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Early neurological wake-up test in intubated patients with traumatic brain injury

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Abstract

Background Daily wake-up has been implemented widely in intensive care units (ICU) and could improve the patients' prognosis. However, little is known about the benefit of early neurological wake-up test (ENWT) in patients with acute traumatic brain injury (TBI). We aimed to investigate the role of ENWT as a clinical monitoring tool for TBI and its association with prognosis.

Methods This is an observational retrospective study included intubated and continuously sedated TBI in ICU, and all data were extracted from three tertiary hospitals from China. The main exposure of interest was ENWT, defined as cessation of sedation within 24 h after admission. The primary outcome was 28-day mortality. Propensity score matching (PSM) was performed at a 1:1 ratio. Multivariable analyses were further used to adjust for residual confounders.

Results The pre-matched and propensity score-matched cohorts included 1386 and 704 patients, respectively. In the PSM analysis, 28-day mortality was 24.7% (87/352) in the ENWT group and 37.2% (131/352) in the control group. ENWT was associated with lower 28-day mortality (hazard ratio [HR], 0.57; 95% CI, 0.44–0.76; $P<0.001$). ENWT was also associated with lower in-hospital mortality (odds ratio [OR], 0.54; 95% CI, 0.38–0.77; $P=0.001$), and higher discharge-home rate (OR, 1.83; 95% CI, 1.19–2.83; $P=0.006$). A sensitivity analysis using the entire cohort also demonstrated lower 28-day mortality (HR, 0.58; 95% CI, 0.44–0.75; $P<0.001$). However, it should be noted that ENWT was related to a higher rate of delirium during ICU stay (OR, 1.66; 95% CI, 1.21–2.26; $P=0.001$). Further analysis demonstrated that tracheostomy during ICU stay led to a significant difference in 28-day mortality.

Conclusion ENWT was associated with a lower risk-adjusted 28-day mortality in acute TBI patients. A higher rate of tracheostomy may partly contribute to this relationship.

Keywords Traumatic brain injury, Mechanical ventilation, Sedation, Neurological wake-up test, Prognosis

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Introduction

Annually, at least 69 million people worldwide sustain traumatic brain injury (TBI), and about 5.48 million people suffer severe TBI, which has become a significant global burden of disability and death [1]. In prehospital setting, several TBI needs tracheal intubation, mechanical ventilation and continuous sedation [2]. Sedation has become an integral part of neurocritical care treatment protocols, which allows a reduction of the intracranial pressure (ICP) and the cerebral metabolic rate, thus limiting the risk of secondary ischemic insult [3]. However, continuous sedation could make the assessment of the neurological status difficult, and also has adverse effects because excessive doses of sedatives may lead to significant morbidity and mortality [4–6].

An early neurological wake-up test (ENWT), defined as interruption of sedation within 24 h and evaluation of the patient's level of consciousness after initial imaging assessment, allows a rapid neurological reassessment after the stabilization of the TBI patients [7]. Actually, clinical examination remains a golden standard for monitoring TBI even in the presence of several advanced neuromonitoring techniques [8]. The physical examination couldn't be replaced by either the brain imaging nor other neurogical monitoring methods [9]. In general ICU, a wake-up and breathe protocol that similar to the neurological wake-up test resulted in reduced ICU stay and better outcomes [6]. To date, there are few reports evaluating the ENWT in TBI, and there are no clinical guidelines for advocating or opposing this practice. In a randomized control trial that applying a daily interruption of continuous sedation strategy in a small group of TBI patients, the authors didn't observe a significant decreased length of mechanical ventilation or ICU stay [10]. Although the neurological wake-up test was found to induce stress response and resulted in transient increased ICP levels [11, 12], it didn't significantly alter the focal cerebral oxygenation and exacerbate the brain injury [12].

The past reports are limited by the small sample size, and more importantly, they did not apply mortality as the primary clinical outcome. Also, the potential association of ENWT with prognosis in TBI patients requires further confirmation. In this study, we aimed to investigate the role of ENWT as a clinical monitoring tool for TBI and its association with mortality.

Material and methods

Data source

This is a multicenter, retrospective cohort study using data collected between November 2016 and October 2023. All ethics committees of the study sites approved the study (IIT20230299B-R1), and written informed consent was waived due to its respective property. This research was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13].

Study population

We searched for consecutive patients with TBI from the Tongji Hospital, Central Hospital of Wuhan and the First Affiliated Hospital of Zhejiang University School of Medicine. The inclusion criteria were: 1) intubated TBI patients confirmed by a brain Computed Tomography scan (CT); 2) presentation to the hospital within 24 h post-injury; 3) patients were continuously sedated and mechanically ventilated on admission. We excluded patients who: 1) had an ICU stay of <24 h; 2) were hemodynamically instable; 3) with elevated ICP (>20 mmHg) if received ICP monitoring; 4) with unstable airway, spine or vent status; 5) with other injuries except for TBI that have an AIS ≥ 3; 6) received craniectomy or other surgery within the first 24 h. Severe TBI was defined as having a Glasgow Coma Scale (GCS) ≤ 8, and mild/or moderate TBI were defined as having a GCS of 9–15 with significant abnormalities at initial CT scan [14].

Exposure and outcomes

The exposure was ENWT, defined as cessation of continuous sedation within 24 h after ICU admission and evaluation of the patient's level of consciousness. The primary outcome was 28-day mortality. Secondary outcomes included in-hospital mortality, one-year all-cause mortality, delirium, discharge-home rate, ventilator associated pneumonia, length of ICU stay, length of hospital stay, and length of invasive mechanical ventilation. The special therapeutic interventions after 24 h from admission including craniectomy and tracheostomy during ICU stay were also recorded. It should be noted that discharge-home rate was used as a proxy for the secondary outcome, since previous researches have indicated that being discharged home was linked to better long-term neurological function for TBI patients [15–17].

Covariates

We collected initial GCS and patients' records after ICU admission, including age, sex, admission location, first care unit, Richmond Agitation-Sedation Scale (RASS), Charlson comorbidity index, Simplified Acute Physiology Score II (SAPS II), Acute Physiology Score III (APS III), SOFA score and ICP monitoring on the first day. We extracted information on comorbidities, such as coronary heart disease, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, liver disease, diabetes mellitus, malignant cancer, rheumatic disease, and sepsis, based on the International Classification

of Diseases coding systems (ICD-9 or ICD-10). We extracted initial records of vital signs (heart rate, mean arterial pressure, ventilatory frequency, body temperature and SpO2), laboratory tests (white blood cell count, platelet count, glucose, hemoglobin, potassium, sodium, calcium, chloride, creatinine, blood urea nitrogen, international normalized ratio, and partial thromboplastin time), and related complications during the ENWT procedure (hemodynamic instability, elevated ICP, and unstable ventilation status).

Statistical analysis

As a retrospective analysis, we performed no priori statistical analysis on the sample size, and all eligible patients were included to improve the statistical power. The study cohort was divided into two groups: those who received ENWT and those who did not. The missing rate of each variable is shown in Table S1. We conducted multiple imputation to estimate missing values for each variable that with a missing rate of less than 25% [18]. The variance inflation factor (VIF) was applied to estimate multicollinearity among variables. A VIF of <5 for each variable indicated the absence of multicollinearity (Tables S2 and 3) [19].

Continuous covariates are presented as median (interquartile range [IQR]) or mean (standard deviation [SD]) based on the normality of the data distribution, and analyzed using either the Student's t test or the Manne-Whitney U-test as appropriate. Categorical variables are reported as number and percentage, and analyzed by Chi-Squared test or Fisher's exact test. Cox proportional-hazards regression model was applied to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the association between ENWT and 28-day mortality. Logistic regression models were used to generate the odds ratio (OR) with 95% CI for dichotomous secondary outcomes. We used Hodgese-Lehmann estimators to calculate the median difference (MD) with 95% CI for continuous secondary outcomes. For all statistics, a two-tailed P value that less than 0.05 was defined statistically significant. The statistical analyses were performed using the RStudio software (RStudio Inc.)

Propensity score matching

We performed primary analyses in the matched cohort to investigate the association between ENWT and primary and secondary outcomes. Propensity score matching (PSM) was performed to adjust variables between the groups received or didn't receive ENWT. The probability of receiving ENWT for each patient was obtained using a logistic regression model. The potential variables in the propensity score model for matching cohort included age, sex, Richmond Agitation-Sedation Scale, first care unit, prehospital GCS, Charlson Comorbidity Index, SOFA, SAPS II and APS III. The matching was performed based on a nearest-neighbour 1:1 matching scheme within a calliper width of 0.1 without replacement. The balance of characteristics between the groups with and without ENWT before and after PSM was evaluated using standardised mean difference (SMD), with a value of <0.1 indicating good balance [20]. In the matched cohort, covariates with a P value <0.05 in the univariable analysis were entered into the multivariable analysis for adjustment, including heart rate, mean arterial pressure, body temperature, SpO2, glucose, and sodium level (Table 1).

Subgroup analyses

Exploratory subgroup analyses in the matched cohort based on age, sex, Charlson Comorbidity Index, and GCS were performed.

Sensitivity analyses

We conducted sensitivity analyses using the entire cohort to test the robustness of the findings observed in the matched cohort. Variables with a $P<0.05$ in univariable analysis were entered into multivariable analysis for adjustment, including age, first care unit, admission location, Charlson Comorbidity Index, SOFA, SAPS II and APS III, coronary heart disease, congestive heart failure, liver disease, ventilatory frequency, body temperature, SpO2, glucose, hemoglobin, sodium, creatinine, blood urea nitrogen, international normalized ratio, and partial thromboplastin time.

Causal mediation analysis

Causal mediation analysis (CMA) [21, 22] is a statistical method for separating the total effect of a clinical intervention into direct and indirect effects. The analysis reports include the average causal mediation effect (ACME), average direct effect (ADE), as well as total effect. In this study, we used the ENWT as the "treatment" and the tracheostomy during ICU stay, craniectomy and length of invasive mechanical ventilation as mediator variables to explore whether the effect of ENWT on the primary outcome was mediated through the mediator variables mentioned above.

Results

Patient selection

The process of patient selection was shown in Fig. 1. A total of 3992 records were identified. After excluding 2606 unqualified records, 1386 intubated patients with TBI were included in the entire cohort, among which 1013 (72.1%) received an ENWT during their ICU stay. The matched cohort included 704 patients (352 in each group).

Table 1 Baseline characteristics before and after propensity score matching

Variables	Before propensity score matching				After propensity score matching			
	Patients without ENWT ($n=373$)	Patients with ENWT ($n=1013$)	P	SMD	Patients without ENWT ($n=352$)	Patients with ENWT ($n=352$)	P	SMD
Age (years), median (IQR)	62.9 [49.8, 78.9]	60.1 [41.2, 76.6]	0.008	0.181	62.7 [48.8, 79.3]	64.9 [49.5, 79.5]	0.451	0.052
Sex			0.21	0.079			0.319	0.081
Female	145 (38.9)	355 (35)			215 (61.1)	201 (57.1)		
Male	228 (61.1)	658 (65.0)			137 (38.9)	151 (42.9)		
First care unit, n (%)			< 0.001	0.492			0.904	0.057
Medical ICU	56 (15.0)	75 (7.4)			51 (14.5)	48 (13.6)		
Neurogical ICU	115 (30.8)	184 (18.2)			100 (28.4)	107 (30.4)		
Surgical ICU	202 (54.2)	754 (74.4)			201 (57.1)	197 (56.0)		
Traumatic brain injury, n (%)			0.001	0.291			0.448	0.198
Laceration and contusion	20 (5.3)	87 (8.6)			81 (23.0)	71 (20.2)		
Compression of brain	88 (23.5)	143 (14.1)			10 (2.8)	8 (2.3)		
Concussion	12 (3.2)	26 (2.6)			22 (6.2)	31 (8.8)		
Subarachnoid hemorrhage	59 (15.7)	174 (17.2)			50 (14.2)	62 (17.6)		
Mixed subarachnoid, subdural, and extradural hemorrhage	54 (14.4)	170 (16.8)			54 (15.3)	44 (12.5)		
Subdural hemorrhage	87 (23.2)	237 (23.4)			86 (24.4)	89 (25.3)		
Unspecified intracranial hemorrhage	31 (8.3)	75 (7.4)			33 (9.4)	25 (7.1)		
Unspecified intracranial injury	24 (6.4)	99 (9.8)			16 (4.5)	22 (6.2)		
Richmond Agitation-Sedation Scale	-1 [-4, 1]	0 [-4, 1]	0.044	0.056	0 [-4, 1]	-1 [-4, 1]	0.845	0.135
Prehospital GCS, median (IQR)	9 [6, 12]	10 [7, 12]	0.397	0.112	8 [5, 10]	8 [6, 11]	0.759	0.038
Neurological severity			0.066	0.114			0.397	0.072
Mild/or moderate TBI	65 (17.4)	134 (13.2)			57 (16.2)	48 (13.6)		
Severe TBI, n (%)	308 (82.6)	879 (86.8)			295 (83.8)	304 (86.4)		
Admission location			< 0.001	0.217			0.816	0.023
Emergency room	225 (60.3)	715 (70.6)			218 (61.9)	214 (60.8)		
Others	148 (39.7)	298 (29.4)			134 (38.1)	138 (39.2)		
Charlson Comorbidity Index, median (IQR)	4.0 [1.0, 5.0]	3.0 [0.0, 5.0]	0.001	0.175	4.0 [1.0, 5.0]	4.0 [1.0, 6.0]	0.551	0.028
Severity of illness at admission								
SOFA, median (IQR)	5 [3, 8]	4 [2, 6]	< 0.001	0.379	5 [3, 7]	5.0 [3, 7]	0.798	0.034
SAPS II, median (IQR)	38 [30, 47]	34 [27, 43]	< 0.001	0.304	38 [29, 46]	37.0 [29, 46]	0.98	0.001
APS III, median (IQR)	43 [31, 62]	37 [28, 50]	< 0.001	0.346	42 [30, 59]	42.0 [30, 56]	0.655	0.054
ICP monitoring on the first day, n (%)	63 (16.9)	100 (9.9)	< 0.001	0.472	63 (17.9)	67 (19.0)	0.699	0.016
Coexisting conditions								
Coronary heart disease	46 (12.3)	87 (8.6)	0.046	0.123	41 (11.6)	42 (11.9)	1	0.009
Congestive heart failure	67 (18.0)	123 (12.1)	0.007	0.163	59 (16.8)	50 (14.2)	0.405	0.071
Cerebrovascular disease	91 (24.4)	204 (20.1)	0.1	0.102	85 (24.1)	77 (21.9)	0.531	0.054
Chronic pulmonary disease	49 (13.1)	100 (9.9)	0.1	0.102	45 (12.8)	54 (15.3)	0.386	0.074
Liver disease	38 (10.2)	54 (5.3)	0.002	0.182	34 (9.7)	21 (6.0)	0.092	0.138
Diabetes mellitus	73 (19.6)	199 (19.6)	1	0.002	64 (18.2)	79 (22.4)	0.19	0.106

Table 1 (continued)

Variables	Before propensity score matching				After propensity score matching			
	Patients without ENWT ($n=373$)	Patients with ENWT ($n=1013$)	P	SMD	Patients without ENWT ($n=352$)	Patients with ENWT ($n=352$)	P	SMD
Malignant cancer	15 (4.0)	43 (4.2)	0.974	0.011	14 (4.0)	15 (4.3)	1	0.014
Rheumatic disease	8 (2.1)	15 (1.5)	0.534	0.05	7 (2.0)	8 (2.3)	1	0.02
Sepsis	238 (63.8)	631 (62.3)	0.649	0.031	220 (62.5)	231 (65.6)	0.432	0.065
Vital signs, median (IQR)								
Heart rate (beats/min)	84.9 [76.0, 98.6]	83.6 [73.2, 95.4]	0.052	0.136	85.1 [76.0, 98.6]	82.2 [71.7, 95.2]	0.011	0.212
Mean arterial pressure (mm Hg)	79.1 [74.2, 86.2]	80.3 [74.3, 87.0]	0.296	0.074	80.0 [74.6, 86.7]	78.1 [72.8, 84.6]	0.016	0.161
Ventilatory frequency (breaths/min)	19.0 [16.8, 21.5]	18.2 [16.4, 20.5]	< 0.001	0.268	19.0 [16.8, 21.4]	18.2 [16.5, 20.8]	0.052	0.159
Body temperature (°C)	37.0 [36.6, 37.4]	37.2 [36.9, 37.6]	< 0.001	0.333	37.0 [36.6, 37.4]	37.2 [36.8, 37.5]	0.025	0.128
SpO2 (%)	98.4 [97.0, 99.4]	98.9 [97.9, 99.6]	< 0.001	0.35	98.4 [97.1, 99.4]	98.8 [97.7, 99.6]	0.001	0.253
Laboratory tests, median (IQR)								
WBC count (k/uL)	12.0 [8.9, 16.1]	12.3 [9.6, 15.6]	0.586	0.017	12.1 [9.1, 16.0]	12.3 [9.5, 15.5]	0.774	0.01
Platelet (k/uL)	190.1 [139.2, 244.2]	194.0 [148.0, 243.0]	0.424	0.028	189.8 [140.7, 243.8]	182.8 [136.0, 239.7]	0.387	0.054
Glucose (mg/dL)	139.0 [119.6, 167.1]	133.2 [115.5, 153.3]	< 0.001	0.242	137.9 [119.1, 162.9]	132.2 [115.2, 152.9]	0.016	0.204
Hemoglobin (g/dL)	11.2 [9.6, 12.7]	11.5 [10.1, 12.9]	0.022	0.145	11.3 [9.7, 12.7]	11.2 [9.7, 12.5]	0.635	0.025
Potassium (mmol/L)	4.1 [3.7, 4.4]	4.0 [3.7, 4.3]	0.129	0.112	4.0 [3.7, 4.4]	4.0 [3.8, 4.3]	0.573	0.061
Sodium (mmol/L)	140.5 [138.0, 143.0]	140.0 [137.5, 142.0]	0.003	0.2	140.6 [138.0, 143.0]	140.0 [137.4, 142.0]	0.004	0.224
Calcium (mmol/L)	8.3 [7.8, 8.8]	8.3 [7.8, 8.7]	0.276	0.094	8.2 [7.8, 8.8]	8.3 [7.8, 8.7]	0.963	0.001
Chloride (mmol/L)	106.0 [103.0, 109.5]	106.0 [102.8, 109.0]	0.631	0.067	106.0 [103.0, 109.8]	106.0 [102.8, 109.3]	0.582	0.093
Creatinine (mg/dL)	0.9 [0.7, 1.2]	0.9 [0.7, 1.1]	< 0.001	0.197	0.9 [0.7, 1.2]	0.8 [0.7, 1.1]	0.085	0.06
Blood urea nitrogen (mg/dL)	16.8 [12.0, 22.4]	15.0 [11.1, 21.0]	0.004	0.179	16.5 [12.0, 22.0]	15.7 [12.0, 23.0]	0.952	0.023
International normalized ratio	1.2 [1.1, 1.4]	1.1 [1.1, 1.3]	0.002	0.215	1.2 [1.1, 1.4]	1.2 [1.1, 1.4]	0.594	0.071
Partial thromboplastin time, s	13.0 [12.0, 15.1]	12.9 [11.8, 14.3]	0.025	0.215	13.0 [11.9, 14.9]	13.1 [12.0, 15.1]	0.429	0.068
Alkaline phosphatase, U/L	72.8 [55.0, 101.7]	69.0 [54.0, 95.0]	0.198	0.169	73.5 [56.0, 101.7]	70.0 [55.6, 102.0]	0.741	0.086
Aminotransferase aspartate, U/L	54.0 [31.0, 147.9]	48.2 [29.0, 112.9]	0.035	0.196	54.0 [31.0, 149.4]	53.5 [29.2, 123.5]	0.314	0.184
Total bilirubin, mg/dL	0.6 [0.4, 1.2]	0.6 [0.4, 1.0]	0.501	0.154	0.6 [0.4, 1.0]	0.7 [0.4, 1.1]	0.331	0.057
ENWT related complications								
Hemodynamic instability, n (%)	57 (15.3)	61 (6.0)	< 0.001	0.304	48 (13.6)	34 (9.7)	0.127	0.124
Elevated ICP, n (%)	6 (1.6)	17 (1.7)	1	0.005	6 (1.7)	6 (1.7)	1	< 0.001
Unstable ventilation status, n (%)	36 (9.7)	54 (5.3)	0.006	0.165	29 (8.2)	26 (7.4)	0.779	0.032

ENWT early neurological wake-up test, *GCS* Glasgow coma scale, *IQR* interquartile range, *ICP* intracranial pressure, *SD* standard deviation, *SMD* standardised mean difference, *SOFA* Sequential Organ Failure Assessment, *SAPS* Simplified Acute Physiology Score, *APS* Acute Physiology Score, *WBC* white blood cell

Cohort characteristics

Table 1 displays the baseline characteristics before and after PSM. In the original cohort, patients who received ENWT were younger and more likely to be treated in surgical ICU, had lower Charlson Comorbidity Index, SOFA, SAPS II and APS III scores, and had lower prevalence of coexisting conditions, including coronary heart disease, congestive heart failure and liver disease (all $P<0.05$). The imbalances in variables were significantly improved after PSM between the groups, with an absolute SMD < 0.1 (Fig. S1). In the matched cohort, the RASS did not differ between the two groups before initiating ENWT ($P=0.845$). The Kernel density plot depicts the timing of initiating ENWT (Fig. S2), the median time to perform ENWT was 2.0 h (IQR 1.0–6.0) after admission.

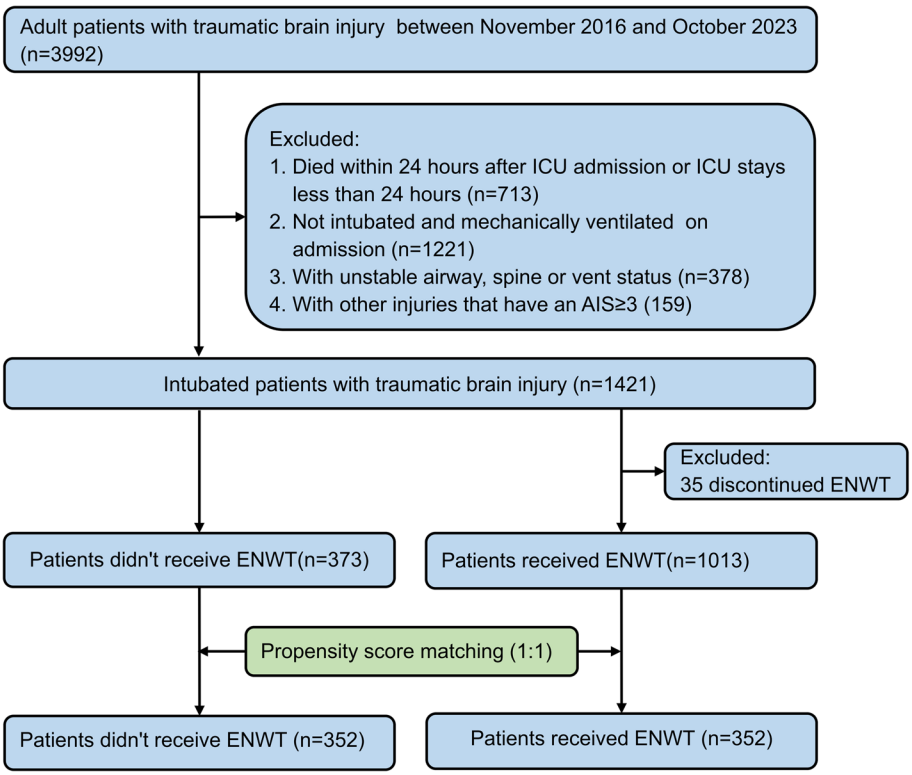

Fig. 1 Flow chart of patient selection

Primary outcome

The 28-day mortality rate was 24.7% (87/352) in the ENWT group and 37.2% (131/352) in the no performed group. Cox Proportional Hazard Model analysis found a lower adjusted risk for 28-day mortality when patients received ENWT in the univariable analysis (HR, 0.55; 95% CI, 0.42–0.72; $P<0.001$) as well as in the multivariable analysis (HR, 0.57; 95% CI, 0.44–0.76; $P<0.001$) (Table 2). Figure 2 shows the Kaplane-Meier curve for 28-day mortality according to weather the patients received ENWT or not in the matched cohort. Besides, we also found that ENWT was related to better long-term prognosis, with lower one-year all-cause mortality in both the univariable analysis (HR, 0.54; 95% CI, 0.40–0.74; $P<0.001$) as well as in the multivariable analysis (HR, 0.64; 95% CI, 0.50–0.81; $P<0.001$) (Table 2).

Subgroup analyses

Figure 3 shows the results of subgroup analyses for 28-day mortality in the matched cohort. Except for patients with age ≥ 65 years (HR, 0.79; 95% CI, 0.55–1.14; $P=0.202$) or patients with Charlson Comorbidity Index ≥ 6 (HR, 0.90; 95% CI, 0.54–1.50; $P=0.683$), ENWT was associated with significant lower mortality in all other subgroup analyses.

ENWT related complications

For TBI patients, many clinicians concerned about the safety of ENWT during the process of sedation interruption or lightening. We observed no significant difference between patients with and without ENWT, in terms of elevated ICP during the first five days in ICU (Fig. S3), hemodynamic instability, and unstable ventilation status during the neurological wake-up test procedure (Table 1). However, it should be noted that ENWT was associated with a higher risk of delirium after adjust for confounders (OR, 1.66; 95% CI, 1.21–2.26; $P=0.001$).

Sensitivity analyses

The 28-day mortality rate was 16.9% (171/1013) in the ENWT group and 37.0% (138/373) in the no performed group. Figure S4 shows the Kaplane-Meier curve for 28-day mortality in the entire cohort. ENWT was associated with lower 28-day mortality in both the univariable analysis (HR, 0.37; 95% CI, 0.30–0.47; $P<0.001$) and the multivariable analysis (HR, 0.58; 95% CI, 0.44–0.75; $P<0.001$).

Secondary outcomes

In-hospital mortality and discharge-home rate

The in-hospital mortality rate was 25.6% (90/352) in the ENWT group and 38.4% (135/352) in the control group.

Table 2 The association of early neurological wake-up test with outcomes in the matched cohort

Clinical Outcome	Patients without ENWT (*n* = 352)	Patients with ENWT (*n* = 352)	Univariable analysis		Multivariable analysis[a]	
			HR/OR/MD (95% CI)	P	HR/OR/MD (95% CI)	P
Primary outcome						
28-day mortality[b], n (%)	131 (37.2)	87 (24.7)	0.55 (0.42–0.72)	< 0.001	0.57 (0.44–0.76)	< 0.001
Secondary outcomes						
In-hospital mortality[c], n (%)	135 (38.4)	90 (25.6)	0.55 (0.40–0.76)	< 0.001	0.54 (0.38–0.77)	0.001
Discharge-home[c], n (%)	60 (17.0)	85 (24.1)	1.55 (1.07–2.24)	0.02	1.83 (1.19–2.83)	0.006
Ventilator associated pneumonia[c], n (%)	31 (8.8)	44 (12.5)	1.48 (0.91–2.40)	0.114	1.41 (0.84–2.36)	0.194
Delirium during ICU stay[c], n (%)	68 (19.3)	97 (27.6)	1.59 (1.17–2.26)	0.01	1.66 (1.21–2.26)	0.001
One-year all-cause mortality[c], (%)	177 (50.3)	125 (35.5)	0.54 (0.40–0.74)	< 0.001	0.64 (0.50–0.81)	< 0.001
Length of ICU stay (days) [d], median (IQR)	3.3 [1.9, 7.6]	4.9 [2.4, 10.3]	0.91 (0.45–1.47)	< 0.001	/	/
Length of hospital stay (days) [d], median (IQR)	7.2 [3.0, 16.6]	10.7 [5.6, 21.0]	2.87 (1.70–4.06)	< 0.001	/	/
Length of invasive mechanical ventilation (hours)[d], median (IQR)	25.0 [10.0, 61.2]	30.0 [15.0, 94.2]	6.0 (2.99–10.00)	< 0.001	/	/
Craniectomy[c], n (%)	38 (10.8)	27 (7.7)	0.69 (0.41–1.15)	0.155	0.73 (0.24–2.23)	0.58
Tracheostomy[c], n (%)	51 (14.5)	85 (18.5)	1.88 (1.28–2.76)	0.001	2.07 (1.96–4.50)	0.045

CI confidence interval, *HR* hazard ratio, *IQR* interquartile range, *MD* median difference, *OR* odds ratio

[a] Adjusted for heart rate, mean arterial pressure, body temperature, SpO2, glucose, and sodium level

[b] HR with 95% CI was calculated using Cox proportional hazards model

[c] OR with 95% CI was calculated using logistic regression model

[d] MD with 95% CI was calculated using Hodgese-Lehmann estimator

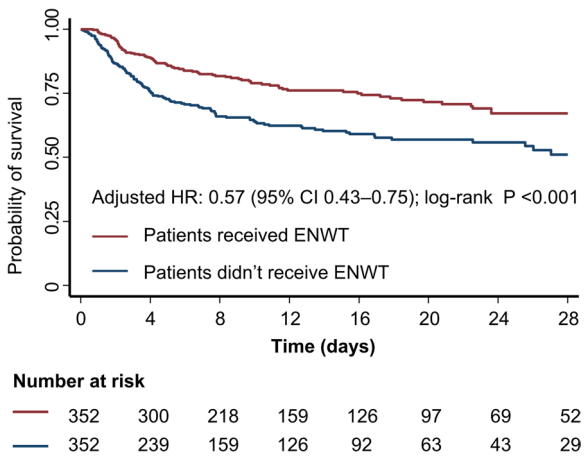

Fig. 2 Kaplane-Meier curve for 28-day mortality according to ENWT application in the matched cohort. The multivariable Cox proportional hazards model was adjusted for heart rate, mean arterial pressure, body temperature, SpO2, glucose, and sodium level

ENWT was associated with lower in-hospital mortality in both the univariable analysis (OR, 0.55; 95% CI, 0.40–0.76; $P < 0.001$) and the multivariable analysis (OR, 0.54; 95% CI, 0.38–0.77; $P = 0.001$) (Table 2). The discharge-home rate was 24.1% (85/352) in the ENWT group and 17.0% (60/352) in the control group. ENWT was associated with higher discharge-home rate in both the univariable analysis (OR, 1.55; 95% CI, 1.07–2.24; $P = 0.02$) and the multivariable analysis (OR, 1.83; 95% CI, 1.19–2.83; $P = 0.006$).

Length of ICU stay and length of hospital stay

The median length of ICU stay was 4.9 days (IQR 2.4–10.3) in the ENWT group and 3.3 days (IQR 1.9–7.6) in the control group. The median length of hospital stay was 10.7 days (IQR 5.6–21.0) in the ENWT group and 7.2 days (IQR 3.0–16.6) in the control group. ENWT was associated with prolonged length of ICU stay (MD, 0.91 days; 95% CI, 0.45–1.47; $P < 0.001$) and hospital stay (MD, 2.87 days; 95% CI, 1.40–4.06; $P < 0.001$) (Table 2).

Other outcomes

No difference was detected regarding ventilator associated pneumonia and craniectomy between the patients with and without ENWT. While the ENWT group had a higher proportion of tracheostomy during the ICU stay, and received longer duration of invasive mechanical ventilation (Table 2).

Causal mediation analysis (CMA)

We then used CMA to explore the direct and indirect effects of ENWT on 28-day mortality. The indirect effect was significant only when the tracheostomy was used as a mediator variable. The total effect was − 0.12

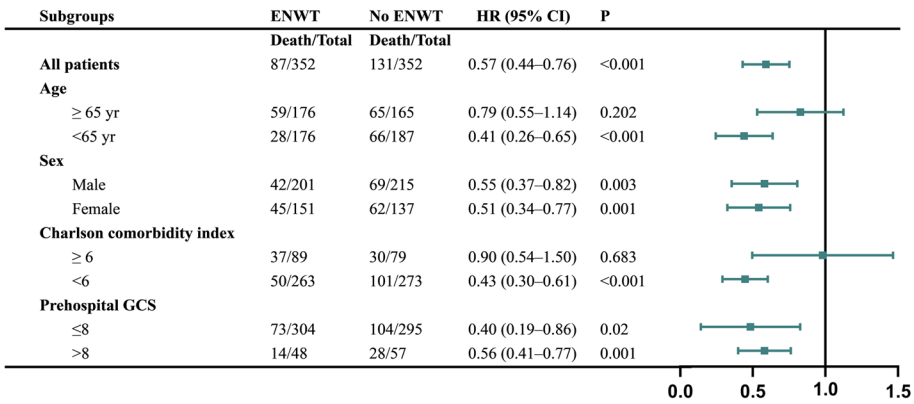

Fig. 3 Subgroup analyses for 28-day mortality in the matched cohort. The multivariable Cox proportional hazards model was adjusted for heart rate, mean arterial pressure, body temperature, SpO2, glucose, and sodium level

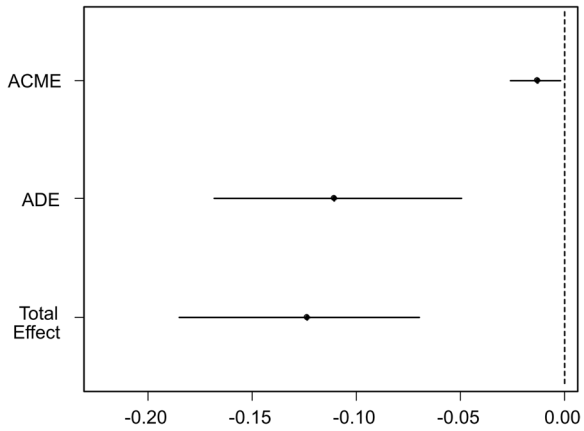

Fig. 4 Causal mediation analysis for tracheostomy

(95% CI − 0.18 to − 0.07; $p < 0.001$), the ACME was − 0.01 (95% CI − 0.03 to 0 approximately; $P < 0.001$), the ADE was − 0.11 (95% CI − 0.17 to − 0.05; $P < 0.001$), and the proportion of the effect mediated was 9.7% (95% CI 1.8% –34%; $P < 0.001$) (Fig. 4). Additionally, an insignificant indirect effect was detected when the craniectomy (ACME − 0.0004; 95% CI − 0.006 to 0 approximately; $P = 0.8$) and length of invasive mechanical ventilation (ACME 0.002; 95% CI − 0.009 to 0.01; $P = 0.56$) (Fig. S5) were used as mediators. We concluded that the beneficial effect of ENWT on 28-day mortality may partly be mediated through the tracheostomy during ICU stay.

Discussion

Main findings

Results from this study indicated an association between ENWT and lower 28-day mortality in patients with TBI. This association was stable in the original and matched cohorts, indicating the robustness of our finding. ENWT was also associated with lower in-hospital mortality, and higher proportion of discharge-home rate.

Relation with previous evidence

In previous reports, up to 40% of TBI patients experienced a clinically neurological deterioration within the first 48 h after ICU admission [23–25], arguing for early and repeated neurological assessments. To date, there are only scarce literatures evaluating the neurological wake-up test for TBI patients. Only one prior randomised controlled trial explored the impact of daily interruption of sedative infusions on TBI patients [10]. However, no benefit was detected in view of the duration of mechanical ventilation and length of intensive care unit stay. It should be noted that these results were based on only 21 TBI patients that received daily interruption of sedative infusions who were compared to 17 TBI controls. In another retrospective trial that describe the characteristics of the TBI patients who received an ENWT [7], the authors found better long-term outcomes in patients with successful ENWT compared to those with failure or absence of ENWT. However, since the TBI patients who didn't receive ENWT in this cohort were more severe than those underwent ENWT, it's unable to get a conclusion whether the ENWT practice should be routinely performed or not based on this research. The results also emphasized that before applying the ENWT procedure careful individualized assessments are required. Several other small clinical trials [11, 26–29] have investigated the impact of neurological wake-up test on the pathophysiological changes of TBI patients and found that although it induced a biochemical stress response, resulted in transient increased ICP and mean arterial blood pressure, no evidence of an exacerbated brain injury was obtained.

In our study, the association between ENWT and lower 28-day mortality in TBI patients was evident in both the original and matched cohorts, and consistent across most of the sub-group analyses and robust in sensitivity analyses. Also, ENWT was associated with lower in-hospital mortality, one-year all-cause mortality and higher discharge-home rate. Together, these findings supported the association between ENWT and improved prognosis in TBI patients.

Possible explanations for findings

The ENWT itself does not affect the clinical outcomes of TBI patients unless it led to therapeutic interventions. Several studies have demonstrated that a timely neurological wake-up test is associated with more rapid intervention delivery in TBI patients. Maas et al. [2] reported that the neurological wake-up test can reliably discover the clinically important neurological improvement or worsening, such as the emergence/exacerbation of focal neurological deficits. Additionally, based on information obtained from the ENWT clinical decision may be more aggressive for deteriorating TBI patients (e.g., surgical treatment, or neuroradiological investigations), or lead to changed ventilator strategies (e.g., earlier extubating, tracheostomy or repeat neurological wake-up) [25, 30]. Unfortunately, which interventions contribute to the beneficial effect of ENWT on mortality remains unproven. We tested several therapeutic interventions to investigate the benefit of ENWT and found that the ENWT group had a higher rate of patients who underwent tracheostomy during ICU stay, and received prolonged length of invasive mechanical ventilation. We then used CMA and uncovered that the beneficial effect of ENWT on 28-day mortality in TBI patients was partly attributed to the tracheostomy.

Implications for clinical practice

The mediating effect of the tracheostomy in TBI treatment has been shown by multiple studies. A retrospective cohort study indicated that TBI patients could benefit from the early tracheostomy, which was associated with a trend of a better 6 months outcome [31]. Further meta-analysis concluded that in patients with TBI early tracheostomy contributes to a lower exposure to secondary insults, and increasing the rate of patient's early rehabilitation and discharge [32]. More researches on the mediation of therapeutic interventions are necessary to assess the effect of ENWT on mortality in TBI patients.

Our results confirmed the benefit of ENWT, however, the factors that could impact the outcomes of TBI patients were complex. From ENWT, we can obtain information on the changes in neurological status that may lead to more active management, reduce the risk for ventilator-associated pneumonias, or shorten the ICU stay; however, interruption of continuous sedation can also induce a stress response that increases the brain metabolism and oxygen consumption [30]. Thus, we should weigh the pros and cons of ENWT in patients with TBI to overcome the related side effects of this procedure.

Study limitations

This study has several limitations. First, due to its retrospective design, the results are subject to unidentified residual confounders (e.g., therapies implemented and the causes of death) and bias despite we used robust statistical methods and covariate adjustment, and the reasons for carrying out or not carrying out an ENWT were not specified. Second, even though the ENWT is safe in most of the patients and may give us useful clinical information about the patient's status, alternate monitoring methods in combination with neuroimaging are suggested in patients showing marked ICP and/or cerebral perfusion pressure changes during this procedure. Third, it is especially in patients with elevated ICP in whom ENWT could be at risk, however, the number of patients received invasive ICP monitoring in this cohort was limited, more evidence is needed in the future to further confirm the safety of ENWT. Lastly, due to its observational nature, the current study only uncovers associations but cannot proven the causal relationships between ENWT and the prognosis of TBI.

Conclusion

In summary, the ENWT was a safe procedure and may associated with better outcomes in TBI patients. The tracheostomy during ICU stay might have partly mediated this effect.

Abbreviations

ENWT	Early neurological wake-up test
PSM	Propensity score matching
HR	Hazard ratio
TBI	Traumatic brain injury
ICP	Intracranial pressure
GCS	Glasgow Coma Scale
SMD	Standardised mean difference
SOFA	Sequential Organ Failure Assessment
SAPS	Simplified Acute Physiology Score
APS	Acute Physiology Score
WBC	White blood cell
ICU	Intensive care units

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Study conception and design: MJ, XFY; Acquisition, analysis, and interpretation of data: MJ, CLL, XPW, YRZ, LGX; Manuscript drafting: MJ; Critical revision for important intellectual content: CLL, YUZ, XCL, XPW; Final approval of the manuscript: all authors. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.M.J. wrote the main manuscript text and prepared Figs. 1–4. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was acquired from the First Affiliated Hospital of Zhejiang University School of Medicine (IIT20230299B-R1), with written informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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