Analysis of D-dimer cut-off values for overt DIC diagnosis in exertional heat illness

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Abstract

The International Society on Thrombosis and Haemostasis (ISTH) scoring system has been used for diagnosing overt disseminated intravascular coagulation (DIC). However, the cut-off points of fibrin-related markers remain unclear. The ability of the ISTH DIC score and Multiple Organ Dysfunction (MODS) score to predict mortality in cases of exertional heat illness (EHI) was tested. In the process, 3 different D-dimer cut-off values for diagnosing overt DIC were evaluated.

Data were obtained on the first day of hospitalization for 76 patients with EHI. The DIC score was calculated according to the ISTH scoring system using 3 D-dimer cut-off values.

In predicting mortality, methods 1 and 2 had the same sensitivity and specificity, which were 85% and 73.2%, respectively. The sensitivity for method 3 was 70%. Furthermore, the specificity of the DIC score for method 3 was 89%, which was higher than that of the other 2 methods. The correlation coefficients of the DIC and MODS scores of these 3 methods were 0.757, 0.748, and 0.756, respectively. For the prediction of mortality, the area under the receiver operating characteristic (ROC) curve for the DIC scores of these 3 methods was 0.838, 0.842, and 0.85, respectively. Furthermore, the area under the ROC curve of the MODS score was 0.927.

The DIC score had a certain predictive power of a poor outcome of EHI patients, but this was not better than the MODS score. The present data may serve as a reference in selecting the appropriate D-dimer cut-off point for the ISTH DIC score.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, CK = Creatine Kinase, Cr = creatinine, DIC = disseminated intravascular coagulation, EHI = exertional heat illness, EHS = exertional heat stroke, FDPs = fibrinogen degradation products, FIB = fibrinogen, FRMs = fibrin-related marker, GCS = Glasgow Coma Scales, ISTH = International Society on Thrombosis and Haemostasis, MODS = Multiple Organ Dysfunction, NPV = negative predictive value, PLT = platelets, PPV = positive predictive value, PT = prothrombin time, ROC = receiver operating characteristic, ROC = receiver operating characteristic, SOFA = Sepsis-Related Organ Failure, TBil = total bilirubin, WBC = leukocyte.

Keywords: D-dimer, DIC score, disseminated intravascular coagulation (DIC), exertional heat illness (EHI)

1. Introduction

Exertional heat illness (EHI) results from dehydration and hyperthermia.[1] Exertional heat stroke (EHS) is the most serious EHI, which is characterized by elevated core temperature (usually

>40°C) and organ system failure, including circulatory failure and central nervous system dysfunction. The mortality for EHS ranges from 21% to 68%.[2,3]

Although the mechanism of tissue injury and death are not well-understood, bleeding and coagulopathy are commonly involved in EHI. Furthermore, the occurrence of disseminated intravascular coagulation (DIC) in heat illness is significantly associated with end-organ failure and poor outcome.[4,5]

Diagnostic criteria for DIC have been established by the International Society on Thrombosis and Haemostasis (ISTH), which created a definition and diagnostic scoring system for overt DIC.[6] The scoring system was established based on routinely available laboratory tests, including platelet count, prothrombin time, fibrin-related marker (D-dimer) or fibrinogen degradation products (FDPs), and fibrinogen. Studies have shown that for predicting DIC, the sensitivity and specificity of the DIC score was 93% and 98%, respectively.[7,8]

The severity of DIC may be associated with mortality.[9,10] In fact, several studies have demonstrated that the DIC score can more reliably predict the mortality of a subgroup of patients than measures such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Multiple Organ Dysfunction (MODS) Score, and the Sepsis-Related Organ Failure (SOFA) score.[6,11,12]

Although the fibrin-related marker (FRM) score is important for the diagnosis of overt DIC, the precise cut-off levels for moderate and strong increases in D-dimer have not been defined.[6,13]

Three sets of D-dimer cut-off values have been published. Hatada et al adopted 2.4 μg/ml and 22.0 μg/ml as D-dimer cut-off

values for contributing to 2 (moderate rise) and 3 (strong rise) points on the ISTH score.[14] Dempfle et al selected 1 μg/ml and 3 μg/ml as cut-off values, earning 2 and 3 points, respectively.[15] Furthermore, Horan et al adopted 0.39 μg/ml and 4 μg/ml as the cut-off points, respectively.[16] These 3 scoring methods were evaluated to calculate the DIC score and evaluate the sensitivity and specificity for poor outcomes in patients with EHI. The investigators also sought to determine the association of these 3 methods with the MODS score as well as the fatality for patients with EHI.

2. Materials and methods

A total of 76 male patients diagnosed with EHI, who were admitted to the Chinese People's Liberation Army General Hospital (39°54'20" N) from July 2005 to August 2014, were included in the present study (median age: 23.1 years old; range: 16–63 years old). Among these patients, 69 patients were soldiers, 4 patients were high school athletes, and the remaining patients included 2 climbers and an actor. Informed consent was obtained from all patients. In cases of impaired consciousness, the informed consent was obtained from family members, friends, or colleagues of the patient. This study was conducted in accordance with the declaration of Helsinki and approval from the ethics committee of the Chinese People's Liberation Army General Hospital. Data were collected within the first 3 hours of hospitalization, including prothrombin time (PT), fibrinogen, platelet count, and D-Dimer (Table 1). Patients who were alive at 28 days after admission were considered survivors.

The 4 laboratory components of the DIC score were determined through routine blood sampling and analyzed in the hospital clinical laboratory. PT was determined through photometric clot detection using a Dade Thrombrel S reagent. Platelet count was determined using an automated system (Sysmex CA-7000) and confirmed with Wright stained peripheral blood smears. The D-dimer titer was determined by latex agglutination using a diagnostic Innovance reagent, while fibrinogen was determined by automated fibrin clot detection using the Nanopia thrombin reagent. All procedures were performed according to the standard practices of our clinical laboratory.

Based on previous studies, 3 D-dimer cut-off values were chosen as the measurement of fibrin-related marker (FRMs) to calculate the ISTH score. This was performed as delineated in Table 1. The cut-offs are presented in Table 2. The DIC scores were calculated for each patient during the first 3 hours of hospitalization. According to the recommendation of ISTH, DIC

Table 2

Cutoff values of D-dimer for DIC Diagnostic Criteria.

	2 points	3 points
Method 1	0.9 μg/ml	3.1 μg/ml
Method 2	0.39 μg/ml	4 μg/ml
Method 3	2.4 μg/ml	22 μg/ml

scores ≥5 were considered "overt DIC." Therefore, each patients DIC score was categorized as ≥5 or <5.

Organ dysfunction was assessed using the MODS score for all patients within 3 hours of admission.

2.1. Statistical analysis

Significant differences between subgroups were tested using t-tests, Mann–Whitney U-tests, or Chi-Squared tests, as appropriate. A P-value of $<.05$ was considered statistically significant. Multiple logistic regression analysis was used to identify factors associated with mortality. The multivariate linear regression analysis was used to analyze the relationships of platelets (PLT), PT, fibrinogen, and D-dimer for the DIC score. Accuracy indices (sensitivity, specificity, negative predictive value [NPV] and positive predictive value [PPV]) were calculated for the DIC scores of the 3 methods against the 28-day outcome. The predicted probabilities of the scoring system were evaluated against the outcome using receiver operating characteristic (ROC) curves. In the present analysis, the power of the models predicted values was derived by calculating the area under the curve (AUC). r DIC scAll statistical analyses were performed using the SPSS 20.0 software package.

3. Results

A total of 76 patients (mean age: 23.12 ± 8.17) diagnosed with EHI were enrolled in the present study. Among these patients, 56 survived, while 20 (26.3%) patients died (Table 3). All patients were male and healthy prior to this episode. The difference in age was not statistically significant between survivors and non-survivors (22.5 ± 7.7 vs 24.8 ± 10.2 years old).

The temperature of all patients was elevated on admission, particularly in non-survivors. On admission, the Glasgow Coma Scales were significantly worse in non-survivors ($P<.05$). Furthermore, PT at admission were significantly longer ($P<.01$) in non-survivors, when compared with survivors, fibrinogen levels were lower ($P=.001$) in non-survivors, when compared

Table 1

International Society of Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) scoring system.

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

  If yes, proceed: if no, do not use this algorithm.

2. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, soluble fibrin monomers, or fibrin degradation products).

3. Score global coagulation test results.

Platelet count (>100, 0; <100, 1; <50, 2)

Elevated fibrin-related marker (e.g., soluble fibrin monomers/fibrin degradation products) (no increase, 0; moderate increase, 2; strong increase, 3)

Prolonged prothrombin time (<3 sec, 0; >3 sec but <6 sec, 1; >6 sec, 2)

Fibrinogen level (>1.0 g/l, 0; <1.0 g/l, 1)

4. Calculate score

If ≥5, compatible with overt DIC; repeat scoring daily;

  If <5, suggestive (not affirmative) of nonovert DIC; repeat next 1–2 days.

Table 3

Characteristics of enrolled EHI patients (mean±SD) on day of admission.

	Survival group (n=56)	Nonsurvival group (n=20)	P
Age	22.54±7.36	24.75±10.15	.301[a]
Tc(°C)	39.70±1.01	40.80±0.77	.000
PLT(×10^9/l)	128.01±68.81	99.5±72.63	.121[a]
PT (s)	22.53±9.68	50.94±12.61	.000[a]
FIB(g/l)	2.26±1.05	1.32±0.9	.001[a]
D-dimer(ug/ml)	1.72±2.08	4.08±2.06	.000[a]
CK(umol/l)	5719.5±15776.64	15362.93±17701.19	.026[a]
Cr(umol/l)	159.81±126.86	298.84±159.49	.000[a]
WBC(×10^{12}/l)	12.46±4.77	15.48±5.61	.023[a]
TBil(umol/l)	48.38±78.98	104.99±87.25	.09[a]
GCS	7.07±4.049	3.9±2.15	.000[b]

[a] t test.
[b] Mann–Whitney U test.
CK = Creatine Kinase, Cr = creatinine, FIB = fibrinogen, GCS = glasgow coma score, PLT = platelets, PT = prothrombin time, TBil = total bilirubin, WBC = leukocyte.

with survivors, and D-dimer levels were higher ($P < .001$) in non-survivors, when compared with survivors. Moreover, there was no significant difference in initial platelet count between these 2 groups of patients ($P = .121$).

The differences in serum creatinine, creatine kinase levels, and leucocyte counts were all statistically significant between non-survivors and survivors on admission (Table 3).

The results of multiple regression analyses showed that hospital mortality was significantly associated with DIC score: method 1 DIC score (odds ratio: 1.694; 95% CI: 1.125–2.551; $P = .012$); method 2 (odds ratio: 1.852; 95% CI: 1.158–2.962; $P = .01$), method 3 (odds ratio: 1.752; 95%CI: 1.185–2.590; $P = .005$) (Table 4).

According to the scoring system suggested by the DIC subcommittee of the ISTH, DIC scores were calculated on the first day. Regardless of which cut-off was applied, the DIC scores were higher in non-survivors and were similar to the MODS scores (Table 5).

However, the calculation of DIC scores was significantly different among these 3 methods. A high degree of correlation between DIC scores calculated using methods 1 and 2 was noted,

Table 5

Admission ISTH DIC scores and MODS of enrolled EHI patients (mean±SD).

	Survival group	Non-survival group	P
DIC score			
Method 1	3.07±2.21	5.85±1.46	.000
Method 2	3.29±2.17	5.95±1.23	.000
Method 3	2.16±1.86	4.8±1.58	.000
MODS score	5.88±3.96	13.2±2.09	.000

Mann–Whitney U test.

and the correlation coefficient was 0.962. The correlation coefficient was 0.935 between methods 1 and 3 and 0.928 between methods 2 and 3 (Fig. 1).

Multivariate linear regression analysis for DIC scores showed that the influence on the DIC score of D-dimer and PT was superior to the other 2 factors, while PLT had less of a contribution to the results than fibrinogen in methods 1 and 2 (Table 6).

The cut-off values in method 3 were far higher than those in methods 1 and 2. None of the scores incorporated the full 3 points for the D-dimer when using method 3, and more patients had zero points than when the other 2 methods were used ($P < .05$, Table 7).

Although the scores were significantly different in these 3 methods, methods 1 and 2 reported identical results in terms of the categorization of overt DIC. The present study revealed that 32 of 76 (42.1%) patients were diagnosed with overt DIC using methods 1 and 2. When method 3 was used, 20 of 76 (26.3%) patients were diagnosed with overt DIC, which was significantly less than the 2 other methods ($P < .05$). For the survivors, 15/56 (26.7%) patients were diagnosed with overt DIC using method 1 or 2. When method 3 was used, 6/56 (10.7%) of survivors were diagnosed with overt DIC.

For predicting mortality, the sensitivity and specificity of DIC scores using methods 1 and 2 were the same: 85% and 73.2%, respectively. The sensitivity of the DIC score using method 3 was 70%, and there was no significant difference among these 3 methods ($P > .05$). The specificity of the DIC score for method 3 was 89.3%, and the difference was statistically significant when

Table 4

Logistic regression analysis on prognosis of EHS patients.

	B	SE	OR	P	95%CI
1					
GCS	−0.332	0.178	0.717	.062	0.506–1.017
Cr	0.004	0.003	1.004	.086	0.999–1.009
WBC	0.08	0.073	1.083	.275	0.938–1.251
Method 1 DIC score	0.527	0.209	1.694	.012	1.125–2.551
2					
GCS	−0.348	0.184	0.706	.059	0.492–1.013
Cr	0.004	0.003	1.004	.09	0.999–1.009
WBC	0.081	0.073	1.084	.269	0.939–1.251
Method 2 DIC score	0.616	0.240	1.852	.01	1.158–2.962
3					
GCS	−0.342	0.179	0.711	.057	0.500–1.010
Cr	0.004	0.003	1.004	.108	0.999–1.009
WBC	0.089	0.074	1.093	.232	0.945–1.264
Method 3 DIC score	0.561	0.200	1.752	.005	1.185–2.590

B = Unstandardized Coefficients, CI = confidence interval, Cr = creatinine, GCS = glasgow coma score, OR = odds ratio, SE = Std. Error, WBC = leukocyte.
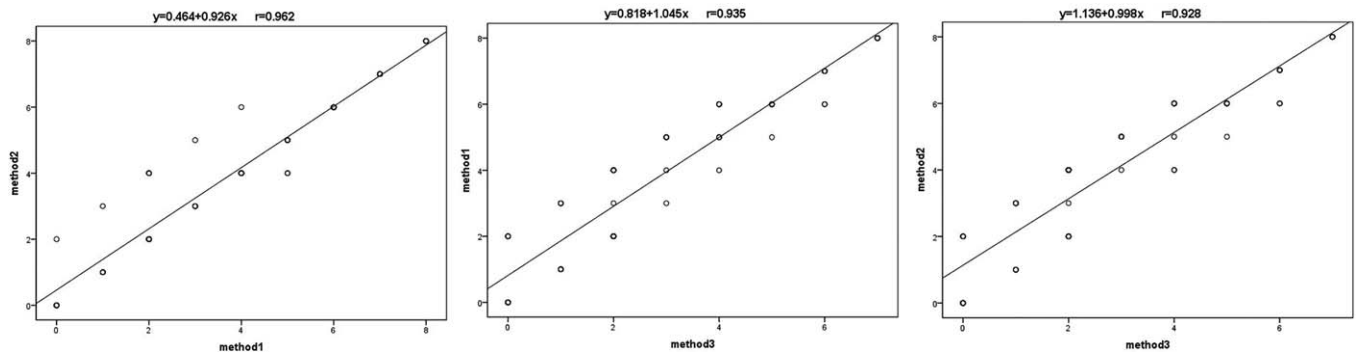
Figure 1. Correlation graphs for 3 method DIC scores (R=0.962 for methods 1 and 2, R=0.935 for method 1 and 3, R=0.928 for methods 2 and 3, P<.05).

Table 6

Multivariate Linear regression Analysis for the DIC score.

	B	Std. Error	Beta	P
Method 1				
PLT	−0.007	0.002	−0.200	.002
PT	0.071	0.011	0.524	.000
FIB	0.577	0.123	0.287	.000
D-dimer	0.575	0.086	0.411	.000
Method 2				
PLT	−0.006	0.002	−0.191	.004
PT	0.063	0.011	0.477	.000
FIB	0.458	0.124	0.234	.000
D-dimer	0.575	0.086	0.411	.000
Method 3				
PLT	−0.006	0.002	−0.240	.000
PT	0.053	0.009	0.511	.000
FIB	0.273	0.1	0.175	.008
D-dimer	0.567	0.07	0.523	.000

Adiust R squre=0.913 for method 1, P=.000; Adiust R squre=0.907 for method 2, P=.000.
Adiust R squre=0.905 for method 3, P=.000.
B = Unstandardized Coefficients, Beta = Standardized Coefficients, FIB = Fibrinogen, PLT = platelet, PT = prothrombin time.

compared with the other 2 methods (P < .05). The PPV of the DIC score using methods 1 and 2 was 53.1%, and the difference was not statistically significant compared with the PPV determined using method 3 (70%, P > .05). The difference in NPV using methods 1 and 2 was statistically significant when compared with that using method 3 (93.2% vs 89%, respectively; P > .05).

The MODS score was associated with the DIC score, and the correlation coefficients between the DIC and MODS scores were as follows: R = 0.757 for method 1, R = 0.748 for method 2, and R = 0.756 for method 3 (Fig. 2).

In analyzing the receiver operating characteristic curve (ROC) for predicting mortality, the areas under the ROC curve of the

DIC scores for methods 1 and 2 were 0.838 and 0.842, respectively. The area under the ROC curve for method 3 was 0.85. The area under the ROC curve for the MODS score was 0.927 (Fig. 3).

4. Discussion

Previous studies have shown that heat stress illness can induce coagulation activation and fibrin formation.[5,17,18] The increasing level of D-dimer and decreased level of fibrinogen reflect the fibrinogen deposits in small and midsize vessels, and this process contributes to organ dysfunction. Thrombocytopenia together with prolonged PT and FRMs reflect the potential for overt DIC in these patients.[19] In the study, fibrinogen and D-dimer levels were significantly higher in the non-survival group than in the survival group. Multivariate linear regression analysis for DIC score in 3 methods showed that both fibrinogen and D-dimer contribute to the results, confirming that fibrin-related markers are the most useful markers for the diagnosis of DIC. This finding differs from other research findings.[20]

Fibrin-related markers are very important for making a diagnosis of DIC, but the cut-off values of FRMs have not yet been clearly established in ISTH overt DIC diagnostic criteria. The present study demonstrates that different D-dimer cut-off values (as FRM) result in different calculated DIC scores. However, in predicting the 28-day mortality, the sensitivity and specificity were the same when 0.39 μg/ml and 4 μg/ml, or 1.0 μg/ml and 3.3 μg/ml, were used as the D-dimer cut-off points. These cut-off levels were so close that the categorical diagnosis of overt DIC was proven to be similar. Selecting 2.4 μg/ml and 22.0 μg/ml as cut-off values increased the specificity but did not have a significant difference in sensitivity for the outcome of mortality at 28 days.

In the present study, it was found that the severity of DIC, as indicated by higher DIC scores, was associated with the severity

Table 7

Number of patients for different Scores of D-dimer of 3 method.

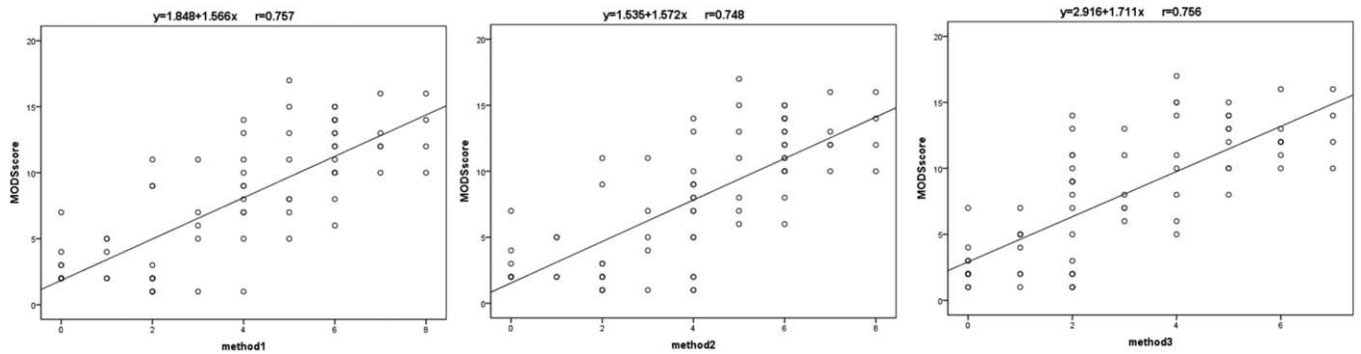|	Method 1			Method 2			Method 3		
	0 point	2 point	3 point	0 point	2 point	3 point	0 point	2 point	3 point
survivor	24	23	9	17	32	7	5	15	0
nonsurvivor	1	6	13	0	7	13	45	11	0
total	25	29	22	17	39	20	50	26	0

Figure 2. Correlation graphs for MODS scores and 3 method DIC scores (R = 0.757 for method 1, R = 0.748 for method 2, and R = 0.756 for method 3, $P < .05$).

of MODS and mortality. But the area under the ROC curves of the MODS scores was greater than that of the DIC scores. For predicting mortality in EHI patients, MODS scores appear to be better than DIC scores, regardless of which DIC scoring method was employed. This finding can help quantify the common opinion that DIC has an effect on mortality in patients with EHI. Coagulation dysfunction may participate in the development of organ failure by promoting inflammatory reactions, endothelial cell injury, and thrombosis. In order to reduce the

mortality associated with DIC in EHI patients, the early diagnosis of DIC in the course of the disease is likely important, with the hope that earlier treatment would improve the clinical outcome.

In terms of D-dimer cut-off values for ISTH overt DIC scores, patients in previous studies suffered from sepsis, trauma, or tumors.[14,15,16] Most of them were much older than the population in the present study and had confounding conditions. In contrast, the present patients that suffered from EHI were
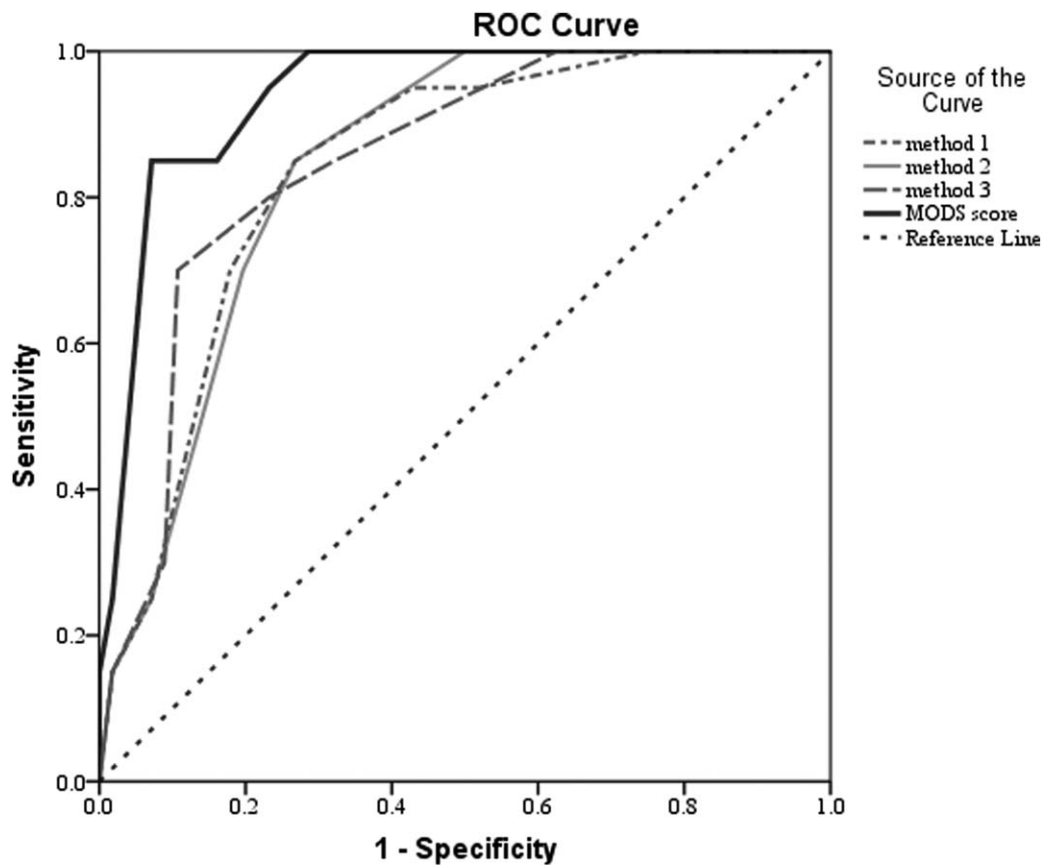

Figure 3. ROC curve of DIC score 1, DIC score 2, DIC score 3, and MODS score (the area under the ROC curve of the DIC scores for methods 1, 2, and 3 were 0.838, 0.842, 0.85. The area under the ROC curve for the MODS score was 0.927).

5

young and healthy. The D-dimer cut-off values described in the previous literature may not be appropriate for EHI patients.

The limit of the study was that it did not include non-exertional heat stress patients, compared to EHI patients. The age of patients with non-exertional heat stress was relatively old and had many complications. At present, there are few studies on the coagulation function of non-exertional heat stress patients. Whether there was more serious coagulation dysfunction is unknown.

In conclusion, DIC scores can predict mortality in patients suffering from EHI, since they predict poor outcome in patients with infections.[21] Furthermore, it was found that higher D-dimer cut-off values lead to increased degrees of specificity, but with decreasing sensitivity. Regarding the high-risk of mortality for EHS patients complicated with DIC, early diagnosis and treatment may be helpful in the management of these patients. Lower D-dimer cut-off values may be better for diagnosing DIC.

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