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Emergency and critical care of severely injured patients

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Emergency and critical care of severely injured patients

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Editorial: Emergency and critical care of severely injured patients

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Editorial on the Research Topic
Emergency and critical care of severely injured patients

Introduction

Severe trauma is among the leading causes of death and morbidity in many age groups around the world. The chain of survival in critically ill injured patients starts on the scene, continues in the emergency department, and carries on in the first surgical phase and in the intensive care unit. The optimal care of such patients depends on both medical treatment and organizational management. Therefore, it is essential to examine both of these aspects if healthcare systems are to optimize the care of critically ill trauma patients in different parts of the world.

Provision of the best available medical care for severely injured patients might result in suboptimal outcomes if prehospital care, or any link in the path of the patients through the chain of survival, is not of similarly high quality. A close look at the various challenges faced by trauma systems—and their potential solutions—in different regions of the world will enable the identification of existing short-comings and may facilitate the exchange of relevant solutions and possible improvements to processes. Both unmet surgical needs and the cost effectiveness of surgical intervention should be addressed and potential solutions should be suggested, including those related to medical, training, and organizational issues.

In emergency and intensive care, many aspects of care are specific to trauma patients, and so general recommendations and guidelines may not cover the precise needs of injured patients in these settings. Furthermore, many treatment options are currently under scientific discussion. Therefore, new research results and a critical appraisal of the relevant up-to-date knowledge is provided to the readers herein.

Non-technical skills and teamwork

A team of experts does not necessarily make an expert team. Starting from this observation, Alexandrino et al. reviewed some of the most important non-technical skills that are required not only in the emergency department, but also in the operating room, and they proposed ways to improve perioperative communication. Furthermore, they give a short appraisal of existing training courses.

Interhospital transfer

The indication and decision of when to transfer a severely injured patient from one to another hospital are complex. Spering et al. described processes followed for the common, countrywide practice of the interhospital transfer of severely injured patients within a highly developed national network of trauma centers. In addition to their epidemiological overview, they were able to identify major factors that resulted in such a transfer. They also presented data indicating that the introduction of a trauma network resulted in an improved transfer policy.

Anticoagulant and antithrombotic drugs

With an increasingly active aging population, greater numbers of injured patients requiring anticoagulant or antithrombotic treatment are presenting challenges to emergency and surgical teams. One study (Yamaji et al.) investigated the impacts of pre-trauma anticoagulant and antithrombotic treatment on mortality in patients with major trauma. They identified differences in outcomes between patients treated with anticoagulant vs. antithrombotic drugs. In this context, a registry study (Fitschen-Oestern et al.) focusing on an elderly population analyzed the effects of the application of tranexamic acid on outcomes in patients who were older than 50 years and receiving pre-existing treatment with anticoagulant or antithrombotic medication. In a third study (Schindler et al.), a high rate of intracranial bleeding was observed in elderly patients who were receiving anticoagulant or antithrombotic treatment before experiencing a low fall. As this observation was also made in asymptomatic patients, the findings hinted at the necessity of performing a head-CT scan in all such patients.

Bleeding control and fracture management

Endovascular intervention techniques may significantly improve bleeding control and outcomes in severely injured patients. However, they require excellent infrastructure and organization, as delayed processes and other obstacles may diminish their potential benefits. Mizuno et al. analyzed the role of a time delay in transcatheter embolization in patients with pelvic fracture, and their findings substantiated the importance of fast intervention.

The Zürich group of Kalbas et al. presented a review and analysis of registry data that examined the best way to decide on the timing of surgical fracture stabilization in patients with multiple injuries. They discussed the values of different parameters and scores, and they propose the use of a decision tree.

Ventilation and early mobilization

Ventilation and mobilization are central interventions during the intensive care treatment of severely injured patients. Although the general guidelines of ventilatory support do also apply to trauma patients, there may be specific conditions (e.g., pulmonary contusion, inhalation injury) that require more individualized treatment. Meregildo-Rodríguez et al. looked at the ventilation of patients with cervical spinal cord injury who may have specific requirements due to the lack of a primary lung injury and a lack of respiratory-muscle activity. The authors presented a systematic review with a special focus on tidal volumes.

The role and potential advantages of early mobilization in ventilated patients is still a Research Topic under discussion. Wang et al. present another meta-analysis, this time including only randomized controlled trials. They suggested taking a differentiated view with respect to effects on different outcome parameters.

Prediction and quality indicators

Early identification of patients at increased risk of developing complications may help to enable stratification of patients into specific monitoring or treatment pathways, or for potential inclusion in studies trialing novel therapies. In a single-center study (Xu et al.), a predictive model for the "Persistent Inflammation, Immunosuppression, and Catabolism Syndrome" was developed and evaluated in trauma patients using parameters that are easily obtained. A nomogram for the calculation of risk was presented.

As has already been stressed in another manuscript on this Research Topic, traumatic brain injuries after low falls in the elderly population is of special interest and concern. It would, therefore, be helpful if specific predictors could be used to indicate the likely treatment courses, outcomes, and resource requirements of such patients. The research group of Forssten et al. identified five predictors of complications and mortality in elderly patients presenting with moderate (Glasgow Coma Scale 9–13) traumatic brain injury after ground-level falls through analyzing information from the database of the American College of Surgeons' Trauma Quality Improvement Program.

Mortality is the primary outcome measure in severely injured trauma victims, with excellent methods available for risk adjustment. However, quality indicators for survivors are rare, and most of those that exist lack validated tools for risk adjustments to improve comparability. Using data from the German Trauma Registry, Lefering et al. developed a model that predicts the length of stay of trauma-injury survivors; after using a dataset describing 108,175 patients, they validated the model in another dataset of more than 72,000 patients. They describe the prediction of patient requirements for ICU treatment (with a duration of more than 1 week) and length of ICU stay for these long-term patients. Their results suggest that this tool may be useful for future benchmarking.

The manuscripts presented on our Research Topic cover a wide range of contributions on subjects that appear to be of general interest for providers of care in the emergency departments, early surgical management, and intensive care treatment in addition to describing prediction models and indicators that may be used for quality control and benchmarking. We hope that readers will gain interesting and helpful information and

insights for their own clinical practice and/or stimuli for their own research.

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Retrospective cohort study to determine the effect of preinjury antiplatelet or anticoagulant therapy on mortality in patients with major trauma

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Objective: This study aimed to compare outcomes among patients who sustained major trauma from injury with and without receiving antiplatelet therapy (APT) or anticoagulant therapy (ACT) to test the hypothesis that APT does not increase the risk of mortality. However, ACT increases the mortality risk in the acute phase of trauma.

Methods: Patients registered in the Japanese Observational body for Coagulation and Thrombolysis in Early Trauma 2 between April 2017 and March 2018 who had sustained a severe injury in any anatomic region of the body, as determined using an injury severity score (ISS) $\geq$ 16 were included in this retrospective cohort study. We analyzed the mortality within 24 h from the arrival using a multivariable linear regression analysis adjusted for several confounding variables.

Results: We identified 1,186 eligible participants who met the inclusion criteria for this study: 105 in the APT (cases), 1,081 in the non-antiplatelet therapy (nAPT) group (controls), 65 in the ACT (cases), and 1,121 in the non-anticoagulant therapy (nACT) group (controls). The mortality within 24 h in the ACT group was significantly higher than in the nACT group (odds ratio 4.5; 95%CI: 1.2–16.79; p = 0.025); however, there was no significant difference between the two groups with or without the antiplatelet drug (odds ratio 0.32; 95%CI: 0.04–2.79; p = 0.3) administration. Other outcomes, like the 28-day mortality, mortality at discharge, and surgery for hemostasis, were not significantly different between regular users and non-users of either antiplatelet or anticoagulant drugs.

Conclusion: Regular antiplatelet medications did not increase mortality within 24 h, 28 days, or at discharge in patients with major trauma, suggesting that standard treatment, including surgery, is sufficient.

KEYWORDS

trauma, antiplatelet therapy, anticoagulant therapy, cohort study, J-OCTET 2, injury

1. Introduction

A quarter to half of the patients with major trauma in some countries are over the age of 60 years due to an aging society, particularly in the West and Japan (1–3). Elderly patients with trauma are different from younger patients in residual physiological functions, the complexity of comorbidities, types of regular medications, and mechanisms of injury (1, 2).

Previous studies have shown that starting antiplatelet therapy (APT) before injury significantly increases mortality risk and unfavorable outcomes in patients with traumatic brain injury (TBI) (3–6). However, some studies suggest no link between APT and increased mortality in TBI (7–9). To the best of our knowledge, it is unclear how APT before injury affects overall trauma mortality. Therefore, to test the hypothesis that pre-injury APT does not increase the risk of mortality; however, anticoagulant therapy (ACT) increases it in the acute phase of trauma, this study aimed to compare outcomes among injured patients with major trauma with and without administration of APT or ACT.

2. Materials and methods

2.1. Study oversight and design

We conducted a retrospective cohort study between April 2017 and March 2018 using the Japanese Observational study for Coagulation and Thrombolysis in Early Trauma 2 (J-OCTET 2) during the observation period. Tohoku University institutional research ethics committee approved the use of the J-OCTET 2 (approval #2020-1-898, approved on January 15, 2021). Furthermore, the Gifu University institutional ethics committee approved this study (approval #2022-141, approved on October 12, 2022). In addition, the institutional ethics committees of Gifu University Graduate School of Medicine approved the substitution of an opt-out notice of informed consent from patients due to the retrospective nature of the study, whose design was based on computerized data with anonymous selection.

2.2. Study patients

Overall, data from 1,213 patients with trauma were registered in the J-OCTET 2 between April 2017 and March 2018. They had an injury severity score (ISS) $\geq$ 16, indicating a severe injury in any region. The following were the exclusion criteria: (1) cases in which consent to participate was not obtained, (2) time of injury was unclear, (3) the patient was transferred from a different hospital, (4) declined active treatment, (5) had a cardiopulmonary arrest on arrival, (6) had a burn injury, and (7) pregnancy, or had coexisting cirrhosis of the liver in the J-OCTET 2. Additionally, we excluded cases with missing data on oral medications from our analysis.

2.3. Data collection

We collected the following data from the electronic medical records: age, sex, ISS, time from accident to hospital arrival, drug history, Charlson Risk Index, systolic blood pressure (SBP) on arrival, heart rate (HR) on arrival, the respiratory rate on arrival, Glasgow coma scale score, lactate level, fibrinogen (Fbg) level, hemoglobin (Hb) level, platelet level, Focused Assessment with Sonography for Trauma (FAST), and prehospital care. The six FAST search sites are the pericardiac cavity, bilateral thoracic cavity, Morrison fossa, perisplenic fossa, and Douglas fossa. There was no predefined transfusion protocol in this study, including emergency reversal of acute major bleeds in patients on ACT, which was based on the physician's clinical judgment.

2.4. Primary and secondary outcomes

The primary outcome of interest in this study was the mortality within 24 h of arrival. The secondary

Abbreviations: APT, antiplatelet therapy; ACT, anticoagulant therapy; TBI, traumatic brain injury; J-OCTET 2, Japanese Observational study for coagulation and thrombolysis in early trauma 2; ISS, injury severity score; SBP, systolic blood pressure; HR, heart rate; Fbg, fibrinogen; Hb, hemoglobin; PH, Platelet; FAST, Focused Assessment with Sonography for Trauma; FFP, fresh frozen plasma; PC, platelet concentrate.

outcomes included 28 day-mortality, mortality at hospital discharge, surgical hemostatic intervention, transcatheter arterial embolization, and transfusion requirement within 24 h. The transfusion requirement was tabulated and analyzed separately for red blood cells, fresh frozen plasma (FFP), and platelet concentrate (PC).

2.5. Sample size

The sample size in this study was determined based on the number of covariates included in the statistical model for the primary analysis and overfitting (10) and based on data availability.

2.6. Statistical analysis

Continuous data were described using the median and interquartile range, and categorical data were described using frequencies with proportions. To evaluate the effect of regular use of anticoagulants and antiplatelet drugs on accidental trauma, we conducted a multivariable linear regression analysis adjusted for covariates, including age, ISS, time from accident to hospital arrival, Charlson Risk Index, SBP, HR, RR, lactate, Glasgow coma scale score, on arrival. FFP and PC were included as covariates only in analyses whereby the mortality within 24 h of arrival, 28-day mortality, and mortality at hospital discharge were the objective variables. The covariates were selected as potential confounders *a priori* based on previous studies (11) and expert advice from a physician in the field. The number of covariates was restricted enough to avoid overfitting. The degree of overfitting of the regression model was confirmed by the optimal parameter obtained from the calibration plots from 150 bootstrap validations. Based on the optimal parameter < 0.2, the model was determined not to be overfitting. We also evaluated the effects of the antiplatelet drug or anticoagulant use on the secondary outcomes. Binary outcomes were evaluated similarly using a multivariable logistic regression model as in the primary analysis. For continuous outcomes without normality, the multivariable proportional odds logistic regression model was used to evaluate the association with the antiplatelet drug or anticoagulant use. Proportional odds logistic regression, also known as ordinal logistic regression, is a popular model for ordinal categorical outcome variables, which also works well for skewed continuous outcomes using ranks of data. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using R software (version 4.2.1; available at http://www.r-project.org) (12).

3. Result

3.1. Baseline characteristics

Overall, 1,213 patients were enrolled between April 2017 and March 2018. The analysis included 1,186 eligible participants who met the criteria of this study: 105 in the APT (cases), 1,081 in the non-antiplatelet therapy (nAPT) group (controls), 65 in the ACT (cases), and 1,121 in the non-anticoagulant therapy (nACT) group (controls). **Table 1** summarizes the clinical characteristics of the patients (**Table 1**). There were no significant differences in sex, time from accident to hospital arrival, Glasgow coma scale score at arrival, or FAST findings at any site between the two groups with or without antiplatelet use. Age, Charlson Risk Index, SBP, and Fbg level were higher in the APT group than in the control group. ISS, HR, RR, lactate level, Hb level, and platelet counts were lower in the APT group than in the control group. There were no significant differences in sex, ISS, SBP, Glasgow coma score, or FAST findings at any site between the two groups with or without anticoagulant use. Age, time from accident to hospital arrival, Charlson risk index, and Fbg level was higher in the ACT group than in the control group. HR, RR, Lac level, Hb level, and platelet counts were lower in the ACT group than in the control group.

3.2. Outcomes

3.2.1. Primary outcomes

Table 2 presents the outcome variables of our study. The mortality rate within 24 h was 2.9–7.7%, and the overall mortality was 5.6% (66 of 1,186 patients). The mortality within 24 h in the ACT group was significantly higher compared to the nACT group (odds ratio 4.5; 95%CI: 1.2–16.79; $p = 0.02$); however, there was no significant difference between the two groups with or without antiplatelet drug administration (odds ratio 0.32; 95%CI: 0.04–2.79; $p = 0.3$).

3.2.2. Secondary outcomes

There were no significant differences in the 28-day mortality, mortality at discharge, or surgery for hemostasis between regular users and non-users of either antiplatelet or anticoagulant drugs. The number of patients who received TAE was 147 (13.1%) and 1 (1.6%) in the nACT and ACT groups, respectively; the rate of TAE was significantly lower in the ACT group with an odds ratio of 0.08; 95%CI: 0.01–0.64; $p = 0.018$. For transfusion volume, RBC transfusion was significantly lower in the ACT group (odds ratio 0.34; 95%CI: 0.15–0.78; $p = 0.011$), whereas FFP and PC transfusions were significantly higher in the APT group (FFP; odds ratio 2.22; 95%CI: 1.22–4.05; $p = 0.009$ and PC; odds ratio 3.16; 95%CI: 1.55–6.42; $p = 0.002$).

TABLE 1 Clinical characteristics of the participants.

			Using of antiplatelet drugs			Using of anticoagulant		
Variable	*N*	Overall, *N* = 1,186[a]	No, *N* = 1,081[a]	Yes, *N* = 105[a]	*P*-value[b]	No, *N* = 1,121[a]	Yes, *N* = 65[a]	*P*-value[b]
Age	1,186	66 (47, 77)	64 (45, 76)	79 (70, 84)	< 0.001	64 (46, 76)	80 (71, 85)	< 0.001
Sex	1,186				0.735			0.325
Female		338 (28.5%)	310 (28.7%)	28 (26.7%)		316 (28.2%)	22 (33.8%)	
Male		848 (71.5%)	771 (71.3%)	77 (73.3%)		805 (71.8%)	43 (66.2%)	
ISS	1,186	22.0 (17.0, 29.0)	22.0 (17.0, 29.0)	20.0 (16.0, 25.0)	0.025	22.0 (17.0, 29.0)	25.0 (17.0, 25.0)	0.588
Time_from_accident_to_hospital_arrival	1,170	44.0 (33.0, 61.0)	44.0 (33.0, 60.0)	46.0 (35.0, 63.8)	0.330	44.0 (33.0, 60.0)	52.0 (36.5, 80.5)	0.003
Charlson risk index	1,040	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	2.0 (1.0, 3.0)	< 0.001	0.0 (0.0, 1.0)	2.0 (0.8, 2.0)	< 0.001
SBP_on_arrival	1,178	134.0 (110.0, 156.8)	132.0 (110.0, 155.0)	148.0 (123.0, 174.0)	< 0.001	133.0 (110.0, 156.0)	140.0 (120.0, 158.0)	0.244
HR_on_arrival	1,185	84.0 (72.0, 100.0)	85.0 (72.0, 101.0)	78.0 (69.0, 90.0)	0.001	84.5 (72.0, 101.0)	79.0 (68.0, 90.0)	0.008
RR_on_arrival	1,179	20.0 (17.0, 24.0)	20.0 (17.2, 24.0)	18.0 (16.0, 23.0)	0.016	20.0 (17.0, 24.0)	18.0 (16.0, 21.0)	0.025
GCS_on_arrival	1,186	14.0 (10.0, 15.0)	14.0 (10.0, 15.0)	14.0 (12.0, 15.0)	0.717	14.0 (10.0, 15.0)	14.0 (12.0, 15.0)	0.68
Lactate_on_arrival	1,054	2.4 (1.7, 3.7)	2.5 (1.7, 3.9)	1.6 (1.2, 2.2)	< 0.001	2.5 (1.7, 3.8)	1.7 (1.5, 2.2)	< 0.001
Fbg_on_arrival_2	1,007	241.0 (191.0, 290.0)	238.0 (185.0, 283.0)	287.0 (226.8, 337.0)	< 0.001	239.0 (188.2, 286.0)	276.0 (244.0, 333.0)	< 0.001
Hb_on_arrival	1,181	13.1 (11.7, 14.5)	13.2 (11.8, 14.6)	12.5 (11.2, 13.7)	< 0.001	13.2 (11.8, 14.5)	11.6 (10.7, 13.2)	< 0.001
Plt_on_arrival	1,180	21.4 (17.1, 26.0)	21.6 (17.4, 26.4)	18.4 (14.8, 22.2)	< 0.001	21.6 (17.4, 26.3)	17.9 (14.1, 20.9)	< 0.001
FAST (pericardiac cavity)	1,024				0.211			0.300
Negative		1,004 (98.0%)	925 (98.2%)	97 (96.3%)		950 (98.1%)	54 (96.4%)	
Positive		20 (2.0%)	17 (1.8%)	3 (3.7%)		18 (1.9%)	2 (3.6%)	
FAST (Lt. thoracic cavity)	1,026				0.659			0.619
Negative		1,007 (98.1%)	927 (98.2%)	80 (97.6%)		951 (98.0%)	56 (100.0%)	
Positive		19 (1.9%)	17 (1.8%)	2 (2.4%)		19 (2.0%)	0 (0.0%)	
FAST (Rt. thoracic cavity)	1,026				> 0.999			> 0.999
Negative		1,010 (98.4%)	929 (98.4%)	81 (98.8%)		954 (98.4%)	56 (100.0%)	
Positive		16 (1.6%)	15 (1.6%)	1 (1.2%)		16 (1.6%)	0 (0.0%)	
y FAST (Morrison fossa)	1,025				0.250			0.166
Negative		981 (95.7%)	900 (95.4%)	82 (98.8%)		925 (95.5%)	56 (100.0%)	
Positive		44 (4.3%)	43 (4.6%)	1 (1.2%)		44 (4.5%)	0 (0.0%)	

(Continued)

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TABLE 1 (Continued)

Variable	*N*	Overall, *N* = 1,186[a]	Using of antiplatelet drugs			Using of anticoagulant		
			No, *N* = 1,081[a]	Yes, *N* = 105[a]	*P*-value[b]	No, *N* = 1,121[a]	Yes, *N* = 65[a]	*P*-value[b]
FAST (perisplenic cavity)	1,025				0.160			0.394
Negative		998 (97.4%)	916 (97.1%)	82 (100.0%)		942 (97.2%)	56 (100.0%)	
Positive		27 (2.6%)	27 (2.9%)	0 (0.0%)		27 (2.8%)	0 (0.0%)	
FAST (Douglas fossa)	1,025				0.715			0.649
Negative		999 (97.5%)	918 (97.3%)	81 (98.8%)		945 (97.5%)	54 (96.4%)	
Positive		26 (2.5%)	25 (2.7%)	1 (1.2%)		24 (2.5%)	2 (3.6%)	
Pre_hospital_care	1,185	235 (19.8%)	219 (20.3%)	16 (15.2%)	0.249	221 (19.7%)	14 (21.9%)	0.632

[a]Median (IQR); *n* (%). [b]Wilcoxon rank sum test; Fisher's exact test. ISS, injury_severity_score; SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate; GCS, Glasgow coma scale; Fbg, fibrinogen; Hb, hemoglobin; Plt, platelet count; FAST, Focused Assessment with Sonography for Trauma.

3.2.3. Sub-group analysis

Additionally, a sub-group analysis excluding TBI with an abbreviated injury scale of three or more points was performed (Table 3). After excluding TBI with an abbreviated injury scale of three or more points, 519 patients were remaining, with 36 administered APT and 15 with ACT. However, they survived for 24 h in both cases. Overall mortality rates within 24 h, 28-day mortality, and mortality at hospital discharge were 2.5, 4.1, and 4.8%, respectively.

4. Discussion

This study highlights the regular use of antiplatelet drugs did not increase mortality within 24 h, 28-day mortality, or mortality at hospital discharge; however, the use of anticoagulants increased mortality within 24 h. Furthermore, it suggests that standard treatment, including surgery, is sufficient even when treating patients with trauma who are regularly administered antiplatelet drugs.

Geriatric trauma has been increasingly common in the Western and Japan, related to population aging. In the UK, more than a quarter of patients with trauma are over 75 years old, which has obvious implications for national and local healthcare planning, particularly for Major Trauma Centers and Emergency Departments (13). It has been reported that the percentage of patients with geriatric trauma has increased, with 47.8% of the Dutch Trauma Registry being over 65 years old in 2014 and 52.9% of the Japanese Nationwide Trauma Registry being over 60 years old between 2004 and 2015 (14, 15). Several studies reported the risk of mortality is 2.5–5.6 times higher in patients with geriatric trauma (16–19). It was reported that the mechanisms and patterns of injury among elderly patients differ from those among younger individuals. The most common site of injury in the elderly is the extremity, and often ground-level falls rather than high-energy trauma; however, age can be an independent risk factor for mortality (20). Thus, in geriatric trauma, even low-energy trauma often leads to severe trauma due to original physical vulnerability, involvement of comorbidities, and current oral medications that negatively affect pathophysiology and treatment.

Recently, the number of elderly patients with trauma who must be administered anticoagulant or antiplatelet drugs due to cardiovascular and cerebrovascular diseases or genetic diseases has been gradually increasing (21–23). Preinjury ACT has long been found to influence mortality and unfavorable outcomes significantly. Lee et al. reported that preinjury ACT was associated with a higher risk of overall mortality (OR 2.12, 95%CI 1.79–2.51, $p < 0.00001$), in-hospital mortality (OR 2.04, 95%CI 1.66–2.52, $p < 0.00001$), intracranial hemorrhage (OD 1.99, 95%CI 1.61–2.45, $p < 0.00001$), and shorter length of hospital stay (MD 0.50, 95%CI 0.03–0.97, $p = 0.04$) in a systematic review and meta-analysis (24). Brain tissue injury

TABLE 2 Multivariable binary/proportional odds logistic analysis.

			Using of antiplatelet drugs				Using of anticoagulant			
Outcome	N	Overall, *N* = 1,186	No, *N* = 1,081[a]	Yes, *N* = 105[a]	Odds ratio (95% CI)	*P*-value[b]	No, *N* = 1,121[a]	Yes, *N* = 65[a]	Odds ratio (95% CI)	*P*-value[b]
Mortality within 24 h	1,185				0.32 (0.04, 2.79)	0.3			4.5 (1.2, 16.79)	0.025
Died		66 (5.6%)	63 (5.8%)	3 (2.9%)			61 (5.4%)	5 (7.7%)		
Survived		1,119 (94.4%)	1,017 (94.2%)	102 (97.1%)			1,059 (94.6%)	60 (92.3%)		
28 day-mortality	1,164				0.63 (0.21, 1.89)	0.406			1.2 (0.42, 3.47)	0.736
Died		114 (9.8%)	104 (9.8%)	10 (9.5%)			107 (9.7%)	7 (10.8%)		
Survived		1,050 (90.2%)	955 (90.2%)	95 (90.5%)			992 (90.3%)	58 (89.2%)		
Mortality at hospital discharge	1,182				0.49 (0.16, 1.52)	0.216			1.05 (0.36, 3.09)	0.927
Died		129 (10.9%)	118 (11.0%)	11 (10.5%)			120 (10.7%)	9 (13.8%)		
Survived		1,053 (89.1%)	959 (89.0%)	94 (89.5%)			997 (89.3%)	56 (86.2%)		
Surgery for hemostasis	1,183	190 (16.1%)	175 (16.2%)	15 (14.3%)	1.66 (0.74, 3.7)	0.215	181 (16.2%)	9 (14.1%)	0.79 (0.30, 2.12)	0.644
TAE	1,184	148 (12.5%)	138 (12.8%)	10 (9.5%)	1.52 (0.64, 3.60)	0.341	147 (13.1%)	1 (1.6%)	0.08 (0.01, 0.64)	0.018
RBC transfusion	1,172	0.0 (0.0, 560.0)	0.0 (0.0, 280.0)	0.0 (0.0, 280.0)	1.59 (0.86, 2.95)	0.139	0.0 (0.0, 560.0)	0.0 (0.0, 0.0)	0.34 (0.15, 0.78)	0.011
FFP transfusion	1,171	0 (0.0, 480.0)	0.0 (0.0, 720.0)	0.0 (0.0, 360.0)	2.22 (1.22, 4.05)	0.009	0.0 (0.0, 720.0)	0.0 (0.0, 0.0)	0.37 (0.17, 0.82)	0.014
PC transfusion	1,167	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	3.16 (1.55, 6.42)	0.002	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.74 (0.3, 1.81)	0.505

[a]Statistical data are presented as the median (interquartile range) or *n* (%). [b]Statistical tests performed: multivariable logistic regression; multivariable proportional odds logistic regression. TAE, transcatheter arterial embolization; RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

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TABLE 3 Outcome variables excluding TBI with abbreviated injury scale of 3 or more points.

			Using of antiplatelet drugs		Using of anticoagulant	
Outcome	*N*	Overall, *N* = 519	No, *N* = 483[a]	Yes, *N* = 36[a]	No, *N* = 504[a]	Yes, *N* = 15[a]
Mortality within 24 h	518					
Died		13 (2.5%)	13 (2.7%)	0 (0.0%)	13 (2.6%)	0 (0.0%)
Survived		505 (97.5%)	469 (97.3%)	36 (100.0%)	490 (97.4%)	15 (100.0%)
28 day-mortality	508					
Died		21 (4.1%)	19 (4.0%)	2 (5.6%)	21 (4.3%)	0 (0.0%)
Survived		487 (95.9%)	453 (96.0%)	34 (94.4%)	472 (95.7%)	15 (100.0%)
Mortality at hospital discharge	517					
Died		25 (4.8%)	23 (4.8%)	2 (5.6%)	25 (5.0%)	0 (0.0%)
Survived		492 (95.2%)	458 (95.2%)	34 (94.4%)	477 (95.0%)	15 (100.0%)
Surgery for hemostasis	517	82 (15.9%)	79 (16.4%)	3 (8.3%)	80 (15.9%)	2 (13.3%)
TAE	518	85 (16.4%)	79 (16.4%)	6 (16.7%)	85 (16.9%)	0 (0.0%)
RBC transfusion	510	0.0 (0.0, 560.0)	0.0 (0.0, 560.0)	0.0 (0.0, 420.0)	0.0 (0.0, 560.0)	0.0 (0.0, 0.0)
FFP transfusion	510	0 (0.0, 480.0)	0.0 (0.0, 720.0)	0.0 (0.0, 360.0)	0.0 (0.0, 600.0)	0.0 (0.0, 0.0)
PC transfusion	508	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

[a]Statistical data are presented as the median (interquartile range) or *n* (%). TAE, transcatheter arterial embolization; RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

stimulates the tissue factor pathway of coagulation in blunt TBI, resulting in various degrees of systemic bleeding tendency and coagulopathy (25–27). In our study, patients who were administered antithrombotic drugs with anticoagulant and antiplatelet before injury were significantly older; nevertheless, only patients administered ACT had significantly elevated mortality. Although the registry study does not allow for a detailed examination, the extremely low rate of TAE in the ACT group suggested that the patients may have had trauma requiring surgery for hemostasis in relative terms, or they may have had multiple bleeds non-amenable to TAE. There was no significant difference in the 28 day-mortality or mortality at hospital discharge in the ACT group, however, since the half-life of anticoagulants, especially DOACs, is at most 12 h, the effect of pre-injury medication was minor, and since the prognosis of severe trauma itself can be affected by definitive treatment during the so-called "golden hour," only early mortality was considered significant. Therefore, there may be justification for discontinuing anticoagulant drug administration when patients who are administered ACT suffer major trauma.

In contrast, Yuval et al. reported that antithrombotic drugs such as anticoagulants and antiplatelet drugs did not significantly increase mortality or blood transfusion requirements among patients with major trauma, including patients with head trauma (28). Thus, the efficacy of APT before the injury and continued administration of antiplatelet drugs after injury remains controversial. Initially, it was reported that discontinuing APT administration increased the risk of thromboembolism significantly, especially in patients with coronary heart disease. Moreover, the risk of coronary thrombosis after withdrawal of APT is greater than the risk of surgical bleeding (29). However, the risk of stroke is relatively low, with only approximately 2% occurring within 30 days of APT discontinuation (30).

Several reports revealed that APT before the injury was significantly associated with increased mortality and unfavorable outcomes in blunt TBI (4–6). In a systemic review and meta-analysis, Batchelor et al. reported a slightly increased risk of death in patients administered APT with blunt TBI (3). Others have reported an increased need for surgery, higher hospitalization rates, and poor discharge status in moderate patients with head trauma administered APT (7). Jones et al. also reported a high incidence of intracranial rebleeding episodes in similar situations (31). Conversely, several studies revealed no significant association between mortality due to APT and head injury (7, 8). To exclude the effect of coagulopathy induced by TBI on the outcomes, patients with concomitant TBI with an abbreviated injury scale of 3 or more points were excluded from the subgroup analysis. However, the extremely low mortality rates in both the APT and ACT groups precluded statistical analysis, and the effect of TBI on outcomes could not be determined in this study.

There is no clear evidence of the effect of preinjury APT on mortality and other outcomes, particularly for trauma other than single TBI. Furthermore, the ability of platelet transfusion to reverse platelet inhibition remains unclear. Two systematic reviews and meta-analyses exist on the effect of early surgery in the trauma treatment of hip fractures in patients on APT before the injury, which is slightly different from the study on the impact of APT. Both studies revealed that early surgery for patients on APT who had hip fractures was associated with increased transfusion rates; however, a decreased mortality

and length of hospital stay (32, 33). While some studies found no significant association between APT administration before major trauma injury and mortality or other outcomes, other studies reported increased mortality and rebleeding rates (8, 9, 31, 34). We could not examine single and double APT in this study; nonetheless, Ferraris et al. reported that patients with APT have significantly more comorbidities and worse outcomes with DAPT than SAPT in either case (35). Furthermore, examining whether aspirin or thienopyridines were administered was not possible but clinically there was no differential management of patients. One interesting study suggests that APT administration before trauma injury is associated with a decreased risk of lung dysfunction, multiple organ failure, and possibly death in high-risk patients with blunt trauma who received transfusions. This finding suggests that platelets are involved in the development of organ dysfunction, according to the author (36). As noted above, there is no consensus on how preinjury APT affects mortality and other outcomes of major trauma, not only a head injury. In the present study, there was no significant difference in mortality between the time point with or without APT before the injury. Considering the disadvantages of APT drug withdrawal, the results may support a treatment policy without discontinuing APT and delaying surgery.

This study had some limitations. First, our observations were limited to a relatively small population; a larger and more racially diverse data set should be the focus of future studies. Second, the groups were not randomized. Third, we could not distinguish single and dual platelet therapy or figure out medication compliance because data were obtained from an observational registry. Fourth, because of no prior development of transfusion protocols in this study, it was impossible to assess whether there was any arbitrary influence on the administration of RBCs, FFP, and PC. Therefore, a prospective study with a predefined protocol is desirable in the future.

5. Conclusion

Our findings suggest that patients administered AC have a higher risk of early mortality than patients not administered AC or AP despite the limitations of the study. In contrast, the mortality risk for patients administered AP remains unchanged. These results provide encouraging data regarding the approach to trauma care among patients receiving AP, despite the lack of reversible agents. However, further studies are needed to clarify the benefits and risks associated with AP.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request. Requests to access these datasets should be directed to the corresponding author HO, hideshi@gifu-u.ac.jp.

Ethics statement

The Tohoku University Institutional Research Ethics Committee approved the use of the J-OCTET 2 (approval #2020-1-898, approved on January 15, 2021). Furthermore, the Gifu University Institutional Ethics Committee approved this study (approval #2022-141, approved on October 12, 2022). The Institutional Ethics Committees of Gifu University Graduate School of Medicine approved the substitution of an opt-out notice of informed consent from patients due to the retrospective nature of the study, whose design was based on computerized data with anonymous selection. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

FY, HO, RK, YKa, GY, YM, YKi, TF, TM, NK, TD, TY, SY, and SO: treatment of the patients. FY and RK: writing—original draft. FY, RK, and HO: writing—review and editing. TI: data management and analysis. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cranial CT is a mandatory tool to exclude asymptomatic cerebral hemorrhage in elderly patients on anticoagulation

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Background: Traumatic brain injury (TBI) after falls causes death and disability with immense socioeconomic impact through medical and rehabilitation costs in geriatric patients. Diagnosing TBI can be challenging due to the absence of initial clinical symptoms. Misdiagnosis is particularly dangerous in patients on permanent anticoagulation because minimal trauma might result in severe intracranial hemorrhage. The aim of this study is to evaluate the diagnostic necessity of cranial computed tomography (cCT) to rule out intracranial hemorrhage, particularly in the absence of neurologic symptoms in elderly patients on permanent anticoagulation in their premedication.

Patients and methods: Retrospective cohort analysis of elderly trauma patients (≥ 65 years) admitted to the emergency department (ED) of the level-1-trauma center of the University Hospital Frankfurt from 01/2017 to 12/2019. The study included patients who suffered a ground-level fall with suspected TBI and subsequently underwent CT because of preexisting anticoagulation.

Results: A total of 227 patients met the inclusion criteria. In 17 of these patients, cCT showed intracranial hemorrhage, of which 14 were subdural hematomas (SDH). In 8 of the patients with bleeding showed no clinical symptoms, representing 5% (n = 160) of all symptom-free patients. Men and women were equally to suffer a post-traumatic hemorrhage. Patients with intracranial bleeding were hospitalized for 14.5 (±10.4) days. Acetylsalicylic acid (ASA) was the most prescribed anticoagulant in both patient cohorts—with or without intracerebral bleeding (70.6 vs. 77.1%, p = 0.539). Similarly, patients taking new oral anticoagulant (NOAC) (p = 0.748), coumarins, or other platelet inhibitors ($p > 0.1$) did not show an increased bleeding incidence.

Conclusion: Acetylsalicylic acid and NOAC use are not associated with increased bleeding risk in geriatric trauma patients (≥ 65 years) after fall-related TBI. Even in asymptomatic elderly patients on anticoagulation, intracranial hemorrhage occurs in a relevant proportion after minor trauma to the head. Therefore, cCT is an obligatory tool to rule out cerebral hemorrhage in elderly patients under anticoagulation.

KEYWORDS

TBI, anticoagulation, cerebral hemorrhage, elderly, geriatric TBI, computertomografie

Introduction

Severe traumatic brain injury (TBI) caused by road traffic accidents and falls are the overall main causes of death and disability with immense socioeconomic impact through loss of productivity as well as medical and rehabilitation costs (1–3). About one-third of seniors older than 65 years of age fall at least one time a year, and 60–70% of them fall again within a year. Along with fall-related fractures, TBI is one of the most common injury patterns caused by minor injury mechanisms like ground level falls in this population (4, 5).

In TBI, primary brain damage occurs due to rupture of vessels and direct damage to brain tissue which results subsequently in cerebral hemorrhage, axonal shear injury and secondary brain damage, like cerebral edema. In these cases, a phasic course can be observed clinically, with initial loss of conciseness (LOC), transient clearing, and secondary unconsciousness (6). In addition to irreversible primary brain damage by cell death, the outcome after TBI is largely determined by secondary brain damage due to hypoxia or intracranial pressure (7, 8). Therefore, prompt diagnosis and appropriate treatment are crucial to achieve optimal outcome.

Major clinical symptoms of brain injury include, i.e., LOC, amnesia, decreased vigilance or vomiting. Subjective minor symptoms are headache, nausea, dizziness, or double vision. Primary mild or even absent symptoms can complicate the diagnosis of relevant TBI because injury severity does not always correlate with the extent of the initial functional impairment (6, 9).

The diagnostic and therapeutic approach to TBI is initially based on the accident mechanism, the presence and severity of neurologic symptoms, and furthermore depends on existing risk factors. Patients without neurological symptoms and corresponding risk factors can be monitored clinically without radiological diagnostics (10). In the presence of neurological symptoms and/or risk factors, native cranial computed tomography (cCT) is considered the gold standard in the primary diagnosis of TBI with respect to the assessment of intracranial damage. In addition to its high sensitivity and specificity, cCT has short examination times and is ubiquitously available (11, 12). A disadvantage of cCT is the radiation exposure to the patient with an average effective dose of 2.6 mSv. Since delayed or undiagnosed intracranial injuries lead to high subsequent costs due to permanent health damage, cCT is also cost-effective when correctly indicated (13).

Older patients are often treated for vascular or cardiac disease with regular use of anticoagulant medications to prevent and/or treat thromboembolic events. These drugs include antiplatelet agents [e.g., acetylsalicylic acid (ASA)], new oral anticoagulants (NOACs), coumarins (vitamin K antagonists), unfractionated and low-molecular-weight heparins (UFH, LMWH), Especially in Anglo-American countries, but also in Germany, the use of ASA for primary prevention of cardiovascular diseases is widespread. Among them, almost half of those over 70 years of age take ASA daily (14). All substance groups inhibit physiological blood clotting in different ways and thus generally increase the risk of bleeding following trauma. It is particularly dangerous to underestimate the severity of a TBI in patients on anticoagulant medication due to probable relevant progression of an intracranial hematoma caused by the insufficient blood clotting (10, 12). While there is a growing consensus and S1-guidelines for the diagnosis and care of patients with TBI, management in older patients, particularly those taking anticoagulant medications, remains elusive due to a lack of evidence (9).

Therefore, the aim of this study is to evaluate the diagnostic value of cCT regarding intracranial hemorrhage particularly in the absence of neurologic symptoms in elderly patients on common permanent anticoagulation.

Materials and methods

Patients and study setting

We retrospectively reviewed the cohort of geriatric trauma patients (≥ 65 years) admitted to the level-1-trauma center of the University Hospital Frankfurt from 01/2017 to 12/2019. The following inclusion criteria were defined: All patients aged ≥ 65 years on long-term anticoagulant medication admitted to the emergency department (ED) after minor trauma (ground-level fall) with suspected TBI. In addition, all included patients underwent cCT because of their anticoagulant medication, regardless of whether they had symptoms of TBI. Patients with suspected severe injuries due to the trauma mechanism who were referred to trauma bay were excluded from the analysis.

The analysis is based on a detailed retrospective review of patient charts evaluating demographic and clinical data. This further includes information on injury patterns, comorbidities, prehospital and in-hospital management, and the process of care in the hospital, as well as examination, laboratory results and outcome data.

Ethics

The study was performed at the University Hospital Frankfurt, Goethe University after approval by the Institutional Review Board (2021-90) in accordance with the Declaration of Helsinki and following STROBE guidelines and the RECORD guidelines for observational studies (Reporting of studies Conducted using Observational Routinely Collected Data) (14, 15).

Statistical analysis

Continuous normally distributed variables were summarized using means ± standard deviation (SD). Values are reported as mean for continuous variables and as percentages for categorical variables. The *p*-values for categorical variables were derived from the two-sided Fisher's exact test, and for continuous variables from the Mann–Whitney U test. Significant values were adjusted by the Bonferroni *post hoc* test. A p-value < 0.05 was considered to be statistically significant ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$). All analyses were performed using the Statistical Package for Social Sciences (SPSS for Mac©), version 26 (SPSS Inc., Chicago, IL, USA).

Results

During the 36-month study period, $n = 227$ patients met the inclusion criteria (≥ 65 years, multimorbidity, TBI, cCT, minor trauma mechanism and anticoagulant therapy). In $n = 17$ (7.5%) patients, cranial CT scan on the day of admission to the ED revealed post-traumatic intracranial hemorrhage.

The incidence of post-traumatic hemorrhage in the elderly is not related to gender

Table 1 shows demographic and clinical characteristics stratified by the incidence of post traumatic intracranial bleeding. Men and women were almost equally likely to suffer a post-traumatic hemorrhage, and the mean of age of both cohorts was about 81 years. All patients with proven bleeding were hospitalized with a mean length of stay (±SD) of 14.5 (±10.4) days. In total, 17.6% of these patients spent 2.2 (±7.0) days on Intensive Care Unit (ICU).

In comparison, patients without hemorrhage were less often hospitalized (31% of $n = 210$, $p < 0.001$) and had a significantly shorter in-hospital stay of 2.2 (±4.6) days ($p < 0.001$). None of them were monitored on ICU ($p < 0.001$).

In both groups, relevant previous diseases were documented in the medical history, which were mainly of cardiac entity (> 80%). Mean laboratory coagulation parameters (Quick, INR, PTT) showed normal values in both groups.

ASA and NOAC use are not associated with increased bleeding risk in geriatric trauma patients

Patient charts were screened for documented premedication, especially regarding the type of anticoagulant (Figure 1). ASA was the most prescribed anticoagulant in these geriatric patients with TBI. ASA was found without significant difference ($p = 0.539$) in the premedication of 70.6% ($n = 12$) patients with and 77.1% ($n = 162$) patients without bleeding. A total of 34 trauma patients were on new oral anticoagulants (NOAC), of whom 8.8% ($n = 3$) presented with intracerebral hemorrhage and 91.2% ($n = 31$) did not ($p = 0.748$). Five patients took coumarins (Vitamin K antagonists, phenprocoumon/warfarin). Another 29 of the 227 patients were on other platelet aggregation inhibitor than ASA [(PAI), like clopidogrel or ticagrelor] but none of them showed higher risk for post-traumatic hemorrhage ($p > 0.1$). In total, 9 of 227 (4%) patients were taking low-molecular-weight heparin (LMWH). Among them intracerebral hemorrhage was significantly more frequent (23.5 vs. 2.4%, $p < 0.001$).

TABLE 1 Demographic and clinical characteristics stratified by the incidence of post-traumatic intracranial bleeding.

	Bleeding		
	Positive $n = 17$	Negative $n = 210$	p-value
Sex (male; %)	41.2	47.1	0.64
Age (years; mean ± SD)	81 ± 10	81 ± 7	0.67
Outpatient (%)	0	69.0	<0.001
Inpatient (%)	100	31.0	<0.001
Hospitalization (days; mean ± SD)	14.5 ± 10.4	2.2 ± 4.6	<0.001
ICU (%)	17.6	0	<0.001
ICU (days, mean ± SD)	2.2. ± 7.0	0	<0.001
Mortality (%)	5.9	0	<0.001
Co-morbidity			
Cardiac (%)	82.4	81.9	0.22
Neurologic (%)	0	9.5	0.38
Coagulation parameters			
Quick (%; mean ± SD)	91.7 ± 22.5	87.6 ± 1.2	0.31
INR (mean ± SD)	1.1 ± 0.4	1.2 ± 0.42	0.36
PTT (s; mean ± SD)	28.94 ± 3.2	27.9 ± 5.1	0.15
Thrombocytes (/µl; mean ± SD)	257 ± 92	223 ± 69	0.1

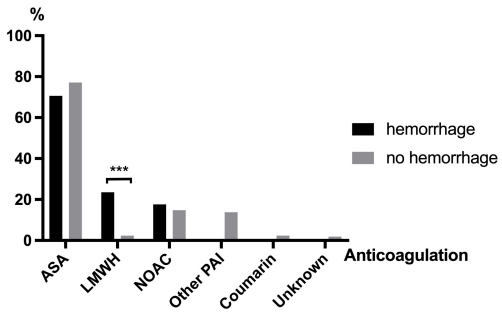

FIGURE 1
Anticoagulants taken in patients with and without cerebral hemorrhage after TBI (ASA, acetylsalicylic acid; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulants; PAI, platelet aggregation inhibitor). *$p \leq 0.05$, **$p \leq 0.01$, and ***$p < 0.001$.

Subdural hematoma is the most common bleeding entity in geriatric patients

Figure 2 shows the distribution of different bleeding entities of geriatric patients (≥ 65 years) after TBI. In total, 17 of 227 patients suffered intracerebral hemorrhage after TBI. In 12 patients a subdural hematoma (SDH, Figure 3) was documented, 2 patients suffered subarachnoid hemorrhage (SAH), and 3 scans showed an intracerebral hemorrhage (ICH, Figure 3) with simultaneous occurrence of SDH ($n = 2$) and SAH ($n = 1$), respectively.

Amnesia is the most sensitive major symptom for intracerebral hemorrhage after TBI in elderly

The anamnesis and first clinical examination of the patients were analyzed for major [amnesia, loss of consciousness (LOC), vomiting] and minor (headache, dizziness) symptoms of TBI (Figure 4). In total, $n = 67$ patients suffered from at least one of the aforementioned symptoms, of which 7.5% had hemorrhage. Overall, patients with cerebral hemorrhage showed significantly more neurological symptoms than patients without hemorrhage (52.9 vs. 27.5%, $p = 0.028$). However, 8 of 17 (47.1%) patients did not show any symptoms despite the detection of cerebral hemorrhage. Patients with post-traumatic hemorrhage were significantly more likely to have amnesia (17.6 vs. 3.8%, $p = 0.11$). LOC (6.7 vs. 11.8%, $p = 0.430$) and vomiting (4.3 vs. 5.9%, $p = 0.758$) occurred with

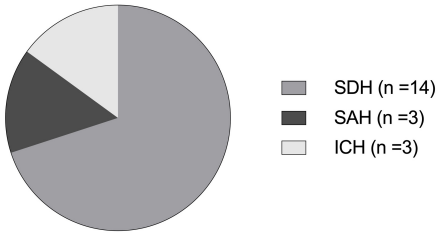

FIGURE 2
Distribution of different bleeding entities of geriatric patients (≥ 65 years) after TBI. In some patients, different bleeding entities were present simultaneously: SDH, subdural hematoma (n = 14); SAH, subarachnoid hemorrhage (n = 3); ICH, intracerebral hemorrhage (n = 3).

similar frequency in both cohorts. Minor symptoms such as headache (5.7 vs. 5.9%, p = 0.977) and dizziness (2.6 vs. 0%, p = 0.520) were also reported with similar frequency. Considering the different bleeding entities, patients with SDH suffered significantly more often from minor intracranial pressure symptoms (13.4% > 3.8%, p = 0.007). The remaining entities SAH and ICH showed no relevant difference to the clinical examination results from the patients without hemorrhage. Patients with post-traumatic symptoms after TBI were hospitalized significantly more often independent from the proof of an intracranial hemorrhage (47.8 vs. 31.3%, p = 0.018). In asymptomatic patients (n = 160) who received CT for minor trauma due to existing anticoagulation, bleeding was detected in 8 patients (5%). In this group, 107 patients were taking ASA at prophylactic doses, among whom 5 patients (4.7%) suffered bleeding. The eight patients who suffered from an intracranial bleeding underwent intensive care therapy, no further patient lacking of symptoms was treated on ICU. In this subgroup, 42 patients were treated as outpatients (26.3%).

Discussion

This retrospective study analyzed data of 227 geriatric patients of a level-1 trauma center over a 3-year period with TBI who underwent a subsequent cCT scan because of anticoagulant premedication. In 17 patients, cCT examination showed post-traumatic intracerebral hemorrhage, of which SDH was the most common. ASA and NOAC use were not associated with increased bleeding risk. But in about half of these patients, bleeding occurred even in the absence of symptoms, which accounted for 5% of all symptom-free patients. Of 160 asymptomatic patients, 107 patients were taking ASA at prophylactic doses, of whom 5 patients (4.7%) experienced bleeding.

Life expectancy is increasing, which results in a higher number of accidents in the geriatric age group (≥ 65 years). In addition to relevant accident mechanisms such as falls from great heights or traffic accidents, accidents with minor injury mechanisms like ground level falls often result in relevant injuries in this group (16, 17). In this study men and women were almost equally affected by post-traumatic intracranial hemorrhage, and the mean age of both cohorts was 81 years of age. Based on a prior analysis of admission diagnoses from 2019 at the University hospital Frankfurt, it was shown that the elderly suffer head injuries at a 1:1 ratio between men and women (8). In most cases, a multi-functional gait disorder is present, usually caused by risk factors such as decreased strength, coordination disorders, and visual impairment. In geriatric traumatology, the focus has been on main diagnoses such as fractures of the femur, the pelvis, or the spine (18, 19). Meanwhile, TBI after a fall, is one of the most common injury entities in patients of advanced age (6).

The most important finding of this study answers the question whether routine cCT in elderly patients on permanent anticoagulants, is statistically and medically appropriate. The results with regard to ASA is particularly interesting. In addition to NOAC and the combination of PAIs, which are mostly used therapeutically, the preventive use of ASA is very common and discussed critically. ASA is an integral part of the secondary prevention of cardiovascular disease. Patients who have already suffered a myocardial infarction or ischemic stroke are usually prescribed ASA at doses of up to 100 mg/day. For primary prevention in patients, however, ASA administration is controversial. Especially in Anglo-American countries, but also in Germany, the uncritical use of ASA in the primary prevention of cardiovascular disease is widespread. Among them, almost half of those over 70 years of age take ASA daily. In 2018 alone, three studies questioning the preventive benefits of low-dose ASA were published. In addition to the ARRIVE and ASCEND trials that compared healthy subjects with at-risk groups, the ASPREE ("Aspirin in Reducing Events in the Elderly") trial analyzed population over an age of 65. The absolute benefit of primary prevention appears to be small, but there was evidence of an increased risk of bleeding in the elderly, as well as in all other age groups. According to the meta-analysis, there is a 31% increase in intracranial hemorrhage with ASA treatment (20). In this study, it was shown that cerebral hemorrhage is not significantly increased by the use of ASA, NOAC or other PAI. Nevertheless, even in the absence of any neurological symptoms, about 5% of the patients in our study on prophylactic ASA medication showed an intracranial bleeding, which strengthens the necessity to perform cCT even following minor head trauma in elderly patients on any anticoagulant medication.

Special care is required in the diagnosis of older patients with TBI (18). Intracranial hemorrhages may remain masked for a long time, especially in elderly patients. It has been described that the use of anticoagulants is associated with an increased risk of bleeding, especially due to traumatic causes. And the use of anticoagulant medications is associated with a high risk of occult intracranial hemorrhage, i.e., without correlating symptoms (5, 10). Thus, the major challenge in diagnosing acute cerebral hemorrhage in the elderly is that the patient's initial symptoms often do not match the radiologic findings (21). It is not surprising that cCT is also performed significantly more often after admission to the ED in those over 65 years of age who are significantly more likely to have relevant preexisting conditions and anticoagulation (22). The diagnostic and therapeutic approach to TBI is initially based on the accident mechanism, the presence and severity of neurologic symptoms, and depending on existing risk factors. Patients with moderate to severe TBI (GCS < 13 points) usually undergo immediate cCT to quickly diagnose a possible intracranial injury (10). A 2017 study recommends routine cCT after a fall, especially in all patients older than 85 years. Although all 737 study participants were clinically stable and had a GCS of 15, 437 patients underwent cCT after clinical examination, which revealed intracranial hemorrhage in one third of the patients (21). According to statistics from the Federal Office of Germany, approximately 165,600 patients > 65 years of age were hospitalized nationwide in 2018 due to a head injury sustained in any accident (23, 24). In this study patients presenting with post-traumatic symptoms after TBI were hospitalized significantly more often. Even though patients with documented hemorrhage had a

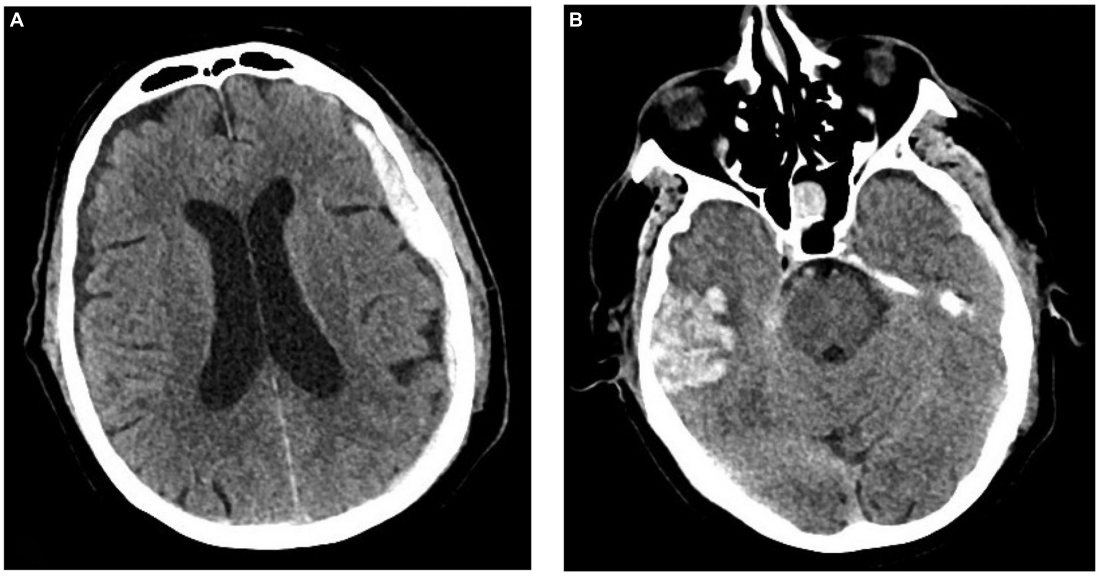

FIGURE 3
Exemplary cranial CT images of a 73-year-old male patient admitted to the emergency department of the University Hospital Frankfurt after a ground-level fall under ASA premedication. The CT scan shows the simultaneous presence of a subdural hematoma **(A)** and an intracerebral hemorrhage **(B)**. ©Department of Diagnostic and Interventional Radiology, University Hospital Frankfurt, Frankfurt am Main, Germany.

significant longer in-hospital stay and ICU treatment. For elderly, rapid recovery is essential because mobility and independence are more difficult to regain than in younger patients. However, it is essential for avoiding and minimizing the need for long-term care (25). There is professional discourse but no clear guideline yet to perform cCT in patients with mild or no symptoms of TBI who are taking anticoagulant medications to rule out possible intracranial hemorrhage (10, 21, 26). Despite minor trauma mechanisms, 17 of 227 patients in this study experienced cerebral hemorrhage. However, in almost 50% of these cases, an intracranial bleeding was detected despite the presence of clinical symptoms. Among these, retrograde amnesia occurred significantly more frequent in patients with post-traumatic hemorrhage. Retrograde amnesia is a mostly temporary form of memory loss regarding events that occurred after the causative event for the amnesia. It is one of the major symptoms of acute brain injury (6). In the elderly, clinical occult hemorrhages occur more frequently because symptoms of increased intracranial pressure may develop later due to the already reduced brain mass. Especially SDH, which is the most common entity of cerebral hemorrhage in the elderly, just like in this study, may remain asymptomatic for a longer time due to its pathophysiology in reduced brain mass (12, 27). Whereby certainly a relevant proportion of geriatric already suffer relevant limitations of memory and retrograde amnesia must be discussed in this context.

Of particular interest were the results showing that the use of NOACs did not lead to increased rate of bleeding in the included patients. However, due to the small number of cases compared to ASA, no conclusive statements can be made. Although we demonstrated an increased incidence of intracranial hemorrhage with LMWH therapy in this study, outpatient use of this agent is uncommon and, to that extent, has reduced validity for the general use of a cCT in geriatric TBI patients on anticoagulation.

On the basis of the data presented here, we continue to believe that the calculated use of cranial CT in geriatric patients with TBI on anticoagulation cannot be dispensed. This is mainly due to the high number of clinically occult hemorrhages that were only diagnosed by cCT. And especially under ASA, which is currently used inflationary in cardiovascular prophylaxis, a not negligible number (5%) of intracerebral bleeding occurred.

Limitations of the study

The most important limitation is the retrospective nature of the data analysis. Another limitation is the single center study design, which only reflects the urban demographics of a large city. This may have a limiting influence on the generalizability of our study results, and it is possible that these results are not applicable to all trauma situations. Overall, the number of positive findings was low, limiting the comparability of patients with intracranial hemorrhage. Nevertheless, the main message of this study is supported by the

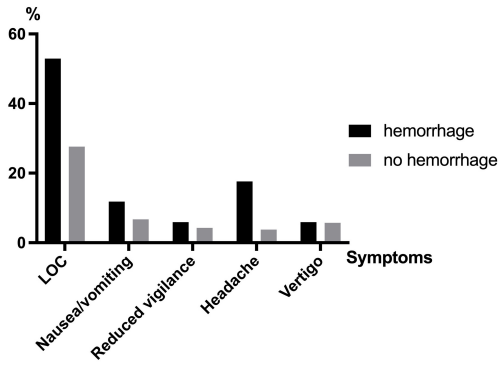

FIGURE 4
Major and minor symptoms in patients with and without cerebral hemorrhage after TBI (LOC, loss of consciousness).

positive results, because in these cases there is a relevant change in the clinical procedure, such as monitoring in the hospital and the basic risk or general indication for CT in ASA and NOAC intake.

Conclusion

Acetylsalicylic acid and NOAC use are not associated with increased bleeding risk in geriatric trauma patients (≥ 65 years) after fall-related TBI. Nevertheless, in almost 50% of cases, intracranial bleeding occurs even in the absence of neurological symptoms, independent from the type of anticoagulant medication. Therefore, cCT is a mandatory tool to exclude cerebral hemorrhage in elderly patients on anticoagulation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study has been conducted after approval by the Institutional Review Board of the University Hospital of the Goethe University Frankfurt (2021-90).

Author contributions

PS designed the study, established the methods, performed the statistical analysis, and revised the manuscript. CS carried out data analyses, obtained the ethical approval for human analyses, performed the statistical analysis, and wrote the first draft of the manuscript. AB collected data and carried out data analyses. IM and KE critically reviewed the manuscript. MW and RV contributed intellectually to the completion of the study. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The effects of early mobilization in mechanically ventilated adult ICU patients: systematic review and meta-analysis

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Background: The effects of early mobilization (EM) on intensive care unit (ICU) patients remain unclear. A meta-analysis of randomized controlled trials was performed to evaluate its effect in mechanically ventilated adult ICU patients.

Methods: We searched randomized controlled trials (RCTs) published in Medline, Embase, and CENTRAL databases (from inception to November 2022). According to the difference in timing and type, the intervention group was defined as a systematic EM group, and comparator groups were divided into the late mobilization group and the standard EM group. The primary outcome was mortality. The secondary outcomes were ICU length of stay, duration of mechanical ventilation (MV), and adverse events. EM had no impact on 180-day mortality and hospital mortality between intervention groups and comparator groups (RR 1.09, 95% CI 0.89–1.33, $p = 0.39$). Systemic EM reduced the ICU length of stay (LOS) (MD −2.18, 95% CI −4.22–−0.13, $p = 0.04$) and the duration of MV (MD −2.27, 95% CI −3.99–−0.56, $p = 0.009$), but it may increase the incidence of adverse events in patients compared with the standard EM group (RR 1.99, 95% CI 1.25–3.16, $p = 0.004$).

Conclusion: Systematic EM has no significant effect on short- or long-term mortality in mechanically ventilated adult ICU patients, but systematic EM could reduce the ICU LOS and duration of MV.

KEYWORDS

early mobilization, mechanical ventilation, ICU, mortality, ICU length of stay

1. Introduction

Mechanically ventilated patients in ICUs are usually associated with short- or long-term complications, which are associated with increased mortality and mechanically ventilated duration, the longer length of ICU LOS and hospital LOS, reduced quality of life, and increased utilization of medical care (1). While the patients are being mechanically ventilated, EM has been proposed as a promising intervention to counteract these complications, and research suggests that it is a safe and feasible intervention (2, 3).

There was evidence of the feasibility of EM to strengthen muscles (4–6), improve Medical Research Council (MRC) and Barthel Index scores (7), and reduce the incidence of ICU-acquired weakness (8, 9), delirium rate (4, 10), and physical disability post–intensive care (11). It also prevented the occurrences of vein thrombosis, ventilator-associated pneumonia, and pressure sores (7, 12). Moreover, it shortens the duration of MV, length of ICU stay, and hospitalization (13, 14).

However, numerous studies found EM with no or inconclusive evidence for a benefit. Many meta-analyses have concluded that EM of ICU patients has no effects on improvements in the functional status, muscle strength, quality of life (QOL) or health care utilization outcomes, ICU LOS, hospital LOS, ICU mortality and hospital mortality (15, 16), and physical function- and mental health-related quality of life at 2–3 months and 6 months post-hospital discharge (12, 17). Most importantly, questions have recently arisen not only about the impact of EM on long-term outcomes but also about its safety. In an international, multicenter, randomized, controlled trial of 750 mechanically ventilated adult ICU patients, the TEAM study investigators and the ANZICS clinical trials group showed that an increase in EM did not improve survival, but it was associated with increased adverse events (18). On the other hand, because there is no unified concept of "early" in the EM literature, most studies believe that any mobilization activity is early if is commenced any time during the course of MV (19) or between 48 and 72 h after the start of MV (20, 21).

Therefore, based on a lack of consensus with published findings about the effects of EM in patients requiring MV in ICU, a meta-analysis of RCTs was conducted to comprehensively assess the benefits and adverse effects of EM in critically ill patients and requiring MV.

2. Methods

2.1. Protocol and registration

This study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22). The protocol has been registered on the international prospective register of systematic reviews website (PROSPERO: https://www.crd.york.ac.uk/prospero/), and the registration number is CRD42022380303.

2.2. Eligibility criteria

Studies were included according to the following inclusion criteria: (1) Population: adult patients (≥18 years old) requiring MV at enrollment or during the ICU stay. (2) Design: RCT published in English. (3) Intervention: patients in the intervention group received systematic EM. Based on previously published meta-analyses (23), systematic EM was defined as any physical or occupational therapy targeting muscle activation, initiated within 3 days after ICU admission and performed according to a clearly defined protocol or specific clinical criteria in all eligible patients.

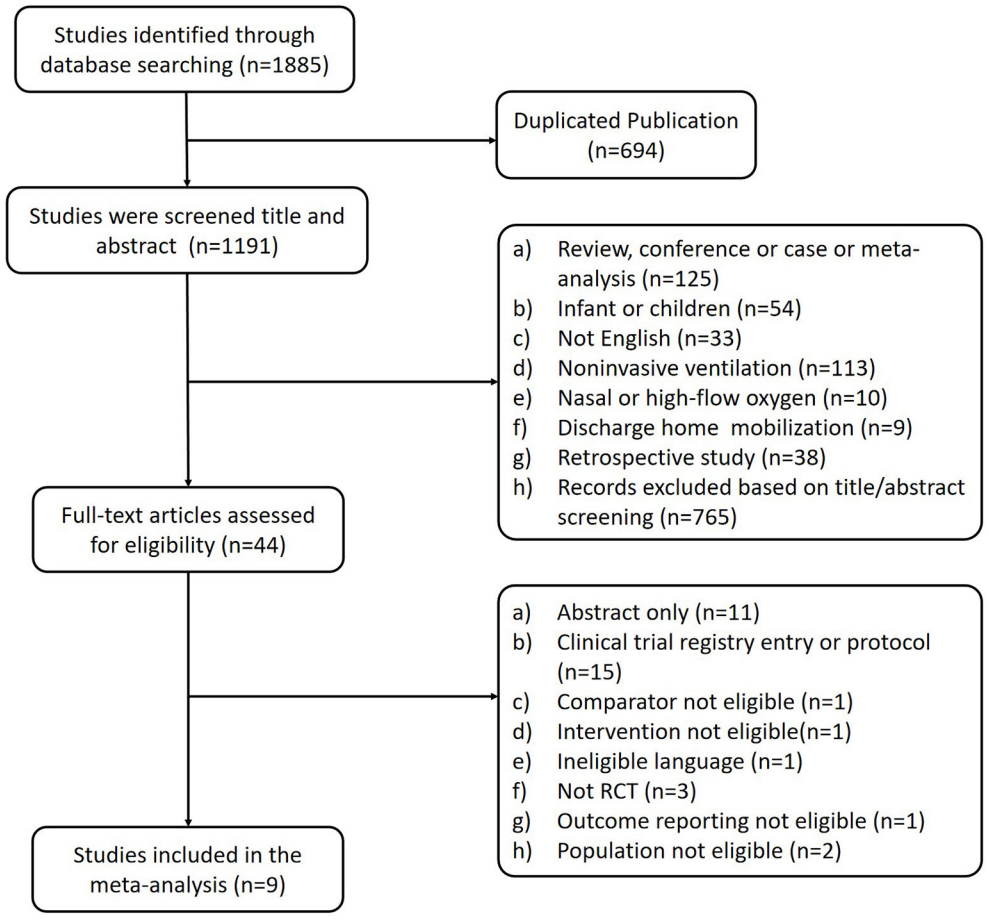

FIGURE 1
PRISMA flow diagram of the study selection.

TABLE 1 Summary of included studies and study participants.

Study	Country, timeframe	Population	Group	No. of participants	Females *n* (%)	Age Mean (SD)/ Median (IQR)	APACHEII score Mean (SD)/ Median (IQR)	Patient admission diagnoses
Schweickert et al. (2)	USA, 2005–2007	Adult ICU patients, mechanically ventilated < 72 h, independent at baseline	Intervention	49	29 (59.2)	57.7 (36.3–69.1)	20.0 (15.8–24.0)	Lung injury (56%), COPD exacerbation (10%), acute exacerbation of asthma (9%), sepsis (15%), hemorrhage (3%), malignancy (3%), other (5%)
			Comparator	55	23 (41.8)	54.4 (46.5–66.4)	19.0 (13.3–23.0)	
Dong et al. (31)	China, 2010–2012	Adult ICU patients, mechanically ventilated between 48 and 72 h with expected ventilation of ≥ 1 week, clear consciousness, cardiovascular and respiratory stability	Intervention	30	9 (30.0)	55.3 (16.1)	15.0 (4.2)	Abdominal infections (18%), ARDS (32%), sepsis (7%), severe acute pancreatitis (15%), pneumonia (23%), COPD exacerbation (5%)
			Comparator	30	10 (33.3)	55.5 (16.2)	16.0 (4.1)	
Hodgson et al. (4)	Australia/New Zealand, 2013–2014	Adult ICU patients, mechanically ventilated within 72 h of ICU admission	Intervention	29	8 (25.9)	64 (12)	19.8 (9.8)	N/A
			Comparator	21	12 (57.1)	53 (15)	15.9 (6.9)	
Morris et al. (33)	USA, 2009–2014	Adult ICU patients, acute respiratory failure requiring mechanical ventilation	Intervention	150	84 (56.0)	55 (17)	NA	Acute respiratory failure (98%), coma (2%)
			Comparator	150	82 (54.7)	58 (14)	NA	
Schaller et al. (10)	USA/Germany, 2011–2015	Adult surgical ICU patients, mechanically ventilated for < 48 h and for at least further 24 h, functionally independent at baseline	Intervention	104	39 (37.5)	66 (48–73)	16 (12–22)	Visceral surgery (27%), vascular surgery (17%), ENT and ophthalmological surgery (10%), transplant surgery (4%), neurosurgery (3%), orthopedic surgery (3%), thoracic surgery (3%), gynecological surgery (2%), urological surgery (1%), plastic surgery (1%), medical or neurological diagnosis (6%), trauma (26%)
			Comparator	96	35 (36.5)	64 (45–76)	17 (11–22)	
Dong et al. (13)	China, 2012–2015	Adult patients, prolonged mechanical ventilation > 72 h, eligible for coronary artery bypass surgery	Intervention	53	33 (62.3)	62.6 (12.8)	16.3 (4.2)	Coronary artery bypass surgery (100%)
			Comparator	53	31 (58.5)	60.2 (15.1)	17.2 (4.3)	
Eggmann et al. (32)	Switzerland, 2012–2016	Adult ICU patients, expected to stay on mechanical ventilation for at least 72 h, independent before critical illness	Intervention	58	22 (37.9)	65 (15)	23.0 (7.0)	Cardiac surgery (18%), neurology/neurosurgery (8%), other surgery (12%), gastroenterology (12%), trauma (4%), respiratory insufficiency (22%), hemodynamic insufficiency (23%), other (2%)
			Comparator	57	16 (28.1)	63 (15)	22.0 (8.0)	

(Continued)

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TABLE 1 (Continued)

Study	Country, timeframe	Population	Group	No. of participants	Females *n* (%)	Age Mean (SD)/ Median (IQR)	APACHEII score Mean (SD)/ Median (IQR)	Patient admission diagnoses
Dong et al. (30)	China, 2019–2020	Adult ICU patients, Prolonged MV (> 72 h), clear consciousness, cardiovascular and respiratory stability, no history of chronic mental illness or COPD	Intervention	39	NA	59.05 ± 17.61	15.90 ± 6.01	N/A
			Comparator	41	NA	64.44 ± 14.72	17.78 ± 8.40	
Hodgson et al. (18)	Australia/ New Zealand/ Germany/ Ireland/UK/ Brazil, 2018–2021	Adult ICU patients (≥ 18 years of age), mechanical ventilation, condition was sufficiently stable to make mobilization potentially possible	Intervention	371	128 (34.5)	60.5 ± 14.8	18.2 ± 6.8	Sepsis (66.3%), Trauma (3.9%), COVID-19 (2.3%), others (27.5%)
			Comparator	370	146 (39.5)	59.5 ± 15.2	18 ± 6.9	

(4) Comparators: patients in the control group received late mobilization (i.e., mobilization initiated 3 days or more after ICU admission) or standard EM (i.e., mobilization initiated within 3 days but less systematic) (23). (5) Outcomes: the primary outcome was mortality (including 180-day mortality and hospital mortality). The secondary outcomes were ICU LOS, duration of MV, and adverse events.

Studies that enrolled patients with pediatric, animal, or cell-based studies and studies published in narrative reviews, abstracts, commentaries, editorials case reports, and duplicate publications were excluded.

2.3. Information sources and search strategy

A computerized literature search was performed in Medline, Embase, and CENTRAL databases (from inception to November 2022) by two independent investigators using the keywords "intensive care unit," "early mobilization," "mechanical ventilation," and "randomized controlled trial," as well as their respective synonyms and derivations. The exact search strategy is provided in Supplementary File 1. The publication language was restricted to English.

After deduplication, two reviewers independently screened the titles and abstracts of all articles in order to detect the potential studies. Disagreements during the review process were resolved through discussion or consultation with an experienced senior reviewer. The pooled full-text references were then assessed to select eligible studies and when disagreement occurred, the dealing method is the same as mentioned above.

2.4. Data extraction

Two independent investigators adopted a standard collection form to extract related data from the included trials. The following information was extracted from each study: first author, year of publication, country, number of patients in intervention groups and comparator groups, patients' baseline characteristics, patient admission diagnoses, intervention description, time to first intervention, intervention frequency, intervention duration, and adverse events. Discrepancies between the researchers were resolved through discussion or arbitration by a third researcher.

2.5. Risk of bias assessment

The risk of bias in included studies was assessed using the Cochrane risk of bias tool, and the overall risk of bias for an individual trial was classified as high risk (when the risk of bias was high in at least one domain), low risk (when the risk of bias was low in all domains), or unclear (when the risk of bias was unclear in at least one domain) (24).

TABLE 2 Details on study interventions and comparators.

Study	Group	Intervention description	Time to first intervention Median (IQR) (days)	Intervention frequency	Intervention duration Mean (SD)/ Median (IQR)
Systematic early mobilization vs. Standard early mobilization					
Dong et al. (31)	Intervention	Heading up actively, transferring from the supine position to sitting position, sitting at the edge of the bed, sitting in chair, transferring from sitting to standing, ambulating bedside and changed every 2 h	N/A	Twice daily	According to the condition of patients
	Comparator	Not described	N/A	N/A	N/A
Schaller et al. (10)	Intervention	Early, goal-directed mobilization algorithm: the goal for a specific day was set either to level 0 (no mobilization), level 1 (passive range of motion exercises in the bed), level 2 (sitting), level 3 (standing), or level 4 ambulation)	N/A	Once daily	Depending on the condition of patients
	Comparator	Standard care except for early, goal directed mobilization	N/A	Once daily	N/A
Eggmann et al. (32)	Intervention	Motor-assisted bed-cycle, standard exercises for both upper and lower limbs exercises for both upper and lower limbs, in-bed exercise, sitting, standing and walking	2.0 (1.4–2.8) after ICU admission	maximum 3 times daily, 7 days per week	25 min (19.5–27)
	Comparator	European standard Physiotherapy including early mobilization, respiratory therapy and passive or active exercises	2.0 (1.4–2.8) after ICU admission	Once daily	18 min (14–21)
Dong et al. (30)	Intervention	Rehabilitation therapy consisted of six levels: level 0, turning over; level 1–2, sit up; level 3, sitting on the edge of bed; level 4, standing up or sitting in a chair; level 5, moved from the bed and walked	N/A	N/A	Tailored depending on the condition of patients
	Comparator	Standard care	N/A	N/A	N/A
Hodgson et al. (18)	Intervention	Senior physiotherapists led the intervention and participated in interdisciplinary discussions and reviews of a safety checklist	N/A	Once daily	20.8 ± 14.6 min
	Comparator	The level of mobilization that was normally provided in each ICU	N/A	Once daily	8.8 ± 9.0 min
Systematic early mobilization vs. Late mobilization					
Schweickert et al. (2)	Intervention	Passive range of motion, active-assisted and active-independent exercises, bed mobility exercises, Sitting balance activities, transfer training, pre-gait exercises and walking	1.5 (1.0–2.1) after intubation	Once daily	0.3 h (0.2–0.5) per day during ventilation 0.2 h (0.1–0.3) per day without ventilation
	Comparator	standard care with physical and occupational therapy delivered as ordered by the primary care team	7.4 (6.0–10.9) after intubation	N/A	0.0 h (0.0–0.0) per day during ventilation 0.2 h (0.0–0.4) per day without ventilation
Morris et al. (33)	Intervention	Passive range of motion, physical therapy and progressive resistance exercise	1 (0–2) after ICU admission	3 times daily, 7 days a week	N/A
	Comparator	Weekday physical therapy when ordered by the clinical team	7 (4–10) after ICU admission	5 days a week	N/A
Dong et al. (13)	Intervention	head up, transferring from supination to sitting, sitting on the edge of bed, sitting in a chair, transferring from sitting to standing, and walking along a bed	N/A	Twice daily	N/A
	Comparator	Received rehabilitation therapy with the help of family after leaving the ICU	N/A	N/A	N/A
Hodgson et al. (4)	Intervention	Functional activities comprising walking, standing, balance exercises, sitting in or out of bed, sitting and rolling (the patient could receive assistance from staff or equipment but the patient actively participated in the exercise at the highest functional level)	3 (2–4) after ICU admission	Once daily	About 30–60 min depending on the condition of patients
	Comparator	Passive movements (the same mobilization equipment was available in both the control group and the intervention group)	4 (3–5) after ICU admission	Once daily	About 5–10 min per day

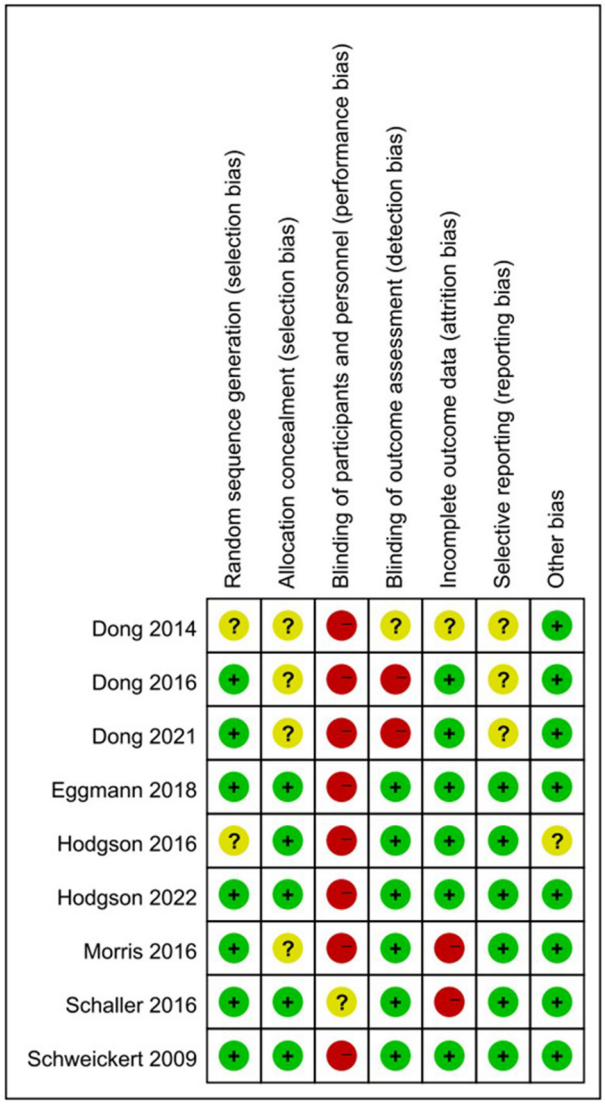

FIGURE 2
Risk of bias assessment for the included studies.

2.6. Data synthesis

Considering these studies differ in the timing and type of interventions, results are reported stratified by a comparator category (systematic EM, late mobilization, and standard EM). According to these studies (23, 25, 26), eligible comparators were categorized as: systematic EM (i.e., mobilization initiated within 3 days of admission to the ICU with), late mobilization (i.e., mobilization initiated 3 days or more after ICU admission), standard EM (i.e., mobilization initiated within 3 days but less systematically, or without clear initiated timing for mobilization). It is worth mentioning that one of these studies included an intervention description of the control group that received mobilization therapy after leaving the ICU (the ICU LOS is 18.3 ± 4.2 days), so this was defined as within the late mobilization category.

All statistical analyses were performed in this study using Review Manager 5.4 version (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). For continuous variables (e.g., ICU LOS and duration of MV), mean differences (MDs) with 95% CIs were calculated using the inverse-variance (I-V) test, while for dichotomous variables (e.g., mortality and adverse events), risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel (M-H) test. In this study, some trials presented the indicators as a median and interquartile range (IQR), which were transferred into mean and standard deviation (SD) (27, 28). Comparable results were shown by fixed- or random effects and 95% confidence intervals.

Study heterogeneity was assessed by using the I^2 statistics (29). If significant heterogeneity ($I^2 < 50\%$) was present, the fixed-effects model was used. Otherwise, the random-effects model was used. A two-sided P-value of ≤ 0.05 was considered to be statistically significant.

3. Results

3.1. Search results

Figure 1 shows the study selection process. The initial search identified 1,885 publications, of which 694 were excluded because of duplication. After reviewing the titles and abstracts, 1,147 were excluded because these articles' research type, population, or language were unqualified. After browsing full-text, nine RCTs ($n = 1{,}756$ patients) were eligible for inclusion and analysis in this meta-analysis (2, 4, 10, 13, 18, 30–33).

3.2. Study characteristics

The baseline characteristics of the included studies are presented in Table 1. Of the nine trials included, seven were published after 2015, while only two were published before that year, one in 2009 (2) and the other in 2014 (31). The included studies provided data from 883 people randomized to the intervention group and 873 people in the control group. In addition to the study conducted by Dong (30), the remaining eight trials reported the male-to-female ratio, which was about 42% in the intervention group and 43% in the comparator group. The mean age of the intervention group and the comparator group was similar, and the age difference in only two articles was large (4, 30), which may be due to the small sample size of the two trials and random error in sampling. Eight studies reported primary study outcomes [180-day mortality (18, 32, 33) and hospital mortality (2, 4, 10, 13, 31)], and these studies reported secondary outcome measures: ICU LOS (2, 4, 10, 13, 30–33), duration of MV (2, 4, 13, 30–32), and adverse events (2, 4, 10, 18, 30–33).

Considering the difference between studies in the timing and type of interventions, some results are reported stratified by a comparator category (systematic EM, late mobilization, and standard EM). According to the study definition, five studies were classified (10, 18, 30–32) as comparing systematic EM vs. standard EM, and the other four studies (2, 4, 13, 33) were classified as systematic EM vs. late mobilization (in Table 2). Different studies

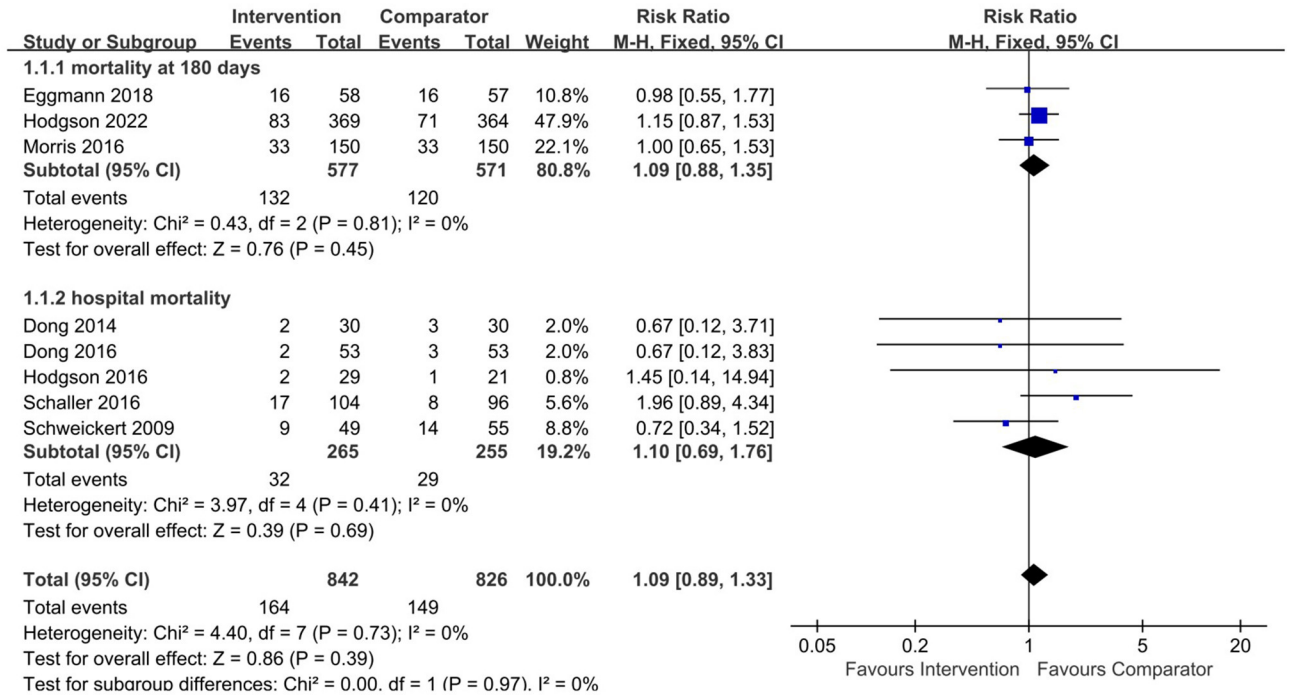

FIGURE 3
Forest plot for early mobilization on effect mortality in the included studies. Intervention group = systematic early mobilization group, Comparator = late mobilization or standard early mobilization.

intervene in different ways, including head up, transferring from supination to sitting, standing, and walking, and other goal-oriented mobilization protocols. The frequency of intervention was once daily, twice daily, or three times daily. The duration of the intervention ranged from 20 to 60 min in the intervention group and from 0 to 0.2 h in the control group (in Table 2).

3.3. Risk of bias assessment

The details of the risk of bias assessment are summarized in Figure 2. Seven studies (78%) were at low risk of bias of the random sequence generation. A suitable method of allocation concealment was used in five studies (56%). Because the patients in the intervention group needs to rehabilitate, blinding of participants and personnel was not possible, and eight studies (89%) were at high risk of bias. Six studies (67%) reported blinding of the outcome assessment. Incomplete outcome data may exist in two studies (22%), and three studies (33%) could be reporting selective.

3.4. Mortality

As shown in Figure 3, eight studies reported mortality at different time points. Among them, three studies (18, 32, 33) reported 180-day mortality that included 577 patients in the intervention group (the systematic EM group) and 571 patients in the comparator group (the late mobilization group and the standard EM group), and there was no significant difference in 180-day mortality between the two groups (RR 1.09, 95% CI 0.88–1.35, $I^2 = 0\%$, test for overall effect: Z = 0.76, $p = 0.45$). As for hospital mortality, there were five studies included in this analysis with 520 patients (2, 4, 10, 13, 31), and no significant difference was found in mortality between the two groups (RR 1.10, 95% CI 0.69–1.76, $I^2 = 0\%$, test for overall effect: Z = 0.39, $p = 0.69$). The results of subgroup analysis showed no difference in mortality between the systematic EM group and standard EM or the late mobilization group at any time points (RR 1.09, 95% CI 0.89–1.33, $I^2 = 0\%$, test for overall effect: $Z = 0.86$, $p = 0.39$).

3.5. ICU length of stay

Eight studies reported the relationship between EM and ICU LOS. In the subgroup analysis, there are four studies that adopted systematic EM and late mobilization (2, 4, 13, 33), and no significant difference was found between these two groups (MD −2.38, 95% CI −6.37–1.62, $I^2 = 93\%$, test for overall effect: Z = 1.17, $p = 0.24$). In addition, the other four studies (10, 30–32) had an impact on systemic EM and standard EM for LOS in ICU. Compared with the standard EM group, there was a statistically significant reduction of ICU LOS in the systematic EM group (MD −2.10, 95% CI −3.27–−0.94, $I^2 = 0\%$, test for overall effect: Z = 3.54, $p < 0.001$). A pooled analysis of these studies showed a significant mean difference and favored the systematic EM group (MD −2.18, 95% CI −4.22–−0.13, $I^2 = 85\%$, test for overall effect: Z = 2.08, $p = 0.04$, n = 1,015) (Figure 4).

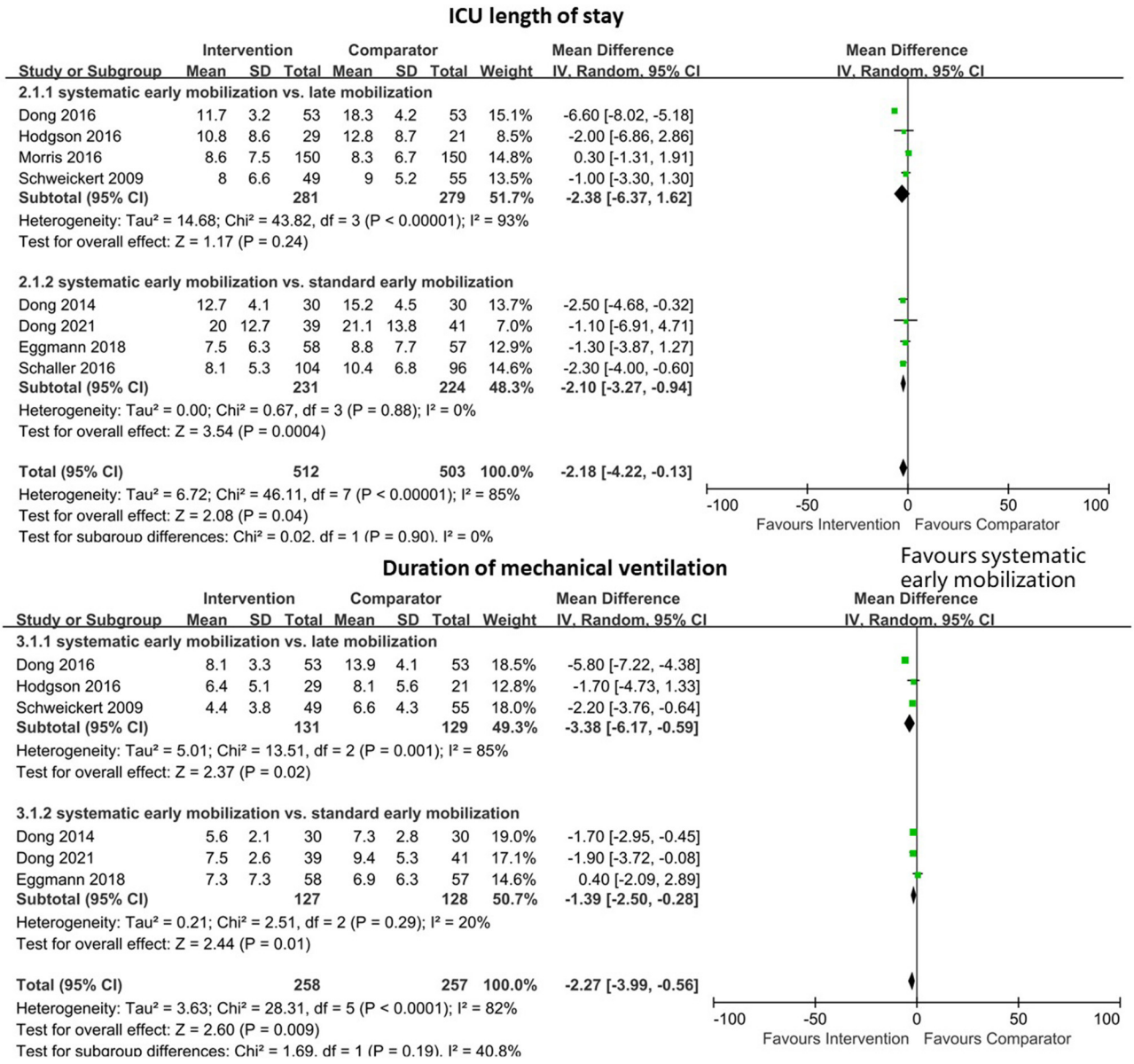

FIGURE 4
Forest plot for early mobilization effect on ICU length of stay in the included studies.

3.6. Duration of mechanical ventilation

Six studies analyzed 515 patients who reported the duration of MV. The pooled analysis of the data indicated a decreased trend in the duration of MV following systematic EM (MD −2.27, 95% CI −3.99–−0.56, I^2 = 82%, test for overall effect: Z = 2.60, p = 0.009) (Figure 4). In the subgroup analysis, there was a statistically significant mechanically ventilated duration in the systematic EM group, compared with the late mobilization group (2, 4, 13) and the standard EM group (30–32) (MD −3.38, 95% CI −6.17–−0.59, I^2 = 85%, test for overall effect: Z = 2.37, p = 0.02 and MD −1.39, 95% CI −2.50–−0.28, I^2 = 20%, test for overall effect: Z = 2.44, p = 0.01, respectively) (Figure 4).

3.7. Adverse events

A total of eight trials with 1,650 patients reported different adverse events among participants. These trials reported adverse events including decreased desaturation, agitation, dislodgement of arterial line or nasogastric tube, dyspnea, dizziness, cardiac arrhythmia, altered blood pressure, and cerebrovascular accident (2, 4, 10, 18, 30–33). The adverse events were not significantly different between the systemic EM group and the late mobilization group (RR 1.35, 95% CI 0.05–33.52, I^2 = 86%, test for overall effect: Z = 0.18, p = 0.85) (2, 4, 33). However, there were more adverse events in the systemic EM group compared to the standard EM group (RR 1.99, 95% CI 1.25–3.16, I^2 = 0%, test for overall effect: Z = 2.89, p = 0.004) (10, 18, 30–32) (Figure 5).

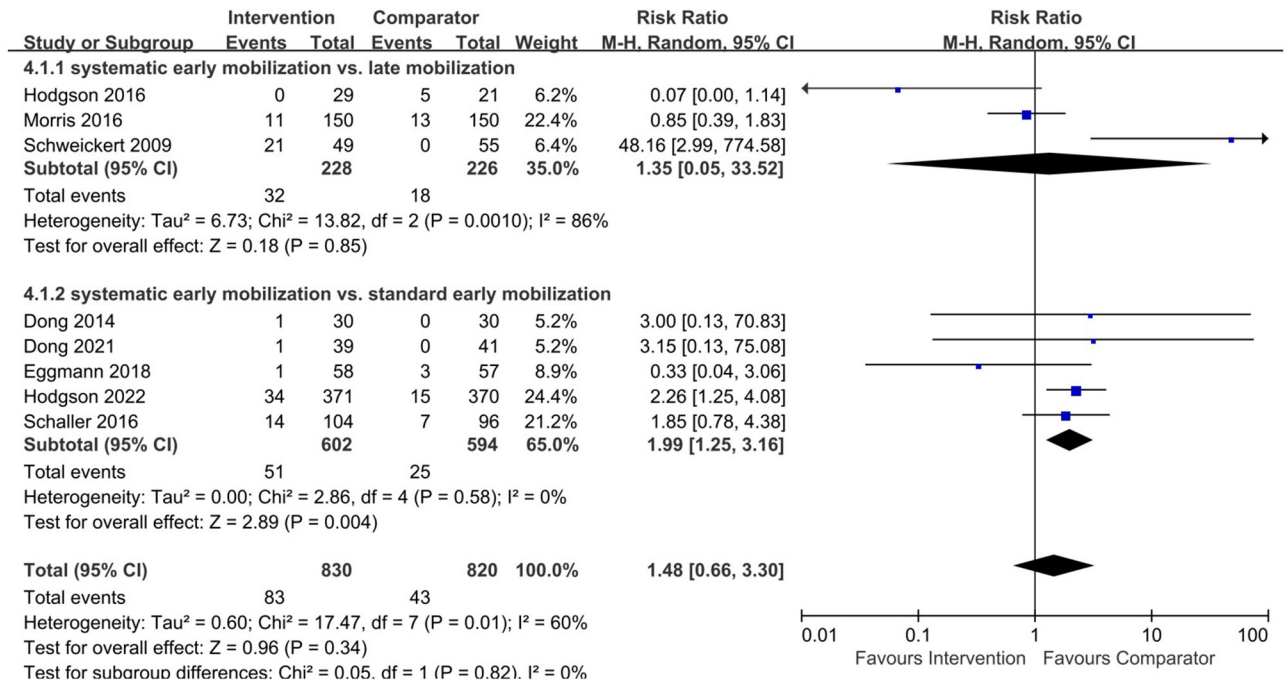

FIGURE 5
Forest plot for early mobilization effect on adverse events in the included studies.

4. Discussion

This meta-analysis included 9 RCTs, and it was found that systematic EM had no effect on short- or long-term mortality in mechanically ventilated adult ICU patients, but it could reduce the LOS in ICU and the duration of MV. While systemic EM may increase the incidence of adverse events in patients compared with standard EM.

The meta-analysis found that EM in the ICU had no effects on 180 days mortality and hospital mortality. There have been many studies on the impact of EM on mortality in ICU patients. After comparing the effects of EM and late mobilization, standard EM or no mobilization, Dominik (23) argued that none of them had any effect on patients' short-term mortality (hospital mortality) and long-term mortality (6-month mortality), which the current study findings support. A systematic review (34) about the impact of mobilization on the mortality of ICU patients demonstrated that mobilization had no positive effects on short- or long-term mortality. The results were consistent with the present study findings, but the current meta-analysis was the inclusion of a multicenter, high-quality, large-population RCTS study published in the New England Journal in October 2022 (18), which added strong evidence to the results.

This study showed that both ICU LOS and the duration of the mechanical ventilator were approximately reduced by 2 days in the EM group. The included four studies (10, 30–32) comparing the length of ICU stay between systematic EM and standard EM showed little heterogeneity and a significant difference between the two groups, suggesting systematic EM within 3 days of ICU admission can effectively reduce the length of ICU stay. Similar results have been found in other systematic reviews. Klem et al. (35) suggested that EM can shorten ICU stay by 1 day but has no effect on the total hospital LOS and also about the effects of systematic EM on the duration of the mechanical ventilator. Zhang et al. (36) reported the same positive results in a systematic review. Monsees et al. (37) also implied the same trend toward a reduction in the duration of mechanical ventilators with EM. It is thought that EM can reduce ICU-acquired weakness (38), which may associate with a prolonged duration of mechanical ventilator (39, 40).

In terms of safety and adverse events, there were eight trials that reported adverse events. Hodgson (18) reported 34 patients with adverse events in the EM group and 15 patients with adverse events in the usual care group, suggesting that the incidence of adverse events in the EM group was higher than that in the usual care group ($P = 0.005$). While in the other studies, there was no difference in the incidence of adverse events between the intervention group and the comparator group. Although serious adverse events were very rare, they still occurred. For example, Schweickert (38) reported a case of desaturation of <80%. Therefore, it is believed that the initiation of EM should be very cautious.

There are some limitations in this study. First, some of the included studies had small sample sizes. In three studies (4, 30, 31), there were <100 total participants, which is more likely to overestimate the effects. Second, our conclusions may be limited by the poor quality and bias of some of the studies. The performance bias and detection bias in these two articles are high-risk, and selection bias and reporting bias are unclear (13, 30). Third, the definition of EM is not clear in those included studies. Some studies

suggest that it should be limited to 3 days (25, 26), while others suggest that it should be limited to 7 days (23). Different definitions may lead to different subgroups, which may affect results. In addition, some other factors cannot be ignored, such as the mode and duration of mobilization treatment, which vary greatly between studies. The lack of detailed information may affect the accuracy of this study.

5. Conclusion

Although EM does not improve short- or long-term mortality in mechanically ventilated adult ICU patients, this systematic review found that systematic EM could reduce the ICU LOS and duration of MV, but it may increase the incidence of adverse events compared with standard EM, which suggest that EM should be initiated carefully. However, given the potential limitations of this study and the substantial heterogeneity among the included trials, the results of this study should be interpreted with caution. Further large-scale and well-conducted RCTs are needed to validate our current findings.

Author contributions

XO: conceptualization and supervision. LiW: methodology and writing—review and editing. LiW and YH: formal analysis. LiW, YH, XZ, YZ, and LuW: data curation. LiW and LuW: writing—original draft preparation. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1202754/full#supplementary-material

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Development and validation of a nomogram for predicting persistent inflammation, immunosuppression, and catabolism syndrome in trauma patients

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Background: Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PIICS) is a significant contributor to adverse long-term outcomes in severe trauma patients.

Objective: The objective of this study was to establish and validate a PIICS predictive model in severe trauma patients, providing a practical tool for early clinical prediction.

Patients and methods: Adult severe trauma patients with an Injury Severity Score (ISS) of ≥16, admitted between October 2020 and December 2022, were randomly divided into a training set and a validation set in a 7:3 ratio. Patients were classified into PIICS and non-PIICS groups based on diagnostic criteria. LASSO regression was used to select appropriate variables for constructing the prognostic model. A logistic regression model was developed and presented in the form of a nomogram. The performance of the model was evaluated using calibration and ROC curves.

Results: A total of 215 patients were included, consisting of 155 males (72.1%) and 60 females (27.9%), with a median age of 51 years (range: 38–59). NRS2002, ISS, APACHE II, and SOFA scores were selected using LASSO regression to construct the prognostic model. The AUC of the ROC analysis for the predictive model in the validation set was 0.84 (95% CI 0.72–0.95). The Hosmer-Lemeshow test in the validation set yielded a χ^2 value of 14.74, with a value of p of 0.098.

Conclusion: An accurate and easily implementable PIICS risk prediction model was established. It can enhance risk stratification during hospitalization for severe trauma patients, providing a novel approach for prognostic prediction.

KEYWORDS

nomogram, persistent inflammation, immunosuppression, catabolism syndrome, trauma score, trauma prediction, ICUAW

Introduction

The majority of severe trauma patients require treatment in the intensive care unit (ICU). Due to improvements in clinical treatment and care in recent years, the mortality rate of these patients has decreased (1, 2). However, surviving patients often experience prolonged stays in the ICU and enter a state of Chronic Critical Illness (CCI) (1, 3). In 2012, Gentile et al. coined the term Post-Intensive Care Syndrome (PIICS) and defined its clinical determinants as Persistent Inflammation, Immunosuppression, and Catabolism Syndrome. These determinants include prolonged hospitalization (>14 days), inflammation (C-reactive protein levels >150 μg/dL), immune suppression (lymphocyte count <800/μL), and catabolism (weight loss >10% during hospitalization or BMI <18.5 kg/m^2) (1, 4). PIICS is characterized by prolonged dysregulation of the inflammatory response, immune dysfunction, and catabolic state, resulting in a range of adverse outcomes, including infection, organ dysfunction, and impaired wound healing (2, 5). Early identification and prediction of PIICS in trauma patients are crucial for optimizing patient management and improving long-term prognosis.

The development and validation of predictive models specifically designed for trauma patients can assist healthcare professionals in identifying high-risk individuals and preventing PIICS-related complications (6). Predictive models can integrate clinical and demographic variables, provide early risk stratification, and facilitate targeted interventions. Currently, there is a primary focus on predictive models for PIICS in critically ill patients in different clinical settings, such as sepsis and major surgeries (6, 7). However, trauma patients present unique challenges and characteristics (5). The pathological mechanisms underlying the development of PIICS in trauma patients are not yet clear, and factors such as the severity of the injury, anatomical location, and surgical interventions may significantly influence the risk and trajectory of PIICS (5, 8–10). Therefore, there is a need to establish a robust dataset encompassing diverse demographic characteristics, injury severity, clinical variables, and biomarker measurements, and employ advanced statistical techniques and machine learning algorithms to derive predictive models with good discriminative and calibration abilities, enhancing their applicability in clinical practice.

This study aims to develop and validate a predictive model specifically for severe trauma patients to predict PIICS. The model will incorporate clinical and injury-related variables to provide physicians with a reliable tool for assessing the risk of PIICS in individual trauma patients. By identifying high-risk patients early on, healthcare professionals can implement targeted interventions to modulate dysregulated inflammatory responses and alleviate the occurrence and progression of PIICS-related complications. This effective prediction approach can be utilized to reduce the risk of PIICS-related complications and improve patient recovery and long-term health.

Materials and methods

A prospective survey was conducted from October 2020 to September 2022 to collect data from severe trauma patients aged 18 and above admitted to the Trauma Intensive Care Unit (ICU) of Tongji Hospital, Huazhong University of Science and Technology School of Medicine. Clinical data within 24 h of admission were assessed and recorded, including age, gender, mechanism of injury (MOI), body mass index (BMI), Injury Severity Score (ISS), Nutritional Risk Screening 2002 (NRS 2002), Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II score (APACHE II score). Laboratory examinations at admission included hemoglobin (g/L), lymphocyte count (*10^9/L), albumin (g/L), and lactate (mmol/L). The BMI was calculated as weight divided by height squared (kg/m^2). 14 days after admission, the relevant indicators of PIICS were recorded and evaluated. Specific indicators include inflammation (C-reactive protein level), immune suppression (lymphocyte count), and catabolism (weight loss during hospitalization or BMI). This research plan has been approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number: TJ-IRB20230214). According to the guidelines, the study satisfied the conditions to waive the requirement for informed consent from individual participants. Therefore, informed consent was waived by Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. All procedures were carried out following relevant guidelines and regulations.

Definition of PIICS

According to Gentile et al.'s study in 2012, PIICS was defined as Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (1). The clinical determinants of PIICS were prolonged hospitalization (>14 days), inflammation (C-reactive protein levels >150 μg/dL), immune suppression (lymphocyte count <800/μL), and catabolism (weight loss >10% during hospitalization or BMI <18.5 kg/m^2) (1, 2).

Statistical analysis

Patients were divided into PIICS and non-PIICS groups based on the occurrence of PIICS during hospitalization. Normally distributed data were presented as means and standard deviations (SDs), while non-normally distributed data were presented as medians and interquartile ranges (IQRs). Differences between groups were evaluated using unpaired *t*-tests or the Mann–Whitney *U* test for continuous variables. Frequency tables were generated for categorical variables and analyzed using chi-square or Fisher's exact tests. Univariate logistic regression was performed to explore risk factors for adverse outcomes during hospitalization. Factors with a value of $p < 0.2$ were entered into the multivariate regression model. The results of the final model were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

Patients were randomly allocated to a training set and a validation set in a 7:3 ratio. In the training set, the least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation was used to select the appropriate variables, with λ set at one standard error (SE). A logistic regression model was developed to predict the occurrence of adverse outcomes during hospitalization, and the predictive performance of the prognostic model was internally validated in the validation set. The final

TABLE 1 Comparison of characteristics between PIICS and No-PIICS patients.

Variables	PIICS cases ($n = 79$)	No-PIICS cases ($n = 136$)	Total patients ($n = 215$)	Value of p
Gender				0.181
Male	52	103	155	
Female	27	33	60	
Age (year)	53 (43–60)	49 (37–58)	51 (38–59)	0.122
MOI (n)				0.296
Vehicle collision	46	90	136	
Fall	12	22	34	
Others	21	24	45	
Injury region				0.573
Head	20	37	57	
Thorax	16	28	44	
Abdomen	17	28	45	
Pelvis	10	8	18	
Spine	6	10	16	
Extremity	10	25	35	
Pelvis	10	8	18	
BMI	23.75 (20.50–33.05)	24.06 (21.73–29.35)	24.22 (10.90–30.11)	0.426
NRS2002 score	3 (2–4)	2 (1–3)	3 (1–3)	0.0002
ISS score	27 (21–34)	22 (17–31)	25 (19–33)	0.003
APACHE II score	11 (9–15)	11 (7–11)	11 (8–13)	0.002
SOFA score	5 (2–7)	3 (2–4)	3 (2–5)	0.0008
Lymphocyte (*10^9/L)	0.92 (0.61–1.355)	0.91 (0.65–1.31)	0.91 (0.63–1.34)	0.813
Hb (g/L)	96 (82–105)	103 (89–116)	98 (85–114)	0.022
Alb (g/L)	31.8 ± 5.5	33.4 ± 4.7	32.4 ± 5.1	0.062
Serum creatinine (umol/L)	57 (46–83)	64 (53–76)	63 (50–76)	0.256
hs-CRP (mg/L)	55.2 (28.5–109.5)	48 (12.4–77.8)	33.8 (29.5–37.1)	0.084
Emergency surgery	17	25	42	0.719

model was presented graphically. Goodness of fit was assessed using the Hosmer-Lemeshow test. Calibration curves and receiver operating characteristic (ROC) curves were plotted to analyze the discriminative ability and calibration of the model. Statistical analysis was performed using R version 4.0.2 with relevant packages.

Results

Descriptive data

A total of 215 patients were included, with 155 males (72.1%) and 60 females (27.9%). The median age was 51 years (38–59). The most common mechanisms of injury were traffic accidents in 136 cases (63.3%), followed by falls in 34 cases (15.8%). The median BMI was 24.22 kg/m^2 (10.90–30.11). The top three body regions with the most severe injuries were the head and neck (26.5%), abdomen (20.1%), and chest (20%). The median NRS 2002 and ISS scores were 3 (1–3) and 25 (19–33), respectively.

Factors associated with PIICS

Based on the occurrence of PIICS, patients were divided into the PIICS group (79 cases) and the non-PIICS group (136 cases). There were statistically significant differences between the PIICS and non-PIICS groups in terms of NRS2002 score, ISS score, APACHE II score, and SOFA score ($p < 0.05$) (Tables 1, 2).

Logistic regression analysis

Univariate logistic regression analysis revealed that independent factors associated with the occurrence of PIICS included NRS2002 score (HR 1.46, 95% CI 1.19–1.82), ISS score (HR 1.05, 95% CI 1.02–1.08), APACHE II score (HR 1.11, 95% CI 1.04–1.20), SOFA score (HR 1.17, 95% CI 1.07–1.32), albumin (HR 0.94, 95% CI 0.88–0.99), and hs-CRP (HR 1.01, 95% CI 1.00–1.01). Multivariate logistic regression analysis identified NRS2002 score (HR 1.29, 95% CI 1.02–1.65) as an independent factor associated with PIICS (Table 3).

TABLE 2 Baseline characteristics of 215 participants.

Variables	Training set (*n* = 150)	Validation set (*n* = 65)	Total patients (*n* = 215)	Value of *p*
Gender				0.7601
Male	109	46	155	
Female	41	19	60	
Age (year)	51 (38–60)	50 (39–57)	51 (38–59)	0.5041
BMI	24.33 (20.98–28.38)	23.90 (21.20–31.43)	24.22 (10.90–30.11)	0.7307
NRS2002 score	3 (1–3)	3 (2–4)	3 (1–3)	0.0458
ISS score	24 (19–29)	26 (20–34)	25 (19–33)	0.4140
APACHE II score	11 (8–13)	11 (8–13)	11 (8–13)	0.9681
SOFA score	3 (2–5)	3 (2–7)	3 (2–5)	0.7315
Lymphocyte (*10^9/L)	0.91 (0.64–1.35)	0.95 (0.62–1.31)	0.91 (0.63–1.34)	0.9318
Hb (g/L)	98 (85–112)	99 (88–117)	98 (85–114)	0.6785
Alb (g/L)	32.9 ± 4.7	32.7 ± 5.9	32.8 ± 5.1	0.0555
Serum creatinine (umol/L)	63 (51–78)	61 (48–73)	63 (50–76)	0.2561
hs-CRP (mg/L)	35.0 (29.6–38.2)	33.8 (29.8–35.8)	33.8 (29.5–37.1)	0.0430
Emergency surgery	32	10	42	0.4077

TABLE 3 Logistic regression for factors associated with PIICS.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p* value	HR	95%CI	*p* value
Gender	0.63	0.32–1.25	0.1823			
Age	1.01	0.99–1.04	0.2657			
BMI	0.99	0.96–1.04	0.8516			
NRS2002	1.46	1.19–1.82	0.0004	1.29	1.02–1.65	0.0356
ISS	1.05	1.02–1.08	0.0033	1.02	0.98–1.06	0.2014
APACHE II score	1.11	1.04–1.20	0.0042	1.08	0.99–1.17	0.0645
SOFA score	1.17	1.07–1.32	0.0021	0.97	0.90–1.04	0.2329
Lymphocyte	0.90	0.53–1.49	0.6881			
Hb	0.99	0.98–1.00	0.2148			
Alb	0.94	0.88–0.99	0.0494	0.97	0.90–1.04	0.3812
Serum creatinine	1.00	0.99–0.99	0.9894			
hs-CRP	1.01	1.00–1.01	0.0403	1.01	0.98–1.04	0.4794
Emergency surgery	1.15	0.52–2.50	0.7192			

LASSO analysis

The LASSO regression with 10-fold cross-validation was performed on a training set of 150 patients. The results of the 10-fold cross-validation are shown in Figures 1A,B. The model achieved the maximum AUC when λ was set to the minimum mean squared error (λ min, 0.04905988) and included 4 variables. When λ was set to the minimum mean squared error plus one standard error (λ1 SE, 0.1133347), the model included no variables, but still achieved a high AUC. The relationship between the regression coefficients of each factor and λ is shown in Figure 1B. As λ increased, the regression coefficients gradually decreased. The final predictive model included NRS2002, ISS, APACHE II, and SOFA, with λ set at min (0.04905988).

Nomogram

A predictive model for the occurrence of PIICS during hospitalization in critically ill adult trauma patients was constructed using the selected factors (NRS2002, ISS, APACHE II, and SOFA). The model was presented in a nomogram (Figure 2). The nomogram showed that higher total scores were associated with a higher risk of PIICS. For example, if a critically ill trauma patient

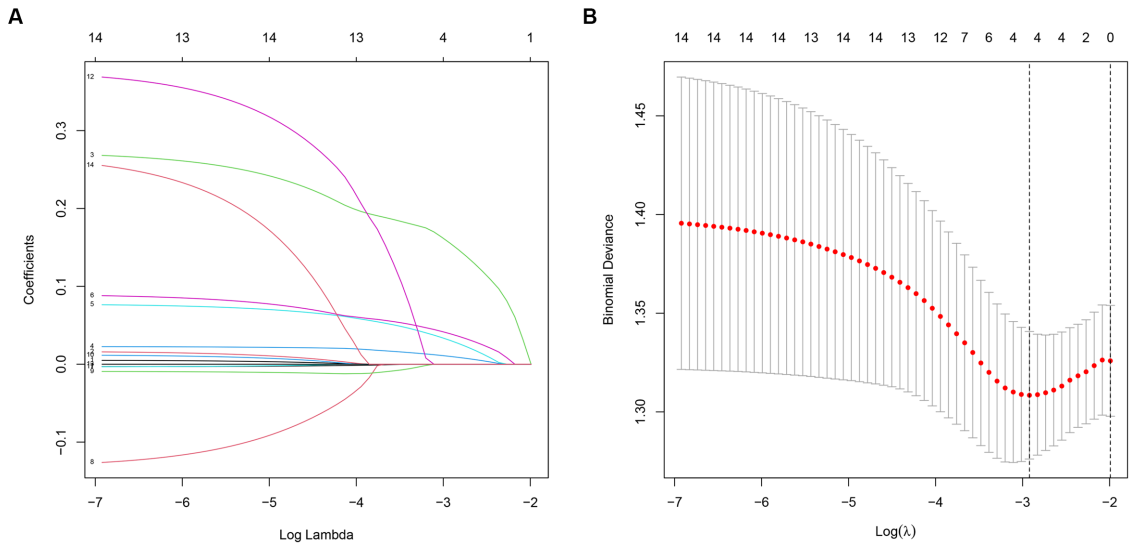

FIGURE 1
(A) The relationship between model AUC and log (λ) is shown by LASSO regression with 10-fold cross-validation. **(B)** LASSO regression (dashed line λ = 1 SE).

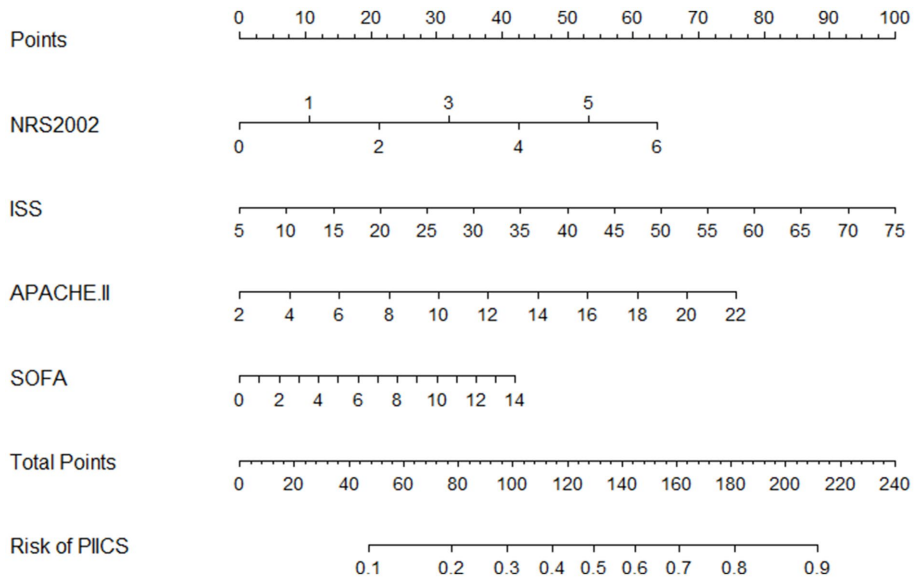

FIGURE 2
Nomogram prognostic model of PICS in patients with severe trauma during hospitalization.

had NRS2002, ISS, APACHE II, and SOFA scores of 2, 20, 10, and 6 at admission, respectively, the corresponding scores on the nomogram were 21, 31, and 17, resulting in a total score of 90 and an estimated probability of developing PIICS during hospitalization of 27%.

Predictive model performance

The performance of the prognostic model was evaluated through 1,000 bootstrapped samples to assess model calibration and potential overfitting. Calibration plots for PIICS prediction in the training and validation sets are shown in Figures 3A,B, respectively. The calibration of the PIICS model was assessed using the Hosmer-Lemeshow test. The results showed $\chi^2 = 6.40$, $p = 0.699$ for the training set and $\chi^2 = 14.74$, $p = 0.098$ for the validation set. Both value of ps were greater than 0.05, indicating an acceptable level of model fit.

Differentiation

The ROC curves for the PIICS model in the modeling and validation sets of trauma patients are shown in Figures 4A,B, respectively. The discriminatory ability of the model was evaluated using the C-index. The C-index was 0.67 (95% CI 0.57–0.78) for the modeling set and 0.84 (95%

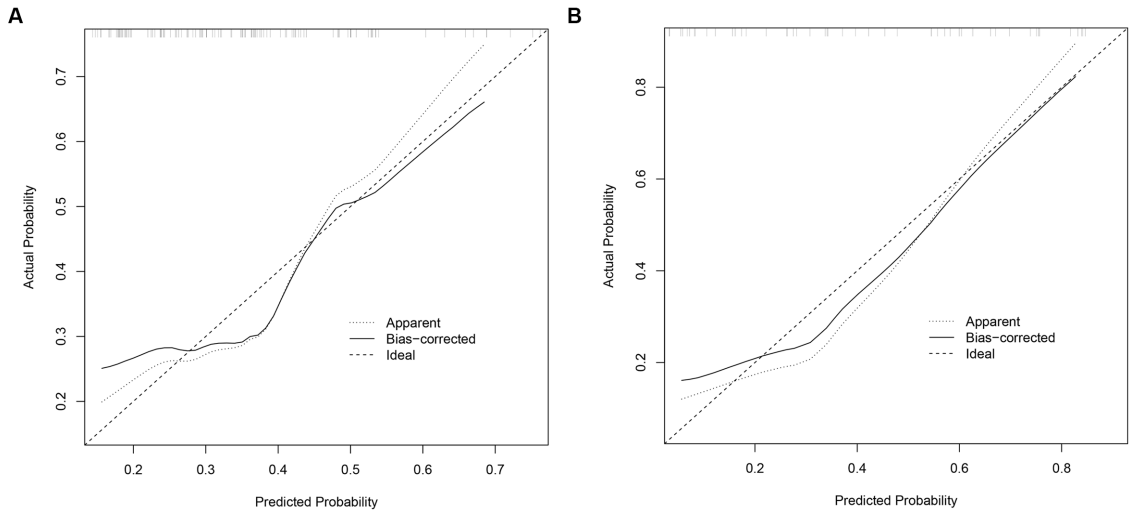

FIGURE 3
(A) Calibration diagram of the training set. **(B)** Calibration diagram of the validation set.

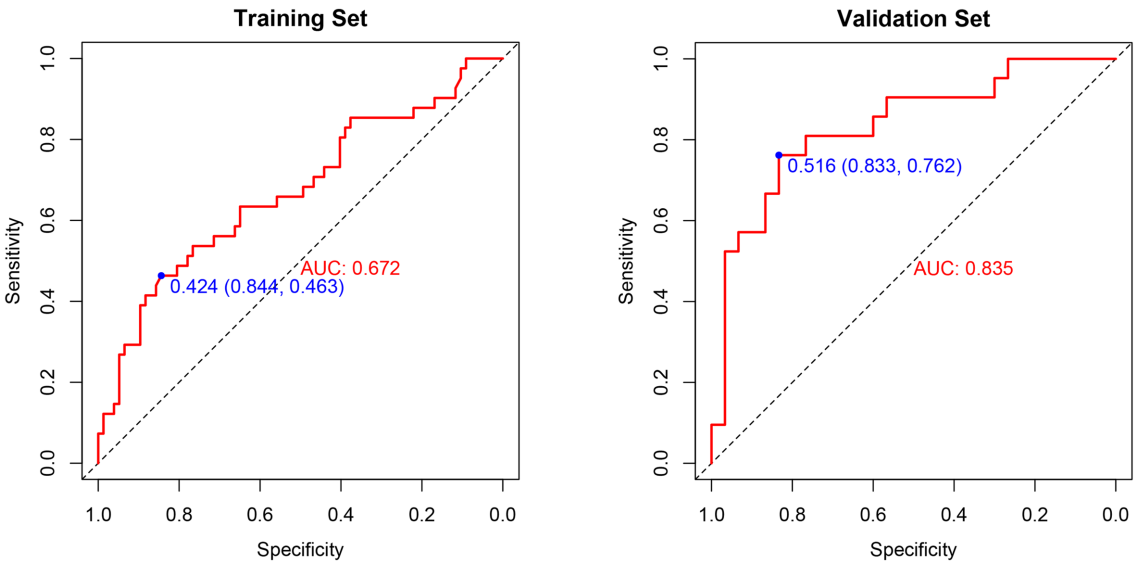

FIGURE 4
(A) ROC curve analysis of the prognostic model and various trauma scores in the training set. **(B)** ROC curve analysis of the prognostic model and various trauma scores in the validation set.

CI 0.72–0.95) for the validation set, indicating a moderate discriminatory ability of the predictive model in both the training and validation sets.

Decision curve analysis (DCA) curve

The clinical decision curves showed that the prognostic model had a considerable net benefit compared to the two extreme reference lines, both in the modeling and validation sets (Figures 5A,B). In the modeling set, the model had a higher net benefit when the risk threshold ranged from 0.15 to 0.62, while in the validation set, the model had a higher net benefit when the risk threshold ranged from 0.02 to 0.81.

Discussion

In our study, we employed rigorous methods to develop and validate the nomogram, and obtaining a series of findings. (a) We retrospectively collected a large amount of data from severely traumatized patients and identified potential risk factors associated with the development of PIICS. These factors included demographic characteristics, injury severity scores, and other relevant clinical parameters. (b) Through multivariate analysis, we identified the most significant predictors and incorporated them into the nomogram. (c) The LASSO regression combined with 10-fold cross-validation was used to select four risk factors, including NRS2002, ISS, APACHE II, and SOFA, to construct a logistic model for predicting the risk of

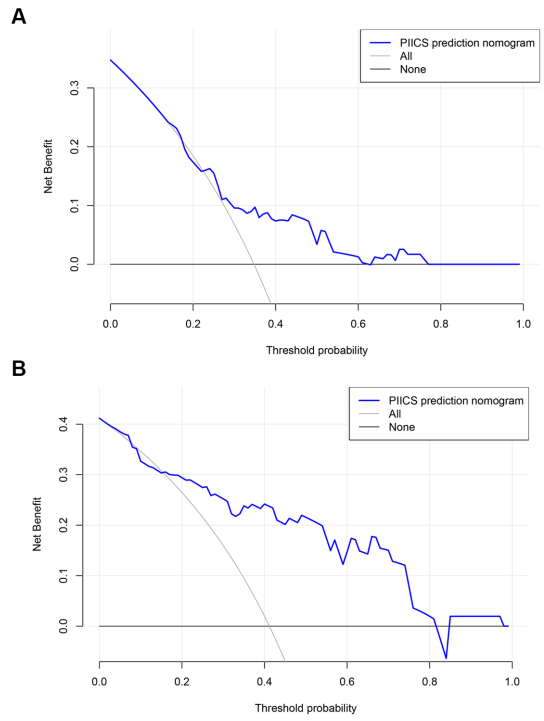

FIGURE 5
(A,B) The clinical decision curves showed that the prognostic model.

PIICS in severely traumatized patients. These findings provide an effective way to screen out PIICS early in our clinical work and may have a positive impact on patient care.

Various scoring systems with potential for predicting poor outcomes in severe trauma have been explored. NRS2002 is a tool for assessing nutritional risk in patients, considering factors such as nutritional intake, weight changes, and illness status to evaluate the level of nutritional risk (11). It has been reported to have predictive value in complications of severe trauma and is highly correlated with increased length of hospital stay (LOS) (12). ISS is a scoring system that assesses the severity of trauma based on the location and severity of injuries and is the most commonly used prognostic score in clinically severe multiple trauma patients (13, 14). APACHE II considers physiological indicators (e.g., blood pressure, respiratory rate, body temperature) and illness status (e.g., chronic diseases, age) to determine patient severity and prognosis (15) and has good performance in assessing in-hospital mortality in emergency trauma patients (16). The SOFA scoring system is used to assess the severity of multiorgan dysfunction in critically ill patients and has better performance in predicting mortality in both non-trauma and trauma patients (17, 18). However, individual scoring systems have limitations in predicting the complex complication of PIICS. Developing an early predictive model for PIICS is an important step in the prevention and management of complications in severe trauma (19). Therefore, an increasing number of studies have focused on exploring predictive factors for the occurrence of PIICS.

Different models have been developed for predicting fatigue syndrome and poor outcomes in elderly trauma patients (22–22), which have demonstrated good predictive and evaluative capabilities in trauma patients. By combining multiple variables and their respective weights, the nomogram provides a visualized model for risk prediction (23, 24), enabling clinicians to make effective predictions of the probability of PIICS occurrence in individual patients. This can aid in identifying high-risk patients and implementing targeted interventions, such as immunomodulatory therapy or nutritional support (25), to mitigate the progression of PIICS and its associated complications.

Compared to traditional prediction models or scoring systems, this model offers several advantages. Firstly, it incorporates a wide range of variables that capture the complexity of trauma patients developing PIICS. This comprehensive approach enhances the accuracy of risk prediction. Secondly, it provides a practical tool for clinicians to conduct real-time risk assessments in clinical practice. By inputting a patient's clinical data into the model, an immediate estimation of the likelihood of PIICS development can be obtained, enabling early intervention.

Although our study has strengths, there are also limitations to consider. Firstly, the retrospective design introduces inherent biases and potential confounding factors. Prospective validation in well-designed cohorts would be valuable to confirm the generalizability of the nomogram. Secondly, our nomogram was developed and validated in a specific population of severely traumatized individuals, and its performance needs to be evaluated in other patient populations or healthcare settings. Furthermore, further validation in different centers or countries is required to ensure its applicability.

Conclusion

In conclusion, the prognostic model developed in this study demonstrates good accuracy and discriminative ability. Developing and validating a predictive model specifically for PIICS in trauma patients is a crucial step toward personalized and proactive management of this complex syndrome. By utilizing existing data and analytical techniques, improving the prediction of risk stratification for severe trauma patients during hospitalization provides valuable insights for clinicians.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by this research plan has been approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number: TJ-IRB20230214). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LX, ZK, DW, YL, and CW undertook the research, LX and YW wrote the main manuscript text and prepared figures. ZL, XB, and YW revised

the article critically for important intellectual content and final approval of the version to be submitted. All authors contributed to the design of the study and the writing of the manuscript and reviewed the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Evaluation of the interhospital patient transfer after implementation of a regionalized trauma care system (TraumaNetzwerk DGU®) in Germany

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Purpose: The aim of the study was to evaluate how many patients are being transferred between trauma centers and and their characteristics in the 2006 initiated TraumaNetzwerk DGU® (TNW). We further investigated the time point of transfer and differences in outcome, compared to patients not being transferred. We wanted to know how trauma centers judged the performance of the TNW in transfer.

Method: (1) We analyzed the data of the TraumaRegister DGU® (TR-DGU) from 2014–2018. Included were patients that were treated in German trauma centers, maximum AIS (MAIS) >2 and MAIS 2 only in case of admission on ICU or death of the patient. Patients being transferred were compared to patients who were not. Characteristics were compared, and a logistic regression analysis performed to identify predictive factors. (2) We performed a survey in the TNW focussing on frequency, timing and communication between hospitals and improvement through TNW.

Results: Study I analyzed 143,195 patients from the TR-DGU. Their mean ISS was 17.8 points (SD 11.5). 56.4% were admitted primarily to a Level-I, 32.2% to a Level-II and 11.4% to a Level-III Trauma Center. 10,450 patients (7.9%) were transferred. 3,667 patients (22.7%) of the admitted patients of Level-III Center and 5,610 (12.6%) of Level-II Center were transferred, these patients showed a higher ISS (Level-III: 18.1 vs. 12.9; Level-II: 20.1 vs. 15.8) with more often a severe brain injury (AIS 3+) (Level-III: 43.6% vs. 13.1%; Level-II: 53.2% vs. 23.8%). Regression analysis showed ISS 25+ and severe brain injury AIS 3+ are predictive factors for patients needing a rapid transfer. Study II: 215 complete questionnaires (34%) of the 632 trauma centers. Transfers were executed within 2 h after the accident (Level-III: 55.3%; Level-II: 25.0%) and between 2–6 h (Level-III: 39.5%; Level-II: 51.3%). Most trauma

centers judged that implementation of TNW improved trauma care significantly (Level III: 65.0%; Level-II: 61.4%, Level-I: 56.7%).

Conclusion: The implementation of TNW has improved the communication and quality of comprehensive trauma care of severely injured patients within Germany. Transfer is mostly organized efficient. Predictors such as higher level of head injury reveal that preclinical algorithm present a potential of further improvement.

KEYWORDS

trauma, trauma care, interhospital transfer, trauma care system, TraumaRegister DGU®, TraumaNetwork DGU®, polytrauma management

Introduction

Major trauma remains the main cause of disability and death worldwide, especially among young and economically active adults (1). Regionalization of trauma care within a network of hospitals was initiated in Germany in 2006 (2). This initiative was started due to an increasing number of hospitals quitting from trauma care of severely injured patients at that time. Evaluation of the quality of care showed significant regional differences in mortality rate (2). Emergency services complained about difficulties to find hospitals ready to admit trauma patients. Reasons for this were inadequate reimbursement of hospitals, a reduction of staff in the emergency rooms and a shift towards economically more interesting elective patients (2, 3). The Implementation of TraumaNetzwerk DGU® (TNW) was completed in 2015. Today Germany is covered by 50 regionalized trauma care networks. Each network consists of designated trauma centers Level-I-III that support each other according to defined guidelines and regulations (4). Experience from such trauma systems and the effort to optimize trauma care reveal improvement of patient's outcome over the last 20 years in Germany (2), the Netherlands, Norway (5), the United Kingdom (5, 6) and the United States (6, 7). It appears that a structured and nationally organized trauma care from the scene of accident to rehabilitation has a higher impact on outcome than any single medical intervention (6). Elements of this systematic approach are the Level III national interdisciplinary guideline (S3-LL) (8), the nationwide implementation of Advanced Trauma Life Support (ATLS) in Germany since 2003 and the continuous feedback from the German Trauma Register (TraumaRegister DGU®, TR-DGU) since 1993 to ensure quality of care within the regionalized networks (3, 8).

The aim of a nationwide structured trauma system such as the TNW is to assure comprehensive quality of trauma care nationwide, measured by survival and quality of life (2–4, 8, 9). It therefore attempts to strengthen the quality of care also in rural areas and smaller hospitals through cooperation between trauma centers of different levels of trauma care. It is supposed to create a network that provides a foundation to initially admit trauma patients to any participating trauma center, stabilize them according to defined trauma care standards and to organize rapid secondary interhospital transfer of severely injured patients if necessary (2–6, 10, 11).

Providing trauma care in designated trauma centers can save lives and prevent long-term disability (6), thus direct transportation of severely injured patients to designated centers, while bypassing closer non-specialized facilities, is considered beneficial. Few studies have analysed the relationship between mortality rate and primary or secondary transport to a Level-I Trauma Center (9, 11–14). These studies have been exclusively conducted in paramedic staffed prehospital emergency systems without physicians being involved on scene (13, 14). Hamada et al. (11) were most recently able to show in France that the direct vs. secondary transport of severely injured patients seem to not have an influence on their outcome in a physician-based prehospital trauma team. Elderly severely injured patients though seem to be at risk of a preclinical undertriage and favourably transported to the nearest trauma center regardless of its grade of speciality (15). In all these scenarios though, we do not know enough about these patients to estimate their outcome if they had been transported to a center with a higher level of trauma care.

Although multiple quality indicators have been identified as predictors for improved outcome of severely injured patients being treated in such national trauma systems, it has been impossible to prove the benefit for patients, who are in need of a rapid transfer in the early stage of trauma management. There are many factors associated with the decision to transfer trauma patients to a Level-I Trauma Center, influencing the final decision making process.

The purpose of this study was to evaluate how many patients are being transferred between trauma centers within the TNW and who they are. We further wanted to investigate when they were transferred and if their outcome differed compared to patients that were not transferred. Finally, we wanted to know how trauma centers judged the performance of the TNW, including transfer management, communication and aftercare of the patients.

Methods

The TraumaRegister DGU®

The TraumaRegister DGU® (TR-DGU) of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie, DGU) started 1993. The aim of this multi-centre database is the pseudonymised and standardized documentation of severely injured patients. Data are collected prospectively in four consecutive time phases from the site of the incident until discharge from hospital: (A) prehospital phase, (B) emergency/resuscitation room and initial surgery, (C) intensive care unit, and (D) discharge. Documentation includes

detailed information on demographics, injury patterns, comorbidities, prehospital and in-hospital management, course on intensive care unit, relevant laboratory findings including transfusion data, and outcome. Included are patients who are admitted to hospital via the resuscitation room and subsequently receive intensive or intermediate care and patients who arrive at hospital with vital signs and die before admission to the intensive care unit.

The infrastructure for documentation, data management, and data analysis is provided by the Academy for Trauma Surgery (Akademie der Unfallchirurgie GmbH, AUC), which is affiliated with the German Trauma Society. Scientific leadership is provided by the Committee on Emergency Medicine, Intensive Care and Trauma Management (Sektion NIS) of the German Trauma Society. Participating hospitals submit their pseudonymised data to a central database via a web-based application. Scientific data analysis is approved according to a peer review procedure established by Sektion NIS.

The participating hospitals are primarily located in Germany (90%), but a growing number of hospitals in other countries contribute data as well (i.e., Austria, Belgium, Finland, Luxembourg, Slovenia, Switzerland, the Netherlands, and the United Arab Emirates). Currently, approximately 30,000 cases (basic group of patients) from more than 650 hospitals are entered into the database per year. Participation in TR-DGU is voluntary. For hospitals associated with the TNW, the entry of at least a basic data set is compulsory for reasons of quality assurance. Approximately 50% of all cases, however, are documented on the base of the standard dataset.

Study I: analysis of the TraumaRegister DGU®

The first study included patients from the registry admitted to a German hospital between 2014 and 2018. Patients with a maximum AIS ≥ 3 (MAIS ≥3) and patients with a MAIS 2 who died or were treated on an intensive care unit were included. The evaluation was performed for Level I, II and III Trauma Centers. The control group consisted of primary admissions without transfer (within the first 48 h). An exact matching of patients transferred out from one hospital and then admitted to another hospital was not possible due to the lack of a uniform case identifier but the patients are either labeled as being transferred or primarily treated in the TraumaRegister DGU®. Furthermore, date and time of transfers were removed from the scientific dataset due to data protection reasons.

For descriptive statistics mean with SD was used for continuous measurements, and *n* with percent was used for categorical variables. In addition, a logistic regression analysis was performed in primary admitted patients to identify factors associated with an early transfer out (dependent variable) from Level-II and III Trauma Centers. Independent variables were young age (<16), injury severity (ISS <16 /16–24, 25+), intubation prehospital, unconsciousness (Glasgow Coma Scale GCS ≤ 8) and serious head injury (AIS 3+). Results are shown as odds ratios with 95% confidence intervals.

Statistics were performed with SPSS® (Version 24, IBM Inc., Armonk, NY, United States).

This study is in accordance with the publication guideline of the TR-DGU and is registered under the TR-DGU project ID 2019–020.

Study II: survey with questionnaire distributed to trauma centers

The second study was a survey with a questionnaire that was distributed to 632 Trauma Centers that take part in the TNW. The idea was to collect the trauma centers perception of daily life reality. We therefore developed a questionnaire that addressed relevant questions in the context of patient transfer between trauma centers. The following five topics were included in the questionnaire: (1) Frequency of patient transfer independently from injury severity, (2) Timing of patient transfer, (3) Communication around the patient transfer, (4) Management of the aftercare of severely injured transferred patients, and (5) General subjective perception of the impact of TNW.

The administrators of all German certified trauma centers ($n = 632$) where contacted via email, including an online link to participate in this survey and anonymously evaluated afterwards. If the questionnaire was not returned within 4 weeks a second memo was sent to the trauma centers. For descriptive statistics mean with SD was used and *n* with percent was used for categorical variables for every trauma center level.

Results

Study I: data from the TraumaRegister DGU®

143,195 patients met the inclusion criteria of whom 69.9% were male, the mean age was 52.1 years (SD 22.5) and the mean ISS was 17.8 points (SD 11.5). 132,086 patients were primary admitted to a trauma center, the other patients were transfers. Among the primary admitted patients, 121,636 patients (92.1%) were definitely treated at the hospital of initial admission and 10,450 (7.9%) were transferred to another trauma center. 54.1% were admitted primarily to a Level-I, 33.7% to a Level-II and 12.2% to a Level-III Trauma Center. The overall mortality rate of the study population was 9.8%.

Transfer depending on designated level of trauma care

Most of the severely injured patients were treated primarily in the trauma center that they got initially admitted to (92.2%) (Table 1; Figure 1). Of the 11,191 patients (7.8%), who were transferred to another trauma center, 3,667 patients (22.7%) were transferred out from Level-III and 5,610 patients (12.6%) were transferred out from Level-II trauma centers. Among the 11,109 cases documented as secondary admissions, most cases were received by Level-I Trauma Centers ($n = 9,280$; 83.5%) while only 1,613 patients (14.5%) were received by Level-II Trauma Centers (Table 1).

Patients at level-III trauma centers

The mean ISS in the group of transferred patients was 18.1 points compared to 12.9 points in patients that had not been transferred out.

TABLE 1 Comparison of demographic and injury data of study patients primary admitted to a Level-II or Level-III Trauma Center who were either treated in that hospital, or transferred out early to another hospital (<48 h) and of patients transferred in to Level-I and -II Trauma Centers, compared to those admitted and treated in these trauma centers.

Level of care	Level III		Level II			Level I	
	Treated	Transfer out	Treated	Transfer out	Transfer in	Treated	Transfer in
	n = 12,458	*n* = 3,667	*n* = 38,899	*n* = 1,613	*n* = 1,613	*n* = 70,279	*n* = 9,280
Age (years)	55 (23)	53 (22)	53 (22)	50 (22)	59 (22)	50 (22)	56 (23)
Children (<16 years)	2.00%	3.70%	2.60%	5.20%	2.50%	4.30%	3.70%
Male sex (%)	65.70%	69.80%	68.00%	71.90%	67.60%	71.00%	70.00%
ISS (mean)	12.9 (8.5)	18.1 (9.3)	15.8 (10.2)	20.1 (10.3)	19.9 (10.2)	19.1 (12.4)	21.2 (11.3)
AIS Head 3+ (%)	13.90%	30.40%	23.80%	31.20%	58.20%	38.60%	57.40%
AIS Thorax 3+ (%)	35.20%	30.40%	37.60%	31.20%	28.50%	38.30%	32.00%
AIS Abdomen 3+ (%)	6.70%	10.70%	8.50%	8.90%	8.70%	9.60%	10.20%
GCS < 9 (%)	4.30%	9.70%	9.20%	14.70%	–	20.60%	–
Blood transfusion (%)	3.10%	4.80%	4.40%	4.90%	4.80%	8.60%	7.60%
Emergency surgery (%)	14.50%	10.60%	21.70%	10.90%	23.60%	27.40%	25.90%
Whole-body CT (%)	61.20%	65.70%	76.10%	70.30%	26.00%	83.80%	34.60%
Admission at night (%)	34.50%	37.80%	36.60%	41.00%	43.10%	38.10%	48.00%
Admitted to ICU	85.70%	44.90%	90.00%	50.70%	89.70%	92.70%	96.10%
Estimated risk of death (based on RISC II) (%)	5.70%	8.60%	7.90%	9.80%	–	11.60%	–
Hospital mortality (%)	5.70%	–	8.60%	–	13.30%	12.30%	12.90%

ISS, injury severity score; AIS, abbreviated injury scale; GCS, Glasgow coma scale; CT, computed tomography; ICU, intensive care unit.

The transferred patients showed twice as often a low GCS (3–8) compared to the non-transferred patients and suffered from a severe head Injury (AIS 3+) more often (43.6% vs. 13.9%). Emergency surgery had been performed less often in transferred patients (10.6% vs. 14.5%). The time of admission as well as other severe injuries (AIS 3+) such as thoracic trauma and abdominal injuries did not show a difference in the two groups (Table 1). Level-III Trauma Centers transferred out every third child (35%), unknown whether to a Level-I Trauma Center or to a designated pediatric trauma center.

Patients at level-II trauma centers

Patients admitted to Level-II Trauma Centers and rapidly transferred out showed more often a relevant (AIS 3+) brain injury (53.2% vs. 23.8%) compared to patients treated in the Level-II Trauma Centers. They were more often unconscious (GCS 3–8, 14.7% vs. 9.2%) and their mean ISS was higher (20.1 points vs. 15.8 points). Emergency surgery was performed half as often in the transferred group (10.9% vs. 21.3%). No differences were seen in thoracic injuries, abdominal injuries and blood transfusions (Table 1).

Patients at level-I trauma centers

Patients being transferred to Level-I Trauma Centers within 48 h after the initial trauma were older (56 vs. 50 years) and showed a higher mean ISS (21.0 vs. 19.1 points) compared to patients primarily admitted to a Level-I Trauma Center. A severe traumatic brain injury (AIS 3+) was seen more often compared to the primarily admitted patient group (58% vs. 39%). The mean/median duration of stay on the ICU was longer in transferred patients (9.2/4 vs. 6.8/2 days). There was no difference in abdominal and thoracic injuries. Half of the transferred patients were admitted to the Level-I Trauma Center during night time (50%). There were no significant differences in mortality between transferred and primarily treated patients at Level-I Trauma Centers (13.1% vs. 12.3%) (Table 1).

Time of transfer

Patients who were transferred within the TNW were mostly rapidly transferred. 90% of transfers occured within the first 24 h, 70% were transferred within 6 h after initial admission to a trauma center. The median duration of stay in the first trauma center before being transferred was 2.8 h (Figure 2).

Patients being transferred to a level-I trauma center

At time of admission at a Level-I Trauma Center, 40% of the transferred patients had already been intubated, only 7% were in shock and coagulopathy was observed in 15%. More than half of the patients (57%) had received some type of CT-scan prior to the transfer. 35% were taken to get a whole-body CT after having been transferred and admitted to a Level-I Trauma Center. Most transferred patients (64%) got directly admitted to intensive care unit (ICU) after management in the Trauma Resuscitation Unit (TRU). 28% of the transferred patients were taken directly from the TRU to the operating theatre (Table 1).

Predictors for transfer

An additionally performed logistic regression analysis ($n = 52{,}130$ from Level II and III) with the dependent variable *early transfer out* (within 48 h after admission) showed that a severe traumatic brain

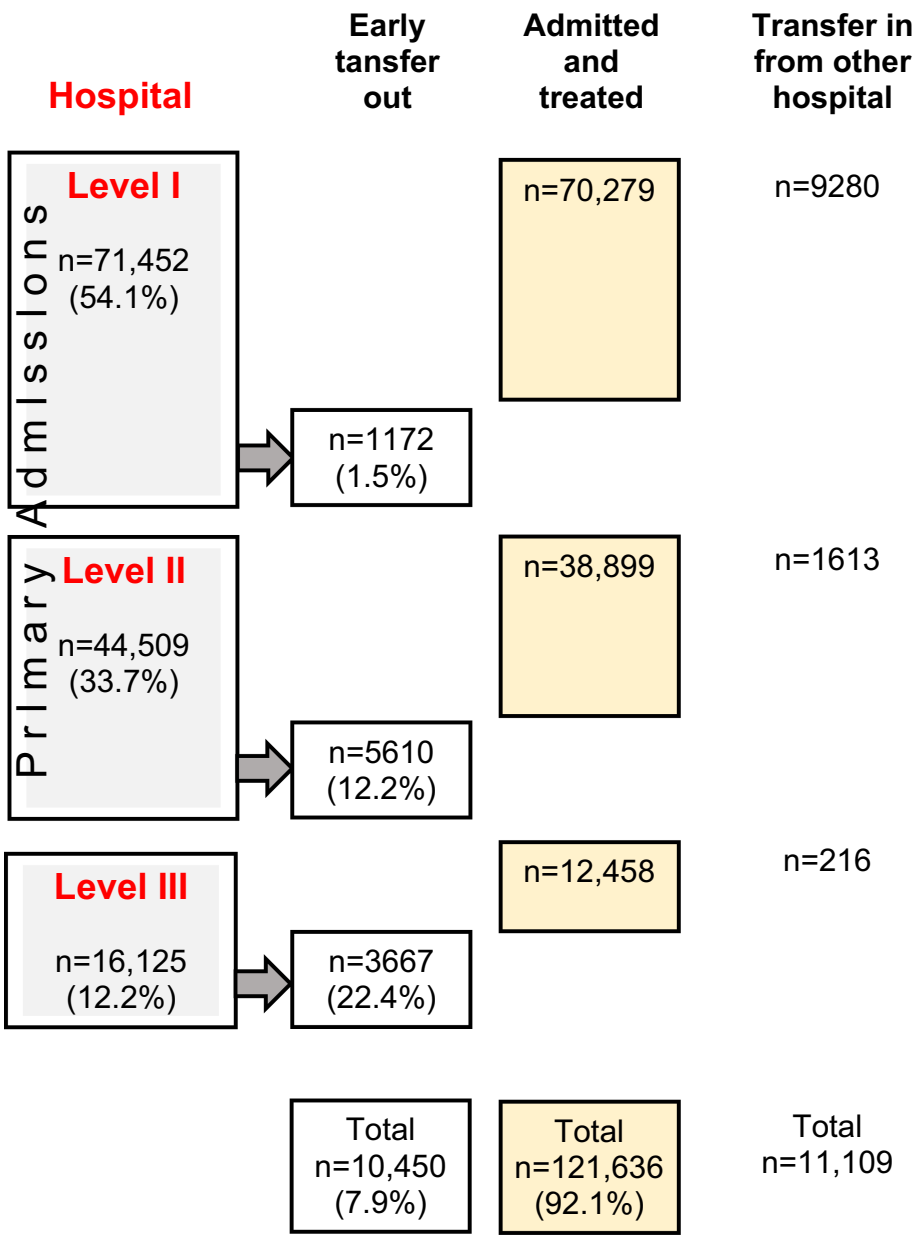

FIGURE 1
Transfer depending on designated level of trauma care, data from TR-DGU.

injury (AIS 3+) with an OR of 2.83 [CI 2.67–3.01] is a predictor for early transfer and so is severe trauma (ISS 25+) with an OR = 2.52 [CI 2.35–2.71]. Age ≤ 16 is also seen as a predictor for an early transfer with an OR of 1.59 [CI 1.39–1.83]. Prehospital intubation was no predictor for early transfer, on the contrary, these patients were less transferred with an OR = 0.62 [0.54–0.67] (Table 2).

Study II: data acquisition through a questionnaire within the TNW

Out of 632 contacted trauma centers within Germany, 215 (34%) replied and handed in a completed questionnaire. 25.6% of the replies came from Level-I, 35.8% from Level-II and 38.6% from Level-III Trauma Centers.

Reason for transfer

Out of the replies from the questionnaire the main reason for transfer (83.6%) were medical specialty (i.e., neurosurgery, cardio-thoracic-surgery, burns) for Level III and II Trauma Centers followed by transfer due to overall higher level of trauma care and capacity problems in ICU or OR. Capacity problems were also a top 4 reason for transfer out of Level I Trauma Centers as well as repatriation, which was as well a frequent reason for receiving transferred patients in Level-III Trauma Centers (Table 3).

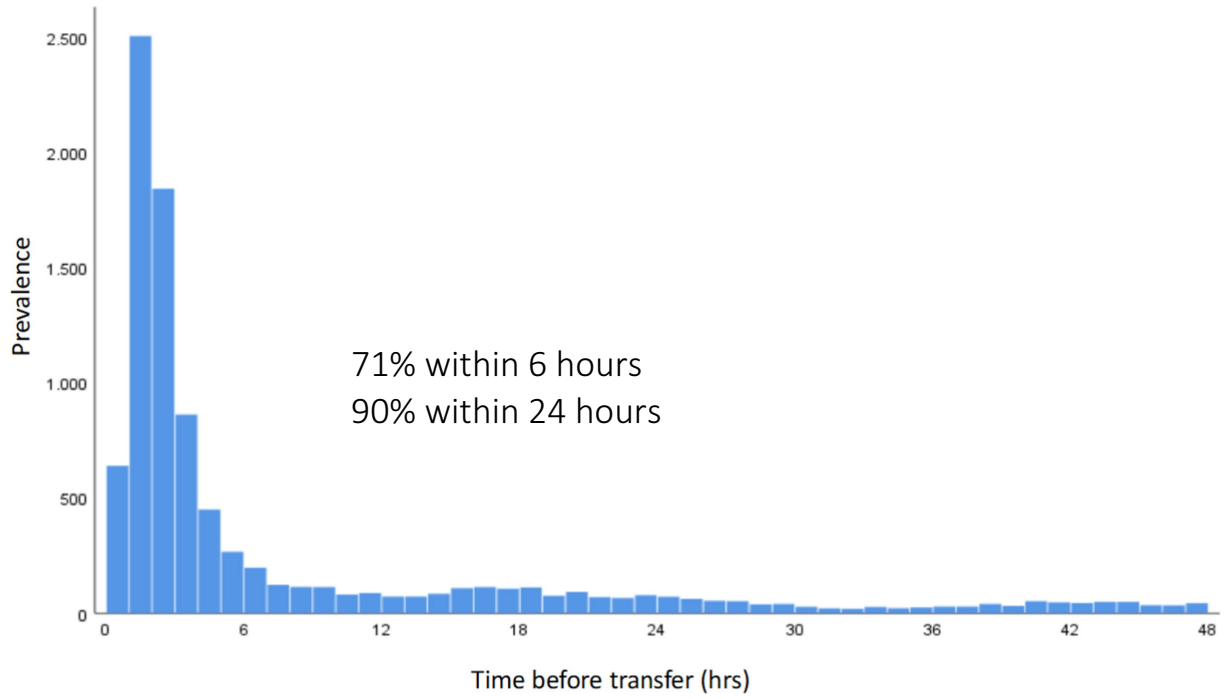

FIGURE 2
Time until transfer (hours) in all patients transferred out within 48 h after admission. The average and median time until transfer was 7.9 and 2.8 h, respectively.

TABLE 2 Logistic regression analysis in patients primary admitted to Level II and Level III trauma centers, with early transfer out as dependent variable.

	Odds ratio (OR)	95% CI for OR	*p* value
Head injury AIS 3+	2.83	2.67–3.01	<0.001
ISS 25+ (ref: <16)	2.52	2.35–2.71	<0.001
ISS 16–24 (ref: <16)	1.84	1.73–1.96	<0.001
Young age (<16 years)	1.59	1.39–1.83	<0.001
Shock on admission	1.07	0.96–1.20	0.223
Admission during the night	1.06	1.00–1.11	0.041
Need for blood transfusion	1.00	0.89–1.13	0.985
GCS 3–8	0.99	0.89–1.10	0.876
Admission during the weekend	0.88	0.83–0.92	<0.001
Old age (65+ years)	0.67	0.63–0.71	<0.001
Intubation prehospital	0.60	0.54–0.67	<0.001
Constant	0.10		

52,130 patients have had complete data in all predictor variables. Predictors were ordered according to decreasing odds ratio (OR). An OR > 1.0 favours an early transfer to another hospital while an OR < 1 did not. Nagelkerke's r^2 was 0.11.

Frequency and timing of patient transfer independently from injury severity

The data analysis of the questionnaire showed that the majority of patients were estimated being transferred within 2–6 h after accident (rapid/early transfer) (Figure 3). The Level-III Trauma Centers showed the highest rate of rapid transfer (94.8% < 6 h). If Level-III Trauma Centers had received patients to their hospital, they mostly received "late transferred" patients (50% after >24 h) (See Figure 4).

Communication around the patient transfer

Being one of the major criteria in assessing the quality and the process of patient transfer, communication before and after the transfer played a relevant role in the survey. The respondents rated the general communication between the trauma centers with "good". The communication was mostly (92.2%–100%) via direct doctor to doctor call. Requested transfers from Level-III or Level-II to Level-I were described in 3.0%–8.4% as delayed due to capacity problems, this

TABLE 3 "What are the 4 main reasons why your Trauma Center has received or transferred patients?"; data from the questionnaire in %.

	Level III		Level II		Level I	
	Received	Transferred	Received	Transferred	Received	Transferred
Higher level of designated Trauma Care within TNW	/	76.7	76.7	52.6	51.4	/
Insufficient ICU-capacity	27.3	26.0	26.0	12.8	28.6	20.3
Insufficient OR-capacity	20.5	20.5	9.6	10.3	25.7	8.5
Medical speciality (Neurosurgery, Cardio-Thoracic-Surgery, Burn-Unit etc.)	9.1	83.6	83.6	76.9	31.4	50.2
Complication	4.5	9.6	9.6	7.7	7.1	8.5
Repatriation	52.3	8.2	8.2	16.7	37.1	32.2
Other	3.2	1.4	1.4	5.1	11.4	22

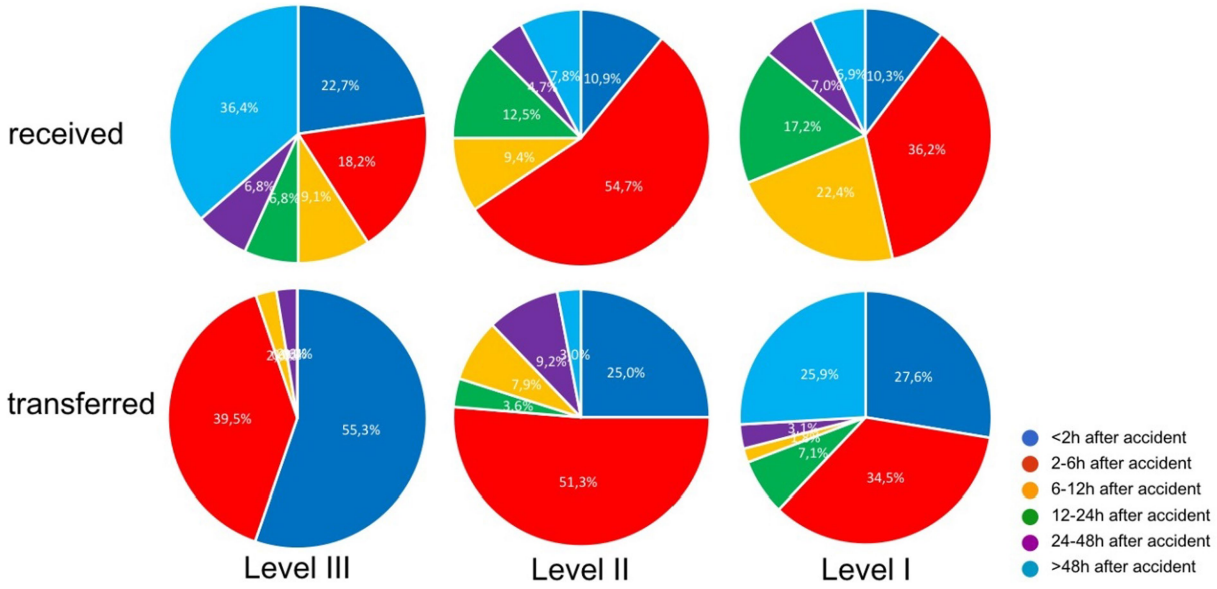

FIGURE 3
Transfer-timing in comparison of received versus transferred patients in dependence of the level of trauma care (Level-I, -II, and -III Trauma Center), in percent; data from the questionnaire.

occasionally (9.2%) happened in the other direction (Level-I to Level-II/III) as well (See Table 4).

Not only the communication prior to a patient transfer is of interest, but also afterwards, to ensure quality or optimize the process. While 75% of the receiving trauma centers responded that they sent out discharge letters to the transferring trauma centers regularly, only 55% of the transferring hospitals responded that they frequently received a discharge letter from the receiving trauma center. An immediate feedback on the quality of the transfer occurs in only 20% (Table 5).

Management of the aftercare of severely injured transferred patients

The respondents of the questionnaire stated that initially transferred patients got sent back after surgical and/or intensive care treatment in 10%–15% to the initial transferring trauma center. Regarding to the answers, the aftercare of former polytraumatized patients mostly takes place in Level-I Trauma Centers. 49% of them indicated, that they manage the aftercare of the initially transferred polytraumatized patients *regularly*, 42% seldomly. Independently of a transfer, 40% of the Level-I Trauma Centers indicate to manage the aftercare of polytraumatized patients at all. This applies to 30% of the Level-II and 20% of the Level-III Trauma Centers.

General subjective appraisal of the TNW

The participating trauma centers were asked if they felt that overall TNW had improved the care of severely injured patients. Most participants judged that TNW was functioning mostly or very well with some improvement of the overall management Many trauma centers judged that implementation of TNW improved trauma care significantly (Figure 5).

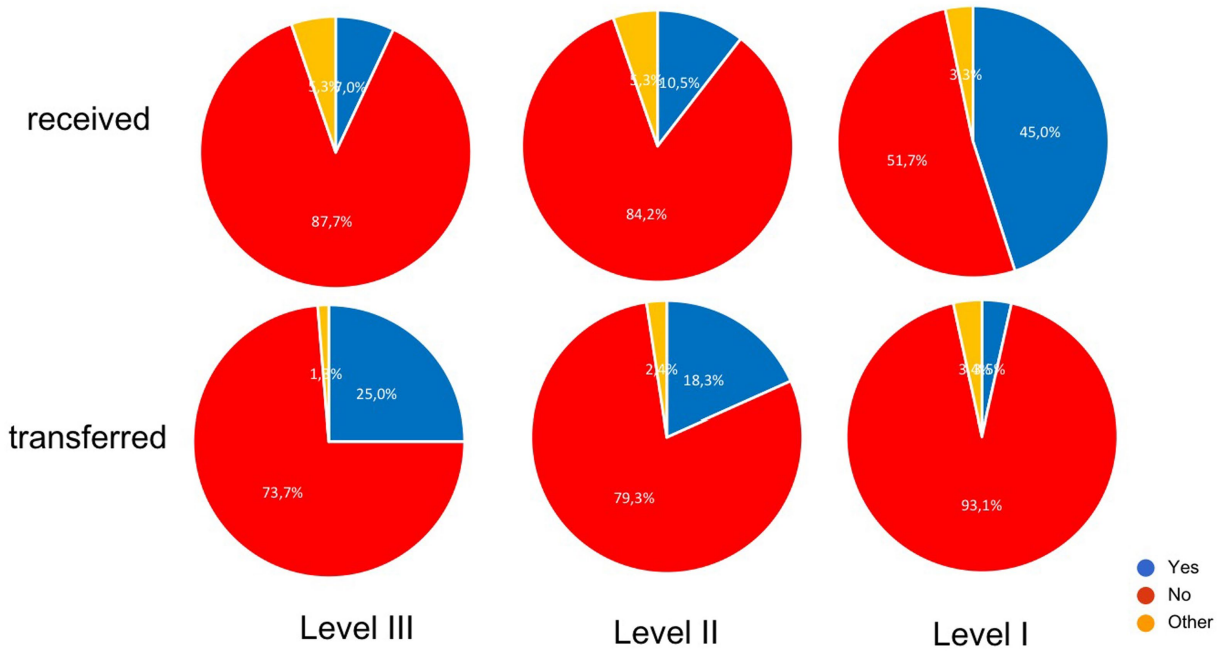

FIGURE 4
Evaluation of the questionnaire, if the trauma centers have been receiving more patients through a trauma-network-managed transfer. Level-III Trauma Centers have been transferring more patients in 25% and Level-I Trauma Center have been receiving more patients in 45% since the TNW had been established.

TABLE 4 Data transfer of diagnostics; data from the questionnaire in %.

	Level III		Level II		Level I	
	Received	Transferred	Received	Transferred	Received	Transferred
Transmitted prior to transfer via telecommunication (i.e., Tkmed®)	38.5	73.6	40.6	73.4	58.3	51.9
Together with patient via data medium (i.e., CD)	51.9	23.6	56.5	22.8	40.0	46.3
Only in written format	2.4	1.4	0.0	0.0	0.0	0.0
Other	7.2	1.4	2.9	3.8	1.7	1.8

TABLE 5 Communication after transfer; data from the questionnaire in %.

	Level III		Level II		Level I	
	Received	Transferred	Received	Transferred	Received	Transferred
Direct Feedback after transfer	73.6	30.7	75.7	41.5	58.3	51.8
Discharge letter of patient's clinical course	60.8	60.8	58.4	53.7	78.0	53.6
Collective overall evaluation	13.5	13.5	18.1	16.0	12.1	13.0

Discussion

The presented data allow some detailed insight to interhospital transfer of severely injured patients within the TNW in Germany.

The results show that Level-I and Level-II Trauma Centers carry the main load in receiving and finally treating severely injured patients of the TNW. 92.2% of these patients were treated up to their discharge in the trauma center they were primarily admitted to. The high percentage of patients treated in the hospital they were primaly admitted to seems to be an indicator for a good working prehospital triage system. Similar findings show Tiruneh et al. for transferd patients in Israel. In the evaluated population only 9.5% of the patients been transferred to another Trauma Center. Those patients were similar to our results more often under 16 years and had more often severe head injuries. Tiruneh et al. showed a greater risk of in-hospital mortality, we could not show this for our population taking the limitations (i.e., RISC Score) into account (16).

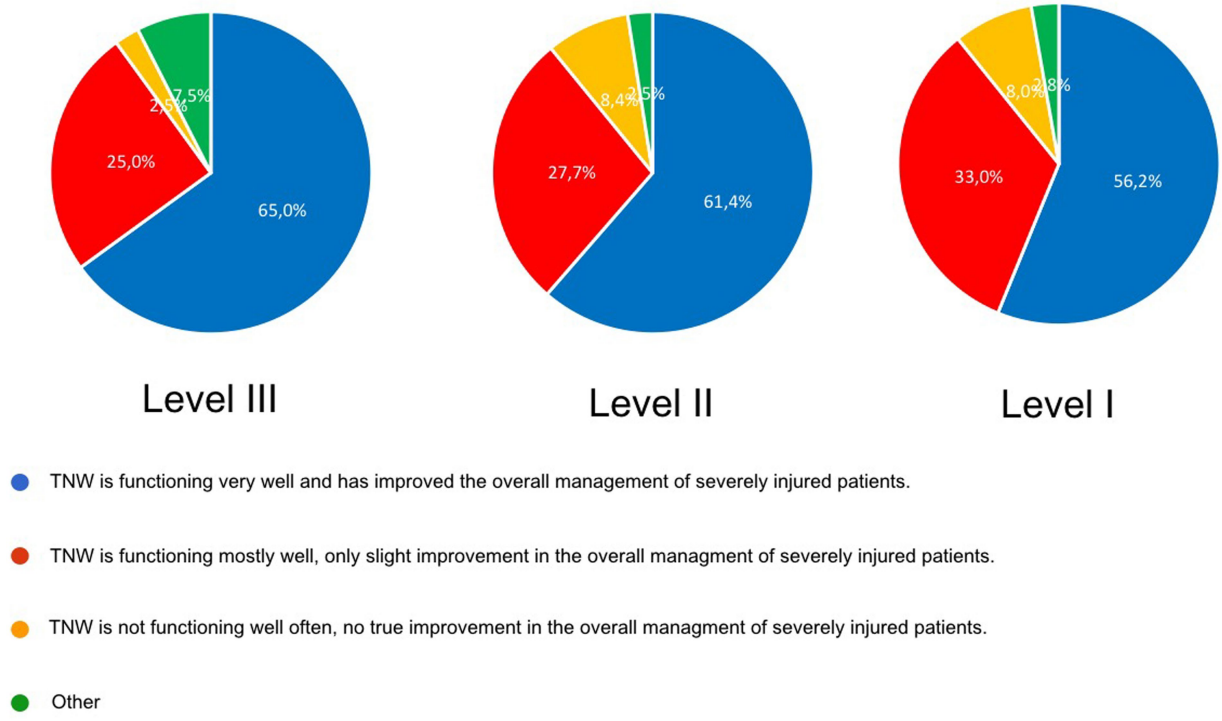

FIGURE 5
General evaluation of the improvement of patient transfer and management of severely injured patients since establishment of the TNW; data from the questionnaire.

Schneppendahl et al. (17) have also analyzed data from the TR-DGU, at an earlier period of time (2002–2007) before initiation of the nationwide TNW and found 84.2% of patients to be treated at the hospital they were initially admitted to until discharge (17). Compared to that earlier study the number of initially correct admissions seems to rise (92.2% vs. 84.2%). This could be a result of successful networking within the TNW and an improved communication and training between prehospital emergency medical services and admitting trauma centers.

The fact that transferred patients were more severely injured might as well show successful networking if patients were stabilized in the lower level Trauma Center and transferd afterwards.

Joosse et al. (18) were able to show in their subgroup analysis for transferred patients with severe traumatic brain injuries in the Netherlands prolonged accident-to-surgery-times and a worse outcome. But there might be a bias due to only transferring patients who were stable enough for being transferred in the first place.

The short time between admission and transfer might also be an achievement of the TNW.

This is in concordance with the answers from the survey, where respondents stated, that the predominant reasons for a needed transfer are due to specific medical specialties and necessity of a higher level of trauma care.

Interesting enough, the survey also revealed a lack of resources being stated as a reason for early transfer of patients.

On one side one could argue that the responsibility of TNW could be to balance out limited resources and still secure a good quality of care. On the other side it should be discussed that any transfer that has not been initiated due to medical reasons but due to a lack of resources, is a potential risk to patient safety and the quality of care. The data can therefore provide arguments for sufficient resource deployment for safely treating emergencies comprehensively.

The implementation of TNW aimed for improvement of communication and cooperation between trauma centers of different levels of trauma care. The survey addressed several items of pre- and post-transfer communication which was rated mostly good. This goal seems to be accomplished.

From the answers of the survey, it appears that transfer requests are not submitted in a standardized way. As mentioned before the main link between trauma centers is a non-standardized phone call. Within the regionalized networks trauma telephone numbers of the participating hospitals are published within the network and are quite well known. Submission of patient documents in a standardized way before transferring the patient could optimize the process. Some trauma centers take advantage of telecommunicative options that have been implemented within the TNW. TK-med® offers the possibility to submit patient documents including x-rays and CT Scans in a safe and standardized way. The survey did not go in further details why TK-med® had not been used more often when transferring patients. Availability as well as user friendliness could be possible reasons and should be addressed in future surveys. Standardized documentation of the patients demographics as well as the injury pattern and the actual vital status including radiographic findings could be easily transmitted via TK-med® so that receiving hospitals already have original data before the patient arrives, in order to be better prepared and allocate necessary resources (19). Devecki et al. also showed a decrease in time before

transfer after implementing a transfer protocol, one must consider the fact that these patients were transfer between Non-trauma Centers and Trauma centers (20).

The perception of direct feedback after transferring a patient has been rated differently by the transferring vs. receiving trauma centers. There seems to be space for future improvement. Especially the overall evaluation of the transferring process after the patient has been discharged only takes place in about 13%–18% of the cases. But this is one of the major fields for securing quality or potentially optimizing processes.

The aftercare of former severely injured patients seems to be a complex issue. The respondents stated that occasionally patients get sent back to the initial trauma center for further treatment or rehabilitation (10%–15%) but the majority of overall aftercare of the patients within an outpatient department takes place in Level-I Trauma Centers.

Thus resources need to be discussed within the TNW to provide aftercare concepts of severely injured patients.

The survey also addressed the question of a subjective overall judgement whether implementation of TNW has improved the management and the quality of care of severely injured patients or not. Most respondents judged that TNW had a somehow positive impact on the management of trauma patients. If we try to judge the effect of TNW on trauma patient care, overall measured by objective data (study I) and subjective perception (study II) good reasons could be announced, that TNW has improved the management and the quality of patient care significantly. This is especially true as TNW was initiated when more and more hospitals quit from trauma care for economical reasons.

Conclusion

The implementation of TNW has improved the communication and quality of comprehensive trauma care of severely injured patients within Germany. By defining standards, working out guidelines and regulations, the primary allocation of patients has improved and so has the standard of care within the trauma centers of different levels of trauma care. If transfer is necessary, it is mostly organized and performed in an efficient matter. Although the transferring process seems to be working well, predictors such as higher level of head injury reveal that preclinical algorithm also present a potential of further improvement. So does the communication after a transfer has taken place to ensure and optimize high quality processes. A standardized protocol including a transfer-document should be implemented and existing resources should be used. The aftercare of severely injured patients needs to be focused on in future TNW-projects.

Limitation

The main limitation of this study is the fact that the data of the transferred patients cannot be linked within the TR-DGU with those being received at the receiving trauma centers. Thus, the prehospital data is partly missing. The expected mortality rate (RISC-II-Score) cannot be calculated due to missing data of the transferring process.

The data collected in the German TR-DGU is not necessarily complete especially if the transfer takes place rapidly. Patients who died before a planned transfer are not included and some patients are transferred due to unknown, non-medical reasons.

Another limitation is the retrospective design of our study. The questionnaire has been sent out to the trauma centers, but only about 30% have handed in their replies. Interpretation of these subjective judgements and ratings needs to put into a sensitive and cautious surrounding to avoid false consequences.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

CS: Writing – original draft, Writing – review & editing, Conceptualization, Investigation. DB: Writing – review & editing, Data curation, Methodology. SR: Writing – review & editing. BB: Writing – review & editing. RH: Writing – review & editing. WL: Writing – review & editing. RL: Formal analysis, Writing – review & editing. HD: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1298562/full#supplementary-material

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Non-technical skills and teamwork in trauma: from the emergency department to the operating room

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Management of a trauma patient is a challenging process. Swift and accurate clinical assessment is required and time-sensitive decisions and life-saving procedures must be performed in an unstable patient. This requires a coordinated response by both the emergency room (ER) and operating room (OR) teams. However, a team of experts does not necessarily make an expert team. Root cause analysis of adverse events in surgery has shown that failures in coordination, planning, task management and particularly communication are the main causes for medical errors. While most research is focused on the ER trauma team, the trauma OR team also deserves attention. In fact, OR team dynamics may resemble more the ER team than the elective OR team. ER and OR trauma teams assemble on short notice, and their members, who are from different specialties and backgrounds, may not train regularly together or even know each other beforehand. And yet, they have to perform high-risk procedures and make high stake decisions, in a time-sensitive manner. The airline industry has long recognized the role of team training and non-technical skills (NTS) in reducing hazards. The implementation of the so called crew resource management or crisis resource management (CRM) has significantly made airline travel safer and the transposition to the medical context, with specific training in non-technical skills, has also brought great benefits. In fact, it is clear that adoption of non-technical skills (NTS) in healthcare has led to an increase in patient safety. In this narrative review we recapitulate some of the key non-technical skills and their relevance in trauma, with a focus on both the emergency department (ER) and the operating room (OR) teams, as well as on the transition of care from one to the other. Also, we explore the use of debriefing the team, as well as the roles of NTS training in both undergraduate and postgraduate settings. We review some of the existing trauma training courses and their roles in developing NTS. Finally, we briefly address the challenges posed by the development of trauma hybrid operating rooms.

KEYWORDS

trauma, non-technical skills, training, human factors, emergency room, operating room

> *"In crisis we do not rise to the level of our expectations, we fall to the level of our training".*
> Archilochus, Greek poet and soldier, *circa* 645 BCE

Introduction

Management of a trauma patient is a challenging process. Swift and accurate clinical assessment is required, time-sensitive decisions and life-saving procedures must be performed in an unstable patient, often with incomplete information and under intense time pressure. This requires a coordinated response by both the emergency room (ER) and operating room (OR) teams. These teams are multidisciplinary, consisting of doctors of distinct specialties and nurses, all of whom are highly motivated to excel at their technical and decision-making skills. Usually, all have previously attended training programs in order to acquire and develop these individual skills.

However, a team of experts does not necessarily make an expert team. Root cause analysis of adverse events in surgery has shown that failures in coordination, planning, task management and particularly communication are the main causes for medical errors (1). Moreover, transitions in healthcare are fraught with mishaps in communication (2) and several studies have confirmed that most severe errors in trauma resuscitation are related to failures in communication (3, 4).

While most research is focused on the ER trauma team, the trauma OR team also deserves attention. In fact, OR team dynamics may resemble more the ER team than the elective OR team. ER and OR trauma teams assemble on short notice, and their members, who are from different specialties and backgrounds, may not train regularly together or even know each other beforehand. And yet, they have to perform high-risk procedures and make high stake decisions, in a time-sensitive manner. Thus, the stage is set for "a perfect storm" of errors and poor outcomes (5).

The airline industry has long recognized the role of team training and non-technical skills (NTS) in reducing hazards. The implementation of the so called crew resource management or crisis resource management (CRM) has significantly made airline travel safer and the transposition to the medical context, with specific training in non-technical skills, has also brought great benefits (6). In fact, it is clear that adoption of NTS in healthcare has led to an increase in patient safety (7).

In this narrative review we recapitulate some of the key non-technical skills and their relevance in trauma, with a focus on both the emergency department (ER) and the operating room (OR) teams, as well as on the transition of care from one to the other. Also, we explore the use of debriefing the team, as well as the roles of NTS training in both undergraduate and postgraduate settings. We review some of the existing trauma training courses and their roles in developing NTS. Finally, we briefly address the challenges posed by the development of trauma hybrid operating rooms.

Non-technical skills in trauma

Non-technical skills (NTS) are social and cognitive skills that interfere with task performance and completion (8). Either in the ER or the OR context, proper team function requires that all team members, and particularly the team leader, should not only be knowledgeable and proficient in their clinical and technical skills, but also have a clear understanding of the critical role of NTS.

There are several NTS particularly relevant for trauma management:

- Situational awareness
- Role allocation
- Decision-making
- Leadership
- Communication

Situational awareness

Situational awareness is defined as "*the perception of elements in the environment within a volume of time and space, the comprehension of their meaning and the projection of their status in the near future*" (9).

This means that the practitioner, usually the team leader, should go beyond the immediately available information, integrate all current data with previous knowledge and expand the consciousness both in physical space and in time. This is considered one of the most important NTS and usually requires some degree of clinical experience and previous exposure to similar situations. However, with adequate simulation-based training it can also be developed by the junior trainee (10).

Situational awareness starts immediately with prehospital notification. The prehospital notification is ideally provided using the AT-MIST (Age, Time, Mechanism, Injuries, Signs, Treatment) mnemonic. Although only indicative, it can provide a glimpse of the potential clinical status of the patient and likely needs, such as activating the massive hemorrhage protocol and other resources, such as the trauma OR. A trigger for damage control surgery can start at this stage.

After patient arrival and during primary survey, situation awareness is also required during the assessment of the patient's response to resuscitation. The availability of resources, physical and human, as well as the environment, come into play when deciding the predicted course of action. An example of the proper use of situational awareness is the branching decision process taking place inside the team leader's mind well ahead of the information required to take the decision being available. For instance, immediate transfer to the OR vs. further resuscitation while an extended focused assessment sonogram in trauma – eFAST exam is ordered; laparotomy if eFAST positive for peritoneal fluid vs. thoracotomy if positive eFAST for pericardial fluid. The patient may just be undergoing the eFAST scan and these scenarios and subsequent branching decisions are being processed by the trauma team leader well in advance.

While the team leader should maintain situational awareness at all times during the ER resuscitation, it may be difficult for all the team members to keep up. In fact, it may not be desirable, especially when some of them are performing technical procedures requiring focus vision. However, it is incumbent upon the team leader of the trauma ER to periodically share the status and plan with all team members. This can be achieved with a Stop procedure, or Team-Time-Out. When clinically possible, i.e., not interfering with immediate resuscitation efforts, this time-out can be useful to share situational awareness with all the team (11).

Intraoperatively it can also be difficult for all team members to attain and maintain situational awareness. During the operation both the surgeon and the anesthesiologist will have to perform delicate procedures requiring focus vision, causing a potential decrease in

situation awareness. Since there may be unexpected intraoperative adverse events it is paramount that situational awareness can alternate between the shared team leaders of the trauma team – surgeon and anesthesiologist. A tool to prevent this is the use of routine situation reports, or "sit reps" (12), actually a form of intraoperative Team-Time-Out. During these, provided there is temporary control of bleeding, the entire team briefs with a concise update. A useful structure for this is the TBCS (Time, Blood, Clotting, Surgical) mnemonic, first developed in the military advanced surgical hospitals, but easily transferable to the civilian setting (Figure 1).

The first three items of the TBCS refer to physiological variables and are reported by the anesthesiologist. The last item consists of surgical findings and plan and is reported by the surgeon. By using the TBCS tool, the entire trauma OR team can be regularly updated, and situational awareness shared with the members.

Another option is for the lead surgeon to share situational awareness with an assistant surgeon. With a two-surgeon team, it is helpful that one of the two can maintain situational awareness, especially when the operating surgeon is on focus vision. Nonetheless, both surgeons' attention may be required in the operative field at times, making the use of intraoperative timeouts essential to keep situational awareness. The same can also work in a two-anesthesiologists team, with one performing procedures and another maintaining situational awareness. However, this should not replace the regular use of intraoperative timeouts.

Finally, situational awareness should not only cover the patient, the resources and the context, but should also contemplate the team members. Some team members may be overwhelmed, while others may be unused. These may create a sense of disenchantment with trauma resuscitation that may compromise the current resuscitation efforts and future trauma scenarios. The team leader(s) should recognize and anticipate this, properly reallocating roles and assigning new tasks.

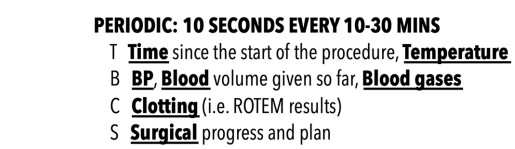


FIGURE 1
TBCS (Time, Blood, Clotting, Surgical) mnemonic for intraoperative time-outs in trauma damage control surgery.

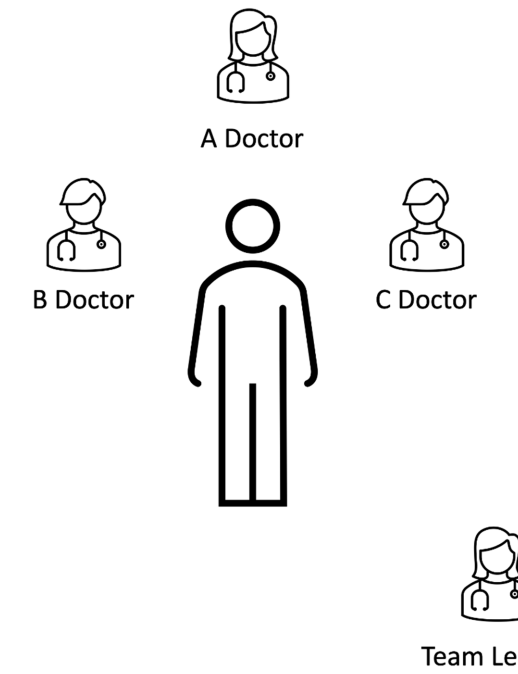


FIGURE 2
Typical role allocation of a trauma team according to the European Trauma Course. However, other options exist, depending on local protocols. Importantly, roles should be allocated and a team leader clearly designated.

Role allocation

Role allocation is critical in the ER setting, where the team can be particularly diverse (13). While the role of team leader is usually performed by either trauma surgeon or emergency physician (14), other team members can be flexibly allocated, according to their expertise and level of comfort. One example is the anesthesiologist, who by essence of training is extremely well suited to lead a team, can manage most airway scenarios, is proficient in analgesia and sedation, and is thus usually allocated the role of Airway (A) doctor. Moreover, the inclusion of the anesthesiologist in the ER trauma team has the added advantage of providing continuity of care should the patient require operative treatment.

Other trauma team roles are: the B (Breathing) doctor, assessing ventilation and performing thoracostomy and placement of chest drainage; the C (Circulation) doctor, assessing circulatory status, obtaining venous access and performing bleeding control procedures, such as application of pelvic binder (Figure 2). Multiple medical specialties are allocatable to these functions, with emergency medicine and trauma and emergency surgery obvious options. Clear allocation of ER nurses to each position is also desirable. In fact, a trauma team can be composed of sub-teams, each with its own responsibilities. Ultimately, all report to the team leader.

Role allocation may be dynamic. A good example is during airway management. While simple maneuvers can be provided by the A-doctor, drug-assisted intubation will require a reallocation of roles, for instance for drug administration, manual restriction of spinal movements and handing the laryngoscope and tube. The team leadership may even be temporarily handed over to the A-person, if he/she is an experienced provider. Other procedures requiring an assistant (such as placing a chest drain or a pelvic binder) will also require reassigning the team members to new tasks. Moreover, the team leader may have to briefly discuss or consult with another specialist and in order to prevent the loss of situational awareness, temporarily handover the leadership to another team member.

Allocation of roles within the team should adapt to local resources. In one of the authors' institution trauma team training program, the simulations follow the composition of the trauma team, not vice versa. The motto that inspires the trauma team training program is: "We simulate like we work and work like we simulate." A rigid team structure would be hard to follow and have little compliance, while a more realistic approach is expected to work much better.

While in the ER role allocation is flexible, with some members able to perform multiple tasks, it is usually more rigid and obvious in the OR: the surgeons will perform the operation, and the anesthesiologist will manage general anesthesia and resuscitation. However, some degree of role allocation is also required in the trauma OR, for instance for contacting the blood bank, placing lines, bringing extra equipment. A good moment to do this is during patient handover from the ER to the OR, when all the operative team should brief. The scrub and anesthesia nurses should have their roles clearly defined, and all team members' names should be clearly identified. After this initial OR team briefing, the surgeon and anesthesiologist can brief their respective nursing staff with more detail (see below – Six-step approach to perioperative communication).

The surgeon's role during induction also requires allocation, particularly because the patient may require a surgical airway, or a chest decompression for a tension pneumothorax after positive pressure ventilation. A member of the surgical team should be clearly allocated for this function, should the need arise.

While the best person should be designated to the proper position, in selected cases junior or more inexperienced team members may assume positions in order to provide proper exposure and training, and enable a rotation of functions. As usual, good judgement in balancing patients' needs with training issues is mandatory. These members should be actively involved in the debriefing, to provide the maximum from the learning opportunity of participating in a trauma team (see below).

Role allocation, like most NTS, requires excellent communication between the team members.

Decision-making

It is often said that good judgement comes with experience and that experience comes with bad judgement. Taking a neuroscience approach, we can divide the thought process used in decision making in two distinct pathways: type 1 and type 2. Type 1 decisions are based on pattern recognition, intuitive and require little mental effort. It is used for simple, daily tasks. Type 2 decisions use deductive processes, are logical, concept-based, require mental work and are thus slower (15).

The way we use these two processes in task performance is well exemplified when we walk in the street. While walking in the streets of our hometown we use mental shortcuts, with fast and automatic processes (type 1). However, when walking the streets of a foreign town (without an online map) we have to use deductive reasoning to find our way, taking considerably more time and mental effort (type 2).

Although we use the two decision-making processes interchangeably in our daily life, in stressful scenarios, our brain, for evolutionary reasons, is prompted to use type 1 decisions (15). A good example of the importance of the decision-making process is in the management of the bleeding patient. Both the experienced and the inexperienced surgeon will initially control bleeding with simple maneuvers, for instance, digital or manual compression of a bleeding artery. A less experienced surgeon will likely try to immediately perform direct suture or clamping of the vessel (type 1 decision), often without proper exposure, without obtaining proximal or distal control, and without taking the time to inform the team. However, the experienced surgeon will more likely pause and assess the available options, communicate with the anesthesiologist to check on the patient status, report the findings and the plan, allocate roles (improve lighting and exposure) and gather more resources (all type 2 decisions).

Simulation-based learning, by recreating "under test conditions, phenomena that are likely to occur in actual performance" (16) is particularly helpful in demonstrating the value of the decision-making process. When exposed to a critical scenario under artificial "classroom" conditions, i.e., a clinical case discussion, participants will rarely fail and will indicate the correct course of action. This means that type 2 decisions are mostly followed. However, if exposed to the same clinical scenario under simulated conditions, many more type 1 decisions are likely to occur. In the author's opinion, this is one of the most important advantages of simulation-based training in trauma management.

However, not all type 1 decisions are necessarily wrong. For example, simple airway maneuvers, such as chin lift or jaw thrust (with restriction of cervical spine motion), or compression of external bleeding, are safe and can be expeditiously performed by a relatively inexperienced practitioner without much mental effort, and without incurring in patient hazards. However, key interventions, such as obtaining a definitive airway, decompressing a hemo- or pneumothorax, starting blood transfusion and taking the patient to OR, all fraught with complications and risks to the patient, should have the benefit of a pondered decision.

While training and experience may attenuate the trend toward repetitive type 1 use, a helpful tool is the use of intra-resuscitation or intraoperative time-outs (11, 17). These allow the entire team to reassess the situation and share concerns. A pause before action, in essence.

Another tool is the training of crisis containment strategies. One of these is the identification of the "surprise and startle" reaction. This technique has been developed for the training of airline crews in dealing with severe, unexpected inflight events, and is potentially transferable to the OR scenario. Airline pilots are trained to clearly identify the event and the response. They should avoid precipitous, type 1 decisions, and are trained to respond in a protocol manner, the "Stop-Aviate-Navigate-Communicate" protocol. The same can be trained for trauma teams (18), whereby a stop procedure and focus on the basics (ABC's for the ER team, TBCS for the OR team). By identifying the event as a surprise, team members will force a stop, redirect the focus and weigh the options.

Leadership

There is ample evidence to support the clear designation of a trauma team leader in the ER (19, 20). Although most trauma team leaders are surgeons (14), emergency physicians can also take up this role (21). However, much more relevant than the specialty *per se*, the attributes of a good trauma team leader are enabling input from the team members and using concise communication (22). Experienced trauma team leaders are associated with reduced time for resuscitation and for decision-making (23).

In the trauma OR, leadership is ideally a shared one. While the indication for surgery, i.e., the decision to operate, rests on the surgical team leader, the actual conduct of the operation requires shared

decisions with the anesthesiologist. This is clearly demonstrated by the fact that most indications for damage control strategy (arterial pH and lactate, temperature, coagulopathy) (24), as well as the response to resuscitation, are physiologic variables easily obtained and updated by the anesthesiology team. Thus, a shared leadership can ideally take into account both what is happening in the surgical field and how is the patient's physiology.

While the technical conduct is in the decision sphere of the surgeon, it is desirable that the anesthesiologist assumes a leadership role at critical moments, particularly during induction, or during severe unexpected events, such as cardiocirculatory arrest. For instance, a sudden intraoperative hemodynamic collapse may only be managed with cross-clamping of the aorta, and this may have to be indicated by the anesthesiologist. Another time for this reallocation of leadership is when the surgeon's focus is too narrow to allow for a comprehensive view of the case, for instance during a procedure requiring focus, such as placing an intra-arterial shunt. Yet another example is during direct heart compressions, through a thoracotomy. The surgeon's focus is directed at making sure the field is dry, the aortic clamp is not slipping and on the efficiency of the bimanual compressions. Thus, at this stage the anesthesiologist should assume a leadership role, deciding on drugs and timing of internal paddle defibrillation. Ego issues should not interfere with the patient management, as the most important person in the OR is, and always will be, the patient. As usual, good cooperation and excellent communication between surgeon and anesthesiologist is mandatory for this "two-headed" brain to work (25).

Good leadership means more that accomplishing the team's mission – a live patient with the most severe injuries treated and with significant physiological reserve to recover in intensive care. Team leaders should also assess how the team members performed, how they felt and how can the team improve. This is discussed in more detail below ("Debriefing the team" section).

Communication

As is obvious from the previous sections, communication is, by far, the most important NTS. Good communication is a team's greatest asset, or its greatest drawback. In fact, it is estimated that 70 to 80% of healthcare errors are due to poor communication (26). Fortunately, there are rules for proper communication in emergency scenarios.

Both peri-resuscitation and perioperative communication should use the principles of closed-loop communication, which are:

- Direct communication, using name
  - o Both prearrival ED team and preoperative OR team briefings should serve to know names and allocate roles
- Visual contact, if possible.
  - o An exception to this is in the intraoperative setting, as the surgeon may not be able to do this if the surgical field requires attention.
- The recipient acknowledges the message and confirms that the message was clearly understood, and the task completed

Closed loop communication is associated with increased speed and efficiency of tasks in the resuscitation setting (27). The authors compare closed-loop communication to communication using the WhatsApp instant message platform, where there is a clear symbology for a sent, received and seen message. However, only when the sender receives the reply is a message truly understood (Figure 3).

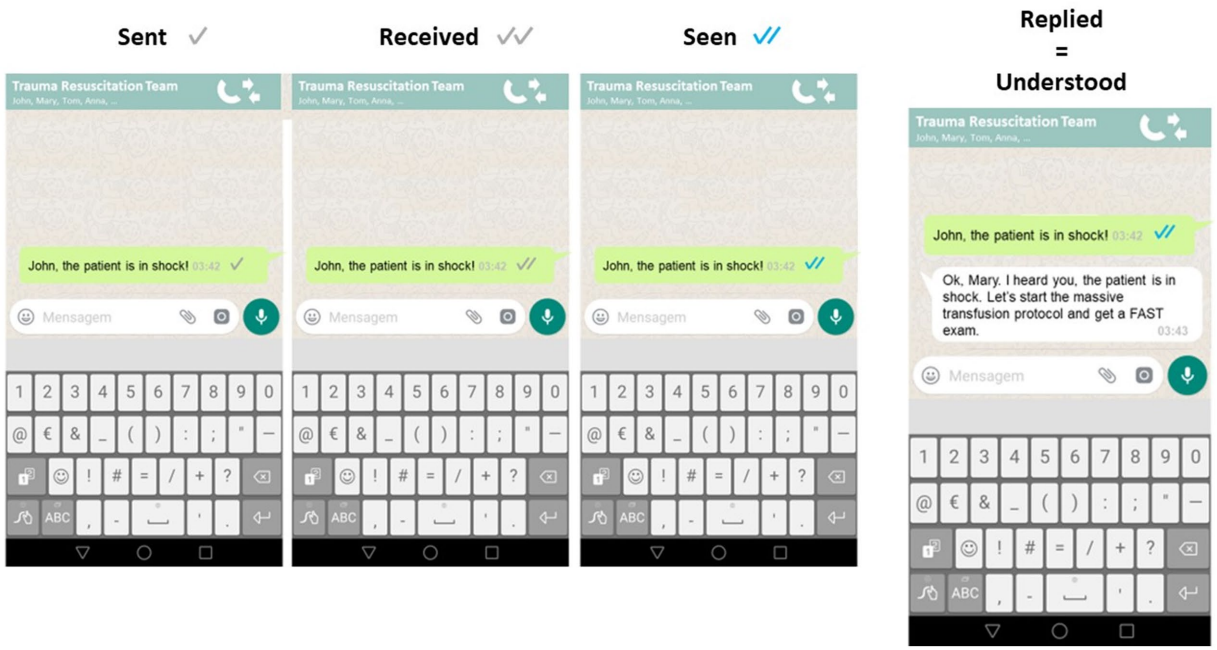


FIGURE 3
Clear symbology for sent, received and seen messages in WhatsApp. However, only when the receiver replies, does the sender really acknowledge that the message has been read and understood. This is translatable to communication in the trauma ER and OR.

Communication starts well before the operation starts, is mandatory during the operation, and is essential after the operation is concluded. Nonetheless, there should be safeguards to avoid over communication. A good rule of thumb is to see communication as a drug or as surgical instrument, i.e., it should be used in the proper timing and dosing. Interrupting the anesthesiologist during a difficult airway, or the surgeon during a difficult supraceliac aortic clamping can easily disrupt the focus. During these moments, only game changing information should be provided, such as sudden patient deterioration, or severe, unexpected intraoperative events. Again, this follows the strategy of the sterile cockpit rule of aviation, whereby during critical times only relevant information needs to be shared (28).

Perioperative communication – the six-step approach

The authors' group has developed a framework for communication in trauma management (25) – the six-step approach to perioperative communication in trauma. This stems from the recognition that there are key moments in the trauma patient's path through the immediate preoperative, intraoperative and immediate postoperative periods, that mandate that the whole team is coordinated. Relevant data such as the patient's physiology, suspected injuries, needed resources, and potential hazards should be shared.

This can be achieved with a communication strategy consisting of six distinct stages (Table 1):

Step 1 – Before patient arrival – OR team notice

- A prehospital notification of the ER of a severely injured patient should prompt immediate trauma team activation and mobilization of resources (for instance, radiology, massive hemorrhage protocol, as well as preparation of the OR for a damage control procedure).
- Although precise information is rarely obtained at this stage, several key data from the AT-MIST should alert the OR team to ensure surgical material and anesthetic equipment are ready.
- In one of the authors' institution, activation of the OR is designated by a specific "Code Orange." This clearly informs the OR staff that a trauma patient will be arriving in the ER and may require emergency surgery. An operating theatre is booked with a team on standby until further notice from the team leader.
- At this stage it is desirable that both surgeon and anesthesiologist incorporate the ER trauma team; if not, step 3 becomes even more relevant.

Step 2 – After patient arrival in ER – Decision and preparation for emergency surgery

- Decision for emergency surgery should be swiftly communicated to the remaining OR team, including OR nurses, as well as assistant surgeons and anesthetic team (if not already present in the ER trauma team). This ensures that everything is ready to receive the patient in the operating room.
- Again, in one of the author's institution a clear indication for emergency surgery is indicated by a warning of a "Code Red" to the OR team. The trauma team leader makes clear to the OR staff that the patient is immediately moving to the OR.
- While this turns a potential activation into a real one, the preliminary steps taken in Step 1 have made this stage easier.
- Surgical and anesthetic teams may take this time to brief the respective OR nursing teams (scrub and anesthetic) of specific requirements (for instance, thoracotomy tray, drugs). However, the authors advise that a trauma surgery protocol is the safest option.
- In some circumstances steps 1 and 2 are done together, for instance when patients arrive unannounced to the ER.

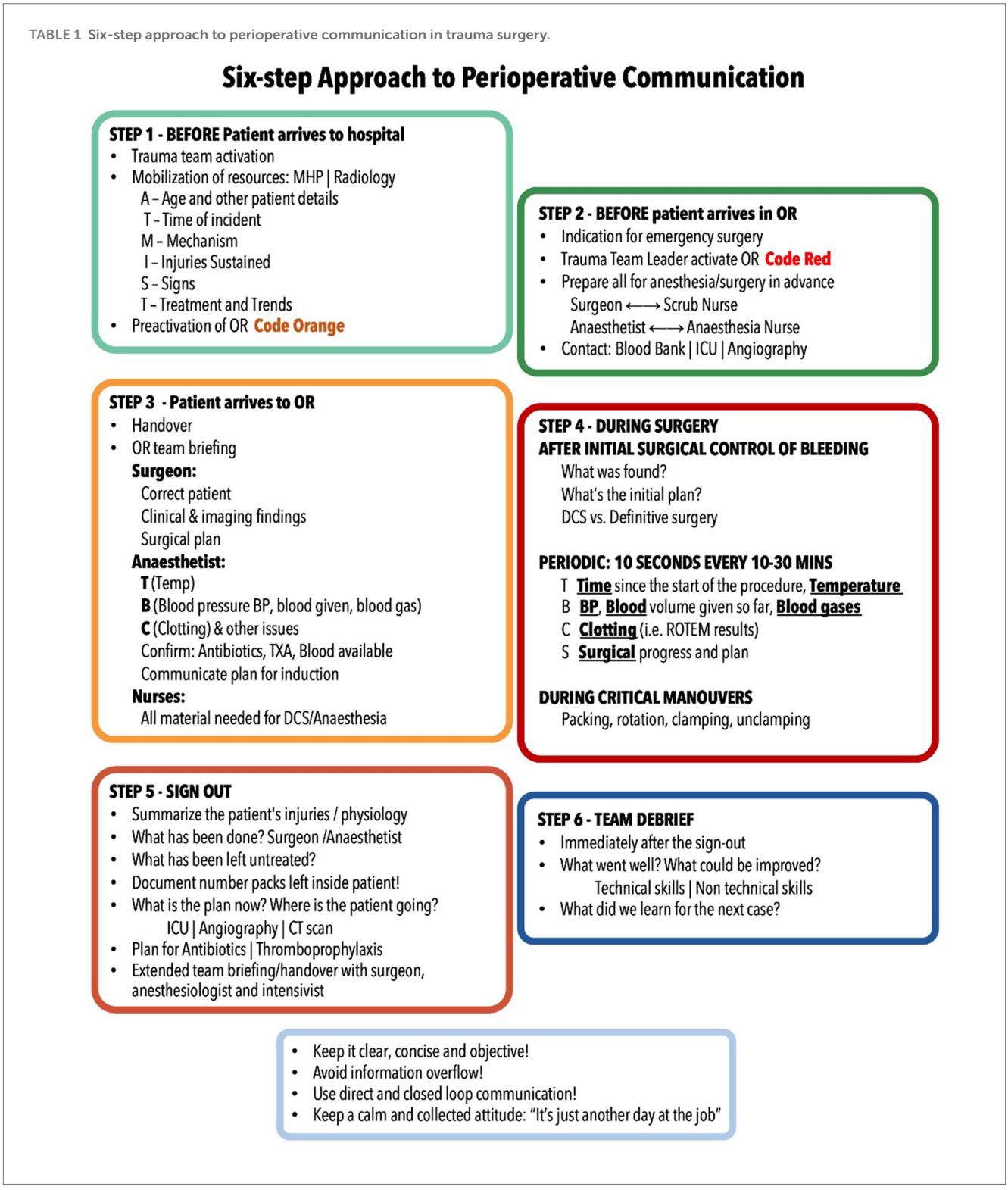
Step 3 –Before surgery – Preoperative communication

- This is a key moment in the OR and a potentially hazardous one. It starts with a handover of information from the ER team to the OR team, particularly if the anesthesiologist was not already present in the ER resuscitation. The OR nurses should be updated of the status, potential injuries and required resources. It is paramount that the OR nursing team be clearly allocated to positions - anesthesiology, scrub and circulating nurses – and quickly receive further information; all the team members' names should be known.
- A key moment is anesthetic induction and there is real potential for patient deterioration. Loss of airway ("cannot intubate, cannot ventilate" scenario), tension pneumothorax and immediate cardiovascular collapse (due to loss of muscle tone and cardiovascular depression from anesthetic drugs in a shocked patient) require that anesthesiology and surgical teams coordinate their action. The surgical team should be scrubbed and gowned, and the patient prepped, before induction. Good role allocation and shared leadership are required, as well as optimal communication.
- Immediately before the incision, if time allows, there should be a brief pause in which the entire OR team agrees on the surgical plan, the patient's clinical status, and to confirm that all materials, drugs, and blood products are available.

Step 4 – During surgery – Intraoperative communication.

- During surgery, immediate control of bleeding is the priority and once this is achieved the surgeon should request a short time-out. This will allow the team to pause, update status and reassess, avoiding spiraling into repeated type 1 decisions. This time out, using the TBCS tool, will be useful to grasp the physiology and the response to treatment, and plan the next move.
- A particularly hazardous moment is the opening of the peritoneum, which can cause loss of tamponade effect. Closed-loop communication is mandatory between operating surgeon and lead anesthesiologist at this stage.
- Regular intraoperative communication at intervals, again using the TBCS, will allow the team to "steer" the patient's status more accurately; indeed, a patient initially planned to have a damage control procedure that recovers well with damage control resuscitation may be treated with definitive surgery.
- The decision to perform either a damage control or a definitive procedure should be clearly announced to the whole team.
- Communication should also be used during or, ideally, immediately after intraoperative adverse events, again using the TBCS.

TABLE 1 Six-step approach to perioperative communication in trauma surgery.



- Intraoperative communication is also critical during key surgical manouvers that have significant physiologic impact, such as liver mobilization, major vessel clamping and unclamping, hepatic or renal hilar clamping, or heart manipulation. This requires closed-loop communication in order to properly coordinate the team.

Step 5 – Sign Out – Before patient leaving the OR

- This is another critical moment. Both the surgical (swab and instrument count, injuries found, procedures performed and timing of expected second-look) and anesthetic records (blood products, venous accesses, drugs, physiological status, past medical history from records) should be summarized and known by the respective surgical and anesthetic team leaders. The number of packs and the predicted timing of the second-look procedure should be clearly recorded and repeated by the team.

- The probabilities of other associated injuries being present should be addressed at this stage and the patient's status reviewed, in order to decide between immediate transfer to CT (if not already done) or to the intensive care unit (ICU).
- Again, the TBCS tool is helpful to summarize what was done and what was the response.
- Contact with the ICU team, ideally started at step 2, is mandatory at this stage to update the patient's status and define a plan (for instance, timing of second-look or definitive abdominal closure).
- The authors recommend that these trauma scenarios should be handled no differently from any other complex case which requires a multidisciplinary team meeting, such as an oncology patient. In fact, trauma patients can, by extent of injuries and physiological instability, be much more complex than many cancer patients. This trauma MDT is paramount for patient outcome.

Stage 6 – Team debriefing

- A trauma damage control operation can be an intense and at time off-putting experience, causing moral damage to the team members and potentially contributing to feelings of helplessness and burnout; this is particularly true when there was significant interpersonal tension or communication issues, or when the patient died in the OR. This requires a formal debriefing, which is explored in detail in the following section.

Debriefing the team

Every trauma case is a learning opportunity, and debriefing is an invaluable tool to achieve this. However, it can be difficult to assemble the whole team after the trauma call or after the operation. There are several potential obstacles: reallocation to other clinical tasks, termination of shifts, lack of belief in debriefing and fear of accusation of misconduct. Nonetheless, it is desirable to gather the team, particularly after a challenging case, and conduct a formal debriefing. Good judgement is mandatory, as many team members may be on the defensive. In one of the author's experience, a good way to prompt debriefing is to have the facilitator clearly state that every team member performed at the best of their individual skills and that the debriefing will only focus on the teamwork. This may help in removing some barriers to a frank discussion. Emphasizing that participation in the debriefing is voluntary, not mandatory, and that all shared information is confidential, is also desirable.

There are several strategies to conduct a postcritical debriefing. One such methods is the STOP – Summarize/Things that went well/Opportunities to improve/Points to action and responsibilities (29). When possible, the authors use a pedagogical structure for debriefing that can be used after simulation based training, the RDAT (Reactions, Description, Analysis, Questions? and Take-home message) (Figure 4) (30). With this method, the participants start by expressing feelings (Reactions phase) that can interfere with review of the facts (Description phase) and exploration (Analysis phase). After allowing for questions or doubts, the participants are invited to identify points for improvement (Take-home message).

In our experience the more junior the team member, the more they are willing to take part in the debriefing. The team leader should see this as a learning opportunity. Another purposed benefit of debriefing is the promotion of team cohesion (31), which is one of the key features of well-functioning teams (32).

In a worldwide snapshot of trauma team function and training, 15 and 23% of respondents reported that they performed debriefing always and often, respectively. A possible way to improve this is to promote debriefing practices in the undergraduate setting (see below). The authors recommend that team leaders should have formal training in debriefing techniques.

Trauma team training focusing on non-technical skills

Trauma teams are not automatically formed simply by assembling a group of providers. Although human beings are social animals, the ability to function in a highly efficient team is not innate and requires attention to NTS. This has deserved increasing focus in recent years and there is compelling evidence to support the incorporation of NTS training into undergraduate and postgraduate settings, particularly in trauma. In fact, NTS has transcended trauma care and is spreading to other non-trauma surgical settings (33–35).

The European Trauma Course (ETC) was the first course to recognize this and specifically train NTS in the trauma setting (36). The ETC expanded on the training of clinical decision-making and

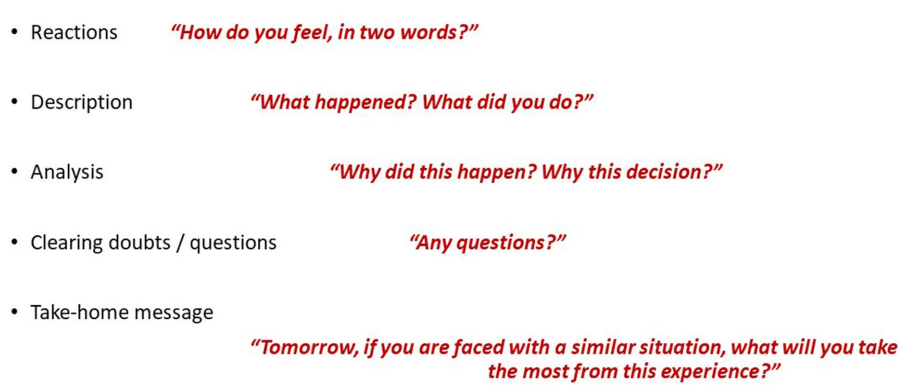


FIGURE 4
RDAT structure for post-resuscitation debriefing – Reactions/Description/Analysis/Questions?/Take-home message.

technical skill acquisition promoted by the Advanced Trauma Life Support (ATLS) course. More recently, the ATLS program's 10th Edition has implemented teamwork training (37). For the authors, course instructors in both ATLS and ETC courses, rather than competing, the two courses add to each other. While ATLS provides the fundamentals of trauma care for the trauma team member, ETC promotes NTS for the trauma team members and team leader.

Regarding intraoperative teams, several notable courses, such as the NOTSS course (38), aim at improving patient safety in the perioperative setting. In the authors' opinion, another way to achieve this is to include NTS in the already existing trauma courses. In a sense replicating in the OR setting what the ETC has done for the ER teams. The Definitive Surgical Trauma Care (DSTC), Definitive Anesthetic Trauma Care (DATC), Definitive Perioperative Nurses Trauma Care (DpNTC) courses are an excellent opportunity for this and allow the entire operating room team to participate in joint training sessions. Here the technical, decision-making and communication skills of surgeons, anesthesiologists and nurses are put to work in the immersive environment of a simulated damage control operating room.

Although the importance of NTS in trauma team function is well recognized, there is little real-world information on how teams are trained. In a recent survey, only 33% of hospitals provided trauma team training. Moreover, 60% of the trauma team members reported having had postgraduate training on NTS with only 24% at the undergraduate level (14). Regarding team training courses for the ER teams, the European Trauma Course was the most popular, immediately followed by local in-house courses. However, most trauma teams do not have the benefit of regular, simulation-based training.

NTS teaching in undergraduate education

Undergraduate teaching aims to promote the acquisition of knowledge, skills and attitudes. However, emphasis has been mostly placed on individual, rather than teamwork skills. This undoubtedly produces well prepared junior doctors, but it is questionable whether these will successfully integrate clinical teams and become good team members, particularly in the emergency setting. Moreover, training for trauma teams is still rare from a global perspective, and even rarer in undergraduate education (14).

Fortunately, there is evidence that early training in NTS can not only lead to the acquisition, but also the retention, of NTS (39) and this has gained significant attention in recent years. Numerous studies have been conducted to explore the integration and effectiveness of teaching non-technical skills to medical students. Communication skills represent a cornerstone of non-technical competencies in Medicine. Studies have shown that enhanced communication skills lead to improved patient satisfaction, adherence to treatment, and even clinical outcomes. Simulation-based training and role-playing exercises have been shown to be effective in improving students' ability to convey complex medical information in a patient-friendly manner (40).

Teamwork and leadership skills are also emphasized. Collaborative learning environments have been introduced in medical education, with group-based activities and interprofessional training to prepare future healthcare professionals for effective teamwork (41).

Moreover, promotion of debriefing habits is paramount in undergraduate education (42). The authors hope that the next generation of doctors has been trained in teamwork, is aware of the relevance of NTS and has gained the habit of debriefing the critical scenario.

Future perspectives: hybrid room teams and NTS

In a typical clinical scenario, the trauma patient streamlines from prehospital handover to an ER team and, if surgical indication arises, to an OR team. Subsequently, the patient may undergo angioembolization in the interventional radiology (IR) suite. Such handovers are fraught with hazards and can contribute to deterioration of clinical practice (2). However, the development of hybrid rooms, with integrated resuscitation, imaging, surgical and angiography capacity, means that the same team can take care of the patient (43). This Trauma Hybrid Operating Room (THOR) concept not only mandates specific training in technical skills, but also poses significant challenges regarding NTS. Joining in the same room team elements with different skillsets (resuscitation, operating, imaging and endovascular) and backgrounds (ER, OR, IR) will require not only protocols and organization, but also a critical understanding of NTS from all participants. To the authors' knowledge this has not been addressed specifically. As more and more institutions adopt the THOR concept, specific team training courses may arise for this particular context, incorporating NTS training alongside with technical skills training. The DSTC-DATC-DpNTC courses, given their flexibility and ability to incorporate add-on modules, could present an opportunity to provide team training for the very specific THOR context.

Conclusion

Managing a severely injured trauma requires that every team member is at the best of his/her individual technical skills. But this is not enough, as outstanding individual work does not guarantee excellent team performance. Proficiency in non-technical skills, particularly the use of communication, are paramount to a good outcome. Fortunately, training opportunities are increasingly available, either with the ETC and inhouse courses, for ER teams; or with the joint DSApNTC courses, for OR teams. The inclusion of NTS in undergraduate curricula is a welcome step and will make the future doctors individually excellent, but also excellent team members and leaders. The future of trauma management will undoubtedly include hybrid rooms, and special attention should be given to training these teams in NTS.

Author contributions

HA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration,

Supervision, Validation, Writing – original draft, Writing – review & editing. BM: Investigation, Writing – original draft, Writing – review & editing. LF: Validation, Writing – original draft, Writing – review & editing. SB: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Predictors of outcomes in geriatric patients with moderate traumatic brain injury after ground level falls

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Introduction: The elderly population constitutes one of the fastest-growing demographic groups globally. Within this population, mild to moderate traumatic brain injuries (TBI) resulting from ground level falls (GLFs) are prevalent and pose significant challenges. Between 50 and 80% of TBIs in older individuals are due to GLFs. These incidents result in more severe outcomes and extended recovery periods for the elderly, even when controlling for injury severity. Given the increasing incidence of such injuries it becomes essential to identify the key factors that predict complications and in-hospital mortality. Therefore, the aim of this study was to pinpoint the top predictors of complications and in-hospital mortality in geriatric patients who have experienced a moderate TBI following a GLF.

Methods: Data were obtained from the American College of Surgeons' Trauma Quality Improvement Program database. A moderate TBI was defined as a head AIS $\leq$ 3 with a Glasgow Coma Scale (GCS) 9–13, and an AIS $\leq$ 2 in all other body regions. Potential predictors of complications and in-hospital mortality were included in a logistic regression model and ranked using the permutation importance method.

Results: A total of 7,489 patients with a moderate TBI were included in the final analyses. 6.5% suffered a complication and 6.2% died prior to discharge. The top five predictors of complications were the need for neurosurgical intervention, the Revised Cardiac Risk Index, coagulopathy, the spine abbreviated injury severity scale (AIS), and the injury severity score. The top five predictors of mortality were head AIS, age, GCS on admission, the need for neurosurgical intervention, and chronic obstructive pulmonary disease.

Conclusion: When predicting both complications and in-hospital mortality in geriatric patients who have suffered a moderate traumatic brain injury after a ground level fall, the most important factors to consider are the need for neurosurgical intervention, cardiac risk, and measures of injury severity. This may allow for better identification of at-risk patients, and at the same time resulting in a more equitable allocation of resources.

KEYWORDS

ground level fall, traumatic brain injury, geriatric, complications, prediction

1 Introduction

A ground level fall (GLF) is defined as "inadvertently coming to rest on the ground, floor or other lower level" (1). GLFs are responsible for 15% of all emergency department visits in the USA and account for 25–33% of all injuries among the elderly (2–4). The financial burden of fall-related injuries is also substantial, with estimated costs exceeding $30.4 billion in the United States alone (5). The likelihood of experiencing such an event increases significantly with age, particularly among individuals aged 80 years and above (1). Given the growing elderly population worldwide, the incidence of traumatic brain injuries (TBI) from GLFs is expected to rise as well (6, 7), leading to an even greater burden on medical, rehabilitation, and nursing care resources.

While approximately 20% of all hospital admissions for TBI fall under the classification of moderate severity, this particular group of patients has unfortunately been overlooked in research efforts (8). Additionally, limited knowledge exists regarding older adults with TBIs from a population-based perspective, which directly contributes to the absence of clear treatment guidelines for those with moderate TBIs in this vulnerable patient population (9, 10). To enhance care of this patient category, improve quality of life, and decrease costs of care, it is essential to identify factors that can be used to predict complications and mortality as well as mitigate these adverse outcomes, if possible. The aim of this study was therefore to determine the most critical variables for predicting in-hospital complications and mortality in geriatric patients who have suffered a moderate TBI after a GLF. The hypothesis was that these adverse outcomes would in large part be predicted by variables already present at hospital admission. By doing so, the goal is to lay the groundwork for delivering better and more targeted care to this specific patient population.

2 Materials and methods

The primary outcome of the study was in-hospital complications, and the secondary outcome was in-hospital mortality. The study is a retrospective register-based cohort study utilizing the data from the 2013–2019 American College of Surgeons' Trauma Quality Improvement Program (ACS TQIP) database containing anonymous patient data based on approximately 900 participating level one trauma centers across the United States. All relevant/applicable ethical permits were in place prior to the commencement of this study. The study adhered to the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines throughout (11). Information retrieved for this study included age, sex, comorbidities, abbreviated injury scale (AIS), injury pattern, interventions, discharge disposition, and complications. All geriatric patients (65 years or older) who suffered a moderate TBI as a result of a GLF were initially screened for inclusion in the current study. In line with previous literature, a moderate TBI was defined as a head AIS ≤ 3, GCS 9–13 with an AIS ≤ 2 in all other body regions (12, 13). Patients were excluded listwise if they were missing data, in order to facilitate a complete case analysis. These previously listed inclusion and exclusion criteria were selected to better delineate the predictive factors for outcome after TBI, i.e., by excluding severe or significant injuries (AIS 3 and above in all other body regions) unrelated to the TBI.

2.1 Statistical analysis

In-hospital complications were defined as myocardial infarction, cardiac arrest with CPR, stroke, deep vein thrombosis, pulmonary embolism, acute respiratory distress syndrome, urinary tract infection, pneumonia, surgical site infection, sepsis, decubitus ulcer, unplanned intubation, unplanned admission to the operating room, and unplanned admission to the intensive care unit. Patients were divided based on if they did or did not experience an in-hospital complication. Continuous data that did not follow a normal distribution were summarized using medians and interquartile ranges, while continuous data that followed a normal distribution was presented as means and standard deviations. The statistical significance of differences in continuous variables was determined using the Mann–Whitney *U*-test for non-normally distributed data and Student's *t*-test for normally distributed data. Categorical data was summarized with counts and percentages. Differences between these variables were evaluated using the Chi-squared test or Fisher's exact test, as appropriate.

A logistic regression (LR) model was fitted, with in-hospital complications as the outcome variable and age, sex, injury severity score (ISS), highest AIS in each region, intracranial injuries, neurosurgical intervention, Revised Cardiac Risk Index (RCRI) (14, 15), shock index, vitals on admission to the emergency room (systolic blood pressure, pulse rate, temperature, oxygen saturation, respiratory rate), Glasgow Coma Scale (GCS) on admission to the emergency room, as well as comorbidities (hypertension, history of peripheral vascular disease, functionally dependent health status, chronic obstructive pulmonary disease, smoking status, cirrhosis, coagulopathy, currently receiving chemotherapy for cancer, metastatic cancer, drug use disorder, alcohol use disorder, and major psychiatric illness) as the explanatory variables (16–18). Preadmission anticoagulant therapy was unable to be included as a covariate given over 38% of cases were missing these data. The relative importance of the explanatory variables in predicting in-hospital complications was evaluated using permutation importance (PI) as described by Altmann et al. (19) The PI was calculated by evaluating to what degree a specific value [1 − Area under the receiver-operating characteristic curve (AUC)] was changed by the suppression of a particular variable. Instead of removing each variable from the dataset, the PI method masks each variable's information by rearranging the variable's values. This process was repeated 10 times to account for the randomness of permutations. The relative importance of each variable in the model was presented as the average increase in 1-AUC compared to the AUC in a model that included all variables without any permutations. The above steps were also repeated for in-hospital mortality as the outcome in the LR models. While the LR models are used to derive the predictive importance, the coefficients themselves are not presented as they would be biased and lack clinical relevance given the presence of multicollinearity in the models.

Statistical significance was defined as a two-sided $p < 0.05$. The statistical analysis was conducted using statistical programming language R 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) with the aid of the tidyverse, DALEX, pROC, haven, and cowplot packages (20).

3 Results

A total of 7,489 patients met the study inclusion criteria (Figure 1). Patients who experienced in-hospital complications were more often male (53.2% vs. 46.9%, $p = 0.008$) and had a higher cardiac risk as measured by the RCRI (RCRI ≥2: 17.3% vs. 9.4%, $p < 0.001$). Most comorbidities were more prevalent among patients who experienced an in-hospital complication (Table 1). This subgroup was more likely to have suffered a more severe head injury (Head AIS 3: 61.8% vs. 44.3%, $p < 0.001$) and present with a lower initial GCS (GCS ≤11: 40.5% vs. 34.0%, $p = 0.017$). This is reflected in the fact that traumatic subdural hematomas (25.9% vs. 16.2%, $p < 0.001$), subarachnoid hemorrhages (24.4% vs. 17.4%, $p < 0.001$), and cerebral contusions were more common in patients who suffered a complication (15.8% vs. 8.6%, $p < 0.001$), which corresponded to a greater need for neurosurgical intervention (9.4% vs. 1.5%, $p < 0.001$). Patients who experienced a complication were also likelier to be more severely injured overall, being found to frequently have suffered a more severe spine (Spine AIS 2: 11.5% vs. 6.0%, $p < 0.001$) and abdomen injuries (Abdomen AIS 2: 0.6% vs. 0.4%, $p = 0.024$) (Table 2). Similar patterns were observed when comparing the patients who died to those who survived their hospital stay (Supplementary Tables S1, S2). Overall, 6.5% of patients suffered a complication and 6.2% died during their hospital stay (Table 3).

The full LR model for in-hospital complications contained a total of 38 variables and resulted in an acceptable predictive ability, with an AUC of 0.71 (95% Confidence Interval: 0.68–0.74) (21). The top five predictors of in-hospital complications in this model were the need for neurosurgical intervention, the RCRI, coagulopathy, spine AIS, and ISS (Figure 2).

The full LR model for in-hospital mortality contained the same 38 variables and also resulted in an acceptable predictive ability, with an AUC of 0.77 (95% Confidence Interval: 0.75–0.79) (21). The top five predictors of in-hospital mortality in this model were head AIS, age, GCS on admission, the need for neurosurgical intervention, and chronic obstructive pulmonary disease (Figure 3).

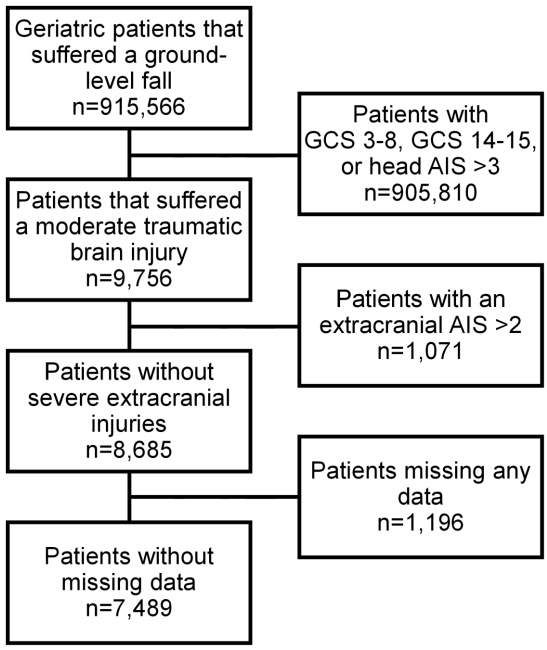

FIGURE 1
Flow chart describing selection of sample population.

4 Discussion

This study represents the first of its kind, investigating predictors of complications and mortality in moderate TBIs. Although previous studies, like the one conducted by Dams-O'Connor et al., highlight that the proportion of elderly patients who suffer a moderate TBI following a GLF is smaller (5%) compared to mild and severe TBIs (84%), the actual number of affected elderly individuals would still be quite substantial, amounting to several thousand elderly patients annually in the United States alone (22, 23). Furthermore, while 80–88% of mild TBI patients recover most or all function, approximately 15% of geriatric moderate TBI lose their lives and up to 80% continue to face significant disabilities even after recovery (6, 9, 22).

Despite this significant impact on patients' lives, the research gap between moderate TBIs and their mild or severe counterparts is vast, leading to a paucity in clear guidelines for effectively treating and managing patients with moderate TBIs (9, 10). In light of this, the current investigation aimed to address this issue by identifying predictors of complications and mortality in geriatric patients with moderate TBIs. Such insights can be invaluable to healthcare professionals, providing them with better tools to assess and manage patients. The need for neurosurgical intervention was found to be the most important predictor of complications, followed by the patients' RCRI, coagulopathy, spine AIS, and ISS. The best predictors of in-hospital mortality were head AIS, followed by age, GCS on admission, the need for neurosurgical intervention, and chronic obstructive pulmonary disease. The need for neurosurgical intervention uniquely stood out as the only predictor of both complications and mortality.

Contrary to previous research that has shown a link between age and an increased frequency of complications following trauma as well as worse outcomes in moderate TBI, age was not identified as one of the top predictors of complications in this study (8, 24, 25). This difference may be attributable to the exclusive focus on geriatric patients, and beyond a certain threshold, age may have a lesser impact on in-hospital complications. Prior investigations that explored age and complications typically examined wider age ranges. Furthermore, this study did not incorporate frailty as a factor, which could be more important than chronological age alone in predicting patient outcomes. Conversely, hypertension and GCS being among the top 10 most important predictors is in line with previous research, which has found that comorbidities and GCS following injury have a strong association with higher rates of complications (24–26).

While predictors of outcome according to the Glasgow Outcome Scale, and other classifications are more common, there are few studies looking at predictors of in-hospital complications following TBI, and none that specifically examine moderate TBI in isolation. Due to the lack of research focused solely on moderate TBI, the results of this study are compared with others that performed the statistical analysis on different groupings of TBI severity. The association between the need for neurosurgical intervention and complications following a TBI has garnered substantial support in academic

TABLE 1 Demographics of geriatric patients who suffered a moderate TBI as a result of a GLF.

	No complication (*N* = 7,002)	Any complication (*N* = 487)	*p*-value
Age, median [IQR]	79 [73–84]	78 [72–83]	0.030
Sex, n (%)			0.008
Female	3,719 (53.1)	228 (46.8)	
Male	3,283 (46.9)	259 (53.2)	
RCRI*, n (%)			<0.001
0	4,158 (59.4)	233 (47.8)	
1	2,185 (31.2)	170 (34.9)	
2	546 (7.8)	67 (13.8)	
3	104 (1.5)	14 (2.9)	
≥4	9 (0.1)	3 (0.6)	
Hypertension, n (%)	4,269 (61.0)	344 (70.6)	<0.001
Previous myocardial infarction, n (%)	124 (1.8)	11 (2.3)	0.381
Congestive heart failure, n (%)	581 (8.3)	64 (13.1)	<0.001
History of peripheral vascular disease, n (%)	87 (1.2)	11 (2.3)	0.063
Cerebrovascular disease, n (%)	888 (12.7)	71 (14.6)	0.254
Non-independent functional status, n (%)	1,702 (24.3)	92 (18.9)	0.008
Currently receiving chemotherapy for cancer, n (%)	58 (0.8)	7 (1.4)	0.197
Metastatic cancer, n (%)	125 (1.8)	10 (2.1)	0.598
COPD, n (%)	696 (9.9)	70 (14.4)	0.002
Current smoker, n (%)	439 (6.3)	44 (9.0)	0.021
Chronic renal failure, n (%)	245 (3.5)	31 (6.4)	0.002
Diabetes mellitus, n (%)	1,755 (25.1)	157 (32.2)	<0.001
Cirrhosis, n (%)	86 (1.2)	11 (2.3)	0.060
Coagulopathy, n (%)	568 (8.1)	79 (16.2)	<0.001
Drug use disorder, n (%)	114 (1.6)	10 (2.1)	0.598
Alcohol use disorder, n (%)	390 (5.6)	45 (9.2)	0.001
Major psychiatric illness, n (%)	877 (12.5)	68 (14.0)	0.393

*Patients received one point for each of the following: a history of ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, and renal insufficiency (acute kidney injury or chronic kidney disease) (14, 15).
TBI, Traumatic brain injury; GLF, Ground-level fall; RCRI, Revised Cardiac Risk Index; COPD, chronic obstructive pulmonary disease.

literature (27–30). Omar et al., for example, recognized neurosurgical intervention as a top predictor of complications, drawing the same conclusion as the present study (30). This finding was also indirectly echoed by Scheetz, who determined that the most significant predictor of in-hospital complications was a major operating room procedure (31). Additionally, in accordance previous investigations including Omar et al., injury severity was found to hold substantial weight in predicting complications in the current analysis (24, 25, 30). However, these studies included all TBI severities.

The results of this study could have several clinical applications. Primarily, they can be utilized to identify elderly patients who are at higher risk of in-hospital complications or mortality following a TBI. By identifying these high-risk individuals, healthcare providers can allocate resources more efficiently and design tailored care plans to address their specific needs. Targeted interventions can be implemented to minimize the risks altogether, leading to improved TBI outcomes. One such intervention, supported by previous research, involves the use of beta-blockers. Studies have demonstrated that beta-blockers can effectively reduce cardiac complications, which are a primary extracranial cause of death associated with TBI, and even decrease mortality following severe TBI (32, 33). Notably, approximately 20% of patients exhibit cardiac pathology as revealed by post-mortem examinations; this damage closely resembles that found in individuals suffering from conditions like pheochromocytoma or cocaine overdose (34). In addition to cardiac considerations, closely monitoring intracranial physiological variables, such as intracranial pressure and cerebral perfusion pressure, could be critical. This is especially important given the close correlation between neurological intervention and complications (35).

Furthermore, the results of this study could serve as a valuable foundation for developing clinical decision-making tools, such as risk prediction models, to aid in the care of geriatric patients with moderate TBI. By leveraging the insights gained from this research, healthcare professionals can make more informed decisions and tailor treatment plans to individual patients' needs. This, in turn, may lead to the creation of best practice guidelines

TABLE 2 Clinical characteristics of geriatric patients who suffered a moderate TBI as a result of a GLF.

	No complication (*N* = 7,002)	Any complication (*N* = 487)	*p*-value
Injury severity score, median [IQR]	8.0 [4.0–10]	9.0 [5.0–10]	<0.001
Head AIS, n (%)			<0.001
1	1,808 (25.8)	91 (18.7)	
2	2,092 (29.9)	95 (19.5)	
3	3,102 (44.3)	301 (61.8)	
Face AIS, n (%)			0.151
Injury not present	4,337 (61.9)	304 (62.4)	
1	2,020 (28.8)	127 (26.1)	
2	645 (9.2)	56 (11.5)	
Neck AIS, n (%)			0.069
Injury not present	6,963 (99.4)	482 (99.0)	
1	33 (0.5)	3 (0.6)	
2	6 (0.1)	2 (0.4)	
Spine AIS, n (%)			<0.001
Injury not present	6,518 (93.1)	429 (88.1)	
1	66 (0.9)	2 (0.4)	
2	418 (6.0)	56 (11.5)	
Thorax AIS, n (%)			0.080
Injury not present	6,655 (95.0)	453 (93.0)	
1	228 (3.3)	20 (4.1)	
2	119 (1.7)	14 (2.9)	
Abdomen AIS, n (%)			0.024
Injury not present	6,875 (98.2)	470 (96.5)	
1	102 (1.5)	14 (2.9)	
2	25 (0.4)	3 (0.6)	
Upper extremity AIS, n (%)			0.638
Injury not present	5,671 (81.0)	390 (80.1)	
1	982 (14.0)	68 (14.0)	
2	349 (5.0)	29 (6.0)	
Lower extremity AIS, n (%)			0.861
Injury not present	6,140 (87.7)	423 (86.9)	
1	691 (9.9)	51 (10.5)	
2	171 (2.4)	13 (2.7)	
External/Other AIS, n (%)			0.460
Injury not present	6,784 (96.9)	469 (96.3)	
1	217 (3.1)	18 (3.7)	
2	1 (0.0)	0 (0.0)	
Epidural hematoma, n (%)	28 (0.4)	5 (1.0)	0.060
Traumatic subdural hematoma, n (%)	1,131 (16.2)	126 (25.9)	<0.001
Traumatic subarachnoid hemorrhage, n (%)	1,219 (17.4)	119 (24.4)	<0.001
Cerebral contusion, n (%)	601 (8.6)	77 (15.8)	<0.001
Diffuse axonal injury, n (%)	18 (0.3)	2 (0.4)	0.377
Neurosurgical intervention, n (%)	106 (1.5)	46 (9.4)	<0.001
Shock index, median [IQR]	0.57 [0.47–0.69]	0.58 [0.48–0.70]	0.228

(Continued)

TABLE 2 (Continued)

	No complication (*N* = 7,002)	Any complication (*N* = 487)	*p*-value
Systolic blood pressure on admission, mean (SD)	148 (±29.8)	151 (±32.1)	0.039
Pulse rate on admission, mean (SD)	85.3 (±19.4)	88.8 (±20.1)	<0.001
Temperature on admission, median [IQR]	37 [36–37]	37 [36–37]	0.648
Oxygen saturation on admission, median [IQR]	97 [95–99]	97 [95–99]	0.788
Respiratory rate on admission, mean (SD)	18.8 (±4.6)	19.2 (±5.1)	0.043
Glasgow Coma Scale on admission, n (%)			0.017
13	3,259 (46.5)	205 (42.1)	
12	1,358 (19.4)	85 (17.5)	
11	1,080 (15.4)	78 (16.0)	
10	814 (11.6)	69 (14.2)	
9	491 (7.0)	50 (10.3)	

TBI, traumatic brain injury; GLF, ground-level fall; AIS, abbreviated injury severity score.

TABLE 3 Crude outcomes in geriatric patients who suffered a moderate TBI as a result of a GLF.

	No complication (*N* = 7,002)	Any complication (*N* = 487)	*p*-value
In-hospital mortality, n (%)	348 (5.0)	120 (24.6)	<0.001
Any complication, n (%)	0 (0.0)	487 (100.0)	<0.001
Myocardial infarction	0 (0.0)	30 (6.2)	<0.001
Cardiac arrest with CPR	0 (0.0)	47 (9.7)	<0.001
Stroke	0 (0.0)	35 (7.2)	<0.001
DVT	0 (0.0)	42 (8.6)	<0.001
Pulmonary embolism	0 (0.0)	11 (2.3)	<0.001
ARDS	0 (0.0)	19 (3.9)	<0.001
Urinary tract infection	0 (0.0)	75 (15.4)	<0.001
Pneumonia	0 (0.0)	54 (11.1)	<0.001
Surgical site infection	0 (0.0)	4 (0.8)	<0.001
Sepsis	0 (0.0)	32 (6.6)	<0.001
Decubitus ulcer	0 (0.0)	34 (7.0)	<0.001
Unplanned intubation	0 (0.0)	126 (25.9)	<0.001
Unplanned admission to the OR	0 (0.0)	7 (1.4)	<0.001
Unplanned admission to the ICU	0 (0.0)	145 (29.8)	<0.001

TBI, traumatic brain injury; GLF, ground-level fall; DVT, deep vein thrombosis; ARDS, acute respiratory distress syndrome; OR, operating room; ICU, intensive care unit.

specifically designed for this vulnerable patient population. One such tool for identifying at-risk patients is the RCRI, which was found to be the second most important predictor of complications. The RCRI relies on six objective data points that can be readily obtained during admission without requiring invasive tests. Early identification of high-risk patients using the RCRI can facilitate appropriate allocation of resources and expertise, ensuring that patients receive the most suitable and timely interventions (14, 15, 36).

This study possesses several notable strengths that contribute to its credibility and potential impact. One of the most significant strengths is the substantial sample size obtained from a national database, namely the ACS TQIP dataset. This large sample size helps mitigate the risk of random errors and enhances the generalizability of the findings to a broader population of trauma patients in the United States. Additionally, the utilization of the ACS TQIP dataset, a comprehensive database specifically designed to capture trauma patient data, minimizes the potential for selection bias, thus increasing the study's external validity. However, there are limitations that warrant careful consideration. While the study identifies certain variables as potential predictors of future complications or mortality, it is crucial to note that these associations do not imply causality between the variables and the outcomes. Instead, the findings highlight potential correlations that warrant further investigation into the complex interplay of these factors in influencing patient outcomes following a TBI. The study's scope was also limited to the variables available in the database, which meant that detailed information regarding

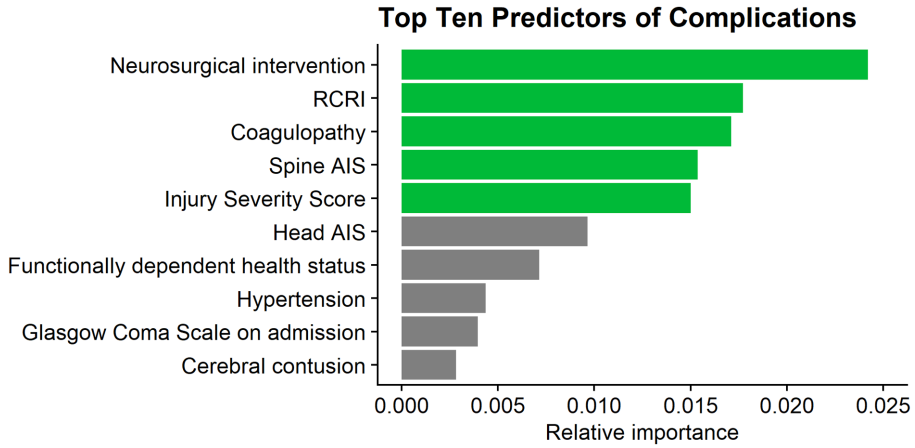

FIGURE 2
Top 10 predictors of complications. RCRI, Revised Cardiac Risk Index; AIS, abbreviated injury severity score.

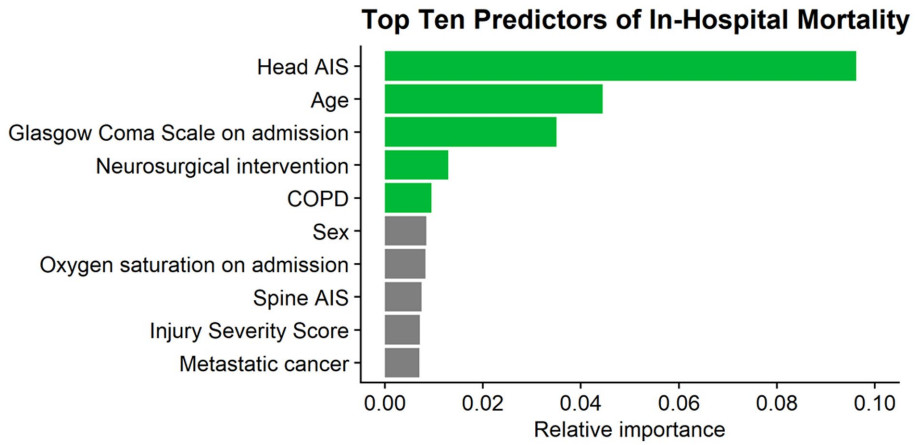

FIGURE 3
Top 10 predictors of mortality. AIS, abbreviated injury severity score; COPD, chronic obstructive pulmonary disease.

computerized tomography findings, indications for surgical intervention, and other possibly important variables were unavailable. Moreover, as with any retrospective study design, there is a risk of non-differential misclassification arising from errors in data entry. Data may also be biased toward specific demographics or conditions, leading to a lack of heterogeneity and potentially limiting the generalizability of the results. Finally, as the data stems from multiple sources, differences in data collection and recording practices across sources can introduce inconsistencies. Preadmission anticoagulant therapy, a potentially critical covariate influencing patient outcomes, was also excluded, as approximately 38% of cases lacked this data. Furthermore, the absence of frailty as a factor in the dataset is another potential limitation. The inclusion of frailty as an assessment tool, such as the Clinical Frailty Scale, could have provided valuable insights into patient outcomes. Research has consistently demonstrated that frailty is a more accurate predictor of outcomes than age alone across various fields of study, underscoring the significance of its inclusion in contexts like this study (37, 38).

5 Conclusion

The findings from our study reveal important predictors for in-hospital complications and mortality in geriatric patients with moderate traumatic brain injuries following ground level falls. However, to maximize the impact of these findings, further investigations are warranted. Future studies should explore how these predictors can be integrated into clinical decision-making tools, such as risk prediction models, to assist healthcare professionals in assessing and managing geriatric patients with moderate traumatic brain injury effectively. Additionally, the development of evidence-based guidelines tailored specifically for moderate TBI treatment in this population is imperative.

Data availability statement

The datasets presented in this article are not readily available because due to TQIP data restrictions by American College of

Surgeons. Requests to access the datasets should be directed to mohsenishahin@yahoo.com and/or the American College of Surgeons.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

SF: Formal analysis, Investigation, Writing – original draft, Methodology. RA: Writing – original draft, Formal analysis, Conceptualization, Investigation, Supervision. MF: Writing – review & editing, Formal analysis, Methodology, Data curation, Software, Visualization. MR: Writing – review &a editing, Formal analysis, Conceptualization, Investigation, Supervision, Validation. BS: Writing – review & editing, Data curation, Formal analysis, Project administration, Resources, Supervision, Validation. SM: Project administration, Supervision, Writing – original draft, Data curation, Methodology, Conceptualization, Funding acquisition, Investigation, Resources, Validation.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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A short decision time for transcatheter embolization can better associate mortality in patients with pelvic fracture: a retrospective study

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Background: Early use of hemostasis strategies, transcatheter arterial embolization (TAE) is critical in cases of pelvic injury because of the risk of hemorrhagic shock and other fatal injuries. We investigated the influence of delays in TAE administration on mortality.

Methods: Patients admitted to the Advanced Critical Care Center at Gifu University with pelvic injury between January 2008 and December 2019, and who underwent acute TAE, were retrospectively enrolled. The time from when the doctor decided to administer TAE to the start of TAE (needling time) was defined as "decision-TAE time."

Results: We included 158 patients, of whom 23 patients died. The median decision-TAE time was 59.5 min. Kaplan–Meier curves for overall survival were compared between patients with decision-TAE time above and below the median cutoff value; survival was significantly better for patients with values below the median cutoff value ($p = 0.020$). Multivariable Cox proportional hazards regression analysis revealed that the longer the decision-TAE time, the higher the risk of mortality ($p = 0.031$). TAE duration modified the association between decision-TAE time and overall survival ($p = 0.109$), as shorter TAE duration (procedure time) was associated with the best survival rate (p for interaction = 0.109).

Conclusion: Decision-TAE time may play a key role in establishing resuscitation procedures in patients with pelvic fracture, and efforts to shorten this time should be pursued.

KEYWORDS

transcatheter arterial embolization, pelvic injury, mortality, hemostasis strategies, retrospective study

1 Introduction

Pelvic injury is often associated with hemorrhagic shock and other fatal injuries (1). Hemorrhage-related mortality rate may be as high as 40%, and overall mortality rate in these patients may be 10–32%, even if hospitalized in a level 1 trauma center (2–5). In the emergency department (ED), the definitive treatments to achieve timely hemodynamic stabilization in patients with pelvic injury include transcatheter arterial embolization (TAE) and pre-peritoneal packing (PPP) (1, 6, 7); other treatments include arterial cross-clamping and resuscitative endovascular occlusion of the aorta (REBOA) (8, 9).

The literature contains many reports on the relative advantages of TAE and PPP (10–13); TAE, a less invasive procedure, has become widely accepted as a safe and efficacious substitute for direct surgical intervention (10). Conversely, considerable delays in performing embolization and a lack of readily available experts in angiography have been highlighted (10, 12). The mortality rates of patients treated with TAE range from 16 to 50% (14, 15), which is higher than that of patients treated with PPP (12).

Recent reports suggest that early administration of TAE results in low mortality rates; and the so-called "door-to-angioembolization time" should be shorter for better outcomes (4, 16). The true effectiveness of shortening the delay before administration of TAE can be confirmed using "decision-TAE time," which represents the time from the decision to administer TAE to its actual administration.

In this study, we aimed to investigate how decision-TAE time influenced mortality in patients with pelvic trauma.

2 Materials and methods

2.1 Study design and ethics statement

This observational study used retrospectively collected data and adhered to the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement. The study protocol is available. Ethics approval was obtained from the medical ethics committee of Gifu University Graduate School of Medicine, Gifu, Japan (Institutional Review Board approval No. 2020-061). The need for informed consent from the patients was waived by the medical ethics committee of the institution because of the study's retrospective nature. This study adhered to the ethical guidelines for medical and health research involving humans, established by the Japanese government.

2.2 Study setting

Gifu University Hospital (Gifu-shi, Japan) is the only advanced critical care center in this region. The region includes catchment areas populated by approximately 2 million people. Patients with pelvic injury who underwent acute TAE were included, if they were admitted to Gifu University's advanced critical care center between January 2008 and December 2019. The attending emergency physicians were responsible for the trauma survey and treatment of these patients in the ED. Emergency physicians and interventional radiologists were involved in the decision-making process. In our institution, interventional radiologists and the equipment required for TAE are available 24 h a day, 365 days a year.

2.3 Selection criteria

Patients who received TAE for pelvic fracture injury from trauma, including other injuries, were enrolled in this study. Patients with out-of-hospital cardiac arrest, without a response to resuscitation, with missing data on the time course of TAE, and those who underwent PPP were excluded. We identified the patients using the facility's diagnosis codes: pelvic fracture, pelvic ring fracture, iliac fracture, pubic fracture, ischial fracture, sacral fracture, acetabular fracture, and hip fracture dislocation. All the data including demographic and biological data on admissions, treatment process, and outcomes were collected from medical records.

2.4 Treatment

At the advanced critical care center at Gifu University Hospital, we established a treatment algorithm based on the Eastern Association for the Surgery of Trauma recommendations (6). Patients who could not undergo computed tomography (CT) scan owing to hemodynamic instability were directly sent to undergo TAE. Some of them could not be prepared for TAE because of the risk of death or because PPP had just been performed; hence, TAE was added if needed. Other patients underwent a CT scan, and immediate TAE was initiated if necessary. If transferred patients had already undergone a CT and there was enough information to make a decision, additional examinations were bypassed and the patients were directly sent to undergo TAE. They were treated according to the algorithm shown in Figure 1. In some cases, REBOA was utilized, based on emergency physicians' decisions. All patients needed TAE for hemostasis.

2.5 Definition of parameters

Emergency physicians decided to administer TAE when: (1) the CT scan indicated massive hemorrhage from pelvic injury, or (2) the patient was hemodynamically unstable and did not undergo a CT scan or was transferred from another hospital after a CT scan. When the CT scan indicated massive hemorrhage, the decision-TAE time was defined as the time from starting the CT to TAE (CT-TAE group: CT group). When the patient did not undergo a CT scan or was transferred after a CT scan, the decision-TAE time was defined as the time from arrival at the ED to the administration of TAE (door-TAE group: DT group) (Figure 2).

Demographic and biological data on admission were collected from medical records. The injury severity score and the abbreviated injury score by body area (head, chest, abdomen, pelvis, and extremities) were calculated for each patient, and defined as "severe" if they scored ≥3 points.

Abbreviations: TAE, Transarterial catheter embolization; REBOA, Resuscitative endovascular occlusion of the aorta; GCS, Glasgow coma scale; DT, Door-to-TAE; SBP, Systolic blood pressure; CT, Computed tomography; ED, Emergency department; PPP, Pre-peritoneal packing; ISS, Injury severity score; RTS, Revised trauma score.

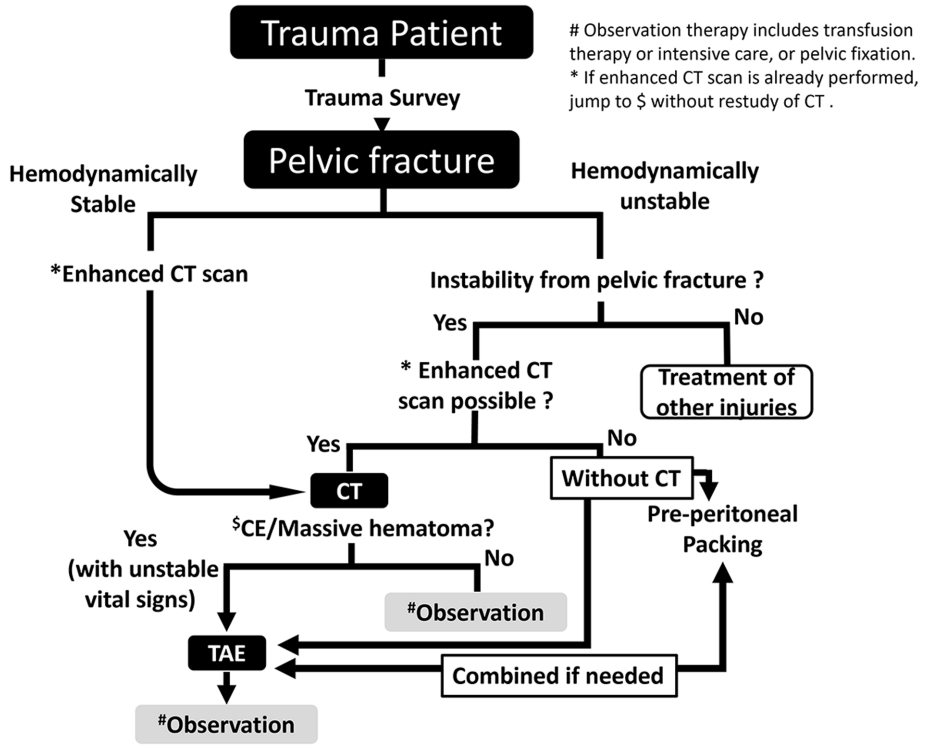

FIGURE 1
Treatment algorithm for pelvic injury. CT, computed tomography; TAE, transarterial catheter embolization.

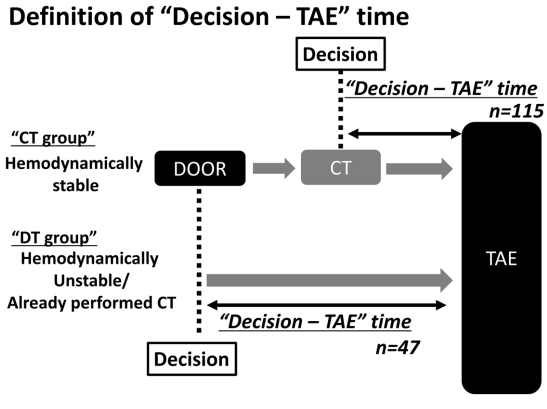

FIGURE 2
Definition of "Decision-TAE" time In the CT (CT-TAE) group, the decision-TAE time is defined as the time from the start of CT to the administration of TAE. In the door-TAE group, the decision-TAE time is defined as the time from arrival to administration of TAE. TAE, transarterial catheter embolization; CT, computed tomography.

2.6 Outcomes

The primary outcome of this study was the time from the end of TAE to death. There were 10 secondary outcomes, including parameters associated with TAE (decision-TAE time, number of arteries involved in TAE, localizations, embolic materials, TAE duration time, and number of secondary TAEs), treatment with REBOA, surgical management for pelvic fractures, length of hospital stay, and causes of death.

2.7 Statistical analysis

The baseline characteristics of the patients and the continuous variables were expressed as median and interquartile range (IQR) and categorical variables as counts and percentages. The sample size was calculated according to feasibility and not power, to avoid overfitting of the statistical model (17). For the primary analysis, Cox proportional hazards regression analysis was performed to confirm the effect of decision-TAE time on the time from the end of TAE administration to death. As age and sex are important characteristics affecting mortality (18, 19), the Cox proportional hazards model was adjusted for them to avoid confounding by patient baseline characteristics (18, 19). GCS and transfer were also incorporated into the model as covariates based on the previous report (20) and background of the study, as they are strongly related to outcome and decision-TAE time. Sensitivity analysis with GCS replaced by ISS or RTS was performed to confirm the robustness of the Hazard ratio for decision-TAE time. A sensitivity analysis of another perspective was also performed using a model with CT/DT group added as a covariate (Table 1).

To avoid overfitting, the number of covariates was limited to two or three (21). Therefore, if the calculated optimism parameter was <0.2, the model was not considered overfitting, even with the above four variables as covariates. The optimism (22) was estimated using 150 bootstrap resamples. Optimism assesses the magnitude of overfitting of regression model (a value less than 0.2 is considered as good) and was calculated using C-statistics by bootstrap samples. Subgroup analysis by DT group and CT group were performed using univariate Cox regression models (Supplementary Table S1).

TABLE 1 Multivariable Cox proportional hazards regression model.

Analysis	Factors	HR	95% LCI	95% UCI	*p* value
Primary analysis	Decision-TAE time	1.009	1.001	1.016	0.031
	GCS	0.812	0.735	0.898	<0.001
	Transfer	0.803	0.308	2.095	0.654
	Age	1.003	0.980	1.026	0.800
	Sex: female	0.339	0.116	0.991	<0.001
Sensitivity analysis 1	Decision-TAE time	1.009	1.001	1.018	0.025
	GCS	0.815	0.738	0.900	<0.001
	Transfer	0.618	0.189	2.022	0.426
	Age	1.002	0.979	1.025	0.037
	Sex: female	0.289	0.090	0.925	<0.001
	DT group	1.722	0.443	6.703	0.433
Sensitivity analysis 2	Decision-TAE time	1.007	0.999	1.015	0.073
	ISS	1.080	1.034	1.128	0.001
	Transfer	0.559	0.197	1.582	0.273
	Age	1.020	0.993	1.047	0.017
	Sex: female	0.260	0.086	0.784	0.001
	DT group	1.670	0.482	5.786	0.419
Sensitivity analysis 3	Decision-TAE time	1.011	1.003	1.019	0.010
	RTS	0.738	0.617	0.883	0.001
	Transfer	0.431	0.134	1.389	0.158
	Age	1.007	0.982	1.033	0.010
	Sex: female	0.230	0.076	0.700	0.002
	DT group	1.539	0.394	6.013	0.535

Multivariable Cox regression: TAE duration time				
Factors	HR	95% LCI	95% UCI	*p* value
TAE duration time	0.889	0.482	1.639	0.707
Age	1.007	0.984	1.032	0.543
Sex: female	0.365	0.135	0.989	0.048

Multivariable Cox regression: decision-TAE time. HR, hazard ratio; CI, confidence interval; UCI, upper CI; LCI, lower CI; TAE, transarterial catheter embolization; GCS, Glasgow coma scale.

Kaplan–Meier estimation calculated the cumulative survival rate for each group divided by the median of the decision-TAE time. The difference in the cumulative survival rate between the two groups was confirmed using the log-rank test.

Similar to the model used for the primary analysis, the effects of the end of TAE administration on death were analyzed. In this secondary analysis, GCS score and transfer were not included as covariates because they were not related to the end of TAE administration. Additionally, an interaction term (decision-TAE time * TAE duration) was incorporated into the Cox proportional hazards model to test whether the effect of decision-TAE time on mortality was modified by including TAE duration. The hazard ratio for a unit increase in decision-TAE time or TAE duration with a 95% confidence interval was reported in each Cox proportional hazards analysis. A sensitivity analysis was performed using the Fine–Gray subdistribution hazard model, treating death from head trauma as a competing risk. Parameters that could influence the decision-TAE time on arrival were summarized for each group by dividing decision-TAE time into quartiles, and comparisons between groups were conducted using a Fisher's exact test for categorical variables and a Kruskal–Wallis test for continuous variables. Imputation was not used for missing data because no data were missing for the primary outcome. A value of *p* (two-sided) <0.05 was considered significant. No adjustment was made for multiple comparisons because all analyses were exploratory. All statistical analyses were performed using the R version 4.2.2.[1]

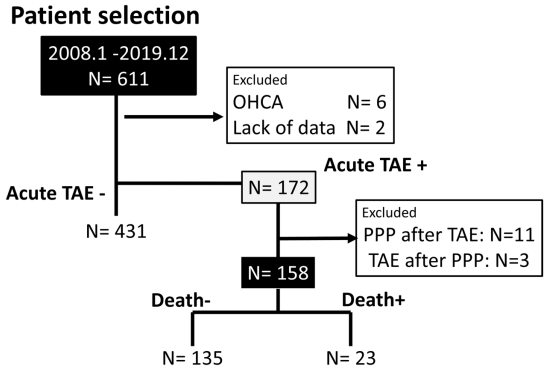

FIGURE 3
Patient selection. Flowchart diagram of eligible and excluded patients. OHCA, out-of-hospital cardiac arrest; TAE, transarterial catheter embolization; PPP, pre-peritoneal packing.

3 Results

3.1 Patient demographics

In total, 611 patients with pelvic fractures were included in this study. A flowchart of the inclusion process is shown in Figure 3.

Six patients with out-of-hospital cardiac arrest and two patients with missing data were excluded. Acute TAE was performed in 172 patients, and 14 patients were excluded because they had undergone PPP with TAE, which may have influenced the effects of TAE on hemostasis. Previously, PPP and TAE have been reported as "complementary procedures" performed to stop bleeding (23, 24). Although complementary (23, 25), PPP and TAE could be effective as a single or combined strategy, depending on the situation. In total, 158 (25.9%) patients met the inclusion criteria.

Table 2 summarizes the patients' clinical characteristics. This study included 94 males (59.5%) and 64 females (40.5%), with a median age of 74 years. Eighty patients (50.6%) were transferred from other hospitals. The median injury severity score was 25. The proportion of patients with severe anatomic injuries with an abbreviated injury score ≥ 3 was the highest for the pelvis, followed by

1 https://www.r-project.org/

TABLE 2 General demographics of the patients with pelvic fracture who received acute angioembolization for pelvic injury.

Factors	No. (%) or Median (25, 75%) (*N* = 158)
Age (y/o)	74 (61, 81)
Sex	
Male	94 (59.5%)
Female	64 (40.5%)
Antiplatelet drug	26 (16.5%)
Anticoagulant drug	12 (7.6%)
Transfer, *n* (%)	80 (50.6%)
ISS (score)	25 (16, 34)
Severe anatomic injuries, *n* (%)	
Head AIS≧3	40 (25.3%)
Chest AIS≧3	54 (34.2%)
Abdomen AIS≧3	26 (16.5%)
Pelvis AIS≧3	124 (78.5%)
SBP upon ED arrival (mmHg)	110 (87, 132)
GCS upon ED arrival (total)	14 (13, 15)
Pelvic fracture type, *n* (%)	
Tile OTA classification	
A1	6 (3.8%)
A2	11 (7.0%)
A3	3 (1.9%)
B1	44 (27.9%) (including 5 associated acetabular fractures)
B2	26 (16.5%) (including 3 associated acetabular fractures)
B3	16 (10.1%) (including 1 associated acetabular fracture)
C1	23 (14.6%) (including 1 associated acetabular fracture)
C2	7 (4.4%)
C3	5 (3.1%)
Unknown	1 (0.6%)
Sacral fracture	2 (1.2%)
Acetabular fracture	14 (8.9%)
Indications for TAE	
1. Contrast extravasation on CT scan	134 (84.8%)
2. Massive hematoma on CT scan	13 (8.2%)
3. Unstable hemodynamics	11 (7.0%)
DT group, *n* (%)	45 (28.5%)
CT group, *n* (%)	113 (71.5%)

ISS, injury severity score; AIS, Abbreviated injury score; TAE, transcatheter arterial embolization; DT, door-to-TAE, SBP, systolic blood pressure; GCS, Glasgow coma scale; OTA, Orthopaedic Trauma Association; CT, Computed tomography; ED, Emergency department.

the chest, head, and abdomen (78.5, 34.2, 25.3, and 16.5%, respectively). The median systolic blood pressure on arrival was 110 mmHg, and the median GCS score was 14. The Tile Orthopaedic Trauma Association classifications and indication for TAE are presented in Table 2. There was an unknown fracture type in one patient because of the lack of a CT scan.

3.2 Relationship between mortality and decision-TAE time

The median decision-TAE time was 59.5 min (IQR: 40–87 min). Twenty-three patients died, and the mortality rate was 14.6%. Patients with decision-TAE time < 59.5 min had significantly higher survival rates than those with decision-TAE time ≥ 59.5 min ($p = 0.02$) as per the Kaplan–Meier curves (Figure 4). The hazard ratio was plotted when the reference was fixed at 105 min.

The multivariable Cox proportional hazards regression model adjusted for age, sex, GCS score, and transfer revealed that the longer the decision-TAE time, the higher the risk of mortality (Table 1). The optimism parameter was 0.168, indicating that the model was not overfitting. The results from the model with the CT/DT group added as a covariate also showed that the decision-TAE time was significant, thus achieving robustness of the results. After adjusting for age and sex, TAE duration was not significantly associated with mortality (Table 1). We also performed sensitivity analysis using Fine-Gray subdistribution hazard model with competing risk of death resulting from head trauma (Supplementary Table S2).

Although the interaction between TAE duration and decision-TAE time was not significant ($p = 0.109$), it indicated that TAE duration modified the effect of decision-TAE time on mortality (Figure 5).

3.3 Patient outcomes

The total number of arteries involved during TAE was 455, with a median value of three (IQR: 2–4). The locations of the arteries and embolic materials are summarized in Supplementary Tables S3, S4, respectively. There were 6 (3.8%) cases of REBOA. Two patients (1.3%) underwent secondary TAE for hemostasis. Sixty-eight patients (43.0%) underwent surgical management for pelvic fractures, including external fixation in 16 patients (10.1%) and internal fixation in 59 patients (37.3%). The median hospital length of stay was 26 (IQR: 11–41) days. The cause of death was unstable hemodynamics in three patients (1.9%), severe head trauma in nine patients (5.7%), unstable hemodynamics and severe head trauma in three patients (1.9%), and other causes including sepsis or respiratory failure in eight patients (5.1%). Patient outcomes are summarized in Table 3.

4 Discussion

The primary finding of this study was that long decision-TAE time resulted in a high risk of mortality. Sensitivity analysis with GCS replaced by RTS which both could represent the severity of patients based on the physiologic status, indicated that decision-TAE time was still significant. Moreover, although the actual TAE duration did not have a significant influence on decision-TAE time, the interaction between TAE duration and decision-TAE time was significant, indicating that TAE duration modified the effect of decision-TAE time on mortality.

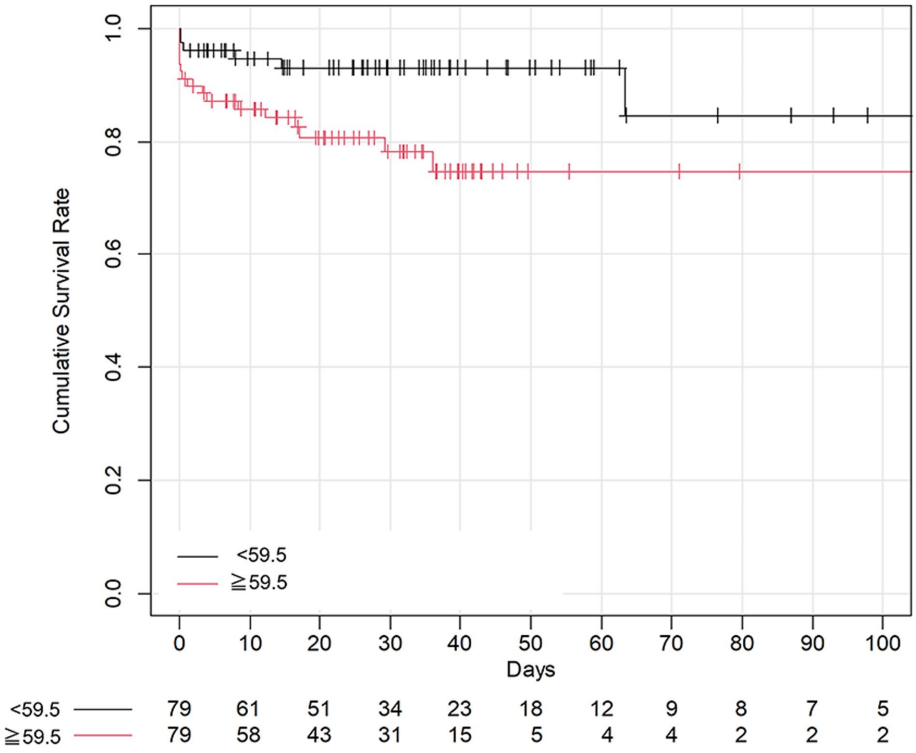

FIGURE 4
Kaplan–Meier curves of overall survival. The vertical axis shows the cumulative survival rate by Kaplan–Meier estimation. The horizontal axis shows the number of days since the baseline day. Marks in the curve indicate data censoring. The Kaplan–Meier curves of overall survival are compared, and a significant difference is observed between the patients above and below the median cutoff value for decision-TAE time ($p = 0.02$). TAE, transarterial catheter embolization.

Some reports have suggested the importance of early TAE for improving mortality (4, 15, 16, 26). In clinical settings, many variations exist in the circumstances surrounding patient delivery to the ED, and the patient's condition upon delivery (27, 28), including the presence of associated injuries, severity of said injuries, and differences in vital signs (29). Moreover, they may have been transferred from another hospital and previously treated by prehospital medical professionals (30, 31). Physicians must decide upon a treatment plan for these patients, taking these factors into consideration (32). Hence, the actual effectiveness of shortening the delay from decision-making to actual TAE administration can be confirmed by analyzing the time from the decision to administer TAE to its administration and effect on the outcomes (29).

Reportedly, the time to angioembolization is longer than the time to PPP, partly owing to the higher availability of orthopedic surgeons compared with that of interventional radiologists (7, 12, 33); furthermore, TAE may be delayed at night or on weekends based on reports of other catheter-based interventions (16, 34, 35). In our institution, interventional radiologists and the equipment required for TAE are available at all times. Therefore, staff and equipment availability was not an issue in this study. The overall decision-TAE time was 60 min, even after performing other resuscitation procedures. Although PPP may have advantages over TAE, such as early start time (7, 12), most patients with pelvic fracture, even if unstable, can be managed with primary TAE strategies at centers with 24-h availability of interventional radiologists (36).

The effectiveness of REBOA for patients with unstable pelvic fractures has been reported (8, 9). In this study, there were seven (4.4%) cases of REBOA; however, there were no clear indications for REBOA in patients with pelvic fracture. Moreover, the consensus on REBOA indications, ideal patient populations, and outcomes is undecided, even among trauma specialties (37); therefore, further studies are needed. In our facility, we aim to complete TAE within 60 min, including treatment of other bleeding injuries. Our intervention analysis showed that TAE duration modified the effect of decision-TAE time on mortality, though the relationship between TAE duration and mortality was undetermined. Our results, as outlined in Figure 5, showed that patients with a decision-TAE time ≥ 105 min benefited from a long TAE duration, whereas patients with a decision-TAE time < 105 min benefitted from a short TAE duration. When the decision-TAE time increased from 105 min to 115 min, the risk increased by 1.15, 1.1, and 1.08 times for cases with TAE duration times of 40, 55, and 75 min, respectively. When the decision-TAE time was extended by an additional 10 min to 125 min, the risk increased by 1.3, 1.23, and 1.15 times, respectively. Conversely, when the decision-TAE time was reduced by 10 min from 105 min to 95 min, the risk was 0.88, 0.9, and 0.93 times, respectively. If the TAE time was reduced from 105 min to 20 min, the risk increased by 0.77, 0.81, and 0.86 times, respectively. This suggests that short decision-TAE and short procedure times might lead to improved mortality outcomes. To the best of our knowledge, this is the first study to discuss the relationship between TAE duration and mortality, as previous reports only speculated on this relationship.

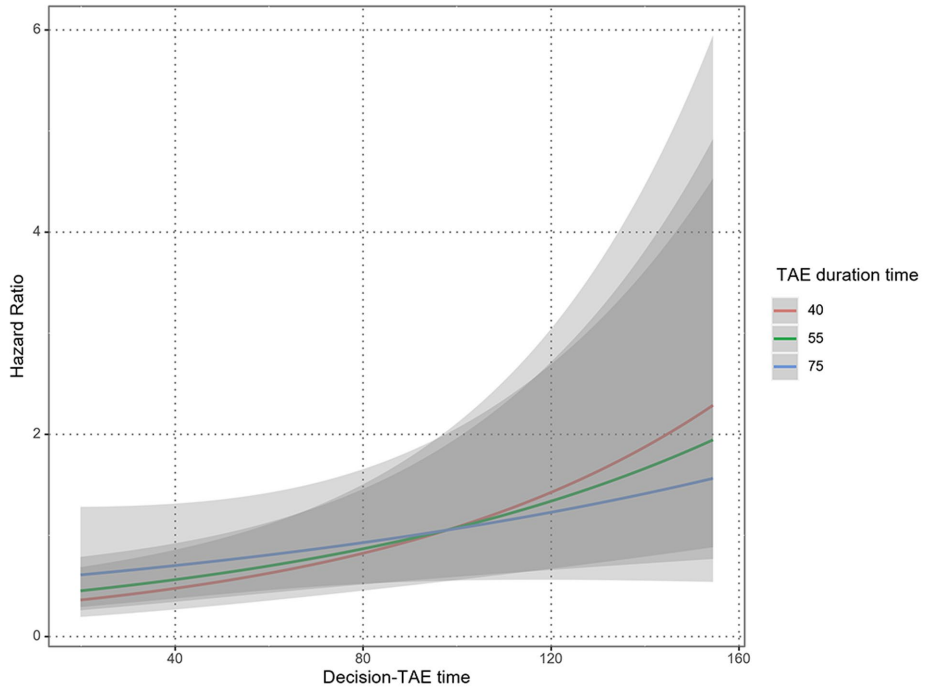

FIGURE 5
Interaction between TAE duration and decision-TAE time. Predicted plots of hazard ratios by Performed TAE time with median decision-TAE time as a reference are shown; the three solid lines correspond to the 25th, 50th, and 75th percentile of Performed TAE time, respectively. The gray shaded areas indicate 95% confidence intervals. Although the interaction between TAE duration and decision-TAE time is not significant ($p = 0.109$), TAE duration modified the effect of decision-TAE time on mortality. TAE, transarterial catheter embolization.

TABLE 3 Outcomes of the patients with pelvic fracture who received acute angioembolization for pelvic injury ($N = 158$).

Factors	No. (%) or Median (25, 75%)
Surgical management	68 (43.0%)
External fixation	16 (10.1%)
Internal fixation	59 (37.3%)
Combined REBOA	6 (3.8%)
Secondary TAE for hemostasis	2 (1.3%)
Mortality, *n* (%)	23 (14.6%)
Mean hospital length of stay (day)	26 (11, 41)
Reasons for death	
(1) Unstable hemodynamics, *n* (%)	3 (1.9%)
(2) Severe head trauma, *n* (%)	9 (5.7%)
(3) (1) and (2), *n* (%)	3 (1.9%)
(4) Other reasons, *n* (%)	8 (5.1%)

REBOA, resuscitative endovascular occlusion of the aorta; TAE, transarterial catheter embolization.

We could not confirm the factors that influenced the decision-TAE time, except for hospital transfer; the expected parameters that could influence the severity of the patient's condition, such as ISS, vital signs, and even associated injuries, were not related to decision-TAE time. Additionally, the transferred patients underwent TAE within a short duration, indicating that fast CT scanning can reduce decision-TAE time; hence, the development of fast imaging strategies is essential. Recent reports have suggested the effectiveness of hybrid emergency room systems (38, 39), hybrid operation rooms (40), and mobile angiography systems (41) for treating patients with trauma. These systems consist of an angiography-CT machine in a trauma resuscitation room and have the potential to provide new evidence in this field.

This study has some limitations. First, the performance of CT scan was dependent on the patient's mode of admission; hence, we could not determine the severity of the patient's condition based on the CT/DT stratification. The small number of CT/DT subgroups did not allow multivariable analysis. Caution may be warranted in univariable analysis results because the effects of confounding factors could not be excluded. Second, we could not clarify the actual durations of "decision time," meaning that other decision-TAE times could be established, and if so, the results would change. Third, the results of this study cannot be generalized to other facilities that do not have the same interventional radiology coverage and equipment. Fourth, as the decision on treatment with REBOA was made by physicians, we could not analyze the impacts of REBOA in this study. Fifth, the time course of patients with pelvic injury varies according to their status; for some, there may be time to perform a CT scan before TAE because their vital signs are relatively stable, whereas for others, this may not be possible (42). Sixth, the impact of head injury or other injuries which could have a lethal impact on mortality, could not be separated. In patients with pelvic trauma, some patients with severe head injury were potentially included. Thus, the treatment strategy should be established based on overall injuries.

In conclusion, overall survival was significantly different between the patients above and below the median cutoff value for decision-TAE time, and the longer the decision-TAE time, the higher the risk of

mortality. Our results suggest that decision-TAE time plays a key role in establishing resuscitation procedures in patients with pelvic fracture; thus, efforts to shorten the decision-TAE time are warranted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the medical ethics committee of Gifu University Graduate School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the need for informed consent from the patients was waived by the medical ethics committee of the institution because of the study's retrospective nature. The manuscript presents research on animals that do not require ethical approval for their study.

Author contributions

YM: Data curation, Writing – original draft. TM: Writing – original draft, Writing – review & editing. HO: Conceptualization, Supervision, Writing – review & editing. TI: Data curation, Methodology, Supervision, Writing – original draft. NK: Data curation, Writing – review & editing. MI: Data curation, Writing – review & editing. RK: Data curation, Writing – review & editing. TF: Data curation, Writing – review & editing. TY: Data curation, Writing – review & editing. SN: Data curation, Writing – review & editing. HK: Data curation, Writing – review & editing. MM: Conceptualization, Supervision, Writing – review & editing. SY: Conceptualization, Supervision, Writing – review & editing. SO: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1329167/full#supplementary-material

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Does tranexamic acid have a positive effect on the outcome of older multiple trauma patients on antithrombotic drugs? An analysis using the TraumaRegister DGU®

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Background: Acute hemorrhage is one of the most common causes of death in multiple trauma patients. Due to physiological changes, pre-existing conditions, and medication, older trauma patients are more prone to poor prognosis. Tranexamic acid (TXA) has been shown to be beneficial in multiple trauma patients with acute hemorrhage in general. The relation of tranexamic acid administration on survival in elderly trauma patients with pre-existing anticoagulation is the objective of this study. Therefore, we used the database of the TraumaRegister DGU® (TR-DGU), which documents data on severely injured trauma patients.

Methods: In this retrospective analysis, we evaluated the TR-DGU data from 16,713 primary admitted patients with multiple trauma and age > =50 years from 2015 to 2019. Patients with pre-existing anticoagulation and TXA administration (996 patients, 6%), pre-existing anticoagulation without TXA administration (4,807 patients, 28.8%), without anticoagulation as premedication but TXA administration (1,957 patients, 11.7%), and without anticoagulation and TXA administration (8,953 patients, 53.6%) were identified. A regression analysis was performed to investigate the influence of pre-existing antithrombotic drugs and TXA on mortality. A propensity score was created in patients with pre-existing anticoagulation, and matching was performed for better comparability of patients with and without TXA administration.

Results: Retrospective trauma patients who underwent tranexamic acid administration were older and had a higher ISS than patients without tranexamic acid donation. Predicted mortality (according to the RISC II Score) and observed mortality were higher in the group with tranexamic acid administration. The regression analysis showed that TXA administration was associated with lower mortality rates within the first 24 h in older patients with anticoagulation as premedication. The propensity score analysis referred to higher fluid requirement, higher requirement of blood transfusion, and longer hospital stay in the group with tranexamic acid administration. There was no increase in complications. Despite higher transfusion volumes, the tranexamic acid group had a comparable all-cause mortality rate.

Conclusion: TXA administration in older trauma patients is associated with a reduced 24-h mortality rate after trauma, without increased risk of thromboembolic events. There is no relationship between tranexamic acid and overall mortality in patients with anticoagulation as premedication. Considering pre-existing anticoagulation, tranexamic acid may be recommended in elderly trauma patients with acute bleeding.

KEYWORDS

multiple trauma, TraumaRegister DGU®, hemorrhage, anticoagulation as premedication, tranexamic acid

Introduction

Uncontrolled hemorrhage is one of the leading causes of mortality and morbidity in multiple trauma patients worldwide (1). A high number of trauma patients with bleeding present a coagulopathy on hospital admission (2). The presence of coagulopathy is associated with an increased incidence of multiple organ failure (3).

According to the national S3 guideline, the administration of tranexamic acid (TXA) in multiple trauma patients with massive bleeding is recommended. Several studies have shown that tranexamic acid administration reduces the risk of mass transfusion and mortality in trauma patients (4–6). Especially in patients with acute bleeding, the risk of death can be safely reduced (6). TXA blocks the formation of plasmin by inhibiting the proteolytic activity of plasminogen activators. This inhibits plasmin in its ability to lyse fibrin (7).

However, TXA is rarely used due to the risk of thrombosis in some patient groups (8, 9). Especially if not all pre-existing conditions and medications are known, as in a preclinical emergency setting, there are still reservations about the administration of TXA. Most studies examine polytrauma patients in general but do not focus separately on high-risk groups.

Along with the aging population, multiple trauma in the elderly has increased over the last few decades (10). Reduced physiological reserve and the existence of multiple medical comorbidities present additional challenges to management (10). In contrast to younger trauma patients, elderly patients experience significantly higher mortality rates and complications after multiple traumas (11).

The following study aims to evaluate the administration of TXA in the emergency room management of older multiple trauma patients with pre-existing anticoagulation. We used the TraumaRegister DGU® to evaluate if the administration of TXA is associated with higher survival rates in elderly trauma patients with anticoagulation as premedication and if there is a higher frequency of complications such as thromboembolic events after TXA administration.

Methods

TraumaRegister DGU®

The TraumaRegister DGU® (TR-DGU) of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie, DGU) was founded in 1993. The aim of this multi-center database is the pseudonymized and standardized documentation of severely injured patients.

Data are collected prospectively in four consecutive time phases from the site of the accident until discharge from the hospital: (A) prehospital phase, (B) emergency room and initial surgery, (C) intensive care unit, and (D) discharge. The documentation includes detailed information on demographics, injury patterns, comorbidities, pre- and in-hospital management, a course on intensive care unit, and relevant laboratory findings including data on transfusion and outcome of each individual. The inclusion criterion is admission to the hospital via the emergency room with subsequent ICU/ICM care or reaching the hospital with vital signs and dying before admission to the ICU.

The infrastructure for documentation, data management, and data analysis is provided by the AUC—Academy for Trauma Surgery (AUC—Akademie der Unfallchirurgie GmbH)—a company affiliated to the German Trauma Society. Scientific leadership is provided by the Committee on Emergency Medicine, Intensive Care and Trauma Management (Sektion NIS) of the German Trauma Society. Participating hospitals submit their data pseudonymized into a central database via a web-based application. Scientific data analysis is approved according to a peer review procedure laid down in the publication guideline of the TraumaRegister DGU®.

The participating hospitals are primarily located in Germany (90%), but a growing number of hospitals from other countries contribute data as well (at the moment from Austria, Belgium, China, Finland, Luxembourg, Slovenia, Switzerland, Netherlands, and the United Arab Emirates). Currently, over 28,000 cases from almost 700 hospitals are entered into the database per year. Participation in the TraumaRegister DGU® is voluntary. For hospitals associated with the TraumaNetzwerk DGU®, however, the entry of at least a basic data set is obligatory for reasons of quality assurance.

Study cohort

Primary admitted patients who were treated in Germany between 2015 and 2019 were included (Figure 1). Further including criteria were age $\geq$ 50 years, and the worst injury severity level according to the Abbreviated Injury Scale should be 3 or more (MAIS 3+).

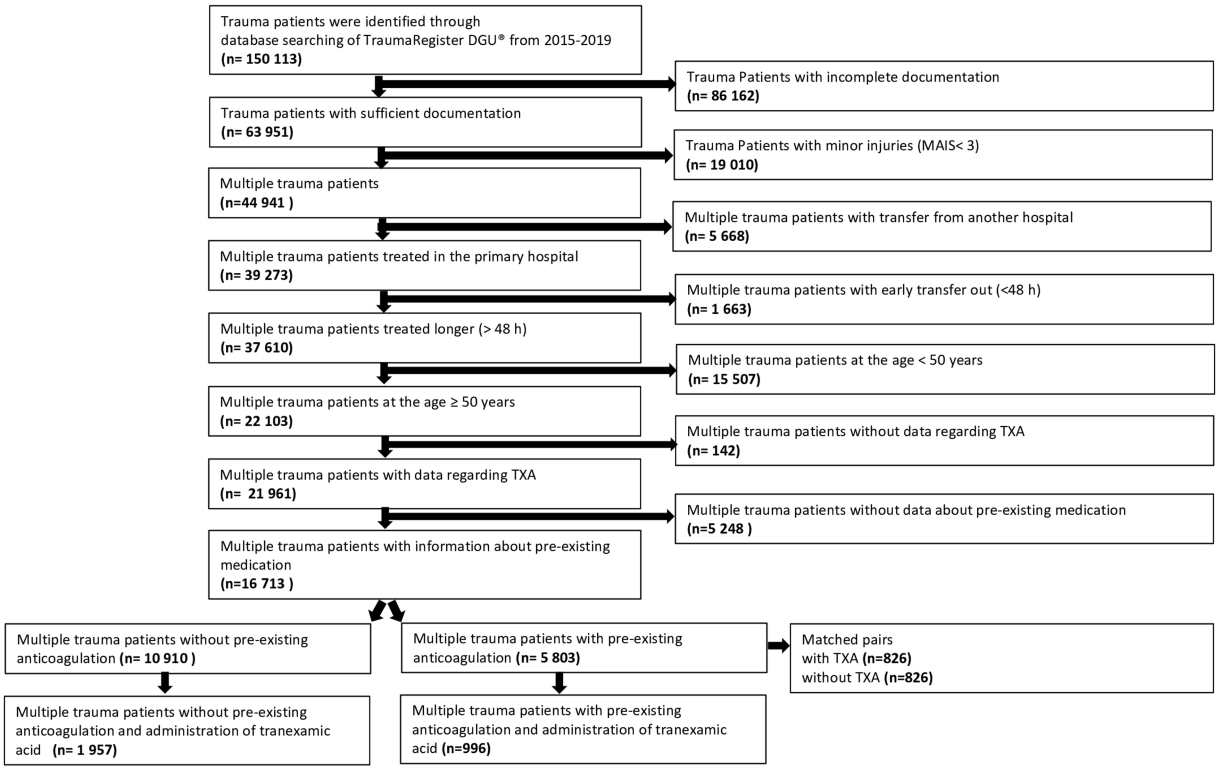

FIGURE 1
Patient selection flow chart of multiple trauma patients with pre-existing anticoagulation and tranexamic acid administration. Multiple trauma patients at the age >50 years and pre-existing anticoagulation were analyzed regarding tranexamic acid administration during trauma care. For the propensity score study, multiple trauma patients with anticoagulation as premedication and tranexamic acid administration were matched with multiple trauma patients with pre-existing anticoagulation without tranexamic acid administration.

Patients treated at local (level 3), regional (level 2), and supra-regional (level 1) trauma centers and whose treatment was documented with the complete dataset were included in the evaluation. The centers are classified in the TraumaNetzwerk DGU® according to the level of care (level I, II, and III) within the German healthcare system (12).

Patients documented with the basic dataset only were excluded since TXA administration was missing. Patients with incomplete data regarding pre-existing anticoagulation were excluded as well. Only primary admissions were considered without transfer-in patients (no data about prehospital TXA) and early transfers out (no outcome data). A total of 16,713 patients qualified for this investigation. Patients were divided into two groups depending on the intake of antithrombotic drugs prior to admission. Again, two subgroups were formed based on the administration of tranexamic acid.

Variables

TXA administration has been documented both in the prehospital setting as well as in the emergency room within 3 h after trauma. Tranexamic acid 0.5–1 g was administered slowly intravenously as an injection solution. It was documented whether tranexamic acid was given preclinically, at the emergency room, or preclinically and at the emergency room. The exact time of administration within 3 h after trauma was not documented.

The outcome was defined as in-hospital mortality, mortality within 24 h after admission, the requirement of blood transfusion until intensive care unit (ICU) admission, hospital stay, stay at ICU, and occurrence of thromboembolic events.

Pre-existing anticoagulation prior to admission was defined as the regular intake of either antiplatelet drugs, vitamin K antagonists, direct oral anticoagulation, or heparinoids. The pre-existing anticoagulation was taken regularly. The information on anticoagulation as prior medication was provided by the patients, relatives, and the general practitioner. Single doses were not included.

The Revised Injury Severity Score II (RISC II) was applied as a prognostic parameter. The RISC II score is validated for risk of death prediction in severely injured patients. Calculation includes type and severity of injury, mechanism of trauma, age, sex, ASA score, pupil reaction and size, motor function, blood pressure, and laboratory parameters such as INR, base excess, hemoglobin, and cardio-pulmonary resuscitation (13).

Study approval

The presented study was approved by the local ethics committee of the medical faculty of Kiel University (D491/21). The publication is in line with the publication guidelines of the TraumaRegister DGU® and registered as TR-DGU project ID-2020-043.

Statistical methods

Statistical analyses were performed with SPSS 24.0 (IBM, Armonk, NY, United States). Continuous and categorical variables are presented as mean with standard deviation (SD) or as numbers (percentages), respectively. Expected mortality was calculated based on the Revised Injury Severity Classification score, version II (RISC II). This score combines 13 different early prognostic factors available shortly after admission. It has been developed and validated with TR-DGU data (13). Multivariable analyses using logistic regression models were performed to identify the adjusted effects of TXA administration on hospital mortality. In addition to the RISC II score, further adjustments were made for the trauma center level of care and pre-existing anticoagulation. Results are presented as odds ratios (OR) with 95% confidence intervals (95% CI). To assess the independent impact of tranexamic acid in patients with anticoagulation as premedication, a propensity score matching was performed. A logistic regression model was used to determine the propensity score, which is the probability of TXA administration (Table 1). Patients with and without TXA administration were then matched according to the propensity score (± 1%). In total, 5,482 patients were available for propensity score matching. Patients with and without tranexamic acid administration were matched. A total of 826 pairs were found. Outcome data were then compared using Pearson's chi-squared test. A significance level of $p < 0.05$ was applied.

Results

A total of 16,713 patients at the age of ≥50 years could be included in this study. In total, 2,953 patients (17.7%) received tranexamic acid (Figure 1). A distinction was made between four groups: patients with pre-existing anticoagulation and administration of tranexamic acid (996 patients, 6%), patients without pre-existing anticoagulation and administration of tranexamic acid (1,957 patients, 11.7%), patients with pre-existing anticoagulation without tranexamic acid (4,807 patients, 28.8%), and patients without both pre-existing anticoagulation and administration of tranexamic acid (8,953 patients, 53.6%).

In summary, 13,760 patients did not receive tranexamic acid (82.3%), 948 patients received tranexamic acid preclinically (5.7%), 1,700 patients received tranexamic acid at the emergency room (10.2%), and 305 patients received tranexamic acid preclinically and at the emergency room (1.8%). Concerning 2,953 patients who received tranexamic acid, 32.1% received tranexamic acid preclinically, 57.6 patients received tranexamic acid at the emergency room, and 10.3% received tranexamic acid preclinically and/or at the emergency room.

Pre-existing coagulation disorders based on regular intake of antithrombotic drugs were present in 5,803 patients (35%, Figure 1). The antithrombotic drugs used by these patients were acetylsalicylic acid (53.7%), direct oral anticoagulants (20.8%), vitamin K antagonists (21.9%), or heparin (2.7%). Trauma patients with pre-existing anticoagulation received tranexamic acid in 996 cases (17.2%) and patients without pre-existing coagulation disorders received tranexamic acid in 1,957 cases (17.9%).

First, we compared patients with and without pre-existing anticoagulation (Table 2). Patients without anticoagulation as premedication (NA) were younger than patients with pre-existing anticoagulation (A) (average age 65 versus 77 years). Patients who received tranexamic acid were younger in both patient collectives (Table 2).

The average ISS was 21.0 in both patient groups, but patients with tranexamic acid administration had a significantly higher ISS (NA: 28.1, A: 25.9). RISC II was significantly higher in the patient group with anticoagulation as premedication (23.6) than in patients without anticoagulation (9). Patients who received tranexamic acid achieved generally a higher RISC II (NA: 20.1, A: 34.7). Hospital mortality was higher in the group with anticoagulation as premedication, both with (36.8) and without tranexamic acid (26.1). The proportion of patients who received blood transfusions was 10 times higher in both patient groups with tranexamic acid administration (Table 2).

To investigate the relationships between pre-existing anticoagulation and tranexamic acid administration on all-cause mortality, we performed a regression analysis with trauma patients with and without anticoagulation at the age of ≥50 years. The administration of tranexamic acid was not associated with lower mortality in the whole patient collective (OR 0.96, 95% CI 0.84–1.09) (Table 3), but the administration of tranexamic acid had a positive effect on mortality within 24 h: OR = 0.84 (0.71–0.99) ($p = 0.041$) (Table 4). The presence of pre-existing anticoagulation is more likely to cause death within 24 h (OR = 1.28 (1.10–1.48) $p = 0.001$).

A regression analysis was performed only for multiple trauma patients (at the age of ≥50 years) with pre-existing anticoagulation. Neither trauma center level of care nor tranexamic acid administration

TABLE 1 Mean age, injury severity score, RISC II score and observed mortality of multiple trauma patients with and without anticoagulant therapy ($n = 16,713$).

	No anticoagulation as premedication (NA)			Anticoagulation as premedication (A)		
	No TXA 8,953 (53.6%)	TXA 1,957 (11.7%)	Total 10,910 (65.3%)	No TXA 4,807 (28.8%)	TXA 996 (6%)	Total 5,803 (34.7%)
Age, years, mean (SD)	65.3 (11.6)	63.0 (10.5)	64.9 (11.4)	77.1 (10.0)	75.1 (10.5)	76.8 (10.1)
ISS, points, mean (SD)	19.5 (9.6)	28.1 (13.5)	21.0 (10.9)	20.0 (9.3)	25.9 (12.2)	21.0 (10.1)
Expected mortality based on RISC II (%)	9.0	20.1	11.0	23.6	34.7	25.5
Hospital mortality, (%), mean	9.8	20.2	11.7	26.1	36.8	28.0
Blood transfusion (%), mean	3.2	33.4	8.6	3.4	32.5	8.4

ISS: Injury severity score, RISC II revised injury severity classification version 2.

TABLE 2 Multivariable analysis using a logistic regression model with overall death as a dependent variable of trauma patients with or without anticoagulation before admission (n = 16,713).

	Regression coefficient	Standard error	Odds ratio (95% CI)	p-value
RISC II score	−0.874	0.016	0.42 (0.40–0.43)	<0.001
Hospital level of care				
Level 1	−0.06	0.07	0.94 (0.82–1.09)	0.411
Level 2	−0.27	0.18	0.76 (0.54–1.08)	0.129
Anticoagulative therapy	0.183	0.056	1.20 (1.08–1.34)	0.001
Administration of TXA	−0.042	0.067	0.96 (0.84–1.09)	0.528

The influence of level of trauma center, pre-existing anticoagulation, and administration of tranexamic acid on death was evaluated. RISC II: revised injury severity classification version 2, TXA: tranexamic acid.

TABLE 3 Multivariable analysis using a logistic regression model with death within 24 hours after admission as a dependent variable of trauma patients with or without anticoagulation before admission (n = 16,713).

	Regression coefficient	Standard error	OR (95% CI)	p-value
RISC II score	−0.79	0.02	0.45 (0.44–0.47)	<0.001
Hospital level of care				
Level 1	−0.18	0.11	0.84 (0.68–1.03)	0.093
Level 2	0.20	0.24	1.22 (0.76–1.96)	0.405
Anticoagulative therapy	0.24	0.08	1.28 (1.10–1.48)	0.001
Administration of TXA	−0.18	0.09	0.84 (0.71–0.99)	0.041

The influence of level of care, pre-existing anticoagulation, and tranexamic acid administration on death within 24 hours after trauma was examined. RISC II: revised injury severity classification version 2, TXA: tranexamic acid.

TABLE 4 Multivariable analysis using a logistic regression model with death during hospital stay (A) death within 24 hours (B) as a dependent variable only of trauma patients with anticoagulation as premedication (n = 5,803).

	Regression coefficient	Standard error	OR (95% CI)	p-value
(A)				
RISC II score	−0.84	0.02	0.43 (0.41–0.45)	<0.001
Hospital level of care				
Level 1	−0.08	0.1	0.92 (0.76–1.11)	0.39
Level 2	−0.26	0.23	0.77 (0.49–1.22)	0.27
Administration of TXA	−0.01	0.1	0.99 (0.83–1.2)	0.95
(B)				
RISC II score	−0.81	0.03	0.44 (0.2–0.47)	<0.001
Hospital level of care				
Level 1	−0.13	0.14	0.88 (0.67–1.14)	0.32
Level 2	0.34	0.30	1.41 (0.78–2.56)	0.26
Administration of TXA	−0.26	0.12	0.77 (0.61–0.98)	0.03

The influence of level of care and tranexamic acid administration on death was examined.

showed an effect on all-cause mortality (tranexamic acid OR = 0.99 (0.83–1.2) (p = 0.95) (Table 1, A). Administration of tranexamic acid showed a positive effect on 24 h-mortality of patients with pre-existing anticoagulation OR = 0.77 (0.61–0.98) (p = 0.05) (Table 1, B).

In order to better compare patients with pre-existing anticoagulation, propensity score matching was performed in patients with and without tranexamic acid administration (n = 5,482). Matching was performed considering different variables listed in Table 5. A total of 826 pairs of patients could be found with identical propensity scores (= probability to receive TXA).

Table 6 presents the data for those matched pairs of propensity scores. Slightly more men received TXA (TXA: 566 (68.5%), No TXA: 519 (62.8%), p = 0.015). In the emergency room, obvious differences occurred for volume administration (TXA: 1,532 ± 1727, No TXA: 959 ± 1,097, p < 0.001) and blood transfusion (TXA: 218 (26.4%), No TXA: 74 (9%), <0.001).

TABLE 5 Multivariate logistic regression analysis with, prehospital TXA' as dependent variable, in patients with anticoagulation therapy before admission (n = 1,652).

	Regression coefficient	Standard error	Odds ratio
Age ≥ 60 years	−0.155	0.137	0.86
AIS abdomen ≥3	0.421	0.150	1.52
AIS extremities ≥3	0.336	0.101	1.40
ISS, per point	0.023	0.004	1.02
Isolated trauma	−0.142	0.107	0.87
Penetrating injury	0.712	0.224	2.04
Systolic blood pressure < 100 mmHg	0.360	0.107	1.43
Helicopter transport	0.497	0.091	1.64
Prehospital treatment			
Intubation	0.171	0.100	1.19
Chest tube	−0.810	0.243	2.36
Pelvic binder	0.775	0.147	2.17
CPR	−0.810	0.229	0.45
I.v. fluid administration (reference: unknown)			
Up to 500 mL	0.059	0.165	1.06
Up to 1,000 mL	0.486	0.173	1.60
Up to 2,000 mL	0.815	0.197	2.26
> 2,000 mL	1.252	0.411	3.50
I.v. fluids 2	0.486	0.173	1.60
I.v. fluids 3	0.815	0.197	2.26
I.v. fluids 4	1.252	0.411	3.50
Hemoglobin ≤ 8 g/dl	0.749	0.162	2.11
Catecholamines	0.929	0.097	2.53
Level 1 trauma center	−0.237	0.114	0.79
Level 2 trauma center	−1.139	0.376	0.32

The calculated probabilities for receiving TXA (rounded percentages) were used as propensity score for the following matching. TXA: tranexamic acid, ASA: American society of anesthesiologists, ISS: injury severity score, SBP: systolic blood pressure, INR: international normalized ratio, i.v.: intravenous, ER: emergency room, Prbc: packed red blood cells, FFP: fresh frozen plasma, RISC II: revised injury severity classification version 2, ICU: intensive care unit, LOS: length of stay.

There were minor differences with regard to RISC II (TXA: 32.4 ± 31.3, No TXA 31 ± 32.9, p = 0.404), mortality within 24 h [TXA: 120 (14.5%), No TXA: 140 (16.9), p = 0.177], and all-cause mortality [TXA: 294 (35.6%), No TXA: 274 (33.2%), p = 0.300]. Differences were not significant.

Hospital stay [TXA: 14 (6-24), No TXA: 12 (4-22), p = 0.006] and ICU length of stay [TXA:7 (2-16), No TXA: 4 (1-12), p < 0.001] were significantly longer for patients who received tranexamic acid (Table 6). We did not find a relevant difference in thromboembolic complications [TXA:26 (3.3%), No TXA 24 (3.1%), p = 0.823].

Discussion

Acute uncontrolled bleeding remains one of the most common causes of death after severe injuries (14). Tolerance to extended blood loss in older patients is limited due to reduced physiological reserve (15, 16).

Blood loss causes hypoperfusion, which leads to tissue damage, immune response, and activation of the coagulation system, resulting in trauma-associated coagulopathy (17). Bleeding-associated coagulopathy correlates, in turn, with the development of organ failure (17).

A key component of trauma-induced coagulopathy represents systemic fibrinolysis (18). Tranexamic acid, an inhibitor of the fibrinolysis system, can reduce blood loss in trauma patients (6). Several studies have documented that tranexamic acid administration reduces mortality in trauma patients without increasing the risk of thromboembolic complications (19, 20). There is little data to date on the effect of tranexamic acid in patients with pre-existing conditions and prior medication.

Depending on the study and patient population, tranexamic acid was used in 10–15% of included multiple trauma patients (4). In the study of Curry et al., only 6% of trauma patients with coagulation disorders and 11.7% without coagulation disorders received tranexamic acid as medication, which seems low considering acute hemorrhage is responsible for 40% of mortality in polytrauma patients (21).

According to manufacturer's guidelines, tranexamic acid should not be administered to patients with certain coagulation disorders,

TABLE 6 We performed propensity score matching in patients with anticoagulation as premedication.

	TXA administered	No TXA	*p*-value
	N = 826	*N* = 826	
Age, years, mean (SD)	75.6 (10.2)	76.1 (10.1)	0.367
Male sex, *n* (%)	566 (68.5)	519 (62.8)	0.015
ASA classification 3/4, *n* (%)	475 (59.6)	486 (61.9)	0.346
Anticoagulant before admission:			
Antiplatelet agents, *n* (%)	427 (51.7)	446 (54.0)	0.349
Vitamin K antagonists, *n* (%)	200 (24.2)	170 (20.6)	0.077
Direct oral anticoagulants, *n* (%)	168 (20.3)	178 (21.5)	0.545
Parenteral anticoagulants, *n* (%)	21 (2.5)	22 (2.7)	0.877
Blunt trauma, *n* (%)	774 (96.6)	778 (96.2)	0.994
ISS, points, mean (SD)	24.4 ± 11.1	23.8 ± 12.0	0.309
SBP preclinical, mmHg, mean ± SD	137.4 ± 39.1	136.3 ± 37.8	0.582
SBP at ER, mmHg, mean ± SD	130.4 ± 37.4	129.2 ± 35.2	0.505
Hemoglobin, g/dL, mean ± SD	11.8 ± 2.5	12.0 ± 2.4	0.044
Base excess, mmol/L, mean ± SD	−2.1 ± 5.1	−2.0 ± 5.2	0.679
INR, mean ± SD	1.6 ± 1.0	1.5 ± 0.8	0.029
I.v. fluids prehospital, mL, mean ± SD	762 ± 511	766 ± 514	0.879
I.v. fluids at ER, mL, mean ± SD	1,532 ± 1,727	959 ± 1,097	<0.001
Expected mortality based on RISC II (mean)	32.4%	31.0%	0.404
ICU LOS, days, median (IQR)	7 (2–16)	4 (1–12)	<0.001
Hospital LOS, days, median (IQR)	14 (6–25)	12 (4–22)	0.006
24 h mortality, *n* (%)	120 (14.5)	140 (16.9)	0.177
Hospital mortality, *n* (%)	294 (35.6)	274 (33.2)	0.300
Blood transfusion before ICU admission, *n* (%)	218 (26.4)	74 (9.0)	<0.001
Mass transfusion (≥ 10 pRBC) (%)	18 (2.2)	2 (0.2)	<0.001
Thromboembolic event, *n* (%)	26 (3.3)	24 (3.1)	0.823
Unconsciousness (GCS 3–8)	253 (31.5%)	240 (30.7%)	0.745
Prehospital CRP (cardiac arrest)	28 (3.4%)	29 (3.5%)	1.00

Patients with tranexamic acid administration were matched with patients without tranexamic acid administration. We investigated the effect of tranexamic acid administration in patients with comparable injury severity. Study outcome after propensity matching ($n = 1{,}652$) is shown in Table 5. TXA tranexamic acid, pRBC packed red blood cells.

consumptive coagulopathy, renal disease, and known seizures. Several preconditions in combination with tranexamic acid administration are associated with a high risk of complications (22, 23). Limited data on trauma patients with special pre-existing conditions and premedication might cause restrained use of tranexamic acid. Increased age of the population has led to a rise in bleeding trauma patients with pre-existing anticoagulation (24). Depending on age and comorbidities, several changes in coagulation such as fibrinogen rise, factor VIII, and VWF rise are found, some fibrinolysis markers increase, and platelets are more active (25, 26). Such patients are not treated uniformly, even in major trauma centers.

In our evaluation, polytrauma patients, both with and without anticoagulation as premedication, who received tranexamic acid were younger and more severely injured than patients without tranexamic acid. Blood transfusion, RISC II, and mortality rate were significantly higher in the groups with tranexamic acid due to patients' age and overall conditions (Table 2). Imach et al. evaluated trauma patients from the TraumaRegister DGU® with and without administration of tranexamic acid without age restriction and showed comparable results in terms of age and injury severity (4). In most evaluations, tranexamic acid was used more in younger patients with hemodynamic instability than in older patients (27, 28). RISCII and the mortality rate of the tranexamic acid group without anticoagulation were comparable with other evaluations (4). RISC II and the mortality rate of patients with anticoagulation as premedication and tranexamic acid were significantly higher than the group without anticoagulation as premedication (Table 2). RISC II includes worst and second-worst injury, age, INR, blood pressure, hemoglobin, and ASA (13). Higher ASA scores, low hemoglobin, and low blood pressure cause higher RISCII and mortality in patients with pre-existing anticoagulation.

Pre-existing coagulation disorders made mortality likely after trauma, while administration and timing of tranexamic acid within the first 3 h had no significant effect on total mortality when all patients at the age of ≥50 years were included. Considering the mortality within the first 24 h after trauma, death became more likely

with pre-existing anticoagulation while the administration of tranexamic acid made death less likely.

Our results correlated with previous findings of patients without age limitation, which demonstrated a reduction in mortality with the administration of tranexamic acid in the first hours after trauma (4, 29). A relation in all-cause mortality in patients receiving anticoagulation as premedication could not be demonstrated in our regression analysis after tranexamic acid administration. Regarding the associations of tranexamic acid with total mortality, there seems to be a great variability depending on the study population, medical care, and pre-existing conditions (30). Using sensitivity analysis, Karl et al. demonstrated reduced 1-month mortality after tranexamic acid administration in the context of a meta-analysis (30). Depending on injury severity and timing of tranexamic acid administration, Neeki et al. demonstrated a reduction in all-cause mortality (31). The combination of injuries may also play a role in the associations of tranexamic acid with all-cause mortality. A reduction in all-cause mortality could not be detected in patients with severe brain injuries.

Result heterogeneity is caused by patient characteristics, such as injury severity, since not all evaluations examined patient groups of comparable age, similar injuries, and injury severity (30).

The timing and dosage of tranexamic acid also play a role. Tranexamic acid administration has an early antifibrinolytic effect within 4 h after trauma (32). Administration of tranexamic acid treatment within 3 h of injury reduces the risk of hemorrhage death by approximately one-third (19, 23). The benefit of tranexamic acid administration decreased by 10% for every 15 min of treatment delay until 3 h after injury, when there was no benefit (33).

Additionally, due to the manufacturer guidelines, the elimination half-life of tranexamic acid is approximately 3 h. After intravenous administration of 10 mg/kg body weight, approximately 90% of tranexamic acid is excreted within the first 24 h. Therefore, the effect of tranexamic acid is limited by time (34).

Older trauma patients are known to have higher rates of complications after multiple trauma than young patients (35). Pre-existing medical conditions have an impact on mortality rate but lose their effect with increasing injury severity (36). For better comparability, a propensity score matching was performed to compare patients with pre-existing anticoagulation at the same age with similar injury severity.

Lower mean hemoglobin concentration and higher mean INR (international normalized ratio) were demonstrated in the group with tranexamic acid administration. The INR and Hb (hemoglobin) are variables that are included in RISC II (13). We could not find a significant difference in RISC II between both groups.

Patients of the tranexamic acid group demonstrated higher blood loss, which probably led to the administration of tranexamic acid. As a result of higher blood loss, blood transfusions were given more frequently in the group with tranexamic acid administration (Table 6). Blood transfusion and mass transfusion are often associated with more medical interventions, longer hospital stay, and higher mortality (37). Patients with tranexamic acid administration had a longer hospital stay and a longer stay at ICU. Transfusion of blood products and the number of transfused units show a correlation with thromboembolic events (38). Although transfusion of blood and mass transfusion were significantly higher in the group receiving tranexamic acid, no more thromboembolic events occurred than in the group without tranexamic acid administration. Therefore, older trauma patients with anticoagulation as premedication do not show more complications after tranexamic acid administration, just like younger multiple trauma patients with tranexamic acid administration (39).

Bleeding and mass transfusions are associated with an increase in mortality (37). Significant higher mass transfusion in the tranexamic acid group did not cause higher mortality than patients without tranexamic acid administration.

The tranexamic acid relation appears to be less pronounced in older trauma patients than in younger patients (40). Patients with anticoagulation as premedication and tranexamic acid administration appear to have a survival advantage in the first 24 h after trauma, which disappears in terms of total mortality.

Conclusion

Pre-existing anticoagulation in elderly patients has an impact on mortality after polytrauma. After tranexamic acid administration, a reduction in mortality was demonstrated compared to the calculated RISC II. A reduction in all-cause mortality for all patients at the age of >50 years could not be verified. A reduction in the 24 h-mortality could be demonstrated for patients with anticoagulation as premedication and tranexamic acid administration.

In propensity score matching, no higher complication rates were demonstrated in the tranexamic acid group. Despite lower hemoglobin and more mass transfusions, the tranexamic acid group was associated with a similar mortality rate.

Limitations

This is a retrospective analysis of data provided by the TraumaRegister DGU®. Data of patients at the age of ≥50 years were included. Most studies define older trauma patients as above the age of 60, but different age limitations can be found in the literature. For our evaluation, we chose the age limit of 50 years because the share in anticoagulation as premedication increases significantly at this age. The risk of complications as thromboembolic events also increases from the age of 50.

We focused on pre-existing anticoagulation and donation of tranexamic acid. The information on anticoagulation as premedication and regular use was provided by the patient, family members, and the family doctor. Information on patient compliance is not documented in the TraumaRegister DGU®.

Multiple trauma patients who died before hospitalization were not included. Patients who were transferred after admission could not be included due to missing data. Only the data of patients up to discharge from the primary treating hospital were evaluated.

One pitfall of large trauma registries is that a complete data set is not available for every patient, so only existing data can be evaluated. Data on the ASA score and on anticoagulation as premedication were evaluated. Precise information about pre-existing conditions and additional prior medication is not documented in the TraumaRegister DGU®.

The included patients were treated by different emergency physicians and emergency teams, whose level of training and experience in emergency care was not considered.

For this reason, the results and conclusions on older trauma patients with anticoagulation as premedication and tranexamic acid administration are limited.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The presented study was approved by the local ethics committee of the medical faculty of Kiel University (D491/21). The publication is in line with the publication guidelines of the TraumaRegister DGU® and registered as TR-DGU project ID-2020-043.

Author contributions

SF-O: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. GF: Conceptualization, Investigation, Writing – original draft. NK: Conceptualization, Investigation, Writing – original draft. RL: Data curation, Methodology, Writing – review & editing. SL: Methodology, Supervision, Writing – review & editing. OS: Methodology, Supervision, Writing – review & editing. TK: Methodology, Supervision, Writing – review & editing. MM: Methodology, Supervision, Writing – review & editing. AS: Supervision, Writing – review & editing. TraumaRegister DGU: Data curation, Writing – review & editing.

TraumaRegister DGU

The TraumaRegister DGU® (TR-DGU) of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie, DGU) is a multicenter database. The aim of the TraumaRegister DGU® is a pseudonymized and standardized documentation of severely injured patients.

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Conflict of interest

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High vs. low tidal volume and pulmonary complications in patients with cervical spinal cord injury on mechanical ventilation: systematic review

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Introduction: Cervical spinal cord injury (CSCI) patients on mechanical ventilation often lack standardized guidelines for optimal ventilatory support. This study reviews existing literature to compare outcomes between high tidal volume (HTV) and low tidal volume (LTV) strategies in this unique patient population.

Methods: We searched for studies published up to August 30, 2023, in five databases, following a PECO/PICO strategy. We found six studies for quantitative analysis and meta-analyzed five studies.

Results: This meta-analysis included 396 patients with CSCI and mechanical ventilation (MV), 119 patients treated with high tidal volume (HTV), and 277 with low tidal volume (LTV). This first meta-analysis incorporates the few studies that show contradictory findings. Our meta-analysis shows that there is no significant statistical difference in developing VAP between both comparison groups (HTV vs. LTV) (OR 0.46; 95% CI 0.13 to 1.66; $p > 0.05$; I^2: 0%), nor are there differences between the presence of other pulmonary complications when treating with HTV such as acute respiratory distress syndrome (ARDS), atelectasis, onset of weaning.

Conclusion: In patients with CSCI in MV, the use of HTV does not carry a greater risk of pneumonia compared to LTV; in turn, it is shown as a safe ventilatory strategy as it does not establish an increase in other pulmonary complications such as ARDS, atelectasis, the onset of weaning nor others associated with volutrauma. It is necessary to evaluate the role of HTV ventilation in this group of patients in primary RCT-type studies.

KEYWORDS

cervical spinal cord injury, tidal volume, mechanical ventilation, ventilator associated pneumonia, systematic review, meta-analysis

1 Introduction

Cervical spinal cord injury (CSCI) usually entails the need for constant ventilatory support as mechanical ventilator (MV), requiring mechanical ventilation immediately after the injury in most cases (1–3).

The management of ventilatory support in CSCI patients is not standardized according to their specific needs, since existing management protocols based on multiple clinical trials for optimal mechanical ventilation settings are designed for patients with acute respiratory distress syndrome (ARDS) without neurological injury (4–7). In these protocols it is suggested that an optimal tidal volume (TV) is 4 to 6 ml or 6 to 8 ml, since this range is considered safe due to the lower incidence of atelectasis, barotrauma and mortality (8, 9). However, there is a lack of research regarding optimal ventilator settings in people with acute CSCI.

Currently guidelines on acute spinal cord injury recommend high tidal volume (HTV) up to of >15 ml/kg predicted body weight (10). Peterson et al. (4) carried an investigation in patients with CSCI connected to MV and observed that patients managed with high tidal volumes had a lower frequency of ventilator-associated pneumonia (VAP), shorter duration of weaning time, and lower incidence of atelectasis compared to a low tidal volume group (LTV) (4). Other studies performed in CSCI populations reported that HTV management was not associated with major complications, suggesting that it is safe to use (5, 7, 11–13).

In CSCI patients with HTV exposure, the maximum values of airway pressure with higher volumes than the standard do not usually exceed 30 cm H_2O due to the flaccidity of muscle tone in these patients, representing a potential benefit (14, 15). On the contrary, LTV fail to compensate for profound muscle weakness, and is associated with an increased need for sedation, mucosal obstruction, decreased surfactant production and increased incidence of atelectasis (16–21). It has even been reported that in quadriplegic patients a lower TV translates into greater dyspnea (11).

Due to the lack of consensus and a high level evidence on adequate ventilatory support settings in the CSCI population, we performed a systematic review and meta-analysis to revisit the recommendations that are being widely followed and provide data that will support decision making in regards to the respiratory support.

2 Materials and methods

2.1 Search strategy

Our systematic review was performed following the guidelines outlined in the Cochrane Handbook for Systematic Reviews (22), PRISMA (23), and AMSTAR 2 (24). The protocol was preregistered in PROSPERO (CRD42023452844). Thorough searches were conducted across multiple databases, including MEDLINE (PubMed), Scopus, EMBASE, Web of Science, Science Direct and the Cochrane Library. Database screening involved the application of thesaurus (MeSH, Emtree, etc.), free terms, and their synonyms. Using boolean operators, we implemented our PECO/PICO strategy (Population: adult patients with cervical spinal cord injury in mechanical ventilation; Exposure: ventilation with high tidal volume; Comparator: ventilation with normal tidal volume; Outcome: ventilator-associated pneumonia OR intrahospital mortality OR total weaning days OR other pulmonary complications). Keywords included terms related to exposure, such as "cervical spinal cord injury" OR "cervical spinal cord trauma" OR "tidal volume," and outcome-related terms, such as "ventilator-associated pneumonia" OR "pulmonary complications." The detailed search strategy is available in the (**Supplementary Table 1A**).

All the articles identified through primary and secondary screenings were compiled using Zotero® 6.0.15. Following the duplicate removal, the documents were stored in the Rayyan® tool, where two authors (EDMR and MCCC) conducted individual screenings of titles and abstracts independently (blinded). The selection of studies was achieved through consensus, and in instances of disagreement, a third researcher served as the arbitrator (GAVT). The chosen papers underwent a second full-text review to assess eligibility. A secondary manual search of reference lists and citing articles of included publications were also reviewed to increase the identification of relevant studies. The selection process is explained in detail in **Figure 1**.

2.2 Selection criteria

We included observational studies (RCS) and randomized controlled trials (RCTs) that included adult patients (≥18) diagnosed with CSCI in need of MV assistance for more than 2 weeks and less than 6 months, with cervical lesions classified as AIS A, B, or C and initiated without pre-existing pulmonary pathology. We included articles published up until August 30, 2023, with no restrictions on date or language. Case reports, case series, and duplicated publications were excluded.

2.3 Outcomes

The primary outcome the frequency of VAP, defined as the occurrence or progression of new pulmonary infiltrates with at least two of three signs: temperature >38 or <36, leukocytosis or leukopenia, or left deviation of immature forms (10%), along with tracheobronchial purulent discharge (11, 12). Secondary outcomes included the presence of acute respiratory distress syndrome (ARDS), atelectasis, and composite mortality (VAP and overall mortality).

2.4 Data extraction

Two independent researchers, blindly, gathered and extracted relevant details of each included study using and standardized spreadsheet, including authors names, country and year of publication, clinical and epidemiological characteristics of the population, number of participants and cases, measures of association, confounding factors, and the outcomes. For dichotomous and time-to-event variables, we compiled odds ratios (OR), risk ratios (RR) and hazard ratios (HR) with 95% confidence intervals (CI 95%). Missing data were reported when appropriate.

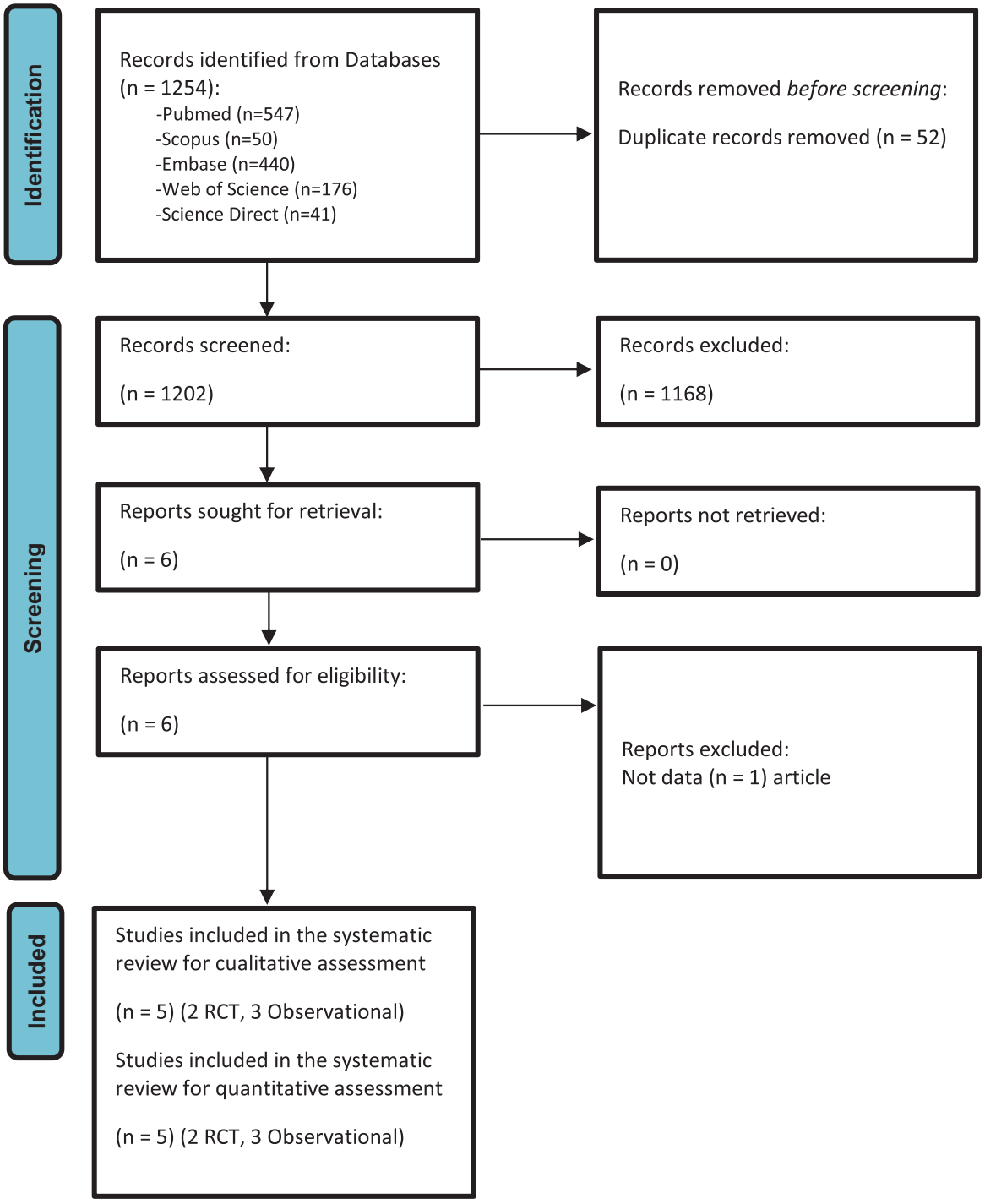

FIGURE 1
PRISMA 2020 flow diagram of the selection process of the primary studies included.

2.5 Statistical analysis

We used the Mantel-Haenszel method in the meta-analysis to pool adjusted ORs with 95% CIs. All studies reported pooled ORs, none RRs. We conducted this meta-analysis using R® 4.2.226 software. To summarize the quantitative synthesis, we used forest plots with the library meta, function metabin, and Mantel-Haenszel method with Restricted Maximum Likelihood (REML) for tau (2). Our protocol stated that we would examine heterogeneity among studies with Cochran's *Q*-test and Higgins I^2 statistic. If heterogeneity was not statistically significant ($p > 0.10$, I^2 statistics <40%), we would use a fixed effects model. On the other hand, we would use a random effects model if heterogeneity was statistically significant (22). We conducted sensitivity a using the function InfluenceAnalysis. Subgroup analysis could not be performed due to the small number of patients in the studies collected.

2.6 Quality assessment

We assessed the potential risk of bias using both the Risk Of Bias In Non-randomized Studies–of Exposure (ROBINS-E) (25) and the Cochrane risk-of-bias tool for randomized trials (RoB 2) (26). To examine the possibility of publication bias, we employed a funnel plot and Egger's test calculation (27).

Two researchers (EDMR and MCCC) assessed the certainty of the evidence (CoE) of the study outcomes for each outcome based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria (28, 29). Any discrepancies between the reviewers were resolved through discussion with the leading researcher (GAVT).

3 Results

3.1 Search results and study characteristics

Six records were included (4, 5, 7, 11, 12, 30) in the qualitative synthesis in our review (**Table 1**). Afterward, five articles remained for the meta-analysis (**Supplementary Table 1B**), three observational studies (4, 7, 10) and two RCTs (11, 12) (**Figure 1**); with a total of 396 MV patients enrolled, 119 patients with HTV, and 277 with LTV. Among the studies included for qualitative analysis, five were conducted in the USA (4, 5, 7, 11, 30) and one in India (12).

In this investigation, the authors use different definitions about TV, but in general, HTV are considered to be values greater than 15 ml/kg. For example, Peterson: HTV 20 ml/kg, LTV median of 15 ml/kg; Wong: HTV 20 ml/kg, LTV 8–10 ml/kg; Fenton: HTV 20 ml/kg LTV 10 ml/kg; Korupolu: HTV greater than 15 ml/kg LTV less than 15 ml/kg; Hatton: HTV initiates an up-titration protocol for TV from 10 to 20 ml/kg considering this value finally, LTV or standard less than 10 ml/kg; Sengupta HTV up to 15 ml/kg LVT 6–8 ml/kg).

Therefore, TV over 15 ml/kg are considered HTV, and volumes less than this are considered standard or LTV since the controls usually have less than 10 ml/kg except for Peterson (4, 5, 7, 11, 12, 30). The primary outcome across all studies was the presence of VAP, defined as the occurrence or progression of new pulmonary infiltrates with at least two of three signs: temperature >38 or <36, leukocytosis or leukopenia, or left deviation of immature forms (10%), along with tracheobronchial purulent discharge (11, 12). The HTV group developed fewer than 50 cases of VAP, while the LTV group had 130 cases.

Additional demographic characteristics of the study population are documented in **Table 1**.

3.2 Risk of bias in studies

Among the five studies included in our meta-analysis, two were RCTs assesed as "some concerns" risk of bias (11, 12), attributable to the absence of blinding, but no other transgressions were identified in other stages of the study protocol. In contrast, two RCS studies were assesed as "some concerns" risk of bias (7, 30) and one "high" risk of bias (4) (**Table 2**).

3.3 Risk of VAP

We conducted an initial meta-analysis including five studies (two RCTs and three observational studies). The analysis revealed that among 119 patients subjected to HTV, 50 exhibited VAP, whereas among 277 patients receiving LTV, 130 developed VAP. The meta-analysis indicated an absence of a significant relationship between the presence of VAP and HTV used (OR 0.78; 95% CI 0.20 to 3.02; $p > 0.05$), with an unacceptably high heterogeneity (I^2: 63%) (**Figure 2A**).

Due to the limited number of studies, subgroup analysis could not be performed. However, a sensitivity analysis through Influence Analysis revealed that excluding Hatton et al. (30), who behaved as an outlier (**Figure 2B**), the overall results showed a trend indicating that ventilation with HTV may provide protection against VAP (OR 0.46; 95% CI 0.13 to 1.66; $p > 0.05$) with no heterogeneity (I^2: 0%) (**Figure 2C**).

3.4 Risk of VAP and mortality

Only three studies assessed a composite outcome (VAP and mortality) (7, 12, 30). There was no significant difference in VAP and mortality rates among patients ventilated with both HTV and LTV (OR 1.04; 95% CI 0.04–29.27) with unacceptable high heterogeneity (I^2: 84%) (**Figure 3A**). Upon further investigation of heterogeneity using Influence Analysis, it was identified that Korupolu et al. (7) acted as a significant outlier (**Figure 3B**). Upon excluding this, the analysis demonstrated that ventilation with HTV emerged as a protective factor for the composite outcome under consideration (OR 0.48; 95% CI 0.30 to 0.79; $p < 0.05$) with no heterogeneity (I^2: 0%) (**Figure 3C**).

3.5 Risk of other pulmonary complications

When analyzing potential complications associated with HTV, in terms of atelectasis, there is no heightened occurrence in the HTV compared to the LTV group (OR 0.45; 95% CI 0.02 to 9.28; $p > 0.05$), with no heterogeneity detected (I^2: 0%). Similarly, the incidence of complications after tracheostomy did not differ between the HTV and LTV groups (OR 0.45; 95% CI 0.00 to 165.22; $p > 0.05$) without heterogeneity (I^2: 0%). The most recent study by Sengupta et al. (12) exclusively provides data on ARDS showing no significant difference between the HTV and LTV ventilation groups (OR 0.30; 95% CI 0.08 to 1.11; $p > 0.05$).

It was not feasible to conduct a meta-analysis for other crucial outcomes, as these data were presented solely in a single study, including parameters such as the time of weaning onset and isolated mortality (**Figure 4**).

TABLE 1 General characteristics of included studies.

References, country	Design	Participants	Exposition	Outcome	Adjustment factors	OR / RR / HR (95% CI)
Peterson et al. (4), EEUU	RCS	Patients with complete tetraplegia for injury at the C3-C4 level, need for 24 h ventilatory support at admission, and successful weaning at discharge between 1983 and 1993. *N* = 42 patients: 19 with high tidal volume ventilation (HTV) and 23 with low tidal volume (LTV). The mean age of the HTV group was 31 years, and of the LTV group was 29 years. Of the total number of patients, 5 were women.	Mechanically ventilated patients who at 2 weeks after admission had an inspiratory tidal volume greater than 20 ml/kg (mean = 25.3 ml/kg; range = 20.3 ± 32.2 ml/kg) vs. patients with inspiratory tidal volume less than 20 ml/kg (mean = 15.5 ml/kg; range = 11.6 ± 19.4 ml/kg).	Successful weaning, duration of mechanical ventilation, pneumonia.	None	No measures of association are reported
Wong et al. (5), EEUU	RCS	Patients with acute tetraplegia due to upper cervical spinal cord injury (C1–C4) admitted 2 years prior to the start of the study. N: 24. Of which 22 were males and 2 females. Mean age was 33.4 years (SD: 16.6). Patients of different ethnicities [African-American (N: 3), Asian (N: 3), Hispanic (N: 7) and white (N: 11)], and etiologies (gunshot wound, motor vehicle accident, fall, diving accident, cervicomedullary tumor, bicycle accident, sports accident) were included. Body mass index had a mean of 25.82 (SD: 16.6).	Quadriplegic patients who received respiratory support with MV according to the protocols of the center to which they were admitted (tidal volume from 12 ml/kg ideal body volume, high-frequency percussive ventilation, mechanical insufflation and exsufflation) vs. baseline respiratory status at the time of admission to the center. Consider HTV at 20 ml/kg vs. standard volumes 8–10 ml/kg	AIS impairment classification, incidents of pneumonia, MV disconnection attempts, types of intervention provided in ventilatory support, patient respiratory findings.	None	No measures of association are reported
Fenton et al. (11), EEUU	RCT	Patients older than 18 years with subacute traumatic tetraplegia less than 6 months, C3–C6 level injuries, non-functional motor preservation as assessed by the AIS scale and requiring continuous mechanical ventilation were randomized to the standard or high tidal volume group. *N* = 33. Patients with diaphragmatic paralysis were excluded	All patients were initially ventilated at 10 ml/kg ideal weight with a PEEP of 5 cm H_2O for 72 h and then randomized to ventilation with standard tidal volume (10 ml/kg PEEP) or high tidal volume (20 ml/kg PEEP). The use of PEEP is the standard of care at this center and was maintained at 5 cm in both groups.	Safety of exposure to high tidal volumes, weaning time, incidence of pulmonary events (pneumonia, barotrauma, ARDS).	None	There was no significant difference in the number of days to weaning between the two treatment groups. The odds of adverse pulmonary events did not differ between the two groups, and the odds of developing VAP did not differ between the two groups. OR = 1.56 (p = 0.1597).
Korupolu et al. (7), EEUU	RCS	Patients with spinal cord injury requiring mechanical ventilation with tracheostomy admitted between 2015 and 2019. *N* = 140. Patients with injury older than 1 year, ARDS, younger than 18 years, severe dysphagia were excluded.	Patients were divided into two groups according to the maximum VT received calculated as ml/kg PBW, patients who received a volume less than 15 ml/kg were included in the moderate VT group (VTM = 50), while those who received a volume greater than 15 ml/kg were included in the high VT group (HTV = 34).	Incidence of pneumonia, adverse events, time elapsed from admission to weaning.	Age, sex, tidal volume at admission	Incidence of pneumonia in HTV vs. MTV. RR = 4.3 p = 0.01; CI 95% 1.5–12, the probability of pulmonary adverse effects in the HTV vs. MTV group. OR = 5.4; CI 95% 1.8–17

(Continued)

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TABLE 1 (Continued)

References, country	Design	Participants	Exposition	Outcome	Adjustment factors	OR / RR / HR (95% CI)
Hatton et al. (30), EEUU	RCS	Patients with acute cervical SCI due to trauma older than 16 years admitted to that center between the years 2011 to 2018. $N = 181$. Patients with MV less than 2 days, ARDS and a score less than 5 on the abbreviated head injury scale were excluded. Median age was 47 years.	Patients on MV who received tidal ventilation at high volume (mean tidal volume: 10.8 cc/kg PBW) vs. ventilation at standard volume (mean tidal volume: 7.6 cc/kg PBW). HTV initiates an up-titration protocol for TV from 10 to 20 ml/kg considering this value finally, LTV or standard less than 10 ml/kg	Ventilator-associated pneumonia, days from admission to VAP, days from admission to tracheostomy, ventilatory dependency at discharge, discharge disposition, hospital mortality.	Age, ISS, level of injury, type of trauma, completeness of spinal cord injury, mechanical ventilator dependence on day 30, hospital stay.	Ventilation to HTV is associated with an increased risk of pneumonia. RR = 1.96 95% CI 1.55–2.17, $p = 0.06$ HTV was also associated with increased risk of ventilator dependency. RR = 2.07 95% CI 1.48–2.71 $p < 0.001$.
Sengupta et al. (12), India	RCT	Patients with acute traumatic cervical spinal cord injury admitted to NICU within 24 h of injury with requirement for mechanical ventilation, admitted between September 2018 and April 2019. $N = 56$. Patients with associated head or chest injury, history of aspiration, OSA, body mass index greater than 30 kg/m^2 were excluded.	Patients were randomly assigned by computerized block system to two groups, high tidal volume group (12–15 ml/kg IBW) and low tidal volume group (6–8 ml/kg IBW).	Successful weaning, barotrauma, atelectasis, VAP, ARDS, duration of treatment, hospital stay, mortality	None	No measures of association are reported

TV, volume tidal; HTV, high tidal volume; LTV, low tidal volume; RCS, retrospective cohort study; RCT, randomized controlled trial; ISS, injury severity score; AIS, abbreviated injury scale; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome; VAP, ventilator associated pneumonia; ICU, intensive care unit; NICU, neurotrauma intensive care unit; IBW, ideal body weight; PBW, predicted body weight.

TABLE 2 Risk of bias of the included studies.

References, country	Study design	Tool	Conclusion
Peterson et al. (4), EEUU	RCS	ROBINS-E	High risk
Wong et al. (5), EEUU	RCS	ROBINS-E	High risk
Fenton et al. (11), EEUU	RCT	RoB 2	Some concerns
Korupolu et al. (7), EEUU	RCS	ROBINS-E	Some concerns
Hatton et al. (30), EEUU	RCS	ROBINS-E	Some concerns
Sengupta et al. (12), India	RCT	RoB 2	Some concerns

RCS, retrospective cohort study; RCT, randomized controlled trial; ROBINS-E, risk of bias in non-randomized studies–of Exposure; RoB 2, version 2 of the Cochrane tool for assessing risk of bias in randomized trials.

3.6 GRADE assessment

We used GRADE to assess the certainty of evidence (CoE) for the presence of VAP in five studies that involved 396 patients. Despite the small number of studies, we found no evidence of publication bias [Egger's test (27): 1.79; 95% CI −3.14 to 6.72; $p > 0.1$] (**Figure 5**). **Table 3** shows that the percentage of VAP in the HTV group was lower (−6.1%, 95% CI −27.7 to 20), but this difference was not statistically significant with a low certainty of evidence.

4 Discussion

This is the first systematic review and meta-analysis that investigates the effect of MV with HTV compared to LTV in patients with CSCI and its association with pulmonary complications and other undesirable respiratory outcomes. We found that there is no significant difference in the presence of VAP as the main outcome in patients with CSCI on MV if HTV vs. LTV is used (OR 0.48; 95% CI 0.30 to 0.79; $p < 0.05$; I^2: 0%). In turn, there is no significant difference regarding the frequency of pulmonary complications such as ARDS, atelectasis, complications after TQT or delays on initiation of weaning in the HTV group compared to those in the LTV group. However, due to the very limited number of primary studies, the results are inconclusive and should be interpreted with caution.

The main complication in patients with CSCI is VAP, which causes significant morbidity and mortality. Therefore, it is necessary to prevent it and start the weaning the patient with CSCI from the MV as soon as possible; only then can the quality of life be improved and healthcare costs reduced (31–34). Poor lung expansion and secretion clearance lead to the development of pneumonia (35). Therefore, the concept of using HTV in patients with CSCI lies in the fact that the ventilatory pathophysiology in patients with CSCI is different from that in a critically ill patient with lung injury, given that there is less compliance of the respiratory system, composed of the thoracic

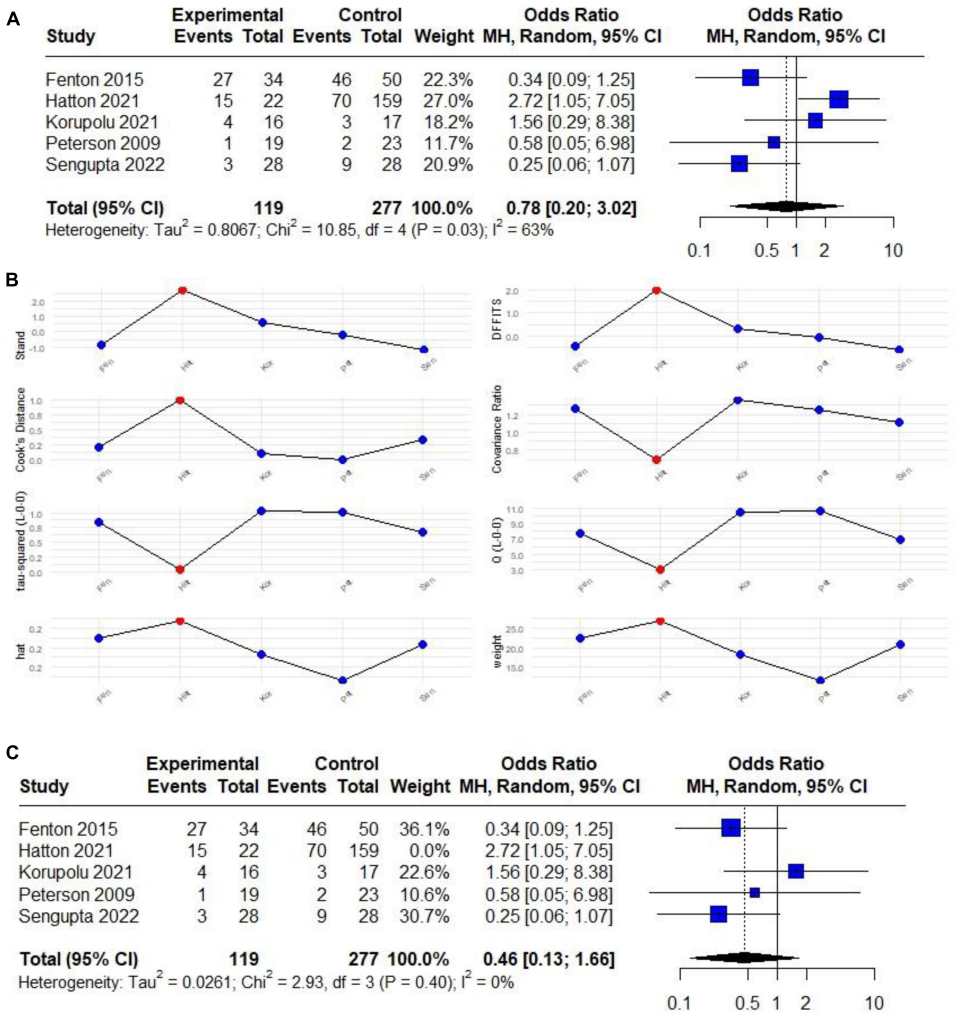

FIGURE 2
(A) Forest plot of the effect of HTV compared with LTV on the risk of developing VAP in patients with CSCI (RCTs and observational) studies. **(B)** Plot of the influence analysis considering (RCTs and observational) studies included in the initial meta-analysis to determine a high heterogeneity, revealing that Hatton behaves like an outlier study. **(C)** Forest plot of the effect of HTV compared with LTV on the risk of developing VAP in patients with CSCI without outlier study.

cage and lung parenchyma. Additionally, the absence of adequate use of abdominal muscles makes achieving adequate TV for these patients more challenging (16, 35, 36). It is reasonable to think that using HTV would lead to controlled overdistension, inducing more outstanding production of surfactant in type II pneumocytes and the alveoli and, therefore, prevent complications such as VAP and atelectasis, among other pulmonary complications (11, 12, 35). Something similar is based on the fact that Gattinoni and Pesenti's concept of "baby lung" does not intuitively apply to the generally healthy lungs of patients with CSCI. Tetraplegic patients often experience air hunger when LVT ventilation is used, even with normal $PaCO_2$, and there is evidence that HTV ventilation may improve weaning success from MV (37, 38).

There are only two RCTs published to date that evaluate MV-dependent CSCI patients and outcomes associated with pulmonary complications (11, 12). Sengupta et al. (12) carried out an RCT, the most currently published, in patients with CSCI where they evaluated the use of HTV compared to LTV and its effect on outcomes such as days to achieve MV release, VAP, atelectasis, and ARDS, enrolling a total of 28 patients for each study group (experimental and control). They found that although there is a higher frequency of VAP in the LTV group compared to HTV (32.14 vs. 10.71%, p: 0.05), there is no statistical significance. The author, when evaluating the role of using HTV with respect to the presence of ARDS, length of hospital stay, and use of vasopressor support, did not find significant differences concerning the LTV group. Only 4 (14%) patients with ARDS were in the HTV group compared to 10 patients (36%) in the LTV group. However, without statistical significance ($p = 0.14$), although there is no data on the PEEP values used in the ARDS groups, higher peak pressure values are shown in HTV vs. LTV (29 vs. 19 mmHg, $p < 0.01$), probably attributed to HTV and PEEP but without more significant evidence of injuries due to barotrauma (pneumothorax, VILI, among others). This demonstrates that the use of HTV is safe. This study is one of the few that assesses mortality as an isolated outcome, where no difference is evident, considering more deaths in the LTV group (9 patients, 37%) compared to the

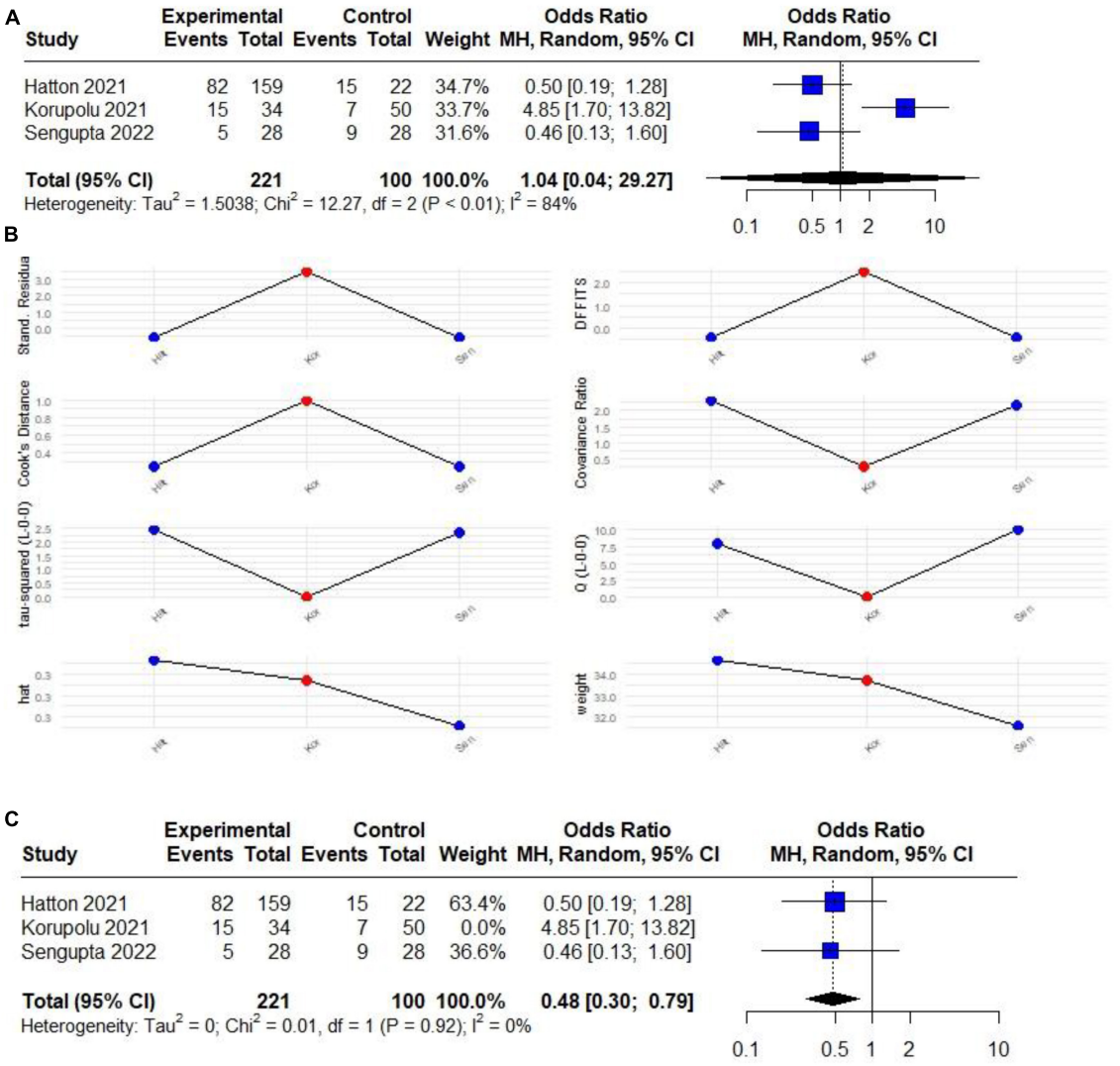

FIGURE 3
(A) Forest plot of the effect of HTV compared with LTV on the risk of developing a composite outcome (VAP and mortality) in patients with CSCI (RCTs and observational) studies. **(B)** Plot of the influence analysis considering (RCTs and observational) studies included in the initial meta-analysis to determine a high heterogeneity, revealing that Korupolu behaves like an outlier study. **(C)** Forest plot of the effect of HTV compared with LTV on the risk of developing a composite outcome (VAP and mortality) in patients with CSCI without outlier study.

HTV group (5 patients, 18%), but without statistical significance ($p = 0.22$).

On the other hand, Fenton et al. (11) conducted an RCT with 35 tracheotomized patients with CSCI (at level C3-C6) MV dependant, using high TV (HTV, experimental group) at values of up to 20 ml/kg per PBW compared to the control group with 10 ml/kg by PBW of TV (LTV, control group). They found no significant difference in the frequency of VAP in both groups (OR 1.56; $p > 0.05$). Of the total of 7 VAPs found, four were from the LTV group, and three were from the HTV group. They also did not find a significant difference in the presence of ARDS or other complications resulting from barotrauma, concluding that it may be safe to use HTV in patients with CSCI based on those above and on the quantification of forced vital capacity (FVC) of both groups of 1231 ml (HTV group) and 1122 (LTV group), with no significant difference ($p > 0.05$). These findings suggest that using HTV is not harmful and should be evaluated in RCTs with larger population.

In contrast to the two RCTs mentioned, a RCS carried out by Korupolu et al. (7) evaluated the use of HTV as a risk factor for VAP, incorporating 84 patients with CSCI tracheostomized on MV, making up the HTV group with 34 patients and 50 patients in the LTV group. They found that there is a greater risk of VAP with the use of HTV (RR 4.3; 95% CI 1.5 to 1.2; p: 0.01), and although in the general characteristics of the patients, the HTV group has a TV (ml) of 875 vs. 750 in the LTV group, and in the same way the peak pressure (mmHg) 21 vs. 19, respectively; they conclude in the multivariate analysis that the increase of 1 ml in the TV is associated with a lower risk of VAP (RR 1.28; 95% CI 1.1 to 1.6; p: 0.02), including mortality when analyzed as a composite outcome (VAP plus mortality) (OR 1.4; 95% CI 1.1 to 1.8; p: 0.01). It is striking in this study by Korupolu et al. (7) that, on the contrary, in its general characteristics, the group of patients who have HTV has a lower TV compared to the group of patients with LTV. In addition, this study does not

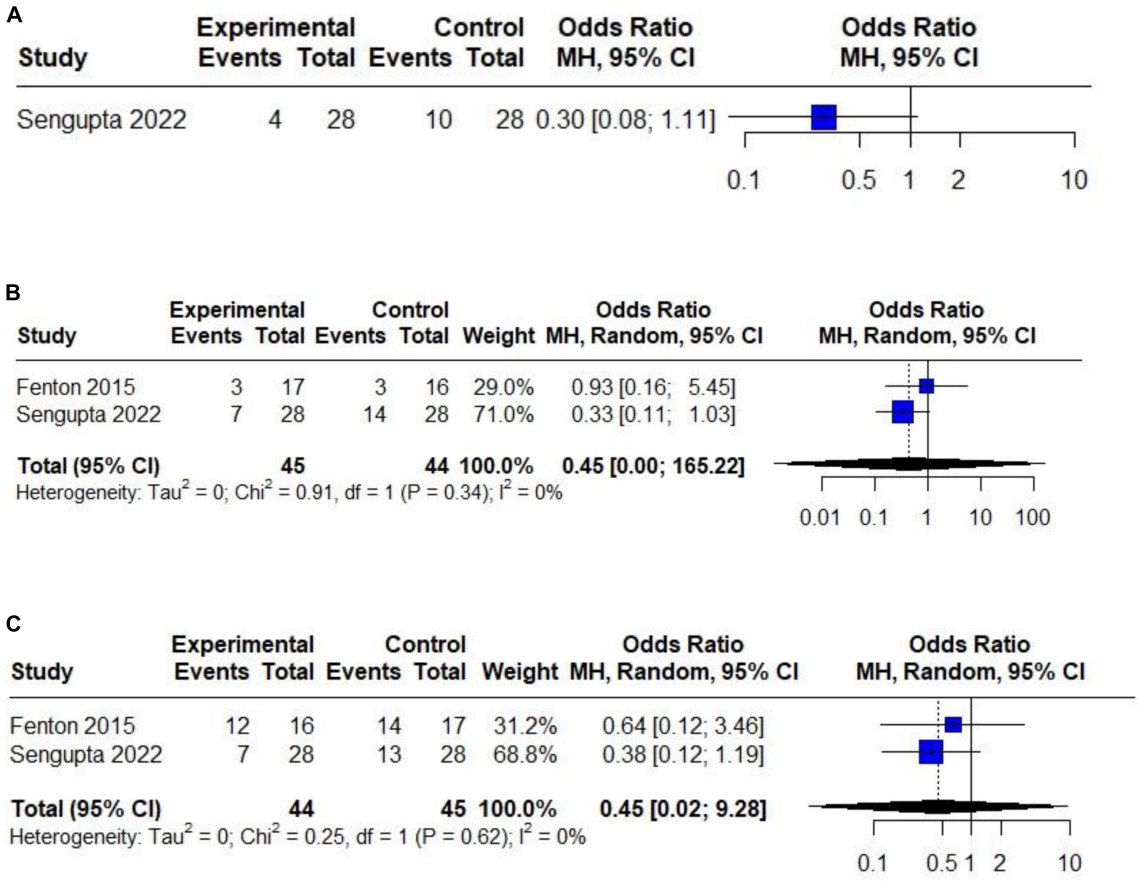

FIGURE 4
Forest plot of the effect of HTV compared with LTV in patients with CSCI on the risk of developing: **(A)** ARDS (only one RCT). **(B)** Atelectasis (only two RCTs). **(C)** complications after tracheostomy (only two RCTs).

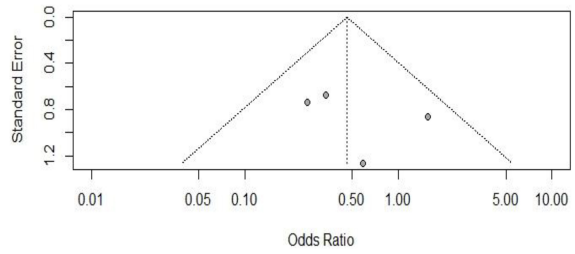

FIGURE 5
Funnel plot of the included studies in the meta-analysis on the effect of developing VAP in patients with CSCI considering observational and RCTs studies without outlier.

carry out sample selection through a probabilistic method, the confounding variables are not necessarily the most appropriate, and the HTV group was considerably older compared to the LTV group. Therefore, the conclusions mentioned above must be interpreted with caution.

The postulated mechanism by which HTV should lead to a lower rate of VAP and other pulmonary complications has yet to be fully understood. However, it is rationally and physiopathological based on the concept that using restrictive TV (LTV or standard, as per our investigation) at 6–8 ml/kg is based on protective lung principles supported by the Acute Respiratory Distress Syndrome (ARDS) Network (13). It is necessary to understand that the evidence supporting lower mortality with low tidal volumes proceed from patients with specific lung pathologies. In contrast, patients with an initial CSCI typically have healthy lungs, suggesting they benefit from using HTV for the aforementioned physiopathological reasons (4, 16, 36).

In addition to the complication due to VAP in patients with CSCI, the presence of atelectasis is a non-negligible situation. The two RCTs that assess this complication found no differences between the presence of atelectasis and the use of tidal volume in HTC or LTV. Fenton et al. (11) report 100% compliance in both groups. Sengupta et al. (12), on the other hand, found a more significant number of atelectasis in the LTV group compared to HTV in 18 patients (64%) compared to 13 patients (46%), respectively, suggesting, again, that the use of HTV can help reduce complications such as atelectasis without entailing problems associated with volutrauma or barotrauma in VM. The same authors also do not report differences in the rate of complications when performing tracheostomy in these groups of patients.

Although there are no significant differences in mortality, in our meta-analysis, when evaluating as a composite outcome (VAP and mortality), excluding Korupolu et al. (7) for behaving as an

TABLE 3 Certainty of the evidence (CoE) through GRADE.

Outcome No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Sin (HTV)	Con (HTV)	Difference	
396 participants: (5 studies)	OR 0.87 (0.41 to 1.43)	46.9%	40.8% (19.2 to 67.1)	6.1% fewer (27.7 fewer to 20.2 more)	⊕⊕◯◯ Low

They show a 6.1% lower risk of developing VAP in patients with CSCI using HTV than LTV, but without showing a statistically significant difference and with a low degree of certainty. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; OR, odds ratio; HTV, high tidal volume.

outlier, we found a reduction in the rate of VAP and mortality in the HTV use group up to 52% less (RR: 0.48; 95% CI 0.30 to 0.79; I^2: 0%) but larger RCT-type studies are needed to demonstrate what is stated in this research.

Our study has numerous strengths. Firstly, we carried out a comprehensive search strategy, which covered six essential databases and clinical trial registers. Secondly, we utilized a rigorous methodology to conduct our review and meta-analysis, which included a thorough quality assessment of studies and a statistical analysis that accounted for heterogeneity. Thirdly, as there was no statistical heterogeneity, it suggests that our findings are dependable and robust. Moreover, the results of individual studies are consistent.

It is important to note that our study has some limitations. First, only a few completed studies have explicitly addressed our PECO/PICO question. Second, the studies included in our meta-analysis were a mix of observational (three) and RCTs (two), with observational studies being more prone to bias than RCTs. Third, while most of the studies used HTV values over 15 ml/K PWB (4, 7, 11, 12, 30), one study used similar but different management points (5). Finally, due to the limited number of studies available, we had to analyze both observational and RCTs, considering the moderate risk of bias found in the reported observational studies.

5 Conclusion

Our study suggests that there is no significant difference in the development of VAP as a complication when using HTV compared to LTV in patients with CSCI in MV, nor are there differences in the presentation of other pulmonary complications such as ARDS, atelectasis, and onset of MV weaning. There is also no evidence that there are more complications associated with volutrauma in the HTV group, indicating that this strategy could be safe. In the composite outcome, when evaluating both VAP and mortality, the results suggest a lower rate of VAP and mortality by up to 52% after excluding outliers. The conclusions above have a low level of evidence. RCTs are necessary to demonstrate the effectiveness of using HTV in patients with CSCI or to rule it out definitively and to be able to couple this evidence into management guidelines.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

EM-R: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project administration, Software, Supervision, Writing – original draft. GV-T: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project administration, Software, Supervision, Writing – original draft, Methodology, Resources, Validation, Validation, Writing – review and editing. CQ-C: Data curation, Formal Analysis, Methodology, Resources, Visualization, Writing – original draft. MC: Funding acquisition, Investigation, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. JC-C: Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Writing – review and editing. JP-P: Conceptualization, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Fracture fixation in polytraumatized patients—From an interdisciplinary early total/appropriate care to the safe definitive surgery concept

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The strategies for the timing of fracture fixation in polytrauma patients have changed with improvements in resuscitation and patient assessment. Specifically, the criteria for damage control have been formulated, and more precise parameters have been found to determine those patients who can safely undergo primary definitive fixation of major fractures. Our current recommendations are supported by objective and data-based criteria and development groups. Those were validated and compared to existing scores. This review article introduces the concept of "safe definitive surgery" and provides an update on the parameters used to clear patients for timely fixation of major fractures.

KEYWORDS

polytrauma, safe definitive surgery, fracture management, borderline patient, multiply injured patients

Introduction

After most surgeons avoided performing major surgeries on patients with questionable clinical status, our group determined the clinical parameters that are relevant for the prediction of complications. This analysis led to the application of early definitive fracture fixation, starting within 24 h after injury. As this practice implies the exclusion of risk factors, it was named "safe definitive surgery" (SDS).

Following a development phase, the criteria adopted in an independent database proved that, after sorting out the exceptional cases requiring damage control, it is of value to allow for fixing fractures in a timely fashion, most of them within 24 h after admission. One of the milestones indicating the change in management of treatment was obvious in a recent survey among international surgeons. The survey indicated that a fixed timeline is no longer followed. Instead, the fixation strategy follows the stability of parameters, and fixation within the 24-h limit continues to prevail.

The SDS was developed based on parameters that currently appear to be required to allow for a timely fixation of major fractures, with respect to the patient's physiological response. The criteria have been summarized in a review article in 2005 (1), which has recently been updated (2). Our article summarizes the key strategies applied, such as (a)

the inclusion of set resuscitation criteria (3); (b) the application importance of utilizing multiple physiological parameters for the assessment of patients; (c) the value of serial reassessments over the course of resuscitation (4–7); and (d) the timely fixation of patients within the 24-h timeline (8).

Methods

Development group

In this review, the development of several treatment strategies was summarized and supported by data from a large database (2). The data were stratified into three different time periods. In group 1, 867 patients (23.6%) were treated prior to 2001 (before the introduction of damage control techniques). Groups 2 and 3 consisted of a total of 2,801 patients, of which 1,262 patients (45.1%) were treated between 2003 and 2008 [the incorporation of damage control techniques for major fractures (Group 2)] and 1,539 patients (54.9%) were treated after 2009 [after introducing changes in nonsurgical management, e.g., after the introduction of transfusion and fluid management guidelines (Group 3)]. These three groups constituted the development group.

Validation group

The validation group consisted of another database, which was used to compare several existing assessment scores. The database utilized the parameters of 3,888 patients who were treated before 2022. It compared four different scales: (a) the so-called clinical grading system (CGS, based on a simple review of parameters in 2005); (b) the modified clinical grading system (mCGS, a modification of the first review based on 750 patients collected from a database in Cleveland, which featured fewer parameters than the CGS); (c) the early appropriate care (EAC) protocol (based on 1,443 patients who were treated in Cleveland between 1999 and 2006); and (d) the polytrauma grading score (PTGS) (11,436 patients who were treated before 2020 from the German Trauma Registry).

Outcome parameters

In the development group, the parameters considered were mortality rate, ventilation time, intensive care unit (ICU) stay and complications, such as the incidence of pneumonia, the incidence of sepsis, death from shock, and death from head trauma.

Discussion

The time frame to determine fracture care as "early," "appropriate," or "delayed" has been under discussion for a long time. In order to allow for safe definitive fixation of major fractures, resuscitation has to be obviously completed. Some authors have argued that completion of resuscitation has been achieved within 24 h after the injury, though this is subject to debate until robust evidence emerges, which includes the absence of vasopressors, the reduction of acid–base status, the normalization of platelet counts and rotational thromboelastometry (ROTEM) values, and the absence of a positive fluid balance (Table 1).

TABLE 1 Criteria for laboratory values and parameters that should normalize within 24 h after injury (e.g., borderline patient with responsive physiology) to allow for safe definitive surgery.

Parameter group	Criteria for normal	Duration until normal
Shock	Vasopress. infusion <3 ml/h or absent	4–6 h
Acid base changes	2–2.5 mmol/L	12–24 h
Platelet count (ROTEM)	>90.000 or rising (acc. to system)	8–12 h
Fluid balance	I/o ratio balanced without vasopressors	24 h
Severe chest injury	Absence or reduction of lung contusion	24 h

The criteria to distinguish between different time periods of fracture care might be based on several criteria, such as (a) the time elapsed after an injury, (b) the completion of normalization of parameters summarized under "resuscitation," or (c) convenience aspects (e.g., the availability of operating rooms). The last mentioned criterion has been added recently, and it became evident that having room to take care of acute emergencies is a feasible option to reduce delays caused by technical operating room availability. Regarding the time elapsed after an injury, this criterion has been the major determinant in the transition era when the term "early total care" was coined. Furthermore, it occurred when early fracture care was proven to be more beneficial than waiting a week to 10 days in the fear of the patient developing a systemic fat embolism syndrome. Despite the lack of clear-cut guidelines for resuscitation, mass transfusions or endpoints were considered as clearance for going to the operating room. The authors who advocated that all fractures (major long bones and others) should be stabilized within a time frame did so in the absence of data to support this idea. The development of the criteria above, namely resuscitation guidelines, led to a different method of care, and the variation between 36 and 48 h was evident, even within the same clinical group, as depicted in Table 2.

Subsequently, clinical parameters were advocated to control for the effects of resuscitation (3). Among these parameters were acid–base changes and lactate clearance, and the first publication to use the term "lactate clearance" examined lactate levels at 8, 16, 24, 36, and 48 h after injury (2 mmol/L served as the threshold level). The authors clearly concluded that, usually, the survival rate of polytrauma patients with severe hemorrhage was 75%. In these patients, the lactate levels had to be normalized within 24 h (4), that is, a lactate level of 2.0 mmol/L should be achieved, which is in accordance with the majority of the relevant literature (5).

One of the hallmark study series has been popularized by Dezman et al. The authors reported on patients treated between 2010 and 2012 who had the lactate level of >3 mmol/L at admission.

TABLE 2 The discussion about optimal early definitive care in patients cleared for surgery: Is timing (24/36/48 h) crucial or lab criteria only?

Author	Year	Origin country/city	Timeline 24 h	Concept	Lab criteria
O'Toole	2009	Baltimore/USA	24	ETC	Resuscitation/lactate (<2 mmol)
Schreiber	2011	Pittsburgh/leeds	24	DCO	4 categories
Vallier	2013	Cleveland/USA	24	ETC	Lactate (<4 mmol/L)
Dienstknecht	2013	Aachen/GER	24	DCO	4 categories
Nahm	2014	Cleveland/USA	24	EAC	Lactate (<4 mmol/L)
Weinberg	2015	Cleveland/USA	36	EAC	–
Pape	2015	Aachen/Ger	<24	SDS	4 cat
Giannoudis	2016	Leeds/GB	<24	PRISM	Mult. categories
Vallier	2016	Cleveland/USA	36	EAC	Lactate (<4 mmol/L)
Childs	2017	Cleveland/USA	24	EAC	Lactate (<4 mmol/L)
Blockhuis	2017	Utrecht/NL	<24	SDS	–
Pape	2019	Zurich/SUI	<24	SDS	4 categories (see Table 5), surgery asap
Volpin	2021	Haifa/ISR	24	DCO/SDS	–
Halvachizadeh	2021	Zurich/SUI	<24	SDS	4 categories (see Table 5), Surgery asap
Scherer	2022	Zurich/SUI	<24	SDS	4 categories (see Table 5), surgery asap
Blaesius	2022	Aachen/GER	24	ETC/SDS	PTGS score
Pfeifer	2023	Zurich/SUI	<24	SDS	4 categories (see Table 5), Surgery asap
Halvachizadeh	In press	Zurich/SUI	<24	SDS	4 categories (see Table 5), Surgery asap

Variability of lactate threshold levels and recommendations of surgical timing in the orthopedic literature since 2010.

The timeline for blood sampling was 24 h post admission. The authors describe a subgroup of patients that normalized their lactate levels within 24 h, and this group was named the "*high clearance*" group. Another group that did not improve their lactate levels within this time frame was named the "*poor clearance*" group. Thus, the timeline of completion of resuscitation is usually 24 h. Along these lines, the authors concluded the superiority of 24 h lactate clearance over using the lactate value only at admission (6, 7).

Kucukdurmaz et al. in their discussion regarding the EAC vs. Damage Control Orthopedics (DCO) approaches examined the 24 h lactate value, which should not exceed more than 2.5 mmol/L, and focused on late respiratory complications (9). Stahel et al. observed that the closure of the abdomen can be performed in close proximity to fracture fixation of the femur, i.e., in one surgical session (10). As mentioned earlier, there have been changes even in the group that developed the EAC protocol, as they initially started at a threshold level of 4 mmol/L of lactate on admission and reduced it to 2.5 mmol/L.

More recently, coagulopathy has been similarly in focus and has become a major determinant of discussing whether a patient is stable, borderline, or unstable (11). Our group has developed reviews to address the issue of threshold levels to separate these clinical entities. Similar trends were followed by Regnier in 2012, when focusing on the value of lactate (5), and by Shapiro et al., who examined 576 trauma patients where the endpoint was mortality (12).

Timing of fracture fixation in the context of physiological stability

Historically, there appeared to be a consensus on the implementation of an early definitive care approach, and most centers attempted to follow the rules of Bone and Johnson (13).

Later, operating room (OR) availability has been on focus, and many countries have taken the initiatives to develop a "dedicated trauma room" in order to allow for rapid access. Nevertheless, some centers have been cautious and claimed that the completion of resuscitation has to be achieved before fixation. Moreover, surgeon preference was discussed rather than patient criteria after the completion of resuscitation. Therefore, some authors accepted a delay in the fixation of the first major fracture, and timelines changed from 24 to 36 h under many circumstances (Table 2). There has been a development in utilizing different endpoints of resuscitation within departments in the last few years, including acid–base changes along with coagulation and physiological parameters, such as blood pressure, which has led

TABLE 3 Comparison of the U.S. vs. EU trauma system.

Parameter/time after accident	USA	EU
Rescue		
Type of training	Trained paramedics 12 M., EMTs Param. exam.	Trained physicians completed residency, then 1 year resc. course, proof of ATLS, or polytrauma course
Max. tx. on scene	Intubation, CPR	Intubation, CPR, chest drain, central line, ultrasound (some)
Admission		
ER treatment	Emerg. Med. or Gen surgeon	Shock room leaders Unfallchirurg and anesthesia
Organization of surgical care	Gen. surgeon consults Orthop. trauma	Unfallchirurg
Aftertreatment	Orthopedic trauma surgeon	Unfallchirurg

to a considerable improvement of the classification options, as summarized recently (11).

One of the hallmarks of the development against a set timeline has been a survey conducted among experienced surgeons. The surgeons responded by stating that the timing of surgery no longer uses a fixed timeline, as initiated before, but a physiology-based approach is utilized (11). This use of approach is in line with our own concept, as proposed in the SDS protocol, and Prompt-Individualised-Safe Management (PRISM) concept by Giannoudis et al. (14, 15).

The influence of trauma systems on the team approach and timing of fracture care

The organization of trauma care differs between the US and many regions in Europe (Table 3). These differences concern the rescue crew, where, in the US, trained paramedics usually perform a "scoop and run" approach to bring the patient to the closest hospital. More recently, this approach has been reinforced by the fact that hospital chains have become stronger and taken over the rescue issue by choosing which particular hospital should be served first. These economic principles would overcome the stipulations in the certification processes governed by state regulations. The issues about quality control have not been formally addressed, as the National Trauma Data in the US database does not cover secondary complications.

In Europe, a different approach is adopted. First, a rescue personnel should have completed residency, followed by certain emergency medicine courses and at least one other course, such as Advance Trauma Life Support (ATLS), the Polytrauma course, or the European Trauma Course (16). In Switzerland, these courses are also included in the newly developed trauma surgery education, which requires certain exposure after completion of the surgical or orthopedic residency (https://sgact.ch/schwerpunkt-spez-traumatologie).

The in-hospital treatment is also substantially different. In the US, the multiply injured patient is admitted by a general surgeon, who then consults the orthopedic service in case of fractures (Table 3). In contrast, the admission team in most European health centers consists of both anesthesia and trauma surgery specialists who perform diagnostic procedures in parallel and usually perform an emergency computed tomographic (CT) scan within the first minutes after admission. The certification process to be accepted as a major trauma center includes certain diagnostic criteria, such as the "time to CT scan." It is one of the important quality criteria, which are reported during the annual feedback conducted at the annual regional trauma congress (https://www.traumaregister-dgu.de/index.php).

These and other factors may be involved in the fact that the German Trauma Registry (TR-DGU) incentivises all level I trauma centers to have the diagnostics completed within 2–3 h and life-threatening procedures performed within the same time frame, including the definitive procedure.

Current status of decision-making for patients with major fractures according to the SDS concept

The concept of "safe definitive surgery" (SDS) relies on serial measurements of several representative physiological parameters and on the dynamic reevaluation of the patient's physiology during the course of resuscitation and operative interventions (8).

The initial assessment and first treatment measures in the polytrauma patient are highly standardized and follow the principles of ATLS (16). ATLS is a program aimed at restoring the derailment of the patient's physiology, typically caused by either insufficient oxygenation, insufficient perfusion of the end organ, or a combination of both. Although these initial measures have been taken, the timing and sequence of operative procedures are not specified (17). There is a general consensus that definitive operative procedures should be performed once the patient's physiology has been sufficiently restored. However, there is still little agreement on how to reliably quantify the restoration of patient's physiology (18).

The approach used in the past was the ubiquitous application of damage control strategies on the first day and the conversion to a definitive stabilization in the so-called window of opportunity after several days. If applied in an unreflected fashion, however, damage control strategies might lead to relevant restrictions of patient positioning, prolonged immobilization, and delayed definitive surgeries, resulting in an unjustifiable lengthening of hospital stay (19). The concept of early appropriate care (EAC) has been proposed to clear patients for rapid fracture fixation (20). However, this approach included only one aspect of the pathophysiology (acid–base changes) and is dependent on only one measurement (on admission). Several studies have argued that repeat measurements and the inclusion of multiple parameters yield a superior predictive power of unfavorable outcomes. Dezman et al. showed the superior predictive capability of 24 h mortality by utilizing serial lactate

TABLE 4 Development of scores to determine the state of multiply injured patients on admission, separated by evidence level.

	Names	Level of evidence	Pathophysiological changes included			
			Shock (Acid/Base)	Coagulopathy	Hypothermia	Soft tissue injury
Pape, 2005	CGS	Level IV	Multiple	Multiple	Temp.	Multiple
Dienstknecht, 2013	No name	Level III	BD	PTT	–	Multiple
Nahm 2013	mCGS	Level III	Acidosis	Platelets	Temp.	AIS
Vallier, 2013	EAC	Level II	Acidosis	–	–	–
Hildebrand, 2014	PTGS	Level III	BD, pRBC	INR	–	ISS
Halvachizadeh, 2020	SDS concept	Level II	BD, pRBC, BP	PTT, platelets	Temp.	AIS/ISS

BD, base deficit; BP, blood pressure; INR, international normalized ratio; pRBC, packed red blood cells; PTT, partial thromboplastin time.

measurements and coined the term lactate clearance (6). Moreover, Halvachizadeh et al. have determined that the combination of several parameters, including hemorrhage, coagulation, acid–base status, and soft tissue damage, provide superior predictive power of complications than using only one physiological parameter (21). Indeed, applying the parameters from the Polytrauma Grading Score, which include systolic blood pressure, international normalized ratio (INR), thrombocyte count, base deficit, packed red blood cells, and the new injury severity score (NISS), significantly increased the predictive capabilities for the development of sepsis, pneumonia, and other late complications (21, 22). An overview of several published scores is provided in Table 4.

In view of these considerations, SDS proposes to evaluate patients using a combination of parameters and to perform repeat measurements, allowing a dynamic reassessment based on the response to resuscitation and operative interventions.

The choice of parameters used in SDS is based on the understanding of the pathophysiological posttraumatic response, especially of the interplay of hypothermia, coagulopathy, hemorrhage, and tissue injury (23). An overview of the most relevant parameters is presented in Table 3. These parameters have been shown to adequately estimate the physiological response to severe trauma and resuscitative efforts. They significantly influence the patients' clinical course and have been recently validated by a systematic review, which aimed to identify thresholds that are indicative of a higher rate of adverse outcomes in polytrauma (11).

Hemorrhage may be identified by systolic blood pressure, lactate, and hemoglobin levels; coagulopathy may be identified by INR or viscoelastic tests ROTEM and hypothermia may be identified by body temperature. There is a recent consensus among leading surgeons (unpublished to date) that the classification of tissue injuries remains challenging and varies between body regions. Traumatic brain injury (TBI) can be evaluated using the intracranial perfusion pressure (ICP), cerebral perfusion pressure (CPP), and the presence of a midline shift, while thoracic tissue trauma can be assessed using the Thorax Trauma Severity Score (TTSS) (24). Abdominal injuries are most frequently graded using the Moore or the American Association for the Surgery of Trauma (AAST) classifications (25). Further parameters that should be considered are the overall injury severity (i.e., NISS), the injury pattern, the number of fractured long bones, and the number of required blood transfusions (26). Based on these parameters, "unstable" or "borderline" stable patients can be identified, and the timing of fracture fixation can be adjusted accordingly (Table 5). It is important to note, however, that these categories are dynamic and that patients can improve or deteriorate depending on their response to resuscitative measures and operative interventions. This process is visualized in Figure 1.

In a study that included 3,668 polytraumatized patients, a significant decrease in early mortality, overall mortality, and complication rates since the introduction of optimized transfusion and fluid management guidelines was observed (2). This report is in line with the survey indicated above, where there is no longer a set timeline, but the stability of parameters is regarded as the endpoint.

In line with these reports, the surgeon panel agreed on the following hierarchy of surgical interventions builds: (a) life-saving operations (i.e., patent airway, pneumothoraces, and uncontrollable hemorrhage); (b) central nervous system (CNS)-saving operations (i.e., severe traumatic brain injury, and spinal cord injury); (c) limb-saving operation (i.e., vascular injuries, mangled extremities, and compartment syndrome); and (d) operations preserving local function and preventing local complications (e.g., open fractures and severe dislocation).

Further considerations should include expected blood loss, post-interventional systemic inflammatory response, potential (pulmonary) complications (e.g., avoid reamed intramedullary nailing in patients with severe chest trauma), patient positioning, duration of immobilization, and pain control. Moreover, the combined operation time should generally not exceed 6 h, and the complexity of fractures needs to be assessed in accordance with the individual surgeons' skills. Finally, it also remains pivotal to evaluate local factors that might prohibit definitive fixation and drive musculoskeletal temporary surgery such as contamination and severe soft tissue trauma (27).

In view of these considerations, the polytrauma section of the European Society for Trauma and Emergency Surgery (ESTES) has led an initiative to introduce a definition for "major fracture(s)" in the multiply injured patient (28, 29). A recent systematic review showed that, over the last decades, the timing of fixation of pelvic and spinal fractures gained importance in the treatment of polytrauma patients, which is likely due to

TABLE 5 Threshold levels of parameters to separate stable from borderline patients apply four different categories (20).

Category	Parameter	Threshold—borderline	Threshold—unstable
Hemorrhage	SBP (mmHg)	<100	<90
	Lactate (mmol/L)	>2	>4
	Hemoglobin (g/dl)	<9	<7
	PBRC (on first day)	>2	>8
Hypothermia	Body temperature (°C)	<35	<33
Coagulopathy	INR	>1.2	>1.5
ROTEM	Extem CT (s)	>60	>80
	Extem MCF (mm)	<60	<45
	Fibtem MCF (mm)	<12	<5
TEG	ACT (s)	>110	>128
	MA (mm)	<60	<55
	LY30 (%)	>3	>5
Tissue injury			
Brain	ICP (mmHg)	>15	>20
	CPP (mmHg)	<70	<60
	Midline shift (mm)	>5	≥5
Chest	TTSS	>6	>7
Abdomen	Moore classification	>2	>3

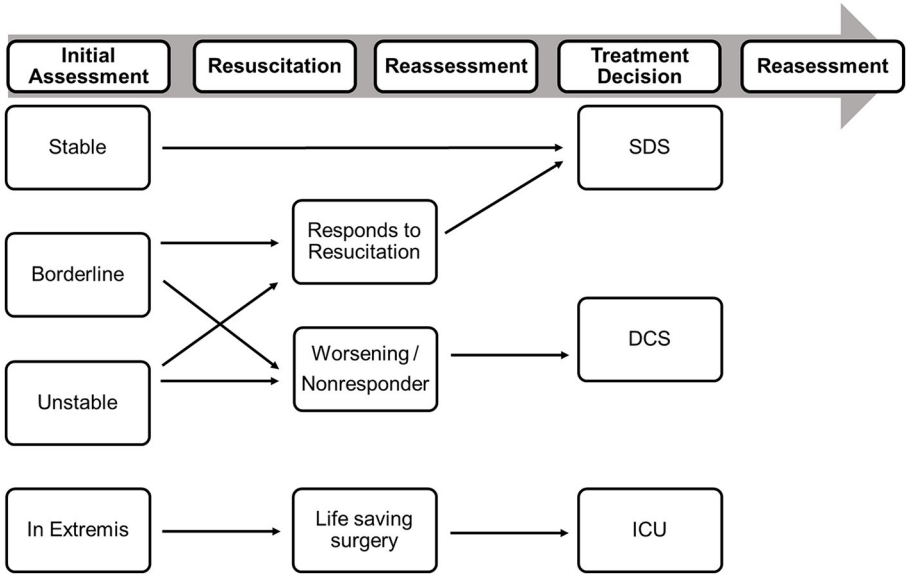

FIGURE 1
Decision-making in Polytrauma patients should be based on the initial assessment of the patient physiology and on the response to resuscitative measures. DCS, damage control surgery; ICU, intensive care unit [modified from Pape et al. (8)].

improved diagnostic tools and less invasive operative techniques. Another important finding was that hemodynamic stability And injury-specific factors (e.g., associated soft tissue injuries) have increased in importance over time, while chest injury and TBI have always been important factors in perioperative decision-making (28).

Another recent study presented the results of an international expert opinion questionnaire that focused on factors to be considered to adjust the physiological insult through surgery, coining the term "surgical load." This study confirmed that surgical sequencing should be performed according to the risk of bleeding, fracture complexity, and the anatomic region. Open surgical

procedures as well as surgeries on the trunk, greater articulations, and long bones seem to lead to a higher surgical load than their minimally invasive counterparts or operations on the distal extremities (30).

Nevertheless, there has not yet been a comprehensive grading of the surgical priorities based on the anatomical region of injury. It rather seems that further injury- and patient-specific factors should play a superior role in determining the sequence of operative fixation. This is further emphasized by the recent revision of the abbreviated injury scale, which gives higher scores for fractures if they are open, or associated with severe soft tissue injury (31).

Conclusion

The understanding of the pathophysiology of patients with polytrauma continues to improve. Besides the physiological effect of the initial traumatic load, this understanding also includes the impact of resuscitative efforts and surgical interventions. The concept of "safe definitive surgery" builds on this knowledge to enable timely and safe fracture fixation in severely injured patients, to be completed within 24 h after admission for patients who do not require a damage control approach. It is important to perform reassessment of patients intraoperatively.

International and multidisciplinary groups of experts are currently preparing consensus statements for fracture fixation in patients with severe concomitant injuries. Another promising approach might be to investigate advanced analytical tools (e.g., proteomic, metabolomic, and lipidomic analyses, and real-time immunofluorescence) in polytrauma patients to further extend the insight into the systemic posttraumatic response and to identify potential new markers for point-of-care resuscitation.

Author contributions

YK: Data curation, Writing—original draft, Writing—review & editing, Visualization. S-MH: Writing—review & editing, Investigation, Project administration, Validation. AK: Writing—review & editing, Formal analysis, Supervision. FK: Data curation, Visualization, Writing—original draft, Writing—review & editing. RP: Project administration, Writing—review & editing, Visualization. GW: Conceptualization, Methodology, Writing—review & editing, H-CP: Conceptualization, Data curation, Investigation, Writing—original draft, Writing—review & editing.

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Conflict of interest

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Prediction of prolonged length of stay on the intensive care unit in severely injured patients—a registry-based multivariable analysis

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Purpose: Mortality is the primary outcome measure in severely injured trauma victims. However, quality indicators for survivors are rare. We aimed to develop and validate an outcome measure based on length of stay on the intensive care unit (ICU).

Methods: The TraumaRegister DGU of the German Trauma Society (DGU) was used to identify 108,178 surviving patients with serious injuries who required treatment on ICU (2014–2018). In a first step, need for prolonged ICU stay, defined as 8 or more days, was predicted. In a second step, length of stay was estimated in patients with a prolonged stay. Data from the same trauma registry (2019–2022, n = 72,062) were used to validate the models derived with logistic and linear regression analysis.

Results: The mean age was 50 years, 70% were males, and the average Injury Severity Score was 16.2 points. Average/median length of stay on ICU was 6.3/2 days, where 78% were discharged from ICU within the first 7 days. Prediction of need for a prolonged ICU stay revealed 15 predictors among which injury severity (worst Abbreviated Injury Scale severity level), need for intubation, and pre-trauma condition were the most important ones. The area under the receiver operating characteristic curve was 0.903 (95% confidence interval 0.900–0.905). Length of stay prediction in those with a prolonged ICU stay identified the need for ventilation and the number of injuries as the most important factors. Pearson's correlation of observed and predicted length of stay was 0.613. Validation results were satisfactory for both estimates.

Conclusion: Length of stay on ICU is a suitable outcome measure in surviving patients after severe trauma if adjusted for severity. The risk of needing prolonged ICU care could be calculated in all patients, and observed vs. predicted rates could be used in quality assessment similar to mortality prediction. Length of stay prediction in those who require a prolonged stay is feasible and allows for further benchmarking.

KEYWORDS

trauma and injuries, intensive care, length of stay, registries trauma and injuries, registry, prediction models

Introduction

Most initiatives for quality assessment of the treatment of severely injured patients focus on mortality as primary outcome. This is reasonable since mortality rates range from 5% to 20% depending on the inclusion criteria. The German TraumaRegister DGU® (TR-DGU) of the German Trauma Society (DGU) considers reduction of hospital mortality as its primary aim as well. This registry includes severely injured patients admitted to hospital with trauma team activation who needed intensive care, or died. Specific scoring and prediction systems have been developed and validated to estimate the risk of death [RISC (1) and RISC II (2)]. Participating hospitals receive annual quality reports where observed and predicted mortality are compared.

However, for surviving patients only process parameter have been implemented as quality indicators (3). Length of Stay (LoS) in hospital or on the intensive care unit (ICU) could well be considered as a relevant outcome measure in survivors (4). A shorter length of stay would also be preferable from an economic point of view. But an unadjusted comparison of LoS data across hospitals would be misleading since LoS depends on several factors. Usually, a more severely injured patient would require a more intense therapy, and sometimes repeated operations, associated with a longer LoS (5). There are also patient-related factors with an effect on LoS, like age or concomitant diseases, especially in the elderly. Finally, also complications like (multiple) organ failure, or sepsis, determine the required LoS. For example, Böhmer et al. found that, after adjustment, a sepsis would prolong the ICU stay by 8 days, and organ failure would prolong ICU stay by 2–8 days on average, depending on the failing organs (5).

The present analysis aims to predict LoS on ICU as a means of benchmarking hospital treatment. However, LoS is not easy to predict since LoS data are rather skewed with a large number of patients requiring a short stay only, and a much smaller number of cases with a rather long need for intensive care. This small group of patients who require a prolonged LoS on ICU consume a considerable amount of resources (6). Several models to predict LoS on ICU exist already (7), but they focus on all cases and not just on prolonged ICU stay, or consider a mixed ICU population, or they did not include relevant predictors specifically for trauma patients available in our registry. According to Kramer et al., we followed a two-step approach to LoS prediction in survivors (6): In a first step we aimed to predict the probability for a prolonged ICU stay, and in a second step ICU LoS was sought to be predicted in those patients requiring a prolonged stay.

Methods

This is a retrospective analysis of existing registry data from surviving patients with severe injuries The derived models were validated with contemporary data from the same registry, imitating the application of these models.

TraumaRegister DGU®

The TraumaRegister DGU® (TR-DGU) of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie, DGU) was founded in 1993. The aim of this multi-center database is a pseudonymized and standardized documentation of severely injured patients.

Data are collected prospectively in four consecutive time phases from the site of the accident until discharge from hospital: (A) Pre-hospital phase, (B) Emergency room and initial surgery, (C) Intensive care unit and (D) Discharge. The documentation includes detailed information on demographics, injury pattern, comorbidities, pre- and in-hospital management, course on the intensive care unit (ICU), relevant laboratory findings including data on transfusion, and outcome of each individual. The inclusion criterion is admission to hospital via the emergency room (trauma team activation) with subsequent intensive or intermediate care. Patients who reached the hospital with vital signs but died before admission to ICU were included as well.

The infrastructure for documentation, data management, and data analysis is provided by AUC—Academy for Trauma Surgery (AUC—Akademie der Unfallchirurgie GmbH), a company affiliated to the German Trauma Society. The scientific leadership is provided by the Committee on Emergency Medicine, Intensive Care and Trauma Management (Sektion NIS) of the German Trauma Society. The participating hospitals submit their data pseudonymised into a central database via a web-based application. Scientific data analysis is approved according to a peer review procedure laid down in the publication guideline of TR-DGU.

The participating hospitals are primarily located in Germany (90%), but a rising number of hospitals of other countries contribute data as well (presently Austria, Belgium, Finland, Luxembourg, Slovenia, Switzerland, The Netherlands, and the United Arab Emirates). Currently, approx. 30,000 cases from over 650 hospitals are entered into the database per year. Participation in TR-DGU is voluntary. For hospitals associated with TraumaNetzwerk DGU®, however, the entry of at least a basic data set is mandatory for reasons of quality assurance.

This study was conducted according to the publication guideline of the TR-DGU and registered as project number 2016-012.

Patients

For the development set, surviving patients documented in TR-DGU were selected from a 5 year period (January 2014–December 2018). Only cases admitted to a German trauma center and treated on an intensive care unit (ICU) were considered. Patients with minor injuries defined as Maximum Abbreviated Injury Scale (MAIS) severity grade one were excluded. Primary admitted cases who were not transferred out within 48 h, as well as cases transferred in from other hospitals were considered. This left 109,793 survivors from 670 hospitals for analysis. Before excluding the non-survivors from the development set, mortality rate was 9.7% in those admitted to ICU, and another 1.6% died before admission to ICU.

Patients were further excluded due to the following reasons: Length of stay on ICU not documented ($n = 6$); late transfer in from another hospital with >3 days between accident and transfer (n = 563); transferred out before day 30 in a condition that still required intensive care (intensive care treatment not terminated; $n = 1{,}063$). After these exclusions data of 108,178 patients were available.

The results of this analysis were validated in a second set of patients documented in TR-DGU from 2019 to 2022, using the same inclusion and exclusion criteria.

Data collection system of TR-DGU allows to document length of intensive care in days or hours. If ICU stay was documented in hours, the respective days were calculated as a decimal number, and parts of a day were counted as a separate day. So, all LoS ranging from 1 to 24 h were counted as 1 day, and 25 h then counted as 2 days, and so on.

Organ failure was documented as Sequential Organ Failure Assessment (SOFA) score grade 3 or 4 for five organ systems: lung/respiration, coagulation, heart/blood pressure, liver, kidney, and the central nervous system (8). Organ failure and sepsis were documented as binary variable (yes/no) during the ICU stay.

For number of injuries, only injuries with an AIS severity level of 2 or more were counted. Often, AIS 1 injuries were not completely documented, and their impact on length of stay could be neglected. Furthermore, the number of injuries were truncated at 13. Only 1.9% of cases had more than 13 diagnoses documented (maximum 29), but without a further effect on LoS.

Statistics

Since the distribution of LoS data were heavily skewed with a long tail to the right (Figure 1), standard regression analysis would violate the requirements of this method. Therefore, we followed an approach previously used and published by Kramer and Zimmerman (6). According to their approach, we first defined a threshold for prolonged intensive care. We decided to use a cut-off of 7 days, which means that an ICU stay lasting longer than 1 week (8 days or more) was considered as a prolonged ICU stay. This cut-off was chosen both for clinical and methodological reasons. Short ICU stays often depend more on the availability of beds than on the clinical condition. Furthermore, when including a large number of short ICU stays in a model, then the regression algorithm aims to fit these short stays rather than identifying reasons for a prolonged stay.

After 1 week nearly 80% of patients had left the ICU already. We then considered factors available before first ICU admission to estimate the probability of a prolonged ICU stay using logistic regression analysis. This analysis was performed on the total population of 108,178 cases. Based on the coefficients of the model, a formula was provided to calculate the probability of requiring a prolonged ICU stay. Predicted and observed values were compared, and discrimination was assessed by the area under the receiver operating characteristic (ROC) curve.

In a second step we only used cases with a prolonged ICU stay and tried to predict their length of stay. This analysis would allow including all information until day 7. Similar to the approach of Kramer & Zimmerman, we truncated rather long ICU stays at day 30 for this analysis. This linear regression analysis with a truncated LoS (range 7–30 days) was calculated on 23,830 cases.

Odds Ratios (OR) from logistic regression analysis as well as coefficients from linear regression analysis were presented with their respective 95% confidence intervals.

Counts were presented as percentage, and continuous measures were presented as mean with standard deviation (SD), or as median with quartiles in case of skewed distributions. For observed vs. predicted length of stay, the mean absolute error (MAE) and the root mean squared error (RMSE) were reported. All analyses were performed using SPSS statistical software (version 29, IBM Inc., Armonk NY, United States).

Results

A total of 108,178 severely injured survivors who required intensive care were documented in TR-DGU within a 5 years period. The mean age was 50 years, and 70% of patients were males (Table 1). The average Injury Severity Score (ISS) was 16.2 points. Many patients

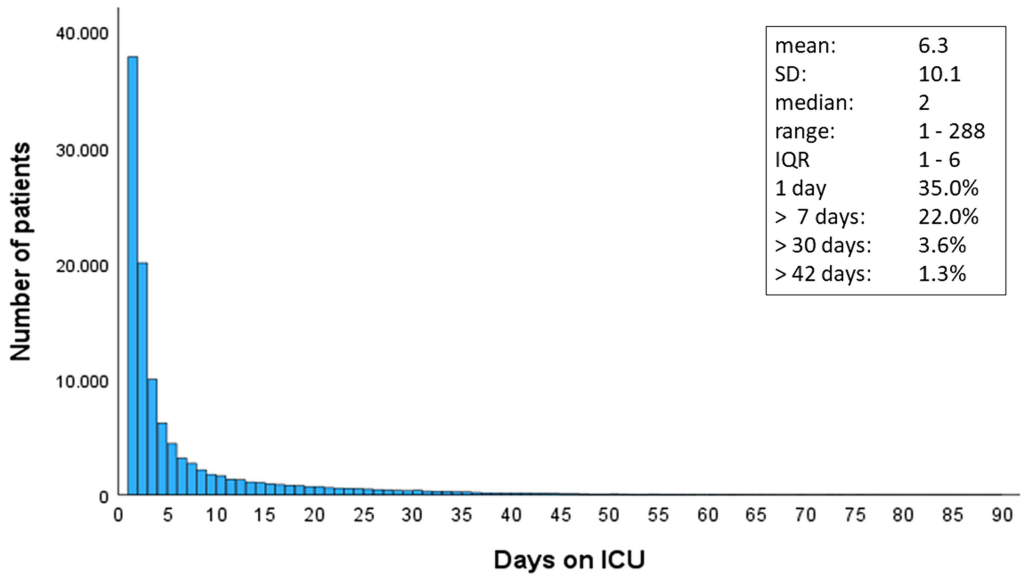

FIGURE 1
Distribution of length of stay in ICU in 108,178 surviving patients with severe injuries. SD, standard deviation; IQR, inter-quartile range.

required a short ICU stay only (Figure 1); the median LoS was 2 (IQR 1–6) days. Thirty-five percent were discharged within 24 h.

Prediction of prolonged ICU stay

A prolonged ICU stay of more than 7 days was observed in 23,830 patients (22.0%). These patients differed in many aspects from those with a shorter ICU stay (Table 1). They had about twice as many injuries, and their ISS nearly doubled (13.6 vs. 25.5 points). Mechanical ventilation was observed in 79.3% of cases with a prolonged ICU stay, as compared to only 15.5% in cases with a shorter stay.

Patients with a prolonged ICU stay were responsible for 71.5% of all ICU days, and for 92.7% of all ventilation days.

Logistic regression analysis was used to develop a prediction model for prolonged ICU stay. The following measures were considered as potential predictors: age; sex; pre-injury status (according to the American Society of Anaesthesiologists (ASA) classification); number of injuries; transfer in from another hospital within 3 days; worst injury severity level (AIS); relevant injury (AIS 3+) in the following body regions: head, thorax, abdomen, spine, and extremities; shock (systolic blood pressure ≤ 90 mmHg pre-hospital or on admission); need for blood transfusion before ICU admission; and need for ventilation on admission to ICU. The number of injuries was the only continuous predictor in the model. The reference category of a categorical predictor was selected based on the lowest risk category so that the remaining categories received an OR above 1.00. The following variables were eliminated from the model due to a minor impact (OR < 1.20): sex and relevant injury of the thorax, the abdomen, and the extremities. The remaining predictors are presented in Figure 2, the full model is given in Supplementary Table 2A. Nagelkerke's R^2 of this model was 0.541.

The most important predictors were need for ventilation (OR 10.45, CI_{95} 10.03–10.89) and survivors with MAIS 6 (OR 12.56, CI_{95}

TABLE 1 Basic data and potential predictors for a prolonged need for intensive care (>7 days) in all patients.

	Short ICU stay	Prolonged ICU stay	Total
Patients	*N* = 84,348	*N* = 23,830	*N* = 108,178
Transfer in from other hospital	6.4%	12.7%	7.8%
Age (years)	49.3 (22.1)	52.8 (21.2)	50.0 (21.9)
Male sex	69.7%	72.9%	70.4%
Injury Severity Score (ISS)	13.6 (7.8)	25.5 (11.6)	16.2 (10.1)
Serious head injury (AIS 3+)	21.0%	49.4%	27.2%
Serious thoracic injury (AIS 3+)	30.4%	50.8%	34.9%
Serious abdominal injury (AIS 3+)	4.8%	12.4%	6.5%
Serious injury of the spinal cord (AIS 3+)	5.6%	13.1%	7.2%
Serious injury of the extremities (AIS 3+)	18.9%	31.9%	21.7%
Penetrating trauma	3.9%	3.3%	3.7%
Number of injuries	3 (2–5)	6 (4–8)	4 (3–6)
Pre-injury status			
ASA 1	56.7%	44.6%	54.1%
ASA 2	29.1%	34.4%	30.2%
ASA 3/4	14.2%	21.0%	15.7%
Blood transfusion before ICU admission	2.4%	15.7%	5.4%
Shock with BP ≤ 90 mmHg prehospital or on admission	3.0%	12.7%	5.1%
Intubated/ventilated on ICU	15.5%	79.3%	29.5%
Sepsis	0.5%	16.4%	4.4%
Multiple organ failure	2.9%	40.7%	13.0%
OF Lung/respiration	2.3%	31.8%	10.1%
OF heart/blood pressure	5.0%	43.5%	15.3%
OF coagulation	2.3%	15.0%	5.7%
OF liver	0.1%	2.0%	0.6%
OF kidney	0.6%	5.8%	2.0%
OF central nervous system	3.3%	32.2%	11.0%

OF, organ failure; ICU, intensive care unit; ASA, American Society of Anaesthesiologists classification; BP, (systolic) blood pressure.

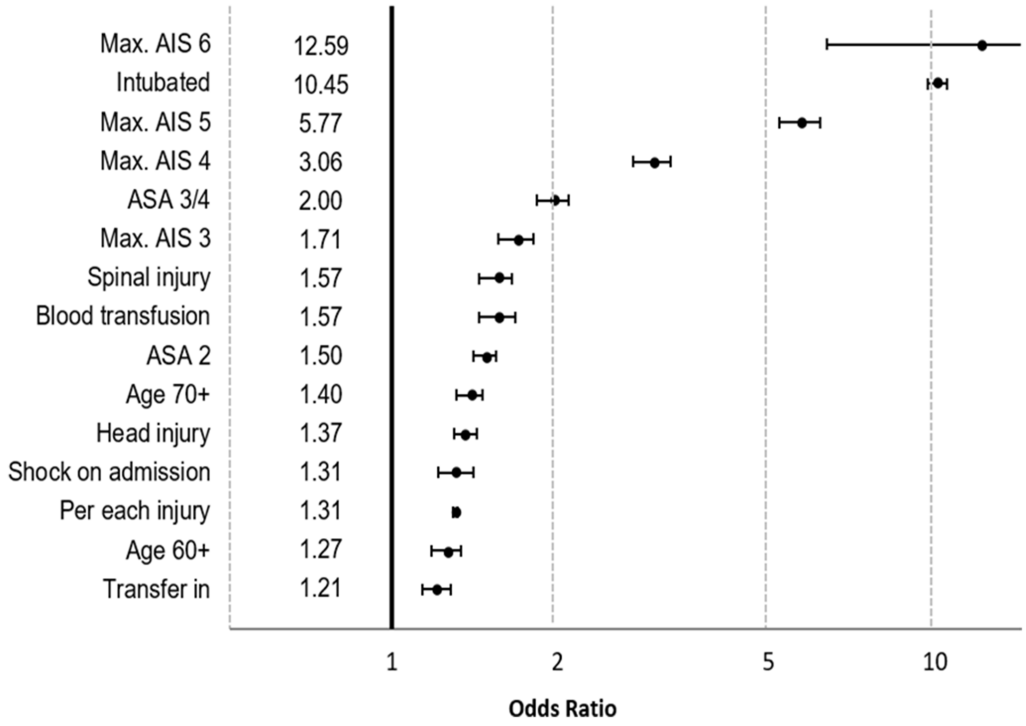

FIGURE 2
Results of logistic regression analysis for prediction of prolonged ICU stay. Effects are presented as odds ratios with 95% confidence intervals.

6.49–24.43; $n = 81$; mostly high cervical spine injury). Based on the coefficients of the model, a formula was derived for calculation of the risk for prolonged ICU stay (Table 2). According to this formula, 21.9% of patients were expected to need a prolonged ICU stay. Figure 3 compares observed and predicted risk for a prolonged ICU stay in patients with different risk levels. The majority of patients (58.2%) had a low probability <10% for a prolonged ICU stay.

Length of stay prediction

In a second step only survivors with a prolonged ICU stay were considered (at least 8 days; $n = 22{,}830$). Patients with a very prolonged ICU stay ($n = 3{,}906$; 16.4%) were not excluded but their LoS was truncated at 30 days for this analysis. The linear regression analysis used the same predictors as in the first step, plus the information whether a case was still intubated and ventilated at day 8.

All predictors, except for "transfer in," had an effect size of at least 0.2 days on LoS and were included in the final model. Number of injuries and severity level of the worst injury (max AIS) had a linear effect on LoS, but age did not. Table 3 describes the final linear model where the coefficients correspond to days. The R^2 was 0.40 so that nearly half of the variation could be explained by the model. Table 4 gives the final formula for calculating the expected number of days on ICU. Starting with the constant term (9.4 days) values of 0.2 to 8.8 were added in case of the respective finding. Requiring ventilation beyond day 7 is by far the strongest predictor (+8.8 days), and only thoracic trauma reduces the estimated LoS.

The observed length of stay in this group was 18.0 days (SD 7.8; median 16; IQR 11–25; range 8–30). The mean value for the estimated length of stay was 17.9 days (SD 15.6; median 15.6; IQR 13–23; range 9.9–28.0). Observed and predicted values were highly correlated ($r = 0.633$) (Figure 4). The mean absolute error (MAE) was 5.0 days, and the root mean squared error (RMSE) was 6.1 days.

Validation

Using the same inclusion and exclusion criteria, a total of 72,062 patients from TR-DGU (2019–2022) were available for validating the previous results. Table 5 summarizes the results. Figures 5, 6 present observed and expected values per year for both measures, risk of requiring a prolonged ICU stay and expected LoS in patients with a prolonged stay.

Discussion

The aim of this project was to establish a benchmark for surviving patients in external quality control. While adjusted risk of death prediction is established in nearly all trauma registries, only few outcome indicators are available for survivors. Besides quality of life assessment (which is hard to implement), complication rates and length of stay are candidates (9). We agree with Kramer who stated in a recent review that "ICU LoS predictions should not be used for individual patients, but can be useful for benchmarking efficiency across ICUs and patient groups" (6). Both measures, however, require an adjustment for injury severity, like mortality. Excellent hospitals that could prevent severe cases from dying will have more organ failure and longer intensive care in survivors.

TABLE 2 Formula for calculating the risk of prolonged ICU stay (8 or more days).

Predictor	Reference	Points weights	
Constant	---	**−4.83**	
Age	<60 years	**+0.24**	if 60–69 years old
		+0.33	if 70 years or older
Number of injuries	---	**+0.27**	per each injury (max. 13)
Worst injury	AIS 2	**+0.54**	if AIS = 3
		+1.12	if AIS = 4
		+1.75	if AIS = 5
		+2.53	if AIS = 6
Head injury	AIS 0–2	**+0.32**	if AIS 3–6
Spinal injury	AIS 0–2	**+0.45**	if AIS 3–6
Ventilation on ICU	No	**+2.35**	if ventilated
Pre-injury status	ASA 1	**+0.40**	if ASA = 2
		+0.69	if ASA = 3 or 4
Blood transfusion before ICU admission	no	**+0.45**	if yes
Shock pre-clinical or on admission	no	**+0.27**	if yes
Transfer in from other hospital	no	**+0.19**	if yes
Let **X** be the sum of point weights per case. Using the exponential function with Euler's number **e**, the risk of prolonged ICU stay is then calculated as: RISK = $\mathbf{e}^X/(1+\mathbf{e}^X)$.			

For values in the reference category, no points were added. The point weights were derived from the coefficients of the logistic regression analysis (full model: see Supplementary Table 2A). Bold values are used in the formula for calculating the risk of prolonged ICU stay.

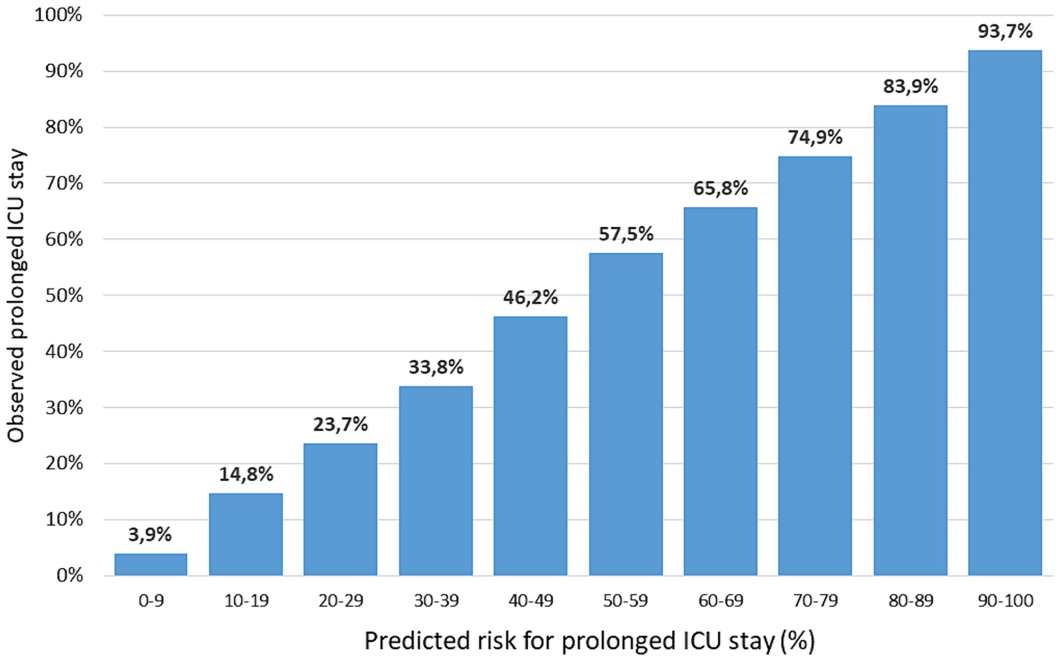

FIGURE 3
Observed (vertical axis) and predicted (horizontal axis) risk of prolonged ICU stay in the development set. Predicted risk is grouped in 10 categories of equal range; sample sizes per category range from 2,892 (90–100) to 63,011 (0–9).

Previous attempts to measure resource use include the Standardized Resource Use (SRU) quantification published by Rothen et al. (10) which is plotted against the standardized mortality rate (SMR). This approach has been developed in a general ICU population including all patients, also non-survivors. It estimates expected ICU LoS per survivor in different severity strata, and cumulated expected number of days were compared to observed ones. However, this approach also distributes resources used in non-survivors among the

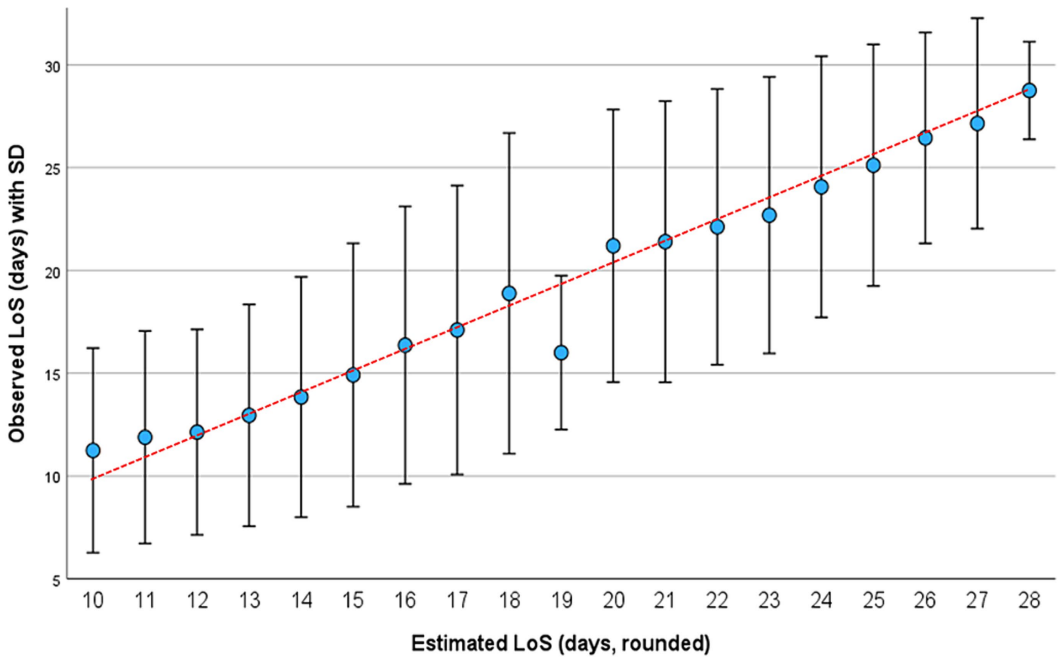

FIGURE 4
Observed (vertical axis) and estimated (horizontal axis) LoS on ICU in 23,830 patients of the validation set. Long stays were truncated at 30 days. Results are presented as mean with standard deviation (SD).

TABLE 3 Results of linear regression analysis of length of stay on ICU for 23,830 patients with a prolonged ICU stay (8–30 days).

Parameter	Prevalence	Coefficient	95% CI
Age ≥ 50 years	57.2%	0.49	0.30–0.68
Male sex	72.9%	0.56	0.39–0.74
Pre-injury status			
ASA 2	33.5%	0.61	0.41–0.81
ASA 3 or 4	21.0%	1.09	0.85–1.33
Maximum AIS severity (2–6)*	---	0.21	0.11–0.31
Number of injuries (1–13)*	---	0.26	0.22–0.29
Serious head injury	49.4%	0.40	0.21–0.60
Serious thoracic injury	50.8%	−0.57	−0.75–−0.38
Serious abdominal injury	12.4%	0.51	0.26–0.76
Serious spinal injury	13.1%	0.84	0.60–1.09
Serious extremity injury	31.9%	0.77	0.57–0.96
Blood transfusion	15.7%	0.97	0.73–1.20
Shock	12.7%	0.44	0.20–0.69
Ventilated on ICU	79.3%	0,65	0.43–0.88
Ventilated > 7 days on ICU	47.0%	8.82	8.64–9.00

*Variable with multiple values; coefficient is the effect per one point.

surviving patients, and therefore SRU is strongly correlated to mortality and the SMR. The present approach is limited to survivors only, and it uses LoS predictors specifically available for severe trauma patients only.

Prediction of length of stay is a methodological challenge since data are rather skewed. Several methods were suggested in the literature where each methods has its strengths and weaknesses (7, 11, 12). We applied the approach of Kramer et al. which has some appealing properties: The first step is a classical binary prediction model for a prolonged ICU stay. In a second step, LoS will be predicted in those patients with a prolonged stay only. This means that for the large number of patients with a limited need for intensive care no LoS

TABLE 4 Formula for calculating the estimated number of days on ICU in patients with prolonged ICU stay (8–30 days).

Estimated ICU LoS =	9.4 days	(constant)
	+0.5 days	if age ≥ 50 years
	+0.6 days	if male sex
	+0.6 days	if pre-injury status was ASA 2
	+1.0 days	if pre-injury status was ASA 3/4
	+0.25 days	multiplied with number of injuries (1–13)
	+0.2 days	multiplied with maximum AIS severity (2–6)
	+0.4 days	if serious head injury (AIS 3+)
	−0.6 days	if serious thoracic injury (AIS 3+)
	+0.5 days	if serious abdominal injury (AIS 3+)
	+0.8 days	if serious spinal injury (AIS 3+)
	+0.8 days	if serious injury of the extremities (AIS 3+)
	+1.0 days	if blood transfusion before ICU admission
	+0.4 days	if shock preclinical or on admission
	0.7 days	if ventilated on ICU
	+8.8 days	if still ventilated on day 7

TABLE 5 Summary results from the development and validation dataset.

	Development dataset	Validation dataset
Years	2014–2018	2019–2022
Number of patients	*n* = 108,178	*n* = 72,062
ICU length of stay (days)*	2 (1–6)	2 (1–6)
	6.3 days	5.7 days
Prolonged ICU stay (>7 days)	*n* = 23,830	*n* = 14,243
	22.0%	19.8%
Expected rate of patients with a prolonged ICU stay	21.9%	20.8%
Area under the ROC curve, with 95% confidence interval	0.903 (0.900–0.905)	0.895 (0.892–0.898)
For patients with prolonged ICU stay		
Length of stay (range 8–30)*	16 (11–25)	15 (10–25)
	18.0	17.5
Estimated length of stay (days)*	15.6 (13.3–22.8)	14.8 (13.2–22.6)
	17.9	17.5
Pearson's correlation of observed and predicted length of stay	0.613	0.611

*Median with IQR, mean.

prediction will be performed. It has been reported that including also patients with a short ICU stay will lead to a model that very much focuses on these short stay patients, and prediction of longer stays become uncertain (13, 14).

Also most recently published LoS prediction models like the one by Peres et al. perform a parallel prediction of the risk of a long stay (15). But like other prediction models, their intention is an early identification of long stay patients, including non-survivors, in a general intensive care unit.

In our study 78% of patients left ICU within 1 week. This cut-off value was chosen based on clinical reasoning since major complications like sepsis or multiple organ failure usually would require more than 1 week of intensive care. In short stay patients, it is less important whether LoS was 2, 3, or 4 days. Such a decision often depends on organizational or other reasons rather than solely on the patient's condition. So the first step is calculated in all cases, and the focus is on needing a substantial amount of intensive care.

Only in a second step LoS is directly predicted using a regression analysis. As previously recommended, very long stays were truncated at 30 days (14, 16). In our study only 3.6% of cases had a stay of more than 30 days. Among these cases with a very long ICU stay only one third required a stay longer than 42 days. But those cases would seriously influence the prediction model.

Our first model was able to identify several predictors for a prolonged intensive care in survivors. As expected, the severity (here: worst AIS severity level) and the number of injuries are the strongest predictors, combined with the need for mechanical ventilation in ICU. Also pre-existing diseases (pre-injury ASA status) and higher age predict a prolonged ICU stay. Among specific injuries, spinal cord and head injuries were relevant predictors while injuries to the rest of the body only showed a marginal additional effect, after adjustment for severity. The final model was able to explain a lot of the observed variation (Nagelkerke's $R^2 = 0.54$). The validation of this model in the years 2019–2022 showed good results, with only 1.0% difference between observed and predicted rates. This difference is mainly based on the most recent 2 years where less patients needed a prolonged ICU stay. This might be the continuation of a previously published trend of shorter ICU length of stay observed by Böhmer et al. (17) in the same registry. It might reflect improvements in intensive care in the early care, but this is speculative.

Moore et al. also tried to predict LoS on ICU in severe trauma patients (9). They found that injury severity (worst AIS in six body regions) and age each contributed more than one third of the explained variation of the model. The remaining predictors (comorbidities, mechanism of injury, transfer, GCS, repeated ICU visit) together explained the rest. This is similar to risk of death prediction where injury severity and age also are the most important predictors. The prediction model of Kramer and Zimmerman who also predicted a prolonged ICU stay first (more than 5 days) used a general ICU population (6). They also found that the need for

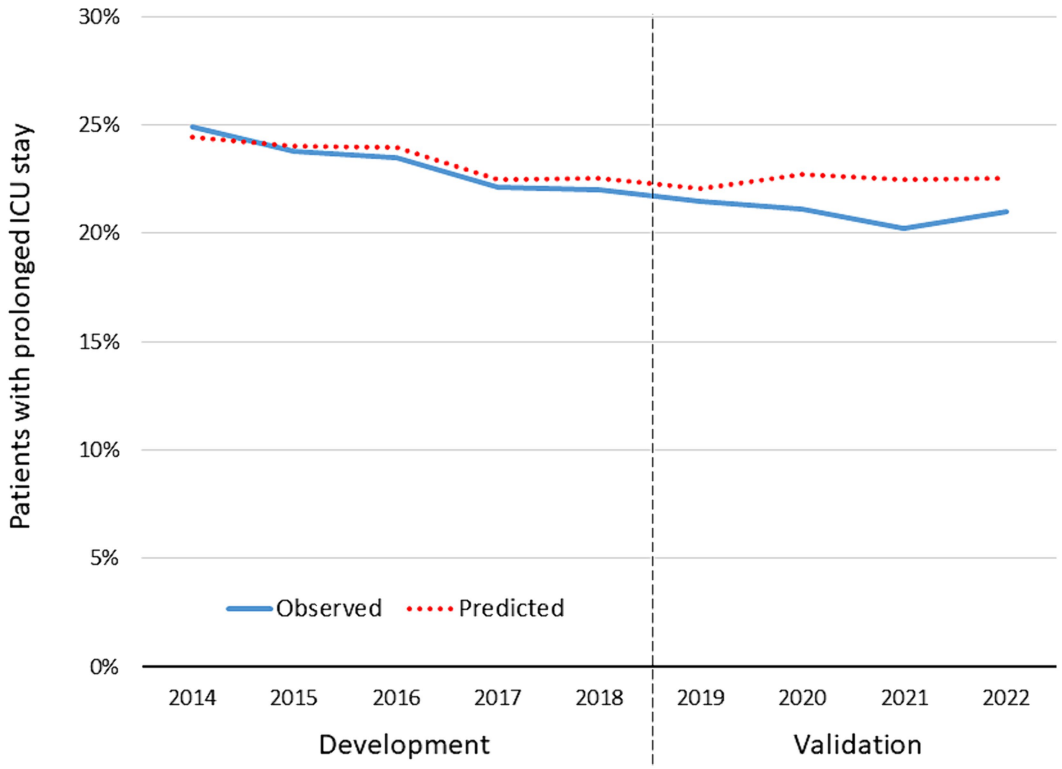

FIGURE 5
Observed and expected rate of patients with a prolonged ICU stay in survivors treated on ICU (n = 180,240). The years 2014–2018 served as development data for the prediction model; the years 2019–2022 served as validation for the model.

ventilation on day one was highly predictive. They found an even higher effect for "unable to assess GCS" which is obviously associated with sedation and mechanical ventilation. Since trauma patients were just a small subgroup in the data of Kramer and Zimmerman, they used the general Acute Physiology Score [from APACHE IV (14)] instead of injury severity. Other authors used similar general severity scores, like the Simplified Acute Physiology Score (SAPS II) or the Mortality Prediction Model (MPM) (18, 19).

The second model is a linear regression predicting length of stay, truncated at 30 days, in patients with prolonged ICU stay. We used real days here, and not a transform of LoS, so that the coefficients could directly be interpreted as number of days in the final model. There is one exceptional factor among the predictors, which is need for a prolonged need for artificial ventilation on day 8. This finding would add 8.8 days to the constant value of 9.4 days. None of the other predictors had a similar effect size. The only predictor with a negative weight was thoracic trauma (−0.6 days).

The outstanding importance of artificial ventilation for LoS prediction has also been found in previous analyses. Peres et al., for example, found ventilation to be the most important factor, applying various machine-learning approaches (15).

Validation of predicted LoS showed a nearly perfect concordance with observed LoS. During the validation phase LoS was about 0.5 days shorter than in the development phase. This corresponds with the slightly lower risk for a prolonged stay observed in the first model.

Future studies in this area will focus on further validation analyses with existing LoS prediction models, like Standardized Resource Use (SRU) (10) and their applicability in the subset of trauma ICU patients. The Standardized Length of Stay Ratio (SLOSR) approach showed already improved results compared to SRU (20). The focus on survivors only, as we did here, does not require to limit resources in non-survivors. Thus long ICU stays in patients who finally died will not affect the LoS estimation. Our approach could serve as a perfect complement to severity-adjusted mortality prediction, and the combination of both seems promising [as Rothen et al. did (10)]. Further analyses will focus on early complications in patients with less than 7 days on ICU.

Limitations

Length of stay prediction is not an easy task, as mentioned above. The approach which we used may not be the best strategy. Other methods including transformations, machine learning, or different regression models may have reached superior results. However, the observed R^2 values were large enough to support an application in benchmarking. Furthermore, the formulas we derived for calculating expected need for a prolonged ICU stay, as well as LoS, are based on coefficients rounded to one decimal. This seemed to be reasonable regarding the respective confidence intervals. Furthermore, using days instead of some transformation thereof might be suboptimal, but on the other hand, the results could directly be interpreted as days. This is an advantage when communicating the results to clinicians.

The validation period coincides with the COVID pandemic. During that phase, intensive care has been challenged a lot, and therapeutic changes may have occurred. However, separate analyses from the

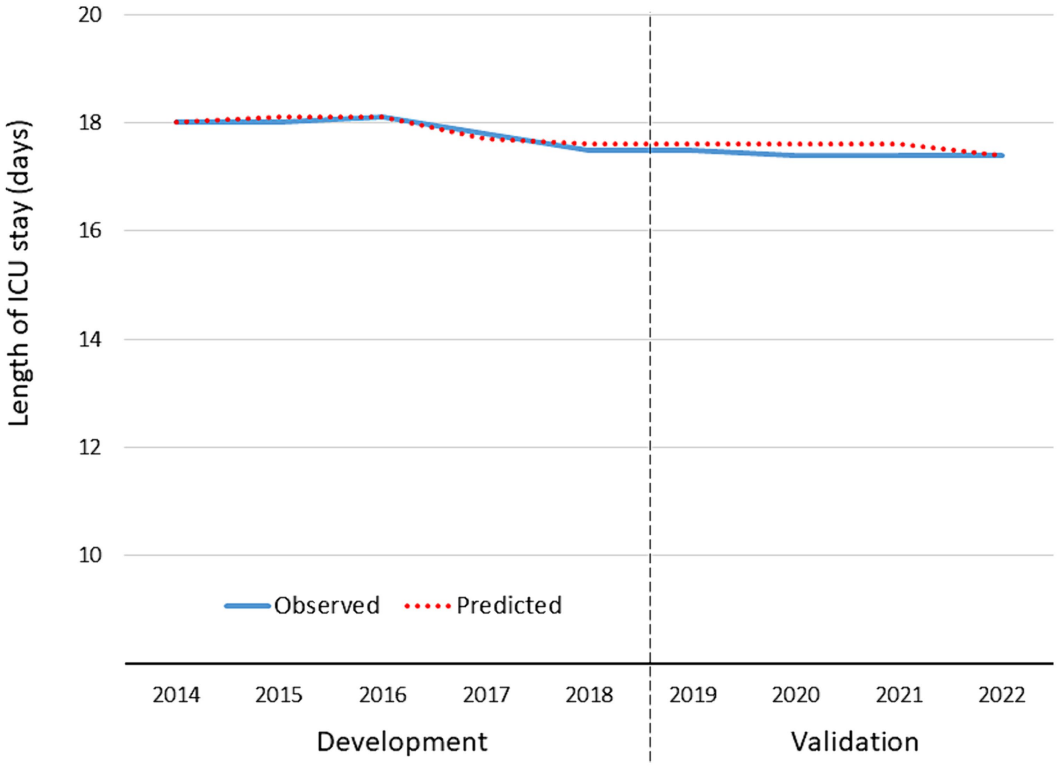

FIGURE 6
Observed and expected average length of ICU stay in patients with a prolonged ICU stay > 7 days (n = 38,064). The years 2014–2018 served as development data for the prediction model; the years 2019–2022 served as validation for the model.

TR-DGU did not suggest that less trauma patients received intensive care, nor that length of stay did change during the pandemic (21).

As has been observed in the past, intensive care is rather resource-consuming, and economic challenges may have future impact on ICU length of stay. Thus a continuing re-validation and potential calibrations are mandatory.

Finally, such models will not necessarily reflect the situations in other countries. The results may depend on the availability of ICU beds, and on how intensive care is refunded.

Conclusion

Length of stay on ICU is an adequate outcome measure in survivors after severe trauma and could be used in benchmarking after adjustment for severity. We developed a prediction model for a prolonged ICU stay (>7 days), and an estimator for LoS in patients who needed intensive care for more than 1 week. Both instruments were validated and will be used in future quality reports.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: according to the guidelines of the German Trauma Society (DGU) and the Akademie der Unfallchirurgie (AUC GmbH) who runs the registry, data from TR-DGU are not publicly available. However, applications for analyses could be forwarded to AUC. The corresponding author will answer requests for data details regarding the present project. Requests to access these datasets should be directed to support-tr@auc-online.de.

Ethics statement

The present study is exclusively based on routinely collected data gathered for the purpose of legally required external quality control. Thus no patient consent was required. Our responsible ethics committee (University Witten/Herdecke, Germany) decided regarding a previous similar request (reference no. 64/2018) that no separate vote is required when such de-personalized data are analyzed.

Author contributions

RL: Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. CW: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

TraumaRegister DGU

Committee on Emergency Medicine, Intensive Care and Trauma Management (Sektion NIS) of the German Trauma Society (DGU).

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Conflict of interest

RL declares that his institution (University Witten/Herdecke) has an ongoing service agreement with AUC GmbH (Akademie der Unfallchirurgie; the owner of the TraumaRegister DGU) which includes the statistical support in registry data analysis.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1358205/full#supplementary-material

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