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Original Article

Comparison of serum IL-18, IL-1β and caspase-1 levels in patients with chronic venous insufficiency and coronary artery bypass grafting

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Abstract

Aim: Chronic venous insufficiency (CVI) and coronary artery disease requiring coronary artery bypass grafting (CABG) are both associated with systemic inflammation. Inflammasome-mediated pathways involving caspase-1, interleukin-1Beta (IL-1β), and interleukin-18 (IL-18) contribute to vascular inflammation. This study compared circulating inflammasome-related biomarkers and hematological inflammatory indices between patients with CVI and CABG.

Material and Methods: This prospective observational study included 40 patients (20 with CVI and 20 undergoing elective CABG). Serum IL-18, IL-1β, and caspase-1 concentrations were measured using enzyme-linked immunosorbent assay (ELISA). Hematological inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), were calculated from complete blood counts. Group comparisons were performed using the Mann–Whitney U test, correlations using Spearman's rank correlation analysis, and adjusted analyses using analysis of covariance (ANCOVA) controlling for age and sex.

Results: In the unadjusted analyses, serum IL-18, IL-1β, and caspase-1 levels were significantly higher in the CABG group than in the CVI group (all $p < 0.05$). Neutrophil count, NLR, and SII were also significantly higher in CABG patients, whereas platelet counts were higher in the CVI group. The SII showed a positive correlation with IL-18 in the CABG group ($r = 0.655$, $p = 0.021$). After adjustment for age and sex, only serum caspase-1 remained independently associated with the study group, whereas differences in IL-1β and IL-18 were no longer statistically significant.

Conclusion: Although CABG patients exhibited greater inflammasome-related inflammatory activity than CVI patients in unadjusted analyses, only serum caspase-1 remained independently associated with disease status after adjustment for demographic variables. Caspase-1 may, therefore, represent a more robust biomarker of inflammasome activation in advanced coronary artery disease.

Keywords: Interleukin18; interleukin1β; caspase1; venous insufficiency; coronary artery bypass

INTRODUCTON

Chronic venous insufficiency (CVI) represents a widespread vascular pathology characterized by compromised anatomical structure and retrograde flow within the venous framework [1]. At its core, the driving etiology involves persistent venous hypertension secondary to valvular failure, which initiates downstream microvascular disturbances, endothelial stress, and macroscopic structural changes [2]. Clinically, CVI exhibits a broad spectrum of presentations, extending from minor telangiectasias and prominent varicose veins to severe lower-limb edema and recalcitrant stasis ulcerations [3]. Clinical assessment of chronic venous disease has been standardized using validated severity scoring systems, facilitating objective evaluation of disease severity, treatment response, and longitudinal clinical outcomes [4].

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Epidemiological studies and contemporary clinical reviews indicate that chronic venous insufficiency represents a substantial healthcare burden in Western countries, although reported prevalence varies according to the study population and diagnostic criteria [5-7]. Increasing evidence suggests that chronic venous disease and atherosclerotic cardiovascular disease share several common inflammatory and endothelial mechanisms [8,9]. Despite these similarities, comparative studies directly evaluating inflammatory pathways in venous and arterial vascular diseases remain limited. In addition, large prospective population-based cohorts have provided valuable insights into the relationship between vascular disease burden, systemic inflammation, and long-term cardiovascular outcomes, highlighting the clinical importance of inflammatory pathways in vascular disease [10,11].

Among the specific molecular pathways governing modern vascular research, the activation of intracellular multiprotein complexes known as inflammasomes has gained significant attention. Sustained inflammatory triggers prompt endothelial impairment, continuous leukocyte recruitment, localized reactive oxygen species production, and structural arterial remodeling, all accelerating cardiovascular deterioration [12]. Specifically, inflammasome assembly activates caspase-1, which processes the precursor forms of Interleukin1 Beta (IL-1β) and Interleukin18 (IL-18) into their biologically active forms [12–14]. Emerging evidence suggests that inflammasome activation also contributes to the pathogenesis of chronic venous disease. Increased expression of pro-inflammatory cytokines and activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome have been associated with endothelial dysfunction, venous wall remodeling, and chronic inflammation in patients with chronic venous disease [12,15]. However, comparative studies simultaneously evaluating circulating caspase-1, IL-1β, and IL-18 levels in patients with chronic venous insufficiency and advanced coronary artery disease remain scarce.

While interest in the inflammatory foundations of macrovascular and microvascular syndromes has expanded, comparative research directly measuring these precise circulating biomarkers across different vascular beds is limited. To address this gap, this investigation aimed to comparatively assess serum concentrations of caspase-1, IL-1β, and IL-18 via Enzyme-Linked Immunosorbent Assay (ELISA) in a defined cohort of patients managed with coronary artery bypass grafting (CABG) for severe coronary disease against individuals presenting with established peripheral CVI.

MATERIAL AND METHODS

Study Design and Ethical Approval

This prospective, observational, single-center study was conducted at a tertiary university hospital between April 2024 and December 2024. The study protocol was approved by the Institutional Clinical Research Ethics Committee of the participating university (Decision No: 2024/26, Registration No: 24-KAEK-070; approval date: 14 March 2024). The study was performed in accordance with the principles of the Declaration of Helsinki and reported according to the STROBE guidelines for observational studies. No randomization or blinding procedures were applied due to the observational design of the study. Patients were enrolled consecutively during the study period. Written informed consent was obtained from all participants prior to their inclusion in the study.

Study Population

A total of 40 patients were included in the study and divided into two groups: CVI group (n = 20) and CABG group (n = 20). The CVI group consisted of patients diagnosed with chronic venous insufficiency corresponding to the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) class C3, with documented great saphenous vein reflux on duplex ultrasonography and a vein diameter greater than 5.5 mm. The CABG group included patients scheduled for elective isolated coronary artery bypass grafting due to advanced coronary artery disease.

Inclusion and Exclusion Criteria

Inclusion criteria were age over 18 years, a confirmed diagnosis of CVI (CEAP C3) or an indication for elective CABG, and the provision of written informed consent. Exclusion criteria included the presence of acute infection or inflammatory disease, autoimmune or chronic inflammatory disorders, active malignancy, recent acute myocardial infarction or emergency surgery, severe hepatic or renal dysfunction, and the use of systemic corticosteroids or immunosuppressive therapy. Patients receiving chronic corticosteroid treatment were excluded due to potential effects on systemic inflammatory markers.

Blood Sampling and Laboratory Analysis

Peripheral venous blood samples were collected under standardized conditions. In the CABG group, samples were obtained after overnight fasting immediately before anesthesia induction. Blood was drawn into serum separator tubes, allowed to clot for 30 minutes at room temperature, and then centrifuged at 4000 rpm for 10 minutes. Serum samples were stored at −80°C until analysis. Serum IL-18, IL-1β, and caspase-1 levels were measured using commercially available ELISA kits according to the manufacturers' instructions, and concentrations were expressed in pg/mL.

Hematological Parameters

Complete blood count parameters were obtained using an automated hematology analyzer. Inflammatory indices were calculated, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), which was defined as the platelet count multiplied by the neutrophil count divided by the lymphocyte count.

Study Endpoints

The primary endpoint was the comparison of serum IL-18, IL-1β, and caspase-1 levels between the CVI and CABG groups. Secondary endpoints included comparisons of hematological inflammatory indices (NLR, PLR, SII) and correlations between inflammasome markers and inflammatory indices.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.0 (GraphPad Software Inc., San Diego, CA, USA). Additionally, sample size and statistical power evaluation were performed using G*Power software (version 3.1.9.7). The normality of distribution was assessed using the Shapiro–Wilk test. Although most continuous variables did not demonstrate a normal distribution, data are presented as mean ± standard deviation (SD) for descriptive purposes, and categorical variables are presented as numbers and percentages. Continuous variables were compared between two independent groups using the Mann–Whitney U test, while categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Spearman's rank correlation analysis was used to assess correlations between variables. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

The study included 40 patients, comprising 20 patients with CVI and 20 patients undergoing CABG. The mean age was significantly higher in the CABG group than in the CVI group (55.00 ± 6.61 vs. 47.26 ± 13.56 years, p = 0.010). The proportion of male patients was also significantly higher in the CABG group (70% vs. 40%, p = 0.002). In contrast, body mass index (BMI) was significantly higher in the CVI group than in the CABG group (29.4 ± 4.8 vs. 26.3 ± 3.9 kg/m², p = 0.020) (Table 1).

Table 1. Demographic characteristics of the study population

Parameters		CVI Group (n = 20)	CABG Group (n = 20)	*p value*
Age, (years)		47.26 ± 13.56	55.00 ± 6.61	**0.010***
BMI (kg/m²)		29.40 ± 4.80	26.30 ± 3.9	**0.020***
Sex, n (%)	**Male**	8 (40 %)	14 (70 %)	**0.002***
	Female	12 (60 %)	6 (30%)	
Smoking status, n (%)	**Never**	8 (40 %)	8 (40 %)	*0.800*
	Current	7 (35 %)	6 (20 %)	
	Former	5 (25%)	8 (40 %)	
Diabetes Mellitus, n (%)	**No**	17 (85 %)	8 (40 %)	**0.008***
	Yes	3 (15 %)	12 (60 %)	
Hypertension, n (%)	**No**	14 (70 %)	7 (35%)	*0.056*
	Yes	6 (30 %)	13 (65%)	
Hyperlipidemia, n (%)	**No**	20 (100%)	12 (60%)	**0.003***
	Yes	0 (0%)	8 (40%)	
Beta blocker use, n (%)	**No**	18 (90%)	12 (60%)	*0.065*
	Yes	2 (10%)	8 (40%)	
Statin use, n (%)	**No**	14 (70 %)	10 (50%)	*0.330*
	Yes	6 (30 %)	10 (50%)	
ASA use, n (%)	**No**	18 (90%)	8 (40 %)	**0.002***
	Yes	2 (10%)	12 (60 %)	
Clopidogrel use, n (%)	**No**	20 (100%)	14 (70 %)	**0.020***
	Yes	0 (0%)	6 (30 %)	

Data are presented as mean ± SD for continuous variables and as n (%) for categorical variables. Continuous variables were compared using the Mann–Whitney U test, while categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was defined as p < 0.05. Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CVI, chronic venous insufficiency; SD, standard deviation.

As detailed in Table 2, white blood cell (WBC) counts did not differ significantly between the groups (p = 0.15). However, neutrophil counts were significantly higher in the CABG group than in the CVI group (5.28 ± 2.72 vs. 3.91 ± 2.24, p = 0.013), whereas lymphocyte counts were significantly lower (1.90 ± 1.00 vs. 2.56 ± 1.20, p = 0.001). Platelet counts were significantly higher in the CVI group than in the CABG group (291 ± 103.01 vs. 229 ± 57.4, p = 0.033). Similarly, both the neutrophil-to-lymphocyte ratio (NLR) (3.49 ± 2.86 vs. 1.62 ± 0.49, p = 0.010) and the systemic immune-inflammation index (SII) (632.2 ± 333.3 vs. 462 ± 169, p = 0.005) were significantly higher in the CABG group. In contrast, the platelet-to-lymphocyte ratio (PLR) did not differ significantly between the groups (p = 0.33) (Table 2).

Table 2. Comparison of hematological and inflammatory parameters between CVI and CABG groups

Parameters	CVI Group (n=20)	CABG Group (n=20)	p value
WBC (10^3/µL)	7.22 ± 1.85	6.46 ± 1.88	0.150
Neutrophil (10^3/µL)	3.91 ± 2.24	5.28 ± 2.72	**0.013***
Lymphocyte (10^3/µL)	2.56 ± 1.20	1.90 ± 1.00	**0.001***
Platelets (10^3/µL)	291 ± 103.01	229 ± 57.40	**0.033***
NLR	1.62 ± 0.49	3.49 ± 2.86	**0.010***
PLR	121.3 ± 49.06	139.9 ± 59.80	0.330
SII	462 ± 169	632.2 ± 333.30	**0.005***

WBC, neutrophil, lymphocyte, and platelet counts and the NLR, PLR, and SII were compared between the groups. Data are presented as mean ± SD. Comparisons between groups were performed using the Mann–Whitney U test. Statistical significance was defined as p < 0.05. Abbreviations: CABG, coronary artery bypass grafting; CVI, chronic venous insufficiency; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; SII, systemic immune-inflammation index; WBC, white blood cell.

Spearman's rank correlation analysis demonstrated a significant positive correlation between the SII and serum IL-18 levels in the CABG group (r = 0.655, p = 0.021) (Table 3).

Comparative serum evaluations for IL-1β, IL-18, and caspase-1 are illustrated in Figure 1. Circulating concentrations of all three inflammasome-related biomarkers were significantly higher in the CABG group than in the CVI group (p ≤ 0.01) (Figure 1).

Table 3. Spearman correlation analysis of IL-18 and SII inflammatory indices in CABG patients

Variable	Correlation with Serum IL-18 (r)	p-value
SII	0.655	**0.021***

Correlation analysis was performed using Spearman's rank test. Statistical significance was defined as p < 0.05. Abbreviations: IL 18, interleukin-18; pvalue, probability value; SII, Systemic Immune-Inflammation Index.

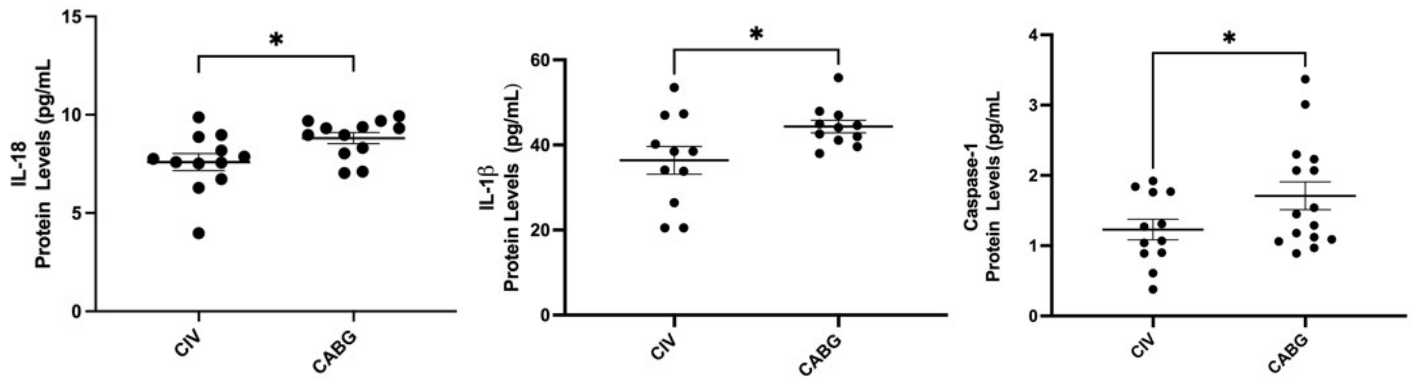


Figure 1. Comparison of serum IL-18, IL-1β, and caspase-1 levels between patients with CVI and those undergoing CABG. Serum inflammatory biomarker levels were measured using ELISA. Comparisons between groups were performed using the Mann–Whitney U test. *p < 0.05, **p < 0.01, and ***p < 0.001. Abbreviations: CABG, coronary artery bypass grafting; CVI, Chronic venous insufficiency; IL 18, interleukin-18; IL-1β, interleukin-1Beta.

Multivariate Adjusted Analysis (ANCOVA)

Because significant baseline differences in age and sex were observed between the chronic venous insufficiency (CVI) and coronary artery bypass grafting (CABG) groups, an analysis of covariance (ANCOVA) was performed to evaluate whether the observed differences in circulating biomarkers remained significant after adjustment for these potential confounders.

After adjustment for age and sex, the difference in serum caspase-1 levels between the study groups remained statistically significant ($F(1,17) = 18.720$, $p < 0.001$, partial $\eta^2 = 0.524$), indicating that the association was independent of these demographic variables. In contrast, the between-group differences in serum IL-1β ($F(1,19) = 3.616$, $p = 0.073$, partial $\eta^2 = 0.160$) and IL-18 ($F(1,23) = 0.490$, $p = 0.491$, partial $\eta^2 = 0.021$) were no longer statistically significant after adjustment. These findings suggest that demographic factors may partially account for the observed differences in IL-1β and IL-18, whereas serum caspase-1 appears to be a more robust marker distinguishing patients with advanced coronary artery disease from those with chronic venous insufficiency.

DISCUSSION

The present study compared circulating inflammasome-related biomarkers and hematological inflammatory indices between patients with chronic venous insufficiency (CVI) and those undergoing coronary artery bypass grafting (CABG). In the unadjusted analyses, serum caspase-1, IL-1β, and IL-18 concentrations were significantly higher in the CABG group, indicating increased inflammasome-related inflammatory activity in advanced coronary artery disease. However, after adjustment for age and sex using ANCOVA, only the difference in serum caspase-1 remained statistically significant, whereas the differences in IL-1β and IL-18 were attenuated. These findings suggest that demographic factors may partially influence circulating IL-1β and IL-18 concentrations, while serum caspase-1 appears to be less affected by these variables. Therefore, caspase-1 may represent a more robust indicator of inflammasome activation when comparing inflammatory responses between different vascular diseases. Nevertheless, these findings should be interpreted cautiously and require confirmation in larger, age- and sex-matched cohorts [14-16].

The persistence of elevated serum caspase-1 after multivariable adjustment is biologically plausible. Caspase-1 is the key effector enzyme activated following inflammasome assembly and is directly responsible for the maturation of IL-1β and IL-18. Beyond cytokine processing, caspase-1 also mediates pyroptotic cell death and amplifies vascular inflammation through multiple downstream pathways. Experimental and clinical studies have demonstrated that excessive inflammasome activation contributes to endothelial dysfunction, plaque progression, and plaque instability in atherosclerosis. Our findings, therefore, suggest that upstream inflammasome activation, represented by caspase-1, may better differentiate advanced coronary artery disease from chronic venous insufficiency than circulating downstream cytokine concentrations alone [14-17].

Interestingly, the differences observed for IL-1β and IL-18 in the unadjusted analyses were attenuated after adjustment for age and sex. This finding is biologically reasonable because circulating interleukin concentrations are known to be influenced by both aging and sex-dependent immune regulation. Aging is characterized by chronic low-grade inflammation ("inflammaging"), which is associated with increased production of several pro-inflammatory cytokines, including IL-1β and IL-18. Likewise, sex hormones modulate innate immune responses and cytokine secretion, contributing to inter-individual variability in circulating inflammatory mediators. Consequently, the higher IL-1β and IL-18 concentrations observed in the unadjusted analyses may have been partially attributable to baseline demographic differences rather than disease status alone [18-20].

The hematological inflammatory findings further support the presence of enhanced systemic inflammation in patients undergoing CABG. Higher neutrophil counts, NLR, and SII values observed in the CABG group are consistent with previous studies demonstrating that these indices reflect systemic inflammatory activation and predict adverse cardiovascular outcomes. Furthermore, the positive correlation between serum IL-18 and SII observed in the CABG group suggests that inflammasome activation is closely linked with systemic immune-inflammatory status. Although IL-18 was not independently associated with disease status after adjustment, its correlation with the SII indicates that it remains a useful indicator of the overall inflammatory burden in patients with advanced coronary artery disease [21-23].

Although chronic venous insufficiency is primarily caused by venous hypertension and valvular dysfunction, inflammation also contributes to disease progression [5]. Increased IL-1β levels and NLRP3 inflammasome activation have been reported in patients with chronic venous disease, supporting the role of inflammasome-related pathways in venous wall remodeling [12,24]. Our findings suggest that systemic inflammasome activity is less pronounced in chronic venous insufficiency than in advanced coronary artery disease. Nevertheless, the presence of measurable inflammasome-related biomarkers indicates that inflammation is involved in the pathophysiology of chronic venous insufficiency [5,25]. Recent advances in the treatment of iliofemoral venous thrombosis further emphasize the importance of inflammatory mechanisms in venous disease [26].

Several limitations should be considered when interpreting these findings. First, this was a single-center study with a relatively small sample size, limiting statistical power. Second, although age and sex were adjusted using ANCOVA, residual confounding cannot be completely excluded because of the limited cohort size. Third, inflammasome activity was assessed using circulating serum biomarkers without complementary

molecular or histopathological analyses. Larger multicenter studies with age- and sex-matched populations are warranted to validate whether caspase-1 consistently remains an independent marker of vascular inflammasome activation and to further clarify the influence of demographic factors on circulating IL-1β and IL-18 concentrations.

CONCLUSION

In conclusion, our findings indicate that inflammasome-related inflammatory pathways are involved in both coronary artery disease and chronic venous insufficiency. Although serum IL-1β, IL-18, and caspase-1 levels were higher in the unadjusted analyses of patients undergoing CABG, adjustment for age and sex demonstrated that only serum caspase-1 remained independently associated with disease status. These findings suggest that circulating IL-1β and IL-18 concentrations may be partially influenced by demographic factors, whereas serum caspase-1 appears to be less susceptible to these effects and may serve as a more consistent indicator of inflammasome activation in advanced coronary artery disease. Nevertheless, larger prospective studies with age- and sex-matched cohorts are needed to validate these observations and to further clarify the clinical utility of inflammasome-related biomarkers in vascular diseases.

Ethics Committee Approval: This study was approved by the Ethics Committee of Tokat Gaziosmanpasa University Hospital (approval number: 14.03.2024, 24-KAEK-070).

Patient Consent for Publication: Written informed consent was obtained from all patients included in the study.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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