Linking Comorbidity and Inflammation: The Role of Comorbidity Polypharmacy Score in Chronic Limb-Threatening Ischemia

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Introduction: Chronic limb-threatening ischemia (CLTI) is a severe manifestation of peripheral artery disease, frequently associated with multimorbidity and polypharmacy. Chronic low-grade inflammation plays a pivotal role in atherosclerosis progression, and hematologic markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are gaining value as prognostic tools.
Aim: To investigate the relationship between the Comorbidity-Polypharmacy Score (CPPS) and inflammatory biomarkers in patients undergoing elective revascularization for CLTI.
Methods: This retrospective study included 442 CLTI patients treated at the Vascular Surgery Unit, University of Siena. CPPS was calculated by summing the number of chronic diseases and long-term medications, stratifying patients into 4 groups: mild, moderate, severe, and morbid. Pre-operative bloodwork was analyzed to calculate NLR, PLR, and SII. Statistical analysis included ANOVA and linear regression.
Results: CPPS distribution was mild (22.6%), moderate (54.3%), severe (21.9%), and morbid (1.2%). Inflammatory markers increased significantly with CPPS severity. Mean NLR rose from 3.1 ± 2.1 in mild to 5.8 ± 3.7 in morbid ($P < 0.001$), PLR from 145.0 ± 89.5 to 227.2 ± 112.9 ($P < 0.001$), and SII from 835.7 ± 707.6 to 1710.6 ± 944.0 ($P < 0.001$). Hemoglobin decreased from 13.6 ± 2.1 g/dL to 11.5 ± 1.7 g/dL ($P = 0.03$). Linear regression showed significant positive correlations between CPPS and NLR ($R^2 = 0.28$), PLR ($R^2 = 0.35$), and SII ($R^2 = 0.33$).
Conclusions: Higher CPPS is associated with elevated inflammatory markers and declining hemoglobin, suggesting that multimorbidity and polypharmacy contribute directly to systemic inflammation. CPPS, alongside NLR, PLR, and SII, may support risk stratification and personalized management in CLTI patients.

INTRODUCTION

Chronic low-grade inflammation is increasingly recognized as a central driver of **multimorbidity**, particularly in atherosclerotic diseases such as **lower extremity artery disease (LEAD)**. These conditions rarely occur in isolation and often coexist with diabetes, chronic kidney disease, or Chronic Obstructive Pulmonary Disease (COPD), forming a self-reinforcing network of inflammatory

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pathologies. Inflammation promotes endothelial dysfunction, immune activation, and plaque instability, mechanisms that accelerate vascular damage and systemic deterioration. This biological chaos is amplified by **immunosenescence** and behavioral factors like poor diet, smoking, and stress, creating a vicious cycle of progressive multimorbidity.[1,2] In older adults, immunosenescence amplifies this process, tipping the immune balance further toward a persistent, dysregulated inflammatory state known as inflammaging.[3]

The systemic inflammatory burden in these vascular diseases is measurable: elevated levels of C-Reactive Protein, IL-6, and other markers are consistently associated with worse prognosis and faster disease progression.[4] This inflammatory milieu interacts with behavioral and environmental contributors—smoking, poor diet, sedentary behavior, psychosocial stress—creating a vicious cycle where atherosclerosis and inflammation reinforce one another.[5]

Overlaying all of this is the pervasive challenge of polypharmacy, the concurrent use of multiple medications, often 5 or more, to manage multiple chronic conditions. In the context of LEAD and other cardiovascular disease, patients are frequently prescribed antiplatelet agents, statins, antihypertensives, glucose-lowering therapies, anticoagulants, and more. Paradoxically, medications intended to reduce inflammation or cardiovascular risk can sometimes exacerbate systemic stress or impair immune responses.[6] This complex pharmacological web can worsen frailty, further fuel chronic inflammation, and ultimately undermine the very outcomes these treatments aim to improve.

The Comorbidity-Polypharmacy Score (CPPS), which integrates the number of chronic conditions and concurrent medications, has emerged as a powerful tool to quantify patient complexity and predict adverse outcomes.[7] High CPPS values correlate with increased hospitalizations, treatment burden, and mortality, especially in patients with cardiovascular comorbidities. In this context, polypharmacy is not just a logistical issue; it can fuel inflammation through drug–drug interactions, immune dysregulation, and reduced physiological reserve.

Emerging hematological markers of systemic inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory index (SII) are gaining diffusion as accessible, low-cost prognostic tools. These indices, easily derived from routine complete blood counts, have been independently associated with disease severity, cardiovascular risk, and poor outcomes in patients with LEAD, carotid artery stenosis, and other atherosclerotic diseases.[8–12] Their value lies not only in their predictive ability but also in their potential role in guiding treatment intensity and follow-up frequency in multimorbid patients. As we move toward more personalized and resource-conscious care, such biomarkers may become essential tools in bridging the gap between complex pathophysiology and pragmatic clinical decision-making.

From this background, the present study's aim is to investigate the potential relation between CPPS and hematological inflammatory biomarkers in patients undergoing elective endovascular revascularization procedures for CLTI condition.

MATERIALS AND METHODS

This retrospective study analyzed a cohort of consecutive patients admitted to the Vascular Surgery Unit at the University of Siena between 2017 and 2018. All patients underwent elective peripheral vascular revascularization procedures for a diagnosis of CLTI.

The population selected for the analysis was already studied to validate CPPS as a predictive tool for major outcomes after CLTI revascularization procedures.[13] Patient data were extracted from electronic hospital records. Each hospitalization was retrospectively reviewed, with attention to clinical history, ongoing medications, preoperative bloodwork, and the types of procedures performed. Among the most frequently observed comorbidities were coronary artery disease (with or without previous interventions), hypertension (defined either by elevated blood pressure or ongoing treatment), diabetes (diagnosed based on standard glucose thresholds or ongoing therapy), COPD (including chronic bronchitis, emphysema, or asthma), chronic kidney disease (serum creatinine >1.2 mg/dL), and a history of smoking. Other common conditions included congestive heart failure, cerebrovascular disease (stroke or TIA), cancer, dyslipidemia, and atrial fibrillation.

To evaluate polypharmacy, all prescription medications intended for chronic use were included in the CPPS, regardless of therapeutic class, including noncardiovascular drugs such as psychiatric agents, analgesics, or respiratory therapies. Over-the-counter agents, supplements, and topical treatments were excluded unless they were explicitly prescribed for continuous use and documented in the medical record. In line with a recent publication,[13]

we used the CPPS to quantify each patient's comorbidity and medication burden. The CPPS was calculated by summing the number of chronic conditions and the number of chronically prescribed drugs at the time of preoperative evaluation. Based on this total, patients were stratified into 4 groups: mild (0−7), moderate (8−14), severe (15−21), and morbid (>21).

We also examined pre-operative lab data, focusing on white blood cell count, neutrophils, lymphocytes, and platelets. From these, we derived inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), the latter calculated as (neutrophils × platelets)/lymphocytes.

To minimize potential confounding effects, patients with documented acute infections, recent surgeries (<30 days), trauma, or other acute inflammatory conditions at the time of preoperative evaluation were excluded from the analysis.

The main aim of the study was to explore whether there was a relationship between CPPS and systemic inflammatory markers in patients undergoing elective revascularization for CLTI.

The study was conducted in accordance with the Declaration of Helsinki (2013 revision). The local ethics committee reviewed the study and approved a waiver of informed consent, given its retrospective, observational nature and exclusive reliance on existing patient records.

Statistical Analysis

Continuous data were shown as mean values ± standard deviation (SD). Categorical variables were expressed as fractions. Analysis of variance was used for independent tests to compare groups on continuous variables after demonstrating a normal distribution of the data. One-way analysis of variance (ANOVA) analysis was performed within and between-group comparisons for continuous data. Chi-square tests were performed for categorical data analysis. Linear regression analysis was used to evaluate the relation between variables.

A *P*-value inferior to 0.05 has been considered statistically significant in all the statistical tests. All statistical analyses were performed with GraphPad Prism 10.1.1 (GraphPad Software Inc, San Diego, Calif) and Jamovi 2.3.18.0 (Sydney, Australia). We present this article by the STROBE reporting checklist.

Table I. Baseline characteristics of population study

Variables	Total population ($N = 442$)
Age (mean ± SD)	76.5 ± 9.9
Male (*N*,%)	272 (64.5%)
Hypertension (*N*,%)	379 (85.7%)
Dyslipidemia (*N*,%)	312 (70.6%)
CAD (*N*,%)	163 (36.9%)
CHF (*N*,%)	101 (22.8%)
Cerebrovascular Disease (*N*,%)	81 (18.3%)
AF (*N*,%)	78 (17.6%)
COPD (*N*,%)	86 (19.6%)
CKD (*N*,%)	123 (27.8%)
Dialysis	16 (3.6%)
DM (*N*,%)	201 (45.5%)
Malignancy (*N*,%)	42 (9.5%)
Smoking habit (*N*,%)	
Current Smoker	93 (21%)
Former Smoker	119 (26.9%)
Barthel at Admission (mean ± SD)	77.4 ± 28.6
N° of comorbidities (mean ± SD)	3.6 ± 1.9
N° of drugs (mean ± SD)	7.5 ± 3.4
CPPS (mean ± SD)	10.9 ± 4.7
Rutherford Classification (*N*,%)	
III	123 (27.8%)
IV	111 (25.2%)
V	208 (47%)
VI	0 (0%)
Multilevel PAD location (*N*,%)	240 (54.3%)
Location of arterial PAD (*N*,%)	
Aorto-iliac	72 (16.3%)
Femoral district	307 (69.4%)
Popliteal segment	211 (47.7%)
Below-the-knee	216 (48.8%)

Abbreviations: CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; AF: Atrial Fibrillation; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus: PAD: Peripheral Artery Disease; CPPS: Comorbidity-Polypharmacy Score; SD: Standard Deviation.

RESULTS

Baseline Features

The study included 442 patients (mean age 76.5 ± 9.9 years; 61.5% male). As shown in Table I, cardiovascular risk factors were highly prevalent: hypertension (85.7%), dyslipidemia (70.6%), CKD (27.8%), and diabetes (45.5%). Patients were on an average of 7.5 ± 3.4 medications (range 0−18).

Most were admitted for CLTI, classified per Rutherford as grade III (27.8%), IV (25.2%), and V (47%). Atherosclerosis involved the femoral segment in 69.4%, popliteal in 47.7%, and below-the-knee arteries in 48.8%. Multilevel disease was present in 54.3% (Table I).

Table II. Preoperative Inflammatory markers of the population study stratified for CPPS subgroups

Variables	Mild CPPS ($N = 100$, 22.6%)	Moderate CPPS ($N = 240$; 21.9%)	Severe CPPS ($N = 97$; 21.9%)	Morbid CPPS ($N = 5$; 1.2%)	P Value
Leukocyte (1000/mL) (mean ± SD)	8.6 ± 3.3	8.4 ± 2.5	9.1 ± 3.8	9.4 ± 2.8	0.6
Neutrophil (1000/mL) (mean ± SD)	5.7 ± 2.9	5.7 ± 2.3	7.8 ± 11.4	8.4 ± 8.2	0.04
Lymphocyte (1000/mL) (mean ± SD)	2.1 ± 1.3	1.9 ± 0.7	1.7 ± 0.7	1.5 ± 0.7	0.8
Platelets (1000/mL) (mean ± SD)	259.2 ± 88.3	265.5 ± 100.5	259.1 ± 91.5	301.9 ± 63.9	<0.001
NLR (mean ± SD)	3.1 ± 2.1	3.8 ± 3	5.2 ± 7.6	5.8 ± 3.7	<0.001
PLR (mean ± SD)	145 ± 89.5	172.3 ± 117.9	179 ± 71.1	227.2 ± 112.9	<0.001
SII (mean ± SD)	835.7 ± 707.6	1137.2 ± 1351.1	1417.7 ± 2604.6	1710.6 ± 944	<0.001
Hb (g/dL) (mean ± SD)	13.6 ± 2.1	12.8 ± 2.1	12.1 ± 1.9	11.5 ± 1.7	0.03

Abbreviations: SD: Standard Deviation; NLR: Neutrophil-to-Lymphocyte ratio; PLR: Platelet-to-Lymphocyte ratio, SII: Systemic Inflammatory Index.

Comorbidity-Polypharmacy Score and Inflammatory Markers Analysis

The population was divided into 4 groups based on CPPS: 22.6% (100/442) have mild CPPS, 54.3% (240/442) have moderate CPPS, 21.9% (97/442) have severe CPPS, and only 1.2% (5/442) have morbid CPPS status. The 4 subgroups revealed significant differences in terms of perioperative blood sample values.

Based on the data presented in Table II, there is a clear and progressive association between the severity of the CPPS and systemic inflammatory markers.

Notably, as highlighted in Figure 1, neutrophil counts rise significantly with CPPS severity, from a mean of 5.7 ± 2.9 × 10^9/L in mild/moderate CPPS groups to 7.8 ± 11.4 and 8.4 ± 8.2 × 10^9/L in the severe and morbid CPPS groups, respectively ($P = 0.04$), while lymphocyte counts show a nonsignificant decreasing trend, resulting in a sharp elevation in NLR. NLR climbs from 3.1 ± 2.1 in mild CPPS to 5.8 ± 3.7 in morbid CPPS ($P < 0.001$), underlining an increasingly dysregulated immune profile.

Similarly, PLR increases markedly across groups, peaking at 227.2 ± 112.9 in morbid CPPS ($P < 0.001$), likely reflecting both inflammatory and prothrombotic shifts. The SII, which integrates neutrophils, platelets, and lymphocytes, demonstrates a dramatic upward trajectory, more than doubling from 835.7 ± 707.6 in mild CPPS to 1710.6 ± 944 in morbid CPPS ($P < 0.001$), highlighting the cumulative burden of immune activation.

Interestingly, platelet count alone also rises significantly with CPPS, from a mean of 259.2 ± 88.3 to 301.9 ± 63.9 × 10^9/L ($P < 0.001$), which may reflect ongoing systemic inflammation or subclinical vascular stress. Concurrently, hemoglobin levels decline significantly as CPPS worsens ($P = 0.03$), possibly due to chronic disease-related anemia or the additive effect of medications and systemic illness.

Figure 2 illustrates the positive linear relationship between the CPPS and 3 inflammatory indices, NLR, PLR, and SII.

Panel 2A demonstrates a statistically significant upward trend between CPPS and NLR values. The regression equation (Y = 0.2506 × CPPS + 1.618) indicates that for each unit increase in CPPS, the NLR increases by approximately 0.25, suggesting a clear association between rising comorbidity/polypharmacy burden and systemic neutrophilic inflammation and lymphocyte suppression.

Panel 2B shows a similar pattern for PLR, with a steeper regression slope (Y = 6.703 × CPPS + 101.8), indicating that each unit rise in CPPS corresponds to an average increase of 6.7 units in PLR. This reinforces the pro-inflammatory and pro-thrombotic shift seen in patients with more complex clinical profiles.

Panel 2C highlights the relationship between CPPS and SII values. Equation (Y = 78.28 × CPPS + 379.8) reflects a robust linear association, with wide data dispersion but a clear positive trend. This suggests that as patients accumulate comorbidities and medications, their systemic immune-inflammatory burden—captured comprehensively by SII—increases significantly.

DISCUSSION

The study confirmed how CPPS relates to chronic inflammation biomarkers and NLR, PLR, and SII in

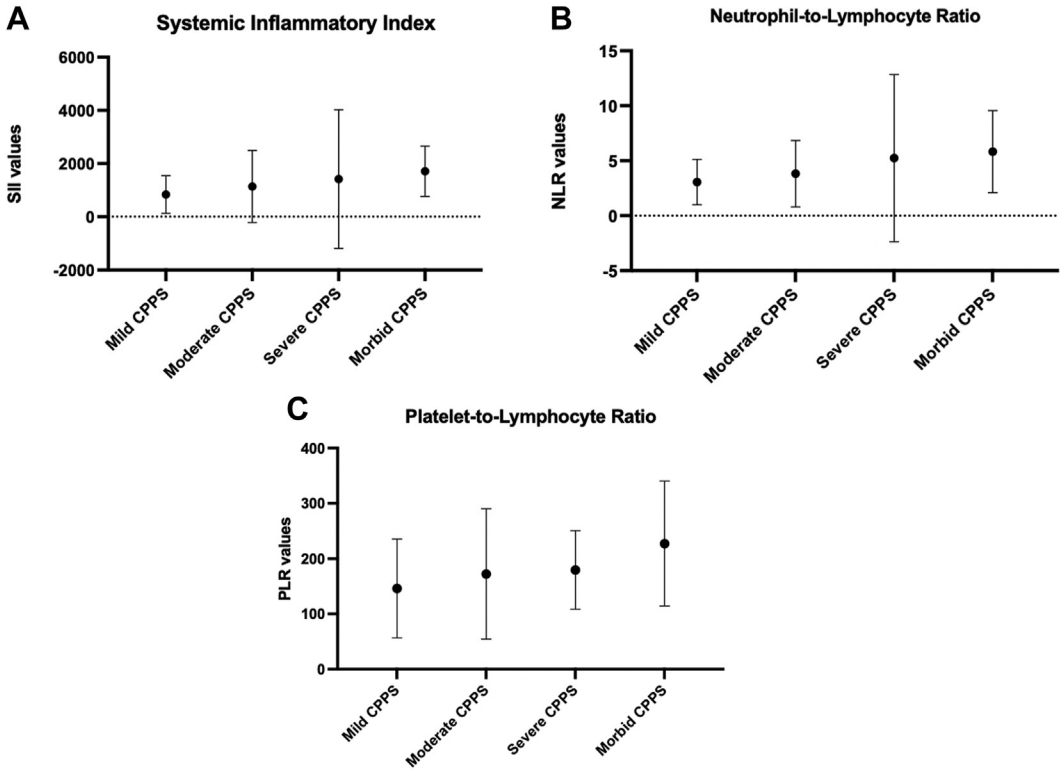

Fig. 1. Inflammatory indices stratified by CPPS categories. Bar graphs with mean ± standard deviation (SD) showing the distribution of inflammatory markers across CPPS groups (mild, moderate, severe, morbid): **(A)** Systemic Immune-Inflammation Index (SII), **(B)** Neutrophil-to-Lymphocyte Ratio (NLR), and **(C)** Platelet-to-Lymphocyte Ratio (PLR).

a linear trend, highlighting that the cumulative burden of comorbidities and drug intake directly impact the subclinical inflammation level. These findings further validate the utility of these simple, cost-effective indices in stratifying clinical risk and inflammatory burden in complex vascular patients, such as those with CLTI or other advanced atherosclerotic conditions and supporting the notion that multimorbidity and polypharmacy are not only clinical management challenges but also direct contributors to a pro-inflammatory state in complex vascular patients.

As CPPS increases, these inflammatory indices also show a consistent upward trend, reflecting the mounting immune dysregulation in patients burdened by multiple comorbidities and complex pharmacological regimens. This relationship highlights how the combined effect of disease burden and polypharmacy actively contributes to a sustained, subclinical inflammatory state. These markers, which are simple, inexpensive, and derived from routine blood counts, demonstrate strong potential in stratifying inflammatory risk and identifying high-risk patients, particularly in the setting of CLTI and other advanced vascular conditions.

The findings also reinforce the concept that multimorbidity and polypharmacy are not passive clinical descriptors, but rather dynamic factors that directly influence the patient's biological environment. Chronic diseases often drive persistent low-grade inflammation, while polypharmacy can intensify this through drug-induced immune modulation, organ stress, or cumulative side effects. Together, they form a cycle that fuels vascular deterioration and complicates therapeutic decision-making.

In the arterial wall, chronic inflammation plays a central role in the initiation and progression of atherosclerosis. Inflammatory cells such as monocytes and macrophages infiltrate the intima, where they engulf oxidized low-density lipoproteins, forming foam cells and perpetuating the development of atherosclerotic plaques. This process is amplified by pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, which promote endothelial dysfunction, upregulate adhesion

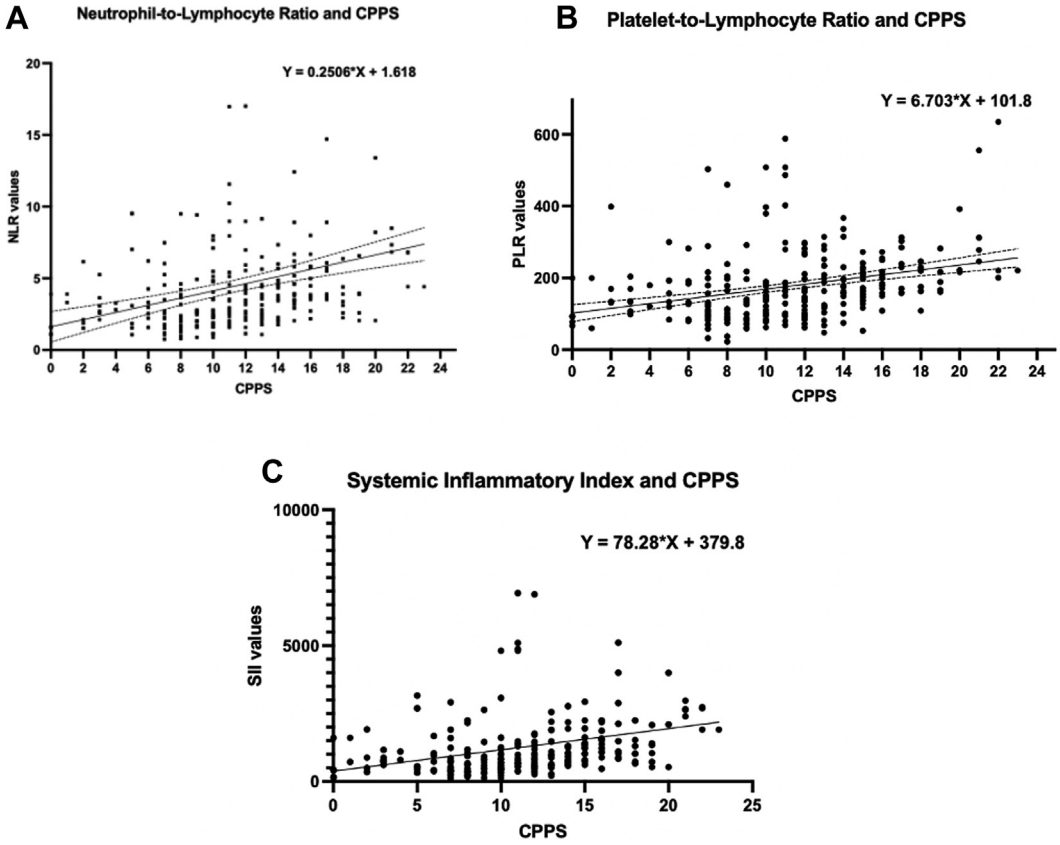

Fig. 2. Correlation between CPPS and inflammatory indices (linear regression analysis). Scatter plots demonstrating the linear association between the Comorbidity-Polypharmacy Score (CPPS) and 3 systemic inflammatory markers: **(A)** Neutrophil-to-Lymphocyte Ratio (NLR), **(B)** Platelet-to-Lymphocyte Ratio (PLR), and **(C)** Systemic Immune-Inflammation Index (SII).

molecules, and sustain a pro-atherogenic microenvironment.[14] These inflammatory cascades do not occur in isolation; rather, they are perpetuated by systemic risk factors such as smoking, diabetes, hypertension, and chronic kidney disease—many of which are common in multimorbid patients.

In the context of LEAD, this inflammatory-driven atherogenesis results in progressive arterial narrowing and occlusion, particularly in the femoropopliteal and tibial segments. Clinically, this manifests as intermittent claudication in early stages and can progress to CLTI, characterized by ischemic rest pain, nonhealing ulcers, or gangrene. These complications are not only debilitating but also carry a substantial risk of major amputation and mortality if not promptly treated.[15] Data from large registries and cohort studies have shown that patients with CLTI have a 1-year amputation rate of up to 30% and a 1-year mortality rate exceeding 25%, comparable to or worse than many forms of cancer.[16]

Importantly, LEAD is not merely a localized vascular problem but a powerful marker of systemic atherosclerosis and global vascular risk. The presence of LEAD significantly increases the risk of myocardial infarction, stroke, and cardiovascular death. Furthermore, its prognostic impact is magnified in the presence of multimorbidity, especially diabetes and CKD. In diabetic patients, LEAD progresses more rapidly and is often more diffuse and distal, making revascularization more challenging. Studies have shown that diabetics with LEAD have higher rates of restenosis, limb loss, and mortality after both endovascular and surgical interventions compared to nondiabetics.[17] Similarly, CKD is independently associated with increased vascular calcification, impaired endothelial repair, and a hypercoagulable state, all of which worsen LEAD outcomes. Patients with both LEAD and CKD have been found to have up to 3-fold higher risk of amputation and death compared to those without renal impairment.[18]

These associations are further exacerbated by the underlying systemic inflammatory state common to

all these conditions. Elevated biomarkers such as CRP, IL-6, NLR, and SII have been shown to correlate with both the presence and severity of LEAD. For example, a recent meta-analysis found that patients with elevated NLR had significantly worse amputation-free survival and higher rates of adverse limb events.[19] This positions inflammation not only as a mechanistic driver but also as a clinically useful biomarker for identifying high-risk individuals and guiding therapy.

In summary, inflammation lies at the molecular core of LEAD, mediating plaque development, progression, and destabilization. Its clinical expression in the lower limbs, ranging from claudication to CLTI, is both a manifestation of and a contributor to systemic vascular decline. The presence of comorbid conditions such as diabetes and CKD amplifies this inflammatory burden and significantly worsens outcomes, reinforcing the need for integrated, inflammation-aware management strategies in this vulnerable population.

An additional and clinically meaningful finding is the progressive decline in hemoglobin levels associated with increasing CPPS, suggesting a link between multimorbidity/polypharmacy burden and anemia. As CPPS severity increases—from mild to morbid—mean Hb values drop significantly. This decline likely reflects the cumulative impact of chronic disease, systemic inflammation, and medication burden on erythropoiesis and iron metabolism. Chronic inflammation promotes functional iron deficiency, suppresses erythropoietin production, and impairs the bone marrow response.[20,21]

Moreover, polypharmacy can directly exacerbate this process: medications such as antiplatelet agents, anticoagulants, NSAIDs, proton pump inhibitors, and certain antihypertensives are well-known contributors to gastrointestinal blood loss, renal dysfunction, or bone marrow suppression.[22,23] In high-risk vascular patients, such as those with CLTI, reduced hemoglobin levels are independently associated with poorer wound healing, higher perioperative risk, increased rates of amputation, and elevated all-cause mortality.[24] Thus, the observed inverse relationship between CPPS and hemoglobin not only reflects a biological consequence of inflammation and treatment complexity but also underscores the need for vigilant screening and proactive management of anemia as part of a comprehensive, risk-informed care strategy in this vulnerable population.

An important translational implication of our findings is the potential integration of CPPS and inflammatory biomarkers into existing risk stratification models for patients with CLTI. Current frameworks, such as the PREVENT III score,[25] emphasize clinical and anatomical factors but do not account for pharmacological burden or systemic inflammation. Incorporating CPPS, along with NLR, PLR, and SII, could improve prognostic precision by capturing underlying immune dysregulation and treatment complexity. This may allow for better identification of vulnerable patients, more tailored perioperative planning, and stratified follow-up intensity. Future prospective studies are warranted to validate such integrative approaches.

Limitations

This study has several limitations inherent to its retrospective and observational design. First, data were extracted from electronic medical records, which may be subject to documentation bias or incomplete reporting. Second, while the CPPS offers a practical measure of clinical complexity, it does not account for disease severity or drug interactions, which may also influence inflammatory responses. Third, inflammatory markers such as NLR, PLR, and SII, although valuable and accessible, can be affected by acute events or subclinical conditions not fully captured in the dataset. Additionally, the small size of the morbid CPPS subgroup restricts the statistical power to draw firm conclusions for that category. Finally, as this was a single-center study, generalizability to other populations or healthcare settings may be limited. Prospective, multicenter studies are warranted to validate these findings and assess their applicability in broader clinical practice.

CONCLUSION

This study highlights the pivotal role of chronic inflammation in the clinical complexity of patients with CLTI, particularly within the context of multimorbidity and polypharmacy. The progressive increase in inflammatory markers, NLR, PLR, and SII, across rising CPPS categories underscores a strong, quantifiable relationship between systemic immune activation and disease burden. Concurrently, the significant decline in hemoglobin levels with higher CPPS further reflects the biological and functional impact of this chronic inflammatory state. Collectively, these findings support the use of CPPS and inflammatory indices as practical tools for risk stratification, enabling more personalized, inflammation-aware care for high-risk vascular patients. Integrating these markers into clinical practice may help guide therapeutic intensity, identify vulnerable individuals earlier, and ultimately

improve outcomes in this fragile and growing patient population.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Edoardo Pasqui: Writing — review & editing, Writing — original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giulia Casilli:** Writing — review & editing, Investigation, Data curation. **Tommaso Anichini:** Writing — review & editing, Formal analysis, Data curation. **Eleonora Cerbini:** Writing — review & editing, Validation, Formal analysis, Data curation. **Leonardo Pasquetti:** Writing — review & editing, Investigation, Data curation. **Giuseppe Galzerano:** Writing — review & editing, Writing — original draft, Investigation, Formal analysis, Conceptualization. **Gianmarco de Donato:** Writing — review & editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

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