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ORIGINAL RESEARCH

Identification of Co-Diagnostic Genes and Potential Therapeutic Targets for Asthma and Sepsis Through Mendelian Randomization and Immune Infiltration Analysis

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Background: Evidence suggests a bidirectional relationship between asthma and sepsis, but the mechanisms are unclear. This study explores the co-diagnostic genes and molecular links between asthma and sepsis using Mendelian Randomization (MR) and bioinformatics methods, and further validates the findings through clinical data, aiming to identify potential therapeutic targets and drugs.

Methods: Protein Quantitative Trait Loci (pQTL) data from an Icelandic population were used for two-sample MR analysis. Differential expression analysis identified common genes. Gene Ontology and KEGG enrichment analyses explored biological functions. Receiver Operating Characteristic (ROC) curves validated gene performance, and immune cell infiltration was analyzed using CIBERSORT. Drug targets were predicted using DrugSigDB and validated by molecular docking. Clinical data of the three groups of people were collected, and baseline analysis, ROC curve analysis, and comparison of the expression levels of *CXCL8* were carried out.

Results: At the genetic level, 435 genes related to asthma and 1,385 genes related to sepsis were identified, with 141 common genes. Further findings showed that there were 247 differentially expressed genes in asthma and 2,878 differentially expressed genes in sepsis, and 65 common differentially expressed genes were enriched in immune and inflammatory pathways. The key gene *CXCL8* exhibited excellent diagnostic performance and was closely related to immune cell subsets. Based on the research results, ten potential therapeutic drugs were screened, and seven of them were verified by molecular docking. Clinical sample testing results show that *CXCL8* is closely related to asthma and sepsis.

Conclusion: *CXCL8* may be a biomarker for both asthma and sepsis. Immune cells like monocytes, macrophages, and T cells may drive comorbid progression. Potential drug candidates were identified, offering new insights for future research on these diseases.

Keywords: MR, machine learning, molecular docking, asthma, sepsis, *CXCL8*

Introduction

Asthma is recognized as a heterogeneous disease[1] and remains a widespread global health issue, imposing a significant economic burden worldwide.[2] An estimated 241 million people are affected by asthma, with both its morbidity and mortality rates remaining high.[3] The disease is characterized by airway inflammation and hyperresponsiveness.[4] Genetic, epigenetic, and environmental factors all contribute to the development of asthma.[5] Patients typically present with expiratory dyspnea and wheezing, often accompanied by shortness of breath, chest tightness, or cough.[6,7] Furthermore,

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asthma is frequently associated with comorbidities such as gastroesophageal reflux disease, allergic rhinitis, obesity, depression, diabetes, and cardiovascular disease.[8] Currently, asthma diagnosis primarily relies on pulmonary function tests, exhaled nitric oxide measurements, sputum eosinophil counts, allergen tests, chest imaging, and blood gas analysis. Its treatment mainly uses glucocorticoid therapy, in addition to β receptor agonists, leukotriene modulators, theophylline and other drugs.[6,7] Topical and systemic glucocorticoid therapy is effective in controlling asthma; however, it is associated with several side effects, including central weight gain, hypertension, insulin resistance, type 2 diabetes, and osteoporosis.[9] Additionally, current methods for evaluating and treating severe asthma have notable limitations.[10] Consequently, there is an urgent need to explore novel approaches for the diagnosis and treatment of asthma.

Sepsis is a clinical syndrome triggered by an abnormal immune response to infection,[11] characterized by life-threatening multi-organ dysfunction.[12] The progression of sepsis can be divided into two stages: (i) an initial systemic inflammatory response syndrome, which may lead to multi-organ failure and septic shock; (ii) the subsequent compensatory anti-inflammatory response syndrome, a stage that results in sepsis-induced immunosuppression, heightening the risk of secondary infections and contributing to mortality.[13] Annually, approximately 48.9 million people worldwide are diagnosed with sepsis, with around 11 million deaths, accounting for 19.7% of global mortality.[14] It is also the leading cause of death among pediatric patients.[15] Sepsis is a heterogeneous condition, causing a variety of infections from diverse pathogens, each resulting in distinct patterns of organ damage.[16] Currently, the treatment of sepsis primarily relies on bundled management, including rapid cardiopulmonary resuscitation, intravenous antibiotic therapy, and source control.[17,18] While these approaches have shown some effectiveness, they are also fraught with limitations.[19] The timely selection and administration of antibiotics are crucial, as delayed or inappropriate antibiotic use is associated with higher mortality.[20] Emerging therapies, such as glucocorticoids and immunomodulation, are under investigation, but robust evidence supporting their efficacy remains lacking. Despite the gradual standardization of sepsis treatment protocols, significant challenges persist, and further research is essential to enhance therapeutic outcomes.[21]

Although asthma and sepsis differ significantly in terms of pathogenesis and clinical manifestations, there is an underlying intrinsic connection between the two, primarily involving immune system dysfunction and inflammatory responses. Macrophage activation and polarization are thought to play a pivotal role in the onset and progression of both diseases,[22,23] while the complement system is extensively implicated in their pathogenesis.[24] Additionally, the structure and function of gut microbes are closely linked to the development of asthma,[25] and the gut microbiota also plays a crucial role in the onset and progression of sepsis.[26] Both asthma and sepsis are known to disrupt the body's acid-base and electrolyte balance.[27,28] In this study, we integrated the gene expression data from both diseases, systematically analyzed their shared Differentially Expressed Genes (DEGs) using bioinformatics methods, and employed Protein Quantitative Trait Loci (pQTL) colocalization recognition sites as Single Nucleotide Polymorphisms (SNPs) for Mendelian Randomization (MR) analysis to identify common genes. By examining these shared genes, we aim to uncover their roles in immune responses and inflammatory processes, as well as explore potential co-regulatory mechanisms. Finally, we further validated the associations between the common genes and the diseases through the analysis of clinical patient data. This study highlights the connections and common factors influencing both asthma and sepsis, offering significant insights into their pathogenesis and suggesting new directions for potential therapeutic targets.

Materials and Methods

Study Design

In this study, we identified co-diagnostic genes for asthma and sepsis through pQTL MR analysis and comprehensive bioinformatics approaches. We evaluated the expression levels and diagnostic potential of these biomarkers. In our MR analysis, SNPs associated with pQTLs were selected as instrumental variables (IVs).[29,30] Subsequently, immune infiltration analysis and candidate drug evaluations were conducted. Figure 1 is the flow chart of this study. At the same time, this study included 295 research subjects, among whom there were 99 patients with sepsis and 106 patients with asthma. Through a systematic analysis of the clinical cohort data, the associated characteristics of asthma and sepsis were explored from an actual clinical perspective.

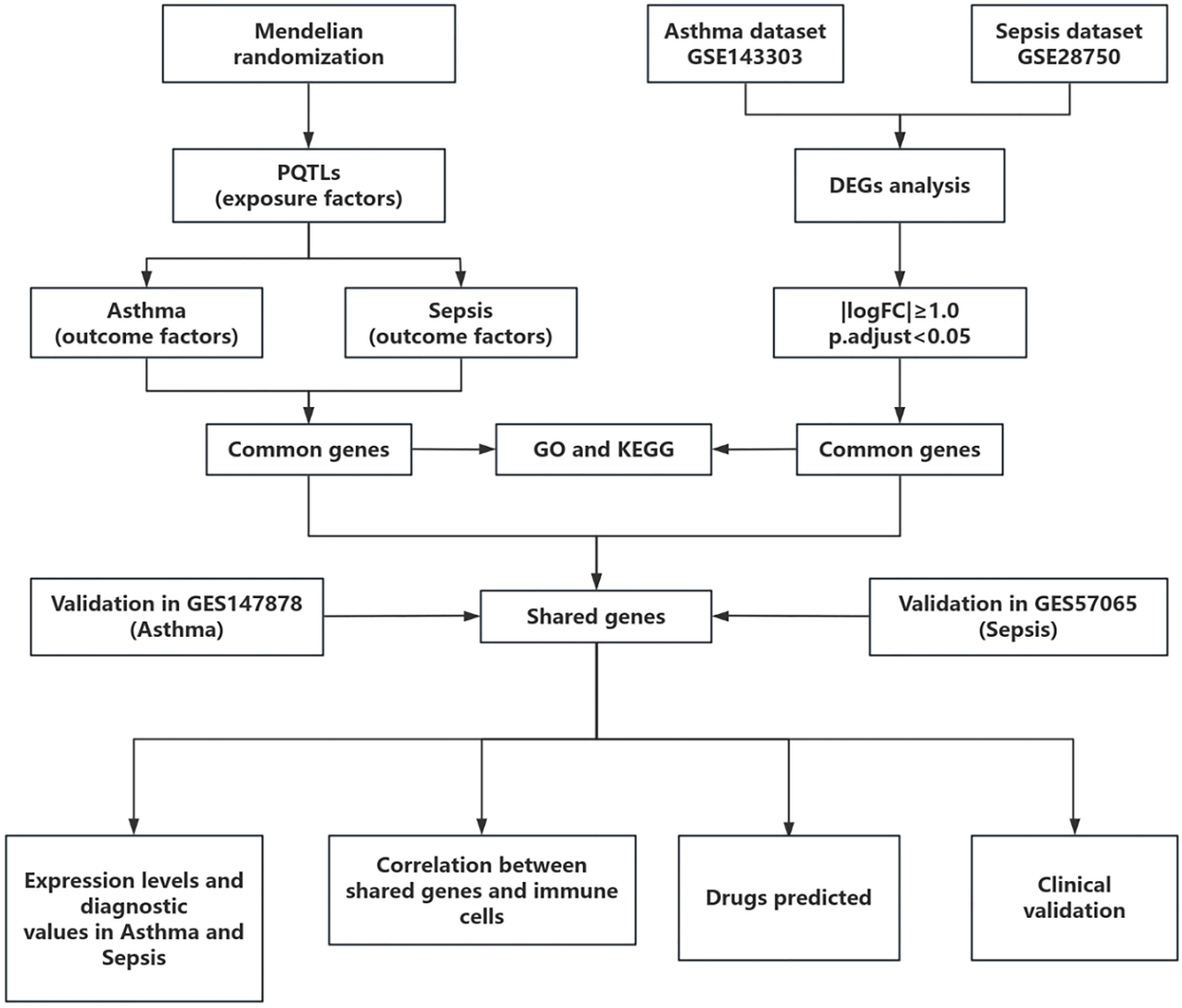

Figure 1 The flow chart of the study.

Data Sources

pQTL data for human plasma proteins were sourced from a previous study,[31] which conducted a Genome-wide Association Study (GWAS) on plasma protein levels measured using 4907 aptamers in 35,559 Icelandic individuals. This study identified 18,084 associations between genetic variants and plasma protein levels (denoted as pQTLs), with 19% involving rare variants (Minor Allele Frequency < 1%).

For the MR analysis, we used summary-level data from the largest publicly available GWAS database (https://gwas.mrcieu.ac.uk/) for each trait (Table 1). Asthma and sepsis data were extracted from the MRC Integrative Epidemiology

Table 1 The Study Details of the Asthma and Sepsis Datasets in the Mendelian Randomization Analysis

Trait	Dataset	Year	Sample Size	Number of Controls and Cases	Population
Asthma	ukb-b-18113	2018	462,933	53,598 cases and 409,335 controls	European
Sepsis	ieu-b-4980	2021	486,484	11,643 cases and 474,841 controls	European

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Table 2 The Basic Information of Gene Expression Omnibus Datasets Used in This Study

GSE Number	Platform	Samples	Source Type	Disease	Group
GSE143303	GPL10558	47 cases and 13 controls	Bronchial endothelial cells	Asthma	Discovery
GSE147878	GPL10558	60 cases and 13 controls	Bronchial endothelial cells	Asthma	Validation
GSE28750	GPL570	10 cases and 20 controls	Peripheral blood	Sepsis	Discovery
GSE57065	GPL570	28 cases and 25 controls	Peripheral blood	Sepsis	Validation

Unit database and the UK Biobank. All participants were of European ancestry to minimize potential race-related biases in the analysis.

The gene expression datasets for asthma and sepsis were obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/).[32] The following criteria were applied to guide the search process:[1] The samples were sourced from Homo sapiens;[2] The experimental data were of the microarray type;[3] The datasets included both control groups and disease groups;[4] The total number of samples in each cohort was at least 10. Eventually, four GEO datasets, namely GSE143303, GSE28750, GSE147878 and GSE57065 were selected as the datasets for asthma and sepsis. Among them, GSE143303 related to asthma and GSE28750 related to sepsis were designated as the discovery cohorts. GSE147878 and GSE57065 were used to validate the hub genes of asthma and sepsis respectively. The detailed information of the above-mentioned datasets is presented in Table 2.

The clinical validation part of this study was conducted in the health management centers of three tertiary general hospitals in southern China, including 90 healthy individuals, 106 asthma patients, and 99 sepsis patients. Demographic data and clinical indicators were systematically collected, and the expression of *CXCL8* in serum was detected by enzyme-linked immunosorbent assay (ELISA). This study was approved by the Institutional Review Board of The Third Xiangya Hospital of Central South University (Ethics Approval No.23911) and adhered to the principles of the Declaration of Helsinki. All necessary approvals were obtained from the government and the Health and Wellness Committee. A broad consent form was used in this study, which was signed by each participant before undergoing the physical examination. All personal information was anonymized during the analysis and reporting process to ensure confidentiality and privacy.

Selection of IVs and Data Coordination in MR Analysis

We included genome-wide significant SNPs with a P value $< 5 \times 10^{-8}$. The SNPs were clustered based on Linkage Disequilibrium (LD) (window size = 10,000 kilobases, $r^2 < 0.001$). The level of LD was estimated based on the 1000 Genomes Project for European samples.[33] If a specific exposure-related SNP was not present in the outcome dataset, a proxy SNP was used as the LD marker. In MR analysis, palindromic and ambiguous SNPs were excluded from the IVs.[34] The F-statistic was calculated from the variance explained by the SNPs in each exposure, using the formula $[(N - K - 1)/K]/[R^2/(1 - R^2)]]$, where K is the number of genetic variants and N is the sample size. In this study, weak IVs with an F-statistic < 10 were removed.[35,36] The minor allele frequency was required to be > 1%.

MR Analysis of pQTL

We utilized pQTL datasets as exposure factors and GWAS for asthma and sepsis as outcomes to identify causal proteins and genes associated with both conditions. Inverse Variance Weighting (IVW) was applied to meta-analyze and combine the Wald ratios of causal effects for each SNP.[34,37] Then, the MR-Egger[38] and weighted median[39] methods are used to supplement IVW. According to different validity assumptions, different methods are used to obtain MR Estimates. The application of the IVW method assumes that all SNPs are valid IVs, allowing for accurate estimation of causal effects. The MR-Egger method, on the other hand, evaluates directed pleiotropy by interpreting the intercept as an estimate of the average pleiotropy of the genetic variation. In contrast, the weighted median method offers higher accuracy, with smaller standard deviation, and remains robust in the presence of horizontal pleiotropy. Even when up to 50% of the genetic variations are invalid IVs, the weighted median provides consistent estimates.[40]

Sensitivity Analysis

The causal direction of each extracted SNP with respect to the exposure and the outcome was tested using the MR Steiger filtering method.[41] This method calculates the variance explained by the instrumental SNPs in both the exposure and the outcome, and tests whether the variance in the outcome is less than that in the exposure. A "TRUE" MR Steiger indicates that the causal direction is consistent with the hypothesis, whereas a "FALSE" result implies the reverse causality, ie, the SNP influences the outcome rather than the exposure; such SNPs are therefore excluded.

Cochran's Q statistic and funnel plots were used to assess the heterogeneity among SNPs.[42,43] The MR-Egger intercept method[38] and the MRPRESSO method[44] were employed to detect horizontal pleiotropy. If outliers were identified and removed, the MR causal estimates were recalculated. If heterogeneity persisted despite their removal, a random effects model was applied to assess the stability of the results, as this model is less sensitive to the influence of weaker SNP-exposure associations. A leave-one-out analysis was conducted to evaluate the impact of each SNP on the overall causal estimate.

Identification of DEGs

All raw datasets were preprocessed, including background adjustment and normalization, using the "affy" package in R software (version 4.3.0). Probes were mapped to gene symbols based on the GPL10558 and GPL570 platforms (Affymetrix Human Genome U133 Plus 2.0 Array). For genes matched by multiple probes, the mean value was selected as the gene expression level. The "Limma" R package was then used to identify DEGs in both the asthma and sepsis datasets. The thresholds for DEGs were set as an adjusted p-value < 0.05 and $|\log2 \text{ fold change (FC)}| \geq 0.5$. The "ggplot2" and "pheatmap" R packages were employed to create volcano plots and clustering heatmaps for DEGs. Venn diagrams were generated using the "Venn" package to identify common DEGs between asthma and sepsis.

2.7 Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) cg pathway enrichment analysis.

DAVID (Database for Annotation, Visualization and Integrated Discovery) 6.8 (https://david.ncifcrf.gov/tools.jsp) is a gene function classification tool used to perform enrichment analysis on common genes (cg) for implementing GO.[45] The enriched GO terms are categorized into Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) ontologies. To understand the biological functions of common genes (cg), we uploaded the common genes (cg) to the DAVID database (a gene function classification tool, https://david.ncifcrf.gov/tools.jsp).[46] The significant enrichment thresholds for GO and KEGG analyses were set as $p < 0.05$ and a count ≥ 2.

Expression Analysis and Diagnostic Evaluation of Candidate Biomarkers

The "ggplot2" package was employed to visualize the expression levels of candidate biomarkers in both the control and disease groups ($p < 0.05$). The Area Under Curve (AUC) of the Receiver Operating Characteristic (ROC) curve was calculated, and the "pROC" package was used to assess the diagnostic accuracy of the candidate biomarkers.

Immune Infiltration Analysis

The datasets we used were GSE143303 (asthma) and GSE28750 (sepsis). CIBERSORT, a deconvolution algorithm, was employed to determine the composition of 22 immune cell types based on gene expression data. The "CIBERSORT" software package was used to analyze immune cell infiltration, while the "ggplot2", "corplot", and "vioplot" packages were utilized for visualizing the results. Spearman correlation analysis was performed to assess the relationships between immune cells and candidate biomarkers.

Evaluation of Candidate Drugs

The enrichment platform was used to explore the relationships between drug molecules and hub genes, with data sourced from the Drug Signature Database (DSigDB, https://tanlab.ucdenver.edu/DSigDB). Currently, this database contains 22,527 gene sets, including 17,389 drugs, covering 19,531 genes.[47] The three-dimensional structures of drug target molecules were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/)[48] and saved in the SDF file format. The 3D

structures of key gene targets were retrieved from the Protein Data Bank (PDB; https://www.rcsb.org/) database[49] and saved as files in the PDB format. AutoDock Vina[50] and PyMol 1.8.1 (Schrödinger, http://www.pymol.org/) were used for molecular docking and visualization analysis to display the interaction forces between drug molecules and gene targets.

Methodology of Clinical Characteristics Analysis

The demographic characteristics of the study population were systematically collected and analyzed, including age, sex, weight, and BMI, along with vital signs (blood pressure) measured at admission. For continuous variables, all data were presented in the form of mean ± standard deviation (SD), and for categorical variables, they were presented in the form of counts (percentages). One-way analysis of variance (ANOVA) was used to evaluate the differences of continuous variables among the three groups, and the chi-square test was applied to categorical variables.

Assessment of Diagnostic Biomarkers via ROC Curves

ROC curves were generated to assess the diagnostic performance of candidate biomarkers. Sensitivity (true - positive rate) was plotted on the y - axis, and 1 - Specificity (false - positive rate) was plotted on the x - axis. The Area Under the Curve (AUC) values were calculated to quantify the overall diagnostic accuracy of the biomarkers. For each biomarker, multiple threshold settings were considered to obtain different pairs of sensitivity and 1 - Specificity values, which were then connected to form the ROC curves.

CXCL8 Levels in Different Patient Groups

Samples were collected from normal subjects, asthma patients, and sepsis patients. We measured *CXCL8* concentrations in samples from the three groups using an enzyme-linked immunosorbent assay (ELISA) kit. The data were presented as a combination of scatter plots and box plots. The box plots display the median, inter - quartile range (IQR), and the whiskers typically extend to 1.5 times the IQR. Dots and triangles represent individual data points for each group. One - way ANOVA was used to compare the *CXCL8* levels among the three groups.

Statistical Analysis

Statistical analyses were performed using R software (version 4.3.0), with a p-value threshold of < 0.05 considered statistically significant. The "TwoSampleMR" package was utilized for conducting the MR analysis.[51] MR-Pleiotropy RESidualS and Outliers and Robust Adjusted Profile Score were computed using the R packages "MRPRESSO" and "MR.RAPS" respectively. Additionally, we performed a PhenoScanner search to evaluate all known phenotypes associated with the genetic instruments used in our analysis. For the screening of DEGs, module genes, enrichment analysis, transcription factor-gene networks, gene-microRNA networks, and immune infiltration analysis, a p-value threshold of less than 0.05 was considered statistically significant. We utilized SPSS software for descriptive statistics of the data and comparison of differences between groups. Prism software, on the other hand, was employed to create intuitive graphs to better present the analysis results.

Results

MR Analysis of pQTL in Relation to Asthma and Sepsis

MR analysis was conducted to investigate the relationship between pQTLs and asthma in an Icelandic population. This analysis identified 435 genetically determined proteins significantly associated with asthma, using a significance threshold of $P < 0.05$. The detailed results are provided in Supplementary Table S1. Similarly, an MR analysis was performed to examine the association between pQTLs and sepsis in the same population, revealing 1,385 genetically determined proteins significantly linked to sepsis, also with a $P < 0.05$ threshold. The comprehensive findings are outlined in Supplementary Table S2. To identify overlapping genetic factors between asthma and sepsis, the intersection of genes significantly associated with both conditions was determined, which comprised 141 genes, offering insights into potential shared genetic mechanisms between asthma and sepsis. The detailed list of these intersecting genes is available in Supplementary Table S3.

Sensitivity Analysis

Sensitivity analyses were conducted to examine and address the potential pleiotropy in causal estimates. Cochran's Q test and funnel plots revealed no significant heterogeneity or asymmetry in the causal relationships among these SNPs (Supplementary Table S4, Supplementary Figure S1, and S2). The influence of each SNP on the overall causal estimate was validated through leave-one-out analysis (Supplementary Figure S3 and S4). By systematically removing each SNP and re-performing the MR analysis on the remaining SNPs, we observed consistent results, which indicate that the inclusion of all SNPs contributed to a significant causal association.

Functional Enrichment Analysis of Intersected Genes from pQTL Analysis

Using GO and KEGG pathway enrichment analyses, we explored the biological characteristics and pathways of the 141 intersected genes identified through pQTL analysis. The GO analysis yielded 122 terms, including 71 BP, 21 CC, and 30 MF. The top 15 most significant terms, comprising 5 each from BP, CC, and MF, are presented here. In BP, the main enrichments were observed in multicellular organism development (P<0.001), neutrophil chemotaxis (P<0.001), positive regulation of kinase activity (P<0.001), positive regulation of cell migration (P<0.001), and response to virus (P<0.001). For CC, the primary enrichments were in extracellular region (P<0.001), extracellular space (P<0.001), cell surface (P<0.001), plasma membrane (P<0.001), and receptor complex (P<0.001). In MF, the main enrichments included transmembrane receptor protein tyrosine kinase activity (P<0.001), chemokine activity (P<0.001), CCR chemokine receptor binding (P<0.001), insulin-like growth factor binding (P<0.01), and serine-type endopeptidase activity (P<0.01).

The KEGG pathway enrichment analysis identified 28 pathways, with the top 5 most significant ones: cytokine-cytokine receptor interaction (P<0.001), viral protein interaction with cytokine and cytokine receptor (P<0.001), JAK-STAT signaling pathway (P<0.001), Measles (P<0.01), and Toll-like receptor signaling pathway (P<0.01). The results from the GO and KEGG enrichment analyses are depicted in Figure 2, with complete details provided in Supplementary Table S5. These findings suggest a strong association between asthma and sepsis in relation to inflammatory responses and immune processes.

Identification of DEGs

In the asthma dataset (GSE143303), a total of 247 DEGs were identified, comprising 127 upregulated genes and 120 downregulated genes (Figure 3A). In the sepsis dataset (GSE28750), a total of 2878 DEGs were identified, including 1376 upregulated genes and 1482 downregulated genes (Figure 3B). Cluster heatmaps based on all DEGs in asthma and sepsis, respectively (Figure 3C and D). Using a Venn diagram, a total of 65 common DEGs were identified between asthma and sepsis (Figure 3E).

Functional Enrichment Analysis of Common DEGs

Functional enrichment analysis using GO and KEGG pathways was performed to explore the biological characteristics and pathways of the 65 common DEGs. The GO analysis identified 55 terms, including 35 BP, 11 CC, and 9 MF. The 15 most significant terms, comprising 5 BP, 5 CC, and 5 MF, were presented. BP was primarily enriched in inflammatory responses (P<0.001), response to lipopolysaccharide (P<0.001), neutrophil activation (P<0.01), apoptotic processes (P<0.01), and cellular response to lipopolysaccharide (P<0.01). CC was mainly enriched in extracellular region (P<0.001), extracellular space (P<0.01), extracellular exosome (P<0.01), collagen-containing extracellular matrix (P<0.01), and external side of the plasma membrane (P<0.01). MF was enriched in protein binding (P<0.001), calcium-dependent protein binding (P<0.01), identical protein binding (P<0.01), signaling receptor binding (P<0.01), and protein homodimerization activity (P<0.01).

The KEGG pathway enrichment analysis highlighted 12 pathways, with the five most significant presented here: Cell cycle (P<0.01), Hepatitis B (P<0.01), Diabetic cardiomyopathy (P<0.05), Human T-cell leukemia virus 1 infection (P<0.05), and Oocyte meiosis (P<0.05). The results of the GO and KEGG enrichment analyses are shown in Figure 4, with the complete findings listed in Supplementary Table S6. These findings suggest a strong association between asthma and sepsis in relation to inflammatory responses and immune processes.

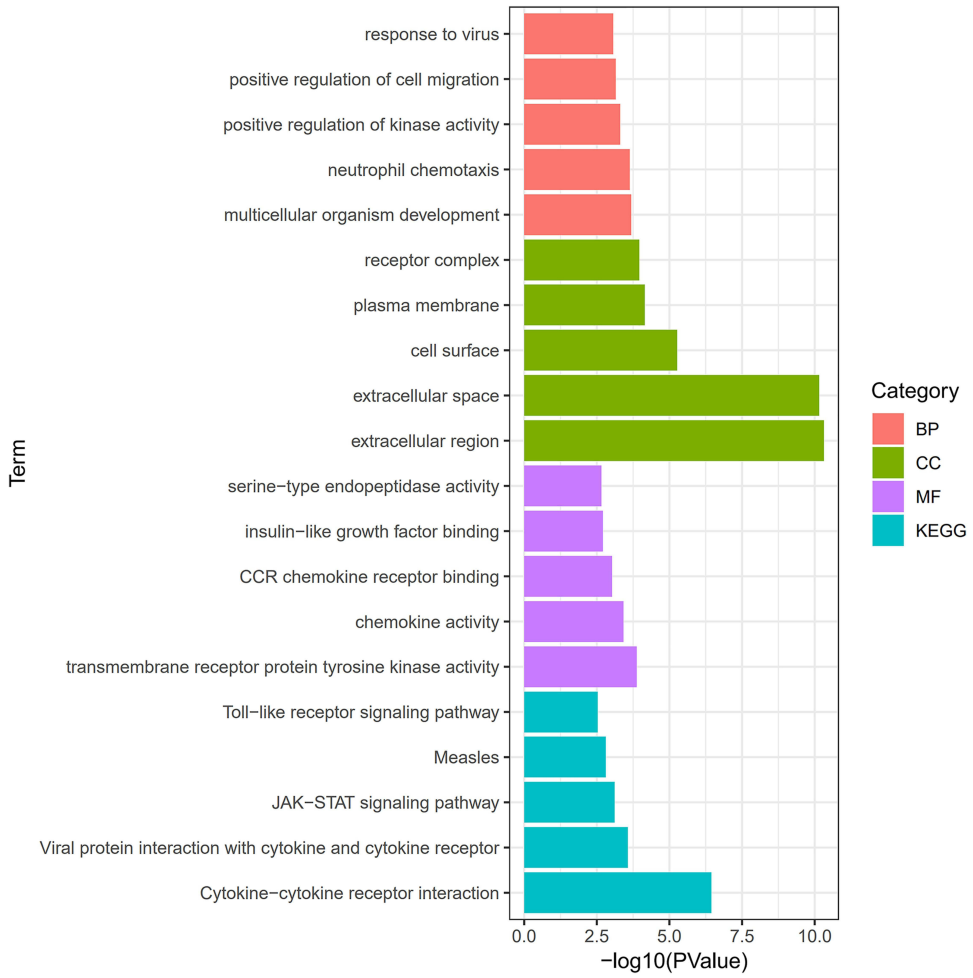

Figure 2 The functional enrichment analysis of intersection genes obtained from Protein Quantitative Trait Loci analysis between asthma and sepsis.

Diagnostic Value and Validation of Candidate Biomarkers

By intersecting the 141 genes identified from the pQTL analysis with the 65 DEGs, we identified *CXCL8* as the overlapping gene, as shown in Figure 5. To validate whether *CXCL8* functions as a diagnostic biomarker for both asthma and sepsis, we further analyzed its expression levels and diagnostic performance. As illustrated in Figure 6A, the expression level of *CXCL8* was significantly higher in the asthma disease group compared to the control group. In contrast, in the sepsis dataset, the expression level of *CXCL8* was significantly lower in the disease group than in the control group (Figure 6B). ROC curve analysis demonstrated that *CXCL8* exhibits excellent predictive performance for both asthma and sepsis. (Figure 6C and D): for the asthma dataset (GSE143303), *CXCL8* achieved an AUC of 0.833 (95% CI: 0.707–0.930); for the sepsis dataset (GSE28750), *CXCL8* achieved an AUC of 0.840 (95% CI: 0.670–0.960).

To further assess the accuracy of the candidate biomarkers, we validated them in two external datasets: GSE147878 for asthma and GSE57065 for sepsis. Consistent with previous findings, the expression of this biomarker was significantly upregulated in the disease group of the validated asthma dataset (Figure 6E). In the validated sepsis dataset, the biomarker expression was significantly lower in the disease group compared to the control group (Figure 6F). ROC curve analysis further confirming its strong diagnostic value (Figure 6G and H). In summary, these findings suggest that *CXCL8* holds promise as a diagnostic biomarker for both asthma and sepsis.

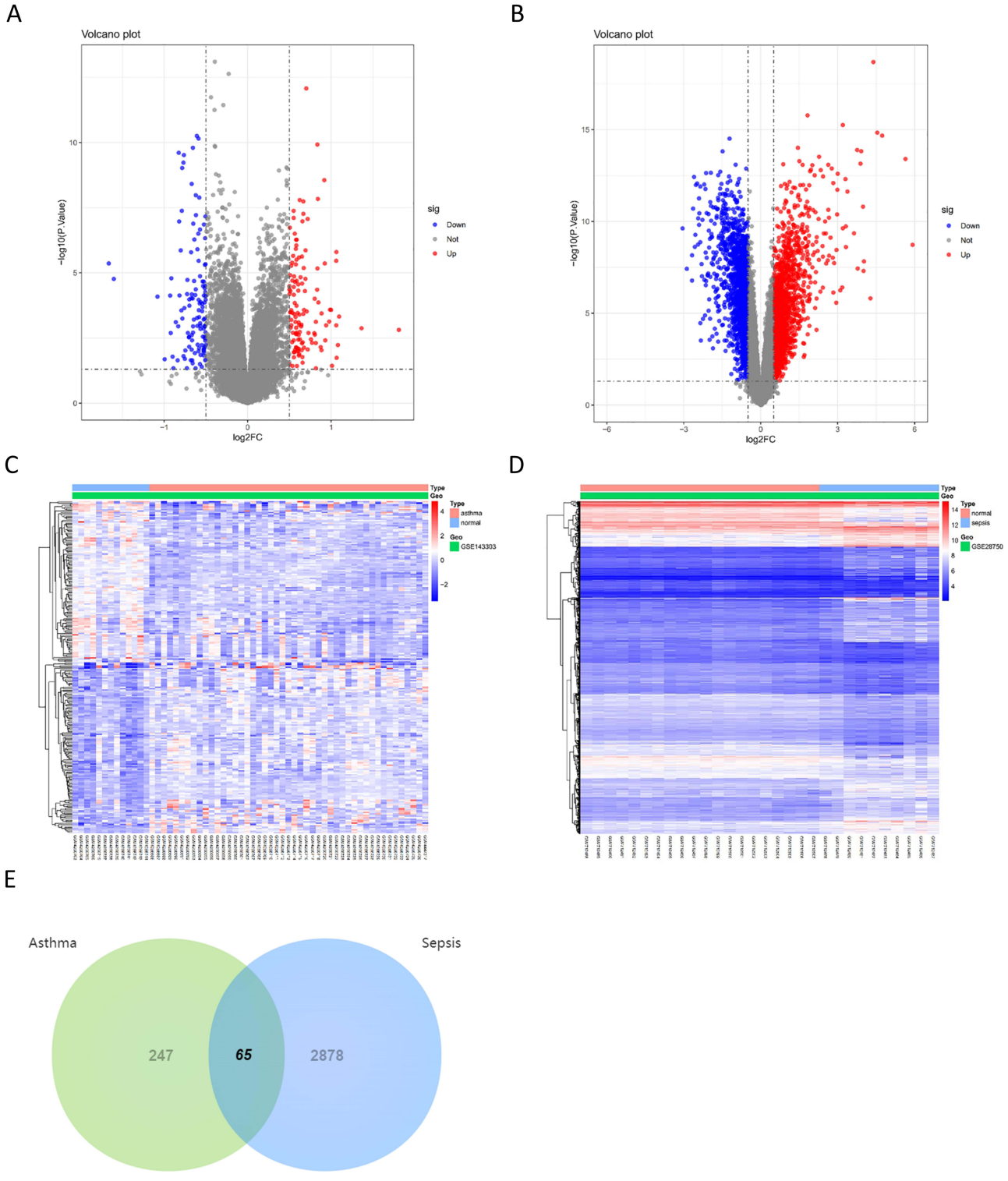

Figure 3 The identification of DEGs. (**A** and **B**) Volcano plots of all DEGs in asthma (GSE143303) and sepsis (GSE28750). (**C** and **D**) Heatmaps of all DEGs in asthma (GSE143303) and sepsis (GSE28750). (**E**) Venn diagram of the intersection of DEGs in asthma and sepsis.

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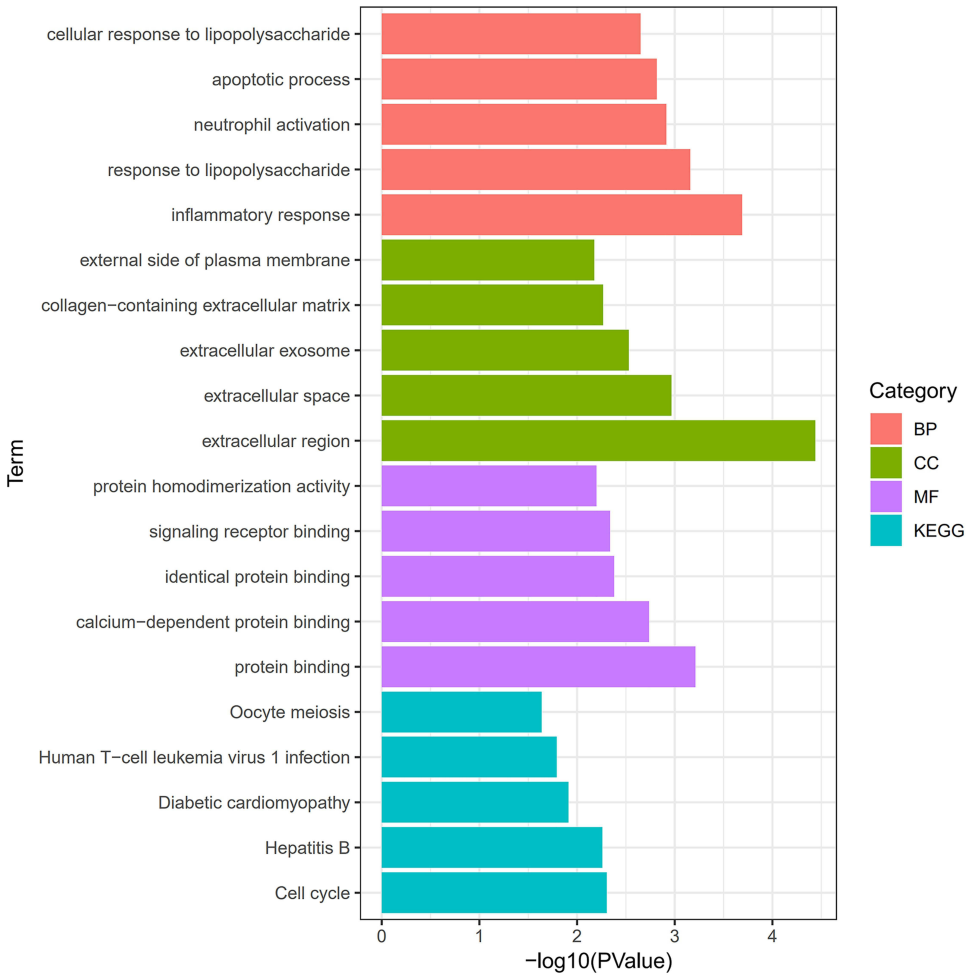

Figure 4 The functional enrichment analysis of common DEGs between asthma and sepsis.

Immune Cell Infiltration Analysis

Asthma and sepsis are both immune-mediated diseases; therefore, CIBERSORT was employed to analyze the proportions of immune infiltrating cells in these conditions. Figure 7A and B depict the distribution of 22 types of immune cells in each sample for asthma and sepsis, respectively. The correlation heatmaps between individual immune cells are shown in Figure 7C and D, with Figure 7C representing asthma and Figure 7D representing sepsis.

Furthermore, we observed that T cells CD4 memory resting, T cells regulatory (Tregs), Macrophages M2, and Mast cells resting exhibited dysregulated levels between normal and asthma samples (Figure 7E). Similarly, B cells memory, Plasma cells, T cells CD8, T cells CD4 naïve, T cells follicular helper, Macrophages M0, Macrophages M1, Dendritic cells resting, Mast cells resting, and Neutrophils showed dysregulated levels between normal and sepsis samples (Figure 7F).

Additionally, we conducted a correlation analysis between the shared biomarker and immune cells. The results revealed that in asthma samples, *CXCL8* was negatively correlated with T regulatory cells (Tregs) and resting mast cells, while showing a positive correlation with activated memory CD4+ T cells and neutrophils (Figure 7G). In sepsis samples, *CXCL8* was negatively correlated with neutrophils, Macrophages M2, and Macrophages M0, and positively correlated with T cells CD8, T cells CD4 naïve, and T cells CD4 memory activated (Figure 7H). These findings indicate that *CXCL8* is closely related to immune cells such as macrophages.

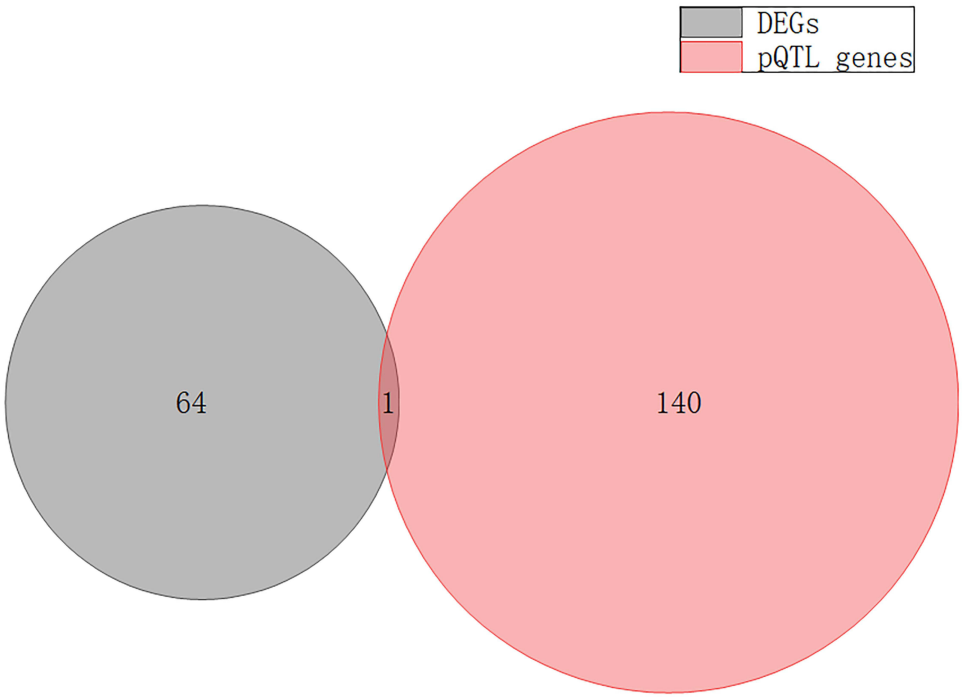

Figure 5 The intersection of results obtained from Protein Quantitative Trait Loci analysis and differential expression gene analysis.

Identification of Candidate Drugs

We utilized the DSigDB database on the Enrichr platform to identify potential drugs targeting the *CXCL8* gene, resulting in 608 gene-drug associations, with detailed findings provided in Supplementary Table S7. We extracted the top 10 drugs ranked by adjusted p-values, including GLYOXAL CTD 00006046, Leupeptin CTD 00001574, 6401–97-4 CTD 00000925, Chromium (III) Chloride CTD 00001073, glutaraldehyde CTD 00006033, amoxicillin CTD 00005390, Diatrizoic acid CTD 00005787, Beclomethasone 17-monopropionate CTD 00002649, proscillaridin CTD 00006639, and ibuprofen TTD 00008500 (Table 3).

The molecular targets of the screened drugs and their corresponding genes were subjected to molecular docking. Protein structures of the gene targets were retrieved from the PDB database, while drug molecule ligands were obtained from PubChem for docking analysis. The molecular docking results showed that the binding energies of the ligands 6401–97-4 CTD 00000925, amoxicillin CTD 00005390, Diatrizoic acid CTD 00005787, proscillaridin CTD 00006639, and ibuprofen TTD 00008500 with potential gene targets were less than −4.5 KJ/mol, indicating low conformational energy and strong binding activity of these drug ligands with the gene targets (Table 4). Notably, Leupeptin CTD 00001574 and Chromium (III) Chloride CTD 00001073 did not have their three-dimensional structures found in PubChem, and the docking results for Beclomethasone 17-monopropionate CTD 00002649 showed that the drug molecule did not form hydrogen bonds with the corresponding gene. Therefore, only 7 drug targets were validated in the molecular docking process, as shown in Figure 8.

Demographic and Clinical Feature Differences Among Groups

The study compared clinical characteristics among normal subjects (n=90), asthma patients (n=106), and sepsis patients (n=99). The specific results of clinical data analysis are shown in Table 5. Significant differences were observed across groups. Age showed that normal subjects had a mean age of 35.21±7.804 years, younger than asthma patients (54.34 ±14.546 years) and sepsis patients (48.63±11.353 years) ($p<0.001$). The proportion of individuals aged ≥ 65 years was 0% in normal subjects, 25.47% in asthma patients, and 14.14% in sepsis patients ($p<0.001$). Regarding gender, the percentage of females was 70% in normal subjects, 37.74% in asthma patients, and 76.77% in sepsis patients ($p<0.001$).

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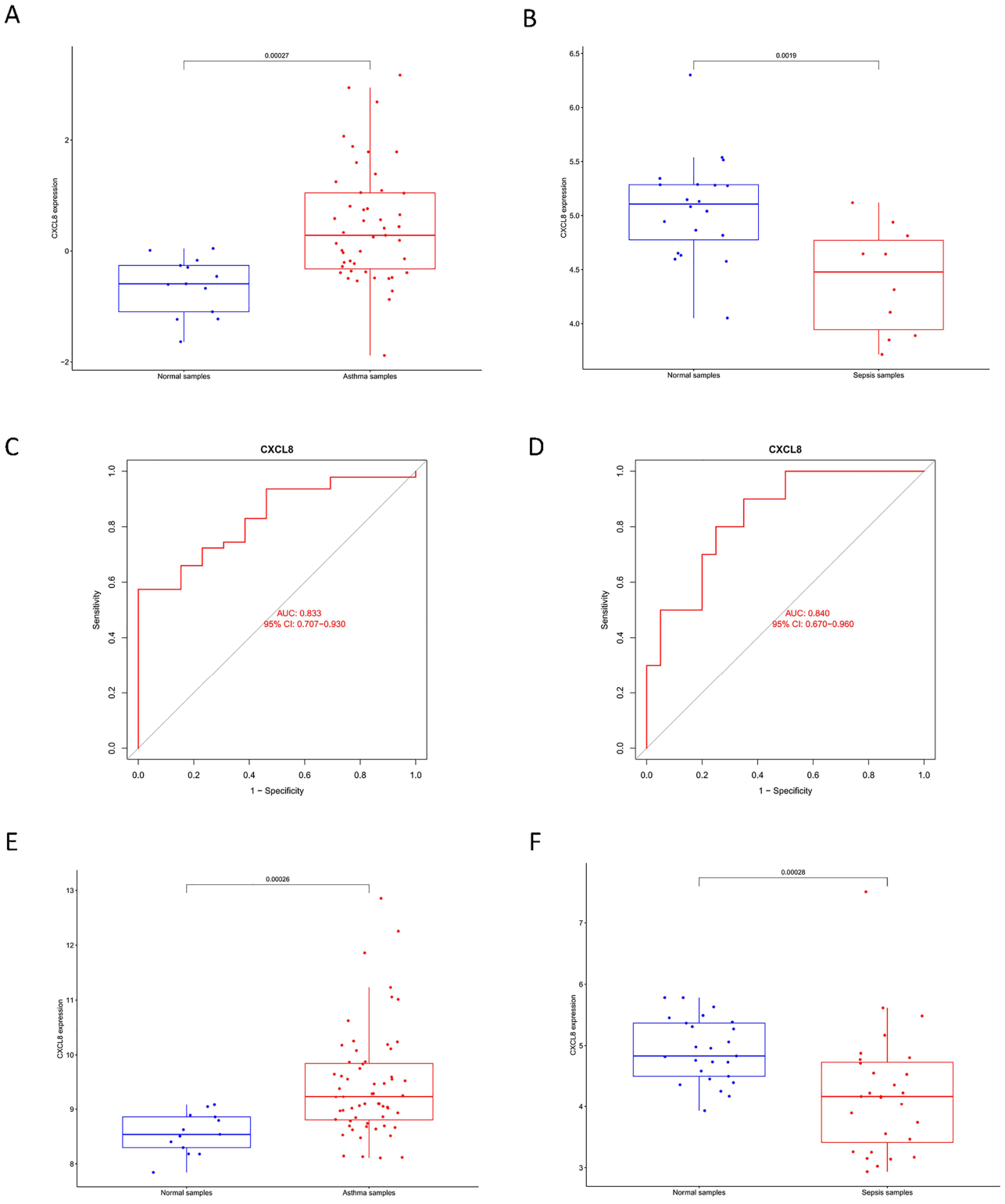

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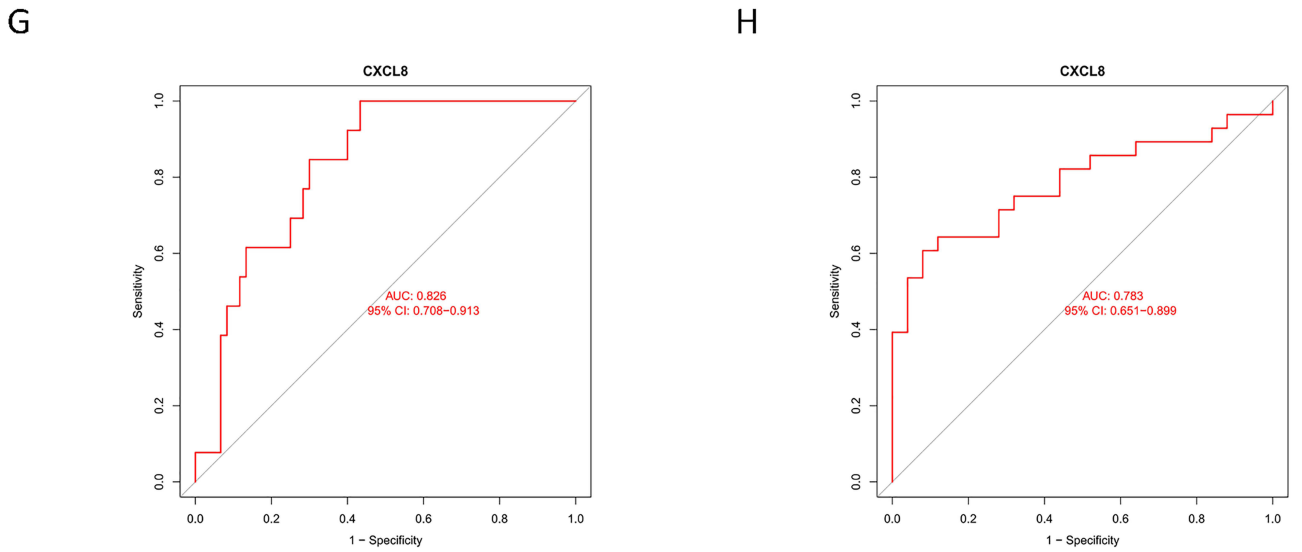


Figure 6 The evaluation of the diagnostic value of the candidate biomarkers in the discovery and validation datasets. (**A**) The expression difference of the shared gene in the asthma (GSE143303) discovery dataset. (**B**) The expression difference of the shared gene in the sepsis (GSE28750) discovery dataset. (**C**) ROC curve of the shared gene in the asthma (GSE143303) discovery dataset, and (**D**) The ROC curve of the shared gene in the sepsis (GSE28750) discovery dataset. (**E**) The expression difference of the shared gene in the asthma (GSE147878) validation dataset. (**F**) The expression difference of the shared gene in the sepsis (GSE57065) validation dataset, (**G**) The ROC curve of the shared gene in the asthma (GSE147878) validation dataset. (**H**) The ROC curve of the shared gene in the sepsis (GSE57065) validation dataset.

Mean weight and BMI also varied significantly among the three groups ($p<0.001$). For vital signs upon admission, both systolic and diastolic blood pressure were significantly different across the groups ($p<0.001$).

Diagnostic Performance of Biomarkers and CXCL8 Expression in Sepsis and Asthma

The diagnostic performance of biomarkers was evaluated via ROC curves. Curve A exhibited an Area Under the Curve of 0.999, with a specificity of 0.99 and a sensitivity of 1 (Figure 9A). Curve B had an AUC of 0.998, a specificity of 1, and a sensitivity of 0.022 (Figure 9B). These findings indicated that the biomarkers demonstrated high diagnostic accuracy under different performance metrics.

Furthermore, the expression levels of *CXCL8* were measured. As depicted in the box - and - whisker plot, normal subjects had the lowest *CXCL8* levels (22.85±3.622 pg/mL), followed by asthma patients (59.33±36.99 pg/mL), and sepsis patients had the highest levels (147.40±99.82 pg/mL) (Figure 10). There were significant differences in *CXCL8* levels among the three groups ($p<0.001$).

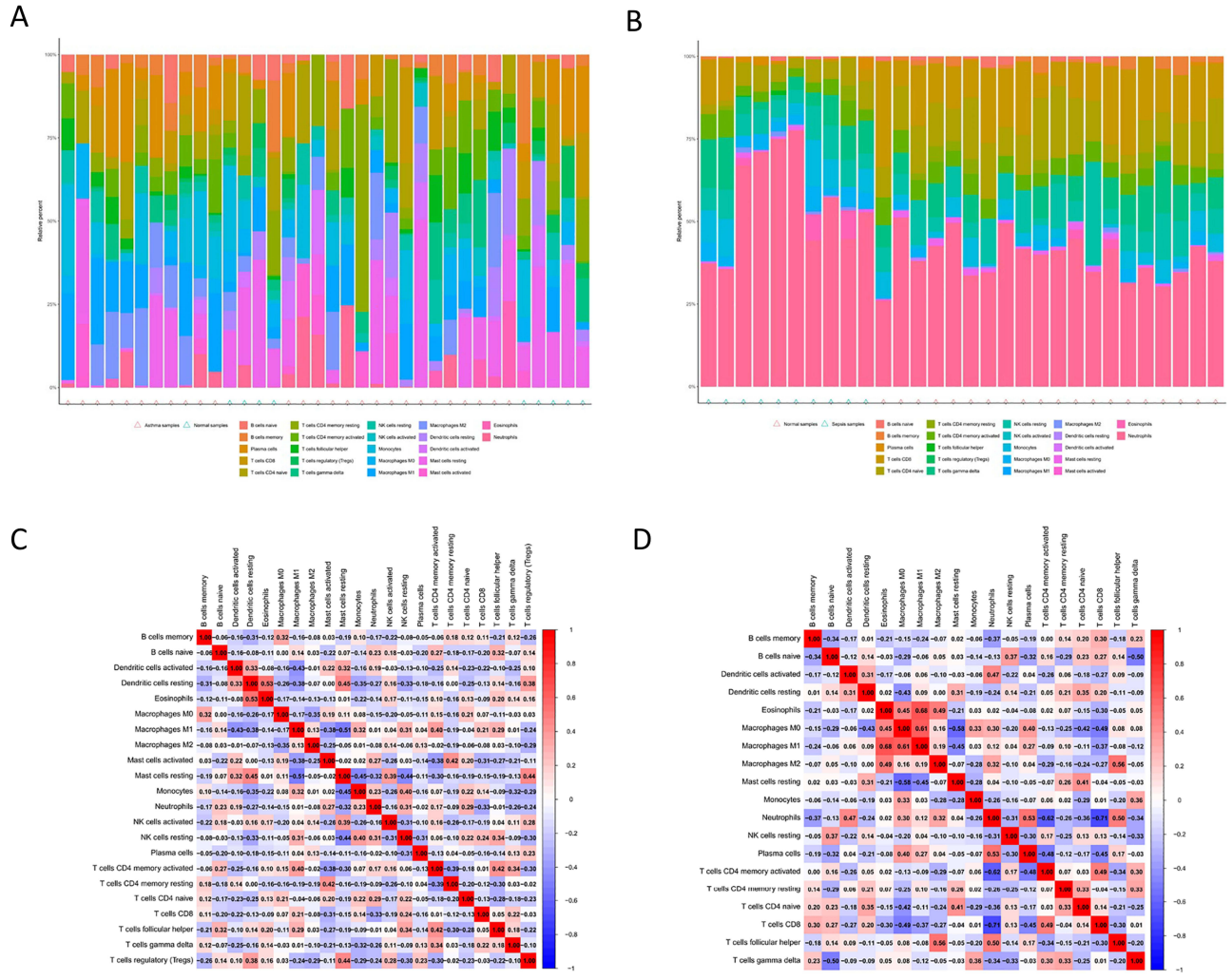
Discussion

There are about 251 million patients suffering from asthma worldwide, with high morbidity and mortality,[3] imposing a huge burden on the world economy.[2] Sepsis is a life-threatening infectious disease with an extremely high mortality rate, closely associated with septic shock and multiple organ dysfunction.[52] In recent years, the incidence of sepsis has increased and been consumed a large amount of medical and health resources.[53] Research exploring the relationship between asthma and sepsis is currently limited, yet evidence suggests a connection between the two diseases, with a complex and not fully understood pathophysiological mechanism. Previous studies have identified potential mechanisms for asthma and sepsis individually; however, no study has yet examined their common underlying mechanisms. In this paper, we employ pQTL MR analysis, along with comprehensive bioinformatics and immune infiltration analyses, to investigate the shared transcriptional features between asthma and sepsis, as well as the role of immune cells in this relationship.

Initially, we conducted MR analysis of pQTLs in the Icelandic population, identifying 435 and 1,385 proteins significantly associated with asthma and sepsis, respectively, and pinpointing 141 intersection genes. We then identified 247 DEGs in the asthma dataset and 2,878 DEGs in the sepsis dataset, with 65 common DEGs. Functional enrichment

analysis revealed that these genes were primarily involved in innate and adaptive immune responses, as well as inflammatory processes. Overall, these findings suggest that the regulation of immune responses and cytokine secretion may serve as a key link between asthma and sepsis. Through analysis of the intersection genes and DEGs identified in the MR study, we identified *CXCL8* as a key diagnostic gene shared between asthma and sepsis. Compared to the control group, *CXCL8* expression was significantly elevated in asthma patients, while its expression was markedly reduced in sepsis patients. Furthermore, ROC analysis demonstrated the potential of *CXCL8* as a diagnostic biomarker for both diseases, with all AUC values exceeding 0.75, emphasizing its crucial role in the pathogenesis and diagnosis of asthma and sepsis. Additionally, based on the results of the clinical validation, we found that *CXCL8* is indeed closely related to both asthma and sepsis. Using DSigDB, we predicted 10 potential drug compounds targeting this hub gene, seven of which exhibited stable binding in molecular docking, supporting the feasibility of these drugs as treatment options. These predicted drugs may serve as therapeutic targets for asthma and sepsis, though their functions and molecular pathways require further validation through cell experiments and clinical studies.

Our study identified the *CXCL8* gene as a key intersection gene for both asthma and sepsis, suggesting its potential as a diagnostic biomarker for these conditions. Also known as the *IL-8* gene, *CXCL8* encodes a CXC chemokine, initially recognized as a low molecular weight protein with potent neutrophil chemotactic activity.[54] Its product is a precursor protein containing 99 amino acids. After treatment, it produces an active protein, 77 amino acids in non-immune cells,



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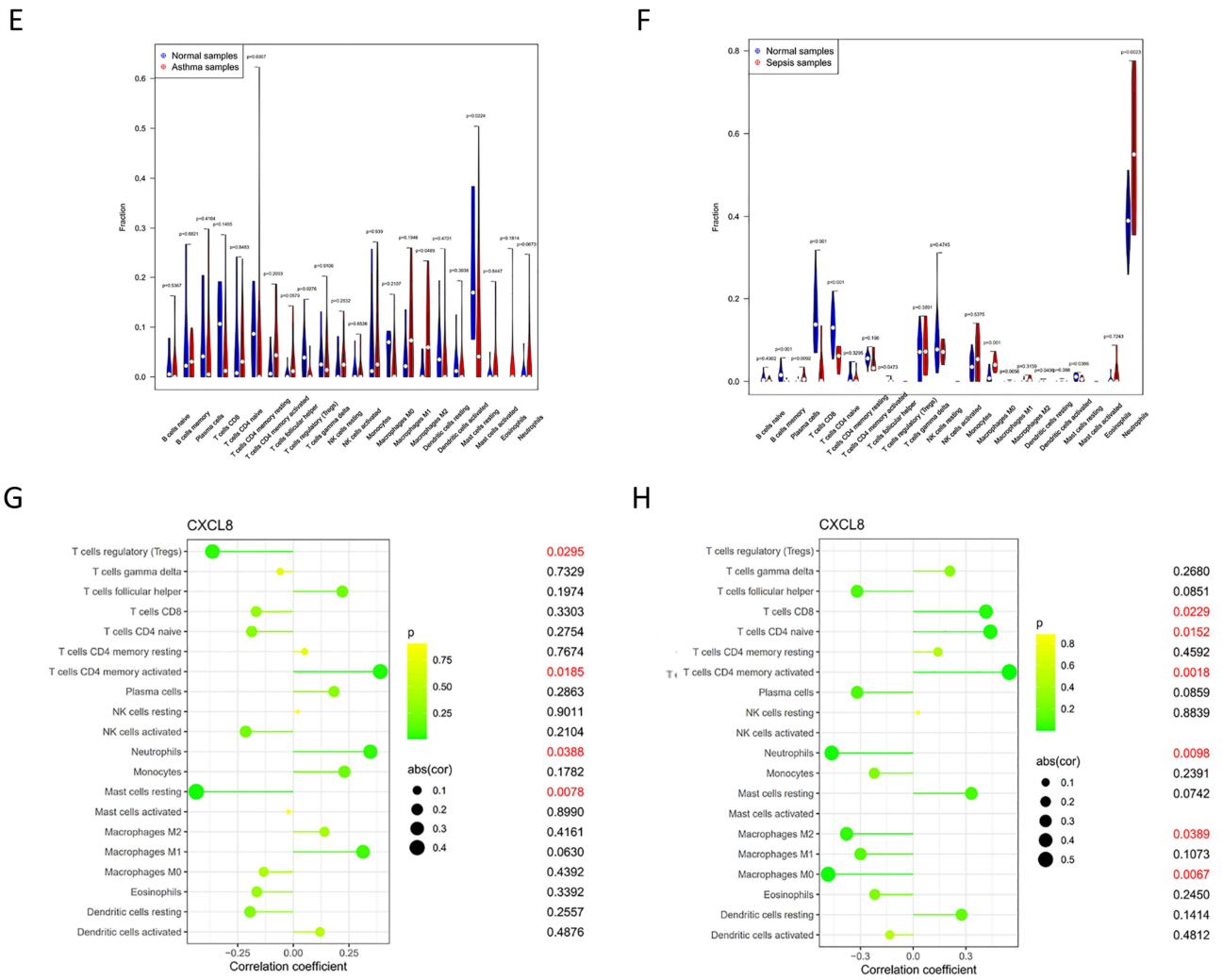

Figure 7 The immune cell infiltration analysis. (**A**–**D**) The percentages of 22 immune cells identified by the CIBERSORT algorithm in the asthma dataset (GSE143303) and the sepsis dataset (GSE28750). (**E** and **F**) Box plots showing the proportions of immune cells in disease and control groups of asthma and sepsis patients. (**G**) The correlation between *CXCL8* and infiltrating immune cells in asthma and normal samples. (**H**) The correlation between *CXCL8* and infiltrating immune cells in sepsis and normal samples.

and 72 amino acids in monocytes and macrophages.[55] CXCL8 transmits signals by binding to CXCR1 and CXCR2 G protein-coupled receptors. The *CXCL8* gene is expressed in a variety of cells and is closely related to inflammatory responses, tumor development, and immune regulation.[55] Previous studies have shown that the CXCL8-CXCR1/2 axis

Table 3 The Top 10 Predicted Drug Compounds

Term	P-value	Adjusted P-value	Combined Score
GLYOXAL CTD 00006046	5.50E-04	0.005906171	150,029.821
Leupeptin CTD 00001574	5.50E-04	0.005906171	150,029.821
6401-97-4 CTD 00000925	5.50E-04	0.005906171	150,029.821
Chromium (Iii) Chloride CTD 00001073	5.50E-04	0.005906171	150,029.821
Glutaraldehyde CTD 00006033	5.50E-04	0.005906171	150,029.821
Amoxicillin CTD 00005390	5.50E-04	0.005906171	150,029.821
Diatrizoic acid CTD 00005787	5.50E-04	0.005906171	150,029.821
Beclomethasone 17-monopropionate CTD 00002649	5.50E-04	0.005906171	150,029.821
Proscillaridin CTD 00006639	5.50E-04	0.005906171	150,029.821
Ibuprofen TTD 00008500	5.50E-04	0.005906171	150,029.821

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Table 4 The Corresponding IDs and Docking Binding Energies of Each Drug Ligand with Potential Gene Targets

Term	PubChem CID	Genes	PDB ID	Vina Score (kJ/mol)
GLYOXAL CTD 00006046	7860	*CXCL8*	5D14	−2.4
6401-97-4 CTD 00000925	80812	*CXCL8*	5D14	−6.1
Glutaraldehyde CTD 00006033	3485	*CXCL8*	5D14	−3.8
Amoxicillin CTD 00005390	33613	*CXCL8*	5D14	−6.3
Diatrizoic acid CTD 00005787	2140	*CXCL8*	5D14	−5.5
Proscillaridin CTD 00006639	5284613	*CXCL8*	5D14	−8.0
Ibuprofen TTD 00008500	3672	*CXCL8*	5D14	−6.2

plays an important role in the pathogenesis of inflammatory diseases such as asthma.[56] Some small molecule CXCR1/2 inhibitors, CXCL8 release inhibitors, and CXCL8 and CXCR1/2 neutralizing antibodies are in advanced clinical trials for asthma treatment,[56] providing new ideas for the clinical treatment of asthma. For neonatal asthma, a decrease in CXCL8 is associated with an increased risk of early asthma endpoints.[57] Recent studies have found that *IL-8/CXCL8* is overexpressed in lung tissues of patients with severe asthma and lung tissues of asthmatic mouse models, which is a potential target for the treatment of severe asthma.[58] The *CXCL8* gene is also closely related to sepsis, and IL-8/CXCL8 is significantly associated with the risk of sepsis.[59,60] Currently, numerous studies have investigated the relationship between *CXCL8* expression, its associated pathways, and sepsis-related complications. Specifically, *CXCL8* expression has been identified as a risk factor for heart failure in patients with sepsis;[61] Inhibition of *CXCL8* expression in serum and kidney can prevent sepsis-induced acute kidney injury;[62] *CXCL8* is a key mediator in the progression of septic hepatitis and liver failure.[63] The above results suggest that the *CXCL8* gene is associated with both asthma and sepsis, highlighting its potential as a common diagnostic marker for these conditions and an important target for their treatment. In our study, GO-term, KEGG-pathway and immune-infiltration analyses revealed that both asthma and sepsis are tightly linked to immune-related cascades. Functional enrichment analyses revealed that the two datasets significantly share the core CC terms “extracellular region” and “extracellular space”. This indicates that, irrespective of disease context, *CXCL8*-mediated effects are exerted preferentially within the extracellular micro-environment, consistent with its role in regulating cytokine expression and providing a spatial basis for the shared pathogenesis of the two disorders. As a cytokine-encoding gene, *CXCL8* plays a pivotal role in initiating and modulating these immune pathways.[55] Taken together with the published evidence, it is reasonable to predict that *CXCL8*—identified here as a shared disease gene—exerts its effects on both disorders by regulating immunological processes and immune-cell functions (eg, macrophage), thereby representing a critical diagnostic and therapeutic target.

Macrophages are key immune cells whose primary functions include recognizing, engulfing, and digesting foreign microorganisms, dead cells, and other particulate matter. They play a crucial role in immune defense and the maintenance of tissue homeostasis.[64] Macrophage polarization refers to the different functions and phenotypes of macrophages under different microenvironment stimulation, which are usually divided into M1 and M2 types.[65] The former is involved in combating pathogens and mediating inflammatory responses through the secretion of pro-inflammatory factors and phagocytosis, while the latter promotes tissue repair and the resolution of inflammation by releasing anti-inflammatory factors. Macrophage polarization plays a crucial role in maintaining immune homeostasis, participating in immune regulation and tissue repair, and its dysregulation may be linked to the onset and progression of various diseases.[66] Our study found that Macrophages M2 showed a dysregulated level between normal samples and asthma samples, and Macrophages M0 and Macrophages M1 showed a dysregulated level between normal samples and sepsis samples through immune cell infiltration analysis, indicating that asthma and sepsis are closely related to macrophage activation and polarization. Some relative studies have confirmed these results.[22,23] As mentioned above, allergic asthma is related to airway inflammation and airway hyperresponsiveness, in which macrophages play an important role. Under different microenvironment stimulation, macrophages will polarize into M1 and M2 types and play different roles, which has a

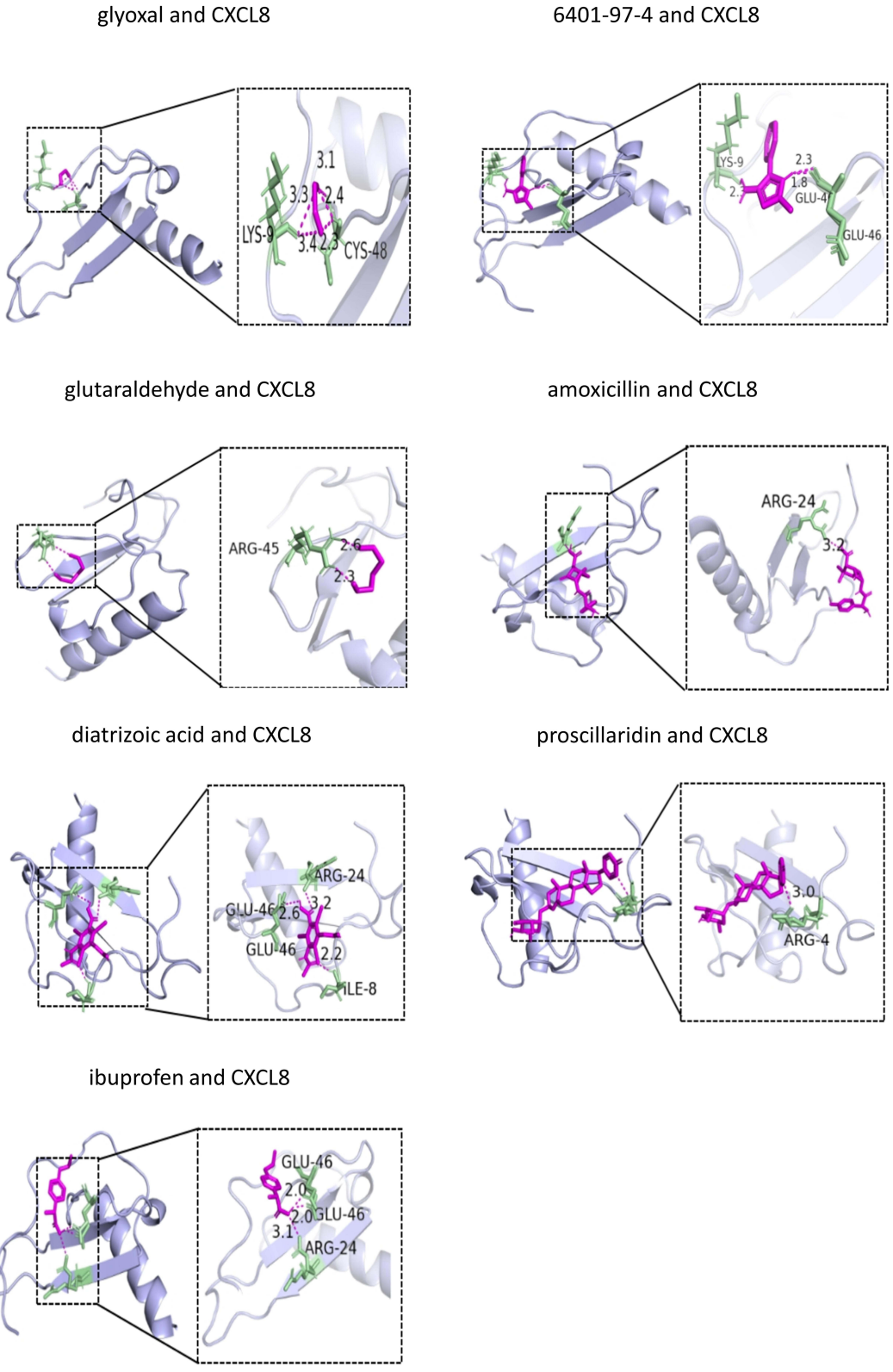

Figure 8 The schematic diagrams of molecular docking for the 7 drugs.

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Table 5 Clinical Characteristics and Biomarker Levels of Normal Subjects, Asthma Patients, and Sepsis Patients

Characteristics	Normal	Asthma	Sepsis	*p* value
	(n = 90)	(n = 106)	(n = 99)	
Age, years—Mean ± SD	35.21 ± 7.804	54.34 ± 14.546	48.63 ± 11.353	<0.001
Age ≥ 65 years	0(0)	27(25.47)	14 (14.14)	<0.001
Females	63(70)	40 (37.74)	76 (76.77)	<0.001
Males	27(30)	66(62.26)	23 (23.23)	
Weight, kg—Mean ± SD	59.77 ± 11.133	63.96 ± 10.870	67.91 ± 12.477	<0.001
BMI, kg/m^2—Mean ± SD	22.85 ± 3.622	24.43 ± 3.377	25.06 ± 3.414	<0.001
Vital signs upon admission—Mean ± SD				
Systolic BP, mm Hg	112.54 ± 14.078	127.50±19.357	125.61 ± 14.301	<0.001
Diastolic BP, mm Hg	68.29 ± 11.082	76.04 ± 12.812	77.57 ± 11.149	<0.001
CXCL8	22. 85±3.622	59.33±36.99	147.40±99.82	<0.001

profound impact on the pathogenesis of asthma.[67] The activation and polarization of macrophages also play an important role in the occurrence and development of sepsis, which can provide antibacterial defense for the body.[68,69] In addition, the activation and polarization of macrophages are closely related to multiple sepsis complications, including acute lung injury,[70,71] cardiomyopathy,[72] liver injury[73,74] and so on, suggesting macrophage activation and polarization may serve as common factors in the pathogenesis of both asthma and sepsis.

Additionally, our study identified the *CXCL8* gene as a common diagnostic biomarker for both asthma and sepsis, which was negatively correlated with M0 and M2 macrophages. This finding further corroborates the role of macrophage activation and polarization in the pathophysiology of both diseases. CXCL8 has been shown to induce M2 macrophage polarization, and this polarization, in turn, promotes the continued expression and secretion of *CXCL8*, forming a positive feedback, which is closely related to gastric cancer,[75] colorectal cancer,[76] cervical cancer,[77] pancreatic cancer,[78]

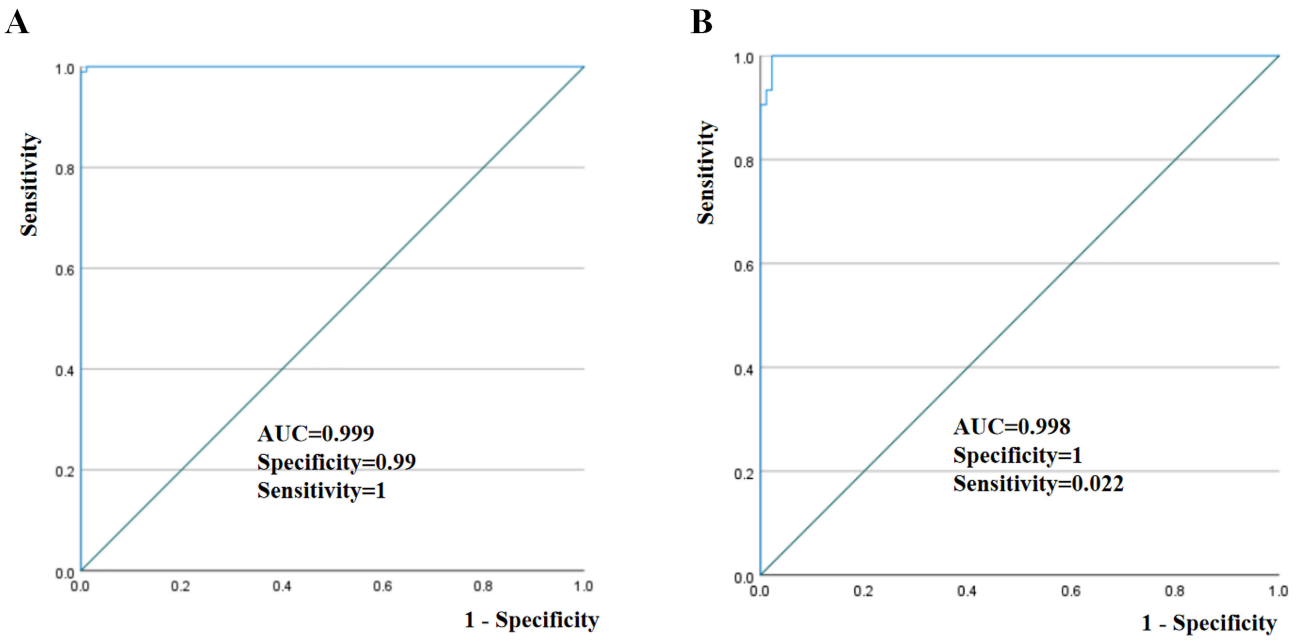

Figure 9 Analysis of ROC curves of diagnostic biomarkers for sepsis (**A**) and asthma (**B**).

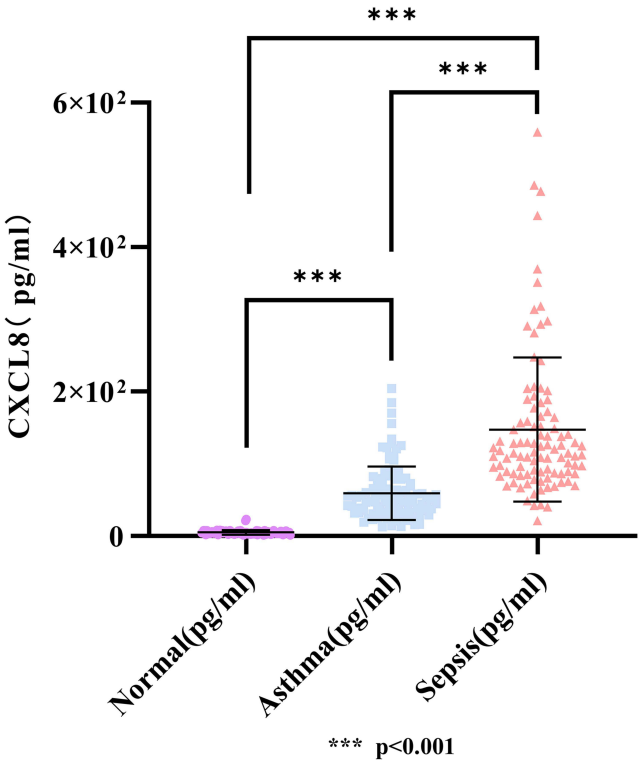

Figure 10 *CXCL8* expression levels in normal subjects, asthma patients, and sepsis patients.

periodontitis[79] and other systemic diseases. Based on our research findings, we hypothesize that this process may also be implicated in the onset and progression of asthma and sepsis.

The strength of this study lies in the use of Icelandic human plasma-derived pQTL data for MR analysis. This novel dataset minimizes the risk of errors associated with population duplication. Additionally, bioinformatics methods were employed to screen relevant genes, assess their expression levels, and evaluate their diagnostic efficacy. Potential therapeutic drugs targeting these genes were identified, and molecular simulations were performed, yielding high data accuracy and strong clinical relevance. Subsequently, we confirmed the accuracy and reliability of the aforementioned analysis results through clinical validation. However, some limitations exist. Firstly, the sample size of the dataset used is relatively small. Moreover, this study lacks data on patients with both asthma and sepsis. Future research should aim to collect larger datasets and incorporate comorbidity data. Additionally, the results require further validation through subsequent in vivo and in vitro experiments. More importantly, as a widely expressed cytokine-encoding gene, CXCL8 is markedly up- or down-regulated in many other disorders and can influence their onset and progression through multiple pathways, including COPD[80–82] and pneumonia[83,84] in the respiratory system. Serum IL-8 levels also serve as a shared diagnostic biomarker for both COPD and asthma.[82] This overlap inevitably reduces its diagnostic specificity, so clinical signs and symptoms must be used to rule out confounding diseases before CXCL8 can be considered a reliable biomarker. Despite these limitations, the preliminary identification of these biomarkers provides a foundation for generating new hypotheses to guide future investigations.

This study is the first to explore the relationship between asthma and sepsis using bioinformatics approaches, yielding promising statistical results that align with existing evidence and demonstrate significant innovation. By employing a variety of analytical methods, this research explores genes and regulatory factors linked to asthma, sepsis, and immune cells, while predicting relevant cellular signaling pathways and potential therapeutic targets. These findings offer valuable research directions for both basic and clinical medical research in the future, provide bioinformatics evidence for asthma and sepsis-related studies, and propose new avenues for future research and drug development in this field.

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Conclusion

In the MR analysis, we established a causal relationship between asthma and sepsis; however, further investigation is required to explore additional risk factors as potential mediators. Through GEO analysis, we identified two diagnostic genes, *CXCL8*, along with co-regulatory pathways and immune characteristics shared by asthma and sepsis. Additionally, we screened potential therapeutic drugs targeting these diagnostic genes, offering a novel strategy for the clinical management of asthma and sepsis. Immune cell infiltration analysis revealed a strong association between macrophage activation and polarization with both asthma and sepsis. Clinical validation has confirmed that CXCL8 is indeed closely related to both asthma and sepsis. These findings provide a theoretical framework for understanding the molecular mechanisms underlying asthma complicated by sepsis, encompassing genetic factors, signaling pathways, and immune infiltration.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available in the GWAS database (https://gwas.mrcieu.ac.uk/), the UK Biobank (https://www.nature.com/collections/bpthhnywqk), GEO repository (https://www.ncbi.nlm.nih.gov/gds/?term=), PubChem (https://pubchem.ncbi.nlm.nih.gov/) and PDB (https://www.rcsb.org/).

Statement of Ethics

The study protocol and consent forms were approved by the Ethics Committee of the Third Xiangya Hospital (No. 23911), with all procedures followed by the World Medical Association Declaration of Helsinki, and all essential permissions were obtained from the government and health commission. All personal information was anonymized during analysis and reporting to ensure confidentiality and privacy.

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The authors gratefully acknowledge the voluntary participation of all the study subjects.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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