SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-63634

UDK 577.1 : 61 ISSN 1452-8258

J Med Biochem 45: 1–8, 2026

Original paper
Originalni naučni rad

ROLE OF INFLAMMATORY BIOMARKERS (IL-6, TNF-α, CRP), PLATELET ACTIVATION (CD62P, PAC-1, GPIIB/IIIA), EXPLORATORY GENE EXPRESSION ANALYSIS (SERPINE1, F3) AND PREDICTIVE MODELING BETWEEN DEPRESSION AND THROMBOSIS RISK

ULOGA INFLAMATORNIH BIOMARKERA (IL-6, TNF-α, CRP), AKTIVACIJE TROMBOCITA (CD62P, PAC-1, GPIIB/IIIA), EKSPLORATORNE ANALIZE GENSKE EKSPRESIJE (SERPINE1, F3) I PREDIKTIVNOG MODELOVANJA U ODNOSU IZMEĐU DEPRESIJE I RIZIKA OD TROMBOZE

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Summary

Background: Over 280 million people suffer from depression worldwide, a psychiatric disorder that is increasingly associated with thrombotic events like deep vein thrombosis (DVT) and pulmonary embolisms (PE). There is still a lack of understanding of the biological pathways linking depression to thrombosis, including systemic inflammation, platelet hyperactivity, and abnormal coagulation. This study aims to elucidate these mechanisms by analysing inflammatory and coagulation biomarkers, assessing platelet function, and identifying independent risk factors for thrombosis.

Methods: A case-control study was conducted with 500 participants: 250 diagnosed with major depressive disorder (MDD) and 250 healthy controls. Key inflammatory markers (IL-6, TNF-α, CRP) and coagulation factors (D-dimer, fibrinogen) were quantified using enzyme-linked immunosorbent assay (ELISA) and quantitative polymerase chain reaction (qPCR). A prespecified exploratory qPCR analysis of SERPINE1 and F3 was planned to explore potential prothrombotic mechanisms. However, these data were not included in the final inferential analysis. Platelet activation was evaluated by flow cytometry. This used CD62P (P-selectin) expression, PAC-1 binding, and GPIIb/IIIa activation. A 12-month longitudinal follow-up was performed. Multivariate regression models identified independent predictors of thrombosis risk.

Kratak sadržaj

Uvod: Više od 280 miliona ljudi širom sveta pati od depresije, psihijatrijskog poremećaja koji se sve češće dovodi u vezu sa trombotskim događajima poput duboke venske tromboze (DVT) i plućne embolije (PE). I dalje ne postoji dovoljno razumevanja bioloških puteva koji povezuju depresiju i trombozu, uključujući sistemsku inflamaciju, hiperaktivnost trombocita i poremećaje koagulacije. Cilj ove studije je bio da razjasni ove mehanizme analizom inflamatornih i koagulacionih biomarkera, procenom funkcije trombocita i identifikacijom nezavisnih faktora rizika za trombozu.

Metode: Sprovedena je studija tipa slučaj–kontrola sa 500 ispitanika: 250 sa dijagnozom velikog depresivnog poremećaja (MDD) i 250 zdravih kontrolnih ispitanika. Ključni inflamatorni markeri (IL-6, TNF-α, CRP) i koagulacioni faktori (D-dimer, fibrinogen) su kvantifikovani primenom ELISA metode i kvantitativne lančane reakcije polimeraze (qPCR). Unapred planirana eksploratorna qPCR analiza gena SERPINE1 i F3 je sprovedena radi ispitivanja potencijalnih protrombotskih mehanizama, ali ovi podaci nisu uključeni u završnu inferencijalnu analizu. Aktivacija trombocita je procenjena protočnom citometrijom, analizom ekspresije CD62P (P-selektin), vezivanja PAC-1 i aktivacije GPIIb/IIIa. Sprovedeno je longitudinalno praćenje u trajanju od 12 meseci. Za identifikaciju nezavisnih prediktora rizika od tromboze korišćeni su multivarijantni regresioni modeli.

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Results: Participants with depression exhibited significantly elevated levels of inflammatory and prothrombotic biomarkers compared to controls ($p<0.001$). Markers of platelet activation were notably upregulated, indicating a hypercoagulable state. Multivariate regression analysis identified depression severity (OR=2.10, 95% CI: 1.80–2.45), IL-6 levels (OR=1.92, 95% CI: 1.65–2.30), and platelet activation (OR=2.50, 95% CI: 2.05–3.00) as strong independent predictors of thrombosis risk ($p<0.001$).
Conclusion: Depression is an independent risk factor for thrombosis, mediated through pathways involving systemic inflammation and platelet hyperactivity. These findings underscore the importance of integrating psychiatric evaluation into thrombosis risk assessment protocols and suggest potential benefits of targeted anti-inflammatory or antiplatelet strategies in high-risk psychiatric populations.

Keywords: depression, thrombosis, inflammation, platelet activation, endothelial dysfunction, biomarkers, risk prediction

Rezultati: Ispitanici sa depresijom su imali značajno povišene nivoe inflamatornih i protrombotskih biomarkera u poređenju sa kontrolnim ispitanicima ($p<0,001$). Markeri aktivacije trombocita su bili izrazito povećani, što ukazuje na hiperkoagulabilno stanje. Multivarijantna regresiona analiza je identifikovala težinu depresije (OR=2,10; 95% CI: 1,80–2,45), nivoe IL-6 (OR=1,92; 95% CI: 1,65–2,30) i aktivaciju trombocita (OR=2,50; 95% CI: 2,05–3,00) kao snažne nezavisne prediktore rizika od tromboze ($p<0,001$).
Zaključak: Depresija predstavlja nezavisan faktor rizika za trombozu, uz učešće mehanizama kao što su sistemska inflamacija i hiperaktivnost trombocita. Ovi nalazi naglašavaju značaj uključivanja psihijatrijske procene u protokole procene rizika od tromboze i ukazuju na potencijalne koristi ciljanih antiinflamatornih ili antitrombocitnih strategija kod visokorizičnih psihijatrijskih pacijenata.

Ključne reči: depresija, tromboza, inflamacija, aktivacija trombocita, endotelna disfunkcija, biomarkeri, procena rizika

Introduction

Major depressive disorder (MDD) is a leading cause of global disability, affecting approximately 280 million people with a lifetime prevalence of 10–20% (1). Beyond its profound psychological and social burdens, MDD is increasingly recognized as a significant risk factor for cardiovascular disease (CVD) and venous thromboembolism (VTE) (2). Epidemiological studies suggest that, compared with individuals without depression, patients with MDD have a higher risk of venous thromboembolism (VTE); for example, a population-based cohort study reported a 1.38-fold increased risk, and a meta-analysis found adjusted odds ratios of 1.29 for depression-related DVT and PE (3, 4).

The pathophysiological link is hypothesized to involve chronic low-grade inflammation, platelet dysfunction, and endothelial impairment, yet the precise molecular mechanisms remain incompletely defined (5, 6).

The relationship between depression and thrombosis is bidirectional. Depression is linked to a proinflammatory state and increased coagulation, which can promote clot formation (7, 8). Acute thrombotic events can trigger or worsen depressive symptoms via neuroinflammation and oxidative stress (9). Depression treatment, especially SSRIs, may alter platelet function, further complicating this relationship (10). Research often relies on cross-sectional designs, small samples, and lacks adequate control for confounding factors such as lifestyle and medication use. These issues produce inconsistent findings and hinder causal inference (11, 12). A critical unmet need is the identification of robust, independent predictors of thrombosis risk specific to individuals with depression, disentangled from traditional cardiovascular risk factors. This study aims to address these gaps through a comprehensive, longitudinal investigation that integrates advanced biomarker profiling, functional platelet analysis, and sophisticated statistical modelling.

Study objectives

1. To quantify inflammatory (IL-6, TNF-α, CRP) and coagulation (D-dimer, fibrinogen) biomarkers in individuals with MDD compared to healthy controls.
2. To evaluate the degree of platelet activation and hyperreactivity in depression using flow cytometry analysis.
3. To investigate the temporal progression of thrombosis risk through longitudinal monitoring of biomarker levels and clinical events.
4. To determine independent predictors of thrombosis risk in depression using multivariate logistic regression and Cox proportional hazards modelling.
5. To develop an integrative risk assessment framework combining molecular, clinical, and statistical data for the early identification of high-risk individuals.

Literature review

Accumulating evidence implicates chronic inflammation as a central mechanism linking depression to thrombotic risk. Meta-analyses consistently report elevated levels of pro-inflammatory cytokines,

including IL-6, TNF-α, and the acute-phase reactant CRP, in patients with MDD (13, 14). These inflammatory mediators promote endothelial dysfunction by reducing nitric oxide bioavailability and increasing expression of vascular adhesion molecules, thereby creating a prothrombotic vascular milieu (15).

Parallel research highlights the role of platelet hyperactivation. Studies using flow cytometry have demonstrated significantly increased expression of activation-dependent platelet markers, such as P-selectin (CD62P) and the activated fibrinogen receptor (GPIIb/IIIa), in depressed individuals compared to controls (16, 17). This state of platelet hyperactivity enhances platelet aggregation and adhesion, contributing to a hypercoagulable phenotype.

Longitudinal cohort studies and Mendelian randomization analyses provide stronger evidence for a potential causal relationship, showing that depressive symptoms and genetic liability to depression are associated with an increased incidence of VTE, independent of conventional risk factors (18, 19). However, significant heterogeneity exists across studies due to variations in diagnostic criteria, sample characteristics, and methodological approaches (20). A notable limitation is the frequent failure to adequately account for the effects of psychotropic medications, particularly SSRIs, which possess mild antiplatelet properties and may confound associations (21).

While techniques such as ELISA and flow cytometry are cornerstones of biomarker research, they have limitations. ELISA measurements can be influenced by inter-assay variability and may not distinguish between active and inactive protein isoforms (22). Flow cytometry assessments of platelet function are sensitive to pre-analytical variables such as venepuncture technique and sample processing time. Multivariate regression analyses, though valuable for controlling confounders, may suffer from residual confounding and do not establish causality (23, 24).

Current evidence is constrained by the predominance of cross-sectional studies, small and homogenous samples, and a lack of integrated longitudinal biomarker profiling alongside rigorous psychiatric assessment (12, 25). Furthermore, the development and validation of clinically applicable predictive models of thrombosis risk in psychiatric populations remain underexplored. The present study was designed not to discover entirely new biomarkers, but to integrate established inflammatory, platelet, and coagulation-related signals within a single clinical phenotype cohort and to examine their combined association with thrombotic risk in depression.

Methodology

Study design and participants

A 12-month longitudinal case-control study was conducted. A total of 500 participants were recruited: 250 meeting DSM-5 criteria for MDD (confirmed by Hamilton Depression Rating Scale [HDRS] score ≥17 or Beck Depression Inventory [BDI] score ≥20) and 250 age-, gender-, and body mass index (BMI)-matched healthy controls. Exclusion criteria included a history of diagnosed coagulation disorders, thromboembolic events, major cardiovascular disease (myocardial infarction, stroke), autoimmune diseases, immunosuppressive therapy, pregnancy, and other major psychiatric disorders (e.g., schizophrenia, bipolar disorder). Antidepressant medication use was recorded as a binary variable (yes/no). Due to limitations in detailed pharmacological data collection, specific classes of antidepressants (e.g., SSRIs vs. non-SSRIs) were not systematically categorized for subgroup analysis.

Biomarker analysis

Fasting venous blood samples were collected at baseline and at 3, 6, and 12-month follow-ups. Plasma was isolated for biomarker quantification.

- ELISA: Commercially available kits were used to measure plasma concentrations of IL-6, TNF-α, CRP, D-dimer, and fibrinogen. All assays were performed in duplicate.
- qPCR: RNA was extracted from whole blood, reverse-transcribed to cDNA, and analysed via qPCR for expression levels of genes implicated in coagulation pathways (e.g., SERPINE1, *F3*). qPCR for SERPINE1 and F3 was prespecified as an exploratory mechanistic assay to assess potential coagulation-related transcriptional changes. Because no analysable gene-expression dataset was available for final reporting, these results are not presented as part of the primary findings.

Platelet activation assessment

Whole blood samples were analysed by flow cytometry within 2 hours of collection. Platelets were stained with fluorescently labelled monoclonal antibodies against:

- CD62P (P-selectin) to assess alpha-granule secretion.
- PAC-1 antibody to detect the activated conformation of the fibrinogen receptor GPIIb/IIIa.

- An antibody targeting activated GPIIb/IIIa. Measurements were taken under resting conditions and following stimulation with a low dose of ADP.

Statistical analysis

Data are presented as mean ± standard deviation or percentages. Group comparisons for continuous variables were made using independent t-tests or Mann-Whitney U tests. Categorical variables were compared using Chi-square tests.

- Multivariate Logistic Regression was employed to identify baseline factors independently associated with a composite endpoint of thrombotic events (DVT, PE, stroke, MI) during follow-up, adjusting for age, gender, BMI, smoking status, and medication use. The main outcome was specified as a composite of thrombotic events, including venous (deep vein thrombosis, pulmonary embolism) and arterial (myocardial infarction, ischemic stroke). This approach was adopted to account for the overall thrombotic risk associated with depression, considering common underlying mechanisms such as systemic inflammation, endothelial dysfunction, and platelet activation.
- Antidepressant use (yes/no) was included as a covariate in multivariate regression models to account for its potential influence on platelet function and coagulation pathways.
- Cox Proportional Hazards Modelling was used to analyse time-to-event data for thrombotic outcomes over the 12 months.

All analyses were performed using SPSS version 26.0 and R software, with a two-tailed p-value <0.05 considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Review Board of [Institution Name, blinded for review]. All participants provided written informed consent. Data were anonymized and stored securely in accordance with ethical guidelines.

Results

Participant characteristics

The depressed and control groups were well-matched for age, gender, and BMI. As expected, the prevalence of smoking and antidepressant use was significantly higher in the MDD group. However, detailed classification of antidepressant subtypes (e.g., SSRI vs. non-SSRI) was not available for subgroup-level analysis.

Biomarker analysis

As shown in *Table I*, participants with MDD had significantly elevated plasma levels of all measured inflammatory and coagulation biomarkers compared to healthy controls ($p<0.001$ for all). Effect sizes (Cohen's d) were large, ranging from 1.6 for CRP to 2.2 for D-dimer.

Platelet activation

Flow cytometry analysis revealed markedly heightened platelet activation in the MDD group (*Table II*). The percentages of platelets expressing CD62P, binding PAC-1, and showing activated GPIIb/IIIa were approximately two-fold higher in depressed participants than in controls (all $p<0.001$), with large effect sizes. A composite platelet activation score was calculated to provide an integrated measure of platelet reactivity. Individual markers (CD62P expression, PAC-1 binding, and GPIIb/IIIa activation) were first standardized (z-scores), and the composite score was derived as the mean of these standardized values.

Longitudinal changes

Longitudinal tracking over 12 months showed a gradual, modest decline in biomarker levels among

Table I Comparison of inflammatory and coagulation biomarkers.

Biomarker	Depressed Group (Mean ± SD)	Control Group (Mean ± SD)	p-value	Effect Size (Cohen's d)
IL-6 (pg/mL)	5.8±1.2	2.4±0.7	<0.001	1.8
TNF-α (pg/mL)	4.2±1.1	1.8±0.5	<0.001	1.7
CRP (mg/L)	3.5±0.8	1.2±0.4	<0.001	1.6
D-dimer (ng/mL)	750±150	350±90	<0.001	2.2
Fibrinogen (mg/dL)	450±100	300±80	<0.001	1.9

Table II Comparison of platelet activation markers.

Platelet Marker	Depressed Group (%)	Control Group (%)	p-value	Effect Size (Cohen's d)
CD62P (P-selectin)	65.2±12.1	30.5±8.4	<0.001	2.1
PAC-1 Binding	55.4±10.8	20.7±6.9	<0.001	1.9
GPIIb/IIIa Activation	72.1±13.5	38.2 9.7	<0.001	2.3

Table III Longitudinal biomarker trends in the depressed group.

Time Point	IL-6 (pg/mL)	D-dimer (ng/mL)	Platelet Activation (%)*
Baseline	5.8±1.2	750±150	65.2
3 Months	5.5±1.1	720±140	63.5
6 Months	5.2±1.0	690±130	60.8
12 Months	4.8±0.9	650±120	58.1

*Mean of CD62P, PAC-1, GPIIb/IIIa activation

Table IV Multivariate predictors of thrombosis risk.

Predictor Variable	Adjusted Odds Ratio	95% Confidence Interval	p-value
Depression Severity (HDRS)	2.10	1.80–2.45	<0.001
IL-6 Level (per pg/mL)	1.92	1.65–2.30	<0.001
D-dimer Level (per 100 ng/mL)	2.35	1.95–2.80	<0.001
Platelet Activation Score	2.50	2.05–3.00	<0.001
Age (per 10 years)	1.40	1.20–1.65	0.003
BMI (per 5 kg/m2)	1.30	1.10–1.50	0.02
Smoking Status (Yes vs. No)	1.60	1.30–1.90	0.005

depressed participants (*Table III*). However, at all-time points, including the 12-month assessment, IL-6, D-dimer, and platelet activation levels remained significantly elevated compared with baseline control levels ($p<0.01$).

Predictive modelling

Due to sample size limitations and the distribution of the events, separate analyses for arterial and venous thrombotic events were not performed. Multivariate logistic regression analysis identified several independent predictors of incident thrombotic events during follow-up (*Table IV*). After adjusting for confounders, depression severity (per HDRS point), baseline IL-6 level, and the composite platelet activation score, reflecting the integrated activity of CD62P, PAC-1, and GPIIb/IIIa, showed a strong association with thrombosis risk, emerged as the strongest predictors, with odds ratios exceeding 1.9. Traditional risk factors like age, BMI, and smoking were also significant but had lower effect magnitudes.

Discussion

This study provides robust evidence that major depressive disorder is associated with a distinct prothrombotic phenotype characterized by systemic inflammation, platelet hyperactivity, and coagulation activation. The significantly elevated levels of IL-6, TNF-α, CRP, D-dimer, and fibrinogen align with prior

meta-analytic findings (13, 14) and corroborate the hypothesis that chronic low-grade inflammation is a key mediator linking mood disorders to vascular pathology (15). The large effect sizes observed suggest these differences are not only statistically significant but also clinically relevant.

While the longitudinal study design facilitates better understanding of temporal relationships, the current findings should be interpreted as associations rather than conclusive evidence of causality. Residual confounding from unmeasured or undertreated confounders, including chronic stress, dietary factors, lack of physical activity, and genetic predisposition, cannot be entirely ruled out in observational studies. Therefore, the current findings are best interpreted as biologically plausible associations that require confirmation (26).

The principal finding is pronounced platelet hyperactivation in depressed individuals, as evidenced by a 2- to 3-fold increase in CD62P expression, PAC-1 binding, and activated GPIIb/IIIa. This extends earlier work by Izzi et al. and Amadio et al. (15, 16) and strongly supports the concept of depression as a state of heightened platelet reactivity. This functional alteration likely represents a direct mechanistic contributor to increased clotting risk, potentially through enhanced platelet adhesion and aggregate formation at sites of vascular injury.

The longitudinal data offer novel insight into the persistence of this prothrombotic state. Although biomarker levels showed a slight downward trend over 12 months, possibly reflecting treatment effects or regression to the mean, they remained substantially above healthy control levels. This suggests that the thrombogenic milieu in depression is not merely an acute epiphenomenon but may represent a persistent state. However, confirmation in remitted patients and longer follow-up studies would be needed (27).

The multivariate regression analysis yielded crucial prognostic information. The identification of depression severity, IL-6, and platelet activation as powerful independent predictors of thrombosis risk, even after adjusting for traditional cardiovascular risk factors, underscores the unique contribution of the psychiatric condition itself. This argues against attributing the association solely to comorbid lifestyle factors and highlights the need for thrombosis risk assessment protocols that explicitly incorporate psychiatric evaluation (20).

Clinically, these findings support a more integrated approach to risk assessment rather than a replacement for standard thrombosis workup. For example, in patients with moderate-to-severe MDD, particularly those undergoing major surgery or those with additional cardiovascular risk factors, a brief psychiatric assessment could be considered alongside routine thrombotic risk evaluation, and inflammatory or coagulation markers such as CRP or D-dimer may be considered when clinically indicated as part of individualized risk stratification. This should be viewed as a pragmatic suggestion for future care pathways rather than a formal screening recommendation (20, 21).

A biologically plausible explanation for the observed association between depression severity and thrombotic risk is that more severe depressive symptoms may reflect greater neuroendocrine and autonomic stress dysregulation. Chronic activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system may promote a pro-inflammatory state, including increased IL-6 signalling, while simultaneously priming platelets toward a hyper reactive phenotype. In this framework, IL-6 may contribute to platelet hyper-responsiveness, thereby linking affective burden to thrombo-inflammatory risk. This interpretation remains speculative, but it is consistent with current mechanistic literature connecting stress biology, inflammation, and platelet activation (28, 29).

The composite thrombotic outcome, comprising arterial and venous thrombosis, needs careful interpretation. These conditions have distinct underlying pathophysiological mechanisms but share common features, including systemic inflammation, endothelial dysfunction, and platelet activation. The composite thrombotic outcome in this study was designed to encompass the global thrombotic phenotype associated with depression. Arterial and venous thrombosis, although different, have some similarities. We recognize this, and the study's limitation is the lack of stratified analysis. More studies with larger sample sizes should be conducted to perform a sensitivity analysis to identify possible differences (10, 16).

Several limitations should be acknowledged. First, while longitudinal, the 12-month follow-up period may be insufficient to capture the long-term trajectory of thrombotic risk in depression. Second, the observational design precludes definitive causal conclusions; the identified associations, though adjusted for key confounders, may still be influenced by unmeasured variables. Third, while carefully controlled, flow cytometry results can be sensitive to pre-analytical variables (25). Fourth, although SERPINE1 and F3 were prespecified exploratory molecular targets, no interpretable qPCR dataset was available for final analysis; therefore, these genes could not be evaluated as outcome measures in the present study. Fifth, one of the limitations of this study was its lack of stratification regarding antidepressant drugs. In particular, SSRIs have been reported to affect platelet activity by inhibiting serotonin uptake, thereby exerting antiplatelet effects.

There was no subgroup analysis based on different classes of antidepressant drugs, and this may have led to some confounders. It is recommended that further studies be done to stratify antidepressant drugs comprehensively. Also, future research should employ longer follow-up periods, interventional designs (e.g., trials of anti-inflammatory agents), and incorporate multi-omics approaches to elucidate causal pathways further and identify novel therapeutic targets (26).

Conclusion

In conclusion, this study demonstrates that depression is independently associated with a significantly increased risk of thrombosis, driven by a triad of systemic inflammation, platelet hyperactivation, and coagulation dysregulation. The persistence of this prothrombotic state over time, along with the strength of biomarker-based predictors, reinforces the clinical relevance of these findings. Integrating assessment of depression severity and relevant biomarkers such as IL-6 and platelet activation markers into routine cardiovascular risk evaluation could enhance the early identification of high-risk individuals. Future efforts should focus on translating these mechanistic insights into targeted prevention strategies and evaluating their efficacy in improving outcomes for patients with depression. In conclusion, major depressive disorder was associated with a prothrombotic biomarker profile characterized by inflammation, platelet activation, and coagulation dysregulation. These findings may help refine future risk stratification frameworks, pending external validation (30, 31).

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Received: March 10, 2026
Accepted: April 14, 2026