

Clinical Characteristics of Asymptomatic Thromboembolism in Psychiatric Inpatients: A Retrospective Study

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Purpose: Venous thromboembolism (VTE) poses a significant threat to individuals' health, yet its correlation with mental disorders remains underappreciated. Here, we conducted a retrospective analysis to explore the characteristics of psychiatric patients presenting with VTE.

Methods: We retrospectively analyzed psychiatric inpatients with elevated plasma D-dimer levels at the Mental Health Center, First Affiliated Hospital, Zhejiang University School of Medicine, from January 2014 to January 2022. The inclusion criteria comprised comprehensive demographic and clinical profiles, including laboratory and imaging findings.

Results: A cohort of 33 eligible patients was included, with plasma D-dimer levels ranging from 880 to 10,700 µg/L FEU. Significantly higher D-dimer levels were observed in patients diagnosed with severe mental disorders (SMD), such as schizophrenia and bipolar disorder, compared to those with mild mental disorders (MMD), including depression and anxiety disorders ($p = 0.007$). Furthermore, individuals receiving antipsychotic medications for less than one year exhibited elevated D-dimer levels compared to those on treatment for over one year ($p = 0.005$). However, normalization of D-dimer levels did not demonstrate a significant association with psychiatric diagnosis or treatment duration ($p > 0.05$).

Conclusion: Our findings suggest that patients diagnosed with SMD or those undergoing antipsychotic treatment for less than one year may have elevated D-dimer levels, indicating a potential predisposition to VTE severity. This underscores the importance of recognizing VTE risk in individuals with severe mental disorders and warrants further investigation into the impact of antipsychotic treatment duration on thrombotic risk.

Keywords: asymptomatic thromboembolism, D-dimer, psychiatric disorder, risk factors

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), stands as the third most prevalent cardiovascular disorder, with an overall incidence ranging from 1 to 2 per thousand inhabitants.^{1,2} VTE is acknowledged as a multifactorial disorder, and associated risk factors, such as psychosocial elements, have garnered increased attention.^{3,4} Recent findings highlight VTE as a significant contributor to sudden death among inpatients with psychiatric disorders.⁵

Estimates from the global burden of disease position psychiatric disorders among the top 20 causes of disability.⁶ Previous investigations have shown that individuals with psychiatric disorders typically experience a reduced life expectancy, on average, by at least 10 years compared to the general population, primarily due to an elevated risk of cardiovascular disease.⁷⁻⁹ Notably, approximately 4% of unanticipated sudden deaths among psychiatric patients are linked to PE, with VTE incidence

peaking at 11.6% within a three-month timeframe in this population.^{10,11} Moreover, reports suggest an exponential increase in VTE incidence with advancing age, particularly among patients older than 40 years.¹² However, diagnosing VTE among psychiatric patients presents significant challenges, potentially attributed to factors such as the sedative effects of medications, immobilization, or psychopathological symptoms. Furthermore, symptomatic VTE occurrences could lead to fatal outcomes. Consequently, early screening for asymptomatic VTE, identification of potential triggering factors, and implementation of effective diagnostic measures among psychiatric patients are imperative.

In this study, we undertook a retrospective investigation targeting asymptomatic venous thromboembolism (VTE) among psychiatric inpatients, conducting a comprehensive analysis of the demographic and clinical characteristics of this cohort.

Methods

Participants

The study received approval from the Institutional Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine. Informed consent was waived due to the retrospective nature of the study. Discharge diagnoses were used as search terms in the hospital's electronic medical record system to identify psychiatric inpatients from January 2014 to January 2022 at the Mental Health Center, First Affiliated Hospital, Zhejiang University School of Medicine. Mental disorder diagnoses followed the criteria outlined in the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders.

Inclusion criteria involved individuals meeting specific conditions: D-dimer levels exceeding 700 μ g/L FEU (the upper normal limit), confirmation of VTE through arteriovenous color Doppler ultrasonography of the lower limbs or computed tomography angiography of the pulmonary artery, and an absence of known VTE symptoms such as pain, swelling, difficulty breathing, or hemoptysis. Exclusion criteria included arterial thromboembolism, coagulation dysfunction, severe abnormalities in liver and kidney function, serious infections, gastrointestinal diseases leading to dehydration, recent surgery or trauma, physical limitations, sedentary or bedridden status for extended periods, and pregnancy or lactation.

Measures

The study involved gathering patients' demographic data, clinical profiles, and results from laboratory and imaging tests. This included information such as age, gender, height, weight, smoking history, duration and diagnosis of psychosis, history of cerebrovascular disease and hypertension, psychotropic medication usage, and plasma D-dimer levels both before and after anticoagulant therapy. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters).

The clinical presentation of asymptomatic VTE is characterized by the absence of obvious symptoms such as swelling or pain in the legs, chest pain, breathing difficulties, or hemoptysis. Diagnosis relies on elevated D-dimer levels and imaging, i.e., PE reveals the presence of pulmonary thrombosis by computed tomography pulmonary angiography (CTPA), while DVT reveals the presence of venous thrombosis by vascular ultrasound.

Data Analysis

The analysis of the collected data was executed with SPSS, version 21.0. To better elucidate our research findings, we utilized GraphPad Prism 9.4.0 for data visualization. The Mann-Whitney *U*-test was used to assess the difference between the two numerical variables. Categorical variables are checked precisely by Fisher. The results are presented as mean, standard deviation, and median (minimum–maximum) values for quantitative data and as frequency (*n*) and percentage (%) values for categorical data. Two-sided, $p < 0.05$ was considered statistically significant.

Results

Demographic Characteristics

Our study included 33 psychiatric patients who met the specific inclusion and exclusion criteria. Among them, 24 cases presented with asymptomatic VTE manifested as pulmonary embolism (PE), and 9 were diagnosed with deep vein thrombosis (DVT). The distribution of mental health diagnoses included 12 patients with anxiety disorder (AD), 11 with major depressive

disorder (MDD), 6 with schizophrenia (SCZ), and 2 with bipolar disorder (BD). Other diagnoses comprised somatoform disorder (SD) and alcoholic dependence syndrome (ADS), each in one patient. Patients were categorized into major mental disorder (SMD) and mild mental disorder (MMD) groups based on severity, with SMD diagnoses including SCZ, BD, SD, and ADS, and MMD diagnoses including AD and MDD.

Treatment regimens involved atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and other psychotropic medications. The duration of antipsychotic medication usage varied from 1 month to 20 years. Sedative drugs, like benzodiazepines (e.g., alprazolam), were administered in 17 patients (51.5%), while atypical antipsychotic drugs (e.g., olanzapine and clozapine) were prescribed in 14 cases (42.4%). Additionally, 13 patients had hypertension, and 21 patients had a history of cerebrovascular disease. Detailed demographic characteristics are presented in [Table 1](#)

Factors Associated with Plasma Levels of D-Dimer

Plasma D-dimer levels were routinely measured within the first few days of hospitalization, with a mean observed level of $4060.00 \pm 2824.88 \mu\text{g/L FEU}$, ranging from 920 to $10700 \mu\text{g/L FEU}$, significantly surpassing the normal range of $0\text{--}700 \mu\text{g/L FEU}$. Analysis revealed a correlation between pre-treatment D-dimer levels, the severity of mental illness, and medication duration. Specifically, patients diagnosed with severe mental disorders (SMD) exhibited higher D-dimer levels compared to those diagnosed with mild mental disorders (MMD) ($p=0.007$) ([Figure 1](#)). Moreover, patients receiving antipsychotic medication for less than a year demonstrated elevated D-dimer levels relative to those treated for more than a year ($p=0.005$) ([Figure 2](#)). However, no significant association was observed between pre-treatment D-dimer levels and factors such as thrombus type, history of hypertension, or cardiovascular disease ($p>0.05$).

The Recovery of D-Dimer Levels After Anticoagulant Treatment

Following the diagnosis of VTE, patients typically undergo conventional anticoagulant therapy, commonly involving subcutaneous injections of low-molecular-weight heparin (LMWH) or oral warfarin, typically administered over a duration of approximately one week.¹³ In our study, 27 patients (81.8%) received conventional LMWH treatment, while the remaining 6 (18.2%) were administered oral warfarin for a similar duration.

After initiating treatment, D-dimer levels were reassessed. Among the patients, 26 (78.8%) showed a significant reduction in plasma D-dimer levels, with 16 (48.5%) returning to within the normal D-dimer range. Notably, the reduction in D-dimer levels following treatment, as well as the normalization of D-dimer values, were observed independently of factors such as gender, age, and type of mental illness, among others. Detailed features are outlined in [Table 2](#).

Table 1 Clinical Demographic Characteristics of Patients

Characteristics	Total (33), N (%)
Gender (Male/Female)	9 (27.3)/24 (72.7)
Age (≤ 65 / >65), years old	13 (39.4)/20 (60.6)
BMI (≤ 24.9 / >24.9), kg/m ²	19 (57.6)/14 (42.4)
Hypertension History (Yes/No)	13 (39.4)/20 (60.6)
Cerebrovascular disease History (Yes/No)	21 (63.6)/12 (36.4)
Type of psychosis (MMD/SMD)	23 (69.7)/10 (30.3)
Duration of illness (≤ 12 / >12), months	9 (27.3)/24 (72.7)
Duration of antipsychotic medication (≤ 12 / >12), months	16 (48.5)/17 (51.5)
Atypical antipsychotic drugs (Yes/No)	14 (42.4)/19 (57.6)
Sedation application history (Yes/No)	17 (51.5)/16 (48.5)
Thrombosis type (PE/DVT)	24 (72.7)/9 (27.3)

Abbreviations: BMI, body mass index; MMD, mild mental disorder; SMD, severe mental disorder; PE, pulmonary embolism; DVT, deep-vein thrombosis.

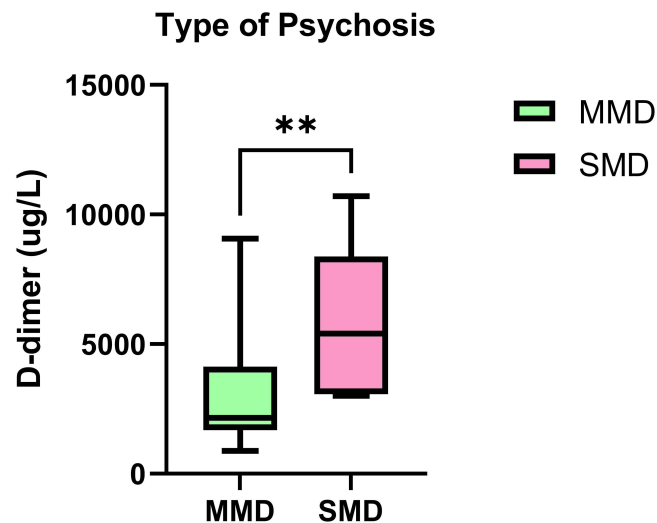


Figure 1 D-dimer levels in the diagnosis of different psychiatric disorders. D-dimer levels in the diagnosis of different psychiatric disorders. Patients diagnosed with SMD exhibited higher levels than those diagnosed with MMD ($p=0.007$). The Mann-Whitney *U*-test was used for statistical analysis, with $**p < 0.01$. **Abbreviations:** MMD, mild mental disorder; SMD, severe mental disorder.

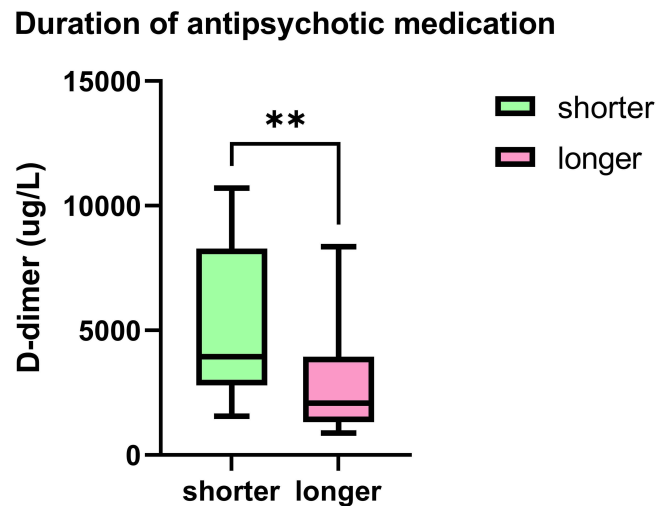


Figure 2 D-dimer levels at different treatment durations. D-dimer levels at different treatment durations. Patients on antipsychotics for less than a year exhibited higher D-dimer levels compared to those treated for more than a year ($p=0.005$). The Mann-Whitney *U*-test was used for statistical analysis, with $**p < 0.01$. Shorter: receiving antipsychotic medication for less than 1 year; longer: receiving antipsychotic medication for more than 1 year.

Discussion

VTE poses a significant challenge in hospitals, requiring careful attention. The D-dimer test is reliable for ruling out VTE in outpatient and emergency settings,^{14,15} and also works well for hospitalized patients.¹⁶ Notably, individuals with psychosis have a higher risk of VTE,^{17–19} highlighting the importance of regularly checking their D-dimer levels for asymptomatic VTE. Our study reveals significant findings regarding patients diagnosed with asymptomatic VTE. Specifically, individuals diagnosed with severe mental disorders (SMD) had higher D-dimer levels compared to those with mild mental disorders (MMD). Additionally, patients in their first year of antipsychotic medication showed elevated D-dimer levels compared to those with a longer medication duration.

D-dimer, a marker indicating fibrinolysis activity, plays a vital role in diagnosing VTE.²⁰ Our study found differences in D-dimer levels among patients with asymptomatic VTE, with lower levels seen in those with mild mental disorders (MMD) compared to severe mental disorders (SMD) ($p=0.007$). This difference might be because SMD patients tend to be less physically active, which can increase the risk of VTE.²¹ Higher D-dimer levels at VTE diagnosis could also

Table 2 Recovery of D-Dimer Levels in Patients After Anticoagulant Therapy

Characteristics	Not Recovered (17) N (%)	Recovered (16) N (%)	P-value
Gender			
Male	7 (41.2)	2 (12.5)	0.118
Female	10 (58.8)	14 (87.5)	
Age, years old			
≤65	5 (29.4)	8 (50.0)	0.296
>65	12 (70.6)	8 (50.0)	
BMI, kg/m ²			
≤24.9	9 (52.9)	10 (62.5)	0.728
>24.9	8 (47.1)	6 (37.5)	
Hypertension History			
Yes	7 (41.2)	6 (37.5)	1.000
No	10 (58.8)	10 (62.5)	
Cerebrovascular disease History			
Yes	9 (52.9)	12 (75.0)	0.282
No	8 (47.1)	4 (25.0)	
Type of psychosis			
MMD	12 (70.6)	11 (68.8)	1.000
SMD	5 (29.5)	5 (31.3)	
Duration of illness, months			
≤12	6 (35.3)	3 (18.8)	0.438
>12	11 (64.7)	13 (81.2)	
Duration of antipsychotic, months			
≤12	9 (52.9)	7 (43.8)	0.732
>12	8 (47.1)	9 (56.3)	
Atypical antipsychotic drugs			
Yes	9 (52.9)	5 (31.2)	0.296
No	8 (47.1)	11 (68.8)	
Sedation application history			
Yes	7 (41.1)	10 (62.5)	0.303
No	10 (58.2)	6 (37.5)	
Thrombosis type			
PE	13 (76.5)	11 (68.8)	0.708
DVT	4 (23.5)	5 (31.3)	
Use of LMWH			
Yes	13 (76.5)	13 (86.7)	0.659
No	4 (23.5)	2 (13.3)	

Abbreviations: BMI, body mass index; MMD, mild mental disorder; SMD, severe mental disorder; PE, pulmonary embolism; DVT, deep-vein thrombosis; LMWH, low molecular weight heparin.

suggest a higher chance of recurrence and a worse prognosis,²² as seen in COVID-19 patients.²³ Therefore, SMD patients with high D-dimer levels may have a poorer outlook regarding VTE.

A seven-year follow-up study found a higher risk of VTE in people taking antidepressants, possibly due to drug-induced blood clotting.²⁴ Possible mechanisms may involve the drug-induced hypercoagulable state, manifested by increased platelet aggregation, antiphospholipid antibodies, hyperprolactinemia, and metabolic symptoms.^{12,25} Similarly, conventional antipsychotics have been linked to increased VTE risk, especially in the first few months of treatment.²⁶ The nested case-control study showed that individuals who had been prescribed antipsychotics within the past 24 months had a higher risk of VTE than non-users, and that the risk was approximately double for patients who had started the new drug within the past three months.²⁷ This seems to suggest that antipsychotics should initially have a higher risk of blood clots. Our study supported these findings, showing higher D-dimer levels in patients on antipsychotic medication for up

to one year ($p=0.005$). This suggests a higher risk of severe VTE in the first year of treatment. The possible reason is that patients who are just starting treatment may experience lifestyle changes, including reduced activity, which may increase the risk of blood clots. Additionally, during the early stages of treatment, physicians may be adjusting drug doses to achieve optimal efficacy, and higher doses may be associated with an increased risk of blood clots. The specific mechanism needs further exploration.

The risk of thrombosis is related to the duration of the patient's disease. A longitudinal cohort study shows that individuals with mental disorders have elevated risk for subsequent cardiovascular disease, particularly in the first year after diagnosis.²⁸ However, in our study, no significant difference was found between D-dimer and disease course ($p > 0.05$). Studies suggest that the type of medication influences D-dimer levels, with first-generation antipsychotics and sedatives being correlated with a higher risk of VTE.^{26,29,30} In addition, atypical antipsychotics were associated with a higher risk of VTE than conventional antipsychotics.²⁷ However, our study found no significant correlation between D-dimer levels and the use of sedative drugs ($p > 0.05$). We also analyzed the relationship between the use of atypical antipsychotics and D-dimer, and there was no correlation between the two ($p > 0.05$). Additionally, only two patients were prescribed low potency antipsychotics, rendering the data insufficient for statistical analysis.

In future studies, we can stratify patients according to duration of antipsychotic medication and type of disease to make a risk assessment model. Aiming at accurately identifying high-risk patients, early identification and early intervention, and the implementation of targeted preventive measures can ultimately reduce the incidence of VTE and improve the overall health outcomes of psychiatric patients.

Our study has several limitations. The small sample size, retrospective design, and lack of control groups may limit the strength of our findings. Additionally, being conducted at a single center may restrict the generalizability of the results. The absence of imaging assessments and long-term follow-up after discharge are further limitations. Future research should address these limitations by increasing sample sizes, involving multiple centers, incorporating control groups, extending follow-up periods, and conducting comprehensive imaging-based prognostic assessments.

Conclusion

In a nutshell, this retrospective study investigated 33 psychiatric patients diagnosed with asymptomatic VTE during hospitalization. Our findings suggest that individuals with SMD or those in the initial year of antipsychotic medication displayed elevated D-dimer levels compared to those with MMD or longer medication duration. Notably, patients with heightened D-dimer levels, particularly early in antipsychotic treatment or with an SMD diagnosis, warrant careful monitoring and clinical intervention.

Data Sharing Statement

Datasets of this study are available from the corresponding author on reasonable request.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the First Affiliated Hospital, Zhejiang University School of Medicine. We have erased patient personal information to ensure that no information will be leaked and patients waived signing informed consent for the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest related to the subject of this study.

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