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ORIGINAL RESEARCH

Frailty Predicts in-Hospital Death in Traumatic Brain Injury Patients: A Retrospective Cohort Study

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Background and Aim: Traumatic brain injury (TBI) is a severe public health problem in elderly patients, and frailty is associated with higher mortality rates in older patients. This study aims to assess the prognostic value of frailty in patients with TBI.

Methods: Clinical data from 348 TBI patients treated at Affiliated Kunshan Hospital of Jiangsu University and Kunshan Hospital of Traditional Chinese Medicine between December 2018 and December 2020 were retrospectively collected. Univariate and multivariate logistic regression analyses were used to determine risk factors affecting in-hospital mortality, and receiver operating characteristic (ROC) curves were plotted to assess the discriminatory power of the frailty index. Frailty was assessed using the FRAIL scale, where FRAIL stands for Fatigue, Resistance, Ambulation, Illness, and Loss of weight, with each item scored as 0 or 1.

Results: Using the FRIAL questionnaire, 122 patients had low frailty and 226 had high frailty. Multivariate logistic regression analysis showed that high frailty was a risk factor for in-hospital mortality in TBI patients ($P<0.001$, OR=2.012 [1.788–2.412]). The proportion of infections occurring in the two groups was statistically different ($P=0.015$), with severely infected TBI patients being more likely to develop complications. The ROC curve showed an area under the curve for the FRAIL score of 0.845 [0.752–0.938].

Conclusion: Frailty is an important risk factor for in-hospital mortality in elderly TBI patients, and more attention should be paid to patients with high levels of frailty. Clinicians should consider the degree of frailty when assessing TBI and making treatment decisions.

Keywords: frailty, traumatic brain injury, in-hospital mortality, prognosis

Introduction

Traumatic brain injury (TBI) is a significant public health problem worldwide, with more than 50 million people affected annually.[1,2] Falls and traffic accidents are the leading causes of TBI, particularly in older adults, and the incidence of TBI is increasing in individuals aged 65 years and above. Within this age group, frailty is more prevalent than in younger age groups and is associated with a wide range of geriatric conditions. Therefore, it is crucial to assess the role of frailty after TBI and propose coping methods to mitigate its effects on TBI outcomes.[3,4]

Previous studies have also investigated the impact of frailty or weakness on TBI outcomes. Abdulle et al[5] reported that frailty affects mild traumatic brain injury, which accounts for approximately 80% to 90% of all traumatic brain injuries, in older adults and is associated with poor long-term outcomes, even though most patients recover within 6 months without the need for specialized treatment. In recent years, there has been increased awareness of frailty in neurosurgery, which exhibits a high degree of heterogeneity. A literature review by Pazniokas[6] revealed several studies indicating that increased frailty is correlated with higher rates of complications and increased mortality. This is because

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frail elderly patients are less able to manage themselves and are more vulnerable, particularly those who require surgery after TBI. Joseph's findings indicated that frailty triples the likelihood of failure to resuscitate in older trauma patients.[7]

Although frailty has been widely recognized as being associated with adverse health outcomes in elderly patients, its specific impact on TBI patients has not been adequately studied. With the increasing global trend of aging, the incidence of TBI in the elderly population has also risen significantly. Since frailty is more prevalent in this population, it may influence the treatment options and prognosis for TBI patients. However, there is still a lack of sufficient research focused on this particular group. The objective of this study was to evaluate the degree of frailty in TBI patients and investigate its impact on patient outcomes. Additionally, potential interventions aimed at reducing in-hospital mortality and improving prognosis were explored.

Materials and Methods

Patient Selection

This retrospective cohort study included TBI patients treated at the Department of Neurosurgery in Affiliated Kunshan Hospital of Jiangsu University and Kunshan Hospital of Traditional Chinese Medicine between December 2018 to December 2020. TBI was defined as brain injury caused by external forces, including concussion, brain contusion, traumatic epidural hemorrhage, traumatic subdural hematoma, and traumatic cerebral hemorrhage. The diagnosis of TBI was confirmed by two imaging specialists who issued a joint report on brain CT and MRI findings. All cases were subjected to strict inclusion and exclusion criteria, which were (1) confirmed diagnosis of TBI, (2) age > 70 years, and (3) no treatment before admission; exclusion criteria were (1) death within 24 hours of admission (2) no FRAIL questionnaire (3) combined malignancy (4) incomplete clinical information. This retrospective study was approved by the Ethics Committee of Affiliated Kunshan Hospital of Jiangsu University and followed the Declaration of Helsinki. All patients provided informed consent. Laboratory tests, such as routine blood, urine, liver and kidney function, electrolytes, and blood and urine amylase, were conducted within six hours of emergency admission. Imaging studies, such as head CT or MRI, were also performed. The diagnosis of traumatic brain injury was established through a multidisciplinary discussion between neurologists, neurosurgeons and imaging physicians.

Questionnaire for FRAIL Scores

The FRAIL scale is a well-researched tool with demonstrated reliability, validity, and ease of implementation in clinical practice, making it a practical choice for assessing frailty in elderly patients[8–10] The FRAIL score is a 5-point scale where each item, including activity tolerance, walking fatigue, exertional fatigue, number of comorbidities, and recent weight loss, is scored as 1. Two professional follow-up specialists administered the questionnaire to patients after receiving appropriate training and briefing. Patients were categorized into low frailty (FRAIL score 0–1) or high frailty (FRAIL score 2–5) based on their questionnaire results. If the patient was unable to answer the questions for any reason, the professionals usually consulted with family members and/or emergency contacts to complete the questionnaire on behalf of the patient.[8]

Clinical Data Collection

Clinical information was extracted from Affiliated Kunshan Hospital of Jiangsu University and Kunshan Hospital of Traditional Chinese Medicine's medical record system and collected by professional data collectors. This information included gender, age, spine trauma, mechanism of injury, use of hemostatic agents upon admission, hypotension (BP ≤ 90) on arrival, Glasgow Coma Scale (GCS) score on admission, admission destination, type of TBI, injury site, hypoxia, surgical interventions, and vital signs on admission (systolic blood pressure in mmHg, diastolic blood pressure in mmHg, heart rate in bpm, and body temperature in °C).[11]

Data Analysis

The *t*-test was used when two groups of continuous variables conformed to a normal distribution. The rank sum test was used for continuous variables that did not conform to a normal distribution. The chi-square or Fisher's exact test was used when the two groups were categorical variables. Variables with P<0.05 were first screened by univariate logistic regression analysis and then included in multivariate logistic regression analysis to screen out risk factors and determine the efficacy of the FRAIL index to predict in-hospital mortality using receiver operating characteristic curves (ROC).

All data in the text were analyzed using SPSS 25.0 (IBM, Armonk, New York, USA), and P<0.05 (two sides) was considered statistically significant. Images were drawn using R language (version 4.0.5) and GraphPad Prism (version: 8.0). Sample size estimation was performed before the study using PASS (version: 11.0).

Results

Baseline Information of Low Frailty and High Frailty Group

FRAIL has a maximum score of 5, with a total of five items, each with a score of 0 or 1. A total of 58 patients scored 0 (Orange), 64 patients scored 1(Blue), 50 patients scored 2 (Cyan), 61 patients scored 3(Red), 81 patients scored 4 (Purple), and 34 patients scored 5 (Black)(Figure 1).

A total of 348 patients, including 122 with low frailty and 226 with high frailty, were included in the study based on strict inclusion and exclusion criteria (Figure 2). In the low frailty group, 73 (59.8%) were males, while in the high frailty group, 165 (73.0%) were males, with a significant difference between the two groups (p=0.015). The highly frail group was relatively older (P=0.041), had a higher proportion of admissions with hemostatic agents at 79.6% (P=0.048), lower GCS score at admission, with 28.3% of patients having a total score of 3–8, which was higher than the low frailty group (p=0.047). Additionally, the number of multiple injury sites was higher in the highly frail group, with 114 single injury sites (80.4%), compared to 69.7% in the low frailty group (p<0.001). On admission, highly frail patients had a higher temperature, with a median temperature of 36.9°C (P=0.032), and 57 patients were admitted to the ICU, accounting for 25.2%, which was higher than the proportion of patients with low frailty (P=0.009). No statistically significant differences were observed between the two groups in the remaining variables (Table 1).

Analysis of Risk Factors Affecting in-Hospital Death Using Univariate and Multivariate Logistic Regression

Univariate and multifactorial logistic regression analyses were performed for all patients, and variables for which univariate logistic regression yielded P<0.05 were included in the multivariate logistic regression model. Variables that

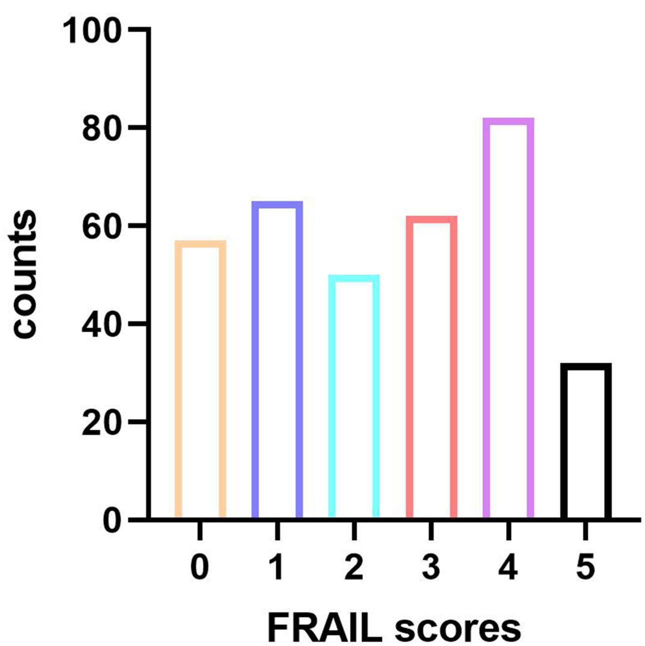

Figure 1 Number of people with different FRAIL scores.

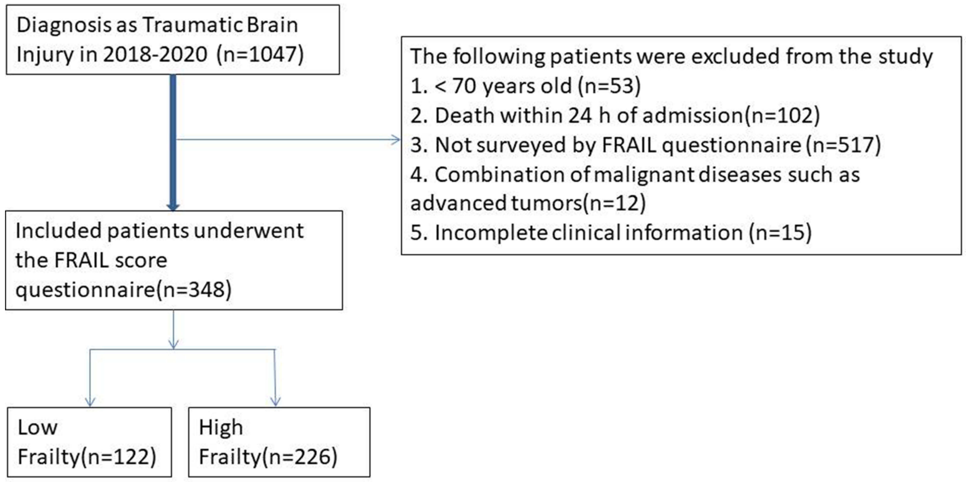

Figure 2 Inclusion and exclusion table for patients with TBI.

were statistically significant in the univariate analysis included Age (P=0.018), Hypotension (BP≤90) on arrival (P=0.041), GCS score on admission (P<0.001), and Frailty (P<0.001). The final multivariate logistic regression results were BMI<25 (OR=0.788, 95% CI: 0.517–0.912, P<0.001 vs >80), Hypotension (BP≤90) on arrival's No (OR=0.912, 95% CI: 0.831–0.975, P=0.012 vs Yes), GCS score on admission's severe (OR=0.877, 95% CI: 0.681–0.913, P<0.001 vs

Table 1 Baseline Characteristics in TBI Patients with Different Levels of Fatigue (N = 348)

		Low Frailty (n=122)	High Frailty (n=226)	P-value[‡]
Gender				0.015
	Male Female	73 (59.8) 49 (40.2)	165 (73.0) 61 (27.0)	
Age				0.041
	<80 y ≥80 y	100 (82.0) 22 (18.0)	163 (72.1) 63 (17.9)	
Spine Trauma				0.393
	No Yes	104 (85.2) 18 (14.8)	201 (88.9) 25 (11.1)	
Mechanism of injury				0.253
	Traffic accident High fall Stumble Others[§]	83 (68.0) 22 (18.0) 12 (9.8) 5 (4.2)	140 (62.0) 36 (15.9) 30 (13.3) 20 (8.8)	
Use of hemostatic agents on admission[‡]				0.048
	No Yes	37 (30.3) 85 (69.7)	46 (20.4) 180 (79.6)	
Hypotension (BP ≤ 90) on arrival				0.503
	No Yes	120 (98.4) 2 (1.6)	219 (96.9) 7 (3.1)	

(*Continued*)

Table 1 (Continued).

		Low Frailty (n=122)	High Frailty (n=226)	P-value‡
GCS score on admission				0.047
	Severe (3–8) Moderate (9–12) Mild (13–15)	24 (19.7) 16 (13.1) 82 (67.2)	64 (28.3) 41 (18.1) 121 (53.6)	
Admission Destination				0.009
	General ward Intensive Care Unit	106 (86.9) 16 (13.1)	169 (74.8) 57 (25.2)	
Type of TBI				0.732
	Diffuse brain injury Focal brain injury Uncategorized	65 (53.3) 44 (36.1) 13 (10.6)	128 (56.6) 79 (35.0) 19 (8.4)	
Injury site				0.001
	1 2 ≥ 3	85 (69.7) 30 (24.6) 7 (5.7)	114 (50.4) 79 (35.0) 33 (14.6)	
Hypoxia				0.625
	No Yes	104 (85.2) 18 (14.8)	197 (87.2) 29 (12.8)	
Surgical interventions				0.797
	Decompressive craniectomy Hematoma evacuation	43 (35.2) 51 (41.8)	75 (33.2) 97 (42.9)	
Vital signs in admission				
Systolic blood pressure (mmHg)		122 (105–140)	120 (103–137)	0.288
Diastolic blood pressure (mmHg)		73 (66–87)	70 (56–84.5)	0.317
Heart rate (bpm)		97 (85–120)	103 (84–123.5)	0.102
Body temperature (°C)		36.4 (36.1–37.0)	36.9 (36.4–37.3)	0.032

Notes: The values in parentheses are percentages unless indicated otherwise. ‡ χ^2 test with Yates' correction, § Sharps injuries, firearm injuries, etc, ‡Use of anticoagulants or antiplatelet drugs.
Abbreviations: TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; BP, Blood pressure.

Moderate; OR=0.566, 95% CI: 0.322–0.782, P<0.001 vs Mild) and Frailty's High (OR=2.012, 95% CI: 1.788–2.412, P<0.001 vs Low) were significantly associated with in-hospital death (Table 2). For the particular variable of frailty, the multivariate obtained OR was the largest of all variables.

Comparison of Complications in Patients with TBI with Low and High Frailty

In the low frailty group, there were 12 patients (9.8%) with neurological complications; in the high frailty group, there were 36 patients (15.9%) with neurological complications, with no statistical difference between the two groups. For non-neurological complications, there was a statistical difference in the proportion of infections that occurred in the two groups (p=0.015)(Table 3).

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Table 2 Univariate and Multivariate Logistic Regression Analysis of Risk Factors Associated with in-Hospital Mortality in All Patients

Variables	Univariate Analysis			Multivariate Analysis		
	P	HR	95% CI	P	HR	95% CI
Gender	0.132					
Male		Ref	–			
Female		0.812	0.417–1.335			
Age (years)	0.018			<0.001		
≥80		Ref	–		Ref	–
<80		0.893	0.776–0.925		0.788	0.517–0.912
Spine Trauma	0.554					
Yes		1.105	0.897–1.354			
No		Ref	–			
Mechanism of injury	0.232					
Traffic accident		Ref	–			
High fall		1.312	0.678–2.122			
Stumble		0.784	0.388–1.318			
Others		1.121	0.912–1.432			
Use of hemostatic agents on admission	0.556					
Yes		Ref	–			
No		0.849	0.493–1.463			
Hypotension (BP ≤ 90) on arrival	0.041			0.012		
Yes		Ref	–		Ref	–
No		0.856	0.566–0.932		0.912	0.831–0.975
GCS score on admission	<0.001			<0.001		
Severe (3–8)		Ref	–		Ref	–
Moderate (9–12)		0.877	0.681–0.913		0.877	0.681–0.913
Mild (13–15)		0.566	0.322–0.782		0.566	0.322–0.782
Admission Destination	0.388					
General ward		Ref	–			
Intensive Care Unit		1.229	0.598–2.527			
Type of TBI	0.712					
Diffuse brain injury		Ref	–			
Focal brain injury		1.026	0.507–2.077			
Uncategorized		0.712	0.289–1.750			
Injury site	0.122					
1		Ref	–			
2		1.123	1.088–1.312			
≥ 3		1.237	0.993–1.433			
Frailty	<0.001			<0.001		
Low		Ref	–		Ref	–
High		1.977	1.679–2.338		2.012	1.788–2.412

Abbreviations: OR, Odds ratios; TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; BP, Blood pressure.

Plotting Receiver Operating Curves (ROC) for Frailty Score as Well as Significant Variables

ROC curves were used to demonstrate the extent to which each variable predicted in-hospital death in patients with TBI, showing the ROC curves for Age, GCS score, and FRAIL score with 1-specificity in the horizontal coordinate and sensitivity in the vertical coordinate. As seen in the figure, the area under the curve for Age was 0.656 (95% CI:0.552–0.761), the GCS score was 0.691 (95% CI:0.585–0.796), and the FRAIL score was 0.845 (95% CI:0.752–0.938) (Figure 3). The optimum cutoff value for each index was determined using the maximum Youden index for sensitivity + specificity-1. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of Age at the

Table 3 Comparison of TBI Complications in Different Fatigue Groups (N = 348)

		Low Frailty (n=122)	High Frailty (n=226)	P-value‡
Neurological complication				0.143
	No	110(90.2)	190(84.1)	
	Yes	12(9.8)	36(15.9)	
Non-neurological complication				
Circulatory				1.000
	No	120(98.4)	221(97.8)	
	Yes	2(1.6)	5(2.2)	
Respiratory				1.000
	No	121(99.2)	224(99.1)	
	Yes	1(0.8)	2(0.9)	
Digestive				1.000
	No	121(99.2)	224(99.1)	
	Yes	1(0.8)	2(0.9)	
Urinary				1.000
	No	121(99.2)	223(98.7)	
	Yes	1(0.8)	3(1.3)	
Coagulation				1.000
	No	121(99.2)	223(98.7)	
	Yes	1(0.8)	3(1.3)	
Infection				0.015
	No	118(97.5)	205(90.7)	
	Yes	3(2.5)	21(9.3)	

Notes: The values in parentheses are percentages unless indicated otherwise. ‡ χ^2 test or Fisher's test.
Abbreviation: TBI, Traumatic Brain Injury.

optimum cutoff value were 0.813, 0.500, 0.639, 0.565, and 0.769, respectively; the GCS scores were 0.781, 0.613, 0.681, 0.610 and 0.774, respectively; and FRAIL scores of 0.844, 0.800, 0.850, 0.771 and 0.865, respectively (Table 4).

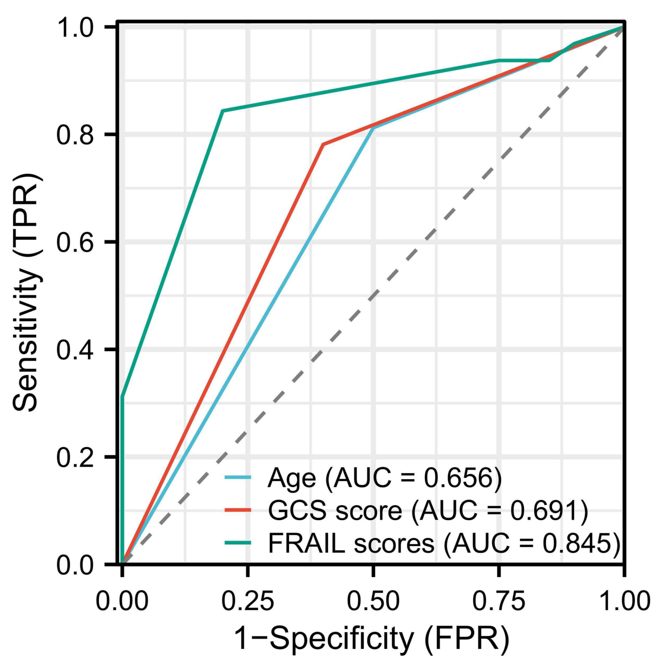

Figure 3 Age, GCS score and FRAIL score of the receiver operating curve.

Table 4 Predictive Value of Risk Factors for in-Hospital Mortality

Predictors	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Age	0.656(0.552–0.761)	0.639	0.813	0.500	0.565	0.769
GCS score	0.691(0.585–0.796)	0.681	0.781	0.613	0.610	0.774
FRAIL scores	0.845(0.752–0.938)	0.820	0.844	0.800	0.771	0.865

Abbreviations: GCS, Glasgow Coma Scale; AUC, areas under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

Discussion

Frailty is a complex and multifaceted condition that varies widely among individuals, manifesting through different physiological, cognitive, and social dimensions. This heterogeneity arises from the fact that frailty is influenced by a combination of factors such as age, comorbidities, and lifestyle, leading to diverse clinical presentations. Some individuals may exhibit physical frailty (eg, muscle weakness, fatigue), while others may experience cognitive decline or psychosocial issues. As a result, frailty does not present uniformly across all patients, making it a heterogeneous indicator that can complicate both diagnosis and prognosis.[12,13] As frailty is also highly correlated with age, and traumatic brain injury tends to more severely affect patients who are older, it is essential to explore the relationship between frailty and traumatic brain injury. In this study, which included 348 patients with TBI who were hospitalized in neurosurgery, we found that the level of frailty was significantly associated with an increased risk of in-hospital mortality among patients with TBI. Furthermore, our study demonstrated that high frailty was an independent risk factor for in-hospital mortality in patients with TBI. These findings suggest that the assessment of frailty may serve as an important tool for identifying patients with TBI who are at higher risk for adverse outcomes, including mortality, and potentially allow for earlier interventions and improved clinical management. However, further research is needed to better understand the mechanisms underlying the relationship between frailty and TBI, and to identify potential strategies for mitigating this risk factor in clinical practice.

Frailty is widely recognized as a syndrome of decreased reserve and stress resistance, resulting from the cumulative decline of multiple physiological systems. However, its measurement and classification among patients remain highly variable, with various methods for measuring frailty currently available.[14–16] Earlier studies, such as those conducted by Fried et al, identified frailty phenotypes in older adults based on the presence of three or more of the following criteria: unexpected weight loss (10 pounds or more within the past year), self-reported exhaustion, weakness (measured through grip strength), slow walking speed, and low levels of physical activity.[17] These criteria provide a potential basis for the clinical assessment of frailty and for future research to develop standardized measurements of frailty that can be used to guide interventions. In recent years, other researchers have developed different criteria for assessing frailty, such as Searle et al[18], who created a frailty index that links deficit accumulation to individual mortality risk, providing a more precise approach to the assessment of frailty. The assessment tool used in our study, the FRAIL scale, is a quantitative score-based assessment developed by Gleason et al[8] to quantify fatigue, resistance, aerobic capacity, illness, and weight loss. It has been used to stratify elderly surgical patients and implement perioperative care, and was found to be effective in differentiating the frailty of our TBI patients, thus improving our analysis of the relationship between frailty and TBI.

Our study, following the FRAIL questionnaire, identified frailty as a significant risk factor for in-hospital mortality in patients with TBI, contributing to the literature on the association between frailty and trauma.[19–21] The likelihood of frailty is greater in elderly patients, and its effects on aging are manifold. Bellal et al[7] conducted a prospective study showing that frailty tripled the probability of failure to resuscitate in elderly trauma patients. Therefore, it is essential to be aware of the frailty status of elderly patients treated in Level I trauma centers. Sastry et al[22] found that frailty was associated with a higher likelihood of receiving high-intensity interventions (such as in-hospital ventilators or discharge to a care facility) among 100 elderly patients with TBI surveyed, suggesting that patients with TBI who are accompanied by frailty should receive priority attention in neurosurgical wards to avoid further damage. An international team of researchers, including those from CENTER-TBI and TRACK-TBI, developed and externally validated a frailty index, which demonstrated that higher scores were associated with greater frailty and a significantly increased risk of adverse outcomes.[23] They recommended that patients with high frailty index in TBI should be identified early enough to allow for individualized rehabilitation programs, which could mitigate the effects of frailty in TBI patients. Using data from the US National Injury Database of nearly 700,000 patients with TBI, Tang et al[24] showed that frailty was an independent predictor of poor prognosis, including the need for longer duration of ventilator support, and ultimately led to higher mortality and morbidity, independent of injury severity.[25]

Previous studies have investigated various factors that affect the prognosis of patients with TBI. Ozyurt et al[26] concluded that both gender and age differences influence the prognosis of TBI, with male patients having a higher mortality rate and experiencing more complications in older patients. Flaherty et al[27] predicted moderate to severe TBI using the lactate to albumin ratio, with higher ratios indicating a greater likelihood of survival, making it a useful prognostic indicator for treatment decisions at the time of TBI patient assessment. Birle et al[28], on the other hand, predicted all-cause mortality in craniocerebral injury using the systemic inflammatory response index, which reduced confounding bias by PSM. They found that high inflammatory response is associated with a high risk of death within 30 days of hospitalization and mortality within one year of discharge, concluding that combining inflammatory factors is a better predictor than a single predictor.

There are several limitations to this study. Firstly, it is a retrospective study, which may introduce selection bias and confounding bias. Additionally, the study was performed at a single-center, so further data from other centers are needed to support our findings. Secondly, the degree of frailty was assessed using only the FRAIL questionnaire, which may be subject to information bias. The use of additional questionnaires could have provided a more comprehensive assessment of frailty in our patients.

Conclusion

Frailty, as assessed by the FRAIL questionnaire, is a significant risk factor for in-hospital mortality in elderly patients with TBI. Given the strong association between high frailty scores and adverse outcomes, it is recommended that clinicians assess frailty at the time of injury diagnosis. The FRAIL scale, due to its simplicity, reliability, and ease of implementation, can be a practical tool for this purpose. By integrating frailty assessment into the initial evaluation of TBI patients, clinicians can better stratify risk, tailor treatment decisions, and potentially improve patient outcomes.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent Statement

This research was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Affiliated Kunshan Hospital of Jiangsu University. Informed consent was obtained from all subjects and/or their legal guardian(s).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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