E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/15.01.107

Research Article

High-Sensitivity C - reactive protein As an Independent Predictor of Cardiovascular Complications in Chronic Obstructive Pulmonary Disease

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Received: 25.03.25, Revised: 23.04.25, Accepted: 13.05.25

ABSTRACT
Background: Systemic low-grade inflammation is believed to link chronic obstructive pulmonary disease (COPD) with excess cardiovascular (CV) morbidity. High-sensitivity C-reactive protein (hsCRP) is an inexpensive, stable biomarker of this inflammatory state, yet its prospective prognostic value in COPD is uncertain.
Objective: To determine whether baseline hsCRP independently predicts incident composite CV events over 12 months in clinically stable COPD and to consider implications for emerging anti-inflammatory pharmacology and drug-safety monitoring.
Methods: In a prespecified sub-study of our echocardiographic cohort, 126 consecutive out-patients (June 2016 – May 2019) with post-bronchodilator $FEV_1/FVC < 0.70$ and ≥ 6 weeks clinical stability were followed for 12 months. Baseline hsCRP was measured by immunonephelometry (Siemens BN II) and dichotomised at 3 mg L^{-1}. The primary end-point was first occurrence of composite CV events (non-fatal myocardial infarction, stroke/TIA, hospitalised heart failure or CV death) adjudicated by blinded cardiologists. Multivariable Cox regression adjusted for age, sex, pack-years, GOLD grade, hypertension, diabetes and ischaemic heart disease.
Results: Median hsCRP was 3.8 mg L^{-1} (IQR 2.1–6.2); 54 % of patients exceeded 3 mg L^{-1}. Twenty-six events occurred (event rate 21 %): heart-failure hospitalisation 12, non-fatal MI 7, stroke/TIA 4, CV death 3. Event incidence was 31 % in the high-hsCRP group versus 9 % when ≤ 3 mg L^{-1} ($p = 0.002$). hsCRP > 3 mg L^{-1} doubled risk (adjusted HR 2.12, 95 % CI 1.01–4.46; $p = 0.047$). Adding hsCRP to a clinical model improved the C-statistic from 0.70 to 0.77 ($p = 0.03$) and net re-classification index by 0.21.
Conclusions: Baseline hsCRP > 3 mg L^{-1} independently predicts short-term CV events in COPD. Routine inflammatory profiling could refine risk stratification and guide inclusion in anti-inflammatory drug trials.

Keywords: COPD; Hscrp; Cardiovascular Risk; Inflammation; Colchicine; Pharmacovigilance.

INTRODUCTION

Cardiovascular disease accounts for almost half of the excess mortality observed in chronic obstructive pulmonary disease (COPD) (1). A compelling mechanistic link is systemic low-grade inflammation: interleukin-6 released from activated pulmonary macrophages stimulates hepatic synthesis of C-reactive protein (CRP), while circulating CRP amplifies complement activation and endothelial dysfunction (2). In the general population, high-sensitivity CRP (hsCRP) ≥ 3 mg L^{-1} identifies individuals at "high cardiovascular risk" (3) and marks residual inflammatory risk despite optimal lipid-lowering therapy (4). Whether the same threshold prospectively predicts cardiovascular (CV) events in COPD—independently of airflow limitation—has been little explored, particularly in South-Asian cohorts.

The question is timely. Contemporary COPD management frameworks (GOLD 2024) emphasise comorbidity assessment but provide limited guidance on inflammatory biomarkers (5). Meanwhile, anti-inflammatory cardio-metabolic strategies—including sodium–glucose cotransporter-2 inhibitors, low-dose colchicine and interleukin-1 or interleukin-6 blockade—are advancing toward widespread clinical use. Regulatory agencies now expect

biomarker-guided pharmacovigilance to balance efficacy with safety. Establishing hsCRP as a COPD-specific CV predictor could therefore improve clinical risk stratification and optimise trial design.

Against this background, we prospectively examined whether baseline hsCRP predicts 12-month composite CV events in clinically stable COPD after adjustment for traditional risk factors, smoking burden and lung-function severity.

MATERIALS AND METHODS

Design and Participants

This prospective observational study was nested within our 2016–2019 COPD echocardiography cohort (ethical approval GMCH/Resp/2016-19). Consecutive out-patients aged ≥ 40 years with spirometric COPD (post-bronchodilator $FEV_1/FVC < 0.70$) and clinical stability of at least six weeks were eligible. Exclusion criteria included systemic inflammatory or malignant disease, recent acute coronary syndrome, chronic dialysis and glucocorticoid therapy > 5 mg prednisolone-equivalent daily.

Baseline Assessment

Detailed history, GOLD 2024 spirometric grade (5), modified Medical Research Council (mMRC) dyspnoea score, comorbidities and medications were recorded. Fasting venous hsCRP was quantified by immunonephelometry (analytical imprecision < 5 %). Echocardiographic indices of diastolic function and pulmonary pressures were collected but excluded from the primary prediction model to prevent over-adjustment.

Outcome Definition

The primary end-point was time to first composite CV event—non-fatal myocardial infarction, stroke/transient ischaemic attack, hospitalised heart failure (HFpEF or HFrEF) or CV death— during 12-month follow-up. Two cardiologists, blinded to hsCRP status, adjudicated events against standard criteria.

Statistical Analysis

Patients were stratified by hsCRP ≤ 3 versus > 3 mg L^{-1}. Survival free of events was estimated by Kaplan–Meier and compared with the log-rank test. Cox proportional-hazards models adjusted for age, sex, pack-years, GOLD grade, hypertension, diabetes and prior ischaemic heart disease. Model performance was evaluated by change in Harrell's C-statistic and category-less net- reclassification index using methods of Harrell (6). Analyses used SPSS v28; two-sided $p < 0.05$ was considered significant.

RESULTS

Table 1: Baseline Characteristics According to Hscrp

Variable	hsCRP ≤ 3 mg L^{-1} (n = 58)	RP > 3 mg L^{-1} (n = 68)	p
Age, y	63 ± 8	66 ± 8	0.04
Male, %	76	78	0.82
GOLD 3–4, %	23	46	0.01
Hypertension, %	36	54	0.04
Diabetes, %	17	29	0.12
Prior ischaemic heart disease, %	26	34	0.34
PaO_2, mm Hg	69 ± 8	64 ± 9	0.002

Table 2: Cox Multivariable Predictors of 12-Month Composite CV Events

Predictor	Adjusted HR (95 % CI)	p
hsCRP > 3 mg L^{-1}	**2.12 (1.01–4.46)**	0.047
GOLD grade 3–4	1.89 (1.00–3.57)	0.049
Hypertension	1.74 (1.03–2.93)	0.040
Age (per 5 y)	1.12 (0.91–1.37)	0.29
Diabetes	1.31 (0.70–2.47)	0.40
Prior IHD	1.27 (0.69–2.35)	0.44

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DISCUSSION

In this prospective South-Asian cohort, baseline hsCRP > 3 mg L^{-1} doubled the 12-month risk of major cardiovascular events in COPD, independent of age, lung-function severity and conventional risk factors. The absolute 31 % event rate in the high-hsCRP stratum underscores the inflammatory burden of COPD and approximates the 28 % one-year heart-failure admission rate reported in the ESC-HF registry for COPD–HFpEF overlap (7,8). Our data extend earlier cross- sectional associations (2) by demonstrating incremental prognostic utility (ΔC = 0.07; NRI = 0.21) and support hsCRP as a practical risk-enrichment biomarker. Therapeutic implications are immediate. Low-dose colchicine lowered CV events in COLCOT and LoDoCo-2 (9, 10) and is now entering COPD-specific trials that require elevated hsCRP for enrolment. Ziltivekimab, an IL-6 ligand antibody, achieved 77 % hsCRP reduction and is advancing to phase III cardiovascular outcome studies with planned COPD sub-analyses (11). Dual CCR2/CCR5 inhibition with cenicriviroc also attenuates systemic CRP but mandates stringent pulmonary safety monitoring (12). By identifying patients at highest inflammatory risk, hsCRP may streamline recruitment and enable targeted pharmacovigilance.

Strengths of our study include prospective design, blinded event adjudication and multivariable adjustment. Limitations comprise single-centre scope, modest sample size, a 12-month horizon and absence of serial hsCRP measurements, precluding assessment of on-therapy kinetics. Nonetheless, the independent signal observed warrants validation in larger multicentre cohorts with broader biomarker panels and longer follow-up.

CONCLUSION

An hsCRP concentration > 3 mg L^{-1} independently identifies COPD patients at two-fold higher short-term cardiovascular risk. Incorporating hsCRP into routine COPD assessment could refine referral thresholds, guide inclusion in anti-inflammatory drug trials and sharpen post-marketing pharmacovigilance.

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