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ASSOCIATION BETWEEN SYSTEMIC INFLAMMATORY BIOMARKERS AND THE RISK OF MULTIMORBIDITY IN PATIENTS WITH NON-COMMUNICABLE DISEASES: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Multimorbidity, the coexistence of two or more chronic non-communicable diseases (NCDs), is increasing globally and is strongly associated with adverse clinical outcomes. Systemic inflammation is considered a potential shared biological mechanism underlying multimorbidity; however, evidence from clinical populations remains limited. The objective of the study is to evaluate the association between systemic inflammatory biomarkers and multimorbidity among patients with NCDs in a hospital-based cross-sectional study.

Materials and Methods: A cross-sectional study was conducted among adult patients (≥18 years) with diagnosed NCDs. Multimorbidity was defined as the presence of ≥2 chronic conditions. Data on sociodemographic and clinical variables were collected using structured questionnaires and medical records. Serum levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), fibrinogen, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were measured using standard laboratory methods. Statistical analyses included group comparisons, correlation analysis, multivariable logistic regression, and ROC curve analysis.

Result: Patients with multimorbidity showed significantly higher levels of all inflammatory biomarkers compared to those with a single NCD ($p<0.001$). IL-6 demonstrated the strongest correlation with multimorbidity burden ($r=0.58$, $p<0.001$). After adjustment for confounders, IL-6 (AOR=3.84, 95% CI: 2.31–6.37) and hs-CRP (AOR=3.29, 95% CI: 2.01–5.39) were independent predictors of multimorbidity. The combined biomarker model showed high discriminatory performance (AUC=0.903).

Conclusion: Systemic inflammatory biomarkers, particularly IL-6 and hs-CRP, are strongly associated with multimorbidity among patients with NCDs. These biomarkers may serve as useful tools for risk stratification and early identification of individuals at high risk of complex disease burden.

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Keywords: Multimorbidity, Non-communicable diseases, Systemic inflammation, IL-6; hs-CRP, Biomarkers, Cross-sectional study.

INTRODUCTION

Multimorbidity, commonly defined as the coexistence of two or more chronic conditions within an individual, has emerged as a major global public health challenge.[1,2] The growing burden of non-communicable diseases (NCDs), including cardiovascular diseases, diabetes mellitus, chronic respiratory diseases, chronic kidney disease, and cancer, has substantially increased the prevalence of multimorbidity worldwide. Multimorbidity is associated with reduced quality of life, functional impairment, increased healthcare utilization, polypharmacy, and premature mortality, thereby imposing significant clinical and economic burdens on healthcare systems.[3,4]

Although the mechanisms underlying multimorbidity remain incompletely understood, accumulating evidence suggests that chronic low-grade systemic inflammation may represent a common biological pathway linking multiple chronic diseases. Persistent activation of inflammatory processes contributes to endothelial dysfunction, insulin resistance, oxidative stress, immune dysregulation, and tissue remodeling, all of which are implicated in the pathogenesis and progression of several NCDs.[5,6] This phenomenon, often described as "inflammaging," is characterized by sustained elevations of circulating inflammatory mediators and has been proposed as a key driver of age-related disease accumulation and multimorbidity.[7]

Several inflammatory biomarkers have been investigated as potential indicators of multimorbidity risk. Among these, C-reactive protein (CRP) and interleukin-6 (IL-6) have consistently demonstrated positive associations with the number and severity of chronic conditions.[5,6] Longitudinal evidence from community-based cohorts indicates that elevated IL-6 levels predict a faster accumulation of chronic diseases over time, suggesting a potential causal role of systemic inflammation in multimorbidity development.[8,9] Furthermore, recent systematic reviews have identified inflammatory biomarkers, particularly IL-6 and CRP, among the most frequently reported biological markers associated with multimorbidity across diverse populations.[10-12]

Despite growing recognition of inflammation as a shared pathogenic mechanism, evidence regarding the relationship between systemic inflammatory biomarkers and multimorbidity among patients already living with NCDs remains limited, particularly in low- and middle-income countries where the burden of NCDs is rapidly increasing. Most previous studies have focused on individual diseases rather than evaluating multimorbidity as a distinct clinical entity. Consequently, there is a need to identify accessible and clinically applicable biomarkers that can facilitate early risk stratification and improve understanding of the biological pathways underlying disease clustering.[13]

Therefore, the present cross-sectional study aimed to investigate the association between systemic inflammatory biomarkers and the risk of multimorbidity among patients with non-communicable diseases. Understanding these associations may provide insights into shared pathophysiological mechanisms and support the development of targeted preventive and therapeutic strategies for individuals at high risk of complex multimorbid conditions.

MATERIALS AND METHODS

Study Design and Study Population: This hospital-based cross-sectional study was conducted among adult patients (≥18 years) diagnosed with one or more non-communicable diseases (NCDs), including hypertension, diabetes mellitus, cardiovascular disease, chronic respiratory disease, chronic kidney disease, and cancer. Eligible participants were recruited

consecutively from outpatient and inpatient departments during the study period. Patients with acute infections, autoimmune diseases, active inflammatory conditions, recent surgery or trauma, pregnancy, or incomplete clinical data were excluded.

Assessment of Multimorbidity and Clinical Characteristics: Sociodemographic data, lifestyle factors, anthropometric measurements, and clinical characteristics were collected using a structured questionnaire and verified through medical records. Multimorbidity was defined as the presence of two or more physician-diagnosed chronic conditions in the same individual. Participants were categorized into a single NCD group and a multimorbidity group (≥2 NCDs). Information on disease duration, medication use, smoking status, alcohol consumption, and body mass index (BMI) was also recorded.

Measurement of Systemic Inflammatory Biomarkers: Fasting venous blood samples were collected under standardized conditions. Serum levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and fibrinogen were measured using validated enzyme-linked immunosorbent assay (ELISA) kits and standard laboratory protocols. Complete blood count parameters were additionally used to calculate the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Internal and external quality-control procedures were implemented to ensure analytical accuracy and reproducibility.

Statistical Analysis: Data were analyzed using SPSS version 30 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), whereas categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the independent t-test, Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Multivariable logistic regression analysis was used to evaluate the association between inflammatory biomarkers and multimorbidity after adjusting for age, sex, BMI, smoking status, and other potential confounders. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were reported. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 420 patients with non-communicable diseases (NCDs) were included in the analysis. The mean age of the study population was 58.4 ± 12.7 years, and 231 (55.0%) participants were male. Overall, 258 (61.4%) participants met the criteria for multimorbidity (≥2 chronic conditions), whereas 162 (38.6%) had a single NCD. Participants with multimorbidity were significantly older than those with a single NCD (61.9 ± 11.4 vs. 52.8 ± 13.1 years, $p<0.001$). The prevalence of obesity, smoking, and physical inactivity was also significantly higher among multimorbid individuals. Detailed baseline characteristics are presented in [Table 1].

In [Table 2], Significantly elevated levels of all evaluated inflammatory biomarkers were observed among participants with multimorbidity. The largest between-group differences were noted for hs-CRP and IL-6 concentrations. Mean hs-CRP levels were nearly two-fold higher in multimorbid patients than in those with a single NCD (5.8 ± 2.4 vs. 2.9 ± 1.7 mg/L, $p<0.001$). Similarly, IL-6, TNF-α, fibrinogen, NLR, and PLR demonstrated significant elevations in the multimorbidity group (all $p<0.001$).

[Table 3], The number of chronic diseases per participant showed significant positive correlations with all inflammatory markers. IL-6 exhibited the strongest correlation with multimorbidity burden ($r=0.58$, $p<0.001$), followed by hs-CRP ($r=0.54$, $p<0.001$) and TNF-α ($r=0.49$, $p<0.001$). [Table 4] shows, After adjustment for age, sex, BMI, smoking status, physical activity, and disease duration, elevated inflammatory biomarkers remained independently associated with multimorbidity.

Participants in the highest biomarker categories demonstrated substantially greater odds of multimorbidity. IL-6 emerged as the strongest independent predictor (AOR=3.84, 95% CI: 2.31–6.37,

p<0.001), followed by hs-CRP (AOR=3.29, 95% CI: 2.01–5.39, p<0.001). Receiver operating characteristic (ROC) analysis demonstrated good discriminatory performance for multimorbidity. IL-6 yielded the highest diagnostic accuracy (AUC=0.842), followed by hs-CRP (AUC=0.816). Combining all biomarkers significantly improved discrimination (AUC=0.903) in table 5.

[Figure 1] illustrates the distribution of major NCD combinations among participants, showing the most frequent coexistence patterns such as hypertension with diabetes and cardiovascular disease clusters. [Figure 2] demonstrates a graded increase in multimorbidity prevalence across hs-CRP quartiles, reflecting a clear dose–response relationship between systemic inflammation and disease burden. [Figure 3] presents the progressive rise in IL-6 levels with increasing number of chronic diseases, visually supporting the concept of inflammation-driven multimorbidity and reinforcing a linear inflammatory escalation with disease accumulation.

Table 1: Demographic and Clinical Characteristics According to Multimorbidity Status

Variable	Single NCD (n=162)	Multimorbidity (n=258)	p-value
Age (years), mean ± SD	52.8 ± 13.1	61.9 ± 11.4	<0.001
Male sex, n (%)	82 (50.6)	149 (57.8)	0.148
BMI (kg/m²), mean ± SD	24.9 ± 3.8	28.1 ± 4.6	<0.001
Current smokers, n (%)	29 (17.9)	71 (27.5)	0.025
Physical inactivity, n (%)	56 (34.6)	137 (53.1)	<0.001
Disease duration (years), median (IQR)	4 (2–7)	9 (5–14)	<0.001

Table 2: Comparison of Inflammatory Biomarkers Between Study Groups

Biomarker	Single NCD	Multimorbidity	p-value
hs-CRP (mg/L)	2.9 ± 1.7	5.8 ± 2.4	<0.001
IL-6 (pg/mL)	4.7 ± 1.9	8.9 ± 3.5	<0.001
TNF-α (pg/mL)	7.8 ± 2.8	12.6 ± 4.2	<0.001
Fibrinogen (mg/dL)	314 ± 58	402 ± 71	<0.001
NLR	2.11 ± 0.84	3.67 ± 1.21	<0.001
PLR	122 ± 39	169 ± 52	<0.001

Table 3: Correlation of Inflammatory Biomarkers with Number of Chronic Conditions

Biomarker	Correlation Coefficient (r)	p-value
hs-CRP	0.54	<0.001
IL-6	0.58	<0.001
TNF-α	0.49	<0.001
Fibrinogen	0.43	<0.001
NLR	0.47	<0.001
PLR	0.39	<0.001

Table 4: Multivariable Logistic Regression for Predictors of Multimorbidity

Variable	AOR	95% CI	p-value
Age (>60 years)	2.41	1.51–3.86	<0.001
BMI (per kg/m² increase)	1.12	1.06–1.18	<0.001
Smoking	1.67	1.01–2.76	0.044
hs-CRP (highest tertile)	3.29	2.01–5.39	<0.001
IL-6 (highest tertile)	3.84	2.31–6.37	<0.001
TNF-α (highest tertile)	2.72	1.61–4.61	<0.001
Fibrinogen (highest tertile)	2.18	1.31–3.62	0.003

Table 5: ROC Analysis for Prediction of Multimorbidity

Biomarker Model	AUC	95% CI	Sensitivity (%)	Specificity (%)
hs-CRP	0.816	0.775–0.857	79.1	73.4
IL-6	0.842	0.804–0.879	81.8	76.5
TNF-α	0.791	0.747–0.835	75.6	71.3
Fibrinogen	0.748	0.701–0.795	70.2	68.9
Combined Model	0.903	0.874–0.931	86.8	82.4

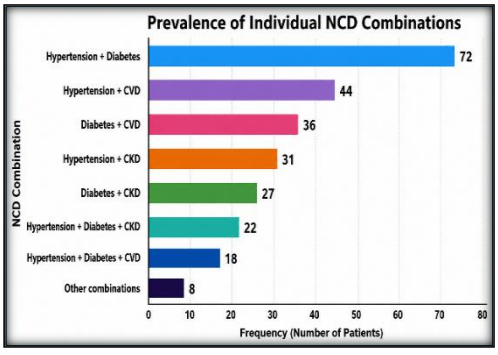

Figure 1: Prevalence of Individual NCD Combinations

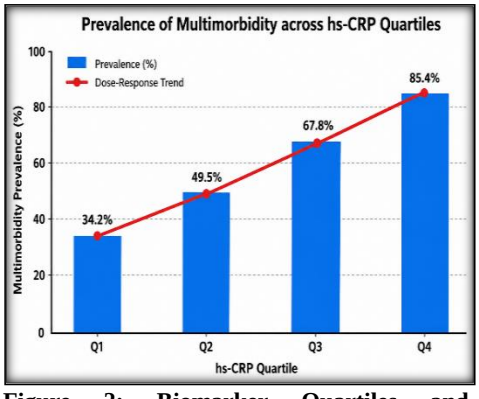

Figure 2: Biomarker Quartiles and Prevalence of Multimorbidity

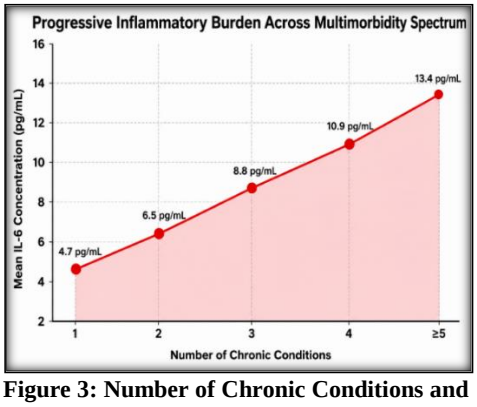

Figure 3: Number of Chronic Conditions and Mean IL-6 Levels

DISCUSSION

The present study demonstrates a strong and independent association between systemic inflammatory biomarkers (hs-CRP, IL-6, TNF-α, fibrinogen, NLR, and PLR) and multimorbidity burden among patients with non-communicable diseases (NCDs). The findings support the concept that chronic low-grade inflammation is a central biological mechanism underlying the clustering of chronic diseases. Similar observations have been reported by St Sauver et al,[1] who demonstrated that elevated inflammatory biomarkers are closely linked with multimorbidity and biologic aging, reinforcing the role of inflammation as a shared pathophysiological pathway across multiple conditions.

In the current study, IL-6 emerged as the strongest predictor of multimorbidity, followed by hs-CRP. This aligns with Cheong et al,[2] who showed that inflammatory and metabolic markers significantly predict both incidence and progression of multimorbidity as well as mortality risk in aging populations. Likewise, Ornago et al,[3] identified IL-6 and CRP as part of a core biomarker signature distinguishing multimorbid individuals from healthy aging populations, suggesting that inflammatory dysregulation is not only associated with disease presence but also with disease complexity and clustering.

The graded increase in inflammatory markers with higher disease burden observed in this study is consistent with longitudinal findings from Botoseneanu et al,[4] who reported that inflammation and glycemic dysregulation jointly contribute to functional decline in multimorbid individuals. Our findings further extend this evidence by demonstrating a clear dose–response relationship between IL-6 levels and number of chronic conditions, supporting a progressive inflammatory escalation model of multimorbidity.

In the Indian context, the high prevalence of multimorbidity observed in our cohort is consistent with population-based evidence reported by Pattanaik et al,[5] who demonstrated a substantial burden of chronic disease clustering among older adults in India. These findings highlight the growing public health challenge of multimorbidity in low- and middle-income countries, where health systems are primarily designed for single-disease management rather than integrated care.

The present study also aligns with systematic evidence synthesized by Zazzara et al,[6] who identified inflammatory biomarkers as among the most consistently reported biological indicators of multimorbidity across diverse populations. Similarly, Friedman and Shorey,[8] emphasized inflammation as a central mechanism linking multimorbidity with disability, suggesting that inflammatory dysregulation contributes not only to disease coexistence but also to functional impairment.

Furthermore, our findings are supported by Vetrano et al,[7] who demonstrated a strong association between frailty and multimorbidity, with inflammation acting as a key shared biological substrate. This reinforces the interconnected nature of frailty, aging, and multimorbidity. Additional evidence from Gaylord et al,[9] highlights that inflammatory biomarkers represent stable indicators of biological aging trajectories, further supporting their relevance in multimorbidity research.

The predictive performance of IL-6 observed in our study is also consistent with population-based findings by Zhao et al,[14] who reported significant associations between elevated IL-6 levels and adverse brain health outcomes, suggesting that systemic inflammation contributes to multi-organ vulnerability. Similarly, Pan and Ma,[11] demonstrated the clinical relevance of inflammatory markers in frailty, further strengthening the translational significance of our findings.

Mechanistically, the synergistic elevation of inflammatory markers observed in multimorbidity may reflect persistent immune activation, oxidative stress, and endothelial dysfunction triggered by coexisting metabolic and chronic conditions. This is supported by Shin,[12] who reported synergistic inflammatory amplification in patients with coexisting diabetes and periodontitis, indicating that multimorbidity may further intensify systemic inflammatory burden. Additionally, Guo et al,[13] demonstrated that lifestyle factors significantly influence circulating immune markers, suggesting that modifiable behavioral determinants may partially mediate inflammation-driven multimorbidity.

This study has certain limitations. Its cross-sectional design precludes causal inference between inflammatory biomarkers and multimorbidity. The reliance on single-time biomarker measurements may not capture temporal variations in inflammatory status. Additionally, residual confounding due to unmeasured variables such as dietary patterns, genetic predisposition, and environmental exposures cannot be excluded. Finally, as the study was conducted in a single tertiary care setting, generalizability to the broader population may be limited.

Overall, the findings highlight systemic inflammation—particularly IL-6 and hs-CRP—as central biological correlates of multimorbidity, supporting their potential role as clinically relevant biomarkers for early risk stratification and integrated disease management strategies in patients with NCDs.

CONCLUSION

This study demonstrates a significant and independent association between systemic inflammatory biomarkers and multimorbidity among patients with non-communicable diseases. Elevated levels of hs-CRP, IL-6, TNF-α, fibrinogen, NLR, and PLR were strongly linked with increased multimorbidity burden, with IL-6 emerging as the most robust predictor. The findings support the hypothesis that chronic low-grade systemic inflammation is a key shared biological mechanism underlying the clustering of chronic diseases. The observed dose–response relationship between inflammatory markers and number of comorbid conditions further reinforces the role of inflammation in disease progression and complexity.

From a clinical perspective, routinely available inflammatory biomarkers may serve as valuable tools for early risk stratification, prognostic assessment, and integrated management of patients with multiple chronic conditions. Incorporating inflammatory profiling into routine clinical evaluation may help identify high-risk

individuals and support more personalized, preventive healthcare strategies.

Future longitudinal and multi-center studies are warranted to establish causal pathways and explore whether targeted anti-inflammatory interventions can reduce the development or progression of multimorbidity.

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