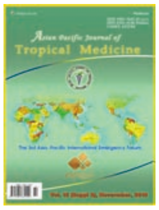

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Combined anatomic and physiologic scoring systems for predicting in-hospital mortality in ICU patients with severe trauma: A multicenter observational cohort study

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ABSTRACT

Objective: To evaluate the ability of new injury severity score (NISS), acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ), Glasgow coma scale (GCS), a combination of NISS and GCS, a combination of APACHE Ⅱ and GCS, a combination of NISS and APACHE Ⅱ to predict all-cause mortality of patients with severe trauma in mainland China.

Methods: This was a multicenter observational cohort study conducted in the ICU of the Chonggang General Hospital, Daping Hospital of the Army Medical University and Affiliated Hospital of Zunyi Medical College from January 2012 to August 2016. The score of NISS, APACHE Ⅱ, GCS, a combination of NISS and GCS, a combination of APACHE Ⅱ and GCS, a combination of NISS and APACHE Ⅱ were calculated based on data from the first 24 hours of ICU admission. Data were processed with Student's *t*-test, *chi*-square test, and receiver operating characteristic (ROC) curve of six scoring systems. Calibration was assessed with the Hosmer-Lemeshow test. The primary endpoint was death from any cause during ICU stay.

Results: A total of 852 and 238 patients with severe trauma were assigned to the derivation group and validation group, respectively. Area under the ROC curve (AUC) was 0.826 [95% confidence interval (*CI*)=0.794-0.855)] for NISS, 0.802 (95% *CI*=0.768-0.832) for APACHE Ⅱ, 0.808 (95% *CI*=0.774-0.838) for NGCS, 0.859 (95% *CI*=0.829 -0.886) for NISS+NGCS, 0.864 (95% *CI*=0.835-0.890) for APACHE Ⅱ+NGCS, 0.896 (95% *CI*=0.869-0.929) for NISS+APACHE Ⅱ in the derivation cohort. Similarly, the score of NISS+APACHE Ⅱ was also better than the other five scores in the validation cohort (AUC=0.782; 95% *CI*=0.725-0.833) and had a good calibration (*P*=0.41).

Conclusions: Taking into account anatomical and physiological parameters completely, the combination of NISS and APACHE Ⅱ performs better than NISS, APACHE Ⅱ, NGCS, NISS+NGCS, APACHE Ⅱ+NGCS for predicting mortality in ICU severe trauma patients. It is needful to develop models that contain various types of accessible predictors (demographic variables, injury cause/mechanism, physiological and anatomical variables, *etc.*) as comprehensive as possible.

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1. Introduction

According to the WHO report, the global mortality caused by severe trauma (especially traffic injury) remains high[1]. If the wound infection following injury is not well controlled, it can be further developed into local infection, endogenous infection (such as intestinal infection) or nosocomial infection (such as surgical infection, ventilator-associated pneumonia, *etc.*), and then evolved to sepsis, multiple organ dysfunction syndrome even death, which seriously threaten the health of patients[2]. Consequently, in the event that we make an early prediction and diagnosis for trauma patients with complications, their prognosis will be better improved.

The predictive indicators for post-traumatic mortality are mainly composed of epidemiological information of patients (such as gender, age, injury mechanism and severity, *etc.*)[3-7], physiological and biological indicators (such as blood lactate, activated prothrombin time, inflammatory cytokines, vital signs, plasma arginine bioavailability, *etc.*)[8-12]. In addition, Injury Severity Score (ISS), New Injury Severity Score (NISS), APACHE system, Revised Trauma Score (RTS), Glasgow Coma Scale (GCS) and Trauma & Injury Severity Score (TRISS) are well-known for predicting mortality in trauma patients. However, some researches on death prediction in trauma patients used physiological and biological indicators alone, or trauma score plus biochemical index[13,14], which did not fully consider the bias of univariate prediction and weak prediction ability.

Previously published finding has indicated that the ISS can be replaced by the NISS which takes the three most severe injuries regardless of body region into account[15], and NISS shows better predictive value than ISS both in adult and pediatric trauma population[16]. Owing to the extremely poor physiological status of critically ill patients in a trauma center, the APACHE scoring system was developed. APACHE Ⅱ and Ⅲ are widely used for predicting outcomes of trauma patients[17]. The GCS following modification is most commonly used to evaluate the severity of traumatic brain injury, in adults as well as in children, which are also used as a predictor of mortality[18]. A systematic review showed that the basic TRISS model was perceived as outdated and adding more predictors to it did not always prove higher performance in the general trauma population[19]. Although there are many different trauma scales for predicting patients' outcomes following trauma, the combined application of the scoring system is extremely limited in mainland China. Therefore, the aim of this multicenter observational cohort study was to evaluate the ability of NISS, APACHE Ⅱ, GCS, a combination of NISS and GCS, a combination of APACHE Ⅱ and GCS, a combination of NISS and APACHE Ⅱ to predict mortality in ICU severe trauma patients.

2. Materials and methods

2.1. Study design and setting

All data in the derivation group and validation group were collected at the ICU of Chonggang General Hospital, Daping Hospital of the Army Medical University and Affiliated Hospital of Zunyi Medical College from January 2012 to August 2016.

2.2. Ethics with study approval

This multicenter observational cohort study was performed after receiving institutional review board approval from the Chonggang General Hospital, Daping Hospital and Affiliated Hospital of Zunyi Medical College. The Human Ethics Committee of the Third Affiliated Hospital of Army Medical University approved the study procedures and consent form (approval number 2014-51).

2.3. Patients

A total of 1 090 patients with severe trauma hospitalized in ICU were included, and all met the following criteria: $\geqslant$16 years old, incoming ICU within 24 hours after injury, the length of ICU stay $\geqslant$48 hours; ISS$\geqslant$16 and without coexisting illness. Patients who abandoned treatment or transferred to another hospital were excluded.

2.4. Data collection

The primary endpoint was death from any cause during hospital stay. The clinical data of demographical characteristics, physiological and biological indicators were collected and NISS, APACHE Ⅱ, NGCS, NISS+NGCS, APACHE Ⅱ+NGCS, NISS+APACHE Ⅱ score of patients on the first day of ICU admission were calculated and compared between two groups. NISS is the improvement on the basis of the ISS, which adds to the squares of the three highest scoring Abbreviated Injury Scale injuries no matter the affected body area[20]. APACHE Ⅱ is a revised version of APACHE-Ⅰ, which consists of age scores, acute physiology scores, and chronic health scores cited the weights of 45 acute diseases[21]. A score of 15 minus the original GCS to get the modified GCS named NGCS.

2.5. Data analysis

Data within two groups were compared by Student's t test for continuous variables and *chi*-square test for categorical variables. The area under the receiver operator characteristic (ROC) curves (AUC) of the six scoring systems was compared and calibration was evaluated using the Hosmer-Lemeshow statistic. DeLong-DeLong non-parametric test was used to analyze the predictive ability of these six scoring systems and P<0.05 was considered significant. All analyses were performed with SAS 9.3.

3. Results

A total of 1090 severe trauma patients were enrolled from 1 January 2012 to 15 August 2016. There were 852 patients with severe trauma in the 2012-2014 derivation database and 238 valid cases in the 2015-2016 database, respectively (Figure 1).

3.1. Results of derivation cohort

A total of 852 participants with severe trauma were studied, including 684 males (80.28%) and 168 (19.72%) females. Mean ages in death group and survival group were (48.32±15.75) years, (45.51±13.68) years, respectively. The demographic information is summarized in Table 1. The most common causes of severe trauma were road traffic injuries (50.35%), followed by falling from a high place (31.22%), blunt instrument injuries (10.92%), sharp instrument injuries (4.58%), assault (2.11%) and others (0.83%). In the end, the overall mortality of patients in ICU was 33.75%. The scores of NISS, APACHE Ⅱ, NGCS, NISS+NGCS, APACHE Ⅱ+NGCS, and NISS+APACHE Ⅱ in the death group were significantly higher than survival group (P<0.001).

Figure 2A shows the ROC curves of these six scoring systems for mortality prediction. The area under ROC curves was 0.826 for NISS, 0.802 for APACHE Ⅱ, 0.808 for NGCS, 0.859 for NISS+NGCS, 0.864 for APACHE Ⅱ+NGCS, 0.896 for NISS+APACHE Ⅱ, and the NISS + APACHE Ⅱ showed the best calibration (χ^2=3.06, P=0.47).

DeLong-DeLong non parametric test results of AUC were as follows: NISS versus APACHE Ⅱ, P=0.391; NISS versus NGCS,

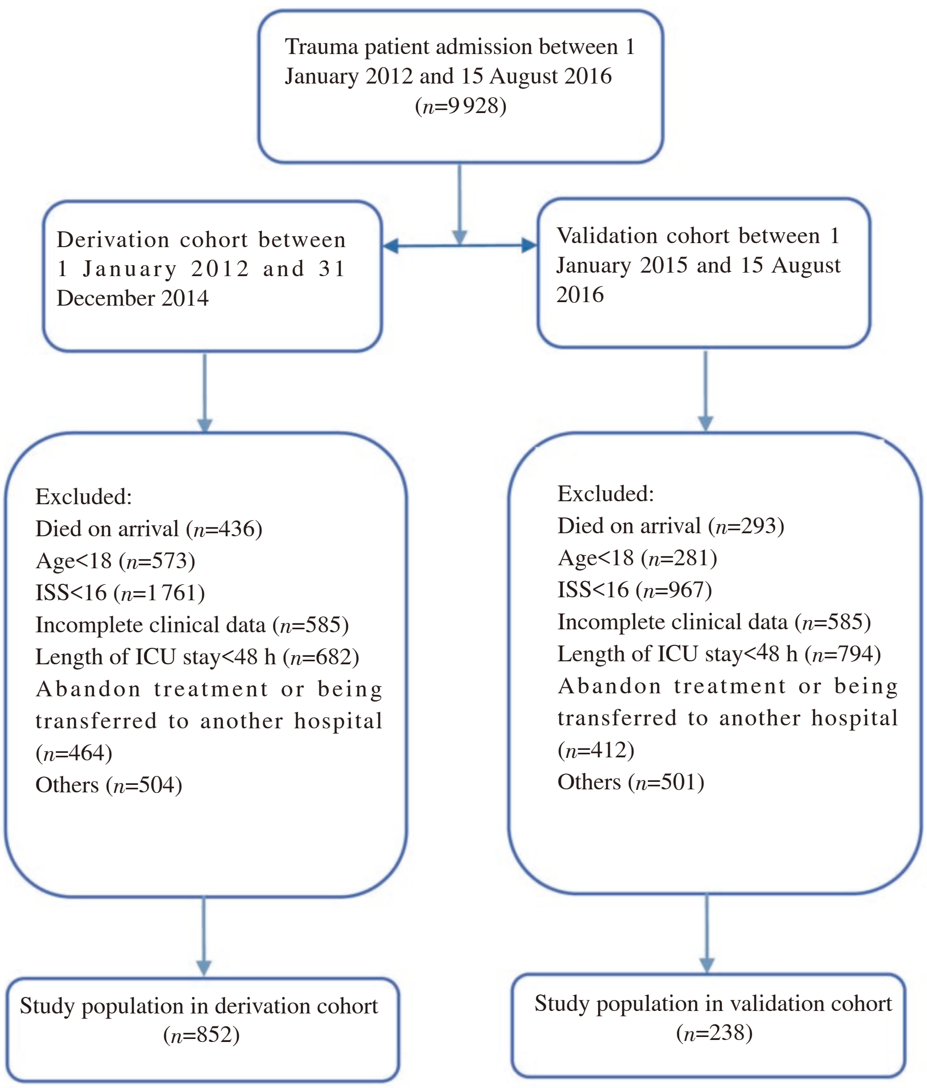

Figure 1. Chart flow.

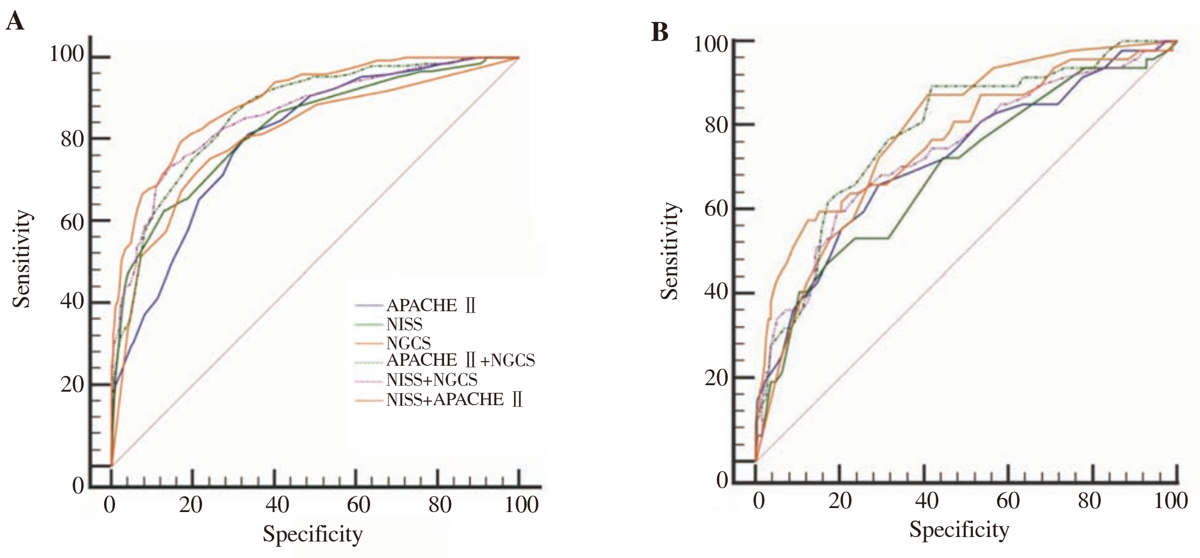

Figure 2. ROC curves of six scoring systems in derivation cohort (A) (n=852) and in validation cohort (B) (n=238).

Table 1. Comparison of demographic information between the death group and the survival group in the derivation cohort (n=852).

Variables	Death group (n=215)	Survival group (n=637)	χ^2/t	P
Gender			0.604	0.439
Female	39	129		
Male	176	508		
Age (Mean ± SD, years)	48.32 ±15.75	45.51 ±13.68	1.836	0.273
Intensive care unit stay (Mean ± SD, d)	17.25 ±30.63	15.71 ±19.40	1.184	0.519
Causes of trauma			2.976	0.080
Road traffic injury	111	318		——
Falling	65	201		——
Blunt object	23	70		——
Sharp object	10	29		——
Assault	4	14		——
Other	2	5		——
Scores				
NISS	41.62±11.21	30.50±8.23	7.213	<0.001
APACHE Ⅱ	24.37±7.28	16.86±5.61	8.441	<0.001
NGCS	8.60±4.35	3.79±2.90	6.270	<0.001
NISS+NGCS	50.57±13.38	35.86±10.82	8.025	<0.001
APACHE Ⅱ+NGCS	30.04±9.82	20.64±7.93	9.292	<0.001
NISS+APACHE Ⅱ	64.48±13.55	47.43±11.20	9.711	<0.001

Table 2. Efficacy of the six scoring systems in the derivation cohort.

Items	NISS	APACHE Ⅱ	NGCS	NISS+NGCS	APACHE Ⅱ+NGCS	NISS+APACHE Ⅱ
AUC (95%*CI*)	0.826 (0.794-0.855)	0.802 (0.768-0.832)	0.808 (0.768-0.832)	0.859 (0.829 -0.886)	0.864 (0.835-0.890)	0.896 (0.869-0.929)
Best cut-off point	40	18	6	43	24	56
Se (%)	62.67	81.33	75.33	73.33	86.00	79.33
Sp (%)	86.85	66.38	75.86	85.34	70.47	82.97
PV+ (%)	82.66	70.75	71.16	83.68	83.73	82.33
PV- (%)	69.94	78.05	82.95	74.73	75.46	80.05
RL+	4.77	2.42	3.12	5.00	2.91	4.66
RL-	0.43	0.28	0.33	0.31	0.20	0.25
J	0.50	0.48	0.51	0.59	0.57	0.62
PR (%)	85.09	84.67	84.90	86.13	86.84	87.54

AUC: area under the curve; Se: sensitivity; Sp: specificity; PV+: positive predictive value; PV-: predictive value; RL+/-: likelihood ratio; J: Youden's index; PR: precision rate.

P=0.449; NISS versus APACHE Ⅱ+NGCS, *P*=0.117; NISS versus NISS+NGCS, *P*<0.001; NISS versus NISS+APACHE Ⅱ, *P*<0.001; APACHE Ⅱ versus NGCS, *P*=0.818; APACHE Ⅱ versus APACHE Ⅱ+NGCS, *P*<0.001; APACHE Ⅱ versus NISS+NGCS, *P*=0.030; APACHE Ⅱ versus NISS+APACHE Ⅱ, *P*<0.001; NGCS versus APACHE Ⅱ+NGCS, *P*<0.001; NGCS versus NISS+NGCS, *P*=0.003; NGCS versus NISS+APACHE Ⅱ, *P*<0.001; APACHE Ⅱ +NGCS versus NISS+NGCS, *P*=0.807; APACHE Ⅱ+NGCS versus NISS+APACHE Ⅱ, *P*=0.045; NISS+NGCS versus NISS+APACHE Ⅱ, *P*=0.002.

The best cut-off points for mortality prediction were 40 (sensitivity=62.67%; specificity=86.85%) for NISS, 18 (sensitivity=81.03%; specificity=66.38%) for APACHE Ⅱ, 6 (sensitivity=75.33%; specificity=75.86%) for NGCS, 43 (sensitivity=73.36%; specificity=85.34%) for NISS+NGCS, 24 (sensitivity=86.00%; specificity=74.47%) for APACHE Ⅱ+NGCS, 56 (sensitivity=79.45%; specificity=87.93%) for NISS+APACHE Ⅱ (Table 2).

3.2. Results of validation cohort

A total of 238 participants with severe trauma were studied, including 186 males (78.15%) and 52 (21.85%) females. The mean ages in death group and survival group were (48.38±14.26) years, (46.36±14.35), years, respectively. The demographic information is summarized in Table 3. In the end, the overall mortality of patients in ICU was 19.75%. The scores of NISS, APACHE Ⅱ, NGCS, NISS+NGCS, APACHE Ⅱ+NGCS, and NISS+APACHE Ⅱ in the death group were significantly higher than survival group (*P*<0.001). Figure 2B shows the ROC curves of these six scoring systems for mortality prediction. The area under ROC curves were 0.690 for NISS, 0.719 for APACHE Ⅱ, 0.739 for NGCS, 0.740 for NISS+NGCS, 0.763 for APACHE Ⅱ+NGCS, 0.786 for NISS+APACHE Ⅱ, and the NISS + APACHE Ⅱ showed the best calibration (χ^2=4.34, *P*=0.41) (Table 4). DeLong-DeLong non parametric test results of AUC were as follows in Table 4.

Table 3. Comparison of demographic information between the death group and the survival group in the validation cohort (*n*=238).

Variables	Death group (*n*=47)	Survival group (*n*=191)	χ^2/*t*	*P*
Gender			0.465	0.495
Female	12	40		
Male	35	151		
Age (Mean ± SD, years)	48.38 ±14.26	46.36 ±14.35	0.892	0.386
Intensive care unit stay (Mean ± SD, d)	17.36 ±22.03	14.65 ±19.90	0.498	0.414
Cause of trauma			1.463	0.062
Road traffic injury	21	98		——
Falling	10	54		——
Blunt object	7	19		——
Sharp object	5	11		——
Assault	3	6		——
Other	1	3		——
Scores				
NISS	41.09±14.18	32.44±10.11	5.263	<0.001
APACHE Ⅱ	21.89±7.09	16.36±6.16	3.015	<0.001
NGCS	8.43±3.66	4.07±2.16	5.685	<0.001
NISS+NGCS	49.51±16.47	36.51±12.35	6.151	<0.001
APACHE Ⅱ+NGCS	30.32±8.73	20.43±9.00	4.647	<0.001
NISS+APACHE Ⅱ	62.98±15.01	48.80±12.08	5.971	<0.001

Table 4. Efficacy of the six scoring systems in the validation cohort.

Items	NISS	APACHE Ⅱ	NGCS	NISS+NGCS	APACHE Ⅱ+NGCS	NISS+APACHE Ⅱ
AUC (95%*CI*)	0.690 (0.651-0.722)	0.719 (0.673-0.734)	0.739 (0.701-0.768)	0.743 (0.680-0.771)	0.763 (0.718-0.805)	0.786 (0.737-0.829)
Best cut-off point	41	19	4	45	21	57
Se (%)	46.81	65.96	87.23	59.57	89.36	87.45
Sp (%)	83.25	70.68	59.16	80.63	58.12	77.43
PV+ (%)	73.65	69.23	66.27	68.78	71.79	82.05
PV- (%)	61.01	67.49	65.36	72.47	73.54	67.26
RL+	2.79	2.25	2.14	3.08	2.13	4.57
RL-	0.64	0.48	0.22	0.50	0.18	0.49
J	0.30	0.37	0.46	0.40	0.48	0.47
PR(%)	83.42	84.18	84.56	85.34	85.12	86.73

AUC: area under the curve; Se: sensitivity; Sp: specificity; PV+: positive predictive value; PV-: predictive value; RL+/-: likelihood ratio; J: Youden's index; PR: precision rate.

4. Discussion

To a large extent, the prognoses of severe trauma patients in ICU are depended on patients' characteristics, such as injury severity, and the scoring system is the main method to measure the severity of trauma. Considering the heterogeneity of patients, it is inappropriate to apply only one trauma scoring model for all trauma population. Various scoring systems have been developed in recent decades to predict mortality or survival of trauma patients, and ISS, Abbreviated Injury Scale, NISS, APACHE Ⅱ and GCS are frequently used in mainland China. According to the results of our study, the combination of NISS and APACHE Ⅱ performed better than the other five scores (NISS, APACHE Ⅱ, NGCS, NISS+NGCS, APACHE Ⅱ+NGCS) during mortality prediction in severe trauma patients.

Among all patients in this study, cases due to road traffic injuries accounted for the highest proportion, followed by high-falling injuries, blunt injuries, sharp injuries and assaults, which were consistent with the distribution of trauma types in other studies[22,23]. NISS was proposed by Osler[20] based on ISS and demonstrated correlation with the length of hospital stay and mortality of severe trauma patients inn ICU[24]. Besides, several studies found that NISS was superior to ISS for predicting functional recovery and mortality in road traffic injuries and skeletal trauma[25], so NISS was selected to use in this study. However, Dewar *et al.*[26] found that neither NISS nor ISS could predict the occurrence of post-traumatic multiple organ failure. This discordance between the results can be mainly attributed to the use of anatomical score alone.

APACHE Ⅱ consists of age score, acute physiology score, and chronic health score, which can better reflect the patients' physiological status. Multiple studies showed that APACHE Ⅱ had some ability to predict the death of emergency trauma patients and ICU trauma patients[27-29]. In contrast, our study found that the predictive efficacy of APACHE Ⅱ was lower with the minimum AUC (0.802) among six scoring systems, implying that the physiological score used alone was inadequate to predict the mortality of trauma patients. GCS is better stool to evaluate the level of consciousness in trauma patients, especially those with brain traumatic injury (TBI). Yousefzadeh-Chabok *et al.*[18] declared that GCS might be a better predictor of mortality in children trauma cases compared to ISS (AUC: 0.997 versus 0.929, P<0.05). McNett *et al.*[30] found that GCS performed better than FOUR scores when predicted 24 h and 72 h mortality after TBI (24 h FOUR versus GCS: 0.913, 0.935; 72 h FOUR versus GCS: 0.837, 0.884). In this study, we found that NGCS after modification had analogical AUC to APACHE Ⅱ (0.808 versus 0.802, P>0.05). This is in contrast to Zali *et al.*[31]. They compared the ability to predict mortality and functional outcome of GCS and APACHE Ⅱ in ICU patients with multiple trauma, and found that APACHE Ⅱ was superior to GCS since it involved the principle physiologic parameters of patients (AUC: 0.892±0.028 versus 0.621±0.029, P<0.05).

On account of the lower accuracy of a single scoring system, some researchers investigated the predictive efficacy among combined scoring systems. Kahloul *et al.*[32] compared the predictive performance of two anatomic scales (ISS, NISS) with two physiologic scales (Revised Trauma Scale, Simplified Acute Physiology Scale Ⅱ) in 1 136 trauma patients. They found that the combination of NISS with SAPS Ⅱ, or combination of ISS with SAPS did not improve the prediction performance. However, our study findings showed a better predictive value of the combination of anatomic scale with physiologic one (NISS+APACHE Ⅱ, AUC=0.896). In addition, our previous study found that the combination of NISS with APACHE Ⅱ was superior to NISS and APACHE Ⅱ used alone for multiple organ dysfunction syndrome diagnosis in ICU severe trauma patients[33]. In fact, scoring systems that incorporate anatomic and physiologic variables are beneficial in predicting the mortality of trauma patients. Combination of APACHE Ⅱ with NGCS and combination of NISS with NGCS did not show high predictive value, which might be related to the calculation method of GCS itself. The GCS scale does not include pupil and sensory examinations, language assessment of patients with artificial airways, and that was why Majdan *et al.*[34] used GCS and pupillary reaction to predict six-month mortality in patients with TBI. It also lacks indicators for assessing the severity of coma, such as brain-stem function and breathing patterns and it fails to fully reflect the patients' physiology because the subtle neurological system changes could not be found. Notably, the combined application of NISS and APACHE Ⅱ has comprehensive manifestation in anatomy and physiology aspects so that it could show the severity of the injury.

Our study has limitations that should not be neglected. First, this evaluation included 852 cases who met the inclusion criteria, hence, prospective verification is needed for multi-center of severe trauma patients. Second, although we trained medical technicians before the study, there were still computational errors during calculation. Finally, this study focused on severe trauma patients (ISS⩾16) who were in critical condition. In order to obtain comprehensive results, trauma patients who had ISS<16 and admission within 24 hours should be considered in subsequent studies.

Taking into account anatomical and physiological parameters completely, the combination of NISS and APACHE Ⅱ performed better than NISS, APACHE Ⅱ, NGCS, NISS+NGCS, APACHE Ⅱ +NGCS as predicting mortality of severe trauma patients in ICU. These findings provide basis for developing diagnostic models that contain various types of accessible predictors (demographic variables, injury cause/mechanism, physiological and anatomical variables *etc.*).

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

H.P.L. had an initial idea. X.Y.M., H.J.J., B.W. designed the study. X.Y.M., H.J.J., L.X.T., Q.W., J.Y.Z. collected the derivation cohort clinical data. Z.G.H., W.T., T.C. collected the validation cohort clinical data. X.Y.M., H.J.J., L.X.T., J.Y.Z. proofread all data. X.Y.M., H.J.J. summarized, extracted and processed all results. X.Y.M., H.J.J., B.W. assessed and statistically analyzed the data. X.Y.M., H.J.J., H.P.L. drafted the manuscript. All author read and revised the manuscript, and approved the final submission. H.P.L. and B.W. take responsibility for completeness and accuracy of the data and analyses.

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