVAL PREDICTION IN THE AGEING BLUNT TRAUMA POPULATION: A COHORT STUDY

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ABSTRACT

Introduction The overestimation of survival predictions in the ageing trauma population results in negative benchmark numbers in hospitals that mainly treat elderly patients. The aim of this study was to develop and validate a modified Trauma and Injury Severity Score (TRISS) for accurate survival prediction in the ageing blunt trauma population.

Methods This retrospective study was conducted with data from two Dutch Trauma regions. Missing values were imputed. New prediction models were created in the development set, including age (continuous or categorical) and Anesthesiologists Physical Status (ASA). The models were externally validated. Subsets were created based on age (≥75 years) and the presence of hip fracture. Model performance was assessed by proportion explained variance (Nagelkerke R^2), discrimination (Area Under the curve of the Receiver Operating Characteristic, AUROC) and visually with calibration plots. A final model was created based on both datasets.

Results No differences were found between the baseline characteristics of the development dataset (n = 15,530) and the validation set (n = 15,504). The inclusion of ASA in the prediction models showed significant improved discriminative abilities in the two subsets (e.g. AUROC of 0.52 [95% CI: 0.46, 0.58] vs. 0.74 [95% CI: 0.69, 0.78] for elderly patients with hip fracture) and an increase in the proportion explained variance ($R^2 = 0.32$ to $R^2 = 0.35$ in the total cohort). The final model showed high agreement between observed and predicted survival in the calibration plot, also in the subsets.

Conclusions Including ASA and age (continuous) in survival prediction is a simple adjustment of the TRISS methodology to improve survival predictions in the ageing blunt trauma population. A new model is presented, through which even patients with isolated hip fractures could be included in the evaluation of trauma care.

INTRODUCTION

Accurate survival predictions are necessary for reliable comparisons of the quality of care between centers. The Dutch Trauma Registry (DTR) is a nationwide registry collecting trauma data of approximately 80.000 admitted patients annually in the Netherlands[1,2]. The DTR updated the coefficients of the Trauma and Injury Severity Score (TRISS) and used this updated TRISS for evaluation of trauma care[1,3]. This model has accurate survival predictions when looking at the trauma population in general, but showed an overestimation of survival in the elderly trauma patient[4,5].

Patients with isolated hip fractures are often excluded from trauma registries[6]. Nevertheless, the purpose of the trauma registry is to document and gain insight into the full spectrum of admitted trauma patients, including the elderly[7]. In 2016, 18.2% of the Dutch population was aged 65 years or older and it is expected that this number will increase to 26.5% in 2040[8]. Because the elderly remain more active later in life, it is likely that the proportion of elderly trauma patients will increase as well. Hence, the Dutch trauma registry includes patients with isolated hip fractures, and includes them for the evaluation of quality of care. Currently, almost 20% of the registry comprises elderly patients with hip fracture. Because survival predictions will be overestimated in the elderly, the benchmark numbers (e.g. W-statistic [Ws][9]) provided from the updated TRISS are negatively biased, especially in hospitals that mainly treat elderly patients[5].

Previously developed scoring systems for elderly with hip fracture, like the Nottingham Hip Fracture Score[10], are often based on variables that are not collected in the Dutch trauma registry (e.g. comorbidities present at time of hip fracture[11,12], the abbreviated mental test score [AMTS][13] or frailty[11,13]) and could therefore not be applied to the Dutch trauma population. Other previously developed models based on the TRISS methodology incorporated age as a categorical or continuous predictor and added comorbidity to the survival prediction model[14–19]. Although these models have the potential for accurate predictions in the total (and ageing) Dutch trauma population, the models were not solely assessed to the elderly trauma population and patients with isolated hip fractures were often excluded from the analyses.

Benchmark numbers should be comparable and accurate among all trauma subsets. Predictors for survival models should be reliable for the total trauma population and should be readily available from the trauma registry. The aim of this study was to develop and validate a modified TRISS with simple and minimal adjustments with variables available in the Dutch trauma registry.

METHODS

Patient selection

This research was a retrospective cohort, conducted with registry data from two of the eleven trauma regions in the Netherlands: Network Emergency Care Brabant and Network Emergency Care Euregio. The first region included 12 emergency departments and was located in the South of the Netherlands, and the latter region was located in the east of the Netherlands with 4 emergency departments. Both regions included one level I trauma center and both regions included rural as urban areas.

The registry collected data from patients with injury that were admitted to one of the hospitals of the two regions after visiting the Emergency Department (ED) within 48 hours after trauma, independent of injury severity. Also, patients who died in the ED or secondary referrals were registered. Patients who were dead on arrival were excluded. Data was anonymized prior to access.

Two datasets were created, based on year of admission. The development set consisted of all observations from 2015 from the two regions (N = 16,095), including elderly patients (with hip fracture). The validation set consisted of all observations from 2016 (N = 16,073), including elderly patients (with hip fracture).

Data collection and predictors

Information about the injury, prehospital and hospital physiological data, Abbreviated Injury Scale (2008) (AIS08)[20], and demographic variables were collected. The Dutch trauma registry did not include information about comorbidities other than the Anesthesiologists Physical Status (ASA)[21].

The prehospital Eye (E), Motor (M), and Verbal (V) components of the Glasgow Coma Scale (GCS)[22] and prehospital Respiratory Rate (RR) were used for patients who were sedated before arrival in the hospital. Also, the prehospital value for the V component of the GCS and RR were selected for intubated patients. Patterns of missing values for the survival predictors were analyzed. Missing values were considered Missing at Random (MAR) and missing predictor variables were imputed according to multiple imputation[23]. Missing values were imputed 30 times in both the development and validation set, according to the maximum percentage of missing values. The development set consisted of 3.5%, 3.6%, 3.7%, 28.8%, 9.9%, 1.1% and 9.2% missing values for E, M, V, RR, Systolic Blood Pressure (SBP), ISS and ASA respectively. The validation set consisted of 2.1%, 2.1%, 2.2%, 27.0%, 8.9%, 0.7% and 8.2% missing values for E, M, V, RR, SBP, ISS and ASA respectively. The imputation processes were assessed with convergence plots, which showed no trends.

Patients with penetrating injury (development set: N = 523 [3.2%] and validation set: N = 525 [3.3%]) were excluded, because the number of deaths was too low to assess the model performances adequately. Also, patients with unknown mechanism of injury (development set: N = 42 [0.3%] and validation set: N = 47 [0.3%]) were excluded from further analyses.

Model development

Coefficients were calculated for five different models in the development dataset, with increasing number of parameters in the models and in-hospital mortality as outcome (Table 1). Model 1 is the updated TRISS as used in the Dutch Trauma Registry, with coefficients from 2015[1]. The other models were adjusted with age as categorical or continuous variable, and/or ASA was added to the model. The assumption of linearity in the logit was assessed for all linear variables.

If no deviant model performances were found between the development dataset and the validation dataset because characteristics between sets were closely related, a final model was developed in a combined dataset (combining development dataset and validation dataset, N = 31,034)[24]. Year of admission was included and assessed as predictor in this final model.

TABLE 1. Variables that are incorporated in the different models.

	GCS	SBP	RR	ISS	Age			ASA
	Coded[a]	Coded[a]	Coded[a]	Linear	Dichotomous	Categorical	Continuous	Categorical[b]
Model 1	X	X	X	X	X			
Model 2	X	X	X	X	X			X
Model 3	X	X	X	X		X		
Model 4	X	X	X	X		X		X
Model 5	X	X	X	X			X	
Model 6	X	X	X	X			X	X

Abbreviations: ASA, Anesthesiologists Physical Status; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; RR, Respiratory Rate; SBP, Systolic Blood Pressure.

[a] Variables were coded according to the Revised Trauma Score calculations.

[b] ASA classification; ASA-1: a normal healthy patient, ASA-2: a patient with mild systemic disease, ASA-3: a patient with severe systemic disease, ASA-4: a patient with severe systemic disease that is a constant threat to life.

Subsets

The models were developed in the total trauma population. Because previous research showed poor performance of the updated TRISS in the elderly with and without hip fracture[5], two subsets were created in both the development and the validation dataset to validate the performance of the new models. The first subset consisted of elderly patients ≥75 years. The second subset consisted of patients suffering hip fracture, defined as ≥65 years with AIS08-codes 853161.3, 853162.3, 853151.3 and 853152.3, and ISS≤13.

Statistical analysis

Data was reported according to the Transparent Reporting of a multivariable prediction model for individual Prognosis Or Diagnosis (TRIPOD) statement[25]. Because the models were pre-specified, the shrinkage principle is applied; the regression coefficients were meant for less extreme predictions, i.e. a better calibration. A shrinkage factor was calculated with s as uniform shrinkage factor and shrunk regression coefficients were calculated as $s*\beta$. The shrinkage factor (s) is based on the following formula: $s = (\text{Model } \chi^2 - df) / \text{Model } \chi^2$, with model χ^2 as the difference in 2log likelihood between the model with and without predictors and df as the degrees of freedom of the number of predictors considered for the model[26,27]. The intercept was recalculated, based on the shrunken coefficients.

The proportion of variance that is explained by the model is calculated with Nagelkerke R square (R^2)[28]. Model performance was assessed by discrimination and calibration. Discrimination was measured using the Area Under the curve of the Receiver Operating Characteristic (AUROC). Differences between AUROC were considered significant when the 95% Confidence Intervals (CI) did not overlap, implying a p-value <0.01 for the difference in AUROC.

Calibration was assessed visually with calibration plots. The models were externally validated by calculating the survival prediction for each model using the shrunken coefficients in the validation set, and were assessed on performance in both the validation set as in its subsets. Data cleaning and multiple imputation were done using IBM SPSS version 24 (Chicago, USA). R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for the drawing of the calibration curves. Calibration curves were created based on cubic splines.

TABLE 2. Patient characteristics for the development and validation set.

	Development set			Validation set		
	Total	**≥75 years**	**≥65 years with hip#[b]**	**Total**	**≥75 years**	**≥65 years with hip#**
N	15,530	5,369	2,599	15,504	5,405	2,689
Age (mean, SD)	54.8 (29.1)	84.2 (7.0)	81.8 (8.0)	54.8 (29.2)	84.1 (7.1)	81.8 (8.0)
Male (N, %)	7672 (49.4)	2572 (34.6)	801 (30.8)	7764 (50.1)	2584 (35.0)	774 (28.2)
ASA (N, [%])[b]						
1	6865 (44.2)	403 (7.5)	229 (8.8)	6898 (44.5)	397 (7.3)	231 (8.6)
2	5649 (36.4)	2773 (51.6)	1280 (49.2)	5630 (36.3)	2824 (52.2)	1301 (48.4)
3	2928 (18.9)	2140 (39.9)	1062 (40.9)	2842 (18.3)	2106 (39.0)	112 (4.2)
4	88 (0.6)	53 (1.0)	28 (1.1)	134 (0.9)	78 (1.4)	45 (1.7)
Mortality (N, %)	375 (2.4)	279 (5.2)	205 (4.2)	322 (2.1)	233 (4.3)	179 (3.8)
E (N, [%])[c]						
Normal	14462 (93.1)	5035 (93.8)	2490 (95.8)	14626 (94.3)	5164 (95.5)	2604 (96.8)
Abnormal	1068 (6.9)	334 (6.2)	109 (4.2)	878 (5.7)	241 (4.5)	85 (3.2)
M (N, [%])[c]						
Normal	14675 (94.5)	5087 (94.7)	2490 (95.8)	14889 (96.0)	5209 (96.4)	2606 (96.9)
Abnormal	855 (5.5)	282 (5.3)	109 (4.2)	615 (4.0)	196 (3.6)	83 (3.1)
V (N, [%])[c]						
Normal	13971 (90.0)	4832 (90.0)	2398 (92.3)	14058 (90.7)	4903 (90.7)	2491 (92.6)
Abnormal	1559 (10.0)	537 (10.0)	201 (7.7)	1446 (9.3)	502 (9.3)	198 (7.4)
RR (N, [%])[c]						
Normal	15203 (97.9)	5267 (98.1)	2554 (98.3)	15148 (97.7)	5297 (98.0)	2649 (98.5)
Abnormal	327 (2.1)	102 (1.9)	45 (1.7)	356 (2.3)	108 (2.0)	40 (1.5)
SBP (N, [%])[c]						
Normal	14995 (96.6)	5262 (98.0)	2559 (40)	15050 (97.1)	5306 (98.2)	2659 (98.9)
Abnormal	535 (3.4)	107 (2.0)	40 (1.5)	454 (2.9)	99 (1.8)	30 (1.1)
ISS (median, IQR)	4 (2, 9)	9 (4, 9)	9 (9, 9)	4 (2, 9)	9 (4, 9)	9 (9, 9)

Abbreviations: ASA, Anesthesiologists Physical Status; E, Eye component of the Glasgow Coma Scale; hip#, hip fracture; IQR, Inter Quartile Range; ISS, Injury Severity Score; M, Motor component of the Glasgow Coma Scale; ref, reference group; RR, Respiratory Rate; SBP, Systolic Blood Pressure; V, Verbal component of the Glasgow Coma Scale.

[a] Patients with hip fractures were defined as ≥65 years with AIS08-codes 853161.3, 853162.3, 853151.3 and 853152.3, and ISS<13.

[b] ASA classification; ASA-1: a normal healthy patient, ASA-2: a patient with mild systemic disease, ASA-3: a patient with severe systemic disease, ASA-4: a patient with severe systemic disease that is a constant threat to life.

[c] Normal values for E, M and V were 4, 6 and 5 respectively. Normal value of RR was considered between 10 and 29 per minute and the normal value for SBP was >89 mm Hg.

RESULTS

Patient characteristics

Development set

A total of 15,530 observations were used for the model development (Table 2). The mortality rate in the total population was 2.4% (n = 375) and 49.4% (n = 7,672) was male. Mean age was 54.8 years (SD: 29.1) and the median (Interquartile Range [IQR]) ISS was 4 (2–9). The population consisted of 5,369 patients equal to or older than 75 years and a total of 2,599 patients (16.7%) were ≥65 years with a hip fracture.

Validation set

A total of 15,504 observations were used for external validation (Table 2). The mortality rate in the validation set was 2.1% (n = 322) and 50.1% (n = 7,764) was male. Mean age was 54.8 years (SD: 29.2) and the median (Interquartile Range [IQR]) ISS was 4 (2–9). A total of 5,405 patients were equal to or older than 75 years and a total of 2,689 patients (17.3%) were ≥65 years with a hip fracture. No differences were found between the baseline characteristics of the development dataset and the validation set.

Performances

The coefficients of the models were shown in Table 3. The assumption of linearity in the logit was met for all continuous predictors, indicating that there were no transformations necessary. The shrinkage factors were very close to 1, indicating no overfit (s = 0.99).
The explained variance in model 1 was lower compared to all other models (R^2: 0.27 vs. 0.32 to 0.35 respectively) (Table 3). The highest R^2 was found in model 4 (R2 : 0.35).
The discriminative ability of the models for the total validation dataset and its subsets were shown in Table 3. Discrimination improved significantly after restructuring the age component (from AUROC 0.85 [95% CI: 0.83, 0.87] for model 1 to 0.88 [95% CI: 0.87, 0.90] for model 5 with age as linear predictor) (Table 3). After inclusion of the ASA classification, the discriminative ability increased to 0.91 (95% CI: 0.90, 0.93). The validation subset with the elderly showed an discriminative ability of 0.68 (95% CI: 0.65, 0.72) for model 1, with an significant increase of discriminative ability for model 6 (0.78 [95% CI: 0.75, 0.81]). The validation hip fracture cohort showed a significant increase in discriminative ability between model 1 and model 6 (AUROC: 0.52 [95% CI: 0.46, 0.58] and AUROC: 0.74 [95% CI: 0.69, 0.78] respectively). The inclusion of ASA in the prediction models showed significant higher discriminative abilities in the two subsets.
Calibration curves for the elderly in the validation set were shown in Figure 1. There was an overestimation of the survivors in the elderly for model 1. The models that incorporate age as categorical or continuous predictor improved calibration. No differences were found between the calibration curves with categorical or continuous age predictor (results

not shown). Including ASA as predictor in addition to the age variable showed a small improvement in calibration.

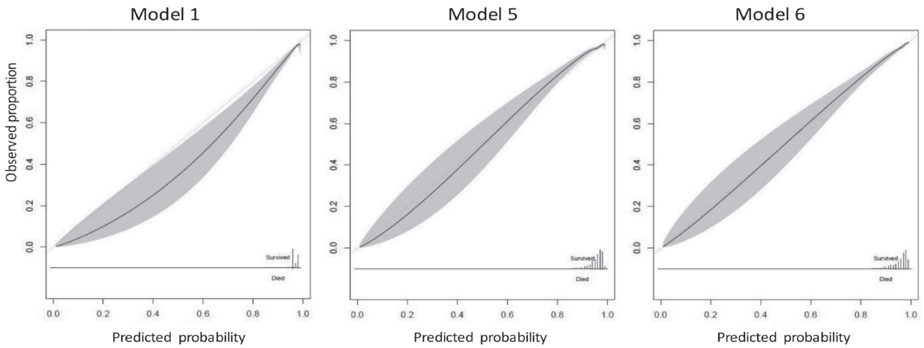

FIGURE 1. Calibration curves of model 1 (left), model 5 (middle) and model 6 (right) in the elderly subset (≥75 years) of the validation cohort.

TABLE 3. The predictors in the different survival prediction models with the coefficients calculated with logistic regression in the development set, including the discriminative ability of each of the models in the development set and validation set and among the elderly trauma patients.

Predictor	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
		coefficient		coefficient		coefficient		coefficient		coefficient		coefficient
GCS coded[a]	linear	0.710	linear	0.678	linear	0.788	linear	0.745	linear	0.769	linear	0.728
SBP coded[a]	linear	0.311	linear	0.326	linear	0.361	linear	0.351	linear	0.393	linear	0.383
RR coded[a]	linear	0.560	linear	0.598	linear	0.610	linear	0.620	linear	0.654	linear	0.656
ISS	linear	-0.111	linear	-0.122	linear	-0.127	linear	-0.134	linear	-0.127	linear	-0.133
Age	0-54	ref	0-54	ref	0-9	0.190	0-9	0.112	linear	-0.074	linear	-0.059
	>54	-2.788	>54	-1.779	10-19	0.073	10-19	-0.015				
					20-29	-0.173	20-29	0.007				
					30-39	ref	30-39	ref				
					40-49	1.046	40-49	1.276				
					50-59	-1.400	50-59	-0.759				
					60-69	-1.986	60-69	-1.236				
					70-79	-3.155	70-79	-2.208				
					80-89	-3.917	80-89	-2.803				
					90+	-4.379	90+	-3.222				
ASA[b]			ASA-1	ref			ASA-1	ref			ASA-1	ref
			ASA-2	-1.232			ASA-2	-0.810			ASA-2	-0.718
			ASA-3	-2.343			ASA-3	-1.695			ASA-3	-1.632
			ASA-4	-3.074			ASA-4	-2.585			ASA-4	-2.513
Constant		0.894		1.549		1.060		1.434		3.301		3.363
R^2	0.27		0.32		0.33		0.35		0.32		0.35	

TABLE 3. Continued.

Predictor	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
AUROC (95% CI)[c]						
Development	0.85 (0.84, 0.87)	0.89 (0.88, 0.90)	0.89 (0.88, 0.90)	0.91 (0.89, 0.92)	0.89 (0.88, 0.90)	0.91 (0.89, 0.92)
Validation	0.85 (0.83, 0.87)	0.90 (0.89, 0.92)	0.88 (0.87, 0.90)	0.91 (0.90, 0.92)	0.88 (0.87, 0.90)	0.91 (0.90, 0.93)
AUROC (95% CI) – the elderly[d]						
Validation	0.68 (0.65, 0.72)	0.78 (0.75, 0.81)	0.70 (0.66, 0.74)	0.78 (0.75, 0.81)	0.70 (0.66, 0.74)	0.78 (0.75, 0.81)
AUROC (95% CI) – with hip#[e]						
Validation	0.52 (0.46, 0.58)	0.71 (0.66, 0.76)	0.62 (0.56, 0.67)	0.73 (0.69, 0.78)	0.62 (0.57, 0.68)	0.74 (0.69, 0.78)

Abbreviations: ASA, Anesthesiologists Physical Status; AUROC, Area Under Receiver Operating Characteristic; CI, Confidence Interval; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; ref, reference group; R^2, Nagelkerke R-square; RR, Respiratory Rate; SBP, Systolic Blood Pressure.

[a] Variables were coded according to the Revised Trauma Score calculations.

[b] ASA classification; ASA-1: a normal healthy patient, ASA-2: a patient with mild systemic disease, ASA-3: a patient with severe systemic disease, ASA-4: a patient with severe systemic disease that is a constant threat to life.

[c] AUROC (95% CI) in the total development set (n=15,530) and validation set (n=15,504).

[d] AUROC (95% CI) in the elderly of the validation set (n=5,405).

[e] AUROC (95% CI) in the hip fracture cohort of the validation set (n=2,696). Patients with hip fractures were defined as ≥65 years with AIS08-codes 853161.3, 853162.3, 853151.3 and 853152.3, and ISS≤13.

Final model

The final model was developed in a combination dataset (n = 31,034) including both the development as the validation set, because baseline characteristics and model performances were equal in both datasets (Tables 2 and 3). Year of injury was not significant as predictor with a coefficient close to 0, and was therefore excluded from the model. ASA and age (continuous) were included in the final model, based on the best performances from the validation study. The shrinkage factor indicated no overfit (s = 1.00). The formula and coefficients of the final model are presented below:

$$\mathrm{P(survival)} = \frac{1}{1+e^{-b}} \text{ ,}$$

with b = 4.418 + 0.747*GCS + 0.273*SBP + 0.411*RR – 0.133*ISS – 0.055*Age – 0.546*ASA 2 –1.626*ASA 3–2.929*ASA 4.

R^2 for the final model was 0.35 with a AUROC of 0.91 (95% CI: 0.90, 0.92). The AUROC was 0.78 (95% CI: 0.76, 0.80, n = 10,774) in the elderly subset and 0.73 (95% CI: 0.70, 0.76, n = 5,288) for elderly patients (≥ 65 years) with hip fracture. The calibration curve showed high agreement between observed survival proportions and predicted survival probabilities in the elderly (Figure 2).

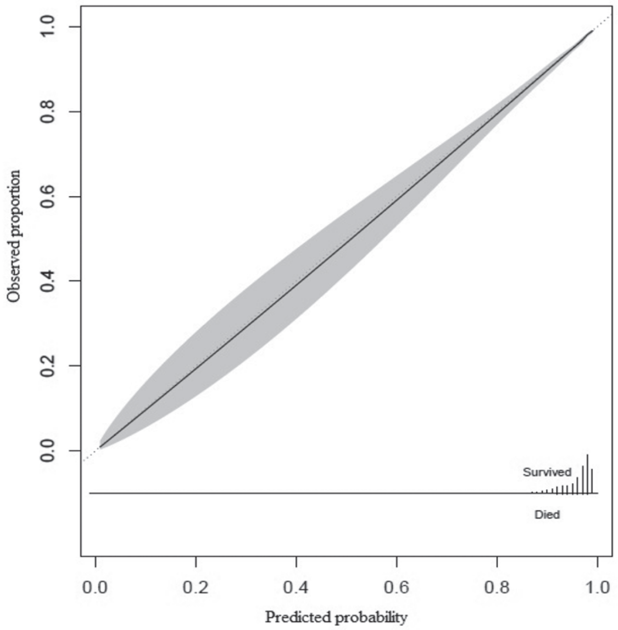

FIGURE 2. Calibration curve of the final model in the elderly subset (≥ 75 years) of the validation cohort.

DISCUSSION

Adequate predictions are necessary to compare the quality of care between centers. It has been shown previously that the updated TRISS is not an adequate prediction model in the elderly trauma population. To provide more accurate predictions in trauma subsets in the current ageing trauma population, we believe that only small adjustments in the TRISS methodology could be sufficient, without developing a complex new model. This study showed that small adjustments of the traditional TRISS model improved the predictive performance, especially in the elderly.

Many different models were developed to provide accurate predictions for trauma populations around the world[29]. Although TRISS has several known shortcomings, it is still one of the international standards for evaluating the quality of trauma care and showed to be adequate for survival prediction in general[29–31]. Survival predictions of the updated TRISS in different subsets of the trauma population showed overestimation of survival in the older trauma patients. This implies that the quality of care in hospitals that mainly treat elderly patients seems to be worse than hospitals treating younger patients. These misleading outcomes could be adjusted by incorporating simple available variables in the formula, i.e. age as categorical (with more than 2 categories) or as a continuous variable in the TRISS. Although some studies showed an equivalent performance after these adjustments of age in the TRISS model[14,32], others showed better predictive ability[33,34]. The latter is also reflected in this study. The models showed an improvement of predictive ability in the general trauma population and calibration of the adjusted models improved significantly in the elderly. For benchmark purposes, re-categorization or restructuring of age is a beneficial small adjustment to improve survival predictions and benchmark numbers.

In addition, the elderly trauma population suffers often from comorbidities. Comorbidity can be expressed in many different ways. Prediction models that incorporate comorbidity include for example ASA and the Charlson Comorbidity Index[18,35–38]. Comorbidity can also be dichotomized or incorporated as a continuous variable; in which the presence of comorbidity or the amount of comorbidities are measured respectively[14–16,39,40]. Data on comorbidity in trauma patients has to be collected manually and is an extensive and time consuming effort. ASA classification is automatically coded in the medical records of patients who needed surgery and could relatively easy be included in the trauma registry. However, previous research showed some contradictions concerning ASA. On the one hand, the ASA scale is suggested to be a reliable mean of classifying pre-existing comorbidity in trauma patients[40] and showed to be an independent predictor of mortality after trauma[39]. On the other hand, it is suggested that ASA is a subjective and inconsistent measure, which could vary between observers[41–43]. It is therefore possible that other comorbidity measures provide different results compared to ASA. Nevertheless, this study showed an improvement of the predictive ability after including ASA in the prediction models, especially in the elderly subset with a hip fracture.

This retrospective study has several limitations. Although the discriminative ability of the new model in elderly patients with hip fracture was adequate (AUROC of 0.73), it could be much higher. Other variables are considered important predictors for mortality in geriatric trauma patients (e.g. frailty and AMTS)[10,44,45]. The Dutch Trauma Registry did not incorporate these measures, hence comparison between other models and this new presented model could not be made. However, this model is used as prognostic tool for the evaluation of trauma care, based on a population wide registry and is not used for diagnostic purposes. Therefore, we believe the high agreement between observed survival and predicted survival probabilities as shown in the calibration curves is of more importance. In addition, this study used in-hospital mortality as outcome measure. This outcome could be subject to bias by differences in hospital discharge practices[46]. Hospitals in which patients were longer admitted might have higher in-hospital mortality rates compared to hospitals in which patients were quickly discharged to other facilities. However, the alternative, e.g. 30-day mortality, is only incorporated in the Dutch trauma registry from 2014 onwards and is often missing (40% in 2014 and 24% in 2015).

Conclusion

The inclusion of age as categorical or continuous predictor and ASA in survival prediction is a simple and effortless adjustment of the TRISS methodology to improve predictive ability and calibration in the ageing Dutch blunt trauma population. A new model is presented, through which even patients with isolated hip fractures could be included in the evaluation of trauma care.

REFERENCES

1. WAR LTR. Landelijke Traumaregistratie-Toelichting uitkomstevaluatie 2017. TRISS model Nederlandse coëfficiënten en SMR. Resultaten 2017 regio: Netwerk Acute Zorg Brabant. 2018.
2. Ringdal KG, Coats TJ, Lefering R, Di Bartolomeo S, Steen PA, Røise O, et al. The Utstein template for uniform reporting of data following major trauma: a joint revision by SCANTEM, TARN, DGU-TR and RITG. *Scand J Trauma Resusc Emerg Med.* 2008;16(1):7.
3. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. *J Trauma.* 1987;27(4):370–378.
4. De Jongh M. A. C., Verhofstad MHJ, Leenen LPH. Accuracy of different survival prediction models in a trauma population. *Br J Surg.* 2010;97(12):1805–1813.
5. de Munter L, Polinder S, Nieboer D, Lansink KW, Steyerberg EW, de Jongh MA. Performance of the modified TRISS for evaluating trauma care in subpopulations: a cohort study. *Injury.* 2018;49(9):1648– 1653.
6. Gomez D, Haas B, Hemmila M, Pasquale M, Goble S, Neal M, et al. Hips can lie: impact of excluding isolated hip fractures on external benchmarking of trauma center performance. *J Trauma.* 2010;69 (5):1037–1041.
7. Bergeron E, Lavoie A, Belcaid A, Ratte S, Clas D. Should patients with isolated hip fractures be included in trauma registries? *J Trauma.* 2005;58(4):793–797.
8. Statistics Netherlands (CBS). Trends in the Netherlands. 2016.
9. Younge P, Coats T, Gurney D, Kirk C. Interpretation of the Ws statistic: application to an integrated trauma system. *J Trauma.* 1997;43(3):511–515.
10. Maxwell MJ, Moran CG, Moppett IK. Development and validation of a preoperative scoring system to predict 30 day mortality in patients undergoing hip fracture surgery. *Br J Anaesth.* 2008;101(4):511– 517.
11. Nijmeijer WS, Folbert EC, Vermeer M, Slaets JP, Hegeman JH. Prediction of early mortality following hip fracture surgery in frail elderly: The Almelo Hip Fracture Score (AHFS). *Injury.* 2016;47(10):2138– 2143.
12. Bouamra O, Jacques R, Edwards A, Yates DW, Lawrence T, Jenks T, et al. Prediction modelling for trauma using comorbidity and 'true' 30-day outcome. *Emerg Med J.* 2015;32(12):933–938.
13. Krishnan M, Beck S, Havelock W, Eeles E, Hubbard RE, Johansen A. Predicting outcome after hip fracture: using a frailty index to integrate comprehensive geriatric assessment results. *Age Ageing.* 2013;43(1):122–126.
14. Bergeron E, Rossignol M, Osler T, Clas D. Improving the TRISS methodology by restructuring age categories and adding comorbidities. *J Trauma.* 2004;56(4):760–767.
15. Cinelli SM, Brady P, Rennie CP, Tuluca C, Hall TS. Comparative results of trauma scoring systems in fatal outcomes. *Conn Med.* 2009;73(5):261–265.
16. Moore L, Lavoie A, Turgeon AF, Abdous B, Le Sage N, Imond M, et al. Improving Trauma mortality prediction modeling for blunt trauma. *J Trauma.* 2010;68(3):698–705.
17. Moore L, Hanley JA, Turgeon AF, Lavoie A, Eric B. A new method for evaluating trauma centre outcome performance: Tram-adjusted mortality estimates. *Ann Surg.* 2010;251(5):952–958.
18. Gabbe BJ, Magtengaard K, Hannaford AP, Cameron PA. Is the Charlson Comorbidity Index useful for predicting trauma outcomes? *Acad Emerg Med.* 2005;12(4):318–321.
19. Bouamra O, Wrotchford A, Hollis S, Vail A, Woodford M, Lecky F. A new approach to outcome prediction in trauma: A comparison with the TRISS model. *J Trauma.* 2006;61(3):701–710.
20. Gennarelli TA, Wodzin E. Abbreviated injury scale 2005: update 2008. Russ Reeder; 2008.
21. Dripps R. New classification of physical status. *Anesthesiology.* 1963;24:111.
22. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet.* 1974;304(7872):81–84.

23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med.* 2011;30(4):377–399.
24. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal–external, and external validation. *J Clin Epidemiol.* 2016;69:245–247.
25. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC medicine.* 2015;13(1):1.
26. Van Houwelingen J, Le Cessie S. Predictive value of statistical models. *Stat Med.* 1990;9(11):1303– 1325.
27. Copas JB. Regression, prediction and shrinkage. J R Stat Soc.Series B Methodol 1983:311–354. 28. Nagelkerke NJ. A note on a general definition of the coefficient of determination. *Biometrika.* 1991;78 (3):691–692.
29. de Munter L, Polinder S, Lansink K, Cnossen M, Steyerberg E, de Jongh M. Mortality prediction models in the general trauma population: A systematic review. *Injury.* 2017;48(2):221–229.
30. Domingues CdA, Nogueira LdS, Settervall CHC, Sousa, Sousa RM. Performance of Trauma and Injury Severity Score (TRISS) adjustments: an integrative review. *Rev Esc Enferm USP.* 2015;49(Spec):138– 146.
31. Stoica B, Paun S, Tanase I, Negoi I, Chiotoroiu A, Beuran M. Probability of survival scores in different trauma registries: a systematic. *Chirurgia (Bucur).* 2016;111(2):115–119.
32. Kilgo PD, Meredith JW, Osler TM. Incorporating recent advances to make the TRISS approach universally available. *J Trauma.* 2006;60(5):1002–1008.
33. Schluter PJ. Trauma and Injury Severity Score (TRISS): Is it time for variable re-categorisations and recharacterisations? *Injury.* 2011;42(1):83–89.
34. Kimura A, Chadbunchachai W, Nakahara S. Modification of the Trauma and Injury Severity Score (TRISS) method provides better survival prediction in Asian blunt trauma victims. *World J Surg.* 2012;36(4):813–818.
35. Jones JM, Skaga NO, Søvik S. Norwegian survival prediction model in trauma: modelling effects of anatomic injury, acute physiology, age, and co-morbidity. *Acta Anaesthesiol Scand.* 2014;58(3):303–315
36. Thompson HJ, Rivara FP, Nathens A, Wang J, Jurkovich GJ, MacKenzie EJ. Development and validation of the mortality risk for trauma comorbidity index. *Ann Surg.* 2010;252(2):370–375.
37. Willis CD, Gabbe BJ, Jolley D, Harrison JE, Cameron PA. Predicting trauma patient mortality: ICD [or ICD-10-AM] versus AIS based approaches. *ANZ J Surg.* 2010;80(11):802–806.
38. Davie G, Cryer C, Langley J. Improving the predictive ability of the ICD-based Injury Severity Score. *Inj Prev.* 2008;14(4):250–255.
39. Skaga NO, Eken T, Søvik S, Jones JM, Steen PA. Pre-injury ASA physical status classification is an independent predictor of mortality after trauma. *J Trauma.* 2007;63(5):972–978.
40. Ringdal KG, Skaga NO, Steen PA, Hestnes M, Laake P, Jones JM, et al. Classification of comorbidity in trauma: The reliability of pre-injury ASA physical status classification. *Injury.* 2013;44(1):29–35.
41. Cohen ME, Bilimoria KY, Ko CY, Richards K, Hall BL. Effect of subjective preoperative variables on risk-adjusted assessment of hospital morbidity and mortality. *Ann Surg.* 2009;249(4):682–689.
42. Burgoyne LL, Smeltzer MP, Pereiras LA, Norris AL, Armendi AJ. How well do pediatric anesthesiologists agree when assigning ASA physical status classifications to their patients? *Pediatr Anesth.* 2007;17(10):956–962.
43. Haynes S, Lawler P. An assessment of the consistency of ASA physical status classification allocation. *Anaesthesia.* 1995;50(3):195–199.
44. Joseph B, Pandit V, Khalil M, Kulvatunyou N, Zangbar B, Friese RS, et al. Managing Older Adults with Ground-Level Falls Admitted to a Trauma Service: The Effect of Frailty. *J Am Geriatr Soc.* 2015;63 (4):745–749.

45. Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Hashmi A, Green DJ, et al. Superiority of frailty over age in predicting outcomes among geriatric trauma patients: a prospective analysis. *JAMA surgery.* 2014;149(8):766–772.
46. R Rydenfelt K, Engerstro¨m L, Walther S, Sjo¨berg F, Stro¨mberg U, Samuelsson C. In-hospital vs. 30-day mortality in the critically ill-a 2-year Swedish intensive care cohort analysis. *Acta Anaesthesiol Scand.* 2015;59(7):846–858.

PART II

PREDICTION OF NON-FATAL OUTCOME AFTER TRAUMA

6

THE FUNCTIONAL CAPACITY INDEX AS PREDICTOR FOR HEALTH STATUS AFTER TRAUMA

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Submitted.

ABSTRACT

Introduction Trauma could have a serious impact on health status (HS). The aim of this study was to (1) assess the predictive value of the functional capacity index (FCI) for 12-month HS in the trauma population compared to the injury severity score (ISS) and most severe abbreviated injury scale (max-AIS) and (2) assess different possibilities to incorporate multiple injuries into one FCI score.

Methods Adult injury patients (≥18 years), admitted from August 2015 until November 2016 within 48 hours after injury to an ICU or a ward in the Netherlands and survived to hospital discharge, were included in the study. HS was measured with the EuroQol-5D-3L (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS) 12 months after injury. Missing values were imputed. Correlations were calculated between HS and the FCI, combination scores of the FCI, ISS and max-AIS. The predictive value was assessed univariable and multivariable, in addition to age and comorbidity.

Results A total of 3,063 (31% of total eligible patients) and 2,328 (24% of total eligible patients) patients completed the EQ-5D and EQ-VAS at 12 months after injury respectively. The highest correlation was found for the EQ-5D utility and the minimal FCI-score (min-FCI) ($\rho = 0.167$, $p<0.001$). R^2 increased significantly to 14.4% for the EQ-5D utility score after the addition of min-FCI to the multivariable regression model with ISS, comorbidity and age as predictors. Max-AIS showed to be the best predictor for the EQ-VAS.

Conclusion FCI only predicts a small proportion of the variability for HS 12 months after injury. AIS-max and ISS showed to be better predictors. Nevertheless, next to ISS, age and comorbidity, the FCI significantly improved prediction of HS. FCI combination scores for multiple injuries showed no additive predictive ability compared to the FCI.

INTRODUCTION

Trauma is one of the leading causes of death and disability[1,2]. While mortality rates following injury decreased the last decades in developed countries, there is a high prevalence of morbidity among survivors[3,4]. This requires an extension of focus for the evaluation of trauma care quality to non-fatal outcome.

Injury severity is a well-known predictor for mortality in the trauma population. The Abbreviated Injury Scale (AIS)[5] provides a severity score for every sustained injury. The Injury Severity Score (ISS)[6] combines these AIS severities into one score to deal with multiple injuries, by adding the square of the three most severe injuries in three different body regions. Both the maximal AIS severity and the ISS are used in survival prediction models.

Predictors for non-fatal outcome are not yet clearly defined. MacKenzie et al. (1996)[7] designed the Functional Capacity Index (FCI) to reflect functional limitations or reduced capacity one year after injury. It is an aggregated score across ten dimensions of function (e.g. visual, cognitive, speech). The FCI scores are linked to anatomic descriptions, provided through the AIS-codes. The scores originally range from 0 to 100, but the AIS dictionary was extended with an updated and truncated version of the FCI (pFCI08) ranging from 1 (worst functional limitation) to 5 (no functional limitation) after the update of AIS-codes in 2008 (AIS08)[5].

The use of the FCI in trauma outcome studies is scarce[8-14]. McMurry et al. (2015) developed whole body scores for the FCI that account for multiple injuries but can only be calculated by knowing the original algorithm which is not available[8,12,15]. Other studies that included patients with multiple injuries assumed that the worst injury, and thus the lowest FCI score, was equivalent to the overall functional loss[7,16]. However, this method was never validated[9]. A recent study assessed multiple methods to comprise one FCI score accounting for multiple injuries. Although this study was only performed in major injury, they concluded that it did not improve prediction compared with AIS-based scores[14].Trauma could have a major impact on the patients' perceived health status, also in patients with minor injury[17,18]. Health status (HS) is defined as the impact of disease on patients' physical, psychological, and social functioning[19]. It is possible that the FCI could be a valuable predictor for poor HS 12 months after injury in the total clinical trauma population. The aim of this study was to (1) assess the predictive value of pFCI08 for 12-month HS in the trauma population in comparison with the ISS and AIS-max and (2) assess different possibilities to incorporate multiple injuries into one FCI score.

METHODS

Participants

All adult injury patients, aged ≥18, who were admitted from August 2015 until November 2016, within 48 hours after injury to an ICU or a ward in one of the ten hospitals in the county Noord-Brabant, the Netherlands, and survived to hospital discharge were included in the study. Patients with insufficient knowledge of the Dutch language, with a pathological fracture, or with no place of residence were excluded from the study. If patients were unable to complete the questionnaire due to dementia or other neurological conditions, a proxy informant was asked to complete the questionnaires (i.e. family member or caregiver).

Design and data collection

This multicenter prospective observational cohort study is part of the Brabant Injury Outcome Surveillance (BIOS-study)[20]. Ethical approval was received from the Medical Ethics Committee Brabant, the Netherlands (project number NL50258.028.14).

A nurse or medical doctor distributed the first questionnaire if eligible patients were still admitted to the hospital. Eligible patients that were discharged one week after injury were informed by a research member via telephone and a questionnaire was sent to the home address. Patients had the opportunity to start participating in the BIOS-study at 1 week, 1 month and 3 months. All eligible patients were asked to complete a questionnaire at one week, one month, three months, six months and one year after injury. Follow-up questionnaires were sent by post or by e-mail, based on the preference of the patient.

An elaboration on the study design can be found elsewhere[20]. All participants signed an informed consent.

All follow up questionnaires from the BIOS study included post-injury HS. Injury characteristics and pre hospital data from the Brabant Trauma Registry (BTR) were linked to the BIOS data.

Patients who initially did not participate in the (follow-up questionnaires of the) BIOS-study were asked to complete a short version of the questionnaire, to increase response. The short questionnaire did not include proxy assessment.

Predictors

The predictive ability of ISS and most severe AIS08 score (max-AIS) were assessed and compared to the predictive value of FCI, which was based on three different calculations:

- Min-FCI: Categorical variable indicating the lowest pFCI08 score for all body regions ranging from 1 (worst possible functional state) to 5 (perfect state).
- FCI-score 3: First, the pFCI08 was recoded to 1 (perfect functional state) to 5 (worst functional state). The three worst pFCI08 scores for three different body regions (according to the AIS08) were squared, possible range from 1 (perfect functional state) to 75 (worst possible functional state).
- FCI-score 9: First, the pFCI08 was recoded to 1 (perfect functional state) to 5 (worst possible functional state). The worst pFCI08 scores for all body regions (according to the AIS08) were squared, possible range from 1 (perfect functional state) to 225 (worst possible functional state).

The latter two options were based on the fact that multiple injuries in different body regions result in lower health status compared to the single injuries and were constructed for this study.The Injury Severity Score (ISS) was calculated using the AIS 2008 dictionary for injury coding[5].

Other variables

The FCI was developed in a healthy population aged 18 to 35 years sustaining a single injury. Therefore, age and comorbidity are variables that should be accounted for when assessing the predictive ability of the pFCI08. Age was available for all eligible patients in the BIOS-study. Comorbidity was collected with the American Society of Anesthesiologists (ASA) physical status classification system and was automatically merged to the BIOS-study from the BTR.

Outcome assessment

Outcome measures were the EuroQol-5 dimensions with 3 levels of severity (EQ-5D-3L) and the EuroQol Visual Analogue Scale (EQ-VAS) 12 months post injury. The EQ-5D-3L measures HS in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension consisted of three severity levels: no problems, moderate problems or severe problems. A utility score (i.e. HS) was calculated using a scoring algorithm, ranging from 0 (dead) to 1 (perfect health). The EQ-VAS is a vertical scale with end points of 0 (worst health you can imagine) to 100 (best health you can imagine).

Statistical analysis

Missing values for HS (3.3%, N=104) 12 months after injury for patients that participated at 12 months, but had missing item scores, were imputed according to multiple imputation with 15 imputations and 5 iterations using the multivariate imputation by chained equations (MICE) procedure[21]. The imputation model included utility scores of the outcome variables from all follow-up questionnaires, baseline measures, patient characteristics and injury characteristics.

Baseline characteristics were determined for the total BIOS-study population and for the participants 12 months after injury. Differences between responders and non-responders were assessed with chi-square for categorical variables or Mann-Whitney U tests for continuous variables. Mean scores for the EQ-5D utility score and EQ-VAS 12 months after injury according to the FCI-score 3 were calculated and graphically displayed in patients aged ≤69 years. The predictive value of min-FCI, FCI-score 3, FCI-score 9, ISS08 and AIS-max for HS 12 months post injury were assessed in the clinical trauma population that completed the EQ-5D questionnaire 12 months after injury. First, Spearman (ρ) correlation between predictors and HS was calculated. FCI-score 3 and FCI-score 9 were closely correlated (r=0.998) and showed similar values for most of the patients. FCI-score 9 was therefore omitted for further analyses. The FCI-score 3 and ISS were transformed to accomplish linearity between dependent and independent variables (inverse transformation and log-transformation respectively). Next, statistical significance of the regression coefficients and explained variability (R^2) were determined in univariable linear regression. The predictive value was assessed in multivariable analyses, including age and comorbidity to the models. Multicollinearity was assessed with the Variance Inflation Factor (VIF), with VIF above 10 indicating a multicollinearity problem. If no multicollinearity problem was found, a second multivariable model was developed that included an FCI measure and an injury severity measure. Nested models were compared by using the F-test. A p-value<0.05 was considered statistically significant. Sensitivity analyses were performed on elderly patients (>69 years) and on severely injured patients (ISS>15)). Multiple imputation was performed in the statistical program R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed in IBM SPSS version 24.0 (Chicago, USA).

RESULTS

Baseline characteristics

A total of 9,774 trauma patients were eligible to participate in the BIOS-study, of whom 31% (N=3,063) and 28% (N=2,328) completed the 12 month follow-up EQ-5D questionnaire and EQ-VAS respectively (Figure 1). Participants that completed the EQ-5D had a median ISS (IQR) of 6 (4-9) and were mostly patients that sustained injuries at home (59%, N=1,821) or by traffic accidents (27%, N=840) (Table 1). Max-AIS ranged from 1 (N=2,438, 25%) to 5 (N=65, 1%) in the total population of the BIOS-study. The AIS region with most acquired injury was lower extremity, followed by head.

The vast majority of participants were coded as healthy or as patients with mild systemic disease according to the ASA classification (31% [N=944] and 51% [N=1,566] respectively in the EQ-5D cohort and 34% [N=794] and 48% [N=1,125] respectively in the EQ-VAS cohort). Overall, responders of the EQ-5D utility score and EQ-VAS at 12 months were more severely injured and more healthy compared to the non-responders.

The EQ-5D utility score and EQ-VAS score 12 months after injury in patients aged ≤69 was highest among patients in the lowest FCI-score 3 category (FCI-score 3: 1-8). The higher the FCI-score 3, the lower the EQ-5D utility score and EQ-VAS score 12 months after injury (Figure 2).

TABLE 1. Patient characteristics of all eligible patients for the BIOS-study and the participants at 12 months that completed the EQ-5D questionnaire and the EQ-VAS.

	Total eligible patients BIOS-study	**participants EQ-5D 12 months[a]**		**participants EQ-VAS 12 months[a]**	
			p-value[c]		**p-value[c]**
N	9774 (100)	3063 (32)		2328 (24)	
Male gender (N, %)	4736 (49)	1438 (47)	.075	1132 (49)	.715
Age (median [IQR])	69 (50-82)	68 (55-79)	.668	67 (54-78)	<.01
ISS (median [IQR] and N [%])	5 (3-9)	6 (4-9)	<.001	5 (4-9)	<.001
1-3	2505 (26)	631 (21)		466 (20)	
4-8	2917 (30)	1043 (34)		814 (35)	
9-15	3484 (36)	1221 (40)		920 (40)	
≥16	438 (5)	168 (5)		128 (6)	
unknown	430 (4)	-		-	
max-AIS (N, %)			<.001		<.001
1 (least severe)	2438 (25)	624 (20)		461 (20)	
2	3026 (31)	1098 (36)		859 (37)	
3	3386 (35)	1220 (40)		918 (39)	
4	233 (2)	95 (3)		69 (3)	
5 (most severe)	65 (1)	26 (1)		21 (1)	
unknown	626 (6)	-		-	

TABLE 1 Continued.

	Total eligible patients BIOS-study	**participants EQ-5D 12 months[a]**		**participants EQ-VAS 12 months[a]**	
			p-value[c]		**p-value[c]**
Number of disabling injuries (N, %)			.188		<.05
1	4662 (48)	1577 (51)		1201 (52)	
2-4	3754 (38)	1241 (41)		934 (40)	
>4	666 (7)	245 (8)		193 (8)	
unknown	692 (7)	-		-	
AIS region[b] (N, %)					
Head	3005 (31)	891 (29)		661 (28)	
Face	1451 (15)	412 (13)		319 (14)	
Thorax	1198 (12)	422 (14)		326 (14)	
Abdomen	229 (2)	61 (2)		52 (2)	
Spine/Neck	812 (8)	279 (9)		219 (9)	
Upper extremity	2219 (23)	758 (25)		576 (25)	
Lower extremity	4807 (49)	1765 (58)		1346 (58)	
Missing	729 (8)	-		-	
Cause of injury (N, %)			<.001		<.001
Violence	205 (2)	24 (1)		20 (1)	
traffic	2133 (22)	840 (27)		654 (28)	
work	337 (3)	129 (4)		105 (5)	
at home	5417 (55)	1821 (59)		1349 (58)	
sports	468 (5)	211 (7)		175 (8)	
other	121 (1)	39 (1)		25 (1)	
unknown	1093 (11)	-		-	
ASA (N, %)			<.001		<.001
1 (healthy)	2458 (25)	944 (31)		794 (34)	
2	3627 (37)	1566 (51)		1125 (48)	
3	1817 (19)	526 (17)		391 (17)	
4 (severe threat to life)	62 (1)	27 (1)		18 (1)	
unknown	1810 (19)	-		-	
worst FCI score (N, %)			<.001		<.001
5 (best functional status)	4938 (51)	1528 (50)		1165 (50)	
4	3424 (35)	1243 (41)		929 (40)	
3	310 (3)	117 (4)		96 (4)	
2	323 (3)	136 (4)		110 (5)	
1 (worst functional status)	87 (1)	39 (1)		28 (1)	
unknown	692 (7)	-		-	

[a] missing values of participants were manually searched for in patients' medical records or imputed according to multiple imputation with multivariate imputation by chained equations (MICE) procedure.

[b] patients that had at least one injury in the region head, face, thorax, abdomen, spine/neck, upper extremity or lower extremity. Differences were not assessed between responders and non-responders, because patients could be included in more than one category (if multiple body regions were injured).

[c] differences were assessed between responders and non-responders, with chi-square for categorical variables and Mann-Whitney U tests for continuous variables.

Abbreviatons: AIS, Abbreviated injury score; ASA, American Society of Anesthesiologists physical status; FCI, functional capacity index; IQR, Inter Quartile Range (Q1-Q3); ISS, Injury Severity Score; mCIRS, modified Cumulative Illness Rating Scale; N, number;

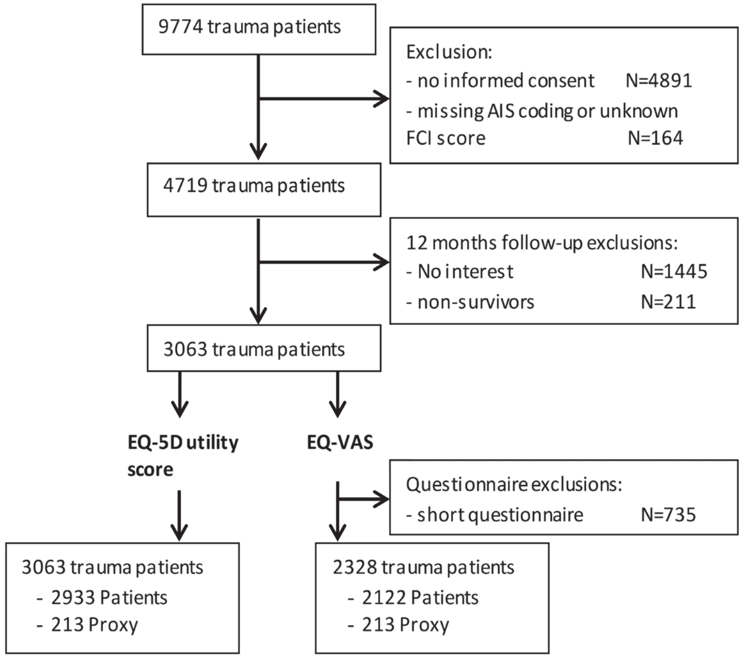

FIGURE 1. Flow diagram of participants at 12 month follow-up in the BIOS-study.

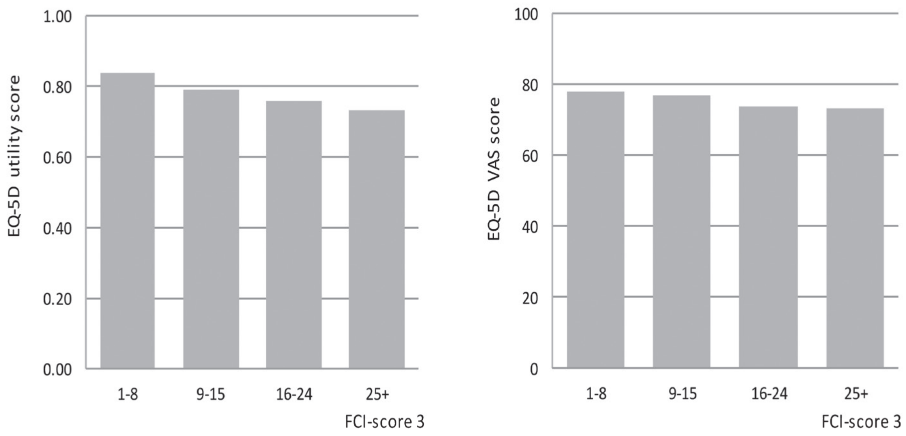

FIGURE 2. Mean EQ-5D utility score and EQ-VAS score 12 months after injury for patients aged ≤69 years according to categories of the FCI-score 3.

Correlation

The highest correlation with the EQ-5D utility score was found for the min-FCI (ρ = 0.167, p<0.001), followed by the max-AIS (ρ = -0.152, p<0.001). The highest correlation with the EQ-VAS score was found for the max-AIS (ρ = -0.133, p<0.001), followed by the min-FCI (ρ = 0.089, p<0.001). Pearson correlation between EQ-5D utility score or EQ-VAS score and ISS08 were ρ = -0.123 and ρ = -0.113 respectively, both p<0.001.

Predictive values

A lower pFCI08 was associated with a lower utility score 12 months after injury (Table 2). R^2 in the univariate analysis ranged from 1.0% for the ISS08 to 5.0% for max-AIS. Although R^2 was highest for max-AIS, only two categories of AIS score showed significant regression coefficients. Linear regression with pFCI08 as categorical predictor (min-FCI) resulted in a R^2 of 2.9%, which increased to 14.4% after adjustment of age and comorbidity. F-change showed that the addition of min-FCI, FCI-score 3, ISS08 and max-AIS significantly increased the predictive ability next to age and ASA.
Univariate analysis to predict EQ-VAS with the min-FCI, FCI-score 3, ISS08 or max-AIS showed an R^2 of 1.6%, 0.5%, 0.7% and 3.3% respectively, indicating that the predictors explain less variability for the EQ-VAS score than for the EQ-5D utility score. Not all regression coefficients of the min-FCI were significant for predicting the EQ-VAS. The multivariable linear regression showed a proportion explained variability ranging from 15.4% for the FCI-score 3 and ISS08 to 16.0% for max-AIS.

A second multivariable model is constructed by adding ISS08 to the regression model (VIF < 10) (Table 3). R^2 significantly increased to 14.5% for the EQ-5D utility score with min-FCI as predictor. The proportion explained variability only increased significantly in predicting the EQ5D-utility after addition of the min-FCI or the FCI-score 3 next to age, ASA and ISS08. Sensitivity analyses on the subset aged >69 years (N=1437 for EQ-5D utility score and N=992 for EQ-VAS) showed that the min-FCI significantly improved the models in predicting the EQ-5D utility and the EQ-VAS (Supplemental table 1). The FCI-score 3 only improved the predictive ability of the model for the EQ-5D utility.
Sensitivity analyses on severely injured patients (N=168 for EQ5D utility score and N=128 for EQ-VAS) showed that the FCI-score 3 significantly improved the predictive ability of the models predicting both EQ-5D utility and EQ-VAS (Supplemental table 2). The min-FCI only improved the predictive ability of the model for the EQ-VAS.

TABLE 2. Regression coefficients including the 95% confidence interval and R^2 for univariable and multivariable linear regression predicting EQ-5D utility score or EQ-VAS score 12 months after injury.

Predictor	**Univariable analyses**		**Multivariable analyses -** models also including age and ASA	
	EQ5D utility	**EQVAS**	**EQ5D utility**	**EQVAS**
min-FCI				
1 (worst functional status)	-0.09 (-0.17, -0.01)*	-2.55 (-9.27, 4.18)	-0.13 (-0.25, -0.07)***	-6.03 (-12.31, 0.24)
2	-0.05 (-0.09, -0.01)*	-1.49 (-5.04, 2.05)	-0.08 (-0.14, -0.05)***	-3.80 (-7.10, -0.50)*
3	-0.05 (-0.10, 0.00)*	-0.55 (-4.28, 3.18)	-0.06 (-0.08, 0.01)*	-1.07 (-4.56, 2.42)
4	-0.09 (-0.11, -0.08)***	-4.82 (-6.37, -3.27)***	-0.06 (-0.08, -0.04)***	-1.97 (-3.46, -0.48)**
5 (best functional status)	ref	ref	ref	ref
R^2 (R^2 change)[c]	**2.9%**	**1.6%**	**14.4%** (1.6%)	**15.6%** (0.5%)
F-change (df)[a]	**-**	**-**	**13.64 (4)*** **	**3.26 (4)***
FCI-score 3[b]	0.19 (0.13, 0.25)***	-8.83 (3.74, 13.91)**	0.16 (0.10, 0.22)	6.91 (2.15, 11.66)
R^2 (R^2 change)[c]	**1.1%**	**0.5%**	**13.7%** (0.8%)	**15.4%** (0.3%)
F-change (df)[a]	**-**	**-**	**29.88 (1)*** **	**8.37 (1)** **
ISS08[c]	-0.08 (-0.10, -0.05)***	-4.50 (-6.63, -2.37)***	-0.05 (-0.08, -0.03)***	-2.90 (-4.90, -0.90)**
R^2 (R^2 change)[c]	**1.0%**	**0.7%**	**13.4%** (0.6%)	**15.4%** (0.3%)
F-change (df)[a]	**-**	**-**	**19.16 (1)*** **	**8.33 (1)** **
max-AIS				
1 (least severe)	ref	ref	ref	ref
2	0.01 (-0.02, 0.04)	1.68 (-0.35, 3.70)	0.00 (-0.02, 0.03)	1.04 (-0.86, 2.93)
3	-0.11 (-0.13, -0.08)***	-5.47 (-7.47, -3.48)***	-0.06 (-0.09, -0.03)***	-2.49 (-4.41, -0.58)*
4	0.02 (-0.04, 0.08)	0.22 (-4.30, 4.74)	-0.03 (-0.08, 0.02)	-2.66 (-6.90, 1.56)
5 (most severe)	-0.15 (-0.26, -0.04)**	-5.21 (-12.99, 2.57)	-0.14 (-0.23, -0.05)**	-8.29 (-15.55, -1.03)*
R^2 (R^2 change)[c]	**5.0%**	**3.3%**	**14.2%** (1.3%)	**16.0%** (0.9%)
F-change (df)[a]	**-**	-	**11.78 (4)*** **	**6.35 (4)*** **

[a] F-change was based on the addition of the predictor to the model including age and ASA
[b] inverse transformation of FCI-score 3 and log-transformation of ISS08
[c] R^2 change is the change in R^2 by adding the predictor to the multivariable model
*p<0.05, **p<0.01, ***p<0.001
Abbreviatons: AIS, Abbreviated injury score; ASA, American Society of Anesthesiologists physical status; CI, Confidence Interval; FCI, functional capacity index; ISS, Injury Severity Score;

TABLE 3. Regression coefficients with 95% confidence interval and R^2 for multivariable linear regression predicting EQ-5D utility score or EQ-VAS score 12 months after injury.

	EQ5D utility[a]	**EQVAS**[a]
min-FCI		
1	-0.11 (-0.19, -0.04)**	-4.52 (-11.03, 2.00)
2	-0.08 (-0.12, -0.04)***	-3.57 (-6.88, -0.26)*
3	-0.05 (-0.10, -0.01)*	-0.68 (-4.20, 2.84)
4	-0.05 (-0.07, -0.03)***	-1.45 (-3.05, 0.14)
5	ref	ref
R^2 (R^2 change)[c]	**14.5%** (1.0%)	**15.7%** (0.3%)
F-change (df)[c]	**9.38 (4)*** **	**1.92 (4)**
FCI-score 3[b]	0.13 (0.06, 0.20)***	4.76 (-0.55, 10.07)
R^2 (R^2 change)[c]	**13.9%** (0.4%)	**15.5%** (0.1%)
F-change (df)[c]	**14.91 (1)*** **	**3.18 (1)**

Multivariable regression models were adjusted for age, ASA and ISS08 (log transformed)
[b] inverse transformation of the FCI-score 3
[c] F-change was based on the addition of the predictor to the model with age, ASA and ISS
*p<0.05, **p<0.01, ***p<0.001
Abbreviatons: ASA, American Society of Anesthesiologists physical status; CI, Confidence Interval; FCI, functional capacity index; ISS, Injury Severity Score;

DISCUSSION

The pFCI08 is a simple and readily available score, developed to predict functional status in trauma patients 12 months after injury. Although FCI only predicts a small proportion of the variability of HS, it is a predictor for HS 12 months after injury. The min-FCI (a categorical variable indicating the worst FCI in a person) is a better predictor for HS compared to the FCI-score 3 (a continuous score that combines multiple injuries).

Validation studies with the original FCI showed poor performances and low to moderate correlations, especially in patients with lower-extremity injury[22-24]. The revised FCI was first validated in 2005. This preliminary validation study concluded that this updated FCI score improved predictions of experienced functional loss compared to the original version of the FCI for patients experiencing lower extremity trauma[25]. In 2016, McMurry et al. validated a combination score for the FCI for multiple injuries in different body regions and concluded that the FCI was identified as a significant predictor for the physical component of the Short Form 36 (SF-36)[15]. However, a recent review described several limitations of this paper and suggested that the paper did not provide sufficient evidence that the revised FCI predicts functional outcome[9].

A recent study from Palmer et al. (2019)[14] stated that the FCI did not consistently increase predictive value for all items of the EQ-5D. However, the analyses were only conducted in severely injured patients and they did not take into account the EQ-5D utility score. Nevertheless, their results were mostly similar with our results. Because the FCI and AIS-based severity did not show collinearity, they could both be included in the prediction model resulting in better predictions. This way, the FCI could add prognostic value in predicting non-fatal outcome.

This study has several limitations. The pFCI08 is developed in a dataset with the following characteristics: (I) the patient survives the injury, (II) The patient is aged between 18 and 34 years, without comorbidities prior to injury, (III) The acute care and rehabilitation received after injury is appropriate and timely and (IV) the patient only sustained one injury. According to the assumptions mentioned above, the pFCI08 could only be used in a selective patient group. The patients in our study have survived during the 12 months after sustaining the injury. A validation study from 2017 suggested that the age limits in the development of pFCI08 were unnecessarily restrictive, and could be broadened[8]. Also, the AIS-dictionary states that the FCI was developed in a trauma population with an age-range of 18 to 65 years. The trauma population in this study ranged from 18 years to 100 years, with adjustment for age in the multivariable models. Besides, the sensitivity analyses showed that the pFCI08 significantly improved the predictive ability of the models. The third assumption, regarding timely and appropriate received acute care, could not be assessed in this study. However, because the care is given in a developed country and time to travel to hospital is minimal in the county Noord-Brabant, we assume that care was appropriately and timely received. Besides, the FCI-score accounted for multiple injuries, but showed no improvement in predictive ability compared to the pFCI08.

Last, the low follow-up rate of patients that completed the HS questionnaire 12 months after injury (32% of total) could have introduced selection bias, differences were found between responders and non-responders.

We computed a FCI-score 3 related to the method for ISS-calculation, but only 45.2% of the patients suffered multiple injuries. It is possible that the score could not perform optimally because of the low prevalence of multiple FCI scores and thus a lack of variability in the score. Next to age and comorbidity, many other important factors have been found to predict HS and other non-fatal outcome, e.g. gender, educational level and psychological status of the patient[17,26-28]. These factors have probably more predictive ability for HS compared to FCI. Future research should consider all these factors for prediction of non-fatal outcome. Trauma care is improved the last decades and will improve even further. This could require an updated version of the pFCI08 every few years. While the pFCI08 is a widely available score and is easy applicable in prediction of non-fatal injury outcomes, the development of an updated version FCI is a time-consuming matter[7].

In conclusion, this study showed that the FCI predicts a small proportion of the variability for HS 12 months after injury. AIS-max and ISS showed to be better predictors. Nevertheless, next to ISS, age and comorbidity, the FCI significantly improved prediction of HS. FCI scores for multiple injuries showed no additive predictive ability compared to the FCI. As there is no easily accessible alternative, the FCI should be considered and assessed as possible predictor for non-fatal outcome after injury beside other well-known predictors, including an AIS-based variable. However, more research is needed to provide an alternative with better prognostic ability compared to the pFCI08.

REFERENCES

1. Morrison A, Stone DH. Trends in injury mortality among young people in the European Union: a report from the EURORISC working group. *J adolesc Health.* 2000;27(2):130-135.
2. Polinder S, Meerding WJ, Mulder S, Petridou E, van Beeck E. Assessing the burden of injury in six European countries. *Bull World Health Organ.* 2007;85:27-34.
3. Vles WJ, Steyerberg EW, Essink-Bot M, Van Beeck EF, Meeuwis JD, Leenen LP. Prevalence and determinants of disabilities and return to work after major trauma. *J Trauma.* 2005;58(1):126-135.
4. MacKenzie EJ, Rivara FP, Jurkovich GJ, Nathens AB, Frey KP, Egleston BL, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med.* 2006;354(4):366-378.
5. Gennarelli TA, Wodzin E. Abbreviated injury scale 2005: update 2008. Russ Reeder; 2008.
6. Baker SP, o'Neill B, Haddon Jr W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma.* 1974;14(3):187-196.
7. MacKenzie EJ, Damiano A, Miller T, Luchter S. The development of the functional capacity index. *J Trauma.* 1996;41(5):799-807.
8. Palmer C, Gabbe B, Cameron P. Revised Functional Capacity Index as a predictor of outcome following injury. *Br J Surg.* 2017;104(13):1874-1883.
9. Palmer CS, Cameron PA, Gabbe BJ. A review of the revised Functional Capacity Index as a predictor of 12 month outcomes following injury. *Injury.* 2017;48(3):591-598.
10. Poplin GS, Harris RB, Pollack KM, Peate WF, Burgess JL. Beyond the fireground: injuries in the fire service. *Inj Prev.* 2012;18(4):228-233.
11. Breeze J. Predicting outcomes of fragmentation injuries sustained by soldiers wearing new methods of ballistic face protection. *J Oral Maxillofac Surg.* 2013;71(9):e99.
12. McMurry TL, Sherwood C, Poplin GS, Seguí-Gómez M, Crandall J. Implications of functional capacity loss and fatality for vehicle safety prioritization. *Traffic Inj Prev.* 2015;16(sup2):S140-S145.
13. Barnes J, Morris A. A study of impairing injuries in real world crashes using the Injury Impairment Scale (IIS) and the predicted Functional Capacity Index (PFCI-AIS). *Ann Adv Automot Med.* 2009;53: 195-205.
14. Palmer CS, Cameron PA, Gabbe BJ. Comparison of revised Functional Capacity Index scores with Abbreviated Injury Scale 2008 scores in predicting 12-month severe trauma outcomes. *Inj Prev.* 2019; Published Online First: 30 March 2019.
15. McMurry TL, Poplin GS, Crandall J. Functional recovery patterns in seriously injured automotive crash victims. *Traffic Inj Prev.* 2016; 17(sup1):21-26.
16. Segui-Gomez M. Application of the Functional Capacity Index to NASS CDS data. Application of the Functional Capacity Index to NASS CDS data. National Highway Traffic Safety administration. 1996.
17. Polinder S, van Beeck EF, Essink-Bot ML, Toet H, Looman CW, Mulder S, et al. Functional outcome at 2.5, 5, 9, and 24 months after injury in the Netherlands. *J Trauma.* 2007;62(1):133-141.
18. Wad MS, Laursen T, Fruergaard S, Morgen SS, Dahl B. Survival and health related quality of life after severe trauma– a 15 years follow up study. *Injury.* 2018;49(2):191-194.
19. De Vries J. Chapter 16: Quality of life assessment. In: *Assessment in behavioral medicine, Vingerhoets A (ed).* 2001;353-370.
20. de Jongh MA, Kruithof N, Gosens T, van de Ree CL, de Munter L, Brouwers L, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: the Brabant Injury Outcome Surveillance (BIOS) study. *Inj Prev.* 2017;23(1):59-2016-042032. Epub 2016 May 6.
21. van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE. 1999; PG/VGZ/99.054.

22. Schluter PJ, Neale R, Scott D, Luchter S, McClure RJ. Validating the functional capacity index: a comparison of predicted versus observed total body scores. *J Trauma.* 2005;58(2):259-263.
23. MacKenzie EJ, Sacco W, Luchter S, Ditunno J, Staz CF, Gruen G, et al. Validating the Functional Capacity Index as a measure of outcome following blunt multiple trauma. *Qual Life Res*. 2002;11(8):797-808.
24. McCarthy ML, MacKenzie EJ. Predicting ambulatory function following lower extremity trauma using the functional capacity index. *Accid Anal Prev.* 2001;33(6):821-831.
25. Gotschall CS. The Functional Capacity Index, second revision: morbidity in the first year post injury. *Intl J Inj Contr Saf Promot*. 2005;12(4):254-256.
26. Gabbe BJ, Simpson PM, Harrison JE, Lyons RA, Ameratunga S, Ponsford J, et al. Return to work and functional outcomes after major trauma. *Ann Surg*. 2016;263(4):623-632.
27. Gabbe BJ, Simpson PM, Sutherland AM, Wolfe R, Fitzgerald MC, Judson R, et al. Improved functional outcomes for major trauma patients in a regionalized, inclusive trauma system. *Ann Surg.* 2012;255(6):1009-1015.
28. Holtslag HR, van Beeck EF, Lindeman E, Leenen LP. Determinants of long-term functional consequences after major trauma. *J Trauma.* 2007;62(4):919-927.

SUPPLEMENTAL TABLES

TABLE 1. Sensitivity analyses: regression coefficients with 95% confidence interval for predicting EQ-5D utility score or EQ-VAS score 12 months after injury in patients >69 years

	EQ-5D utility[a]	**EQ-VAS**[a]
min-FCI		
1	-0.08 (-0.27, 0.11)	-2.12 (-22.06, 17.83)
2	-0.02 (-0.13, 0.08)	1.77 (-7.26, 10.80)
3	-0.02 (-0.10, 0.06)	-0.39 (-6.85, 6.07)
4	-0.05 (-0.08, -0.02)**	-3.93 (-6.56, -1.30)**
5	ref	ref
R^2 (R^2 change)[c]	**16.2%** (0.8%)	**16.7%** (0.6%)
F-change (df)[d]	**2.68 (4)***	**2.40(4)***
FCI-score 3[b]	0.12 (0.00, 0.23)*	8.21 (-1.51, 17.93)
R^2 (R^2 change)[c]	**15.8%** (0.2%)	**16.2%** (0.2%)
F-change (df)[d]	**4.19 (1)***	**2.88 (1)**

[a] Multivariable regression models were adjusted for age, ASA and ISS08 (log transformed)
[b] inverse transformation of the FCI-score 3
[c] R^2 change is the change in R^2 by adding the predictor to the multivariable model
[d] F-change was based on the addition of the predictor to the model with age, ASA and ISS
*p<0.05, **p<0.01, ***p<0.001
Abbreviatons: ASA, American Society of Anesthesiologists physical status; CI, Confidence Interval; FCI, functional capacity index; ISS, Injury Severity Score;

TABLE 2. Sensitivity analyses: regression coefficients with 95% confidence interval for predicting EQ-5D utility score or EQ-VAS score 12 months after injury in patients with ISS>15

	EQ-5D utility[a]	**EQ-VAS**[a]
min-FCI		
1	-0.08 (-0.19, 0.02)	-3.50 (-11.04, 4.04)
2	-0.11 (-0.24, 0.02)	-12.20 (-21.27, -3.13)**
3	-0.08 (-0.23, 0.06)	-2.39 (-13.41, 8.62)
4	-0.15 (-0.27, -0.04)*	-11.63 (-19.96, -3.29)**
5	ref	ref
R^2 (R^2 change)[c]	**8.8%** (5.0%)	**16.1%** (8.7%)
F-change (df)[d]	**2.17 (4)**	**3.08 (4)***
FCI-score 3[b]	0.29 (0.1, 0.57)	21.67 (0.72, 42.62)*
R^2 (R^2 change)[c]	**6.3%** (2.5%)	**10.5%** (3.1%)
F-change (df)[d]	**4.28 (1)***	**4.20 (1)***

[a] Multivariable regression models were adjusted for age, ASA and ISS08 (log transformed)
[b] inverse transformation of the FCI-score 3
[c] R^2 change is the change in R^2 by adding the predictor to the multivariable model
[d] F-change was based on the addition of the predictor to the model with age, ASA and ISS
*p<0.05, **p<0.01, ***p<0.001
Abbreviatons: ASA, American Society of Anesthesiologists physical status; CI, Confidence Interval; FCI, functional capacity index; ISS, Injury Severity Score;

7

PREDICTING HEALTH STATUS IN THE FIRST YEAR AFTER TRAUMA

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ABSTRACT

Introduction Although mortality rates following major trauma are continuing to decline, a growing number of patients are experiencing long-term disability. The aim of this study was to identify factors associated with health status in the first year following trauma and develop prediction models based on a defined trauma population.

Methods The Brabant Injury Outcome Surveillance (BIOS) study was a multicentre prospective observational cohort study. Adult patients with traumatic injury were included from August 2015 to November 2016 if admitted to one of the hospitals of the Noord-Brabant region in the Netherlands. Outcome measures were EuroQol Five Dimensions 5D-3L (EQ-5D™ utility and visual analogue scale (VAS)) and Health Utilities Index (HUI) 2 and 3 scores 1 week and 1, 3, 6 and 12 months after injury. Prediction models were developed using linear mixed models, with patient characteristics, preinjury health status, injury severity and frailty as possible predictors. Predictors that were significant ($P < 0.050$) for one of the outcome measures were included in all models. Performance was assessed using explained variance (R^2).

Results In total, 4883 patients participated in the BIOS study (50.0% of the total), of whom 3366 completed the preinjury questionnaires. Preinjury health status and frailty were the strongest predictors of health status during follow-up. Age, sex, educational level, severe head or face injury, severe torso injury, injury severity, Functional Capacity Index score, co-morbidity and duration of hospital stay were also relevant in the multivariable models predicting health status. R^2 ranged from 35% for EQ-VAS to 48% for HUI 3.

Conclusion The most important predictors of health status in the first year after trauma in this population appeared to be preinjury health status and frailty.

INTRODUCTION

In the Netherlands, almost 80 000 patients were admitted to hospital owing to injury in 2017[1]. Although mortality rates from trauma are declining, a growing number of patients are experiencing long-term disability, including many young patients whose health status could suffer greatly[2–4].

Prediction models provide (inter)national norms for trauma care quality, which are useful for comparisons between countries, regions or hospitals. Although trauma is recognized as a leading cause of morbidity, the quality of trauma care is evaluated mainly by survival[5]. Evaluation of the quality of trauma care might go beyond counting deaths, and take into account the non-fatal consequences of trauma[2]. One of the non-fatal consequences is impaired perceived health status, defined as the perceived impact of a disease on the patient's social, physical and emotional

functioning[6]. Previous studies[7–11] reported possible predictors for worse health status, such as greater age, female sex, higher Injury Severity Score (ISS), presence of co-morbidity, and frailty in the elderly. A recent study[12] showed that unemployment before injury and pre-existing mental health were additional predictors for different dimensions of health status. However, many of these studies were based on only a subset of the trauma population. The aim of this study was to identify factors associated with health status in the first year following trauma and develop prediction models based on a defined trauma population.

METHODS

This study was part of the Brabant Injury Outcome Surveillance (BIOS) study, which was registered at ClinicalTrials.gov (NCT02508675); the protocol has been published previously[13]. Patients were included if they were admitted to an ICU or ward in the Noord-Brabant region of the Netherlands within 48h after injury and survived to hospital discharge between August 2015 and November 2016. Patients were required to be fluent in Dutch and had a minimum age of 18 years. Patients with pathological fractures were excluded. If patients were incapable of completing the self-reported questionnaires, they were completed by a proxy where possible. All participating patients and the proxy informants provided signed informed consent, and the study was approved by the Medical Ethics Committee Brabant (NL50258.028.14).

Questionnaires were distributed by a nurse or doctor if patients remained in hospital 1 week after injury. For patients discharged within 1 week after injury, a member of the research team informed the patient about the study by telephone, and questionnaires were sent by post. Patients were asked to complete a questionnaire at 1 week and 1, 3, 6 and 12 months after injury. Follow-up questionnaires were sent by post or e-mail, according to individual patient preference. Participants who did not complete a follow-up questionnaire were invited to participate again at the next time point.

The Brabant Trauma Registry (BTR) collected data on non-fatal outcomes at 3, 6, 12 and 24 months after injury as part of the Recovery After Injury (RAI) study, including health status measured using the EuroQol Five Dimensions EQ-5D-3L™ (EuroQol Group, Rotterdam, the Netherlands). Because both studies had identical inclusion criteria and questionnaires, only non-participants in the BIOS study were invited to complete this short RAI questionnaire. The EQ-5D™ utility scores were extracted and merged with those from the BIOS study. The RAI study did not include proxy assessment.

Predictors

Patient characteristics

Patient characteristics (age, sex, educational level, socioeconomic status (status score) and frailty before injury, preinjury health status) were collected from the questionnaires and electronic medical records.

Educational level was measured as the highest completed degree, certificate or diploma of education and was structured in three categories. Patients with primary education or preparatory secondary vocational education, or without a diploma were considered to have a low educational

level. Middle educational level included patients who completed university preparatory education, senior general secondary education or senior secondary vocational education and training. Patients who completed university of applied science or an academic degree were considered to have a high educational level.

Status score was based on home postcode. All postcodes in the Netherlands correspond to a specific status score, based on the level of education, income and percentage unemployment in the neighbourhood; the score ranges from –6.75 to 3.06, with a lower value indicating low status and vice versa. In 2014, the mean status score in the Netherlands was 0.28[14].

Preinjury frailty was assessed with the Groningen Frailty Index (GFI). The GFI was measured only in patients aged 65 years or more at 1 week or 1month after injury. A sum score of at least 4 was considered to indicate frailty. All patients younger than 65 years were considered not to be frail (with a total GFI score of 0).

All patients who completed a questionnaire at 1 week and 1 month after injury also completed the EQ-5D-3L™ questionnaire and EQ visual analogue scale (VAS) about their preinjury health status.

Finally, the norm scores for EQ-5D™ utility and EQ-VAS for the Dutch population were considered as potential predictors15. Norm scores were created based on sex and age categories.

Injury characteristics

Data about the injury were extracted from the BTR, including Abbreviated Injury Scale (AIS) region, hip fracture, ISS, admission to ICU, Functional Capacity index (FCI), ASA fitness grade and duration of hospital stay. Body regions injured and ISS were based on 2008 AIS codes16. Only serious or severe injuries, defined as those with an AIS score of at least 3, were classified by body region. Body regions were combined in four categories for the analyses: head and face, torso (abdomen and thorax), extremity (upper and lower), and neck and spine injury. Patients with a hip fracture were defined as elderly patients (65 years or older), with an isolated fracture of the proximal femur (AIS 2008 codes 853151.3, 853152.3, 853161.3 and 853162.3), with an ISS of no more than 13.

The FCI was included as a categorical variable; the lowest FCI value for all injuries sustained in each patient was used. FCI values can be found in the AIS 2008 codebook dictionary16 and ranged from 1 (worst functional limitation) to 5 (no functional limitation).

Outcome assessment

Outcome measures were scores on the EQ-5D-3L™, EQ-VAS and the Health Utilities Index (HUI; Health Utilities, Dundas, Ontario, Canada). The EQ-5D™ measures health status in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression[17]. Each dimension has three possible levels: no problems, moderate problems or severe problems. A utility score (EQ-5D™ utility) was calculated, ranging from 0 representing death to 1 for full health. A negative utility score indicates a health status worse than death. The

Dutch tariffs were used for this study to calculate EQ-5D-3L™ preference weights18. The EQ-VAS ranged from 0 at the bottom (worst possible health state) to 100 at the top (best possible health state). The proxy use of the EQ-5D-3L™ and EQ-VAS has been validated in an injury cohort[19].

HUI is used to measure general health status[20,21]. It consists of 15 questions, divided into seven HUI Mark 2 (HUI 2) questions and eight HUI Mark 3 (HUI 3) questions. A utility score was calculated using an algorithm to quantify health status, where dead scores 0 and perfect health scores 1. The proxy use of the HUI has been validated in patients who have had a stroke[22].

The EQ-5D-3L™ was included at all time points in both the BIOS and RAI studies. The HUI and EQ-VAS were included at all time points in the BIOS study, but were not used in the RAI study.

Statistical analysis

Results are reported according to the TRIPOD guidelines[23]. Missing values for participants who completed the preinjury assessment (169 (5%) with missing EQ-5D-3L™ preinjury items and 100 (3%) with missing preinjury EQ-VAS scores) were imputed by means of multiple imputation with 15 imputations and five iterations using the multivariable imputation by chained equations procedure[24]. Only participants who completed preinjury assessment were included for further modelling. Missing follow-up EQ-5D™ utility, EQ-VAS, HUI 2 and HUI 3 for patients who died during the 12-month follow-up period were set to 0.

Linear mixed models with random intercepts were used for all potential predictors, with EQ-5D™ utility, EQ-VAS, HUI 2 and HUI 3 as outcome measures. The ability to predict health status (based on explained variance, R^2) of the norm scores was compared with the predictive ability of the preinjury EQ-5D™ utility and EQ-VAS scores. The variable that was least time-consuming to collect (based on the length of the questionnaire and difficulty of collection) and with the highest predictive ability was included in the multivariable model if the predictor had $P < 0.200$ in the univariable analyses. R^2 ranges from 0% to 100%, and is the most common performance measure for continuous outcomes[25]. Backward selection was used for the multivariable linear regression models, with $P > 0.050$ for exclusion. Predictors that were beneath the threshold of 0.050 for at least one of the outcome variables in the multivariable analyses were included in all prediction models. The same predictors were included in the prediction models to enable comparison of regression coefficients.

Sensitivity analyses were undertaken to assess the effect of exclusion of subsets on the regression coefficients of the models. Regression coefficients were compared between the total clinical trauma population and the clinical trauma population excluding elderly patients with hip fracture or excluding patients who were admitted to ICU. Performance of the models was assessed using R^2.

Analyses were done in SPSS® version 24 (IBM, Armonk, New York, USA) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

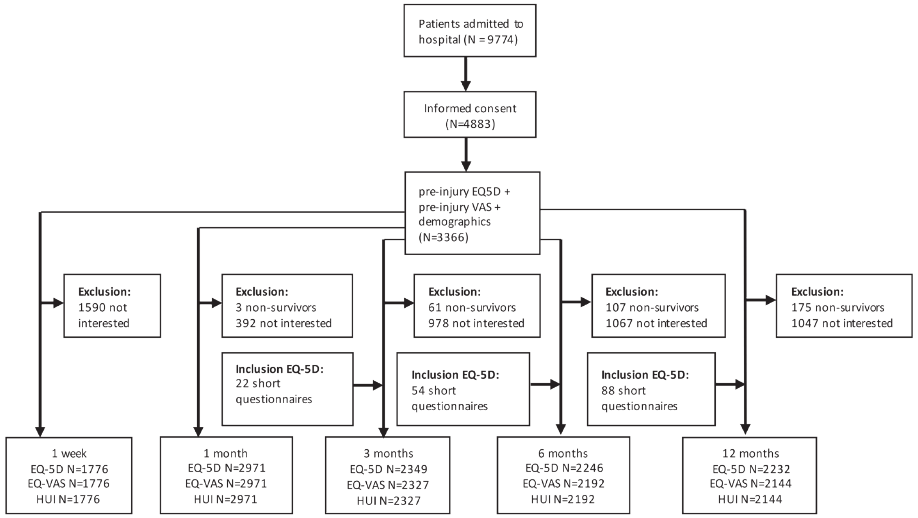


FIGURE 1. Flow diagram summarizing health status questionnaire completion during the first year after injury.
EQ-5D™, EuroQol Five Dimensions; EQ-VAS, EuroQol visual analogue scale; RAI, Recovery After Injury; HUI, Health Utilities Index.

TABLE 1. Characteristics of the total cohort, participants who completed at least the preinjury questionnaire and non-participants who were excluded from analyses

	Total cohort‡		**Participants§**		**Non-participants**	
	N	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
No. of patients (%)	9,774	100.0	3,366	34.4 (33.5, 35.4)	6,408	65.6 (64.6, 66.5)
Male sex	4,736	48.5 (47.5, 49.4)	1702	50.6 (48.9, 52.3)	3,034	47.3 (46.1, 48.6)
Age in years*	64.3 (21.2)		63.7 (18.7)		64.7 (22.4)	
Length of hospital stay†	4 (2-8)		4 (2-8)		4 (2-9)	
Missing	720	7.4 (6.8, 7.9)	-		486	7.6 (6.9, 8.2)
ISS	2505	25.6 (24.8, 26.5)	806	23.9 (22.5, 25.4)	1708	26.7 (25.6, 27.7)
1-3	2917	29.8 (28.9, 30.8)	1132	33.6 (32.0, 35.2)	1794	28.0 (26.9, 29.1)
4-8	3484	35.6 (34.7, 36.6)	1261	37.5 (35.8, 39.1)	2230	34.8 (33.6, 36.0)
9-15	332	3.4 (3.0, 3.8)	132	3.9 (3.3, 4.6)	201	3.1 (2.7, 3.6)
16-24	106	1.1 (0.9, 1.3)	35	1.0 (0.7, 1.4)	66	1.0 (0.8, 1.3)
≥25	430	4.4 (4.0, 4.8)	-	-	409	6.4 (5.8, 7.0)
Missing						
AIS region¶	428	4.4 (4.0, 4.8)	143	4.2 (3.6, 4.9)	285	4.4 (3.9, 5.0)
Head	18	0.2 (0.1, 0.3)	8	0.2 (0.1, 0.4)	10	0.2 (0.1, 0.3)
Face	404	4.1 (3.7, 4.5)	180	5.3 (4.6, 6.1)	224	3.5 (3.0, 3.9)
Thorax	66	0.7 (0.5, 0.8)	27	0.8 (0.5, 1.1)	39	0.6 (0.4, 0.8)
Abdomen	120	1.2 (1.0, 1.4)	49	1.5 (1.1, 1.9)	71	1.1 (0.9, 1.4)
Spine	4	0.0 (0.0, 0.1)	2	0.1 (0.0, 0.1)	2	0.0 (0.0, 0.1)
Neck	29	0.3 (0.2, 0.4)	17	0.5 (0.3, 0.7)	12	0.2 (0.1, 0.3)
Upper extremity	2755	28.2 (27.3, 29.1)	977	29 (27.5, 30.6)	1778	27.7 (26.7, 28.8)
Lower extremity						
Hip fracture	2123	21.7 (20.9, 22.5)	683	20.3 (18.9, 21.6)	1440	22.5 (21.4, 23.5)
Trauma centre level	2287	23.4 (22.6, 24.2)	910	27 (25.5, 28.5)	1377	21.5 (20.5, 22.5)
I	5431	55.6 (54.6, 56.6)	1731	51.4 (49.7, 53.1)	3700	57.7 (56.5, 58.9)
II	2056	21 (20.2, 21.8)	725	21.5 (20.2, 22.9)	1331	20.8 (19.8, 21.8)
III						
Minimal FCI	410	4.2 (3.8, 4.6)	171	5.1 (4.3, 5.8)	244	3.8 (3.3, 4.3)
1-2 (worse state)	3734	38.2 (37.2, 39.2)	1398	41.5 (39.9, 43.2)	2374	37 (35.9, 38.2)
3-4	4938	50.5 (49.5, 51.5)	1797	53.4 (51.7, 55.1)	3206	50 (48.8, 51.3)
5 (best possible state)	692	7.1 (6.6, 7.6)	-	-	584	9.1 (8.4, 9.8)
Missing						
ASA	2458	25.1 (24.3, 26.0)	1165	34.6 (33.0, 36.2)	1494	23.3 (22.3, 24.3)
I	3627	37.1 (36.2, 38.1)	1551	46.1 (44.4, 47.8)	2330	36.4 (35.2, 37.5)
II	1817	18.6 (17.8, 19.4)	613	18.2 (16.9, 19.5)	1321	20.6 (19.6, 21.6)
III	62	0.6 (0.5, 0.8)	37	1.1 (0.7, 1.5)	47	0.7 (0.5, 0.9)
IV	1810	18.5 (17.7, 19.3)	-	-	1216	19 (18, 19.9)
Missing						
Educational level	2563	26.2 (25.4, 27.1)	1737	51.6 (49.9, 53.3)	893	13.9 (13.1, 14.8)
Low	1267	13 (12.3, 13.6)	942	28 (26.5, 29.5)	351	5.5 (4.9, 6.0)
Middle	885	9.1 (8.5, 9.6)	687	20.4 (19.0, 21.8)	213	3.3 (2.9, 3.8)
High	5059	51.8 (50.8, 52.8)	-	-	4951	77.3 (76.2, 78.3)
Missing						
Status score*	0.18 (0.95)		0.26 (0.93)		0.16 (0.95)	

Values in parentheses are percentages with 95% confidence intervals unless indicated otherwise; values are *mean(SD) and †median (IQR). ‡Totals for all patients without imputation. §Missing values for participants were imputed. ¶Patients who had at least one injury with an Abbreviated Injury Scale (AIS) score of 3 or higher in the head, face, thorax, abdomen, spine, neck, upper extremity or lower extremity region.

Abbreviations: ISS, Injury Severity Score; FCI, Functional Capacity Index.

RESULTS

In total, 9774 patients were asked to complete the questionnaires. Only patients who completed at least the preinjury questionnaire were included in this study (3366 patients, 34.4 % of the total cohort) (Figure 1).

The mean(SD) age of the participants was 63.7(18.7) years and 50.6% were men (Table 1). The median duration of hospital stay after injury was 4 (IQR 2–8) days. Some 37.5% of participants had an ISS of 9–15 and 53.4% had a minimum FCI score of 5. The prevalence of hip fracture among the participants was 20.3%. According to the ASA classification, 34.6% of the participants were healthy (ASA grade I) and 1.1% had severe systemic disease with constant threat to life (ASA grade IV). Most participants had a low level of education (51.6%) and the mean(SD) status score was 0.26(0.93).

Participants were more likely to be healthy (ASA grade I or II) with a higher status score and were more often highly educated compared with non-participants. Participants were more severely injured or more often admitted to a level I trauma centre than non-participants (Table 1).

Overall, the mean EQ-5D™ utility, EQ-VAS and HUI scores increased over time (Figure 2). The smallest increment in health status was found between 6 and 12 months after injury. Participants at 1 week reported higher preinjury scores than those who participated at other time points.

Health status as predictor

Preinjury EQ-5D™ utility score (R^2 in univariable model ranging from 22% for EQ-VAS to 33% for HUI 2 and HUI 3) and preinjury EQ-VAS (R^2 in univariable model ranging from 15% for EQ-5D™ utility to 27% for HUI 3) were the strongest predictors for all outcome variables (Table 2).

Norm scores for the EQ-5D™ utility and the EQ-VAS were omitted from further analyses, because their predictive ability was much lower than preinjury values of health status questionnaires. The preinjury EQ-VAS was used in further analyses because this value was least time-consuming to collect and had a relatively high predictive ability.

Prediction models

Frailty and the preinjury EQ-VAS were the strongest predictors for all health status outcome measures. The explained variance for preinjury EQ-VAS ranged from 15% for EQ-5D™ utility to 27% for HUI 3 in univariable analyses (Table 2). The explained variance for frailty ranged from 15% for EQ-VAS to 29% for HUI 3 in univariable analyses (results not shown).

Age, sex, educational level, severe head or face injury, severe torso injury, ISS, FCI score, ASA grade, duration of hospital stay, preinjury EQ-VAS score and frailty were predictors of health status in the first year after trauma (Table 3). The regression coefficients show the expected difference in outcome for a 1-unit higher value of the predictor, with values for all other predictors being identical.

Explained variance was 36, 35, 44 and 48% for EQ-5D™ utility, EQ-VAS,HUI 2 and HUI 3 respectively. Health status increased over the 12 months after injury with regression coefficients of 0.291 for EQ-5D™ utility, 14.620 for EQ-VAS, 0.168 for HUI 2 and 0.281 for HUI 3.

The explained variance for the measurements at different follow-up times increased for all health status outcomes by duration: from 14% at 1 week to 41% at 12 months for EQ-5D™ utility, from 17% at 1 week to 41% at 12 months for EQ-VAS, from 18% at 1 week to 49% at 12 months for HUI 2, and from 22% at 1 week to 51% at 12 months for HUI 3.

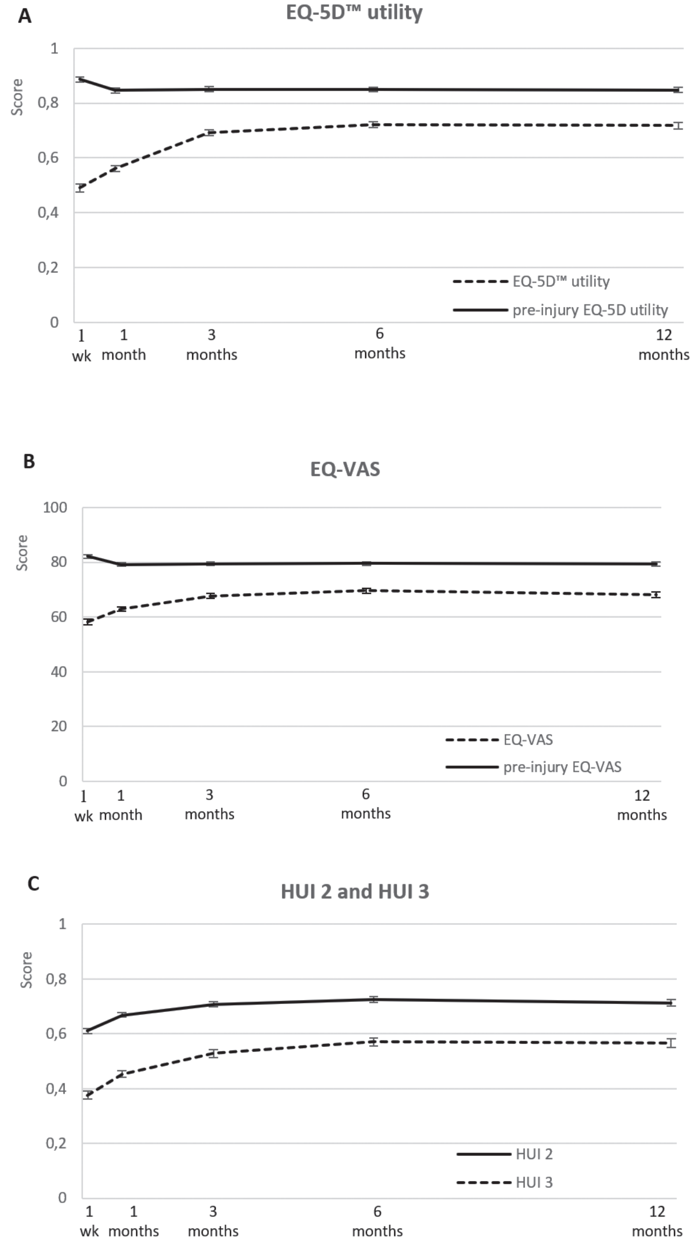
No significant differences were found between the regression coefficients of the models developed in the total clinical trauma population, and those of the clinical trauma population excluding patients with hip fracture or excluding patients admitted to the ICU (Supplemental Tables 1 and 2).

TABLE 2. Univariable analyses and explained variance between pre-injury HS measures and the norm values and health status measures in the first year after trauma.

	First year after trauma			
	EQ-5D™ utility	**EQ-VAS**	**HUI 2**	**HUI 3**
Preinjury EQ-5D™ utility				
Regression coefficient	0.68 (0.65, 0.72)	46.71 (44.27, 49.15)	0.64 (0.61, 0.66)	0.90 (0.86, 0.94)
R^2 (%)	24	22	33	33
Preinjury EQ-VAS				
Regression coefficient	0.01 (0.01, 0.01)	0.63 (0.60, 0.66)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
R^2 (%)	15	25	25	27
Norm EQ-5D™ utility				
Regression coefficient	1.77 (1.59, 1.96)	122.94 (109.15, 136.74)	2.00 (1.85, 2.16)	2.98 (2.75, 3.20)
R^2 (%)	7	6	13	14
Norm EQ-VAS				
Regression coefficient	0.02 (0.02, 0.03)	1.68 (1.47, 1.89)	0.03 (0.02, 0.03)	0.04 (0.04, 0.04)
R^2 (%)	5	5	9	10

Values in parentheses are 95% confidence intervals. EQ-5D™, EuroQol Five Dimensions; EQ-VAS, EuroQol visual analogue scale; HUI, Health Utilities Index; R^2, explained variance.

FIGURE 2. Mean scores on health status questionnaires during follow-up.



A EuroQol Five Dimensions (EQ-5D™) B EuroQol visual analogue scale (EQ-VAS) C Health Utilities Index (HUI).

Preinjury values plotted at each time point represent scores obtained at 1 week or month after injury for patients who completed postinjury questionnaires at that time point. Error bars represent 95% confidence intervals.

TABLE 3. Regression coefficients and explained variance for health status measures in multivariable linear mixed models.

	First year after trauma			
	EQ-5D™ utility	**EQ-VAS**	**HUI 2**	**HUI 3**
Age	0.001 (0.000, 0.001)	0.030 (-0.007, 0.068)	-0.001 (-0.001, 0.000)	-0.001 (-0.002, -0.001)
Female gender	-0.049 (-0.063, -0.034)	-1.955 (-2.993, -0.917)	-0.033 (-0.044, -0.022)	-0.045 (-0.062, -0.029)
Educational level				
Low*	0	0	0	0
Middle	0.006 (-0.011, 0.024)	0.062 (-1.175, 1.299)	0.008 (-0.005, 0.022)	0.020 (0.000, 0.040)
High	0.027 (0.008, 0.046)	-0.175 (-1.525, 1.175)	0.023 (0.008, 0.038)	0.037 (0.016, 0.058)
Head or face injury†	0.078 (0.038, 0.117)	4.485 (1.659, 7.311)	0.063 (0.032, 0.094)	0.049 (0.004, 0.094)
Torso injury†	0.038 (0.001, 0.075)	2.391 (-0.217, 4.998)	0.044 (0.016, 0.072)	0.049 (0.007, 0.090)
ISS	-0.005 (-0.007, -0.003)	-0.468 (-0.623, -0.312)	-0.004 (-0.006, -0.003)	-0.005 (-0.008, -0.003)
FCI				
1 (worse status)	-0.018 (-0.101, 0.065)	1.853 (-4.047, 7.752)	-0.049 (-0.113, 0.015)	-0.109 (-0.200, -0.019)
2	-0.107 (-0.143, -0.071)	-2.469 (-5.011, 0.072)	-0.057 (-0.085, -0.029)	-0.092 (-0.132, -0.051)
3	-0.061 (-0.097, -0.025)	-1.194 (-3.769, 1.382)	-0.038 (-0.066, -0.009)	-0.068 (-0.108, -0.027)
4	-0.047 (-0.064, -0.029)	-0.700 (-1.949, 0.549)	-0.027 (-0.040, -0.013)	-0.034 (-0.054, -0.015)
5 (best status)*	0	0	0	0
ASA				
I*	0	0	0	0
II	0.023 (0.004, 0.042)	2.206 (0.850, 3.561)	0.015 (0.001, 0.030)	0.016 (-0.006, 0.038)
III	-0.046 (-0.073, -0.019)	-3.210 (-5.153, -1.267)	-0.056 (-0.076, -0.035)	-0.066 (-0.096, -0.036)
IV	-0.066 (-0.150, 0.019)	-4.274 (-10.304, 1.757)	-0.083 (-0.149, -0.017)	-0.078 (-0.160, 0.005)
Length of stay at hospital (days)	-0.009 (-0.010, -0.008)	-0.524 (-0.622, -0.426)	-0.007 (-0.008, -0.006)	-0.009 (-0.011, -0.008)
Frailty	-0.159 (-0.183, -0.135)	-6.841 (-8.463, -5.219)	-0.150 (-0.169, -0.132)	-0.232 (-0.258, -0.206)
Pre-injury EQ-VAS	0.004 (0.003, 0.004)	0.498 (0.464, 0.533)	0.004 (0.003, 0.004)	0.005 (0.005, 0.006)
Follow-up measurements				
1 week*	0	0	0	0
1 month	0.130 (0.118, 0.142)	9.107 (8.225, 9.990)	0.116 (0.108, 0.125)	0.160 (0.148, 0.171)
3 months	0.241 (0.229, 0.254)	13.763 (12.848, 14.677)	0.156 (0.147, 0.165)	0.235 (0.223, 0.246)
6 months	0.293 (0.280, 0.305)	15.892 (14.968, 16.815)	0.177 (0.168, 0.186)	0.282 (0.271, 0.294)
12 months	0.291 (0.279, 0.303)	14.620 (13.701, 15.539)	0.168 (0.159, 0.177)	0.281 (0.269, 0.292)
Constant	0.248 (0.192, 0.303)	21.117 (17.229, 25.006)	0.454 (0.411, 0.497)	0.127 (0.067, 0.188)
R^2 (%)				
Overall	**36**	**35**	**44**	**48**
Follow-up measurements				
1 week	14	17	18	22
1 month	27	34	46	47
3 months	33	35	47	49
6 months	40	37	48	50
12 months	41	41	49	51

Values in parentheses are 95% confidence intervals. *Reference category. †Patients who had at least one injury in the head or face region, or in the thorax or abdomen (torso) region with an Injury Severity Score (ISS) of at least 3.

Abbreviations: EQ-5D™, EuroQol Five Dimensions; EQ-VAS, EuroQol visual analogue scale; HUI, Health Utilities Index; FCI, Functional Capacity Index; R^2, explained variance.

DISCUSSION

The most important predictors of health status in the year after trauma were preinjury health status and frailty, reflecting that it is essential to consider the baseline condition when assessing post-traumatic scores. Other factors influencing health status included: age, sex, educational level, severe head or face injury, severe torso injury, ISS, FCI score, ASA grade and duration of hospital stay. The model predicting HUI 3 had the highest explained variance (48%), followed by the model predicting HUI 2 (44%).

There are many different tools for measuring different concepts of quality of life. Van Beeck and colleagues[26] provided guidelines for injury-related disability measurement in follow-up studies and suggested use of the EQ-5D-3L™ in combination with the HUI 3 as a common base for health outcome measures, as these cover all relevant health domains. The collection of two questionnaires per patient after trauma is not ideal. An alternative could be to collect the EQ-VAS score, which can be obtained quickly and easily, together with the HUI 3, which is most sensitive to age and co-morbidity and thus highly relevant in the ageing trauma population[27]. However, the HUI has a license fee that may not be affordable for all registries or hospitals.

Previously identified predictors for long-term functional consequences after trauma[7–12] were also relevant in the present study. An unexpected finding of this study is that patients with a severe head or face injury, or a severe torso injury had a better health status than patients without such injuries. Similar findings were reported in other studies of traumatic brain injury and traumatic spinal cord injury[28,29]. A possible explanation could be that patients' perception of their health status may change after severe injury, owing to a change in internal standards or values, resulting in a surprisingly high health status score. This phenomenon is called response shift, which was postulated based on the disability paradox: 'people with significant disability report a good quality of life, although this may seem counterintuitive to most external observers'[30,31].

Preinjury health status scores should ideally be collected prospectively to avoid bias. This was practically not feasible in the context of the present study. Retrospectively collected preinjury health status scores are consistently higher than population norms because of recall bias and response shift[32]. Nevertheless, they are considered to be more appropriate for the evaluation of postinjury health status in the trauma population than general population norm scores[33]. Although preinjury EQ-5D™ utility was shown to be a better predictor, preinjury EQ-VAS was included in the models as it is easy to collect.

In this study, longer hospital stay was associated with reduced health status in the first year after trauma. Early complications of trauma and surgery have been shown to increase the duration of hospital stay and also to have a negative impact on health status for injured patients[34,35]. Another explanation could be that length of stay reflects injury severity, because patients with more severe injury were more likely to have a longer hospital stay.

Although many predictors are available from trauma registries, others (frailty, preinjury health status and educational level) are not, and should be assessed manually. Preinjury EQ-VAS scores and data on educational level are easy to collect, for example when patients are discharged from hospital. Frailty, however, is more complex. A recent review[36] showed that frailty does not have a clear international standard or definition, and suggested that frailty measurement should be incorporated into routine care for elderly patients.

The explained variance of almost 50% was considered acceptable for a comprehensive concept such as health status. Although mortality rates are declining, survival is still an important outcome after trauma. Survival prediction models in combination with a model for health status may ultimately prove a useful approach to evaluate the quality of trauma care. However, many predictors of outcome in the present study are independent of treatment or injury.

One limitation of this study was the low rate of completed health status questionnaires in the first year after trauma. In total, 34.4% of the initial sample was used in this study. Differences in baseline characteristics between participants and non-participants were found, indicative of selection bias, which could have affected the results. Nevertheless, the study population was large enough, and the calculated shrinkage factors indicated no overfitting.

This study was conducted in only one region of the Dutch trauma population, which could limit the generalizability of the models. The models could be useful for comparable trauma populations, but are limited to variables that are relevant for the Dutch trauma population and are available from the data set or registry. The authors recommend external validation of the present findings in other comparable trauma populations (other regions in the Netherlands or neighbouring countries) to further investigate the usefulness of the models. The prediction models are developed in the total clinical trauma population and are not applicable to subsets of this population (such as patients with major trauma or brain injury). Different prediction models, possibly with other outcome measures (such as Glasgow Outcome Scale - Extended or quality of life after brain injury) are needed for these important subsets. Finally, frailty was measured only in participants aged at least 65 years. Participants younger than this were considered not to be frail in this study. Although it is unlikely, this assumption could be false and might have influenced the results.

REFERENCES

1. Landelijke Netwerk Acute Zorg (LNAZ). Annual Report of the Dutch Trauma Registry: Traumazorg in beeld 2013–2017. LNAZ: Utrecht, 2018.
2. Segui-Gomez M, MacKenzie EJ. Measuring the public health impact of injuries. *Epidemiol Rev.* 2003;25:3–19.
3. Vles WJ, Steyerberg EW, Essink-Bot ML, van Beeck EF, Meeuwis JD, Leenen LP. Prevalence and determinants of disabilities and return to work after major trauma. *J Trauma.* 2005;58(1):126–135.
4. Holtslag HR, van Beeck EF, Lichtveld RA, Leenen LP, Lindeman E, van derWerken C. Individual and population burdens of major trauma in The Netherlands. *Bull World Health Organ.* 2008;86(2):111–117.
5. de Munter L, Polinder S, Lansink KW, Cnossen MC, Steyerberg EW, de Jongh MA. Mortality prediction models in the general trauma population: a systematic review. *Injury.* 2017;48(2):221–229.
6. De Vries J. Quality of life assessment. In: *Assessment in Behavioral Medicine.* Brunner-Routledge: London, 2001; 353–370.
7. Gabbe BJ, Simpson PM, Lyons RA, Ameratunga S, Harrison JE, Derrett S et al. Association between the number of injuries sustained and 12-month disability outcomes: evidence from the injury-VIBES study. *PLoS One.* 2014;9(12):e113467.
8. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg.* 2010;210(6):901–908.
9. Holtslag HR, van Beeck EF, Lindeman E, Leenen LP. Determinants of long-term functional consequences after major trauma. *J Trauma.* 2007;62(4):919–927.
10. Haagsma JA, Polinder S, Olff M, Toet H, Bonsel GJ, van Beeck EF. Posttraumatic stress symptoms and health-related quality of life: a two year follow up study of injury treated at the emergency department. *BMC Psychiatry.* 2012;12:1.
11. van Delft-Schreurs CC, van Bergen JJ, de Jongh MA, van de Sande P, Verhofstad MH, de Vries J. Quality of life in severely injured patients depends on psychosocial factors rather than on severity or type of injury. *Injury.* 2014;45(1):320–326.
12. Gabbe BJ, Simpson PM, Cameron PA, Ponsford J, Lyons RA, Collie A et al. Long-term health status and trajectories of seriously injured patients: a population-based longitudinal study. *PLoS Med.* 2017;14(7):e1002322.
13. de Jongh MA, Kruithof N, Gosens T, van de Ree CL, de Munter L, Brouwers L et al.; BIOS-group. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: the Brabant Injury Outcome Surveillance (BIOS) study. *Inj Prev.* 2017;23(1):59.
14. Sociaal en Cultureel Planbureau (SCP). Frequently Asked Questions; updated 2018. https://www.scp.nl/Onderzoek/Lopend_onderzoek/A_Z_alle_lopende_onderzoeken/Statusscores [accessed 19 May 2018].
15. Stolk E, Krabbe P, Busschbach J. Using the Internet to collect EQ-5D norm scores: a valid alternative? Scientific Plenary Meeting of the EuroQol Group Proceedings, The Hague, 2007;153–165.
16. Gennarelli TA,Wodzin E. Abbreviated Injury Scale 2005: Update 2008. Association for the Advancement of Automotive Medicine: Barrington, 2008.
17. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199–208.
18. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ.* 2006;15(10):1121–1132.
19. Gabbe BJ, Lyons RA, Sutherland AM, Hart MJ, Cameron PA. Level of agreement between patient and proxy responses to the EQ-5D health questionnaire 12 months after injury. *J Trauma Acute Care Surg.* 2012;72(4):1102–1105.

20. FurlongW, Feeny D, Torrance G. Health Utilities Index (HUI) Procedures Manual: Algorithm for Determining HUI Mark 2 (HUI2)/Mark 3 (HUI3) Health Status Classification Levels, Health States Single-attribute Level Utility Scores and Overall Health-related Quality of Life Utility Scores from 15-item Self-complete Health Status Questionnaires. Health Utilities: Dundas, 2000.
21. Horsman J, FurlongW, Feeny D, Torrance G. The health utilities index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes.* 2003;1:54.
22. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and health utilities index. *Stroke.* 2004;35(2):607–612.
23. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement. *BMC Med.* 2015;13:1.
24. van Buuren S, Oudshoorn K. Flexible Multivariate Imputation by MICE. PG/VGZ/99.054. TNO: Leiden, 1999.
25. Steyerberg EW. Evaluation of performance. *In: Clinical Prediction Models: a Practical Approach to Development, Validation, and Updating, Gail M, Tsiatis A, Krickeberg K, Wong W, Sarnet J (eds).* Springer Science & Business Media: New York, 2010;255–280.
26. Van Beeck EF, Larsen CF, Lyons RA, Meerding WJ, Mulder S, Essink-Bot ML. Guidelines for the conduction of follow-up studies measuring injury-related disability. *J Trauma.* 2007;62(2):534–550.
27. Polinder S, Haagsma JA, Bonsel G, Essink-Bot ML, Toet H, van Beeck EF. The measurement of long-term health-related quality of life after injury: comparison of EQ-5D and the health utilities index. *Inj Prev.* 2010;16(3):147–153.
28. Ulvik A, Kvåle R,Wentzel-Larsen T, Flaatten H. Quality of life 2-7 years after major trauma. *Acta Anaesthesiol Scand.* 2008;52(2):195–201.
29. Rivers CS, Fallah N, Noonan VK, Whitehurst DG, Schwartz CE, Finkelstein JA et al.; RHSCIR Network. Health conditions: effect on function, health-related quality of life, and life satisfaction after traumatic spinal cord injury. A prospective observational registry cohort study. *Arch Phys Med Rehabil.* 2018;99(3):443–451.
30. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med.* 1999;48(11):1507–1515.
31. Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. *Soc Sci Med.* 1999;48(8):977–988.
32. Scholten AC, Haagsma JA, Steyerberg EW, Van Beeck EF, Polinder S. Assessment of pre-injury health-related quality of life: a systematic review. *Popul Health Metr.* 2017;15(1):10.
33. Watson WL, Ozanne-Smith J, Richardson J. Retrospective baseline measurement of self-reported health status and health-related quality of life versus population norms in the evaluation of post-injury losses. *Inj Prev.* 2007;13(1):45–50.
34. Mondello S, Cantrell A, Italiano D, Fodale V, Mondello P, Ang D. Complications of trauma patients admitted to the ICU in level I academic trauma centers in the United States. *BioMed Res Int.* 2014; 473419.
35. Holbrook TL, Hoyt DB, Anderson JP. The impact of major in-hospital complications on functional outcome and quality of life after trauma. *J Trauma.* 2001;50(1):91–95.
36. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. *Eur J Intern Med.* 2016;31:3–10

SUPPLEMENTAL TABLE 1

Sensitivity analyses; regression coefficients and 95% Confidence Interval for the EQ-5D utility, EQ-VAS, Health Utility Index (HUI 2 and HUI 3) for the clinical trauma population excluding patients that were admitted to the ICU (excluded patients N=249) after multivariable linear mixed models.

	EQ-5D utility	EQ-VAS	HUI 2	HUI 3
Age	0.001 (0.001, 0.002)	0.055 (0.016, 0.095)	-0.001 (-0.001, 0.000)	-0.001 (-0.002, -0.001)
Female gender	-0.047 (-0.063, -0.032)	-1.741 (-2.813, -0.669)	-0.031 (-0.043, -0.019)	-0.045 (-0.062, -0.028)
Educational level				
Low[a]	0	0	0	0
Middle	0.005 (-0.013, 0.024)	0.140 (-1.136, 1.416)	0.009 (-0.005, 0.023)	0.017 (-0.003, 0.038)
High	0.029 (0.009, 0.048)	0.161 (-1.234, 1.556)	0.025 (0.010, 0.040)	0.035 (0.013, 0.057)
Head or face injury[b]	0.098 (0.050, 0.146)	5.185 (1.767, 8.602)	0.070 (0.032, 0.107)	0.045 (-0.010, 0.099)
Torso injury[b]	0.039 (-0.005, 0.083)	2.880 (-0.265, 6.024)	0.043 (0.008, 0.077)	0.049 (0.000, 0.098)
ISS	-0.007 (-0.009, -0.004)	-0.592 (-0.790, -0.395)	-0.005 (-0.007, -0.003)	-0.005 (-0.008, -0.002)
FCI				
1 (worse status)	0.071 (-0.083, 0.224)	8.397 (-2.465, 19.260)	0.039 (-0.079, 0.156)	0.015 (-0.145, 0.175)
2	-0.111 (-0.149, -0.073)	-2.883 (-5.550, -0.216)	-0.058 (-0.088, -0.029)	-0.095 (-0.137, -0.053)
3	-0.064 (-0.103, -0.025)	-1.408 (-4.147, 1.330)	-0.043 (-0.073, -0.012)	-0.082 (-0.124, -0.039)
4	-0.038 (-0.056, -0.019)	-0.085 (-1.418, 1.248)	-0.022 (-0.036, -0.007)	-0.032 (-0.053, -0.012)
5 (best status)[a]	0	0	0	0
ASA				
1 (healthy)[a]	0	0	0	0
2	0.023 (0.003, 0.043)	2.086 (0.690, 3.483)	0.017 (0.002, 0.032)	0.016 (-0.007, 0.039)
3	-0.044 (-0.073, -0.016)	-3.103 (-5.119, -1.088)	-0.052 (-0.074, -0.031)	-0.068 (-0.099, -0.036)
4 (severe sys-temic disease)	-0.056 (-0.143, 0.031)	-3.997 (-10.320, 2.326)	-0.077 (-0.146, -0.009)	-0.081 (-0.169, 0.007)
Length of stay at hospital (days)	-0.011 (-0.012, -0.009)	-0.617 (-0.741, -0.492)	-0.008 (-0.009, -0.006)	-0.010 (-0.012, -0.008)
Frail	-0.164 (-0.188, -0.139)	-6.850 (-8.510, -5.190)	-0.152 (-0.171, -0.133)	-0.233 (-0.260, -0.206)
Pre-injury VAS	0.004 (0.003, 0.004)	0.510 (0.475, 0.546)	0.004 (0.003, 0.004)	0.006 (0.005, 0.006)

SUPPLEMENTAL TABLE 1

	EQ-5D utility	EQ-VAS	HUI 2	HUI 3
Follow-up measurements				
T1 (1 week)[a]	0	0	0	0
T2 (1 month)	0.126 (0.114, 0.138)	9.066 (8.163, 9.969)	0.114 (0.105, 0.123)	0.157 (0.145, 0.168)
T3 (3 months)	0.234 (0.221, 0.246)	13.424 (12.486, 14.362)	0.153 (0.144, 0.162)	0.230 (0.218, 0.242)
T4 (6 months)	0.283 (0.270, 0.295)	15.386 (14.439, 16.334)	0.172 (0.162, 0.181)	0.275 (0.263, 0.287)
T5 (12 months)	0.281 (0.269, 0.294)	14.120 (13.179, 15.062)	0.164 (0.155, 0.173)	0.276 (0.265, 0.288)
Constant	0.238 (0.182, 0.295)	19.681 (15.689, 23.673)	0.447 (0.403, 0.491)	0.118 (0.055, 0.180)

[a] Reference category of categorical variable

[b] patients that had at least one injury in the region head or face, or in the region thorax or abdomen (torso) with an injury severity of at least 3.

Abbreviations: ASA, American society of anesthesiologists classification; FCI, Functional Capacity Index; ISS, Injury Severity Score;

SUPPLEMENTAL TABLE 2

Sensitivity analyses; regression coefficients and 95% Confidence Interval for the EQ-5D utility, EQ-VAS, Health Utility Index (HUI 2 and HUI 3) for the clinical trauma population excluding patients with hip fracture (ISS<15) after multivariable linear mixed models.

	EQ-5D utility	EQ-VAS	HUI 2	HUI 3
Age	0.001 (0.000, 0.001)	0.030 (-0.013, 0.072)	-0.001 (-0.001, 0.000)	-0.001 (-0.002, 0.000)
Female gender	-0.061 (-0.078, -0.044)	-2.566 (-3.737, -1.395)	-0.040 (-0.053, -0.027)	-0.051 (-0.070, -0.032)
Educational level	0	0	0	0
Low[a]	0.010 (-0.010, 0.029)	-0.162 (-1.544, 1.220)	0.006 (-0.009, 0.021)	0.021 (-0.002, 0.044)
Middle	0.036 (0.014, 0.058)	-0.186 (-1.717, 1.344)	0.024 (0.007, 0.040)	0.045 (0.021, 0.070)
High				
Head or face injury[b]	0.078 (0.038, 0.119)	4.283 (1.486, 7.079)	0.055 (0.024, 0.086)	0.045 (-0.001, 0.092)
Torso injury[b]	0.042 (0.004, 0.081)	2.747 (0.115, 5.379)	0.042 (0.013, 0.070)	0.054 (0.011, 0.097)
ISS	-0.004 (-0.007, -0.002)	-0.440 (-0.602, -0.277)	-0.003 (-0.005, -0.001)	-0.005 (-0.007, -0.002)
FCI	-0.006 (-0.088, 0.077)	2.737 (-2.920, 8.394)	-0.038 (-0.100, 0.024)	-0.090 (-0.182, 0.002)
1 (worse status)	-0.099 (-0.135, -0.063)	-1.824 (-4.336, 0.688)	-0.047 (-0.075, -0.020)	-0.080 (-0.121, -0.039)
2	-0.056 (-0.093, -0.018)	-0.925 (-3.499, 1.648)	-0.034 (-0.062, -0.006)	-0.057 (-0.099, -0.015)
3	-0.057 (-0.080, -0.035)	-0.999 (-2.563, 0.565)	-0.021 (-0.038, -0.003)	-0.039 (-0.065, -0.014)
4	0	0	0	0
5 (best status)[a]				
ASA	0	0	0	0
1 (healthy)[a]	0.013 (-0.009, 0.034)	1.711 (0.225, 3.197)	0.009 (-0.007, 0.025)	0.009 (-0.016, 0.034)
2	-0.045 (-0.079, -0.012)	-2.639 (-5.004, -0.275)	-0.047 (-0.072, -0.022)	-0.068 (-0.106, -0.031)
3	-0.147 (-0.267, -0.028)	-8.831 (-17.757, 0.095)	-0.144 (-0.232, -0.056)	-0.145 (-0.278, -0.012)
4 (severe sys-temic disease)				
Length of stay at hospital (days)	-0.010 (-0.012, -0.009)	-0.599 (-0.708, -0.490)	-0.008 (-0.010, -0.007)	-0.011 (-0.013, -0.009)
Frail	-0.136 (-0.166, -0.107)	-5.430 (-7.455, -3.404)	-0.145 (-0.168, -0.121)	-0.220 (-0.254, -0.186)
Pre-injury VAS	0.003 (0.003, 0.004)	0.480 (0.438, 0.521)	0.003 (0.003, 0.004)	0.005 (0.004, 0.006)

SUPPLEMENTAL TABLE 2

	EQ-5D utility	EQ-VAS	HUI 2	HUI 3
Follow-up measurements	0	0	0	0
T1 (1 week)[a]	0.121 (0.107, 0.134)	8.623 (7.632, 9.614)	0.110 (0.100, 0.120)	0.155 (0.142, 0.168)
T2 (1 month)	0.244 (0.230, 0.258)	14.141 (13.110, 15.173)	0.155 (0.145, 0.166)	0.235 (0.222, 0.249)
T3 (3 months)	0.305 (0.291, 0.319)	16.907 (15.861, 17.952)	0.181 (0.171, 0.191)	0.291 (0.277, 0.305)
T4 (6 months)	0.308 (0.294, 0.322)	16.510 (15.472, 17.548)	0.175 (0.165, 0.185)	0.288 (0.275, 0.302)
T5 (12 months)				
Constant	0.277 (0.211, 0.342)	22.577 (18.001, 27.152)	0.472 (0.422, 0.523)	0.147 (0.074, 0.221)

[a] Reference category of categorical variable

[b] patients that had at least one injury in the region head or face, or in the region thorax or abdomen (torso) with an injury severity of at least 3.

Abbreviations: ASA, American society of anesthesiologists classification; FCI, Functional Capacity Index; ISS, Injury Severity Score;

8

PROGNOSTIC FACTORS FOR POOR RECOVERY AFTER TRAUMA: A PROSPECTIVE MULTICENTRE COHORT STUDY

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Submitted.

ABSTRACT

Introduction. The identification of trauma patients at high risk for poor recovery could enable clinicians to tailor treatment. This study aimed to determine (I) prognostic factors for poor health status and (II) recovery patterns during the first two years after injury in the clinical trauma population.

Methods. A prospective longitudinal cohort study followed adult injury patients admitted to a Dutch hospital between August 2015 and November 2016. The EuroQol-5-dimensions-3-level (EQ-5D-3L) and a cognition item were collected at 1 week, 1, 3, 6, 12, and 24 months after injury. Prognostic factors and recovery patterns were assessed with linear mixed models for the EuroQol Visual Analogue Scale (EQ-VAS) and the EQ-5D-3L utility score and with logistic mixed models for the EQ-5D-3L dimensions and cognition.

Results. Fifty percent (n=4883/9774) of eligible patients completed at least one questionnaire. Health status was especially low during the first six months after injury (mean EQ-5D utility[SD] ranged from 0.49[0.32] at 1 week to 0.79[0.25] at 24 months). The dimensions mobility, pain/discomfort and usual activities improved up to 2 years after injury. Lower pre-injury health status, frailty and longer length of stay were important prognostic factors for poor recovery. Spine injury, lower and upper extremity injury showed to be prognostic factors for problems after injury. Traumatic brain injury was a prognostic factor for problems with cognition.

Conclusion. This study contributes to the increase in knowledge of recovery patterns and could be a starting point to develop prediction models for specific injury classifications for the implementation of personalized medicine.

INTRODUCTION

Trauma, defined as a physical injury, is one of the leading causes of disability and affects millions of people worldwide each year. The number of survivors after trauma increased the last decades, due to the improvement of trauma care[1-3]. Many patients suffer physical, psychological or cognitive impairments, resulting in a reduction of their health status (HS).

The trauma population is a heterogeneous group of patients. Patients are from various age groups with many different injury patterns, in both severity and body region. In addition, type of accident (e.g. falls, road traffic accident) and mechanism of injury (e.g. bleeding, fracture) can be diverse. The identification of patients at high risk of poor health status outcome could enable clinicians to tailor treatment in which patients are referred to specialized care and rehabilitation at an early stage of their recovery.

Most previous studies on prognostic factors for poor recovery were conducted in major or severe trauma patients population[4-12], traumatic brain injury patients[7,13] or assessed on a small follow-up trauma population[14]. In addition, studies were based on long follow-up measurement[10]. Last, pre-injury health status was not measured or taken into account by determining the prognostic factors for health status in previous studies. Research that take into account the total clinical trauma population during the first two years of their recovery is scarce[15]. In addition, different recovery patterns can be expected in, for example, brain injury patients and patients suffering from lower/upper extremity injury.

This study aimed (I) to determine prognostic factors for poor health status and (II) determine recovery patterns after injury during the first two years after injury in the clinical trauma population and in specific injury classifications.

METHODS

Study design and participants

Data was obtained from the Brabant Injury Outcome Surveillance (BIOS)[16]. The BIOS-study is a prospective observational cohort study in which health status, costs, functional and psychological outcomes were assessed in the first 24 months after trauma in injured patients. The study was approved by the Medical Ethics Committee Brabant (NL50258.028.14).

All adult (≥18 years) patients admitted to a hospital in the region Noord-Brabant (the Netherlands) from 1 August 2015 to 30 November 2016 due to an injury and who survived to hospital discharge were included in this study. Patients without sufficient knowledge of the Dutch language or with pathological fractures were excluded. A proxy informant (caregiver or family member) was asked to complete the self-administered questionnaires if patients were incapable of participating in the BIOS-study. The questionnaires were sent by post or electronically at one week, one month, three months, six months, twelve months and 24 months after injury. All participants, patients or proxy informants, signed informed consent. Patients were asked to complete a shorter version of the questionnaire at three months, six months, twelve months and 24 months after injury to increase response. This short version incorporates only a small collection of the questions that are included in the BIOS-study. Injury characteristics were collected in the Brabant Trauma Registry and, for participating patients, merged to the BIOS-data.

Outcome

Health status was measured with the EuroQol-5D-3L (EQ-5D)[17]. This questionnaire consists of the EQ-5D descriptive system and the EQ-visual analogue scale (EQ-VAS). The EQ-5D descriptive system comprised the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension could be answered in three levels: no problems, some problems and severe/extreme problems.

A summary score of these five dimensions (EQ-5D utility) can be calculated by using the Dutch tariffs[18]. This utility score ranged from 0 (death) to 1 (perfect health). The EQ-VAS is a vertical visual analogue scale with 0 indicating the worst imaginable health state and 100 indicating the best imaginable health state.

Cognition was added as additional dimension to the EQ-5D questionnaire. Respondents were asked to describe their or, in case of proxy, the patients' state of health, concerning cognition (e.g. memory, concentration). Similar to the other dimensions, answer options were based on three levels: no problems, some problems and severe problems.

HS was measured at each time point during follow-up in both patient and proxy questionnaires. The EQ-5D (including the cognition dimension) and EQ-VAS were also measured pre-injury, by asking participants at one week or one month and proxy informants at one month for the patients' health status before sustaining the injury. The EQ-VAS was not included in the short questionnaire.

Prognostic factors

Previous research showed that higher age[5-7,15], female sex[5,7,8,12,15], low education[5,9], pre-injury employment status[4,5,13], presence of comorbidities[8,9,15], presence of hip/lower extremity/spine or head injury[5,9,14,15], longer length of stay[6,14] and admission to the intensive care (IC)[5,6,14] are prognostic factors for poor outcome after injury. The association between injury severity and health status was inconsistent[6,9-11,14,19].

Sociodemographic variables

Possible prognostic factors for health status that were measured in the BIOS-study were sex, age, educational level (low, middle or high), pre-injury work status (yes/no), frailty and pre-injury health status. Educational level was categorized in three levels as the highest completed degree, diploma of education; low (primary education, preparatory secondary vocational education or without diploma), middle (university preparatory education, senior general secondary education or senior secondary vocational education and training), and high (academic degree or university of applied science). Frailty was measured at one week or one month after injury with the Groningen Frailty Index (GFI) in patients ≥65 years[20]. A sum-score of ≥4 was considered frail. Patients <65 years were considered not frail. Pre-injury health status was measured at 1 week or 1 month after injury with the EQ-5D-3L, referring to the health status of the patients prior to injury.

Clinical variables

Possible other clinical prognostic factors for health status were length of hospital stay, injury severity score, admission to the intensive care (yes/no), presence of comorbidities and the functional capacity index. Comorbidities were measured with the American Society of Anaesthesiologists (ASA) physical status classification system ranging from 1 (healthy patient) to 4 (severe systemic disease that is a constant threat to life). The functional capacity index and injury severity score were based on the Abbreviated Injury Scale (AIS) codes (AIS-90, update 2008)[21].

Injury Classification

The Abbreviated Injury Scale (AIS) codes (AIS-90, update 2008)[21] were used to create injury group classifications representing the most common types of injuries. In total, 14 injury groups were created: 3 lower extremity injury groups (pelvic injury, hip fracture, and tibia fracture/complex foot fracture or distal/shaft femur fracture), 2 upper extremity injury groups (shoulder and upper arm injury, and radius, ulna or hand fracture), 2 head injury groups(AIS-head≤2, and AIS-head≥3), 1 face injury group, 2 thorax injury groups (thorax injury, and rib fracture), 2 abdomen injury (AIS-abdomen≤2, and AIS-abdomen≥3) and 2 spine injury (spinal cord injury/brachial plexus lesion, and stable vertebral fracture/disc injury). Patients who suffer multiple injuries could be classified in one or more injury group classifications.

Data analysis

Baseline characteristics of participants were compared with non-participants, using chi-square for categorical variables or the Mann-Whitney U test for non-normal distributed data. Descriptive statistics included the median with the interquartile range (IQR) for continuous variables. Missing baseline characteristics and missing utility scores were imputed according to multiple imputation by using the Multivariate Imputations by Chained Equations (MICE) procedure with 15 imputations and 5 iterations[22]. The imputation model included baseline characteristics, injury characteristics and summary scores of the follow-up questionnaires to capture associations with missingness as completely as possible.

Multicollinearity was checked based on the Variance Inflation Factor (criterion: VIF > 10). Prognostic factors were assessed for poor health status outcome with EQ-5D utility and EQ-VAS as outcome measures. Regression coefficients with corresponding 95% confidence interval (CI) were reported. The dimensions of the EQ-5D descriptive system were dichotomized into 0=no problems and 1=some problems/extreme problems. Logistic mixed models with random intercepts were used to assess prognostic factors for poor outcome for the six dimensions of the EQ-5D (e.g. mobility, self-care, usual activities, pain/discomfort, anxiety/depression and cognition). All potential prognostic factors were included in the multivariable regression models to calculate adjusted Odds Ratios and corresponding 95% CI.

Recovery patterns were determined by changing the reference category of the time variable in linear mixed models for health status and logistic mixed models for the dimensions of health status, adjusted for the prognostic factors. Recovery patterns for the items of the EQ-5D were assessed in detail for injury classifications that showed to be statistically significant for the dimensions in the total multivariable model.

Analyses were conducted in the statistical programs R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS version 24 (Chicago, USA) and results were reported according to the TRIPOD guidelines[23].

RESULTS

Baseline characteristics

A total of 4883 patients (50% of total, N=9774) completed at least one questionnaire of the BIOS study of whom 48% (N=2,329) was male (Figure 1, Table 1). The median age was 68 years with an IQR of 53-80 years. Responders had a median injury severity score of 5 (IQR [4-9]) and most of the patients were classified as healthy or as patients with mild systemic disease (N=3,879, 79%). A total of 358 patients (7%) were admitted to the intensive care unit. Compared to the non-responders, participants were more severely injured, were more often admitted to a level I trauma centre, were more often admitted to the intensive care unit, had lower functional capacity index values, and were more often healthy (measured with the ASA classification). The majority of the responders had low educational level (N=2,670, 55%) and 38% of the responders (N=1,278) had a job prior to injury.

Health status over time

The mean (SD) EQ-5D utility score ranged from 0.49 (0.32), 0.56 (0.30), 0.69 (0.27), 0.76 (0.25), 0.77 (0.26) and 0.79 (0.25) at 1 week, 1, 3, 6, 12 and 24 months respectively (Figure 2a). The mean (SD) EQ-VAS score ranged from 58.26 (20.45), 63.02 (20.46), 69.48 (18.56), 72.97 (17.28), 73.50 (18.08) and 75.58 (17.88) at 1 week, 1, 3, 6, 12 and 24 months respectively. Patients reported the most recovery during the first 6 months, with a little improvement up to 12 months. The first month, patients reported most problems for pain/discomfort, usual activities, mobility and self-care (Figure 2b). During the 24 month follow-up, the percentage of patients reporting problems for pain/discomfort, usual activities and mobility were highest. Two years after injury 49% (95% CI: 47, 51) of the patients reported problems for pain/discomfort, 43% (95% CI: 41, 45) reported problems for mobility, 41% (95% CI: 39, 43) reported problems for usual activities, 25% (95% CI: 23, 27) reported for cognition, 20% (95% CI: 18, 22) reported problems for anxiety/depression and 19% (95% CI: 17, 21) for self-care.

Prognostic factors

Lower pre-injury health status, frailty and longer length of stay at hospital were important significant prognostic factors for both decreased health status during the first two years after trauma (Table 2). Increasing age is a protective factor for self-care, usual activities, pain/discomfort, anxiety/depression and cognition, but no significant association was found for mobility. Female sex showed to be a significant prognostic factor for all outcomes, except for mobility.

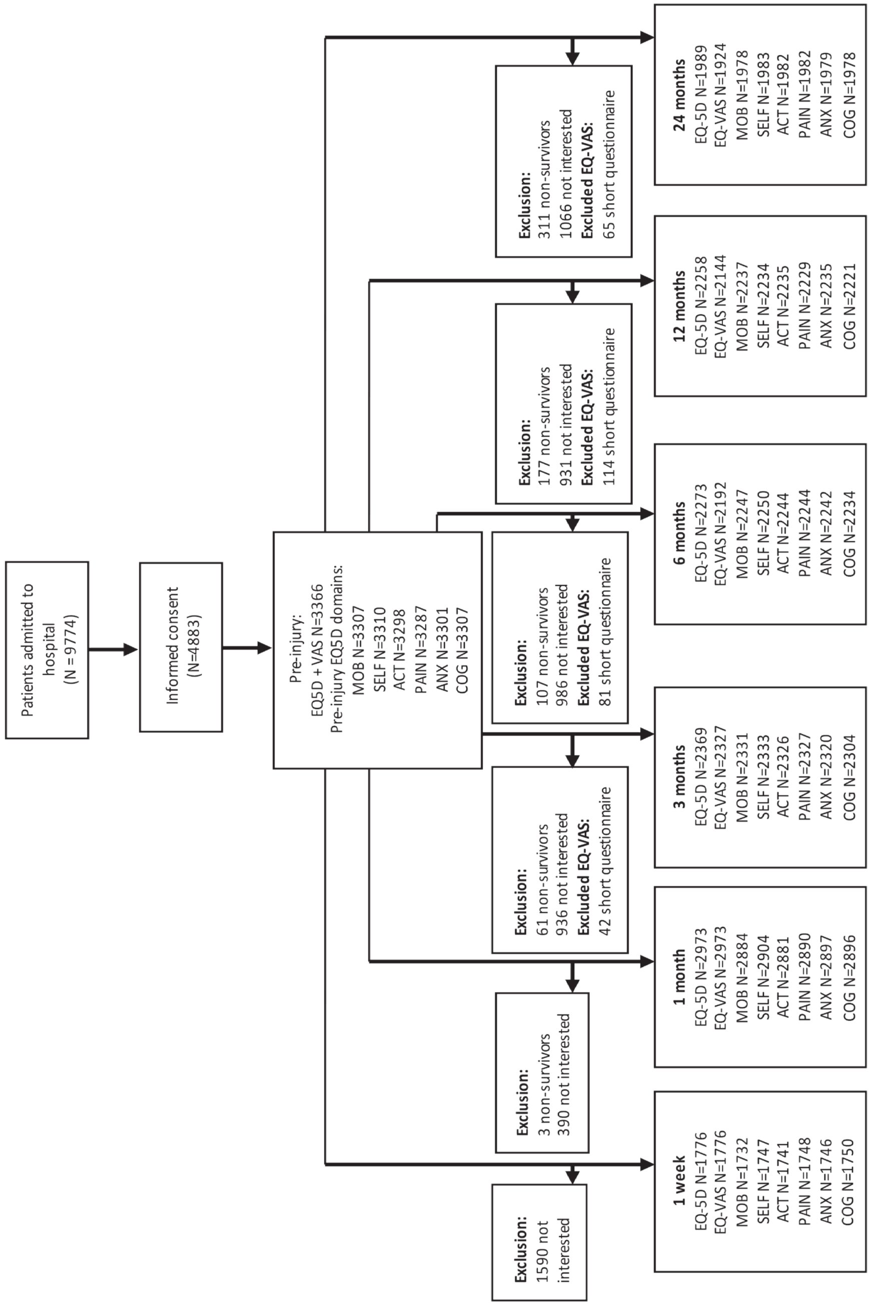

FIGURE 1. flow diagram of study participation of the BIOS-study.
Abbreviations: ACT, Usual activities; ANX, Anxiety/depression; COG, Cognition; MOB, Mobility; PAIN, Pain/discomfort; SELF, Self-care.

TABLE 1. Patient characteristics tables of responders and non-responders of the BIOS-study

	Responders[a]	Non-responders	p-value
N (%)	4883	4891	
Male (%)	2329 (48)	2407 (49)	0.13
Age (median, IQR)	68 (53-80)	70 (46-84)	0.26
ASA classification (N, %)			
1 (healthy)	1531 (31)	1195 (24)	0.00
2	2348 (48)	1657 (34)	
3	950 (19)	1046 (21)	
4 (severe systemic disease)	54 (1)	40 (1)	
Missing	-	953 (20)	
Injury Severity Score (median, IQR)	5 (4-9)	5 (2-9)	0.00
Length of stay at hospital (median, IQR)	4 (2-8)	4 (2-8)	0.02
Functional capacity index (N, %)			0.00
1-2 (worse state)	248 (5)	169 (4)	
3-4	2074 (42)	1721 (35)	
5 (best possible state)	2561 (52)	2473 (51)	
Missing	-	528 (11)	
Injury classification (N, %)			
Pelvic injury	293 (6)	151 (3)	
Hip fracture	1266 (26)	1099 (23)	
Tibia, complex foot or femur fracture	569 (12)	505 (10)	
Shoulder and upper arm injury	473 (10)	417 (9)	
Radius, ulna or hand fracture	308 (6)	283 (6)	
Head injury with AIS <=2	1324 (27)	1443 (30)	
Head injury with AIS >=3	186 (4)	181 (4)	
Facial injury	249 (5)	303 (6)	
Thoracic injury	198 (4)	162 (3)	
Rib fracture	451 (11)	398 (8)	
Abdominal injury	87 (2)	89 (2)	
Spinal cord injury	36 (1)	30 (1)	
Stable vertebral fracture or disc injury	27 (1)	10 (0)	
Pelvic injury	301 (6)	249 (5)	
Mechanism of injury			
Home and leisure	2957 (61)	2582 (53)	
Traffic	1272 (26)	895 (18)	
Occupational	205 (4)	144 (3)	
Sport	321 (7)	165 (3)	
Self-harm	18 (0)	27 (1)	

TABLE 1. Continued.

	Responders[a]	**Non-responders**	**p-value**
Violence	64 (1)	149 (3)	
Other	46 (1)	42 (1)	
missing		887 (18)	
Admission to intensive care unit (N, %)	358 (7)	292 (6)	0.00
Educational level (N, %)*			
Low	2670 (55)	-	
Middle	1305 (27)	-	
High	908 (19)	-	
Pre-injury work status*	1278 (38)	-	

[a] missing variables were imputed
*variables were only collected in responders
Abbreviations: ASA, American Society of Anaesthesiologists Classification; IQR, Inter Quartile Range; N, Number.

Lower extremity injury showed to be a prognostic factor for health status , mobility, self-care, usual activities and pain-discomfort. Upper extremity injury was a prognostic factor for health status , self-care, usual activities and pain/discomfort. Spine injury showed to be a prognostic factor, although not always significant, for health status , mobility, self-care, usual activities and pain/discomfort. Traumatic brain injury showed to be a prognostic factor for problems with cognition.

Recovery patterns

Most recovery occurred in the first 6 months (Table 3). Health status measured with the EQ-5D utility improved significantly during the first year after injury and health status measured with the EQ-VAS significantly increased during the 24 months after injury (although not significant at twelve months compared to six months). Patients reported to have significantly less problems with mobility, usual activities and pain/discomfort 24 months after injury compared to twelve months after injury.

Patients with spine injury showed improved mobility up to three months after injury, whereas patients with lower extremity injury showed less mobility problems up to twelve months after injury (Table 4). Upper and lower extremity injury showed the same recovery pattern during the first two years for self-care. Patients with spine injury showed improvement up to six months compared with three months after injury for self-care.

Patients with upper extremity and spine injury reported less problems for usual activities at twelve months after injury compared with six months after injury. Recovery mostly occurred up until twelve months after injury, except for pain/discomfort. Patients with lower extremity injury reported significant less problems at 24 months compared to twelve months for pain/discomfort.

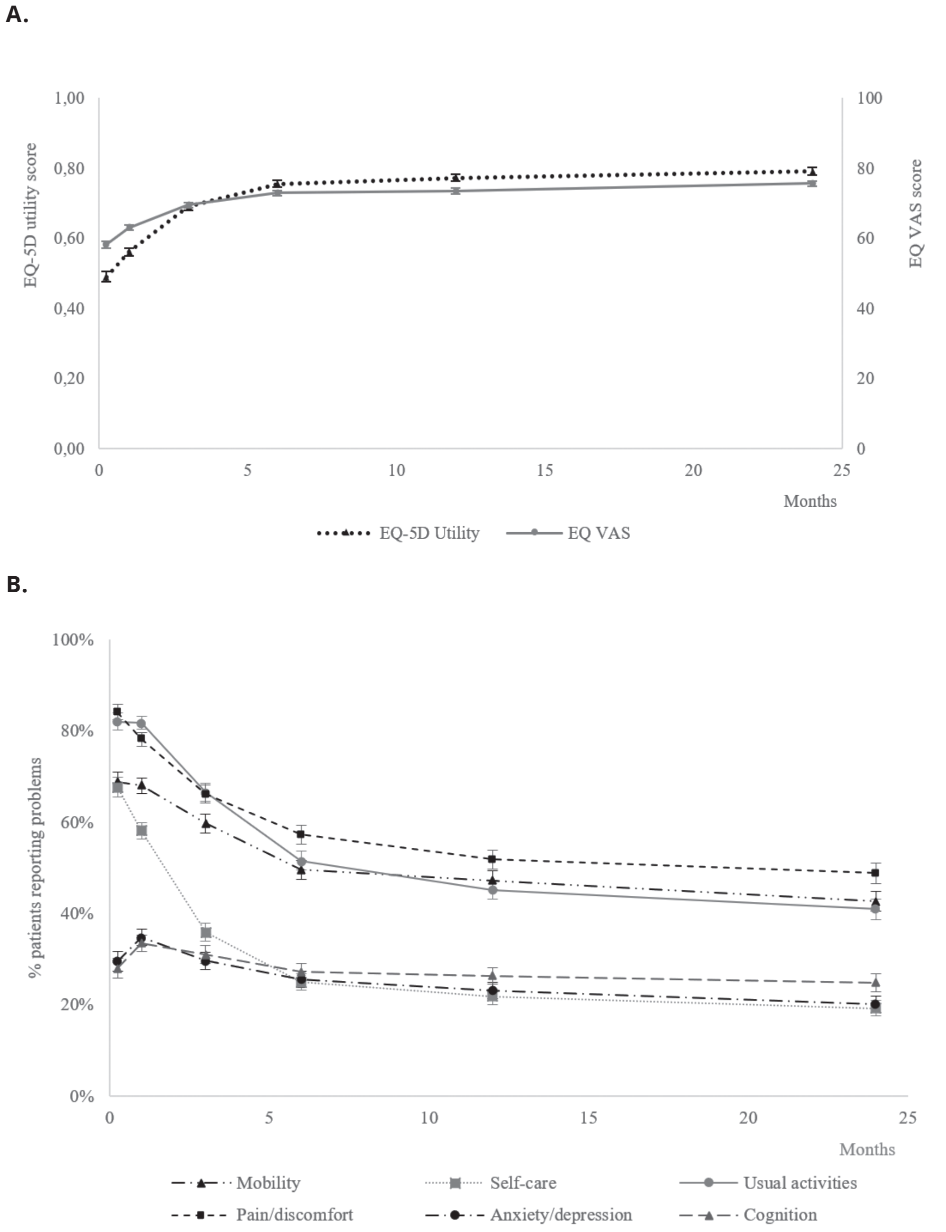

FIGURE 2. (A) Health status scores (95% CI) and **(B)** % patients reporting problems (95% CI) on the dimensions of the EQ-5D-3L.

TABLE 2. Regression coefficients in multivariable linear mixed models for the EQ-5D utility and the EQ-VAS and odds ratios in multivariable logistic mixed models for the dimensions of HS.

	During the first two years after injury							
	Linear regression coefficients (95% CI)		Odds Ratios (95% CI)					
	EQ-5D utility	EQ-VAS	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/ depression	Cognition
Female sex	-0.03 (-0.04, -0.01)	-1.43 (-2.30, -0.55)	1.08 (0.91, 1.29)	1.08 (0.95, 1.22)	1.51 (1.32, 1.72)	1.56 (1.35, 1.80)	2.02 (1.62, 2.51)	2.01 (1.54, 2.63)
Age (years)								
18 - 24	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
25 - 44	0.01 (-0.03, 0.04)	-0.32 (-2.87, 2.24)	1.13 (0.70, 1.83)	0.88 (0.61, 1.28)	1.18 (0.82, 1.71)	1.08 (0.72, 1.61)	0.97 (0.53, 1.77)	0.84 (0.41, 1.72)
45 - 64	0.05 (0.02, 0.09)	1.22 (-1.15, 3.60)	1.20 (0.76, 1.87)	0.79 (0.56, 1.13)	0.89 (0.63, 1.26)	0.81 (0.55, 1.18)	0.37 (0.21, 0.66)	0.37 (0.19, 0.73)
65 - 74	0.12 (0.08, 0.16)	6.43 (3.76, 9.10)	0.84 (0.51, 1.38)	0.55 (0.38, 0.82)	0.53 (0.36, 0.78)	0.51 (0.33, 0.78)	0.10 (0.05, 0.20)	0.14 (0.07, 0.31)
≥ 75	0.09 (0.05, 0.13)	4.98 (2.22, 7.73)	1.39 (0.82, 2.33)	0.98 (0.66, 1.46)	0.64 (0.43, 0.96)	0.45 (0.29, 0.70)	0.13 (0.07, 0.26)	0.42 (0.19, 0.92)
Nr of comorbidities								
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	-0.03 (-0.04, -0.01)	-2.72 (-3.79, -1.65)	1.45 (1.18, 1.77)	1.19 (1.03, 1.39)	1.29 (1.11, 1.51)	1.23 (1.04, 1.46)	1.65 (1.27, 2.15)	1.36 (0.99, 1.88)
≥2	-0.05 (-0.07, -0.04)	-4.08 (-5.30, -2.87)	2.13 (1.69, 2.68)	1.62 (1.38, 1.91)	1.84 (1.54, 2.20)	1.80 (1.47, 2.20)	2.34 (1.74, 3.13)	2.01 (1.40, 2.87)
Injury Severity Score[b]	-0.01 (-0.02, 0.00)	-0.93 (-1.53, -0.33)	1.10 (0.98, 1.23)	1 (0.92, 1.09)	1.08 (0.99, 1.18)	0.92 (0.83, 1.01)	1.12 (0.97, 1.30)	1.27 (1.05, 1.52)
Length of stay at hospital (days)								
1 - 2	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
3 - 7	-0.05 (-0.07, -0.03)	-3.40 (-4.52, -2.29)	2.14 (1.73, 2.64)	1.56 (1.33, 1.84)	1.72 (1.47, 2.03)	1.69 (1.40, 2.04)	1.69 (1.27, 2.25)	1.15 (0.81, 1.62)
8 - 14	-0.10 (-0.12, -0.08)	-6.24 (-7.70, -4.77)	3.21 (2.39, 4.29)	2.60 (2.12, 3.19)	2.67 (2.13, 3.35)	2.15 (1.68, 2.75)	2.73 (1.90, 3.92)	1.77 (1.13, 2.76)
≥ 15	-0.15 (-0.18, -0.12)	-9.32 (-11.43, -7.22)	6.07 (3.80, 9.69)	3.42 (2.51, 4.66)	3.97 (2.77, 5.71)	2.43 (1.66, 3.55)	4.15 (2.48, 6.95)	2.81 (1.47, 5.37)
Functional Capacity Index								
1 (worse state)	-0.07 (-0.15, 0.00)	-0.89 (-6.27, 4.48)	1.51 (0.57, 4.06)	1.79 (0.87, 3.71)	1.14 (0.51, 2.54)	1.00 (0.42, 2.41)	1.46 (0.41, 5.19)	1.63 (0.31, 8.57)
2	-0.06 (-0.10, -0.03)	-1.22 (-3.57, 1.12)	1.89 (1.19, 3.01)	1.94 (1.42, 2.66)	1.59 (1.12, 2.27)	1.28 (0.87, 1.89)	1.57 (0.89, 2.77)	0.67 (0.32, 1.38)
3	-0.03 (-0.07, 0.00)	-0.48 (-2.84, 1.89)	2.11 (1.34, 3.31)	1.47 (1.08, 2.02)	1.88 (1.32, 2.68)	1.14 (0.78, 1.66)	1.10 (0.62, 1.95)	0.91 (0.44, 1.86)
4	-0.03 (-0.05, -0.01)	-0.04 (-1.50, 1.43)	1.62 (1.22, 2.15)	1.57 (1.29, 1.93)	1.42 (1.14, 1.77)	1.28 (1.01, 1.63)	1.03 (0.72, 1.48)	0.57 (0.36, 0.91)
5 (best possible state)[a]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Injury classification[c]								
Pelvic injury	-0.04 (-0.07, -0.02)	-1.64 (-3.37, 0.10)	2.74 (1.96, 3.83)	1.29 (1.02, 1.64)	0.97 (0.74, 1.25)	1.33 (0.99, 1.78)	0.67 (0.43, 1.04)	0.57 (0.33, 0.98)
Hip fracture	-0.01 (-0.04, 0.02)	-0.34 (-2.20, 1.52)	2.62 (1.82, 3.79)	1.28 (0.99, 1.66)	1.05 (0.79, 1.40)	1.04 (0.76, 1.41)	0.90 (0.57, 1.42)	1.00 (0.57, 1.77)

TABLE 2. Continued.

	During the first two years after injury							
	Linear regression coefficients (95% CI)		Odds Ratios (95% CI)					
	EQ-5D utility	EQ-VAS	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/ depression	Cognition
Tibia, complex foot or femur fracture	-0.05 (-0.07, -0.02)	-1.14 (-2.75, 0.48)	6.85 (4.97, 9.44)	1.27 (1.02, 1.58)	1.71 (1.33, 2.18)	1.34 (1.03, 1.76)	0.8 (0.53, 1.19)	0.71 (0.43, 1.18)
Shoulder and upper arm injury	-0.03 (-0.06, -0.01)	-2.00 (-3.44, -0.55)	0.56 (0.42, 0.74)	2.22 (1.82, 2.71)	1.58 (1.28, 1.96)	2.05 (1.60, 2.61)	1.01 (0.7, 1.44)	0.71 (0.46, 1.12)
Radius, ulna or hand fracture	-0.02 (-0.04, 0.00)	-0.59 (-2.31, 1.12)	0.42 (0.30, 0.58)	1.46 (1.16, 1.85)	1.22 (0.95, 1.57)	1.23 (0.93, 1.63)	1.44 (0.94, 2.19)	0.87 (0.51, 1.48)
Head injury with AIS <=2	0.02 (0.01, 0.04)	0.64 (-0.41, 1.70)	0.78 (0.64, 0.96)	0.57 (0.49, 0.67)	0.77 (0.66, 0.90)	0.85 (0.72, 1.01)	1.15 (0.88, 1.49)	2.91 (2.12, 4.01)
Head injury with AIS >=3	0.04 (0.00, 0.08)	2.07 (-0.66, 4.80)	0.86 (0.51, 1.43)	0.92 (0.62, 1.37)	0.78 (0.52, 1.17)	0.90 (0.58, 1.39)	1.20 (0.62, 2.34)	3.29 (1.45, 7.49)
Facial injury	0.02 (0.00, 0.05)	0.78 (-1.15, 2.70)	0.52 (0.35, 0.75)	0.75 (0.56, 1.00)	0.67 (0.51, 0.89)	0.67 (0.49, 0.91)	1.10 (0.68, 1.78)	1.21 (0.68, 2.16)
Thoracic injury	0.06 (0.03, 0.10)	3.11 (0.77, 5.46)	0.54 (0.35, 0.84)	0.56 (0.40, 0.78)	0.55 (0.40, 0.78)	0.68 (0.47, 1.00)	0.58 (0.32, 1.05)	0.60 (0.29, 1.24)
Rib fracture	-0.01 (-0.03, 0.01)	-0.07 (-1.61, 1.48)	1.07 (0.80, 1.43)	1.02 (0.81, 1.27)	0.93 (0.74, 1.16)	1.63 (1.26, 2.11)	0.96 (0.65, 1.41)	0.85 (0.53, 1.36)
Abdominal injury	0.02 (-0.02, 0.06)	1.68 (-1.27, 4.63)	0.63 (0.36, 1.09)	0.57 (0.36, 0.88)	0.67 (0.44, 1.02)	0.56 (0.35, 0.90)	0.93 (0.45, 1.95)	1.55 (0.65, 3.69)
Spinal cord injury	-0.06 (-0.16, 0.04)	-3.03 (-9.85, 3.80)	1.86 (0.53, 6.60)	1.33 (0.53, 3.33)	1.35 (0.47, 3.88)	11.61 (2.86, 47.17)	0.92 (0.18, 4.71)	0.30 (0.04, 2.35)
Stable vertebral fracture or disc injury	-0.06 (-0.08, -0.03)	-4.16 (-5.99, -2.33)	1.31 (0.93, 1.84)	1.67 (1.30, 2.15)	1.79 (1.37, 2.34)	2.45 (1.79, 3.35)	1.14 (0.72, 1.79)	0.82 (0.47, 1.42)
Admission to Intensive Care Unit	0.00 (-0.02, 0.03)	-0.47 (-2.35, 1.41)	0.81 (0.56, 1.18)	1.01 (0.77, 1.32)	1.04 (0.78, 1.38)	1.08 (0.79, 1.49)	0.77 (0.48, 1.23)	2.22 (1.26, 3.91)
Pre-injury work status	0.00 (-0.02, 0.02)	-0.23 (-1.62, 1.17)	0.73 (0.57, 0.95)	0.94 (0.78, 1.14)	1.01 (0.83, 1.23)	1.12 (0.90, 1.40)	0.74 (0.53, 1.04)	0.92 (0.61, 1.39)
Educational level								
Low[a]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Middle	0.00 (-0.01, 0.02)	0.39 (-0.66, 1.43)	0.94 (0.77, 1.15)	0.96 (0.83, 1.11)	0.93 (0.80, 1.08)	1.07 (0.90, 1.26)	0.71 (0.55, 0.92)	1.05 (0.77, 1.45)
High	0.02 (0.00, 0.03)	0.36 (-0.76, 1.49)	0.91 (0.73, 1.13)	0.99 (0.84, 1.15)	0.75 (0.64, 0.89)	0.82 (0.68, 0.98)	0.64 (0.48, 0.86)	1.06 (0.75, 1.51)

TABLE 2. Continued.

	During the first two years after injury							
	Linear regression coefficients (95% CI)		**Odds Ratios (95% CI)**					
	EQ-5D utility	**EQ-VAS**	**Mobility**	**Self-care**	**Usual activities**	**Pain/discomfort**	**Anxiety/ depression**	**Cognition**
Frailty	-0.09 (-0.11, -0.07)	-5.12 (-6.54, -3.71)	2.38 (1.75, 3.24)	1.79 (1.46, 2.20)	2.07 (1.63, 2.62)	1.48 (1.18, 1.87)	4.94 (3.55, 6.86)	4.37 (2.89, 6.61)
Pre-injury status^{d}	0.49 (0.45, 0.53)	0.47 (0.44, 0.50)						
No problems^{a}			Ref	Ref	Ref	Ref	Ref	Ref
Moderate/ severe problems			13.58 (10.62, 17.36)	20.02 (15.50, 25.86)	6.39 (5.20, 7.86)	6.12 (5.09, 7.36)	30.22 (21.62, 42.25)	371.77 (224.34, 616.10)

Time was included as categorical variable in the analyses

[a] Reference category

[b] Regression coefficients and odds ratios (95%) represents a 4 unit increase on the ISS scale.

[c] Regression coefficients and odds ratios (95% CI) for patients suffering the injury compared to patients not having the injury.

[d] Regression coefficients (95% CI) for pre-injury EQ-5D utility score and the pre-injury EQ-VAS for EQ-5D utility and EQ-VAS respectively. Odds ratios (95% CI) for pre-injury moderate and severe problems on the dimensions of the EQ-5D questionnaire (pre-injury mobility, Self-care, Pain/discomfort, Anxiety/depression and cognition respectively for the columns).

Abbreviations: AIS, Abbreviated Injury scale; ASA, American Society of Anaesthesiologists Classification; CI, Confidence Interval; Ref, Reference Category.

TABLE 3. Change in health status and the dimensions of health status over time in multivariable linear and logistic mixed models.

	1 month vs 1 week	**3 months vs 1 month**	**6 months vs 3 months**	**12 months vs 6 months**	**24 months vs 12 months**
Linear regression coefficients (95% Confidence Interval)*					
EQ-5D utility	0.13 (0.12, 0.14)	0.12 (0.11, 0.13)	0.06 (0.05, 0.07)	0.01 (0.00, 0.02)	0.00 (-0.01, 0.02)
EQ-VAS	8.48 (7.70, 9.26)	5.97 (5.28, 6.69)	3.12 (2.36, 3.87)	0.24 (-0.52, 1.01)	0.98 (0.19, 1.76)
Odds Ratios (95% Confidence Interval)*					
Mobility	0.51 (0.41, 0.63)	0.38 (0.32, 0.46)	0.38 (0.31, 0.46)	0.85 (0.70, 1.03)	0.79 (0.65, 0.97)
Self-care	0.25 (0.21, 0.30)	0.14 (0.12, 0.17)	0.34 (0.28, 0.41)	0.73 (0.59, 0.91)	1.03 (0.82, 1.30)
Usual activities	0.67 (0.54, 0.83)	0.22 (0.19, 0.27)	0.31 (0.26, 0.37)	0.61 (0.52, 0.73)	0.82 (0.69, 0.98)
Pain/discomfort	0.46 (0.37, 0.56)	0.36 (0.30, 0.42)	0.51 (0.44, 0.61)	0.68 (0.58, 0.80)	0.84 (0.71, 1.00)
Anxiety/ depression	0.99 (0.82, 1.21)	0.70 (0.59, 0.84)	0.70 (0.58, 0.85)	0.83 (0.68, 1.02)	0.89 (0.72, 1.11)
Cognition	0.85 (0.68, 1.06)	0.91 (0.75, 1.12)	0.62 (0.49, 0.77)	1.09 (0.86, 1.38)	1.15 (0.91, 1.45)

*Regression coefficients and odds ratios in longitudinal analyses adjusted for sex, age, American Society of Anaesthesiologists Classification, Injury Severity Score, length of stay at hospital, Functional Capacity Index, Injury classifications, admission to intensive care unit, pre-injury work status, educational level, frailty and pre-injury status

TABLE 4. Change in the dimensions of health status over time in multivariable logistic mixed models for different injury classifications

	Adjusted Odds Ratios (95% Confidence Interval)*				
	1 month vs 1 week	**3 months vs 1 month**	**6 months vs 3 months**	**12 months vs 6 months**	**24 months vs 12 months**
Mobility					
Lower extremity[1]	0.78 (0.48, 1.27)	0.24 (0.16, 0.35)	0.17 (0.12, 0.23)	0.54 (0.41, 0.70)	0.79 (0.60, 1.03)
Spine[2]	0.12 (0.05, 0.30)	0.18 (0.08, 0.37)	0.37 (0.17, 0.81)	1.01 (0.47, 2.22)	0.70 (0.31, 1.60)
Self-care					
Lower extremity[1]	0.33 (0.24, 0.44)	0.66 (0.52, 0.84)	0.75 (0.58, 0.95)	0.66 (0.49, 0.88)	1.05 (0.77, 1.43)
Upper extremity[3]	0.19 (0.11, 0.32)	0.09 (0.06, 0.15)	0.25 (0.16, 0.40)	0.51 (0.30, 0.87)	0.72 (0.40, 1.31)
Spine[2]	0.25 (0.11, 0.57)	0.05 (0.02, 0.11)	0.15 (0.06, 0.34)	0.55 (0.21, 1.43)	1.43 (0.52, 3.93)
Usual activities					
Upper extremity[3]	0.40 (0.22, 0.73)	0.20 (0.13, 0.32)	0.25 (0.17, 0.38)	0.61 (0.40, 0.90)	0.76 (0.50, 1.15)
Spine[2]	0.48 (0.17, 1.30)	0.11 (0.05, 0.25)	0.24 (0.12, 0.49)	0.30 (0.15, 0.60)	1.71 (0.58, 2.38)
Pain/discomfort					
Lower extremity[1]	0.42 (0.30, 0.59)	0.53 (0.41, 0.69)	0.49 (0.39, 0.63)	0.66 (0.52, 0.84)	0.75 (0.59, 0.96)
Upper extremity[3]	0.49 (0.27, 0.87)	0.27 (0.17, 0.43)	0.48 (0.32, 0.73)	0.52 (0.35, 0.78)	0.78 (0.52, 1.18)
Spine[2]	0.35 (0.12, 0.98)	0.29 (0.13, 0.64)	0.62 (0.30, 1.27)	0.19 (0.09, 0.39)	1.27 (0.64, 2.50)
Anxiety/depression					
Spine[2]	0.69 (0.33, 1.43)	0.92 (0.49, 1.74)	0.64 (0.32, 1.27)	0.81 (0.40, 1.64)	0.87 (0.41, 1.85)
Cognition					
Traumatic Brain Injury[4]	0.72 (0.50, 1.02)	0.85 (0.60, 1.18)	0.69 (0.48, 0.99)	0.91 (0.63, 1.32)	1.15 (0.79, 1.68)

*Odds Ratios in longitudinal analyses adjusted for sex, age, American Society of Anaesthesiologists Classification, Injury Severity Score, length of stay at hospital, Functional Capacity Index, Injury classifications, admission to intensive care unit, pre-injury work status, educational level, frailty and pre-injury status

[1] Patients with pelvic injury, hip fracture or tibia, complex foot or femur fracture

[2] Patients with spinal cord injury or stable vertebral fracture or disc injury

[3] Patients with shoulder and upper arm injury or radius, ulna or hand fracture

[4] Patients with Traumatic brain injury, independent of injury severity

DISCUSSION

In this multicentre prospective cohort study, we found that patients reported problems up until two years after injury. Health status was especially low during the first six months after injury, in which patients often reported problems in most of the dimensions of health status. Lower pre-injury health status, frailty and longer length of stay at hospital were prognostic factors for both decreased health status and reporting problems in the dimensions during the first two years after trauma. For the EQ-5D dimensions mobility, usual activities and pain/discomfort less problems were reported at two years compared to one year after trauma, as for the other dimensions we found no decrease in reported problems after one year.

Previous research showed that age is a prognostic factor for reduced health status[9,15,24]. In contrast, results from this study showed improved overall health status. This could be explained by the addition of the strong risk-factors pre-injury health status and frailty in the multivariable adjusted models. Indicating that not the increase of age is a prognostic factor for poor health status, but the patients' health status before injury. Not all elderly patients are frail nor are they in poor health. With the ageing population, frailty and pre-injury health status are essential to consider when assessing recovery patterns in injury patients. Higher age was a prognostic factor for problems with mobility and self-care but showed to be a protective factor for other dimensions of the EQ-5D. The latter is in line with a recent study, stating that the relationship between age and the dimensions of EQ-5D differed[4].
The addition of the cognitive dimension on the EQ-5D has previously been shown to improve classification and validity, especially in patients with TBI[25,26]. In line with these findings, this study showed that patients with TBI were at risk on developing cognitive problems after injury. It has been suggested previously that most patients with mild TBI patients recover fully within three to six month, although some patients with mild TBI and patients with more severe TBI suffer persistent cognitive problems[27-29]. Our study showed that TBI patients reported to be recovered after six months, in line with the recovery pattern of mild TBI patients. This is possibly due to the fact that most responders of the BIOS-study suffered mostly mild TBI (27%) compared to moderate/severe TBI (4%). Further evaluation of these subgroups with more specific outcome measures are necessary to determine their recovery patterns.

In line with previous studies, this study showed that female sex is a prognostic factor for poor health status after injury[4,5,7,8,12,15,30]. It has been suggested that problems were more often reported in females, in contrast to males, who dismiss there complaints more often. Another explanation could be that women experience more psychological impact, resulting in lower health status.

Except for longer length of stay at the hospital, no injury related characteristics were found to be prognostic factors for anxiety/depression complaints. These results suggest that psychological problems after injury are mainly based on patient characteristics, which is confirmed in previous research[31,32].

Although the large prospective longitudinal design of this study is a major strength, there are also some limitations. First, only 50% of the patients responded to the BIOS-study. We found differences in injury and patient characteristics between responders and non-responders of the BIOS-study, e.g. responders were more severely injured compared to the non-responders, indicating selection bias. Next, it is also possible that selective dropout has occurred. We suspect that patients who were fully recovered were less likely to respond to the follow-up questions, resulting in an overestimation of complaints after injury.

We acknowledge that long-term non-fatal outcomes should be incorporated in the trauma registry[33]. These outcomes could be used to inform caregivers and patients about their expected recovery patterns. However, pre-injury health status is essential in predicting short and long-term outcome after injury and should therefore also be included in the registry. Furthermore, the dimensions of the EQ-5D and health status showed to have different recovery patterns for different injury classifications. Non-fatal outcome should not only be focused on health status, but especially on the different dimensions.

Although patients showed to be recovered after six months for the dimensions anxiety/depression and cognition, the dimensions mobility, pain/discomfort and usual activities still improved 2 years after injury. These results contribute to the increase in knowledge of recovery patterns and could be a starting point to develop prediction models for specific injury classifications for the implementation of personalized medicine.

REFERENCES

1. Liberman M, Mulder DS, Lavoie A, Sampalis JS. Implementation of a trauma care system: evolution through evaluation. *J Trauma*. 2004;56(6):1330-1335.
2. Cameron PA, Gabbe BJ, Cooper DJ, Walker T, Judson R, McNeil J. A statewide system of trauma care in Victoria: effect on patient survival. *Med J Aust*. 2008;189(10):546.
3. Moore L, Hanley JA, Turgeon AF, Lavoie A. Evaluation of the long-term trend in mortality from injury in a mature inclusive trauma system. *World J Surg*. 2010;34(9):2069-2075.
4. Gabbe BJ, Simpson PM, Cameron PA, Ponsford J, Lyons RA, Collie A, et al. Long-term health status and trajectories of seriously injured patients: A population-based longitudinal study. *PLoS Medicine.* 2017;14(7):e1002322.
5. Christensen MC, Banner C, Lefering R, Vallejo-Torres L, Morris S. Quality of life after severe trauma: results from the global trauma trial with recombinant Factor VII. *J Trauma.* 2011;70(6):1524-1531.
6. Sluys K, Häggmark T, Iselius L. Outcome and quality of life 5 years after major trauma. *J Trauma*. 2005;59(1):223-232.
7. Steel J, Youssef M, Pfeifer R, Ramirez JM, Probst C, Sellei R, et al. Health-related quality of life in patients with multiple injuries and traumatic brain injury 10 years postinjury. *J Trauma.* 2010;69(3):523-531.
8. Ringburg AN, Polinder S, van Ierland, Marie Catherine P, Steyerberg EW, van Lieshout EM, Patka P, et al. Prevalence and prognostic factors of disability after major trauma. *J Trauma.* 2011;70(4):916-922.
9. Holtslag HR, van Beeck EF, Lindeman E, Leenen LP. Determinants of long-term functional consequences after major trauma. *J Trauma.* 2007;62(4):919-927.
10. Ulvik A, Kvåle R, Wentzel-Larsen T, Flaatten H. Quality of life 2–7 years after major trauma. *Acta Anaesthesiol Scand.* 2008;52(2):195-201.
11. Harris I, Dao ATT, Young J, Solomon M, Jalaludin BB, Rae H. Factors predicting patient satisfaction following major trauma. *Injury.* 2007;38(9):1102-1108.
12. Holbrook TL, Hoyt DB. The impact of major trauma: quality-of-life outcomes are worse in women than in men, independent of mechanism and injury severity. *J Trauma*. 2004;56(2):284-290.
13. Andelic N, Hammergren N, Bautz-Holter E, Sveen U, Brunborg C, Røe C. Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. *Acta Neurol Scand*. 2009;120(1):16-23.
14. Sampalis JS, Liberman M, Davis L, Angelopoulos J, Longo N, Joch M, et al. Functional status and quality of life in survivors of injury treated at tertiary trauma centers: what are we neglecting? *J Trauma.* 2006;60(4):806-813.
15. Polinder S, van Beeck EF, Essink-Bot ML, Toet H, Looman CW, Mulder S, et al. Functional outcome at 2.5, 5, 9, and 24 months after injury in the Netherlands. *J Trauma.* 2007;62(1):133-141.
16. de Jongh MA, Kruithof N, Gosens T, van de Ree CL, de Munter L, Brouwers L, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: the Brabant Injury Outcome Surveillance (BIOS. study. *Inj Prev.* 2017;23(1):59-2016-042032.
17. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.
18. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ.* 2006;15(10):1121-1132.
19. Aitken LM, Davey TM, Ambrose J, Connelly LB, Swanson C, Bellamy N. Health outcomes of adults 3 months after injury. *Injury.* 2007;38:19-26.
20. Steverink N, Slaets J, Schuurmans H, van Lis M. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). *Gerontologist*. 2001;41(Special Issue 1):236-237.

21. Gennarelli TA, Wodzin E. Abbreviated injury scale 2005: update 2008. Russ Reeder; 2008.
22. van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE. 1999; PG/VGZ/99.054.
23. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for individual Prognosis or diagnosis (TRIPOD): Explanation and ElaborationThe TRIPOD Statement: explanation and elaboration. *Ann Intern Med.* 2015;162(1):W1-W73.
24. Gabbe BJ, Simpson PM, Harrison JE, Lyons RA, Ameratunga S, Ponsford J, et al. Return to work and functional outcomes after major trauma. *Ann Surg*. 2016;263(4):623-632.
25. Geraerds A, Bonsel GJ, Janssen MF, de Jongh M, Spronk I, Polinder S, et al. The added value of the EQ-5D with a cognition dimension in injury patients with and without traumatic brain injury. *Qual Life Res.* 2019;28(7):1931-1939.
26. Ophuis RH, Janssen MF, Bonsel GJ, Panneman MJ, Polinder S, Haagsma JA. Health-related quality of life in injury patients: the added value of extending the EQ-5D-3L with a cognitive dimension. *Quality Life Res*. 2019;28(7):1941-1949.
27. Frencham KA, Fox AM, Maybery MT. Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *J Clin Exp Neuropsyc*. 2005;27(3):334-351.
28. Carroll L, Cassidy JD, Peloso P, Borg J, Von Holst H, Holm L, et al. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004;36(0):84-105.
29. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am.* 2014;37(1):1-11.
30. Bazarian JJ, Blyth B, Mookerjee S, He H, McDermott MP. Sex differences in outcome after mild traumatic brain injury. *J Neurotrauma.* 2010;27(3):527-539.
31. Quale AJ, Schanke A, Frøslie KF, Røise O. Severity of injury does not have any impact on posttraumatic stress symptoms in severely injured patients. *Injury.* 2009;40(5):498-505.
32. Wiseman TA, Curtis K, Lam M, Foster K. Incidence of depression, anxiety and stress following traumatic injury: a longitudinal study. *Scand J Trauma Resusc Emerg Med.* 2015;23(1):29.
33. Haider AH, Herrera-Escobar JP, Al Rafai SS, Harlow AF, Apoj M, Nehra D, et al. Factors Associated With Long-Term Outcomes After Injury: Results of the Functional Outcomes and Recovery After Trauma Emergencies (FORTE) Multicenter Cohort Study. *Ann Surg.* 2018;Epub ahead of print.

9

PREVALENCE AND PROGNOSTIC FACTORS FOR PSYCHOLOGICAL DISTRESS AFTER TRAUMA

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ABSTRACT

Objective: To describe the prevalence and prognostic factors of symptoms of anxiety and depression and posttraumatic stress symptoms (PTSS) after injury in the clinical trauma population.

Design: Multicentre prospective observational cohort study.

Setting: Ten hospitals in Noord-Brabant, the Netherlands.

Participants: 4,239 adult trauma patients admitted between August 2015 and December 2016

Interventions: Patients were asked to complete a questionnaire at one week, and one, three, six and twelve months after injury.

Main Outcome Measures: The Hospital Anxiety and Depression Scale was used to assess anxiety and depressive symptoms and the Impact of Event Scale was used to assess PTSS.

Results: The prevalence of symptoms of anxiety and depression decreased from 10% and 12% respectively at one week after injury to 7% and 7% at twelve months after injury. Acute traumatic stress symptoms were present in 13% at one week and PTSS was prevalent in 10% of the participants at twelve months after injury. Strong prognostic factors for poor psychological outcome in multivariable logistic mixed models were pre-injury frailty, psychological complaints and non-working status pre-injury, female gender, low educational level and accident category (i.e. traffic accident, work-related or accidents at home compared to sport injuries).

Conclusion: Psychological distress is a common health problem during the first year after injury. Important prognostic factors for psychological distress include psychological complaints before injury and frailty. Early recognition of psychological problems after injury could facilitate discussion between caregivers and patients and improve recovery.

INTRODUCTION

Annually, almost 80,000 patients are admitted to a hospital after injury in the Netherlands[1]. Mortality rates in the trauma population decreased over the last decades in countries with advanced health care, causing an expansion of the focus to non-fatal consequences after trauma[2].

Trauma patients often suffer short- and long-term psychological distress[3,4]. Psychological distress is a general term to describe a state of emotional suffering that interferes with the level of functioning, and could be characterized by posttraumatic stress symptoms (PTSS), and symptoms of depression and anxiety[5]. Previous research showed that higher psychological distress after trauma was associated with higher experienced disability, lower health related quality of life and lower self-reported recovery[6-10].

Published literature about the prevalence of psychological distress after injury and its prognostic factors among the general trauma population is scarce, because most studies are based on specific subsets of the trauma population, e.g. specific injuries, road traffic accidents or the working (male) population[11-19]. Previous studies showed prevalence rates of symptoms of anxiety and depression or PTSS in the general trauma population of 4% to 24%, 6% to 42% and 2% to 30% respectively post-injury[3,20,21]. However, these studies were often conducted in a small sample size or were not assessed over time.

Many effective interventions are available to treat patients with psychological distress after injury[22]. However, health care givers often do not recognize patients suffering psychological distress. Early identification of patients who are vulnerable for developing subsequent psychological sequelae could help caregivers to recognize patients with a high risk of psychological distress and could benefit patient functional recovery, rehabilitation and wound healing[21,23-27]. Previous studies in cancer-related diseases showed that early identification of psychological distress is successful, it is likely to benefit communication and referral and increases patient well-being[28,29].

This study aimed to describe the prevalence and prognostic factors of symptoms of anxiety and depression, and PTSS during the first year after injury in the clinical trauma population.

METHODS

Participants

This prospective cohort study was part of the Brabant Injury Outcome Surveillance Study (BIOS-study)[30]. Adult injury patients (≥18yrs) who were admitted between August 2015 and November 2016, within 48 hours after injury to an ICU or a ward in the region Noord-Brabant, the Netherlands, and survived to hospital discharge were included in this study. Patients with a pathological fracture, insufficient knowledge of the Dutch language or with no place of residence were excluded. If patients were unable to complete the questionnaires, a proxy informant was asked to complete the questionnaires.

Design

The BIOS-study is a multicenter prospective observational cohort study. Patients were asked to complete a questionnaire on paper or digitally at one week, one, three, six and twelve months after injury. Patients who did not complete the questionnaire one week after trauma, were asked to participate from one month or three months onwards. Patients who did not respond to a questionnaire were considered non-responders for that time point, but were asked again to participate in the following questionnaire. Patients who did not completed questionnaires up until three months were asked to complete a short version of the questionnaire to increase response. The short questionnaire did not include proxy assessment nor did it include digital assessment. An elaboration on the study design can be found elsewhere[30].

All patients who participated in the BIOS-study signed an informed consent. The study was approved by the Medical Ethics Committee Brabant (NL50258.028.14). Data was anonymized prior to access.

Data collection

Patient characteristics were collected for all patients (i.e. gender, educational level, comorbidities and living situation). Follow-up questionnaires from the BIOS-study included health status, psychological and functional outcome. The short questionnaire included demographics, health status and the Impact of Event Scale (IES) (the latter was excluded in the short version of the questionnaire for patients who were ≥65years and suffered hip fracture).

Patients who participated at one week or one month after trauma completed a questionnaire including pre-injury psychological complaints and pre-injury frailty. Pre-injury psychological complaints were measured with the anxiety/depression domain of the EuroQol-5D-3L questionnaire[31]. Frailty was measured with the Groningen Frailty Index (GFI)[32] in patients ≥65 years old, with GFI≥4 indicating frailty[33]. Patients <65 years old were considered not frail. Education was categorized in low (no diploma, primary education or preparatory secondary vocational education), middle (university preparatory education, senior general secondary education or senior secondary vocational education and training) or high (university of applied science or an academic degree). Comorbidities were measured with the American Society of Anesthesiologists physical status classification (ASA)[34], ranging from 1 (healthy) to 4 (severe systematic disease, constant threat to life).

Injury characteristics and prehospital data from the Brabant Trauma Registry were merged with the BIOS data. The Injury Severity Score (ISS) was calculated according to the Abbreviated Injury Scale 2008 (AIS08)[35].

Outcome measures

The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depressive symptoms[36]. The HADS consists of fourteen questions, seven for symptoms of anxiety (HADS-A) and seven for depressive symptoms (HADS-D). All questions have a 4-point response scale and the scores for both subscales ranged from 0 to 21. A higher subscale score indicates greater severity of symptoms for anxiety and depression with a subscale value of ≥11 indicating a probable case[37]. The HADS has shown to be valid in patients with traumatic brain injury and has been used in several studies with trauma patients[38-40].

The IES was used to assess PTSS[41]. The IES consists of 15 items of which the patient could use a 4-point scale (0=not at all, 1=rarely, 3=sometimes and 5=often) whether the statement is present during the last seven days. A total score for the IES could be calculated, ranging from 0 to 75. A sum score of ≥35 was considered as PTSS[42]. Previous research showed that the IES is a reliable measure for subjective distress and could be used as a repeated measure to track subjective distress over time[43]. In addition, the Dutch version of the IES showed to be valid[44]. PTSS could be measured from one month after injury. The IES is also assessed at one week after injury, indicating symptoms of acute traumatic stress disorder. If at least one of the outcome measures was above the cut-off value, the patient was considered psychological distressed.

Analysis

Missing sum scores ranged from 5.6% (N=165) at six months to 6.5% (N=117) at one week after injury for the HADS-A and from 5.3% (N=156) at six months to 6.3% (N=167) at one month after injury for the HADS-D. Missing items of the HADS were first imputed with individual subscale means according to the half-rule (at least half of the items were answered)[45]. Missing baseline characteristics, missing IES values and the remaining missing HADS sum scores were imputed according to multiple imputation with 15 imputations and 5 iterations using the multivariate imputation by chained equations procedure[46]. The imputation model included demographics, baseline measures, injury characteristics and follow-up questionnaires.

Patient characteristics were compared between responders and non-responders, with a Mann-Whitney U tests and Chi-square tests for continuous and categorical variables, respectively. ASA category 3 and 4 (N=43), and the Functional Capacity Index (FCI) category 1 (N=49) and 2 were combined, due to low prevalence.

Patients who were admitted due to intentional injury (i.e. self-inflicted and violence) were excluded from further analyses. Patients who were admitted to the hospital due to self-inflicted injury (N=12) already have indication for appropriate psychological support after admission. Patients who were admitted due to violence (N=56) were not included, due to the low number of patients and high prevalence of psychological distress.

Potential prognostic factors were gender, age, educational level, psychological complaints pre-injury, ASA, length of hospital stay (LOS), FCI, accident category, injury region based on AIS08, ISS and work status before injury. Continuous variables were scaled to their standardized values (subtracting the mean and divided by the standard deviation). Prognostic factors were determined with logistic mixed models.

Odds ratios (OR) for the prognostic factors at each follow-up time point were calculated using the interaction term between each prognostic factor and time point in a multivariable logistic mixed model, adjusted for all other factors. The reference category of the time variable was changed to calculate the main effects of the prognostic factors at each time point.

Analyses were conducted in the statistical programs IBM SPSS version 24 (Chicago, USA) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient participation and characteristics

A total of 9,774 patients were asked to participate in the BIOS-study (Figure 1). Responders of the questionnaire were significantly younger compared to the non-responders (62.4[SD:18.7] and 65.8[SD:22.8] years respectively) (Table 1). Responders were more often healthy (with ASA=1 for 35% vs 22%), had a shorter LOS (mean LOS 6.2[SD:5.5] vs 6.9[SD 7.2]) and were more often admitted to the ICU (8% vs 6%) and a level I trauma center (26% vs 21%) compared to the non-responders. A total of 4,239 patients (43%) completed at least one IES questionnaire and 3,388 patients (35%) completed at least one HADS questionnaire. Half of the responders reported to be low educated. A total of 363 responders reported to have depression or anxiety pre-injury and 487 patients were considered frail. Of the working-age population (<65 years old) 24% (N=403) of the participants of the HADS questionnaire and 26% (N=537) of the participants of the IES questionnaire reported to have no job prior to injury.

Prevalence of psychological distress

Psychological distress was prevalent in 23% (N=414) of the participants at one week and in 14% (N=361) at twelve months after injury (Figure 2). Participants reported most often to have only one of the following complaints: PTSS, symptoms of anxiety or depression (13% at one week, 9% at twelve months after injury) followed by the co-occurrence of all three complaints (3% in the first three months after injury, 2% at twelve months after injury).

Prevalence of anxiety symptoms ranged from 10% (N=169) at one week to 7% (N=157) at twelve months post-injury. Symptoms of depression reduced from 12% (N=208) at one week to 7% (N=156) at twelve months post-injury. Acute traumatic stress symptoms were prevalent in 13% (N=226) at one week and PTSS was prevalent in 10% (N=267) of the participants at twelve months after injury.

The prevalence of symptoms of anxiety, symptoms of depression and PTSS in patients who were admitted due to violence were 39%, 35% and 50% at one week after injury respectively and 44%, 27% and 43% at twelve months after injury respectively.

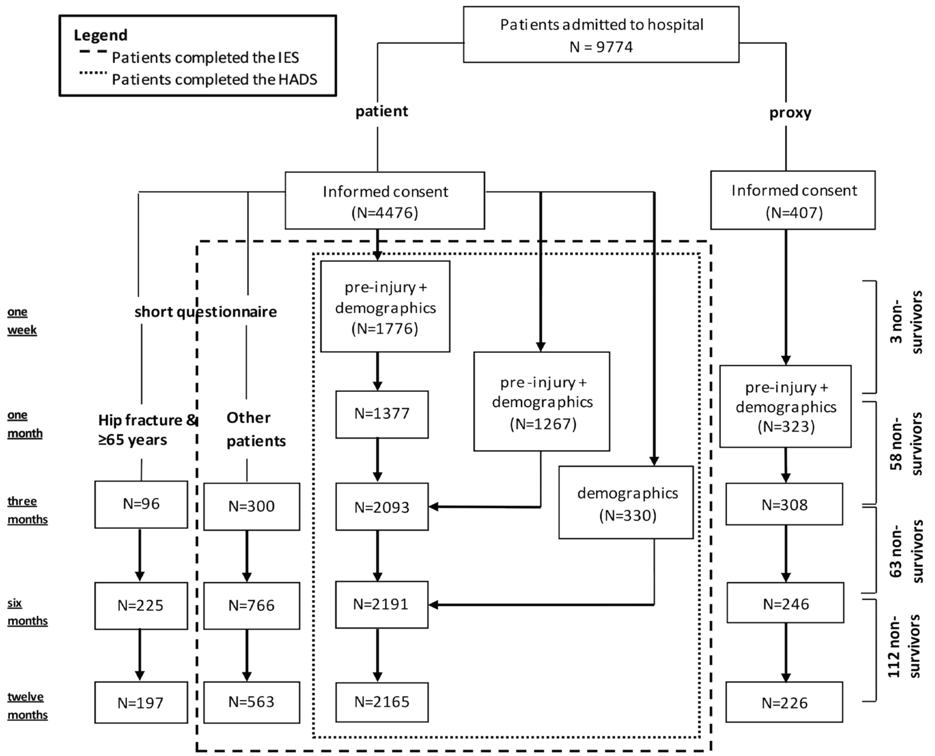


FIGURE 1. Flow diagram of participation in BIOS-study.

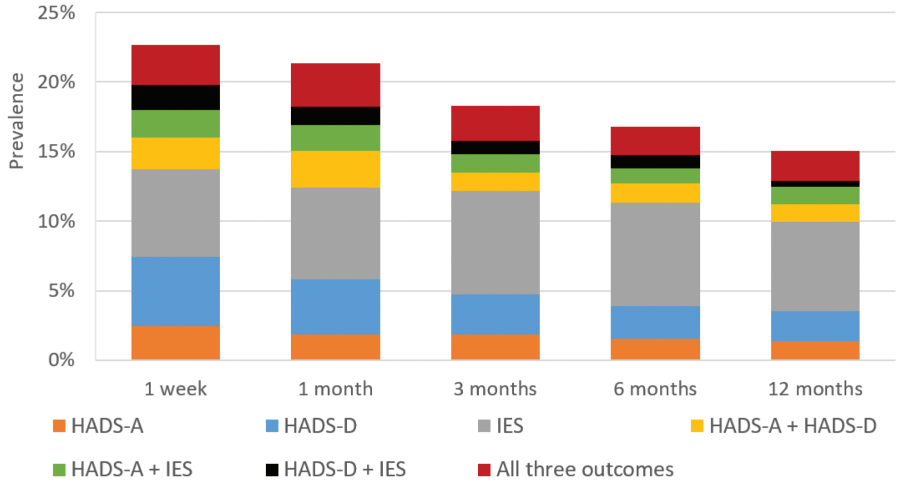


FIGURE 2. Prevalence of patients with psychological distress (at least one of the outcome measures above cut-off) in the first year after injury, and percentages of co-occurrence of psychological distress.

TABLE 1. Patient characteristics in the total cohort and the responders who completed the Impact of Event Scale (IES).

	Total cohort	Responders^a	Non-responders	p-value
N (%)	9,774 (100)	4239 (43)	5535 (57)	
Male (%)	4736 (49)	2161 (51)	2575 (47)	$p < 0.001$
Age (median, IQR)	69 (50-82)	65 (51-77)	73 (48-85)	$p < 0.001$
ASA classification (N, %)				$p < 0.001$
1 (healthy)	2458 (25)	1502 (35)	1224 (22)	
2	3627 (37)	2056 (49)	1949 (35)	
3	1817 (19)	638 (15)	1348 (24)	
4 (severe systemic disease)	62 (1)	43 (1)	51 (1)	
Missing	1810 (19)	-	953 (17)	
ISS (median, IQR)	5 (3-9)	5 (3-9)	6 (3-9)	$p < 0.001$
LOS (median, IQR)	4 (2-8)	4 (2-7)	5 (2-9)	$p < 0.001$
FCI (N, %)				$p < 0.001$
1-2 (worse state)	410 (4)	234 (6)	184 (3)	
3-4	3734 (38)	1541 (36)	2254 (41)	
5 (best possible state)	4938 (51)	2464 (58)	2569 (46)	
Missing	692 (7)	-	528 (10)	
Accident category (N, %)				$p < 0.001$
At home	5499 (56)	2320 (55)	3179 (57)	
Traffic incident	2133 (22)	1194 (28)	939 (17)	
Work related	337 (3)	192 (5)	145 (3)	
Sport	468 (5)	299 (7)	169 (3)	
Violence	205 (2)	54 (1)	151 (3)	
Self-inflicted	39 (0)	12 (0)	27 (0)	
Missing	1093 (11)	168 (4)	925 (17)	
Region of injury with AIS≥3 (N, %)				
Upper/lower extremity	2780 (28)	980 (23)	1800 (33)	$p < 0.001$
Spine/neck	124 (1)	72 (2)	52 (1)	$p < 0.01$
Head/face	442 (5)	206 (5)	236 (4)	$p = 0.160$
Torso	450 (5)	257 (6)	193 (3)	$p < 0.001$
Injury classifications (N, %)				
Pelvic injury	444 (5)	276 (7)	168 (3)	
Hip fracture	2365 (24)	778 (18)	1587 (29)	
Tibia, complex foot or femur fracture	1074 (11)	543 (13)	531 (10)	
Shoulder and upper arm injury	890 (9)	444 (11)	446 (8)	

TABLE 1. Continued.

	Total cohort	Responders[a]	Non-responders	p-value
Radius, ulna or hand fracture	591 (6)	293 (7)	293 (5)	
Head injury with AIS <=2	2767 (28)	1268 (30)	1499 (27)	
Head injury with AIS >=3	367 (4)	168 (4)	199 (4)	
Facial injury	552 (6)	242 (6)	310 (6)	
Thoracic injury	360 (4)	193 (5)	167 (3)	
Rib fracture	939 (10)	529 (13)	410 (7)	
Abdominal injury	227 (2)	109 (3)	118 (2)	
Spinal cord injury	37 (0)	27 (1)	10 (0)	
Stable vertebral fracture or disc injury	550 (6)	290 (7)	260 (5)	
Admission to IC (N, %)	650 (7)	318 (8)	332 (6)	p < 0.001
Admission to trauma center (N, %)				p < 0.001
Level I	2287 (23)	1112 (26)	1175 (21)	
Level II	5431 (56)	2253 (53)	3178 (57)	
Level III	2056 (21)	874 (21)	1182 (21)	

[a] Missing values for the responders were imputed.

Abbreviations: AIS, Abbreviated Injury Scale; ASA, American Society of Anesthesiologists physical status classification; FCI, Functional Capacity Index; IC, Intensive Care; IQR, Inter Quartile Range; ISS, Injury Severity Score; LOS, Length of Stay; N, number

Prognostic factors for psychological distress

Univariable analyses showed that female gender, psychological complaints pre-injury, frailty and longer LOS at hospital were prognostic factors for symptoms of anxiety, depression and post-traumatic stress during one year after injury (Table 2). Low educational level, upper/lower extremity injury (AIS≥3), no work status prior to injury and accidents at home or work also showed to be prognostic factors for at least one of the outcome measures.

In the multivariable analyses, psychological complaints pre-injury, frailty and longer LOS at hospital were prognostic factors for all three outcome measures (anxiety and depressive symptoms and PTSS (Table 2). An additional prognostic factor for depressive symptoms was female gender (OR:1.33 [95% CI:0.79,2.22]). Additional prognostic factors for PTSS were female gender (OR:1.66 [95% CI:1.07,2.59]) and traffic accident (OR:3.12 [95% CI:1.16,8.39] with sport injury as reference) (Supplemental file 1).

Short- and long-term prognostic factors

Short-term prognostic factors (first three months) for symptoms of anxiety were younger age, low educational level, longer LOS and frailty (Supplemental file 2). Long-term prognostic factors (three to twelve months) were female gender and younger age.

Longer LOS was a prognostic factor for short-term symptoms of depression. No long-term prognostic factors were found. Younger age and female gender were short-term prognostic factors for PTSS and long term prognostic factors were longer LOS and low educational level.

TABLE 2. Univariable and multivariable odds ratios with 95% CI for prognostic factors of anxiety, depressive symptoms and post-traumatic stress symptoms (PTSS) measured with the HADS-A, HADS-D and IES respectively.

	HADS-A		HADS-D		IES	
	Univariable	**Multivariable**	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
Age[a]	1.09 (0.81, 1.45)	0.67 (0.43, 1.06)	1.21 (0.92, 1.58)	0.87 (0.58, 1.30)	1.04 (0.84, 1.28)	0.72 (0.51, 1.03)
Female gender	1.86 (1.13, 3.08)	1.67 (0.93, 2.99)	1.61 (1.01, 2.55)	1.33 (0.79, 2.22)	1.78 (1.26, 2.53)	1.66 (1.07, 2.59)
Frail pre-injury	4.03 (2.04, 7.97)	2.53 (1.07, 5.98)	5.39 (2.82, 10.31)	3.43 (1.59, 7.39)	2.93 (1.68, 5.13)	1.81 (0.89, 3.66)
Education						
Low	Ref	Ref	Ref	Ref	Ref	Ref
Middle	0.65 (0.35, 1.20)	0.69 (0.35, 1.38)	0.83 (0.48, 1.44)	1.12 (0.62, 2.04)	0.66 (0.41, 1.05)	0.71 (0.42, 1.19)
High	0.46 (0.22, 0.95)	0.65 (0.30, 1.41)	0.59 (0.31, 1.12)	1.04 (0.53, 2.02)	0.43 (0.24, 0.79)	0.60 (0.33, 1.09)
Work status prior to injury	0.61 (0.35, 1.07)	1.04 (0.46, 2.34)	0.62 (0.38, 1.03)	1.05 (0.52, 2.12)	0.62 (0.45, 0.84)	0.71 (0.39, 1.32)
Pre-injury anxiety/ depression complaints	40.12 (18.15, 88.71)	33.97 (13.85, 83.29)	31.50 (13.94, 71.18)	22.53 (9.92, 51.19)	12.14 (5.94, 24.84)	9.05 (4.34, 18.88)
ASA						
1 (healthy)	Ref	Ref	Ref	Ref	Ref	Ref
2	1.46 (0.80, 2.66)	1.30 (0.63, 2.69)	1.08 (0.65, 1.80)	0.78 (0.41, 1.47)	1.35 (0.94, 1.94)	1.18 (0.67, 2.06)
3 - 4 (severe)	2.08 (0.98, 4.41)	1.38 (0.48, 3.95)	2.64 (1.39, 5.01)	1.71 (0.70, 4.14)	1.49 (0.90, 2.46)	1.04 (0.46, 2.36)
ISS[a]	0.99 (0.76, 1.29)	0.84 (0.47, 1.49)	1.22 (0.97, 1.53)	1.27 (0.80, 2.02)	0.97 (0.80, 1.18)	0.78 (0.50, 1.19)
Spine neck[b]	0.93 (0.11, 7.82)	0.92 (0.09, 9.81)	1.68 (0.31, 9.27)	0.63 (0.08, 4.88)	1.76 (0.49, 6.29)	2.23 (0.40, 12.45)
Head face[b]	0.85 (0.22, 3.28)	0.70 (0.11, 4.51)	1.11 (0.35, 3.48)	0.56 (0.12, 2.49)	0.91 (0.34, 2.41)	0.94 (0.25, 3.54)
Torso[b]	0.94 (0.32, 2.80)	1.15 (0.22, 5.94)	0.99 (0.37, 2.66)	0.55 (0.14, 2.21)	0.84 (0.38, 1.88)	1.27 (0.37, 4.32)
Upper/Lower extremity[b]	1.07 (0.60, 1.92)	1.43 (0.48, 4.21)	1.54 (1.01, 2.35)	1.15 (0.47, 2.82)	1.00 (0.78, 1.28)	1.07 (0.48, 2.38)
Accident category						
At home	3.17 (0.83, 12.01)	1.79 (0.45, 7.01)	2.36 (0.80, 6.97)	1.26 (0.44, 3.63)	2.81 (1.08, 7.31)	2.16 (0.80, 5.80)
Traffic	2.55 (0.64, 10.13)	2.37 (0.61, 9.20)	1.79 (0.58, 5.56)	1.70 (0.60, 4.85)	2.80 (0.64, 7.55)	3.12 (1.16, 8.39)
Work	1.73 (0.27, 11.32)	1.42 (0.22, 9.22)	1.87 (0.41, 8.51)	2.07 (0.51, 8.44)	2.55 (1.04, 10.16)	2.81 (0.76, 10.35)
Sport	Ref	Ref	Ref	Ref	Ref	Ref
FCI						
1 - 2 (worst limitation)	1.37 (0.47, 4.03)	1.24 (0.38, 4.04)	1.56 (0.57, 4.25)	0.94 (0.31, 2.86)	1.05 (0.42, 2.61)	0.89 (0.33, 2.38)
3	0.76 (0.19, 3.10)	0.69 (0.16, 2.97)	0.91 (0.26, 3.24)	0.64 (0.17, 2.36)	0.88 (0.30, 2.59)	0.78 (0.26, 2.36)
4	0.85 (0.48, 1.51)	0.55 (0.24, 1.27)	1.19 (0.71, 1.98)	0.74 (0.37, 1.50)	0.93 (0.60, 1.45)	0.75 (0.41, 1.38)
5 (no limitation)	Ref	Ref	Ref	Ref	Ref	Ref
Admission to IC	1.17 (0.45, 3.04)	0.97 (0.27, 3.44)	1.44 (0.62, 3.36)	0.77 (0.26, 2.29)	1.30 (0.71, 2.38)	1.24 (0.48, 3.22)
LOS[a]	1.35 (1.06, 1.72)	1.44 (1.01, 2.06)	1.69 (1.28, 2.22)	1.71 (1.22, 2.40)	1.29 (1.05, 1.59)	1.41 (1.05, 1.91)
Follow-up measurements						
1 week	Ref	Ref	Ref	Ref	Ref	Ref
1 month	1.06 (0.72, 1.58)	1.11 (0.75, 1.64)	0.80 (0.57, 1.12)	0.77 (0.55, 1.08)	0.94 (0.64, 1.37)	0.91 (0.63, 1.30)
3 months	0.55 (0.36, 0.82)	0.59 (0.39, 0.90)	0.37 (0.25, 0.54)	0.42 (0.29, 0.61)	0.76 (0.53, 1.09)	0.75 (0.52, 1.07)
6 months	0.45 (0.29, 0.68)	0.57 (0.37, 0.88)	0.35 (0.24, 0.51)	0.39 (0.27, 0.58)	0.53 (0.37, 0.75)	0.52 (0.36, 0.74)
12 months	0.48 (0.31, 0.74)	0.51 (0.32, 0.80)	0.25 (0.17, 0.37)	0.25 (0.17, 0.37)	0.48 (0.34, 0.70)	0.45 (0.30, 0.65)

[a] Continuous variables were scaled.

[b] Patients were selected in this category if AIS≥3 for this region.

Abbreviations: ASA, American society of anesthesiologists classification; FCI, Functional Capacity Index; IC, Intensive Care; ISS, Injury Severity Score; Ref, Reference Category.

DISCUSSION

Psychological distress was prevalent in 23% of the patients one week after injury and decreased to 14% of the patients twelve months after injury. Prognostic factors for poor psychological outcome were pre-injury frailty, psychological complaints and non-working status pre-injury, female gender, low educational level and accident category (i.e. traffic accident, work-related or accidents at home compared to sport injuries). Psychological complaints pre-injury and frailty were the most important prognostic factors for psychological distress.

Prevalence of psychological distress among patients who were admitted due to intentional injury (i.e. self-inflicted or violence) was high, which is in line with previous literature[47-49], indicating that those patients should be monitored or evaluated carefully. Therefore, prognostic factors were only based on patients who did not suffer intentional injury.
In line with previous research, prognostic factors for psychological distress were mainly patient characteristics, whereas injury characteristics were not[23,50,51]. Even though previous research showed that ICU admission is a prognostic factor for the development of psychological distress after injury[24,52], this study does not support this evidence. A longer LOS possibly reflects social indication or (medical) complications following their injury.
Psychological distress could result in lower health related quality of life, indicating poor recovery after injury[53]. The prognostic factors discussed in this study could help clinicians to recognize patients suffering psychological distress and guide them to discuss those problems to improve recovery. Psychologists might be needed to discuss issues with personality traits, coping strategies and social support, which were previously suggested as predictors of psychological distress[54,55]. We did not include such characteristics and could therefore not confirm their relevance as potential prognostic factors. A more comprehensive study, including the prognostic factors assessed in this study and the previously described factors should aim to develop a valid and simple prediction model for psychological distress after injury. Such a prediction model could help triage patients who are at risk on developing psychological distress after injury at an early stage.

Study limitations

The first limitation considers the possibility to generalize the results to other trauma populations. The BIOS-study is considered representative for the total trauma population in the Netherlands as it contains urban as well as rural areas and includes level I, level II, and level III trauma centers. However, only 43% of all patients participated and differences were found between baseline characteristics of responders and non-responders implying that selection bias could have occurred. Furthermore, it is likely that selective dropout occurred. Patients who were fully recovered were probably less likely to complete the follow-up questionnaires compared to patients who still perceived complaints after their injury, resulting in an overestimation of prevalence rates of psychological distress.
Second, this study was based on self-reported questionnaires. Official diagnosis of mental health problems should be conducted with a structured interview, according to the statistical manual for psychiatric disorders[56]. The questionnaires in this study only suggest psychological complaints and could be used to refer patients for further evaluation by a psychologist. In addition, the IES only measures two out of three clusters of PTSS[41].

Conclusions

Psychological distress is a common health problem during the first year after injury. The most important prognostic factors for psychological distress were psychological complaints before injury and frailty. Early recognition of psychological problems could facilitate discussions between caregivers and patients and could improve recovery after injury.

REFERENCES

1. Landelijke Netwerk Acute Zorg (LNAZ). *Annual report of the dutch trauma registry: Traumazorg in beeld 2013 - 2017. 2018*.
2. Patton GC, Coffey C, Sawyer SM, et al. Global patterns of mortality in young people: A systematic analysis of population health data. *The lancet*. 2009;374(9693):881-892.
3. Wiseman TA, Curtis K, Lam M, Foster K. Incidence of depression, anxiety and stress following traumatic injury: A longitudinal study. *Scand J Trauma Resusc Emerg Med*. 2015;23(1):29.
4. Bryant RA, O'donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. *Am J Psychiatry*. 2010;167(3):312-320.
5. Drapeau A, Marchand A, Beaulieu-Prévost D. Epidemiology of psychological distress. In: *Mental illnesses-understanding, prediction and control*. InTech; 2012.
6. Richmond TS, Kauder D, Hinkle J, Shults J. Early predictors of long-term disability after injury. *Am J Crit Care*. 2003;12(3):197-205.
7. Di Gallo A, Parry-Jones WL. Psychological sequelae of road traffic accidents: An inadequately addressed problem. *Br J Psychiatry*. 1996;169(4):405-407.
8. Sutherland AG, Alexander DA, Hutchison JD. The mind does matter: Psychological and physical recovery after musculoskeletal trauma. *J Trauma*. 2006;61(6):1408-1414.
9. Baranyi A, Leithgöb O, Kreiner B, et al. Relationship between posttraumatic stress disorder, quality of life, social support, and affective and dissociative status in severely injured accident victims 12 months after trauma. *Psychosomatics*. 2010;51(3):237-247.
10. Kellezi B, Coupland C, Morriss R, et al. The impact of psychological factors on recovery from injury: A multicentre cohort study. *Soc Psychiatry Psychiatr Epidemiol*. 2017;52(7):855-866.
11. Mason S, Turpin G, Woods D, Wardrope J, Rowlands A. Risk factors for psychological distress following injury. *Br J Clin Psychol*. 2006;45(2):217-230.
12. Mason S, Wardrope J, Turpin G, Rowlands A. The psychological burden of injury: An 18 month prospective cohort study. *Emerg Med J*. 2002;19(5):400-404.
13. Andruszkow H, Deniz E, Urner J, et al. Physical and psychological long-term outcome after traumatic brain injury in children and adult patients. *Health Qual Life Outcomes*. 2014;12(1):26.
14. Mayou R, Bryant B, Ehlers A. Prediction of psychological outcomes one year after a motor vehicle accident. *Am J Psychiatry*. 2001;158(8):1231-1238.
15. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. *Pain*. 2005;114(1):141-148.
16. Sigurdardottir S, Andelic N, Røe C, Schanke A. Depressive symptoms and psychological distress during the first five years after traumatic brain injury: Relationship with psychosocial stressors, fatigue and pain. *J Rehabil Med*. 2013;45(8):808-814.
17. Whelan-Goodinson R, Ponsford JL, Schonberger M, Johnston L. Predictors of psychiatric disorders following traumatic brain injury. *J Head Trauma Rehabil*. 2010;25(5):320-329.
18. Shalev AY, Freedman S, Peri T, et al. Prospective study of posttraumatic stress disorder and depression following trauma. *Am J Psychiatry*. 1998;155(5):630-637.
19. Skogstad L, Tøien K, Hem E, Ranhoff AH, Sandvik L, Ekeberg Ø. Psychological distress after physical injury: A one-year follow-up study of conscious hospitalised patients. *Injury*. 2014;45(1):289-298.
20. Haagsma JA, Polinder S, Olff M, Toet H, Bonsel GJ, van Beeck EF. Posttraumatic stress symptoms and health-related quality of life: A two year follow up study of injury treated at the emergency department. *BMC Psychiatry*. 2012;12(1):1.
21. O'donnell ML, Bryant RA, Creamer M, Carty J. Mental health following traumatic injury: Toward a health system model of early psychological intervention. *Clin Psychol Rev*. 2008;28(3):387-406.

22. Bisson J, Andrew M. *Psychological treatment of post-traumatic stress disorder (PTSD).* Wiley New York, NY; 2007.
23. Wiseman T, Foster K, Curtis K. Mental health following traumatic physical injury: An integrative literature review. *Injury*. 2013;44(11):1383-1390.
24. Zatzick D, Jurkovich GJ, Rivara FP, et al. A national US study of posttraumatic stress disorder, depression, and work and functional outcomes after hospitalization for traumatic injury. *Ann Surg*. 2008;248(3):429-437.
25. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: Methods and mechanisms. *Immunol Allergy Clin North Am*. 2011;31(1):81-93.
26. Ponsford J, Hill B, Karamitsios M, Bahar-Fuchs A. Factors influencing outcome after orthopedic trauma. *J Trauma*. 2008;64(4):1001-1009.
27. O'Donnell ML, Creamer MC, Parslow R, et al. A predictive screening index for posttraumatic stress disorder and depression following traumatic injury. *J Consult Clin Psychol*. 2008;76(6):923-932.
28. Kazak AE, Barakat LP, Ditaranto S, et al. Screening for psychosocial risk at pediatric cancer diagnosis: The psychosocial assessment tool. *J Pediatr Hematol Oncol*. 2011;33(4):289-294.
29. Ryan H, Schofield P, Cockburn J, et al. How to recognize and manage psychological distress in cancer patients. *Eur J Cancer care*. 2005;14(1):7-15.
30. de Jongh MA, Kruithof N, Gosens T, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: The brabant injury outcome surveillance (BIOS) study. Inj Prev. 2017;23(1):59-2016-042032. Epub 2016 May 6.
31. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
32. Steverink N, Slaets J, Schuurmans H, van Lis M. Measuring frailty: Developing and testing the GFI (groningen frailty indicator). *Gerontologist*. 2001;41(Special Issue 1):236-237.
33. Peters LL, Boter H, Buskens E, Slaets JP. Measurement properties of the groningen frailty indicator in home-dwelling and institutionalized elderly people. *J Am Med Dir Assoc*. 2012;13(6):546-551.
34. Dripps R. New classification of physical status. *Anesthesiology*. 1963;24:111.
35. Gennarelli TA, Wodzin E. *Abbreviated injury scale 2005: Update 2008*. Russ Reeder; 2008.
36. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.
37. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale: An updated literature review. *J Psychosom Res*. 2002;52(2):69-77.
38. Bocci MG, Grieco DL, Lochi S, et al. Defining needs and goals of post-ICU care for trauma patients: Preliminary study. *Minerva Anestesiol*. 2016;82(1):22-29.
39. Whelan-Goodinson R, Ponsford J, Schönberger M. Validity of the hospital anxiety and depression scale to assess depression and anxiety following traumatic brain injury as compared with the structured clinical interview for DSM-IV. *J Affect Disord*. 2009;114(1):94-102.
40. Whittaker R, Kemp S, House A. Illness perceptions and outcome in mild head injury: A longitudinal study. *J Neurol Neurosurg Psychiatry*. 2007;78(6):644-646.
41. Horowitz M, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. *Psychosom Med*. 1979;41(3):209-218.
42. Wohlfarth TD, van den Brink W, Winkel FW, ter Smitten M. Screening for posttraumatic stress disorder: An evaluation of two self-report scales among crime victims. *Psychol Assess*. 2003;15(1):101.
43. Sundin EC, Horowitz MJ. Impact of event scale: Psychometric properties. *Br J Psychiatry*. 2002;180:205-209.
44. van der Ploeg E, Mooren T, Kleber RJ, van der Velden, Peter G, Brom D. Construct validation of the *dutch* version of the impact of event scale. *Psychol Assess*. 2004;16(1):16.
45. Bell ML, Fairclough DL, Fiero MH, Butow PN. Handling missing items in the hospital anxiety and depression scale (HADS): A simulation study. *BMC research notes*. 2016;9(1):479.

46. van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE. 1999;PG/VGZ/99.054.
47. Santiago PN, Ursano RJ, Gray CL, et al. A systematic review of PTSD prevalence and trajectories in DSM-5 defined trauma exposed populations: Intentional and non-intentional traumatic events. *PloS one*. 2013;8(4):e59236.
48. Mello-Silva ACC, Brasil VV, Minamisava R, Oliveira LM, Cordeiro JABL, Barbosa MA. Quality of life and psychological trauma in firearm violence victims. *Texto Contexto Enferm*. 2012;21(3):558-565.
49. Pajonk F, Ruchholtz S, Waydhas C, Schneider-Axmann T. Long-term follow-up after severe suicide attempt by multiple blunt trauma. *European psychiatry*. 2005;20(2):115-120.
50. Wiseman TA, Curtis K, Lam M, Foster K. Incidence of depression, anxiety and stress following traumatic injury: A longitudinal study. *Scand J Trauma Resusc Emerg Med*. 2015;23(1):29.
51. Quale AJ, Schanke A, Frøslie KF, Røise O. Severity of injury does not have any impact on posttraumatic stress symptoms in severely injured patients. *Injury*. 2009;40(5):498-505.
52. Corrigan I, Samuelson KA, Fridlund B, Thomé B. The meaning of posttraumatic stress-reactions following critical illness or injury and intensive care treatment. *Intensive Crit Care Nurs.* 2007;23(4):206-215.
53. Kendrick D, Kelllezi B, Coupland C, et al. Psychological morbidity and health-related quality of life after injury: Multicentre cohort study. *Qual Life Res*. 2017;26(5):1233-1250.
54. Myhren H, Ekeberg Ø, Tøien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. *Critical Care*. 2010;14(1):R14.
55. Birkeland MS, Nielsen MB, Hansen MB, Knardahl S, Heir T. Like a bridge over troubled water? A longitudinal study of general social support, colleague support, and leader support as recovery factors after a traumatic event. *Eur J Psychotraumatol*. 2017;8(1):1302692.
56. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5®).* American Psychiatric Pub; 2013.

SUPPLEMENTAL FILE 1

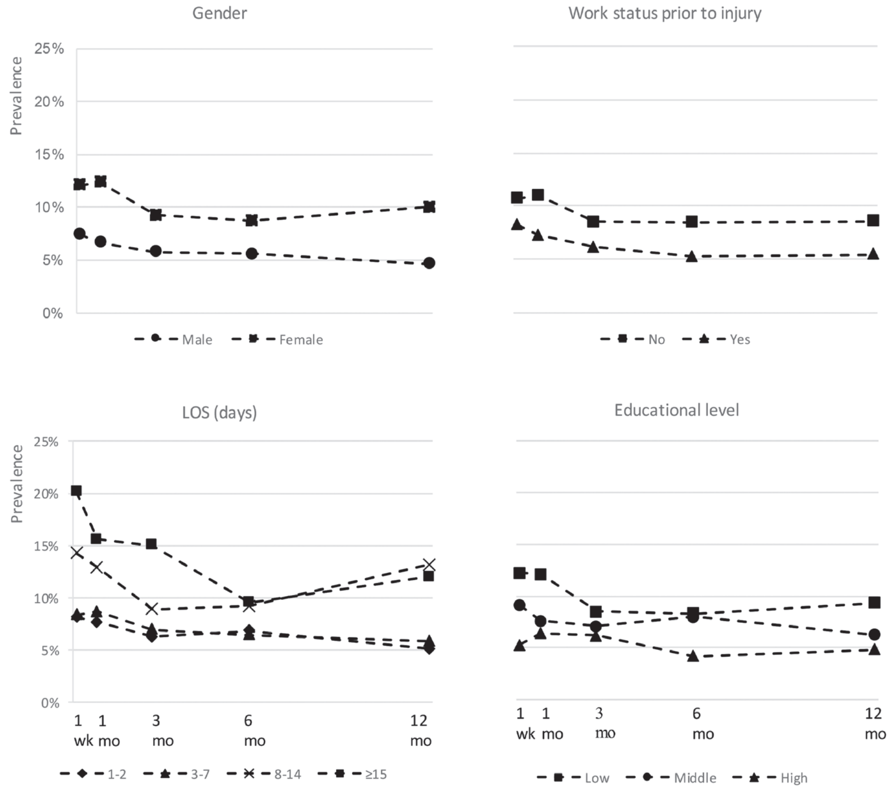


FIGURE 1. Percentage of responders in the first year after injury with poor psychological outcome for the HADS-A, based on gender, pre-injury employment, length of stay (LOS) in hospital and educational level.

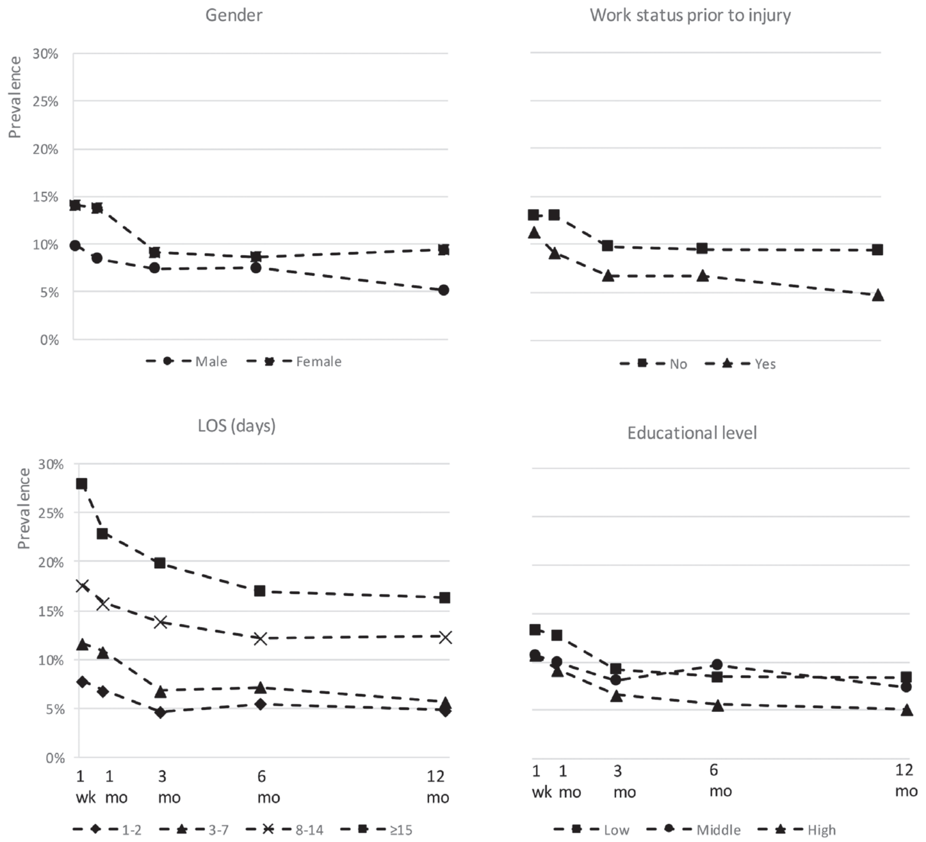


FIGURE 2. Percentage of responders in the first year after injury with poor psychological outcome for the HADS-D, based on gender, pre-injury employment, length of stay (LOS) in hospital and educational level.

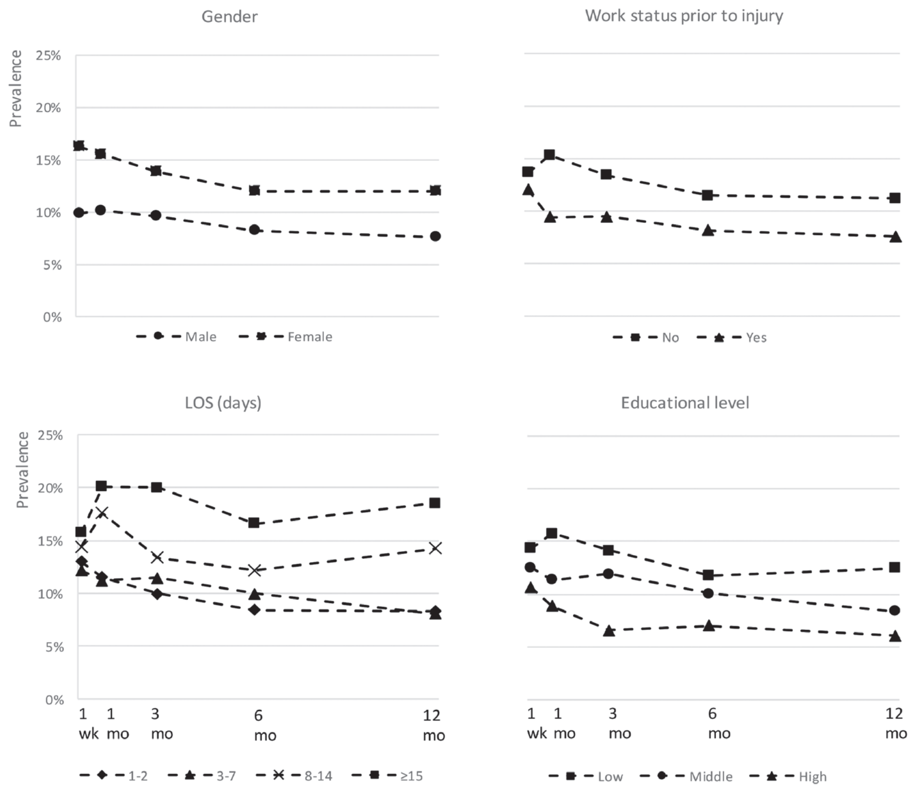


FIGURE 3. Percentage of responders in the first year after injury with poor psychological outcome for the IES, based on gender, pre-injury employment, length of stay (LOS) in hospital and educational level.

SUPPLEMENTAL FILE 2

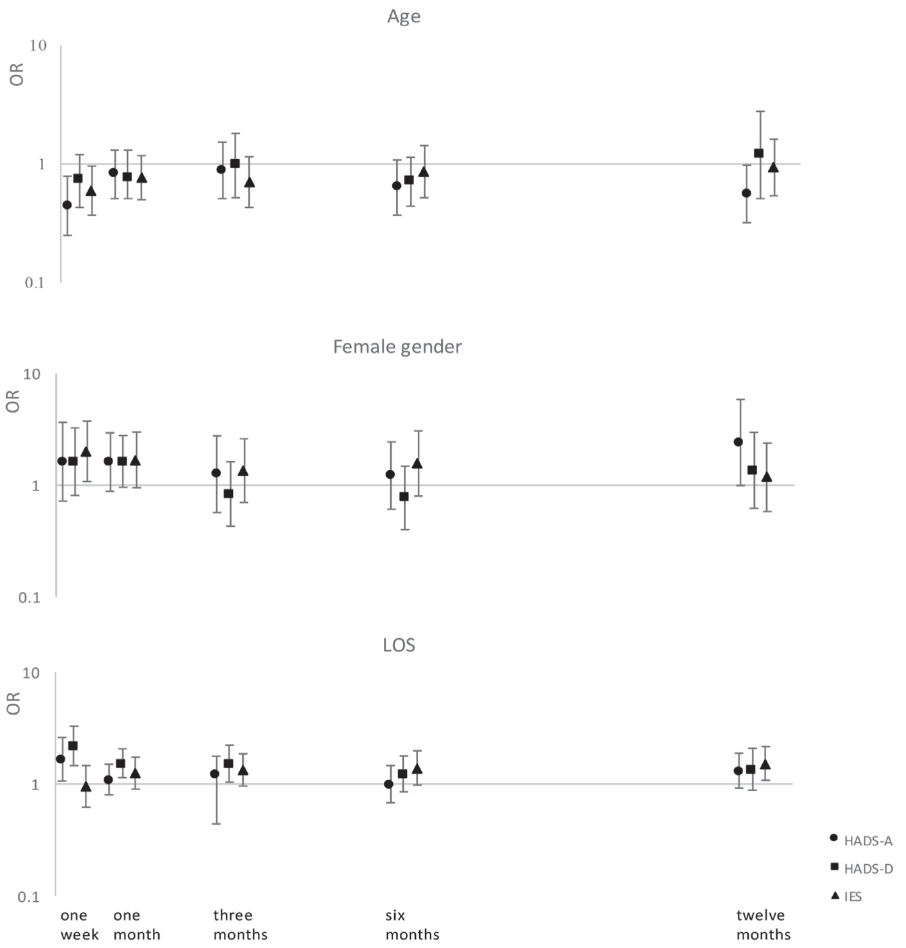
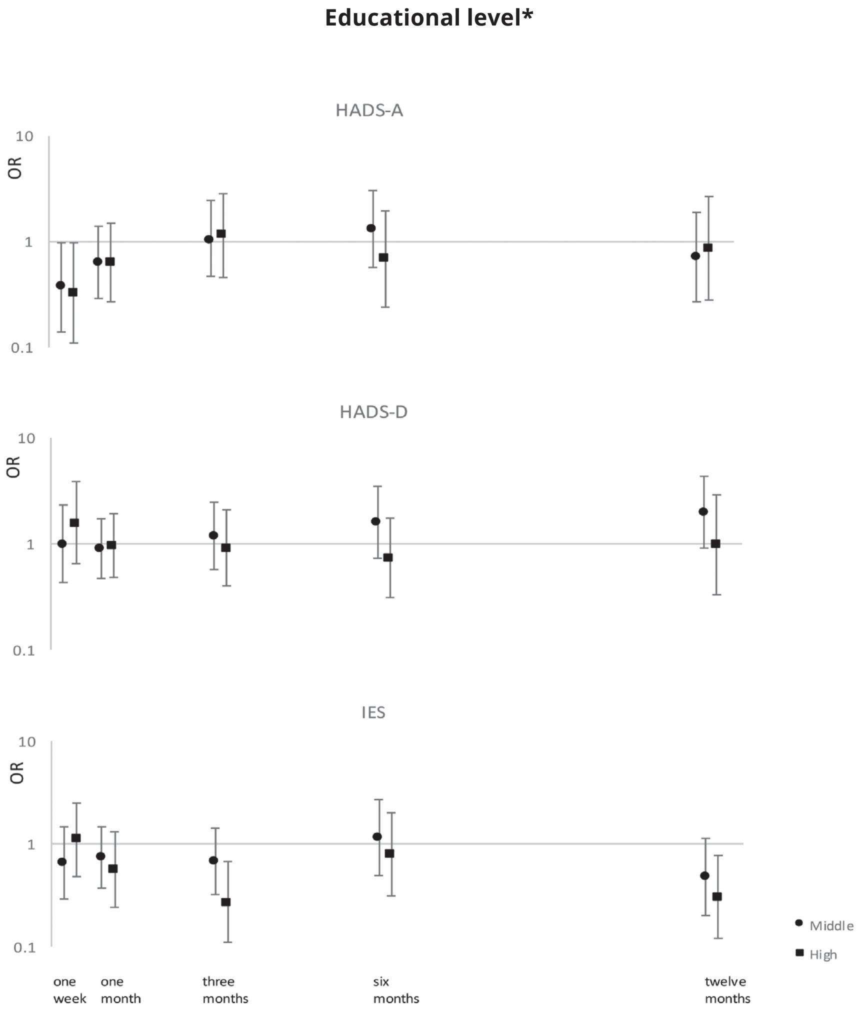


FIGURE 1. OR (95% CI) of the prognostic factors age, female gender and length of stay (LOS) at hospital for each follow-up time point for symptoms of anxiety, depression and post-traumatic stress.



*low educational level = reference category

FIGURE 2. OR (95% CI) for educational level for each follow-up time point for symptoms of anxiety, depression and post-traumatic stress.

10

PROGNOSTIC FACTORS FOR MEDICAL AND PRODUCTIVITY COSTS, AND RETURN TO WORK AFTER TRAUMA

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Submitted.

ABSTRACT

Aim The aim of this study was to determine prognostic factors for medical and productivity costs, and return to work (RTW) during the first two years after trauma in a clinical trauma population.

Methods This prospective multicentre observational study followed all adult trauma patients (≥18 years) admitted to a hospital in Noord-Brabant, the Netherlands from August 2015 through November 2016. Health care consumption, productivity loss and return to work were measured in questionnaires at 1 week, 1, 3, 6, 12 and 24 months after injury. Data was linked with hospital registries. Prognostic factors for medical costs and productivity costs were analysed with log-linked gamma generalized linear models. Prognostic factors for RTW were assessed with Cox proportional hazards model. The predictive ability of the models was assessed with McFadden R^2 (explained variance) and c-statistics (discrimination).

Results A total of 3785 trauma patients (39% of total study population) responded to at least one follow-up questionnaire. Mean medical costs per patient (€9,710) and mean productivity costs per patient (€9,000) varied widely. Prognostic factors for high medical costs were higher age, female gender, spine injury, lower extremity injury, severe head injury, high injury severity, comorbidities, and pre-injury health status. Productivity costs were highest in males, and in patients with spinal cord injury, high injury severity, longer length of stay at the hospital and patients admitted to the ICU. Prognostic factors for RTW were high educational level, male gender, low injury severity, shorter length of stay at the hospital and absence of comorbidity.

Conclusions Productivity costs and RTW should be considered when assessing the economic impact of injury in addition to medical costs. Prognostic factors may assist in identifying high cost groups with potentially modifiable factors for targeted preventive interventions, hence reducing costs and increase RTW rates.

INTRODUCTION

Trauma is considered an important public health problem. Almost 80,000 patients (47 patients per 10,000 inhabitants) were affected by an injury in 2017 in the Netherlands[1]. Furthermore, trauma is a major cause of death, and both short- and long-term disability in young adults[2].

The economic burden of injury consists of both medical and productivity costs. Medical costs are rising the last decades, making it an important societal and political topic[3]. These high costs are mainly due to the high number of (minor) injuries and the increase costs of health care[4]. Productivity costs are based on the period of absence from work. Although most individuals with minor injuries rapidly recover and return to their daily activities, a significant part of the patients suffer long-term disabilities resulting in a long period of absenteeism at work[5].

Previous research on the economic burden of injury has focused mainly on specific injuries or age groups[6-9]. One study focused on health care costs and productivity costs of both minor and severe injuries[10]. Risk groups were identified, based on external cause, injury groupings, age and sex. They concluded that elderly females with hip fracture, young men with traffic injury or soccer injuries and bicycle or motorcycle injuries among all ages are known risk groups for high costs[10]. Previous research on return to work (RTW) provided prognostic factors for patients with traumatic brain injury (TBI)[11,12], patients with work-related injuries[13,14], major trauma[15] and extremity injury[16] and included, among others, the following prognostic factors: age, multiple injuries, injury severity and gender.

The prediction of costs and RTW after injury can enable policymakers to prioritize prevention and quality of care improvement, based on patient characteristics, pre-injury status and comorbidities of the patients. Prevention, intervention strategies and medical practice can target costly patients to reduce the economic burden. To our knowledge, no prediction models for medical costs, productivity costs and RTW in the total clinical trauma population have been developed.

The aim of this study was to determine prognostic factors of medical costs, productivity costs and RTW during the first two years after trauma in the clinical trauma population.

METHODS

Study design

This study was performed with data from the Brabant Injury Outcome Surveillance (BIOS) study[17]. The BIOS study is a prospective observational follow-up cohort study that was approved by the Medical Ethics Committee Brabant (NL50258.028.14) and was registered at ClinicalTrials.gov (NTC02508675). The BIOS study enrolled all adult (≥18 years) trauma patients admitted to a ward or ICU in the region Noord-Brabant, the Netherlands, from August 2015 through November 2016 because of an injury. Exclusion criteria were insufficient knowledge of the Dutch language, no place of residence, or hospital admission due to pathological fractures.

Questionnaires were completed by a proxy if patients were incapable of completing the self-reported questionnaires. All participants or proxy informants signed informed consent. Patients or proxy informants were asked to complete the self-reported questionnaires at 1 week, 1, 3, 6, 12 and 24 months after injury.

Outcome measures

Outcome measures were medical costs (in-hospital and post-hospital costs), productivity costs and RTW.

In-hospital costs involved the treatments and all activities during admission (i.e. emergency department visit, diagnostics, admission to ICU and ward and transport to hospital). In-hospital activities were registered after trauma and were obtained from the trauma registry and hospital registries.

The self-reported questionnaires at 1, 3, 6, 12 and 24 months after injury included the Institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire (iMCQ)[18]. The iMCQ is a non-disease specific questionnaire for measuring post-hospital costs. Patients reported the number of appointments with medical specialists, whether they received home care, and stay or treatment at a medical facility. The questionnaires at 12 and 24 months after injury informed on homecare, GP consult, company doctor consult, psychologist and physiotherapist visit only.

Unit costs of health care activities were retrieved from a cost-reference manual[19]. Costs of diagnostics were based on unit costs from hospital price lists, the Dutch health care authority (NZa) and previous research[20-27]. Health care use was multiplied with the costs per unit. In-hospital costs and post-hospital costs were calculated by multiplying all activities with the corresponding unit price[28].

The self-reported questionnaires also included the iMTA Productivity cost questionnaire (iPCQ)[29,30] to assess RTW and to facilitate calculation of costs concerning productivity loss. Patients were asked about RTW and the period of absenteeism. The costs of productivity loss were calculated with the friction cost method. This method estimates the costs of productivity loss based on an average individual earning of a certain friction period; theoretical time until another unemployed person replaced the individual who is absent. In line with previous research the friction period was set at 85 working days[19]. If working hours of patients were missing, these missing values were replaced with the national mean specified for sex. According to Statistics Netherlands (CBS) (2019)[31] the mean working hours for men were 36 hours per week and the mean working hours for women were 26 hours per week. Productivity loss was calculated by multiplying the missed working hours with the mean Dutch hourly wage rate, also specified for sex[19]. Productivity costs were calculated for the working age population (18-67 years). For the calculation of total mean costs (medical + productivity costs), productivity costs for patients aged >67 and patients without paid employment were equal to 0.

Prognostic factors

Patient characteristics

Possible patient-related prognostic factors for all outcome measures were gender, age, educational level, pre-injury frailty, living situation and pre-injury health status which were collected from the questionnaires. Educational level was categorized in low (primary education or preparatory secondary vocational education, or no diploma), middle (university preparatory education, senior general secondary education or senior secondary vocational education and training), and high (university of applied science or an academic degree). Pre-injury frailty was measured with the Groningen Frailty Index (GFI)[32] at 1 week or 1 month (if patients did not participate at 1 week after injury) in patients aged ≥65. A sum score of 4 or higher for the GFI was considered frail and patients under 65 years were considered not frail. Pre-injury health status was measured with the EQ-5D-3L 1 week or 1 month (if patients did not participate at 1 week after injury). A utility score was calculated by using the Dutch tariffs[33].

Clinical variables

Clinical variables and injury characteristics were collected with the Brabant Trauma Registry (BTR). Data from the BTR was linked with data from the BIOS-study. Possible clinical prognostic factors for medical costs, productivity costs and RTW were the presence of comorbidities, cause of injury (7 categories: home/leisure, traffic, occupational, sport, self-harm, violence or other), Injury Severity Score (ISS), the functional capacity index (FCI), injury classification and Length of Stay (LOS). The FCI and ISS were based on the Abbreviated Injury Scale (AIS) codes (AIS-90, update 2008)[34].

AIS was used to create injury group classifications representing the most common types of injuries. In total, 14 injury groups were created: 3 lower extremity (pelvic injury, hip fracture, and tibia fracture / complex foot fracture or distal/shaft femur fracture), 2 upper extremity (shoulder and upper arm injury, and radius, ulna or hand fracture), 2 head (AIS-head≤2, and AIS-head≥3), 1 face, 2 Thorax (thorax injury, and rib fracture), 2 abdomen (AIS-abdomen≤2, and AIS-abdomen≥3) and 2 spine (spinal cord injury or brachial plexus lesion, and stable vertebral fracture or disc injury) injury groups. Patients who suffered multiple injuries were classified in multiple injury group classifications. LOS was not considered as prognostic factor for in-hospital costs because LOS was directly used to calculate medical costs.

Statistical analysis

Results are reported according to the TRIPOD guidelines[35]. Analyses were performed in SPSS V.24 (statistical package for social sciences, Chicago, Illinois, USA) and R version 3.4.2 (R foundational for statistical computing, Vienna, Austria).

Patient characteristics were compared between responders and non-responders, with Mann-Whitney U tests and Chi-square tests for continuous and categorical variables respectively. Mean, median and interquartile range (IQR) of total costs, medical costs and productivity costs were calculated.

Missing baseline characteristics were imputed according to multiple imputation by using the Multivariate Imputations by Chained Equations (MICE) procedure with 15 imputations and 5 iterations[36]. The imputation model included baseline characteristics, injury characteristics and summary scores of the follow-up questionnaires. Missing outcome values were excluded from analyses (n=264 for medical costs).

Prognostic factors for medical costs and productivity costs were assessed with with log-linked gamma generalized linear models (GLM). The predictive ability was measured with explained variance (McFadden pseudo-R^2). The relative difference in mean costs (exp[parameter estimate]) with 95% Confidence Interval (CI) were reported for the three models.

Prognostic factors for RTW were assessed with a Cox proportional hazards model. The analyses for RTW and productivity costs included patients aged ≤67 years who had paid employment prior to injury (n=1236). The period of absenteeism (weeks) was set as time variable and RTW (1=RTW, 0=no RTW) as the dependent variable. The proportional hazards assumption (the ratio of the hazards for patients was constant over time) was checked visually with Kaplan-Meier curves. Hazard Ratios (HR) and 95% CI were reported. The predictive ability of the model was assessed with the C-statistic (a measure of goodness of fit for binary outcomes). A p-value of <0.05 was considered statistically significant.

TABLE 1. Patient characteristics for the research population; responders and non-responders

	Responders to BIOS[a]	**Non-responders**	**p-value***
n	3785	5989	
Mean age (SD)	64.2 (18.9)	64.4 (22.5)	0.529
Females (n)	1911 (50.5%)	3127 (52.2%)	0.097
Median ISS (IQR)	5 (4-9)	5 (2-9)[b]	<0.001
Mean ISS (SD)	6.6 (5.0)	6.2 (4.7)[b]	
Median LOS (IQR)	4 (2-8)	4 (2-8)[c]	0.537
Admission to ICU (n)	284 (7.5%)	366 (6.1%)	<0.01
Injury classification (n)			
Pelvic injury	250 (6.6%)	194 (6.5%)	
Hip fracture	979 (25.9%)	1386 (23.1%)	
Tibia, complex foot or femur fracture	443 (11.7%)	631 (10.5%)	
Shoulder and upper arm injury	354 (9.4%)	536 (8.9%)	
Radius, ulna or hand fracture	243 (6.4%)	348 (5.8%)	
Head injury with AIS ≤ 2	1013 (26.8%)	1754 (29.3%)	
Head injury with AIS ≥ 3	143 (3.8%)	224 (3.7%)	
Facial injury	196 (5.2%)	356 (5.9%)	
Thoracic injury	161 (4.3%)	199 (3.3%)	
Rib fracture	421 (11.1%)	518 (8.6%)	
Abdominal injury AIS ≤ 2	74 (2.0%)	102 (1.7%)	
Abdominal injury AIS ≥ 3	29 (0.8%)	37 (0.6%)	
Spinal cord injury	18 (0.5%)	19 (0.3%)	
Stable vertebral fracture or disc injury	238 (6.3%)	312 (5.2%)	

[a] missing items for responders to the BIOS questionnaires were imputed
[b] missing values: 406
[c] missing values: 456
*Student's t-test with unequal variance for age, Mann-Whitney U tests for ISS and LOS and Chi-square tests for gender and admission to ICU.
Abbreviations: AIS, Abbreviated Injury Scale; ICU, Intensive Care Unit; IQR, Inter Quartile Range; ISS, Injury Severity Score; n, number; SD, Standard Deviation

RESULTS

Patient and study characteristics

A total of 3785 trauma patients (39% of total study population, n=9774) completed at least one follow-up questionnaire on health care use and RTW in the context of the BIOS-study (Supplemental Figure 1). Responders had a mean age (SD) of 64.2 (18.9) years and 1911 (50.5%) were female (Table 1). The median ISS (IQR) was 5 (4-9) and the median (IQR) length of stay at the hospital was 4 (2-8) days.

Responders (n=3785) were more often admitted to the intensive care unit (ICU), and were more severely injured, according to the ISS (median [IQR] 5 [4-9] and 5 [2-9] respectively) compared to the non-responders (n=5989).

Costs of trauma

Mean total costs per respondent were €12,970 (median: €7,290, IQR: €4,010-€15,960) (Table 2), of which medical costs comprised 75% and productivity costs comprised 25%. Highest mean total costs and medical costs per patient based on injury classifications were found in patients with spinal cord injury (mean: €36,720, 67% medical costs and 33% productivity costs [median €20,690, IQR: €10,200-€69,070]), followed by patients with severe abdominal injury (mean: €31,540, 72% medical costs and 28% productivity costs [median €18,200, IQR: €9,040-€44,390]) (Figure 1a). Patients with ISS>15 also showed high mean medical and high mean productivity costs per respondent (€24,380 and €18,770 respectively).

Mean medical costs per patient were €9,710 (median: €4,900, IQR: €2,780-€9,300) All variables showed significant associations with medical costs in the univariable GLM (Supplemental Table 1). Higher age was independently associated with increased medical costs in the multivariable GLM (Table 3). Medical costs were on average 1.77 (95% CI: 1.48, 2.12) times higher in patients aged ≥75 compared to patients aged 18-44. Pelvic injury, tibia, complex foot or femur fracture, severe head injury, severe abdominal injury, spinal cord injury or stable vertebral fracture/disc injury were associated with increased medical costs. Besides, female gender, higher ISS and ≥2 comorbidities were prognostic factors for higher medical costs compared to male gender, low ISS and no comorbidities respectively. McFadden R^2 of the multivariable model was 31,5%.

TABLE 2. mean and median (IQR) total costs in euros (€) of medical and productivity loss costs in the clinical trauma in population in the first two year after trauma.

	Total costs[c] (€) N=3172		**Medical costs (€) N=3521**		**Productivity loss costs[a] (€) N=1032**	
	Mean	Median (IQR)	Mean	Median (IQR)	Mean	Median (IQR)
Total study population	12970	7290 (4010-15960)	9710	4900 (2780-9300)	9000	7410 (2770-14900)
Age (years)						
18-44	13560	9290 (4460-18620)	6040	2800 (1910-5450)	8630	6880 (2640-14970)
45-64	14110	9820 (4880-19600)	7160	4000 (2480-7100)	9280	7750 (3300-14970)
65-74[b]	9020	5060 (3120-9060)	8780	4980 (3060-8730)	7130	3770 (2120-10080)
≥75	14140	7090 (4120-15590)	14140	7090 (4120-15590)		
Gender						
Male	12900	7180 (3860-18540)	8090	4070 (2380-7740)	10480	9660 (2940-16760)
Female	13020	7360 (4130-14520)	11310	5700 (3320-11150)	6490	6160 (2640-10080)
Educational level						
Low	13090	7210 (3980-15490)	11020	5650 (3220-11510)	10590	9880 (4500-16760)
Middle	12840	7440 (3980-16800)	8010	4140 (2390-7510)	9590	8620 (3090-16760)
High	12780	7300 (4070-15180)	8570	4050 (2460-7410)	6900	5200 (2150-10850)
Injury classifications						
Pelvic injury	19620	11620 (6340-16740)	16010	8820 (4750-17570)	14110	14900 (9360-18620)
Hip fracture	15400	8200 (4850-18130)	14230	6920 (4360-14460)	9670	9170 (5440-14970)
Tibia, complex foot or femur fracture	15870	10220 (5220-21490)	11330	5860 (3610-11210)	11100	10080 (4470-16760)
Shoulder and upper arm injury	12870	8630 (4980-16540)	9660	5700 (3130-9330)	9110	7750 (3520-14180)
Radius, ulna or hand fracture	14560	8780 (4530-20400)	9550	4840 (2600-10090)	10590	9300 (3740-16760)
Head injury AIS ≤ 2	9970	5230 (3010-11990)	7060	3430 (2180-6700)	7340	5240 (2040-12440)
Head injury AIS ≥ 3	17620	8650 (5440-21500)	14450	6660 (4020-15420)	12680	13930 (6100-17180)
Facial injury	13260	6590 (3270-15100)	8660	3530 (2260-7980)	8830	6200 (2650-12400)
Thoracic injury	18450	13600 (6500-22610)	12520	6820 (4100-11960)	12200	10970 (5990-16760)
Rib fracture	14570	8670 (4730-17770)	10020	5400 (3150-9260)	10420	9240 (4230-16760)
Abdominal injury AIS ≤ 2	15810	8430 (4010-15870)	11480	4970 (2690-13020)	8290	6880 (2730-12460)
Abdominal injury AIS ≥ 3	31540	18200 (9040-44390)	22660	10080 (5730-33460)	12640	10840 (5910-18620)
Spinal cord injury	36720	20690 (10200-69070)	24540	11870 (5460-32570)	14640	16760 (7750-18620)
Stable vertebral fracture or disc injury	18110	12460 (5710-22360)	12350	6240 (3430-11730)	12370	12400 (7450-16760)

TABLE 2. Continued.

	Total costs[c] (€) N=3172		Medical costs (€) N=3521		Productivity loss costs[a] (€) N=1032	
	Mean	Median (IQR)	Mean	Median (IQR)	Mean	Median (IQR)
ISS						
1-3	7830	4360 (2610-8560)	5160	2670 (1900-4720)	5590	2950 (1550-8370)
4-8	11980	7380 (3970-15660)	7870	4210 (2570-7760)	9650	8510 (3490-15510)
9-15	15090	8570 (4950-18560)	12670	6580 (4130-12090)	10610	9900 (5450-16760)
>15	24380	16660 (8220-32910)	18770	9780 (5830-22380)	13460	13940 (8860-18620)
External cause						
Home and leisure	13230	7280 (4020-15130)	11300	5610 (3290-11250)	8780	7580 (3050-13860)
Traffic	11930	6910 (3900-15400)	8090	4270 (2440-7740)	8210	6600 (2650-13100)
Occupational	20370	19920 (4730-27240)	7830	3450 (2100-7600)	14640	7450 (16760-16760)
Sport	10980	7840 (4130-16020)	4500	3090 (2190-5020)	8320	6840 (2660-13530)
Self-harm	11830	9290 (3170-20770)	7850	6680 (3150-13100)	7600	7000 (1340-14430)
Violence	10460	5240 (3990-9240)	7140	3250 (1530-5410)	7880	5070 (1980-12470)
Other	11500	6110 (3570-18270)	7900	3710 (1950-11740)	6470	4980 (1160-12450)

[a] Productivity loss costs were only assessed for patients aged 18-67 years with paid employment before injury (N=1236, 204 missing productivity loss costs).
[b] Category changed to 65-67 for productivity loss costs.
[c] Total costs were only calculated for patients with both known medical costs and productivity loss costs.
Abbreviations: AIS, Abbreviated Injury Scale; CI, Confidence Interval; HS, Health Status; ISS, Injury Severity Score; LOS, Length of Stay; NA, Not Applicable.

Average productivity costs per respondent were €9,000 (median: €7,410, IQR: €2,770-€14,900) within the working population. Highest mean productivity costs per patient were found in patients with spinal cord injury (€14,640, median: €16760, IQR: €7,750-€18,620) and pelvic injury (€14,110, median: €14,900, IQR: €9,360-€18,620) (Figure 1b). Mean productivity costs were also high in patients who were admitted due to occupational injury (mean €14,640 per patient) and in patients with ISS>15 (mean: €13,460 per patient).

Number of comorbidities, pre-injury health status and age showed not to be associated with productivity costs in the univariable GLM (Supplemental Table 1). In contrast with the univariable GLM, lower age showed to be associated with higher productivity costs in the multivariable GLM. Prognostic factors for increased productivity costs were male gender, low educational level, stable vertebral fracture/disc injury, higher ISS, higher LOS, occupational injury and admission to the ICU in the multivariable GLM (Table 3). McFadden R^2 of the multivariable model was 19,8%.

RTW

Within the working age population (18-67 years, n=1964) a total of 1,236 patients (63%) reported to have paid employment prior to injury, of which 131 patients (11%) had a missing value for time to event. For patients with known outcome (n=1105), median survival weeks was 8 (IQR: 2.5-17.7). A total of 180 patients were censored due to loss to follow-up (Figure 2). At 12 months after injury, 82% (n=905) of the patients with known outcome returned to work and 5% (n=59) did not return to work.

Age, gender, number of comorbidities and pre-injury health status showed no significant association with RTW in the univariable Cox regression analyses (Supplemental Table 1). Prognostic factors for RTW in the multivariable analyses were higher age (HR: 1.48 [95% CI: 0.88, 2.49]), male gender (HR: 1.22 [95% CI: 1.05, 1.41]), higher educational level (HR: 1.27 [95% CI: 1.06, 1.53] for middle and HR: 2.10 [95% CI: 1.74, 2.55] for high educational level compared to low educational level) and patients with a sport injury (HR: 1.31 [95% CI: 1.06, 1.63] compared to patients with home and leisure injury) (Table 3). Injury classifications with decreased probability on RTW were tibia, complex foot or femur fracture (HR: 0.70 [95% CI: 0.56, 0.88]) and stable vertebral fracture/disc injury (HR: 0.66 [95% CI: 0.50, 0.87]). Besides, higher ISS and longer LOS showed a decreased probability on RTW. C-statistic of the multivariable Cox-regression model was 0.700 (95% CI: 0.682, 0.718).

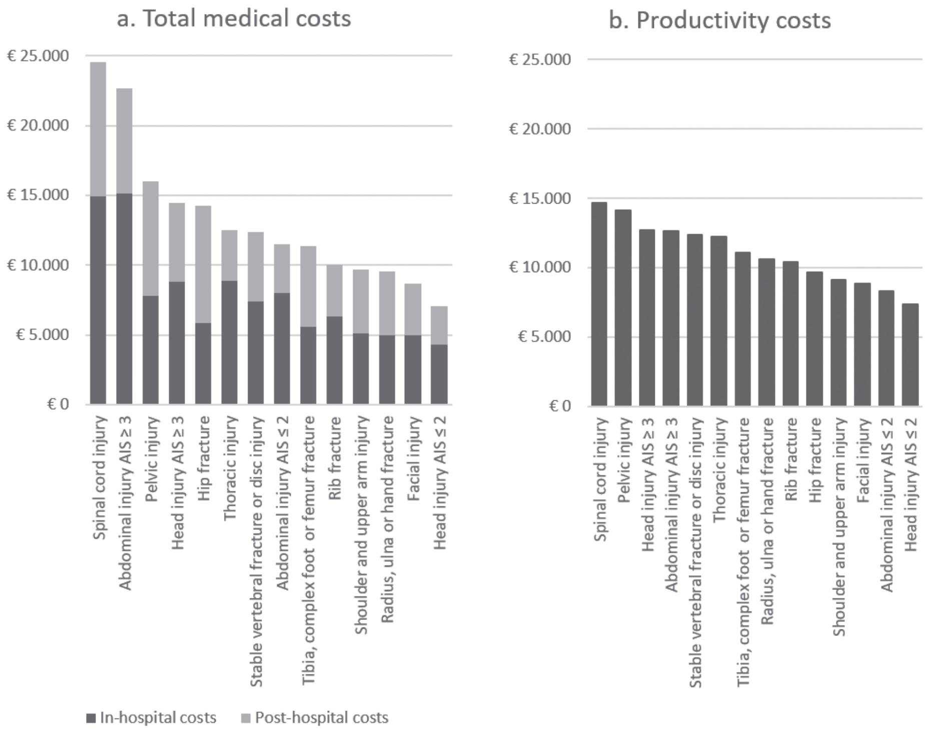


FIGURE 1ab. Medical and productivity costs (€) for the most common injury classifications ordered from high to low costs.

TABLE 3. The relative difference with multivariable generalized linear models for medical costs and productivity costs and multivariable cox proportional hazards model for RTW in the first two years after trauma.

	Generalized linear models		**Cox proportional hazards model**
	Medical costs N=3109[d]	Productivity costs N=939[e,f]	RTW N=1015[e,g]
	Exp(E) (95% CI)	Exp(E) (95% CI)	Hazard Ratio (95% CI)
Age (years)			
18-44	Ref	Ref	Ref
45-64	1.16 (1.00, 1.34)	0.96 (0.86, 1.07)	1.08 (0.92, 1.26)
65-74[b]	1.25 (1.05, 1.48)	0.62 (0.45, 0.87)	1.48 (0.88, 2.49)
≥75	1.77 (1.48, 2.12)	NA	NA
Female gender	1.13 (1.03, 1.25)	0.68 (0.62, 0.76)	0.82 (0.71, 0.95)
Educational level			
Low[a]	Ref	Ref	Ref
Middle	0.92 (0.82, 1.03)	0.93 (0.82, 1.05)	1.27 (1.06, 1.53)
High	1.07 (0.94, 1.21)	0.71 (0.62, 0.80)	2.10 (1.74, 2.55)
Injury classifications			
Pelvic injury	2.01 (1.66, 2.44)	1.18 (0.95, 1.46)	0.84 (0.61, 1.15)
Hip fracture	1.19 (0.99, 1.44)	1.02 (0.82, 1.27)	0.87 (0.63, 1.20)
Tibia, complex foot or femur fracture	1.58 (1.34, 1.86)	1.14 (0.98, 1.33)	0.70 (0.56, 0.88)
Shoulder and upper arm injury	1.12 (0.95, 1.32)	1.00 (0.86, 1.17)	0.98 (0.78, 1.23)
Radius. ulna or hand fracture	1.00 (0.83, 1.21)	1.14 (0.96, 1.36)	0.80 (0.62, 1.02)
Head injury with AIS ≤ 2	0.86 (0.76, 0.97)	0.87 (0.77, 0.98)	1.04 (0.88, 1.23)
Head injury with AIS ≥ 3	1.58 (1.18, 2.12)	1.06 (0.78, 1.46)	0.87 (0.55, 1.39)
Facial injury	1.12 (0.91, 1.38)	0.92 (0.75, 1.11)	0.92 (0.70, 1.22)
Thoracic injury	1.07 (0.83, 1.38)	0.93 (0.74, 1.17)	1.09 (0.78, 1.53)
Rib fracture	1.02 (0.86, 1.21)	0.99 (0.84, 1.17)	1.20 (0.94, 1.51)
Abdominal injury AIS ≤ 2	0.93 (0.66, 1.32)	0.79 (0.59, 1.04)	1.62 (1.08, 2.42)
Abdominal injury AIS ≥ 3	1.81 (1.06, 3.09)	0.85 (0.58, 1.25)	1.54 (0.86, 2.78)
Spinal cord injury	2.62 (1.34, 5.11)	1.28 (0.68, 2.40)	0.66 (0.28, 1.59)
Stable vertebral fracture or disc injury	1.29 (1.06, 1.57)	1.39 (1.15, 1.67)	0.66 (0.50, 0.87)
ISS			
1-3	Ref	Ref	Ref
4-8	1.11 (0.96, 1.29)	1.36 (1.17, 1.57)	0.72 (0.59, 0.89)
9-15	1.50 (1.25, 1.80)	1.40 (1.15, 1.70)	0.62 (0.47, 0.82)
>15	1.89 (1.37, 2.60)	1.27 (0.91, 1.77)	0.67 (0.42, 1.07)
Length of stay at hospital (days)	NA[c]		
1-2		Ref	Ref
3-7		1.25 (1.10, 1.43)	0.74 (0.61, 0.89)
8-14		1.50 (1.24, 1.81)	0.53 (0.40, 0.70)
>14		1.54 (1.15, 2.08)	0.41 (0.26, 0.65)
External cause			
Home and leisure[a]	Ref	Ref	Ref
Traffic	0.97 (0.87, 1.09)	0.97 (0.86, 1.09)	1.03 (0.87, 1.23)
Occupational	1.08 (0.86, 1.36)	1.30 (1.08, 1.57)	0.79 (0.60, 1.04)
Sport	0.68 (0.56, 0.83)	0.91 (0.78, 1.06)	1.31 (1.06, 1.63)
Self-harm	0.96 (0.40, 2.32)	0.66 (0.31, 1.40)	0.89 (0.27, 2.89)
Violence	1.08 (0.69, 1.69)	0.95 (0.65, 1.40)	1.22 (0.69, 2.14)
Other	0.95 (0.58, 1.56)	0.88 (0.53, 1.45)	1.41 (0.69, 2.86)
ICU admission	NA[c]	1.27 (1.02, 1.58)	0.82 (0.59, 1.14)

TABLE 3. Continued.

	Generalized linear models		**Cox proportional hazards model**
	Medical costs N=3109[d]	Productivity costs N=939[e,f]	RTW N=1015[e,g]
	Exp(E) (95% CI)	Exp(E) (95% CI)	Hazard Ratio (95% CI)
Number of comorbidities	Ref	Ref	Ref
0[a]	1.11 (0.98, 1.24)	0.97 (0.86, 1.09)	1.05 (0.88, 1.25)
1	1.35 (1.18, 1.54)	1.01 (0.86, 1.20)	0.92 (0.71, 1.18)
≥2			
Frail	1.06 (0.91, 1.24)	NA[c]	NA[c]
Pre-injury health status	0.63 (0.49, 0.82)	0.90 (0.58, 1.40)	1.69 (0.86, 3.31)
Intercept	5102.99 (3761.04, 6923.74)	8370.42 (5342.99, 13113.25)	NA
McFadden R²	**31.5%**	**19.8%**	**NA**
C-statistic (95% CI)	**NA**	**NA**	**0.700 (0.682. 0.718)**

[a]Reference category of categorical variable. [b]Category changed to 65-67 for productivity loss costs and RTW. [c]variables were not considered as predictors. [d]missing values: 23 Number of comorbidities, 389 Pre-injury health status, 264 medical costs. [e]working population N=1236. [f]missing values: 3 Nr of comorbidities, 90 Pre-injury health status, 204 missing productivity loss costs. [f]missing values: 18 status RTW, 113 time to event, 87 Pre-injury health status, 3 Number of comorbidities.

Abbreviations: AIS, Abbreviated Injury Scale; CI, Confidence Interval; ISS, Injury Severity Score; NA, Not Applicable.

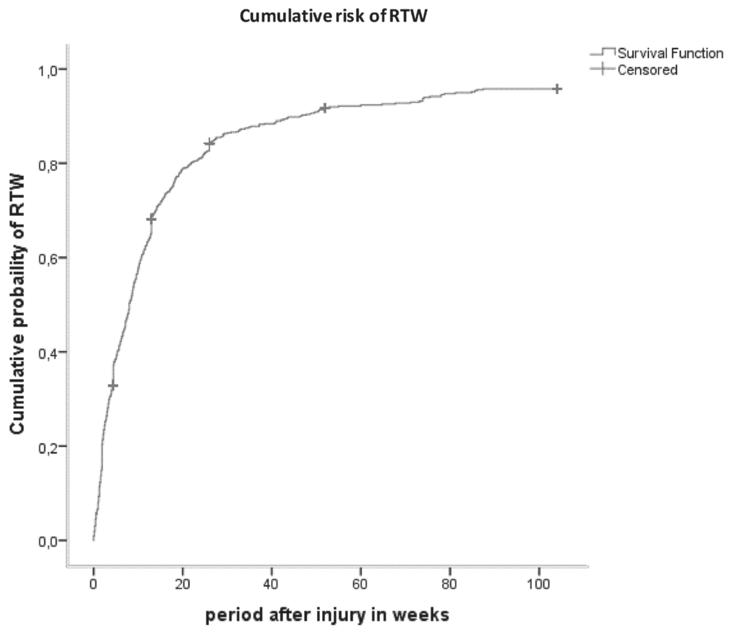


FIGURE 2. Cumulative probability of RTW after trauma in the working age study population during 24 months of follow-up (n=1105).

DISCUSSION

This study explored prognostic factors of medical costs, productivity costs and RTW after trauma during 24 months of follow-up. A stable vertebral fracture or disc injury and higher ISS were independently associated with higher medical costs, higher productivity costs and longer period of absenteeism at work. Although female gender and higher age were prognostic factors for higher medical costs, they were also both associated with lower productivity costs after adjustment for confounding. A total of 5% of the patients with paid employment did not return to work at 12 months after injury. Important prognostic factors for RTW were higher educational level, higher age, low ISS and low LOS.

Costs

In line with previous studies, higher age and female sex were associated with higher medical costs[10,37]. No clear trend was found between mean total costs per respondent and age, probably due to a different pattern in productivity costs among age categories. Other variables such as high ISS, specific body regions (abdomen, spine and brain injury) and LOS were also identified as prognostic factors for medical costs in a review[38].

Female sex is a prognostic factor for higher medical costs, but is also associated with lower productivity costs. The lower productivity costs might be explained by the fact that women more often work part-time compared to men in the Netherlands[39].
A Dutch study on the economic burden of injury reported the highest health care costs for hip fracture patients (€20,000 per patient)[10]. Although our study showed that hip fractures were in the top 5 of high medical costs (€14,230 per patient), several other injury classifications were considerably more expensive. However, the prevalence of hip fractures in the injury cohort is high, so this could have more impact on health care consumption and costs compared to the relatively low prevalence of more costly injuries (e.g. spinal cord injury or abdominal injury with AIS≥3).

RTW

A previous study on RTW in major trauma patients also found comorbidities, pre-injury disability, and presence of spinal cord injury as prognostic factors for no RTW[40]. They also stated that older age was a prognostic factor for no RTW, in contrast to our results. This could be explained by different study population (major trauma vs all trauma).
Previous research found an association between unemployment and poor recovery[41,42]. This association is probably interchangeable; patients who experience for example pain or distress after trauma are more likely for no RTW and patients who are back at work soon after their injury, have a better recovery[43]. These factors can be influenced by tailored interventions. Future research should focus on these specific modifiable physical complaints and psychological distress after trauma and the medical costs and RTW. Interventions can help with the recovery, which could result in lower medical costs and sooner RTW.
Our study showed that the probability of RTW decreased over time, but did not stabilize up to 24 months after injury. In contrast with RTW rates in moderate to severe TBI patients[44], in which RTW rates remained stable between 1 and 10 years after injury, RTW rates could still increase with time in our study population. A longer follow-up is necessary to conclude which patients remain unemployed.

Strengths and limitations

A strength of this study is the large study population with six follow-up measurement, including short-term (1 week) and long-term (two years). This study design allows to calculate costs and RTW in detail and could give an overview of costs and RTW in the total clinical trauma population. Furthermore, to our knowledge, this was the first attempt to develop prediction models for the total trauma population for both medical as productivity costs and also RTW. Productivity costs were based on the friction cost method. This method does not discriminate between patients who are 90 days absent at work or 2 years absent at work. Although there are no extra productivity costs, it does affect society and the patient. Therefore, a strength of this study is the addition of RTW (in days) up to 2 years after injury as outcome.
An important limitation in this study is that educational level is not taken into account for the calculation of productivity costs. Although different average wages were used for males and females, no distinction was made between average wages of the different educational levels. The analyses showed that high educational level was a prognostic factor for RTW, indicating that patients with high educational level were sooner back at work after trauma compared to patients with low educational level. However, because the wages per hour were similar to patients with low educational level, the significant result of high educational level as prognostic factor for lower productivity costs probably only indicates this shorter period of absenteeism at work instead of actually lower productivity costs. Future studies should assess this with average wages that are corrected for educational level.
Another limitation of this study is the use of self-reported questionnaires which are prone to recall-bias. Patients were asked about care consumption and RTW over the period between the previous questionnaire and the current questionnaire. This period increased from 1 week for the first questionnaire to 12 months for the last follow-up questionnaire.
Next, the primary aim of the BIOS-study is to determine physical and psychological outcome after injury. This means that only survivors of an injury were included in the BIOS-study. Patients who did not survive until one week after trauma were excluded and costs were not calculated (n=219, 2% of the BIOS-study population).

Last, patients who were fully recovered were probably more likely to be lost to follow-up and differences between responder and non-responders indicate that more severely injured patients participated. This non-response bias could result in an overestimation of both medical and productivity costs.

Implications

The findings of this study showed high medical costs, high productivity costs and long absenteeism from work. An intervention to help patients to earlier return to work after sustaining a trauma could reduce productivity costs and decrease the period of absenteeism at work. Considering the differences in prognostic factors for medical costs and productivity costs, it is important that medical costs and productivity costs are both taken into account and analysed separately. The identified prognostic factors in this study were all easy to detect patient and injury characteristics. This enables health practitioners and policy makers to inform patients and induce prevention interventions to reduce medical costs and productivity costs.

Conclusion

Although many prognostic factors resulted in both higher medical costs as higher productivity costs, some factors showed differential effects. Productivity costs and RTW should be considered when assessing the economic impact of injury in addition to medical costs. Prognostic factors may assist in identifying high cost groups with potentially modifiable factors for targeted preventive interventions, hence reducing costs and increase RTW rates.

REFERENCES

1. Landelijke Netwerk Acute Zorg (LNAZ). Annual report of the dutch trauma registry: Traumazorg in beeld 2013 - 2017. 2018.
2. World Health Organization. Injuries and violence: The facts 2014. 2014;WO700(August).
3. Xu K, Soucat A, Kutzin J, et al. Public spending on health: A closer look at global trends. 2018;WHO/HIS/HGF/HFWorkingPaper/18.3.
4. McClure RJ, Douglas RM. The public health impact of minor injury. *Accid Anal Prev.* 1996;28(4):443-451.
5. Clay FJ, Newstead SV, Watson WL, McClure RJ. Determinants of return to work following non-life-threatening acute orthopaedic trauma: A prospective cohort study. *J Rehabil Med.* 2010;42(2):162-169.
6. Hartholt KA, van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: Injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* 2011;71(3):748-753.
7. Scholten AC, Polinder S, Panneman MJ, Van Beeck EF, Haagsma JA. Incidence and costs of bicycle-related traumatic brain injuries in the netherlands. *Accid Anal Prev.* 2015;81:51-60.
8. de Putter CE, Selles RW, Polinder S, Panneman MJ, Hovius SE, van Beeck EF. Economic impact of hand and wrist injuries: Health-care costs and productivity costs in a population-based study. *J Bone Joint Surg Am.* 2012;94(9):e56.
9. Polinder S, Iordens GI, Panneman MJ, et al. Trends in incidence and costs of injuries to the shoulder, arm and wrist in the netherlands between 1986 and 2008. *BMC Public Health.* 2013;13(1):531.
10. Polinder S, Haagsma J, Panneman M, Scholten A, Brugmans M, Van Beeck E. The economic burden of injury: Health care and productivity costs of injuries in the Netherlands. *Accid Anal Prev.* 2016;93:92-100.
11. Wäljas M, Iverson GL, Lange RT, et al. Return to work following mild traumatic brain injury. *J Head Trauma Rehabil.* 2014;29(5):443-450.
12. Shames J, Treger I, Ring H, Giaquinto S. Return to work following traumatic brain injury: Trends and challenges. *Disabil Rehabil.* 2007;29(17):1387-1395.
13. Berecki-Gisolf J, Clay FJ, Collie A, McClure RJ. Predictors of sustained return to work after work-related injury or disease: Insights from workers' compensation claims records. *J Occup Rehabil.* 2012;22(3):283-291.
14. He Y, Hu J, Yu ITS, Gu W, Liang Y. Determinants of return to work after occupational injury. *J Occup Rehabil.* 2010;20(3):378-386.
15. Vles WJ, Steyerberg EW, Essink-Bot M, Van Beeck EF, Meeuwis JD, Leenen LP. Prevalence and determinants of disabilities and return to work after major trauma. *J Trauma.* 2005;58(1):126-135.
16. MacKenzie EJ, Bosse MJ, Kellam JF, et al. Early predictors of long-term work disability after major limb trauma. *J Trauma.* 2006;61(3):688-694.
17. de Jongh MA, Kruithof N, Gosens T, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: The brabant injury outcome surveillance (BIOS) study. *Inj Prev.* 2017;23(1):59-2016-042032. Epub 2016 May 6.
18. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Handleiding iMTA medical cost questionnaire (iMCQ). *Rotterdam: iMTA, Erasmus Universiteit Rotterdam.* 2013.
19. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. *Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg.In opdracht van Zorginstituut Nederland.Geactualiseerde versie.* 2015.
20. Upatising B, Wood DL, Kremers WK, et al. Cost comparison between home telemonitoring and usual care of older adults: A randomized trial (tele-ERA). *Telemedicine and e-Health.* 2015;21(1):3-8.

21. Erasmus MC. Passantenprijslijst 2016. https://www6.erasmusmc.nl/cs-patientenzorg/2419534/2419543/3956735/5250821/Internetversie_passantenprijslijst_2016_v3.pdf?view=active. Updated 2016. Accessed 07/24, 2019.
22. Elkerliek. Standaard prijslijst overige zorgproducten. https://www.elkerliek.nl/elkerliek.nl/home/Passantanprijslijst%20Overige%20Zorgproducten%2001042013%20tm%2030062013.pdf. Updated 2013. Accessed 07/24, 2019.
23. Nederlandse Zorgautoriteit. BRCU-2015 bijlage 2 medisch specialisteische behandelingen en tarieven 2011. https://puc.overheid.nl/nza/doc/PUC_11602_22/. Updated 2015. Accessed 07/24, 2019.
24. Nederlandse Zorgautoriteit. Nederlandse zorgautoriteit zorgapplicatie. https://zorgproducten.nza.nl/ZoekZorgproduct.aspx. Updated 2017. Accessed 07/24, 2019.
25. Nederlandse Zorgautoriteit. Tarievenlijst eerstelijnsdiagnostiek. https://docplayer.nl/13384312-Tarievenlijst-eerstelijnsdiagnostiek-bijlage-1-bij-tariefbeschikking-tb-cu-7078-02-van-1-juni-2014.html. Updated 2014. Accessed 07/24, 2019.
26. Rivas. Bio-impedantiemeting. https://www.rivas.nl/voeding-leefstijl/gezondheidsmetingen/cursus/bio-impedantiemeting/?tx_roqcursussenactiviteiten_cursussen%5Baction%5D=show&tx_roqcursussenactiviteiten_cursussen%5Bcontroller%5D=Course&cHash=094076003728918c33f5113ca52651f1. Updated 2019. Accessed 07/24, 2019.
27. Zeelandcare. Passanten prijslijst DBC-OVP zorgproducten. https://zeelandcare.com/sites/default/files/Prijslijst%20Passanten%20DBC-OVP%20zorgproducten%202018.pdf. Updated 2018. Accessed 07/24, 2019.
28. Geraerds AJLM, Haagsma JA, de Munter L, Kruithof N, de Jongh MAC, Polinder S. Medical and productivity costs after trauma: Comparison across injury severity groups. *Manuscript submitted for publication*. 2019.
29. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Handleiding iMTA productivity cost questionnaire (iPCQ). *Rotterdam: iMTA, Erasmus Universiteit*. 2013.
30. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA productivity cost questionnaire: A standardized instrument for measuring and valuing health-related productivity losses. *Value Health*. 2015;18(6):753-758.
31. CBS. Working population; working time. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/82647NED/table?dl=17FC9. Updated 2019. Accessed 07/24, 2019.
32. Steverink N, Slaets J, Schuurmans H, van Lis M. Measuring frailty: Developing and testing the GFI (groningen frailty indicator). *Gerontologist*. 2001;41(Special Issue 1):236-237.
33. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The dutch tariff: Results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ*. 2006;15(10):1121-1132.
34. Gennarelli TA, Wodzin E. *Abbreviated injury scale 2005: Update 2008*. Russ Reeder; 2008.
35. Moons KG, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and ElaborationThe TRIPOD statement: Explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.
36. van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE. 1999;PG/VGZ/99.054.
37. Meerding WJ, Mulder S, Van Beeck EF. Incidence and costs of injuries in the netherlands. *Eur J Public Health*. 2006;16(3):271-277.
38. Willenberg L, Curtis K, Taylor C, Jan S, Glass P, Myburgh J. The variation of acute treatment costs of trauma in high-income countries. *BMC Health Serv Res*. 2012;12(1):267.
39. Centraal Bureau voor de Statistiek. Werkzame beroepsbevolking: Deeltijd. https://www.cbs.nl/nl-nl/achtergrond/2017/33/werkzame-beroepsbevolking-deeltijd. Updated 2017. Accessed 08/27, 2019.
40. Collie A, Simpson PM, Cameron PA, et al. Patterns and predictors of return to work after major trauma: A prospective, population-based registry study. *Ann Surg*. 2019;269(5):972-978.
41. Hodgson CL, Haines KJ, Bailey M, et al. Predictors of return to work in survivors of critical illness. *J Crit Care*. 2018;48:21-25.
42. Cancelliere C, Donovan J, Stochkendahl MJ, et al. Factors affecting return to work after injury or illness: Best evidence synthesis of systematic reviews. *Chiropr Man Therap*. 2016;24(1):32.
43. Waddell G, Burton AK. *Is work good for your health and well-being?* The Stationery Office; 2006.
44. Howe EI, Andelic N, Perrin PB, et al. Employment probability trajectories up to 10 years after moderate-to-severe traumatic brain injury. *Front Neurol*. 2018;9:1051.

SUPPLEMENTAL TABLE 1

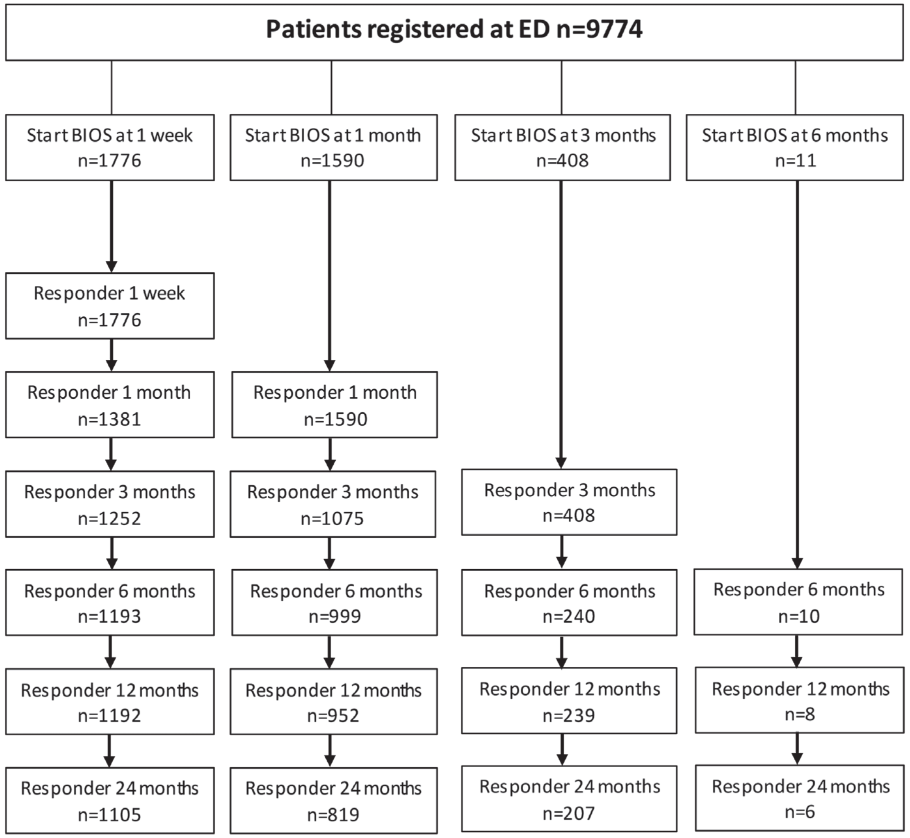
The relative difference with univariable generalized linear models for medical costs and productivity costs and univariable cox proportional hazards model for RTW in the first two years after trauma.

	Generalized linear models		**Cox proportional hazards model**
	Medical costs N=3521[d]	Productivity costs N=1236[e,f]	RTW N=1236[e,g]
	Exp(E) (95% CI)	Exp(E) (95% CI)	Hazard Ratio (95% CI)
Age (years)			
18-44	Ref	Ref	Ref
45-64	1.19 (1.01-1.39)	1.07 (0.97, 1.19)	0.93 (0.82, 1.07)
65-74[b]	1.45 (1.22, 1.73)	0.60, 1.13)	0.92 (0.57, 1.49)
≥75	2.34 (2.00, 2.74)	NA	NA
Female gender	1.40 (1.26, 1.55)	0.62 (0.57, 0.68)	0.91 (0.80, 1.05)
Educational level	Ref	Ref	Ref
Low[a]	0.73 (0.64, 0.83)	0.91 (0.81, 1.02)	1.28 (1.09, 1.51)
Middle	0.78 (0.67, 0.90)	0.65 (0.58, 0.74)	2.05 (1.73, 2.42)
High			
Injury classifications[f]			
Pelvic injury	2.08 (1.70, 2.54)	1.51 (1.24, 1.84)	0.57 (0.43, 0.76)
Hip fracture	2.31 (2.02, 2.64)	1.20 (1.01, 1.44)	0.65 (0.51, 0.83)
Tibia, complex foot or femur fracture	1.60 (1.36, 1.89)	1.39 (1.21, 1.60)	0.56 (0.46, 0.68)
Shoulder and upper arm injury	1.25 (1.05, 1.49)	1.08 (0.93, 1.26)	0.84 (0.68, 1.04)
Radius, ulna or hand fracture	1.01 (0.83, 1.24)	1.19 (1.00, 1.40)	0.85 (0.67, 1.07)
Head injury AIS ≤ 2	0.82 (0.72, 0.93)	0.79 (0.71, 0.89)	1.14 (0.98, 1.33)
Head injury AIS ≥ 3	2.09 (1.61, 2.70)	1.61 (1.25, 2.08)	0.45 (0.31, 0.67)
Facial injury	1.14 (0.91, 1.42)	0.99 (0.82, 1.19)	0.91 (0.70, 1.17)
Thoracic injury	1.10 (0.83, 1.44)	1.20 (0.97, 1.49)	0.91 (0.67, 1.22)
Rib fracture	1.09 (0.91, 1.30)	1.11 (0.95, 1.30)	1.03 (0.83, 1.29)
Abdominal injury AIS ≤ 2	0.92 (0.64, 1.32)	0.75 (0.57, 0.98)	1.43 (0.98, 2.09)
Abdominal injury AIS ≥ 3	1.56 (0.87, 2.80)	1.08 (0.74, 1.57)	1.02 (0.60, 1.74)
Spinal cord injury	3.85 (1.92, 7.73)	1.51 (0.85, 2.68)	0.46 (0.20, 1.04)
Stable vertebral fracture or disc injury	1.30 (1.06, 1.59)	1.44 (1.22, 1.71)	0.63 (0.49, 0.80)
ISS			
1-3	Ref	Ref	Ref
4-8	1.53 (1.33, 1.75)	1.72 (1.53, 1.94)	0.54 (0.46, 0.63)
9-15	2.46 (2.15, 2.81)	1.89 (1.66, 2.16)	0.45 (0.37, 0.54)
>15	3.64 (2.85, 4.66)	2.40 (1.95, 2.95)	0.33 (0.25, 0.45)
Length of stay at hospital (days)	NA[c]		
1-2		Ref	Ref
3-7		1.44 (1.29, 1.60)	0.60 (0.51, 0.69)
8-14		1.98 (1.69, 2.31)	0.41 (0.33, 0.51)
>14		2.22 (1.72, 2.85)	0.27 (0.18, 0.39)
External cause			
Home and leisure[a]	Ref	Ref	Ref
Traffic	0.72 (0.64, 0.81)	0.93 (0.83, 1.03)	1.09 (0.94, 1.27)
Occupational	0.69 (0.54, 0.89)	1.66 (1.40, 1.97)	0.74 (0.58, 0.94)
Sport	0.40 (0.26, 1.87)	0.95 (0.83, 1.10)	1.43 (1.18, 1.73)
Self-harm	0.69 (0.26, 1.87)	0.87 (0.42, 1.82)	0.73 (0.24, 2.26)
Violence	0.63 (0.39, 1.04)	0.89 (0.62, 1.27)	1.39 (0.83, 2.33)
Other	0.70 (0.39, 1.26)	0.75 (0.45, 1.24)	1.41 (0.72, 2.76)
ICU admission	NA[c]	1.58 (1.34, 1.87)	0.61 (0.48, 0.77)
Number of comorbidities			
0[a]	Ref	Ref	Ref
1	1.46 (1.29, 1.65)	1.03 (0.92, 1.16)	0.94 (0.80, 1.10)
≥2	2.02 (1.79, 2.28)	1.08 (0.92, 1.26)	0.84 (0.67, 1.04)
Frail	1.67 (1.46, 1.92)	NA[c]	NA[c]
Pre-injury health status	0.32 (0.25, 0.40)	1.09 (0.71, 1.68)	1.85 (0.99, 3.46)

[a]Reference category of categorical variable, [b]Category changed to 65-67 for productivity loss costs and RTW, [c]variables were not considered as predictors. [d]missing values: 23 Number of comorbidities, 389 Pre-injury health status, 264 medical costs. [e]working population N=1236. [f]missing values: 3 Nr of comorbidities, 90 Pre-injury health status, 204 missing productivity loss costs. [f]missing values: 18 status RTW, 113 time to event, 87 Pre-injury health status, 3 Number of comorbidities.

Abbreviations: AIS, Abbreviated Injury Scale; CI, Confidence Interval; ISS, Injury Severity Score; NA, Not Applicable.

SUPPLEMENTAL FIGURE 1



SUPPLEMENTAL FIGURE 1. Flow diagram of study participation; the total number of unique patients that responded to the questionnaire on health care use and RTW was 3785.

II

GENERAL DISCUSSION

The main aim of this thesis was to evaluate, develop and validate models for predicting fatal and non-fatal outcome after trauma in the Netherlands. This chapter will describe the main findings of this thesis and addresses methodological considerations. Furthermore, implications and recommendations for future research and policy are discussed.

Main findings

Part I - Prediction of fatal outcome after trauma

The first part of this thesis studies prediction models for mortality, the traditional outcome for the evaluation of trauma care and addresses the first research question:

I. How can we improve and utilize prediction models for fatal outcome after trauma?

A total of 258 different models were found in the literature to predict mortality in the general trauma population of which the TRISS model is the most commonly used model **(Chapter 2)**. Several methodological limitations were found in the development and validation of these models: (I) not all models were developed using an adequate sample size with sufficient events per predictor variable, (II) cases with missing values were often excluded, (III) variables were often dichotomized or categorized to be included in the models and (IV) not all variables in the models were readily available from the trauma registry.

Registry data often contain missing values. Multiple imputation could be a valid method to deal with these missing data **(Chapter 3)**. Differences in imputation models did influence outcome evaluation. The inclusion of supplementary variables in the imputation models had no additional value.

Outcome comparisons with the TRISS model should be interpreted with care **(Chapter 4)**. Performance of the TRISS model was adequate in the total clinical Dutch trauma population but was poor to moderate in the older patients. This could simply be improved by adding a comorbidity measure to the model and by using the age variable as a continuous predictor **(Chapter 5)**. A new model was presented, which enables the inclusion of elderly patients with an isolated hip fracture in the evaluation of quality of trauma care.

Part II - prediction of non-fatal outcome after trauma

The second part of this thesis describes innovative models to predict non-fatal outcomes and addresses the second research question:

II. To what extent can we predict non-fatal outcome after trauma?

The functional capacity index should be considered as a possible predictor for non-fatal outcome as it predicts a small proportion of the variability for health status 12 months after injury **(Chapter 6)**. However, a FCI score that incorporated multiple injuries did not increase the prognostic ability.

Health status was especially low during the first six months after injury **(Chapter 7-8)**. The most important predictors were pre-injury health status and frailty, reflecting that baseline condition of the patient is essential to consider when predicting health status after injury. Additional factors influencing health status included age, sex, educational level, severe head or face injury, severe torso injury, ISS, ASA grade and duration of hospital stay. The EuroQol Visual Analogue Scale (EQ-VAS) and the Health Utility Index Mark 3 (HUI 3) were considered the best outcome measures (compared with the EQ-5 dimensions utility score and the HUI 2), with an explained variance for the models of 35% and 48% respectively. The dimensions mobility, pain/discomfort and usual activities improved up to 2 years after injury.

Psychological distress after injury is a common health problem. The prevalence of psychological distress ranged from 23% to 14% at one week and 12 months after injury respectively **(Chapter 9)**. Prognostic factors for poor psychological outcome were pre-injury frailty, psychological complaints and non-working status prior to injury, female gender and low educational level.

Although most prognostic factors resulted in both higher medical costs as higher productivity costs, some factors showed differential effects (e.g. gender and age) **(Chapter 10)**. Productivity costs and RTW should be considered when assessing the economic impact of injury in addition to medical costs. Prognostic factors may assist in identifying high cost groups with potentially modifiable factors for targeted preventive interventions, hence reducing costs and increase RTW rates.

Methodological considerations

Results from this thesis are conducted in two different types of cohorts. Results in chapter 2-5 were based on a retrospective cohort, while results in chapter 6-9 were from a multicenter prospective cohort. Both cohorts have methodological strengths and weaknesses to address our research questions (Table 1).

Generalizability

This thesis provided studies in which all clinical trauma patients from the region Noord-Brabant were included. This region is considered representative for the total Dutch clinical trauma population, as it combines rural and urban areas. Noord-Brabant has 12 emergency departments, including one level I trauma center[1]. Furthermore, Noord-Brabant has 2.5 million inhabitants, representing 14.7% of the total Dutch population.

Although the retrospective studies in this thesis were generalizable to the Dutch clinical trauma population, it could be questioned whether this is also true for international comparisons. Previous research showed large differences between the pre-hospital care of the Netherlands and Germany[2]. The mode of transport to the trauma centers differed greatly. Possibly due to the high hospital density and thus short distances, most patients in the Netherlands were transported with the ambulance, whereas patients in Germany were often transported with the helicopter. Long distance travel to reach the emergency department could result in lower in-hospital mortality, because patients did not survive long enough to reach the hospital[3,4]. In addition, it has been shown previously that mechanism of injury, race and health insurance status are strong predictors for outcome disparities after trauma in the United States[5-7]. Patients with blunt injury, who have insurance and who are white (in comparison with Blacks, Hispanics and Asians) are less likely to die after sustaining an injury. Insurance status does not play an important role in predicting outcome after injury in the Dutch trauma population, because the vast majority (99.9%) of the Dutch population is insured[8]. Race is another factor that does not play a major role in outcome prediction in the Netherlands. Differences in outcome for race can probably partly be explained by educational level or social economic status. However, the traditional outcome measurement prediction models does not include race or insurance status, and could therefore not influence prediction outcomes. In contrast, blunt and penetrating injury is included as predictor in the models. In 2017 was 10.2% of the nonelderly (≤64 years) population uninsured in the United States[9]. Furthermore, penetrating injury in the Netherlands accounts for 2.9% of the injuries, whereas in other countries penetrating injury could be responsible for 20-60% of all injuries[1,10,11].

In the prospective Brabant Injury Outcome Surveillance (BIOS) study we found differences in patient characteristics for responders and non-responders. Responders were on average younger, more often healthy and more likely to be severely injured, with a longer length of stay at the hospital. The short-term questionnaire (1 week) was completed by younger patients who were more healthy but with minor injuries. This possibly resulted in an underestimation of the short-term problems after injury. Furthermore, it is likely that selective drop-out occurred; patients who were fully recovered did not respond to the follow-up questionnaire. This could have resulted in an overestimation of problems at long-term follow-up.

These differences suggest that the developed prediction models could not be generalizable to other trauma populations, in which the previous described factors play an important role in outcome prediction. However, the models could be generalizable to other developed countries, with high density hospitals, mostly insured patients and with a low prevalence of penetrating injury.

TABLE 1. Methodological considerations concerning the results from this thesis

Methodological considerations		**Retrospective** (chapter 2-5)	**Prospective** (Chapter 6-10)
Generalizability	International differences between pre-hospital care	X	X
	Outcome disparities due to race, mechanism of injury or health insurance status	X	X
	Non-response bias		X
Outcome measurement	Unstandardized outcome	X	X
	Recall bias		X
	Proxy completion of questionnaires		X
	Collection of data is labour-intensive and expensive	X	X

Outcome measurement: when, what and how?

Although mortality is considered a hard end point, the specific definition of mortality is important. Mortality rates are most often calculated with in-hospital mortality numbers. Early discharge of could result in lower in-hospital mortality rates[12,13]. Previous research suggest to use a standardized follow-up period of mortality, for example 30-day mortality, even though obtaining this information could be challenging because patients are often discharged from hospital at that time point[13].

In countries with advanced health care, mortality rates after trauma decreased the past decades. Approximately 98% of the Dutch trauma patients survives their injury, who often suffer physical, psychological and social consequences[1]. Even though mortality is still an important outcome measure for the evaluation and improvement of trauma care, non-fatal outcome should also be considered.

A strength of the BIOS-study is the prospective cohort design with multiple short-term and long-term follow-up measurements. In addition, all dimensions of recovery after trauma were measured; functional outcome, health related quality of life, psychological outcome, costs and return to work[14].

Pre-injury health status for injured patients is an important baseline measurement. It can be used by clinicians to determine whether patients have returned to their pre-injury status. However, it is unknown which patients will suffer an injury and thus pre-injury health status has to be measured retrospectively. Due to the retrospective collected data, pre-injury data is prone to recall bias. Alternatively, population norm data for health status according to a patients' age and gender can be used[15]. However, the trauma population is not representative of the general population, indicating that pre-injury measurement might be more appropriate[16-18]. Retrospectively collected pre-injury scores are often higher compared to the norm scores[18,19]. A possible explanation could be that patients recall a higher pre injury status because of the suddenly decrease of their functional capacity. Chapter 7 indicates that the predictive ability of retrospectively collected pre-injury is superior to norm data.

Many patients were not able or capable to respond to the questionnaires, due to cognitive complaints or the severity of the injury. Those questionnaires were send to a proxy; family members or caregivers of the patients could complete these questionnaires. In the BIOS-study, 8% of the questionnaires was completed by a proxy informant, those patients were older and more severely injured compared to the other responders. Although previous literature showed that the health status response of proxies was not biased[20], not all questionnaires could be completed by proxies (i.e. the impact of Event Scale and the Hospital Anxiety and Depression Scale). For those outcome measurements, a selective group of patients was not able to respond: severely injured patients and elderly, which could have resulted in an underestimation of reported problems.

Furthermore the outcomes were based on self-reported questionnaires. Although this was the most efficient way to measure all dimensions of recovery for patients, it could be questioned whether unmeasured factors affected the psychometric properties of the self-reported outcome measurement. Recall bias, the mode of administration (e.g. paper, telephone, internet), proxy completion and other life-events could influence the outcome[21]. Furthermore, a trauma is often experienced as a life-event, in which patients are focused on processing the injury and their recovery, especially during the short-term follow-up. Patients were not keen on completing many questionnaires, resulting in a low response rate[22]. Furthermore, the collection of the self-reported questionnaires (often by post) is a labor-intensive process and results in high costs in large study populations[23,24]. The systematic collection of all essential data for outcome predictions and assessments for injury prediction should be more efficient.

Last, not only the collection of the questionnaires but also the purchase of the questionnaire could be a costly process. Several questionnaires require a high license fee, which is possibly not affordable to all registries or hospitals.

Implications for research

In this thesis we addressed newly developed prediction models for both the evaluation of trauma care and for medical practice in trauma care. We mention some implications for future research concerning data collection, i.e. quality, feasibility, and validity.

Collection of data

First of all, baseline characteristics of the patient are important predictors of trauma outcome for both evaluation of trauma care and medical practice in trauma care. This could be administered in the trauma registry or in the electronic medical file. Frailty, educational level and pre-injury health status are variables that should be collected at hospitalization or at discharge in addition to the currently collected variables.

The world's population is ageing and frailty becomes more important for medical research[29]. Dent et al. (2016)[30] conducted a review to determine which measurements could accurately identify frailty and which of these measures should be used in the clinical setting. They concluded that there is not a perfect frailty measurement in existence today. Morley et al. (2013)[31] stated that a worldwide frailty measurement should be incorporated as routine care for older patients in clinical practice. This measurement should comply with the following standards: I) easy and not time-consuming to collect, II) high validity and reliability, III) the tool is able to predict outcome.

To assure that the models are applicable to the wide variety of trauma patients, the collection of non-fatal consequences should be initiated in the trauma registry. Many standardized Patient Reported Outcome Measures (PROMs) are developed over the past decades, but few of them are routinely used in medical care[25]. To avoid labor-intensive work, innovative ways of data collection should be used[32]. Web-based entry has been introduced as a patient reported outcome system[33]. Patients are emailed and directed to a website to complete condition-specific or generic well-being questionnaires. Scores are directly available for the patients and for the medical professionals. A more recent development for the collection of patient reported outcomes is the Patient-Reported Outcome Measurement Information System (PROMIS)[34]. The System provides multiple types of measures; e.g. fixed set of questions for one domain or multiple domains, and Computer Adaptive Tests (CATs). CATs collects dynamically selected items from an item bank based on the patient's previous answer[35]. With a minimal selection of items, it is possible to provide an accurate estimation with a small standard error of measurement of the patients' outcome.

External validation

Last, the developed models in this thesis should be validated externally to support general applicability[36]. The predictive ability (performance measures such as calibration, discrimination and goodness-of-fit) of the models should be accurate in a population that differs from the patients in the Brabant Trauma Registry or BIOS-study[37]. Potential methods for external validation could be temporal (validation in more recent patients), geographical (validation in patients from different centres) or fully independent validation.

Implications for health care and policy

The studies presented in this thesis have also implications for health care and policy. The newly developed prediction models for the evaluation of trauma care can elaborate on more innovative outcomes and can improve predictions. The models for outcome prediction for medical practice can help with decision making, communication and prevention.

Evaluation of trauma care

Although trauma care in the Netherlands is considered to be of high quality, there is always room for improvement. The mortality rates decline and trauma care outcome should be extended with long-term outcome and non-fatal consequences. According to Gruen et al. (2012)[26] the burden of traumatic injury is multidimensional. A list of all deficits framework (LOAD) has been presented, which describes twenty consequences after injury; 12 individual consequences, 3 consequences related to family and close friends and 5 consequences relating to the wider society[27]. Mortality remains an important outcome measure, but should be combined with long-term and non-fatal outcome measures to adequately assess the quality of trauma care[26,28].

Currently, the evaluation of quality of trauma care is assessed graphically with funnel plots. Standardized mortality ratios (SMR) are calculated for each emergency department. The SMR (dots) shows the ratio between observed and expected mortality. The SMR shows how an emergency department performs in their population compared to how it is expected according to the prediction model. The SMR is equal to 1 if the observed outcome is identical to the expected outcome. The line indicate the 95% Confidence Interval (CI) and the dotted line is the 99.9% CI. If the SMR is between the 95% CI lines, observed and expected mortality is not significant different and could be explained by coincidence. If the SMR is outside the 95% CI range but within the 99.9% CI, there is significant difference between observed and expected mortality with a 5% chance the difference could be explained by coincidence. If the SMR is outside the 99.9% CI range, there is only 0.1% chance that the significant difference between observed and expected mortality could be explained by coincidence.

A high SMR indicates more observed mortality than is expected with the prediction model, and thus a poor performance of the hospital. Emergency departments with a poor performance are subject of further research and evaluation of the quality of trauma care.

A low SMR, below the 95% CI showed good performance, compared to the expected mortality with the model.

The newly developed survival prediction model (**chapter 5**) can be used to calculate the SMR's for each emergency department and are shown in figure 1.

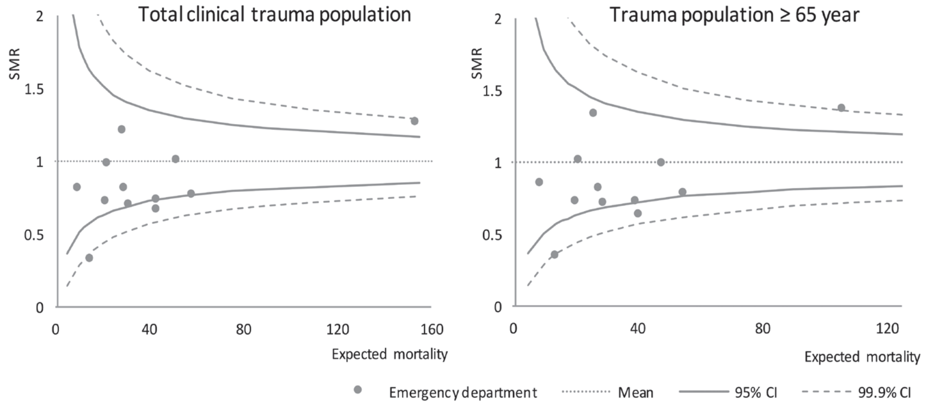


FIGURE 1. Funnel plots; SMR for in-hospital mortality for different emergency departments.

Small hospitals with few patients that mainly treat minor injury have low mortality rates. Mortality as outcome can be useful for complex trauma subsets in which mortality rates are high, such as severe injury, elderly trauma patients or patients with traumatic brain injury. A possibility is that the evaluation of quality of trauma care by using mortality as outcome should be limited to level I trauma centers.

The results of this thesis suggest that predictors of fatal and non-fatal outcome are not identical, indicating that an integrated model could not be used. However, funnel plots of both fatal outcome and non-fatal outcome could be created to give additional information. By using the models that are developed in **chapter 7**, funnel plots can be created for non-fatal outcome (figure 2). The interpretation of the funnel plots for health status is identical to the funnel plots in figure 1.

Medical practice in trauma care

This thesis described prognostic factors for poor recovery after injury, or high medical or productivity costs. The studies can create awareness among health care professionals, patients and policy makers about possible consequences after injury, to help with communication, education and prevention.

Chapter 9 provides prevalence's and prognostic factors for psychological distress during the first year after injury. Patients often suffer from psychological consequences. The assessment of prognostic variables is a first attempt to predict these psychological problems after injury and could create awareness and, hopefully, an extension of focus in recovery after injury. It could enable health care professionals to discuss potential psychological problems with patients and refer patients to receive adequate care.

Furthermore, not only injury-related variables should be considered when assessing a patients recovery. This thesis showed that specific patients characteristics play an important role in the recovery of a patient (e.g. frailty, pre-injury health status, educational level).

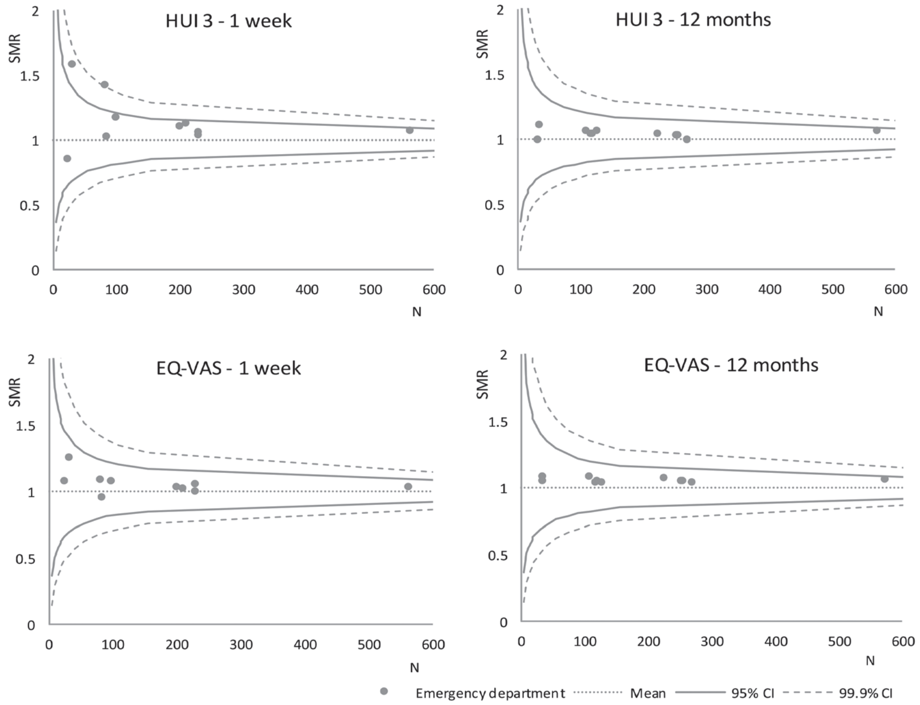


FIGURE 2. Funnel plots; SMR for health status after trauma for different emergency departments.

Overall conclusions

The trauma registry is an important tool for evaluating and benchmarking of the quality of trauma care. The ageing population and outdated TRISS model ensures biased benchmark numbers. Models with better adjustment for the Dutch case-mix are developed and should be used when evaluating the quality of trauma care in the Netherlands.

Mortality will remain an important outcome measure to assess and evaluate the quality of trauma care. However, the focus on trauma outcome has to be extended with non-fatal consequences. For evaluation of non-fatal consequences it is essential to measure baseline

conditions of the patients. The findings of this thesis could enable researchers to further improve the prediction of non-fatal outcomes after trauma. The prediction models could enable health care professionals to discuss potential psychological or physical problems with patients and refer patients to receive adequate care.

Recommendations

This thesis enables to formulate specific recommendations for researchers, policy makers and health care professionals who are working in the trauma field. The recommendations are specified in six categories: methodological, case-mix, outcome measurement, electronic medical file, funding, , and other (Table 2).

TABLE 2. Recommendations for researchers, policy makers and health care professions who are working in the trauma field.

	Recommendations	Researchers	Policy makers	Health care professionals
Methodological	Use an adequate sample size with sufficient events per predictor variable for the development of a prediction model	X		
	Consider multiple imputation to deal with missing variables in registry dataset and maximize efficiency	X		
	Include continuous variables, if possible, in the prediction models to increase predictive ability	X		
	Externally validate the prediction models for non-fatal outcome in this thesis to assess predictive ability in a population that differs from the current study population	X		
Case-mix	Include baseline characteristics of the patients in the cohort studies for better outcome prediction after trauma (e.g. health before injury)	X		
	use prediction models with adequate adjustment for differences in case-mix for a fair evaluation of quality of trauma care	X	X	
	Pay attention to high-risk groups for poor recovery			X

	Recommendations	Researchers	Policy makers	Health care professionals
Outcome measurement	Use the Euroqol Visual Analogue Scale and/or Health Utility Index Mark 3 as outcomes for health status in a large heterogeneous trauma population	X	X	
	collect standardized variables that are widely used around the world to enable (inter)national comparisons and usability of the models	X	X	
	Include non-fatal outcome in the evaluation of quality of trauma care		X	
Electronic medical file	Use variables that are readily available from the trauma registry, to avoid labor-intensive work	X		
	Implement questionnaires in the electronic medical file, enabling health care professionals and patients to use them		X	
	Register all important information about patient and injury correctly in the electronic medical files (trauma-template)			X
	Implement and use prediction models to discuss potential psychological or physical problems with patients and refer high-risk patients to receive adequate care		X	X
Funding	Provide funding for future research on recovery after injury or evaluation of trauma care to enable patient-centered care and increase the quality of trauma care.		X	
	Provide funding to accomplish the registration of additional patient characteristics and non-fatal outcome measures in hospitals		X	
Other	Be aware of possible psychological consequences after injury			X
	Implement and make use of multidisciplinary consultations		X	X

REFERENCES

1. Landelijke Netwerk Acute Zorg (LNAZ). Annual report of the dutch trauma registry: Traumazorg in beeld 2013 - 2017. 2018.
2. Timm A, Maegele M, Lefering R, Wendt K, Wyen H, TraumaRegister DGU. Pre-hospital rescue times and actions in severe trauma. A comparison between two trauma systems: Germany and the netherlands. *Injury*. 2014;45:S43-S52.
3. Simons R, Brasher P, Taulu T, et al. A population-based analysis of injury-related deaths and access to trauma care in rural-remote northwest british columbia. *J Trauma*. 2010;69(1):11-19.
4. Lipsky AM, Karsteadt LL, Gausche-Hill M, et al. A comparison of rural versus urban trauma care. *J Emerg Trauma Shock*. 2014;7(1):41.
5. Haider AH, Chang DC, Efron DT, Haut ER, Crandall M, Cornwell EE. Race and insurance status as risk factors for trauma mortality. *Arch Surg*. 2008;143(10):945-949.
6. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990-2016: Burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444-1472.
7. Greene WR, Oyetunji TA, Bowers U, et al. Insurance status is a potent predictor of outcomes in both blunt and penetrating trauma. *Am J Surg*. 2010;199(4):554-557.
8. Ministerie van Volksgezondheid, Welzijn en Sport, Directie Zorgverzekeringen. VWS - verzekerdenmonitor 2017. 2017.
9. Kaiser Family Foundation. Key facts about the uninsured population. https://www.kff.org/uninsured/fact-sheet/key-facts-about-the-uninsured-population/. Updated 2018. Accessed 02/28, 2019.
10. Søreide K. Epidemiology of major trauma. *Br J Surg*. 2009;96(7):697-698.
11. Dijkink S, Krijnen P, Hage A, et al. Differences in characteristics and outcome of patients with penetrating injuries in the USA and the netherlands: A multi-institutional comparison. *World J Surg*. 2018;42(11):3608-3615.
12. Rydenfelt K, Engerström L, Walther S, Sjöberg F, Strömberg U, Samuelsson C. In-hospital vs. 30-day mortality in the critically ill–a 2-year swedish intensive care cohort analysis. *Acta Anaesthesiol Scand*. 2015;59(7):846-858.
13. Kristoffersen DT, Helgeland J, Clench-Aas J, Laake P, Veierød MB. Comparing hospital mortality–how to count does matter for patients hospitalized for acute myocardial infarction (AMI), stroke and hip fracture. *BMC health Serv Res*. 2012;12(1):364.
14. de Jongh MA, Kruithof N, Gosens T, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: The brabant injury outcome surveillance (BIOS) study. *Inj Prev*. 2017;23(1):59-2016-042032. Epub 2016 May 6.
15. Stolk E, Krabbe P, Busschbach J, Stolk E, Krabbe P, Busschbach J. Using the internet to collect EQ-5D norm scores: A valid alternative. The Hague, The Netherlands: Presented at: 24th Scientific Plenary Meeting of the EuroQol Group, 2009.
16. Wilson R, Derrett S, Hansen P, Langley J. Retrospective evaluation versus population norms for the measurement of baseline health status. *Health Qual Life Outcomes*. 2012;10(1):68.
17. Watson WL, Ozanne-Smith J, Richardson J. Retrospective baseline measurement of self-reported health status and health-related quality of life versus population norms in the evaluation of post-injury losses. *Inj Prev*. 2007;13(1):45-50.
18. Kruithof N, Haagsma JA, de Munter L, Polinder S, de Jongh MA. Comparison of pre-injury recalled health status (HS) data of trauma patients and HS of the general population. *Injury*. 2019.
19. de Graaf MW, Reininga IH, Wendt KW, Heineman E, El Moumni M. Pre-injury health status of injured patients: A prospective comparison with the dutch population. *Qual Life Res*. 2018:1-14.
20. Gabbe BJ, Lyons RA, Sutherland AM, Hart MJ, Cameron PA. Level of agreement between patient and proxy responses to the EQ-5D health questionnaire 12 months after injury. *J Trauma Acute Care Surg*. 2012;72(4):1102-1105.

21. Frost MH, Reeve BB, Liepa AM, et al. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health*. 2007;10:S94-S105.
22. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol*. 2007;17(9):643-653.
23. Van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: The future in epidemiology? *Am J Epidemiol*. 2010;172(11):1292-1298.
24. Ekman A, Litton J. New times, new needs; e-epidemiology. *Eur J Epidemiol*. 2007;22(5):285-292.
25. Nelson EC, Eftimovska E, Lind C, Hager A, Wasson JH, Lindblad S. Patient reported outcome measures in practice. *BMJ*. 2015;350:g7818.
26. Gruen R, Gabbe B, Stelfox H, Cameron P. Indicators of the quality of trauma care and the performance of trauma systems. *Br J Surg*. 2012;99(S1):97-104.
27. Lyons RA, Finch CF, McClure R, van Beeck E, Macey S. The injury list of all deficits (LOAD) framework–conceptualising the full range of deficits and adverse outcomes following injury and violence. *Int J Inj Contr Saf Promot*. 2010;17(3):145-159.
28. Moore L, Stelfox HT, Boutin A, Turgeon AF. Trauma center performance indicators for nonfatal outcomes: A scoping review of the literature. *J Trauma Acute Care Surg*. 2013;74(5):1331-1343.
29. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752-762.
30. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. *Eur J Intern Med*. 2016;31:3-10.
31. Morley JE, Vellas B, Van Kan GA, et al. Frailty consensus: A call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397.
32. Black N. Patient reported outcome measures could help transform healthcare. *BMJ*. 2013;346:f167.
33. Williams D. The myClinicalOutcomes website: Providing real-time, patient-level PROMs data. *Ann R Coll Surg Engl (Suppl).* 2012;94(1):20-21.
34. Ader DN. *Developing the patient-reported outcomes measurement information system (PROMIS). Med Care*. 2007;45(Suppl 1):S1–S2.
35. Petrillo J, Cano SJ, McLeod LD, Coon CD. Using classical test theory, item response theory, and rasch measurement theory to evaluate patient-reported outcome measures: A comparison of worked examples. *Value Health*. 2015;18(1):25-34.
36. Steyerberg EW. Chapter 17: Validation of prediction models. In: Gail M, Tsiatis A, Krickeberg K, Wong W, Sarnet J, eds. In: *Clinical prediction models: A practical approach to development, validation, and updating.* Springer Science & Business Media; 2010:299-311.
37. Steyerberg EW. Chapter 15: Evaluation of performance. In: Gail M, Tsiatis A, Krickeberg K, Wong W, Sarnet J, eds. In: *Clinical prediction models: A practical approach to development, validation, and updating.* Springer Science & Business Media; 2010:255-280.

SUMMARY

Introduction

Trauma, defined as a physical injury, is a global public health problem and is a leading cause of death among young adults. Patient and injury characteristics can be combined in one model to predict outcome after trauma. These prediction models can be valuable for medical research purposes and for medical practice, e.g. for health care providers, health insurers, researchers and policymakers. The models can compare outcomes to support evaluation of quality of care between populations, hospitals, regions or countries and are often applied on population-based data. Besides, prediction models can target the individual patient who is in need for intervention. It can help with decision-making and could give information that can be useful for communication among physicians and patients.

As part of the inclusive trauma care system, the Dutch Trauma Registry (DTR) was introduced in 2007 to measure and improve the quality of trauma care in the Netherlands. The DTR collects characteristics of the patient and the injury, admission related variables and outcome of all patients who are admitted to a hospital within 48 hours after trauma. Patients who were dead on arrival at the hospital were not registered in the DTR. In 2017, approximately 79.000 patients were hospitalized and registered in the DTR due to trauma. The mortality rate in the Netherlands is 2%, indicating that 98% of the trauma population survives.

The main aim of this thesis is to evaluate, develop and validate models for predicting fatal and non-fatal outcome after trauma in the Netherlands. The aim of this thesis was operationalized according to the following objectives, divided in two parts:

I. How can we improve and utilize prediction models for fatal outcome after trauma?
   a. Which outcome prediction models are available for the evaluation of trauma care?
   b. Are predictions from the Trauma and Injury Severity Score (TRISS) model valid for the evaluation of quality of trauma care in the clinical Dutch trauma population?
   c. How could predictions from the TRISS model be improved for the evaluation of quality of trauma care?
II. To what extent can we predict non-fatal outcome after trauma?
   a. What are prognostic factors for health status after trauma?
   b. What are prognostic factors for psychological distress after trauma?
   c. What are prognostic factors for medical costs and return to work after trauma?

Part I: Prediction of fatal outcome after trauma

A total of 258 different models were found in the literature to predict mortality in the general trauma population of which the TRISS model is the most commonly used model. Several methodological limitations were found in the development and validation of these models: (I) not all models were developed using an adequate sample size with sufficient events per predictor variable, (II) cases with missing values were often excluded, (III) variables were often dichotomized or categorized to be included in the models and (IV) not all variables in the models were readily available from the trauma registry. Registry data often contain missing values. Multiple imputation could be a valid method to deal with these missing data. Differences in imputation models did influence outcome evaluation. The inclusion of supplementary variables in the imputation models had no additional value. Performance of the TRISS model was adequate in the total clinical Dutch trauma population but was poor to moderate in the older patients. This could simply be improved by adding a comorbidity measure to the model and by using the age variable as a continuous predictor. A new model was presented, which enables the inclusion of elderly patients with an isolated hip fracture in the evaluation of quality of trauma care.

Part II: Prediction of non-fatal outcome after trauma

The functional capacity index (FCI) should be considered as a possible predictor for non-fatal outcome as it predicts a small proportion of the variability for health status 12 months after injury. However, a FCI score that incorporated multiple injuries did not increase the prognostic ability. Additional factors influencing health status included pre-injury health status, frailty, age, sex, educational level, severe head or face injury, severe torso injury, Injury Severity Score, ASA grade and duration of hospital stay. The most important predictors were pre-injury health status and frailty, reflecting that baseline condition of the patient is essential to consider when predicting health status after injury. The EuroQol Visual Analogue Scale (EQ-VAS) and the Health Utility Index Mark 3 (HUI 3) were considered the best outcome measures (compared with the EQ-5 dimensions utility score and the HUI 2). Psychological distress after injury is a common health problem. The prevalence of psychological distress ranged from 23% to 14% at one week and 12 months after injury respectively. Prognostic factors for poor psychological outcome were pre-injury frailty, psychological complaints and non-working status prior to injury, female gender and low educational level.
Although most prognostic factors resulted in both higher medical costs as higher productivity costs, some factors showed differential effects (e.g. gender and age). Productivity costs and return to work should be considered when assessing the economic impact of injury in addition to medical costs. Prognostic factors may assist in identifying high cost groups with potentially modifiable factors for targeted preventive interventions, hence reducing costs and increase return to work rates.

Discussion

The main aim of this thesis was to evaluate, develop and validate fatal and non-fatal outcome prediction models in the trauma population. A new survival prediction model was developed and validated, which enables the inclusion of elderly patients with an isolated hip fracture in the evaluation of quality of trauma care. Mortality will remain an important outcome measure to assess and evaluate the quality of trauma care. Many patients suffer physical and psychological problems after trauma. This project developed a model to predict health status after trauma for the evaluation of quality of trauma care. Baseline conditions (before injury) are essential to consider in predicting non-fatal outcome. The prediction models can be based on simple clinical characteristics that may also motivate specific interventions in future studies and could help with communication between health professional and patient. Several methodological considerations were discussed. First, although the study population was generalizable to the Dutch clinical trauma population, it could be questioned whether this is also true for international comparisons. Second, standardized outcome measurements should be used to increase the ability for (inter)national comparisons. Next, recall bias, the mode of administration, proxy completion and other life-events could have influenced the outcome.

The results of this thesis resulted in several implications for research. Future studies should focus on educational level, and pre-injury health status and frailty. Those variables are essential for accurate predictions of trauma outcome and should be collected at hospitalization or at discharge in addition to the currently collected baseline variables. Next, to assure that the models are applicable to the wide variety of trauma patients, the collection of nonfatal consequences should be initiated in the trauma registry. Last, the models developed in this theses should be validated externally to support general applicability. The results of this thesis has also implications for health care and policy. The newly developed survival prediction model and health status models can be used for the evaluation of quality of trauma care. Also, the non-fatal prediction models could enable health care professionals to discuss potential psychological and physical problems with patients and refer patients to receive adequate care.

Recommendations

This thesis enables to formulate specific recommendations for researchers, policy makers and health care professionals who are working in the trauma field.

	Recommendations	Researchers	Policy makers	Health care professionals
Methodological	Use an adequate sample size with sufficient events per predictor variable for the development of a prediction model	X		
	Consider multiple imputation to deal with missing variables in registry dataset and maximize efficiency	X		
	Include continuous variables, if possible, in the prediction models to increase predictive ability	X		
	Externally validate the prediction models for non-fatal outcome in this thesis to assess predictive ability in a population that differs from the current study population	X		
Case-mix	Include baseline characteristics of the patients in the cohort studies for better outcome prediction after trauma (e.g. health before injury)	X		
	Use prediction models with adequate adjustment for differences in case-mix for a fair evaluation of quality of trauma care	X	X	
	Pay attention to high-risk groups for poor recovery			X
Outcome measurement	Use the Euroqol Visual Analogue Scale and/or Health Utility Index Mark 3 as outcomes for health status in a large heterogeneous trauma population	X	X	
	Collect standardized variables that are widely used around the world to enable (inter)national comparisons and usability of the models	X	X	
	Include non-fatal outcome in the evaluation of quality of trauma care		X	
Electronic medical file	Use variables that are readily available from the trauma registry, to avoid labor-intensive work	X		
	Implement questionnaires in the electronic medical file, enabling health care professionals and patients to use them		X	
	Register all important information about patient and injury correctly in the electronic medical files (trauma-template)			X
	Implement and use prediction models to discuss potential psychological or physical problems with patients and refer high-risk patients to receive adequate care		X	X
Funding	Provide funding for future research on recovery after injury or evaluation of trauma care to enable patient-centered care and increase the quality of trauma care.		X	
	Provide funding to accomplish the registration of additional patient characteristics and non-fatal outcome measures in hospitals		X	
Other	Be aware of and screen for possible psychological consequences after injury			X
	Implement and make use of multidisciplinary consultations		X	X

SAMENVATTING

Introductie

Trauma, een lichamelijk letsel als gevolg van een ongeval of val, is een wereldwijd probleem voor de volksgezondheid en is een belangrijke doodsoorzaak bij jongvolwassenen. Patiënt- en letselkenmerken kunnen in één model worden gecombineerd om uitkomst na trauma te voorspellen. Deze voorspelmodellen kunnen waardevol zijn voor medische onderzoeksdoeleinden en voor de medische praktijk, bijvoorbeeld voor zorgaanbieders, zorgverzekeraars, onderzoekers en beleidsmakers. De modellen kunnen uitkomsten vergelijken ter ondersteuning van de evaluatie van de kwaliteit van zorg tussen populaties, ziekenhuizen, regio's of landen en worden vaak toegepast op populatiegegevens. Bovendien kunnen voorspelmodellen zich richten op de individuele patiënt die mogelijk een interventie nodig heeft. Het kan ondersteunen bij de besluitvorming en informatie geven die nuttig kan zijn voor communicatie tussen artsen en patiënten.

Als onderdeel van het inclusief traumazorgsysteem is in 2007 de Landelijke Trauma Registratie (LTR) geïntroduceerd om de kwaliteit van traumazorg in Nederland te meten en te verbeteren. De LTR verzamelt kenmerken van de patiënt en het letsel, opname gerelateerde variabelen en uitkomst na trauma van alle patiënten die binnen 48 uur na een trauma in een ziekenhuis worden opgenomen. Patiënten die bij aankomst in het ziekenhuis al zijn overleden, worden niet geregistreerd in de LTR. In 2017 werden ongeveer 79.000 patiënten in het ziekenhuis opgenomen en geregistreerd in de LTR vanwege trauma. Het sterftecijfer in Nederland is 2%, wat aangeeft dat 98% van de traumapopulatie overleeft.

Het hoofddoel van dit proefschrift is het evalueren, ontwikkelen en valideren van modellen voor het voorspellen van fatale en niet-fatale uitkomst na een trauma in Nederland. Het doel van dit proefschrift werd geoperationaliseerd volgens de volgende doelstellingen, verdeeld in twee delen:

I. Hoe kunnen we voorspelmodellen voor een fatale afloop na een trauma verbeteren en gebruiken?
   a. Welke uitkomst voorspelmodellen zijn beschikbaar voor de evaluatie van traumazorg?
   b. Zijn voorspellingen met de Trauma and Injury Severity Score (TRISS) geldig voor de evaluatie van de kwaliteit van traumazorg in de klinische Nederlandse traumapopulatie?
   c. Hoe kunnen voorspellingen uit het TRISS-model worden verbeterd voor de evaluatie van de kwaliteit van traumazorg?

II. In hoeverre kunnen we een niet-fatale afloop na een trauma voorspellen?
   a. Wat zijn voorspellende factoren voor de gezondheidstoestand na een trauma?
   b. Wat zijn voorspellende factoren voor psychologische problemen na een trauma?
   c. Wat zijn voorspellende factoren voor medische kosten en terugkeer naar werk?

Deel I: predictie van fatale uitkomst na trauma

Uit onze systematische literatuurstudie bleek dat er in totaal 258 verschillende modellen zijn om sterfte te voorspellen in de generieke trauma populatie. Het TRISS model wordt het meest gebruikt. Verschillende methodologische beperkingen zijn gevonden bij het ontwikkelen en valideren van deze modellen: (I) de studie populatie is niet altijd groot genoeg om een model te ontwikkelen, (II) patiënten met ontbrekende waarden bij de voorspellende variabelen worden vaak geëxcludeerd, (III) voorspellende variabele worden vaak opgedeeld in categorieën en (IV) niet alle variabelen worden standaard verzameld in de traumaregistratie.

Data van de traumaregistratie bevat vaak ontbrekende waarden. Verschillen in de imputatiemodellen zorgden voor andere uitkomsten bij het meten en vergelijken van kwaliteit van zorg. Een goede manier om hier mee om te gaan is multiple imputatie techniek. De inclusie van aanvullende variabelen, naast de predictoren van het model, zorgde niet voor betere geïmputeerde waarden.

Het TRISS model voorspelt mortaliteit goed in de gehele opgenomen Nederlandse trauma populatie, maar voorspelt mortaliteit slecht tot matig bij oudere patiënten. Dit kan eenvoudig verbeterd worden door comorbiditeit toe te voegen en leeftijd als een continue voorspeller in het model te includeren. Een nieuw model werd gepresenteerd, waardoor oudere patiënten met een geïsoleerde heupfractuur op eerlijke wijze kunnen worden meegenomen in de evaluatie van de kwaliteit van traumazorg.

Deel II: predictie van niet-fatale uitkomst na trauma

De functionele capaciteitsindex is een mogelijke voorspeller voor niet-fatale afloop, aangezien deze een klein deel van de variatie voorspelt voor de gezondheidstoestand 12 maanden na het letsel. De combinatie van FCI-scores van meerdere letsels verhoogde echter niet het voorspellend vermogen om gezondheidsstatus te voorspellen 1 jaar na trauma. Andere factoren die van invloed zijn op de gezondheidstoestand bij traumapatiënten zijn: de gezondheidsstatus en mate van kwetsbaarheid vóór het trauma, leeftijd, geslacht, opleidingsniveau, ernstig hoofd- of aangezicht letsel, ernstig letsel aan de romp, totale letselernst, comorbiditeit en het aantal dagen opname in het ziekenhuis. De belangrijkste voorspellers zijn de gezondheidsstatus en mate van kwetsbaarheid voor het ongeval. Dit geeft aan dat de basisconditie van de patiënt essentieel is om te overwegen bij het voorspellen van de gezondheidstoestand na trauma. De EuroQol Visual Analogue Scale (EQ-VAS) en de Health Utility Index Mark 3 (HUI 3) zijn de beste uitkomstmaten (vergeleken met de EQ-5 dimensies Utility score en de HUI 2), met een verklaarde variantie voor de modellen van respectievelijk 35% en 48%.

Psychologische problemen na trauma zijn een veel voorkomend gezondheidsprobleem. De prevalentie hiervan varieerde van 23% tot 14% na respectievelijk één week en twaalf maanden na het ongeval. Risicofactoren voor een slechte psychologische uitkomst zijn kwetsbaarheid, psychologische klachten en de afwezigheid van een betaalde baan voorafgaand aan het letsel, vrouwelijk geslacht en een laag opleidingsniveau.

Hoewel de meeste voorspellende factoren resulteerden in zowel hogere medische kosten als hogere productiviteitskosten, vertoonden sommige factoren verschillende effecten (bijv. geslacht en leeftijd). Naast medische kosten, moeten ook productiviteitskosten en terugkeer naar werk meegenomen worden bij de berekening van de economische impact van letsel. Voorspellende factoren kunnen helpen bij het identificeren van groepen met hoge kosten met potentieel wijzigbare factoren voor gerichte preventieve interventies, waardoor de kosten worden verlaagd en terugkeer naar werk wordt verhoogd.

Discussie

Het doel van dit proefschrift was om fatale en niet-fatale voorspelmodellen in de traumapopulatie te evalueren, ontwikkelen en valideren. Er is een nieuw overlevingsmodel ontwikkeld en gevalideerd, waarmee oudere patiënten met een geïsoleerde heupfractuur kunnen worden geïncludeerd in de evaluatie van de kwaliteit van de traumazorg. Sterfte blijft een belangrijke uitkomstmaat om de kwaliteit van traumazorg te beoordelen en te evalueren. Veel patiënten hebben fysieke en psychologische problemen na een trauma. Dit project ontwikkelde een model om de gezondheidstoestand na trauma te voorspellen voor de evaluatie van de kwaliteit van traumazorg. Ook is er een scorekaart voor psychologische problemen na trauma ontwikkeld. Basiscondities (vóór letsel) zijn essentieel om mee te nemen bij het voorspellen van niet-fatale uitkomsten. De voorspelmodellen kunnen gebaseerd zijn op eenvoudige klinische kenmerken die mogelijk ook ondersteunen tot de uitvoering van specifieke interventies in toekomstige studies en bij de communicatie tussen zorgverlener en patiënt.

Verschillende methodologische overwegingen werden besproken. Ten eerste, hoewel de onderzoekspopulatie generaliseerbaar was naar de Nederlandse klinische traumapopulatie, kan het zijn dat dit niet het geval is voor de generaliseerbaarheid naar internationale trauma populaties. Ten tweede moeten gestandaardiseerde uitkomstmaten worden gebruikt om internationale vergelijkingen mogelijk te maken. Daarnaast kunnen recall bias, de wijze van deelname (per post of digitaal), proxy deelname en andere levensgebeurtenissen invloed hebben gehad op de uitkomsten.

De resultaten van dit proefschrift resulteerden in verschillende implicaties voor onderzoek. Toekomstige studies moeten zich richten op kwetsbaarheid bij ouderen, opleidingsniveau en de gezondheidstoestand vóór het letsel. Deze variabelen zijn essentieel voor nauwkeurige voorspellingen van trauma uitkomsten en moeten worden verzameld bij ziekenhuisopname of bij ontslag. Daarnaast, zouden niet-fatale uitkomsten na trauma geïntegreerd kunnen worden in de traumaregistratie. Ten slotte moeten de in dit proefschrift ontwikkelde modellen extern worden gevalideerd om de algemene toepasbaarheid te ondersteunen.

De resultaten van dit proefschrift hebben ook implicaties voor de gezondheidszorg en het beleid. Het nieuw ontwikkelde overlevingsmodel en de gezondheidsstatusmodellen kunnen worden gebruikt voor de evaluatie van de kwaliteit van traumazorg. Ook kunnen de niet-fatale voorspelmodellen zorgverleners in staat stellen om mogelijke psychologische en fysieke problemen met patiënten te bespreken en patiënten door te verwijzen voor gepaste zorg.

Aanbevelingen

Dit proefschrift maakt het mogelijk om specifieke aanbevelingen te formuleren voor onderzoekers, beleidsmakers en zorgverleners die in traumazorg werken.

	Aanbevelingen	Onderzoekers	Beleids-makers	Zorg-verleners
Methodologisch	Voor de ontwikkeling van een nieuw voorspelmodel moet de studiepopulatie groot genoeg zijn met voldoende cases per variabele	X		
	Overweeg multiple imputatie methoden om met missende waarden in registratie data om te gaan en de efficiëntie te maximaliseren	X		
	Includeer, indien mogelijk, continue variabele in de voorspelmodellen om het voorspellend vermogen te vergroten	X		
	Valideer de predictiemodellen voor niet-fatale uitkomst uit dit proefschrift extern om het voorspellend vermogen te beoordelen in een populatie die verschilt van de huidige studiepopulatie	X		
Case-mix	Includeer basis karakteristieken van de patiënten in cohort studies voor betere uitkomstpredicties (e.g. gezondheid voor ongeval)	X		
	Gebruik adequate correctie voor verschillen in case-mix voor eerlijke vergelijkingen van de kwaliteit van traumazorg	X	X	
	Besteed aandacht aan de risicogroepen voor slecht herstel			X

	Aanbevelingen	Onderzoekers	Beleidsmakers	Zorgverleners
Meten van uitkomst	Gebruik de EQ-VAS en HUI3 als uitkomsten voor gezondheidsstatus in de grote heterogene trauma populatie	X	X	
	Verzamel gestandaardiseerde variabelen die wereldwijd worden gebruikt om (inter) nationale vergelijking en bruikbaarheid mogelijk te maken	X	X	
	Neem niet-fatale uitkomsten op in de evaluatie van de kwaliteit van traumazorg		X	
Elektronisch medisch dossier	Gebruik variabelen die direct beschikbaar zijn in de traumaregistratie om arbeidsintensief werk te voorkomen	X		
	Implementeer vragenlijsten in het elektronisch medisch dossier, zodat zorgverleners en patiënten deze kunnen toepassen en gebruiken		X	
	Registreer alle belangrijke informatie over patiënt en letsel correct in het elektronisch medisch dossier (trauma-template)			X
	Implementeer en gebruik modellen om mogelijke fysieke of psychologische problemen van patiënten bespreekbaar te maken en hoog-risico patiënten door te verwijzen		X	X
Financiering	Verstrek financiering voor toekomstig onderzoek naar herstel na letsel of evaluatie van traumazorg om patiëntgerichte zorg mogelijk te maken en de kwaliteit van traumazorg te verbeteren		X	
	Verstrek financiering om de registratie van aanvullende patiëntkenmerken en niet-fatale uitkomstmaten in ziekenhuizen te bewerkstelligen		X	
Overig	Houd rekening met mogelijke psychologische gevolgen na trauma			X
	Implementeer en gebruik een multidisciplinair overleg		X	X

LIST OF PUBLICATIONS

Smit ES, de Vries H, **de Munter L,** Hoving C. Depressive symptoms' association with smoking-related cognitions and their influence on smoking cessation behaviour. *OA Epidemiology*. 2013;1(2):13.

de Munter L, Maasland DHE, van den Brandt PA, Kremer B, Schouten LJ. Vitamins and carotenoid intake and risk of head-neck cancer subtypes in the Nehterlands Cohort Study. *Am J Clin Nutr*. 2015; 102;420-432.

de Jongh MAC, Kruithof N, Gosens T, van de Ree CLP, **de Munter L**, Brouwers L, et al. Prevalence, recovery patterns and predictors of quality of life and costs after non-fatal injury: the Brabant Injury Outcome Surveillance (BIOS) study. *Inj Prev*. 2016;0:1-9 doi:10.1136/injuryprev-2016-042032

de Munter L, Polinder S, Lansink KWW, Cnossen MC, Steyerberg EW, de Jongh MAC. Mortality prediction models in the general trauma population: A systematic review. *Injury*. 2017;48(2):221-229.

Kruithof N, de Jongh MAC, **de Munter L**, Lansink KWW, Polinder S. The effect of socio-economic status on non-fatal outcome after injury: A systematic review. *Injury*. 2017;48(3):578-590.

van de Ree CLP, de Jongh MAC, Peeters CMM, **de Munter L**, Roukema JA, Gosens T. Hip fractures in elderly people: Surgery or No Surgery? A Systematic Review and Meta-Analysis. *Geriatr Orthop Surg Rehabil*. 2017;8(3):173-180.

de Munter L, ter Bogt NCW, Hesselink DD, de Jongh MAC. Imputation strategies in the trauma registration. *J Trauma Acute Care Surg*. 2017;83(5):828-836.

de Munter L, Polinder S, Nieboer D, Lansink KWW, Steyerberg EW, de Jongh MAC. Performance of the modified TRISS for evaluating trauma care in subpopulations: A cohort study. *Injury*. 2018;49(9):1648-1653.

Kruithof N, Haagsma JA, Karabatzakis M, Cnossen MC, **de Munter L**, van de Ree CLP, de Jongh MAC, Polinder S. Validation and reliability of the Abbreviated World Health Organization Quality of Life Instrument (WHOQOL-BREF) in the hospitalized trauma population. *Injury*. 2018;49(10):1796-1804.

de Munter L, ter Bogt NCW, Polinder S, Sewalt CA, Steyerberg EW, de Jongh MAC. Improvement of the performance of survival prediction in the ageing blunt trauma population: A cohort study. *PLoS ONE*. 2018;13(12):e0209099.

de Munter L, Polinder S, van de Ree CLP, Kruithof N, Lansink KWW, Steyerberg EW, de Jongh MAC. Predicting health status in the first year after trauma. *Br J Surg*. 2019;106:701-710.

Kruithof N, Haagsma JA, **de Munter L**, Polinder S, de Jongh MAC. Comparison of pre-injury recalled health status (HS) data of trauma patients and HS of the general population. *Injury*. 2019;50(4):890-897.

van de Ree CLP, Landers MJF, Kruithof N, **de Munter L**, Slaet JPJ, Gosens T, de Jongh MAC. Effect of frailty on quality of life in elderly patients after hip fracture: a longitudinal study. *BMJ Open*. 2019;9:e025941.

de Munter L, Polinder S, Haagsma JA, Kuirthof N, van de Ree CLP, Steyerberg EW, de Jongh MAC. Prevalence and prognostic factors for psychological distress after trauma. *Arch Phys Med Rehab*. 2019; In Press.

Geraerds AJLM, Haagsma JA, **de Munter L**, Kruithof N, de Jongh MAC, Polinder S. Medical and productivity costs after trauma. *PLoS ONE*. 2019;14(12):e0227131.

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Leonie

CURRICULUM VITAE

Leonie de Munter was born on July 23, 1987 in Hulst, The Netherlands. After pre-university education (VWO) at the Reynaertcollege, Hulst in 2005, she started her academic training at the Eindhoven University of Technology (TU/e) in biomedical engineering. In 2010 she continued her training in Health Sciences, at Maastricht University. She followed the prevention and health track and earned her BSc degree in 2013.

Subsequently she obtained her MSc in Epidemiology at the same university in 2014. During her master, she was an intern at the Department of Epidemiology studying 'Vitamin and carotenoid intake and risk of head-neck cancer subtypes in the Netherlands Cohort Study'.

In 2015 she started her PhD research focusing on prediction models of fatal and non-fatal outcome measurement in the trauma population in the ETZ-hospital (Elisabeth-TweeSteden Ziekenhuis), Tilburg. This research was performed in close collaboration with the department of Public Health, Erasmus Medical Centre, Rotterdam. Currently, Leonie is working as a researcher at the ETZ-hospital Tilburg.

PHD PORTFOLIO

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Erasmus MC Department:	MGZ
PhD period:	May 2015 – October 2019
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Copromotors:	Dr. S. Polinder
	Dr. M.A.C. de Jongh

	Year	ECTS
1. PhD training		
General courses		
Good Clinical Practice en herregistratie, ETZ, Tilburg, NL	2015+2019	1.2
Scientific writing in English, ETZ, Tilburg, NL	2016	0.5
Integrity Course, Erasmus MC, Rotterdam, NL	2017	0.3
Microsoft Access 2010, ETZ, Tilburg, NL	2017	1.0
Implementatie cursus, ZonMw, Den Haag, NL	2018	0.2
Specific courses		
Logistic Regression (ESP66), NIHES, Rotterdam, NL	2015	1.4
Advanced Analysis of Prognosis Studies (EWP13), NIHES, Rotterdam, NL	2016	0.9
Repeated Measurements (CE08), NIHES, Rotterdam, NL	2017	1.7
Latent Class Analysis, UvT, Tilburg, NL	2019	1.0
Seminars and workshops		
Research meetings Brabant Injury Outcome Surveillance - Tilburg, NL	2015 - 2018	1.2
Research meetings Xperiment Trauma/Neuro TopZorg - Tilburg, NL	2015 - 2017	0.3
Discover your talents for your future Erasmus MC, Rotterdam, NL	2015	0.2
How to start your PhD at Erasmus MC - Rotterdam, NL	2015	0.2
Themabijeenkomsten Netwerk Acute Zorg Brabant - Tilburg, NL	2015 - 2017	0.2
Symposium ‘quality of hospital care’ at Erasmus MC - Rotterdam, NL	2015	0.2
Symposium Dutch Trauma Registry, Utrecht, NL	2015 - 2017	0.3
Trauma TopZorg symposium, ETZ, Tilburg, NL	2015 - 2019	0.5
Symposia ISOQOL-NL, Utrecht, NL	2018 - 2019	0.6

	Year	ECTS
Oral Presentations (inter)national conferences		
Xperiment Trauma/Neuro meeting, Tilburg, NL	2016-2017	2.0
European Congress of Trauma & Emergency Surgery (ECTES), Bucharest, Romania	2017	1.0
Wetenschapsdag, Tilburg, NL	2017-2019	2.0
European Congress of Trauma & Emergency Surgery (ECTES), Valencia, Spain	2018	1.0
Dutch Epidemiology Conference (WEON), Bilthoven, NL	2018	1.0
World Trauma Congress (WTC), San Diego, US (2 presentations)	2018	1.5
International Society for Quality of Life Research Conference (ISOQOL), Dublin, Ireland	2018	1.0
20 jaar traumaregistratie, Utrecht, NL	2019	1.0
Poster Presentations (inter)national conferences		
Trauma TopZorg Symposium, Tilburg, NL	2015	1.0
European Congress of Trauma & Emergency Surgery, Bucharest, Romania	2017	1.0
Wetenschapsdag, Tilburg, NL	2017	1.0
Dutch Epidemiology Conference (WEON), Bilthoven, NL	2018	1.0
Society for Medical Decision Making (SMDM), Leiden, NL (2 posters)	2018	1.5
World Congress of the International Society of Physical and Rehabilitation Medicine (ISPRM), Paris, France (e-poster)	2018	1.0
International Society for Quality of Life Research Conference (ISOQOL), Dublin, Ireland	2018	1.0
International Society for Health Economics and Outcome Research (ISPOR), Copenhagen, Denmark (2 posters)	2019	1.5
2. Teaching		
Interns – Bachelor / Master Psychology	2016 - 2017	2.0