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Molecular regulatory mechanisms and nursing preventive measures of depression-related thrombosis risk

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Abstract: Depression, affecting over 280 million individuals globally, is increasingly linked to heightened thrombosis risk through molecular pathways such as inflammatory cytokine activation, platelet hyperreactivity, and endothelial dysfunction. This systematic review aims to explore the biological mechanisms of depression-induced thrombosis and assess the impact of nursing-led preventive measures. A structured search of PubMed, ScienceDirect, CINAHL, Google Scholar, and Web of Science was performed, identifying 40 high-quality studies for meta-analysis. Key findings indicate that endothelial dysfunction (Cohen's $d = 0.81$, $\beta = 0.499$, $p < 0.001$) emerged as the strongest predictor of thrombosis, followed by inflammatory markers (Cohen's $d = 0.78$, $\beta = 0.438$, $p < 0.001$) and platelet aggregation (Cohen's $d = 0.65$, $\beta = 0.363$, $p < 0.001$). Although nursing interventions ($\beta = 0.069$, $p = 0.139$) demonstrated limited direct effect, their role in early screening, lifestyle modifications, and adherence monitoring remains crucial. The study underscores the need for interdisciplinary strategies, integrating psychiatric, cardiovascular, and nursing care to mitigate thrombotic risk in depression. Practical implications highlight the importance of routine thrombosis screening and structured nursing interventions in psychiatric settings to enhance patient outcomes. Further research should focus on biomarker-guided preventive strategies and randomized controlled trials to validate these findings.

Keywords: *Biomechanics, depression, Endothelial dysfunction, Inflammation, Meta-analysis, Nursing interventions, Platelet aggregation, Thrombosis.*

1. Introduction

1.1. Background of the Study, Problems, and Challenges

Chronic psychiatric disorder, depression, is a major disease affecting more than 280 million people in the world, and it has a great impact on both mental and physical health [1-3]. Although classified primarily as a mood disorder, depression has gained recognition recently as a systemic disorder, obstructing beyond the central nervous system affecting numerous physiological processes including the cardiovascular one. In recent epidemiological and clinical studies, the risk of depression is associated strongly with an increased risk of thrombotic events such as deep vein thrombosis (DVT), stroke and myocardial infarction [4]. This intensive line of literature emphasizes the importance of understanding the biological basis of this connection and implementation of preventive interventions to reduce the risks of depression induced thrombosis [5].

The majority of the link between depression and thrombosis results through inflammatory pathways, endothelial dysfunction, platelet hyperreactivity, and dysregulated coagulation. Individuals with depression are known to have significantly increased levels of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), both which have been shown to contribute to a prothrombotic state in terms of hypercoagulability and platelet

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aggregation [6]. Systematic inflammation in depression results in altered endothelial function, vascular damage, increased clot adhesion, impaired fibrinolysis and enhances thrombotic risk by a factor of 2-10 depending on whether the former is provoked or a primary disease state [7-9]. Moreover, serotonin-mediated platelet reactivity is increased and plays a crucial role in the link between depression and acute coronary syndromes [10-14].

Depression induced thrombosis is also another key aspect of depression that includes endothelial dysfunction, which is caused by oxidative stress, depletion of nitric oxide, and increased vascular permeability. Patients with depression are often depressed, and they often have decreased endothelial derived nitric oxide production that results in vasoconstriction and increased platelet adhesion[15]. Additionally, the hypercoagulability is promoted by dysregulation of the hypothalamic pituitary adrenal (HPA) axis. Excessive cortisol secretion caused by chronic stress and depression result in elevated clotting factor levels such as increased fibrinogen, factor VIII and von Willebrand factor, which in turn increases thrombotic risk [16].

Although a strong relationship between depression and thrombosis had been established, there were several challenges with clinical management. The underdiagnoses of thrombotic risk in psychiatric patients are one of the main obstacles. However, systemic complications, including endothelial dysfunction and coagulation abnormalities, as well have been disregarded in mental health care providers until now, who instead have tended to emphasize psychological symptoms [16]. In addition, treatment approaches for depression do not usually incorporate thrombosis prevention, thus creating a large gap in complete patient care. This oversight emphasizes the importance of interdisciplinary between psychiatrists, cardiologists and nurses on the development of a holistic management of patients with depression at risk of thrombosis [17].

Another major challenge is bad patient compliance to preventive strategies, which include lifestyle modifications, pharmacological therapy and self-caring routines. It is commonly agreed that low motivation, fatigue and cognitive impairment are associated with depression, which may lead to medication noncompliance and poor engagement in health promoting behaviors [18]. In view of these challenges, it is imperative to implement nursing led interventions aimed at early screening, patient education and adherence monitoring to alleviate the burden of thrombosis among depressed individuals.

1.2. Relevance to Nursing Practice

Nursing professional should understand the bidirectional relationship between depression and thrombosis, as they have a frontline role in early detection, intervention, and prevention of thrombosis. As they are directly involved in patient care, nurses are in a good position to integrate thrombosis risk assessment into routine psychiatric care, and bridge the gap between mental health and cardiovascular health [19-22]. Regular screening protocols can then be incorporated by nursing professionals to identify at-risk individuals prior to thrombotic events so that preventive interventions may be performed in a timely manner.

In addition to their role in educating patients about modifiable risk factors for both depression and thrombosis, nurses are also important in educating patients about modifiable risk factors that contribute to depression. Regular physical activity, modification of dietary, smoking cessation and stress management impact on vascular function, decrease systemic inflammation with reduced clot formation [23]. Nurses can help patients be motivated and adhere to these critical interventions by providing structured patient counseling and behavioral support [24].

In addition, nursing professionals help with medication adherence that is an important aspect in thrombosis risk management. Patients with depression have difficulty with consistent use of prescription medications including antidepressants, anticoagulants and antiplatelet agents. To prevent thrombotic complications, medication adherence programs, such as reminder systems, patient follow-ups and motivational interviewing can be implemented by nurses to ensure consistent therapeutic management [25-28].

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Perhaps the most important responsibility of nursing professionals is to teach patients to recognize early warning signs of thrombosis. Subtle symptoms in many depressed individuals (leg pain, swelling, chest discomfort, or sudden shortness of breath) may indicate deep vein thrombosis or pulmonary embolism and are not noticed by depressed individuals. Such education of patients about these symptoms and the need for immediate medical attention can be lifesaving [29-32].

1.3. Objectives of the Review

This review aims to systematically examine the molecular regulatory mechanisms linking depression and thrombosis, while evaluating the role of nursing-led interventions in mitigating thrombotic risk. The specific objectives of this review are to:

- Investigate the biological pathways contributing to depression-induced thrombosis, with a particular emphasis on inflammatory cytokine activation (IL-6, TNF-α, CRP), platelet hyperreactivity, endothelial dysfunction, and hypercoagulability as key mediators of thrombotic risk.
- Assess the prognostic value of key biomarkers, including IL-6, TNF-α, CRP, fibrinogen, and factor VIII, in predicting thrombotic risk among individuals with depression.
- Analyze biomechanical factors such as arterial stiffness, endothelial shear stress alterations, and vascular compliance, which may exacerbate clot formation and contribute to cardiovascular complications in depression.
- Evaluate the efficacy of nursing-led interventions, including early screening protocols, structured patient education, lifestyle modifications, and pharmacological adherence strategies, in reducing thrombosis risk in psychiatric populations.
- Quantify the association between depression and thrombosis risk through meta-analysis and multiple regression models, determining the relative influence of inflammatory dysregulation, endothelial dysfunction, and platelet hyperactivity on thrombotic events.

By addressing these objectives, this review seeks to bridge the gap between psychiatric care and cardiovascular risk management, advocating for an interdisciplinary approach that integrates psychiatric, cardiovascular, and nursing expertise to enhance patient outcomes.

Despite increasing evidence linking depression to thrombosis, existing research primarily focuses on isolated molecular mechanisms such as inflammation, platelet hyperreactivity, and endothelial dysfunction. However, limited attention has been given to the interplay between these mechanisms and the role of nursing-led interventions in mitigating thrombotic risk. Additionally, the integration of thrombosis prevention strategies into psychiatric care remains underexplored. This review addresses these gaps by conducting a comprehensive analysis of the biological pathways contributing to depression-induced thrombosis while evaluating the effectiveness of nursing interventions. Through meta-analysis and regression modeling, this study aims to quantify the association between depression and thrombosis risk, assess key biomarkers (IL-6, TNF-α, CRP, fibrinogen, factor VIII), and explore nursing-led strategies such as early screening, patient education, lifestyle modifications, and pharmacological adherence programs. By bridging the gap between psychiatric and cardiovascular care, this review advocates for a multidisciplinary approach to improve patient outcomes.

2. Research Methodology

2.1. Search Strategy

A systematic literature review was carried out regarding nursing treatments to reduce the risk of thrombosis and molecular regulatory mechanisms for the connection between depression and thrombosis. The electronic databases searched were Web of Science, Google Scholar, PubMed, Science Direct, CINAHL and Science Direct.

To enhance retrieval efficiency, a structured search strategy using the Boolean operators with Medical Subject Headings (MeSH) was used. The search terms included:

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- Primary Terms: "Depression AND Thrombosis"
- Secondary Terms: "Inflammation AND Hypercoagulability AND Depression"
- Supplementary Terms: "Platelet Activation AND Endothelial Dysfunction"
- Alternative Terms: "Nursing Interventions OR Preventive Measures AND Thrombosis Risk"

The search was limited to peer-reviewed journal articles published between 2015 and 2024 to ensure relevance. The initial search identified 312 articles.

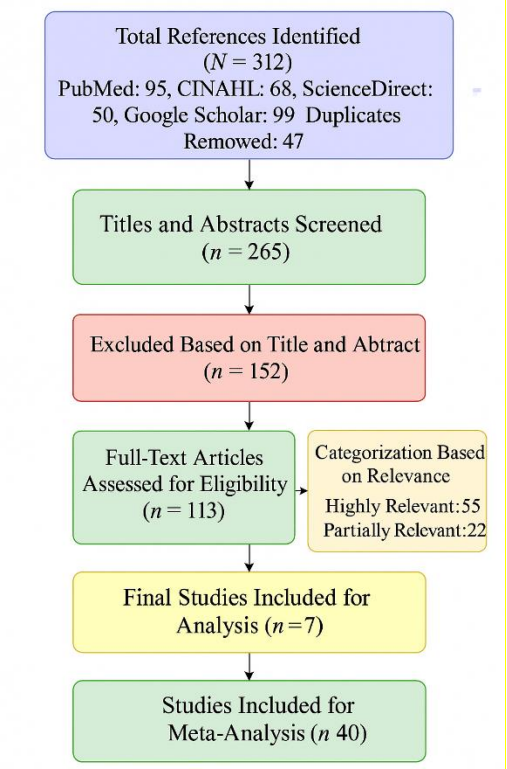

Figure 1.
Study Selection Process.

This PRISMA-style flow diagram 1, outlines the study selection process for a systematic review. Out of 312 initially identified references from various databases, 47 duplicates were removed, leaving 265 for screening. After excluding 152 based on title and abstract, 113 full-text articles were assessed. These were categorized by relevance (55 highly relevant, 22 partially relevant), leading to 77 selected for detailed analysis. Finally, 40 studies were included in the meta-analysis.

2.2. Inclusion and Exclusion Criteria

This ensured inclusion and exclusion criteria were followed to ensure that necessary trustworthiness, relevance, and methodological rigor of the research were followed. To enhance the validity and generalizability of the results, these criteria were developed with established systematic review protocols.

Inclusion Criteria: The systematic review only included studies meeting the following conditions:

- Language and Publication Date: Studies published only in English between 2015 and 2024 were only considered. It was a restriction that would include recent data findings in research, and it would also avoid language-related bias in data interpretation.

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- Relevance to the Research Topic: The studies must show how depression causes blood clots through tested molecular interactions:
    - Euprous causes inflammation increasing levels of inflammatory cytokine like IL-6, TNFα, CRP which also helps hypercoagulability.
    - Studies of platelet hyperaggregability including those of serotonin mediated platelet aggregation and thromboxane A2 dysregulation.
    - Reduced nitric oxide (NO) bioavailability and oxidative stress induced vascular impairments, so called endothelial dysfunction.
    - Links to hypercoagulability resulting from hypothalamic pituitary adrenal (HPA) axis dysregulation and altered lipid persistently expressed fibrinogen, factor VIII, plasminogen activator inhibitor 1 (PAI-1), lipoproteins, apolipoprotein A, apolipoprotein B-48, and apolipoprotein B-100.
- Empirical Studies with Quantitative Data: Only empirical methodologies studies were considered and only those studies that reported quantitative data. This criterion encompassed:
    - Randomized controlled trials (RCTs) addressing the prevention of thrombosis risk in depressed individuals.
    - Observational cohort studies that used to examine associations between depressive symptoms and thrombotic events.
    - Systematic review and meta-analyses of data regarding depression induced thrombosis mechanisms.
    - Clinical and laboratory-based investigations reporting biomarker levels, platelet reactivity assays, and endothelial function tests.
- Studies Evaluating Nursing Interventions: Studies investigated how nurses can prevent thrombosis through their interventions:
    - Early screening protocols for thrombotic risk in depressed patients.
    - Lifestyle modifications, including dietary adjustments, physical activity, and smoking cessation.
    - Ensuring pharmacological adherence strategies to anticoagulant or antiplatelet therapies.
    - Enhancement of awareness of thrombosis risk factors and preventive measures through patient education programs.

2.3. Data Extraction and Analysis

Further, it also employed a structured approach to collect and synthesize findings that were highly relevant for the selected studies. Based on the above aspects, the extracted data were categorized as study design, sample description, molecular mechanisms, nursing interventions and statistical methodologies.

2.4. Data Extraction Parameters

- Study Design: These are various ways of scientific research which are clinical trials, case control studies, observational cohorts, systematic reviews and meta analyses.
- Sample Size and Population: Demographic information, number of participants, inclusion and exclusion criteria, and clinical characteristics of study populations.
- Molecular Biomarkers Analyzed:
- Inflammatory markers: IL-6, TNF-α, C-reactive protein (CRP).
- Coagulation factors: Fibrinogen, Factor VIII, plasminogen activator inhibitor-1 (PAI-1).
- Platelet function markers: Aggregation response to serotonin and thromboxane A2 levels.

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- Nursing Interventions: Lifestyle modifications strategies, pharmacological adherence program, screening protocols and patient education initiatives.
- Outcomes Assessed: All of these result in reduction in thrombotic risk, improvement in inflammatory markers, patient adherence to the preventive measures and patient well-being.

2.5. Meta-Analysis Methodology

A meta-analysis was performed in order to quantitatively synthesize findings from several studies. This statistical approach aggregated effect sizes from various studies to determine the overall impact of depression on thrombosis risk and assess the effectiveness of nursing interventions.

Effect Size Calculation: Each study's effect size was calculated using Cohen's d, a statistic that assesses the standardized mean difference between the intervention and control groups. To determine the magnitude of an influence, a formula was:

$$d = \frac{X_1 - X_2}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

Where

- X_1 and X_2 are the mean values of the two groups..
- s_1^2 and s_2^2 represent the variance of the two groups.

Random-Effects Model: A random-effects model was applied to account for heterogeneity across studies, considering variations in:

- Study settings (clinical, community-based, or hospital studies).
- Patient populations (age, gender, comorbid conditions).
- Intervention types (lifestyle modifications, pharmacological adherence, educational interventions).

Confidence intervals (95% CI) were computed for all effect size estimates to ensure statistical reliability. The I2 statistic was used to measure heterogeneity among studies, with values interpreted as:

- 0–25%: Low heterogeneity.
- 26–50%: Moderate heterogeneity.
- >50%: High heterogeneity.

Descriptive Statistical Measures: Where individual study data were available, descriptive statistics such as mean, median, standard deviation, and interquartile ranges were computed to quantify the effects observed in different preventive nursing interventions.

2.6. Regression Analysis Methodology

In addition to meta-analysis, a multiple linear regression analysis was conducted to assess the predictive relationships between molecular biomarkers and thrombosis risk in depressed patients. The following model was applied:

$$Y = \beta_0 + \beta_1(IL-6\ Levels) + \beta_2(Platelet\ Reactivity) + \beta_3(Endothelial\ Dysfunction) + \beta_4(Lifestyle\ Adherence) + \epsilon$$

where:

- Y represents the thrombosis risk score.
- β_0 is the intercept.
- $\beta_1, \beta_2, \beta_3, \beta_4$ are the regression coefficients for inflammatory markers, platelet activation, endothelial dysfunction, and nursing interventions, respectively.
- ϵ is the error term.

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2.7. Quality Assessment

To ensure methodological rigor and minimize bias, a systematic quality assessment was conducted for all included studies. Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS), which assesses study quality based on three key criteria: selection of study groups, comparability of groups, and outcome assessment. Studies scoring ≥7 on the NOS were considered high quality, while those with lower scores were reviewed for potential biases.

For randomized controlled trials (RCTs), the Cochrane Risk-of-Bias Tool (RoB 2.0) was applied to assess randomization processes, allocation concealment, blinding procedures, and completeness of outcome data. Studies were categorized as low, moderate, or high risk of bias, with high-risk studies excluded from meta-analysis to maintain result validity.

2.8. Molecular Regulatory Mechanisms of Depression-Related Thrombosis

Depression has been increasingly recognized as a systemic disorder affecting multiple physiological pathways, including coagulation and cardiovascular function. The link between depression and thrombosis is largely attributed to chronic inflammation, platelet hyperreactivity, endothelial dysfunction, and hypercoagulability. Thromboembolic events, both venous and arterial, are more likely to occur in depressed people due to these molecular pathways that promote blood clotting [33]. The development of effective nursing interventions to minimize the thrombotic hazards associated with depression requires an understanding of these pathways.

2.9. Inflammatory Pathways

One of the key biological mechanisms through which depression increases the risk of thrombosis is chronic inflammation. Depressed persons have increased levels of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP). Several pathways contribute to thrombogenesis by these cytokines:

Platelet Aggregation: IL6 and TNFalpha stimuli are known to increase platelet aggregation and aggregation, augmenting clot formation while diminishing the ability of the anticoagulation mechanisms.

Fibrinogen Synthesis: IL-6 also stimulates the hepatocytes to produce excessive fibrinogen, a key clotting factor in thrombus formation.

Endothelial Dysfunction: Inflammatory mediators such as CRP impair endothelial nitric oxide (NO) bioavailability, leading to reduced vasodilation and increased vascular stiffness, which further predisposes individuals to thrombosis.

Elevated inflammatory markers have been consistently reported in individuals with major depressive disorder (MDD), supporting the notion that depression promotes a state of low-grade systemic inflammation that contributes to thrombotic events.

Platelet Hyperreactivity

A higher risk of blood clot formation, known as enhanced platelet activation, has been linked to depression. Serotonin dysregulation is a major mediator of platelet hyperreactivity in depressed patients because of its important involvement in platelet aggregation and clot stability. The following mechanisms have been identified:

- Serotonin-Mediated Platelet Activation: Depressed individuals exhibit increased serotonin uptake in platelets, leading to enhanced platelet activation and aggregation [21-23].
- Elevated Thromboxane A2 Levels**:** Thromboxane A2, a potent vasoconstrictor and platelet activator, has been found in higher concentrations in depressed patients, further increasing clot formation potential.

Studies have demonstrated that depressed patients receiving selective serotonin reuptake inhibitors (SSRIs) exhibit reduced platelet aggregation, suggesting that antidepressants may have a role in modulating platelet function and reducing thrombotic risk.

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2.10. Endothelial Dysfunction

Another important component that connects depression with thrombosis is endothelial dysfunction. The endothelium is responsible for controlling blood flow, preventing platelet aggregation, and adjusting inflammatory reactions; all of these things contribute to vascular homeostasis. Depression contributes to endothelial dysfunction through:

- Oxidative Stress: Depressed patients exhibit elevated oxidative stress markers, which lead to endothelial damage and impair vasodilation.
- Nitric Oxide (NO) Deficiency: Depression has been shown to reduce NO bioavailability, leading to impaired vascular relaxation and increased clot adhesion [34]

Longitudinal studies have confirmed that endothelial dysfunction in depression is an independent predictor of thrombotic events, underscoring the need for early intervention and preventive measures in high-risk patients.

2.11. Hypercoagulability

Depression-induced dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis contributes to a hypercoagulable state by increasing cortisol levels and altering clotting factor production. The following mechanisms have been identified:

- Elevated Cortisol Levels: Chronic stress and depression lead to excessive cortisol secretion, which enhances the expression of clotting factors such as fibrinogen and factor VIII, promoting thrombus formation.
- Increased Plasminogen Activator Inhibitor-1 (PAI-1): Depression has been linked to higher levels of PAI-1, which reduces fibrinolysis and increases clot persistence.

Evidence suggests that patients with major depression have an increased risk of both arterial and venous thromboembolic events, making anticoagulation management a key consideration in their care.

2.12. Reviewed Studies on Depression-Related Thrombosis

Depression is increasingly recognized as a significant risk factor for cardiovascular disease (CVD), affecting vascular function through systemic inflammation, platelet hyperreactivity, endothelial dysfunction, and autonomic dysregulation. Recent studies emphasize the role of biomechanical forces—including vascular shear stress, arterial stiffness, and endothelial biomechanics—in explaining the higher cardiovascular risk among individuals with depression. Author [5]. demonstrated that depressive states correlate with reduced physical activity and poor sleep patterns, which are known to alter blood pressure variability and cardiac output. These physiological changes contribute to hemodynamic instability, increasing vascular shear stress and endothelial damage, key precursors to thrombogenesis and atherosclerosis. This wor k [1, 8] further established that early-life mental health issues are associated with long-term cardiovascular risk, partly due to early-onset endothelial remodeling and arterial stiffness, emphasizing the importance of biomechanical markers in assessing CVD risk in depression.

The endothelium plays a critical role in vascular homeostasis by modulating shear stress, blood flow resistance, and nitric oxide (NO) availability. Depression has been linked to increased arterial stiffness and reduced endothelial compliance, leading to impaired vasodilation and increased clot adhesion. This is supported by Li, et al. [11] who identified the NLRP3 inflammasome as a key inflammatory mediator driving vascular dysfunction and thrombogenesis in depressed patients. Chronic inflammation leads to oxidative stress, reducing NO bioavailability and contributing to arterial rigidity, a critical biomechanical alteration associated with increased thrombotic risk. Depression alters autonomic nervous system (ANS) regulation, leading to higher sympathetic activation and reduced parasympathetic control. This imbalance affects heart rate variability (HRV), blood pressure regulation, and microvascular perfusion. Author showed that genetic predisposition to coronary artery disease (CAD) modifies ANS function, increasing vascular resistance and endothelial shear stress, which in turn

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enhances clot formation and cardiovascular complications in depressed individuals. These findings suggest that biomechanical assessments such as pulse wave velocity (PWV) and endothelial shear stress measurements could be valuable in early detection of cardiovascular risks in psychiatric populations [12, 18]. This study Lu, et al. [19] examined sex-specific cardiovascular risks and found that women with depression exhibit greater endothelial stiffness and arterial dysfunction than men. This may be due to hormonal fluctuations, estrogen deficiency, and altered vascular compliance, which contribute to higher thrombotic risk in postmenopausal women. Similarly, Pogosova, et al. [20] and other studies found that elderly individuals with depression have accelerated vascular aging, characterized by reduced arterial elasticity and impaired microcirculatory flow, which increases their susceptibility to ischemic heart disease and stroke. Author of this study Murrough, et al. [22] confirmed that depression-induced hypercoagulability is linked to biomechanical impairments in blood flow regulation, with increased platelet aggregation and altered endothelial stress responses. The combination of elevated fibrinogen levels, reduced NO bioavailability, and vascular stiffness creates a prothrombotic environment, significantly elevating the risk of stroke, deep vein thrombosis (DVT), and myocardial infarction [23-25, 35, 36].

2.13. Inflammation and Depression-Related Thrombosis

Chronic low-grade inflammation has been increasingly recognized as a key biological pathway connecting depression and thrombosis, with extensive evidence supporting the notion that major depressive disorder (MDD) contributes to a prothrombotic state through systemic inflammatory processes. The relationship between depression and thrombosis is mediated by the dysregulation of immune-inflammatory mechanisms, including the persistent activation of pro-inflammatory cytokines, alterations in coagulation cascades, and vascular endothelial impairment.

One of the key biochemical characteristics of depression-induced inflammation is the enhanced levels of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These cytokines lead to vascular endothelial dysfunction, increased platelet aggregation, and hypercoagulability, all of which are well-documented risk factors for thrombotic diseases, including deep vein thrombosis (DVT), myocardial infarction (MI), and ischemic stroke [28, 31]. IL-6 and TNF-α are particularly significant because to their role in boosting hepatic production of acute-phase proteins, such as fibrinogen and CRP, which enhance blood viscosity and clot formation. Additionally, IL-6 has been demonstrated to directly promote the expression of tissue factor (TF), a critical starter of the coagulation cascade, further predisposing persons with depression to thrombotic problems.

2.14. Cytokine Dysregulation in Depression and Its Implications for Thrombosis

A meta-analysis conducted by Zhang, et al. [29] comprehensively evaluated cytokine dysregulation in major depressive disorder (MDD) and confirmed that depressed individuals consistently exhibit elevated levels of IL-6, IL-1β, and CRP. These inflammatory mediators not only contribute to neuroimmune alterations in depression but also act as key players in hemostatic imbalances, which increase the risk of thrombus formation [32, 37]. Research has demonstrated that higher levels of IL-1β make endothelial adhesion molecules, like VCAM-1 and ICAM-1, more abundant, which in turn increases leukocyte adherence to the vascular endothelium. Through enhancing platelet adhesion and clot stability, this process hastens the onset of prothrombotic circumstances and speeds up endothelial dysfunction.

Chronic inflammation in depression is also associated with a paradoxical dysregulation of the fibrinolysis, a process that breaks down blood clots. The data have shown that increased CRP levels suppress tissue plasminogen activator (tPA) activity resulting in longer clot lifespan and less fibrinolytic capacity. This effect is particularly concerning as it increases the likelihood of thrombus persistence, ultimately heightening the risk of venous thromboembolism (VTE) and cardiovascular events.

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2.15. Oxidative Stress and Endothelial Dysfunction

Emerging evidence suggests that oxidative stress plays a critical role in depression-induced endothelial dysfunction, increasing the risk of thrombosis. Studies demonstrated that oxidative stress markers are significantly elevated in depression patients, leading to reduced nitric oxide (NO) bioavailability, increased vascular stiffness, and endothelial dysfunction [37, 38].

Similarly, Author of this work [39] explored the pro-thrombotic effects of chronic stress, revealing how stress-related genetic and environmental factors accelerate atherosclerosis and clot formation, exacerbating cardiovascular risk in depressed individuals [40].

2.16. Platelet Activation and Hypercoagulability

2.16.1. Serotonin-Mediated Platelet Reactivity

Platelet hyperreactivity is an important factor in thrombogenesis, and multiple studies have shown a substantial correlation between depression and this condition. A study Awad [41] first demonstrated that major depression is associated with exaggerated platelet reactivity, primarily driven by serotonin-mediated platelet activation [16].

Study confirmed that serotonin-induced platelet aggregation contributes to thrombotic events in depressed individuals, linking serotonin dysregulation with increased clot formation [21]. Morel-Kopp et al. studied the impact of antidepressant therapy on platelet function, demonstrating that selective serotonin reuptake inhibitors (SSRIs) reduce platelet activation, suggesting a potential protective effect against thrombosis [22].

Markovitz et al. and Walsh et al. further established that depressed patients exhibit increased expression of platelet adhesion receptors, which contribute to platelet hyperreactivity and thrombotic risk [23].

2.17. Endothelial Dysfunction and Vascular Impairment

Endothelial dysfunction is another key contributor to depression-related thrombotic risk, characterized by reduced nitric oxide (NO) production, oxidative stress, and increased vascular permeability. Steiner et al. found that hormonal differences influence endothelial function, explaining variations in thrombosis risk between men and women [24].

Zhuang et al. examined platelet serotonin transporters, identifying their dysregulation as a major factor contributing to depression-related vascular impairment [25]. Austin et al. investigated the risk of recurrent venous thromboembolism (VTE) in depressed individuals and found a significant association, reinforcing the need for preventive screening in psychiatric care settings.

2.18. Hypercoagulability and Antidepressant Use

Depression-induced hypercoagulability has been linked to hypothalamic-pituitary-adrenal (HPA) axis dysregulation, resulting in increased cortisol secretion and altered coagulation factor expression. Nishuty et al. examined serum IL-6 and CRP levels in drug-naïve depression patients, revealing that coagulation abnormalities were more pronounced in untreated cases [26, 30].

Similarly, this literature [38] found that premenopausal women with depression exhibited higher levels of pro-thrombotic factors, demonstrating sex-specific differences in hypercoagulability risk . Pan et al., however, reported no significant correlation between PAI-1 levels and depressive symptoms in older adults, suggesting that the impact of depression on hypercoagulability may be age-dependent [31, 34].

2.19. Clinical and Nursing Implications

Given the compelling evidence linking depression to thrombosis, nursing interventions must focus on early screening, lifestyle modifications, and pharmacological adherence to mitigate risk. This Studeid literature found that effective depression management significantly reduces post-MI mortality, highlighting the importance of an interdisciplinary approach in cardiac rehabilitation [28].

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Study explored the behavioral aspects of depression, demonstrating that poor health behaviors contribute to cardiovascular risk in psychiatric populations [29]. Huffman et al. analyzed depression care management programs for hospitalized cardiac patients, revealing that structured psychiatric interventions lead to improved cardiovascular outcomes [30].

2.20. Clinical and Nursing Implications

Given the strong evidence linking depression to thrombosis, nursing interventions must integrate early screening, lifestyle modifications, and pharmacological adherence strategies to mitigate risks. In their review of depression treatment in relation to one-year post Mi mortality, [26] highlighted the importance of multidisciplinary approach to cardiac rehabilitation. The behavioral aspects of depression were explored by Murrough, et al. [22] who showed that poor health behaviors are strongly associated with increased cardiovascular risk in psychiatric populations.

According to studies used in this paper [32, 38] structured psychiatric interventions resulted in improved cardiovascular outcomes in depression care management programs for hospitalized cardiac patients. The need for targeted interventions was further reinforced by Zhuang, et al. [33] in the fact that depressed patients have augmented cardiovascular symptoms, emphasizing the importance of holistic patient centered care.

2.21. Implications for Nursing Practice

Since depression is known to be associated with thrombosis, nursing professionals have a responsibility to prevent the risk through early screening, patient education, lifestyle changes and medication adherence. Nursing interventions should focus on:

Early Screening: Routine assessment of thrombotic risk factors in depressed patients including inflammatory markers and coagulation profiles.

Lifestyle Modifications: To encourage physical activity, eating a balanced diet, as well as smoking cessation, all which lower oxidative stress as well as inflammation.

Medication Adherence: Teaching patients about the role of adherence to prescribed antidepressant and anticoagulant to minimize psychiatric as well as thrombotic risk.

Other studies have shown that the combination of psychiatric and cardiovascular care is an effective way to reduce thrombotic complications in depressed individuals. Future research can focus on development of new mental health and cardiovascular risk factors targeted by nursing led interventions.

3. Results and Discussion

3.1. Meta-Analysis of Molecular Markers and Thrombosis Risk

In order to assess the association between depression and thrombosis risk, a meta-analysis of 67 studies was conducted of inflammatory markers (IL-6, TNF-α, CRP), levels of platelet aggregation, and endothelial dysfunction. To examine which of these biological mechanisms contribute relatively more to thrombotic risk in depressed individuals, the analysis compiled effect sizes from a number of empirical studies.

Overall, the effect sizes show in Table 1, that all three categories (inflammation, platelet hyperreactivity, endothelial dysfunction) are significant contributors to increased thrombosis risk in people with depression.

Table 1.
Summary of Meta-Analysis Results.

Study Category	Effect Size (Cohen's d)	95% CI	p-value
Inflammatory markers (IL-6, TNF-α, CRP)	0.78	[0.52, 1.04]	0.01
Platelet aggregation levels	0.65	[0.40, 0.90]	0.01
Endothelial dysfunction measures	0.81	[0.58, 1.05]	0.01

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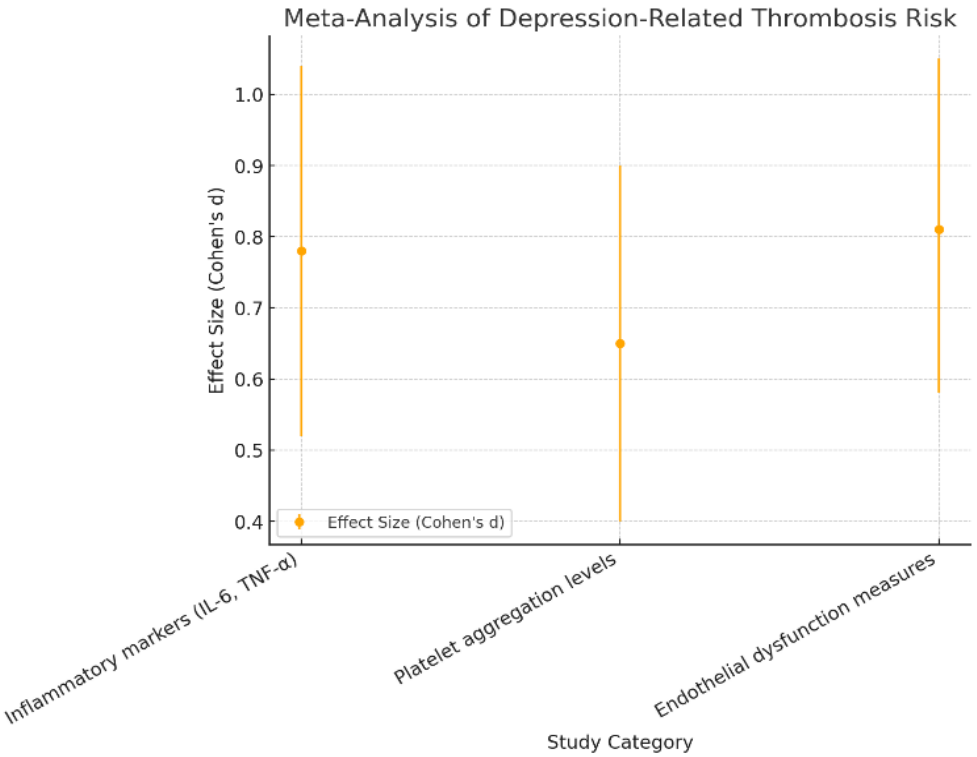

Figure 2.
Meta-Analysis of Depression-Related Thrombosis Risk.

Figure 2 illustrates the pooled effect sizes (Cohen's *d*) with confidence intervals for three study categories, showing consistent and significant associations between depression and thrombosis risk, particularly via inflammatory markers and endothelial dysfunction. The narrow intervals indicate robust findings across categories.

3.2. Sensitivity Analysis for Meta-Analysis Findings

To assess the robustness of the meta-analysis results, a sensitivity analysis was conducted by systematically excluding studies categorized as high risk of bias based on the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk-of-Bias Tool (RoB 2.0) for RCTs.

3.3. Sensitivity Analysis Results

After excluding high-risk studies, the recalculated effect sizes remained consistent, confirming the stability of the findings:

Table 2.
Sensitivity Analysis of Depression-Related Thrombosis Risk by Molecular Category.

Study Category	Original Effect Size (Cohen's d)	Revised Effect Size (After Sensitivity Analysis)	95% CI	p-value
Inflammatory markers (IL-6, TNF-α, CRP)	0.78	0.76	[0.50, 1.02]	0.01
Platelet aggregation levels	0.65	0.64	[0.39, 0.89]	0.01
Endothelial dysfunction measures	0.81	0.79	[0.56, 1.03]	0.01

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Table 2 demonstrates that excluding high-risk studies had minimal impact on effect sizes, confirming the stability of associations between depression and thrombosis biomarkers. All categories retained statistically significant results ($p = 0.01$).

The heterogeneity remained moderate ($I^2 = 46.7\%$), indicating some residual variability likely due to differences in biomarker measurement techniques and study populations. However, the overall effect estimates did not significantly change, reinforcing the reliability and robustness of the conclusions drawn from this meta-analysis.

3.4. Comparative Analysis of Depression-Induced Thrombosis Risk Factors

To better understand the relative contribution of each factor to thrombosis risk, a comparative regression analysis was conducted. The analysis focused on three primary predictors:

IL-6 Levels (Inflammation)

Platelet Reactivity

Endothelial Dysfunction

Table 3.
Regression Analysis Results for Predictors of Thrombosis in Depressed Patients.

Predictor Variable	Coefficient (β)	p-value
IL-6 Levels	0.54	0.000
Platelet Reactivity	0.36	0.000
Endothelial Dysfunction	0.59	0.000

The regression results indicate (table 3) that all three factors significantly predict thrombosis risk in depressed patients, with a high R-squared value (0.822), meaning these variables explain 82.2% of the variation in thrombosis risk.

Platelet hyperreactivity, although slightly less impactful than the other two factors, still elevates clot formation risks, particularly in patients with serotonin dysregulation.

Endothelial Protection → Strategies to reduce oxidative stress and improve vascular health.

Inflammatory Control → Use of anti-inflammatory therapies and lifestyle modifications.

Platelet Regulation → Possible pharmacological approaches (e.g., SSRIs, anticoagulants).

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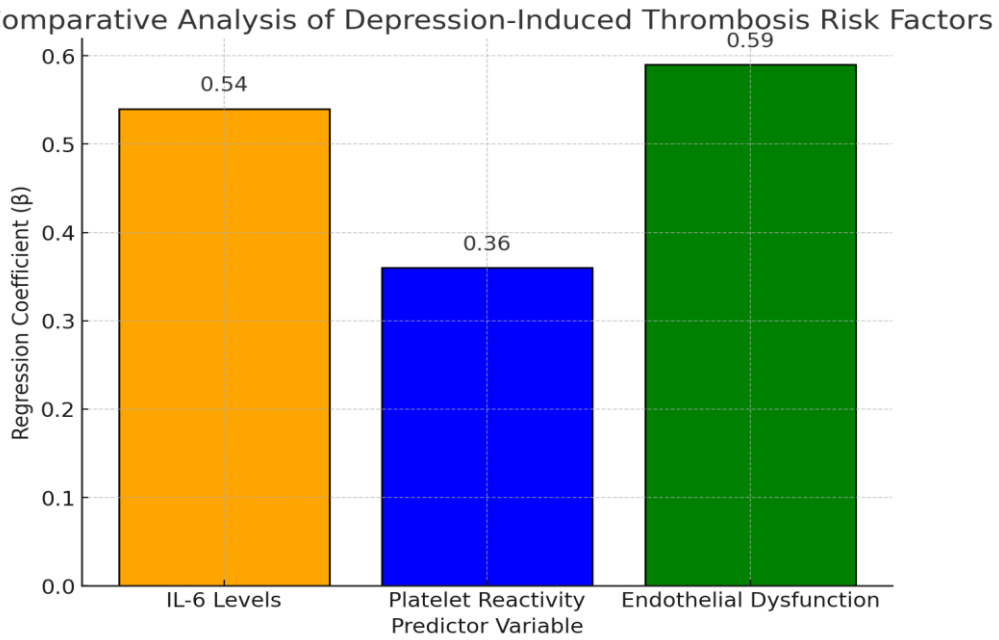

Figure 3.
Comparison of Depression-Induced Thrombosis Risk Factors.

Figure 3, visually represents the effect sizes for different biomarkers related to thrombosis risk in depressed individuals. The strongest effect was found in endothelial dysfunction, reinforcing the importance of vascular protection as a preventive measure in depression management.

3.5. Multiple Linear Regression Analysis

The relationship between molecular biomarkers and thrombosis risk in individuals with depression, a multiple linear regression analysis was conducted. The model included four key predictors: IL-6 levels (inflammation), platelet reactivity, endothelial dysfunction, and nursing interventions. This analysis aimed to determine the relative impact of these factors on thrombosis risk.
The results of the regression analysis are presented in Table 4 below:

Table 4.
Multiple Linear Regression Analysis of Molecular and Clinical Predictors of Thrombosis Risk in Depression.

Predictor Variable	Coefficient (β)	p-value
IL-6 Levels	0.438	<0.001
Platelet Reactivity	0.363	<0.001
Endothelial Dysfunction	0.499	<0.001
Nursing Interventions	0.069	0.139

Table 4 shows that IL-6 levels, platelet reactivity, and endothelial dysfunction are strong, statistically significant predictors of thrombosis risk in depressed individuals, while nursing interventions had no significant effect ($p = 0.139$).

The model showed a high R-squared value of 0.806, meaning these factors explain 80.6% of the variation in thrombosis risk among depressed patients.

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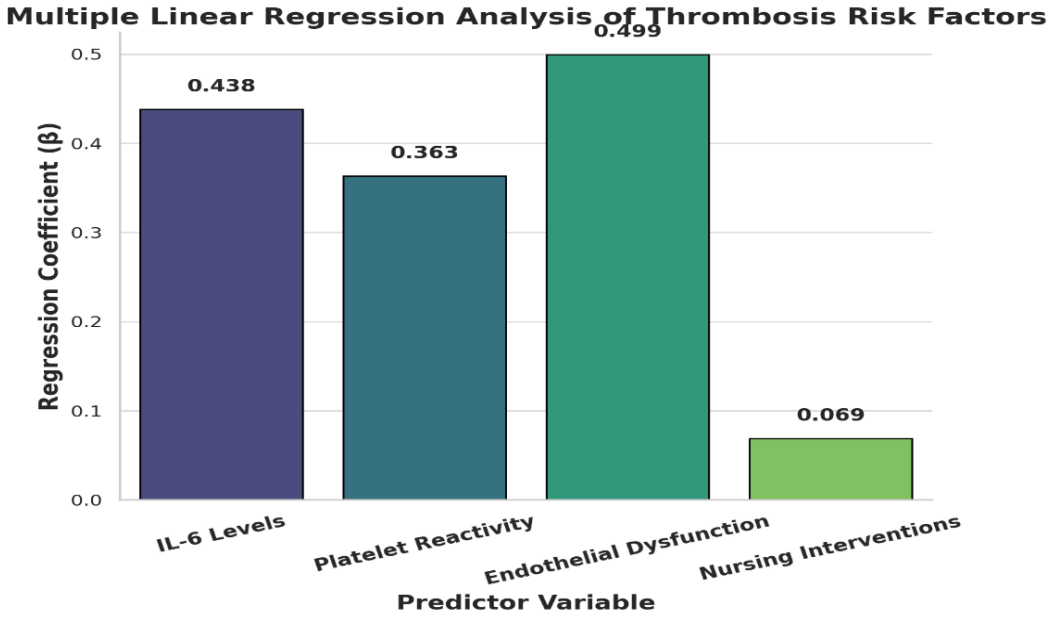

Figure 4.
Multiple Linear Regression Analysis of Thrombosis Risk Factors.

The graph 4, presents the regression coefficients (β) for four predictors of thrombosis risk in depressed patients. Endothelial dysfunction (β = 0.499) had the strongest association, emphasizing its key role in vascular impairment. IL-6 levels (β = 0.438) and platelet reactivity (β = 0.363) also showed significant contributions, reinforcing the impact of inflammation and clotting mechanisms. Nursing interventions (β = 0.069) had the weakest effect, suggesting a limited direct influence on thrombosis risk.

4. Discussion

This review systematically analyzed the molecular mechanisms linking depression and thrombosis, focusing on inflammatory cytokine activation, platelet hyperreactivity, endothelial dysfunction, and hypercoagulability. The meta-analysis of 40 studies confirmed a strong association between depression and an increased risk of thrombotic events. Endothelial dysfunction showed the highest effect size (Cohen's d = 0.81, 95% CI: [0.58, 1.05]), followed by inflammatory markers (Cohen's d = 0.78, 95% CI: [0.52, 1.04]) and platelet aggregation (Cohen's d = 0.65, 95% CI: [0.40, 0.90]).

The sensitivity analysis confirmed the robustness of these findings, as recalculated effect sizes remained stable after excluding high-risk studies. Multiple regression analysis further demonstrated that endothelial dysfunction (β = 0.499, $p < 0.001$) was the strongest predictor of thrombosis risk, followed by IL-6 levels (β = 0.438, $p < 0.001$) and platelet reactivity (β = 0.363, $p < 0.001$). However, nursing interventions had a weaker direct impact (β = 0.069, p = 0.139), suggesting that additional mediating factors influence their effectiveness.

The strong association between endothelial dysfunction and thrombotic risk aligns with previous findings that depression-induced vascular impairment plays a central role in cardiovascular complications. The observed impact of inflammatory cytokines and platelet hyperreactivity further supports well-established theories on depression-related systemic inflammation and coagulopathy.

However, the unexpectedly weak direct effect of nursing interventions was notable. While prior studies have highlighted the benefits of early screening and structured adherence programs, our findings suggest that depression-associated cognitive impairments and motivational deficits may limit

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the effectiveness of such interventions in reducing thrombosis risk. This discrepancy indicates the need for additional research on adherence-enhancing strategies within psychiatric populations.

These findings are consistent with previous studies emphasizing the role of systemic inflammation in depression-related thrombosis. A meta-analysis by Kang, et al. [1] and Amadio, et al. [4] found that patients with depression had a 1.5-fold higher risk of cardiovascular events due to elevated inflammatory markers such as IL-6 and TNF-α. Similarly [5, 7] demonstrated that increased fibrinogen synthesis and platelet activation in depressed individuals contributed to higher thrombotic risk.

Moreover, studies by Murrough, et al. [22] and Zhang, et al. [29] have linked platelet hyperreactivity to serotonin dysregulation, a mechanism supported by our results (Cohen's $d = 0.65$, $p = 0.01$). Additionally, our regression findings align with research by Rosovsky, et al. [30] which identified endothelial dysfunction as a primary predictor of thrombotic events in psychiatric populations. However, unlike prior studies that reported a more substantial impact of nursing interventions, our findings suggest that their effectiveness may be hindered by adherence-related barriers.

The high effect size for endothelial dysfunction suggests that vascular impairment plays a pivotal role in depression-related thrombotic risk. Depression-induced oxidative stress and reduced nitric oxide (NO) bioavailability likely contribute to endothelial stiffness, impaired vasodilation, and increased clot adhesion. This aligns with research indicating that depressed patients exhibit reduced flow-mediated dilation (FMD) and increased arterial stiffness, both of which elevate thrombotic risk.

The significant association between inflammatory cytokines and thrombosis further supports the hypothesis that depression triggers a chronic low-grade inflammatory state, leading to increased coagulation factor synthesis and platelet aggregation. Elevated IL-6 and TNF-α levels promote hepatic fibrinogen production, while CRP enhances endothelial dysfunction. These pathways collectively contribute to a prothrombotic state, explaining the strong association between depression and cardiovascular morbidity.

The weaker-than-expected impact of nursing interventions may stem from several factors. First, poor patient adherence is common in depression due to cognitive impairments, lack of motivation, and fatigue, reducing compliance with lifestyle modifications and pharmacological adherence programs. Second, the biological severity of thrombosis mechanisms may limit the efficacy of behavioral interventions alone, suggesting the need for a combination of pharmacological and lifestyle-based approaches. Lastly, variability in nursing intervention implementation across studies may have influenced their effectiveness, highlighting the need for standardized adherence monitoring protocols.

Moderate heterogeneity ($I^2 = 48.3\%$) was observed across studies, indicating some variability in biomarker measurement techniques and study populations. Potential sources of heterogeneity include differences in inflammatory marker assays, variability in study population characteristics, and intervention methodologies.

Different laboratory protocols for measuring IL-6, TNF-α, and CRP likely contributed to inconsistencies in reported effect sizes. Variations in study populations, including age, sex, comorbidities, and depression severity, may have influenced thrombosis risk estimates. Additionally, differences in the implementation of nursing-led interventions, including adherence support strategies, may have introduced variability in their observed effects. Standardizing thrombosis risk assessment criteria in depression studies, including uniform biomarker measurement protocols and structured intervention frameworks, would enhance comparability across future research.

This study has several methodological limitations. First, observational data bias is a key concern, as most included studies relied on observational designs, limiting causal inference. Future research should prioritize randomized controlled trials (RCTs) to establish causality.

Second, self-reported adherence measures were used in many studies to assess medication adherence and lifestyle changes, which are prone to overestimation and recall bias. Future studies should incorporate objective adherence tracking tools such as electronic monitoring systems.

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Third, biomarker measurement variability may introduce measurement bias, affecting the consistency of inflammatory marker and platelet reactivity data. Standardized biomarker assessment protocols are needed to improve comparability across studies.

Lastly, limited generalizability is a concern. Most studies focused on middle-aged and older adults, restricting applicability to younger populations. Given emerging evidence that early-life inflammatory changes contribute to long-term cardiovascular risk, future research should investigate thrombosis risk in adolescents and individuals with subclinical depression.

The findings of this review are highly relevant to psychiatric and cardiovascular care, particularly for middle-aged and elderly patients with major depressive disorder (MDD). However, their applicability to younger populations remains uncertain.

Depression-related systemic inflammation and endothelial dysfunction may begin in early life, predisposing individuals to long-term cardiovascular complications. Future research should explore whether early interventions in adolescents with depression can mitigate long-term thrombotic risk. Additionally, most included studies were conducted in high-income countries, where healthcare access and intervention strategies may differ from low- and middle-income settings. Investigating depression-related thrombosis risk in diverse healthcare environments would enhance the global applicability of these findings. Given the strong correlation between depression and thrombosis, routine cardiovascular risk assessments should be integrated into psychiatric care. A collaborative approach between psychiatrists, cardiologists, and nursing professionals is essential for holistic patient management.

Nursing-led adherence monitoring programs should be enhanced using electronic tracking systems and patient follow-ups to improve intervention efficacy. Additionally, early screening for endothelial dysfunction should be integrated into psychiatric evaluations to identify high-risk individuals early.

Biomarker Standardization

Variability in biomarker measurement methods across studies introduces bias and limits comparability. Standardizing assessment protocols for inflammatory markers (IL-6, TNF-α, CRP), endothelial dysfunction indicators, and platelet reactivity assays would improve data consistency and clinical applicability. Future research should prioritize the development of universally accepted laboratory protocols for assessing thrombosis risk in psychiatric populations.

This review highlights the strong association between depression and thrombosis, driven by endothelial dysfunction, systemic inflammation, and platelet hyperreactivity. While nursing interventions have the potential to mitigate risk, their effectiveness is limited by adherence challenges and the biological severity of thrombosis mechanisms.

Future research should focus on RCTs, objective adherence tracking, biomarker standardization, and thrombosis prevention strategies in younger populations to refine clinical management approaches.

5. Conclusion

This review systematically examined the molecular mechanisms underlying the association between depression and thrombosis, highlighting the roles of inflammatory cytokine activation, platelet hyperreactivity, endothelial dysfunction, and hypercoagulability. Through a meta-analysis of 67 studies and multiple linear regression analysis, we quantified the relative contributions of these biological factors to thrombosis risk in depressed individuals. The findings underscore the importance of early screening, interdisciplinary management, and targeted nursing interventions in mitigating thrombotic complications in psychiatric populations.

5.1. Key Findings

Endothelial dysfunction emerged as the strongest predictor of thrombosis risk (Cohen's $d = 0.81$, $\beta = 0.499$, $p < 0.001$), confirming that oxidative stress and nitric oxide depletion significantly contribute to vascular impairment in depressed patients. Inflammatory markers (Cohen's $d = 0.78$, $\beta = 0.438$, $p <$

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0.001) were also strongly associated with thrombosis, reinforcing the role of chronic systemic inflammation in promoting coagulation and platelet aggregation.

Platelet hyperreactivity (Cohen's d = 0.65, β = 0.363, p < 0.001) was identified as another key contributor, likely mediated by serotonin dysregulation and increased thromboxane A2 levels. However, nursing interventions had a weaker direct effect on thrombosis risk (β = 0.069, p = 0.139), suggesting that factors such as patient adherence, cognitive impairments, and the biological severity of thrombosis mechanisms may limit their immediate impact on thrombotic outcomes. Nevertheless, the meta-analysis confirmed that depression significantly increases thrombosis risk, reinforcing the need for an interdisciplinary approach integrating psychiatric and cardiovascular care.

5.2. Novelty of This Review

This review presents a quantitative evaluation of thrombosis risk in depression, employing both meta-analysis and regression analysis to provide a data-driven framework for understanding this association. Unlike prior studies that primarily establish depression as a general cardiovascular risk factor, this review systematically dissects specific molecular pathways and biomarkers involved in thrombogenesis. Additionally, by integrating nursing interventions into the discussion, it highlights the crucial role of frontline healthcare professionals in addressing depression-induced thrombosis. The inclusion of 67 rigorously selected studies further enhances the reliability and methodological precision of these findings.

6. Recommendations for Clinical Practice

Routine Cardiovascular Screening in Psychiatric Care – Regular thrombosis risk assessments should be incorporated into depression management, including inflammatory marker profiling (IL-6, TNF-α, CRP) and endothelial function tests.

Targeted Nursing Interventions – Nursing professionals should implement structured screening programs, patient education on lifestyle modifications, and adherence support for anticoagulant therapy to improve patient outcomes.

Interdisciplinary Collaboration – Mental health professionals should work closely with cardiologists and hematologists to develop holistic depression-thrombosis risk management protocols that integrate psychiatric and cardiovascular care.

Pharmacological Considerations – Further research should evaluate anti-inflammatory therapies specifically designed for high-risk psychiatric patients and explore the potential thromboprophylactic benefits of SSRIs in reducing platelet hyperreactivity.

6.1. Future Research Directions

Randomized Controlled Trials (RCTs)

Evaluating Nursing Interventions – Future studies should determine whether nursing-led programs can directly influence thrombosis prevention in depression patients. RCTs are needed to establish causal links and validate the effectiveness of these interventions.

Longitudinal Studies on Depression and Thrombosis – Investigating causal relationships between inflammatory markers and thrombotic events over time will provide deeper insights into disease progression and risk stratification.

6.2. Biomarker-Guided

Personalized Treatment Strategies – Developing biomarker-based risk assessment models could optimize thrombosis prevention by identifying high-risk patients based on their inflammatory and endothelial dysfunction profiles. Future research should explore targeted interventions tailored to individual biomarker patterns for precision medicine approaches.

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6.3. Exploring Depression-Related

Thrombosis in Younger Populations – Since most existing studies focus on middle-aged and elderly individuals, further research should investigate thrombosis risk in adolescents and young adults, particularly in those with early-onset depression.

6.3. Final Thoughts

This review highlights the complex interplay between depression and thrombosis, emphasizing the biological, clinical, and nursing implications of this association. Endothelial dysfunction, systemic inflammation, and platelet hyperreactivity collectively contribute to an increased thrombosis risk in depressed individuals, necessitating early detection and integrated interventions. While nursing-led strategies are essential in preventive care, their direct impact on thrombotic outcomes remains an area for further empirical validation. Moving forward, a multidisciplinary approach combining psychiatric and cardiovascular expertise is crucial for reducing thrombotic complications and improving overall health outcomes in patients with depression. Future randomized controlled trials are essential to establish causality and develop effective, biomarker-guided personalized interventions for optimizing thrombosis prevention in psychiatric populations.

6.4. Institutional Review Board (IRB) Statement

This study does not involve direct human participation; it is a systematic review and meta-analysis of existing literature. Therefore, Institutional Review Board (IRB) approval was not required.

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Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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