Development and internal validation of an improved prognostic model with limited resources (Broaln-MEWS) for predicting 28-day mortality of critical illness: a retrospective cohort study

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Article

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Abstract

Background

Prognostic models in intensive care unit (ICU) were extensively applied in high-income countries, but were limited in lower income countries for lack of resource. A simple prognostic model for easy use in ICU was more attractive. The modified early warning score (MEWS), age, body mass index (BMI), red cell distribution width(RDW), neutrophil to lymphocyte ratio (NLR), lactate (lac) and osmolarity were easily accessible and objective indexes in resource limited settings to predict mortality of patients in ICU. However, using these indexes alone to predict mortality has the disadvantage of insufficient diagnostic efficiency. The usefulness of a combination of these indexes to predict 28-day mortality of critical illness was unclear.

Methods

This was a retrospective cohort study of patients admitted to ICU in MIMIC-III database. A total of 44103 patients older than 14 years were randomly assigned to a development (29402 patients) or validation cohort (14701 patients). Captured variables included demographic characteristics, clinical assessments, laboratory data, acute physiology and Chronic Health Evaluation (APACHE)-II, and MEWS. After identifying independent risk factors of 28-day mortality, we developed a 28-day mortality prediction model with multivariate logistic regression in development cohort. We compared the difference among Broaln-MEWS, APACHE-II, MEWS, RDW, NLR, lac and osmolarity by using area under the receiver operating characteristic curve (AUROC) to calculate discriminative ability, Hosmer-Lemeshow C-Statistic (H/L C-statistic) to assess calibration and Brier score to evaluate accuracy. Finally, the model was validated in the validation cohort and nomogram graph was offered to fast calculate predicted mortality risk.

Results

The 28-day mortality of critical illness was 22.85% in the development cohort. Patients with increased age, MEWS, NLR, RDW, lac, osmolarity and decreased BMI at baseline exhibited higher risks of 28-day mortality. The mortality prediction model (Broaln-MEWS) that incorporated age, BMI, MEWS, RDW, NLR, lac and osmolarity had an AUROC of 0.741 for the developing data, which was higher than that of MEWS (0.669), NLR (0.634), RDW (0.591), lac (0.580), or osmolarity (0.592) alone($p < 0.000$) and slightly lower than APACHE-II (0.747) ($p = 0.060$). The H/L C-statistic of Broaln-MEWS were equal to 9.641($p = 0.291$) and Brier score was 0.103, respectively. Additionally, Broaln-MEWS model demonstrated good discriminative power in the validation group by AUROC that was 0.744 ($p < 0.000$)

Conclusion

The Broaln-MEWS model had higher predictive value for 28-day prognosis in critically illness, which was used easily in resource limited settings.

Introduction

The health condition of ICU patients would be radical change for many factors including previous health status, patient reserve, underestimated illness severity, efficiency of the care, and response to treatment [1]. Though a great leap has been made over these years in the field of critical care, it was only contributed to a small step in lowering the mortality rate of ICU patients, which was still hovering at around 20-40% nowadays because of highly complex and heterogeneous disease spectrum of ICU patients [2, 3].

In clinical practice, ICU prognostic models were critical for correctly evaluating and classifying ICU patients at high risk in assisting clinicians to make wiser medical judgements and ensuring reduction of ICU deaths as well as instilling proper utilization of the already constrained healthcare resources, especially in low- and middle-income countries (LMICs) [4-6]. These systems, as bedside and digital triage tools to identify risk of catastrophic deterioration and death in critical patients, could help us to capture the intensity of resource use and gain better understanding of what is truly ICU-acquired organ dysfunction [7]. The predictive efficiency of frequently-used scoring systems were reported in table1[8-10]. Among these systems, APACHE-II utilized combinations of three critical domains: demographics feature, like age and sex; along with an evaluation of the patient's chronic health status, admission diagnosis, and the worst values of 12 physiological variables during the first 24 hours following ICU admission to calculate the APACHE-II predicted mortality. However, using APACHE-II were time and medical expense-consuming because more than 20 kinds of clinical data needed to be gathered and complete scoring should be finished within 24 hours after clinical reception. Similar to the APACHE-II, sequential organ failure assessment (SOFA) focused on multiple-organ dysfunction was also inconvenient for rapidly assessing ICU patients. Therefore, it may be impractical to apply widely these recommendations in resource-restricted settings like LMICs [11]. MEWS was a simple efficient track-and-trigger system to identify patients who were present or developed with acute illness. It was derived from five common physiological vital signs: respiratory rate, body temperature, systolic blood pressure, pulse rate and level of conscious, which helped to enhance detection of physiological abnormalities, predict ICU admission and in-hospital mortality [12]. The advantages of MEWS included application of easily measurable and available parameters, no increasing burden of disease, suitable for resource limited settings. In the surviving sepsis campaign guidelines, it was recommended as a screening tool to identify and manage critically ill patients [13]. However, MEWS was inferiority to the APACHE II in prediction efficiency of ICU mortality. In a comparative study about predictive efficacy of shock patients’28-day mortality between APACHE-II and MEWS, the AUROC of APACHE-II was 0.785 and the MEWS was 0.614 [10].

An ideal risk scoring system for critically illness should be easy to use, accurate, informative and low cost with great potential to improve health of ICU patients. It was an interesting issue to balance such dilemma based on highly complex and heterogeneous disease spectrum of ICU patients. Some

convenient laboratory indexes such as NLR, RDW, lac and osmolarity. were widely available for predicting ICU mortality in multiple patient populations in the past few years [14-17]. Some reports also showed that the combination of scoring system and simple laboratory indexes can improve the prediction efficiency of traditional scoring system, for example in a 292 shock patients 28-day prognosis analysis, the AUROC (0.696) of a new MEWS based on the conventional MEWS, age and transcutaneous oxygen saturation was superiority to the conventional MEWS (AUROC:0.614) ($p<0.05$) [10]. Therefore, based on the traditional scoring system and simple laboratory indexes, developing a scoring system with high prediction efficiency may be more suitable for use in LMICs

In this study we develop an improved MEWS scoring system using convenient data including age group, BMI group, MEWS, RDW group, NLR , lac and osmolarity group by analyzing the correlation of each variable with 28-day ICU mortality as well as comparing the prediction efficiencies of the different scoring mortality on 28-day prognosis in development group and verifying this model on validation group by using collected clinical data of ICU patients in Medical Information Mart for Intensive Care III (MIMIC-III) database.

Methods

This was a retrospective cohort of patients admitted to the ICU (aged 14 years or older). The outcome was for developing and validating an improved MEWS scoring system for 28-day all-cause mortality of critical illness displaying with nomogram graph. The datasets leveraged in this study were derived from a publicly critical database called MIMIC-III (version 1.4), which contains high-quality health-related data from patients who were admitted to critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012. After completing the National Institutes of Health web-based training course, we obtained approval to access the database (Certification Number: 37764466). Informed consent was not required for all protected health information has been de-identified.

Study population

We reviewed the discharge summaries of all patients admitted to ICU in MIMIC-III database between 2001 and 2012. All ICU patients >14 years of age with measured MEWS within 24 hours after ICU admission were included in this study. Patients with the following criteria were excluded: (1) an age less than 14 years old; (2) patients with readmission within the same hospitalization were excluded and only data of the first ICU admission of hospitalization were selected into final cohort; (3) MEWS could not be calculated due to omission of a measurement within 24 hours after ICU admission. After screening database, a total of 44103 ICU patients were eligible for the current analysis.

Data extraction, management and processing

Demographic, clinical, laboratory data and risk scoring systems were extracted with structured query language by using PostgreSQL tools (version 9.6) or calculated from the following tables: ADMISSIONS, ICUSTAYS, CHARTEVENTS, DIAGNOSIS_ICD, d_items, d_icd_diagnoses, LABEVENTS, PATIENTS

prescriptions and Materialized Views. The demographic information consisted of age, gender, BMI, admission and discharge date of patients'getting into and out of ICU, date of death. The clinical characteristics included preexisting chronic medical conditions or comorbidities (such as congestive heart failure, cardiac arrhythmias, pulmonary circulation abnormality，valvular disease，peripheral vascular disease，hypertension, application of vasoactive drug(used within 48 hours before and after ICU admission)，chronic pulmonary disease, liver disease, peptic ulcer，renal failure, diabetes, hypothyroidism, paralysis, other neurological abnormality, psychoses, depression, solid tumor, metastatic cancer, lymphoma, coagulopathy, blood loss anemia，deficiency anemias，alcohol or drug abuse, rheumatoid arthritis, acquired immune deficiency syndrome. The laboratory parameters included white blood cell counts (WBC), neutrophil-to-lymphocyte ratio (NLR), hemoglobin (Hgb), Red cell distribution width (RDW), platelets, total bilirubin(TBil), aspartate transaminase (AST), alanine transaminase (ALT), blood glucose (glu), blood urea nitrogen (BUN), serum creatinine (Scr), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), PH, PaO_2, $PaCO_2$, SO_2, PaO2/fio2， lactate, sodium, potassium. These lab parameters were selected the worst values measured if they were measured multiple times within 48 hours before and after ICU admission. In these parameters, BMI was calculated as weight(kilograms) /height(meters)^2, NLR as neutrophil to lymphocyte ratio and osmolarity as (2×sodium+potassium) + (glucose/18) + (BUN/2.8). The risk score system included APACHE-II and MEWS. The APACHE-II values of each ICU patient were acquired with the SQL code from Materialized Views of MIMIC-III database. MEWS was calculated according to Table2 [7] and the parameter of MEWS was selected the worst values within 24 hours after ICU admission.

For MIMIC database obscured true ages of patients over 89 years old for privacy policy, we selected age×90/300 as a surrogate age for those patients. In data processing, we selected Winsor means to duplicate outliers. We used multiple imputation by carrying out five imputations to replace missing values for BMI and laboratory parameters to match patients having known values that are most similar to other patients with the missing values. To further examine the effect of age, BMI, RDW and osmolarity, they were further categorized into different levels for analysis with logistic regression models: age level 1 (<60), level 2 (≥60), BMI level 1 (<18.5), level 2 (18.5-28), level 3 (≥28), RDW level 1 (<14.5%), level 2 (≥14.5%), osmolarity level 1 (<300mmoL/L), level 2 (≥300mmoL/L).

Development of the risk prediction model and model validation

The eligible patients were randomly assigned 2:1 to either derivation cohort for model development or internal validation cohort for model verification. We performed an initial analysis of all available demographic, clinical, laboratory data, APACHE-II and MEWS based on patients stratified into survivors and non-survivors group in development cohort. Univariate and multivariate logistic analyses were used for identifying independent predictors of 28-day all-cause mortality of critical illness and developing predictive model. Collinearity analysis were considered for avoiding potential multicollinearity of predictive model. The obtained predictive model was estimated their performance in the validation group by AUROC and its 95% confidence interval (CI). Calibration of the model was assessed by the H/L C-statistic and accuracy of the model by Brier score

Comparison with existing prognostic models

The performance of obtained model was then compared with APACHE-II, MEWS, RDW, NLR, lactate and osmolarity. Discrimination (AUROC), calibration (H/L C-statistic), and accuracy (Brier score) were calculated, respectively.

Nomogram development for the simplified prediction model

The nomogram graph was a graphical tool easily used by clinicians in resource limited environment like no statistical software or online electronic calculator. The nomogram graph was formulated with clinical applicability based on the results of the obtained predictive model.

Statistical analysis

All patients were divided into two cohorts (development vs validation cohort) with completely random method. The distributions of the continuous variables were assessed with Kolmogorov-Smirnov test, and skewed distributions were log normalized (e.g., age, APACHE-II, MEWS, TBil, AST, ALT, BUN, Scr, INR, PT, APTT, SO2). Normally distributed continuous data were expressed as mean ± standard deviations (SD), non-normally distributed continuous data as median (interquartile range [IQR]), and categorical variables as absolute values (percentages), respectively. Descriptive statistics in development cohort was used to summarize patients' baseline data between survivors and non-survivors group with t test for normally distributed data or Mann-Whitney U test for non-normally distributed data and the Chi square test to analyze the differences in categorical variables. The covariates associated with 28-day all-cause mortality (MEWS, NLR, lac, age group, BMI group、RDW group, osmolarity group) were further identified with univariate and multivariate logistic regression analyses. The unadjusted and adjusted odds ratios (OR) for each variable was assessed and reported with p values and 95% CIs. The multivariate logistic regression models (Broaln-MEWS) were built using a forward selection modeling process with a significance level of 0.05. The variables independently associated with 28d mortality (MEWS, NLR, lac, age group, BMI group、RDW group, osmolarity group) were included in this model. Furthermore, potential multicollinearity was tested using a mean variance inflation factor (VIF), with a value of ≥10 indicating multicollinearity. Additionally, we used AUROC to assess discriminative ability in different model including APACHE-II, MEWS, RDW, NLR, lactate and osmolarity. We then applied the obtained model generated on the training dataset to the validation dataset to assess discriminative ability with AUROC and calibration with H/L C-statistic in predicting mortality. To enhance the clinical utility of the model, a nomogram was formulated based on the results of multivariate analysis for model. Overall, all analyses were performed using Stata software version 14.0. A two-sided $p<0.05$ was considered statistical significance.

Results

Study population and baseline characteristics

According to inclusion and exclusion criteria, a total of 679305 ICU patients were selected from the MIMIC-III database. 542707 patients were excluded due to repeated ICU admission, 32089 patients with age <14, and 60406 patients without measured MEWS within 24 hours before and after ICU admission. 44103 admissions with sufficient data were included in the last analysis, including 25063 male (56.83%) and 19040 female patients (43.17%). The mean age of all patients was 63.94±17.18 years. A total of 6177 patients died within 28 days, establishing an initial 28-day mortality rate of 14.01%. The detailed process of study population extraction was shown in Fig. 1. Hypertension (54.08%) was the most common comorbidity, followed by cardiac arrhythmia (29.74%), congestive heart failure (28.13%). In our study, 29402 patients (66.67%) were randomly assigned to the development cohort and 14701 patients (33.33%) to the validation cohort.

Development a risk prediction model for 28-day all-cause mortality of ICU patients

The percentage of 28-day all-cause mortality of critical illness was 14.20% in the development cohort (4176/29402). Table 3 describes the baseline characteristics of these patients. There were significant differences in baseline clinical features, risk scores, laboratory data of patients who died compared with those survived, as summarized in Table 3. Non-survivors were predominantly male and had a statistically significantly higher chronic medical conditions or comorbidities incidence of congestive heart failure, cardiac arrhythmias, pulmonary circulation disease, more likely to require use of vasoactive drug, liver disease, renal failure, paralysis, other neurological disease, solid tumor, metastatic cancer, lymphoma, coagulopathy and lower incidence of valvular disease, hypertension, diabetes, psychoses, depression，alcohol or drug abuse than survivors. Non-survivors were older and had statistically significantly higher values shown in length of ICU stay, APACHE-II, MEWS, WBC, RDW, TBil, INR, PT, APTT, BUN, Scr, glu, lac, NLR, osmolarity，sodium and potassium than survivors. In addition, non-survivors had statistically significantly lower value of Hgb, PLT, AST, ALT, PH, PaO_2, $PaCO_2$, SO_2, PaO_2/fio_2 vs survivors. There were no significant differences in peripheral vascular disease, peptic ulcer, hypothyroidism, blood loss anemia, deficiency anemia, rheumatoid arthritis, acquired immune deficiency syndrome between survivors and non-survivors in development cohort.

In regard to BMI, RDW, NLR and osmolarity, there were significantly graded increase in 28d-mortality rate across decreasing BMI group (BMI (<18.5) 17.53% versus BMI (18.5 to 28) 15.04% versus BMI (>28) 12.88%; p=0.000 for 28d-mortality), increasing age group (age(<60) 8.24% versus age(≥60) 15.51% p=0.000), increasing RDW group (RDW(<14.5%) 8.53% versus RDW(≥14.5%) 16.93% p=0.000) and increasing osmolarity group (osmolarity (<300) 10.34% versus osmolarity (≥300) 16.80% p=0.000) (Figure2a-d). Because MEWS could be obtained by simple calculation, RDW and NLR by routine blood test, lac and osmolarity obtained through portable test tools, we selected age group, BMI group, MEWS, lac, RDW group, NLR and osmolarity group for univariate and multivariate logistic regression analysis. Such selection could achieve the goal of convenient clinical use and avoiding multicollinearity of predictive model, compared with the selection of all variables based on the results of the univariable analyses in development cohort. Table 4 demonstrated that all the selected variables were significantly associated with 28d-mortality in univariate logistic regression analysis, which was same to above

univariable analyses. multivariate logistic analyses also showed that age group, BMI group, MEWS, lac, RDW group, NLR and osmolarity group were independent risk factors for 28d-mortality (Table 4). Unadjusted or adjusted OR and 95% CIs of these variables were showed in Table4. Furthermore, we evaluated potential multicollinearity of above model with VIF. The VIF value of the predictive model for 28d-mortality were equal to 7.93, which did not prompt modifications to the mode. For this predictive model was constructed with MEWS, NLR, lac, age p, BMI group, RDW, and osmolarity, the model was named as“Broaln-MEWS”model. The AUROC of 28-day prognosis using Broaln-MEWS, APACHE-II, MEWS, RDW, NLR, lac and osmolarity for critical illness were shown in Table 5 and Fig. 3. The AUROC for Broaln-MEWS model in predicting 28d mortality was 0.741 with a sensitivity of 70.9%, specificity of 64.3% (p=0.000). The AUROCC of APACHE-II, MEWS, RDW, NLR, lac, osmolarity were 0.747 with a sensitivity of 69.7%, specificity of 72.7%, 0.669 with a sensitivity of 53.6%, specificity of 73.0%, 0.634 with a sensitivity of 61.1%, specificity of 59.4%, 0.591 with a sensitivity of 55.7%, specificity of 57.8%, 0.580 with a sensitivity of 31.1%, specificity of 81.3%, 0.592 with a sensitivity of 47.5%, specificity of 69.3%, respectively. Though the discriminative power of Broaln-MEWS (AUROC 0.741) was lower than APACHE-II (AUROC 0.747), there was no significant difference between the two scores (p=0.060). Notably, statistical differences in AUROC of Broaln-MEWS, MEWS, RDW, NLR, lac or osmolarity were detected (p=0.000), which indicated the Broaln-MEWS score was not inferior to APACHE-II and superior to other risk scores. The calculated H/L C-statistic were displayed in Table 5. Lac, NLR and osmolarity had p values of less than 0.05, but for Broaln-MEWS, APACHE-II, MEWS, RDW. Broaln-MEWS had a score of 9.64 (p=0.291) in predicting 28d-mortality, which suggested that Broaln-MEWS had good predictive ability and statistically acceptable agreement between observed mortality and actual mortality. The outcome of Brier score, suggesting model accuracy in measuring prediction at an individual level, denoted acceptable performance for all models. The Brier score varied from 0.103 for Broaln-MEWS, 0.106 for APACHE-II, 0.113 for MEWS, 0.116 for RDW, 0.115 for lac to 0.118 for NLR.

Internal Validation of Broaln-MEWS score

The developed Broaln-MEWS model was internally validated by using the validation group. Broaln-MEWS model demonstrated good discriminative power in the validation group by AUROC that was 0.744 (95%CI 0.732–0.756, p= 0.000). And the H/L C-statistic was equal to 11.37 (p=0.182) in validation group (Fig.4.).

Nomogram development for Broaln-MEWS score

For the AUROC was limited in understanding how a prediction score worked in clinical practice, the nomogram graph was readily used as a simplified prognostic graphical by clinicians even in resource limited settings such as absence of statistical software or electronic calculators. We translated the model with all integrated significant independent factors into a nomogram using Stata statistical software. The prognostic nomogram graph derived from Broaln-MEWS score for clinical applicability was shown in Figure5.

Discussion

To our knowledge, the retrospective study firstly proposed a simple prognostic model (Broaln-MEWS) combined age group, BMI group, MEWS, RDW group, NLR, lac, osmolarity group to predict 28-day mortality in critically ill patients that was internal validated. The major finding of this study was that AUROC showed that prediction efficiency of 28-day prognosis of Broaln-MEWS was higher than that of the traditional MEWS, NLR, RDW, lac, or osmolarity alone and slightly lower than APACHE-II. But Broaln-MEWS was not inferior to APACHE-II score, statistically.

For ICU patients with features of complicate disease spectrum, longer in-hospital stay and higher medical resource consumption rates, early identification of the death risk of critical illness in ICU with prognostic scoring systems was important for the timely and effective management and intervention. Although there were many scoring systems of critical illness used to distil the complexity into a single measure to quantitate survival probabilities in current clinical practice, we should not ignore the drawbacks and flaws of individual systems. For instance, some assessment tools need many blood tests or scoring items to fill resulting in more time to complete causing delayed interventions or increasing the financial burden of patients. Thus, fast, convenient and cheap evaluation tools were more attractive in clinical practice.

Our study used retrospectively collected variables to predict the development of 28d-mortality in critically ill patients. The selected variables were selected from the previously literature and used in previously ICU risk assessment models. In our study, we demonstrated that non-survivors tended to be older, had lower levels of BMI, and had higher MEWS, RDW, NLR, lac, osmolarity, which indicated that age, BMI, MEWS, NLR, RDW, lac, and osmolarity values may serve as potential prognostic markers in critical illness. In these indexes, MEWS was developed as practical tools that could rapidly and effectively estimate clinical death risk by using only 5 simple and basic physiologic parameters without increasing economic burden of patients, because these parameters could be acquired by electronic medical record, automatically. According to previous observational studies, Moon et al. reported that the introduction of MEWS charts significantly reduced the number of in-hospital cardiac arrest calls (2% vs. 3%; p = 0.004) and in-hospital mortality rates(42% vs. 52%;p = 0.05) [18]. In a study to predict 28-day mortality rate of ICU patients with severe sepsis/septic shock, MEWS was associated with the 28-day mortality rate (OR, 1.462; 95%CI, 1.122 to 1.905; p = 0.005) [19], which was consistent with our study (OR, 1.250; 95%CI, 1.232 to 1.269; p = 0.000). However, some study also found that MEWS has a limited ability to estimate sudden deterioration in patients like cardiac shock [20]. Therefore, MEWS alone to predict mortality rate of critical ill patients requires further investigation. As was well known, sepsis was recognized as a global health problem in ICU. The proportion of ICU-acquired sepsis was 24.4% and the mortality in hospitalized sepsis patients remains very high at 25–30% [21]. Whether patients have sepsis was an important factor affecting the mortality of ICU patients. NLR, as immune-related biomarker, was found to serve as a convenient prognostic marker in septic patients. In a study to predict 28d-mortality in septic patients, Liu et al. reported NLR was associated with the 28-day mortality rate (OR, 1.340; 95%CI, 1.253 to 1.434; p < 0.001) [22]. However, in our study, the OR value was 1.047(95%CI, 1.041 to 1.053; p = 0.000). The reason for this difference was that Liu et al selected patients with sepsis, and the population in our study was all ICU patients, not limited to sepsis. Lac had been usually associated with mortality in different groups of critically ill patients, as seen in cardiogenic, hypovolemic, and septic shock etc. Relative hyperlactatemia

(1.36 to 2.00mmol/L) within the first 24 hours of ICU admission is an independent predictor of hospital and ICU mortality in critically ill patients [16]. RDW represented an index of the variability in size of circulating erythrocytes. The normal range of RDW is 11.0%-14.5%. There were few clinical scenarios resulting in an RDW less than 11.0%, but many disease processes elevating the RDW above 14.5% [23]. A series of studies have demonstrated that RDW shows the predictive value of mortality in patients with heart failure, septic shock, acute respiratory distress syndrome, etc. [14, 24, 25]. In our study, RDW with a threshold of 14.5% showed the strong correlation with the mortality of critical ill patients (OR, 1.762; 95%CI, 1.613 to 1.925; p = 0.000). Our outcome was similar to previous study by Heidi S Bazick et al. (30d mortality RDW 14.7–15.8% OR, 1.69; 95% CI, 1.52–1.86; p < 0.001; >15.8% OR, 2.61; 95% CI, 2.37–2.86; p < 0.001) [23]. In addition, osmolarity, age, and BMI were associated with poor clinical outcomes of critical illness. Osmolarity with thresholds at 300 mmol/L was associated with increased mortality in critically ill patients with cardiac, cerebral, vascular and gastrointestinal admission diagnoses [26], which was consistent with our study (OR, 1.34; 95%CI, 1.252 to 1.464; p = 0.000). In a nationwide ICU mortality study of Poland, younger patient age was associated with ICU survival [3]. Zhigang Xue etc. report patients with BMI < 18.5 kg/m^2 had significantly higher ICU mortality (OR:1.92; 95% CI:1.84–2.01) in Asian hospitalized patients [27]. Our study also revealed that age with thresholds at 60 year and BMI with thresholds at 18.5 and 28 was associated with increased mortality in critically ill patients.

Next, we investigated the factors that independently predicted the 28d mortality in critical illness. Our data showed that the age group, BMI group, MEWS, RDW group, NLR, lac and osmolarity group were independent predictors of the 28-day mortality by using logistic regression analysis. Furthermore, the ROC curves were used to evaluate the predictive power of each of the above independent factors for 28-day mortality of critical illness. It was noticed that APACHE-II had the largest AUC value (0.747), followed by MEW (0.669), RDW (0.634), osmolarity (0.592), NLR (0.591), and lac (0.580) as a single parameter. These outcomes indicated that the predictive power of MEWS, RDW, NLR, lac, or osmolarity was limited and inferior to APACHE-II. For disease complexity and heterogeneity in critical illness, combining different indexes can more accurately reflect the prognosis of ICU patients. For example, the addition of RDW to APACHE-III improved its mortality prediction marginally. Adding RDW to APACHE-III increased AUROC (from 0.9586 to 0.9613) [28]. In our study, we used age, MEWS, NLR, RDW, lac, and osmolarity to predict 28d-mortality. Notably, a significant increasement of AUC (0.741) was found after we combined these parameters as a composite index. The major reasons for this may be related to differences in these indexes reflecting six dimensions of ICU patients from: age to aging degree, BMI to nutritional status, MEWS to general condition, lac to microcirculation, NLR to sepsis and osmolarity to internal environment.

Moreover, we used Brier score to assess model accuracy. In the original work, Broaln-MEWS had a smallest Brier score of 0.103 with comparison of APACHE-II (0.106), MEW (0.113), RDW (0.116), NLR (0.118), lac (0.115) and osmolarity (0.114), indicating that Broaln-MEWS had better accuracy in prediction at an individual level. Additionally, we calculated H/L C-statistic to assess acceptable agreement between observed ICU mortality and actual ICU mortality. Of these proposed models, only Broaln-MEWS and APACHE-II had discrimination greater than 0.70, calibration was adequate (p = 0.291

and p = 0.659 > 0.05), suggesting the assignment of the correct probability at all levels of predicted risk. Finally, the Broaln-MEWS model provided stable evaluation with excellent calibration assessed by use of a validation group (AUROC: 0.744 p = 0.000; H/L C-statistic 11.37 p = 0.182).

Our study had some strengths. First, as far as we know, our work firstly demonstrated the enhanced prognostic prediction value of combination with age, MEWS, NLR, RDW, lac, and osmolarity. Second, the sample size in our study was relatively large to reduce selection bias. Furthermore, we performed different probability models to evaluate Broaln-MEWS model in order to ensure the scientific nature and credibility of the results. Third, these parameters were objective and easily accessible laboratory widely available to clinicians. For instance, RDW and NLR were routinely reported as part of the complete blood count. Forth, it was easy and not time-consuming to calculate 28d-mortality by nomogram graph provided in our study.

Nevertheless, our data were collected retrospectively by MIMIC-III database. It was important to recognize the limitations of our study. First, because our work was a single institutional retrospective study with MIMIC-III database, it was difficult to extrapolate the findings to other hospitals. An external validation in cohorts of other countries was warranted before the conclusion may be generalize. Second, for data collection from MIMIC-III database was incomplete and contained many inaccurate data elements, the bias potential could not be excluded.

Conclusion

In this study we developed an internal validated prediction model (Broaln-MEWS) for 28-day mortality of critically illness admitted to ICU with the use of simple and easy to collect clinical variables. Collectively, our study shows that Broaln-MEWS has higher predictive value for 28-day prognosis in critically ill patients. Additional studies are required to determine whether it could be applied to other patient groups.

Abbreviations

ALT
alanine transaminase
APACHE
acute physiology and chronic Health evaluation
APTT
activated partial thromboplastin time
AST
aspartate transaminase
AUROC
area under the receiver operating characteristic curve
BMI
body mass index
BUN

blood urea nitrogen
CI
confidence interval
glu
blood glucose
Hgb
hemoglobin
H/L C-statistic
Hosmer-Lemeshow C-Statistic
ICU
intensive care unit
lac
lactate
LMICs
low- and middle-income countries
MEWS
modified early warning score
MIMIC-III
Medical Information Mart for Intensive Care III
NLR
neutrophil to lymphocyte ratio
OR
odds ratios
PT
prothrombin time
RDW
red cell distribution width
Scr
serum creatinine
TBil
total bilirubin
WBC
white blood cell counts.

Declarations

Ethical Approval and Consent to participate

Informed consent was not required for all protected health information has been de-identified.

Consent for publication

All the authors give consent to publish this article in Critical Care Journal.

Availability of data and materials

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

Competing interests

The authors have reported that no potential conflicts of interest exist with any companies/ organizations whose products or services may be discussed in this article.

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Authors' contributions

Xianming Zhang and Rui yang contributed to write the manuscript and image acquisition. The two authors contributed equally.

Xiaoying Ji, Hongda chen and Jinwen Cai contributed to literature research, the conception of the study and manuscript editing.

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Tables

Table 1-5 are available in the Supplementary Files section.

Figures

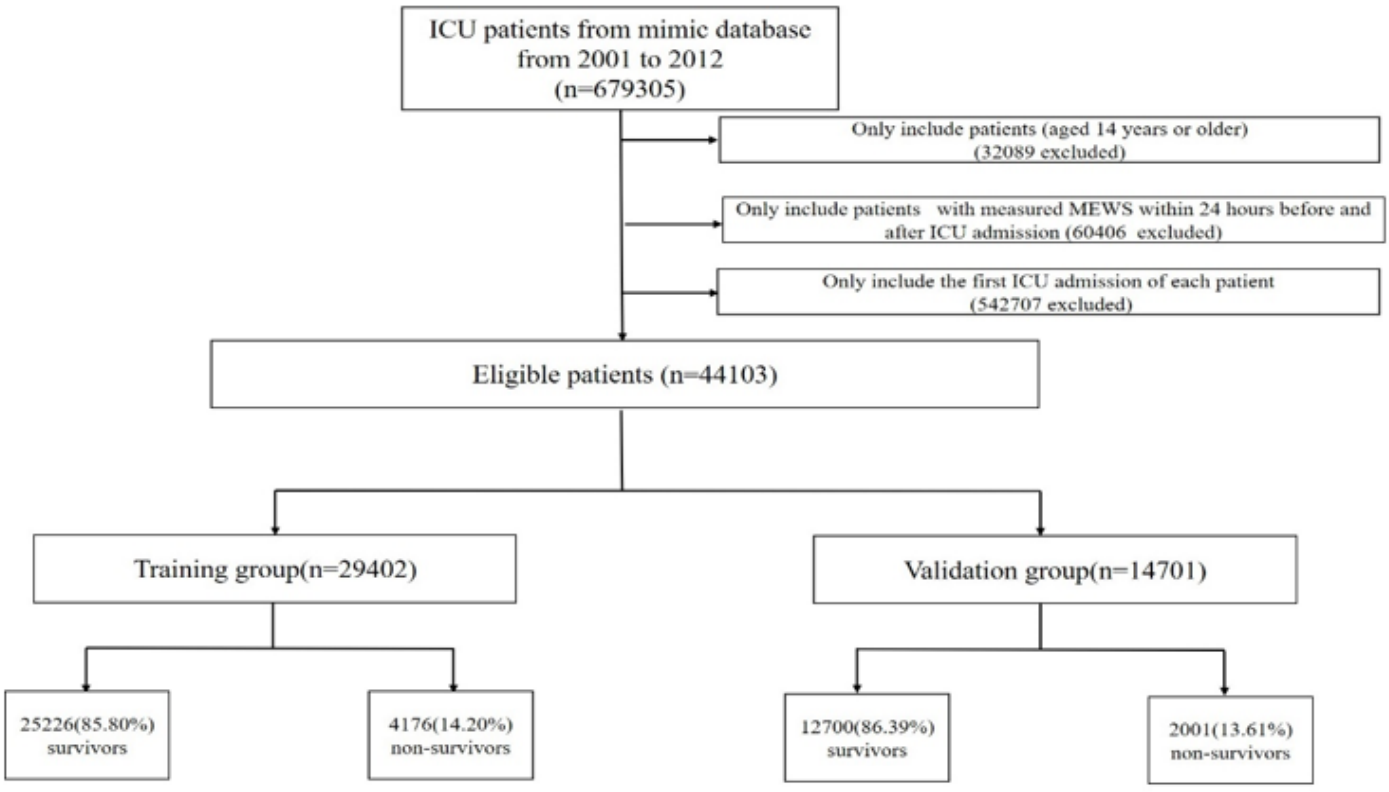

Figure 1

Study population and protocol flowchart.

Flow chart illustrating the major steps in the development and validation of Broaln-MEWS model in this protocol.

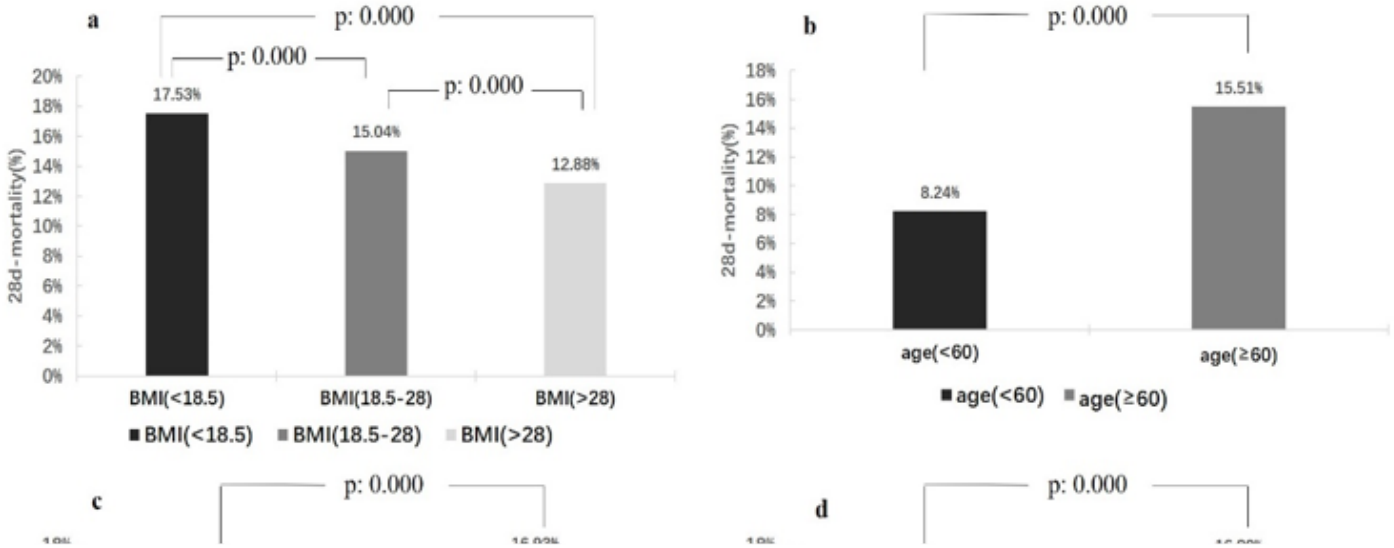

Figure 2

(a-d). Comparisons of 28d mortality among patients with different BMI, age, RDW, and osmolarity group. a.28d-mortality among patients with different BMI group, b.28d-mortality among patients with different age group c. 28d-mortality among patients with different RDW group d. 28d-mortality among patients with different osmolarity group

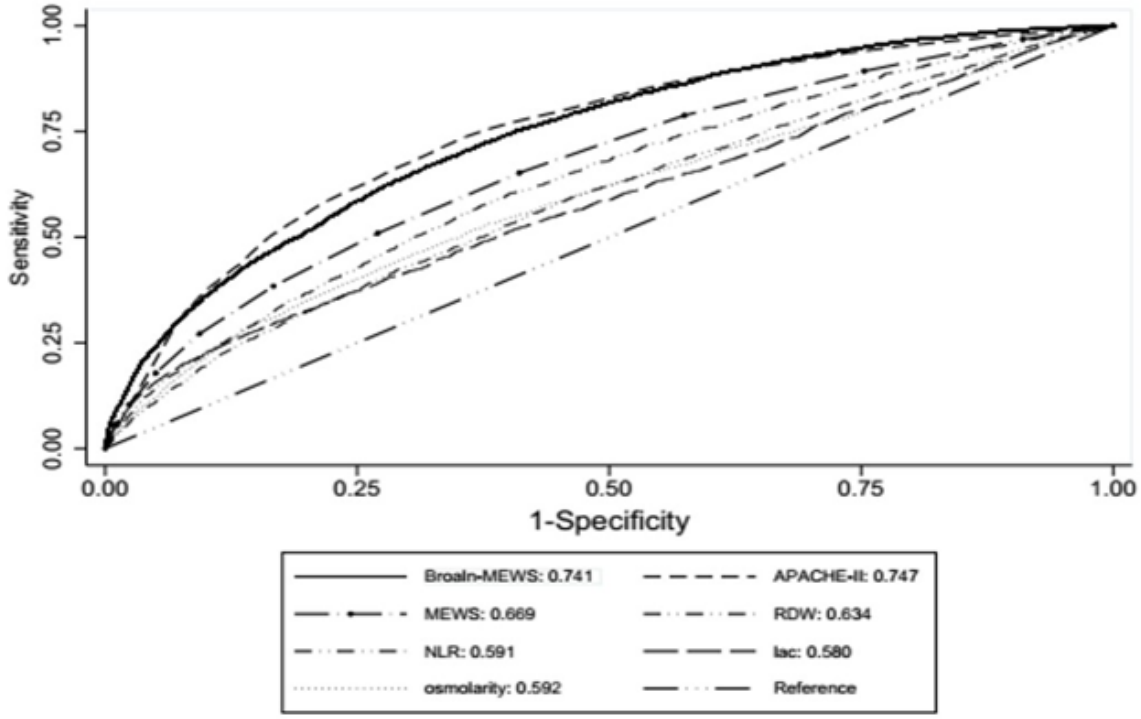

Figure 3

Performance in predicting 28d-mortality of critical illness using Broaln-MEWS, APACHE-II, MEW, RDW, NLR, lac and osmolarity.

The AUROC for Broaln-MEWS, APACHE-II, MEW, RDW, NLR, lac and osmolarity were 0.741, 0.747, 0.634, 0.591, 0.580, 0.59, respectively.

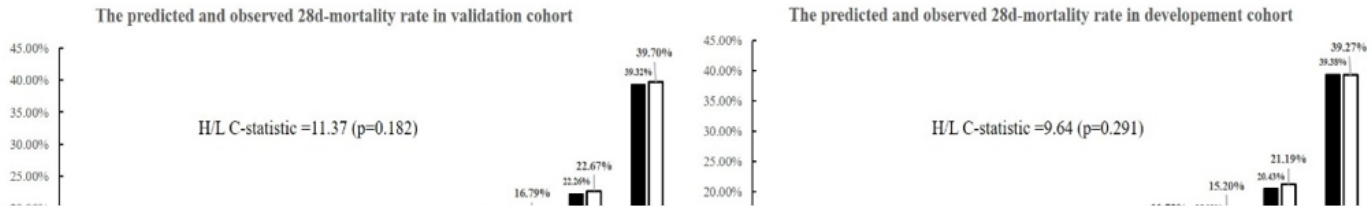

Figure 4

Hosmer–Lemeshow Chi squared statistic is shown for the risk score in both development and validation group.

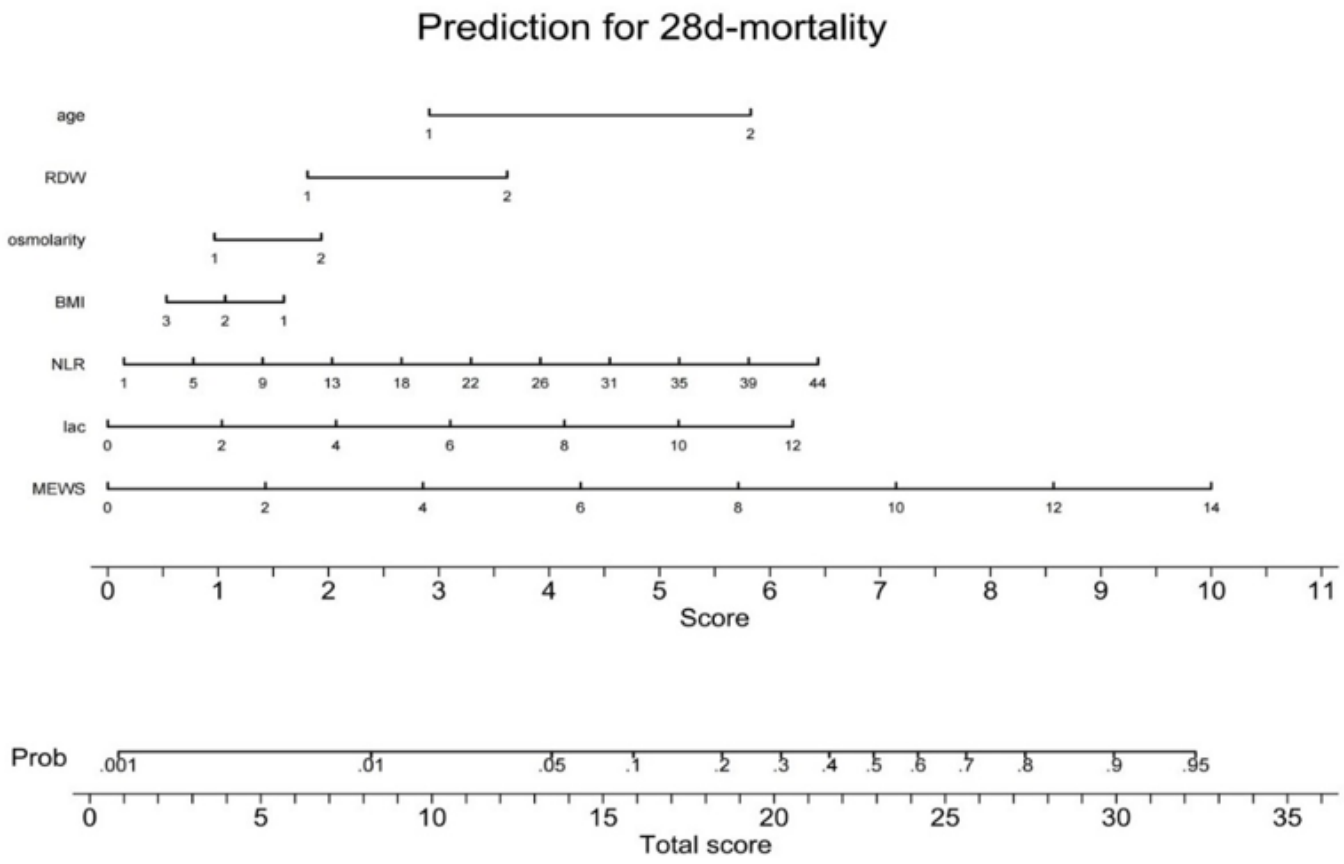

Figure 5

Nomogram graph for Broaln-MEWS model

To use the nomogram graph, an individual patient's predicted mortality risk value for Broaln-MEWS model was located on each variable axis, and a line was drawn upward to find out the corresponding score of each variable state. The sum of these numbers was located on the total score, and a line was drawn to the probability axes to determine the likelihood of 28d-mortality. (BMI: body mass index, lac: lactate, MEWS: modified early warning score, NLR: neutrophil to lymphocyte ratio RDW: red cell distribution width prob: probability)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx