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SCIENTIFIC ARTICLE

Postoperative excessive blood loss after cardiac surgery can be predicted with International Society on Thrombosis and Hemostasis scoring system

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KEYWORDS
Cardiac surgery;
Coagulation;
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Morbidity;
Transfusion

Abstract
Background and objective: Prediction of postoperative excessive blood loss is useful for management of Intensive Care Unit after cardiac surgery. The aim of present study was to examine the effectiveness of International Society on Thrombosis and Hemostasis scoring system in patients with cardiac surgery.
Method: After obtaining approval from the institutional review board, the medical records of patients undergoing elective cardiac surgery using Cardio-Pulmonary Bypass between March 2010 and February 2014 were retrospectively reviewed. International Society on Thrombosis and Hemostasis score was calculated in intensive care unit and patients were divided with overt disseminated intravascular coagulation group and non-overt disseminated intravascular coagulation group. To evaluate correlation with estimated blood loss, student *t*-test and correlation analyses were used.
Results: Among 384 patients with cardiac surgery, 70 patients with overt disseminated intravascular coagulation group ($n = 20$) or non-overt disseminated intravascular coagulation group ($n = 50$) were enrolled. Mean disseminated intravascular coagulation scores at intensive care unit admission was 5.35 ± 0.59 (overt disseminated intravascular coagulation group) and 2.66 ± 1.29 (non-overt disseminated intravascular coagulation group) and overt disseminated intravascular coagulation was induced in 29% (20/70). Overt disseminated intravascular coagulation group had much more EBL for 24 h ($p = 0.006$) and maintained longer time of intubation time ($p = 0.005$).

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Conclusion: In spite of limitation of retrospective design, management using International Society on Thrombosis and Hemostasis score in patients after cardiac surgery seems to be helpful for prediction of the post- cardio-pulmonary bypass excessive blood loss and prolonged tracheal intubation duration.

PALAVRAS-CHAVE
Cirurgia cardíaca;
Coagulação;
Coagulação intravascular disseminada;
Morbidade;
Transfusão

A perda sanguínea excessiva no pós-operatório de cirurgia cardíaca pode ser prevista com o sistema de classificação da Sociedade Internacional de Trombose e Hemostasia (ISTH)

Resumo
Justificativa e objetivo: A previsão de perda sanguínea excessiva no pós-operatório é útil para o manejo em Unidade de Terapia Intensiva (UTI) após cirurgia cardíaca. O objetivo do presente estudo foi examinar a eficácia do sistema de classificação da Sociedade Internacional de Trombose e Hemostasia (*International Society on Thrombosis and Hemostasis* – ISTH) em pacientes submetidos à cirurgia cardíaca.
Método: Após obter a aprovação do Comitê de Pesquisa Institucional, os prontuários de pacientes submetidos à cirurgia cardíaca eletiva usando circulação extracorpórea (CEC) entre março de 2010 e fevereiro de 2014 foram retrospectivamente revisados. O escore ISTH foi calculado na UTI, e os pacientes foram alocados em dois grupos: grupo com coagulação intravascular disseminada (CID) manifesta e grupo com CID não-manifesta. Para avaliar a correlação com a Perda Estimada de Sangue (PES), o teste *t* de Student e as análises de correlação foram utilizados.
Resultados: Dentre os 384 pacientes submetidos à cirurgia cardíaca, 70 pacientes com CID manifesta (n = 20) ou CID não manifesta (n = 50) foram incluídos. As médias dos escores CID na admissão na UTI foram 5,35 ± 0,59 (Grupo CID manifesta) e 2,66 ± 1,29 (Grupo CID não manifesta) e induzida CID manifesta em 29% (20/70). O grupo CID manifesta apresentou PES superior durante 24 horas ($p = 0,006$) e um tempo maior de intubação ($p = 0,005$).
Conclusão: Apesar da limitação do desenho retrospectivo, o uso do escore ISTH para o manejo de pacientes após cirurgia cardíaca parece ser útil para prever a perda sanguínea excessiva pós-CEC e o prolongamento da intubação traqueal.

Introduction

Excessive perioperative bleeding continues to complicate cardiac surgery with Cardio-Pulmonary Bypass (CPB) in spite of improvements in extracorporeal oxygenation and surgical techniques. Patients after cardiac surgery with CPB has various causes of bleeding.[1,2] Defective surgical hemostasis and acquired transient platelet dysfunction mainly cause bleeding in patient with CPB. After starting CPB, hemodilution causes platelet counts to decrease to approximately 50% of preoperative levels rapidly and even is the progressive loss of platelet function and prolonged PT and PTT and low fibrinogen levels are also attributable to dilution coagulopathy. Drug induced causes also attributed the perioperative bleeding[3] and unknown mechanisms contribute to decrease in platelet counts and platelet dysfunction during CPB.[4] In addition, the balance of pro-coagulation and anticoagulation is profoundly disturbed in Cardio-Pulmonary Bypass (CPB) patients. Both extensive contact between blood and non-endothelial surfaces of the bypass circuit and the release and reinfusion of tissue factor lead to increased thrombin generation during CPB.[5–7] These results cause fibrin formation, fibrinolysis, and platelet activation, despite full heparinization.[5,8] Thus, during CPB, it thought that hyper-fibrinolysis is a secondary phenomenon induced by the activation of coagulation factors. Activation of factor XII and thrombin have been demonstrated to induce the release of tissue-type plasminogen activator from endothelium. Therefore, it attenuates the effects of both thrombin and plasmin to maintain coagulation homeostasis during CPB, as unrestricted thrombin and plasmin activation ultimately lead to consumption of coagulation factors and platelets (i.e. a disseminated intravascular coagulation state during CPB).[7,8] Therefore, variable reasons are contributed in the patients undergoing unpredicted excessive blood loss.

The prediction of postoperative excessive blood loss after cardiac surgery with CPB has been hampered by lack of a specific diagnostic test. No single clinical sign or laboratory test has been found to possess sufficient diagnostic accuracy for confirming or rejecting the diagnosis of postoperative excessive blood loss.[9]

Table 1 Scoring system for overt disseminated intravascular coagulation proposed by International Society on Thrombosis and Hemostasis.

	0	1	2
Platelets ($\times 10^3.mL^{-1}$)	>100	50–100	<50
D-Dimer (fibrin-related marker) ($\mu g.mL^{-1}$)	<0.5	0.5–5	>5
Prolonged prothrombin time (s)	>3	3–6	>6
Fibrinogen ($g.L^{-1}$)	>1.0	≤1.0	
If score ≥ 5, compatible with overt DIC			

DIC, disseminated intravascular coagulation.

In 2001, the International Society on Thrombosis and Hemostasis (ISTH) Sub-Committee of the Scientific and Standardization Committee on Disseminated Intravascular Coagulation proposed that the working definition of disseminated intravascular coagulation (DIC) be delineated into two phase. Non-overt DIC represent subtle hemostatic dysfunction while overt DIC recognized its decompensated phase.[10] For overt DIC, a cumulative score of 5 or more from prolonged Prothrombin Time (PT), reduced platelets and fibrinogen, and elevated fibrin-related markers proposed (Table 1). Even bleeding after cardiac surgery has variable causes, we thought the applying ISTH scoring system may be able to predict the postoperative excessive blood loss in patients after cardiac surgery with CPB. The aims of this present study were to investigate the effectiveness of ISTH scoring system in patients after cardiac surgery with CPB.

Method

After obtaining approval from the institutional review board, the medical records of patients aged over 20 years undergoing elective cardiac surgery using CPB between March 2010 and February 2014 were retrospectively reviewed. These demographic and clinical characteristics, perioperative laboratory findings, and postoperative complications were assessed using computerized databases from our institution. Of the 384 patients identified, we only included those ($n = 70$) who underwent valve surgery using CPB in Fig. 1. They did not have an underlying disorder known to be associated with overt DIC. Patients underwent cardiac surgery except valve surgery underwent anesthesia with midazolam, rocuronium, and sufentanil or previous cardiac operation, an underlying disorder known to be associated with overt DIC, or missing peri-operative records were excluded ($n = 314$).

Anesthetic and CPB management

All valve surgery in this study underwent anesthesia with midazolam, rocuronium, and sufentanil. Before initiation of CPB, tidal volume was adjusted to achieve normoventilation with oxygen in air (FiO_2 0.5) and was controlled by means of blood gas analysis to maintain normal arterial carbon dioxide tension.

The operation was generally performed with standard non-pulsatile CPB technique ($2.4\,L.min^{-1}.m^{-2}$) with

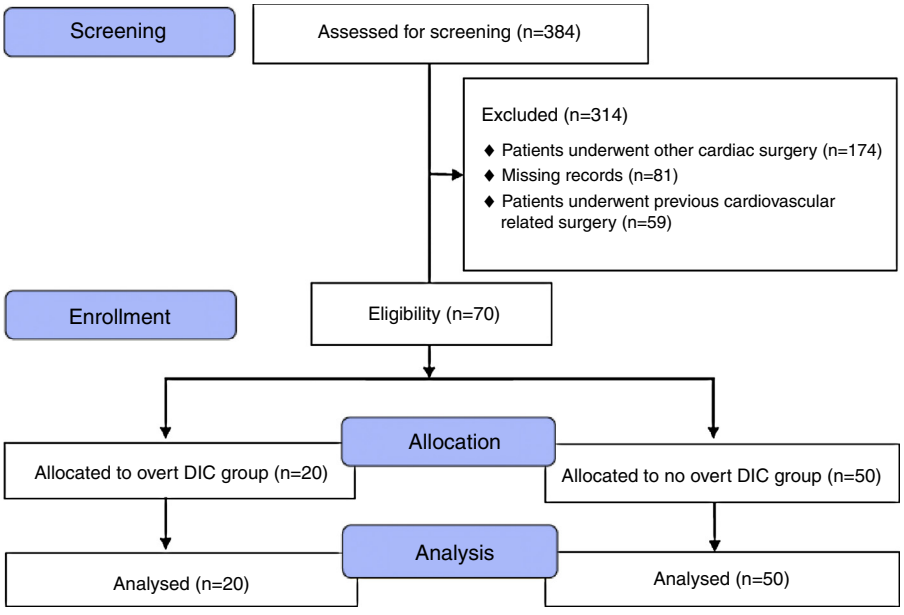

Figure 1 CONSORT flow diagram in this retrospective study. Overt DIC group: DIC score ≥ 5, non-overt DIC group: DIC score < 5. DIC, disseminated intravascular coagulation.

moderate hypothermia (nasopharyngeal temperature 32–34 °C) with the administration of heparin (300 IU.kg^{-1}). Since the report of Mangano et al.,[11] our institute has not used aprotinin in cardiac surgery. Therefore, the activated clotting time was maintained at above 400 s. The circuit was primed with Ringer's lactated solution, albumin, and mannitol. Cardioprotection was achieved with cold blood cardioplegia. After separation from CPB (rectal temperature 36.5–37 °C) anticoagulation activity was reversed with protamine sulfate, given a ratio of 1 mg: 100 IU of heparin.

Laboratory tests and DIC scoring

Perioperative laboratory tests were collected after surgery. Platelet counts, PT, fibrinogen, and Fibrinogen Degradation Products (FDP) were measured by electric impedance methods, scattered light detection method, and latex quantitative immunoassay, respectively.

Based on the ISTH scoring system (Table 1), we calculated the DIC score. The authors considered the overt DIC occurred when a cumulative score of 5 or more from the scoring system. According to the result of DIC score on arrival to ICU, we divided the patients into two groups; Overt DIC group, DIC score ≥ 5, non-overt DIC group, DIC score < 5.

Blood transfusion protocol and criteria for surgical re-exploration for bleeding

Blood product transfusion guidelines were used to standardize transfusion practice. In the postoperative ICU, the threshold for packed Red Blood Cell (pRBC) transfusion was a Hct/Hb less than 0.25/8.0. The indication for postoperative transfusion of random donor platelets or fresh frozen plasma was the presence of excessive bleeding (>200 mL.h^{-1}), and a laboratory demonstrated coagulation defect [platelet count $< 100 \times 10^9$ L, PT or activated partial thromboplastin time (aPTT) $> 1.5 \times$ control value, or fibrinogen level < 1.0 g.L^{-1}].

Postoperatively, blood loss from the mediastinal chest tubes was reported at 6 h, 12 h, and 24 h from the time the patient arrived in the ICU. The 24 h blood loss was documented. The definition of EBL in ICU was greater than 1 L blood loss for 24 h.[12] Surgical re-exploration was considered when bleeding during the first 2 h was greater than 300 mL.h^{-1} or was greater than 200 mL.h^{-1} for 4 h consecutively, with normal coagulation variables.

Patient management protocol

The tracheal extubation criteria were full consciousness, hemodynamic stability, adequate muscle strength and adequate respiration (required positive end-expiratory pressure, $\leq$ to 5 cmH_2O; breathing rate, < 30.min^{-1}) as well as adequate gas exchange value (PaO_2, $\geq$ to 80 mmHg/$FiO_2 = 0.4$; $PaCO_2$, 35–50 mmHg).

As the parameters of postoperative morbidity, intubation time, oxygen index (OI), length of stay in the Intensive Care Unit (ICU), and serum creatinine level for 2 days were retrospectively assessed. Arterial blood gas analysis was performed and the OI was calculated (arterial PO_2/inspired fraction of oxygen) on arrival of ICU.

In accordance with the Acute Kidney Injury Network (AKIN) criteria,[13] the development of postoperative AKI was evaluated based on changes in serum Creatinine (Cr) concentration within 48 h of surgery. Serum creatinine level was examined preoperatively, within 2nd day of ICU.

Statistical analysis

Values are expressed as mean $\pm$ SD or median (25th–75th percentile). To compare the categorical data, chi-square test was used. Continuous variables were expressed as mean $\pm$ SEM compared by means of a parametric (Student *t*-test) or were expressed as median (25th and 75th percentiles) compared by means of a nonparametric (Wilcoxon signed-rank sum) test, on the basis of the distribution of variables. To evaluate correlation with estimated blood loss (EBL), student *t*-test and correlation analyses was used. To identify factors significantly predictive of EBL, univariate and multivariate linear regression analyses was performed. A $p < 0.05$ was considered significant.

Results

During the 4 years period, 384 patients were collected in this study (Fig. 1). Among the patients, 70 patients with overt DIC group ($n = 20$) or non-overt DIC group ($n = 50$) were enrolled. Overt DIC incidence on arrival to ICU was 29% (20/70) in our study population.

Table 2 summarizes clinical characteristics of the 70 patients studied. There were no statistical differences between the groups in preoperative NYHA classification, age, sex, pre-existing co-morbidity and type of surgery. The CPB time did not differ between groups and transfusion except RBC also did not differ between groups (Table 3). However, patients with Overt DIC group had higher D-Dimer score ($p < 0.001$) and lactate level ($p = 0.02$) after surgery (Table 4).

Although transfusion between groups in ICU has no statistical differences, total amount of transfused RBC was higher in Overt DIC group. And, intubation time of overt DIC group was also longer than non-overt DIC group. However, length of stay in the ICU, oxygenation index (arterial PO_2/inspired fraction of oxygen), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and incidence of postoperative AKI were no statistical differences between groups (Table 5).

In addition, these were founded that EBL was higher in Overt DIC group and correlated with occurrence of DIC, DIC score and CPB time (Tables 6 and 7). In addition, in univariate and multivariate analyses, DIC score and CPB time was identified as significantly predictive factors of EBL (Table 8).

Discussion

Our result showed that the DIC score and occurrence of DIC were related to post-operative excessive blood loss and may be related with prolonged mechanical ventilation.

Table 2 Preoperative patients' characteristics.

	Overt DIC group($n=20$)	Non-overt DIC group($n=50$)	p-Value
Age (years)	61.90 ± 9.40	55.56 ± 13.36	0.06
Gender (M/F)	12/8	28/22	0.97
Anti-thrombin (%)	129.45 ± 44.30	124.34 ± 42.79	0.67
NYHA classification	2 (2–3)	2 (2–3)	0.70
Co-morbidity			
Diabetes mellitus (%)	3 (15)	5 (10)	0.68
Hypertension (%)	6 (30)	17 (34)	0.97
Previous stroke (%)	2 (10)	1 (2)	0.19
Atrial fibrillation (%)	7 (35)	15 (30)	0.9
Renal failure (%)	1 (5)	0	1.00
COPD (%)	1 (5)	0	1.00
Type of surgery			0.67
Single valve (%)	17 (85)	38 (76)	
Double valve (%)	3 (15)	12 (24)	
Triple valve (%)		2 (4)	

Values are expressed as average ± SD, number (%), or median (25th–75th percentile). Overt DIC group: DIC score ≥ 5; non-overt DIC group: DIC score < 5.
DIC, disseminated intravascular coagulation; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease.

Table 3 Intraoperative patients' characteristics.

	Overt DIC group($n=20$)	Non-overt DIC group ($n=50$)	p-Value
CPB time (min)	193.25 ± 60.35	187.46 ± 56.75	0.71
Transfusion in the operating room			
Packed RBC (unit)	4 (3–5)	2 (1–3)	0.01[a]
FFP (unit)	1 (0–3)	0 (0–2)	0.80
PLT (unit)	3.5 (0–10)	0 (0–10)	0.91

Values are expressed as average ± SD or median (25th–75th percentile). Overt DIC group: DIC score ≥ 5, non-overt DIC group: DIC score < 5.
DIC, disseminated intravascular coagulation; CPB, cardiopulmonary bypass; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelet.
[a] $p < 0.05$.

Table 4 Postoperative patients' characteristics in ICU.

	Overt DIC group ($n=20$)	Non-overt DIC group($n=50$)	p-Value
D-Dimer ($\mu g.mL^{-1}$)	2.79 (2.01–3.37)	1.35 (0.87–2.28)	<0.001[a]
Lactate ($mmoL.L^{-1}$)	3.25 (2.80–3.90)	2.70 (2.20–3.50)	0.02[a]
Fibrinogen ($mg.dL^{-1}$)	308.19 ± 77.25	324.76 ± 90.14	0.51
PT (INR)	1.97 ± 0.37	1.52 ± 0.23	<0.001[a]
Platelet ($\times 10^3.mL^{-1}$)	84.00 (66.25–95.00)	113.00 (92.00–141.00)	<0.001[a]
EBL (mL)	1502.05 (850.00–1825.00)	895.00 (580.00–1290.00)	0.006[a]
Transfusion in the ICU			
Packed RBC (unit)	1 (0–2)	0 (0–2)	0.50
FFP (unit)	3 (1.5–6)	3 (0–6)	0.58
PLT (unit)	1 (0–3.5)	0 (0–6)	0.97
Total transfusion			
Packed RBC (unit)	5 (4–7)	3 (2–5)	0.01[a]
FFP (unit)	5 (2–7)	4 (0–8)	0.53
PLT (unit)	7 (0–10)	10 (0–10)	0.97

Values are expressed as average ± SD or median (25th–75th percentile). Overt DIC group, DIC score ≥ 5; non-overt DIC group, DIC score < 5.
DIC, disseminated intravascular coagulation; PT, prothrombin time; INR, international normalized ratio; EBL, estimated blood loss; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelet.
[a] $p < 0.05$.

Table 5 Postoperative patients' outcomes.

	Overt DIC group ($n = 20$)	Non-overt DIC group($n = 50$)	p-Value
ICU stay (day)	2.50 (2.00–5.00)	3.00 (2.00–5.00)	0.90
Intubation time (min)	2740.00 (1796.50–4635.00)	1646.50 (1310.00–2390.00)	0.005[a]
Oxygen Index	395.92 ± 138.46	307.05 ± 176.70	0.78
APACHE II	23.76 ± 6.59	21.67 ± 7.90	0.23
Acute kidney injury	5 (25)	16 (32)	0.56
Infection	2 (10)	6 (12)	0.81
CNS manifestation	4 (20)	6 (12)	0.39

Values are average ± SD, number (%), or median (25th–75th percentile). Overt DIC group: DIC score ≥5; non-overt DIC group: DIC score < 5.
DIC, disseminated intravascular coagulation; ICU, Intensive Care Unit; oxygen index: arterial PO_2/inspired fraction of oxygen, APACHE II, Acute Physiology and Chronic Health Evaluation II; CNS, central nervous system.
[a] $p < 0.05$.

Table 6 Correlation with estimated blood loss using student t-test.

Variable	Number	Estimated blood loss (mL)	p-Value
Sex			
Female	30 (43)	1111.00 ± 548.04	0.69
Male	40 (57)	1177.25 ± 121.40	
Stroke			
No	67 (96)	1141.87 ± 691.36	0.69
Yes	3 (4)	1305.00 ± 275.27	
Atrial fibrillation			
No	48 (69)	1155.31 ± 698.06	0.90
Yes	22 (31)	1134.77 ± 649.77	
Non-overt DIC			
No	50 (71)	1136.67 ± 532.43	0.002[a]
Overt DIC			
Yes	20 (29)	1170.80 ± 851.26	

Values are expressed as average ± SD or number (%). Overt DIC, DIC score ≥ 5; non-overt DIC, DIC score < 5.
DIC, disseminated intravascular coagulation.
[a] $p < 0.05$.

Table 7 Correlation with EBL using correlation analysis.

	EBL (mL)	DIC score	CPB time (min)	Age (year)	Anti-thrombin (%)	Lactate (mmoL.L^{-1})
EBL (mL)	1					
DIC score	0.29[a]	1				
CPB time (min)	0.34[a]	0.12	1			
Age (year)	0.20	0.24	0.03	1		
Anti-thrombin (%)	−0.17	−0.59[a]	0.04	−0.15	1	
Lactate (mmoL.L^{-1})	0.13	0.03	0.14	0.11	−0.13	1

EBL, estimated blood loss; DIC, disseminated intravascular coagulation; CPB, cardiopulmonary bypass.
[a] $p < 0.05$.

The working definition of DIC proposed by ISTH has been validated since 2001. In the absence of a reference gold standard for the ISTH overt DIC score, comparison with the Japanese Ministry of Health and Welfare (JMHW) score were important as the best-evidenced working diagnosis to date.[14] The initial reported agreement rate between ISTH and JMHW score was 67.4%.[15] Discordance was due to the JMHW sensitivity to DIC in hematologic malignancies with high fibrinolytic activity. A further study, exclude such cases, demonstrated 93% concordance.[16] Using a different approach with blinded expert assessment, Bakhtiari et al. found sensitivity of 91% and specificity of 97% with the ISTH DIC score.[17] Therefore, the authors have considered the ISTH score may be a trustworthy tool to diagnose post-CPB DIC and postoperative blood loss.

Table 8 Univariate and multivariate linear regression analyses.

Variable	Regression coefficient	Upper limit of the 95% CI	Lower limit of the 95% CI	*p*-Value
Univariate				
DIC score	119.62	25.30	213.94	0.01[a]
CPB time (min)	3.96	1.27	6.66	0.005[a]
Age (year)	10.64	−2.11	23.39	0.1
Anti-thrombin (%)	−7.23	−17.38	2.92	0.16
D-Dimer ($\mu g.mL^{-1}$)	161.72	21.62	301.83	0.02[a]
pRBC (unit)	59.60	25.47	73.73	0.07
Lactate ($mmoL.L^{-1}$)	68.97	−65.26	203.20	0.31
Multivariate				
DIC score	105.27	14.53	196.00	0.02[a]
CPB time (min)	3.61	0.98	6.24	0.008[a]

CI, confidence interval; DIC, disseminated intravascular coagulation; CPB, cardiopulmonary bypass; pRBC, intraoperative packed red blood cell.
[a] $p < 0.05$.

Postoperative bleeding is one of the most common complications of cardiac surgery. Approximately 20% of patients bleed significantly after cardiac surgery, and 5% require re-exploration.[18,19] A surgical cause of bleeding is found in 50% of patients undergoing reoperation for bleeding. In the remainder of patients, the cause is multifactorial and is probably related to the unique circumstances of the surgical procedure.[20] Extensive surgical trauma, prolonged blood contact with the artificial surface of CPB, high doses of heparin, and hypothermia contribute to dysfunction of the coagulation and inflammatory systems that lead to a postoperative coagulopathy. The link between the activation of the coagulation and inflammatory systems during the course of CPB is complex and is related to the generation of acute-phase reactions similar to those seen in sepsis. Therefore, it is often difficult to demonstrate the specific contributing factors of the coagulopathy in any given patient in the operating room or in the Intensive Care Unit (ICU) since the coagulopathy is related to coagulation and inflammatory systems. In addition, it is difficult to demonstrate a clear association between fibrinolysis and EBL after CPB. However, in some studies, markers of fibrinolysis have been found to be related to postoperative EBL. These findings have been supported by the efficiency of the anti-fibrinolytic agents (e.g., aprotinin, tranexamic acid) during CPB in reducing blood loss.[21,22] Our results also showed that the occurrence of DIC in ICU triggered by CPB was related to postoperative EBL.

In conclusion, in this study, to use the ISTH score system for evaluating the occurrence of DIC in patients undergoing cardiac valve surgery was useful and could be predicted post-CPB excessive blood loss and prolonged mechanical ventilation. While this study had a limitation due to retrospective design, these data may help direct further studies and management of patients undergoing cardiac valve surgery.

Conflicts of interest

The authors declare no conflicts of interest.

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