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Early coagulation changes as predictors of adverse outcomes in patients with severe burn and inhalation injuries

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ABSTRACT

Background: Disorders of the coagulation pathway are triggered in patients with severe burn and inhalation injuries in the early stages. There are multiple early coagulation indices identified to correlate with adverse outcomes.

Method: A retrospective analysis of patients with severe burn and inhalation injuries from 12 centers in mainland China was performed to identify early changed coagulation indices with predictive value associated with four major 28-day adverse outcomes (death, anticoagulation, mechanical ventilation, continuous renal replacement therapy) by logistic regression. The optimal cut-off value was also determined by Youden's index.

Results: A total of 433 patients with severe burn and inhalation injuries were included in the study. Activated partial thromboplastin time (APTT) was found to be a risk factor for death, anticoagulation and continuous renal replacement therapy outcomes, while D-dimer was a risk factor for death and mechanical ventilation outcomes. Compared with previous definitions of coagulopathy, the occurrence of adverse outcomes was well predicted by both APTT and D-dimer. Patients were divided into high-risk and low-risk coagulopathy based on APTT and D-dimer cutoff values, with high-risk coagulopathy being an independent risk factor for death. Age, TBSA, lactate level, and pre-hospital infusion volume were identified as independent influencing factors on high-risk coagulopathy.

Conclusion: The coagulation indices APTT and D-dimer in the early post-hospitalization period have a good early warning effect in the severe burn and inhalation injuries population, by which early screening to identify high-risk coagulopathies can be performed and targeted interventions can be implemented.

1. Introduction

Burns lead to coagulation disorders in the early stages. Inhalation injuries, comprising approximately 30 % of all burn injuries, present a significant risk for diverse adverse outcomes, including acute respiratory distress syndrome, sepsis, multiple organ dysfunction syndrome, and mortality [1]. The impact on the respiratory tract is multifaceted and heterogeneous, with thermal injury predominantly affecting the upper respiratory tract, while smoke inhalation induces localized and systemic inflammatory responses, disrupting the barrier function of the lung

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parenchyma. In addition, coagulation pathway disorders induced by inhalation injury play a role in the pathologic process. This not only results in localized hypercoagulation within the lungs but also involves intricate interactions with the inflammatory response [2]. Burn-induced coagulopathy (BIC) has been explored in the early post-burn period [3]. Inhalation injury, as a risk factor, exacerbates this coagulation homeostasis. However, the unique role of inhalation injury and the coagulation pathway is difficult to identify well, and there is a further lack of relevant diagnostic definitions in the more segmented inhalation injury population [4]. Early recognition of coagulation disorders is difficult.

This article undertakes a retrospective analysis of data from multiple centers. The aim is to identify early indicators of coagulation dysfunction with prognostic significance with severe burn and inhalation injuries. Based on this analysis, cut-off values for these indicators are established. Ultimately, these indicators serve as tools to identify a high-risk population exhibiting early coagulation disorders in the context of severe burn and inhalation injuries (Supplemental Figure 1).

2. Method

2.1. Population inclusion and variable selection

We enrolled patients with inhalation injuries associated with burn injuries meeting specific criteria, defined as either a total body surface area (TBSA) of $\geq$ 30 % burns or $\geq$ 10 % third-degree burns. The diagnosis of inhalation injuries was established through fiberoptic bronchoscopy. In classifying the degree of inhalation injury, the following criteria were employed: Mild: Injuries above the vocal folds, encompassing the nose, pharynx, and vocal folds. Moderate: Injuries above the tracheal rump, including the pharynx and trachea. Severe: Injuries extending below the bronchus, involving the bronchus and lung parenchyma. These patients were admitted to 12 prominent tertiary hospitals across mainland China during the period spanning January 01, 2015, to December 31, 2020. To be eligible for inclusion, patients had to be over 18 years of age and admitted to the hospital within 24 hours post-injury. They were also required to have completed relevant clinical laboratory tests. Patients presenting with any of the following conditions were excluded from the study: 1. Comorbid severe trauma. 2. Pregnancy, pre-existing tumors, or severe organ dysfunction before the burn injury occurred. 3. Pre-existing coagulation disorders or a documented history of anticoagulant medication usage before hospital admission. 4. Serious adverse outcomes during hospitalization resulting from unforeseen factors (e.g., suicide, abandonment of treatment, etc.).

Data for this study were extracted from comprehensive in-hospital medical records, encompassing a diverse array of patient information. This included general characteristics such as gender and age, details about the burn condition (causes of injury, TBSA), anamnesis covering hypertension, diabetes mellitus, chronic cardiac disease, and stroke, as well as clinical laboratory tests within 24 hours postburn (covering coagulation, hepatic function, renal function, and arterial blood gases). The length of the patient's hospital stay was also recorded.

Outcomes were defined over a 28-day period and included four main outcomes. The primary outcome was death, while secondary outcomes encompassed the use of therapeutic anticoagulants, mechanical ventilation (MV), and continuous renal replacement therapy (CRRT). Anticoagulant drugs primarily included anticoagulant and antithrombotic medications such as heparin, low molecular weight heparin, or antiplatelet agents.

3. Previous diagnosis of early coagulopathy in burns

In previous studies within the field, two primary categories of acute burn-induced coagulopathy (ABIC) diagnosis in the early stages of burns have been identified (Table 1). Sherren and Geng adhered to the definition of traumatic coagulopathy, characterizing prothrombin time (PT) $>$ 14.6 s, international normalized ratio (INR)$>$ 1.2, or activated partial thromboplastin time (APTT)$>$ 45 s as indicative of coagulopathy in acute burn cases[3,5]. Additionally, Mitra and Kaita employed a different diagnostic approach, defining coagulopathy in burn patients with INR $>$ 1.5 or APTT$>$ 60 s[6,7].

In our study, we adopted these established definitions to categorize early coagulopathies and subsequently compared their predictive efficacy regarding patient outcomes. High-risk coagulopathy01 defined as PT$>$ 14.6 s or INR$>$ 1.2 or APTT$>$ 45 s. High-risk coagulopathy02 defined as INR $>$ 1.5 or APTT $>$ 60 s.

4. Logistic regression analysis screening for coagulation-related variables

Given the potential for multiple covariances between variables, we employed correlation analysis to evaluate the presence of such relationships. Typically, a correlation close to 1 between two factors is indicative of multicollinearity. To further assess the degree of covariance, we referred to the variance inflation factor (VIF)[8], calculated as $VIF = 1 / (1 - R^2)$. Here, R^2 represents the explanatory power of the linear regression model when the particular independent variable is treated as the dependent variable, and the other independent variables function as explanatory variables. If the VIF exceeds 10, the model is considered to exhibit more pronounced multicollinearity.

Logistic regression was employed to investigate the risk factors associated with the outcome variables. Initially, the coagulation indices underwent univariate regression analysis. To account for potential covariates, three variable screening methods were utilized for further analysis[9,10]:1. stepwise multivariate logistic regression: This method, analyzed using the MASS package in the R software, involved forward selecting the combination of models with the smallest Akaike Information Criterion (AIC). 2. Lasso regression: Lasso regression introduced the L1 penalty term to the regression model, facilitating variable selection and reduction. 3. Elastic Net Regression: The Elastic Net method incorporated a combination of both L1 and L2 penalty terms. Both Lasso and Elastic Net regression utilized 10-fold cross validation, generating λ values with a default of 100. The λ value with the smallest mean square error was selected as the variable for screening.

Table 1
Definition of acute burn-induced coagulopathy in the previous publications.

Author	Year	Coagulopathy definition	Incidence	Measure time	Population	Sample	Country
P.B. Sherren	2013	PT$>$ 14.6 s or INR$>$ 1.2 or APTT$>$ 45 s	39.6 %	admission	TBSA$>$ 30 %; all ages	117	England
Rommel P. Lu	2013	INR$\geq$ 1.3, APTT $\geq$ 1.5 times mean normal, and normal PLT	0 %	admission within 12 h post burn	TBSA$>$ 15 %; Age$>$ 18	102	
Biswadev Mitra	2013	INR $>$ 1.5 or APTT$>$ 60 s	37 %	admission $<$ 24 h	TBSA$>$ 20 %; Age$>$ 18	99	Australia
Kang Geng	2020	PT$>$ 14.6 s or INR$>$ 1.2 or APTT $>$ 45 s	31 %	admission $<$ 24 h	TBSA$>$ 50 %; Age$>$ 18	129	China
Yasuhiko Kaita	2020	INR $>$ 1.5 or APTT $>$ 60 s	13.1 %	admission $<$ 24 h	Admission without fluid administration	137	Japan

PT: Prothrombin time; INR: international normalized ratio; APTT: activated partial thromboplastin time; TBSA: total body surface area.

5. Restricted cubic spline

In the real-world research, the association between two variables is often characterized by a non-linear trend. To capture and model this non-linearity, the Restricted Cubic Spline (RCS) method is employed [11]. This technique involves dividing the data range into intervals and fitting a cubic polynomial within each interval, creating a smooth curve. RCS is a widely used approach for analyzing nonlinear relationships. Where a node is a set of predetermined points distributed over the range of the independent variable and is used to join cubic polynomials together to form a continuous, smooth curve. We identify suitable nodes by minimizing the AIC.

6. Determination of optimal cutoff value

Receiver Operating Characteristic (ROC) curve analysis is a prevalent method in clinical medical and epidemiological studies for assessing prediction accuracy[12]. The area under the curve (AUC) is the area under the ROC curve surrounded by the axes, and the closer the value is to 1, the better the prediction ability is. The optimal cutoff point for the cut point is often determined using the Youden index, defined as $Youden = Sensitivity + Specificity - 1$. The Youden index is a metric that aims to maximize the sum of sensitivity and specificity, reaching its maximum value when the combined sensitivity and specificity are optimized.

Patients were divided into high-risk coagulopathy and low-risk coagulopathy based on defined cutoff values. Logistic regression was employed to analyze the association between coagulopathy and death, and analyze possible influencing factors for high-risk coagulopathy.

7. Statistical analysis

Continuous variables are presented as mean (standard deviation) if they exhibit a normal distribution; otherwise, median (interquartile range) is utilized. And differences were assessed using t-tests or Mann-Whitney U-tests. Categorical variables were reported as proportional counts and compared using the chi-square test or Fisher exact test. All statistical analyses were conducted as two-sided tests, with *P*-values less than 0.05 considered statistically significant. Data analysis and graphical representation were performed using the R software. It is important to note that the study received approval from the Ethics Committee of Changhai Hospital, ensuring compliance with ethical standards in research.

8. Results

8.1. Characteristics of the population

A total of 433 burn patients with inhalation injuries were included. The outcomes observed were as follows: 49 (11.32 %) deaths, 187 (43.19 %) patients receiving MV, 16 (3.70 %) patients undergoing CRRT, and 50 (11.55 %) patients receiving anticoagulation. Based on the two previous definitions of ABIC, the incidence of ABIC was found to be 14.1 % and 3.7 %, respectively (Table 2).

Inter-correlations were observed among coagulation-related indices, as revealed by correlation analysis, indicating a strong association between PT, APTT, and INR (Supplemental Figure 2**A**). Furthermore, the analysis of VIF indicators identified significant multicollinearity in the context of the CRRT outcome (Supplemental Figure 2B). This suggests that there are high levels of interdependence among variables related to CRRT in the dataset.

9. APTT and D-dimer are independent risk factors

Univariate logistic regression analyses were conducted for four distinct outcomes, highlighting the significant influence of various coagulation-related indices. Specifically, APTT, D-dimer, INR, and platelet count emerged as significant factors affecting the outcome of death. The administration of anticoagulation therapy was found to be influenced solely by APTT. For the MV outcome, potential influential factors included PT, APTT, D-dimer, INR, Calcium, and platelet count. In the case of CRRT as an outcome, PT, APTT, Thrombin time (TT), D-dimer, INR, and platelet count were identified as influential factors (Fig. 1).

To mitigate the impact of covariance, three algorithms—Stepwise Regression, Lasso, and Elastic Net—were employed to screen for independent influences on different outcomes. The combined results indicated that APTT and D-dimer were independent influences on mortality outcomes, APTT independently affected anticoagulation, and D-dimer was an independent influence on MV. However, only the Stepwise Regression algorithm identified APTT as an independent influence on the CRRT outcome (Fig. 1, Fig. 2**A**).

Table 2
Characteristics of the population.

Characteristic	Overall, N = 433
Gender, n (%)	
Female	123 (28.41 %)
Male	310 (71.59 %)
Age, mean (± SD)	48 (37, 58)
TBSA (%), median (IQR)	60 (45, 80)
Weight(kg), median (IQR)	65 (58, 72)
Cause, n (%)	
Fire	388 (89.61 %)
Corrosive injury	13 (3.00 %)
Scald injury	20 (4.62 %)
Electric injury	12 (2.77 %)
Degree of inhalation injury, n (%)	
mild	169 (39.03 %)
moderate	126 (29.10 %)
severe	138 (31.87 %)
Coagulation index, median (IQR)	
Prothrombin time (s)	11.70 (11.00, 12.80)
APTT (s)	28 (24, 33)
Thrombin time (s)	18.40 (17.00, 20.20)
D-dimer (mg/L)	2.4 (1.1, 6.2)
INR	1.00 (0.94, 1.10)
Fibrinogen (g/L)	2.50 (2.00, 3.13)
Calcium (mmol/L)	2.01 (1.78, 2.17)
Platelet count (10^9/L)	240 (171, 312)
Laboratory tests, median (IQR)	
PH	7.36 (7.32, 7.42)
lactate (mmol/L)	3.80 (2.30, 5.30)
MAP (mmHg)	95 (89, 103)
Serum total bilirubin(μmol/L)	18 (12, 26)
Serum total bilirubin(μmol/L)	73 (58, 93)
Alkaline phosphatase(U/L)	61 (51, 71)
Serum albumin (g/dL)	33 (26, 38)
RBC(10^9/L)	5.35 (4.82, 5.89)
WBC(10^9/L)	20 (15, 27)
Hemoglobin (g/L)	161 (145, 178)
Anamnesis, n (%)	
Hypertension	35 (8.08 %)
Diabetes	14 (3.23 %)
Coronary heart disease	6 (1.39 %)
Stroke	7 (1.62 %)
High-risk coagulopathy01, n (%)	61(14.1 %)
High-risk coagulopathy02, n (%)	16(3.7 %)
Time post burn(hour), median (IQR)	4.0 (2.0, 6.0)
LOS (day), median (IQR)	37 (25, 63)
MV, n (%)	187 (43.19 %)
CRRT, n (%)	16 (3.70 %)
Anticoagulation, n (%)	50 (11.55 %)
Death, n (%)	49(11.32 %)

TBSA: total body surface area; APTT: activated partial thromboplastin time; INR: international normalized ratio; MAP: mean arterial pressure; RBC: red blood cells; WBC: white blood cells; LOS: length of stay. MV: mechanical ventilation; CRRT: continuous renal replacement therapy.
High-risk coagulopathy01: defined as PT> 14.6 s or INR> 1.2 or APTT> 45 s;
High-risk coagulopathy02: defined as INR > 1.5 or APTT > 60 s;

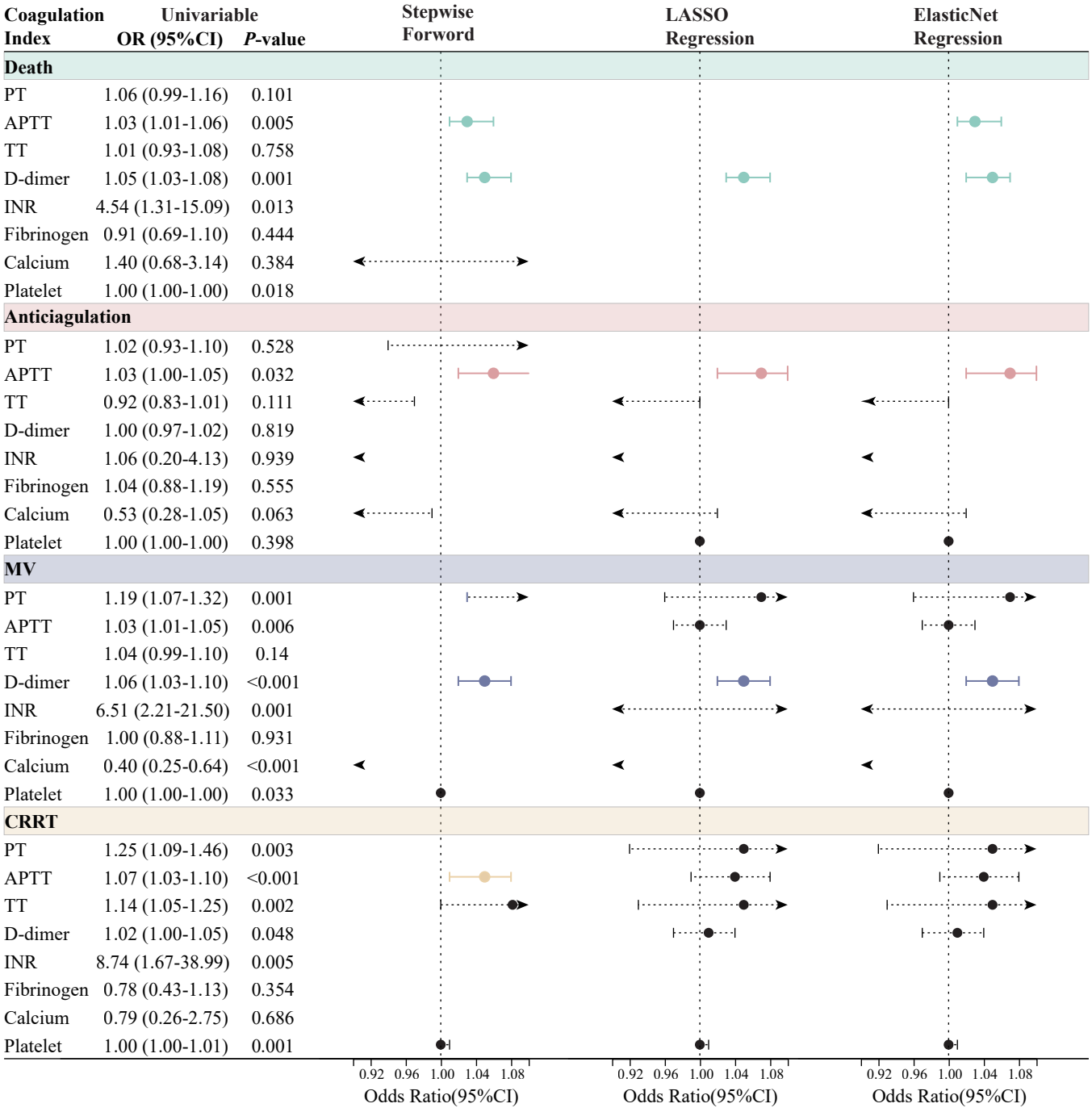

Fig. 1. Logistic regression results for early coagulation indices and different outcomes. It shows the results of the variables screened by the univariate regression analysis, stepwise forward regression, LASSO regression, and elastic network regression algorithms, respectively. PT: Prothrombin time; APTT: activated partial thromboplastin time; TT: Thrombin time; MV: mechanical ventilation; CRRT: continuous renal replacement therapy.

10. Predictive value of APTT and D-dimer

Based on the ROC and AUC, D-dimer demonstrated a higher predictive value for death and MV compared to APTT. The optimal cutoff values for APTT and D-dimer were relatively close among the four outcomes, with an approximate optimal cutoff value of 30 s for APTT when the Youden index was highest for death (31.5 s), anticoagulation (29 s), CRRT (33 s), and MV (29.7 s). For D-dimer, the optimal cutoff value for the four endpoints were centered around 3.3 mg/L for death (3.27 mg/L), anticoagulation (3.27 mg/L), CRRT (3.3 mg/L), and MV (3.39 mg/L), with an exception for the anticoagulation outcome where a cutoff value of 1.83 mg/L with a Youden index of 3.27 mg/L was also acceptable (Fig. 2**B-E**).

As the degree of inhalation injury increased, both D-dimer and APTT indices showed an elevation. The rise in two indices in the lung injury group compared to the upper airway was statistically significant (Supplemental Figure 3**A**). Stratified analyses were performed for age, TBSA, and degree of inhalation injury. Due to the limited number of cases for CRRT, stratification studies of CRRT in populations with TBSA less than 50 are lacking. Notably, after stratification by variable, the AUCs of APTT and D-dimer were consistent across outcomes (Supplemental Figure 3**B**). The optimal cutoff value for APTT appeared to be consistent at 30 seconds, showing a robust predictive effect. However, it was observed that the cutoff values for D-dimer were not the

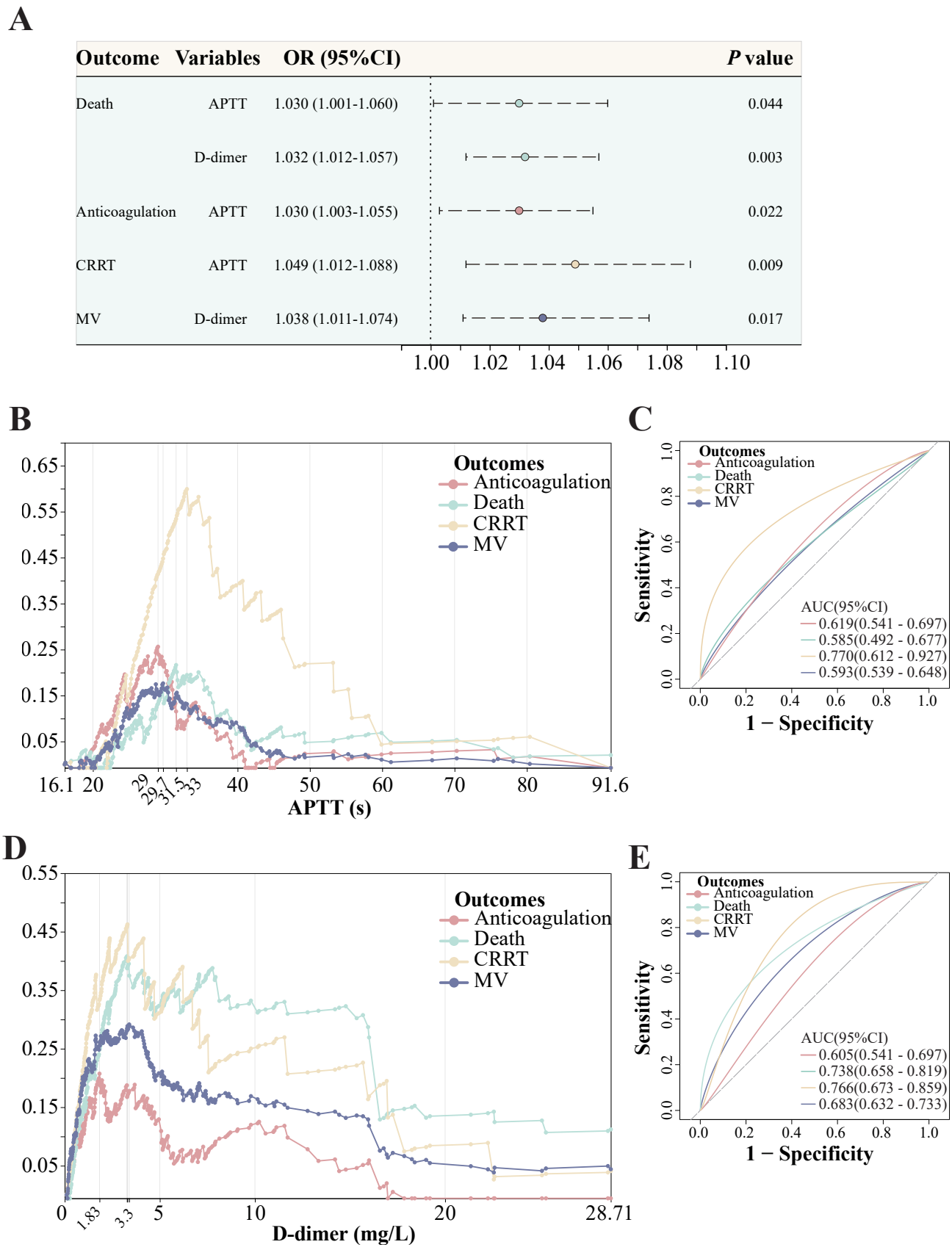

Fig. 2. Analysis of variables with predictive value for outcomes. A is the result of a multifactor logistic analysis after adjusting for age and TBSA. B is the trend of APTT with Youden index in different outcomes. C is the ROC plot of APTT in different outcomes and corresponding AUC values. D is the trend of D-dimer with Youden index in different outcomes. E is the ROC plot of D-dimer in different outcomes and corresponding AUC values. MV: mechanical ventilation; CRRT: continuous renal replacement therapy.

same for different outcomes in individuals older than 60 years and were consistently higher than those in individuals younger than 60 years (Supplemental Figure 3**C-D**).

11. Nonlinear relationship between APTT, D-dimer and outcomes

Based on the results of multivariate logistic regression, further polynomial fits were applied between the continuous variable APTT and the outcome variables (death, anticoagulation therapy, and CRRT). Additionally, polynomial fits were performed between D-dimer and the outcome variables (death and MV). The *P* for trend was statistically significant in all outcomes.

Notably, when APTT exceeded 30 seconds or D-dimer exceeded 3.3 mg/L, the odds ratio (OR) for the corresponding outcome was consistently greater than 1, and as APTT and D-dimer increased, larger OR values were observed. Specifically, a nonlinear relationship was identified between APTT and anticoagulation therapy, as well as APTT and CRRT. Similarly, a nonlinear relationship was identified between D-dimer and MV (Fig. 3**A-E**).

12. Division of high-risk coagulopathies based on APTT and D-dimer

Patients were classified as being at high risk for coagulation disorders based on criteria of APTT $>$ 30 s or D-dimer $>$ 3.3 mg/L. A total of 232 patients (53.58 %) fell into this high-risk category. This classification demonstrated greater effectiveness in predicting the impacts of multiple outcomes compared to previous diagnostic definitions of ABIC (Fig. 3**F**). Variables with $P < 0.05$ in univariate Logistic regression were included as confounders in further analyses of high-risk coagulopathy and death. High-risk coagulopathy was an independent risk factor for death after adjusting for covariates by multivariate Logistic regression analysis (Table 3). Moreover, the study identified multiple factors influencing the development of early coagulation disorders. Following screening by three algorithms, age, TBSA, lactate level, and Pre-hospital infusion volume were identified as independent influences on early coagulation disorders (Table 4).

13. Discussion

Extensive burns exert multi-faceted impacts on the body's coagulation pathways at early stage, involving endothelial damage, hypovolemia, and widespread activation of the immune-inflammatory system[13]. The definition of ABIC has lacked uniformity in previous studies, with some adopting the definition of conventional trauma induced coagulopathy[3]. However, results have exhibited variability across different cohorts. Recognizing the distinct nature of burns, it becomes imperative to conduct a nuanced analysis, particularly within the unique subgroup of inhalation injuries. As a complication of the burn process with severe impairment of respiratory function, inhalation injury can exacerbate the attack on body's coagulation and fibrinolytic systems[2]. In the present study, patients with severe burns and inhalation injuries demonstrated elevated D-dimer levels and decreased serum calcium concentrations, suggesting the presence of hyperfibrinolysis and calcium depletion. These findings align with some previous studies. Early coagulation profiles in burn patients are characterized by hypercoagulability. Damage of inhalation injury to the lung epithelium initiates exogenous coagulation pathways, resulting in localized hypercoagulability within the lungs[14]. This hypercoagulable state promotes excess fibrin deposition in the airways through extravasation, not only heightening airway obstruction but also inducing alterations in airway endothelial permeability[15]. Additionally, previous research has indicated that plasminogen activator inhibitor-1 may play a role in fibrin deposition associated with smoke inhalation lung injury [16]. Furthermore, proteases of the coagulation and fibrinolytic systems appear to play a role in cell recruitment, complement activation, and cytokine production in the progression of inflammation [17].These pathological changes can manifest shortly after injury, underscoring the critical importance of early intervention in coagulation disorders for an improved patient prognosis[18]. Existing evidence indicates that the local application of anticoagulant substances, such as heparin, holds promise in improvement of impaired microcirculation[19]. However, a comprehensive exploration and description of the early coagulation state associated with adverse outcomes remain insufficiently addressed in current field of severe burn and inhalation injuries.

Furthermore, plasma transfusions are integral components of early resuscitation therapy in this population[20]. Consequently, targeting the assessment of coagulation status before fluid resuscitation in individuals with inhalation injuries can effectively manage this uncertainty and ensure the stability of predictive measures.

This study is the first to identify coagulation indicators with early warning value for multiple adverse outcomes based on a large cohort of patients with severe burn and inhalation injuries. In our study, plasma D-dimer and APTT levels assessed within 24 hours post-injury, demonstrated associations with various adverse outcomes. D-dimer, a solubilization product of fibrin, reflects the state of fibrinolysis in the body [21]. Disorders of the fibrinolytic system involved in the progression of lung injury. Another marker of fibrinolysis, the soluble urokinase-type fibrinogen activator receptor, has also been proved to be elevated in the lungs after inhalation injuries, and its systemic levels have prognostic value for patients[22]. Previous investigations have shown that burns are often accompanied by an early elevation of D-dimer level[23]. Noteworthy associations between D-dimer levels at admission and diverse outcomes during hospitalization have been established in trauma patients[24]. Furthermore, D-dimer has exhibited prognostic relevance in patients experiencing a spectrum of lung injuries, encompassing conditions such as COVID-19 and severe pancreatitis[25,26].

APTT, extensively utilized as a diagnostic basis for trauma induced coagulopathy, has received limited validation within severe burn and inhalation injuries populations. Prior investigations have identified APTT as a predictor of mortality in burn patients, where its levels were observed to be higher in death compared to the surviving cohort[27]. APTT is responsive to functional changes in endogenous coagulation pathways, and the observed relative prolongation in population with the adverse outcomes may be attributed to excessive coagulation factor depletion. The early coagulation state in severely burned patients is characterized as highly fragile, with systemic immunoinflammation and widespread activation of the complement system, when combined with inhalation injury, more likely to induce an over-enhanced coagulation response[28]. Within our study population, APTT levels were notably elevated in the mortality compared to the survival group, though all values falling within the lower range of conventional testing. Despite the relatively conservative nature of the optimal cutoff values determined for both D-dimer and APTT, their acceptability is underscored by the systemic endothelial compromise induced by severe burns and the pervasive ischemia-reperfusion injury throughout the body.

After identifying high-risk coagulation disorders based on elevated D-dimer levels and prolonged APTT, several factors were found to contribute to the onset of early coagulation dysfunction following injury. Within the scope of our study, the relationship between the severity of inhalation injuries and coagulation dysfunction was less significant compared to that associated with extensive burns. This discrepancy may be attributed to the primarily localized nature of pulmonary coagulation in inhalation injuries, in contrast to the systemic endothelial activation observed in extensive burns. In addition to advanced age and extensive burns, lactate levels and Pre-hospital infusion volume emerge as significant influencers. Notably, in trauma patients, coagulation disorders often coincide with acidosis and hypothermia[29]. Upon examining our dataset, it became evident that the group experiencing mortality had undergone high prehospital fluid infusion. In the context of extensive burns, prehospital emergency care

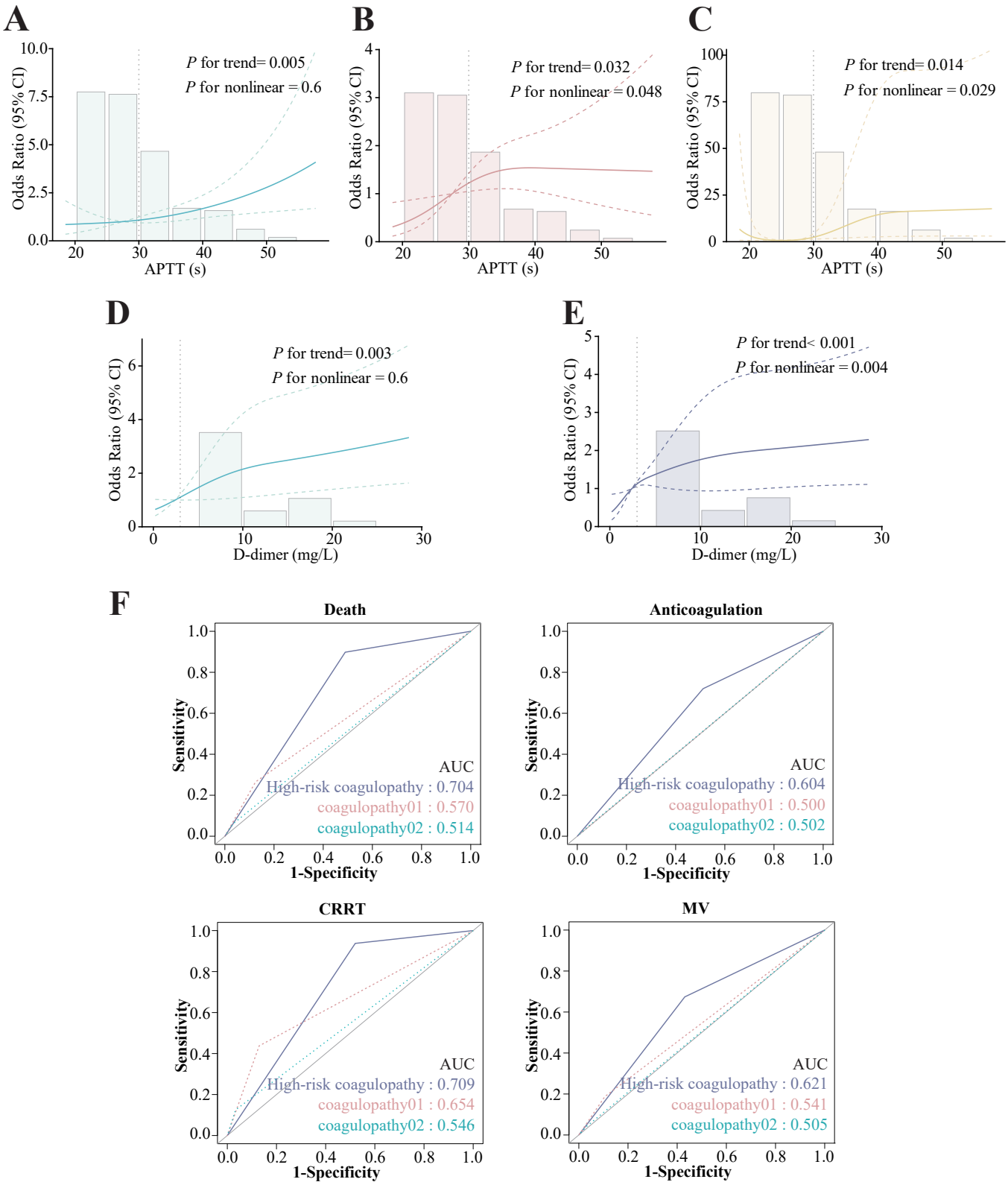

Fig. 3. Non-linear relationship and predictive ability between APTT/D-dimer and different outcomes. A is an RCS plot of APTT versus mortality outcome; B is an RCS plot of APTT versus anticoagulation outcome; C is an RCS plot of APTT versus CRRT outcome; D is an RCS plot of D-dimer versus mortality outcome; E is an RCS plot of D-dimer versus MV outcome; F is a comparison of the predictive ability to classify a population at high risk for coagulation disorders based on the APTT/D-dimer methods and previous definitions. Coagulopathy01: defined as PT> 14.6 s or INR> 1.2 or APTT> 45 s; Coagulopathy02: defined as INR > 1.5 or APTT > 60 s; MV: mechanical ventilation; CRRT: continuous renal replacement therapy.

Table 3
Logistics regression analysis to identify death-relevant variables.

Variables	Univariate regression			Multivariate regression		
	OR	95 % CI	p value	OR	95 % CI	p value
Age	1.05	1.03, 1.07	< 0.001	1.05	1.03, 1.08	< 0.001
TBSA	1.04	1.02, 1.06	< 0.001	1.03	1.01, 1.05	0.01
Degree of inhalation injury						
mild	—	—		—	—	
moderate	2.89	1.13, 7.40	0.027	2.49	0.86, 7.21	0.092
severe	5.89	2.49, 13.96	< 0.001	3.48	1.27, 9.55	0.015
PH	0	0.00, 0.10	< 0.001	0.08	0.00, 3.86	0.199
lactate	1.12	1.04, 1.22	0.005	1.03	0.92, 1.15	0.621
Serum total bilirubin	1.02	1.01, 1.04	0.01	1.01	0.99, 1.03	0.44
Serum Creatinine	1.02	1.01, 1.03	< 0.001	1.01	1.00, 1.02	0.002
Serum albumin	0.95	0.91, 0.98	0.005	1	0.95, 1.05	0.931
WBC	1.04	1.01, 1.06	0.012	1.01	0.97, 1.04	0.705
High-risk coagulopathy	9.17	3.56, 23.64	< 0.001	3.21	1.13, 9.12	0.029

OR: Odds Ratio, CI: Confidence Interval, TBSA: total body surface area, WBC: white blood cell.

Table 4
Logistics regression analysis to identify high-risk coagulopathy-relevant variables.

Variables	Univariate analysis OR (95 %CI, *P* value)	Stepwise-Forword OR (95 %CI, *P* value)	LASSO Regression OR (95 %CI, *P* value)	ElasticNet Regression OR (95 %CI, *P* value)
Age	1.03 (1.01–1.04, p < 0.001)	1.04 (1.02–1.05, p < 0.001)	1.04 (1.02–1.05, p < 0.001)	1.04 (1.02–1.05, p < 0.001)
TBSA	1.04 (1.03–1.05, p < 0.001)	1.03 (1.02–1.05, p < 0.001)	1.03 (1.02–1.04, p < 0.001)	1.03 (1.02–1.04, p < 0.001)
Degree of inhalation injury				
mild	-	-	-	-
moderate	1.14 (0.72–1.81, p = 0.580)	-	1.02 (0.61–1.71, p = 0.945)	1.02 (0.61–1.71, p = 0.945)
severe	2.14 (1.35–3.41, p = 0.001)	-	1.36 (0.79–2.36, p = 0.263)	1.36 (0.79–2.36, p = 0.263)
PH	0.02 (0.00–0.19, p = 0.001)	0.13 (0.01–1.91, p = 0.137)	0.10 (0.01–1.59, p = 0.106)	0.10 (0.01–1.59, p = 0.106)
Lactate	1.20 (1.11–1.31, p < 0.001)	1.15 (1.06–1.26, p = 0.001)	1.15 (1.06–1.26, p = 0.002)	1.15 (1.06–1.26, p = 0.002)
Time post burn	1.05 (1.01–1.10, p = 0.014)	1.05 (1.01–1.10, p = 0.022)	1.05 (1.01–1.10, p = 0.024)	1.05 (1.01–1.10, p = 0.024)
Fluid infusion	1.00 (1.00–1.00, p = 0.001)	1.00 (1.00–1.00, p = 0.027)	1.00 (1.00–1.00, p = 0.036)	1.00 (1.00–1.00, p = 0.036)

High-risk coagulopathy: defined as APTT > 30 s or D-dimer > 3.3 mg/L, OR: odds rate, CI: Confidence Interval, TBSA: total body surface area

strategies aim to avert shock by promptly supplementing crystalloid fluids[30]. However, it is imperative to recognize that excessive crystalloid infusion can lead to the dilution of coagulation factors, potentially exacerbating coagulation disorders. Consequently, some scholars propose prehospital management strategies for traumatic coagulopathy, advocating permissive hypotension to minimize fluid infusion and clotting factor dilution, alongside early plasma supplementation[20]. This approach seeks to strike a balance between preventing shock and mitigating the adverse effects of excessive fluid resuscitation on coagulation dynamics.

Notably, the coagulation and fibrinolytic systems within the body are intricate and multifaceted, making reliance on a singular parameter insufficient to comprehensively address the altered coagulation status. This study has successfully unearthed early coagulation indicators with significant early warning value, yet it is crucial to acknowledge the limitations inherent in exploring changes in coagulation status post-burn solely through these indicators. Platelet counts, for example, offers insights into platelet numbers, it falls short in assessing platelet function. To further guide clinical interventions, early coagulation status associated with adverse outcomes still needs to be revealed by more specialized assays. Viscoelasticity experiments, such as rotational thromboelastometry and thrombelastogram, capture early coagulation changes to a greater extent and have garnered recognition among many scholars[20,31]. Furthermore, to address the depletion of the coagulation system, ongoing monitoring of dynamic changes in coagulation factors is essential for effective clinical interventions. Acknowledging that viscoelasticity experiments are not universally conducted, and given the current absence of comprehensive guidelines and consensus in this field, the indicators identified in this study as possessing early warning value can serve as valuable tools for identifying high-risk patients.

There are still some limitations to this paper. The extrapolation of results from this study warrants further validation, and the predictive value of APTT and D-dimer necessitates additional confirmation within larger-scale cohorts. Thrombelastogram and coagulation factor component test results were not included in the coagulation-related variables. In one case, they were not widely conducted, and in the other case, the purpose of early warning is hoped to be achieved by these routine coagulation indices.

14. Conclusion

We successfully identified early indicators of coagulation, APTT and D-dimer, associated with adverse outcomes in patients with severe burn and inhalation injuries. The identification of patients at high risk for early coagulation disorders through the established cutoff values for these two indicators holds significant potential for facilitating timely interventions.

Moving forward, future studies should explore deeper into the molecular mechanisms governing the coagulation system to enhance our understanding, especially in inhalation injury patients. Additionally, efforts should be directed toward refining predictive models to improve their accuracy, thereby bolstering their clinical utility.

Ethics statement

The retrospective cohort has been approved by the ethics committee of Changhai Hospital (grant NO. CHCE2022–243).

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Authors' contributions

The conception and design of the study: Shengyu Huang, Dan Wang, and Qimin Ma; acquisition of data: Tuo Shen, Shengyu Huang, Yusong Wang, Rui Liu, Haiming Xin, Xiaoliang Li, Zhaohong Chen, and Fei Chang; data analysis: Dan Wang, Qimin Ma, and Shengyu Huang; drafting the article: Shengyu Huang and Dan Wang; revise the article: Feng Zhu

All authors declare

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2025.107373.

Availability of data and materials

All data generated or analysed during this study are included in this published article

References

[1] Mercel A, Tsihlis ND, Maile R, Kibbe MR. Emerging therapies for smoke inhalation injury: a review. J Transl Med 2020;18:141. https://doi.org/10.1186/s12967-020-02300-4.
[2] Hofstra JJ, Vlaar AP, Knape P, Mackie DP, Determann RM, Choi G, et al. Pulmonary activation of coagulation and inhibition of fibrinolysis after burn injuries and inhalation trauma. J Trauma 2011;70:1389–97. https://doi.org/10.1097/TA.0b013e31820f85a7.
[3] Sherren PB, Hussey J, Martin R, Kundishora T, Parker M, Emerson B. Acute burn induced coagulopathy. Burns 2013;39:1157–61. https://doi.org/10.1016/j.burns.2013.02.010.
[4] Ball RL, Keyloun JW, Brummel-Ziedins K, Orfeo T, Palmieri TL, Johnson LS, et al. Burn-induced coagulopathies: a comprehensive review. Shock 2020;54:154–67. https://doi.org/10.1097/shk.0000000000001484.
[5] Geng K, Liu Y, Yang Y, Ding X, Tian X, Liu H, et al. Incidence and prognostic value of acute coagulopathy after extensive severe burns. J Burn Care Res 2020;41:544–9. https://doi.org/10.1093/jbcr/irz178.
[6] Mitra B, Wasiak J, Cameron PA, O'Reilly G, Dobson H, Cleland H. Early coagulopathy of major burns. Injury 2013;44:40–3. https://doi.org/10.1016/j.injury.2012.05.010.
[7] Kaita Y, Nishimura H, Tanaka Y, Suzuki J, Yoshikawa K, Yamaguchi Y. Effect of acute coagulopathy before fluid administration in mortality for burned patients. Burns 2021;47:805–11. https://doi.org/10.1016/j.burns.2020.10.011.
[8] Kim JH. Multicollinearity and misleading statistical results. Korean J Anesth 2019;72:558–69. https://doi.org/10.4097/kja.19087.
[9] Pavlou M, Ambler G, Seaman S, De Iorio M, Omar RZ. Review and evaluation of penalised regression methods for risk prediction in low-dimensional data with few events. Stat Med 2016;35:1159–77. https://doi.org/10.1002/sim.6782.
[10] Vinga S. Structured sparsity regularization for analyzing high-dimensional omics data. Brief Bioinform 2021;22:77–87. https://doi.org/10.1093/bib/bbaa122.
[11] Xu Y, Han D, Xu F, Shen S, Zheng X, Wang H, et al. Using restricted cubic splines to study the duration of antibiotic use in the prognosis of ventilator-associated pneumonia. Front Pharm 2022;13:898630. https://doi.org/10.3389/fphar.2022.898630.
[12] Drożdż K, Nabrdalik K, Kwiendacz H, Hendel M, Olejarz A, Tomasik A, et al. Risk factors for cardiovascular disease in patients with metabolic-associated fatty liver disease: a machine learning approach. Cardiovasc Diabetol 2022;21:240. https://doi.org/10.1186/s12933-022-01672-9.
[13] Glas GJ, Levi M, Schultz MJ. Coagulopathy and its management in patients with severe burns. J Thromb Haemost 2016;14:865–74. https://doi.org/10.1111/jth.13283.
[14] Enkhbaatar P, Pruitt Jr BA, Suman O, Mlcak R, Wolf SE, Sakurai H, et al. Pathophysiology, research challenges, and clinical management of smoke inhalation injury. Lancet 2016;388:1437–46. https://doi.org/10.1016/s0140-6736(16)31458-1.
[15] Keyloun JW, Le TD, Brummel-Ziedins KE, McLawhorn MM, Bravo MC, Orfeo T, et al. Inhalation injury is associated with endotheliopathy and abnormal fibrinolytic phenotypes in burn patients: a cohort study. J Burn Care Res 2022;43:432–9. https://doi.org/10.1093/jbcr/irab102.
[16] Midde KK, Batchinsky AI, Cancio LC, Shetty S, Komissarov AA, Florova G, et al. Wood bark smoke induces lung and pleural plasminogen activator inhibitor 1 and stabilizes its mRNA in porcine lung cells. Shock 2011;36:128–37. https://doi.org/10.1097/SHK.0b013e31821d60a4.
[17] Glas GJ, Van Der Sluijs KF, Schultz MJ, Hofstra JJ, Van Der Poll T, Levi M. Bronchoalveolar hemostasis in lung injury and acute respiratory distress syndrome. J Thromb Haemost 2013;11:17–25. https://doi.org/10.1111/jth.12047.
[18] Prat NJ, Herzig MC, Kreyer S, Montgomery RK, Parida BK, Linden K, et al. Platelet and coagulation function before and after burn and smoke inhalation injury in sheep. J Trauma Acute Care Surg 2017;83:S59–s65. https://doi.org/10.1097/ta.0000000000001472.
[19] Phelps MK, Olson LM, Patel M, Thompson MJ, Murphy CV. Nebulized heparin for adult patients with smoke inhalation injury: a review of the literature. J Pharm Technol 2020;36:130–40. https://doi.org/10.1177/8755122520925774.
[20] Kleinveld DJB, Hamada SR, Sandroni C. Trauma-induced coagulopathy. Intensive Care Med 2022;48:1642–5. https://doi.org/10.1007/s00134-022-06834-7.
[21] Schafer K, Goldschmidt E, Oostra D, Fish J, Russell T, Lurie F. The clinical significance of ultra-high D-dimer levels. J Vasc Surg Venous Lymphat Disord 2022;10:8–13. https://doi.org/10.1016/j.jvsv.2021.06.011.
[22] Backes Y, van der Sluijs KF, Tuip de Boer AM, Hofstra JJ, Vlaar AP, Determann RM, et al. Soluble urokinase-type plasminogen activator receptor levels in patients with burn injuries and inhalation trauma requiring mechanical ventilation: an observational cohort study. Crit Care 2011;15:R270. https://doi.org/10.1186/cc10550.
[23] Lin JC, Chen XD, Xu ZR, Zheng LW, Chen ZH. Association of the circulating supar levels with inflammation, fibrinolysis, and outcome in severe burn patients. Shock 2021;56:948–55. https://doi.org/10.1097/SHK.0000000000001806.
[24] Hayakawa M, Maekawa K, Kushimoto S, Kato H, Sasaki J, Ogura H, et al. High D-dimer levels predict a poor outcome in patients with severe trauma, even with high fibrinogen levels on arrival: a multicenter retrospective study. Shock 2016;45:308–14. https://doi.org/10.1097/SHK.0000000000000542.
[25] Xiang X, Zhang Z, Liu Y, Xu W, Gong J, Yu S, et al. Circulating inflammatory factor levels in the early phase of COVID-19 are associated with the progression of respiratory failure: a single-center retrospective study. J Inflamm Res 2023;16:5249–60. https://doi.org/10.2147/jir.S430221.
[26] Jia M, Xu X, Zhou S, Liu H, Zhao Y, Xu Y, et al. Prediction of acute lung injury in severe acute pancreatitis by routine clinical data. Eur J Gastroenterol Hepatol 2023;35:36–44. https://doi.org/10.1097/meg.0000000000002458.
[27] Zhang TN, Ba T, Li F, Chen Q, Chen ZP, Zhou B, et al. Coagulation dysfunction of severe burn patients: A potential cause of death. Burns 2023;49:678–87. https://doi.org/10.1016/j.burns.2022.05.003.
[28] Lavrentieva A, Kontakiotis T, Bitzani M, Papaioannou-Gaki G, Parlapani A, Thomareis O, et al. Early coagulation disorders after severe burn injury: impact on mortality. Intensive Care Med 2008;34:700–6. https://doi.org/10.1007/s00134-007-0976-5.
[29] Buzzard L, Schreiber M. Trauma-Induced Coagulopathy: What You Need to Know. J Trauma Acute Care Surg 2023. https://doi.org/10.1097/TA.0000000000004170.
[30] Tejiram S, Tranchina SP, Travis TE, Shupp JW. The First 24 hours: burn shock resuscitation and early complications. Surg Clin North Am 2023;103:403–13. https://doi.org/10.1016/j.suc.2023.02.002.
[31] Trauma-induced coagulopathy. Nat Rev Dis Prim 2021;7:29. https://doi.org/10.1038/s41572-021-00270-5.