Factors associated with death and limitation of life-sustaining therapies in patients with traumatic brain injury

Brandi, Giovanna ; Stretti, Federica ; Schüpbach, Reto ; Krones, Tanja ; Bühler, Philipp K ; Steiger, Peter

Abstract: Aim of the Study: A substantial proportion of deaths of patients in the Intensive Care Unit (ICU) follow a decision to limit life-sustaining therapies. Patients with moderate to severe Traumatic Brain Injury (TBI) differ from the general ICU population: They are usually younger, previously healthy, and often with no advance directives. The objective of this study was to identify factors associated with mortality and limitation of life-sustaining therapies in patients with moderate to severe traumatic brain injury in a Swiss academic tertiary care hospital. Methods: This study was a retrospective single center analysis of 170 non-elective admissions to the surgical ICU of a Swiss academic tertiary care hospital over a three-year period. Patients were eligible for the study if diagnosed with moderate to severe blunt TBI, and if the ICU length of stay was at least 48 hrs. Factors associated with mortality were investigated. Results: Mean age was 48 ± 21 years, 72.3% were male, and pre-existing medical conditions were overall rare. Forty-five patients (26.5%) died within 6 months after TBI (Non-survivors group). Most deaths (n=43, 95.5%) occurred after limitation of life-sustaining therapies. In the multiple binary logistic regression model age, Protestant religion, hypoxemia during the rescue phase, a higher category in the Marshall classification and a higher Injury Severity Score were independently associated with death. Conclusion: At our institution, most deaths of patients with moderate to severe TBI occurred after a deliberate decision to limit life-sustaining therapies. This decision was associated with age, spiritual belief of the patient, hypoxemia in the pre-hospital setting, radiological findings, and severity scores. Written advance directives should be encouraged to help surrogate decision makers and physicians in the acute and sudden setting of TBI to respect the patient's willed.

Clinics in Surgery

Research Article
Published: 26 Feb, 2019

Factors Associated with Death and Limitation of Life-Sustaining Therapies in Patients with Traumatic Brain Injury

Giovanna Brandi[1], Federica Stretti[1,2], Reto Schüpbach[1], Tanja Krones[3], Philipp Karl Bühler[1], Peter Steiger[1] and Stephanie Klinzing[1]*

[1]Institute for Intensive Care Medicine, University Hospital of Zurich, Switzerland

[2]Department of Pathophysiology and Transplantation, University of Milan, Italy

[3]Clinical Ethics, University Hospital of Zurich, Switzerland

Abstract

Aim of the Study: A substantial proportion of deaths of patients in the Intensive Care Unit (ICU) follow a decision to limit life-sustaining therapies. Patients with moderate to severe Traumatic Brain Injury (TBI) differ from the general ICU population: They are usually younger, previously healthy, and often with no advance directives. The objective of this study was to identify factors associated with mortality and limitation of life-sustaining therapies in patients with moderate to severe traumatic brain injury in a Swiss academic tertiary care hospital.

Methods: This study was a retrospective single center analysis of 170 non-elective admissions to the surgical ICU of a Swiss academic tertiary care hospital over a three-year period. Patients were eligible for the study if diagnosed with moderate to severe blunt TBI, and if the ICU length of stay was at least 48 hrs. Factors associated with mortality were investigated.

Results: Mean age was 48 ± 21 years, 72.3% were male, and pre-existing medical conditions were overall rare. Forty-five patients (26.5%) died within 6 months after TBI (Non-survivors group). Most deaths (n=43, 95.5%) occurred after limitation of life-sustaining therapies. In the multiple binary logistic regression model age, Protestant religion, hypoxemia during the rescue phase, a higher category in the Marshall classification and a higher Injury Severity Score were independently associated with death.

Conclusion: At our institution, most deaths of patients with moderate to severe TBI occurred after a deliberate decision to limit life-sustaining therapies. This decision was associated with age, spiritual belief of the patient, hypoxemia in the pre-hospital setting, radiological findings, and severity scores. Written advance directives should be encouraged to help surrogate decision makers and physicians in the acute and sudden setting of TBI to respect the patient's willed.

Keywords: Traumatic brain injury; Mortality; Intensive care; Life-sustaining therapies; Withdrawal

OPEN ACCESS

Correspondence:
Giovanna Brandi, Institute for Intensive Care Medicine, University Hospital of Zurich, Zurich, Switzerland, E-mail: giovanna.brandi@usz.ch

Received Date: *11 Jan 2019*
Accepted Date: *22 Feb 2019*
Published Date: *26 Feb 2019*

Citation:
Brandi G, Stretti F, Schüpbach R, Krones T, Bühler PK, Steiger P, et al. Factors Associated with Death and Limitation of Life-Sustaining Therapies in Patients with Traumatic Brain Injury. Clin Surg. 2019; 4: 2341.

Abbreviations

TBI: Traumatic Brain Injury; ICU: Intensive Care Unit; ISS: Injury Severity Score; SDM: Surrogate Decision-Maker; ADs: Advance Directives; CT: Computed Tomography Scan; EOL: End of Life; GCS: Glasgow Coma Scale; AIS-head Abbreviated Injury Scale of the Head Region; SAPS II: Simplified Acute Physiology Score II; LOS: Length of Stay; MV: Days number of days on Mechanical Ventilation; RBCs: Red Blood Concentrates; CRRT: Continuous Renal Replacement Therapy; EDH: Epidural Mass; tSAH: Traumatic Subarachnoid Hemorrhage; GOS: Glasgow Outcome Scale; SD: Standard Deviation; IQR: Interquartile Range; OR: Odd-Ratio; CI: Confidence Interval

Introduction

Despite large regional and cultural variations, a large proportion of deaths in the Intensive Care Unit (ICU) occur after a deliberate process of limiting life-sustaining therapies [1-3]. Several determinants to the decision have been identified, including patient characteristics, disease process, therapeutic interventions, level of the acute care center- due to variation in physicians' perceptions

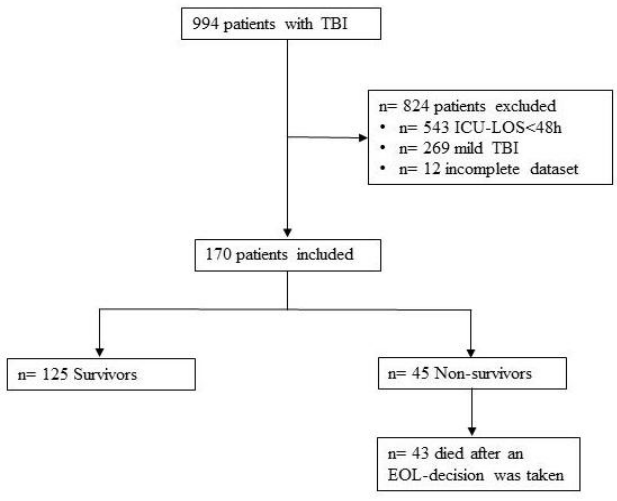

Figure 1: Study population.
Patients included in the study. TBI: Traumatic Brain Injury; ICU-LOS Length of Stay at the Intensive Care Unit; EOL: End of Life

of long-term prognosis and physicians' practice patterns for recommending limitation of life-sustaining therapies-, and Surrogate Decision-Makers (SDM) [2-5].

Traumatic Brain Injury (TBI) is the consequence of an acute and sudden event and represents the leading cause of death and disability in young adults [6]. Patients with moderate to severe TBI differ from the general ICU population. They are generally younger, previously healthy, and in most cases have not discussed or written down Advance Directives (AD) addressing their actual situation [7]. Furthermore, patients with TBI often in the acute phase do not have the possibility to communicate their preferences allowing to base therapeutic options on his or her presumed will. Moreover, SDM might be overwhelmed by the situation and might not serve as surrogate since they never discussed the situation with the patient before the accident. In addition, the existing prognostic models are helpful, but not designed to aid decision making on individual patient level [8-10].

In the past decades, an increasing trend of limitation of life-sustaining therapies has been observed in TBI patients in a Scottish unit [11]. Little is known about the factors contributing to the decision to suspend life-sustaining therapies in patients with TBI. A survey of intensivists, neurosurgeons, and neurologists participating in the care of TBI patients revealed wide variations concerning the use and the assessment of the usefulness of different prognostic predictors and tests (physical exam, Computed Tomography scan (CT), magnetic resonance imaging, and electrophysiology tests). Equally, there are significant uncertainties regarding the determination of prognosis and the decision process to limit life-sustaining therapies among responders [12]. Cote et al. [2] and Thompson et al. [13] identified some head CT-findings and an effect of intensity of care on mortality in patients with TBI. However, estimation of patient's will, religion and spiritual believes which legally have to build the base for the decision and also statistically have an influence were not included in their analysis [14-16]. Exclusion of actual or presumed will from the decision process is particularly problematic, since in some countries-such as Switzerland- respecting the actual or presumed will of the patients is mandatory.

This study aims to describe factors associated with mortality and having influenced the decision to limit life-sustaining therapies in patients with moderate and severe TBI admitted to our unit over a period of three years, and to relate the findings to existing data.

Material and Methods

This retrospective cohort study was performed at the surgical ICU of the University Hospital of Zurich, a level I Swiss Trauma Center, in compliance with the Declaration of Helsinki and the national legal and regulatory requirements, and was approved by the local Ethics Committee (KEK-ZH-Nr. 2016-00332, April 2016). Data acquisition followed the current Swiss regulations with no need for an explicit written informed consent.

Inclusion criteria were admission to the surgical ICU between 1 January 2012 and 30 June 2015 with diagnosis of blunt TBI (ICD Code S00-S09) by identification using the hospital's electronic database (KISIM™, Cistec® Zurich, Switzerland), and aged 16 or older. The classification as moderate or severe was based on the initial Glasgow Coma Scale (GCS <13) before sedation and intubation. Data were collected and medical charts were reviewed from the investigators.

Exclusion criteria were discharge from the ICU and death within 48 hr to avoid the inclusion of patients with initially over-estimated severity and no need of an intensified treatment, e.g. due to alcohol- or drug-influence at the time of trauma [17], and patients who deceased in the emergency room or before a meeting with the SDM was organized. At our institution a meeting with the SDM is held within 48 hrs from injury to identify goals of care based on documented or assumed patient's will. Treatment of TBI patients was based on an internal protocol, referring to international guidelines [18].

Baseline demographic and pre-hospital data, severity and prognostic scores, and intensity of care at the ICU were collected. Baseline demographic data included age, sex, religion, previous medical conditions (stroke, past TBI, epilepsy, diabetes mellitus, cardiovascular disease, use of anticoagulants and antiplatelet agents, psychiatric disorder and history of alcohol or drug abuse), presence of written ADs, and/or information on whether the patient discussed EOL issues with his or her next of kin before trauma. Pre-hospital data covered mechanism of injury (traffic accident, fall or other causes), hypotension (defined as systolic blood pressure <90 mmHg), hypoxemia (defined as SpO2 <90%), and pupillary reactivity during the rescue phase. Pupillary reactivity was considered pathological if one or both pupils presented no response to light. Severity scores included GCS before sedation and intubation, Injury Severity Score (ISS) [19], the Abbreviated Injury Scale of the head region (AIS-head) [20], and the Simplified Acute Physiology Score II (SAPS II) [21]. The IMPACT score, a prognostic model to predict mortality and unfavorable outcomes 6-months after TBI was calculated [22]. The IMPACT model is based on age, clinical findings (GCS motor component, pupillary reactivity), computed tomographic characteristics, secondary insults (hypoxemia, hypotension), and on laboratory values on admission (glucose, hemoglobin).

Intensity of care during the ICU stay was evaluated with the ICU-Length of Stay (LOS), the number of days on Mechanical Ventilation (MV-days), use of vasoactive drugs, amount of Red Blood Concentrates (RBCs), and use of Continuous Renal Replacement Therapy (CRRT). ICU mortality (ICU-mortality) was noted.

The Marshall classification of head injury was used based

Baseline demographic data	All (n=170)	Survivors (n=125)	Non-survivors (n=45)	Survivors vs Non-survivors
Age (years) [mean ± SD]	*48 ± 21*	44 ± 19	61 ± 22	p<0.00001
Sex (male) (%)	*123 (72.3)*	90 (72)	33 (73.3)	n.s.
Religion (%) • 1.Other/unknown • 2.Protestant • 3.Catholic • 4.Islamic	 *69 (40.6)* *52 (30.6)* *43 (25.3)* *6 (3.5)*	 58 (46.4) 29 (23.2) 33 (26.4) 5(4)	 11 (24.5) 23 (51.1) 10 (22.2) 1 (2.2)	 n.s. p=0.015 n.s. n.s.
Written AD (%)	*10 (5.9)*	4 (3.2)	6 (13.3)	p=0.023
EOL issue discussed	*22 (13.0)*	7 (5.6)	15 (34.1)	p<0.001
Stroke (%)	*2 (1.18)*	1 (0.8)	1 (2.2)	n.s.
Past TBI (%)	*14 (8.2)*	8 (6.4)	6 (13.3)	n.s.
Diabetes mellitus (%)	*11 (6.5)*	6 (4.8)	5 (11.1)	n.s.
Cardiac-disease (%)	*54 (31.8)*	34 (27.2)	20 (44.4)	p=0.033
Use of anticoagulants/ antiplatelet agents (%)	*28 (16.5)*	12 (9.6)	16 (35.6)	p<0.0001
Epilepsy (%)	*8 (4.7)*	5 (4)	3 (6.7)	n.s.
Alcohol/drug abuse (%)	*43 (25.3)*	36 (28.8)	7 (15.6)	n.s.
Pre-hospital data				
Cause of injury (%) • 1.Other/unknown • 2.Traffic accident • 3. Fall	 *39 (22.9)* *70 (41.2)* *61 (35.6)*	 34 (27.2) 52 (41.6) 39 (31.2)	 5 (11.1) 18 (40) 22 (48.9)	 n.s. n.s. n.s.
Hypotension (%)	*33 (19.6)*	20 (16.3)	13 (28.9)	n.s.
Hypoxemia (%)	*44 (26.2)*	26 (21.1)	18 (40)	p=0.014
Pathologic pupillary reactivity (%)	*36 (21.2)*	22 (17.6)	14 (31.1)	n.s.

Figure 2: Baseline demographic data and pre-hospital data of the study population.

on the first Computerized Tomography (CT) after trauma [23]. Particularly, the presence of Epidural Hematoma (EDH) and traumatic Subarachnoid Hemorrhage (tSAH) were noted. Long-term functional outcome was assessed with the Glasgow Outcome Scale (GOS) 6 months after trauma with a structured questionnaire and an interview of the patients [24].

For the analysis, patients were split in two groups based on GOS: Survivors includes patients still alive 6 months after injury (GOS ≥ 2), and non survivors includes patients who died 6 months following TBI (GOS 1). For non survivors, time of death (expressed in number of days after TBI), and place of death (ICU or normal ward, long-term care facilities, home) were collected.

The decision to limit life-sustaining therapies was classified as withholding or withdrawing treatment. Withholding treatment defines the decision not to start or increase a life-sustaining intervention (e.g. an order not to resuscitate). Withdrawing treatment refers to the active decision to stop provision of a life-sustaining intervention (e.g. vasopressors). Furthermore, timing of decision to limit the life-sustaining therapies (expressed in number of days after trauma), time of death after the decision (expressed in number of days after the decision was taken), and people involved in the decision (SDM, legal guardian) were collected.

For descriptive statistics, categorical variables were expressed as absolute numbers with percentages, normally distributed quantitative variables as mean ± Standard Deviation (SD) and non-normally distributed variables as median with Interquartile Range (IQR). The Kolmogorov-Smirnov test was used to verify normal distribution of continuous variables. Comparisons between the Survivors and the non survivors were performed with student's t test, Mann-Whitney test, Chi-square or Fisher's exact test, as appropriate. By statistically significant p-value, post-hoc tests were performed, taking into account the multi-comparison procedure. In order to identify risk factors associated with death, potential predictor variables were first selected by univariate analysis. Predictors with $p<0.1$ were entered into a multiple binary logistic regression model and mortality was the outcome variable. Goodness of fit of the regression was performed with the standard regression model [25]. The Odds-Ratios (ORs) were calculated and expressed with the corresponding 95% Confidence Intervals (95% CI). Statistical significance was set at p value <0.05 for all analyses. All analyses were performed using Stata version 12.1 (StatCorp. LP, College Station, TX, USA).

Results

During the study period, 994 patients with TBI were admitted to the surgical ICU. Of those, 170 fulfilled the inclusion criteria of the study (Figure 1). Mean age was 48 ± 21 years and 72.3% of the patients were male. Baseline demographic data, pre-hospital data, severity and prognostic scores, and intensity of care at the ICU of the study population overall are presented in Figure 2-5.

In the Survivors group (n=125, 72% male) mean age was 44 ± 19 years, while in the non-survivors group (n=45) patients were significantly older (mean age 61 ± 22 years, $p<0.0001$; 73.3% male). Baseline data and pre-existing medical conditions are listed in Figure 2. The two groups differed in frequency of cardio-vascular disease and use of anticoagulants/antiplatelet agents, which were significantly higher ($p=0.033$ and $p<0.0001$, respectively) in the non-survivors group. Pre-hospital data are presented in Figure 2. In particular, hypoxemia during the rescue phase occurred significantly more often in the non-survivors group ($p=0.014$).

Based on the Marshall classification, the survivor group includes significantly less patients with categories IV and VI than non-survivors. Furthermore, the rate of tSAH on the first CT-scan was significantly higher in the non-survivors group, as shown in Figure 3.

Concerning severity, based on ISS, SAPS II and IMPACT, patients

CT-findings	All (n=170)	Survivors (n=125)	Non-survivors (n=45)	
Marshall classification (%)				
• category I	*25 (14.7)*	22 (17.6)	3 (6.7)	n.s.
• category II	*59 (34.7)*	48 (38.4)	11 (24.4)	n.s.
• category III	*31 (18.2)*	23 (18.4)	8 (17.8)	n.s.
• category IV	*5 (2.9)*	1 (0.8)	4 (8.9)	p=0.009
• category V	*39 (23)*	30 (24)	9 (20)	n.s.
• category VI	*11 (6.5)*	1 (0.8)	10 (22.2)	p<0.0001
tSAH (%)	*120 (70.6)*	82 (65.6)	38 (84.4)	p=0.017
EDH (%)	*30 (17.6)*	26 (20.8)	4 (8.9)	n.s.

Figure 3: Marshall Classification of the study population.

Severity and prognostic scores	All (n=170)	Survivors (n=125)	Non-survivors (n=45)	Survivors vs Non-survivors
AIS-Head (%)				
• code 1	*26 (15.3)*	23 (18.4)	3 (6.7)	n.s.
• code 2	*27 (15.9)*	24 (19.2)	3 (6.7)	n.s.
• code 3	*61 (35.9)*	45 (36)	16 (35.6)	n.s.
• code 4	*56 (32.9)*	33 (26.4)	23 (51.0)	n.s.
ISS [mean ± SD]	*24.3 ± 12.5*	23.1 ± 12.4	27.8 ± 12.3	p=0.03
SAPS II [median, IQR]	*48 (34-58)*	45 (31-55)	55 (44-62)	p=0.0001
IMPACT-mortality [mean ± SD] (%)	*34.2 ± 20.8*	28.3 ± 18.5	50.6 ± 17.7	p<0.0001
IMPACT-unfavorable outcome [median, IQR](%)	*54 (29-75)*	43 (22-66)	76 (63-85)	p<0.0001
GCS	*6.3 ±3.2*	6.4 ± 3.1	6.1 ± 3.3	n.s.
GCS motor	*3.2 ± 2.0*	3.3 ± 2.0	2.9 ± 2.0	n.s.
GOS	*3.0 ± 1.4*	3.7 ± 0.7	1 ± 0	p< 0.0001

Figure 4: Severity and prognostic scores of the study population.

Intensity of care	All (n=170)	Survivors (n=125)	Non-survivors (n=45)	Survivors vs Non-survivors
ICU-LOS (days) [median, IQR]	*8.6 (3.7–7.7)*	9.7 (3.7-17.0)	6.7 (4.4- 10.9)	n.s.
MV-days (days) [median, IQR]	*4.8 (1.7-11)*	4.3 (1.3-11.7)	6 (3-8)	n.s.
ICU-mortality (%)	*27 (15.9)*	0 (0)	27 (60)	p<0.0001
ICP-probe (%)	*73 (42.9)*	54 (43.2)	19 (42.2)	n.s.
Barbiturate coma (%)	*8 (4.7)*	5 (4)	3 (6.7)	n.s.
Decompressive craniectomy (%)	*23 (13.5)*	16 (12.8)	7 (15.6)	n.s.
Vasoactive drugs (days) [median, IQR]	*3.7 (1.7-7.7)*	3.7 (1.3-8.7)	4.3 (2.7-7.3)	n.s.
CRRT (%)	*9 (5.3)*	6 (4.8)	3 (6.7)	n.s.
RBC (units) [median, IQR]	*1 (0-5)*	1 (0-5)	2 (0-5)	n.s.

Figure 5: Intensity of care for the study population.

in the non-survivors group had higher scores and consequently higher likelihood of unfavorable outcome compared to patients in the survivors group, as shown in Figure 4.

Intensity of care during the ICU stay did not differ between groups, as shown in Figure 5.

The majority of patients of the non-survivors group (n=43; 95.5%) died after a decision to limit life-sustaining therapies. In the majority of the cases life-sustaining therapies were withdrawn (overall, n=38, 22.3%, Survivors *vs.* non-survivors p<0.0001). Patients died 14 ± 16 days after trauma and 2 ± 2.7 days after EOL decision. Overall, only few patients in the study population had written ADs (n=10, 5.9%) or discussed EOL issues at least once with the SDM before TBI (n=22, 13%). In the Non-survivors group presence of written ADs and EOL issues discussion with the SDM prior to TBI were significantly more frequent than in the Survivors group (p=0.023 and p<0.0001, respectively), as shown in Figure 2. A next of kin was the SDM in the majority of the cases (97.6%), in both groups.

In the univariate logistic regression analysis mortality was associated with age (OR 1.04, CI 1.02-1.06, p<0.001), Protestant religion (OR 4.18, CI 1.79-9.74, p=0.001), previous cardio-vascular disease (OR 2.14, CI 1.05-4.34, p=0.035), use of anticoagulants/ antiplatelet agents (OR 5.19, CI 2.21-12.18, p<0.001), hypoxemia during the rescue phase (OR 2.49, CI 1.19-5.20, p=0.015), a higher category in the Marshall classification (OR 1.5, CI 1.20-1.88, p<0.0001), presence of tSAH on the first head-CT scan (OR 2.85, CI 1.17-6.91, p=0.021), code 4 of the AIS-Head (5.34, CI 1.43-19.91, p=0.013), ISS (OR 1.03, CI 1.00-1.06, p=0.033), and SAPS II (OR 1.04, CI 1.02-1.07, p<0.001).

	Univariable logistic regression			Multivariable logistic regression		
variable	OR	95%-CI	p value	OR	95%-CI	p value
Age (per year increase)	1.04	1.02-1.06	<0.001	1.04	1.01-1.06	0.008
Protestant religion (other as reference)	4.18	1.79-9.74	0.001	4.52	1.58-12.96	0.005
Hypoxia (no as reference)	2.48	1.19-5.19	0.015	3.62	1.32-9.89	0.012
Marshall classification (per category increase)	1.5	1.2-1.88	<0.001	1.74	1.29-2.34	<0.001
ISS (per unit increase)	1.03	1.00-1.06	0.033	1.06	1.02-1.10	0.004

Figure 6: Univariable and in multivariable logistic regression analysis.

In the multiple logistic regression model, age, Protestant religion, hypoxemia during the rescue phase, a higher category in the Marshall classification and a higher ISS were independently associated with mortality, as shown in Figure 6.

Discussion

The present study was conducted to evaluate factors associated with mortality in patients with moderate to severe TBI. Few studies have focused on this patient group [2,7,8,13,26], which are usually younger and have less comorbidities than the general critically ill population.

We conducted a multiple binary logistic regression analysis to identify factors associated with mortality. Because mortality occurred in the study population mostly due to non-sudden deaths following EOL decisions, we can speculate that its predictors were also crucial aspects for the decision to limit life-sustaining therapies.

As expected, also in this study TBI primarily affected young and previous healthy individuals. Furthermore, probably due to the sudden nature of TBI in younger patients, the existence of written ADs was extremely low (ca. 6% of the study population) and similar to a previous report [7]. This is notable, since in Switzerland- after the introduction of the new law for the protection of adults (2013) [27] - all inhabitants are encouraged to provide written ADs and to designate a SDM. Older patients with chronic or terminal illnesses and their physicians are more likely to actively fulfill this task, and also physicians in regions where Advance care planning is not part of the health care system actively bring this up with these patients [28,29]. ADs contain personal therapeutic goals and, particular for Switzerland, consent or dissent to specific medical measures. Furthermore, ADs commonly name one or more SDMs who, in case of incapability of decision-making by the patient- as in case of severe TBI, are appointed to decide on behalf of the patient based on documented or presumed patient's will.

In the study population and comparable to previous findings nearly all deaths (95.5%) occurred after an EOL decision [7,26] and, similar to data referring to the critically ill population in the general ICU [1,3], withdrawal of life-sustaining therapies was the most frequent kind of EOL decision. At our unit, these decisions occur only after reviewing any ADs that may exist, after extensive discussions with the SDM, and with the approval of both the family and the care team, which usually includes intensivists, ICU-nurses, neurosurgeons, trauma surgeons, and clinical ethicists. In contrast to individual decision and prognostic scores, this multifactorial approach from several perspectives could help to improve the decision to limit life-sustaining therapies.

Similar to previous studies referring to patients with TBI [26] and to the general ICU population [3,30], increasing age was associated with limitation of life-sustaining therapies. Interestingly and different to the findings from Thompson et al. [13], even though patients in the Non-survivors group were significantly older than patients in the survivors one, both groups received during their ICU stay similar duration of treatment (ICU-LOS, MV-days), frequency of rescue therapies for intracranial hypertension (barbiturate coma, decompressive craniectomy), and general ICU-therapies (vasopressors, CRRT and RBCs), so that we can postulate that an advanced age was associated with death and indirectly with limitation of life-sustaining therapies but not with reduced intensity of treatment per se.

How physician's and patient's religions influence the use of EOL therapies has been rarely investigated [26]. To our knowledge, this is the first study to evaluate the possible role of patient's religion in a population with TBI. The Ethicus study revealed that in the European general ICUs physicians who are Protestant, Catholic, or with no religion more frequently use withdrawal of life-sustaining treatments than physicians who are Greek Orthodox, Jewish, or Moslem. Our results reveal that mortality and indirectly limitation of life-sustaining therapies were also associated with the Protestant religion of the patient. Traditionally, Switzerland has been a country with strong secularism with no state religion, however with an important Protestant and Catholic tradition, which is about evenly balanced within the Swiss population. Even if the patients in the majority of the cases did not participate in the EOL discussion due to the neurological impairment, it seems that their spiritual believes were crucial factors influencing the EOL decision-making.

Similar to the results of Diringer et al. [5] in the setting of a neurology/neurosurgery ICU, the severity of the acute condition, expressed by a higher category in the Marshall classification of head injury and a higher ISS, influences mortality and the decision to limit life-sustaining therapies. Thus, this result shows that decisions to limit life-sustaining therapies are strongly influenced not only by the probability of mortality, but also by the predicted morbidity attributable to the neurological insult. Prognostication which is needed to guide physicians and SDM to approve or refuse medical treatments based on documented or assumed patient's preferences has, however, several limitations. Most prognostic models, in fact, are limited to their use for the first hours or days after TBI only, do not consider the evolution of the cerebral damage several days after trauma, and were not developed with the specific aim of influencing EOL decisions [8]. In addition, physicians` perceptions of neurologic prognosis have an important impact on the decision-making process, even though it is known that this perception is highly variable among physicians and based on personal experience, competence, and spiritual belief [12].

Our study has some limitations. First, it investigated patients admitted to a single ICU in a single institution; consequently it is possible that other institutions or different management styles would yield different results. Furthermore, the outcome variable of the study was mortality. Because almost the totality of deaths followed a redirection of care to limitation of life-sustaining therapies, we postulate that factors associated with death also influenced the EOL-decisions. Additionally, due to the retrospective design of the study, the observed data were limited to the information detailed in the patients' chart and no causal inferences are possible. Finally, because of limitations of our database, we did not investigate the influence of other relevant factors such as, for example, physician's attitudes about futile care that has been shown to influence decisions to limit life-sustaining therapies [3].

Processes leading to a limitation of life-sustaining therapies are complex, variable, and multifactorial, and represent an important topic and issue in particular in neurocritical care. Even if our analysis refers to a regional experience, our findings might contribute to better understand the delicate process of decision-making at the end of life.

In conclusion, the majority of deaths of patients with moderate to severe TBI at our institution follow a decision to limit life-sustaining therapies. Written ADs help SDMs and physicians in the acute and sudden setting of TBI to respect the patient's willed. Their writing should be encouraged in an intensive regionally implemented advance care planning concept even among young people to evoke and support patient's reflections on their preferences for treatment goals in severe TBI also regarding a permanent vegetative or minimally conscious state as a potential outcome [34]. Age, spiritual belief of patients, hypoxemia in the pre-hospital setting, outcome prognostication based on the Marshall classification and the ISS influenced death and indirectly the decision to limit life-sustaining therapies. Due to the conceptual limitation of current prognostication models, improved and multifactorial approaches to predict neurologic outcome are needed.

References

1. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. Am J Respir Crit Care Med. 1997;155:15-20.
2. Cote N, Turgeon AF, Lauzier F, Moore L, Scales DC, Bernard F, et al. Factors associated with the withdrawal of life-sustaining therapies in patients with severe traumatic brain injury: a multicenter cohort study. Neurocrit Care. 2013;18(1):154-60.
3. Sprung CL, Cohen SL, Sjokvist P, Baras M, Bulow HH, Hovilehto S, et al. End-of-life practices in European intensive care units: the Ethicus Study. JAMA. 2003;290(6):790-7.
4. Hakim RB, Teno JM, Harrell FE, Jr., Knaus WA, Wenger N. Factors associated with do-not-resuscitate orders: patients' preferences, prognoses, and physicians' judgments. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Ann Intern Med. 1996;125(4):284-93.
5. Diringer MN, Edwards DF, Aiyagari V, Hollingsworth H. Factors associated with withdrawal of mechanical ventilation in a neurology/neurosurgery intensive care unit. Crit Care Med 2001;29(9):1792-7.
6. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008;7(8):728-41.
7. Robertsen A, Forde R, Skaga NO, Helseth E. Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. Scand J Trauma Resusc Emerg Med. 2017;25:44.
8. Geurts M, Macleod MR, van Thiel GJ, van Gijn J, Kappelle LJ, van der Worp HB. End-of-life decisions in patients with severe acute brain injury. Lancet Neurol. 2014;13(5):515-24.
9. Honeybul S, Gillett GR, Ho KM. Uncertainty, conflict and consent: revisiting the futility debate in neurotrauma. Acta Neurochir (Wien). 2016;158(7):1251-7.
10. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol. 2014;10(2):99-114.
11. Wilson WT, McMillan T, Young AM, White MA. Increased trends in the use of treatment-limiting decisions in a regional neurosurgical unit. Br J Neurosurg. 2017;31(2):254-57.
12. Turgeon AF, Lauzier F, Burns KE, Meade MO, Scales DC, Zarychanski R, et al. Determination of neurologic prognosis and clinical decision making in adult patients with severe traumatic brain injury: a survey of Canadian intensivists, neurosurgeons, and neurologists. Crit Care Med. 2013;41(4):1086-93.
13. Thompson HJ, Rivara FP, Jurkovich GJ, Wang J, Nathens AB, MacKenzie EJ. Evaluation of the effect of intensity of care on mortality after traumatic brain injury. Crit Care Med. 2008;36(1):282-90.
14. Ball CG, Navsaria P, Kirkpatrick AW, Vercler C, Dixon E, Zink J, et al. The impact of country and culture on end-of-life care for injured patients: results from an international survey. J Trauma 2010;69(6):1323-33.
15. Sprung CL, Maia P, Bulow HH, Ricou B, Armaganidis A, Baras M, et al. The importance of religious affiliation and culture on end-of-life decisions in European intensive care units. Intensive Care Med. 2007;33(10):1732-9.
16. Sprung CL, Carmel S, Sjokvist P, Baras M, Cohen SL, Maia P, et al. Attitudes of European physicians, nurses, patients, and families regarding end-of-life decisions: the ETHICATT study. Intensive Care Med. 2007;33(1):104-10.
17. Stocchetti N, Pagan F, Calappi E, Canavesi K, Beretta L, Citerio G, et al. Inaccurate early assessment of neurological severity in head injury. J Neurotrauma. 2004;21(9):1131-40.
18. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24 Suppl 1: S1-106.
19. Baker SP, O'Neill B, Haddon W, Jr., Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14(3):187-96.
20. Gennarelli TA, Wodzin E. AIS 2005: a contemporary injury scale. Injury. 2006;37(12):1083-91.
21. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270:2957-63.
22. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008;5:e165; discussion e65.
23. Marshall LF, Marshall SB, Klauber MR, Van Berkum Clark M, Eisenberg H, Jane JA, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma. 1992;9(1):287-92.
24. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma. 1998;15(8):573-85.
25. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. Stat Med. 1997;16:965-80.
26. Lilley EJ, Williams KJ, Schneider EB, Hammouda K, Salim A, Haider AH, et al. Intensity of treatment, end-of-life care, and mortality for older patients with severe traumatic brain injury. J Trauma Acute Care Surg. 2016;80(6):998-1004.

27. Büchler. Medical law in Switzerland. 2nd edn. Wolters Kluwer Law & Business 2016. 2016.

28. Teno JM, Gruneir A, Schwartz Z, Nanda A, Wetle T. Association between advance directives and quality of end-of-life care: a national study. J Am Geriatr Soc. 2007;55(12):189-94.

29. De Vleminck A, Pardon K, Houttekier D, Van den Block L, Vander Stichele R, Deliens L. The prevalence in the general population of advance directives on euthanasia and discussion of end-of-life wishes: a nationwide survey. BMC Palliat Care. 2015;14:71.

30. Esteban A, Gordo F, Solsona JF, Alia I, Caballero J, Bouza C, et al. Withdrawing and withholding life support in the intensive care unit: a Spanish prospective multi-centre observational study. Intensive Care Med. 2001;27(11):1744-9.

31. Chi JH, Knudson MM, Vassar MJ, McCarthy MC, Shapiro MB, Mallet S, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: a prospective multicenter study. J Trauma. 2006;61(5):1134-41.

32. Oddo M, Levine JM, Mackenzie L, Frangos S, Feihl F, Kasner SE, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery. 2011;69(5):1037-45.

33. Spaite DW, Hu C, Bobrow BJ, Chikani V, Barnhart B, Gaither JB, et al. The Effect of Combined Out-of-Hospital Hypotension and Hypoxia on Mortality in Major Traumatic Brain Injury. Ann Emerg Med. 2017;69(1):62-72.

34. Tolle SW, Teno JM. Lessons from Oregon in Embracing Complexity in End-of-Life Care. N Engl J Med 2017;376(11):1078-82.