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Association Between Inflammatory Biomarkers and Disease Severity in Patients with Chronic Medical Conditions: A Cross-Sectional Study from a Tertiary Care Hospital in South India

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ABSTRACT: ***Background:*** Chronic medical conditions are increasingly recognized as states of persistent low-grade systemic inflammation, with biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and ferritin implicated in disease progression and severity. Data from Indian tertiary care settings, particularly from South India, remain limited. ***Objective:*** To evaluate the association between circulating levels of CRP, IL-6, and ferritin and clinical indices of disease severity in patients with selected chronic medical conditions (type 2 diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and rheumatoid arthritis).

Methods: A cross-sectional observational study was conducted over seven months (November 2021 to May 2022) in a tertiary care hospital in South India. Thirty adult patients with established chronic medical conditions were recruited. Severity was graded using condition-specific validated tools. Serum CRP, IL-6, and ferritin were measured by standardized immunoassays. Associations were tested using Spearman's correlation and multivariable linear regression.

Results: Median (IQR) biomarker levels were CRP 8.4 (4.1–18.2) mg/L, IL-6 18.5 (9.2–42.7) pg/mL, and ferritin 186 (98–312) ng/mL. All three biomarkers correlated positively with severity scores (CRP: $\rho = 0.68$, $p < 0.001$; IL-6: $\rho = 0.74$, $p < 0.001$; ferritin: $\rho = 0.52$, $p = 0.003$). In adjusted analysis, IL-6 remained independently associated with severity ($\beta = 0.41$, $p = 0.006$). ***Conclusion:*** Inflammatory biomarkers, particularly IL-6, are significantly associated with disease severity across diverse chronic medical conditions in this South Indian cohort. These markers may aid in severity stratification, though larger longitudinal studies are warranted.

Keywords: Inflammatory biomarkers; C-reactive protein; Interleukin-6; Ferritin; Chronic disease; Disease severity; India

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INTRODUCTION

Chronic medical conditions including type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis (RA) constitute a major and growing burden on health systems in India and worldwide. A unifying feature of many of these conditions is chronic low-grade systemic inflammation, which contributes not only to disease progression but also to the development of complications and multimorbidity [1,2]. Unlike acute inflammation, this persistent inflammatory state is characterised by modest but sustained elevations in circulating cytokines and acute-phase proteins, which can be measured in routine clinical laboratory settings.

C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to interleukin-6 (IL-6), is the most widely studied inflammatory biomarker in chronic disease. Elevated high-sensitivity CRP (hs-CRP) has been consistently associated with the presence and severity of T2DM, cardiovascular disease, CKD, and non-alcoholic fatty liver disease in Indian populations [3-5]. IL-6, a pleiotropic pro-inflammatory cytokine, occupies a central position in the inflammatory cascade, driving hepatic CRP production while also exerting local tissue effects that promote insulin resistance, endothelial dysfunction, and fibrosis [6,7]. Ferritin, traditionally regarded as an iron-storage protein, is now recognised as an acute-phase reactant that reflects systemic inflammatory burden and has been linked to adverse outcomes in several chronic conditions [8].

Despite the biological plausibility of these associations, evidence from South India a region with a distinct demographic and cardiometabolic risk profile remains sparse. Most published Indian studies have focused on a single disease entity, limiting the generalisability of findings across the broader spectrum of chronic medical conditions encountered in tertiary care practice. Furthermore, few studies have simultaneously examined multiple biomarkers and their relative contributions to severity, which is essential for identifying the most informative marker for clinical use.

The present study was therefore designed to address this gap by evaluating the association between three accessible inflammatory biomarkers CRP, IL-6, and ferritin and validated indices of disease severity in a cohort of patients with diverse chronic medical conditions attending a tertiary care hospital in South India. By examining these relationships across multiple conditions rather than within a single disease silo, the study aims to provide pragmatic insights relevant to the integrated management of chronic disease in resource-constrained settings.

OBJECTIVE

The primary objective of this study was to determine the association between circulating levels of inflammatory biomarkers (CRP, IL-6, and ferritin) and disease severity in adult patients with chronic medical conditions specifically T2DM, CKD, COPD, and RA presenting to a tertiary care hospital in South India. Severity was assessed using validated, condition-specific instruments: glycaemic control (HbA1c) and complication burden for T2DM, estimated glomerular filtration rate (eGFR) for CKD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grading for COPD, and Disease Activity Score-28 (DAS28) for RA.

The secondary objective was to compare the relative strength of association of each biomarker with severity across the pooled cohort and to explore whether any biomarker demonstrated an independent relationship with severity after adjustment for age, sex, body mass index (BMI), and disease duration. Identifying a parsimonious set of biomarkers that perform consistently across chronic conditions could inform the development of practical severity-stratification tools suitable for use in Indian tertiary care settings.

METHODOLOGY & MATERIALS

This cross-sectional observational study was conducted in the Department of General Medicine and affiliated specialty clinics of a tertiary care hospital in South India over a seven-month period from November 2021 to May 2022. The hospital serves a predominantly urban and peri-urban population and provides both outpatient and inpatient care across medical and surgical specialties. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were: (i) age ≥ 18 years; (ii) established diagnosis of at least one of the following chronic medical conditions T2DM (per American Diabetes Association criteria), CKD (per Kidney Disease: Improving Global Outcomes criteria), COPD (per GOLD criteria), or RA (per American College of Rheumatology/European Alliance of Associations for Rheumatology 2010 criteria); (iii) disease duration ≥ 12 months; and (iv) willingness to provide written informed consent. Exclusion criteria were: (i) acute infection or febrile illness within the preceding four weeks; (ii) current use of immunosuppressive or immunomodulatory therapy (other than disease-modifying anti-rheumatic drugs for RA); (iii) known haematological malignancy or primary haemochromatosis; (iv) pregnancy or lactation; (v) end-stage organ disease with life expectancy < 6 months; and (vi) inability to complete severity assessment due to cognitive or physical impairment.

Data collection procedure: Eligible consecutive patients attending the medicine outpatient department and specialty clinics during the study period were screened. A structured case record form was used to capture demographic data (age, sex, residence, education, socioeconomic status), anthropometric measurements (height, weight, BMI), disease characteristics (type, duration, current medications, comorbidities), and condition-specific severity indices. Severity was operationalized as follows: for T2DM, glycaemic control was categorised as controlled (HbA1c < 7.0%), moderate (7.0–9.0%), or poor (> 9.0%), and complication burden was recorded; for CKD, eGFR was calculated using the CKD-EPI equation and staged according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines; for COPD, post-bronchodilator forced expiratory volume in one second (FEV_1) % predicted was used to assign GOLD grades 1–4; and for RA, DAS28-erythrocyte sedimentation rate (DAS28-ESR) was calculated, with scores > 5.1 indicating high disease activity. A composite severity score was not imposed because the instruments are not directly interchangeable; instead, each condition's validated severity metric was used in condition-specific analyses, and a pooled analysis was conducted using standardized (z-transformed) severity scores within each condition. Venous blood samples (5 mL) were collected in plain and EDTA vacutainers under aseptic precautions. Serum was separated within 2 hours and stored at −80°C until batch analysis. CRP was measured by immunoturbidimetry (normal range: 0–5 mg/L), IL-6 by enzyme-linked immunosorbent assay (normal range: 0–7 pg/mL), and ferritin by chemiluminescent immunoassay (normal range: 23.9–336.2 ng/mL for men; 11–307 ng/mL for women).

Statistical data analysis: Data were entered into Microsoft Excel and analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test. Non-normally distributed variables were summarized as median (interquartile range), and categorical variables as frequency

(percentage). Associations between biomarkers and condition-specific severity scores were assessed using Spearman's rank correlation coefficient. For the pooled analysis, severity scores were standardized within each condition (z-scores) to permit cross-condition comparison. Multivariable linear regression was used to examine the independent association of each biomarker with the standardized severity score, adjusting for age, sex, BMI, and disease duration. Biomarkers were log-transformed where appropriate to approximate normality. A two-sided p-value < 0.05 was considered statistically significant. With a sample size of 30, the study was powered to detect a correlation coefficient of 0.50 at 80% power and $\alpha = 0.05$ (two-tailed); this calculation was performed a priori using G*Power version 3.1.

RESULTS

The study cohort comprised 30 patients (18 men, 12 women) with a median age of 56 (interquartile range [IQR] 48–65) years. The distribution of chronic conditions was: T2DM (n = 12, 40.0%), CKD (n = 9, 30.0%), COPD (n = 6, 20.0%), and RA (n = 3, 10.0%). Median disease duration was 6 (IQR 3–10) years. The median BMI was 24.8 (IQR 22.1–27.6) kg/m². Comorbid hypertension was present in 18 patients (60.0%), and 8 patients (26.7%) had two or more chronic conditions. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1. Baseline demographic and clinical characteristics of the study cohort (N = 30)

Characteristic	Value
Age, years, median (IQR)	56 (48–65)
Male sex, n (%)	18 (60.0)
BMI, kg/m², median (IQR)	24.8 (22.1–27.6)
Disease duration, years, median (IQR)	6 (3–10)
Chronic condition, n (%)	
Type 2 diabetes mellitus	12 (40.0)
Chronic kidney disease	9 (30.0)
COPD	6 (20.0)
Rheumatoid arthritis	3 (10.0)
Comorbid hypertension, n (%)	18 (60.0)
≥ 2 chronic conditions, n (%)	8 (26.7)
Haemoglobin, g/dL, median (IQR)	12.1 (10.8–13.4)
Serum albumin, g/dL, median (IQR)	3.8 (3.4–4.2)
eGFR, mL/min/1.73 m², median (IQR)	62 (38–88)

Biomarker levels were elevated relative to reference ranges in a substantial proportion of participants. Median CRP was 8.4 (IQR 4.1–18.2) mg/L, with 21 patients (70.0%) having CRP > 5 mg/L. Median IL-6 was 18.5 (IQR 9.2–42.7) pg/mL, with 24 patients (80.0%) exceeding 7 pg/mL. Median ferritin was 186 (IQR 98–312) ng/mL, and 9 patients (30.0%) had levels above the sex-specific upper limit of normal. Biomarker distributions by primary condition are presented in Table 2.

Table 2. Inflammatory biomarker levels by primary chronic condition

Condition (n)	CRP, mg/L, median (IQR)	IL-6, pg/mL, median (IQR)	Ferritin, ng/mL, median (IQR)
T2DM (12)	7.2 (3.8–14.5)	16.4 (8.1–35.2)	172 (105–284)
CKD (9)	12.6 (6.4–24.8)	28.7 (14.3–56.1)	214 (128–368)
COPD (6)	9.8 (5.1–17.3)	22.5 (11.8–44.6)	198 (112–302)
RA (3)	5.4 (2.9–11.7)	14.2 (6.8–26.5)	148 (92–231)
Overall (30)	8.4 (4.1–18.2)	18.5 (9.2–42.7)	186 (98–312)

All three biomarkers demonstrated statistically significant positive correlations with condition-specific severity scores. CRP showed a strong correlation ($\rho = 0.68$, $p < 0.001$), IL-6 showed the strongest correlation ($\rho = 0.74$, $p < 0.001$), and ferritin showed a moderate correlation ($\rho = 0.52$, $p = 0.003$). In the pooled analysis using standardized severity z-scores, the pattern was consistent (CRP: $\rho = 0.65$, $p < 0.001$; IL-6: $\rho = 0.72$, $p < 0.001$; ferritin: $\rho = 0.49$, $p = 0.006$). In multivariable linear regression adjusted for age, sex, BMI, and disease duration, log-transformed IL-6 remained independently associated with the standardized severity score ($\beta = 0.41$, 95% CI 0.13–0.69, $p = 0.006$),

whereas CRP (β = 0.22, 95% CI −0.08 to 0.52, p = 0.142) and ferritin (β = 0.14, 95% CI −0.12 to 0.40, p = 0.281) did not retain statistical significance. The regression model explained 58.3% of the variance in severity (adjusted R^2 = 0.583, F(7,22) = 4.87, p = 0.002). Correlation and regression findings are summarized in Table 3.

Table 3. Correlation and adjusted association of inflammatory biomarkers with disease severity

Biomarker	Spearman's ρ (condition-specific severity)	p-value	Adjusted β (95% CI) for standardized severity*	p-value
CRP (log)	0.68	< 0.001	0.22 (−0.08 to 0.52)	0.142
IL-6 (log)	0.74	< 0.001	0.41 (0.13–0.69)	0.006
Ferritin (log)	0.52	0.003	0.14 (−0.12 to 0.40)	0.281

**Adjusted for age, sex, BMI, and disease duration; model adjusted R^2 = 0.583.*

DISCUSSION

This study demonstrates that circulating levels of CRP, IL-6, and ferritin are elevated in patients with diverse chronic medical conditions attending a South Indian tertiary care hospital and that all three biomarkers correlate positively with validated indices of disease severity. Notably, IL-6 emerged as the biomarker most strongly and independently associated with severity after adjustment for potential confounders. These findings align with the growing recognition of chronic low-grade inflammation as a shared pathogenic pathway across cardiometabolic, renal, respiratory, and autoimmune diseases, and they extend previous single-disease observations from India to a clinically heterogeneous cohort [2,5,9].

The strong correlation between IL-6 and severity is biologically coherent. IL-6 is a proximal cytokine that orchestrates the hepatic acute-phase response, including CRP synthesis, while also exerting tissue-level effects that drive insulin resistance, glomerular injury, airway remodelling, and synovial inflammation [6,7]. In T2DM, IL-6 has been shown to impair insulin signalling and predict glycaemic deterioration; in CKD, elevated IL-6 is associated with faster eGFR decline and cardiovascular events; in COPD, IL-6 correlates with airflow limitation and exacerbation frequency; and in RA, IL-6 is a validated therapeutic target and a marker of disease activity [7,11,13]. The present finding that IL-6 outperformed CRP in adjusted models is consistent with the cytokine's upstream position in the inflammatory cascade and suggests that IL-6 may capture inflammatory burden more sensitively than downstream acute-phase proteins. Similar observations have been reported in Indian cohorts, including a study of patients with multi-organ involvement in which IL-6 demonstrated the strongest correlation with the number of affected organs [13].

Ferritin, although significantly correlated with severity in unadjusted analysis, did not retain independence in the multivariable model. This may reflect confounding by anaemia of chronic disease, which is highly prevalent in CKD and RA, and by the acute-phase behaviour of ferritin, which can fluctuate with transient inflammatory stimuli [8,14]. Nonetheless, the moderate correlation observed is clinically meaningful and supports the inclusion of ferritin in a multi-marker panel rather than as a standalone severity indicator. CRP, while strongly correlated in univariate analysis, also lost statistical significance after adjustment, possibly owing to collinearity with IL-6 and the modest sample size. The persistence of IL-6 as an independent predictor despite these constraints strengthens the robustness of the finding.

These results have several implications. First, they support the feasibility of measuring a small panel of inflammatory biomarkers particularly IL-6 to complement condition-specific severity assessment in resource-limited tertiary care settings. Second, they underscore the value of a cross-disease approach: rather than treating inflammation as a disease-specific epiphenomenon, clinicians may benefit from viewing it as a shared therapeutic target, with implications for anti-inflammatory strategies that transcend traditional disease boundaries. Third, the findings contribute much-needed South Indian data to a literature dominated by North Indian and Western cohorts, highlighting the importance of regional validation of biomarker–severity relationships. However, the study also reinforces that no single biomarker is sufficient; the moderate-to-strong correlations observed indicate that inflammatory markers should be interpreted alongside clinical severity tools rather than as replacements for them [9,15].

LIMITATIONS OF THE STUDY

This study has several limitations that warrant consideration. The sample size of 30 is modest, which limits precision and precludes robust subgroup analyses by individual chronic condition; the study was powered to detect a correlation of 0.50, and smaller but clinically relevant associations may have been missed. The cross-sectional design cannot establish temporality or causality whether inflammation drives severity, severity drives inflammation, or both

reflect a common upstream process remains unresolved. The pooled analysis relied on standardized severity scores derived from different instruments, which, while pragmatic, may not fully capture the nuances of each condition. Single-timepoint biomarker measurements may be influenced by transient fluctuations, and although acute infection was excluded, subclinical inflammatory stimuli cannot be entirely ruled out. The cohort was drawn from a single tertiary care centre, and referral bias may have enriched the sample with more severe cases, limiting generalisability to primary care or community populations. Finally, important confounders such as medication adherence, physical activity, dietary patterns, and socioeconomic factors were not comprehensively captured, and residual confounding therefore remains possible.

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CONCLUSION

In this cross-sectional study of 30 patients with chronic medical conditions attending a tertiary care hospital in South India, circulating levels of CRP, IL-6, and ferritin were elevated and correlated significantly with condition-specific indices of disease severity. IL-6 demonstrated the strongest and most consistent association, remaining an independent predictor of severity after adjustment for age, sex, BMI, and disease duration. These findings support the utility of inflammatory biomarkers particularly IL-6 as accessible adjuncts to clinical severity assessment in chronic disease management and reinforce the concept of chronic low-grade inflammation as a transdiagnostic pathogenic mechanism relevant to Indian patients.

From a clinical and research perspective, the results argue for the incorporation of a brief inflammatory biomarker panel into routine assessment protocols for chronic diseases in tertiary care, while cautioning against reliance on any single marker in isolation. Larger, longitudinal, multi-centre studies with adequate power for condition-specific analyses are needed to validate these findings, establish clinically meaningful cut-offs, and determine whether serial monitoring of IL-6 or a multi-marker score can predict disease progression, treatment response, and adverse outcomes. Such evidence would inform the development of pragmatic, inflammation-informed strategies for chronic disease management in South India and comparable settings.

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