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Correlation of Dynamic D-dimer Levels with Mortality in COVID-19 Patients with Type 2 Diabetes Mellitus

Correlación de los niveles dinámicos de dímero D con la mortalidad en pacientes con COVID-19 y diabetes mellitus tipo 2

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SUMMARY

Background: *Hypercoagulation characterized by elevated D-dimer has been reported in COVID-19 patients. This condition is aggravated in Type 2 Diabetes Mellitus (T2DM) patients through various mechanisms. This study aimed to analyze the correlation of dynamic D-dimer levels with mortality in COVID-19 patients with T2DM.*
Methods: *This retrospective study was conducted by taking data on adult COVID-19 patients with T2DM. D-dimer levels were checked serially on days 1, 4, 7, 10 and the last examination before patients died or were discharged. Correlation analysis between D-dimer levels and mortality was performed at each examination.*
Results: *Of a total of 224 COVID-19 and T2DM patients, 26.3% were deceased. Median D-dimer days 1, 4, 7, 10, and last examination in survived patients were 870, 960, 930, 885, 770 and deceased patients were 2 640, 2 620, 3 790, 3 440, 3 520, respectively. Patients who died had consistently higher D-dimer levels across all examinations ($p<0.01$). The results from ROC analysis to predict mortality showed that the highest AUCs obtained on day 10 and at the last examination were 0.87 and 0.92, respectively. Similar results were found in correlation analysis with contingency coefficients 0.447 and 0.523, respectively.*
Conclusion: *Dynamic D-dimer correlates with mortality in COVID-19 patients with T2DM.*

Keywords: *COVID-19, Diabetes Mellitus, D-dimer, Mortality*

RESUMEN

Antecedentes: *Se ha reportado hipercoagulación caracterizada por dímero D elevado en pacientes con*

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COVID-19. Esta condición se agrava en pacientes con diabetes mellitus tipo 2 (T2DM) a través de varios mecanismos. Este estudio tuvo como objetivo analizar la correlación de los niveles dinámicos de dímero D con la mortalidad en pacientes con COVID-19 con DM2.
Métodos: *Este estudio retrospectivo se realizó tomando datos de pacientes adultos con COVID-19 con DM2. Los niveles de dímero D se comprobaron en serie los días 1, 4, 7, 10 y el último examen antes de que los pacientes murieran o fueran dados de alta. En cada examen se realizó un análisis de correlación entre los niveles de dímero D y la mortalidad.*
Resultados: *De un total de 224 pacientes con COVID-19 y DM2, el 26,3 % fallecieron. La mediana de los días 1, 4, 7, 10 del dímero D y el último examen en pacientes sobrevivientes fue 870, 960, 930, 885, 770 y los pacientes fallecidos fueron 2 640, 2 620, 3 790, 3 440, 3 520, respectivamente. Los pacientes que fallecieron tenían niveles de dímero D consistentemente más altos en todos los exámenes (p<0,01). Los resultados del análisis ROC para predecir la mortalidad mostraron que las AUC más altas obtenidas el día 10 y en el último examen fueron 0,87 y 0,92, respectivamente. Resultados similares se encontraron en el análisis de correlación con coeficientes de contingencia de 0,447 y 0,523, respectivamente.*
Conclusión: *El dímero D dinámico se correlaciona con la mortalidad en pacientes con COVID-19 con DM2.*

Palabras clave: *COVID-19, diabetes mellitus, dímero D, mortalidad.*

INTRODUCTION

Corona Virus Disease-19 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). COVID-19 has become a global burden since it was first reported in Wuhan, China, with the number of cases continuing to increase. Various kinds of variants due to mutations have contributed greatly to the increase in COVID-19 cases. Until October 2022, it was reported that the total number of COVID-19 worldwide had reached more than 600 million cases, while in Indonesia more than 6 million cases (1).

Diabetes mellitus is the second most common comorbidity in COVID-19 patients after hypertension, reaching 35.4 %. Diabetes has been known to increase the severity and mortality of COVID-19 (1). A variety of biomarkers are currently used to predict the mortality outcome from COVID-19. D-dimer is a hypercoagulation marker that has long been used in deep vein thrombosis and pulmonary embolism cases and is currently in COVID-19 (2,3). Diabetes mellitus and COVID-19 are closely related to hypercoagulable conditions through overlapping pathophysiological mechanisms (4). The pro-inflammatory conditions in these diseases can induce immunothrombosis. The SARS-CoV-2 virus can directly invade endothelial cells resulting in endothelial dysfunction (5,6), while diabetes also causes endothelial dysfunction due to chronic hyperglycemia and oxidative stress (7). Another mechanism is through the renin-angiotensin system, where ACE2 downregulation in COVID-19 will increase angiotensin-II and decrease angiotensin-1-7 (8), while diabetic patients also have activation of the renin-angiotensin system (9). In the end, pro-inflammatory conditions, endothelial dysfunction, and increased angiotensin-II will lead to a hypercoagulable state.

Inflammatory conditions and coagulopathy in COVID-19 are dynamic processes, where in severe cases, this process can continue and is characterized by an increase in various biomarkers. This study aimed to analyze the correlation between dynamic D-dimer levels and mortality in confirmed COVID-19 patients with diabetes. To our knowledge, this is the first study to analyze this correlation in a population of COVID-19 patients with diabetes.

METHODS

Study Design, Participants, and Data Collection

We conducted a retrospective, analytical study in Dr. Soetomo General Hospital Surabaya, a tertiary referral hospital in Indonesia. A total of 224 patients diagnosed with COVID-19 and type 2 diabetes mellitus (T2DM) from August 1, 2020, to July 31 2021 were enrolled in this study. This study used secondary data taken from medical records.

The diagnosis of COVID-19 was confirmed through a real-time reverse transcriptase-

polymerase chain reaction (RT-PCR), while T2DM was confirmed from past history or HbA1c more than 6.5 at the time of hospitalization. We only included patients hospitalized for at least 7 days, so serial D-dimer data could be obtained. Exclusion criteria included pregnancy, cancer, trauma, history of venous thromboembolism or use of anticoagulants, and incomplete medical record data.

Patients were divided based on the mortality outcome at the end of hospitalization into survived and deceased patients. Data were collected including demographic, symptoms, onset, comorbidities, and laboratory results. Routine laboratory tests such as complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), serum electrolytes, C-reactive protein (CRP), procalcitonin, albumin, blood glucose level, and HbA1c were collected on the admission (day 1). D-dimer levels were collected at five-time points: day 1, 4, 7, 10, and the last examination before the patient died or was discharged. We labeled those as DD 1, DD 4, DD 7, DD 10, and DD last. D-dimer was analyzed using Sysmex CS-2500 with units of nanogram/milliliter (ng/mL).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 for Windows (IBM, Armonk, NY, USA). All data are presented as number (n) and percentage (%) for categorical, median, and range for continuous variables. The normality of data distribution was tested using Kolmogorov-Smirnov. The difference between the two groups was compared using an independent t-test or Mann-Whitney U test as appropriate. The receiver operating curve (ROC) was constructed to evaluate the D-dimer levels in predicting death. The area under the curve (AUC) was calculated, with higher values indicating better discriminatory ability. The correlation between D-dimer level and mortality was assessed by the contingency coefficient, and the odds ratio (OR) was assessed using the optimal cut-off value from the ROC curve. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Demography, clinical characteristics, and laboratory results

A total of 224 patients with COVID-19 and T2DM were included in this study. 165 (73.7 %) patients survived until hospital discharge, while 59 (26.3 %) died. The median age was 54 (25-83) years, male patients were 51.3 %. Most of the patients had a history of diabetes of fewer than 5 years and were first diagnosed during hospitalization. The most common comorbidity was hypertension, followed by chronic kidney disease, coronary artery disease, and others. The median length of hospitalization was 6 days and the length of stay for most patients was more than 14 days. Among survived patients, 53.9 % were severe cases, and all deceased patients were severe cases. Demographic data and clinical characteristics of the patients can be seen in Table 1.

The patient's laboratory results at admission can be seen in Table 2. The blood glucose showed higher results in deceased patients (257 vs. 233), while HbA1c was higher in survived patients (8.6 vs. 9.3). Several inflammatory markers were higher in deceased patients including white blood cells (9.12 vs 8.39), neutrophils (7.56 vs 6.49), NLR (7.6 vs 5.4), CRP (10.7 vs 8), and procalcitonin (0.37 vs 0.2).

Dynamic D-dimer changes based on mortality outcome

In our study, D-dimer values were obtained from all patients on DD 1, DD 4, DD 7, and DD last (survived patients 165 vs. deceased patients 59), but on DD 10 several patients had been discharged or died (survived patients 130 vs. deceased patient 36). The results of our study showed that deceased patients had higher median D-dimer levels than survived patients consistently across all examinations. The difference is statistically significant with p value < 0.001 (Table 3).

Table 1. Clinical characteristics of COVID-19 patients with T2DM on the initial admission

Variable	**All patients (N = 224)**	**Survived (N = 165)**	**Death (N = 59)**
Age (years)			
Median (range)	54 (25-83)	54 (25-82)	56 (32-83)
Sex			
Male	115 (51.3 %)	84 (50.9 %)	31 (52.5 %)
Female	109 (48.7 %)	81 (49.1 %)	28 (47.5 %)
Diabetes onset, years (mean±SD)	3.63±4.65	3.56±4.84	3.81±4.10
First diagnosed	72 (32.1 %)	57 (34.5 %)	15 (25.4 %)
< 5 years	92 (41.1 %)	64 (38.8 %)	28 (47.5 %)
5-10 years	31 (13.8 %)	23 (13.9 %)	8 (13.6 %)
> 10 years	29 (12.9 %)	21 (12.7 %)	8 (13.6 %)
Comorbidity			
Hypertension	89 (39.7 %)	59 (35.8 %)	30 (50.8 %)
CKD	13 (5.8 %)	6 (3.6 %)	7 (11.9 %)
CAD	11 (4.9 %)	7 (4.2 %)	4 (6.8 %)
Stroke	9 (4.0 %)	6 (3.6 %)	3 (5.1 %)
Chronic pulmonary disease	11 (4.9 %)	9 (5.5 %)	2 (3.4 %)
Hepatitis B	10 (4.5 %)	8 (4.8 %)	2 (3.4 %)
Symptom onset, days			
Median (range)	6 (2-14)	6 (2-14)	6 (3-14)
Symptom			
Cough	171 (76.3 %)	125 (75.8 %)	46 (78.0 %)
Shortness of breath	153 (68.3 %)	108 (65.5 %)	45 (76.3 %)
Fever	136 (60.7 %)	98 (59.4 %)	38 (64.4 %)

CAD: coronary artery disease; CKD: chronic kidney disease

Table 2. Laboratory findings of the COVID-19 patients with T2DM on the initial admission

Laboratory Median (range)	All patients (N = 224)	Survived N = 165)	Death (N = 59)
Hemoglobin (g/dL)	13.3 (6.7-16.8)	13.3 (7.1-16.8)	13.1 (6.7-16.7)
White blood cells (x10^9/L)	8.61 (2.72-42.97)	8.39 (2.72-26.09)	9.12 (3.74-42.97)
Neutrophil (x109/L)	6.76 (1.93-41.34)	6.49 (1.93-23.77)	7.56 (2.64-41.34)
Lymphocyte (x10^9/L)	1.11 (0.30-3.39)	1.15 (0.30-3.04)	1.03 (0.51-3.85)
Platelet (x10^9/L)	258 (16-980)	268 (16-712)	232 (95-980)
BUN (mg/dL)	15 (2-110)	14 (2-90)	23 (5-110)
Creatinin (mg/dL)	1.0 (0.4-15.6)	0.9 (0.4-10.8)	1.3 (0.4-15.6)
AST (U/L)	49 (13-233)	46 (13-233)	65 (18-226)
ALT (U/L)	43 (8-368)	40 (8-368)	46 (14-320)
Plasma glucose (mg/dL)	236 (20-624)	233 (20-590)	257 (83-624)
HbA1c (g%)	8.9 (5.5-19.7)	9.3 (5.6-19.7	8.6 (5.5-17.3)
NLR	5.9 (1.1-43.7)	5.4 (1.5-35)	7.6 (1.1-43.7)
CRP (mg/L)	9.0 (0.1-37.9)	8.0 (0.1-37.9)	10.7 (0.9-37)
Prokalsitonin (ng/mL)	0.23 (0.01-100.00)	0.2 (0.01-3.63)	0.37 (0.01-100.00)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio

Table 3. D-dimer results on serial examination during hospitalization

D-dimer, median (ng/mL)	Survived (N = 165)	Death (N = 59)	p-value
DD 1	870	2 640	< 0.001
DD 4	960	2 620	< 0.001
DD 7	930	3 790	< 0.001
DD 10	885	3 440	< 0.001
DD last	770	3 520	< 0.001

Survived patients had relatively stable dynamic D-dimer changes in the range of 500-1 000 ng/dL, while the deceased patient had a sharp increase in D-dimer on day 7, followed by a slight decrease on day 10. On the last examination, D-dimer levels were not much different from day 10 (Figure 1).

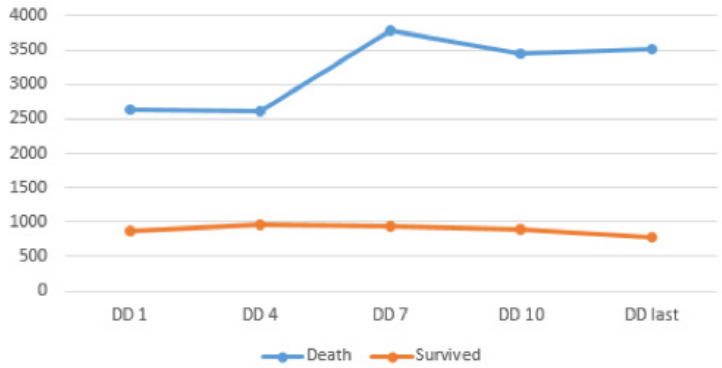

Figure 1. Dynamic D-dimer levels changes (in ng/dL) in COVID-19 patients with T2DM during hospitalization.

Correlation of dynamic D-dimer levels with mortality

The area under the curve of D-dimer levels on DD 1, DD 4, DD 7, DD 10, and DD last is shown in Figure 2 and Table 4. All of them show values more than 0.7, indicating good predictive values for mortality. Apparently, the higher AUCs were obtained with increasing examination time, from 0.759 on DD 1 to 0.865 on DD 10, also the highest AUC was obtained at DD last (0.920). We didn't show the AUC of DD 10 in Figure 2 because of the different numbers of patients.

D-dimer cut-off values as the optimal threshold for predicting mortality in COVID-19 patients with diabetes were shown in Table 4. The correlation of dynamic D-dimer levels with mortality can be seen from the contingency coefficient and odds ratio. In our study, we found a correlation between D-dimer and mortality better

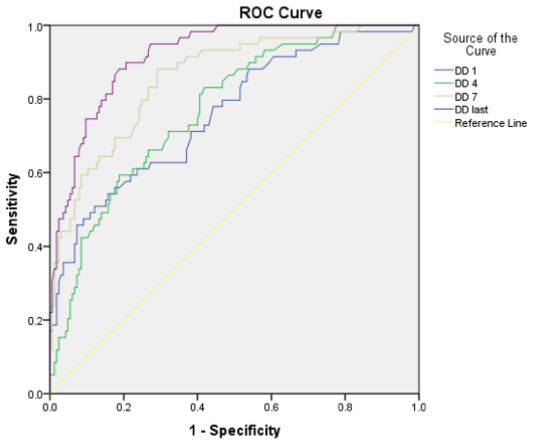

Figure 2. ROC curves of dynamic D-dimer as a predictor of mortality.

on later examinations. Contingency coefficient and OR were obtained respectively on DD 1 0.25 and 3.33 (1.78-6.21), then continued to increase until DD 10 0.45 and 13.35 (5.47-32.6). The highest value was obtained at DD last. All correlation analyses had p< 0.001.

Table 4. AUCs, cut-off values, and correlation analysis between dynamic D-dimer levels with mortality

D-dimer	AUC	Cut off	OR	Contingency coefficient	P value
DD 1	0.759	1 225	3.33 (1.78-6.21)	0.250	< 0.001
DD 4	0.772	1 560	5.22 (2.72-10.01)	0.329	< 0.001
DD 7	0.858	1 770	11.06 (5.43-22.52)	0.438	< 0.001
DD 10	0.865	1 520	13.35 (5.47-32.6)	0.447	< 0.001
DD last	0.920	1 565	23.98 (10.86-52.95)	0.523	< 0.001

Abbreviations: AUC, area under the curve; OR, odds ratio

DISCUSSION

This study was conducted in a referral hospital, so most of the patients were severe cases, thus contributing to the high mortality rate (26.3 %). This result is different from several studies in China which reported about 60 % were non-severe cases (10,11). The median age in this study is consistent with a meta-analysis study (12) but differs from a multicenter study in France (CORONADO study) that showed an older mean age (69.8±13.0 years) (13). Our study also found patients with relatively young age who already had diabetes, with the youngest being 25 years old. Type 2 diabetes mellitus at a young age is currently a burden with an increasing trend and is associated with lifestyle, obesity, and some non-modifiable factors such as genetics.

Most of the patients in our study had a history of diabetes for less than 5 years, followed by a first diagnosed diabetes reaching 32.1 %. A study in China reported slightly different results in first-diagnosed diabetes of 20.8 %, while the CORONADO study reported a mean duration of diabetes of 13.6±10.9 years, with first-diagnosed diabetes only 3.1 % (13). The higher rate of first-diagnosed diabetes compared to other studies is because this condition is more common in developing countries. Indonesia ranks third in the country with the highest number of newly diagnosed diabetes in the world, which is 14.3 million people (14). Another contributing factor is the possibility of COVID-19-induced diabetes, where the invasion of the SARS-CoV-2 on pancreatic beta cells can cause acute disturbances of insulin secretion or even destruction of the beta cells (15). A large number of patients with first-diagnosed diabetes is a burden, especially in developing countries like Indonesia, where new patients are often diagnosed with very high HbA1c levels or various complications. When these patients suffer from COVID-19, they are at a higher risk of experiencing a worse outcome.

The most common comorbidity in our study was hypertension. A meta-analysis reported hypertension reaching 21.4 % in COVID-19 patients (16), Cariou et al. even reported a very high rate of 77.2 % (13). The next most common comorbidities are CKD, CHD, and stroke, with a prevalence of less than 10 %. These three diseases are micro-vascular and macro-vascular complications of T2DM. COVID-19 patients with diabetes have more comorbidities than those without diabetes (17). These conditions also contribute to a higher mortality rate in COVID-19 patients with diabetes due to the higher risk of coagulopathy and organ dysfunction.

We found a high glycemic profile with plasma glucose > 200 and HbA1c > 8.5. A cohort study in the UK showed poor glycemic control before hospital admission and HbA1C levels were associated with higher mortality

in COVID-19 patients (18), however, the CORONADO study reported no association between them (13). The severity of COVID-19 is related to the dysregulated immune response, resulting in a cytokine release syndrome characterized by an increase in pro-inflammatory cytokines, and this condition is exacerbated by hyperglycemia. Patients with COVID-19 with diabetes have decreased lymphocytes and increased neutro-phils, interleukin-6, ferritin, and CRP (19). Finally, diabetes and hyperglycemia in COVID-19 are associated with the worsening condition, Acute respiratory distress syndrome (ARDS), and mortality (20). Glucose-lowering agents, especially insulin, play an important role in the management of COVID-19 with diabetes, especially in hospitalized patients where metabolic stress is generally more severe (19,21). Therefore, it is essential to closely monitor and manage blood glucose levels in COVID-19 patients with diabetes to reduce complications and mortality.

D-dimer levels in our study were consistently higher in deceased patients than in survived patients across all examinations. Long et al. reported similar results to our study, in which D-dimer was examined at baseline, days 3-5, and composite endpoints. D-dimer levels were higher in deceased patients than survived patients, and also higher in later examinations (22). We found that D-dimer levels of survived patients tended to be stable in the range of 500-1000 ng/mL, while deceased patients increased on day 7 and decreased slightly on day 10. Huang et al. reported different results, D-dimer levels on days 1, 3, 7, and 15 continued to increase in deceased patients (23). The clinical course of COVID-19 can be divided into three phases, starting at the beginning of infection (phase 1), then sometimes progressing to pulmonary involvement (phase 2), and less frequently experiencing systemic inflammation (phase 3). Severe COVID-19 occurs in phase 3 which is characterized by cytokine release syndrome, coagulopathy, and ARDS. Phase 2 generally occurs 5-7 days after onset. In the next 5-7 days, a small proportion (about 10 %-15 %) of patients progress to phase 3 which can be fatal, with mortality estimated at 20-30 % (24). In our study, patients presented to the hospital at a median of 6 days of symptom onset. Deceased patients may present in a severe condition (phase 3) so the D-dimer has a high initial value, although some patients may present in phase 2 which progresses to phase 3 and die. By day 7, all patients should be in phase 3 which may explain the increase in D-dimer compared to days 1 and 4.

We performed the ROC analysis to predict mortality in COVID-19 patients with diabetes and determine the cut-off levels on serial D-dimer tests. The cut-off values of the D-dimer can be seen in table 3. The ROC curve analysis showed the AUC at DD 1, DD 4, DD 7, DD 10, and DD last were 0.759, 0.772, 0.858, 0.865, and 0.92, respectively. Our study also shows a significant correlation between dynamic D-dimer and mortality, with contingency coefficients 0.25, 0.329, 0.438, 0.447, 0.523, and odds ratios 3.33, 5.22, 11.06, 13.35, and 23.98, respectively. A meta-analysis reported that patients with high D-dimer levels were at increased risk of mortality with an OR 3.28 (3.00-3.58, $p< 0.001$). The cut-off value of D-dimer in that study varied from 500, 1 000, and 2 000, to more than 2 000 ng/mL (25). Long et al. made ROC curve analysis of D-dimer to predict mortality at days 1, 3-5, and composite endpoint with AUC results from 0.742, 0.818, and 0.851, respectively (22). We can see that D-dimer correlates with mortality better with increasing examination days. The best correlation was found at the last examination before the patient died or was discharged, but it could not be used as a predictor of death because of the uncertainty of the examination time.

The hypercoagulation associated with COVID-19 is a process involving the virus itself, immune response, and ACE2 dysregulation (5,26). The SARS-CoV-2 infection will activate an aggressive inflammatory response, especially in uncontrolled diabetes patients where the immune system is impaired, will trigger uncontrolled production of pro-inflammatory cytokines and even cytokine storms. This hyperinflammatory condition will induce endothelial damage and excessive thrombin formation (19). The longer the history of diabetes, the greater the risk of endothelial dysfunction and micro-vascular or macro-vascular complications, which results in an even greater hypercoagulable condition (27). In addition, organ damage and hypoxemia due to COVID-19 also stimulate thrombosis by

increasing blood viscosity and activating the hypoxia-inducible transcription factor-dependent signaling pathway, leading to decreased blood flow, endothelial dysfunction, and further inflammation (25).

The main causes of death in COVID-19 include ARDS, sepsis with organ failure, and septic shock (28). However, it should be noted that hypercoagulable conditions can contribute to various thrombosis manifestations that can lead to death. The thrombosis manifestations include pulmonary embolism, micro-thrombosis in the lungs or known as pulmonary intravascular coagulopathy, macro-thrombosis, and micro-thrombosis in other organs such as the brain, heart, liver, and even systemic thrombosis (29). In our hospital, most of the COVID-19 patients died from respiratory failure and organ failure due to sepsis. However, we did not find a diagnosis of pulmonary embolism because CT angiography was not performed. We believe that the incidence of a pulmonary embolism due to COVID-19 in our hospital is quite high considering the high number of patients who died from respiratory failure with very high D-dimer levels.

However, this study had several limitations, such as a relatively small sample size, limited available data from the medical record, and a single-center study in one referral hospital. For more accurate and precise results, and wider generalizability of the findings, prospective studies, and a larger sample size are required to confirm the findings further.

CONCLUSION

The results of this study showed that a hypercoagulation characterized by an elevated D-dimer was likely present in patients with COVID-19 and T2DM at the early stage. Hypercoagulation is strongly related to disease progression and mortality outcomes. This can be seen from the higher levels of D-dimer in deceased patients, and the tendency for relatively higher levels on later examination. Correlation analysis also showed a stronger correlation between D-dimer levels and mortality on later examination. Therefore, the D-dimer levels should be monitored as early as possible to detect hypercoagulation-related complications thereby decreasing the morbidity and mortality of COVID-19 patients, especially those with diabetes.

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Conflict of Interest

The authors have no conflict of interest to declare.

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