Effect of frailty on 6-month outcome after traumatic brain injury: a multicentre cohort study with external validation

*Stefania Galimberti, Francesca Graziano, Andrew I R Maas, Giulia Isernia, Fiona Lecky, Sonia Jain, Xiaoying Sun, Raquel C Gardner, Sabrina R Taylor, Amy J Markowitz, Geoffrey T Manley, Maria Grazia Valsecchi, Giuseppe Bellelli, Giuseppe Citerio, on behalf of the CENTER-TBI and TRACK-TBI participants and investigators**

Summary

Background Frailty is known to be associated with poorer outcomes in individuals admitted to hospital for medical conditions requiring intensive care. However, little evidence is available for the effect of frailty on patients' outcomes after traumatic brain injury. Many frailty indices have been validated for clinical practice and show good performance to predict clinical outcomes. However, each is specific to a particular clinical context. We aimed to develop a frailty index to predict 6-month outcomes in patients after a traumatic brain injury.

Methods A cumulative deficit approach was used to create a novel frailty index based on 30 items dealing with disease states, current medications, and laboratory values derived from data available from CENTER-TBI, a prospective, longitudinal observational study of patients with traumatic brain injury presenting within 24 h of injury and admitted to a ward or an intensive care unit at 65 centres in Europe between Dec 19, 2014, and Dec 17, 2017. From the individual cumulative CENTER-TBI frailty index (range 0–30), we obtained a standardised value (range 0–1), with high scores indicating higher levels of frailty. The effect of frailty on 6-month outcome evaluated with the extended Glasgow Outcome Scale (GOSE) was assessed through a proportional odds logistic model adjusted for known outcome predictors. An unfavourable outcome was defined as death or severe disability (GOSE score ≤4). External validation was performed on data from TRACK-TBI, a prospective observational study co-designed with CENTER-TBI, which enrolled patients with traumatic brain injury at 18 level I trauma centres in the USA from Feb 26, 2014, to July 27, 2018. CENTER-TBI is registered with ClinicalTrials.gov, NCT02210221; TRACK-TBI is registered at ClinicalTrials.gov, NCT02119182.

Findings 2993 participants (median age was 51 years [IQR 30–67], 2058 [69%] were men) were included in this analysis. The overall median CENTER-TBI frailty index score was 0·07 (IQR 0·03–0·15), with a median score of 0·17 (0·08–0·27) in older adults (aged ≥65 years). The CENTER-TBI frailty index score was significantly associated with the probability of an increasingly unfavourable outcome (cumulative odds ratio [OR] 1·03, 95% CI 1·02–1·04; p<0·0001), and the association was stronger for participants admitted to hospital wards (1·04, 1·03–1·06, p<0·0001) compared with those admitted to the intensive care unit (1·02, 1·01–1·03 p<0·0001). External validation of the CENTER-TBI frailty index in data from the TRACK-TBI (n=1667) cohort supported the robustness and reliability of these findings. The overall median TRACK-TBI frailty index score was 0·03 (IQR 0–0·10), with the frailty index score significantly associated with the risk of an increasingly unfavourable outcome in patients admitted to hospital wards (cumulative OR 1·05, 95% CI 1·03–1·08; p<0·0001), but not in those admitted to the intensive care unit (1·01, 0·99–1·03; p=0·43).

Interpretation We developed and externally validated a frailty index specific to traumatic brain injury. Risk of unfavourable outcome was significantly increased in participants with a higher CENTER-TBI frailty index score, regardless of age. Frailty identification could help to individualise rehabilitation approaches aimed at mitigating effects of frailty in patients with traumatic brain injury.

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Introduction

Traumatic brain injury in high-income countries is becoming most prominent in older people,[1,2] and ageing in this setting is strongly associated with poorer outcomes.[3] Chronological age, injury severity, and clinical and tomographic data are customarily used as early descriptors and predictors of outcome post injury.[1] However, the widely used traumatic brain injury prognostic models (ie, CRASH and IMPACT),[4,5] which incorporate age along with other indicators of trauma severity, only explain approximately 35% of variance in outcome.

Assessing the patient's status before traumatic brain injury through the evaluation of frailty might better inform prognosis. Frailty is a consequence of cumulative decline in many physiological systems across the lifetime. It reflects, as a state of vulnerability, poor resolution of homoeostasis after a stressor event (eg, traumatic brain injury), with an increased risk

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*CENTER-TBI participants and investigators and TRACK-TBI investigators are listed in the appendix

School of Medicine and Surgery (Prof S Galimberti PhD, F Graziano PhD, G Isernia MD, Prof M G Valsecchi PhD, Prof G Bellelli MD, Prof G Citerio MD) **and Bicocca Bioinformatics Biostatistics and Bioimaging B4 Center** (Prof S Galimberti, F Graziano, Prof M G Valsecchi)**, University of Milano-Bicocca, Milan, Italy; Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium** (Prof A I R Maas PhD)**; School of Health and Related Research, University of Sheffield, Sheffield, UK** (Prof F Lecky PhD)**; Emergency Department, Salford Royal Hospital, Salford, UK** (Prof F Lecky)**; Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, La Jolla, CA, USA** (S Jain PhD, X Sun PhD)**; Department of Neurology** (R C Gardner MD) **and Department of Neurological Surgery** (S R Taylor PhD, A J Markowitz JD, Prof G T Manley PhD)**, University of California, San Francisco, CA, USA; Brain and Spinal Injury Center, Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, CA, USA** (S R Taylor, A J Markowitz, Prof G T Manley)**; Acute Geriatric Unit** (Prof G Bellelli) **and Neurointensive Care Unit** (Prof G Citerio)**, San Gerardo Hospital, Monza, Italy**

Correspondence to:
Prof Giuseppe Citerio, School of Medicine and Surgery, University of Milano-Bicocca, Milan 20100, Italy
giuseppe.citerio@unimib.it

See **Online** for appendix

Research in context

Evidence before this study

We searched PubMed from database inception to June 1, 2021, for studies published in English, excluding experimental studies, case reports, and reviews, using the terms ("frailty [Title/Abstract]" AND "traumatic brain injury[Title/Abstract]") AND "outcome[Title/Abstract]". Only a few small studies evaluated the effects of frailty on outcomes for patients with traumatic brain injury and, specifically, associations of frailty with early (ie, hospital outcome) and mid-term outcomes (ie, 6-month outcome). In the studies of associations of frailty with mid-term outcomes, frailty was frequently assessed with tools that do not fully capture the multidimensional biological and physiological dimensions of frailty and limited their exploration to older adults. Therefore, there is scarce evidence on the impact of frailty in patients with traumatic brain injury.

Added value of this study

Using the method of Rockwood and colleagues from the Canadian Study of Health and Aging, we developed a novel frailty index for patients with traumatic brain injury with data available from CENTER-TBI. The association of frailty with mid-term outcomes (ie, at 6 months after injury) was described. The analytical cohort, composed of 2993 participants admitted to hospital, is—to our knowledge—the largest ever studied and the first to use the accumulation-of-deficits approach in a population of patients with traumatic brain injury. In this approach, the number of variables is the key factor, not a single variable. In fact, in the validation cohort from TRACK-TBI, although only 75% of variables overlap, the findings regarding associations are similar. This exploration of the role of frailty is extendable to retrospective analyses of legacy traumatic brain injury datasets, as well as those being prospectively collected. Frailty is associated with worse outcomes at 6 months and is more evident in less severely injured participants admitted to the ward than those admitted to the intensive care unit.

Implications of all the available evidence

Evaluating frailty in traumatic brain injury is particularly important for patients admitted to hospital wards with less severe trauma. The integration of frailty into available prognostic models could be beneficial. A more targeted approach to considering the effects of frailty on patients from acute care through rehabilitation is probably essential to improve outcomes for these vulnerable patients.

of negative health outcomes. Rockwood and colleagues,[6–8] in the Canadian Study of Health and Aging, developed and validated the Frailty Index as a novel method to define frailty. The Frailty Index encompasses frailty as an accumulation of deficits across various domains. It shows reproducibility, even when accounting for variability in the included items relevant to different clinical conditions and contexts.[9] As expected, frailty increases with age, but also occurs in younger adults.[10] There is substantial evidence that frailty is related to poorer outcomes in individuals admitted to hospital for heterogeneous medical and surgical conditions requiring intensive care, including COVID-19.[11–16] However, only a few small studies have evaluated the effects of frailty in patients with traumatic brain injury and possible associations of frailty with negative early and long-term outcomes.[11–15,17,18] In these studies looking at the associations of frailty with negative outcomes, frailty was assessed with tools that did not fully capture its multiple biological and physiological dimensions, and analyses in these studies were restricted to older adults (>65 years).

In the present study, we aimed to assess whether frailty—captured with an accumulation of deficits approach—is associated with 6-month outcomes in a large cohort of patients with traumatic brain injury. We aimed to develop a frailty index specific to traumatic brain injury, to be used to assess patients' health status at baseline. We subsequently aimed to externally validate this frailty index in a different cohort of patients with traumatic brain injury.

For more on **CENTER-TBI** see https://www.center-tbi.eu/

Methods

Study design and participants

CENTER-TBI is a prospective, longitudinal, observational study of patients with traumatic brain injury presenting within 24 h of injury at 65 hospitals or tertiary centres in 19 countries in Europe.[19] Ethics approval was obtained for each recruiting site. Informed written consent was obtained from patients or their caregivers according to local legislation, for all patients recruited to the CENTER-TBI core dataset, and consent was documented in the electronic case report form.

TRACK-TBI is a prospective, longitudinal observational study of patients with traumatic brain injury enrolled within 24 h of injury at 18 US level I trauma centres. TRACK-TBI was approved by the institutional review board at each site, and all participants either provided written informed consent themselves or a legally authorised representative provided consent on their behalf.

This current analysis of frailty was preregistered on the CENTER-TBI proposal platform on Dec 10, 2019, and the study was approved by the management committee before starting the data analysis. Patients recruited to the CENTER-TBI study comprised the development cohort in this study. We included people with a clinical diagnosis of traumatic brain injury requiring a CT scan and hospital admission to a ward or an intensive care unit within 24 h after injury. Individuals also needed to have data comprising at least 75% of the variables used in the CENTER-TBI frailty index calculation. Finally, an outcome evaluation at 6 months with the extended Glasgow

Outcome Scale (GOSE) was required.[20] Patients from the TRACK-TBI study comprised the validation cohort in this study. Inclusion criteria were the same as for the development cohort. Approval by the management committee before starting the data analysis of the TRACK-TBI cohort was also required.

This article is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (pp 2–7).

Procedures

Participants' baseline characteristics, medical history, injury severity, clinical course and treatment, and outcomes were collected from the CENTER-TBI and TRACK-TBI datasets. Details regarding data collection and extraction have been previously described.[12,13]

We used a cumulative deficit approach to create a CENTER-TBI frailty index. We adopted the principle described by Searle and colleagues[9] to calculate frailty by counting health deficits. These deficits included a variable number of symptoms, signs, diseases, and disabilities, or laboratory, radiographical, or electrocardiographical abnormalities. We assumed that the more deficits a person has, the more likely a person is to be frail. Importantly, there must be a minimum number of variables because estimates are unstable if this number is under a certain threshold (generally, ten variables). The more variables included in a frailty index, the more reliable the estimates become.[9] A frailty index with 30 variables or more is considered sufficiently accurate for the prediction of adverse outcomes.[21] We considered 30 variables from CENTER-TBI, which mapped the burden of comorbidities, currently prescribed medications, and the laboratory tests performed within the first 24 h of admission (appendix pp 11, 12). To generate a robust frailty index, we required that at least 75% of these items were available for each enrolled individual. For each item, a zero score was assigned if the deficit was absent, and a score of 1 indicated its presence. The cutoff for laboratory tests was defined by reported laboratory reference ranges (appendix pp 11, 12). From the individual cumulative

For more on **STROBE reporting guidelines** see www.strobe-statement.org

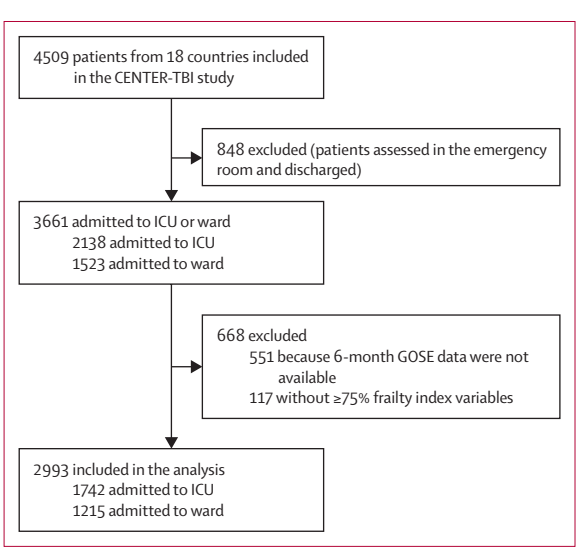

Figure 1: **Study profile**
FI=Frailty Index. GOSE= Glasgow Outcome Scale Extended. ICU=intensive care unit.

	Overall (n=2993)	ICU (n=1742)	Ward (n=1251)	p value
Age, years	51 (30–67)	49 (29–65)	54 (33–69)	<0·0001
Age ≥65 years	859 (29%)	448 (26%)	411 (33%)	<0·0001
Sex				<0·0001
Male	2058 (69)	1264 (73)	794 (64)	..
Female	935 (31%)	478 (27%)	457 (36%)	..
Glasgow Coma Scale at arrival to hospital	14 (8–15)	9 (4–14)	15 (14–15)	<0·0001
Missing data	112 (4%)	82 (5%)	30 (2%)	..
Severity of traumatic brain injury	..	..	..	<0·0001
Mild	1762/2881 (61%)	605/1660 (36%)	1157/1221 (95%)	..
Moderate	322/2881 (11%)	274/1660 (17%)	48/1221 (4%)	..
Severe	797/2881 (28%)	781/1660(47%)	16/1221(1%)	..
Missing data	112 (4%)	82 (5%)	30 (2%)	..
Preinjury ASAPS	..	..	..	0·23
Normal healthy	1705/2971 (57%)	1018/1730 (59%)	687/1241 (55%)	..
Mild systemic disease	958/2971 (32%)	535/1730 (31%)	423/1241(34%)	..
Severe systemic disease	288/2971 (10%)	164/1730 (10%)	124/1241 (10%)	..
Life threatening	20/2971 (1%)	13/1730 (1%)	7/1241 (1%)	..
Missing data	22 (1%)	12 (1%)	10 (1%)	..
Cause of injury	..	..	..	<0·0001
Road traffic incident	1190/2925 (41%)	777/1692 (46%)	413/1233 (34%)	..
Incident fall	1326/2925 (45%)	698/1692 (41%)	628/1233 (51%)	..
Other non-intentional injuries	143/2925 (5%)	63/1692 (4%)	80/1233 (7%)	..
Violence or assault	119/2925 (4%)	54/1692 (3%)	65/1233 (5%)	..
Act of mass violence	1/2925 (<1%)	1/1692 (<0·5%)	0	..
Suicide attempt	37/2925 (1%)	34/1692 (2%)	3/1233 (<0·5%)	..
Other	109/2925 (4%)	65/1692 (4%)	44/1233 (4%)	..
Missing data	68 (2%)	50 (3%)	18 (1%)	..
Injury Severity Score	21 (13–34)	29 (25–41)	10 (9–17)	<0·0001
Missing data	30 (1%)	24 (1%)	6 (<1%)	..
Suspected alcohol involved in the injury	715/2775 (26%)	415/1573 (26%)	300/1202 (25%)	0·42
Missing data	218 (7%)	169 (10%)	49 (4%)	..
Hypotension	246/2858 (9%)	225/1639 (14%)	21/1195 (2%)	<0·0001
Missing data	135 (5%)	103 (6%)	56 (4%)	..
Hypoxia	250/2834 (9%)	227/1639 (14%)	23/1195 (2%)	<0·0001
Missing data	159 (5%)	103 (6%)	56 (4%)	..
Pupillary reactivity	..	..	..	<0·0001
Both reactive	2491/2844 (88%)	1350/1664 (81%)	1141/1180 (97%)	..
Both unreactive	219/2844 (8%)	201/1664 (12%)	18/1180 (2%)	..
One reactive	134/2844 (5%)	113/1664 (7%)	21/1180 (1%)	..
Missing data	149 (5%)	78 (4%)	71 (6%)	..
Cardiovascular history	903 (30%)	492 (28%)	411 (33%)	0·0080
Endocrine disease	373/2991 (13%)	206/1742 (12%)	167/1249 (13%)	0·23
Missing data	2 (<1%)	0	2 (<1%)	..

(Table 1 continues on next page)

	Overall (n=2993)	ICU (n=1742)	Ward (n=1251)	p value
(Continued from previous page)				
Oncologic disease	181/2991 (6%)	95/1740 (6%)	86/1251 (7%)	0·13
Missing data	2 (<1%)	2 (<1%)	0	..
Pulmonary disease	302/2991 (10%)	158/1742 (9%)	144/1249 (12%)	0·032
Missing data	2 (<1%)	0	2 (<1%)	..
Psychiatric disease	396/2975 (13%)	246/1726 (14%)	150/1249 (12%)	0·085
Missing data	18 (1%)	16 (1%)	2 (<1%)	..
Previous traumatic brain injury	239/2831 (8%)	116/1624 (7%)	123/1207 (10%)	0·0050
Missing data	162 (5%)	118 (6%)	44 (4%)	..
Any extracranial injury	1317 (44%)	969 (56%)	348 (28%)	<0·0001
More than two drugs	542 (18%)	297 (17%)	245 (20%)	0·084

Data are median (IQR) or n (%), unless otherwise specified. ASAPS=American Society of Anesthesiologists Physical Status. ICU=intensive care unit.

Table 1: **Baseline characteristics of the CENTER-TBI cohort by stratum (ICU or ward)**

frailty index, potentially ranging from 0 to 30, we obtained a standardised score (range 0–1, with 0 corresponding to no frailty and 1 representing the full expression of frailty). To account for missing values, we divided the cumulative frailty index by the number of non-missing items. Details on construction of the CENTER-TBI frailty index and the robustness of this approach are shown in the appendix (p 9).

Statistical analysis

Categorical variables are described by counts and percentages, and quantitative characteristics are expressed as median (IQR) or mean (SD), as appropriate. Baseline characteristics in the two care pathways (hospital ward or intensive care unit [ICU]) were compared using the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous data. The Mann-Whitney *U* test was also used for between-group comparisons of the CENTER-TBI frailty index.

The relationship between age and the CENTER-TBI frailty index was estimated using a regression model, with a three knots spline on age (at 20 years, 40 years, and 65 years) and corresponding 95% CIs. The association of the CENTER-TBI frailty index with outcome at 6 months (score on GOSE) was assessed with a proportional odds logistic model that was adjusted for predictors of the core IMPACT model[4] (ie, age, motor Glasgow Coma Scale Motor score at admission to hospital, and pupillary reactivity). GOSE was evaluated as an ordinal outcome with four categories: dead (GOSE 1); vegetative state and severe disability (including lower-severe and upper-severe disability, GOSE 2–4); moderate disability (including lower-moderate and upper-moderate disability, GOSE 5–6); and good recoveries (including lower-good and upper-good recovery, GOSE 7–8). Unfavourable outcome was defined as GOSE score of 4 or less. The proportionality assumption was checked for all variables, whereas the linearity assumption was assessed for continuous variables. Additionally, to evaluate the potential differential value of the CENTER-TBI frailty index on older adults (defined as aged ≥65 years according to WHO), an interaction term was assessed with a likelihood ratio test. Analyses were done of cases with complete data and using the MICE algorithm for multiple imputations of missing data (ten imputed datasets)[22] and separately in intensive care unit (ICU) and ward subsets. Results are shown as the cumulative odds ratio (OR) of unfavourable categories, with corresponding 95% CI. ORs refer to each 0·01 increase in the frailty index score.

Model performances were assessed by goodness of fit (Nagelkerke's R^2) and discriminative ability (C statistic). Internal validation used a resampling procedure based on 1000 bootstrap samples for Nagelkerke's R^2 calculation and calibration. Performance criteria in the external validation cohort comprised Nagelkerke R^2 and C statistic. All analyses were done using R, version 4.0.3 (Bunny-Wunnies Freak Out).

CENTER-TBI is registered at ClinicalTrials.gov, NCT02210221; TRACK-TBI is registered at ClinicalTrials.gov, NCT02119182.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 19, 2014, and Dec 17, 2017, 3661 participants from the CENTER-TBI study were admitted to intensive care units or wards. After excluding people without a 6-month GOSE score (n=551), and those without at least 75% of the variables (maximum eight items not available for each individual) included in the CENTER-TBI frailty index method (n=117), 2993 participants remained for this analysis (figure 1). Baseline characteristics were comparable between excluded and included participants (data not shown), confirming that this set of 2993 participants was an unselected sample from the original CENTER-TBI cohort.

The population included in this analysis is described in table 1. The median age was 51 years (IQR 30–67) and the subgroup of older adults represented about a quarter of cases (859 [29%] of 2993 participants); most were men (2058 [69%]). Falls (1326 [45%] of 2925 participants) and road traffic incidents (1190 [41%]) were the most frequent causes of traumatic brain injury. Injury severity was mild-to-moderate in 2084 (72%) of 2881 participants. Median Glasgow Coma Scale score and median Injury Severity Score at hospital arrival were 14 (IQR 8–15) and 21 (13–34), respectively, and 2491 (88%) of 2844 patients with traumatic brain injury had two reactive pupils. 1246 (42%) of 2971 participants had a mild or severe preinjury American Society of Anaesthesiologists' physical status (ASAPS) score with the most frequently reported

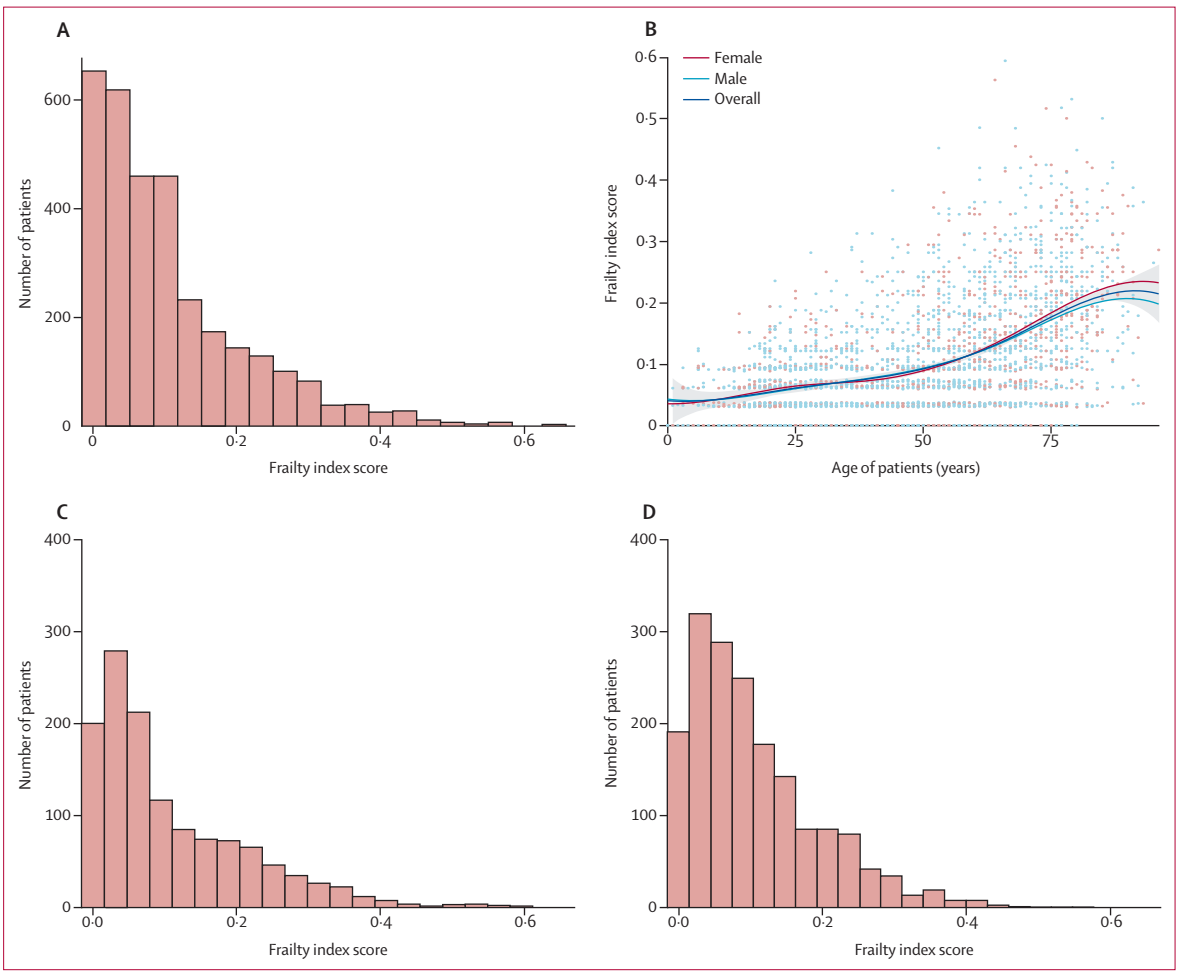

Figure 2: **Description of the CENTER-TBI frailty index**
(A) Overall distribution of the frailty index score. (B) Relationship of age versus frailty index by sex. Distribution of the frailty index score in ICU (C) and ward (D). Frailty increased linearly with ageing at two different rates (ie, different slopes in populations aged <50 years [slope 0·0010] *vs* >50 years [0·0034]), until a plateau was reached around age 75 years, with no difference between sexes (female: <50 years [slope 0·0008] *vs* >50 years [0·0038]; male: <50 years [0·0011] *vs* >50 years [0·0031]). ICU=intensive care unit.

comorbidities being cardiovascular (903 [30%] of 2993 participants), psychiatric (396 [13%] of 2975), and endocrine (373 [13%] of 2991). Almost half of cases used more than two prescribed drugs chronically.

ICU participants were younger (median age 49 years, IQR 29–65) and had a more severe injury (781 [47%] of 1660), as described by median Glasgow Coma Scale of 9 (4–14), a median Injury Severity Score of 29 (25–41), and by the presence of at least one unreactive pupil (314 [19%] 1664). Conversely, participants admitted to the ward were slightly older (54 years, 33–69) and with mild traumatic brain injury (1157 [95%] of 1221), mainly caused by a fall (628 [51%] of 1233).

The distribution of the CENTER-TBI frailty index scores (figure 2A) is right-skewed, with most values clustered in the left tail of the curve. The overall median CENTER-TBI frailty index score in all participants was 0·07 (range 0–0·64, IQR 0·03–0·15) and 527 (18%) participants had a frailty index higher than 0·2. This figure accorded with an absolute accumulation of deficits ranging from 0 to 18 (median 2, IQR 1–4). In adults aged 65 years or older, the overall median CENTER-TBI frailty index score was 0·17 (0–0·64, 0·08–0·27).

Similar median CENTER-TBI frailty index scores were recorded in participants admitted to the ICU (median 0·07, IQR 0·03–0·15) and in those admitted to the ward (median 0·07, 0–0·16; p=0·39; figure 2C and 2D). CENTER-TBI frailty index scores were consistent between those admitted to the ICU and those admitted to the ward in a subset of older adults (p=0·79; data not shown).

Overall, 411 (14%) of 2993 participants died within 6 months (GOSE 1) and 858 (29%) had an unfavourable outcome (GOSE ≤4; a more detailed description of GOSE in four ordered categories overall is in the appendix p 14). The CENTER-TBI frailty index score was

significantly associated with the odds of an increasingly unfavourable outcome in the unadjusted analysis (cumulative OR 1·05, 95% CI 1·04–1·06; p<0·0001) and in the multivariable model (1·03, 1·02–1·04; p<0·0001). Overall, for each 0·033 increase in the CENTER-TBI frailty index score (representing approximately one cumulative deficit), the risk of an increasingly unfavourable outcome at 6 months was increased (cumulative OR 1·11, 95% CI 1·08–1·14). The IMPACT predictors (age, pupil reactivity, and GCS motor score at hospital admission) maintained their significance (table 2). Interaction between frailty and age was non-significant ($p_{interaction}$=0·38). The predicted probabilities of being in one of the four GOSE categories as a function of frailty and age are shown in figure 3. The probability of death increased with higher CENTER-TBI frailty index score and age, and the probability of good recovery decreased with higher CENTER-TBI frailty score and age. The probabilities of intermediate classes of recovery remained relatively constant. These findings were confirmed in analyses that accounted for missing values (appendix p 15).

	Cumulative OR (95% CI)	p value
Frailty index*	1·03 (1·02–1·04)	<0·0001
Age	1·02 (1·01–1·02)	<0·0001
Pupil reactivity	..	..
Both reacting	1·00 (ref)	..
One reacting	2·11 (1·52–2·94)	<0·0001
No pupils reacting	5·39 (3·96–7·37)	<0·0001
GCS motor	..	..
Localises or obeys	1·00 (ref)	..
Normal flexion	4·40 (3·16–6·14)	<0·0001
Abnormal flexion	6·20 (3·91–9·87)	<0·0001
Extension	9·03 (5·48–15·04)	<0·0001
No	5·79 (4·73–7·10)	<0·0001

GOSE has four categories: dead (GOSE 1); vegetative state and severe disability (GOSE 2–4); moderate disability (GOSE 5–6); and good recoveries (GOSE 7–8). For each 0·033 increase in the frailty index score (corresponding approximately to addition of one cumulative deficit), cumulative OR was 1·11 (95% CI 1·08–1·14). GOSE=extended Glasgow Outcome Scale. OR=odds ratio. *OR refers to each 0·01 increase in the frailty index score. GCS=Glasgow Coma Scale.

Table 2: **Results from the proportional odds model on ordered outcome (GOSE 1, GOSE 2–4, GOSE 5–6, GOSE 7–8) in 2827 cases with complete data**

Among patients admitted to the ICU, 318 (19%) of 1649 died within 6 months, and 677 (41%) unfavourable outcomes (GOSE score ≤4) were reported. Among hospital ward admissions, 65 (<1%) of 1178 died within 6 months and 133 (11%) had an unfavourable outcome. The association of the CENTER-TBI frailty index score with risk of an increasingly unfavourable outcome was not as strong in ICU admissions (cumulative OR 1·02, 95% CI 1·01–1·03; p<0·0001; appendix p 16) compared with those admitted to a hospital ward (1·04, 1·03–1·06; p<0·0001; appendix p 17).

Goodness-of-fit of the model in which the CENTER-TBI frailty index score was added to the core IMPACT predictors resulted in a Nagelkerke's R^2 of 31·9 versus 30·2 in the model without the inclusion of the frailty index score, whereas the discriminative ability quantified by the C statistic was 74·2% and 73·2%, respectively. Internal validation with bootstrapping resulted in a Nagelkerke's R^2 of 31·8 and observed outcomes were in line with those predicted in the model with the addition of the CENTER-TBI frailty index score (mean absolute calibration error <0·024; appendix p 19).

From Feb 26, 2014, to July 27, 2018, 1677 participants in the TRACK-TBI study met criteria for this study and were included as an external validation cohort. Compared with the CENTER-TBI cohort, these individuals were younger (median age 39 years, IQR 26–56) and less severely injured (1184 [72%] of 1622 patients had mild disease, appendix p 13). Overall, 123 (7%) of 1677 participants died

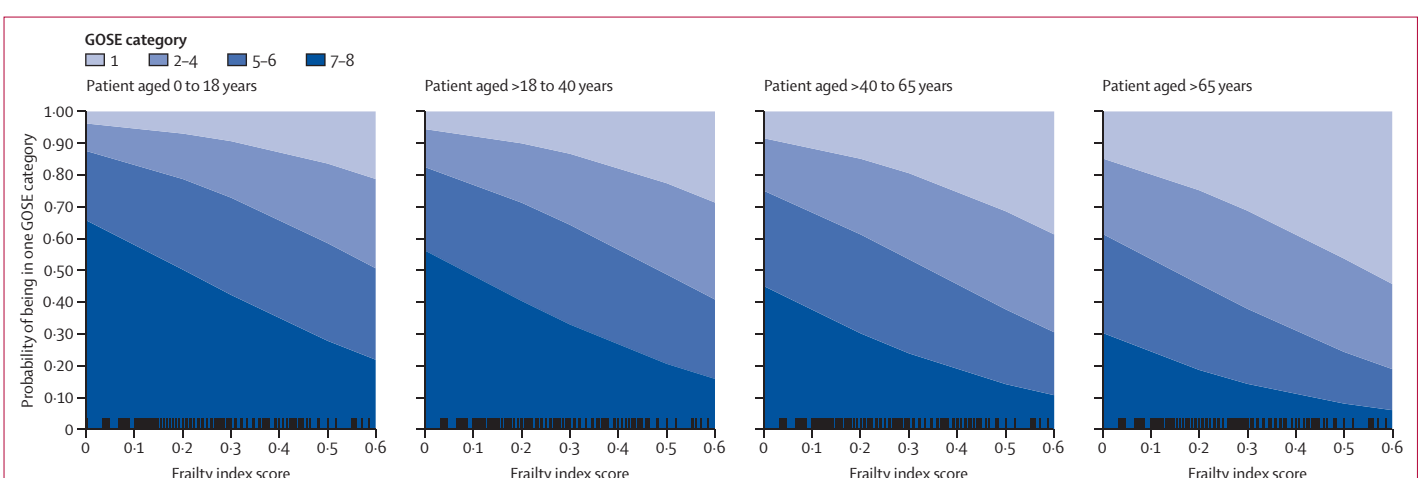

Figure 3: **Stacked probability of being in one of the four GOSE categories, by age and frailty index score**
Each vertical black line represents one patient. Dead=GOSE 1. Vegetative state and severe disability, including lower-severe and upper-severe disability=GOSE 2–4. Moderate disability, including lower-moderate and upper-moderate disability=GOSE 5–6. Good recoveries, including lower and upper good recovery=GOSE 7–8. GOSE=extended Glasgow Outcome Scale.

within 6 months and 316 (19%) had an unfavourable outcome (GOSE ≤4).

The right-skewed shape of the distribution of the CENTER-TBI frailty index in the TRACK-TBI cohort is similar to that observed in CENTER-TBI (appendix p 18). The median overall frailty index score in the TRACK-TBI cohort was 0·03 (IQR 0–0·10), with no differences in this median score noted among participants admitted to the ICU and those admitted to a hospital ward (appendix p 18). A higher frailty index score was significantly associated with increased risk of an increasingly unfavourable outcome, both in the overall analysis (cumulative OR 1·02, 95% CI 1·00–1·03; p=0·025) and for participants admitted to the ward (1·05, 1·03–1·08; p<0·0001), but not for those admitted to the ICU (1·01, 0·99–1·03; p=0·43; appendix p 20). In the validation cohort, the Nagelkerke's R^2 was 28·2 and the C statistic was 0·71.

Discussion

To our knowledge, we present the most comprehensive study on frailty and traumatic brain injury to date, including external validation of the frailty index that we developed. The index we constructed, using data available from CENTER-TBI, was designed to map relevant domains, including 30 variables for the identification of a robust frailty index.[9] We adhered to fundamental assumptions required for such an index to be biologically sensible, accumulating with age, and not displaying early saturation. Additionally, our index was robust to the presence of missing data, as we required that at least 75% of the items were available for each enrolled participant.[9]

In our cohort, frailty index scores were right-skewed (ie, most patients were not frail) and were linearly associated with increasing age, plateauing at age 75 years. 18% of patients had a CENTER-TBI frailty index higher than 0·2, showing that frailty is present in our cohort. As expected, frailty was more commonly reported in older adults but was also present in some younger participants. Nonetheless, not all older participants showed frailty, and we noted a subgroup with a very low frailty index. Participants admitted to the ICU or hospital ward showed a similar preinjury frailty profile, regardless of age.

The effect of the CENTER-TBI frailty index on outcome varied by traumatic brain injury care setting. In the ICU stratum, the effect of frailty on outcome seemed to be overcome by the severity of trauma (ie, when traumatic brain injury was severe, frailty did not affect outcome). However, when traumatic brain injury was not severe, as in participants admitted to the hospital ward, the effect of frailty on mid-term outcome was statistically significant and should be considered in the clinical context. This finding is probably underestimated given our inclusion in this analysis of only hospitalised participants with more severe injuries. Laboratory values had an important role in defining frailty in the ICU cohort, whereas the percentage of missing laboratory values, because they were not routinely collected in less severely injured patients, is higher in the ward cohort. If these data were available, the results would probably be even more significant and we might have observed a larger effect of frailty on outcome.

We externally validated the CENTER-TBI frailty index using data from the large TRACK-TBI cohort. This cohort differs from CENTER-TBI participants by age and severity of injury and, thus, TRACK-TBI patients are at less apparent risk of neurological worsening. Although practical constraints on available data limited the shared items to approximately 75% of variables, the CENTER-TBI frailty index score distribution in TRACK-TBI patients had the same skewed shape observed in CENTER-TBI. Similar results were seen when estimating the association with mid-term ordinal GOSE overall and in participants hospitalised in the ward.

Frailty has been explored in many clinical settings, including critical illness with ICU admission, and has been consistently associated with mortality, complications, prolonged length of hospital stay, post-hospitalisation functional decline, and reduced quality of life.[23] By definition, frailty is a multidimensional condition. Not surprisingly, numerous instruments have been developed to operationalise its measurement. Rockwood and colleagues[7,8] developed a cumulative deficit frailty instrument known as the Frailty Index. This frailty index includes clinical features, functional characteristics, and laboratory measures that are known to be associated with the development of adverse outcomes. Importantly, the Frailty Index is not simply a measure of multimorbidity but rather a multidimensional construct. Deficits in these items are counted, and a score is then expressed as a ratio of the deficits present. In our study, we used a cumulative deficit approach that defined frailty by enumerating health abnormalities, with less attention paid to the specific nature of each problem or its severity.

For all the cohorts in which the Frailty Index has been operationalised, population-relevant deficits have been considered, recognising that variables might be selected to best meet the study populations posited deficits, as we did in our study. Accordingly, in this standard methodological approach, although frailty can be measured in many ways, using different types and numbers of variables, it does not change the primary outcome of frailty, or alter its utility in outcome prediction. As Searle and colleagues[9] noted, it does not matter if one clinical condition has different weights in terms of outcome prediction compared with another condition because the Frailty Index considers the number of deficits only.

Until now, uncertainty has existed as to how frailty might affect outcome after an important stressor event, such as traumatic brain injury, due to a paucity of studies specific to traumatic brain injury and the fact that the accumulation of deficits before the traumatic event has been insufficiently considered.[11,17] Previous traumatic

brain injury cohorts have reported mortality (in-hospital and long term),[24] increased length of stay,[25] effects on discharge destination, and lower quality of life (future falls, disabilities, and cognitive impairment) in the presence of frailty.[26] Moreover, previous studies of frailty in patients with traumatic brain injury have considered only some of these tools. In a meta-analysis by Muscedere and colleagues,[12] ten observational studies were identified, enrolling a total of 3030 patients (927 frail and 2103 fit patients). Six studies used either the seven-item or the nine-item Clinical Frailty Scale, one study[27] used a frailty phenotype (ie, classifies the individuals as frail when three or more of the following five criteria are present: unintentional weight loss, exhaustion, slow walking speed, low physical activity, and low muscle strength; a classification of prefrailty is also possible when only one or two of these criteria are present), and three studies used a frailty index, alone or in combination with the Clinical Frailty Scale. More recent studies used an 11-item frailty index modified from the original accumulation of deficit model and the Tilburg Frailty Indicator.[17] Limits of these tools are the relative arbitrariness of the scoring system and the poor suitability in a working environment such as the ICU. For example, Fried's phenotype frailty tool[27] requires handgrip strength to be measured with a dynamometer, which is not always feasible on the patient's arrival after traumatic brain injury. Moreover, the low number of health deficits assessed might imply poor reliability of the frailty tool. Additionally, the Tilburg Frailty Indicator is composed of questions on sociodemographic variables not directly related to frailty, such as sex, marital status, level of education, lifestyle, and psychological and social functioning, some of which might be difficult to capture from administrative data or in a busy inpatient setting. The 30-item CENTER-TBI frailty index was built per the Rockwood approach with a method similar to that described by Mueller and colleagues[28] and Zeng and colleagues.[29] However, the latter study involved only 155 individuals[29] and used a dichotomised version of the frailty index, thus losing statistical efficiency and finesse of interpretation.

Frailty on its own asserts independent effects on mid-term functional outcome, suggesting that it should be added to age in prognostic models and be considered during initial assessments of traumatic brain injury. Indeed, classic prognostic models (eg, the IMPACT models),[3] along with parameters of injury severity and imaging, consider age alone but not frailty, with increasing age associated with poorer outcome. The individual intrinsic capacity peaks in early adulthood and tends to decline from midlife onwards. However, the trajectories of decline have great variability at an individual level, and some components of capacity might remain stable over the life course. As highlighted by the WHO *Global strategy and action plan on ageing and health*, a hallmark of ageing is the very broad range of individual intrinsic capacity observed across older adults. The process of ageing is not consistent in all people and predicting an individual's intrinsic capacity for a specific class of age might be inappropriate. For this reason, it is neither advisable nor adequate to use age as a surrogate of individual performance in traumatic brain injury outcomes, and our findings are in line with this principle.

We recognise several limitations to our analysis. First, the definition of frailty lacks a generally accepted standard. We developed the CENTER-TBI frailty index according to available variables in our dataset. Compared with other frailty indices, our index omits unavailable variables related to social and daily activities, nutritional status, and measures of cognitive impairment. However, as shown by Rockwood, the cumulative deficits approach can accurately capture frailty because the number of included items is large enough to describe detailed individual health status. We maintain that our exploration should be viewed as robust proof-of-concept research.

Second, we used laboratory data in development of our frailty index, consistent with previous work,[30] but we excluded several variables—eg, haemoglobin and platelets—that could be altered immediately after the traumatic event. To reduce possible effects of missing data, we selected only patients in whom more than 75% of the considered variables were available.

Third, a consensus about a single operational definition of frailty is still lacking after more than 20 years of intensive clinical research. The choice of a deficit accumulation model that incorporates many candidate factors, different from the most widely used operational definition of frailty that describes a phenotype (ie, the biological or syndromic construct), could be criticised. However, in the context of traumatic brain injury, frailty phenotypes seem to be more appropriate to define primary frailty and could potentially be applied in a preclinical context to tailor specific prevention strategies. However, these data are not available in the CENTER-TBI study.

Finally, our study aimed to evaluate associations of frailty with outcomes in traumatic brain injury, but these associations do not imply causation. A limited advantage was noted in terms of goodness of fit when the CENTER-TBI frailty index score was added to the core IMPACT predictors, meaning that the added value of frailty in prognostication is limited in hospitalised patients with traumatic brain injury. However, traumatic brain injury is a complex condition and might not be fully captured by baseline characteristics alone. Indeed, Nagelkerke's R^2 was 30·2 using the core IMPACT variables (ie, without considering the frailty index score), which is in line with published work, and the absolute increment of 1·7 points by including the CENTER-TBI frailty index in the model corresponds to a 5·6% increase in relative terms. The internal discriminative ability of the model considering both core IMPACT predictors and frailty index score (shown in table 2) is better when

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assessed internally (ie, in the CENTER-TBI cohort) than in the external validation cohort (ie, TRACK-TBI cohort). However, it should be emphasised that the C statistic for an ordinal outcome is a conservative measure. Finally, we calibrated the model shown in table 2 because this model is not yet an established prognostic model and work is needed to improve the frailty index.

With the age of patients with traumatic brain injury increasing, and frail patients more prone to experiencing a traumatic event, accurately assessing frailty has growing relevance. Our finding that frailty has a greater effect on outcomes for the subset of patients with less severe trauma advocates for routine assessment of frailty in such patients. Public health prevention strategies (eg, related to road traffic accidents) should be considered. Safer design within houses for older adults, aimed at reducing falls or other accidental trauma, could reduce incidence in this more frail and vulnerable population. Furthermore, systematic screening of frailty in primary care among older patients might help to identify patients at risk of poorer outcome after mild-to-moderate traumatic brain injury. Indeed, initial evidence suggests that frailty might be reversible with appropriate interventions.[31] Finally, during a hospital stay, collecting information on a patient's frailty status could help to individualise rehabilitation approaches aimed at mitigating effects of frailty, and to improve coping with the consequences of traumatic brain injury.

Contributors

SG and FG contributed to raw data verification, data analysis and interpretation, access to raw data, and drafting and critical revision of the article. AIRM, GI, FL, SRB, AJM, GTM, MGV, and GB contributed to data interpretation, and drafting critical revision of the article. SJ, XS, and RCG contributed to raw data verification, data analysis and interpretation, access to raw data of the validation cohort, critical revision of the article, final approval of the version to be published. Giuseppe Citerio contributed to the conception of the work, supervision of the data collection, data analysis and interpretation, access to raw data, and drafting and critical revision of the article. GC is the guarantor of the entire manuscript. All authors had access to all of the data and approved the final version of the manuscript for submission. CENTER-TBI participants and investigators and TRACK-TBI investigators (non-authors contributors) contributed to data collection.

Declaration of interests

GC reports grants, personal fees, and being an advisory board member for Integra and Neuroptics, all outside of the submitted work. All other authors declare no competing interests.

Data sharing

The data supporting the findings in the study are available upon reasonable request to the corresponding author and stored at https://center-tbi.incf.org/_5cf8e3d1c3b0d43708ebef42. Imaging data can be found at https://center-tbi.incf.org/_5cf4dbd0560bb01102b6b28e, data on vitals values at https://center-tbi.incf.org/_5cf4dce9560bb01102b6b28f, and data regarding medications can be found at https://center-tbi.incf.org/_5cf4de0d560bb01102b6b291. We plan to disseminate the results to study participants and or patient organisations on the CENTER-TBI website.

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