Prevalence and Clinical Characteristics of Proximal Deep Venous Thrombosis After a High-density Coronavirus Disease 2019 Cluster in a Japanese Psychiatric Hospital

Authors: Toru Sato,MD[1]; Yoshito Ogihara,MD,PhD[1]; Naoki Fujimoto,MD,PhD[1]; Akihiro Usami,MD[2]; Tatsuya Hamaguchi,MD[2]; Masaki Tanabe,MD,PhD[3]; Ryuji Okamoto,MD,PhD[1]; Shinji Nakase,MD,PhD[2]; Kaoru Dohi,MD,PhD[1]

Affiliations: [1]Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Japan. [2]Department of Psychiatry, Suzuka Kosei Hospital, Suzuka, Japan. [3]Department of Clinical Laboratory, Mie University Hospital, Tsu, Japan.

Short title: Proximal DVT in psychiatric patients with COVID-19

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Address for Correspondence: Yoshito Ogihara,MD,PhD

E-mail: yoshito@clin.medic.mie-u.ac.jp

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Abstract

Background: The prevalence of deep venous thrombosis (DVT) remains unclear in hospitalized psychiatric patients following coronavirus disease 2019 (COVID-19).

Method and Results: We retrospectively investigated the prevalence of proximal DVT in 50 hospitalized patients following COVID-19 in a Japanese psychiatric hospital that had developed a COVID-19 cluster between August and September 2020. The prevalence of proximal DVT was 10.0%. Patients with proximal DVT had lower body weight, and higher maximum D-dimer level and International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE score.

Conclusions: Hospitalized psychiatric patients following COVID-19 are at high risk of DVT and should be carefully followed-up.

Keywords: COVID-19; Deep venous thrombosis; Psychiatry

Background

Since the coronavirus disease-2019 (COVID-19) was first reported in December 2019 in Wuhan, China, COVID-19 has rapidly spread all over the world.[1] Multiple studies reported that patients with COVID-19 developed coagulopathy, leading to thromboembolic complications, especially venous thromboembolism (VTE).[2] In Japan, some recent studies reported COVID-19-associated VTE, although the incidence was lower than other countries.[3] Furthermore, a previous study reported that patients following COVID-19 were at high risk of VTE, such as fatal pulmonary embolism (PE) and proximal deep venous thrombosis (DVT), even after discharge from hospital.[4]

In psychiatric patients, the frequency of occurrence of VTE has been reported to be higher than in non-psychiatric patients, resulting from a hypercoagulable state due to antipsychotic agents, physical immobilization, and underlying inherent coagulant dysfunction.[5] Thus, the incidence of VTE in patients with COVID-19 is likely to be higher in psychiatric patients. In the present study, we performed screening of proximal DVT using portable ultrasonography in psychiatric patients after a high-density COVID-19 cluster in a Japanese psychiatric hospital, and investigated the prevalence and clinical features of proximal DVT.

Methods

Study Design and Study Population

This study was a retrospective single-center cohort study that enrolled patients in a ward of a psychiatric hospital that developed a COVID-19 cluster between August 2020 and September 2020 in Mie prefecture, Japan.

Assessment of proximal DVT

Each patient was referred to an acute care medical hospital for the treatment of COVID-19. The patients who survived returned to the psychiatric hospital and underwent three-point compression ultrasound (3PCUS) by a multidisciplinary team that consisted of a cardiologist, a psychologist, and a clinical psychotherapist. We used a V scan Dual Probe with a 3.4–8.0-MHz linear probe and V scan Extend R2 with a 3.3–8.0-MHz linear probe (GE Healthcare, Chicago, IL, USA). The three points consisted of the bilateral common femoral veins, femoral veins, and popliteal veins, which were checked more than once with adequate compression by the probe until the veins were fully compressed. The patients were placed in the sitting position when feasible; otherwise, in the supine position.[6] Proximal DVT was defined as non-compressibility of the vein or visualization of an intraluminal clot. We collected the patients' data from the hospital charts. Additional patients' information during the treatment of COVID-19 in the acute care medical

hospitals was collected by questionnaires to each physician.

Severity of COVID-19

We defined patients who did not require oxygen as mild COVID-19, those who required oxygen as moderate COVID-19, and those who required mechanical ventilation as severe COVID-19.[3]

Physical function and nutritional status

The controlling nutritional status (CONUT) score and Clinical Frailty Scale (CFS) were calculated at the time of 3PCUS. The CONUT score reflects nutritional status and immunological characteristics by classifying patients into three groups: normal nutritional status (CONUT 0–1), mild malnutrition (CONUT 2–4), and moderate-severe malnutrition (CONUT > 5).[7] The CFS evaluates specific domains including comorbidity, function, and cognition, generating a frailty score ranging from 1 (very fit) to 9 (terminally ill).[8]

VTE risk assessments

Maximum D-dimer level was defined as the highest D-dimer level between the onset of COVID-19 and the time of 3PCUS. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE score was used to assess the risk of VTE in hospitalized medical patients at the time of 3PCUS.[9]

Definition of bleeding and thrombotic events

Major bleeding events were defined according to the International Society on Thrombosis and Haemostasis definitions.[10] Thrombotic events were defined as symptomatic arterial and/or venous thrombotic events diagnosed between the onset of COVID-19 and the time of 3PCUS.

Endpoints

The primary outcome was defined as the prevalence of proximal DVT detected by 3PCUS. In addition, we divided the entire population into two groups based on diagnosis of proximal DVT (patients with proximal DVT or patients without proximal DVT), and compared the patients' clinical information and data between the two groups.

All procedures were in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committees of Mie University Hospital and Suzuka Kosei Hospital after the DVT screening were performed for all patients (Reference number H2021-066). In this study, as we used clinical information obtained in routine clinical practice, we obtained informed consent in the form of an opt-out on the hospital's website and bulletin boards in the hospital. This method is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Statistical Analysis

Categorical variables were presented as numbers and percentages. Continuous variables were presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared with the chi-square test when appropriate; otherwise, the Fisher's exact test was used. Continuous variables were compared using Student's t-test or Mann-Whitney U test based on their distributions. All statistical analyses were performed with Medcalc version 20.015. All reported P values are 2-tailed, and $P < 0.05$ was considered significant.

Results

We identified 59 patients in the ward of the psychiatric hospital that recorded the COVID-19 cluster. Of these, 55 patients developed COVID-19. Five patients died because of COVID-19 with no sign of symptomatic PE. The remaining 50 patients underwent 3PCUS 38.6±8.7 days after the onset of COVID-19 and were enrolled in the study (Figure 1). The time of 3PCUS in the mild, moderate, and severe COVID-19 group were 39.8±9.1 days, 35.5±7.0 days, and 36.7±3.8 days, respectively. The time of maximum D-dimer level were 15(6-24) days after the onset. Those in the mild, moderate, and severe COVID-19 group were 15(7-32) days, 13(4-17) days, and 16(15-17) days,

respectively. In the entire population, the mean age was 68.9±9.7 years, 50.0% were male, and the mean body weight (BW) and body mass index (BMI) were 49.4±9.0 kg and 19.8±3.2 kg/m^2, respectively. The median CONUT score and CFS were 4 points and 6 points, respectively, which indicated mild malnutrition and moderately frail status (Table 1). Antipsychotic agents were prescribed in 43 patients (86.0%) including 36 schizophrenia patients (72.0%). The primary outcome was observed in five patients (10.0%), all of whom had asymptomatic proximal DVT (Figure 1). The incidence of DVT in the mild, moderate, and severe COVID-19 groups was 5.6%, 18.2%, and 33.3%, respectively (Figure 2). Prophylactic anticoagulant therapy was administered in 11 patients (22.0%) in the treatment of COVID-19. The administration rate of prophylactic anticoagulation in the mild, moderate, and severe COVID-19 groups was 16.7%, 18.2%, and 100%, respectively. In mild COVID-19 group, one of 6 patients who received prophylactic anticoagulant therapy and one of 30 patients who did not receive prophylactic anticoagulant therapy had proximal DVT, respectively. In moderate COVID-19 group, two of 9 patients who did not receive prophylactic anticoagulant therapy had proximal DVT (Figure 2). The selection of anticoagulant agents was based on each physician's discretion.

Between the patients with and without proximal DVT, there were no significant

differences in patients' characteristics except for the proportion of BW (40.7±7.1 vs. 50.4±8.6 kg, p = 0.049) (Table 1). In addition, patients with proximal DVT tended to have a lower BMI (16.9±2.5 vs. 21.1±3.1 kg/m^2, p = 0.06), a higher CONUT score (6 vs. 4 points, p = 0.11), and CFS (7 vs. 6 points, p = 0.11). Furthermore, the patients with proximal DVT had significantly higher maximal D-dimer levels (7.8 vs. 1.1 μg/mL, p = 0.03) and IMPROVE VTE scores (2 points vs. 1 point, p = 0.03) (Table 1). No major bleeding or thrombotic events were observed in both groups. .

Following diagnosis of proximal DVT, two of five patients received anticoagulants, whereas the remaining three patients had only undergone follow-up 3PCUS because of anemia and small thrombus. None of them developed symptomatic PE.

Discussion

The main findings of the current study were: (1) The prevalence of proximal DVT following COVID-19 in hospitalized psychiatric patients was 10.0%; (2) the incidence of proximal DVT was relatively high among severe COVID-19 patients despite prophylactic anticoagulant therapy; (3) the patients with proximal DVT showed lower BW with a trend towards lower BMI compared against those without, and tended to have

a higher CONUT score and CFS; and (4) the patients with proximal DVT demonstrated higher maximal D-dimer levels and IMPROVE VTE scores.

In the current study, proximal DVT was observed in 10.0% of 50 psychiatric patients following COVID-19. This prevalence of proximal DVT was relatively high compared with recent reports from Japanese patients with COVID-19, which reported an incidence rate of 0.6% for VTE and 1.9~2.9% for arterial and venous thrombotic events.[11-13] The findings of the present study indicate that hospitalized psychiatric patients could be at a higher risk of COVID-19-associated VTE compared with non-psychiatric patients. Schizophrenia and antipsychotics are known risk factors of VTE due to an increased release of adrenaline, an increased activation of the markers of thrombogenesis, an increased level of the antiphospholipid antibody, and changes in serotonin metabolism in the platelets.[14] In the current study, all but one patient with DVT had schizophrenia and had received antipsychotics, supporting the hypothesis that schizophrenia and antipsychotics lead to an increased incidence of COVID-19-associated VTE. On the other hand, the current study involved screening of proximal DVT for all enrolled patients. A recent review report identified that the rates of COVID-19-associated VTE in studies with ultrasound screening was high compared with those in studies without ultrasound screening.[15] This may partially explain why the occurrence of proximal DVT was high in

the current study; however, it is important to note that 10.0% of the hospitalized psychiatric patients following COVID-19 had proximal DVT with the need for management.

In the current study, the patients following moderate or severe COVID-19 had a high rate of proximal DVT, supporting the findings of other studies that the incidence rate of VTE was high in certain groups of patients, such as ICU patients, with severe COVID-19.[3, 13, 15] As a previous study reported,[16] fatal coagulation abnormalities in severe cases of COVID-19 may be an important risk factor for the occurrence of VTE.

Obesity is a well-known risk factor of VTE.[17] In addition, this finding was also observed in Japanese patients with COVID-19.[3] Contrary to these previous studies, the patients with proximal DVT had lower BW and tended to have low BMI and high CONUT scores compared with those without. This discrepancy may be partly explained by the existence and severity of the psychiatric diseases. The patients with proximal DVT also tended to have high CFS, which may have been ascribed to malnutrition, causing prolonged immobilization time and stasis of blood flow in lower extremities; thus, leading to an increased rate of DVT.

D-dimer is a reliable negative predictive marker for screening of acute VTE. In a previous study involving COVID-19 hospitalized patients, high D-dimer level was

associated with VTE.[18] In addition, IMPROVE VTE score is an extensively validated risk assessment model for the identification of medical hospitalized patients with VTE.[9, 18] Consistent with previous studies, the present study identified high maximal D-dimer and IMPROVE VTE scores in the patients with proximal DVT. Almost all the patients with proximal DVT had VTE risk factors, including immobilization and aging, which compose the IMPROVE VTE score, supporting the association between frailty and VTE occurrence. On the other hand, the specificity of D-dimer and IMPROVE VTE score for COVID-19-associated VTE was also reported to be low.[18] Therefore, screening by imaging should not be performed based on only high D-dimer level or IIMPROVE VTE score because of poor cost-benefit balances. High severity of COVID-19, severe frailty, and high D-dimer and IMPROVE VTE scores in a psychiatric hospitalized patient may alert the clinicians to the possibility of occurrence of VTE. The further accumulation of data from multicenter surveillance is needed to confirm the findings.

Study Limitations

First, the current study was a retrospective single center study based on data from a quite small population; thus, these findings may not accurately reflect the entirety of hospitalized psychiatric patients in Japan. Second, pulmonary imaging procedures could

not be performed because of lack of adequate facilities to diagnose PE in the psychiatric hospital. Thus, the primary outcomes did not include the prevalence of PE. Third, most of the patients with the prophylactic anticoagulation received direct oral anticoagulants, which may have affected the prevalence of proximal DVT and D-dimer levels. Fourth, there are no data on the presence or absence of DVT before the infection of COVID-19 in the present study. Therefore, it is unknown whether and to what extent COVID-19 leads to an increased rate of VTE in psychiatric patients. .

Conclusions

We demonstrated some clinical features of DVT in hospitalized psychiatric patients following COVID-19 in Japan. The prevalence of proximal DVT was high at 10 %. In particular, severe infection, low BW, and high D-dimer levels and IMPROVE VTE scores may lead to an increased rate of VTE. Therefore, the management of VTE may be warranted in COVID-19 psychiatric patients.

Acknowledgements

None.

Data Availability

The deidentified participant data will not be shared.

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Figure Legends

Figure 1. Study flow chart. COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis.

Figure 2. Prevalence of DVT and prophylactic anticoagulant therapy in each category of severity of COVID-19.

Table 1. Patients' characteristics

	Total (n=50)	Patients with DVT (n=5)	Patients without DVT (n=45)	P value
Age, years	68.9±9.7	75.6±5.6	68.2±9.8	0.06
Male sex, n (%)	25 (50.0)	2 (40.0)	23 (51.1)	0.67
Body weight, kg	49.4±9.0	40.7±7.1	50.4±8.6	0.049
Height, cm	158.1±7.5	155±6.4	158.4±7.6	0.68
BMI, kg/m^2	19.8±3.2	16.9±2.5	20.1±3.1	0.06
CONUT score, point	4 (2.25-6)	6 (5-8)	4 (2-6)	0.11
CFS, point	6 (5-7)	7 (7-7)	6 (5-7)	0.11
Schizophrenia, n (%)	36 (72.0)	4 (80.0)	32 (71.1)	1.00
Administration of antipsychotic agents, n (%)	43 (86.0)	4 (80.0)	39 (86.7)	0.55
Comorbidities				
Hypertension, n (%)	10 (20.0)	0 (0)	10 (22.2)	0.57
Diabetes Mellitus, n (%)	5 (10.0)	1 (20.0)	4 (8.9)	0.42
Dyslipidemia, n (%)	4 (8.0)	1 (20.0)	3 (6.7)	0.35
Heart disease, n (%)	2 (4.0)	0 (0)	2 (4.4)	1.00
History of VTE, n (%)	0 (0)	0 (0)	0 (0)	NA
During the treatment of COVID-19				
Hospital ward				
ICU, n (%)	5 (10.0)	1 (20.0)	4 (8.9)	0.42
General ward, n (%)	45 (90.0)	4 (80.0)	41 (91.1)	0.42
VTE risk				
Maximum D-dimer level, μg/mL	1.4 (0.7-5.2)	7.84 (2-14.4)	1.1 (0.6-4)	0.03
IMPROVE VTE Risk score, point	1 (1-2)	2 (2-2)	1 (1-2)	0.03
Physical immobilization, n (%)	10 (20.0)	1 (20.0)	9 (20.0)	1.00
Severity of COVID-19				
Need oxygen, n (%)	14 (28.0)	3 (60.0)	11 (24.4)	0.13
Need mechanical ventilation, n (%)	3 (6.0)	1 (20.0)	2 (4.4)	0.28
Need ECMO, n (%)	0 (0)	0 (0)	0 (0)	NA

Thromboprophylaxis management				
Compression stockings /intermittent pneumatic compression, n (%)	6 (12.0)	1 (20.0)	5 (11.1)	0.49
Anticoagulants, n (%)	11 (22.0)	2 (40.0)	9 (20.0)	0.30
Unfractionated heparin at prophylactic dose, %		0	11.1	0.42
Low-molecular-weight heparin, %		50.0	11.1	
Direct oral anticoagulants, %		50.0	77.8	
Major bleeding or thrombotic events, n (%)	0 (0)	0 (0)	0 (0)	NA

Data are mean (standard deviation), median (interquartile range), or number (percentage).

DVT, deep venous thrombosis; BMI, body mass index; CONUT score, controlling nutritional status score; CFS, clinical frailty scale; ICU, intensive care unit; VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

Figure 1

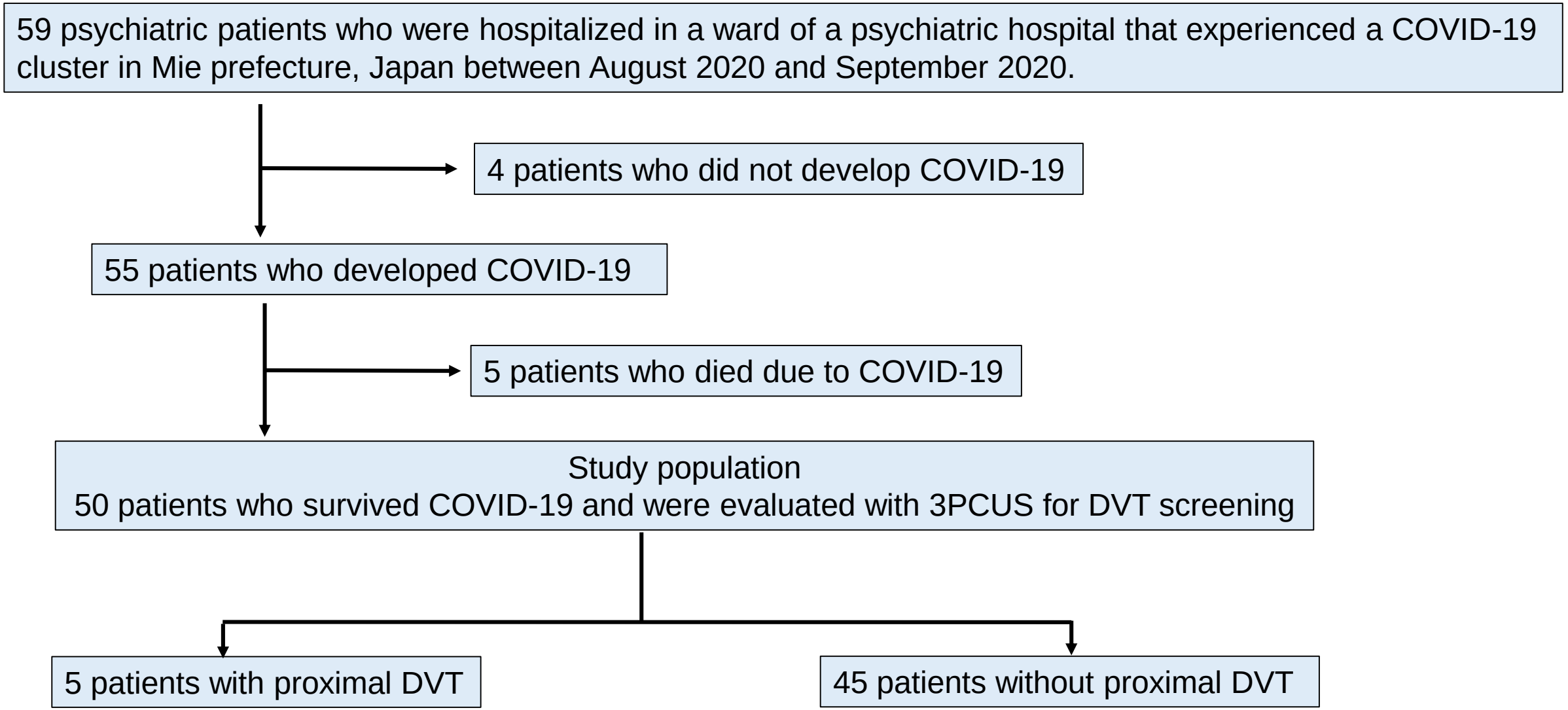
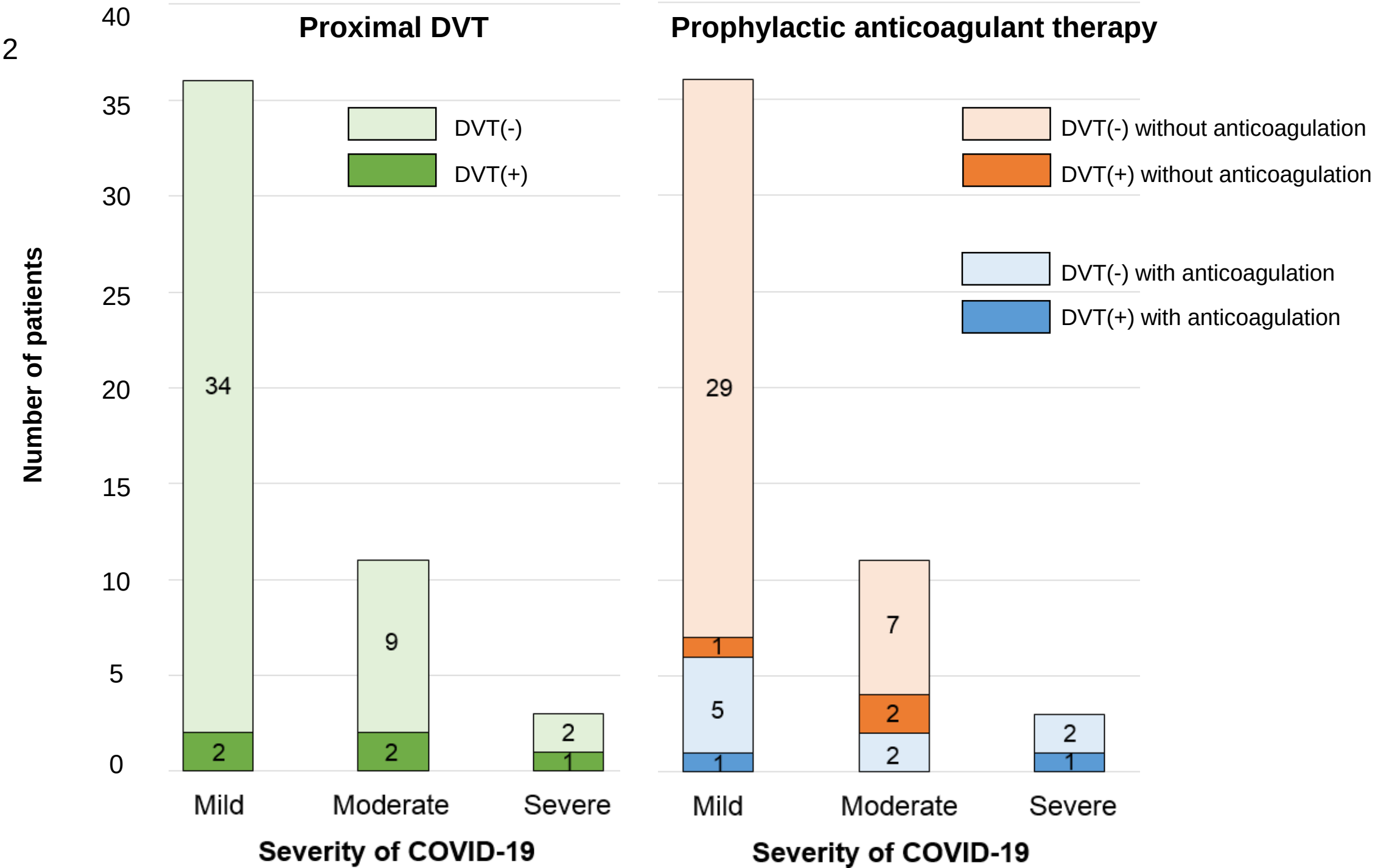

59 psychiatric patients who were hospitalized in a ward of a psychiatric hospital that experienced a COVID-19 cluster in Mie prefecture, Japan between August 2020 and September 2020.
4 patients who did not develop COVID-19
55 patients who developed COVID-19
5 patients who died due to COVID-19
Study population
50 patients who survived COVID-19 and were evaluated with 3PCUS for DVT screening
5 patients with proximal DVT
45 patients without proximal DVT

Figure 2


Proximal DVT
Prophylactic anticoagulant therapy
Number of patients
40
35
30
25
20
15
10
5
0
DVT(-)
DVT(+)
DVT(-) without anticoagulation
DVT(+) without anticoagulation
DVT(-) with anticoagulation
DVT(+) with anticoagulation
34
2
9
2
2
1
29
1
5
1
7
2
2
2
1
Mild
Moderate
Severe
Severity of COVID-19
Mild
Moderate
Severe
Severity of COVID-19