

A Machine Learning Method for Early Stewardship of Invasive Mechanical Ventilation in Patients with Sepsis

Wanjun Liu

the Second Affiliated Hospital of Anhui Medical University

Wenyan Xiao

the Second Affiliated Hospital of Anhui Medical University

Jin Zhang

the Second Affiliated Hospital of Anhui Medical University

Juanjuan Hu

the Second Affiliated Hospital of Anhui Medical University

Shanshan Huang

the Second Affiliated Hospital of Anhui Medical University

Yu Liu

Anhui University

Tianfeng Hua

the Second Affiliated Hospital of Anhui Medical University

Min Yang

yangmin@ahmu.edu.cn

the Second Affiliated Hospital of Anhui Medical University

Research Article

Keywords: Sepsis, Invasive Mechanical ventilation, Clinical phenotype, Machine learning, Web-based tool

Posted Date: February 22nd, 2024

DOI: <https://doi.org/10.21203/rs.3.rs-3970283/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Heterogeneity among mechanically ventilated patients with sepsis makes it challenging to define appropriate treatments. This study aimed to establish a method for identifying high-risk patients in this vulnerable population. To this end, unsupervised machine learning models were used to analyze a large volume of real-world clinical data for determining prognosis in these patients at an early stage.

Methods

The Intensive Care Medical Information Database IV (MIMIC-IV; version 2.0) was used to generate training and test sets. Three datasets were used for further validation: the Intensive Care Medical Information Database III (MIMIC-III, version 1.4), Philips eICU Collaborative Research Database (eICU-CRD; version 2.0), and a local set from the Second Affiliated Hospital of Anhui Medical University.

Results

In the training, test, MIMIC-III, eICU-CRD, and local sets, approximately 9571, 1595, 4821, 6624, and 110 patients, respectively, diagnosed with sepsis who received invasive mechanical ventilation (IMV) on the first day of intensive care unit (ICU) admission were found. Three unique clinical phenotypes were derived based on the training set and were named phenotypes I, II, and III according to the order of clustering results. Patients with phenotype I had a 28-day mortality rate higher than 30% and characteristically presented with concurrent respiratory and circulatory dysfunction, whereas patients with other phenotypes had a better prognosis.

Conclusions

This retrospective exploratory study identified three unique phenotypes in patients with sepsis undergoing mechanical ventilation. These three phenotypes were distinctive and suggested that patients assigned phenotype I are a high-risk group, warranting focused attention during the early ICU stage.

Background

The heterogeneity of sepsis is widely recognized; as a result, patients with the same diagnostic criteria have differential outcomes and healing needs [1–3]. Invasive mechanical ventilation (IMV) is a common modality of treatment for patients with sepsis, with more than 40% of these patients reportedly receiving IMV during hospitalization [4, 5]. The use of IMV in this heterogeneous group should adapt a more refined management plan that may further improve the allocation of healthcare resources as well as therapeutic outcomes [6].

In clinical practice, patients receive IMV for complex and varied reasons. Acute respiratory distress syndrome (ARDS) secondary to sepsis is a common reason for patients receiving IMV [7, 8]. However, pulmonary susceptibility in patients with sepsis undergoing IMV is higher, and a more rapid progression and worsening of the disease and potentially increasing number of complications have been demonstrated in both animal and clinical studies in these populations [9–11]. Nevertheless, there remains a lack of consensus regarding the indications for IMV in patients with sepsis and effective methods for early warning and stewardship promotion in these high-risk patients. Therefore, early identification and differentiation of mechanically ventilated patients with sepsis may benefit treatment, disease assessment, and precision critical care in this vulnerable population.

In this study, we hypothesized that the heterogeneity among patients with sepsis receiving IMV could be differentiated based on the clinical characteristics of the patients. Further, we used unsupervised machine learning models to gain experience from a large volume of real-world clinical data to more efficiently and easily differentiate and predict the prognosis in these patients at an early stage.

Methods

Data Sources

Three large public critical care databases, including the Medical Information Market for Intensive Care IV (MIMIC-IV; version 2.0), the electronic intensive care unit Collaborative Research Database (eICU-CRD; version 2.0), and the Medical Information Market for Intensive Care III (version 1.4, MIMIC-III) and one local dataset from the Second Affiliated Hospital of Anhui Medical University (SAHAMU) were used. We received training on these datasets from the official websites and obtained permission (Record ID: 39691989) to use the databases before embarking on the study. Since the private information of the patients in these datasets was encrypted, the official website was exempt from ethical requirements. The study was reviewed and approved by the Ethics Committee of the SAHAMU before using the local dataset (Approval No. YX2022-146). Information on local cases was collected from the electronic medical record system of the hospital, and informed consent was obtained from each patient. Data from all sources are officially approved and used legally in accordance with relevant policies and guidelines.

Populations and Definitions

This study included patients who met the Sepsis-3 diagnostic criteria and received IMV on the first day of ICU admission. The Sepsis-3 criteria were as follows [12]: patients who simultaneously had a Sequential Organ Failure Assessment (SOFA) score of ≥ 2 and those with suspected infection. A flowchart for patient inclusion is shown in Fig. 1. We included only adult patients who were first admitted to ICU. Furthermore, to reduce bias, patients receiving IMV after 24 h were not included, and for those with repeated IMV, only the data of the first IMV exposure were included in the analysis.

Dataset Partitioning and Variable Extraction

We randomly assigned the MIMIC-IV dataset as the training and test sets in a 6:1 ratio, whereas the other datasets were assigned as validation sets. In these publicly available databases, we used the code packages of officially available standardized query languages to perform variable extraction, whereas, in the local dataset, data were manually extracted from the electronic medical record systems. We extracted variables, including those used for the baseline, modeling, and clinical outcomes. For baseline variables, we extracted demographics, comorbidities, laboratory indices, vital signs, and several scores commonly used in the ICU on the first day of ICU admission. Age, sex, and body mass index were included as demographic variables. Comorbidity variables were extracted based on International Classification of Diseases codes, including myocardial infarction, congestive heart failure, chronic pulmonary disease, severe liver disease, malignancy, and diabetes. Laboratory variables, including white blood cell count (WBC), hemoglobin, platelet count (PLT), serum creatinine, pH, arterial oxygen partial pressure (PaO_2), arterial carbon dioxide partial pressure, PaO_2 /fraction of inspired oxygen [FiO_2] (P/F), and base excess, were extracted from the worst values on the first day of ICU admission. Vital signs, including body temperature, respiratory rate, heart rate, mean arterial pressure and percutaneous oxygen saturation, were monitored continuously, and the time-weighted average was calculated as the area under the time curve of their values divided by time. The extraction directions for all continuous variables are summarized in Additional file 1: Table S1. Moreover, we extracted several composite scores, including the Charlson Comorbidity Index, Glasgow Coma Scale, Simplified Acute Physiological Score II, Oxford Acute Severity of Illness, and SOFA scores. Therapeutic variables, including vasoactive drugs and continuous renal replacement therapy, were extracted as dichotomous variables depending on whether or not they were administered. The timeframe for extracting all variables mentioned above was limited to the first 24 h of ICU admission.

Unsupervised machine learning-based models require variables with representativeness and equivalent scale. We used the six sub-items of the SOFA scores of the included patients on the first day of ICU admission as clustering variables. Clinical outcome variables were compared across phenotypes. In this study, 28-day mortality was defined as the primary outcome. Secondary outcomes included weaning failure, 7-day mortality and ICU mortality. We considered only the first weaning event and defined weaning failure based on the WIND study conducted in 2016 [13].

Data Analysis

In this study, we used the Mann-Whitney U test or Kruskal-Wallis test to compare continuous variables and the chi-square test or Fisher's exact probability method to compare categorical variables; the corresponding data are presented as medians (interquartile range) and frequencies (percentages), respectively.

To avoid the influence of missing values and outliers on data analysis, this study preprocessed data before modeling. First, there were outliers and missing values for a proportion of the data in the database. To avoid the influence of extreme outliers, this study comprehensively considered the distribution of data in clinical practice and databases and excluded data with more than the 99.9th percentile from

continuous monitoring. Variables with more than half of the missing proportion were excluded to avoid missing values influencing the analysis. Multiple imputations were used when the proportion of missing data was < 50%. There were no missing data in the local dataset. Additional file 2: Figure S1 summarizes and displays the missing data for the affected datasets.

Data were clustered using the k-means clustering algorithm. Owing to the randomness of k-means, we compared two methods to designate the optimal number of clusters, the sum of squared errors and the Davies–Boulding index. After clustering, t-distributed Stochastic Neighbor Embedding was used to reduce dimensionality and visualize the data. To further compare and visualize 28-day mortality between groups, we used Kaplan–Meier (K–M) curves to plot 28-day mortality and corresponding 95% confidence intervals (95% CI) between groups and compared them using the log-rank test. The Mann–Kendall test was used for trend analysis. The k-means algorithm used in this study was based on Euclidean distances, and a new sample was assigned by comparing its minimum Euclidean distance from the original clustering center. Furthermore, for multiple rates of exposure factors between the two phenotypes, we used odds ratios (OR) based on the logistic regression model.

In this study, we used R (version 4.1.3) and Python (version 3.7.3) for modeling, statistics and graphing. A P-value of < 0.05 was considered statistically significant.

Results

Patients and Baseline

The MIMIC-IV, MIMIC-III, eICU-CRD, and local datasets included 11,166, 4,821, 6,624 and 110 patients, respectively (Fig. 1). The patient median age was similar in the four datasets, and the proportion of male patients was > 50%. However, there were distinctions, such as myocardial infarction, which accounted for 19.2% of the MIMIC-IV dataset and only 8.2% of the local dataset (Additional file 3: Table S3). The MIMIC-IV dataset included the largest number of patients and had a relatively low proportion of missing data; hence, we chose it as the basis for the model building (Additional file 2: Figure S1). The MIMIC-IV dataset was assigned to the training set in 85%, and the other datasets were assigned to the validation sets (Fig. 1).

Subsequently, we used the six sub-items of the SOFA score for clustering using the k-means clustering algorithm, the sum of squared errors (SSE), and the Davies–Bouldin Index (DBI) to select the optimal number of clusters. In the three clusters, the instantaneous change in SSE and DBI indices maintained a locally small value based on the k-means clustering algorithm, leading us to eventually classify this group into three phenotypes based on the subitem score of the SOFA on the first ICU day (Additional file 4: Figure S2).

Characteristics of Organ Injury among Patients with Different Phenotypes

After clustering, we defined the clusters as phenotypes I, II, and III. The six sub-items of SOFA scores among the phenotypes were visually discernible, as shown in the heat map (Fig. 2). Patients with phenotype I had higher SOFA circulation and respiration scores than those with phenotype II and III. Patients with phenotype II had a prominent respiratory score, whereas those with phenotype III had fewer manifestations of organ injury. In addition to the training set, the test and validation sets showed similar performance (Fig. 2). However, there were significant differences in clinical characteristics among patients in the three phenotype groups. To visualize the differences between the embodied phenotypes in more detail, a pairwise comparison among the three phenotypes was performed. Patients with phenotype I always had higher rates of vasoactive drug use, more severe organ injury and higher rates of congestive heart failure than those with phenotypes II or III (Fig. 3). There were also characteristic biological indicators in patients with phenotype I. They had a more acidic internal environment (base excess, pH) than patients with phenotype II and a more pronounced hypoxic presentation than those with phenotype III (Fig. 3). The comparison between patients with phenotypes II and III showed that those assigned phenotype II by the clustering algorithm were more likely to have a higher degree of visceral damage and present primarily with respiration-related metrics (P/F, PaO₂ and respiratory rate; Fig. 3). Furthermore, the above features were observed in the training set and were also consistent across the test set and three validation sets (Table 1, Tables S4–S7).

Table 1
Baseline data of different phenotypes in the training set

	Phenotype I	Phenotype II	Phenotype III	<i>P</i> value
N	3009	3437	3125	
Age (years old)	68 (57, 78)	66 (55, 75)	67 (54, 77)	< 0.001
Male (%)	1787 (59.4)	2140 (62.3)	1846 (59.1)	0.014
BMI (kg/m ²)	28.4 (24.6, 33.5)	29.0 (25.4, 34.0)	26.3 (23.2, 30.2)	< 0.001
Comorbidities				
Myocardial infarction (%)	744 (24.7)	625 (18.2)	472 (15.1)	< 0.001
Congestive heart failure (%)	1132 (37.6)	794 (23.1)	665 (21.3)	< 0.001
Chronic pulmonary disease (%)	871 (28.9)	984 (28.6)	661 (21.2)	< 0.001
Severe liver disease (%)	291 (9.7)	188 (5.5)	152 (4.9)	< 0.001
Malignancy (%)	350 (11.6)	341 (9.9)	299 (9.6)	0.018
Diabetes (%)	973 (32.3)	1024 (29.8)	809 (25.9)	< 0.001
Composite scores				
CCI	6 (4, 8)	5 (3, 7)	5 (3, 7)	< 0.001
GCS	15 (14, 15)	15 (14, 15)	15 (13, 15)	< 0.001
SAPSII	52 (41, 64)	38 (31, 45)	37 (29, 45)	< 0.001
OASIS	45 (38, 50)	37 (32, 42)	37 (33, 42)	< 0.001
SOFA	12 (10, 14)	7 (5, 8)	4 (3, 6)	< 0.001
Laboratory indexes				
WBC (×10 ⁹ /L)	16.5 (11.6, 22.7)	13.9 (10.4, 18.2)	13.3 (10.2, 17.1)	< 0.001
Hemoglobin (g/L)	9.4 (8.0, 11.0)	9.8 (8.5, 11.3)	9.6 (8.3, 11.1)	< 0.001
Platelet count (×10 ⁹ /L)	144 (90, 207)	154 (114, 212)	148 (109, 209)	< 0.001
Serum creatinine (mg/dL)	1.7 (1.1, 2.7)	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	< 0.001
pH	7.2 (7.2, 7.3)	7.3 (7.3, 7.4)	7.3 (7.3, 7.4)	< 0.001

WBC, White blood cell count; PaO₂, Arterial oxygen partial pressure; PaCO₂, Arterial carbon dioxide partial pressure; FiO₂, Fraction inspired oxygen concentration; MAP, Mean arterial pressure; SO₂, Percutaneous oxygen saturation; CRRT, Continuous renal replacement therapy; P/F, PaO₂/FiO₂.

	Phenotype I	Phenotype II	Phenotype III	<i>P</i> value
PaO ₂ (mmHg)	58 (41, 80)	76 (56, 93)	126 (103, 160)	< 0.001
PaCO ₂ (mmHg)	49 (43, 58)	48 (43, 54)	43 (39, 48)	< 0.001
P/F	97 (68, 148)	135 (94, 180)	300 (244, 370)	< 0.001
Base excess (mmol/L)	-7 (-12, -3)	-2 (-5, 0)	-2 (-5, 0)	< 0.001
Vital signs				
Respiratory rate (/min)	21 (18, 26)	18 (16, 21)	17 (15, 19)	< 0.001
Heart rate (/min)	87 (76, 101)	82 (75, 93)	81 (73, 92)	< 0.001
MAP (mmHg)	74 (70, 79)	78 (73, 84)	78 (73, 84)	< 0.001
Body temperature (°C)	36.9 (36.4, 37.4)	36.9 (36.5, 37.3)	36.8 (36.5, 37.2)	0.002
SO ₂ (%)	98 (96, 99)	98 (97, 99)	99 (99, 100)	< 0.001
Urine output (mL/kg/h)	0.5 (0.2, 1.0)	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	< 0.001
Therapeutics				
Vasoactive drugs (%)	2964 (98.5)	1614 (47.0)	1627 (52.1)	< 0.001
CRRT (%)	248 (8.2)	15 (0.4)	17 (0.5)	< 0.001
Tracheotomy (%)	135 (4.5)	122 (3.5)	112 (3.6)	0.094
WBC, White blood cell count; PaO ₂ , Arterial oxygen partial pressure; PaCO ₂ , Arterial carbon dioxide partial pressure; FiO ₂ , Fraction inspired oxygen concentration; MAP, Mean arterial pressure; SO ₂ , Percutaneous oxygen saturation; CRRT, Continuous renal replacement therapy; P/F, PaO ₂ /FiO ₂ .				

Characteristics of Infection-related Indicators among the Phenotypes

We visualized the infection-related indicators in patients included in the MIMIC-IV dataset during the first week. The SOFA scores in patients with phenotype I remained at the highest during the first week, showing a tendency to increase and then decrease (Additional file 5: Figure S3A). Patients with phenotype I had an overall lower PLT and a decreasing trend, followed by an increasing trend, whereas patients with phenotypes II and III had higher initial PLT than those with phenotype I and showed an overall increasing trend (Additional file 5: Figure S3B). In the comparison of inflammatory cells, although Additional file 5: Figure S3C shows a decrease in WBC in all three phenotypes after ICU admission, the overall decreasing trend was not statistically significant. The absolute values of neutrophils, lymphocytes and monocytes in patients with phenotype I were higher than those in patients with phenotypes II and III during the first week of ICU admission (Figure S4D–S4F). Notably, the infection sites and pathogens

associated with the three phenotypes were characteristic. The positive rate of gram-positive bacteria in the hemoculture of patients assigned phenotype I was 5.8%, compared with OR values of 1.75 and 1.73 in patients assigned phenotypes II and III, respectively (Table S8 and Figure S4). In particular, the positive rate of gram-negative bacteria and fungi was more prominent in the hemoculture of patients with phenotype I. Specifically, the OR values of hemoculture for gram-negative bacteria and fungi in patients with phenotype I compared to those with phenotypes II and III were 3.57, 4.11, and 3.49, 4.71, respectively ($P < 0.001$, Figures S5A and S5B). Comparing infection sites, the proportions of pulmonary (33.7%), urologic (14.3%) and intestinal (4.8%) infections were higher in phenotype I patients than in phenotype II patients (Table S8); however, no significant difference in the urologic infection rate was found between phenotype III and I patients ($OR = 1.03$, $P = 0.706$). Nonetheless, patients with phenotype II had lower rates of urologic infection and higher rates of pulmonary infection (OR values of 0.76 and 1.57, respectively) than those with phenotype III ($P < 0.001$, Figure S5C).

Clinical Outcomes in Patients among the Phenotypes

Figure 4 presents the 28-day mortality trend for the three phenotypes using the K–M curve. The 28-day mortality rate in patients with phenotype I was significantly higher, with the 28-day mortality rates in patients with phenotype I in the training, test, MIMIC-III, eICU-CRD, and local validation sets being 38.8%, 36.9%, 44.3%, 37.5%, and 57.1%, respectively, which were significantly higher than those in patients assigned phenotype II or III (Table 2). Concurrently, the 7-day mortality, ICU mortality and weaning failure were higher in patients with phenotype I than in those with the other two phenotypes, which was consistent across the validation set. There was no consistency in the length of ICU stay (LOS) among patients with phenotype I and phenotype II, whereas patients with phenotype III always had the shortest LOS (Table 2).

Table 2
Comparison of clinical outcomes among different phenotypes

Datasets	Outcomes	Phenotype I	Phenotype II	Phenotype III	P value
The training set	7-day mortality (%)	799 (26.6)	196 (5.7)	194 (6.2)	< 0.001
	28-day mortality (%)	1166 (38.8)	399 (11.6)	395 (12.6)	< 0.001
	ICU mortality (%)	1036 (34.4)	291 (8.5)	272 (8.7)	< 0.001
	LOS (Day)	5 [3, 10]	3 [2, 6]	3 [2, 6]	< 0.001
	Weaning failure (%)	1187 (39.4)	476 (13.8)	410 (13.1)	< 0.001
The test set	7-day mortality (%)	133 (25.5)	33 (6.0)	32 (6.1)	< 0.001
	28-day mortality (%)	192 (36.9)	65 (11.9)	60 (11.4)	< 0.001
	ICU mortality (%)	163 (31.3)	46 (8.4)	37 (7.0)	< 0.001
	LOS (Day)	5 [3, 11]	3 [2, 6]	3 [2, 6]	< 0.001
	Weaning failure (%)	189 (36.3)	84 (15.3)	70 (13.3)	< 0.001
The MIMIC-III set	7-day mortality (%)	228 (30.4)	118 (5.8)	213 (10.4)	< 0.001
	28-day mortality (%)	333 (44.3)	244 (12.0)	358 (17.5)	< 0.001
	ICU mortality (%)	274 (36.5)	143 (7.1)	243 (11.9)	< 0.001
	LOS (Day)	6 [3, 12]	3 [2, 7]	3 [2, 6]	< 0.001
	Weaning failure (%)	167 (22.2)	374 (18.5)	325 (15.9)	< 0.001
The eICU-CRD set	7-day mortality (%)	342 (28.5)	406 (8.1)	39 (10.2)	< 0.001
	28-day mortality (%)	450 (37.5)	705 (14.0)	64 (16.8)	< 0.001
	ICU mortality (%)	355 (29.6)	473 (9.4)	38 (10.0)	< 0.001
	LOS (Day)	4 [2, 8]	4 [2, 8]	4 [2, 7]	0.356
	Weaning failure (%)	423 (35.2)	656 (13.0)	60 (15.7)	< 0.001
The Local set	28-day mortality (%)	20 (57.1)	7 (19.4)	1 (2.7)	< 0.001
	LOS (Day)	6 [3, 10]	6 [3, 9]	2 [1, 5]	0.113
	Weaning failure (%)	22 (62.9)	7 (18.4)	1 (2.7)	< 0.001
LOS, Length of ICU stay.					

Clinical Scenarios and a Web-Based Tool

To increase the utility of this study, we used web technology to develop an online tool that could be used to quickly assess patient phenotypes. We fused this subphenotype model with that of our previous study

to create a prediction model capable of dynamically predicting weaning in patients with sepsis (Figure S5) [14]. We further verified its robustness using the receiver operating characteristic curves. This tool is publicly available and accessible at <http://1.15.228.15/frontdoc/sepweaning2.html>. This tool enables clinicians to quickly identify the phenotype of a patient at the initiation of IMV and to determine appropriate responses based on the phenotype.

Discussion

In this study, we proposed that patients with sepsis receiving IMV can be divided into three subphenotypes. We defined them using Roman numerical order as phenotypes I, II, and III. Among these phenotypes, patients assigned phenotype I had the worst prognosis and were characterized by respiratory and cardiovascular dysfunction and an elevated inflammatory response. In contrast, patients with phenotype II had prominent respiratory dysfunction, and patients with phenotype III had the least organ injury; patients assigned to these two phenotypes had comparable prognoses. The subphenotypes showed strong generalizability regardless of the training, test, and validation sets derived from different data sources. Moreover, the three subphenotypes showed good discriminability in terms of clinical characteristics, patterns of organ dysfunction, and prognosis. These phenotypes can be identified at an early stage and provide a reference for the refinement of the management of patients with sepsis receiving IMV.

Sepsis-3 defined suspected infection as a new sepsis criterion; patients with sepsis may not progress to septic shock or multi-organ failure [12]. The etiology of ARDS may be secondary to pulmonary infection, or it may be caused by extra-pulmonary factors such as shock and trauma; the relationship between sepsis and ARDS is cross-cutting and complex. Many studies have shown that patients with sepsis-associated ARDS exhibit different types of inflammatory responses and patterns of organ dysfunction [15–17]. Based on experiences, differentiating and managing high-risk populations can help the effective allocation of medical resources and improve therapeutic efficacy [1, 18, 19]. However, there is currently no reliable method in clinical practice for determining the heterogeneity among such patients. Our study involved a population that exhibited a complex phenotype owing to the simultaneous effects of infection, organ injury, and external forces. Using subphenotypic models, a new approach was provided to understand and differentiate between the clinical characteristics and prognosis of this population. In this study, the three phenotypes were determined according to six sub-items of the SOFA score during the first 24 h of ICU admission and can thus be applied to patients with or without sepsis and can be further generalized to all mechanically ventilated patients. The phenotype model was validated not only in the critical care database but also in the emergency database, with consistent distributions of clinical characteristics and outcomes, and the results were robust.

Previous studies have identified 3–6 clinical subphenotypes of sepsis and ARDS. The sources of these subphenotypes are diverse and include electronic health records, randomized controlled clinical trials, and transcriptomic data [1–3, 18, 19]. In patients with sepsis, a 2017 retrospective study explored genetic subtypes of sepsis known as Mars1 and identified the genotypes most associated with 28-day mortality

[20]. This suggests that gene expression may be the underlying cause of heterogeneity among patients with sepsis. However, diagnosis and classification at the genetic level are time-consuming and labor-intensive. Seymour et al. previously proposed a γ phenotype and a δ phenotype for patients with sepsis, as a hyperinflammatory phenotype and septic shock phenotype, respectively, with similar clinical features and prognosis to those in phenotype I in our study [1]. Analogously, Bhavani et al. categorized patients with sepsis into four phenotypes A, B, C and D, according to the trajectory of their vital signs, with phenotype A and phenotype D patients also characterized by hyperinflammation, hypotension, and poor prognosis [18]. In our study, the characteristic clinical manifestations of patients with phenotype I were high levels of inflammation and circulatory dysfunction, consistent with the two large-scale subphenotype assignment models for sepsis mentioned above. Further, heterogeneity occurs among patients with ARDS. Liu et al. proposed three ARDS phenotypes based on 21 clinical variables, with one phenotype associated with the highest mortality associated with renal dysfunction and acidosis [19]. In our study, patients with phenotype I had an acidic internal environment and renal injury, which can explain the inflammation and perfusion disorders in sepsis and is consistent with the phenotypic characteristics in the ARDS study. However, an increase in creatinine levels rather than a decrease in urine output was the primary contributor to renal injury in patients with phenotype I. In clinical practice, changes in serum creatinine occur later than the development of kidney disease in critically ill populations, suggesting that renal injury in patients with phenotype I may be an initiating factor in the development of the disease. Therefore, it is important to further analyze the etiology and follow-up of patients with phenotype I.

The other two phenotypes in this study also had easily distinguishable clinical features and were of interest. Respiratory dysfunction was the main clinical feature of patients with phenotype II because they had a low P/F ratio, whereas other organic injuries were less pronounced (Fig. 2 and Table 1). In clinical practice, it is common for patients to receive IMV solely for respiratory failure; however, the predominant cause of death in such patients is not isolated respiratory failure but multiple organ injury [21]. Among the three phenotypes, patients with phenotype III had the least organ injury and the best prognosis, and their pathogenic dissemination was comparable to that in patients with phenotype II. Notably, patients with phenotype III still differed from those with phenotype II at the site of infection; however, no associated difference in the short-term prognosis between the two phenotypes was found. Patients with different clinical characteristics but similar clinical outcomes have been identified in a previous study [22]. Furthermore, using early ICU data in the development of subphenotype models, we can use the results of these three phenotypes as variables in our previously developed weaning model, which can be fused to form a dynamic prediction model to predict weaning in patients with sepsis on IMV in real-time. The fused model was shown to have better predictive performance.

This study has some limitations. First, although the classification of patients with sepsis undergoing IMV was relatively simple in terms of results, the calculation of the classification involved SOFA scores, data processing, and clustering algorithms, which are difficult to perform manually. Nevertheless, we developed a web-based tool for computational phenotyping; however, its application remains limited. Second, the training set, the test set, and part of the validation set were constructed based on public

databases in the United States. The sample size of the validated dataset was small and did not include populations from other larger regions, although our local data (Asia) was validated. Therefore, a larger sample size is required for further validation. Third, owing to the lack of data, some results in this study, such as the interpretation of pathogens and infection sites, were not fully validated. Finally, this was a retrospective study, and the evaluation of clinical outcomes for different phenotypes may still be influenced by potential confounding factors, requiring further validation in clinically controlled studies.

Conclusions

This retrospective exploratory study identified three unique phenotypes in patients with sepsis undergoing mechanical ventilation. These three phenotypes are distinctive and suggest that patients assigned phenotype I are a high-risk group, warranting focused attention to this group of patients during the early ICU stage.

Abbreviations

IMV, invasive mechanical ventilation; eICU-CRD, electronic intensive care unit-Collaborative Research Database; ARDS, acute respiratory distress syndrome; CI, confidence interval; DBI, Davies–Bouldin Index; FiO_2 , fraction of inspired oxygen; ICU, intensive care unit; MIMIC-III, Intensive Care Medical Information Database III; MIMIC-IV, Intensive Care Medical Information Database IV; OR, odds ratio; PaO_2 , arterial oxygen partial pressure; SOFA, Sequential Organ Failure Assessment; SSE, Sum of Squared Errors.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Committee of the SAHAMU before using the local dataset (Approval No. YX2022-146). Information on local cases was collected from the electronic medical record system of the hospital and informed consent was obtained from each patient. Data from all sources are officially approved and used legally in accordance with relevant policies and guidelines.

Consent for publication

Availability of data and materials

All of the publicly available datasets can be found at <https://physionet.org/>.

Competing interests

The authors declare that they have no competing interest.

Funding

This study was supported by a research grant from the National Natural Science Foundation of China (No.82072134), the Clinical Research Training Program of the Second Hospital of Anhui Medical University (No.2020LCYB03), the Scientific Research Fund of Anhui Medical University (No.2021xkj166), the Research Fund of Anhui Institute of translational medicine (No.2022zhyx-C46), the Health Research Program of Anhui (No.AHWJ2022b085), and the Natural Science Research Project Funding of Higher Education Institutions Anhui Province (No.2022AH040101).

Authors' contributions

YM, L-WJ, X-WY and ZJ carried out the concepts, design, data acquisition, and manuscript preparation. H-JJ and H-SS carried out literature search, and manuscript preparation. LY and H-TF performed manuscript review, including revision of key technical content and English expression. All authors read and approved the final manuscript.

Acknowledgements

We thank all authors for their contribution to this study.

References

1. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA*. 2019;321:2003-17. <https://doi.org/10.1001/jama.2019.5791>
2. Sweeney TE, Azad TD, Donato M, Haynes WA, Perumal TM, Henao R, et al. Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. *Crit Care Med*. 2018;46:915-25. <https://doi.org/10.1097/CCM.0000000000003084>
3. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med*. 2016;4:259-71. [https://doi.org/10.1016/S2213-2600\(16\)00046-1](https://doi.org/10.1016/S2213-2600(16)00046-1)
4. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA*. 2014;311:1308-16. <https://doi.org/10.1001/jama.2014.2637>
5. Esteban A, Frutos-Vivar F, Ferguson ND, Peñuelas O, Lorente JA, Gordo F, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. *Crit Care Med*. 2007;35:1284-9. <https://doi.org/10.1097/01.CCM.0000260960.94300.DE>
6. Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. *PLOS ONE*. 2015;10:e0125827. <https://doi.org/10.1371/journal.pone.0125827>

7. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526-33. <https://doi.org/10.1001/jama.2012.5669>
8. Zhang P, Liu B, Zheng W, Chen Y, Wu Z, Lu Y, et al. Pulmonary microbial composition in sepsis-induced acute respiratory distress syndrome. *Front Mol Biosci*. 2022;9:862570. <https://doi.org/10.3389/fmolb.2022.862570>
9. Wellman TJ, Winkler T, Costa EL, Musch G, Harris RS, Zheng H, et al. Effect of local tidal lung strain on inflammation in normal and lipopolysaccharide-exposed sheep*. *Crit Care Med*. 2014;42:e491-e500. <https://doi.org/10.1097/CCM.0000000000000346>
10. Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, Varaschin P, et al. Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. *Crit Care*. 2013;17:R63. <https://doi.org/10.1186/cc12594>
11. Müller-Redetzky HC, Will D, Hellwig K, Kummer W, Tschernig T, Pfeil U, et al. Mechanical ventilation drives pneumococcal pneumonia into lung injury and sepsis in mice: protection by adrenomedullin. *Crit Care*. 2014;18:R73. <https://doi.org/10.1186/cc13830>
12. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:775-87. <https://doi.org/10.1001/jama.2016.0289>
13. Béduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, et al. Epidemiology of Weaning Outcome according to a New Definition. The WIND study. *Am J Respir Crit Care Med*. 2017;195:772-83. <https://doi.org/10.1164/rccm.201602-03200C>
14. Liu W, Tao G, Zhang Y, Xiao W, Zhang J, Liu Y, et al. A simple weaning model based on interpretable machine learning algorithm for patients with sepsis: A research of MIMIC-IV and eICU databases. *Front Med (Lausanne)*. 2021;8:814566. <https://doi.org/10.3389/fmed.2021.814566>
15. Mirbeyk M, Saghazadeh A, Rezaei N. A systematic review of pregnant women with COVID-19 and their neonates. *Arch Gynecol Obstet*. 2021;304:5-38. <https://doi.org/10.1007/s00404-021-06049-z>
16. Gong F, Li R, Zheng X, Chen W, Zheng Y, Yang Z, et al. OLFM4 regulates lung epithelial cell function in sepsis-associated ARDS/ALI via LDHA-mediated NF- κ B signaling. *J Inflamm Res*. 2021;14:7035-51. <https://doi.org/10.2147/JIR.S335915>
17. Reilly JP, Wang F, Jones TK, Palakshappa JA, Anderson BJ, Shashaty MGS, et al. Plasma angiopoietin-2 as a potential causal marker in sepsis-associated ARDS development: evidence from Mendelian randomization and mediation analysis. *Intensive Care Med*. 2018;44:1849-58. <https://doi.org/10.1007/s00134-018-5328-0>
18. Bhavani SV, Semler M, Qian ET, Verhoef PA, Robichaux C, Churpek MM, et al. Development and validation of novel sepsis subphenotypes using trajectories of vital signs. *Intensive Care Med*. 2022;48:1582-92. <https://doi.org/10.1007/s00134-022-06890-z>

19. Liu X, Jiang Y, Jia X, Ma X, Han C, Guo N, et al. Identification of distinct clinical phenotypes of acute respiratory distress syndrome with differential responses to treatment. *Crit Care*. 2021;25:320. <https://doi.org/10.1186/s13054-021-03734-y>
20. Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med*. 2017;5:816-26. [https://doi.org/10.1016/S2213-2600\(17\)30294-1](https://doi.org/10.1016/S2213-2600(17)30294-1)
21. Ketcham SW, Sedhai YR, Miller HC, Bolig TC, Ludwig A, Co I, et al. Causes and characteristics of death in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: a retrospective cohort study. *Crit Care*. 2020;24:391. <https://doi.org/10.1186/s13054-020-03108-w>
22. Miller PE, Van Diepen S, Metkus TS, Alviar CL, Rayner-Hartley E, Rathwell S, et al. Association between respiratory failure and clinical outcomes in patients with acute heart failure: analysis of 5 pooled clinical trials. *J Card Fail*. 2021;27:602-6. <https://doi.org/10.1016/j.cardfail.2021.01.018>

Figures

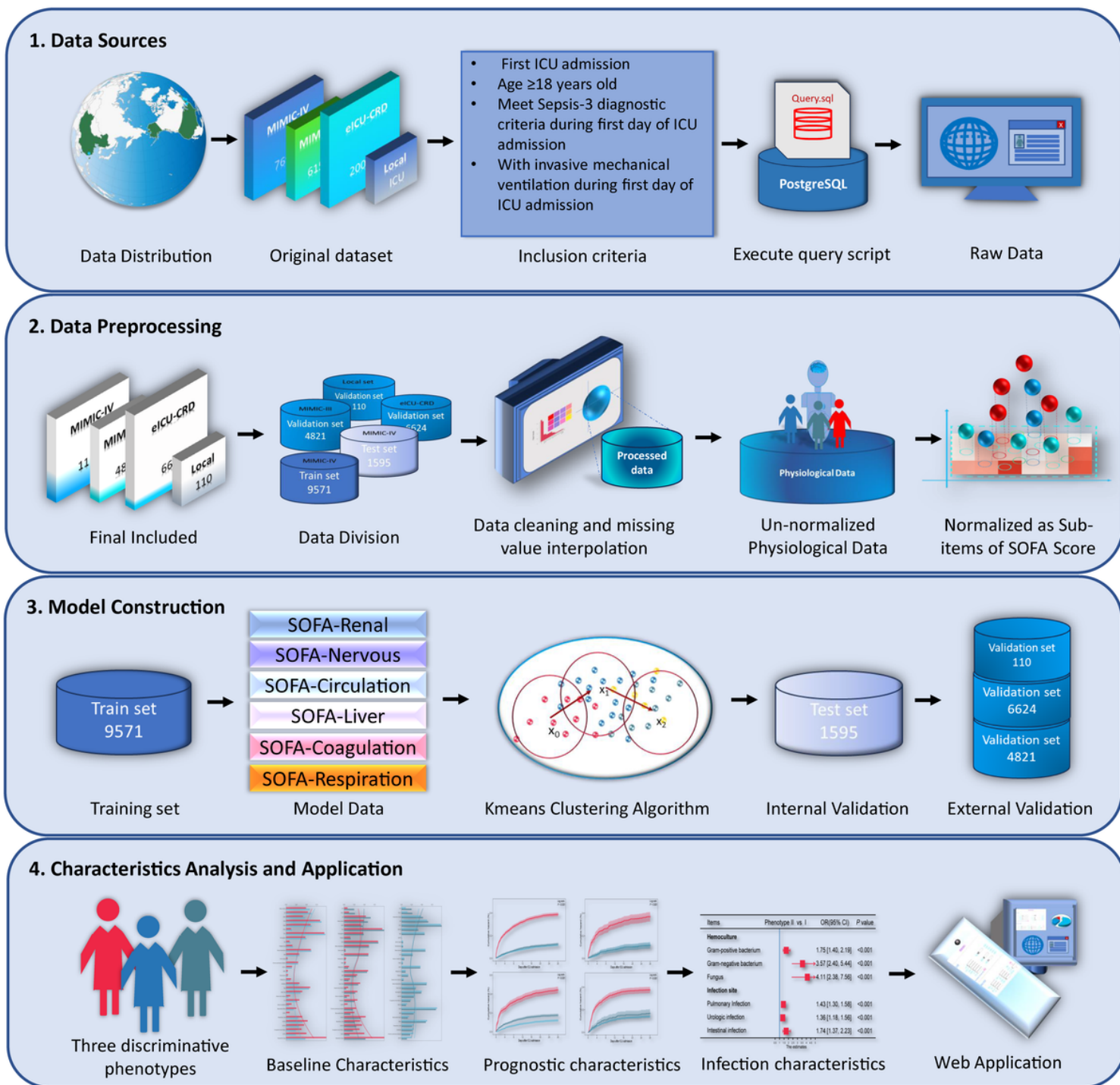


Figure 1

Flowchart of the study design

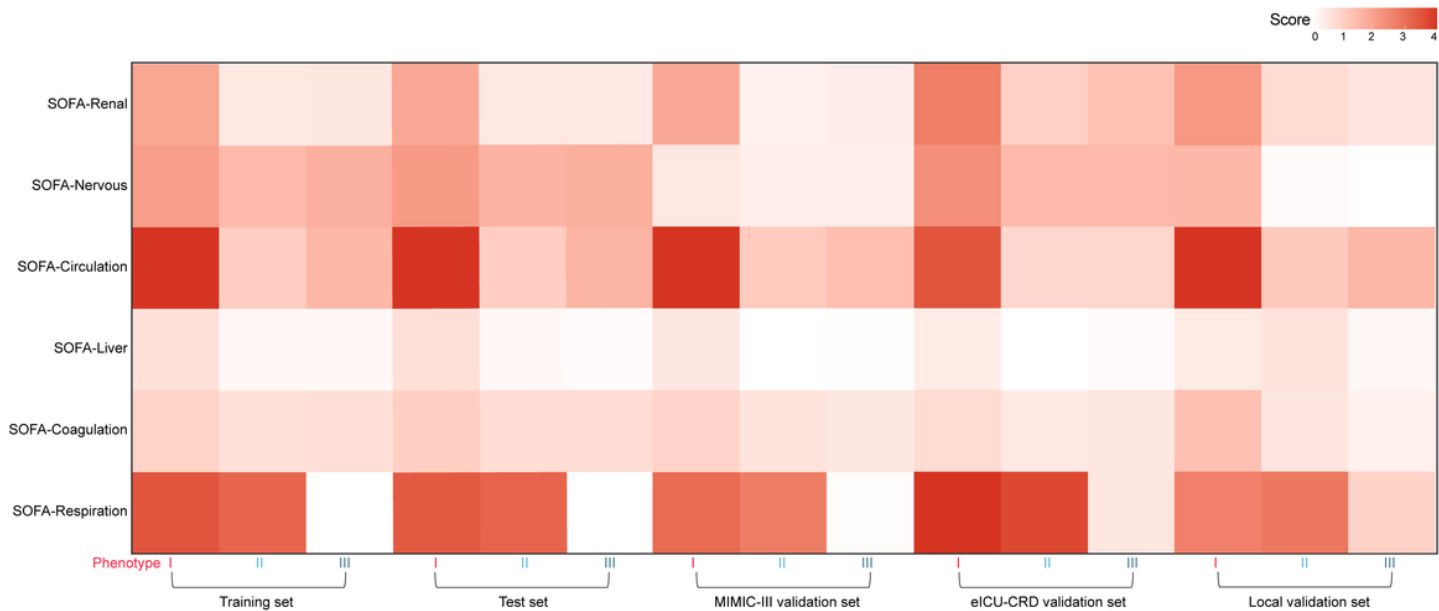


Figure 2

Heatmaps of the mean scores of each subitem of the SOFA score. This figure presents the heatmaps of the mean scores of each subitem of the SOFA score for different phenotypes in the training, test, MIMIC-III, eICU-CRD, and local datasets

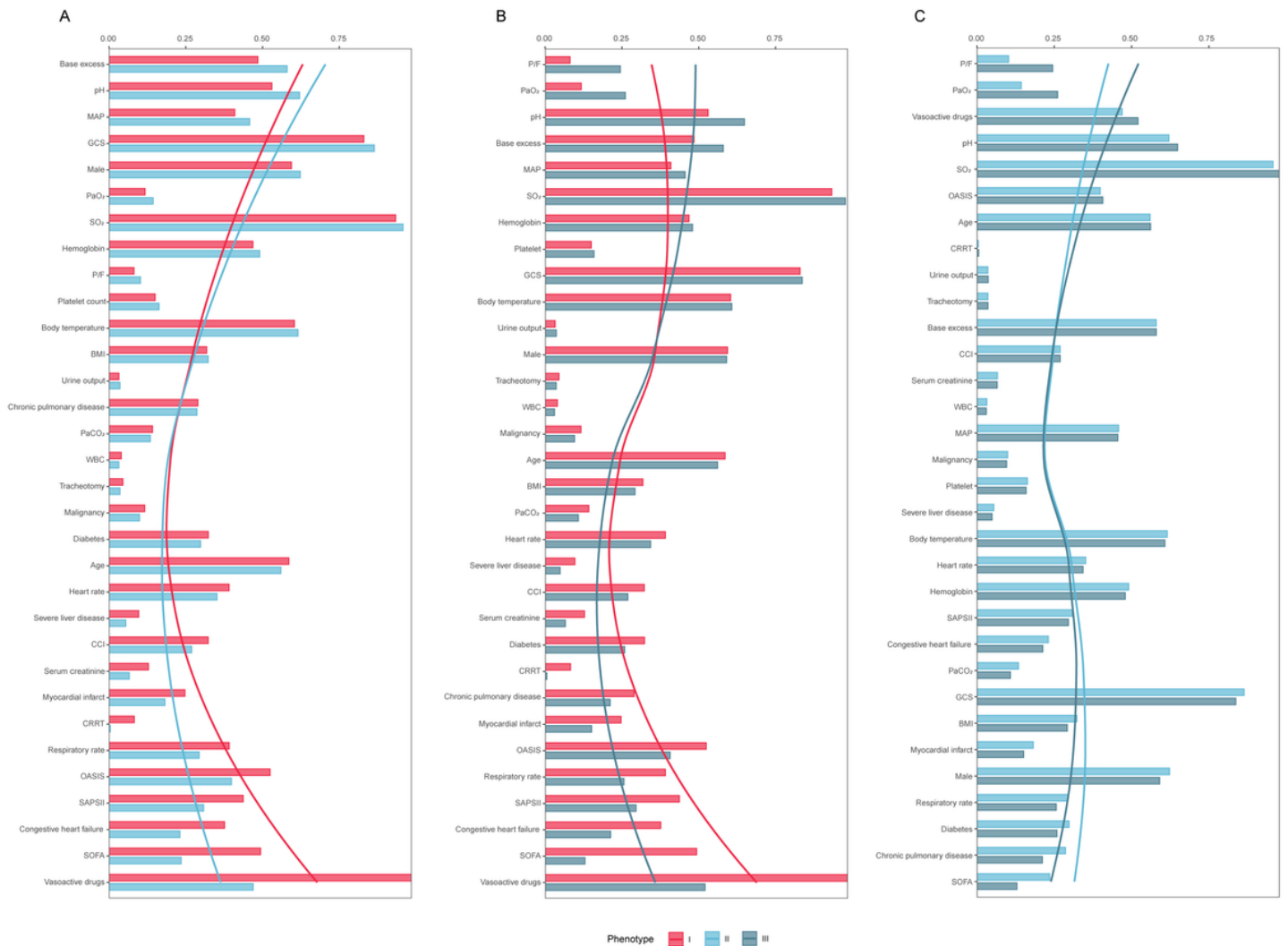


Figure 3

Lateral bar graphs. Lateral bar graphs of phenotype I vs. phenotype II (a), phenotype I vs. phenotype III (b) and phenotype II vs. III (c), ranked according to differences between groups. All baseline variables are normalized to a scale ranging from 0 to 1 to be more suitable for multiple group comparisons.

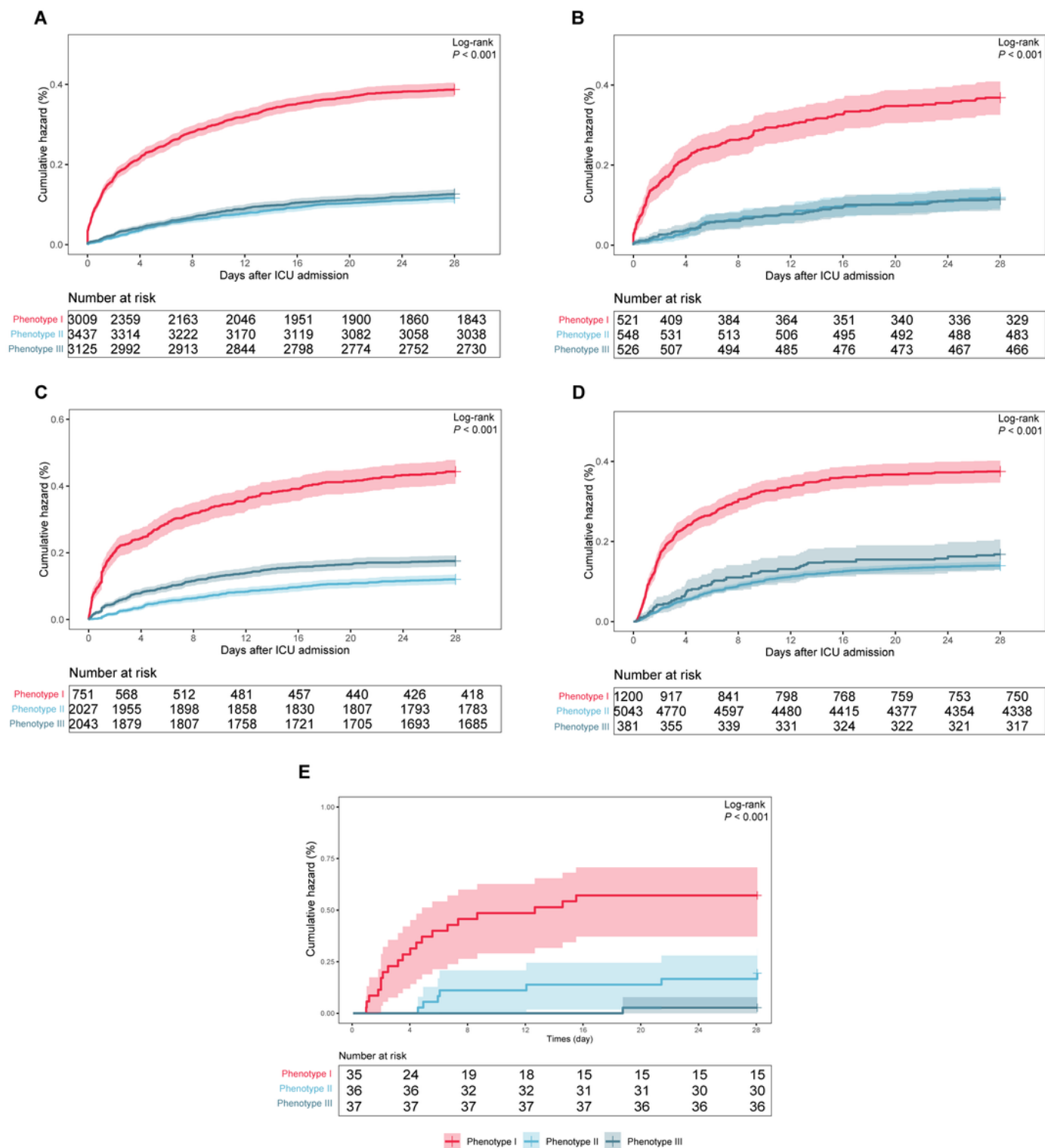


Figure 4

Cumulative curve of 28-day mortality. Cumulative curve of 28-day mortality in patients among the three phenotypes in the training set (a), test set (b), MIMIC-III validation set (c), eICU-CRD validation set (d) and local validation set (e)

Supplementary Files

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

- [FigureS1.tif](#)
- [FigureS2.tif](#)
- [FigureS3.tif](#)
- [FigureS4.tif](#)
- [FigureS5.tif](#)
- [SupplementaryList.docx](#)