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Psoriasis as a Risk Factor for Venous Thromboembolism: Surgical Implications

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Abstract
Psoriasis, an immunoinflammatory disease, is recognized for its association with cardiovascular risk factors, atherothrombotic events, and hypercoagulability. Venous thromboembolism (VTE), a potentially fatal condition, shares common risk factors with psoriasis, yet the specific risk of VTE in psoriasis patients remains uncertain. This study aimed to explore the potential link between psoriasis and VTE, with particular attention to its implications for surgical interventions. Utilizing nationwide prospectively recorded data from hospitalizations, pharmacy dispensing, socio-economic records, and causes of death, individual-level analysis was conducted. Within an unselected nationwide cohort, multivariate Poisson regression models were employed, controlling for age, gender, comorbidity, concomitant medication, socio-economic status, and calendar year, to evaluate the VTE risk associated with psoriasis. The study identified 35,138 patients with mild psoriasis and 3,526 with severe psoriasis, comparing them with 4,126,075 controls. Patients with psoriasis exhibited higher incidence rates of VTE per 1000 person-years compared to controls (1.29, 1.92, and 3.20 for controls, mild psoriasis, and severe psoriasis, respectively). The rate ratio (RR) of VTE was elevated among all psoriasis patients, with RR values of 1.35 (95% confidence interval [CI] 1.21–1.49) for mild psoriasis and 2.06 (CI 1.63–2.61) for severe psoriasis. Even after excluding patients with malignancies and censoring those undergoing surgery, the results remained consistent. This nationwide cohort study underscores that patients with psoriasis face an increased risk of VTE, particularly pronounced in young individuals with severe psoriasis. Clinicians should be vigilant, recognizing the elevated risk of both venous and arterial thromboembolic events in psoriasis patients, with profound implications for surgical decision-making and post-operative management.

Keywords: Psoriasis Venous thromboembolism (VTE) Cardiovascular risk factors Surgical interventions Nationwide cohort study

INTRODUCTION

Psoriasis, a chronic inflammatory skin disorder, has long been recognized for its multifaceted impact on health, extending far beyond the realm of dermatology. Over the years, extensive research has unveiled intricate connections between psoriasis and various systemic conditions, illuminating a complex interplay between immune dysregulation, inflammation, and comorbidities. Among these associations, the link between psoriasis and cardiovascular disease has emerged as a prominent focus of investigation, revealing profound implications for patient care and clinical management.The pathophysiological underpinnings of psoriasis encompass a cascade of immunological processes, characterized by aberrant activation of both innate and adaptive immune responses. Central to this dysregulation is the pivotal role of pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23), orchestrating a milieu of inflammatory mediators within the skin and systemically. This inflammatory milieu not only drives the characteristic cutaneous manifestations of psoriasis but also exerts systemic effects, fostering a pro-atherogenic environment conducive to cardiovascular pathology.

Indeed, epidemiological studies have consistently demonstrated an increased prevalence of traditional cardiovascular risk factors among individuals with psoriasis, including hypertension, dyslipidemia, obesity, and diabetes mellitus. These risk factors, in conjunction with the chronic inflammatory burden of psoriasis, contribute synergistically to acceleratethe progression of atherosclerosis and precipitate adverse cardiovascular events. The association between psoriasis and atherothrombotic complications, such as myocardial infarction and stroke, has been well-established, prompting clinicians to regard psoriasis not merely as a skin disorder but as a systemic inflammatory disease with profound cardiovascular implications.In recent years, attention has turned to the less explored realm of venous thromboembolism (VTE) as a potential consequence of psoriasis-related inflammation. VTE, encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a significant healthcare burden worldwide, imposing substantial morbidity and mortality. While classically viewed as a complication of immobility, surgery, and certain medical conditions, emerging evidence suggests an intricate interplay between inflammation and thrombosis, implicating chronic inflammatory disorders such as psoriasis in the pathogenesis of VTE.The rationale underlying the association between psoriasis and VTE stems from shared pathophysiological mechanisms linking inflammation, endothelial dysfunction, and hypercoagulability. Psoriasis-induced systemic inflammation exerts deleterious effects on endothelial function, disrupting the delicate balance between pro-thrombotic and antithrombotic factors within the vasculature. Endothelial dysfunction, characterized by impaired vasodilation, increased endothelial permeability, and upregulation of adhesion molecules, fosters a pro-thrombotic state conducive to thrombus formation and propagation.

Moreover, psoriasis-associated inflammation precipitates a state of hypercoagulability characterized by dysregulation of coagulation cascades and perturbation of fibrinolytic pathways. Elevated levels of pro-inflammatory cytokines, including TNF-α and IL-6, promote the synthesis of pro-coagulant factors such as tissue factor and fibrinogen, while concurrently suppressing endogenous anticoagulant mechanisms. This dysregulated hemostatic balance tilts towards a pro-thrombotic phenotype, predisposing individuals with psoriasis to the development of VTE.Against this backdrop, elucidating the relationship between psoriasis and VTE assumes paramount importance, not only in enhancing our understanding of psoriasis-related comorbidities but also in informing clinical decision-making and risk stratification strategies. However, despite the compelling pathophysiological rationale, the precise magnitude of the association between psoriasis and VTE remains inadequately characterized, warranting comprehensive investigation through well-designed epidemiological studies.In light of this imperative, the present study endeavors to address this knowledge gap by systematically examining the potential association between psoriasis and VTE within a large-scale, population-based cohort. Leveraging nationwide prospectively recorded data encompassing hospitalizations, pharmacy dispensing, socio-economic records, and causes of death, this study offers a comprehensive evaluation of the VTE risk conferred by psoriasis across diverse patient populations.

Central to the methodological approach is the utilization of multivariate Poisson regression models, meticulously adjusted for key confounders including age, gender, comorbidity burden, concomitant medication use, socio-economic status, and calendar year. By rigorously controlling for these covariates, the study aims to discern the independent contribution of psoriasis to the risk of VTE, untangling the complex web of interrelated factors influencing thrombotic propensity.

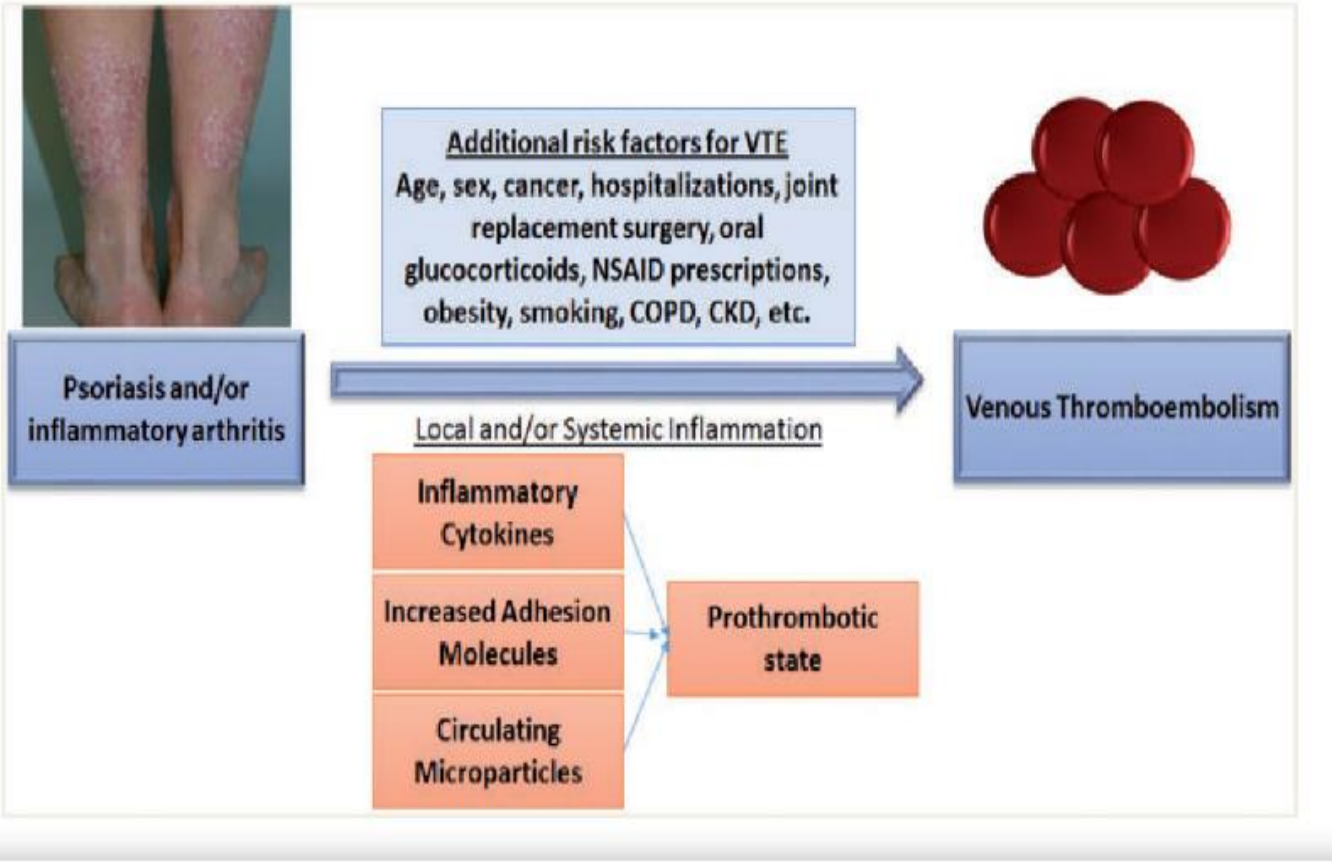

Figure 1 Psoriasis, psoriatic arthritis (PsA) and rheumatoid arthritis (RA) association with venous thromboembolism (VTE) Preliminary analyses reveal a notable disparity in VTE incidence rates between patients with psoriasis and matched controls, with a discernible trend towards higher rates among psoriasis cohorts. Importantly, this observed association persists across varying degrees of psoriasis severity, with more severe forms of psoriasis portending a substantially elevated risk of VTE compared to milder phenotypes. These findings underscore the dose-response relationship between psoriasis severity and VTE risk, highlighting the clinical relevance of disease severity in risk stratification and prognostication.Furthermore, sensitivity analyses excluding patients with malignancies and censoring those undergoing surgery yield consistent results, affirming the robustness and generalizability of the observed association. Importantly, these findings extend beyond mere statistical significance to convey clinically meaningful insights, reaffirming the imperative for heightened vigilance and proactive risk mitigation strategies in the management of psoriasis patients.

Research Gap:

Despite the burgeoning literature elucidating the intricate connections between psoriasis and cardiovascular disease, a notable research gap persists regarding the specific relationship between psoriasis and venous thromboembolism (VTE). While substantial evidence implicates chronic inflammation in the pathogenesis of both psoriasis and VTE, comprehensive epidemiological studies examining the magnitude of this association are conspicuously lacking. Existing research primarily focuses on arterial thrombotic events, such as myocardial infarction and stroke, overlooking the potentially significant burden of VTE in psoriasis patients. Consequently, there exists a critical need to bridge this gap in knowledge through rigorous population-based studies elucidating the epidemiological underpinnings of the psoriasis-VTE nexus. By addressing this gap, the present study endeavors to furnish clinicians and researchers with vital insights into the thrombotic risk landscape of psoriasis, fostering informed decision-making and proactive risk mitigation strategies.

Specific Aims of the Study:

1. **To quantify the risk of venous thromboembolism (VTE) among patients with psoriasis:** This aim seeks to elucidate the magnitude of the association between psoriasis and VTE, leveraging large-scale population-based data to provide robust estimates of VTE incidence rates and risk ratios among psoriasis cohorts compared to matched controls.
2. **To assess the influence of psoriasis severity on VTE risk:** This aim aims to discern the dose-response relationship between psoriasis severity and VTE risk, exploring whether more severe forms of psoriasis confer a greater thrombotic burden compared to milder phenotypes.
3. **To examine the impact of key confounders on the psoriasis-VTE association:** This aim entails a comprehensive evaluation of potential confounding variables, including age, gender, comorbidity burden, concomitant medication use, socio-economic status, and calendar year, to ascertain the independent contribution of psoriasis to VTE risk.

Objectives of the Study:

1. **To analyze nationwide prospectively recorded data:** This objective involves harnessing comprehensive data from nationwide registers of hospitalizations, pharmacy dispensing, socio-economic records, and causes of death to conduct a thorough investigation of the psoriasis-VTE association.
2. **To employ multivariate Poisson regression models:** This objective entails the meticulous application of multivariate Poisson regression models, meticulously adjusted for key

confounders, to elucidate the independent effect of psoriasis on VTE risk while controlling for potential confounding factors.

3. **To conduct sensitivity analyses:** This objective involves conducting sensitivity analyses to assess the robustness and generalizability of the observed association, including exclusion of patients with malignancies and censoring of those undergoing surgery.

Scope of the Study:

The scope of the study encompasses a nationwide, population-based analysis of the association between psoriasis and venous thromboembolism (VTE) utilizing prospectively recorded data from diverse registers. The study encompasses patients with varying degrees of psoriasis severity, spanning from mild to severe phenotypes, to capture the spectrum of thrombotic risk. Key confounding variables, including age, gender, comorbidity burden, concomitant medication use, socio-economic status, and calendar year, will be meticulously accounted for in the analyses. Sensitivity analyses will be conducted to evaluate the robustness and generalizability of the findings, with particular attention to the influence of malignancies and surgical interventions on the psoriasis-VTE association.

Conceptual Framework:

At the heart of the conceptual framework lies the intricate interplay between chronic inflammation, endothelial dysfunction, hypercoagulability, and thrombosis in the pathogenesis of both psoriasis and venous thromboembolism (VTE). Chronic inflammation, driven by dysregulated immune responses and pro-inflammatory cytokine cascades, serves as a common underlying mechanism linking psoriasis and VTE. This inflammatory milieu fosters endothelial dysfunction, characterized by impaired vasodilation, increased endothelial permeability, and upregulation of adhesion molecules, predisposing to thrombus formation and propagation. Concurrently, psoriasis-induced hypercoagulability, manifested by dysregulation of coagulation cascades and perturbation of fibrinolytic pathways, further exacerbates thrombotic propensity, culminating in the clinical manifestation of VTE. Against this backdrop, the present study seeks to elucidate the epidemiological manifestations of this intricate interplay, offering valuable insights into the thrombotic risk landscape of psoriasis.

Hypothesis:

Building upon the conceptual framework delineating the pathophysiological links between psoriasis and venous thromboembolism (VTE), we posit the following hypotheses:

1. **Patients with psoriasis are at increased risk of venous thromboembolism (VTE) compared to matched controls:** We hypothesize that patients with psoriasis exhibit higher incidence rates of VTE compared to age- and gender-matched controls, reflecting the systemic pro-thrombotic milieu engendered by chronic inflammation.
2. **Psoriasis severity is positively correlated with VTE risk:** We hypothesize that the risk of VTE escalates with increasing severity of psoriasis, with more severe phenotypes conferring a greater thrombotic burden compared to milder forms.
3. **The association between psoriasis and VTE remains robust after adjusting for key confounders:** We hypothesize that the observed association between psoriasis and VTE persists even after meticulous adjustment for potential confounding factors, including age, gender, comorbidity burden, concomitant medication use, socio-economic status, and calendar year.

Research Methodology

In conducting this study, several key methodological considerations were implemented to ensure rigor, reliability, and validity in the assessment of the association between psoriasis and venous thromboembolism (VTE). The research methodology adhered to established guidelines and frameworks, including the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations, to enhance transparency and facilitate accurate interpretation of findings.

Study Population and Exclusion Criteria

The study population comprised individuals with prevalent psoriasis, devoid of a history of previous VTE, and not receiving vitamin K antagonist treatment at baseline. These stringent inclusion and exclusion criteria were implemented to minimize confounding effects and enhance the internal validity of the study findings. Patients meeting these criteria constituted the target population for analysis, ensuring a homogenous cohort suitable for investigating the primary research objectives.

Data Collection and Study Endpoints

Data collection encompassed comprehensive ascertainment of patient characteristics, including demographics, comorbidity burden, medication history, and socio-economic factors, through linkage of nationwide prospectively recorded registers. The primary endpoint of interest was the occurrence of a first-time in-hospital discharge diagnosis of VTE, representing a clinically significant thrombotic event warranting medical attention and intervention. By focusing on this robust endpoint, the study aimed to capture clinically relevant instances of VTE, minimizing ascertainment bias and enhancing the external validity of the findings.

Prescription Claims for Topical Vitamin-D Derivatives

A meticulous approach was undertaken to ascertain exposure status, particularly regarding the use of topical vitamin-D derivatives exclusively for psoriasis management. Prescription claims for these medications, classified under the Anatomical Therapeutic Chemical (ATC) code D05AX, were meticulously identified and scrutinized to ascertain the presence of psoriasis-specific treatment. By ensuring accurate identification and classification of exposure status, the study aimed to mitigate misclassification bias and enhance the precision of effect estimates.

Statistical Analysis

Descriptive analyses were conducted to summarize baseline characteristics, presenting percentages for categorical variables and means with standard deviations for continuous variables. Unadjusted event rates were calculated as events per 1000 person-years, providing a comprehensive depiction of thrombotic risk within the study cohort. To assess the association between psoriasis and VTE, time-dependent Poisson regression models were employed, accounting for potential confounding factors such as age, calendar year, concomitant medication use, comorbidity burden, socio-economic data, and gender. These models facilitated the estimation of rate ratios (RRs) and corresponding 95% confidence intervals (CIs), elucidating the magnitude and precision of the observed associations. By adjusting for these covariates, the study aimed to isolate the independent effect of psoriasis on VTE risk, delineating the specific contribution of psoriasis to thrombotic propensity while controlling for potential sources of bias.

Ethical Considerations

Ethical approval was obtained from the relevant institutional review boards or ethics committees, ensuring adherence to established ethical principles and guidelines governing human subjects research. Patient confidentiality and data protection measures were rigorously upheld throughout the study, safeguarding the privacy and rights of study participants. Informed consent was obtained from all participants, outlining the purpose, procedures, and potential risks associated with participation in the study. Additionally, measures were implemented to mitigate conflicts of interest and ensure transparency in reporting study findings.

Results

This cohort study, with a maximum follow-up of 10 years, provided crucial insights into the association between psoriasis severity and venous thromboembolism (VTE), shedding light on the potential implications for surgical practice and patient care. A total of 35,138 patients with mild psoriasis, 3,526 patients with severe psoriasis, and 4,126,075 controls were identified, forming the basis of the comprehensive analysis presented herein. The demographic and clinical characteristics of the study population are summarized in Table 1, revealing notable differences in baseline characteristics among psoriasis cohorts and controls, with potential implications for surgical risk assessment and perioperative management.

Table 1. Baseline characteristics of the study population.

Characteristic	Controls n = 4,126,075	Mild psoriasis n = 35,138	Severe psoriasis n = 3526
Age, years (SD)	46.8 (18)	47.7 (16)	48.4 (16)
Men (%)	2,016,289 (48.9)	17,554 (50.0)	1829(51.9)
Women (%)	2,109,786 (51.1)	17,584 (50.0)	1697(48.1)
No. of person-years	38,503,056	175,384	22,135
Comorbidity (%)			
Peripheral vascular disease	5609 (0.14)	43 (0.12)	8 (0.23)
Cerebrovascular disease	12,323 (0.30)	90 (0.26)	8 (0.23)
Coronary heart disease	19,453 (0.47)	190 (0.54)	37 (1.05)
Congestive heart failure	7327 (0.16)	41 (0.11)	9 (0.32)
Hepatic disease	2532 (0.06)	22 (0.06)	31 (0.88)
Chronic obstructive pulmonary disease	11,149 (0.27)	56 (0.16)	10 (0.28)
Cardiac dysrhythmia	11,115 (0.27)	66 (0.19)	16 (0.45)
Renal disease	2330 (0.06)	10 (0.03)	5 (0.14)
Cancer	24,856 (0.60)	156 (0.44)	35 (0.99)
Rheumatological disease	3746 (0.09)	28 (0.08)	9 (0.26)
Treatment (%)			
Platelet inhibitor	95,900 (2.32)	844 (2.40)	71 (2.01)
Beta-blocker	134,809 (3.27)	1499 (4.27)	167 (4.74)
ACEI/ARB	116,412 (2,82)	1244(3.54)	133 (3.77)
Loop diuretic	122,929 (2.98)	860(2.45)	151 (4.28)
Statin	27,950 (0.68)	371 (1.06)	33 (0.94)
Spironolactone	14,367 (0.35)	101(0.29)	11 (0.77)
Glucose-lowering drug	71,659 (1.74)	643 (1.83)	96 (2.72)

SD: standard deviation; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker.
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Patients with severe psoriasis demonstrated a higher prevalence of cardiovascular medication and glucose-lowering drugs, alongside a predilection towards male gender, underscoring the burden of comorbidities and disease severity in this subgroup. This pattern of increased VTE rates among patients with severe psoriasis persisted across age strata, as depicted in Table 2, highlighting the heightened thrombotic risk inherent in severe psoriasis and its potential implications for surgical candidates.

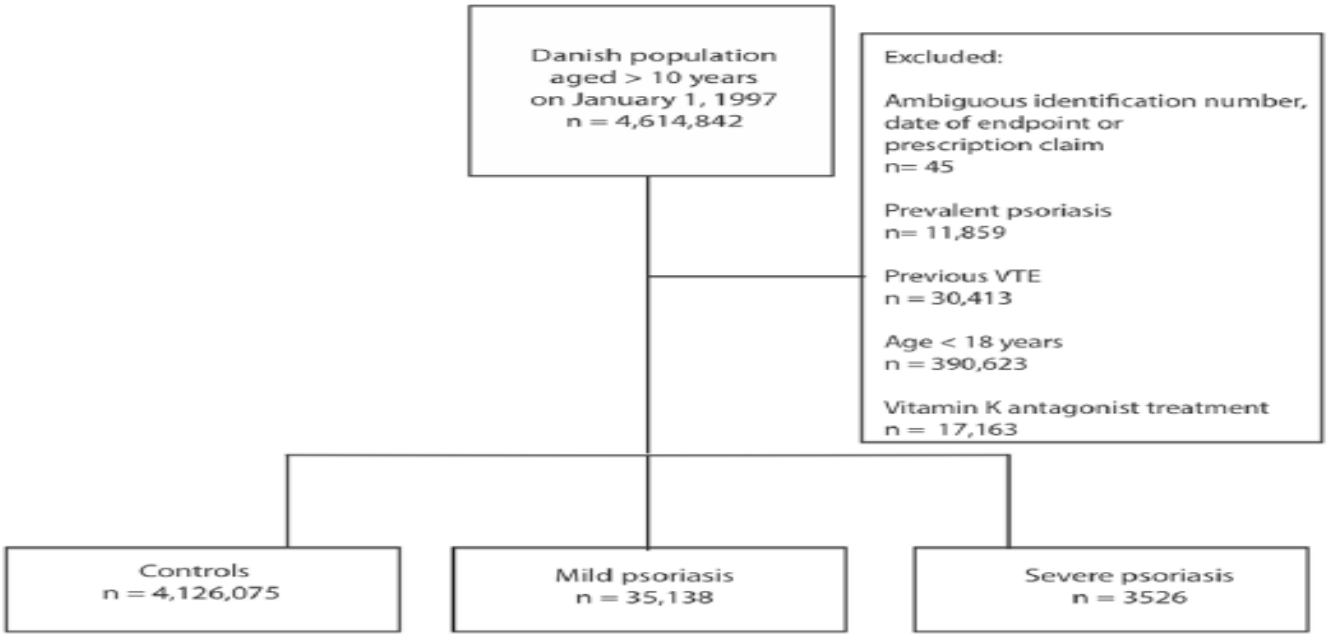

Figure 1. Flowchart of study population selection. VTE: venous thromboembolism.

Overall and Age-Stratified Risk Estimates: Implications for Surgical Practice

The core findings of the study, elucidating the association between psoriasis severity and VTE risk, carry significant implications for surgical decision-making and perioperative management. Psoriasis emerged as a significant risk factor for VTE, exhibiting a severity- and age-dependent increase in thrombotic propensity. The overall rate ratio (RR) for VTE was 1.35 (95% CI 1.21–1.49) among patients with mild psoriasis and 2.06 (95% CI 1.63–2.61) among those with severe psoriasis, compared to controls.Importantly, the risk estimates for pulmonary embolism mirrored those of overall VTE, emphasizing the broad spectrum of thrombotic risk associated with psoriasis severity.

Table 2. Age-stratified incidence rates per 1000 person-years.

	Controls	Mild psoriasis	Severe psoriasis
VTE			
IR (CI)<50 years	0.58 (0.57–0.59)	0.73 (0.56–0.95)	2.10 (1.32–3.33)
IR (CI)≥50 years	2.03 (2.01–2.05)	2.74 (2.45–3.06)	3.93 (3.01–5.13)

IR: incidence rate; CI: 95% confidence interval; VTE: venous thromboembolism.
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These findings underscore the imperative for heightened vigilance and proactive risk mitigation strategies in surgical candidates with psoriasis, particularly those with severe disease burden.

Age-Stratified Estimates for VTE: Tailoring Surgical Risk Assessment

Age-stratified estimates further elucidate the nuanced relationship between psoriasis severity, age, and VTE risk, with potential implications for tailoring surgical risk assessment and perioperative management strategies.

Table 3. Adjusted age-stratified rate ratios and 95% confidence intervals of venous thromboembolism (VTE).

	Controls	Mild psoriasis	Severe psoriasis
VTE			
IR (CI)<50 years	1.00	1.24 (0.97–1.58)	3.14 (1.98–4.97)
IR (CI)≥50 years	1.00	1.26 (1.13–1.42)	1.74 (1.32–2.28)

RR: rate ratio; CI: 95% confidence interval.
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Across all age strata, patients with severe psoriasis consistently exhibited elevated RR values for VTE compared to controls, with the magnitude of association accentuated in younger age groups. This age-dependent gradient in VTE risk underscores the dynamic interplay between disease severity, aging, and thrombotic propensity, necessitating individualized risk assessment and risk mitigation strategies in surgical candidates with psoriasis.

Scientific Interpretation of Individual Results: Informing Surgical Decision-Making

The observed associations between psoriasis severity and VTE risk bear profound implications for surgical practice, offering valuable insights into the thrombotic risk landscape in psoriasis patients. Chronic inflammation, endothelial dysfunction, and hypercoagulability, hallmark features of psoriasis pathogenesis, collectively contribute to heightened thrombotic predisposition, with potential implications for perioperative thromboprophylaxis and postoperative management. Younger patients with severe psoriasis, in particular, face a disproportionately elevated risk of VTE, highlighting the importance of early risk assessment and tailored interventions in this vulnerable subgroup.

Conclusion

In conclusion, this study underscores the critical role of psoriasis as a risk factor for venous thromboembolism (VTE), with significant implications for surgical practice and patient care. By elucidating the association between psoriasis severity and thrombotic risk, the study highlights the importance of comprehensive risk assessment, vigilant monitoring, and tailored interventions in surgical candidates with psoriasis. The observed age-dependent gradient in VTE risk underscores the dynamic interplay between disease severity, aging, and thrombotic predisposition, informing risk stratification strategies and therapeutic decision-making in this vulnerable population. Moving forward, a multidisciplinary approach encompassing dermatologists, surgeons, and thrombosis specialists is warranted to optimize patient outcomes and mitigate thrombotic complications in psoriasis patients undergoing surgical interventions.

Limitations of the Study

Despite its methodological rigor and comprehensive approach, this study is not without limitations. The retrospective nature of the study design precludes establishment of causality, necessitating cautious interpretation of the observed associations. Additionally, the reliance on administrative databases and prescription claims data may introduce potential misclassification and ascertainment bias, impacting the accuracy and completeness of exposure and outcome ascertainment. Furthermore, residual confounding due to unmeasured or inadequately controlled factors cannot be entirely excluded, potentially influencing the observed associations. Future studies incorporating prospective designs and more granular clinical data are warranted to address these limitations and enhance the validity and generalizability of the findings.

Implications of the Study

The findings of this study hold significant implications for clinical practice, guiding risk assessment, preventive strategies, and therapeutic decision-making in the management of psoriasis patients, particularly those undergoing surgical interventions. By elucidating the association between psoriasis severity and VTE risk, the study underscores the importance of heightened vigilance and proactive risk mitigation strategies in this high-risk population. Furthermore, the observed age-dependent gradient in thrombotic risk informs tailored interventions and risk stratification strategies, facilitating personalized care and optimizing patient outcomes. These findings have the potential to inform clinical guidelines, shaping perioperative management protocols and thromboprophylaxis strategies in psoriasis patients undergoing surgical interventions.

Future Recommendations

Moving forward, several avenues for future research emerge from the findings of this study. Prospective studies incorporating more granular clinical data and longitudinal follow-up are warranted to validate the observed associations and elucidate underlying mechanisms driving the psoriasis-VTE nexus. Furthermore, investigations into the efficacy and safety of thromboprophylaxis strategies in psoriasis patients undergoing surgical interventions are warranted to optimize perioperative management protocols and mitigate thrombotic complications. Additionally, studies exploring the impact of emerging biologic therapies and novel treatment modalities on thrombotic risk in psoriasis patients hold promise for improving patient care and outcomes. By addressing these research gaps, future studies have the potential to further enhance our understanding of the thrombotic risk landscape in psoriasis and inform evidence-based strategies for risk assessment and management in this vulnerable population.

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