

Risk factors and novel prognostic score for predicting the 14-day mortality of severe traumatic brain injury patients



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ABSTRACT

Introduction: The mortality of severe traumatic brain injury (TBI) is contributed by the severity of the head injury, associated trauma, and complication during treatment. This study aimed to develop a prognostic scoring system of risk factors that contribute to the 14-day mortality of severe TBI.

Methods: This was a prospective cohort study including 105 severe TBI patients recruited consecutively from March to October 2016. Multivariate analysis with logistic regression was performed to determine the most contributing risk factors. The validation of prognostic factor was performed with ROC, sensitivity and specificity analysis.

Result: There were five significant risk factors of 14-day mortality, which were age > 60 years old (RR: 15.6, 95% CI: 1.88 – 129.95), hypoxia (RR: 17.78, 95% CI: 2.05 – 154.11), GCS 3 – 5 (RR: 34.71, 95% CI: 6.85 – 175.98), effacement of basal cistern (RR: 12.71, 95% CI: 2.61 – 61.95), and traumatic subarachnoid hemorrhage (tSAH) (RR: 7.57, 95% CI: 1.19 – 48.36). The prognostic score ranged from 0 to 6 with the best cut-off point of 1. The best predictive AUC with ROC analysis was 0.817, 81.2% of sensitivity, and 75.0% of specificity.

Conclusion: The proposed prognostic score has shown good predictive ability.

Keywords: mortality risk factor, prognostic score, severe traumatic brain injury, 14-days mortality

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INTRODUCTION

The management of patients with severe traumatic brain injury (TBI) requires expensive resources and a relatively long time of treatment. Even with adequate management, mortality and long-term morbidity are still high. Patients with head injury need to establish risk factors that contribute to the worsening of outcomes as early as possible. It should be done to provide appropriate, accurate and systematic actions and therapies immediately to produce a good prognosis.^{1,2} Further decisions regarding the management of severe TBI patients must involve the patient's family, so informed consent about patient outcomes requires adequate and accurate data. Predicting the outcome of severe TBI patients accurately is important for fund allocations, appropriate clinical decisions and realistic informed consent to the family.

Head injuries are expected to surpass other diseases as a major cause of death and disability in 2020.³ The number of head injury cases in the United States reaches 1.7 million cases each year with deaths reaching 52,000 people, and 10% of them are patients with severe TBI.⁴ In Indonesia, the mortality rate in all severity of head injuries ranges

from 6.17% to 11.22%, with deaths in severe TBI ranging from 25.23% to 37.14%.⁵ Internationally, mortality rate in severe TBI varies between 13% to 33.3%.⁶⁻⁸

The highest proportion of head injury mortality occurs 1 – 2 weeks after the trauma, where 85% of deaths in severe TBI occur in the first 14 days after trauma.⁹ Several prognostic scores were made only by considering clinical factors of head injury severity without considering the effect of complications during treatment.¹⁰⁻¹² Observation for 14 days can be done to assess the influence of head injury severity, accompanying trauma, and complications during treatment.¹³ Besides that, the prognostic assessment 14 days after trauma can also describe Glasgow Outcome Scale (GOS) within six months.¹⁴ Based on that, the authors were interested in developing a validated prognostic scoring system regarding risk factors for 14-day mortality in severe TBI patients.

MATERIAL AND METHODS

A prospective cohort study was conducted on 105 patients over the age of 6 years with severe TBI who came to the Emergency Care Unit of Sanglah General

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Table 1. Characteristic of subjects

Variable	N	%
14-day follow up		
Alive	36	34.3
Dead	69	65.7
Age		
> 60 years old	17	16.2
≤ 60 years old	88	83.8
Sex		
Male	87	16.2
Female	18	83.8
Operation time		
No operation	79	75.2
> 4 hours	17	16.2
≤ 4 hours	9	8.6
GCS on admission		
3 – 5	61	58.1
5 – 6	44	41.9
ISS score		
≥ 30	36	34.3
< 30	69	65.7
Hypotension		
Yes	18	17.1
No	87	82.9
Hypoxia		
Yes	31	29.5
No	74	70.5
Pupil condition		
Bilateral mydriasis	20	19.0
Anisocore	19	18.1
Isocore	66	62.9
Pneumonia		
Yes	19	18.1
No	86	81.9
Central hyperthermia		
Yes	6	5.7
No	99	94.3
Midline shift		
Yes	56	53.3
No	49	46.7
Midline shift (mm)		
≥ 5 mm	35	33.3
< 5 mm	21	20.0
Basal cistern effacement		
Yes	64	61.0
No	41	39.0
Traumatic SAH		
Yes	32	30.4
No	73	69.6
Epidural hematoma		
Yes	32	30.5
No	73	69.5
Subdural hematoma		
Yes	42	40.0
No	63	60.0
Intracerebral hematoma		
Yes	22	20.9
No	83	79.1
Cerebral contusion		
Yes	20	19.0
No	85	81.0

Hospital Denpasar between March and October 2016. Patients with severe TBI with a history of cerebrovascular disease, non-hemorrhagic stroke, hemorrhagic stroke, died before head CT scan was performed, suspected of alcohol intoxication, and patients with a history of pupillary reflex disorder were excluded from this study. All subjects in this study were managed with standard treatment protocol in our hospital. This study protocol had been approved by ethical committee in Sanglah General Hospital.

Eligible subjects were assessed for risk factors that predict the occurrence of death within 14 days. Based on the literature review, we found several important risk factors associated with the occurrence of death within 14 days in severe TBI patients.^{9,13,15-19} Based on our previous observations, we found several important risk factors to be assessed for their effects on the occurrence of death, which were age, sex, GCS score on admission, hypotension, pupillary reflexes, operation time, ISS, pneumonia, central hyperthermia, and head CT scan appearance. All subjects received treatment in accordance with current neurosurgical therapy protocol.

All data were presented dichotomously. We performed a bivariate analysis (chi-square test on the significance limit of $\alpha = 0.05$) to assess the effect of risk factors on mortality within 14 days in severe TBI patients. Multivariate logistic regression was used to assess the influence of each risk factor on the occurrence of death. This analysis resulted as relative risk (RR) with 95% of Confidence Interval (CI) and a significance limit of less than 0.05. The RR of significant risk factors were used as the basis for making prognostic scores. To assess the validity of the scores that have been made, the validity test consists of two stages, which were ROC analysis and assessment of sensitivity and specificity.

RESULTS

Characteristic of subjects

This study was conducted on severe TBI patients who came to the emergency department of Sanglah General Hospital from March 2016 to October 2016. In this period, 105 subjects were included consisting of 87 men (82.8%) with an average age of 37.1 years old. Informed consent were obtained from all subject's closest relative since subjects were unable to give consents. Clinical evaluation of patients was performed after patients were resuscitated. Sixty-one subjects (58.1%) had initial GCS 3 – 5, 39 subjects (37.1%) had abnormal pupils, 18 subjects (17.1%) had hypotension, 31 subjects (29.5%) had hypoxia, and 36 subjects (34.3%) had multi-trauma with ISS ≥ 30. Twenty-

Table 2. Bivariate analysis

Variable	Outcome		RR	95% CI	P-value
	Death	Alive			
Age					
> 60 years old	15 (88.2)	2 (11.8)	1.44	1.13 – 1.83	0.033*
≤ 60 years old	54 (61.4)	34 (36.6)			
Sex					
Male	54 (62.1)	33 (37.9)	0.75	0.57 – 0.97	0.084
Female	15 (83.3)	3 (16.7)			
Operation time					
> 4 hours	8 (47.1)	9 (52.9)	0.68	0.40 – 1.15	0.077
≤ 4 hours	61 (69.3)	27 (30.7)			
Hypotension					
Yes	16 (88.9)	2 (11.1)	1.46	1.15 – 1.85	0.023*
No	53 (60.9)	34 (39.1)			
Hypoxia					
Yes	28 (90.3)	3 (9.7)	1.63	1.29 – 2.06	0.001*
No	41 (55.4)	33 (44.6)			
GCS on admission					
3 – 5	56 (91.8)	5 (8.2)	3.11	1.96 – 4.93	< 0.001*
6 – 8	13 (29.5)	31 (70.5)			
Pupillary anisocore					
Yes	12 (63.2)	7 (36.8)	0.95	0.66 – 1.39	0.795
No	57 (66.3)	29 (33.7)			
Bilateral pupillary mydriasis					
Yes	19 (95.0)	1 (5.0)	1.62	1.32 – 1.98	0.002*
No	50 (58.8)	35 (41.2)			
ISS score					
≥ 30	33 (91.7)	3 (8.3)	1.76	1.37 – 2.25	< 0.001*
< 30	36 (52.2)	33 (47.8)			
Pneumonia					
Yes	11 (57.9)	8 (42.1)	0.86	0.57 – 1.29	0.428
No	58 (67.4)	28 (32.6)			
Central hyperthermia					
Yes	4 (66.7)	2 (33.3)	1.02	0.57 – 1.82	0.960
No	65 (65.7)	34 (34.3)			
Midline shift ≥ 5 mm					
Yes	26 (74.3)	9 (25.7)	1.21	0.92 – 1.58	0.191
No	43 (61.4)	27 (38.6)			
Basal cistern effacement					
Yes	55 (85.9)	9 (14.1)	2.52	1.63 – 3.89	< 0.001*
No	14 (34.1)	27 (65.9)			
Traumatic SAH					
Yes	29 (90.6)	3 (9.4)	1.65	1.31 – 2.09	< 0.001*
No	40 (54.8)	33 (45.2)			
Epidural hematoma					
Yes	17 (53.1)	15 (46.9)	0.75	0.52 – 1.07	0.072
No	52 (71.2)	21 (28.8)			
Subdural hematoma					
Yes	33 (78.6)	9 (21.4)	1.38	1.05 – 1.79	0.023*
No	36 (57.1)	27 (42.9)			
Intracerebral hematoma					
Yes	19 (86.4)	3 (13.6)	1.43	1.13 – 1.82	0.022*
No	50 (60.2)	33 (39.8)			
Cerebral contusion					
Yes	15 (75.0)	5 (25.0)	1.18	0.88 – 1.59	0.331
No	54 (63.5)	31 (36.5)			

*: statistically significant

six subjects underwent surgery with 22 subjects were operated 4 hours after admission. Nineteen subjects experienced pneumonia during treatment (18.1%) and six had central hyperthermia (5.7%). Based on the head CT scan appearance, there were 35 subjects (33.3%) with 5 mm of midline shift, 64 subjects (61.0%) had basal cistern effacement, and 32 subjects (30.4%) had traumatic SAH (tSAH). The study subjects were followed up for 14 days. Sixty-nine subjects died (65.71%) and 36 subjects (34.3%) were alive. In summary, the overall characteristics of the subjects can be seen in [Table 1](#).

Analysis of clinical factors

Bivariate analysis showed 10 significant risk factors for mortality in 14 days. They were age above 60 years old (RR: 1.44, 95% CI: 1.13 – 1.83), hypotension (RR: 1.46, 95% CI: 1.15 – 1.85), hypoxia (RR: 1.63, 95% CI: 1.29 – 2.06), GCS on admission 3 – 5 (RR: 3.11, 95% CI: 1.96 – 4.93), bilateral pupillary mydriasis (RR: 1.62, 95% CI: 1.32 – 1.98), ISS (RR: 1.76, 95% CI: 1.37 – 2.25), basal cistern effacement (RR: 2.52, 95% CI: 1.63 – 3.89), tSAH (RR: 1.65, 95% CI: 1.32 – 2.13), SDH (RR: 1.38, 95% CI: 1.05 – 1.79), and ICH (RR: 1.43, 95% CI: 1.13 – 1.82). The overall results of bivariate analysis can be seen in [Table 2](#).

Significantly associated variables in the bivariate analysis were analyzed with multivariate logistic regression. Based on multivariate analysis, there were five statistically significant risk factors for mortality in 14 days. They were age > 60 years old (RR: 15.6, 95% CI: 1.88 – 129.95), hypoxia (RR: 17.78, 95% CI: 2.05 – 154.11), GCS score on admission 3 – 5 (RR: 34.71, 95% CI: 6.85 – 175.98), basal cistern effacement (RR: 12.71, 95% CI: 2.61 – 61.95), and tSAH (RR: 7.57, 95% CI: 1.19 – 48.36). The results of the multivariate analysis can be seen in [Table 3](#).

Scoring system

Prognosis scores are made by giving different weights to each variable based B value and SE from logistic regression analysis. The tSAH variable with the smallest B/SE ratio was given a score of 1, while the other variables were scored according to their respective ratio, as shown in [Table 4](#) and [Table 5](#). The score can be called good because the area under the curve value is more or equal to 0.7 (AUC 0.817), as seen in [Figure 1](#). Based on the ROC analysis the best cut point can be obtained, namely 1 so that patients with more than 1 scores were categorized as high risk and those who were less than 1 were categorized as low risk. The sensitivity of the severe TBI prognostic score was 81.2% and the specificity was 75.0%. The mortality risk from each total score

Table 3. Multivariate analysis

Variable	RR	95% CI	P-value
Age	15.6	1.88 – 129.95	0.011*
Hypotension	1.45	0.09 – 23.59	0.795
Hypoxia	17.78	2.05 – 154.11	0.009*
GCS on admission	34.71	6.85 – 175.98	< 0.001*
Bilateral mydriasis	5.26	0.31 – 88.12	0.25
ISS score	5.13	0.40 – 65.57	0.208
Basal cistern effacement	12.71	2.61 – 61.95	0.002*
Traumatic SAH	7.57	1.19 – 48.36	0.032*
Subdural hematoma	3.13	0.56 – 17.47	0.194
Intracerebral hematoma	1.36	0.11 – 16.42	0.811

*: statistically significant

Table 4. Generating prognostic score

Variable	B	SE	B/SE	(B/SE)/2.139	Conversion
GCS on admission	3.547	0.828	4.283	2.002	2
Hypoxia	2.878	1.102	2.611	1.220	1
Age	2.749	1.081	2.543	1.188	1
Basal cistern effacement	2.543	0.808	3.147	1.471	1
Traumatic SAH	2.024	0.946	2.139	1.000	1

Table 5. Prognostic scoring

Variable	P-value	95% CI	OR	Score
GCS on admission				
GCS 3-5				2
GCS 6-8	< 0.001	6.85 – 175.98	34.7	0
Hypoxia				
Yes	0.009	2.05 – 154.11	17.8	1
No				0
Age				
> 60 years old	0.011	1.88 – 129.95	15.6	1
≤ 60 years old				0
Basal cistern effacement				
Yes	0.002	2.61 – 61.95	12.7	1
No				0
Traumatic SAH				
Yes	0.032	1.19 – 48.36	7.6	1
No				0

can be seen in Table 6. The higher in total score increases the mortality risk of severe TBI within 14 days.

DISCUSSION

It is important to predict the outcome of severe TBI patients accurately for funding allocation, making appropriate clinical decisions and giving realistic informed consent to the family. The presence of a validated prognosis system can provide us a prediction of good prognosis so more aggressive therapy can be carried out. The prognostic factors in this study were chosen based on several previous studies.¹⁶⁻¹⁹ We found that several variables could be prognostic factors for outcomes of severe TBI patients. They were age, bilateral mydriasis pupil, hypotension, hypoxia, GCS score, ISS, basal cistern effacement, presence of tSAH, SDH and ICH. Among these meaningful variables, five prognostic factors most significantly affected the 14-day mortality of patients with severe TBI. They were age over 60 years, GCS 3 – 5, hypoxia, presence of tSAH, and basal cistern effacement.

Age over 60 has greater risk of death in severe TBI patients. This is consistent with findings from several studies that stated age is an independent predictor of the outcome of head injury patients.²⁰⁻²³ In a study conducted by Heiskanen, it was found that older patients had worse prognosis or outcome, especially at the age above 60 years old.²⁴ This could happen because of the presence of co-morbidities in line with increasing age, reduced brain recovery capacity, decreased blood vessel elasticity, and brain atrophy, which results in susceptibility of dura blood vessels damage after trauma.²²

In hypoxic conditions, there is a failure of energy production, inhibition of oxidative phosphorylation, decreased ATP production, failure of Na⁺ / K⁺ ATPase active transport which triggers influx sodium and efflux potassium, and opening Ca²⁺ channels resulting in massive calcium influx. Calcium accumulation in the cell will cause activation of phospholipase and proteolysis, which triggers the hydrolysis of phospholipids membrane and increased free fatty acid. This will cause irreversible damage to cell membranes, and will eventually result in cerebral edema and increased ICP.^{25,26} This study found that hypoxia is a strong prognostic factor associated with severe TBI patient outcomes. This is consistent with previous studies that state prehospital hypoxia significantly increases the odds ratio of mortality in patients who suffered severe TBI.²⁷⁻²⁹

Low GCS reflects a greater degree of brain damage. In this study, it was found that low GCS score (GCS 3 – 5) is a strong independent risk

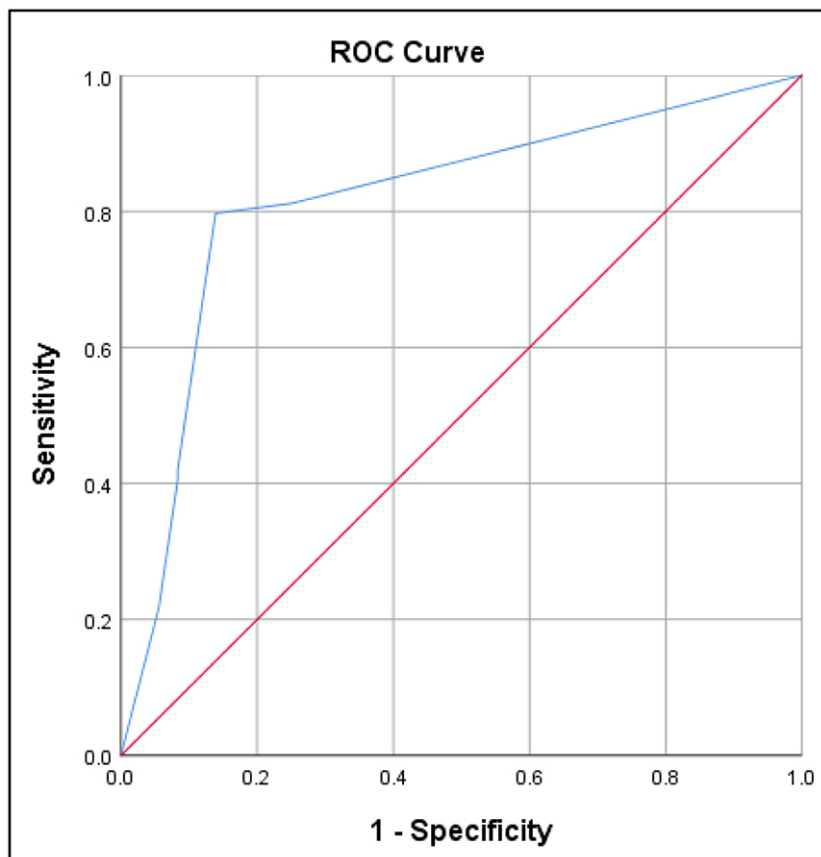


Figure 1. ROC analysis of the prognostic score of 14-day mortality in severe TBI patients. AUC: 0.817, best cut-off point: 1, sensitivity: 81.2%, and specificity: 75.0%.

Table 6. Mortality risk of each total score

Score	Constanta	Coefficient	Y	Mortality risk
1	- 0.562	0.834	0.272	56.75%
2	- 0.562	0.834	1.106	75.04%
3	- 0.562	0.834	1.940	87.43%
4	- 0.562	0.834	2.774	93.93%
5	- 0.562	0.834	3.608	97.36%
6	- 0.562	0.834	4.462	98.83%

$$Y = 0.562 + 0.834 \times \text{total score}; \text{Mortality risk (P)} = 1/(1+\exp(-y)) \times 100 \%$$

factor for the incidence of death within 14 days of severe TBI patients ($p = 0.002$). Low GCS is a risk factor that is almost always present in each study. It indicates the significance of this risk factor for the outcome of head injury patients.^{1,18,30-35}

Compression of the basal cistern is an indicator of increased ICP. Increased intracranial pressure will cause a decrease of blood flow to the brain, which in turn will cause damage to brain tissue. Basal cistern compression on CT scan is a poor predictor of outcome in severe TBI patients. In

this study, we obtained basal cistern effacement as an independent risk factor of mortality within 14 days in patients with severe TBI. This is consistent with the study by Tjahjadi *et al.* that reported basal cistern compression was the most dominant variable in predictors of mortality in severe TBI patients.¹⁵ A higher degree of basal cistern in severe TBI patients results in worse outcomes.³⁶ In this study, we found that most of the patients presented with complete obliteration.

Traumatic SAH is one of the predictors of poor outcome in severe TBI patients. Traumatic SAH can induce secondary vasospasm and cerebral ischemia, which results in the worsening of outcomes.³⁷⁻³⁹ Vasospasm that occurs in tSAH causes cerebral edema, which is one of the factors that increases ICP. Besides that, the presence of SAH shows that the mechanism of trauma tends to be caused by acceleration-deceleration forces that have the potential to cause extensive brain damage.⁴⁰ This study found that tSAH is an independent risk factor for mortality in 14 days of patients with severe TBI. This is in line with previous studies that found head injury patients with a tSAH showed significantly higher mortality.^{41,42} In addition, the presence of tSAH in severe TBI patients was an independent risk factor for poor outcome.^{17,43,44} The extent and location of SAH also influence the increase of ICP and the outcome.⁴⁵ In this study, most of the study subjects showed extensive SAH appearance (grades 3 and 4 according to Fisher Scale for SAH Grading on Admission CT Scan).⁴⁶

CONCLUSION

This prognostic scoring had a good predictive ability because the area under the curve value in the ROC analysis was more or equal to 0.7 (AUC 0.817), with a sensitivity level of 81.2% and a specificity of 75.0%. This prognostic score is expected to provide more realistic informed consent to the patient's family, improved clinical decision making and funding allocation, especially in developing countries where the system and health facilities are still lacking.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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AUTHORS CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection

and analysis were performed by NG, MS, PEM, WN, and PYP. The first draft of the manuscript was written by PEM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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