MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite: Asiri SZA, Melekhovets O, Lobatiuk M, Melekhovets Iu. Rosacea and Chronic Venous Disease: Comorbidity Patterns and Hereditary Risk. *East Ukr Med J.* 2026;14(2):397-406. DOI: https://doi.org/10.21272/eumj.2026;14(2);397-406

ABSTRACT

Sultan Asiri Zuhair Ali
https://orcid.org/0009-0007-4066-9445
Department of Internal and Family Medicine, Scientific and Educational Medical Institute, Sumy State University, Sumy, Ukraine

Oksana Melekhovets
https://orcid.org/0000-0001-9031-7009
Department of Internal and Family Medicine, Scientific and Educational Medical Institute, Sumy State University, Sumy, Ukraine

Mariia Lobatiuk
https://orcid.org/0000-0002-6128-5797
Department of Internal and Family Medicine, Scientific and Educational Medical Institute, Sumy State University, Sumy, Ukraine

Iurii Melekhovets
https://orcid.org/0000-0002-3219-9021
Department of Surgery, Traumatology, Orthopedics and Phthisiology, Scientific and Educational Medical Institute, Sumy State University, Sumy, Ukraine

ROSACEA AND CHRONIC VENOUS DISEASE: COMORBIDITY PATTERNS AND HEREDITARY RISK

Introduction. The pathophysiology of rosacea is driven by complex interactions involving dysregulation of the immune system, neurogenic inflammation, and vascular hyperreactivity. Parallel to this, the hallmark of chronic venous disease (CVD) pathophysiology likely remains in inflammation, possibly triggered by sustained venous hypertension and valvular incompetence. No reliable epidemiological data on comorbidity rosacea with CVD were found in the literature.

The aim was to study the comorbidity of rosacea with chronic venous disease and to determine the impact of positive rosacea and chronic venous disease family anamnesis as risk factors for rosacea using the logistic regression model with the goals of sustainable development, namely, ensuring good health and well-being.

Materials and Methods. A total of 245 individuals were enrolled in the study and allocated between two groups. Rosacea Group included 141 patients who were eligible diagnostic criteria for rosacea [5]. Control Group included 104 participants who have been consulting by a GPs about a healthy lifestyle and had no clinical signs of the Rosacea disease. The mean age of patients in the Control Group was 45.84 ± 14.47 years, in the Rosacea Group it was 44.46 ± 11.26 years. No statistically significant difference was found between the groups (Welch $t = 0.806$; $df = 188$; $p = 0.421$). These findings indicate that age distribution was comparable in both cohorts. To proof the evidence of comorbidity Rosacea with Chronic Venous Disease we assess potential risk factors for the development of rosacea, the presence of Chronic Venous Disease (CVD), rosacea family history (positive family history of rosacea), and CVD family history (positive family history of CVD) were analyzed.

Statistical data analysis was performed using the free software JASP (Version XX, University of Amsterdam, Netherlands). Descriptive statistics were used to assess the age characteristics of the sample; the

Bayesian Binomial Test was used to assess the frequency of clinical signs and anamnestic factors; and the Binary Logistic Regression method was used to calculate the association between risk factors and the probability of developing rosacea.

Results and Discussion. It was found that CVD was detected in 40.8% of patients (n=100), a positive family history of rosacea was identified in 26.9% of patients (n=66), and a positive family history of CVD in 23.3% (n=57) of respondents.

Regression analysis demonstrated statistically significant associations between rosacea and all investigated predictors. The presence of CVD was associated with substantially increased odds of rosacea development (OR = 3.570; 95% CI: 1.987–6.417; $p < 0.001$). Family history of rosacea showed the strongest relationship with disease occurrence (OR = 4.399; 95% CI: 2.172–8.909; $p < 0.001$). This observation indicates a pronounced hereditary component in rosacea susceptibility. A positive family history of Chronic Venous Disease was also independently associated with rosacea (OR = 2.342; 95% CI: 1.189–4.615; $p = 0.014$).

Numerous scientific researches on the comorbidity of rosacea emphasise the significance of this disease and do not limit rosacea only to skin manifestations, considering it within the framework of the exposome theory. Our data confirm the influence of genetic and epigenetic factors (family health history, positive with rosacea or CVD, concomitant rosacea with CVD) on the incidence of rosacea, which can be used in clinical practice for making prognosis and prescribing appropriate treatment with the goals of sustainable development, namely, ensuring good health and well-being.

Keywords: rosacea, chronic vein disease, varicose vein, comorbidity, Odd Ratio, exposome theory, sustainable development.

Corresponding author: *Oksana Melekhovets, Department of Internal and Family Medicine, Scientific and Educational Medical Institute, Sumy State University, Sumy, Ukraine*
e-mail: o.melekhovets@med.sumdu.edu.ua

РЕЗЮМЕ

Султан Асірі Зухейр Алі
https://orcid.org/0009-0007-4066-9445
Кафедра внутрішньої та сімейної медицини, Науково-навчальний медичний інститут, Сумський державний університет, Суми, Україна

Оксана Мелеховець
https://orcid.org/0000-0001-9031-7009
Кафедра внутрішньої та сімейної медицини, Науково-навчальний медичний інститут, Сумський державний університет, Суми, Україна

Марія Лобатюк
https://orcid.org/0000-0002-6128-5797

РОЗАЦЕА ТА ХРОНІЧНА ХВОРОБА ВЕН: ЗАКОНОМІРНОСТІ КОМОРБІДНОСТІ ТА СПАДКОВИЙ РИЗИК

Вступ. Патофізіологія розацеа зумовлена складними взаємодіями, що включають порушення регуляції імунної системи, нейрогенне запалення та судинну гіперреактивність. Паралельно з цим, ознакою патофізіології хронічної хвороби вен нижніх кіецівок, ймовірно, залишається запалення, можливо, спровоковане стійкою венозною гіпертензією та клапанною недостатністю. У літературі за 2010-2026 роки не було знайдено достовірних епідеміологічних даних щодо коморбідності розацеа з ССЗ.

Метою роботи було вивчення коморбідності розацеа з хронічною хворобою вен та визначення впливу позитивного сімейного анамнезу розацеа та хронічних венозних захворювань як факторів ризику розвитку розацеа за допомогою логістичної регресійної моделі відповідно цілям сталого розвитку, а саме забезпеченню доброго здоров'я та благополуччя.

Матеріали та методи. У дослідженні взяли участь 245 осіб, які були розподілені між двома групами. Rosacea Group включала 141

Кафедра внутрішньої та сімейної медицини, Науково-навчальний медичний інститут, Сумський державний університет, Суми, Україна

Юрій Мелеховець
https://orcid.org/0000-0002-3219-9021
Кафедра хірургії, травматології, ортопедії та фтизіатрії, Науково-навчальний медичний інститут, Сумський державний університет, Суми, Україна

пацієнта, що відповідали діагностичним критеріям розацеа. Контрольна група включала 104 учасника, які консультувалися у сімейних лікарів щодо здорового способу життя та не мали клінічних ознак захворювання на розацеа. Середній вік пацієнтів у контрольній групі становив 45,84 ± 14,47 років, у групі з розацеа – 44,46 ± 11,26 років. Статистично значущої різниці між групами не виявлено (Welch t = 0,806; df = 188; p = 0,421). Ці результати свідчать про те, що розподіл за віком був порівнянним в обох когортах. Для підтвердження коморбідності розацеа з хронічним венозним захворюванням ми оцінювали потенційні фактори ризику розвитку розацеа, аналізували наявність хронічного венозного захворювання (ССЗ), сімейний анамнез розацеа (позитивний сімейний анамнез розацеа) та сімейний анамнез ССЗ (позитивний сімейний анамнез ССЗ). Статистичний аналіз даних проводився за допомогою безкоштовного програмного забезпечення JASP (версія XX, Амстердамський університет, Нідерланди). Для оцінки вікових характеристик вибірки використовувалася описова статистика; для оцінки частоти клінічних ознак та анамнестичних факторів було використано баєсівський біноміальний тест; а для розрахунку зв'язку між факторами ризику та ймовірністю розвитку розацеа – метод бінарної логістичної регресії.

Результати та їх обговорення. Було виявлено, що хронічні захворювання вен нижніх кінцівок були виявлені у 40,8% пацієнтів (n=100), позитивний сімейний анамнез розацеа був виявлений у 26,9% пацієнтів (n=66), а позитивний венозний сімейний анамнез – у 23,3% (n=57) респондентів.

Регресійний аналіз продемонстрував статистично значущі зв'язки між розацеа та всіма досліджуваними предикторами. Наявність варикозної хвороби була пов'язана зі суттєво підвищеною ймовірністю розвитку розацеа (ВШ = 3,570; 95% ДІ: 1,987–6,417; p < 0,001). Сімейний анамнез розацеа показав найсильніший зв'язок з виникненням захворювання (ВШ = 4,399; 95% ДІ: 2,172–8,909; p < 0,001). Це спостереження вказує на виражений спадковий компонент у схильності до розацеа. Позитивний сімейний анамнез хронічного венозного захворювання також був незалежно пов'язаний з розацеа (ВШ = 2,342; 95% ДІ: 1,189–4,615; p = 0,014). Численні наукові дослідження коморбідності розацеа підкреслюють значення цього захворювання та не обмежують розацеа лише шкірними проявами, розглядаючи його в рамках теорії експосоми. Наші дані підтверджують вплив генетичних та епігенетичних факторів (сімейний анамнез, позитивний з розацеа або хворобою вен, коморбідність розацеа з венозною хворобою) на захворюваність на розацеа, що може бути використано в клінічній практиці для прогнозування та призначення відповідного лікування з метою реалізації цілей сталого розвитку, а саме забезпечення доброго здоров'я та благополуччя.

Ключові слова: розацеа, хронічне захворювання вен, варикозна хвороба, коморбідність, Odd Ratio, теорія експосом, цілі сталого розвитку.

Автор, відповідальний за листування: *Оксана Мелеховець, кафедра внутрішньої та сімейної медицини, Науково-навчальний медичний інститут, Сумський державний університет, Суми, Україна*
e-mail: o.melekhovets@med.sumdu.edu.ua

INTRODUCTION

Recent advances in modern dermatology allow us to adopt a pathogenetic approach to defining rosacea as a group of neurocirculatory skin diseases with a specific localisation involving all layers of the facial and adjacent skin. The presence of persistent centrofacial erythema is the main clinical symptom in the differential diagnosis of rosacea. The pattern of vascular dysregulation can also be limited to a separate area - the nose, eyes, ears (nose – rhinophyma; eyelids – blepharophyma; earlobes – otophyma; chin – hyatophyma; forehead and area above the bridge of the nose – metaphyma), or extend beyond the facial area to the neck, decollete area.

The pathophysiology of rosacea is driven by complex interactions involving dysregulation of the immune system, neurogenic inflammation, and vascular hyperreactivity. Although this chronic inflammatory skin disease was once regarded as a purely cutaneous disorder, accumulating evidence now associates it with a range of systemic comorbidities [1].

Parallel to this, the hallmark of chronic venous disease (CVD) pathophysiology likely remains in inflammation, possibly triggered by sustained venous hypertension and valvular incompetence. Shear stress changes are directly sensed by endothelial cells, leading to activation and subsequent recruitment of leukocytes and release of proinflammatory agents [2].

Statistical data on the incidence of rosacea vary significantly and range from 1.0 to 22.41% [3]. Chronic venous disease is a widespread clinical condition in Western countries, with a prevalence more than 50% in the adult general population [4]. No reliable epidemiological data on comorbidity rosacea with CVD were found in the literature 2010–2026. But the convergence of these two mechanisms – neurogenic vascular hyperreactivity in rosacea and hemodynamic endothelial injury in CVD – on the same downstream molecular pathways forms the biological basis for postulating their comorbidity.

Based on the pathogenetic features of both diseases, which share common links, it is possible to assume their comorbidity. We were thereby tasked with evaluating the presence of systemic manifestations of venous pathology, specifically varicose veins of the lower extremities, in patients with rosacea. The tools for implementing this task were the objective examination of CVD clinical manifestations, the diagnosis of their clinical class according to the CEAR classification, and the verification of varicose veins using ultrasound. The second task was to conduct a targeted collection of family history regarding the presence of CVD, rosacea or both in two or three generations of blood relatives in the Control Group and Rosacea Group followed by data analysis of a detailed clinical and genealogical survey.

MATERIALS AND METHODS

The study was conducted as part of the Sumy State University research project “Investigation of the comorbid course of noncommunicable diseases to promote a healthy lifestyle and enhance the well-being of the population across different age groups.” In accordance with the Helsinki Declaration, written informed consent was obtained from all patients. Patients were selected from among those undergoing treatment at the clinical base of the Educational and Scientific Medical Institute, “Sumy Clinic of Laser Medicine.”

A total of 245 individuals were enrolled in the study and allocated between two groups. Rosacea Group included 141 patients who were eligible diagnostic criteria for rosacea [5]. Control Group included 104 participants who have been consulting by a GPs about a healthy lifestyle and had no clinical signs of the Rosacea disease. The mean age of the overall cohort was 45.04 ± 12.72 years, ranging from 18 to 79 years.

Prior to intergroup comparison, the distribution of age values was assessed using the Shapiro–Wilk test. No significant deviation from normal distribution was identified ($W = 0.992$; $p = 0.199$). Since Levene’s test demonstrated heterogeneity of variances between groups ($F = 11.72$; $p < 0.001$), Welch’s correction was applied for further analysis (**Table 1**).

Table 1 – Descriptive analysis of the distribution

Descriptive Statistics

	Age
Valid	245
Missing	0
Mean (arithmetic)	45.04
Std. Deviation	12.72
Minimum	18.00
Maximum	79.00

The mean age of patients in the Control Group was 45.84 ± 14.47 years, in the Rosacea Group it was 44.46 ± 11.26 years. No statistically significant difference was found between the groups (Welch $t = 0.806$; $df = 188$; $p = 0.421$). These findings indicate that age distribution was comparable in both cohorts (**Table 2**).

A complete medical history was taken from all patients, including personal history, questions regarding family history of rosacea or varicose veins of the lower extremities, gynecological history, and comorbidities status according to CVD and rosacea. In addition, all patients underwent a general examination to assess the presence of Chronic Venous Disease (CVD) –including

patients with CEAP classes 1–4 as well as a dermatological examination to assess the rosacea.

To proof the evidence of comorbidity Rosacea with Chronic Venous Disease we assess potential risk factors for the development of rosacea, the presence of Chronic Venous Disease (CVD), rosacea family history (positive family history of rosacea), and CVD family history (positive family history of CVD) were analyzed.

Table 2 — Age characteristics of the study groups (0 – Control Group; 1 – Rosacea Group)

Group Descriptives

	Group	N	Mean	SD	SE	Coefficient of variation	Mean Rank	Sum Rank
Age	0	104	45.84	14.47	1.419	0.316	126.4	13150
	1	141	44.46	11.26	0.949	0.253	120.5	16990

Statistical data analysis was performed using the free software JASP (Version XX, University of Amsterdam, Netherlands) [6]. Descriptive statistics were used to assess the age characteristics of the sample; the Bayesian Binomial Test was used to assess the frequency of clinical signs and anamnestic factors; and the Binary Logistic Regression method was used to calculate the association between risk factors and the probability of developing rosacea [7].

The logistic regression model was constructed using the Enter method, with all predictors included in the model simultaneously. The absence of the corresponding symptom (code “0”) was used as the reference category. All variables were represented as dichotomous variables: “1” for the presence of a sign and “0” for the absence of a sign.

To assess the quality of the model, the following were analyzed: Deviance; Akaike Information Criterion (AIC); Bayesian Information Criterion (BIC); Likelihood Ratio Chi-square test ($\Delta\chi^2$); McFadden R^2;Nagelkerke R^2; Tjur R^2; Cox & Snell R^2.

The statistical significance of individual predictors was assessed using Wald test; z-statistic; Odds Ratio (OR); 95% Confidence Interval (95% CI). To verify the stability of the results, the bootstrap resampling method with 5,000 repetitions was used. Bootstrap analysis was performed by calculating the bootstrap estimates; bootstrap standard errors; bias-corrected accelerated confidence intervals (BCa 95% CI). To rule out multicollinearity among independent variables, Multicollinearity Diagnostics were performed to determine Tolerance and Variance Inflation Factor (VIF).

The predictive ability of the logistic model was assessed using Confusion Matrix; Accuracy; Sensitivity (Recall); Specificity; Precision; F-measure; Area Under the ROC Curve (AUC); Brier score.

The following were used for graphical visualization of the results: conditional estimates plots; independent-predicted plots; ROC plot. Results were considered statistically significant at $p < 0.05$.

RESULTS

It was found that CVD was detected in 40.8% of patients (n=100), a positive family history of rosacea was identified in 26.9% of patients (n=66), and a positive family history of CVD in 23.3% (n=57) of respondents.

To investigate selected factors potentially associated with rosacea, a multivariable binary logistic regression analysis was conducted. The regression model included the following predictors: Chronic Venous Disease (CVD), family history of rosacea (Anamnesis rosacea), and family history of Chronic Venous Disease (Anamnesis CVD).

Logistic regression model performance

The constructed logistic regression model showed significantly better fit compared with the intercept-only model ($\Delta\chi^2 = 45.661$; $p < 0.001$), confirming that the included predictors contributed meaningfully to estimating the probability of rosacea occurrence.

Pseudo-R^2 coefficients suggested moderate explanatory ability of the model:

- McFadden $R^2 = 0.137$
- Nagelkerke $R^2 = 0.228$
- Tjur $R^2 = 0.173$
- Cox & Snell $R^2 = 0.170$

Together, these figures mean that approximately one-fifth of the variability in rosacea occurrence can be explained by the variables analysed. The adequacy of the model was also confirmed by the lower AIC and BIC values in the final regression model compared to the null model: AIC: 296.371 vs 336.033;

BIC: 310.377 vs 339.534 (**Table 3**).

Influence of Chronic Venous Disease and family history on rosacea risk

Regression analysis demonstrated statistically significant associations between rosacea and all investigated predictors. The presence of CVD was associated with substantially increased odds of rosacea development (OR = 3.570; 95% CI: 1.987–6.417; $p < 0.001$).

Table 3 — Logistic regression model summary

Logistic Regression

Model Summary - Rosacea

Model	Deviance	AIC	BIC	df	ΔX²	p	McFadden R²	Nagelkerke R²	Tjur R²	Cox & Snell R²
M_0	334.0	336.033	339.534	244			0.000		0.000	
M_1	288.4	296.371	310.377	241	45.661	< .001	0.137	0.228	0.173	0.170

Note. M_1 includes Anamnesis rosacea, CVD, Anamnesis CVD

Family history of rosacea showed the strongest relationship with disease occurrence (OR = 4.399; 95% CI: 2.172–8.909; p < 0.001). This observation indicates a pronounced hereditary component in rosacea susceptibility.

A positive family history of Chronic Venous Disease was also independently associated with rosacea (OR = 2.342; 95% CI: 1.189–4.615; p = 0.014) (**Table 4**).

Table 4 — Logistic regression coefficients

Coefficients

						Wald Test			95% Confidence interval (odds ratio scale)	
Model		Estimate	Standard Error	Odds Ratio	z	Wald Statistic	df	p	Lower bound	Upper bound
M_0	(Intercept)	0.304	0.129	1.356	2.355	5.545	1	.019	1.052	1.747
M_1	(Intercept)	−0.719	0.214	0.487	−3.369	11.35	1	< .001	0.321	0.740
	Anamnesis rosacea	1.481	0.360	4.399	4.114	16.93	1	< .001	2.172	8.909
	CVD	1.273	0.299	3.570	4.255	18.10	1	< .001	1.987	6.417
	Anamnesis CVD	0.851	0.346	2.342	2.460	6.053	1	.014	1.189	4.615

Note. Rosacea level '1' coded as class 1.

Bootstrap validation analysis

To verify the stability of the regression estimates, bootstrap validation with 5000 replications was performed. The bootstrap procedure yielded results comparable to the primary regression model, confirming the robustness of the identified associations.

For Chronic Venous Disease, the bootstrap odds ratio was 3.613 (95% BCa CI: 1.984–6.419). Family history of rosacea demonstrated a bootstrap odds ratio of 4.553 (95% BCa CI: 2.112–9.025), whereas family history of Chronic Venous Disease showed a bootstrap odds ratio of 2.396 (95% BCa CI: 1.127–4.955).

Notably, none of the confidence intervals crossed the reference value of 1.0, indicating stable and statistically reliable estimates across repeated samples (**Table 5**).

Table 5 — Bootstrap coefficients

Bootstrap Coefficients

					95% bca* Confidence interval (odds ratio scale)	
	Estimate	Bias	Standard Error	Odds Ratio	Lower bound	Upper bound
(Intercept)	−0.726	−0.015	0.214	0.484	0.316	0.732
Anamnesis rosacea	1.504	0.037	0.376	4.497	2.112	9.064
CVD	1.292	0.029	0.304	3.641	1.963	6.469
Anamnesis CVD	0.865	0.030	0.385	2.375	1.114	5.042

* Bias corrected accelerated.

Note. Bootstrapping based on 5000 successful replicates.

Note. Coefficient estimate is based on the median of the bootstrap distribution.

Multicollinearity diagnostics

Potential multicollinearity between predictors was assessed before final model interpretation. Tolerance values remained high for all variables:

- CVD – 0.992
- Anamnesis rosacea – 0.984
- Anamnesis CVD – 0.978

At the same time, Variance Inflation Factor (VIF) values were close to 1:

- CVD – 1.008
- Anamnesis rosacea – 1.017
- Anamnesis CVD – 1.023

These findings suggest absence of clinically relevant multicollinearity and confirm that each predictor independently contributed to the regression model.

Predictive accuracy of the model

According to the confusion matrix, the regression model correctly classified 70.61% of all observations. The model demonstrated relatively high sensitivity (81.6%), indicating good ability to correctly identify patients with rosacea. Specificity was lower (55.8%), reflecting moderate performance in distinguishing individuals without the disease.

Additional classification parameters were as follows: accuracy = 0.706; precision = 0.714; F-measure = 0.762; brier score = 0.202; AUC = 0.733.

Overall, these metrics indicate satisfactory predictive performance of the developed model.

Graphical representation of regression findings

Conditional estimates plots demonstrated increasing predicted probability of rosacea in the presence of each investigated predictor. The steepest increase was observed in patients with a positive family history of rosacea, which corresponded to the highest odds ratio identified in the regression analysis (**Fig. 1**).

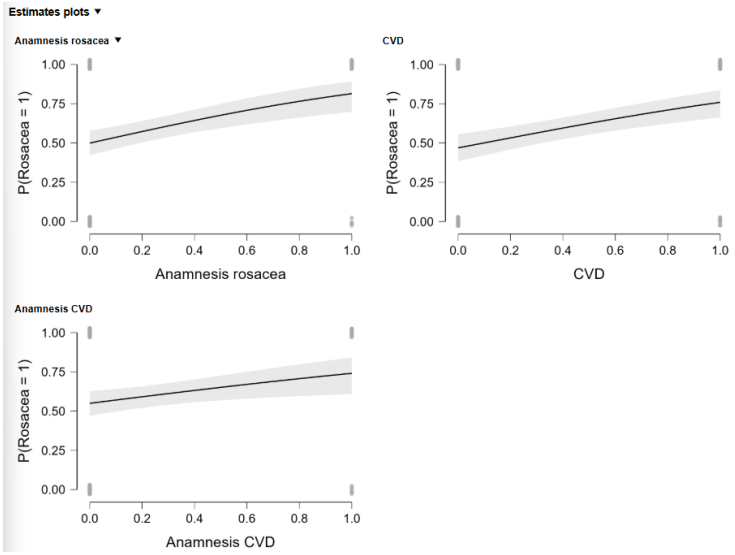

Figure 1— Conditional estimates plots

Independent-predicted plots illustrated a positive linear relationship between the studied predictors and the logit of predicted rosacea probability. All variables showed an upward trend, supporting their positive association with disease occurrence (**Fig.2**).

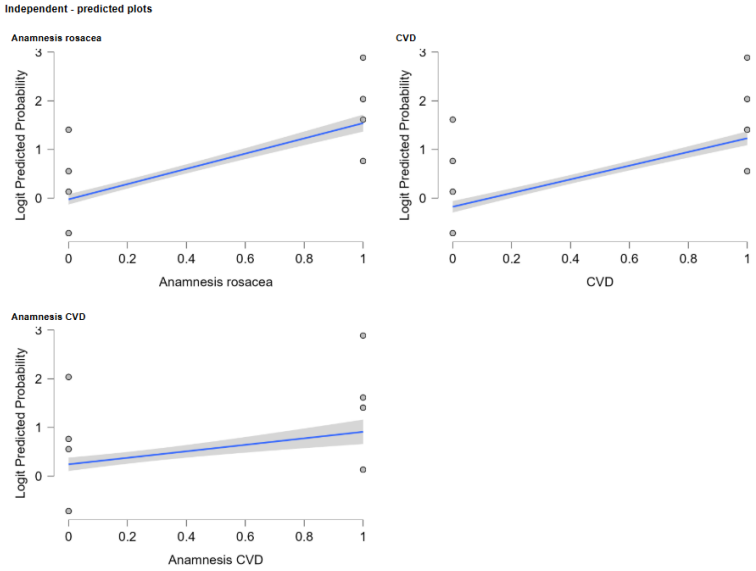

Figure 2 — Independent-predicted plots

The ROC curve demonstrated acceptable discriminative ability of the model. The area under the curve reached 0.733, indicating satisfactory classification performance for predicting rosacea based on CVD and hereditary factors (**Fig. 3**).

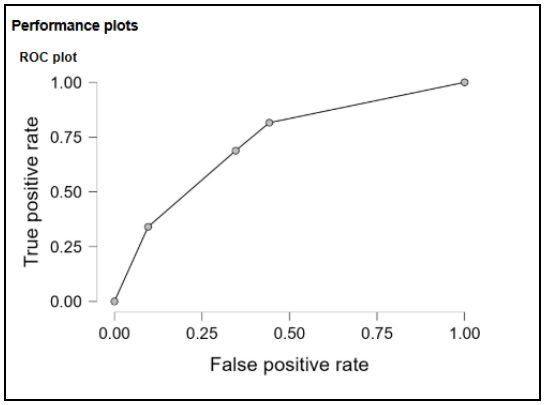

Figure 3 — ROC curve

DISCUSSION

While a dedicated large-scale study specifically linking rosacea to chronic venous disease has not yet been established, the mechanistic overlap – vascular dilation, impaired venous tone, telangiectasia formation – is well recognised. What drives both conditions? Endothelial dysfunction is the central shared pathogenic axis. In chronic venous disease, shear stress changes are directly sensed by endothelial cells, leading to their activation, the subsequent recruitment of leukocytes, and the release of proinflammatory agents – making inflammation the hallmark of CVD pathophysiology, likely triggered by sustained venous hypertension and valvular incompetence. In functional and morphological changes of the venous system of the lower limbs, varicose veins being the most visible manifestation [9–12]. In rosacea, vascular dysfunction plays a central role in pathophysiology, with abnormal reactivity of cutaneous blood vessels and endothelial cell irregularities directly contributing to persistent erythema and telangiectasia. Endothelium-dependent vasomotion implicates nitric oxide (NO), prostacyclin (PGI_2), endothelium-dependent hyperpolarizing factors (EDHF), and endothelin. The role of eNOS is particularly central: local warming of the skin can cause maximal vasodilation in healthy humans and includes roles for both local sensory nerves and nitric oxide. Moreover, all three NOS isoforms – endothelial, neuronal, and inducible – have been reported to contribute to the skin local heating response in different patient populations.

Angiogenesis is an essential process in rosacea, induced by LL-37 from a signal cascade involving microorganisms, VEGF, and MMP-3 from mast cells. Mast cells are equivalently elevated in CVD venous walls, releasing histamine, proteases, and cytokines that perpetuate vascular remodeling [13]. VEGF-A simultaneously acts as both a permeability agent and a pro-remodelling signal: increased expression of VEGF-A seems to determine a significant role in CVD pathogenesis, as it is able to increase venous wall permeability, determining oedema, and to decrease the tone of the vein wall, which may lead to vein dilation with blood stasis in the lower extremities' vein system and subsequent venous hypertension development [14].

The two conditions share a remarkably overlapping molecular language. In rosacea, trigger activation of TLR2 on keratinocytes yields active LL-37, whose actions result in angiogenesis and leukocyte chemotaxis; neuropeptides produced in response to TRP ion channel triggering on neuronal and non-neuronal cells can directly or indirectly result in vasodilation and mast cell activation [15].

Specific TRP subtypes including TRPV1 and TRPV4 are strongly implicated in aberrant neurovascular signaling, contributing to vasodilation, inflammation, and vascular hyperreactivity observed in rosacea – with their activation triggering intracellular Ca^{2+} influx, initiating cascades that promote release of vasoactive and proinflammatory mediators such as nitric oxide, prostaglandin I_2, and endothelium-derived hyperpolarizing factor [16].

On the CVD side, damage to the glycocalyx through chronic distention, low shear stress, or enzymatic MMP cleavage triggers prothrombotic processes as well as increased permeability and leukocyte adhesion – all features that combine in CVD to produce a persistent proinflammatory and prothrombotic environment [17].

The critical research gap remains the absence of a dedicated prospective study. Both conditions peak after age 30, are more prevalent in women, and share genetic risk factors involving vascular wall integrity and immune regulation [18–22]. A case-control or biomarker study pairing rosacea severity with CEAP-classified venous disease would be a high-yield contribution to the literature.

Numerous scientific researches on the comorbidity of rosacea emphasise the significance of this disease and do not limit rosacea only to skin manifestations [23, 24], considering it within the framework of the exposome theory [25, 26].

Our data confirm the influence of genetic and epigenetic factors (family health history, concomitant rosacea with CVD) on the incidence of rosacea, which can be used in clinical practice for making prognosis and prescribing appropriate treatment with the goals of sustainable development, namely, ensuring good health and well-being.

CONCLUSIONS

Logistic regression analysis identified CVD comorbidity, rosacea family anamnesis, and CVD family anamnesis as risk factors for rosacea. Our study demonstrated that patients diagnosed with CVD were more than three times as likely to have rosacea compared with individuals without venous pathology (OR = 3.570). A positive family anamnesis of CVD was also independently associated with rosacea and was associated with a 2-fold increased risk of rosacea (OR = 2.342); a positive family rosacea anamnesis demonstrated the strongest association with disease occurrence (OR = 4.399). Taken together, these results support the concept that vascular abnormalities and inherited predisposition may contribute to rosacea pathogenesis.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING

The study was conducted without financial support within the framework of the research project «Study of comorbidities of non-communicable diseases to ensure a healthy lifestyle and promote the well-being of the population of different age groups» (state registration number 0121U114163; 01.22 - 11.26).

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL CONSIDERATIONS

In accordance with the Helsinki Declaration, written informed consent was obtained from all patients.

REFERENCES

1. Chen LX, Hao PS. The role of skin barrier and immune abnormalities in the pathogenesis of Rosacea. Clin Exp Med. 2025 Oct 25;25(1):324. https://doi.org/10.1007/s10238-025-01859-w. PMID: 41137965; PMCID: PMC12553588.
2. Gwozdzinski, L.; Pieniazek, A.; Gwozdzinski, K. Factors Influencing Venous Remodeling in the Development of Varicose Veins of the Lower Limbs. *Int. J. Mol. Sci.* 2024, *25*, 1560. https://doi.org/10.3390/ijms25031560
3. This systemic review and meta-analysis of 2 databases, PubMed and Embase, JAMA Dermatol 2022 Apr 6;158(6):617–625. https://doi.org/10.1001/jamadermatol.2022.0526
4. Nicolaides A.N., Labropoulos N. Burden and Suffering in Chronic Venous Disease. Adv. Ther. 2019;36 https://doi.org/10.1007/s12325-019-0882-6.
5. Tan J, Almeida LM, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. Br J Dermatol. 2017;176(2):431-438. https://doi.org/10.1111/bjd.15122
6. JASP. A Fresh Way to Do Statistics. Retrieved at: https://jasp-stats.org/
7. Rijnhart, J., Twisk, J., Eekhout, I., & Heymans, M. (2019). Comparisonof logistic-regression based methods for simple mediation analysis with a dichotomous outcome variable. BMC Medical Research Methodology, 19. https://doi.org/10.1186/s12874-018-0654-z.
8. Reinholz M, Ruzicka T, Steinhoff M, et al. Pathogenesis and clinical presentation of rosacea as a key for a symptom-oriented therapy. *J Dtsch Dermatol Ges*. 2016;14(suppl 6):4-15.
9. Davies A.H. The Seriousness of Chronic Venous Disease: A Review of Real-World Evidence. Adv. Ther. 2019;36:5–12. https://doi.org/10.1007/s12325-019-0881-7.
10. Onida S, Davies AH. Predicted burden of venous disease. *Phlebology: The Journal of Venous Disease*. 2016;31(1_suppl):74-79. https://doi.org/10.1177/0268355516628359
11. Diaz JA, Gianesini S, Khalil RA. Glycocalyx disruption, endothelial dysfunction and vascular remodeling as underlying mechanisms and treatment targets of chronic venous disease. Int Angiol. 2024 Dec;43(6):563-590. https://doi.org/10.23736/S0392-9590.24.05339-2. PMID: 39873224; PMCID: PMC11839207.
12. Ortega MA, Fraile-Martínez O, García-Montero C, Álvarez-Mon MA, Chaowen C, Ruiz-Grande F, Pekarek L, Monserrat J, Asúnsolo A, García-Honduvilla N, Álvarez-Mon M, Bujan J. Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. J Clin Med. 2021 Jul 22;10(15):3239. https://doi.org/10.3390/jcm10153239. PMID: 34362022; PMCID: PMC8348673.
13. Lee HJ, Hong YJ, Kim M. Angiogenesis in Chronic Inflammatory Skin Disorders. Int J Mol Sci. 2021 Nov 7;22(21):12035.

https://doi.org/10.3390/ijms222112035. PMID: 34769465; PMCID: PMC8584589.
14. Costa D, Andreucci M, Ielapi N, Serraino GF, Mastroroberto P, Bracale UM, Serra R. Molecular Determinants of Chronic Venous Disease: A Comprehensive Review. Int J Mol Sci. 2023 Jan 18;24(3):1928. https://doi.org/10.3390/ijms24031928. PMID: 36768250; PMCID: PMC9916309.
15. Holmes, A.D. and Steinhoff, M. (2017), Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. Exp Dermatol, 26: 659-667. https://doi.org/10.1111/exd.13143
16. Andrusiewicz A, Khimuk S, Mijas D, Shmorhun B, Nowicka D. Molecular Mechanisms in the Etiopathology of Rosacea-Systematic Review. Int J Mol Sci. 2025 Nov 22;26(23):11292. https://doi.org/10.3390/ijms262311292. PMID: 41373451; PMCID: PMC12692705.
17. Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. *International Journal of Molecular Sciences*. 2018; 19(6):1669. https://doi.org/10.3390/ijms19061669
18. Geng RSQ, Bourkas AN, Mufti A, Sibbald RG. Rosacea: Pathogenesis and Therapeutic Correlates. *Journal of Cutaneous Medicine and Surgery*. 2024;28(2):178-189. https://doi.org/10.1177/12034754241229365
19. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol*. 2017;26(8):659-667.
20. Geng RSQ, Bourkas AN, Mufti A, Sibbald RG. Rosacea: Pathogenesis and Therapeutic Correlates. *Journal of Cutaneous Medicine and Surgery*. 2024;28(2):178-189. https://doi.org/10.1177/12034754241229365
21. Aroni K, Tsagroni E, Kavantzas N, Patsouris E, Ioannidis E. A study of the pathogenesis of rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. Arch Dermatol Res. 2008 Mar;300(3):125-31. https://doi.org/10.1007/s00403-007-0816-z. Epub 2007 Dec 11. PMID: 18071725.
22. Raffetto JD, Khalil RA. Mechanisms of Lower Extremity Vein Dysfunction in Chronic Venous Disease and Implications in Management of Varicose Veins. Vessel Plus. 2021;5:36. https://doi.org/10.20517/2574-1209.2021.16. Epub 2021 May 29. PMID: 34250453; PMCID: PMC8270011.
23. Aksoy B, Ekiz Ö, Unal E, Ozaydin Yavuz G, Gonul M, Kulcu Cakmak S, Polat M, Bilgic Ö, Baykal Selcuk L, Unal I, Karadag AS, Kilic A, Balta I, Kutlu Ö, Uzuncakmak TK, Gunduz K. Systemic comorbidities associated with rosacea: a multicentric retrospective observational study. Int J Dermatol. 2019 Jun;58(6):722-728. https://doi.org/10.1111/ijd.14353. Epub 2018 Dec 21. PMID: 30575019
24. Yi JZ, Chen SX, Lukac D, McGee JS. Systemic comorbidities of rosacea: practice gaps among dermatologists. Arch Dermatol Res. 2022 Dec;314(10):995-997. https://doi.org/10.1007/s00403-021-02279-y. Epub 2021 Sep 12. PMID: 34510277.
25. Passeron T, Krutmann J, Andersen ML, Katta R, Zouboulis CC. Clinical and biological impact of the exposome on the skin. *J Eur Acad Dermatol Venereol*. 2020; 34(Suppl 4): 4–25. https://doi.org/10.1111/jdv.16614
26. Grafanaki K, Bakoli Sgourou D, Maniatis A, Pasmatzi E. The exposomal imprint on rosacea: More than skin deep. J Eur Acad Dermatol Venereol. 2026 Mar;40(3):387-403. https://doi.org/10.1111/jdv.70112. Epub 2025 Oct 13. PMID: 41081484; PMCID: PMC12933707.

Received: 03.05.2026

Accepted for publication: 12.06.2026

Published: 23.06.2026