Full Length Article

Assessment of thromboembolism risk in COVID-19 patients with cardiovascular disease risk factors: Analysis of a Japanese Nationwide Registry☆

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ABSTRACT

Introduction: Patients with COVID-19 and cardiovascular disease risk factors (CVDRF) have been reported to develop coagulation abnormalities frequently. However, there are limitations in conventional predictive models for the occurrence of thromboembolism in patients with COVID-19 and CVDRF.

Methods: Among data on 1518 hospitalized patients with COVID-19 registered with CLAVIS-COVID, a Japanese nationwide cohort study, 693 patients with CVDRF were subjected to least absolute shrinkage and selection operator (LASSO) analysis; a method of shrinking coefficients for reducing variance and minimizing bias to increase predictive accuracy. LASSO analysis was performed to identify risk factors for systemic thromboembolic events; occurrence of arterial and venous thromboembolism during the index hospitalization as the primary endpoint.

Results: LASSO analysis identified a prior systemic thromboembolism, male sex, hypoxygenemia requiring invasive mechanical ventilation support, C-reactive protein levels and D-dimer levels at admission, and congestion on chest X-ray at admission as potential risk factors for the primary endpoint. The developed risk model consisting of these risk factors showed good discriminative performance (AUC-ROC: 0.83, 95 % confidence interval [CI]: 0.77–0.90), which was significantly better than that shown by D-dimer (AUC-ROC: 0.70, 95

% CI: 0.60–0.80) (p < 0.001). Furthermore, systemic embolic events were independently associated with in-hospital mortality (adjusted odds ratio: 3.29; 95 % CI: 1.31–8.00).

Conclusions: Six parameters readily available at the time of admission were identified as risk factors for thromboembolic events, and these may be capable of stratifying the risk of in-hospital thromboembolic events, which are associated with in-hospital mortality, in patients with COVID-19 and CVDRF.

1. Introduction

Previous studies have clearly reported that patients with coronavirus disease-2019 (COVID-19) and cardiovascular disease risk factors (CVDRF) have higher risks of cardiovascular events and mortality than those without CVDRF [1,2] Although one of the leading causes of death in patients with COVID-19 is acute respiratory distress syndrome (ARDS; incidence, 17–41 %) [3], pathological autopsy-based studies also suggest multi-organ thromboembolism as a potential cause of unexplained death [4]. The pathophysiological background of COVID-19-related thromboembolic events has not yet been clarified; however, abnormal increases in coagulation capacity due to severe inflammatory reaction and the weakening of anticoagulation and fibrinolysis in patients with COVID-19 may potentially predispose them to a hypercoagulative state and subsequent thromboembolic events [5]. Indeed, a recent report showed that patients with COVID-19 who experienced sudden worsening of symptoms and sudden death frequently showed markedly elevated D-dimer levels [6], which is associated with the severity of thromboembolism in patients with COVID-19 [7]. However, a limited number of studies have investigated the risk factors for thromboembolic events or the relationships between thromboembolic events and mortality in patients with COVID-19 and CVDRF; currently, the administration of routine anticoagulation therapy before risk stratification for embolic events is not recommended [8–11]. Therefore, we sought to evaluate the prognostic impact of thromboembolic events, to identify the risk factors for thromboembolism, and to develop a risk model capable of predicting thrombotic events in patients with CVDRF hospitalized for COVID-19.

2. Materials and methods

2.1. Study population and endpoints

This study involves a subanalysis of data obtained from the CLAVIS-COVID registry, which is a Japanese nationwide cohort that included data on 1518 patients with COVID-19 who were treated in 49 acute care hospitals between January and May 2020. The study design and findings have been published elsewhere [12–15]. To describe briefly, this registry was designed to investigate the clinical features and outcomes of patients with COVID-19 who had pre-existing or developing cardiovascular disease or CVDRF. Among hospitals in Japan, major acute care hospitals that accommodated patients with COVID-19 were included in this study, which resulted in the enrollment of approximately 9 % (1518 out of 16,851) of all Japanese patients with COVID-19 during the study period. Diagnosis was confirmed with the polymerase chain reaction test for COVID-19 using oropharyngeal swab specimens from all subjects. During the patient enrollment period, the Japanese government mandated that all patients diagnosed with COVID-19 be hospitalized, regardless of severity. CVDRF included hypertension, diabetes, dyslipidemia, and a history or manifestations of heart failure on admission, coronary artery disease, myocardial infarction, peripheral artery disease, valvular heart disease, cardiac arrhythmia, pericarditis, myocarditis, congenital heart disease, pulmonary hypertension, deep vein thrombosis, pulmonary embolism, aortic dissection, aortic aneurysm, cerebral infarction/transient ischemic attack, the use of cardiac devices, heart transplantation, and cardiac arrest. Detailed definitions of each comorbidity have been reported previously [12]. After the exclusion of patients without CVDRF, 693 patients with CVDRF were ultimately included in the study. The primary endpoint was defined as the occurrence of a systemic embolic event, such as ischemic stroke, venous thromboembolism (VTE), myocardial infarction, and systemic arterial embolism observed during the index hospitalization. Enrolled patients were divided into two groups according to whether they experienced the primary endpoint (Fig. 1). The study followed the principles outlined in the Declaration of Helsinki. The study protocol, including the use of opt-out method for obtaining informed consent, was approved by the ethics committee of the Toho University Omori Medical Center (No. M20253) and the local ethics committees of all participating institutions. Furthermore, in accordance with the International Committee of Medical Journal Editors, this clinical study was registered with the University Hospital Medical Information Network Clinical Trial Registry before the first patient was enrolled (UMIN-ID: UMIN000040598).

2.2. Data collection and follow-up

We evaluated patients' baseline characteristics including age, sex, race, body mass index, blood pressure, heart rate, body temperature, respiratory rate, oxygen saturation, histories of smoking, CVDRF and other comorbidities, blood gas analysis, complete blood picture (white blood cell (WBC), differential WBC, and platelet counts, and hemoglobin level), blood chemistry test (albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), renal function parameters (glomerular filtration rate and blood urea nitrogen), levels of serum sodium, serum potassium, C-reactive protein (CRP), procalcitonin, glycated hemoglobin, ferritin, brain natriuretic peptide (BNP), N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), prothrombin time, and D-dimer), abnormal findings on chest radiographs (infiltrative shadow, congestion, and pleural effusion), and treatment regime in the intensive care unit, including the use of invasive mechanical ventilation. In particular, the measurement of CRP and D-dimer was performed in the laboratories of each research facility. Information on prehospital oral medications, including antiplatelet agents, anticoagulants, beta-blockers, renin-angiotensin system inhibitors, angiotensin receptor neprilysin inhibitors, calcium channel blockers, mineralocorticoid receptor antagonists, diuretics, statins, nonsteroidal anti-inflammatory drugs, and steroids was recorded. Abnormal radiography findings were classified by the cardiologist or physician as pneumonia-like infiltrates or congestion, and the presence of pleural effusion was also assessed. As a general rule, intubation was performed when the physician determined that ventilator management with positive pressure ventilation was necessary because oxygenation was not improved by low-flow delivery methods (e.g., simple face mask or non-rebreathing mask). However, the decision for intubation was left to the physician in charge at each facility. In patients who had any missing parameters that were required for calculation of the risk scores, missing values were multiply imputed with the missing-at-random assumption. We generated 20 datasets with imputation using the variables presented in Table 1. Additionally, all laboratory and imaging data were collected at the time of admission, which was at the onset of COVID-19. If the patient did not present with symptoms of COVID-19 at the time of admission, the date of the first positive PCR test was considered as the onset date. The primary endpoints were ischemic stroke and VTE, including deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), myocardial infarction, and systemic arterial thromboembolism. Data on other cardiovascular events, including heart failure, new-onset atrial fibrillation, and myocarditis were also recorded, as they were

identified by previous studies as risk factors of thromboembolism in COVID-19 patients [16]. Additionally, serious adverse events related to COVID-19, such as ARDS, sepsis, and acute kidney injury (AKI), were also investigated. All events during the index hospitalization were diagnosed and reported by the attending physician at each hospital.

2.3. Statistical analysis

Data are expressed as the mean and standard deviation for normally distributed variables and as the median with interquartile range for non-normally distributed data. Categorical data are expressed as numbers and percentages. Group differences were evaluated using the Student's *t*-test or Mann–Whitney *U* test for continuous variables and the chi-squared or Fisher exact test for categorical variables, as appropriate. To evaluate whether the occurrence of thromboembolic events was associated with in-hospital mortality independent of the other known prognostic factors, we performed multivariate logistic regression analysis using the 4C mortality score. This is a risk stratification tool that predicts in-hospital mortality or in-hospital clinical deterioration, defined by any requirement of ventilatory support or critical care, or death. We have previously validated this score in our cohort [17]. For the selection of risk factors, least absolute shrinkage and selection operator (LASSO) analysis was used to identify variables among all parameters collected as baseline characteristics (Table 1). Compared with conventional stepwise multivariable regression modelling, this technique enables a more rigid variable selection and is less likely to overestimate the predictive value even when the number of events is small [18]. Furthermore, to test the performance of the model consisting of identified risk factors, we developed a risk score weighting of the coefficient for selected variables obtained in the multivariable logistic regression model for the composite primary endpoint. The area under the receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated to evaluate the risk discrimination ability of the developed risk model. We further compared the discrimination ability of the developed risk model with D-dimer, which was previously found to be a strong biomarker associated with thromboembolic events in patients with COVID-19 [7]. Statistical significance threshold was set at a two-tailed p-value of <0.05. Statistical analyses were performed using R (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.R-project.org).

3. Results

3.1. Clinical profiles of the study population

The baseline patient profiles are shown in Table 1. The average age of the study population was 68 years, and 65 % of the patients were male. Among the 693 patients with COVID-19 and CVDRF, 35 (5.1 %) experienced the primary endpoint. Patient characteristics of the thromboembolic and non-thromboembolic groups are presented in Table 1. The proportion of male patients, maximum body temperature before hospital admission, and heart rate at admission were significantly higher, while blood pressure and oxygen saturation at admission were significantly lower in the thromboembolic group than in the non-thromboembolic group. Regarding the CVDRF, a higher number of patients had a history of VTE and fewer patients had a history of hypertension in the thromboembolic group than in the non-thromboembolic group. At admission, patients in the thromboembolic group were more likely to show pulmonary congestion on chest radiographs and receive mechanical ventilation than those in the non-thromboembolic group. Blood tests showed that the levels of albumin and sodium were significantly lower, and total bilirubin, alanine aminotransferase, LDH, CRP, D-dimer, prothrombin time, and ferritin levels were significantly higher in the thromboembolic group. Patients in both the groups received oral medications immediately before index hospitalization.

3.2. Outcomes

Among the 35 patients who reached the primary endpoint, 8, 1, 12, 2, and 12 patients had stroke, DVT, PTE, and systemic arterial thromboembolism, respectively, during the hospital stay (median: 24 [interquartile range: 11–29] days) (Table 2). There was no significant difference in the incidence of cardiovascular events, including heart failure, new-onset atrial fibrillation, and myocarditis between those with and without thromboembolic events. However, in terms of serious adverse events, ARDS, sepsis, and AKI occurred significantly more frequently in the thromboembolic group than in the non-

Fig. 1. Study population.
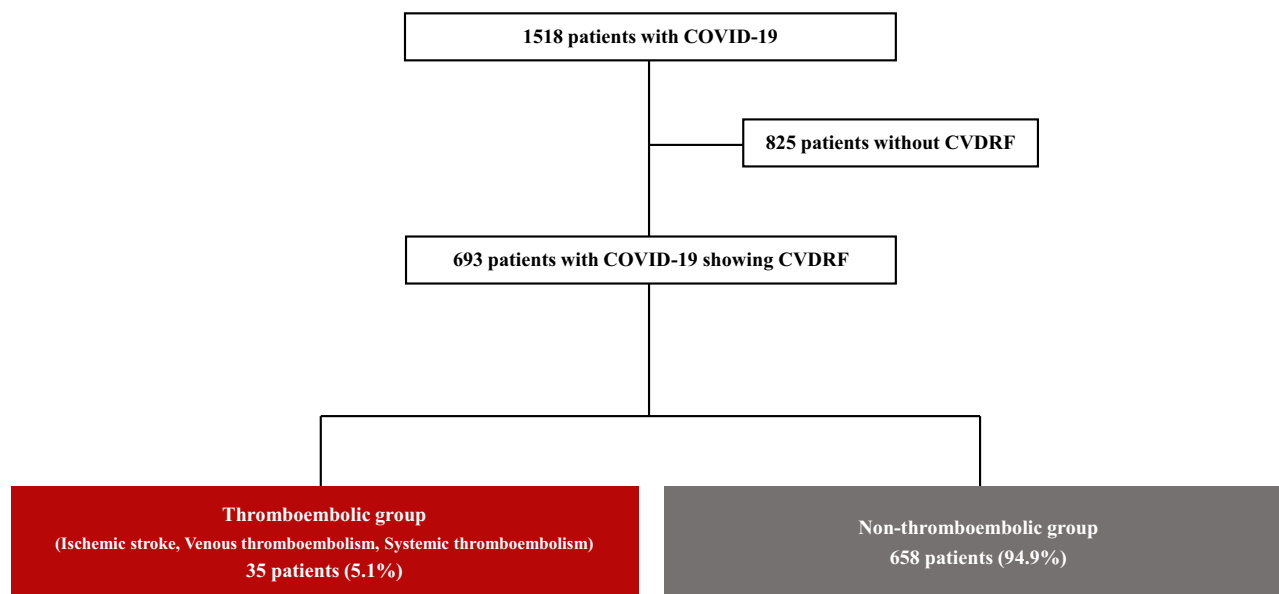Cardiovascular disease risk factors (CVDRF) include the following diseases and states: hypertension, diabetes mellitus, heart failure, coronary artery disease, old myocardial infarction, valvular heart disease, arrhythmia, old cerebral infarction, venous thromboembolism, left ventricular assist device, cardiac implantable electronic device, cardiopulmonary arrest, pericarditis, dissection, and aneurysm.

Table 1
Baseline clinical profile of the study population.

	Non-thromboembolic group n = 658	Thromboembolic group n = 35	Missing (%)	P value
Age, years, (SD)	68.38 (14.98)	66.71 (12.38)	0	0.518
Male patients, (%)	416 (63.2)	33 (94.3)	0	<0.001
Body mass index, kg/m^2, (median [IQR])	23.9 [21.1–26.7]	23.3 [21.3–24.7]	16.3	0.542
Current smoker, (%)	86 (13.1)	1 (2.9)	5.5	0.13
Japanese, (%)	633 (96.2)	33 (94.3)	0	0.903
Vital signs				
Maximum body temperature before hospitalization, °C (median [IQR])	38.0 [37.5–38.5]	38.50 [37.8–38.9]	7.1	0.019
Respiratory rate, breaths/min (median [IQR])	20.0 [16.8–24.0]	20.0 [16.0–25.5]	22.1	0.55
Percutaneous oxygen saturation, % (median [IQR])	96.0 [94.0–98.0]	94.0 [91.5–97.0]	0.6	0.006
Heart rate, beats/min (median [IQR])	85.0 [75.0–97.0]	92.0 [82.0–100.5]	0.9	0.02
Systolic blood pressure, mmHg (median [IQR])	132.0 [119.0–148.0]	126.0 [113.0–137.0]	0.7	0.015
Diastolic blood pressure, mmHg (median [IQR])	78.1 [68.0–89.0]	79.0 [70.0–86.5]	0.9	0.916
CVDRF				
Hypertension, (%)	493 (74.9)	20 (57.1)	0	0.032
Dyslipidemia, (%)	250 (38.0)	19 (54.3)	0	0.08
Diabetes mellitus, (%)	249 (37.8)	17 (48.6)	0	0.274
Atrial fibrillation, (%)	59 (9.0)	1 (2.9)	0	0.345
Sick sinus syndrome, (%)	6 (0.9)	0	0	NA
Atrio ventricular block, (%)	1 (0.2)	0	0	NA
Coronary artery disease, (%)	68 (10.3)	2 (5.7)	0	0.551
Old myocardial infarction, (%)	29 (4.4)	1 (2.9)	0	>0.99
Valvular heart disease, (%)	19 (2.9)	0	0	NA
Prior cerebral infarction, (%)	51 (7.8)	1 (2.9)	0	0.458
Heart failure, (%)	57 (8.7)	3 (8.6)	0	>0.99
Prior venous thromboembolism, (%)	5 (0.8)	3 (8.6)	0	<0.001
Peripheral artery disease, (%)	5 (0.8)	0	0	NA
Others, (%)	37 (5.6)	0	0	NA
Comorbidities				
Chronic obstructive pulmonary disease, (%)	33 (5.0)	2 (5.7)	0	>0.99
Liver cirrhosis, (%)	1 (0.2)	0	0	NA
Chronic kidney disease, (%)	47 (7.1)	1 (2.9)	0	0.581
Malignancy, (%)	63 (9.6)	4 (11.4)	0	0.946
Hemodialysis, (%)	18 (2.7)	1 (2.9)	0	>0.99
Invasive mechanical ventilation, (%)	29 (4.4)	6 (17.1)	0	0.003
Laboratory data				
Albumin, (mg/dL) (median [IQR])	3.3 [2.9–3.8]	2.9 [2.4–3.3]	7.8	0.001
Total bilirubin, (mg/dL) (median [IQR])	0.5 [0.4–0.7]	0.6 [0.5–0.8]	6.5	0.024
AST, (U/L) (median [IQR])	33.0 [25.0–50.0]	38.0 [28.0–53.0]	1.9	0.208
ALT, (U/L) (median [IQR])	26.0 [17.0–42.8]	34.0 [23.0–46.5]	2	0.037
LDH, (IU/L) (median [IQR])	290.5 [226.0–413.0]	366.0 [275.5–489.5]	11	0.005
Blood urea nitrogen, (mg/dL) (median [IQR])	16.6 [12.5–24.0]	20.0 [14.9–26.9]	2	0.091
eGFR (median [IQR])	87.1 [65.7–106.1]	82.5 [64.2–103.6]	2	0.778
Sodium, (mEq/L) (median [IQR])	138.0 [135.0–141.0]	136.0 [132.5–137.0]	2.2	0.001
Potassium, (mEq/L) (median [IQR])	4.0 [3.7–4.3]	4.1 [3.8–4.5]	2.2	0.242
White blood cells, (cells/μL) (median [IQR])	5700.0 [4400.0–7500.0]	6000.0 [5100.0–8400.0]	2.2	0.246
Lymphocytes, (cells/μL) (median [IQR])	941.7 [660.4–1273.2]	850.6 [528.6–1023.0]	6.8	0.057
Neutrophils, (cells/μL) (median [IQR])	4208.5 [2971.4–5719.0]	4886.4 [3536.6–6408.0]	13.3	0.087
Platelets, 10^4/μL (median [IQR])	19.0 [14.8–24.8]	17.4 [12.9–24.2]	2.5	0.439
Hemoglobin, (g/dL) (median [IQR])	13.4 [11.7–14.7]	13.3 [12.1–14.1]	2	0.889
C-reactive protein, (mg/dL) (median [IQR])	5.50 [1.78–11.2]	12.4 [6.58–19.0]	3.8	<0.001
Procalcitonin, (ng/mL) (median [IQR])	0.34 [0.15–1.00]	0.40 [0.11–1.46]	61.9	0.915
HbA1c, (%) (median [IQR])	6.30 [5.94–6.99]	6.40 [5.96–7.01]	43.9	0.711
D-dimer, (μg/mL) (median [IQR])	1.90 [1.10–3.37]	4.06 [2.25–21.09]	33.5	<0.001
PT, (sec) (median [IQR])	22.0 [12.2–71.8]	58.6 [13.9–86.5]	24.1	0.04
Ferritin, (ng/mL) (median [IQR])	572.4 [301.3–1078.1]	1080.2 [802.2–1909.5]	54.3	<0.001
NT-pro BNP, (pg/dL) (median [IQR])	3750.6 [1660.5–8285.3]	3134.6 [265.0–9232.5]	86.3	0.272
BNP, (pg/dL) (median [IQR])	70.4 [37.0–140.3]	93.6 [41.0–207.1]	68.7	0.209
Arterial blood gas				
pH (median [IQR])	7.44 [7.41–7.47]	7.43 [7.40–7.46]	61.6	0.399
PaO$_2$, (mmHg) (median [IQR])	80.6 [72.1–92.2]	83.9 [70.0–99.0]	61.3	0.481
PaCO$_2$, (mmHg) (median [IQR])	35.7 [33.0–39.0]	35.8 [31.0–38.0]	61.5	0.373
SaO$_2$, (%) (median [IQR])	95.0 [93.4–96.2]	95.0 [93.8–97.0]	62	0.349
Lactate, (mg/dL) (median [IQR])	1.29 [1.02–1.89]	1.18 [0.71–1.70]	62.8	0.158
X-ray findings				
Pneumonia like infiltration, (%)	474 (72.0)	30 (85.7)	9.1	0.115
Congestion, (%)	43 (6.5)	10 (28.6)	9.1	<0.001
Pleural effusion, (%)	42 (6.4)	3 (8.6)	9.1	0.873
Prehospital medications				
ACE-i, (%)	34 (5.2)	1 (2.9)	0	0.832
ARB, (%)	219 (33.3)	13 (37.1)	0	0.774
ARNI, (%)	0	0	0	NA
β blockers, (%)	107 (16.3)	4 (11.4)	0	0.601
Ca blockers, (%)	257 (39.1)	9 (25.7)	0	0.161

thromboembolic groups (ARDS: 34.3 % vs. 12.9 %, p = 0.002; sepsis: 22.9 % vs. 7.1 %, p = 0.004; AKI: 20.0 % vs. 8.2 %, p = 0.027).

Moreover, in-hospital mortality was also significantly higher in the thromboembolic group (31.4 % vs. 14.7 %, p = 0.015) (Supplementary Fig. 1). Univariate analysis revealed that thromboembolism was associated with in-hospital mortality (odds ratio (OR): 3.05, 95 % confidence interval (CI): 1.43–6.24, p = 0.003). Moreover, we found that thromboembolism was independently associated with in-hospital mortality even after adjusting for the 4C mortality score (OR: 3.31; 95 % CI: 1.35–7.89, p = 0.007).

3.3. Risk factors for thromboembolic events

LASSO analysis identified male sex (OR: 8.83, 95 % CI: 2.56–55.8), history of embolism (OR: 5.92, 95 % CI: 0.58–46.6), congestion on chest radiographs at admission (OR: 5.25, 95 % CI: 2.01–12.8), use of invasive mechanical ventilation (OR: 3.21, 95 % CI: 1.03–8.79), CRP level at admission (OR: 1.05, 95 % CI: 1.00–1.09), and D-dimer level at admission (OR: 1.01, 95%CI: 1.00–1.02) as the predictors of the primary endpoint (Table 3). The discriminatory performance of the developed risk model (ROC AUC: 0.84, 95 % CI: 0.77–0.90) was significantly better than that of D-dimer alone (ROC AUC: 0.70, 95 % CI: 0.60–0.80) (p < 0.001) (Fig. 2). An exploratory LASSO analysis identified the following risk factors for thromboembolism in critically ill patients, defined as those requiring mechanical ventilation or intensive care unit management: history of atrial fibrillation, history of VTE, Japanese nationality, sex, beta blocker administration at admission, diuretic administration at admission, abnormalities in laboratory parameters such as platelet count, total bilirubin level, prothrombin time, and BNP level at admission, and inflammatory changes and congestion on chest radiographs at admission. The discriminatory performance of this risk model (ROC AUC: 0.98, 95 % CI: 0.96–0.99) was significantly better than that of D-dimer alone (ROC AUC: 0.68, 95 % CI: 0.57–0.78) (p < 0.001) (Supplementary Fig. 2). In addition, LASSO analysis identified the following risk factors for the composite endpoint of mortality and intubation: history of VTE, highest temperature value prior to admission, age, sex, respiratory rate at admission, oxygen saturation at admission, method of oxygenation, history of dialysis, blood pH and blood gas findings at admission, arterial partial pressure of oxygen at admission, beta blocker administration at admission, aspirin administration at admission, abnormalities in laboratory parameters such as platelet count and LDH, albumin, sodium, potassium, CRP, and ferritin levels at admission, and inflammatory changes and congestion on chest radiographs at admission. The ROC AUC of this risk model was 0.93 (95 % CI: 0.90–0.96) with high discriminatory performance (Supplementary Fig. 3).

4. Discussion

The principal finding of this study is that thromboembolic events

Table 2
Clinical outcomes during the index hospitalization.

	Non-thromboembolic group n = 658	Thromboembolic group n = 35	P value
Ischemic stroke/VTE/ Systemic arterial embolism, (%)	0 (0)	35 (100)	NA
Ischemic stroke, (%)	0 (0)	8 (22.9)	NA
VTE, (%)	0 (0)	13 (37.1)	NA
DVT, (%)	0 (0)	1 (2.9)	NA
PTE, (%)	0 (0)	12 (34.3)	NA
Myocardial infarction, (%)	0 (0)	2 (5.7)	NA
Systemic arterial embolism, (%)	0 (0)	12 (34.3)	NA
Heart failure, (%)	4 (0.6)	0 (0)	NA
New atrial fibrillation, (%)	37 (5.6)	2 (5.7)	>0.99
Myocarditis, (%)	2 (0.3)	0 (0)	NA
ARDS, (%)	85 (12.9)	12 (34.3)	0.002
Sepsis, (%)	47 (7.1)	8 (22.9)	0.004
Acute kidney injury, (%)	54 (8.2)	7 (20.0)	0.027
In-hospital death, (%)	97 (14.7)	11 (31.4)	0.015

ARDS = acute respiratory distress syndrome; DVT = deep venous thrombosis; PTE = pulmonary thromboembolism; VTE = venous thromboembolism.

Table 3
Predictive value of each parameter of the new risk model.

Variable	Definition	Beta coefficient	OR	95%CI
Sex	Male	2.18	8.83	2.56–55.8
VTE	Prior venous thromboembolism	1.78	5.92	0.58–46.6
X-ray findings	Congestion on chest X-ray at admission	1.66	5.25	2.01–12.8
Intubation	Use of invasive mechanical ventilation	1.17	3.21	1.03–8.79
CRP	Baseline CRP	0.05	1.05	1.00–1.09
D-dimer	Baseline D-dimer	0.01	1.01	1.00–1.02

CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; VTE = venous thromboembolism.

were observed in 5.1 % of patients with COVID-19 and CVDRF, and thromboembolic events were independently associated with in-hospital mortality. The six readily available at the time of admission, namely, male sex, history of embolism, congestion on chest radiographs at admission, use of invasive mechanical ventilation, CRP level at admission, and D-dimer level at admission, successfully predicted in-hospital thromboembolic events in COVID-19 patients with CVDRF, and the risk model consisting of these parameters performed better than D-dimer alone in terms of discrimination.

Table 1 (*continued*)

	Non-thromboembolic group n = 658	Thromboembolic group n = 35	Missing (%)	P value
MRA, (%)	23 (3.5)	2 (5.7)	0	0.825
NSAIDS, (%)	28 (4.3)	1 (2.9)	0	>0.99
Loop diuretics, (%)	54 (8.2)	2 (5.7)	0	0.834
Statins, (%)	200 (30.4)	14 (40.0)	0	0.312
Aspirin, (%)	70 (10.6)	3 (8.6)	0	0.916
Clopidogrel, (%)	20 (3.0)	1 (2.9)	0	>0.99
Warfarin, (%)	12 (1.8)	2 (5.7)	0	0.328
DOAC, (%)	38 (5.8)	0	0	NA
Steroid, (%)	36 (5.5)	1 (2.9)	0	0.776

ACE-i = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BNP; brain natriuretic peptide; CVDRF = cardiovascular disease risk factor, DOAC = direct oral anticoagulants; eGFR; estimated glomerular filtration rate; HbA1C = hemoglobin A1C; ICU = intensive care unit; LDH = lactate dehydrogenase; MRA = mineralocorticoid receptor antagonist; NSAIDS = non-steroid anti-inflammatory drugs; NT-pro BNP = n-terminal pro-brain natriuretic peptide; PT = prothrombin time, SD = standard deviation.
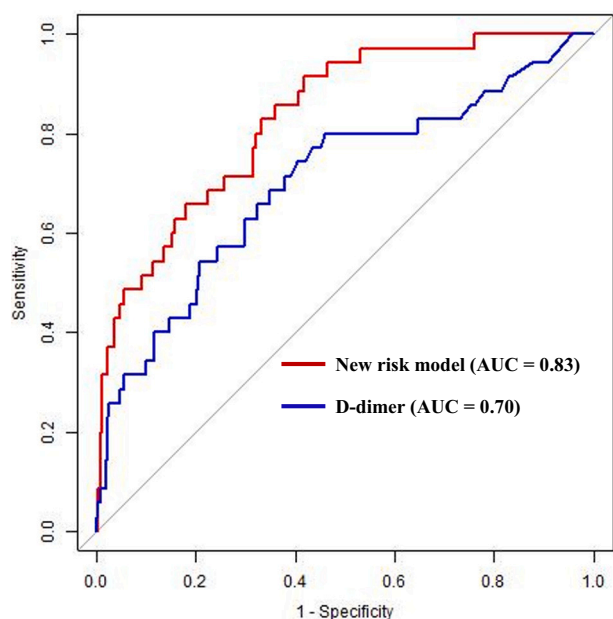
Fig. 2. Comparison of receiver operating curves between with the new risk model and D-dimer alone for thromboembolism.

The median area under the curve for the new risk model is 0.83 (95 % confidence interval: 0.77–0.90) and for D-dimer alone is 0.70 (95 % confidence interval: 0.60–0.80).

4.1. Thromboembolism and in-hospital mortality

A meta-analysis showed that the prevalence of VTE in patients with COVID-19 ranges from 9.5 % to 40.3 %, depending on the frequency of enforcement of VTE screening [19]. However, few studies have evaluated the incidence of arteriovenous thromboembolism in patients with COVID-19. As reported recently, the incidence of arteriovenous thromboembolism varies according to the severity of COVID-19, with approximately 2.6–35 % of patients having thromboembolism (arterial thromboembolism: 0.4–8.3 %) [16,20]. The incidence of arteriovenous thromboembolism in the current study (5.1 %) is consistent with that reported previously; however, the incidence of VTE was very low at 1.8 % (DVT, 0.1 %; PTE, 1.7 %). A possible reason for this difference was that few screening tests for thromboembolism, such as lower extremity venous echocardiography or contrast-enhanced computed tomography, were performed for asymptomatic VTE, since hospitals prioritized the prevention of the spread of the virus among in-hospital patients and clinical staff. The in-hospital mortality rate of patients with CVDRF in the current study was relatively higher than the previously reported rate [21]. In particular, it was high in patients who developed thromboembolism. In summary, the current study may have included patients with CVDRF who had a poorer prognosis but lower chances of being screened for thrombosis than the patients in prior studies. Our data also show that thromboembolism is independently associated with in-hospital mortality; thus, the prediction of thromboembolism is important.

4.2. New risk model of thromboembolism in patients with COVID-19

To the best of our knowledge, little is known about the incidence and risk factors of arteriovenous systemic thromboembolism in patients with COVID-19. D-dimer level alone at admission has been reported to be a possible predictor of thromboembolic events if the patients have substantially high D-dimer levels [22]. However, this methodology does not work well in patients showing a mild increase in D-dimer levels. If the infection site in patients with symptomatic COVID-19 is limited on the lung alveoli at admission, the initiation of systemic inflammation by the release of cytokines—such as interleukin-(IL-)1β, IL-6, and tumor

necrosis factor-α, which are known to induce thromboembolism—may not occur [23]. Recently, a new risk scoring system has been proposed, titled "markers of coagulation and hemostatic activation" (MOCHA); its predictive value for arteriovenous thromboembolism in patients with COVID-19 was reportedly superior to that of D-dimer alone [24]. However, the parameters selected for this scoring system, including plasma D-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex, and fibrin monomer levels, are not routinely evaluated in daily clinical practice, and the feasibility of using this system is not clear. In contrast, the current new risk model comprises high risk substrates for embolism, such sex and history of embolism, and multidimensional evaluation of the general condition of the infection (D-dimer, CRP, radiographic congestion on radiographs, and the need for intubation) that together allow early prediction of embolic complications in COVID-19. The AUC of the new risk model was 0.83, which is higher than that of MOCHA (0.74) and indicates the superior diagnostic performance of our model [24]. Moreover, among high-risk patients with COVID-19 and CVDRF, the predictive value of MOCHA for adverse events has not been validated to date. The current model was found to be able to easily predict thromboembolic events with six parameters that can be measured in daily practice in high-risk patients with CVDRF.

4.3. Limitations

There are several limitations to the current study. First, it was not possible to compare baseline characteristics of patients with CVDRF and those without CVDRF, because we only collected basic data (age, sex, admission and discharge dates, in-hospital outcomes) for patients without CVDRF in this study. In addition, the definition of CVDRF was already determined in the original paper, and data such as BMI and smoking were not included in the current definition of CVDRF. Therefore, it is possible that obesity and smoking, that are known CVDRF, are included in the non-CVDRF group. However, the median BMI of patients with CVDRF was 23.9, and only 17.2 % of patients had a BMI of 27.5 or higher, which is the Asian definition of obesity [25]. Similarly, current smoking was observed in only 12.6 % of patients. Therefore, in patients without CVDRF, among whom obesity and smoking are expected to be prevalent to an even lesser extent, the effect of obesity and smoking on the results are likely to be small. Second, because we evaluated patients with COVID-19 who were hospitalized in Japan, the racial and regional differences in the prevalence and outcomes were unevaluable. Therefore, the current risk model may be difficult to apply directly to patients in other countries. Additionally, the new risk model has not been tested in an external population and requires further investigation in future studies. Third, no routine imaging test for a systemic embolism was performed, partly because the cardiologists were not the attending doctors of the patients enrolled in this study. This may have led to an underestimation of the prevalence of thromboembolic events. Finally, it is important to consider that the data analyzed in this study were collected before the vaccine was administered worldwide and before the emergence of various mutated strains of COVID-19.

5. Conclusions

Using a nationwide registry, the present study showed that six simple parameters readily available at the time of admission may be useful for stratifying the risk of in-hospital thromboembolic events in patients with COVID-19. Incidences of ischemic stroke and systemic embolism are associated with high in-hospital mortality in patients with COVID-19 and CVDRF. Further studies are required to optimize anti-thromboembolic therapy based on individualized risk in patients with COVID-19 and CVDRF.

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CRediT authorship contribution statement

Eiji Shibahashi: Acquisition of data, analysis and interpretation of the data, Drafting of the manuscript.

Kentaro Jujo: Conception and design of the research, Acquisition of data, analysis and interpretation of the data, Drafting of the manuscript.

Shunsuke Kuroda: Acquisition of data, Statistical analysis.

Shingo Matsumoto: Acquisition of data.

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Takeshi Kitai: Acquisition of data.

Taishi Yonetsu: Acquisition of data.

Shun Kohsaka: Acquisition of data, Critical revision of the manuscript for important intellectual content.

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Tetsuo Yamaguchi: Acquisition of data.

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Kenichi Hirata: Critical revision of the manuscript for important intellectual content.

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Yuya Matsue: Acquisition of data, Analysis and interpretation of the data, Critical revision of the manuscript for important intellectual content, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.06.007.

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