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ORIGINAL



Occurrence and timing of withdrawal of life-sustaining measures in traumatic brain injury patients: a CENTER-TBI study

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Abstract

Background: In patients with severe brain injury, withdrawal of life-sustaining measures (WLSM) is common in intensive care units (ICU). WLSM constitutes a dilemma: instituting WLSM too early could result in death despite the possibility of an acceptable functional outcome, whereas delaying WLSM could unnecessarily burden patients, families, clinicians, and hospital resources. We aimed to describe the occurrence and timing of WLSM, and factors associated with timing of WLSM in European ICUs in patients with traumatic brain injury (TBI).

Methods: The CENTER-TBI Study is a prospective multi-center cohort study. For the current study, patients with traumatic brain injury (TBI) admitted to the ICU and aged 16 or older were included. Occurrence and timing of WLSM were documented. For the analyses, we dichotomized timing of WLSM in early (< 72 h after injury) versus later (\geq 72 h after injury) based on recent guideline recommendations. We assessed factors associated with initiating WLSM early versus later, including geographic region, center, patient, injury, and treatment characteristics with univariable and multivariable (mixed effects) logistic regression.

Results: A total of 2022 patients aged 16 or older were admitted to the ICU. ICU mortality was 13% ($n = 267$). Of these, 229 (86%) patients died after WLSM, and were included in the analyses. The occurrence of WLSM varied between regions ranging from 0% in Eastern Europe to 96% in Northern Europe. In 51% of the patients, WLSM was early. Patients in the early WLSM group had a lower maximum therapy intensity level (TIL) score than patients in the later WLSM group (median of 5 versus 10). The strongest independent variables associated with early WLSM were one unreactive pupil (odds ratio (OR) 4.0, 95% confidence interval (CI) 1.3–12.4) or two unreactive pupils (OR 5.8, CI 2.6–13.1) compared to two reactive pupils, and an Injury Severity Score (ISS) if over 41 (OR per point above 41 = 1.1, CI 1.0–1.1). Timing of WLSM was not significantly associated with region or center.

Conclusion: WLSM occurs early in half of the patients, mostly in patients with severe TBI affecting brainstem reflexes who were severely injured. We found no regional or center influences in timing of WLSM. Whether WLSM is always appropriate or may contribute to a self-fulfilling prophecy requires further research and argues for reluctance to institute WLSM early in case of any doubt on prognosis.

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Keywords: Traumatic brain injury, Critical care, Intensive care unit, WLSM

Introduction

A proportion of patients in the ICU dies after withdrawal of life-sustaining measures (WLSM) due to perceived very poor prognosis, deemed incompatible with meaningful recovery. Many patients with very severe brain injury die after WLSM [1]. The occurrence of WLSM in TBI patients is highly variable, ranging from 45% of all deaths in some hospitals, to almost 90% in others [2]. Not only the occurrence of WLSM is highly variable, but also the timing of WLSM is variable across hospitals [3]. Instituting WLSM too early could result in patients dying despite an ultimately acceptable outcome, whereas unduly delayed WLSM could lead to unnecessary burden to patients, families, and clinicians.

In patients with TBI, prognostication and early decision-making is fraught with uncertainty, particularly in the first few hours or days after hospital admission. Clinicians and families often struggle with the prospect of a high chance of persistent severe disability with subsequent prolonged and continued treatment versus the sometimes much smaller chance of an acceptable recovery. Studies have shown that even comatose patients after moderate and severe TBI have substantial probabilities of regaining functional independence [4, 5].

An interval of 72 h between time of injury and WLSM is sometimes used to determine both the initial effect of an injury and the subsequent trajectory of early treatment response [6–8]. The Joint Professional Standards committee and the Neurocritical Care Society (NCS) have also recommended an observation period of up to 72 h in patients with devastating brain injury before WLSM is considered [9]. However, few empirical data on timing and factors associated with timing of WLSM are available [10].

Therefore, we aimed to describe the occurrence and timing of WLSM in TBI patients in European ICUs, and assess factors associated with early versus later WLSM.

Methods

CENTER-TBI study

The Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI, registered at clinicaltrials.gov NCT02210221) study is a prospective cohort study conducted in 63 centers from 18 countries across Europe and Israel between December 2014 and December 2017. Patients were included if they had a clinical diagnosis of TBI, presented to hospital within 24 h after

Take-home message

Withdrawal of life-sustaining measures (WLSM) occurs within 72 h in half of the patients. The occurrence of WLSM varies between regions. The timing of WLSM, however, is not influenced by region or center. WLSM within 72 h occurs mostly in patients with severe TBI affecting brainstem reflexes who were severely injured. Whether WLSM is always appropriate or may contribute to a self-fulfilling prophecy requires further research and argues for reluctance to institute WLSM early in case of any doubt on prognosis.

injury, and had a clinical indication for head computed tomography (CT) scanning.

Patients were excluded if they had a severe preexisting neurological disorder that would confound outcome assessment. Ethics approval was acquired for each center and consent for participation obtained from all patients or their proxies. For more information on the CENTER-TBI study, see previous publications [11, 12].

For this study, we selected patients aged 16 or older, who were admitted to the ICU. Data on patient demographics, injury, imaging, admission, monitoring, treatment, and ICU discharge were extracted. We grouped countries into seven regions: Baltic States (Latvia, and Lithuania), Eastern Europe (Hungary, Romania, and Serbia), Israel, Northern Europe (Denmark, Finland, Norway, and Sweden), Southern Europe (Italy, and Spain), the United Kingdom, and Western Europe (Austria, Belgium, France, Germany, the Netherlands). We excluded regions that had less than five deaths. We specifically focused on patients who did not survive their ICU stay. In an earlier publication of Huijben et al. [13], more information on the whole cohort of ICU patients was reported.

WLSM and timing

In the electronic case report form (e-CRF), life-sustaining measures were defined as “mechanical ventilation; vasoactive medication; CVVH; intravenous fluids”. We considered patients to have died after WLSM if the WLSM date or time was reported, or if the investigators documented a main reason for WLSM in the e-CRF.

To assess the timing of WLSM, we calculated the time until WLSM in hours by taking the difference between time of injury and time of WLSM. If the WLSM date and/or time was missing, we manually imputed the date and/or time with the ICU discharge date and/or time. If ICU discharge date and time were missing, we manually imputed the date and time with the date and time of death. If the time of death was missing, we imputed

12:00 at noon as time of WLSM. For patients who did not survive their ICU stay, ICU discharge date and time was equal to the date and time of death.

Similarly, to assess the time between WLSM and death, we calculated the time until ICU discharge in hours by taking the difference between the time of WLSM and time of ICU discharge.

Statistical analyses

Baseline characteristics are presented as median values with interquartile ranges (IQRs) for continuous variables and as frequencies and percentages for categorical variables. We compared characteristics between patients alive on discharge from ICU to patients who died in the ICU, between patients who died after WLSM and those in whom WLSM was not reported prior to death, and between patients with early WLSM (<72 h) and patients with later WLSM (≥ 72 h). This dichotomization was based on recommendations from the NCS to wait 72 h before instituting WLSM [9].

Furthermore, we collapsed categories 3 and 4 of the American Society of Anesthesiologists Physical Status (ASAPS) classification because category 4 had <10 patients. We also collapsed category V and VI of the Marshall CT classification as grading V and VI could not be differentiated on central review as the raters were not aware of (intent to) surgery. We used the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) core model to calculate the probability of mortality and unfavorable outcome [14]. We dichotomized this probability of mortality and expected unfavorable outcome: if the calculated probability of mortality was >80%, we called it 'a high probability of mortality'. Likewise, if the calculated probability of unfavorable outcome was >80%, we considered it 'a high probability of unfavorable outcome'. Further, we presented box-plots of the predicted probabilities for the different outcome groups (alive, deceased after WLSM, WLSM not reported prior to death, early WLSM, later WLSM).

We used logistic regression models with early versus later WLSM as dependent variable to analyze univariable and multivariable associations with the following variables: age, GCS motor score, and pupillary reaction at baseline, gender, Injury Severity Score (ISS), hemodynamic stability, and geographic region. Baseline scores were measured after stabilization of the patient. All variables were chosen based on clinical judgement. Associations were presented as odds ratios (OR) with 95% confidence intervals (CI). An OR <1 indicated a lower probability of early WLSM, whereas an OR >1 indicated a higher probability of early WLSM. We allowed

for non-linear effects using restricted cubic splines with three knots for ISS.

To assess the influence of region or center, we compared multiple logistic regression models: a fixed-effect model including region to a model without region, a random-effects model with region as random intercept to a model without region as random intercept, and a random-effects model with center as random intercept to a model without center as random intercept. As sensitivity analyses, we fitted the preceding random-effects models in subsets only including centers with 5 or more WLSM, and only in patients with complete data on the timing of WLSM. Models were compared using the likelihood ratio test to determine the significance of the between-center and the between-region influence with the *p* value divided by 2 because the corresponding *p* values require a mixture distribution since the null hypothesis is on the boundary of the parameter space. To address possible concerns about effects of procedures for imputation of missing date and/or time values, we conducted two sensitivity analyses. First, we performed a complete case analysis, excluding all patients with missing information on dates and times of WLSM. Second, we transposed all patients with missing information on date of WLSM to the early group, and re-did the analyses.

The data and the analyses supporting the findings in the study are available upon reasonable request from the corresponding Author (EvV). Version 3.0 of the CENTER-TBI core dataset (data frozen in February 2021) was used in this manuscript. All statistical analyses were performed in R (version 3.6.1) and RStudio (version 1.2.5019), Missing data were imputed using Multivariate Imputation by Chained Equations [15].

Results

Patient characteristics

A total of 2022 patients of 16 years or older were admitted to the ICU. For 1998 patients (99%), the ICU discharge status (deceased or alive) was known. ICU mortality was 13% ($n=267$) (Table S1, appendix). Of these, 229 (86%) patients died after WLSM. The occurrence of WLSM in patients who did not survive their ICU stay varied between regions from 0% in Eastern Europe to 96% in Northern Europe (Table 1).

Of the 229 patients that died after initiating WLSM, 117 patients (51%) had their LSM withdrawn early (<72 h after injury), whereas 112 patients (49%) had their LSM withdrawn later (≥ 72 h after injury). For ten patients (4%), missing time of WLSM was imputed. For 44 patients (19%), missing WLSM date and time were imputed. WLSM was followed by organ donation in 29 patients (25%) in the early group and in 14 patients (13%) in the later group. The median age in the early WLSM group was 61 (IQR 37–75) compared to 60 (IQR

Table 1 Baseline characteristics of deceased patients

	WLSM status		Timing of WLSM	
	No WLSM n = 38	WLSM n = 229	< 72 h n = 117	≥ 72 h n = 112
Patient characteristics				
Age (median [IQR])	67.50 [52.00, 76.50]	60.00 [39.00, 74.00]	61.00 [37.00, 75.00]	60.00 [40.00, 71.25]
Sex male (%)	33 (86.8)	167 (72.9)	86 (73.5)	81 (72.3)
Pre-injury ASAPS classification (%)				
A normal healthy patient	12 (36.4)	86 (42.8)	46 (44.2)	40 (41.2)
A patient with a mild systemic disease	13 (39.4)	79 (39.3)	40 (38.5)	39 (40.2)
A patient with a severe systemic disease	8 (24.2)	36 (17.9)	18 (17.3)	18 (18.6)
Any medical history (%)	24 (64.9)	141 (61.8)	71 (60.7)	70 (63.1)
Region				
Western Europe	12 (31.6)	119 (52)	64 (54.7)	55 (49.1)
Eastern Europe	11 (28.9)	0 (0)	0 (0)	0 (0)
Northern Europe	1 (2.6)	26 (11.4)	14 (12)	12 (10.7)
Southern Europe	9 (23.7)	52 (22.7)	28 (23.9)	24 (21.4)
United Kingdom	5 (13.2)	32 (14)	11 (9.4)	21 (18.8)
Baseline characteristics				
GCS motor baseline (%)				
1	19 (51.4)	142 (64.8)	84 (73.7)	58 (55.2)
2	1 (2.7)	16 (7.3)	10 (8.8)	6 (5.7)
3	2 (5.4)	10 (4.6)	5 (4.4)	5 (4.8)
4	4 (10.8)	14 (6.4)	5 (4.4)	9 (8.6)
5	6 (16.2)	20 (9.1)	5 (4.4)	15 (14.3)
6	5 (13.5)	17 (7.8)	5 (4.4)	12 (11.4)
Pupils baseline (%)				
Both reactive	18 (54.5)	100 (46.3)	30 (26.8)	70 (67.3)
One reactive	2 (6.1)	21 (9.7)	13 (11.6)	8 (7.7)
Both unreactive	13 (39.4)	95 (44)	69 (61.6)	26 (25)
Total ISS (median [IQR])	34.00 [25.00, 45.00]	41.00 [26.00, 75.00]	50.00 [26.00, 75.00]	35.00 [26.00, 50.00]
Major Extracranial Injury (%)	18 (47.4)	132 (57.6)	62 (53)	70 (62.5)
Hypoxia (%)	7 (20.6)	43 (21.8)	27 (26.7)	16 (16.7)
Hypotension (%)	6 (20)	47 (22.8)	30 (28.6)	17 (16.8)
CT characteristics				
Marshall CT classification (%)				
I	1 (3)	8 (3.8)	3 (2.8)	5 (5)
II	6 (18.2)	24 (11.4)	6 (5.5)	18 (17.8)
III	4 (12.1)	40 (19)	25 (22.9)	15 (14.9)
IV	0 (0)	12 (5.7)	8 (7.3)	4 (4.0)
V/VI	22 (66.7)	126 (60)	67 (61.5)	59 (58.4)
Anything present on CT (%)	31 (81.6)	194 (84.7)	102 (87.2)	92 (82.1)
Epidural hematoma present on CT (%)	3 (7.9)	21 (9.2)	9 (7.7)	12 (10.7)
Acute Subdural hematoma present on CT (%)	26 (68.4)	137 (59.8)	79 (67.5)	58 (51.8)
Acute Subarachnoid hemorrhage present on CT (%)	26 (68.4)	137 (59.8)	79 (67.5)	58 (51.8)
ICU admission/treatments				
ICU admission reason (%)				
Mechanical ventilation	20 (52.6)	121 (54.8)	67 (60.4)	54 (49.1)
Frequent neurological observations	5 (13.2)	38 (17.2)	13 (11.7)	25 (22.7)
Hemodynamic invasive monitoring	1 (2.6)	8 (3.6)	4 (3.6)	4 (3.6)
Extracranial injuries	1 (2.6)	4 (1.8)	3 (2.7)	1 (0.9)

Table 1 (continued)

	WLSM status		Timing of WLSM	
	No WLSM n = 38	WLSM n = 229	< 72 h n = 117	≥ 72 h n = 112
Neurological operation	9 (23.7)	22 (10)	9 (8.1)	13 (11.8)
Clinical deterioration	2 (5.3)	28 (12.7)	15 (13.8)	12 (11.5)
Hemodynamic stability upon ICU admission (%)	27 (71.1)	139 (61.2)	62 (53.0)	77 (70)
Intubated upon ICU admission (%)	34 (89.5)	218 (95.2)	112 (95.7)	106 (94.6)
Mechanically ventilated upon ICU admission (%)	34 (89.5)	209 (91.7)	106 (91.4)	103 (92)
ICP monitor present (%)	21 (55.3)	132 (57.6)	44 (37.6)	88 (78.6)
Intubated during hospital stay (%)	37 (97.4)	214 (94.3)	107 (91.5)	107 (97.3)
Tracheostomy during hospital stay (%)	10 (26.3)	16 (7)	3 (2.6)	13 (11.8)
Oxygen administration during hospital stay (%)	32 (84.2)	146 (67.9)	72 (64.3)	74 (71.8)
Intracranial surgery during hospital stay (%)	20 (52.6)	105 (45.9)	40 (34.2)	65 (58)
Extracranial surgery during hospital stay (%)	4 (10.5)	39 (17)	14 (12)	25 (22.3)
ICP control				
Metabolic suppression for ICP control (with high dose barbiturates or propofol) (%)	12 (38.7)	64 (30.6)	18 (17.8)	46 (42.6)
Neuromuscular blockade (paralysis) (%)	7 (22.6)	60 (28.7)	23 (22.8)	37 (34.3)
Intensive hypocapnia for ICP control [PaCO ₂ < 4.0 kPa (30 mmHg)] (%)	6 (19.4)	16 (7.7)	6 (5.9)	10 (9.3)
Hypothermia below 35 °C (%)	4 (12.9)	38 (18.2)	18 (17.8)	20 (18.5)
Decompressive craniectomy	4 (12.9)	39 (18.7)	16 (15.8)	23 (21.3)
Maximum TIL during ICU stay (median [IQR])	6.50 [2.25, 11.75]	8.00 [3.00, 13.25]	5.00 [1.00, 11.00]	10.00 [6.50, 15.00]
Outcomes				
Decision maker of WLSM				
Multidisciplinary	NA	156 (83)	81 (81.8)	75 (84.3)
By a single physician	NA	1 (0.5)	1 (1)	0 (0)
With a relative	NA	31 (16.5)	17 (17.2)	14 (15.7)
Length of hospital stay in days (median [IQR])	6.47 [2.53, 12.94]	3.14 [1.12, 8.84]	1.13 [0.56, 1.87]	8.88 [5.36, 14.32]
Time in hours between injury and WLSM (median [IQR])	NA	68.55 [23.25, 213.00]	23.60 [12.07, 36.55]	213.81 [119.38, 344.37]
Time in hours between WLSM and death (median [IQR])	NA	0.33 [0.00, 6.20]	0.33 [0.00, 7.00]	0.29 [0.00, 4.60]
IMPACT core probability of mortality 80% or higher (%)	3 (9.1)	19 (9.1)	13 (11.8)	6 (6.1)
IMPACT core probability of unfavorable outcome 80% or higher (%)	13 (39.4)	95 (45.5)	66 (60)	29 (29.3)

ASAPS American Society of Anesthesiologists Physical Status; CI confidence interval; CT computed tomography; GCS Glasgow Coma Scale; ICP intracranial pressure; ICU intensive care unit; IMPACT International Mission for Prognosis and Analysis of Clinical Trials in TBI; ISS injury severity score; IQR interquartile range; OR odds ratio; WLSM withdrawal of life-sustaining measures

40–71) in the later WLSM group. The early WLSM group more often had a GCS motor score of 1 (74% versus 55%, respectively), an acute subdural hematoma (68% versus 52%, respectively), hypoxia and hypotension pre-hospital or in the ER (27% versus 17% and 29% versus 17%, respectively). However, intracranial surgery and extracranial surgery were less often performed in the early WLSM group compared to the later WLSM group (34 and 12% versus 58 and 22%, respectively). The maximum TIL score during ICU stay was lower in the early WLSM group compared to the later WLSM

group (median [IQR] 5 [1–11] versus 10 [6.50–15]). Decisions to withdraw LSM were made in consultation with a relative in 17% of the early WLSM group and in 15% in the later WLSM group (Table 1).

In a sensitivity analysis, excluding all patients who went for organ donation after WLSM, 47% of the patients had their LSM withdrawn early (Table S2, appendix).

The median time between injury and WLSM was 69 h (IQR 23–213) (Table 1). In the early WLSM group, the median time was 24 h (IQR 12–37), compared to 214 h (IQR 119–344) in the later WLSM group (Table 1).

Variables associated with early versus later WLSM

In univariable analysis, significant differences in patient characteristics were found between early and later WLSM. Features associated with early WLSM (OR > 1) included one (OR 4.60, CI 1.74–12.17) or two (OR 6.61, CI 3.56–12.27) unreactive pupils compared to both reactive pupils, and a higher total ISS (OR per point 1.03, CI 1.02–1.05). Conversely, hemodynamic stability upon ICU admission (OR 0.48, CI 0.28–0.83) was associated with later WLSM. After adjustment for other variables, one unreactive pupil (OR 3.97, CI 1.28–12.36) or two unreactive pupils (OR 5.80, CI 2.57–13.10) compared to both reactive pupils, and an ISS if over 41 (OR 1.05 per point above 41, CI 1.02–1.08) remained independently associated with early WLSM (Table 2). In a sensitivity analysis that only included patients without missing data on the date and/or time of WLSM, one unreactive pupil compared to both reactive pupils had a comparable association with early WLSM, although no longer statistically significant (OR 3.38, CI 0.73–15.71). In

an exploratory sensitivity analysis in which all patients were included in the early WLSM group when they had missing information on date of WLSM, results were similar as in the primary analyses (Table S3, appendix). Region did not influence early versus later WLSM when comparing a fixed-effect model with and without region (p value of 0.93). Similarly, there were no differences in timing of WLSM between regions or centers in multivariable models with a random intercept for region or center compared to models without (p value of 0.5 in both cases). This was confirmed in a sensitivity analysis, where only centers with > 5 patients who died after WLSM were analyzed.

Probability of mortality and unfavorable outcome using the IMPACT core score

The predicted probabilities for mortality and for unfavorable outcome were highest in the early WLSM group (Figs. 1 and 2). Patients who survived their ICU stay had a high (>80%) predicted probability of mortality and unfavorable outcome

Table 2 Unadjusted and adjusted OR and CI for initiating WLSM early (< 72 h)

Variables	Unadjusted OR	CI	Adjusted OR	CI
Pre-injury characteristics				
Male	1.06	0.59–1.91	1.00	0.49–2.04
ASAPS 1 (ref)	1		1	
ASAPS 2	0.96	0.53–1.75	1.18	0.48–2.92
ASAPS 3	1.05	0.51–2.14	1.41	0.49–4.03
Region				
Western Europe (ref)	1		1	
Northern Europe	1.00	0.43–2.36	0.80	0.28–2.28
Southern Europe	1.00	0.52–1.93	1.15	0.51–2.61
United Kingdom	0.45	0.20–1.02	1.12	0.40–3.17
IMPACT core variables				
Age	1.00	0.99–1.01	1.02	0.99–1.04
GCS motor* 1 (ref)	1		1	
GCS motor 2	0.99	0.35–2.76	0.96	0.29–3.22
GCS motor 3	0.66	0.18–2.36	0.84	0.19–3.80
GCS motor 4	0.34	0.11–1.06	0.53	0.13–2.10
GCS motor 5	0.23	0.08–0.66	0.41	0.11–1.46
GCS motor 6	0.31	0.11–0.93	0.88	0.24–3.22
Pupils both reactive* (ref)	1		1	
Pupils one reactive	4.60	1.74–12.17	3.97	1.28–12.36
Pupils both unreactive	6.61	3.56–12.27	5.80	2.57–13.10
Injury severity				
ISS score per point (< 41)	0.97	0.93–1.02	0.96	0.91–1.01
ISS score per point (> 41)	1.06	1.04–1.09	1.05	1.02–1.08
ICU admission/treatments				
Hemodynamic stability upon ICU admission	0.48	0.28–0.83	0.55	0.28–1.08

ASAPS American Society of Anesthesiologists Physical Status; CI confidence interval; GCS Glasgow Coma Scale; ICU intensive care unit; ISS injury severity score; OR odds ratio; WLSM withdrawal of life-sustaining measures

*GCS motor score and pupils were measured at baseline

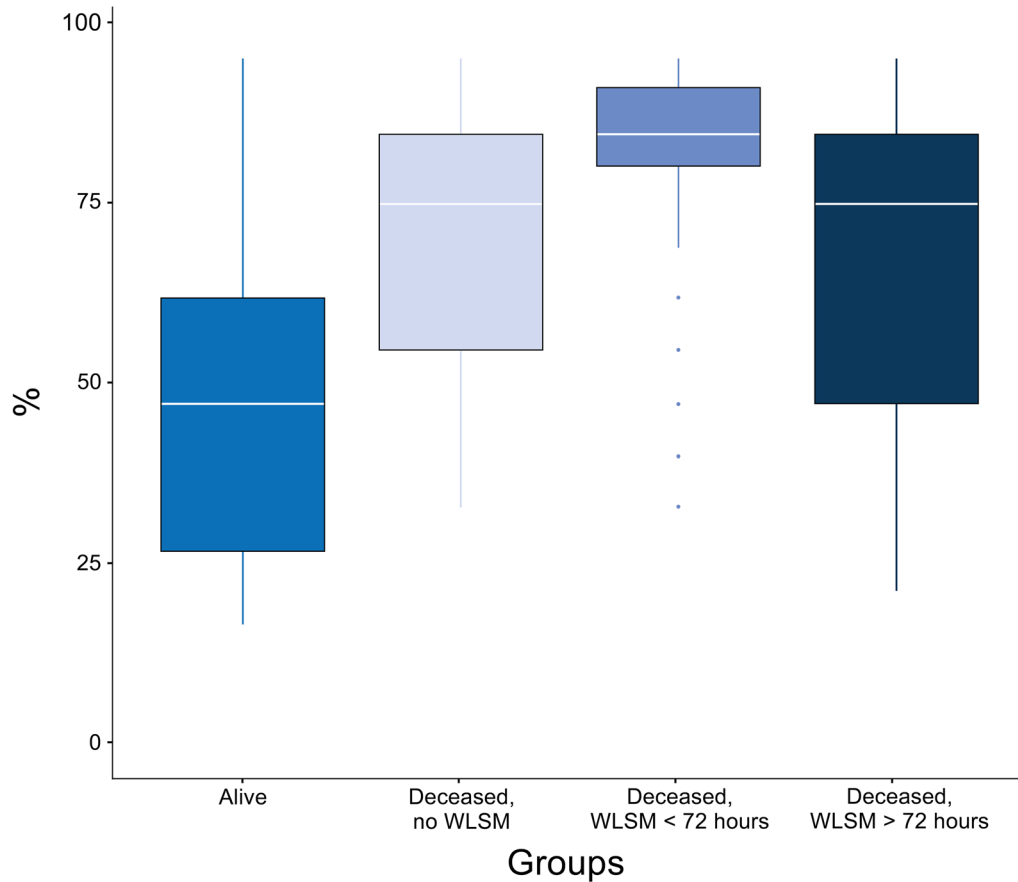


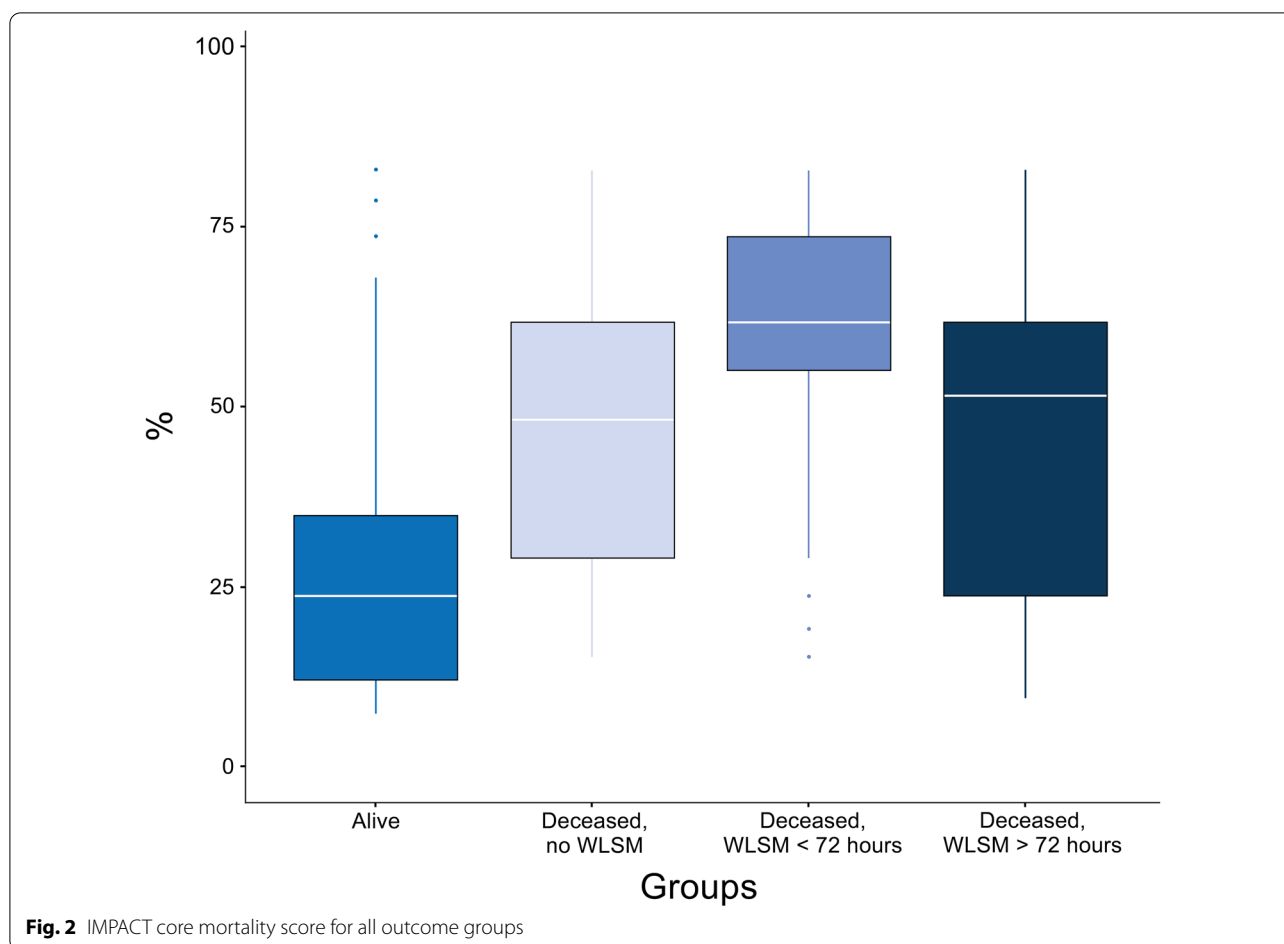
Fig. 1 IMPACT core unfavorable outcome score for all outcome groups

less often than patients who did not survive their ICU stay (1 and 8% versus 9 and 45%, respectively) (Table S1, appendix). Of the 229 patients that died after WLSM, 9% had a high probability of mortality, and 46% had a high probability of unfavorable outcome. Patients who had their LSM withdrawn early compared to later more often had a high probability of mortality and unfavorable outcome (12 and 60% versus 6 and 29%, respectively) (Table 1).

Discussion

We aimed to describe the occurrence and timing of WLSM in patients with TBI, and assess variables associated with early (<72 h) versus later (>72 h) WLSM. We found that 86% of patients dying in the ICU, died after WLSM ranging from 0% in Eastern Europe to 96% in Northern Europe. In half of the patients, WLSM was instituted early. The later WLSM group had a higher maximum TIL during ICU stay compared to the early WLSM group. Variables that were independently associated with early WLSM were one or two unreactive pupils at admission, and a higher ISS. We did not find associations between centers or regions and the timing of WLSM.

First, we found that the occurrence of WLSM varied across regions. This result corresponds with the results of the provider profiling of centers performed prior to study start [3]. A systematic review also reported variation in the prevalence of WLSM on the ICU, ranging from 0 to 84% in over 30 countries across the globe [2]. Some studies suggest that this variation originates from institutional factors [10, 16–21], physician factors [10, 22–25], and religion/geographic factors [25–27]. Variation in earlier studies was not only found between countries, but also within countries [10, 16–18, 28–34], and even within the same department [23]. This could indicate that cultural or regional differences are not the sole trigger of variation in the occurrence of WLSM. Certain patient and ICU factors were previously found to be associated with a higher occurrence of WLSM. These factors include advanced patient age [19], more severe acute or chronic illness [29], the presence of a surrogate decision-maker [35, 36], and non-surgical specialty of the attending physician [37]. Moreover, prior studies reported an increase of WLSM in recent years [17, 34].



Second, we found that having one or two unreactive pupils compared to both reactive pupils, and severe injury, were associated with early WLSM, after adjustment for gender, IMPACT core variables, ASAPS classification, region, and hemodynamic stability upon hospital arrival. In the later WLSM group, a higher maximum TIL score was found, indicating that patients in this group received more (intensive) ICP lowering treatment. Similarly, more patients in the later WLSM group received intracranial surgery compared to patients in the early WLSM group. This may be because these patients have a better prognosis, as perceived by clinicians, or because clinicians are inclined to wait with WLSM to see if the patient responds to a treatment that is initiated. More aggressive therapy could have also been provided to patients that had the highest probability to die. Clinicians may feel the need to do everything they can to save those patients. However, this did not seem the case in our cohort. Although we found regional differences in the occurrence of WLSM, we did not find differences between regions or centers in timing of WLSM. This indicates that the decision for early WLSM is mostly

based on injury characteristics, rather than differences that may be explained by geographic location. Moreover, even though increasing age has been found to be independently associated with the decision to withdraw LSM [18, 38], and even though age is an important factor in prognostic models in TBI [14, 39], we did not find that age was associated with timing of WLSM. This is in line with the conclusion of ethics experts on the Durban World Congress, who concluded that age should not be the sole criterion upon which to decide to WLSM. Furthermore, in a recent publication, differences between men and women in outcomes following TBI have been found [40]. We did not find this difference in sex/gender in the probability of early WLSM.

Third, contrary to the recommendation of the NCS to wait 72 h before instituting WLSM in patients with devastating brain injury [9], half of the patients in our cohort had their LSM withdrawn within this time. Turgeon et al. also found that half of the patients died within 72 h after WLSM [10]. Self-fulfilling prophecies may also exist in TBI [41]. The practice we observe (half of the patients were in the early WLSM group) is clearly not in line with

these recommendations of the NCS. The 72 h waiting period was recommended by the NCS to reduce the risk of self-fulfilling prophecies. A waiting period of 72 h to avoid a self-fulfilling prophecy may not be of any benefit if no care is given during those 72 h. Therefore, clinicians should be willing to treat patients within this timeframe. We hope to further fuel the discussion on what should prevail: avoid a self-fulfilling prophecy at any cost, or prevent unnecessary delay of WLSM. Delaying WLSM and continuing treatment may avoid a self-fulfilling prophecy, but carries a risk of prolonging suffering of patient and relatives, and can lead to false hope for relatives. Early WLSM aims to reduce unnecessary suffering, prevent unnecessary treatment, but carries a risk of increasing potentially avoidable deaths.

Contrary to a self-fulfilling prophecy, a sunk-cost effect could also play a role in the decision-making of clinicians. In the case of sunk-cost effect, clinicians would continue treating a patient because resources have already been invested, even though there is little hope for recovery. Studies into this effect are scarce, but those that have been published so far, have shown that the sunk-cost effect is unlikely to play a role [42, 43].

It seems unlikely that decisions regarding WLSM are driven by expectations of mortality based on validated prediction models. We defined a threshold of 80% as identifying patients with a high expected probability of mortality or unfavorable outcome (using the IMPACT core model). Using this threshold, only one tenth of patients who had their LSM withdrawn had a high probability of mortality, a figure which was identical to the cohort of patients who died without WLSM. Further, although the early WLSM cohort had a higher proportion of patients with high probability of mortality, this was still less than half. It is possible that, rather than expected mortality, these decisions were driven by expectations of unfavorable functional outcome, since survival with severe disability is often portrayed as not being “a life worth living” [44]. However, the conventional dichotomization of level of disability between moderate and severe disability may not match the disability levels which patients find intolerable, and the six-month time point for assessment of outcome may ignore substantial improvements that patients can make beyond 6 months [5, 45]. Even if we do accept these thresholds for “intolerable” disability, it is worrying that nearly half of patients in the WLSM cohort had less than this probability of unfavorable outcome, and that this figure was not substantially different to the proportion of patients expected to have unfavorable outcome in the cohort who died without WLSM. Indeed, even though the early WLSM cohort had a higher proportion of patients with a high probability of unfavorable outcome, over a third still

did not have a high probability of unfavorable outcome. Given the uncertainties in prognostication based on our current knowledge, the clinical choices being made in this context are not easy to explain, and run the risk of inappropriate use of early WLSM.

The figures for later WLSM were similar, with less than half of patients in this cohort having a high expected risk of unfavorable outcome. However, it is well recognized that the level of certainty of the predicted outcome could increase with more observations over time [46], and the failure to respond to therapy or progression of imaging findings may be strong prognostic markers. Indeed, the clinical insights that provide a basis for such later WLSM could provide important insights regarding the choice of time dependent observations into formal prognostic schemes. The ideal timing for decisions regarding WLSM may remain a difficult clinical problem depending on individual patient characteristics (some of which may still be unknown), but, in many instances, delaying such by 72 h may provide greater assurance of their appropriateness.

The timing of WLSM may also be crucial for organ donation. In a population of patients with non-survivable gunshot wounds to the head, donors had longer times from hospital arrival to death and had a longer ICU stay [47]. If there is more time between injury and WLSM, an increase in organ donation may be a secondary outcome. This was seen in the introduction of post cardiac arrest pathways [48, 49]. Furthermore, previous literature found that delay of WLSM in patients with devastating brain injury has the potential to lead to up to 30% more donation after brain death, with patients progressing from potential circulatory death donors to brain death donors [50].

The CENTER-TBI study is unique for its extensive data collection in multiple centers, enrolling TBI patients with varying injury severity across a wide range of European centers. Furthermore, the observational design of the CENTER-TBI study, ensures larger generalizability of the results compared to a clinical trial [51]. However, this study also has limitations which should be considered when interpreting the results. First, all centers participating in CENTER-TBI are characterized by their commitment to TBI research. They might represent a selected sample of the neuro-trauma centers in Europe limiting generalizability. Second, some variation may have existed between investigators in their interpretation of WLSM. In this study, we were looking for an expression of intent, rather than specific interventions being withdrawn or not. This “expression of intent” defines our group of patients where the clinical team ceased to use available options to drive the best outcome, and concentrated at least partially on symptom control and comfort. Third, for statistical reasons, more patients included in the models would have been better.

A higher number of patients would have increased the potential to study associations of other important variables for timing of WLSM, such as imaging characteristics. Fourth, there were some missing data. Missing WLSM dates were manually imputed using the ICU discharge date of the corresponding patient. This could potentially have led to an overestimation of the time between injury and WLSM. To address this concern, we performed two sensitivity analyses. In the first, we performed a complete case analysis, excluding all patients with missing information on date and time of WLSM. In the second, we re-allocated all patients with missing information on date of WLSM to the early group. Both analyses showed similar results as the primary analysis. To lower the impact of missingness of other data, we multiply imputed missing data of variables that were included in our models. Fifth, definitions of the variables concerning brain death in relation to WLSM were not explicit in the e-CRF. In some patients WLSM may have been reported because they had been pronounced brain dead, in which case early WLSM would have been an appropriate decision. We found that WLSM was followed by organ donation in 29 patients in the early WLSM group, and in 14 in the later group. Excluding these patients from the analysis would mean that WLSM was performed early in 47% of all patients undergoing WLSM who did not proceed to organ donation, and may have been potentially inappropriate. This percentage is very similar to the 51% described in the overall cohort, and supports the internal validity of our study. Last, we only gathered information about WLSM, not about withholding life-sustaining measures. Withholding and withdrawal of life-sustaining measures are often considered to be ethically equivalent [52]. However, decision-making may be different between the two given the active versus the passive nature of the two respectively. Thus, our results are not valid for withholding life-sustaining measures.

Future studies should investigate the potential damage done by performing WLSM too early or too late. Furthermore, there should be intensive research on the (early) prediction of outcomes to help clinicians make an initial decision regarding WLSM. Precise data may also inform clinicians on a better timing of WLSM. Existing prediction models can help with this decision-making. However, we should be cautious in the interpretation of these models because they are derived from existing data that was collected more than a decade ago [14, 39]. Therefore, if a self-fulfilling prophecy regarding too early WLSM already exists, this may be fueled by using these models. Thus, updating existing prediction models would be an important step in decreasing uncertainty around (end-of-life) decision-making.

Conclusion

WLSM was performed early (<72 h) in approximately half of the patients in whom it was implemented, and occurs mostly in patients with severe TBI affecting brainstem reflexes who were severely injured. We found no regional or center influences in the timing of WLSM. WLSM may be clinically appropriate. However, clinicians should be cautious of self-fulfilling prophecies. The ideal timing for decisions regarding WLSM remains a difficult clinical problem depending on individual patient characteristics. Further research is required to get insight in these characteristics. Delaying decisions to initiate WLSM by 72 h, as recommended by recent guidelines, may prevent these self-fulfilling prophecies in case of any doubt on a survivable injury.

Supplementary Information

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Author contributions

EvV analyzed the data and drafted the manuscript, and the supplementary tables and figures. All coauthors gave feedback on the manuscript. HL supervised the project. All coauthors gave feedback on (and approved) the final version of the manuscript.

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Availability of data and materials

The data and codes supporting the findings in the study are available upon reasonable request from the corresponding Author (EvV) and are stored at <https://center-tbi.incf.org/>.

Declarations

Conflict of interest

GC is Editor-in-Chief of Intensive Care Medicine. GC reports grants, personal fees as Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics; personal fees from Nestle and UCB Pharma, all outside of the submitted work. DKM reports grants from the European Union and UK National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. The other authors declare that they have no competing interests.

Ethics approval and consent to participate

The Medical Ethics Committees of all participating centers approved the CENTER-TBI study, and informed consent was obtained according to local regulations.

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