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RESEARCH ARTICLE

Prolongation of Peak Time but an Elevated Peak Height of a Clot Wave Form Analysis in Severe Coronavirus Disease 2019

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ABSTRACT

Objective: As coronavirus disease 2019 (COVID-19) is frequently associated with thrombotic diseases, the hemostatic abnormalities in cases of COVID-19 have attracted attention. This study examined the hemostatic abnormalities in patients with severe COVID-19.

Methods: Hemostatic abnormalities were examined based on the activated partial thromboplastin time (APTT) and small amount of tissue factor-induced FIX activation (sTF/FIXa) using a clot waveform analysis (CWA). The anti-Xa activity, C5b-9 and ADAMTS 13 values were also examined in these patients.

Results: CWA-APTT and CWA-sTF/FIXa showed that the peak times were prolonged, but peak heights were increased before anticoagulant therapy. The parameters of the CWA-APTT and CWA-sTF/FIXa were not correlated with the anti-Xa activity. The peak times of the CWA-sTF/FIXa were significantly longer in non-survivors than survivors. Although the plasma levels of C5b-9 and ADAMTS13 activity were markedly decreased in severe COVID-19 patients, there were no significant differences in C5b-9 levels or ADAMTS-13 activity between survivors and non-survivors.

Conclusions: The CWA showed the marked hemostatic abnormalities and hypercoagulability in COVID-19 patients, and anticoagulant therapy might not be monitored by routine APTT.

INTRODUCTION

Since coronavirus disease 2019 (COVID-19) caused the first outbreak in China [1] and COVID-19 infections have now spread from china [2] to worldwide [3], a small proportion of patients with COVID-19 died [4], but approximately 10% of patients developed severe [5] and life-threating acute respiratory distress syndrome (ARDS), especially intensive care unit [6], and many more patients developed mild or moderate illness [7], especially general ward [8]. Following the appearance of the omicron variant of COVID-19 [9], the mortality rate among patients with COVID-19 has been reduced, but the overall incidence of COVID-19 has markedly increased, resulting in a relative increase in deaths among COVID-19 patients. Therefore, the management of COVID-19 complications has become increasingly important in severe stages of COVID-19. There are marked differences in the severity, complications and outcomes of CVID-19 patients between those in the intensive-care unit [6] and the general ward [8].

The thrombotic complications of COVID-19 including pulmonary embolism (PE), deep vein thrombosis (DVT) [10], acute cerebral infarction (ACI) [11], and acute coronary syndrome (ACS) [12], have attracted attentions [13]. There have also been a few cases of disseminated intravascular coagulation (DIC) [14], frequently seen in cases of severe sepsis due to bacterial infection, as well as thrombotic microangiopathy (TMA) [15]. As elevated levels of soluble C-type lectin-like receptor 2 (sCLEC-2) have been reported in COVID-19 patients, suggesting that platelet activation may worsen COVID-19 [15], in the collaboration with the activation of coagulation.

A clot waveform analysis (CWA) is a newly developed approach for evaluating blood coagulabilities [16]. The usefulness of CWA-activated partial thromboplastin time (APTT) and CWA-small amount of tissue factor induced clotting factor IX activation assay (sTF/FIXa) for evaluating the hypercoagulability in malignant neoplasm patients was reported [17].

In the present study, hemostasis assessments using a CWA-APTT or CWA-sTF/FIXa, and ADAMTS-13 activities and C5b-9 levels were examined in severe COVID-19.

MATERIALS AND METHODS

A CWA, C5b-9 level and ADAMTS-13 assays were performed in 48 samples from 17 patients with COVID-19. A CWA was also performed in 183 samples from 183 orthopedic surgery patients before operation, and 20 samples from 20 healthy volunteers. The C5b-9 level measurements and ADAMTS-13 assays were also performed in 96 and 68 healthy volunteers, respectively.

The CWA

The APTT was measured using platelet poor plasma (PPP) and APTT-SP® (Instrumentation Laboratory, Bedford, MA, USA) with an ACL-TOP® (Instrumentation Laboratory), as previously reported [18]. The sTF/FIXa assay was performed using 2,000-fold diluted HemosIL RecombiPlasTin 2G (TF concentration <0.1 pg/ml: Instrumentation Laboratory) and platelet rich plasma (PRP). The CWA was performed as follows: three curves were expressed on the monitor of the ACL-TOP® system [16]. The fibrin formation (FF) curve corresponded to the changes in the absorbance observed while measuring the APTT. The first derivative peak (1st DP) curve corresponded to the coagulation velocity. The second derivative peak (2ndDP) curve corresponded to the coagulation acceleration. The height and time of the FF, 1stDP and 2ndDP curves were called the FFH and FFT, 1stDPH and 1stDPT and 2ndDPH and 2ndDPT, respectively.

Anti-Xa activity

The anti-Xa activity was measured prospectively 1 h after drug intake on Day 1. The anti-Xa activity of edoxaban was measured using STA®-Liquid Anti-Xa (Stago, Asnières-sur-Sreine, France) on a STA®-R Evolution® coagulometer (Stago) with a dedicated test set-up [20]. The anti-Xa assay was calibrated using an edoxaban-specific calibrator set (STA®Edoxaban calibrator) and verified using an edoxaban-specific control set (STA®Edoxaban Control), both developed by Stago.

ADAMTS13 activity assay

The ADAMTS13 activity was measured using a FRETS-VWF73 peptide (Peptide Institute, Osaka, Japan) [19] according to the method reported by Kokame et al [20].

C5b-9 assay

The C5b-9 levels were measured by an enzyme-linked immunosorbent assay (ELISA) using the Human C5b-9 ELISA Set (BD Biosciences, San Diego, CA, USA) [21].

Statistical analyses

The data are expressed as the median (range). The significance of differences between groups was examined using the Mann-Whitney U-test. Although this sample size is not enough to investigate this object, *P* values of <0.05 were considered to indicate a statistically significant difference. All of the statistical analyses were performed using the

Stat-Flex software program (version 6; Artec Co. Ltd, Osaka, Japan).

RESULTS

Eighteen patients with COVID-19 were admitted to the Emergency and Critical Care Center, Mie University Graduate School of Medicine from June 23, to December 15, 2022. Of them, 11 patients were in a critical illness, 5 were in a severe illness, and one was in a mild illness, while 6 died. Thrombotic complications were seen in one with PE, one with acute myocardial infarction, one with DIC and one with TMA (**Table 1**).

Table 1. Subjects

	Age (years)	Sex	Outcome	Thrombosis	Major bleeding	Comorbidity	Heparin	PLT ($x10^{10}$/L)	D-dimer (μg/ml)	Severity
1	59	M	Died	PE	None	PE	Administration	37.2	11.4	Critical illness
2	85	M	Survived	None	None	None	Administration	35.9	3.6	Critical illness
3	64	M	Survived	None	None	None	Administration	42.5	1.8	Critical illness
4	75	M	Survived	None	None	None	Administration	14.9	26.5	Critical illness
5	83	M	Survived	None	None	None	None	15.2	1.6	Severe
6	83	M	Survived	None	None	None	Administration	20.6	3.1	Critical illness
7	83	M	Died	None	None	None	Administration	18.5	2.8	Critical illness
8	84	M	Died	DIC	None	DIC, MOF	None	3.1	1.4	Critical illness
9	65	M	Died	None	None	Sepsis	Administration	8.2	47.0	Critical illness
10	67	M	Survived	None	None	None	Administration	22.6	3.2	Severe
11	64	F	Survived	None	None	Myocarditis	None	18.1	0.7	Severe
12	59	M	Survived	None	None	None	Administration	11.6	0.6	Severe
13	74	M	Survived	AMI	None	AMI	Administration	11.9	1.9	Critical illness
14	79	M	Died	None	None	Myasthenia Gravis	Administration	16.0	1.0	Severe
15	67	F	Died	None	None	None	None	21.8	4.1	Critical illness
16	74	M	Survived	None	None	None	None	42.3	23.4	Critical illness
17	18	M	Survived	TMA	None	TMA	None	0.2	34.6	Mild

PLT, platelet count; PE, pulmonary embolism; DIC, disseminated intravascular coagulation; MOF, multiple organ failure; AMI, acute myocardial infarction.; M, male; F, female; TMA, thrombotic microangiopathy

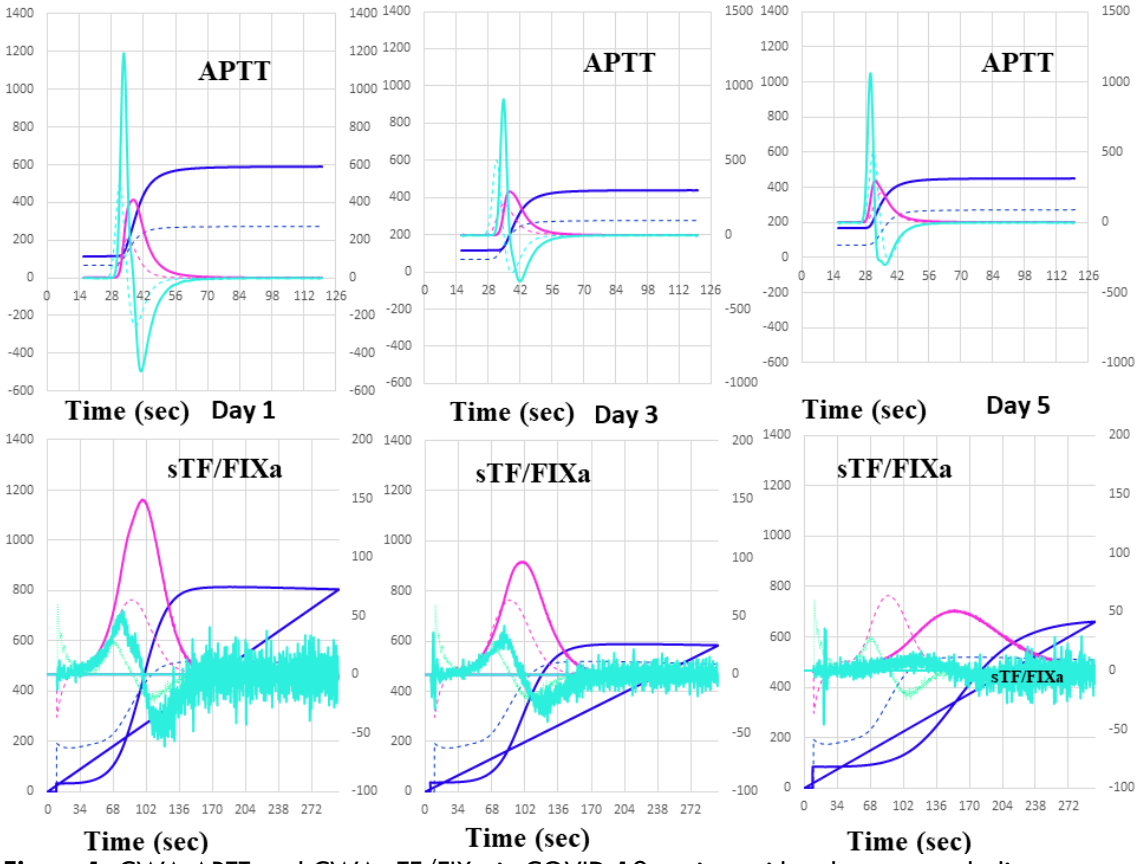

Figure 1. CWA-APTT and CWA-sTF/FIXa in COVID-19 patient with pulmonary embolism
APTT, activated partial thromboplastin time; sTF/FIXa. small amount of tissue factor induced FIX activation assay.

The CWA-APTT showed that the peak heights of the FFC, 1st DP and 2nd DP were heigh on days 1-5, and the CWA-sTF/FIXa showed that the peak heights of the FFC, 1st DP and 2nd DP were markedly high on day 1 but decreased on day 5 (**Figure 1**). Regarding the CWA-APTT, the peak times of the FFC, 1st DP and 2nd DP were significantly longer in patients with COVID-19 than in thoes before orthopedic surgery or healthy volunteers, and the peak heights of FFC and 1st DP were significantly higher in patients with COVID-19 than in patients before orthopedic surgery or healthy volunteers (**Figure 2**). Regarding the CWA-sTF/FIXa, the peak times of the FFC and 2nd DP were significantly longer in patients with COVID-19 than in those before orthopedic surgery, and the peak heights of the FFC and 1st DP were significantly higher in patients with COVID-19 than in those before orthopedic surgery.

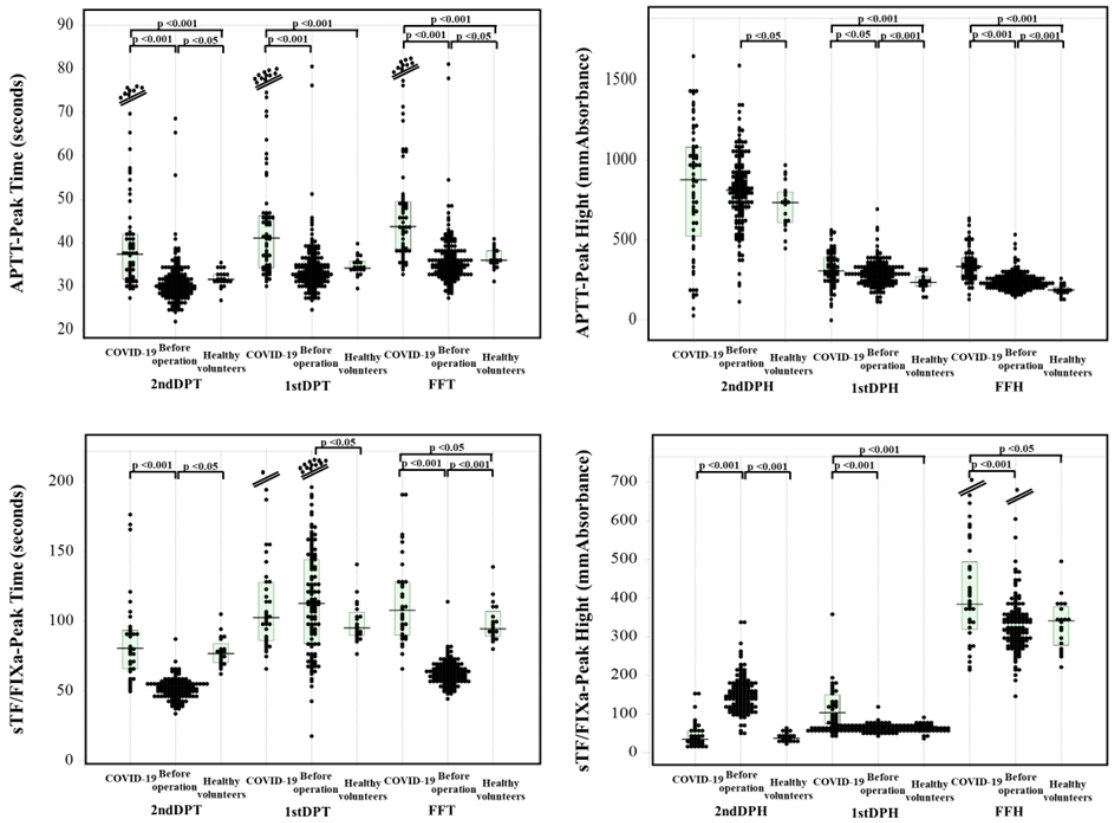

Figure 2. CWA-APTT and CWA-sTF/FIXa in COVID-19 patients, pre-orthopedic surgery patients and healthy volunteers.
APTT, activated partial thromboplastin time; sTF/FIXa. small amount of tissue factor- induced FIX activation assay

Table 2. Correlation between anti-Xa activity and parameters of CWA-APTT or CWA-sTF/FIXa

X	Y = anti-Xa activity	
2nd DPT of APTT	Y = 5.82363 -0.0409X	r = -0.1874
2nd DPH of APTT	Y = -5.6573 + 0.01559X	r = 0.508
1st DPT of APTT	Y = 4.11041 -0.0132X	r = -0.1300
1st DPH of APTT	Y = -7.4494 + 0.03933X	r = 0.4126
FFT of APTT	Y = 4.44994 -0.0171X	r = -0.1440
FFH of APTT	Y = 5.3013 -0.0078X	r = -0.0588
2nd DPT of sTF/FIXa	Y = 18.2075 -0.1977X	r = -0.2848
2nd DPH of sTF/FIXa	Y = 0.62224 + 0.03799X	r = 0.1091
1st DPT of sTF/FIXa	Y = -15.992 + 0.19404X	r = 0.2789
1st DPH of sTF/FIXa	Y = 11.1788 -0.0754X	r = -0.2431
FFT of sTF/FIXa	Y = -15.125 + 0.15966X	r = 0.9716
FFH of sTF/FIXa	Y = 17.7308 -0.0385X	r = -0.4067

CWA, clot waveform analysis; DPT, derivative peak time; DPH, derivative peak height; FFT, Fibrin formation time; FFH, Fibrin formation height
APTT, activated partial thromboplastin time; sTF/FIXa. small amount of tissue factor induced FIX activation assay

Eleven patients were treated with heparin, and 23 samples contained heparin, while 16 did not. Although the CWA-APTT showed that there were no significant differences in the peak times or heights

between plasma samples with and without heparin, the CWA-sTF/FIXa showed that the peak height of the 1st DP was significantly lower in plasma with heparin than in plasma without heparin (**Figure 3**). The anti-Xa activity and the CWA-sTF/FIXa-peak time of FFC showed a close correlation, but the other parameters of the CWA-APTT or CWA-sTF/FIXa were not closely correlated (**Table 2**).

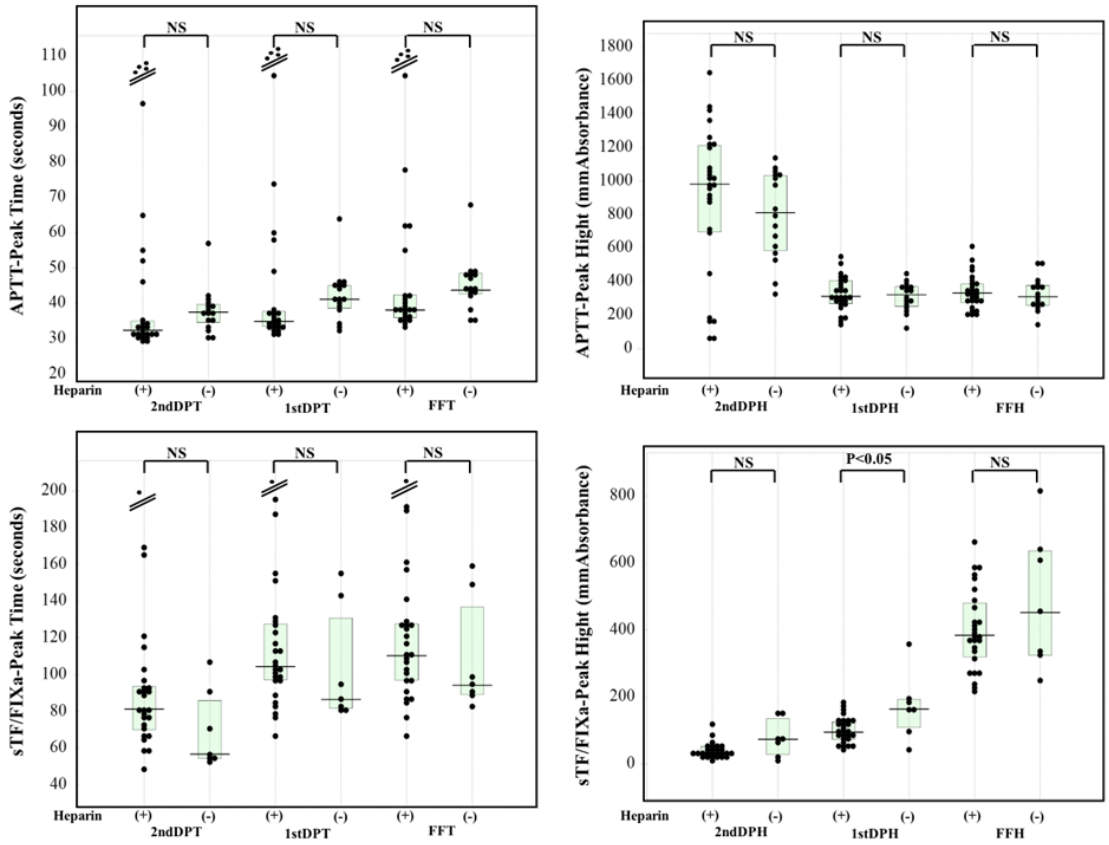

Figure 3. CWA-APTT and CWA-sTF/FIXa in COVID-19 patients treated with and without heparin.
APTT, activated partial thromboplastin time; sTF/FIXa. small amount of tissue factor- induced FIX activation assay

Although there were no significant differences in the CWA-APTT-peak time and height or the CWA-sTF/FIXa-peak height in 35 samples (19 survivors and 16 non-survivors), the peak times of the CWA-sTF/FIXa-FFC, CWA-sTF/FIXa -1st DP or CWA-sTF/FIXa -2nd DP were significantly longer in non-survivors than in survivors (**Figure 4**). The ADAMTS 13 activities were significantly lower in patients with COVID-19, especially in the one patient with TMA (12%) than in others. The plasma levels of C5b-9 were significantly lower in patients with COVID-19 than in healthy volunteers. However, there were no significant differences in ADAMTS13 activities or C5b-9 levels between non-survivors and survivors (**Table3**).

Table 3. ADAMTS13 and C5b-9 levels in healthy volunteers and COVID-19 patients (survivors and non-survivors)

	COVID-19	P	Healthy volunteers	Survivors	P	Non-survivors
ADAMTS-13 Activity (%)	60.9 (36.5-73.4)	P< 0.001	107 (93.7-124)	62.6 (50.2-73.1)	P >0.05	55.8 (31.3-75.3)
C5b-9 (ng/ml)	163 (116-217)	P <0.001	91.3 (61.9-138)	146 (114-332)	P >0.05	173 (137-197)

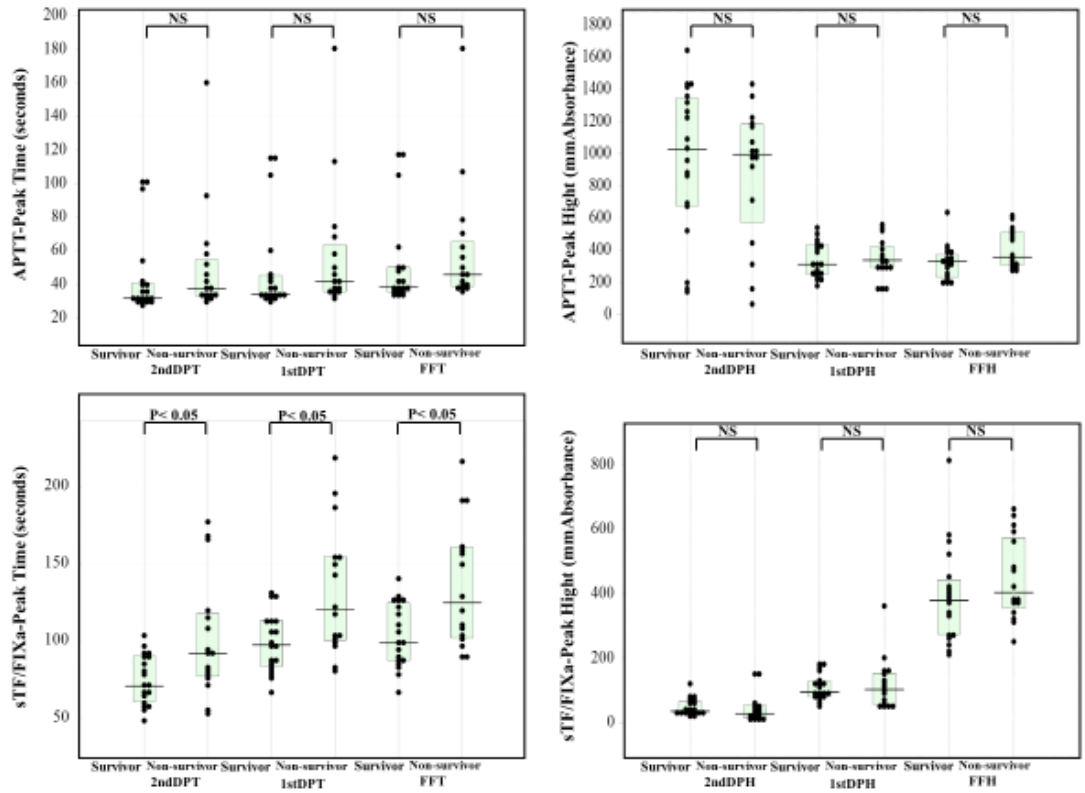

Figure 4. CWA-APTT and CWA- sTF/FIXa in survivors and non-survivors.
APTT, activated partial thromboplastin time; sTF/FIXa, small amount of tissue factor- induced FIX activation assay; NS, not significant

DISCUSSION

While a few complications are observed in general hospitals [7, 8], many patients with severe COVID-19 have thrombotic complications in the intensive- care unit [6]. Marked platelet activation in COVID-19 has been previously reported [14] and prolongation of APTT has been experienced in severe COVID-19 patients in our hospital and thus, hypercoagulability may lead to the development of venous thromboembolism [22].

Regarding the CWA-APTT, the peak time of the FFC, 1st DP or 2nd DP which is generally measured as the routine APTT, were prolonged, and the peak heights of the FFC and 1st DP were elevated in patients with COVID-19. The prolongation of the peak time of the APTT was not reported to be correlated with the bleeding tendency [16]. By contrast, an elevated peak height of the 1st DP has been reported in patients demonstrating malignant neoplasm with thrombosis [17]. Although the prolongation of the peak time of the CWA-APTT is considered to be due to the effect of heparin in our cases, no significant difference in the peak time of the CWA-APTT has been noted between COVID-19 patients treated with and without heparin treatment. The anti-Xa activity was not significantly correlated with the peak time of the CWA-APTT. These finding suggest that COVID-19 patients have a prolonged APTT without the effect of heparin, and the APTT is not well correlated with the heparin concentration in patients with COVID-19. The CWA-APTT was also reported not to be closely correlated with orthopedic surgery patients treated with anti-Xa agents [23].

sTF/FIXa [16], which is based on the diluted prothrombin time, reflects physiological coagulation including thrombin burst [24] and the effects of platelets, and the peak times of the 2ndDP and FFC were prolonged and the peak heights of the 1st DP and FFC, elevated in COVID-19 patients. These data suggest that hypercoagulability exists in patients with COVID-19. As the patient with PE showed an extremely high peak height of the 1st DP, an elevated peak height of the 1stDP may indicate a high risk of thrombosis. In patients with malignant neoplasm, the peak height of the 1st DP was significantly higher than in patients with thrombosis than in those without thrombosis [17]. The peak time of the 1st DP was markedly prolonged in patients with idiopathic thrombocytopenic purpura [25]. The three peak times were significantly longer in non-survivors than in survivors, suggesting that this hemostatic abnormality may reflect a poor outcome.

The decrease in the ADAMTS13 activity did not reach the diagnostic range for thrombotic thrombocytopenic purpura [20] except for in one TMA case, and increased C5b-9 levels were also not in the diagnostic range of atypical hemolytic uremic syndrome [21]. Although there was no significant difference in the ADAMTS13 activity or C5b-9 levels between non-survivors and survivors, these factors may markedly affect the pathological state in patients with COVID-19.

Limitations

This study was small in scale and involved a retrospective study. Most patients had already been treated with heparin, and there were no satisfactory samples without anticoagulants.

Conclusion

The peak time of the CWA-APTT was prolonged in patients with COVID-19, and these patients showed hypercoagulability. A routine APTT assay is not adequate for monitoring heparin treatment. Although ADAMTS-13 activities are decreased and C5b-9 levels are increased in patients with COVID-19, the relationship between these abnormalities and thrombosis has not yet been established.

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