The Association of Coagulation Indicators and Coagulant Agents With 30-Day Mortality of Critical Diabetics

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Abstract
Diabetes, regarded as a global health concerned disease, was focused by the World Health Organization (WHO). Patients with diabetes may have a hypercoagulable and hypo-fibrinolysis state. There is lots of research about cardiovascular effects on diabetes patients, but less about the coagulation system. This study is designed to investigate the relationship between coagulation indicators and 30-day mortality of critical diabetes patients. In this retrospective, single-center study, we included adult patients diagnosed with diabetes. Data, including demographic, complication, laboratory tests, scoring system, and anticoagulant treatment, were extracted from Medical Information Mart for Intensive Care (MIMIC-III). The receiver operating characteristic (ROC) curve and Kaplan-Meier curve were applied to predict the association of mortality and coagulation indicators. Cox hazard regression model and subgroup analysis were used to analyze the risk factors associated with 30-day mortality. A total of 4026 patients with diabetes mellitus were included in our study, of whom 3312 survived after admitted to the hospital and 714 died. Cox hazard regression showed anticoagulant therapy might decrease the risk of 30-day mortality after adjusted. In age <70 subgroup analysis, we found that patients with PTT <26.8 s or lightly increased PT may increase odds of 30-day hospital death (HR, 95%CI, 2.044 (1.376, 3.034), 1.562 (1.042, 2.343)). When age >70, lightly increased PTT may reduce the risk of mortality, but PT >16.3 s, a high level of hypo-coagulation state, increase risk of mortality (HR, 95%CI, 0.756 (0.574, 0.996), 1.756 (1.129, 2.729)). Critical diabetes patients may benefit from anticoagulant agents. The abnormal coagulant function is related to the risk of 30-day mortality.

Keywords
diabetes mellitus, MIMIC, blood coagulation, anticoagulants, mortality

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Introduction
Worldwide, the prevalence rate of diabetes is rising year by year. In 2017, the global prevalence in adults was 8.8% of the world population, and the total number was 424.9 million worldwide. Experts estimated that the population would have a 48% increase to 628.6 million by 2045.1

The typical diabetes mellitus (DM) pathological changes are the thickening of the micro-vessel basement membrane and the disturbance of microcirculation. Microangiopathy is a specific complication of DM which can involve vital organs. Microvascular or macrovascular complications will happen to diabetes patients sooner or later. Microvascular complications include chronic kidney disease, albuminuria, retinopathy, autonomic neuropathy, peripheral neuropathy and erectile dysfunction. Macrovascular complications include coronary artery disease, stroke, transient ischemic attack, carotid artery stenting, carotid endarterectomy, peripheral artery disease, diabetic foot, amputation and heart failure. The global prevalence of microvascular and macrovascular complications was 18% and 13%, respectively.2 Therefore, DM causes multiple organ injury. The most frequently involved organs are kidney and retina, especially.

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Clotting factors are elevated in DM patients, such as fibrinogen, factor VII, factor VIII, factor XI, factor XII, von Willibrand factor and kallikrein. On the contrary, plasma protein C is decline. Some research observed that pro-coagulation biomarker or D-dimer is increased in diabetes patients with microvascular and macrovascular complications. Chronic hyperglycemia leads to the abnormality of vascular. Moreover, a pro-inflammatory and a procoagulant state can result in endothelial dysfunction. Patients with type 2 diabetes mellitus have a hypercoagulable and hypo-fibrinolysis state. And the activation of coagulation may contribute to the increased risk of vascular disease. The activation of aldose reductase, polyl pathway and advanced glycation-end-product formation in DM patients, affects the phosphorylation status and expression of endothelial nitric oxide synthetase, a potent vasodilator that possesses vasodilatory, antiplatelet aggregatory, antiatherogenic and antifibrinolytic.

In Mimic-III database, a study found 10 laboratory tests with the strongest association with mortality. Interestingly, 4 out of 10 are related to coagulation function included partial thromboplastin time (PTT), platelet, total calcium, and INR, respectively. Thus, this study aimed to analyze the association of coagulation indicators with 30-day hospital mortality of diabetes patients at ICU admission.

Methods

Database

The data were acquired from a public and freely available clinical database, MIMIC-III. An extensive and single-center database includes over 38000 ICU patients with their demographic characteristics, diagnosis by ICD-9 codes, physiological index, laboratory tests and medications, admitted to the Beth Israel Deaconess Medical Center, Boston during 2001-2012.

After completing the National Institutes of Health’s Web-based course and passing Protecting Human Research Participants exam, can we apply for the data.

The data of identification were hidden to protect privacy.

Data Extraction

Structured query language (SQL) with PostgreSQL (version 9.6) and open-source development were used to extract MIMIC-III database data. Demographics, laboratory tests, diagnosis, comorbidities, scoring systems, and medication in the first 24 h of ICU admission were collected. Age, body mass index (BMI, weight (kg)/[height(m)]2), gender and ethnicity were extracted as demographics characteristic. Main coagulation parameters were collected in our study, including PTT, international normalized ratio (INR) and prothrombin time (PT). Other laboratory data were also extracted, including albumin (Alb), total bilirubin (TBIL), blood urea nitrogen (BUN), creatinine (Crea), bicarbonate, calcium, glucose (Mean blood glucose level), lactic acid, pH, hematocrit, hemoglobin, red blood cell distribution width (RDW), platelet and white blood cell (WBC). Besides, comorbidities included congestive heart failure (CHF), coronary artery disease (CAD), hypertension, chronic kidney disease (CKD), liver disease, malignancy. Sequential organ failure assessment (SOFA) score, simplified acute physiology score II (SAPS II) and systemic inflammatory response syndrome (SIRS) were calculated for each patient as the severity of illness index. Moreover, our study collected DM patients who received anticoagulants or renal replacement therapy. The following drugs were defined as anticoagulants: heparin, low molecular weight heparin (LMWH), fondaparinux sodium, argatroban, dicoumarol, warfarin, dabigatran, rivaroxaban.

Furthermore, the endpoints of our study were 30-day all-cause mortality from the date of ICU admission.

Population Select Criteria and Outcome

All patients were initially diagnosed with DM according to the International Classification of Disease (ICD)-9 code (code = 250) or diagnosed with DM during hospitalization following by clinical diagnosis of ADA. Patients with the following condition were excluded in our study: (1) age lower than 18 years old; (2) less than 48 hours in ICU; (3) the absence of INR and PTT within 24 hours after ICU admission; (4) only the first ICU stay was considered for patients who admitted more than once.

The outcomes of our study were defined as 30-day hospital mortality.

Statistical Analysis

Descriptive statistics included proportions and frequencies for categorical variables and mean ± standard deviation (SD) for continuous variables. Chi-square test and the Kruskal-Wallis test were used for comparison. The receiver operating characteristic (ROC) curve was applied to measure the sensitivity and specificity of PT, PTT, INR and scoring system in 30-day mortality. The area under the curve (AUC) was also calculated to confirm the quality of coagulation indexes as a predictor of mortality. In order to figure out the relationship between PT, PTT, INR, anticoagulants and 30-day mortality, Kaplan-Meier survival curves (KM) were generated.

Moreover, we used Cox regression hazard model to analyze the association between coagulation indexes, anticoagulants and 30-day mortality. To further understand the relationship of coagulation indexes, anticoagulants and 30-day mortality, a subgroup analysis was conducted classified by age, gender, scoring system, CKD and malignancy. P-value < 0.05 was defined as statistically significant.

Results

Characteristic of the Subjects

Among 46476 ICU admission patients, a total of 4026 ICU inpatients with DM were enrolled in our study and 42450 were excluded (as shown in Figure 1).
The demographic characteristics were displayed in Table 1. Compared to 3312 who survived in our study, 714 of 4026 died after discharge from the hospital in 30 days. The mean age of the former was 74.6 ± 43.6 years old and the latter was 89.7 ± 63.6. The non-survivors were older and stayed longer than the survivors. And there was no difference in gender. We also found that the non-survivors gained high scores in SAPS-II and SOFA, paralleled to mortality. Interestingly, as shown in Table 1, the non-survivor patients were in hypercoagulable state. And whether used anticoagulants were statistically insignificant in survivor and non-survivor patients.

**ROC and KM Curve**

The ROC curve (Figure 2) shows that SAPS-II (AUC = 0.7344) is of better predicting ability than SOFA (AUC = 0.654), PT (AUC = 0.5939), INR (AUC = 0.5874), SIRS (AUC = 0.5812) and PTT (AUC = 0.5563), as an overall scoring system to estimate the severity of disease.

The continuous variables of coagulation values were converted to categorical variables by quartiles derived from Figure 1.

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**Table 1. Baseline Characteristics.**

| Characteristics | 30-day non-survivors, n = 714 | 30-day survivors, n = 3312 | P value |
|-----------------|-------------------------------|---------------------------|---------|
| Age, years      | 89.745 ± 63.635               | 74.594 ± 43.571           | 0.000   |
| BMI             | 34.910 ± 156.892              | 32.667 ± 75.727           | 0.568   |
| Gender, n (%)   |                               |                           |         |
| Female          | 310 (0.077)                   | 1372 (0.341)              | 0.349   |
| Male            | 404 (0.100)                   | 1940 (0.482)              | 0.349   |
| Ethnicity, n (%)|                               |                           |         |
| White           | 466 (0.116)                   | 2208 (0.548)              | 0.500   |
| Black           | 11 (0.003)                    | 79 (0.020)                | 0.213   |
| Yellow          | 55 (0.014)                    | 328 (0.081)               | 0.081   |
| Others          | 182 (0.045)                   | 697 (0.173)               | 0.011   |
| Days of ICU(h)  | 8.253 ± 8.642                 | 6.215 ± 6.824             | 0.000   |
| Scoring systems |                               |                           |         |
| SAPS-II         | 47.769 ± 14.600               | 37.155 ± 12.567           | 0.000   |
| SOFA            | 6.265 ± 3.852                 | 4.600 ± 2.903             | 0.000   |
| SIRS, n (%)     |                               |                           |         |
| 0               | 4 (0.001)                     | 43 (0.011)                | 0.141   |
| 1               | 32 (0.008)                    | 273 (0.068)               | 0.001   |
| 2               | 126 (0.031)                   | 758 (0.188)               | 0.003   |
| 3               | 285 (0.071)                   | 1284 (0.319)              | 0.597   |
| 4               | 267 (0.066)                   | 954 (0.237)               | 0.000   |
| Coagulation parameters |                           |                           |         |
| PTT(s)          | 42.829 ± 28.365               | 38.201 ± 22.916           | 0.000   |
| INR             | 1.670 ± 1.026                 | 1.470 ± 0.847             | 0.000   |
| PT(s)           | 17.214 ± 6.930                | 15.620 ± 6.325            | 0.000   |
| Others laboratory parameters |                       |                           |         |
| Albumin         | 2.939 ± 0.606                 | 3.233 ± 2.671             | 0.003   |
| TBIL            | 2.825 ± 13.707                | 1.316 ± 1.563             | 0.000   |
| Urea nitrogen   | 37.898 ± 25.729               | 27.485 ± 20.249           | 0.000   |
| Creatinine      | 1.684 ± 1.292                 | 1.354 ± 1.260             | 0.000   |
| Bicarbonate     | 22.403 ± 5.256                | 23.874 ± 4.823            | 0.000   |
| Calcium         | 8.195 ± 0.914                 | 8.329 ± 0.830             | 0.000   |
| Glu             | 186.354 ± 89.600              | 180.487 ± 88.965          | 0.111   |
| Lactic acid     | 2.775 ± 2.117                 | 2.278 ± 1.277             | 0.000   |
| pH              | 6.916 ± 0.900                 | 7.012 ± 1.758             | 0.153   |
| Hematocrit      | 31.837 ± 6.235                | 31.873 ± 6.268            | 0.890   |
| Hemoglobin      | 31.837 ± 6.235                | 31.873 ± 6.268            | 0.890   |
| Hypertension    | 383 (0.095)                   | 390 (0.100)               | 0.042   |
| Chronic kidney disease |               |                           |         |
| 0               | 440 (0.109)                   | 2150 (0.534)              | 0.015   |
| 1               | 274 (0.068)                   | 1162 (0.289)              | 0.270   |
| Chronic heart disease |            |                           |         |
| 0               | 685 (0.170)                   | 3142 (0.780)              | 0.001   |
| 1               | 29 (0.007)                    | 170 (0.042)               | 0.001   |
| Cardiac dysrhythmia |            |                           |         |
| 0               | 331 (0.082)                   | 1314 (0.326)              | 0.033   |
| 1               | 383 (0.095)                   | 1990 (0.496)              | 0.011   |
| Chronic kidney disease |                |                           |         |
| 0               | 607 (0.151)                   | 2915 (0.724)              | 0.065   |
| 1               | 107 (0.027)                   | 397 (0.099)               | 0.099   |
| Liver disease   | 367 (0.095)                   | 1338 (0.326)              | 0.011   |
| 0               | 697 (0.173)                   | 3267 (0.811)              | 0.065   |
| 1               | 17 (0.004)                    | 45 (0.011)                | 0.011   |

(continued)
clinical experience. The Kaplan-Meier survival curve of APTT shown a U-shaped relationship with 30-day mortality (Figure 3). Besides, INR and PT’s KM curve revealed that the higher INR or PT, the greater mortality. However, there was no statistical difference whether had anticoagulants according to KM curve of agents.

COX Hazard Regression
To examine the independent predicting value, 714 non-survivors and 3312 survivors were included in 2 models: non-adjusted and adjusted models (Table 2). The later model was adjusted for demographic characteristics (age, gender, ethnicity, BMI), scoring systems (SOFA, SIRS, SAPS II), comorbidities (cardiac dysrhythmia disease, congestive heart failure, hypertension, CKD, liver disease, malignancy), laboratory parameters (albumin, bicarbonate, calcium, creatinine, glucose, hematocrit, hemoglobin, lactic acid, pH, platelet, RDW, TBIL, urea nitrogen, WBC) and therapy (RRT and anticoagulants).

In surprise, after adjusted, anticoagulants were a protected factor for DM patients (HR \(0.710, 95\% (0.585, 0.862)\)) as shown in Table 2.

Subgroup Analysis
The association between coagulation values and anticoagulants and 30-day mortality was performed in subgroup analysis. There was no interaction between INR and 30-day mortality (Tables 3-5).

For elder patients (>70 years), the bigger the PT value is the higher risk of mortality. The HR (95\% CIs) for PT levels 13.2-14.3 s, 14.3-16.3 s and 16.3-150.0 s were 1.244(0.932, 1.662), 1.404(0.979, 2.012) and 1.756(1.129, 2.729), respectively. However, it was a protective factor when the PTT level was 31.3-39.6 s (HR 0.756, 95\% CI (0.574, 0.996)).

On the contrary, for age <70 years, the PT level of 13.2-14.3 s and the PTT level of 16.9-26.8 s had a higher risk of mortality (HR 1.562, 95\% CI (1.042, 2.343), HR 2.044 95\% CI (1.376, 3.034)).

Patients with malignancy, a hypo-coagulable state, PT level more than 16.3 s, showed an increased risk of 30-day mortality (HR 2.305, 95\% CI (1.232, 4.312), P for interaction 0.016).

Table 1. (continued)

| Characteristics       | 30-day non-survivors, n = 714 | 30-day survivors, n = 3312 | P value |
|-----------------------|-------------------------------|-----------------------------|---------|
| Malignancy            |                               |                             | 0.000   |
| 0                     | 522                           | 2722                        | 0.676   |
| 1                     | 192                           | 590                         | 0.147   |
| Anticoagulant         |                               |                             | 0.710   |
| 0                     | 144                           | 645                         | 0.160   |
| 1                     | 570                           | 2667                        | 0.662   |
| Renal replacement      |                               |                             | 0.000   |
| therapy               |                               |                             |         |
| 0                     | 673                           | 3227                        | 0.802   |
| 1                     | 41                            | 85                          | 0.021   |

Table 2. HRs of Coagulation Indicator, Coagulant Drug, and 30-Day Mortality in Different Models.

| Outcome                  | Non-adjusted a | Adjust b |
|--------------------------|---------------|----------|
|                         | HR  | P   | HR  | P   |
| PTT                      |     |     |     |     |
| 16.9-26.8                | 1.180 (0.941, 1.478) | 0.151 | 1.334 (1.058, 1.681) | 0.015 |
| 26.8-31.3                | 1   |     |    |     |
| 31.3-39.6                | 0.927 (0.743, 1.156) | 0.500 | 0.902 (0.721, 1.129) | 0.368 |
| 39.6-150.0               | 1.221 (0.987, 1.511) | 0.066 | 1.138 (0.913, 1.420) | 0.251 |
| PT                       |     |     |     |     |
| 9.2-13.2                 | 1.405 (1.118, 1.766) | 0.004 | 1.312 (1.039, 1.657) | 0.022 |
| 13.2-16.3                | 1.397 (1.074, 1.817) | 0.013 | 1.284 (0.973, 1.694) | 0.077 |
| 16.3-150.0               | 2.093 (1.511, 2.900) | 0.000 | 1.455 (1.033, 2.049) | 0.032 |
| INR                      |     |     |     |     |
| 0.0-1.1                  | 0.971 (0.765, 1.233) | 0.809 | 0.985 (0.775, 1.253) | 0.904 |
| 1.1-1.3                  | 0.919 (0.742, 1.137) | 0.436 | 0.886 (0.709, 1.107) | 0.285 |
| 1.3-1.6                  | 1.069 (0.794, 1.439) | 0.660 | 0.969 (0.713, 1.316) | 0.838 |
| Use drug                 | 0.928 (0.770, 1.189) | 0.429 | 0.710 (0.585, 0.862) | 0.001 |

Abbreviations: BMI, Body Mass Index; ICU, intensive care unit; SAPS-II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; PTT, Partial Thromboplastin Time; PT, Prothrombin Time; INR, International Normalized Ratio; TBIL, Total Bilirubin; GLU, Glucose; RDW, Red Blood Cell; WBC, White Blood Cell; Anticoagulant, Using heparin, low molecular weight heparin, fondaparinux sodium, argatroban, dicoumarol, warfarin, dabigatran, rivaroxaban.

aContinue data are presented as mean ± SD and categorical variables are presented as n (%).
But a hypercoagulable state, when PTT level is less than 26.8 s, also noticed a higher risk of mortality (HR 2.105, 95% CI (1.346, 3.293)).

However, critical DM patients who had used anticoagulants had a decreased risk to mortality, especially elder patients (>70 years, HR 0.726, 95% CI (0.569, 0.925), P < 0.05) and high scores of SAPSII (HR 0.660, 95% CI (0.525, 0.831), P < 0.05) or SOFA (HR 0.607, 95% CI (0.484, 0.762)). Moreover, for CKD patients, treatment with anticoagulants had a significant lower risk of mortality (HR 0.462, 95% CI (0.240, 0.892)) compared to patients without CKD (HR 0.723, (0.590, 0.887)).

**Discussion**

Our study examined the influence of coagulable indicators and coagulant agents of patients admitted to ICU on 30-day mortality. Zheng et al extracted data from the MIMIC database, shown the association of coagulation indicators and mortality with sepsis, and concluded that increased INR related to greater mortality. Another research presented that 1 of the coagulation indicators, PT, is regarded as an independent predictor for 2-year mortality in acute myocardial infarction patients. McClintock compared biomarkers of coagulation and fibrinolysis between survivors and non-survivors, indicating that coagulation and fibrinolysis predict mortality in patients with lung-protective ventilation. Moreover, the levels of thrombomodulin and plasminogen activator inhibitor 1 (PAI) are significantly higher in non-survivors. As peripheral artery disease is a complex condition, Harky et al shown that anticoagulant therapy is paramount to preventing disease.

Several observatories report that the global outbreak of coronavirus disease 2019 (COVID-19) is a hypercoagulable disorder. A retrospective multicenter cohort study about COVID-19 shown that the potential risk factors of older age, high SOFA score, and d-dimer greater than 1μg/mL may have a poor prognosis at an early stage. Half of the patients had comorbidities. And, diabetes ranked as the second common comorbidities after hypertension. Besides, the odds of in-hospital mortality was higher in patients with diabetes. D-dimer and fibrin split products are also shown distinct elevated in other studies of COVID-19 patients while no change with APTT and PT. The study suggested that anticoagulation therapy is regarded as an essential treatment for COVID-19 patients based on the coagulopathy scoring system.

Diabetes is 1 of the metabolic-related diseases. Metabolic syndrome is composed of atherogenic dyslipidemia, elevated blood pressure, insulin resistance and elevated glucose, a prothrombotic state, and a pro-inflammatory state. Also, metabolic syndrome is a multiplex factor for type 2 diabetes.

The incidence of cancer is increasing with age-related to the dysfunction of mitochondrial caused by oxidative stress. Increasing reactive oxygen species (ROS) levels and products of oxidative stress were found in cancer.

APTT reflects the endogenous coagulation system, of which the involved coagulation factors all from the blood. It usually occurs when the blood contacts negatively charged exposed collagen with damaged vascular endothelium. PT reflects an exogenous coagulation system activated by tissue factors in physiological situation, a transmembrane glycoprotein not expressed in blood cells and endothelial cells. Because of the exposed tissue factor’s anchored function, the clotting process is limitedly initiated when blood vessels are injured.
When PT is normal, a prolonged APTT reflects a deficiency of clotting factor as VIII, IX, XI, or XII, high-molecular-weight kininogen, or prekallikrein. The prolonged PT most commonly occurs in hospitalized patients treated with antibiotics and unable to eat, leading to deficient vitamin K. Factors II, VII, IX, and X are the vitamin K–dependent procoagulant proteins. Prolong PT more commonly occur in using anticoagulant like warfarin.

Normal vascular endothelium serves as a barrier to prevent the coagulant factor and platelet from contacting with the subcutaneous components and avoids the activation of the coagulant system and platelet. The vascular endothelium has anticoagulation and antiplatelet function worked by heparin sulfate proteoglycan, thrombomodulin (TM), antithrombin and so on. The imbalance of phosphorylation and dephosphorylation in DM, hyperhomocysteinemia, hypercholesterolemia, or hyperuricemia patients cause dysfunction of endothelium by modulation of vascular endothelial L-arginine/nitric oxide synthetase.

When in a hypercoagulable state, anticoagulant should be applied after excluding systemic diseases such as hemopathy.

| Table 3. Subgroup Analysis of PTT. |
|-----------------------------------|
| PTT        | 16.9-26.8 | 26.8-31.3 | 31.3-39.6 | 39.6-150.0 | \( P \) value |
| Age        |           |           |           |           |               |
| 20.36-69.47| 2013      | 2.044 (1.376, 3.034) | 1 (ref)  | 1.251 (0.840, 1.862) | 1.288 (0.853, 1.945) | 0.017 |
| 69.47-301.28| 2013     | 1.024 (0.764, 1.374) | 1 (ref)  | 0.756 (0.574, 0.996) | 0.990 (0.758, 1.293) |
| Gender     |           |           |           |           |               |
| Female     | 1682      | 1.764 (1.237, 2.515) | 1 (ref)  | 1.077 (0.746, 1.555) | 1.241 (0.861, 1.787) | 0.422 |
| Male       | 2344      | 1.036 (0.747, 1.437) | 1 (ref)  | 0.799 (0.598, 1.068) | 1.169 (0.878, 1.557) |
| SAPS-II    |           |           |           |           |               |
| 6.0-38.0   | 2013      | 1.411 (0.998, 1.996) | 1 (ref)  | 1.058 (0.729, 1.536) | 1.180 (0.809, 1.722) | 0.000 |
| 38.0-114.0 | 2013      | 1.277 (0.953, 1.710) | 1 (ref)  | 0.870 (0.669, 1.130) | 1.077 (0.831, 1.395) |
| SOFA       |           |           |           |           |               |
| 0.0-4.0    | 2013      | 1.731 (1.149, 2.606) | 1 (ref)  | 1.176 (0.755, 1.832) | 1.477 (0.962, 2.268) | 0.528 |
| 4.0-20.0   | 2013      | 1.246 (0.941, 1.650) | 1 (ref)  | 0.860 (0.666, 1.112) | 0.952 (0.737, 1.229) |
| CKD        |           |           |           |           |               |
| 0          | 3522      | 1.452 (1.137, 1.854) | 1 (ref)  | 0.890 (0.697, 1.138) | 1.121 (0.881, 1.426) | 0.106 |
| 1          | 504       | 0.608 (0.269, 1.373) | 1 (ref)  | 0.833 (0.446, 1.557) | 1.168 (0.633, 2.158) |
| Malignancy |           |           |           |           |               |
| 0          | 3244      | 1.112 (0.846, 1.463) | 1 (ref)  | 0.866 (0.666, 1.127) | 1.109 (0.860, 1.429) | 0.521 |
| 1          | 782       | 2.105 (1.346, 3.293) | 1 (ref)  | 1.109 (0.711, 1.729) | 1.156 (0.722, 1.850) |

HR (95%CI) were derived from the Cox hazard regression model. Covariates were adjusted as in adjusted model (Table 2).

| Table 4. Subgroup Analysis of PT. |
|-----------------------------------|
| PT        | 9.2-13.2 | 13.2-14.3 | 14.3-16.3 | 16.3-150.0 | \( P \) for interaction |
| Age       |           |           |           |           |               |
| 20.36-69.47| 2013      | 1.562 (1.042, 2.343) | 1.333 (0.849, 2.094) | 1.215 (0.695, 2.125) | 0.002 |
| 69.47-301.28| 2013     | 1.244 (0.932, 1.662) | 1.404 (0.979, 2.012) | 1.756 (1.129, 2.729) |
| Gender    |           |           |           |           |               |
| Female    | 1682      | 1.448 (1.037, 2.023) | 1.284 (0.844, 1.953) | 1.831 (1.056, 3.176) | 0.240 |
| Male      | 2344      | 1.239 (0.889, 1.726) | 1.294 (0.889, 1.883) | 1.251 (0.802, 1.951) |
| SAPS-II   |           |           |           |           |               |
| 6.0-38.0  | 2013      | 1.393 (0.993, 1.954) | 1.412 (0.927, 2.152) | 1.384 (0.791, 2.420) | 0.000 |
| 38.0-114.0| 2013      | 1.185 (0.878, 1.601) | 1.155 (0.824, 1.621) | 1.538 (1.019, 2.322) | 0.495 |
| SOFA      |           |           |           |           |               |
| 0.0-4.0   | 2013      | 1.656 (1.118, 2.452) | 1.457 (0.877, 2.420) | 1.417 (0.726, 2.767) | 0.103 |
| 4.0-20.0  | 2013      | 1.228 (0.923, 1.635) | 1.213 (0.873, 1.686) | 1.532 (1.021, 2.299) |
| CKD       |           |           |           |           |               |
| 0         | 3522      | 1.205 (0.937, 1.550) | 1.200 (0.886, 1.627) | 1.346 (0.931, 1.946) | 0.016 |
| 1         | 504       | 2.314 (1.173, 4.565) | 1.544 (0.755, 3.158) | 1.400 (0.479, 4.095) |
| Malignancy|           |           |           |           |               |
| 0         | 3244      | 1.226 (0.936, 1.607) | 1.218 (0.875, 1.696) | 1.268 (0.839, 1.917) | 0.016 |
| 1         | 782       | 1.765 (1.077, 2.891) | 1.453 (0.865, 2.441) | 2.305 (1.232, 4.312) |

HR (95%CI) were derived from the Cox hazard regression model. Covariates were adjusted as in adjusted model (Table 2).
The mechanism is thought to be associated with improved overall survival in cancer patients, even in those with impaired liver function. In patients with DIC, prolonged PT or aPTT, the application of fresh frozen plasma (FFP) may be useful, especially for patients with active bleeding.

A study about anticoagulant therapy shown LMWH improves overall survival in cancer patients, even in those with advanced disease. The mechanism is thought to be associated with heparan sulfate chains of cell surface and extracellular matrix proteoglycans, growth factors and their receptors, heparanase, selectins, and the ability to release tissue factor pathway inhibitor from endothelium.

No study had paid attention to the association between coagulation values and mortality. Coagulant index can be easily obtained as a conservative target in metabolic disorders. In the clinical physician may predict patients’ prognosis by these indicators. We also focused on the function of anticoagulant agents in critical diabetes patients.

There were several limitations to our study. First of all, MIMIC-III is a single-center database with limited generalizability. Secondly, we only concentrated on patients admitted to ICU but paid no attention to non-critical patients. Thirdly, insufficient information might lead to bias in the analysis—for example, species, doses and duration time of anticoagulants, the value of fibrinolysis and coagulant factors.

A cohort study about the association of coagulation values or anticoagulants between DM and without DM may further carry out. Although it is suggested that anticoagulants are beneficial to prognosis, more studies and monitoring of coagulation indicators are undoubtedly necessary. In the long term, whether non-critical patients had the same conclusion on the influence of coagulation values regarded to mortality, a multicenter should be in reality.

### Table 5. Subgroup Analysis of Using Anticoagulant.\(^a\)

| Group     | No Use drug (HR (95%CI)) | P for interaction |
|-----------|--------------------------|-------------------|
| Age       |                          |                   |
| 20.36-69.47 | 2013 0.730 (0.525, 1.014) | 0.061             |
| 69.47-301.28| 2013 0.726 (0.569, 0.925) | 0.010             |
| Gender    |                          |                   |
| Female    | 1682 0.687 (0.510, 0.926) | 0.014             |
| Male      | 2344 0.719 (0.554, 0.933) | 0.013             |
| SAPS-II   |                          |                   |
| 6.0-38.0  | 2013 0.742 (0.546, 1.007) | 0.055             |
| 38.0-114.0| 2013 0.660 (0.525, 0.831) | 0.000             |
| SOFA      |                          |                   |
| 0.0-4.0   | 2013 1.006 (0.696, 1.455) | 0.975             |
| 4.0-20.0  | 2013 0.607 (0.484, 0.762) | 0.000             |
| CKD       |                          |                   |
| 0         | 3522 0.723 (0.590, 0.887) | 0.002             |
| I         | 504 0.462 (0.240, 0.892) | 0.021             |
| Malignancy|                          |                   |
| 0         | 3244 0.724 (0.578, 0.907) | 0.005             |
| I         | 782 0.686 (0.454, 1.036) | 0.073             |

\(^a\)HR (95%CI) were derived from the Cox hazard regression model. Covariates were adjusted as in adjusted model (Table 2).

### Conclusions

Critical diabetes patients may benefit from anticoagulant agents, especially for age >70 years, high SOFA scores or SAPS II and CKD patients. APTT showed a U-shaped relationship with 30-day mortality. For age <70 years patients, the abnormality of coagulant function is related to a high risk of mortality. For age >70 years old, lightly increased PT may reduce odds of 30-day hospital death, but over hypo-coagulation state increases the risk of mortality.

### Authors’ Note

Yingxin Huang and Zhihua Zhong contributed equally to this work. Our institution does not require ethical approval for reporting individual cases or case series.

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