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Asthma and Lower Airway Disease

Proteomic and Transcriptomic Signatures of Poor Asthma Symptom Control in the U-BIOPRED Cohort

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ABSTRACT

Background: Controlling asthma symptoms remains challenging. Understanding its molecular mechanisms may provide new insights into asthma pathophysiology. We explored the associations between the transcriptome and proteome in blood and sputum and asthma symptom control.

Methods: This cross-sectional study included asthmatic and healthy adults from the U-BIOPRED cohort. Uncontrolled symptoms were defined as a mean ≥1.5 points on the 5-item asthma control questionnaire. Stability selection using LASSO logistic regression identified genes/proteins associated with symptom control, followed by logistic regression. Analyses were adjusted for age, sex, age of asthma onset, smoking status, body mass index (BMI), FEV_1% predicted, exacerbation history, anti-IgE therapy and urinary steroid levels. The selected variables were compared with healthy controls using linear regression, adjusted for age, sex, BMI, smoking status and urinary steroid levels.

Results: Four serum proteins were selected based on data from 415 asthmatics (median age 52 [41, 61] years; 59% female; 64% uncontrolled). Higher TWEAKR/TNFRSF12A [OR 2.25 (95% CI 1.15, 4.77)] and MBL/MBP-C [1.6 (1.07, 2.42)] levels increased the odds of uncontrolled symptoms, whereas higher MK08/MAPK8 [0.48 (0.29, 0.76)] and CD5L [0.59 (0.41, 0.82)] levels decreased the odds. CD5L levels were significantly lower in severe asthma than in healthy controls [estimate −0.23 (95% CI −0.41, −0.04)]. No associations were found between symptom control and the sputum proteome ($N=90$) or the sputum ($N=96$) and blood ($N=360$) transcriptomes.

Conclusion: Four serum proteins distinguished asthmatics with uncontrolled from controlled symptoms. CD5L levels were also lower in asthmatics with severe disease than in healthy controls, warranting further investigation into its potential therapeutic value.

Other Consortium Study Group members are shown in the Acknowledgements section.

1 | Introduction

Poorly controlled asthma impairs the health-related quality of life and productivity of those affected, exposes them to the side effects of oral corticosteroids (OCS) and increases the risk of emergency room visits, hospitalisations and premature death, contributing significantly to the economic and social burden of the disease [1–4]. Therefore, controlling symptoms and minimising the risk of exacerbations without medication side effects are important goals of asthma management [4].

Incorrect inhaler technique, poor medication adherence, over-reliance on short-acting β_2-agonists, comorbidities, psychosocial factors, or persistent exposure to environmental triggers are common risk factors for poor asthma control [1, 4–9]. Nevertheless, a considerable number of individuals continue to suffer from persistent symptoms and/or recurrent exacerbations even with maximal pharmacological therapy and mitigation of triggering factors [4, 10].

The difficulty in achieving asthma control suggests a possible heterogeneity in the biological mechanisms of the disease [11]. Although some research has investigated the relationship between omics data and asthma control, most studies have focused on the occurrence of exacerbations [12–15], while few have addressed symptom control [16–18]. Exploring the molecular mechanisms associated with symptom control may provide additional insights into the pathophysiology of asthma and support the discovery of alternative therapeutic pathways to improve its management. This study aimed to investigate whether the transcriptome and proteome from blood and sputum were associated with symptom control in adults with asthma.

2 | Methods

2.1 | Study Design and Participants

Data were obtained from the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) study, which included adults with mild-to-severe asthma, as well as healthy controls [19]. All individuals with asthma in U-BIOPRED had a confirmed diagnosis [19]. Severe asthma was defined as having uncontrolled symptoms and/or frequent exacerbations despite taking high doses of inhaled corticosteroids. Adults with asthma who had experienced a severe exacerbation in the previous month or had changed medication within 4 weeks prior to screening were excluded [19]. Ethics committees from the 16 centres involved in recruitment approved the study, and participants signed an informed consent form before data collection [19].

This cross-sectional study included adults with asthma who had proteomic and/or transcriptomic data available and who had their asthma symptom control assessed at baseline. Healthy controls were included based on the availability of their proteomic and/or transcriptomic data.

2.2 | Clinical Assessment

The main variable analysed in this exploratory study was uncontrolled asthma symptoms, defined as a mean score of 1.5 points or higher on the 5-item Asthma Control Questionnaire (ACQ-5) [20]. The ACQ-5 is a 5-item questionnaire used to assess symptom control, with each item scored on a 7-point Likert scale [21, 22]. The total score is the average of all five items, ranging from 0 to 6, with higher scores indicating worse symptom control [21, 22].

Data collection included sociodemographic, anthropometric and clinical data such as age, sex, age at onset of asthma, body weight and height to compute body mass index (BMI; weight in kilogrammes divided by squared height in metres), smoking status, lung function measured by spirometry, self-reported pharmacological treatment and number of exacerbations in the previous 12 months. Inflammatory markers were also measured and included fraction of exhaled nitric oxide (F_{eNO}), serum total immunoglobulin E (IgE), eosinophil and neutrophil counts in the blood and sputum. OCS use was confirmed by the presence of prednisolone or prednisone, methylprednisolone, 16α-OH-prednisolone, 20β-dihydroprednisolone, or desacetyl deflazacort in urine (> 1 ng/mL detection limit). Further information on the data collection protocol can be found elsewhere [19].

2.3 | Transcriptomics and Proteomics Acquisition, Pre-Processing and Analysis

Blood and sputum samples were collected for proteomic and transcriptomic analyses [19]. Transcriptome analysis was performed on RNA from both samples using the GeneChip HT HG-U133 Plus PM Array Plate (Affymetrix, Santa Clara, CA, USA). Affymetrix data were subjected to quality control and pre-processed with the robust multi-array average method [23]. The probes were mapped to gene symbols using annotation data from the HG-U133 Plus PM Array Plate platform. These annotated probe sets were cross-checked against the National Centre for Biotechnology Information databases (version 16.31.0), and any genes flagged as withdrawn were excluded from the analysis. Probe sets mapping to multiple genes were also excluded. Gene expression was estimated by calculating the mean of the average expression values across probe sets. In total, 20,790 genes were included in the transcriptomic analysis. Proteins from sputum supernatants and serum samples were measured with the SOMAscan proteomic assay and reported in relative fluorescent units. The proteomic analysis included 1129 serum and 1125 sputum proteins. Log2-transformed values of gene expression levels and protein abundance were used.

2.4 | Statistical Analyses

Data were downloaded from the tranSMART data management platform [24] and analysed using R statistical software (version 4.4.0), with a significance level set at 0.05.

Normally distributed variables were presented as mean ± standard deviation. Ordinal and non-normally distributed data were reported as median [1st quartile; 3rd quartile]. The absolute and relative frequencies were reported for categorical variables. The baseline characteristics of adults with controlled and uncontrolled symptoms were compared using independent *t*-tests, Welch's *t*-tests or Mann–Whitney *U*-tests for numerical variables, depending on whether the normality and homogeneity of variance assumptions were validated. Comparisons between adults with mild to moderate asthma, severe asthma and healthy controls were performed using one-way ANOVA or Kruskal–Wallis test, followed by post hoc *t*-tests or Mann–Whitney *U*-tests with Bonferroni correction for numerical variables, based on the assumptions of normality and homogeneity of variance. Categorical variables were compared using Pearson's chi-squared test for both group comparisons.

Associations between the transcriptome and proteome of blood and sputum with asthma symptom control were analysed separately, resulting in four datasets: serum proteome, sputum proteome, blood transcriptome and sputum transcriptome. For each dataset, the analysis workflow consisted of the following steps: (1) feature selection using least absolute shrinkage and selection operator (LASSO) logistic regression within a stability selection framework; (2) hypothesis testing of stably selected features using unpenalised logistic regression to obtain unbiased effect estimates; and (3) comparison of significant features across healthy controls and asthma severity groups using linear regression. If no stable features were identified for a given omics in a biological sample, the analysis ended at step 2.

Stability selection was performed using LASSO logistic regression with the R package 'sharp' [25] to identify expressed genes and proteins consistently associated with uncontrolled asthma symptoms, using controlled asthma symptoms as the reference group. LASSO logistic regression was conducted on 500 subsamples, each comprising 50% of the patients. Subsamples of 50% were chosen following a previous approach [26] and supported by the results of simulation studies [27]. Although Bodinier et al. [27] showed that performance plateaus after 50 subsamples, the number was increased to 500 in this study (the maximal available computational capacity) due to the high dimensionality of the data. For each value of the penalty hyperparameter λ within a grid of 100 values, the model was repeatedly fitted, and the frequency with which each feature was selected across subsamples was recorded. Based on each feature's selection proportion, and for each threshold π, features were classified as stably selected, stably excluded, or unstably selected [27]. The grid values for the selection proportion, π, were bounded between 0.6 and 0.9, as recommended [26]. The penalty hyperparameter, λ, and the selection proportion threshold, π, were calibrated by maximising a stability score, defined as the negative log-likelihood under the hypothesis of equiprobability of selection [27]. Age, sex, age of asthma onset, smoking status (ex-smoker vs. former smoker vs. never), BMI, forced expiratory volume in one second as a percentage of predicted (FEV_1% predicted), number of exacerbations in the previous 12 months (0 vs. ≥1 exacerbations) and detection of urinary steroids (yes vs. no) were added as covariates and not penalised. Anti-IgE therapy (user vs. non-user) was also included in the serum proteome and transcriptome analyses but was excluded in the sputum analysis due to the low number of self-reported users. By adjusting for these variables, the analysis aimed to identify molecular features uniquely associated with uncontrolled asthma symptoms rather than overall disease severity or frequency of exacerbations.

Binomial logistic regression was performed to obtain unpenalised estimates for the stably selected features while adjusting for the covariates described above. Multicollinearity was evaluated using the variance inflation factor (VIF < 5), and the overall fit of the model was assessed using the Hosmer–Lemeshow goodness-of-fit test.

If the effects of the stably selected features were significant, gene expression or protein abundances were compared across asthma severities and healthy controls using linear regression (adjusted for age, sex, BMI, smoking status and urinary steroid detection) to determine whether the differences were disease-related. Linearity, homoscedasticity, and normality of residuals were visually inspected using the R package 'performance'. The absence of multicollinearity was also assessed, with a variance inflation factor (VIF) threshold of less than 5.

Listwise deletion was applied to each dataset (serum proteome, sputum proteome, blood transcriptome and sputum transcriptome), excluding patients with missing data on any ACQ-5 item or adjustment covariate. This resulted in dataset-specific sample sizes. The number of missing values for the other variables used to characterize the sample was reported.

3 | Results

The serum and sputum proteome analyses as well as the transcriptome analyses of blood and sputum involved 415, 90, 360 and 96 adults with asthma, respectively (Figure 1). Table 1 summarises the baseline characteristics of the individuals included in each analysis, while Tables S1 and S2 provide further details broken down by asthma symptom control. In the different analyses, adults with asthma had similar characteristics: they were mainly female, middle-aged, non-smokers, had severe asthma and had at least one exacerbation in the last year (Table 1). Individuals with uncontrolled asthma had more severe disease and airway obstruction and a higher frequency of exacerbations compared to individuals with controlled symptoms. In addition, in the serum proteome and blood transcriptome analyses, asthmatics with uncontrolled symptoms were more often female, had a higher BMI and had an increased number of neutrophils in the blood.

Four of the 1129 proteins analysed in serum were selected, with a selection proportion greater than the 65% calibrated threshold (Figure 2A). The most consistently selected protein was mitogen-activated protein kinase 8 (MK08/MAPK8), followed by mannose-binding protein C (MBL/MBP-C), tumour necrosis factor receptor superfamily member 12A or TWEAK receptor (TWEAKR/TNFRSF12A) and CD5 antigen-like (CD5L). All selected proteins were significantly associated with symptom control when adjusted for clinical variables (Figure 2B). Higher

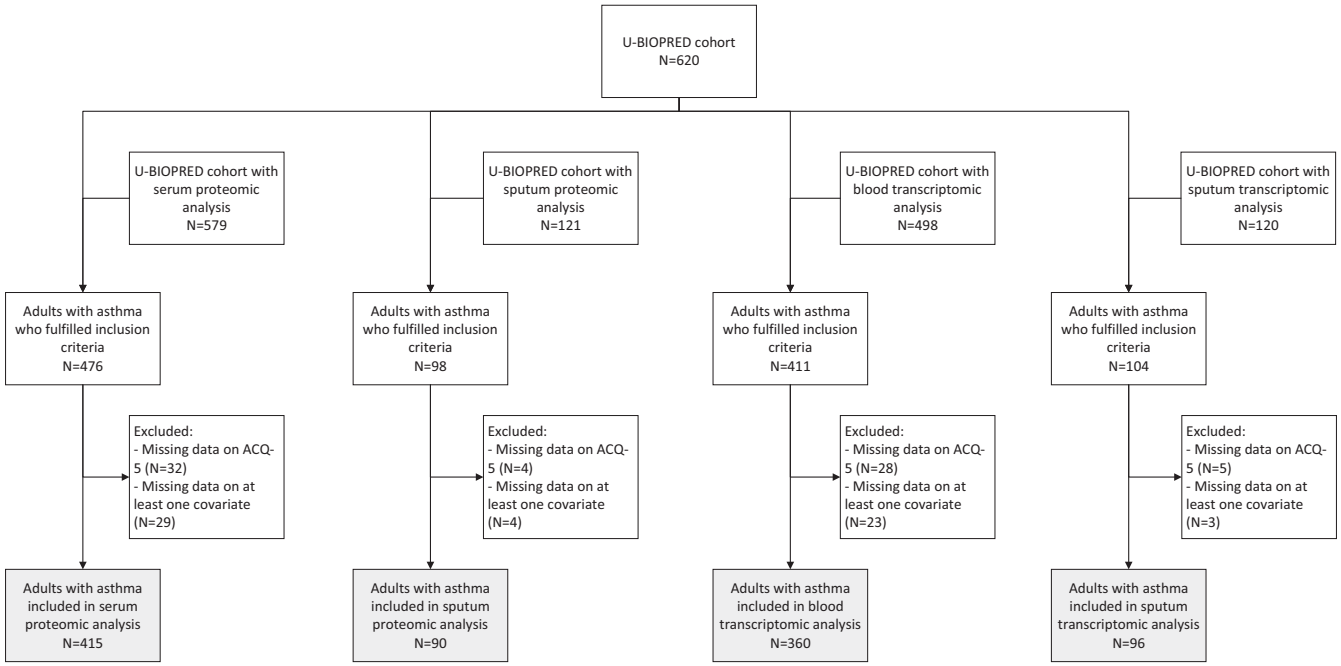

FIGURE 1 | Flow diagram of the adults with asthma included in serum and sputum proteomics analyses, as well as blood and sputum transcriptomic analyses. Covariates included age, sex, age of asthma onset, smoking status, body mass index, FEV1% predicted, exacerbation history, anti-IgE therapy and urinary steroids levels. ACQ-5, 5-item Asthma Control Questionnaire.

levels of TWEAKR/TNFRSF12A [adjusted OR 2.25 (95% CI 1.15, 4.77)] and MBL/MBP-C [adjusted OR 1.6 (95% CI 1.07, 2.42)] increased the odds of uncontrolled asthma. In contrast, higher MK08/MAPK8 [adjusted OR 0.48 (95% CI 0.29, 0.76)] and CD5L levels [adjusted OR 0.59 (95% CI 0.41, 0.82)] reduced the odds of having uncontrolled asthma (Figure 2B). Among the clinical variables used for adjustment, a history of at least one exacerbation in the past year, higher BMI, more severe airway obstruction and female sex were associated with higher odds of uncontrolled symptoms compared with controlled symptoms (Figure 2B).

Of the 1125 proteins analysed in sputum, no consistent association with asthma symptom control was found. Similarly, none of the 20,790 expressed genes analysed in sputum and blood were stably selected.

Ninety-four healthy controls of the U-BIOPRED were included in serum proteomic analysis (Figure S1). Healthy controls exhibited lower levels of F_{eNO}, serum IgE and both blood and sputum eosinophils compared to adults with asthma, with no significant differences observed between asthma severity groups (Table S3). They were also predominantly male, non-smokers, younger, had no detectable steroids in their urine and had lower BMI and blood neutrophil counts than those with severe asthma (Table S3). After adjustment for age, sex, smoking status, BMI and urinary steroid detection, significant differences were found only in serum CD5L levels between individuals with severe asthma and healthy individuals, with lower levels observed in the severe asthma group [adjusted estimate −0.23 (95% CI −0.41, −0.04)] (Table 2). Urinary detectable steroids were also significantly associated with reduced serum CD5L levels [adjusted estimate −0.28 (95% CI −0.43, −0.13)].

4 | Discussion

This study investigated the association between protein abundance and gene expression in blood and sputum with asthma symptom control, independent of important clinical factors including age, sex, onset of asthma, BMI, smoking history, lung function (FEV1% predicted), steroid detection and recent exacerbation history. Four serum proteins were stably selected and significantly associated with asthma symptom control. Serum levels of TWEAKR/TNFRSF12A and MBL/MBP-C were significantly higher in asthmatics with uncontrolled symptoms compared with those with controlled symptoms, whereas MK08/MAPK8 and CD5L levels were lower; however, only CD5L was also significantly reduced in severe asthmatics compared to healthy controls.

The observed associations align with the known biological roles of these proteins in inflammation and immune regulation. TWEAKR/TNFRSF12A, a member of the tumour necrosis factor receptor superfamily, is the receptor for the pro-inflammatory cytokine TWEAK and is expressed on various cell types [28]. The binding of TWEAK to TWEAKR triggers both the NFκB and mitogen-activated protein kinase (MAPK) pathways, leading to inflammation, tissue repair, apoptosis and angiogenesis [28]. However, when highly expressed, TWEAKR/TNFRSF12A may also activate NFκB pathways independently of TWEAK binding [29]. In line with our findings, previous studies have reported higher serum TWEAKR/TNFRSF12A levels in uncontrolled asthma [30] and increased TWEAK expression in the sputum of children with poorly controlled non-eosinophilic asthma [31]. TWEAKR/TNFRSF12A expression is induced by cytokines and growth factors [29], and its upregulation has also been observed in injured tissue and solid tumours, where

TABLE 1 | Overall baseline characteristics of adults with asthma included in serum and sputum proteomics analyses, and blood and sputum transcriptomic analyses.

	Serum proteomics		Sputum proteomics		Blood transcriptomics		Sputum transcriptomics	
	N = 415		*N* = 90		*N* = 360		*N* = 96	
	NA	Overall	NA	Overall	NA	Overall	NA	Overall
Severe asthma	0	342 (82.4)	0	72 (80.0)	0	293 (81.4)	0	77 (80.2)
Age, years	0	52.00 [41.00, 61.00]	0	52.50 [45.00, 59.75]	0	52.00 [41.00, 61.00]	0	53.00 [45.00, 60.25]
Sex, male	0	169 (40.7)	0	39 (43.3)	0	150 (41.7)	0	40 (41.7)
Smoking status	0		0		0		0	
Current smoker		37 (8.9)		11 (12.2)		36 (10.0)		8 (8.3)
Ex-smoker		104 (25.1)		30 (33.3)		86 (23.9)		28 (29.2)
Non-smoker		274 (66.0)		49 (54.4)		238 (66.1)		60 (62.5)
Age of asthma onset, years	0	23.00 [8.00, 40.00]	0	27.00 [10.00, 43.00]	0	23.50 [8.00, 41.00]	0	23.00 [7.00, 40.00]
BMI, kg/m^2	0	26.96 [23.95, 32.04]	0	26.64 [23.48, 32.06]	0	27.25 [23.85, 32.12]	0	26.42 [23.79, 31.09]
Average ACQ-5	0	2.00 [1.00, 3.00]	0	2.10 [1.00, 3.00]	0	2.00 [1.00, 3.00]	0	2.00 [0.95, 3.00]
FEV_1% predicted	0	70.79 [54.28, 87.96]	0	70.27 (21.77)	0	70.97 [54.87, 88.35]	0	69.66 (22.10)
Number of exacerbations[a]	0	2.00 [0.00, 3.00]	0	1.50 [0.00, 3.00]	0	2.00 [0.00, 3.00]	0	2.00 [0.00, 3.00]
Number of exacerbations[a], > 0	0	300 (72.3)	0	62 (68.9)	0	260 (72.2)	0	68 (70.8)
Anti-IgE, user	0	43 (10.4)	0	1 (1.1)	0	39 (10.8)	0	1 (1.0)
OCS, user	5	168 (41.0)	1	33 (37.1)	4	139 (39.0)	1	37 (38.9)
Urinary steroid detection, yes	0	117 (28.2)	0	24 (26.7)	0	89 (24.7)	0	30 (31.2)
F_{eNO}, ppb	22	26.00 [15.00, 48.00]	4	26.75 [17.25, 53.00]	19	26.00 [16.00, 47.00]	3	26.50 [18.00, 49.00]
Serum IgE, IU/mL	8	113.00 [47.00, 317.00]	3	126.00 [51.50, 335.50]	9	112.00 [48.50, 318.00]	3	102.00 [44.50, 205.00]
Blood eosinophils, %	9	3.00 [1.56, 5.53]	1	3.36 [1.78, 6.17]	7	3.00 [1.60, 5.56]	1	3.50 [1.92, 5.62]
Blood eosinophils count, $\times 10^3$cells/μL	9	0.20 [0.10, 0.40]	1	0.24 [0.12, 0.41]	7	0.20 [0.10, 0.40]	1	0.24 [0.12, 0.40]
Blood neutrophils, %	9	60.45 [54.45, 67.86]	1	58.50 [53.85, 65.61]	7	60.00 [53.85, 67.35]	1	58.63 [54.05, 66.25]
Blood neutrophils count, $\times 10^3$cells/μL	9	4.50 [3.44, 6.27]	1	4.13 [3.25, 6.31]	7	4.41 [3.40, 5.93]	1	4.40 [3.50, 6.44]
Sputum eosinophils, %	274	2.48 [0.39, 17.69]	0	2.24 [0.21, 19.27]	234	2.48 [0.57, 14.31]	0	2.66 [0.38, 12.52]
Sputum eosinophil count, cells/μL	274	13.00 [2.00, 84.00]	0	12.00 [1.00, 88.75]	234	13.00 [3.00, 75.75]	0	14.00 [2.00, 69.25]
Sputum neutrophils, %	274	52.29 [29.60, 74.36]	0	48.90 (24.97)	234	50.33 [30.18, 72.27]	0	56.05 [33.99, 77.29]
Sputum neutrophil count, cells/μL	274	259.00 [151.00, 399.00]	0	258.88 (137.99)	234	266.72 (145.30)	0	297.00 [186.50, 416.25]

Note: Categorical variables are reported as *n* (%). Numerical variables are reported as mean (standard deviation) or median [Q1, Q3]. Severe asthma was defined as uncontrolled symptoms and/or frequent exacerbations despite high-dose inhaled corticosteroids.

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; F_{eNO}, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in one second; IgE, immunoglobulin E; NA, not available; OCS, oral corticosteroids; ppb, parts per billion.

[a]In the previous year.

it contributes to inflammation, disease severity and tumour growth [28, 29]. The higher abundance of serum TWEAKR/TNFRSF12A in uncontrolled asthmatics may result from enhanced post-translational regulatory mechanisms through proteolytic ectodomain shedding to control its abundance at the cell surface and its signalling [32]. Such elevated soluble receptor levels could therefore reflect persistent tissue injury and inflammation. Although the TWEAK/TWEAKR axis plays a

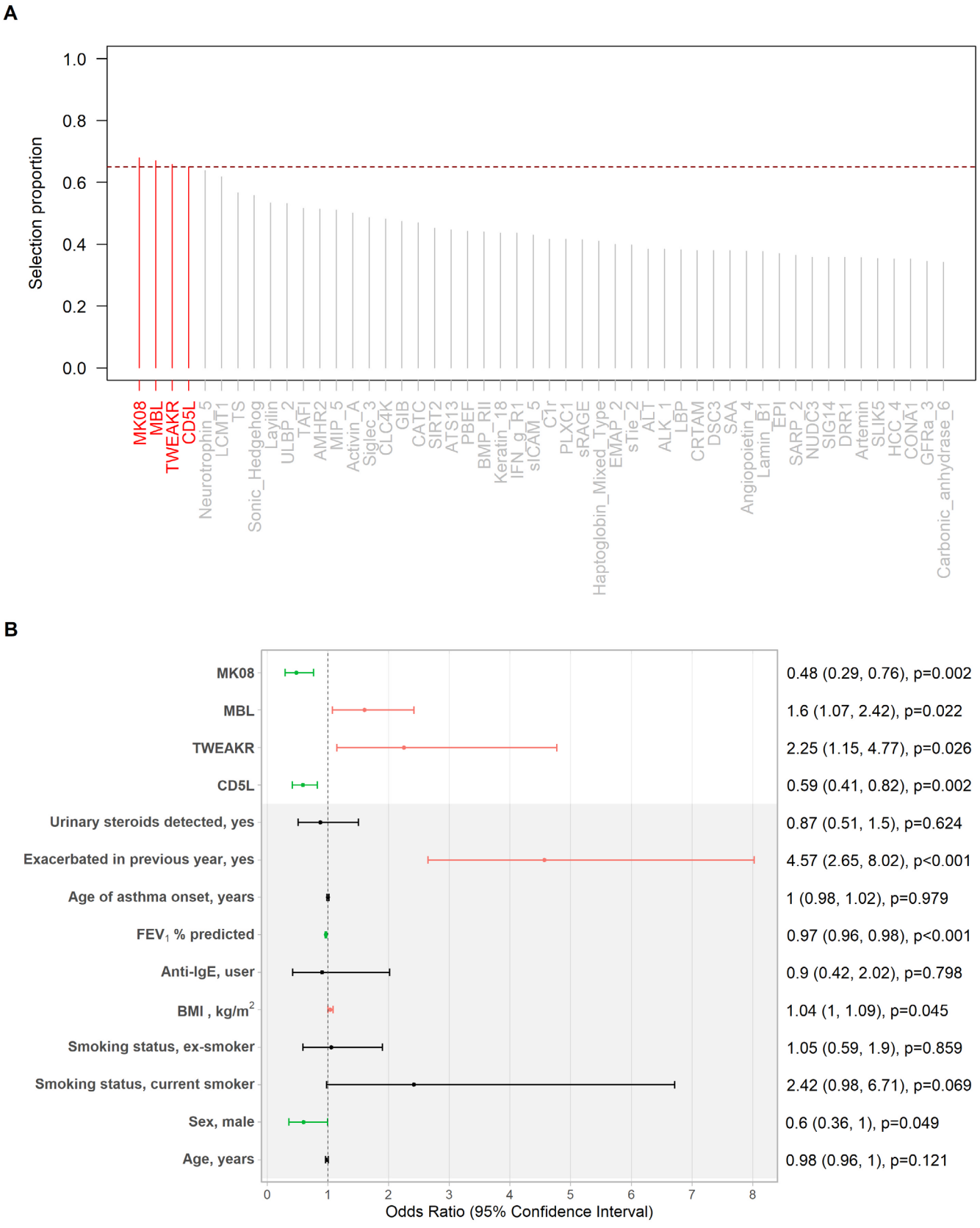

FIGURE 2 | Legend on next page.

FIGURE 2 | (A) Serum proteins identified using stability selection with Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression for asthma symptom control (uncontrolled vs. controlled symptoms); (B) Unpenalised odds ratios (95% confidence intervals) for stably selected proteins in serum, obtained using logistic regression for uncontrolled compared to controlled asthma symptoms, adjusted for clinical covariates ($N = 415$). Red confidence intervals indicate variables that increase the odds of uncontrolled asthma. Green confidence intervals indicate variables that reduce these odds. Black confidence intervals represent non-significant variables. BMI, body mass index; CD5L, CD5 antigen-like; FEV_1, forced expiratory volume in one second; IgE, immunoglobulin E; MBL, mannose-binding protein C; MK08, mitogen-activated protein kinase 8; TWEAKR, tumour necrosis factor receptor superfamily member 12A or TWEAK receptor.

physiological role in tissue repair, its persistent activation may lead to chronic inflammation, hyperplasia and inhibition of tissue repair [28]. Therefore, inhibition of the TWEAK/TWEAKR axis might have therapeutic relevance for asthma [33].

Similar to TWEAKR/TNFRSF12A, higher MBL/MBP-C levels were associated with increased odds of uncontrolled asthma. MBL/MBP-C is an important extracellular pattern-recognition molecule of the innate immune system produced by hepatocytes [34–36]. By binding to bacteria, parasitic protozoans, viruses and fungi, MBL/MBP-C promotes direct opsonisation of pathogens through interaction with collectin receptors in phagocytic cells and activates the lectin complement pathway, leading to complement-dependent opsonisation and generation of proinflammatory anaphylatoxins [34–37]. MBL/MBP-C also promotes the uptake of apoptotic cells by macrophages [38]. Previous studies have shown MBL/MBP-C levels were elevated in individuals with asthma and correlated with blood eosinophils [39, 40]. A study in children with asthma has also found a higher concentration of MBL/MBP-C in more severe cases [41], supporting our findings. Oxidative stress is elevated in severe asthma [42] and may promote MBL/MBP-C synthesis [40, 43], which could explain our observation. Nevertheless, the mechanism leading to increased MBL/MBP-C levels in individuals with uncontrolled asthma symptoms needs to be further elucidated.

Serum MK08/MAPK8 levels were lower in adults with uncontrolled than with controlled asthma. Also known as c-Jun N-terminal kinase 1 (JNK1), MK08/MAPK8 is an intracellular stress-activated protein kinase within the MAPK superfamily, induced by inflammatory and physical stimuli [44]. It is ubiquitously expressed and regulates apoptosis, cytokine production, expression of inflammatory genes and proteins and other signalling pathways [44]. Corticosteroids have been shown to inhibit stress-activated serine–threonine protein kinases, and increased activation of the JNK pathway is reported in asthmatics who do not respond to corticosteroids [45]. Based on this observation, higher MK08/MAPK8 levels would be expected in uncontrolled asthma. However, individuals with uncontrolled symptoms in this study also had higher blood neutrophil counts, and the JNK pathway is not activated in neutrophils in response to certain stimuli, such as TNF-α [46]. In addition, although JNK inhibitors reduced eosinophilic inflammation, airway remodelling and bronchial hyperresponsiveness [47, 48], they did not suppress cytokine expression in neutrophils [46]. Therefore, differences in serum MK08/MAPK8 levels between individuals with uncontrolled and controlled symptoms may suggest differences in intracellular signalling pathway activation across cell types. Since activation of the JNK pathway may promote cell death [49, 50], this could result in the release of intracellular proteins, including JNK1, into the serum. Further validation studies are warranted to confirm these results and determine whether they reflect true biological differences.

Among the identified proteins, CD5L stood out as the only protein that distinguished adults according to asthma symptom control and was also more abundant in healthy controls than in those with severe asthma. This circulating protein, primarily expressed by macrophages, has been shown to inhibit leukocyte apoptosis and regulate inflammatory processes [51]. A recent study showed that treatment with recombinant CD5L suppressed airway inflammation and type 2 immune responses by blocking NLRP3 inflammasome activation in mice with asthma-like inflammation [52], supporting our findings. Other reported anti-inflammatory effects of CD5L include inhibition of macrophage secretion of TNF-α and IL-1β [51, 53, 54], and suppression of Th17 cell pathogenicity [55]. Notably, increased TNF-α and IL-1β levels, Th17 cell immune responses and enhanced NLRP3 inflammasome expression have all been implicated in neutrophilic asthma [56–58]. In a pre-clinical study, inhibiting NLRP3 and IL-1β reduced IL-1β production, neutrophilic inflammation and airway hyperresponsiveness [58]. Beyond asthma, recombinant CD5L has been shown to facilitate the phagocytic clearance of dead cell debris and damage-associated molecular patterns (DAMPs), reducing the inflammatory response in autoimmune arthritis, ischemic stroke, sepsis and kidney injury [59–62], which is relevant given that impaired dead cell clearance and increased DAMP levels have been observed in the airways of asthmatics and may contribute to the neutrophilic asthma phenotype [63]. Our findings and previous literature suggest that reduced CD5L may contribute to impaired regulation of immune homeostasis and inflammation in asthma, thereby leading to poor asthma symptom control. The reduced CD5L levels observed in patients with poor symptom control compared to those with controlled asthma may be an effect of corticosteroid treatment. Although no differences were observed in urinary steroid detection between these groups, most patients with uncontrolled symptoms had severe asthma and were receiving high doses of inhaled corticosteroids. Moreover, when comparing healthy subjects with different asthma severities, urinary steroids were associated with lower CD5L levels. It is possible, therefore, that corticosteroids, while effectively suppressing inflammation, may inadvertently inhibit CD5L, thereby interfering with mechanisms of inflammation resolution.

Nevertheless, elevated levels of this protein have been associated with greater disease severity in chronic obstructive pulmonary disease [64], with more extensive liver damage in chronic liver disease [65], and it has also been implicated in atherosclerosis by promoting macrophage survival, cellular adhesion and lipid

TABLE 2 | Unpenalised coefficient (95% confidence intervals, CI) of individuals with mild to moderate asthma or severe asthma versus healthy controls, obtained using linear regression, for the serum abundance of stably selected proteins, adjusted for age, sex, smoking status, body mass index (BMI) and urinary detection of steroids.

Outcome	Term	Coefficient (95% CI)	*p*
MK08/ MAPK8	Mild to moderate asthma (ref healthy)	0.07 (−0.09, 0.22)	0.400
	Severe asthma (ref healthy)	0.03 (−0.1, 0.17)	0.619
	Age, years	0 (0, 0)	0.891
	Sex, male (ref female)	0 (−0.09, 0.09)	0.966
	Smoking status, current smoker (ref non-smoker)	−0.04 (−0.22, 0.14)	0.659
	Smoking status, ex-smoker (ref non-smoker)	0 (−0.11, 0.11)	0.972
	BMI, kg/m^2	0 (−0.01, 0)	0.317
	Urinary steroids detected, yes (ref no)	0.01 (−0.1, 0.12)	0.861
MBL/ MBP-C	Mild to moderate asthma (ref healthy)	−0.16 (−0.34, 0.03)	0.099
	Severe asthma (ref healthy)	−0.06 (−0.22, 0.1)	0.437
	Age, years	−0.01 (−0.01, 0)	0.001
	Sex, male (ref female)	0.16 (0.05, 0.27)	0.004
	Smoking status, current smoker (ref non-smoker)	0.27 (0.06, 0.48)	0.011
	Smoking status, ex-smoker (ref non-smoker)	0.04 (−0.09, 0.17)	0.518
	BMI, kg/m^2	0 (−0.01, 0)	0.341
	Urinary steroids detected, yes (ref no)	0.04 (−0.09, 0.17)	0.573
TWEAKR/ TNFRSF12A	Mild to moderate asthma (ref healthy)	−0.06 (−0.19, 0.08)	0.404
	Severe asthma (ref healthy)	−0.11 (−0.23, 0)	0.058
	Age, years	0 (0, 0)	0.177
	Sex, male (ref female)	−0.01 (−0.08, 0.07)	0.877
	Smoking status, current smoker (ref non-smoker)	−0.01 (−0.16, 0.14)	0.886
	Smoking status, ex-smoker (ref non-smoker)	−0.06 (−0.15, 0.03)	0.224
	BMI, kg/m^2	0 (0, 0.01)	0.360
	Urinary steroids detected, yes (ref no)	−0.02 (−0.11, 0.08)	0.729
CD5L	Mild to moderate asthma (ref healthy)	−0.18 (−0.39, 0.03)	0.101
	Severe asthma (ref healthy)	−0.23 (−0.41, −0.04)	0.015
	Age, years	0 (0, 0.01)	0.658
	Sex, male (ref female)	0 (−0.12, 0.13)	0.958
	Smoking status, current smoker (ref non-smoker)	0.1 (−0.14, 0.34)	0.432
	Smoking status, ex-smoker (ref non-smoker)	−0.15 (−0.3, −0.01)	0.041
	BMI, kg/m^2	0 (−0.01, 0.01)	0.855
	Urinary steroids detected, yes (ref no)	−0.28 (−0.43, −0.13)	<0.001

Abbreviations: BMI, body mass index; CD5L, CD5 antigen-like; CI, confidence interval; MBL/MBP-C, Mannose-binding protein C; MK08/MAPK8, mitogen-activated protein kinase 8; Ref, reference group; TWEAKR/TNFRSF12A, tumour necrosis factor receptor superfamily member 12A or TWEAK receptor.

accumulation [66]. Future studies are therefore needed to assess whether increasing CD5L levels might offer a viable therapeutic strategy for improving symptom control or whether it would instead exacerbate inflammation and worsen asthma-related outcomes.

In contrast to the serum proteome, neither sputum proteins nor blood or sputum transcripts were consistently selected as being associated with asthma symptom control. Although one study found sputum proteins that distinguished uncontrolled from controlled asthma, the sample size was small [16]. Consistent with our results, previous research did not identify differentially expressed genes (FDR < 5%) in blood between uncontrolled and controlled asthma patients [18]. Clusters based on sputum gene

expression, despite differing in type 2 inflammation, showed comparable symptom control [67], suggesting that transcriptomics may not capture differences in asthma symptom control.

Overall, the negative results in transcriptomic analyses may indicate that differences between uncontrolled and controlled asthma occur primarily at the post-translational level or may be a consequence of the small number of patients relative to the large number of transcripts analysed. Although induced sputum reflects airway biology better than blood, the lack of consistent findings in sputum may suggest that differences in asthma symptom control are due to systemic rather than local airway processes. Indeed, systemic inflammation has been associated with worse asthma control, more frequent exacerbations and more severe asthma [68]. Contamination with squamous epithelial cells may have introduced additional variability, which, together with the relatively small sample size, may have further limited the identification of relevant proteins and genes.

This study has several strengths and limitations that should be recognised. A key strength is the assessment of proteomic and transcriptomic signatures in blood and sputum samples in the context of asthma symptom control, with a relatively large sample size, especially for blood analyses. In addition, a stability selection procedure was applied to improve the identification of relevant genes and proteins. However, the smaller sample size of the sputum analyses may have limited the ability to detect relevant signals. The cross-sectional design of the study also limits the ability to conclude whether the identified proteins are causal determinants of asthma symptom control. Furthermore, the effects of these proteins have not been validated in an independent cohort, which may lead to an overestimation of their true influence on asthma symptom control. Analyses restricted to complete cases may have decreased statistical power and introduced bias. Therefore, future studies should first validate these findings, followed by mechanistic investigations to determine whether modulation of the identified proteins could affect asthma symptom control, and elucidate the underlying biological signalling pathways.

5 | Conclusion

This study identified four serum proteins that distinguished adults with uncontrolled asthma symptoms from those with controlled symptoms. No differences were observed in gene expression in sputum and blood or sputum protein levels. Serum levels of TWEAKR/TNFRSF12A and MBL/MBP-C were higher in individuals with uncontrolled asthma, while MK08/MAPK8 and CD5L were elevated in those with controlled symptoms, even after adjusting for clinical variables. Additionally, serum CD5L levels were lower in severe asthma compared to healthy individuals. Further studies are warranted to confirm these findings in an independent external validation cohort and explore the potential therapeutic value of increasing CD5L levels in asthma.

Author Contributions

J.A. and N.Z.-K. contributed to data curation. J.A. conducted the formal analysis and wrote the original draft. All authors contributed to the conceptualisation, methodology, data interpretation and the review and editing of the manuscript. All authors approved the final version for submission and accept responsibility for the accuracy and integrity of the work.

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Data Availability Statement

The data supporting the findings of this study is available upon reasonable request to the U-BIOPRED steering committee.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Supporting Information.