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A multicenter, prospective evaluation of the Chinese Society of Thrombosis and Hemostasis Scoring System for disseminated intravascular coagulation

Lili Luo[a], Yingying Wu[a], Ting Niu[b], Yue Han[c], Ying Feng[d], Qiulan Ding[e,1], Ruibin Huang[f], Xiaohui Zhang[g,1], Jianming Feng[h], Ming Hou[i], Jun Peng[i], Yan Li[j], Yuhong Zhou[k], Lei Su[l], Linhua Yang[m], Zeping Zhou[n], Feng Xue[o], Jian Gu[p,1], Tienan Zhu[q], Xiaomin Wang[r], Jun Deng[a], Heng Mei[a,*,1], Yu Hu[a,*,1]

[a] Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[b] Department of Hematology, West China Hospital, Sichuan University, Chengdu 610041, China
[c] Department of Hematology, First Affiliated Hospital of Soochow University, Suzhou 215006, China
[d] Department of Hematology, Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, China
[e] Department of laboratory medicine, Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai 200025, China
[f] Department of Hematology, First Affiliated Hospital of Nanchang University, Nanchang 330006, China
[g] Department of Hematology, Peking University People's Hospital, Beijing 100044, China
[h] Department of Hematology, Qinghai Provincial People's Hospital, Xining 810007, China
[i] Department of Hematology, Qilu Hospital of Shandong University, Jinan 250012, China
[j] Department of Hematology, First Hospital of China Medical University, Shenyang 110001, China
[k] Department of Hematology, First Affiliated Hospital of Zhejiang Chinese Medical University, Zhejiang 310006, China
[l] Department of Intensive Care Unit, General Hospital of Guangzhou Military Command, Guangzhou 510010, China
[m] Department of Hematology, Second Hospital of Shanxi Medical University, Shanxi 030001, China
[n] Department of Hematology, Second Affiliated Hospital of Kunming Medical College, Kunming 650101, China
[o] Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China
[p] Department of Hematology, Clinical Medical College of Yangzhou University, Jiangsu 225001, China
[q] Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
[r] Department of Hematology, People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang 830001, China

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ABSTRACT

Introduction: Disseminated intravascular coagulation (DIC) is a severe complication of critical conditions. There are several scoring systems used for the diagnosis of DIC, including the International Society on Thrombosis and Hemostasis (ISTH) Overt-DIC criteria, the Japanese Ministry of Health and Welfare (JMHW) criteria and the Chinese Society of Thrombosis and Hemostasis scoring system for DIC (CDSS). The objective of this prospective study was to evaluate the accuracy and predictive value of the CDSS.

Materials and methods: 1318 patients, aged 18–70 years old and suspected of DIC were enrolled from 18 hospitals across China. Participants were divided into two groups for analysis (group 1, non-hematological diseases; group 2, hematological diseases). 242 patients were excluded because of incomplete data collection and failure to follow-up.

Results and conclusions: The rates of concordance of diagnosis of DIC between the CDSS and two other scoring systems were close to 80%. The area under ROC curves of CDSS had a slight advantage when using the ISTH, JMHW criteria or prognosis as gold standard, respectively. The CDSS DIC was an independent predictor of mortality, and its odds-ratio was superior or comparable to that of the ISTH and JMHW criteria in the two

Abbreviations: DIC, disseminated intravascular coagulation; CDSS, the Chinese Society of Thrombosis and Hemostasis scoring system for DIC; ISTH, the International Society on Thrombosis and Hemostasis; JMHW, the Japanese Ministry Health and Welfare; JAAM, the Japanese Association for Acute Medicine; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; ROC, receiver operating characteristic; AUC, area under ROC curves; PT, prothrombin time; FDP, fibrin/fibrinogen degradation product; APTT, activated partial thromboplastin time; ORs, odds ratios; CIs, confidence intervals; APS, anti-phospholipid syndrome; TTP, thrombotic thrombocytopenic purpura; HIT, heparin-induced thrombocytopenia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndromes

* Corresponding authors at: Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China.
E-mail addresses: hmei@hust.edu.cn (H. Mei), dr_huyu@126.com (Y. Hu).
[1] Collaborative Innovation Center of Hematology, Huazhong University of Science and Technology, Wuhan, Hubei 430022, PR China.

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groups. The CDSS DIC score also had a significant correlation with the APACHE II and SOFA score ($p < 0.05$). In summary, as a quantification standard of the Chinese experts' consensus, the CDSS is conducive to the standardized diagnosis of DIC because of its favorable diagnostic and prognostic utility.

1. Introduction

Disseminated intravascular coagulation (DIC) is a common and severe complication of critical conditions and is highly life-threatening. It presents with a broad spectrum of clinical signs, ranging from prothrombotic state to bleeding or both [1]. As an acquired syndrome resulting from a wide array of underlying diseases, DIC is characterized by systemic intravascular activation of coagulation, induced by and, in turn, deteriorating micro-vascular damage. At its worse, DIC can cause organ dysfunction and multiple hemorrhages [2–5]. Timely intervention and early treatment can significantly improve the outcome of DIC patients [6,7]. Hence, prompt recognition and diagnosis of DIC are essential. However, there is no unique clinical manifestation or laboratory test which can verify or deny a diagnosis of DIC with appropriate sensitivity and specificity [8].

Over the past decades, several DIC diagnostic scoring systems have been developed based on a combination of clinical and laboratory findings. Currently, the three primary diagnostic criteria for DIC are the Japanese Ministry Health and Welfare (JMHW) criteria [9], the International Society on Thrombosis and Homeostasis (ISTH) Overt-DIC criteria [2] and the Japanese Association for Acute Medicine (JAAM) criteria [10]. Many retrospective or prospective studies [9–20], have shown that these criteria are useful for DIC diagnosis, although it is still controversial whether they are optimal in terms of diagnostic and prognostic performance. Wada et al. concluded that the JMHW criteria had poor sensitivity for discerning infection-induced DIC [21]. The ISTH overt-DIC criteria had low sensitivity and high specificity for DIC diagnosed against the JMHW criteria, which could be further improved by adjusting the cut-off values of coagulation tests [11]. Even though it is more sensitive than the JMHW and the ISTH criteria in critically-ill patients, the JAAM criteria showed poor specificity and cannot be applied to all underlying diseases [10]. Thus, it might be confusing for clinicians to choose one optimal diagnostic system for the clinical diagnosis of DIC. Furthermore, the JAAM criteria have been modified by several teams from different perspectives. Toshiaki et al. replaced the systemic inflammatory response syndrome score with antithrombin activity in the JAAM criteria to discriminate DIC in patients with sepsis [22]. Yutaka et al. integrated two endothelial molecular markers into the JAAM criteria, to improve its predictive value in sepsis patients [23]. Besides, the Japanese Society on Thrombosis and Hemostasis proposed the addition of one newly modified diagnostic criteria for DIC based on the underlying pathology [21]. However, the molecule markers adopted in these latter three criteria are not available in most Chinese hospitals. Therefore, these standards have not been universally adopted to diagnose DIC in China.

As early as 1986, the first consensus of Chinese experts on DIC diagnosis was proposed and has been updated several times since [24]. These consensuses consist of qualitative but not quantitative rules, for combining clinical and laboratory findings. However, clinicians often interpret DIC symptoms differently, which makes clinical management quite challenging. Consequently, the rates of both missed diagnosis and misdiagnosis of DIC are high [25], leading to high mortality and medical cost. In 2014, the Chinese Society of Thrombosis and Hemostasis scoring system for DIC (CDSS) was proposed to ameliorate the status quo based on a combination of underlying diseases, clinical manifestations and several available routine coagulation tests [26]. One feature of the CDSS is that, it calculates DIC score separately in cases of hematological diseases. Based on the Chinese experts' consensus and retrospective data, a score of ≥6 is compatible with the diagnosis of DIC in patients with hematological diseases, and ≥ 7 in patients with other causes, respectively [26]. The retrospective study divided the subjects into two groups and then analyzed them independently (group 1: patients without hematological diseases; group 2: those with hematological diseases). That study showed that the CDSS had good diagnostic and prognostic value [26]. However, the study was a single-center retrospective study and further evaluations in multicenter, prospective studies were needed. In 2016, our core center led an eighteen-center prospective study, in which 1076 patients were finally admitted for analysis (753 in group 1 and 323 in group 2). The patients in group 1 were divided into infection group with infection and non-infection group with other underlying diseases [27]. Our study demonstrated that the CDSS has a potential to be developed as an excellent diagnostic and prognostic tool for DIC for both infectious and non-infectious patients [27]. However, the previous study did not enroll patients with hematological diseases. The present study compares the CDSS with two other diagnostic systems from a comprehensive perspective in a larger population with a broader range of pathologies and, demonstrates the potential utility and applicability of the CDSS.

2. Patients and methods

2.1. Ethics statement

This prospective study was performed according to the declaration of Helsinki and approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. During data collection, investigators and data managers were not involved in the clinical diagnosis and treatment of the patients, and the patients' information was kept confidential and de-identified for data management and statistical analyses. Written informed consent was obtained from the patients or, in some special cases, from their relatives.

2.2. Selection criteria

Patients suspected of suffering DIC (age 18–70 years old) with different underlying diseases were enrolled in eighteen medical settings throughout China. The subjects were divided into two groups - those without (group 1) and those with (group 2) hematological diseases [11,26,27]. The associated conditions in patients without hematological diseases (group 1) were the same as those in our previous study [27]. Patients in group 2 had various hematological diseases (including acute myelogenous leukemia [AML], acute lymphocytic leukemia [ALL], multiple myeloma, and lymphoma). The inclusion criteria were as previously described [27]: (1) platelet count ≤ 120×10^9/L (exception to patients in group 2), (2) prolongation of prothrombin time (PT) ≥ 3 s, (3) fibrin/fibrinogen degradation product (FDP) ≥ 10 mg/L, (4) D-dimer ≥ 5 mg/L, (5) fibrinogen ≤ 1 g/L. Patients with the following criteria were excluded [27]: liver cirrhosis classified as Child-Pugh grade C (score 10 or higher) [28], having anti-phospholipid syndrome (APS) based on at least one of the clinical and one of the laboratory criteria [29], thrombotic thrombocytopenic purpura (TTP) based on clinical history, examination and routine laboratory parameters [30], or heparin-induced thrombocytopenia (HIT). Establishing a diagnosis of HIT in patients with complicated medical conditions was challenging, especially in those undergone recent cardiac surgery. In the present study, patients highly suspected of HIT (> 60% chance) according to 4Ts score, were ruled out [31], because most centers in China cannot perform HIT immunoassays and so these were not used in the diagnosis of HIT. The DIC-related markers (PT, activated partial

thromboplastin time (APTT), D-dimer, FDP, PT ratio, fibrinogen) were measured via the STA-R Evolution analyzer using the manufacturer's reagents (Stago, France). Each study center performed their own assays independently.

2.3. DIC diagnosis and treatment

In this study, DIC was diagnosed using the ISTH, the JMHW and the CDSS criteria (Table 1). Abnormal bleeding in the CDSS and JMHW criteria referred to hemorrhage which could not be explained by the underlying diseases. To minimize subjective errors, two experts independently assessed abnormal bleeding. In case of disagreement, the opinion of a third expert was adopted as the final decision. Organ dysfunction defined as a Sequential Organ Failure Assessment (SOFA) score ≥ 2 that could not be explained by underlying diseases. The ISTH overt-DIC criteria did not initially establish definite cut-off values for a "moderately" or "severely" elevated result for the test for fibrin degradation products [2]. Subsequently, D-dimer was recommended as a fibrin-related marker, considering an increase up to 10 times the upper limit of normal (0.5 μg/mL) as moderate, and an increase above this threshold as strong [32]. In the ISTH criteria, D-dimer was used as a fibrin-related marker and was classified as no increase, moderate, or marked increase, which corresponds to D-dimer level < 0.5, 0.5–5, ≥5 (mg/L), respectively [32]. In the CDSS criteria, after the logistic regression determining the diagnostic value of each laboratory parameter and taking both sensitivity and specificity into account, D-dimer level at 5 mg/L and 9 mg/L were considered as critical [26]. The 28-day all-cause mortality was taken as a significant prognostic parameter because it was sometimes difficult to identify the definite causes of deaths in clinical practice. DIC and the underlying diseases or the other complications can form a vicious cycle, which finally results in death. The current primary reference for the treatment of DIC in China is still a consensus of Chinese experts (2012 version), which specifies principles (e.g. alleviating or removing the inciting cause, consideration of anticoagulant thrombosis prophylaxis in high risk patients without active bleeding, and blood component therapy to correct the underlying coagulopathy) but not standardized protocols [4,24,32]. Treatment should be adapted for the circumstances of the individual patient.

2.4. Data sampling and evaluation of patients

Relevant demographic, laboratory and clinical data were collected as previously described [27]. Patients' conditions were scored against the daily SOFA [33] and Acute Physiology and Chronic Health Evaluation (APACHE) II [34] during the monitoring periods. The SOFA score, which correlates with organ dysfunction in critical illnesses, is a globally-used estimation tool for morbidity and mortality [33]. The APACHE II score, closely associated with higher hospital mortality, is a classification system of disease severity [34]. All patients were followed for prognosis until day 28, and the 28-day all-cause mortality was evaluated. Fig. 1 shows the flow chart of this study.

2.5. Statistical analysis

All measurements were reported as the mean ± standard deviation. The data computation and statistical analyses were performed using SPSS 21.0. Comparisons between two groups were made with the unpaired Student's *t*-test for parametric data or Mann-Whitney's *U* test for nonparametric data. Proportions were compared by the *Chi*-square test or paired *Chi*-square test, or Fisher's exact test, if necessary. Receiver operating characteristic (ROC) curves were constructed to compare the diagnostic performance and prognostic value of the sets of the three scoring systems. The larger the area under ROC curves (AUC), the better the diagnostic or prognostic value. The relationship between outcome (dependent variables) and age, gender, or states of DIC diagnosed by one scoring system as explanatory variables, was assessed by binary logistical regression. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs). Correlation was evaluated using the Spearman's rank correlation coefficient. Survival curves were derived by using the Kaplan-Meier method. A value of $p < 0.05$ was considered statistically significant.

Table 1
Criteria for three DIC scoring systems.

Establish	Point	ISTH criteria	JMHW criteria	CDSS criteria
Underlying disease		Necessary	1 point	
Clinical presentation	1	-	■ Bleeding* (1 point) ■ Organ failure (1 point)	■ Abnormal bleeding* ■ Unexplained organ failure ■ shock or microcirculatory disorder ■ Independent of original disease ■ (meet anyone 1 point)
PT, PT ratio		Prolongation of PT	Prothrombin time ratio	Prolongation of PT and APTT
Prolongation of PT	0	< 3 s	≤1.25	PT < 3 s and APTT < 10 s
Prolongation of APPT	1	≥3 s	1.25–1.67	PT ≥ 3 s or APTT ≥ 10 s
	2	≥6 s	> 1.67	PT ≥ 6 s
Fibrin-related marker		D-dimer (ug/mL)	FDP (ug/mL)	D-dimer (μg/mL)
	0	< 0.5	< 10	< 5
	1	-	10–20	-
	2	0.5–5	20–40	5–9
	3	≥5	≥40	≥9
Fibrinogen level (g/L)	0	> 1	> 1.5	> 1
	1	≤1	1–1.5	≤1
	2	-	≤1	–
Platelet counts ($\times 10^3$/μL)	0	> 100	> 120*	> 100
	1	50–100	80–120*	80–100 or ≥50% decrease within 24 h(#)
	2	< 50	50–80*	< 80
	3	-	≤50*	-
Diagnosis of DIC		≥5 points	■ Group 1: ≥7 points ■ Group 2: ≥4 points	■ Group1: ≥7 points ■ Group 2: ≥6 points

DIC, disseminated intravascular coagulation; ISTH, the International Society on Thrombosis and Hemostasis; JMHW, the Japanese Ministry of Health and Welfare; CDSS, the Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrin/fibrinogen degradation product; *: 0 points in patients with hematological malignancies, #: PLT < 50×10^9/L or 50% decrease within 24 hours. means 1 points in patients with hematological diseases; Group 1: patients without hematological diseases; Group 2: patients with hematological diseases.

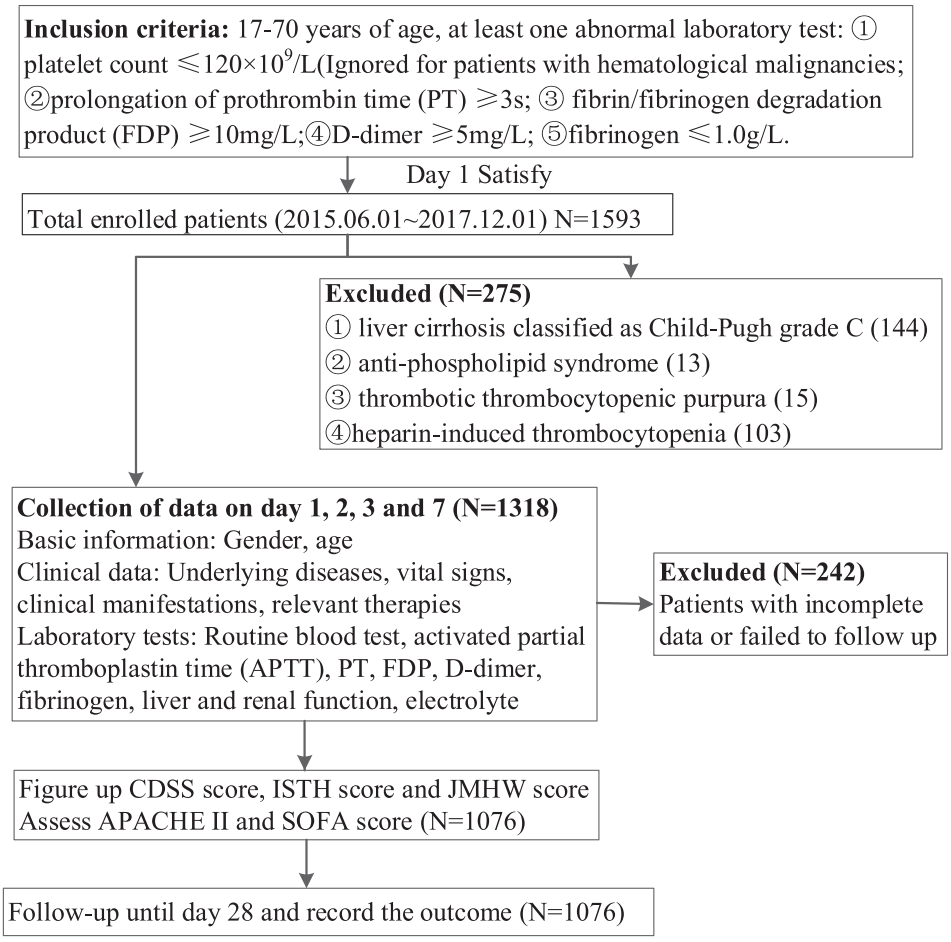

Fig. 1. Study flow. CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

3. Results

3.1. Baseline features of the patients

From June 1, 2015, to December 1, 2017, the 18 centers consented 1593 patients suspected of suffering from DIC based on their laboratory results. According to the exclusion criteria, we excluded 275 patients. We also excluded 242 patients because of incomplete data collection and failure to follow-up. Therefore, 1076 patients were included for analysis. Of the 294 patients receiving heparin, 203 individuals received low molecular weight heparin and the remaining 91 received unfractionated heparins. 753 patients were included in group 1 with a mean age of 48.9 ± 14.1 years, and a male/female ratio of 416:337, 100% overlapping with the previous study [27]. The other 323 patients

Table 2
Diagnostic frequency for DIC and 28-day morality of nonhematologic patients diagnosed with DIC based on ISTH, JMHW and CDSS scoring systems.

patients without hematological diseases	Diagnostic rate (%)			28-day mortality (%)		
	ISTH criteria	JMHW criteria	CDSS criteria	ISTH criteria	JMHW criteria	CDSS criteria
Sepsis/severe infection	51.3(118/230)	51.7(119/230)	56.5(130/230)	62.7(74/118)	64.7(77/119)	63.8(83/130)
Trauma/surgery	20.0(33/165)	22.4(37/165)	23.0(38/165)	42.4(14/33)	43.2(16/37)	42.1(16/38)
Obstetrical calamities	32.3(21/65)	35.4(23/65)	41.5(27/65)	23.8(5/21)	21.7(5/23)	18.5(5/27)
Solid tumor	40.0(24/60)	40.0(24/60)	48.3(29/60)	70.8(17/24)	64.0(16/24)	65.5(19/29)
Pancreatitis	12.1(7/58)	10.3(6/58)	17.2(10/58)	71.4(5/7)	83.3(5/6)	70.0(7/10)
Cardiovascular/cerebrovascular diseases	33.3(18/54)	29.6(16/54)	33.3(18/54)	50.0(9/18)	56.3(9/16)	55.6(10/18)
Autoimmune diseases	16.2(6/37)	8.1(3/37)	13.5(5/37)	33.3(2/6)	66.7(2/3)	40.0(2/5)
Other	35.0(7/20)	45.0(9/20)	55.0(11/20)	57.1(4/7)	55.6(5/9)	63.6(7/11)
Uremia/kidney disease	25.0(6/24)	16.7(4/24)	16.7(4/24)	50.0(3/6)	75.0(3/4)	75.0(3/4)
Hepatic failure	63.2(12/19)	68.4(13/19)	64.7(11/19)	25.0(3/12)	23.1(3/13)	27.3(3/11)
Severe toxic or severe heat stroke	90.0(10/11)	90.0(10/11)	90.0(10/11)	40.0(4/10)	40.0(4/10)	40.0(4/10)
Hemorrhagic shock	70.0(7/10)	70.0(7/10)	80.0(8/10)	57.1(4/7)	71.4(5/7)	62.5(5/8)
Total	35.7(269/753)[a]	36.0(271/753)	40.0(301/753)[b]	53.5((144/269)	55.4(150/271)	54.5(164/301)

DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare; CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; a: $p = 0.0906$ between the ISTH and JMHW criteria; b: $p < 0.001$ for the CDSS compared with other criteria.

in group 2 had a mean age of 42.7 ± 14.4 years, and the male/female ratio was 82:141. Table 2 and Table 3 list the underlying diseases associated with DIC in group 1 and group 2 and reflect almost all the DIC causes. Table 4 describes the characteristics of the patients based on the CDSS.

3.2. Evaluate the diagnostic property of the CDSS

As presented in Tables 2 and 3, the frequency of DIC diagnosis and 28-day mortality varied according to the three scoring systems (ISTH, JMHW, CDSS), consistently with previous studies [10,12,14,16,17]. In group 1, the overall DIC diagnostic rate of the CDSS was the highest ($p < 0.05$), and the mortality rate of the CDSS DIC patients was close to that of the ISTH and JMHW DIC patients. It is worth noting that, the diagnostic rates could not reflect the sensitivity and the specificity, which needed to be combined with the rates of mortality in DIC patients diagnosed by the three criteria. The level of agreement in the diagnosis of DIC was 81.7% between the CDSS and ISTH, and 84.7% between the CDSS and JMHW in group 1 (Fig. 2A and B). Those diagnosed with DIC by CDSS (but not by the ISTH or the JMHW scoring systems) had higher mortality than those diagnosed with DIC by the ISTH and JMHW scoring systems (but not by CDSS). (Fig. 2A 17.4 (4/23) % vs. 43.6 (24/55) %; Fig. 2B 12.5 (2/16) % vs. 34.8(16/46) %). The ISTH and JMHW criteria missed many non-survivors recognized by the CDSS criteria. In group 2, even though fewer patients were diagnosed with DIC according to CDSS ($p < 0.05$), the mortality rate was highest in patients diagnosed with DIC according to CDSS. The rate of concordance in the diagnosis of DIC between the CDSS and the other two criteria was 80.0% (CDSS vs. ISTH), 76.9% (CDSS vs. JMHW), respectively (Fig. 2C and D).

Since there are no current criteria 100% accurate for the diagnosis of DIC, the ISTH, JMHW criteria and prognosis were taken as relative gold standards in comparison with the CDSS. The ROC curves for the ISTH DIC by the CDSS DIC and JMHW DIC were analyzed. The AUC were as following: CDSS 0.900 vs. JMHW 0.897 in group 1(Fig. 3A) and CDSS 0.873 vs. JMHW 0.741 in group 2 (Fig. 3B). The ROC curves for the JMHW DIC by the CDSS DIC and ISTH DIC were also performed. The AUC were as following: CDSS 0.923 vs. ISTH 0.895 in group 1 (Fig. 3C) and CDSS 0.836 vs. ISTH 0.745 in group 2 (Fig. 3D). We also assessed the ROC curves for prediction of death according to DIC diagnosed by the different scoring systems. The AUC were as following: CDSS 0.782 vs. ISTH 0.743 vs. JMHW 0.761 in group 1 (Fig. 3E); CDSS 0.621 vs. ISTH 0.578 vs. JMHW 0.594 in group 2 (Fig. 3F). In group 1, the CDSS had superior sensitivity (CDSS 91.5% vs. JMHW 87.0%, $p = 0.029$; CDSS 94.1% vs. ISTH 86.4%, $p = 0.001$; CDSS 81.2% vs. ISTH 71.3% or JMHW 74.3%, $p < 0.05$), while it had better specificity in group 2 (CDSS 94.6% vs. JMHW 62.0%, $p < 0.001$; CDSS 89.9% vs. ISTH 64.0%, $p < 0.001$; CDSS 48.1% vs. ISTH 32.9% or JMHW 32.9%, $p < 0.05$). In summary, our results indicate that the CDSS outperformed the ISTH and JMHW criteria in terms of sensitivity and specificity in different underlying diseases.

3.3. Prognostic value of the CDSS criteria

The APACHE II, the SOFA score and the 28-day mortality can reflect the illness severity and prognosis [33,34]. As shown in Table 4, compared with the non-DIC patients, CDSS DIC patients had a higher APACHE II, SOFA score and mortality. The CDSS score generally rose with an increase in APACHE II and SOFA score (Fig. 4A and B). The Spearman's rank test demonstrated that the DIC score as determined by the three scoring systems significantly correlated with the APACHE II and SOFA score (Table 5). The Kaplan-Meier survival curves showed that DIC patients diagnosed by the three scoring systems had a much lower survival rate compared to the non-DIC patients (Fig. 4C and D). Furthermore, the logistic regression analysis revealed that DIC was an independent predictor of mortality. Interestingly, the ORs between group 1 and group 2 were conspicuously different (Table 5). In group 1, the ORs of CDSS criteria were 14.1, significantly higher than that of ISTH (8.6) and JMHW criteria (11.4). In group 2, the ORs of CDSS, ISTH and JMHW criteria were 3.1, 2.5, 3.2, respectively. The ROC curve analysis for prediction of death with DIC diagnosed by the three scoring systems showed that the AUC of CDSS was larger than that of ISTH and JMHW in both group 1 and group 2 (Fig. 3E and F). Altogether, the findings above indicated the CDSS score had good prognostic value.

4. Discussion

There is currently no unique assay that can be taken as the gold standard to diagnose DIC. Experts in the field recommend that the diagnosis of DIC be based on the whole clinical picture, taking into consideration the etiology, the condition of the patient and all their available laboratory results [35]. In comparison to the qualitative consensuses, which are lacking in objectivity and regularity, the DIC diagnostic scoring systems could be of use for clinicians. There are three major scoring systems for DIC: the JMHW criteria [9], the ISTH criteria [2] and the JAAM criteria [10]. Each scoring system has its respective drawbacks, and a better alternative is needed. Therefore, the CDSS was proposed, aiming at favorable performance for the diagnosis and prognosis of DIC. The absence of a 100% accurate gold standard for DIC diagnosis is a severe limitation in the assessment of the accuracy of the different DIC diagnostic approaches. Thus, researchers had no alternative but to adopt some eclectic methods. The opinions of independent experts have been taken as the gold standard for the diagnosis of DIC to validate the ISTH overt DIC criteria [12]. Subsequently, Gando S. et al. used the JMHW and ISTH criteria as the alternative standard to evaluate the diagnostic accuracy of the JAAM criteria [10,18]. The Italian Society for Thrombosis and Hemostasis suggested that using the ISTH criteria (grade C) and the JMHW criteria (grade C) to diagnose DIC

Table 3
Diagnostic frequency for DIC and 28-day mortality of hematologic patients diagnosed with DIC based on ISTH, JMHW and CDSS scoring systems.

Underlying disease	Diagnostic rate			28-day all-cause mortality		
Hematological diseases	ISTH criteria	JMHW criteria	CDSS criteria	ISTH criteria	JMHW criteria	CDSS criteria
Non-M3 AML	71.2(74/104)	68.3(71/104)	56.7(59/104)	29.7(22/74)	31.0(22/71)	33.9(20/59)
M3 AML	81.4(70/86)	86.0(74/86)	72.1(62/86)	17.1(12/70)	17.6(13/74)	17.7(11/62)
ALL	59.6(28/47)	56.3(27/48)	38.3(18/47)	35.7(10/28)	37.0(10/27)	44.4(8/18)
Lymphoma	82.9(34/41)	85.4(35/41)	68.3(28/41)	55.9(19/34)	54.3(19/35)	57.1(16/28)
Other	65.4(17/26)	73.1(19/26)	61.5(16/26)	70.6(12/17)	63.2(12/19)	75.0(12/16)
Multiple Myeloma	36.4(4/11)	45.5(5/11)	27.3(3/11)	25·0(1/4)	60.0(3/5)	66.7(2/3)
MDS	50.0(4/8)	37.5(3/8)	37.5(3/8)	0.0(0/4)	0.0(0/3)	0.0(0/3)
Total	71.5(231/323)[a]	72.4(234/323)	58.5(189/323)[b]	32.9(76/231)	33.8(79/234)	36.5(69/189)

DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare; CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndromes; a: $p = 0.0807$ between the ISTH and JMHW criteria; b: $p < 0.001$ for the CDSS compared with other criteria.

Table 4
Patient characteristics based on CDSS status.

	CDSS criteria			CDSS DIC		
	Non-DIC	DIC	*p* value a	Survivors	Non-survivors	*p* value b
Group 1	*n* = 452	*n* = 301		*n* = 137	*n* = 164	
Age, years	48.7 ± 13.8	49.3 ± 14.7	0.554	48.2 ± 14.5	47.7 ± 14.3	0.493
Gender male/female	248/204	168/133	0.798	70/67	86/78	0.816
APACHEII score	11.0 ± 6.2	21.3 ± 11.6	< 0.001	13.9 ± 5.7	27.7 ± 11.5	< 0.001
SOFA score	3.2 ± 3.1	9.4 ± 5.3	< 0.001	6.0 ± 3.2	12.5 ± 4.8	< 0.001
28-day mortality	8.4%(38/452)	54.5%(164/301)	< 0.001			
Group 2	*n* = 134	*n* = 189		*n* = 120	*n* = 69	
Age, years	44.4 ± 13.8	41.4 ± 14.8	0.071	38.8 ± 14.2	46.0 ± 14.8	0.001
Gender male/female	82/52	100/89	0.139	60/60	40/29	0.291
APACHEII score	10.7 ± 3.9	14.7 ± 7.5	< 0.001	11.7 ± 4.1	19.5 ± 9.1	< 0.001
SOFA score	3.6 ± 2.2	6.1 ± 3.4	< 0.001	4.4 ± 1.5	8.6 ± 4.0	< 0.001
28-day mortality	17.4%(16/92)	32.9%(76/231)	< 0.001			

CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; DIC, disseminated intravascular coagulation; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; Group 1: patients without hematological diseases; Group 2: patients with hematological diseases.; a: non-DIC vs. DIC; b: survivors vs. non-survivors.

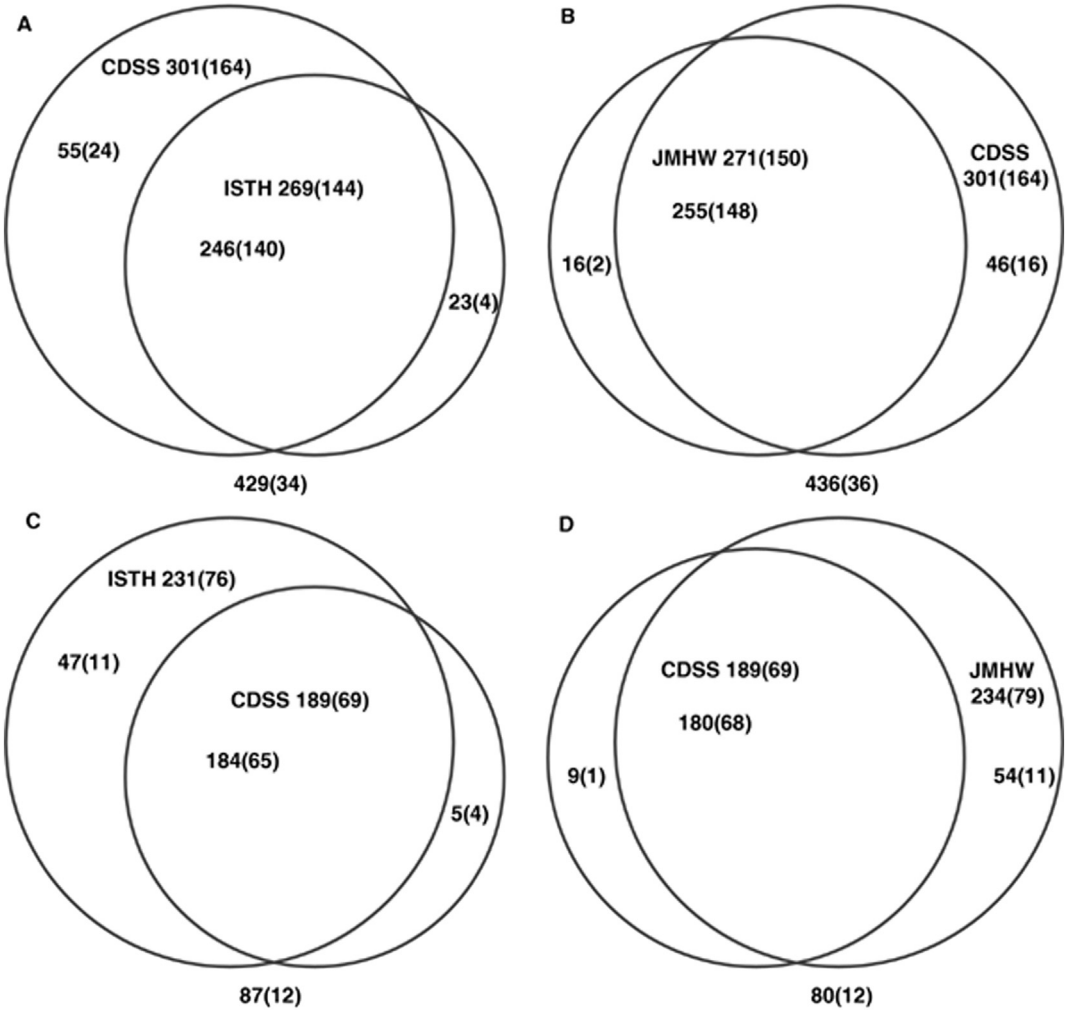

Fig. 2. Relationships of patients diagnosed with DIC diagnosed according to the three DIC scoring systems. (A) and (B), comparisons in group 1 (patients without hematological diseases); (C) and (D), comparisons in group 2 (patients with hematological diseases). The numbers inside the circles show the numbers of DIC patients meeting either criteria, including the common part based on two criteria and separate section just belonging to one criteria; the numbers outside the circles show the numbers of non-DIC patients; the numbers in parentheses indicate the numbers of non-survivors. CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare.

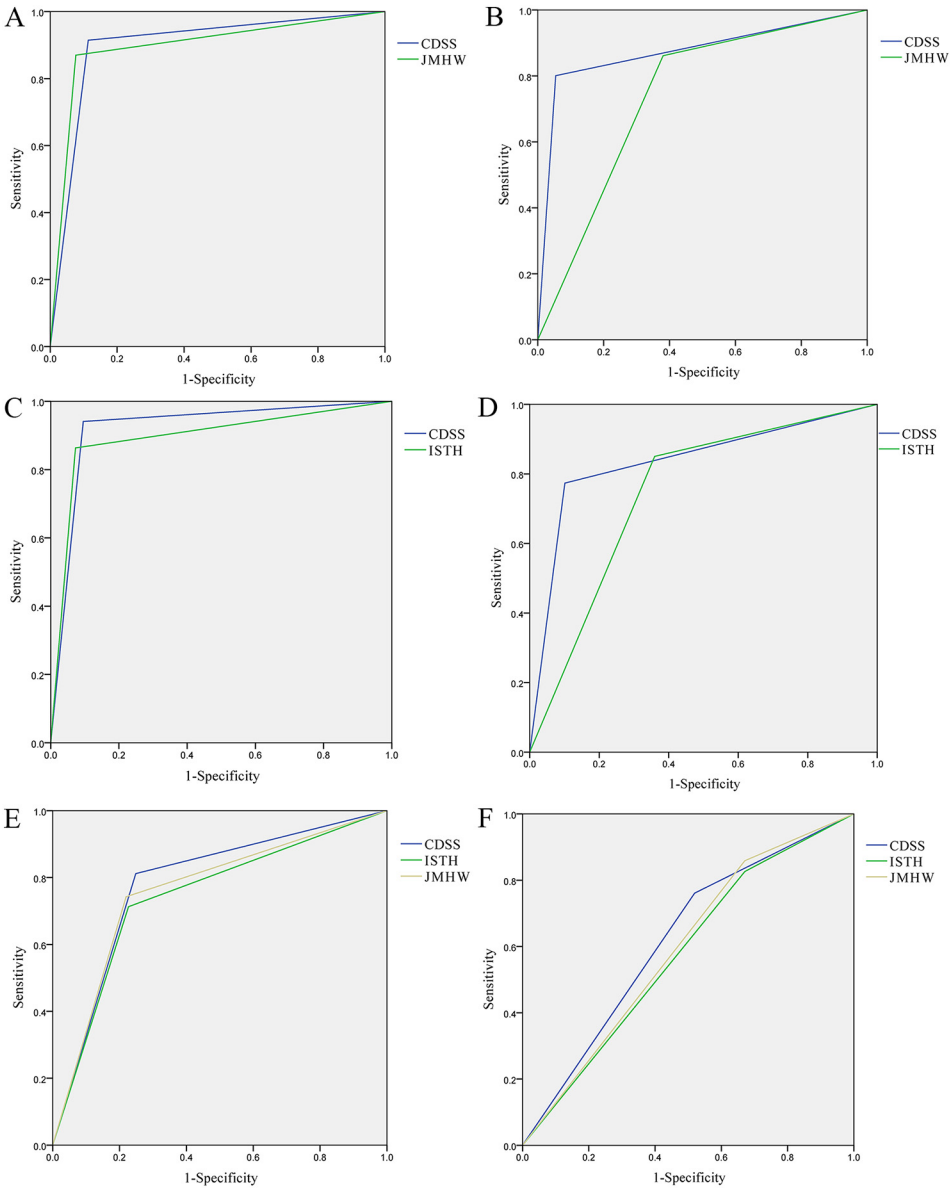

Fig. 3. Comparison of the diagnostic performance of the scoring systems for DIC.
Using the ISTH criteria as the relative gold standard, the area under receiver operating characteristic curves (AUC) of the CDSS was larger than that of JMHW in both group 1(A) and group 2 (B). When the JMHW criteria was the relative gold standard, similar results were observed in group 1 (C) and group 2 (D). If the 28-day mortality was taken as a criterion, the AUC of the CDSS was largest in group 1 (E) and group 2 (F). CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare. Group 1, patients without hematological diseases; group 2, patients with hematological diseases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[32]. In the present study, we adopted the ISTH criteria, the JMHW criteria, and the mortality as the references to evaluate the CDSS.

To assess the CDSS as accurately as possible, we carefully excluded patients who may have had false-positive high DIC scores, such as APS, TTP, HIT and severe liver cirrhosis. Patients who were older than 70 were also not enrolled, because of the complex physical conditions in the elderly population, which may lead to relatively high mortality indepent of DIC. Although the APTT was sensitive to a deficiency or an inhibition of intrinsic phase factors, the APTT results were also prone to be affected by many factors, including artifactual changes and heparin administration [36]. Therefore, prolongation of APTT was not listed as an inclusion criterion.

The differences in the rate of concordance in the DIC diagnosis between the CDSS and the other two criteria (Fig. 2) could be explained by the fact that the three scoring systems were based on different integral rules. Especially in hematological diseases, the ISTH scoring system has a higher emphasis on platelet count, which may lead to over-diagnosis. It should be remembered that, a low platelet count is not specific for DIC patients in the group 2 because of several causes, including clonal expansion of malignant cells, chemotherapy, and pyrexia induced by malignancy itself or an accompanying disease. In non-hematological diseases, the ISTH criteria also don't include typical clinical signs, even though previous studies showed that the DIC patients tended to have typical clinical signs compared with their counterparts without DIC [10,14,18,37]. Finally, both in the CDSS and the JMHW criteria, bleeding is not scored in hematological diseases because it is challenging to discriminate whether it is due to the hematological diseases or caused by DIC or both.

Interestingly, the ORs in group 1 were significantly higher than that in group 2, which could be partly attributed to the severity of the underlying disease. On the other hand, treatment approaches for hematological diseases have been rapidly developed, which significantly ameliorates the outcome for those patients. However, despite reasonable treatment programs, the mortality of sepsis remains high [38]. Therefore, the CDSS may guide clinicians to reasonably allocate limited medical resources because of its higher sensitivity in group 1 and its greater specificity in group 2 compared with the other two criteria.

Altogether, the results indicate that with appropriate sensitivity and specificity in different illnesses, the CDSS scoring system has a certain advantage over the ISTH and the JMHW scoring system, in term of diagnostic and prognostic performance, even though the three scoring systems are based on similar algorithms. Multiple reasons can explain

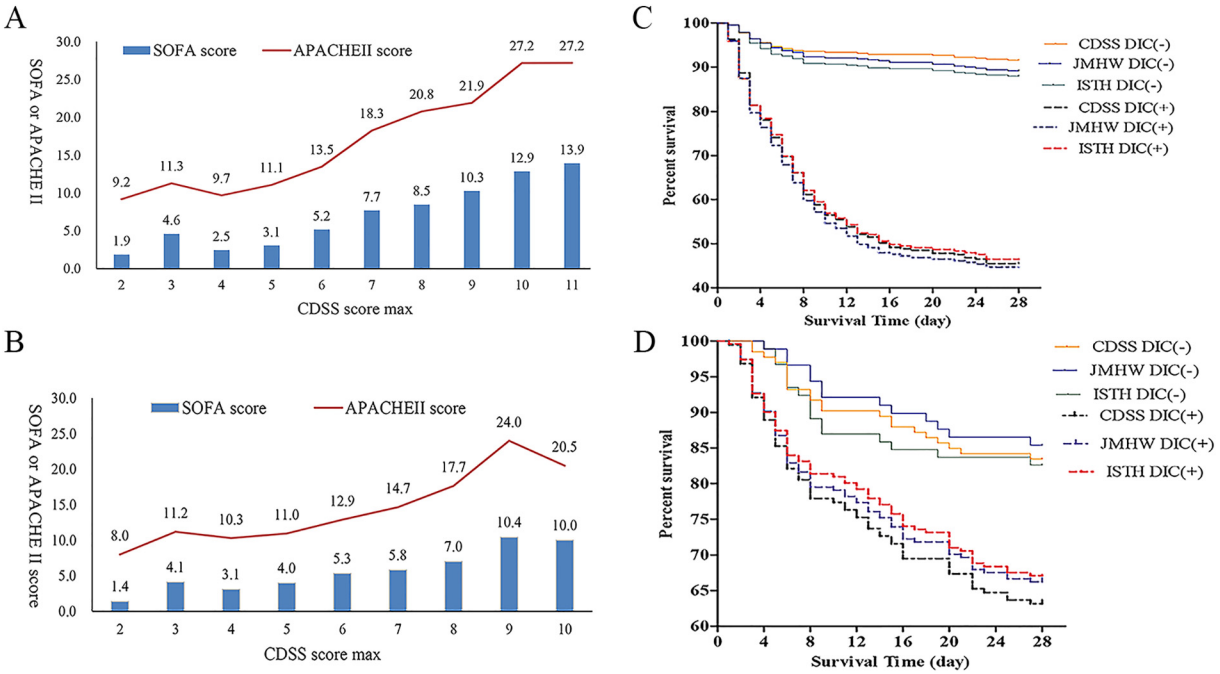

Fig. 4. Prognostic performance of the CDSS. The increase of CDSS DIC score correlated with an increased in APACHE II and SOFA score in both group 1 (A) and group 2 (B); the survival rate was significantly lower in DIC patients than in those without DIC in both group 1 (C) and group 2 (D). CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CDSS, Chinese Society of Thrombosis and Hemostasis Scoring System for DIC; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare. Group 1, patients without hematological diseases; group 2 patients with hematological diseases.

Table 5
Prognostic value of ISTH, JMHW and CDSS scoring systems by underlying disease.

	Group 1			Group 2		
	ISTH criteria	JMHW criteria	CDSS criteria	ISTH criteria	JMHW criteria	CDSS criteria
Sensitivity for 28-day mortality (%)	(144/202) 71.3[a]	(150/202) 74.3[b]	(164/202) 81.2[c]	(76/92) 82.6[g]	(79/92) 85.9[h]	(69/92) 75.0[i]
Specificity for 28-day mortality (%)	(426/551) 75.1[d]	(430/551) 78.0[e]	(414/551) 77.3[f]	(155/231) 32.9[j]	(155/231) 32.9[k]	(111/231) 48.1[l]
AUC*	0.743	0.761	0.782	0.578	0.594	0.621
OR (95%CI)[#] for 28-day mortality	8.6 (5.9–12.5)	11.4 (7.7–16.8)	14.1 (9.3–21.4)	2.5 (1.3–4.5)	3.2 (1.7–6.2)	3.1 (1.8–5.4)
Correlation coefficient with APACHE II score[&]	0.450	0.518	0.511	0.313	0.327	0.358
Correlation coefficient with SOFA score[&]	0.635	0.672	0.646	0.460	0.419	0.423

DIC, disseminated intravascular coagulation; Group 1: patients without hematological diseases; Group 2: patients with hematological diseases; ISTH, International Society on Thrombosis and Hemostasis; JMHW, Japanese Ministry of Health and Welfare; CDSS, Chinese disseminated intravascular coagulation scoring system; AUC, the area under the ROC curve; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; a: $p < 0.001$ between ISTH and CDSS; b: $p = 0.327$ between ISTH and JMHW; c: $p = 0.001$ between CDSS and JMHW; d: $p = 0.119$ between ISTH and CDSS; e: $p = 0.659$ between ISTH and JMHW; f: $p = 0.023$ between CDSS and JMHW; g: $p = 0.118$ between ISTH and CDSS; h: $p = 0.508$ between ISTH and JMHW; i: $p = 0.006$ between CDSS and JMHW; j: $p < 0.001$ between ISTH and CDSS; k: $p = 1.000$ between ISTH and JMHW; l: $p < 0.001$ between CDSS and JMHW; *: $p < 0.001$ for each AUC; #: $p < 0.001$ for each OR; &: $p < 0.001$ for each correlation coefficient.

these results. First, the CDSS considers underlying diseases as an essential scoring item, which can reduce missed diagnosis of the DIC patients without specific etiologies. Second, the CDSS also includes the typical clinical manifestations of DIC, which are important clues to the definite diagnosis of DIC, while these symptoms are not scored in the ISTH criteria, which may hamper its sensitivity. Third, the levels of coagulation factors correlate with hemostasis. The ongoing activation and subsequent exhaustion of coagulation factors in the development of DIC lead to low levels of coagulation factors, reflected by prolonged PT and (or) APTT, which appears to highly correlate with the severity of DIC because of an increased risk of bleeding and mortality [39]. Consistently, our previous work showed that the prolongation of APTT had a significant impact on mortality [26]. Therefore, adding APTT along with PT to the CDSS criteria improve the diagnostic sensitivity. Fourth, the CDSS considers D-dimer rather than FDP as the fibrin-related marker. D-dimer is a known specific marker of secondary fibrinolysis, while FDP cannot differentiate primary and secondary fibrinolysis. DIC is characterized by secondary fibrinolysis, which correlates with the finding that D-dimer has better diagnostic value, and especially has better specificity than FDP in patients at risk for DIC [40,41]. Even though both the ISTH and CDSS criteria consider the D-dimer, striking differences exist in their respective cut-off points. The CDSS has a higher threshold of D-dimer, which can improve its specificity [26]. Fifth, the cut-off values and the importance of platelet count are adjusted in the CDSS [26]. The CDSS also adds the dynamic changes of platelet count as one important integral items, since DIC is an extremely dynamic process. It is imperative to consecutively monitor and reassess after a clinical suspicion of DIC.

The present study also presents some limitations. A limitation may be the lack of a 100% accurate gold standard for DIC diagnosis, which makes a series of studies controversial. Instead, we decided to evaluate the CDSS in comparison with the current leading criteria, because, at present, it seems to be the most appropriate method. With a better understanding of the pathogenesis of DIC, several molecular markers reflecting endothelial injury and hemostatic activation have been found to be reliable indicators for the earlier and more accurate diagnosis of DIC, such as thrombin-antithrombin complex (TAT) and plasminogen activator inhibitor 1 (PAI-1). While Japanese experts have proposed to use several revised criteria, which include those markers [21–23], they cannot be measured in most Chinese hospitals. Therefore, even though the CDSS still considers the conventional coagulation tests, it can still presently be a useful tool for clinicians to recognize and manage DIC in China.

In conclusion, this multi-center prospective study with a large population demonstrated that, in all the common underlying diseases associated with DIC, the CDSS has a favorable capability for the diagnosis and prognosis of DIC with appropriate sensitivity and specificity. At present, its broad application will ensure a standardized diagnosis and treatment of DIC, which can not only improve the patients' diagnosis but will also allow allocating limited medical resources rationally.

Declarations of interest

None.

Acknowledgments

Yu Hu and Hing Mei designed the protocol and obtained funding for the study. Lili Luo, Yingying Wu and Jun Deng collected the data, and all authors were involved in their interpretation. Lili Luo, Yingying Wu and Jun Deng did the assays. Lili Luo and Yingying Wu performed the statistical analysis. Lili Luo and Heng Mei wrote the first draft of this article and all authors contributed to the revisions. We are indebted to all the patients and workers involved in this study for providing us with valuable data.

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