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Population-Scale Plasma Proteomics Reveals Systemic Inflammatory Signatures Associated With Chronic Rhinosinusitis

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To the Editor,

Chronic rhinosinusitis (CRS) is a common inflammatory airway disease, but scalable blood-based biomarkers remain limited [1]. Tissue transcriptomic and proteomic studies using nasal tissue or mucus samples have defined local inflammatory programmes in CRS, yet whether these are detectable systemically at population scale is unclear [2, 3]. Conventional blood biomarkers such as peripheral eosinophil counts and serum periostin capture only a limited portion of the heterogeneous systemic inflammatory response [4]. We analysed UK Biobank Pharma Proteomics Project (UKB-PPP) data to identify circulating proteins and enriched immune pathways associated with CRS and to evaluate how these signatures relate to existing blood-based markers [5].

We analysed Olink Explore 3072 plasma proteomics in 44,344 UKB-PPP participants (725 CRS; 43,619 controls). CRS was defined by hospital ICD-10 codes J32x (chronic sinusitis) or J33x (nasal polyps [NPs]). Ordinary least-squares regression was performed for each of 2923 proteins and 61 routine blood markers, adjusting for age, sex, body mass index, smoking, comorbidities (asthma and atopic dermatitis), systemic steroid use and batch. Significance was determined at false discovery rate (FDR) < 0.01. Pre-ranked pathway enrichment analysis used Gene Ontology Biological Process (GO:BP) gene sets. As secondary analyses, five supervised classification algorithms—penalised logistic regression, random forest, gradient boosting, extreme gradient boosting (XGBoost) and support vector machine (SVM) with a radial basis function kernel—were trained on the differentially expressed features together with clinical covariates and compared with and without proteomic features. Detailed methods and additional results are available in the online repository (see Data Availability Statement).

We identified 46 differentially expressed proteins (45 upregulated, 1 downregulated), with a strongly asymmetric expression pattern in the CRS group (Figure 1A). The upregulated proteins were dominated by markers of tissue remodelling and canonical type 2 (T2) inflammation—particularly eosinophil-related mediators—such as matrix metalloproteinase 10 (MMP10), proteoglycan 2 (PRG2), PRG3, Charcot-Leyden crystal protein (CLC), cystatin SN (CST1), periostin (POSTN), eotaxin-3 (CCL26) and eosinophil cationic protein (RNASE3). Additional upregulated proteins included mucosal and epithelial markers such as WAP four-disulfide core domain protein 2 (WFDC2) and proline-rich protein 4 (PRR4), the proinflammatory cytokine IL-6 and immune-regulatory molecules including Sialic acid-binding Ig-like lectin 8 (SIGLEC8), IL2RA, CD40, CD80 and CCL19. The only significantly downregulated protein was transmembrane protease serine 5 (TMPRSS5). Among routine blood markers, eosinophil count and percentage exhibited the most pronounced elevations in patients with CRS compared with controls, followed by white blood cell count, platelet count and alanine aminotransferase (Figure 1B). Phenotype-stratified analyses showed that CRS with NPs (CRSwNP; $n = 402$) retained the proteomic signature, whereas CRS without NPs ($n = 323$) showed no significant proteins, indicating that the systemic signal is driven primarily by the CRSwNP–associated inflammatory axis.

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Summary

- CRS showed systemic plasma proteomic signals of eosinophilic inflammation and tissue remodelling.
- Plasma proteomics captures non-redundant biological information beyond routine blood markers.

In GO:BP pathway enrichment analysis, the most strongly enriched pathway was extracellular matrix (ECM) disassembly (NES = 1.78, FDR = 0.04), consistent with the proteomic evidence of tissue remodelling. This was followed by regulation of peptidyl-tyrosine phosphorylation (NES = 1.54, FDR = 0.06), leukocyte proliferation and its regulation (NES = 1.41–1.43, FDR = 0.05–0.06) and regulation of immune effector process (NES = 1.38, FDR = 0.06), collectively indicating broad activation of leukocyte signalling cascades.

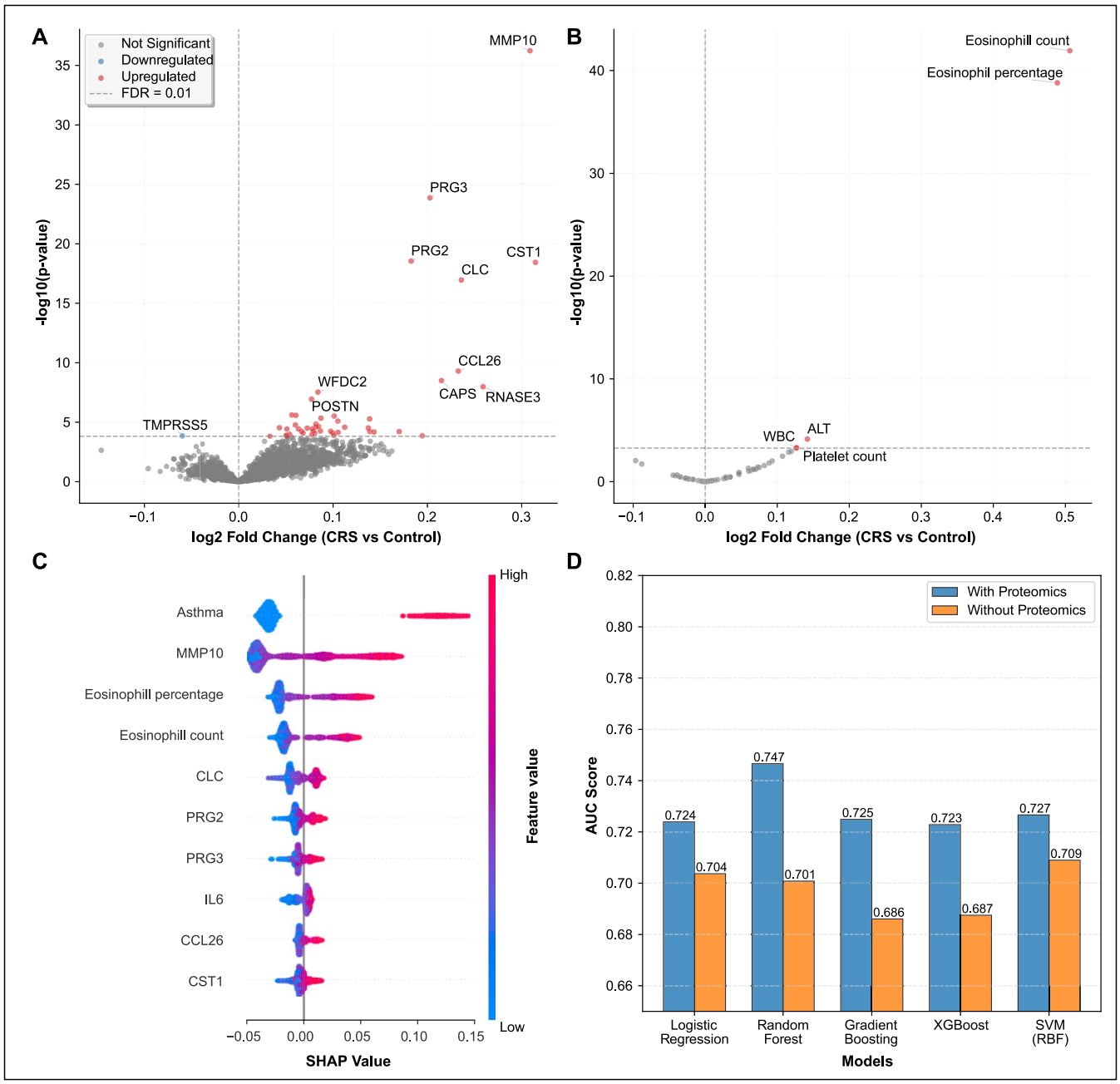

FIGURE 1 | Systemic proteomic signatures and exploratory classification analysis of CRS. (A) Plasma proteins ($n = 2919$) and (B) routine blood cell and chemistry traits ($n = 61$) comparing participants with CRS to control individuals. The x-axis shows log2 fold change, and the y-axis shows the negative log10 adjusted p-value. Red dots indicate significantly upregulated proteins, blue dots indicate significantly downregulated proteins and grey dots represent non-significant proteins. (C) SHAP summary plot illustrating the direction and magnitude of feature impact on model predictions in the random forest model. Each dot represents a participant; colour indicates feature value (red = high, blue = low). (D) Bar charts comparing the test-set AUC of baseline models (routine blood markers and clinical covariates only) versus full models integrating proteomic data across five machine learning algorithms.

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In exploratory classification analyses, the random forest classifier achieved the highest performance as indicated by the area under the receiver operating characteristic curve (ROC-AUC; 0.747). SHAP analysis revealed that comorbid asthma was the single strongest predictor; as a binary feature, its presence exerted a large positive contribution to CRS prediction, followed by MMP10 (Figure 1C). Routine blood markers of T2 inflammation, specifically the eosinophil percentage and count, were also highly ranked. Among proteomic features, CLC, PRG2, PRG3, CST1 and CCL26 were the major contributors, indicating a predominantly T2 inflammatory profile. Despite asthma being the top-ranked feature, sensitivity analyses restricting the CRS group to patients without asthma ($n = 496$) showed that the core proteomic signature remained largely preserved, indicating that the identified systemic signal is not primarily explained by comorbid asthma alone. A parallel comparison of asthma patients without CRS ($n = 4246$) versus controls further showed a distinct proteomic profile, in which MMP10 and other CRS-defining proteins (CST1, POSTN, CCL26) were not prominent, suggesting that the CRS signature is unlikely to be explained by comorbid asthma alone. Adding proteomic features consistently improved discrimination across all five algorithms versus baselines using only selected blood markers and clinical covariates (Figure 1D).

This study defines a systemic proteomic fingerprint of CRS in a population-based cohort. The dominant signals reflect eosinophilic inflammation and ECM remodelling, consistent with known CRS pathobiology [6]. MMP10 and periostin, among the most upregulated proteins, align with the periostin–MMP axis implicated in NP formation [7]. Notably, cystatin SN, previously reported to be elevated in nasal secretions of patients with CRS, was also upregulated in plasma, suggesting that circulating levels may reflect the local inflammatory microenvironment or broader systemic production [8, 9]. While the model's effectiveness is still more appropriate for enhancing risk assessment rather than serving as a standalone diagnostic tool, the steady increase in AUC with the inclusion of proteomic features suggests that plasma proteomics provides unique information that complements standard clinical measures [10]. Limitations include the use of ICD-10 codes rather than symptom-based or endoscopic criteria, precluding endotype-specific analysis and the lack of external validation. Nevertheless, these findings extend tissue-based understanding of CRS to a blood-based, population-scale setting, providing a framework for future studies integrating molecular and clinical phenotyping.

Author Contributions

Dachan Kim: Study design, data collection, data analysis, writing original draft, reviewing and revising the manuscript. Hyung-Ju Cho: Study design, reviewing and revising the manuscript. Chang-Hoon Kim: Study design, reviewing and revising the manuscript. Min-Seok Rha: Study design, data collection, data analysis, funding acquisition, review and revision of the manuscript.

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Ethics Statement

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB 4–2025-1529). Informed consent was waived due to the study's retrospective nature, with data anonymised according to IRB-approved protocols.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data analysed in this study are available through the UK Biobank resource to eligible researchers, subject to application and approval by UK Biobank. Detailed supplementary methods, additional results, supplementary tables, and supplementary figures are available at https://doi.org/10.5281/zenodo.19583286.

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