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Insights into potential mechanisms of asthma patients with COVID-19: A study based on the gene expression profiling of bronchoalveolar lavage fluid

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ABSTRACT

Background: The 2019 novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently a major challenge threatening the global healthcare system. Respiratory virus infection is the most common cause of asthma attacks, and thus COVID-19 may contribute to an increase in asthma exacerbations. However, the mechanisms of COVID-19/asthma comorbidity remain unclear.

Methods: The “Limma” package or “DESeq2” package was used to screen differentially expressed genes (DEGs). Alveolar lavage fluid datasets of COVID-19 and asthma were obtained from the GEO and GSV database. A series of analyses of common host factors for COVID-19 and asthma were conducted, including PPI network construction, module analysis, enrichment analysis, inference of the upstream pathway activity of host factors, tissue-specific analysis and drug candidate prediction. Finally, the key host factors were verified in the GSE152418 and GSE164805 datasets.

Results: 192 overlapping host factors were obtained by analyzing the intersection of asthma and COVID-19. FN1, UBA52, EEF1A1, ITGB1, XPO1, NPM1, EGR1, EIF4E, SRSF1, CCR5, PXN, IRF8 and DDX5 as host factors were tightly connected in the PPI network. Module analysis identified five modules with different biological functions and pathways. According to the degree values ranking in the PPI network, EEF1A1, EGR1, UBA52, DDX5 and IRF8 were considered as the key cohost factors for COVID-19 and asthma. The H₂O₂, VEGF, IL-1 and Wnt signaling pathways had the strongest activities in the upstream pathways. Tissue-specific enrichment analysis revealed the different expression levels of the five critical host factors. LY294002, wortmannin, PD98059 and heparin might have great potential to evolve into therapeutic drugs for COVID-19 and asthma comorbidity. Finally, the validation dataset confirmed that the expression of five key host factors were statistically significant among COVID-19 groups with different severity and healthy control subjects.

Conclusions: This study constructed a network of common host factors between asthma and COVID-19 and predicted several drugs with therapeutic potential. Therefore, this study is likely to provide a reference for the management and treatment for COVID-19/asthma comorbidity.

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1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly spread around the world, leading to damage to the global healthcare system and social economy [1,2]. Inflammation-mediated cytokine storm is a common factor for predisposing to severe COVID-19 complicated by acute respiratory distress syndrome (ARDS), especially in the elderly or severely ill patients [3]. The therapeutic strategies for COVID-19 mainly include immunomodulators, glucocorticoids, antibiotic and antiviral agents. However, there is no specific medicine for the treatment of COVID-19 so far.

Ending the COVID-19 pandemic takes more time than other pandemic diseases in this poor environment [2]. People with chronic respiratory diseases need to be more vigilant about contracting SARS-CoV-2 [4]. Asthma is characterized by recurrent and reversible bronchial limitation that results in variable respiratory symptoms, such as cough, wheezing and shortness of breath [5]. Maintenance treatment with inhaled corticosteroids (ICS) and long-acting β_2 -agonists for asthma can relieve symptoms and reduce the risk of exacerbations [6]. In theory, patients with asthma should be more susceptible to SARS-CoV-2 infection due to a deficient antiviral immune response to respiratory viruses. Some researchers hold the idea that asthma morbidity is associated with the severity and mortality of COVID-19 [7], while others consider that asthma does not contribute to worse outcomes for severe COVID-19 patients [8]. The only consensus is that maintaining asthma control during the COVID-19 pandemic will be beneficial for asthma sufferers [9]. Allergic asthma characterized by blood eosinophilia does not significantly increase the risk of severe COVID-19 compared with nonallergic asthma [10]. Of note, eosinopenia is a biomarker of severe COVID-19 [11] and may be a protective target against excessive inflammatory response [12].

The overexpression of ACE2 (as a receptor of SARS-CoV-2) in lung cells contributes to the susceptibility to SARS-CoV-2 infection [13]. ICS is the cornerstone of asthma management, and asthma patients taking ICS have lower expression of ACE2 [14]. ICS use might alleviate the inflammatory response and lung damage to reduce the risk of infection [15]. Discontinuation of ICS treatment is not recommended for asthma patients due to the untoward effects [16]. However, Sarah L O'Beirne *et al.* show that the expression of ACE2 in the airway of asthma patients receiving long-term ICS treatment will increase, suggesting that patients with COVID-19/asthma comorbidity may suffer a more serious condition [17]. Moreover, Chloe I Bloom *et al.* find that the risk between asthma and COVID-19 is closely related to the asthma phenotype [18]. Therefore, it can be inferred that it is of significance to study the impact of COVID-19/asthma comorbidity on the prognosis of asthma patients complicated by COVID-19.

Viral infections as the main trigger of asthma are often associated with asthma exacerbations. Rhinovirus (RV) and respiratory syncytial virus (RSV), the most common viral infections, are also related to coronavirus infection [19]. Viruses must rely on host cellular factors to successfully promote the replication process. Therefore, virus-host interaction networks are potential targets for the in-depth study of viral infection and pathogenesis [20]. For patients with chronic respiratory diseases, the virus-host interaction relationship will be more complicated. The identification of host factors as drug targets is a potential treatment for patients who suffer from comorbidity with asthma and SARS-CoV-2 infection. To preliminarily explore the relationship between asthma and COVID-19 co-occurrence, we constructed the potential mechanism network of targeted host factors between COVID and asthma by using bioinformatics analysis. The identification of the host factor interaction network might clarify the molecular mechanisms and provide new insights into potential therapeutic targets for COVID-19 and asthma co-occurrence. The detailed flowchart is shown in Fig. 1.

2. Materials and methods

2.1. Transcriptomic data acquisitions

To determine the molecular mechanisms and protein targets shared between SARS-CoV-2 and asthma, we obtained the asthma-related datasets according to the following filter criteria [1]: It originated from the GEO (<https://www.ncbi.nlm.nih.gov/geo/>) database of the National Center for Biotechnology Information (NCBI) [2]; The search keyword was “asthma” [3]; The research type was “expression profiling by array” [3]; The species was “Homo sapiens” [4]; The sample type was bronchoalveolar lavage fluid (BALF) [5]; The dataset must contain control group and asthma group. No suitable COVID-19 dataset was available in the GEO database based on the same search strategy. Thus the datasets recruited in the literature published in Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>) were obtained following the same screening criteria.

The GSE155249 dataset included the BALF samples of 12 patients (10 COVID-19 positives and 2 COVID-19 negatives) [21]. CRA002390 contained the BALF samples of 2 patients (WHU01-2) from Zhongnan Hospital of Wuhan University [22] and 3 healthy BALF samples (Ctrl1-3) [23]. The “DESeq2 package” (v1.26.0) [24] in R was used to screen differential expressed genes (DEGs). The criteria were set as follows: adjusted P -value < 0.05 and $\log_2(\text{fold-change (FC)}) \geq 1$. Genes were selected and normalized to counts per million (CPM) for further analysis. We obtained DEGs from the literature attachments of the data sources for further analysis. The GSE74986 dataset contained 74 BALF samples

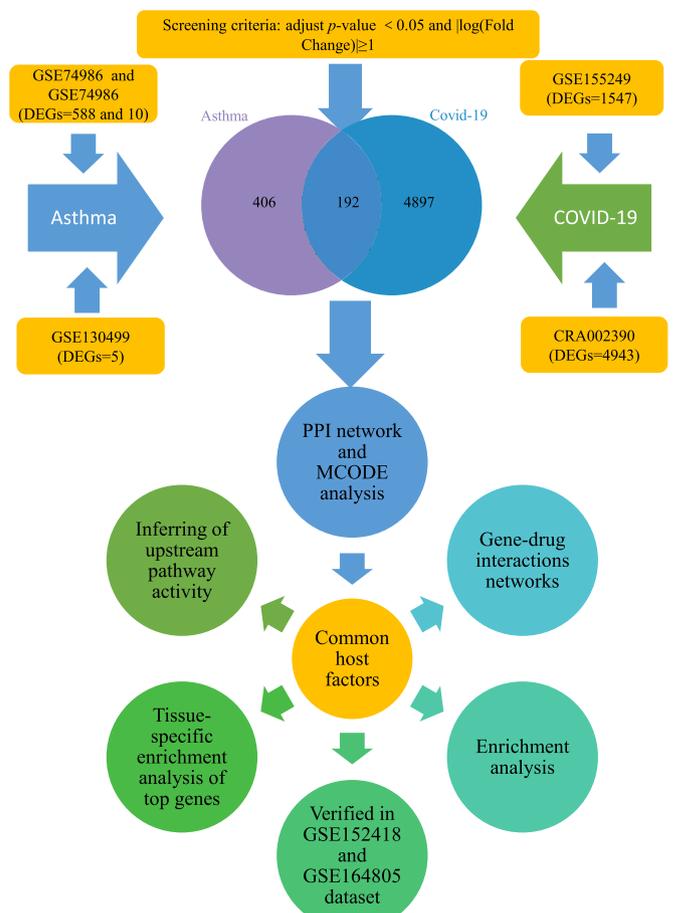


Fig. 1. Flowchart of the procedure of exploring host factor interaction networks between COVID-19 and asthma.

DEGs: differentially expressed genes; MCODE: molecular complex detection; PPI: protein and protein interaction.

of asthma patients and 12 BALF samples of healthy controls [25]. The GSE130499 dataset comprised 118 BALF samples from individuals with asthma and 38 healthy samples, and the GSE67940 dataset included 31 control BALF samples and 83 asthma BALF samples [26]. The detailed information of the datasets was shown in Table 1.

The “GEO2R” and the “limma” package in R [27] were used to obtain DEGs (adjusted P -value < 0.05 and $\log_2 |FC| \geq 1$). Finally, the overlapping host factors between asthma and COVID-19 were received and displayed by the Evenn online website (<http://www.ehbio.com/test/venn/#/>).

2.2. Gene Ontology and pathway enrichment analyses

The DEGs shared between asthma and COVID-19 were biologically classified by enrichment analysis. The “clusterProfiler” package in R [28] (version: 4.1.0) was used for the annotation of common host factors in Gene Ontology (GO; <http://www.geneontology.org/>), including biological processes (BP), cellular component (CC) and molecular function (MF). Kyoto Encyclopedia of Genes and Genomes (KEGG; <https://www.kegg.jp/>) and WIKI pathways enrichment results were generated via the online platform of WEB-based GENE SeT Analysis Toolkit (version 0.61, WebGestalt, <http://www.webgestalt.org/>) by using the “ORA” algorithm [29].

2.3. Protein-protein interaction analysis and network construction

Common host factors were put into the STRING database (version 11.5, <https://string-db.org/>) for generating a protein-protein interaction (PPI) network. The standard of connectivity between protein targets was greater than 0.4 (medium confidence). The PPI network was analyzed and visualized through Cytoscape software (version: 3.6.1, <https://cytoscape.org/>). The “degree” criterion in cytoHubba (<http://apps.cytoscape.org/apps/cytohubba>) was used to perform network topology analysis [30]. Then, module analysis was performed by the Molecular Complex Detection (MCODE) plug in Cytoscape software. Subsequently, the “clusterProfiler” package in R was used for the annotation of modules. The hub common host factors between COVID-19 and asthma were finally obtained based on the above two methods.

2.4. Inferring of upstream pathway activity and tissue-specific enrichment analysis of hub genes

SPEED2 (<https://speed2.sys-bio.net/>) [31] was used to infer upstream pathway activity of the host factor interaction network between asthma and COVID-19. The Bates test was used to quantify the mean rank change in enrichment statistics. And the hub common genes were selected to perform tissue-specific enrichment analysis by using the “Multi Gene Query” function available on the GTEx (V8, <https://www.gtexportal.org/home/>). The heatmap was used to show the expression of the transcripts per million (TPM) values for multiple genes in various tissues.

Table 1

Overview of data sets with their geo-features and their quantitative measurements in this analysis.

Disease name	GEO accession	GEO platform	Total DEGs count	Samples	Up regulated DEGs count	Down regulated DEGs count
Asthma	GSE74986	GPL6480	588	Asthma patients (N = 74); Healthy control (N = 14)	81	507
Asthma	GSE130499	GPL4133	5	Asthma patients (N = 116); Healthy control (N = 38)	1	4
Asthma	GSE67940	GPL6480	10	Asthma patients (N = 73); Healthy control (N = 31)	1	9
COVID-19	CRA002390	/	3943	COVID-19 patients (N = 3); Healthy control (N = 3)	2249	1694
COVID-19	GSE155249	GPL24676	1547	COVID-19 patients (N = 10); Healthy control (N = 2)	242	1305

DEGs: differentially expressed genes.

2.5. Gene-drug interactions networks

STITCH (version: 5.0, <http://stitch.embl.de/>) is a database that uses phenotypic effects, text mining and similarity information of chemical structure to predict the interaction between chemical proteins and small molecules [32]. The STITCH database contains interaction information of more than 68000 different chemical substances and 2200 drugs. The STITCH database was used to predict drugs that have potential therapeutic effects on COVID-19/asthma comorbidity. The gene-drug interaction network was constructed and the importance of a drug was ranked by the value of false discovery rate.

2.6. Verification of the expression levels of key host factors in COVID-19 datasets

The GSE152418 dataset was an RNAseq analysis of PBMCs from 17 COVID-19 subjects and 17 healthy controls. GSM4614985 was a sample obtained from the recovery period of COVID-19 and excluded from the second analysis. GSE164805 was also an RNAseq analysis of the PBMCs that contained 5 healthy controls, 5 mild and 5 severe COVID-19 patients. The clinical information of the two datasets were shown in Table 2 and Table 3. The “Differential expression analyses” function in the COVID19db (<http://hpcc.siat.ac.cn/covid19db/home>) database was used to obtain DEGs and displayed as a heatmap, boxplots and PCA diagram. The “Anova” method was used to analyze the expression differences of key targets in COVID-19 with varying severities and displayed as a boxplot.

2.7. Statistical analysis

All statistical analyses were calculated based on R (version: 4.1.0, <https://www.r-project.org/>). One-way ANOVA was used for the comparison of continuous variables among the three groups, and the *chi-square test* was used for the comparison of categorical variables among the three groups. *Student t-test* was used to judge whether there were differences between the two groups [27]. *Benjamini & Hochberg method* was used to calculate the adjusted P -value (adj. P .Value) and the adj. P .value < 0.05 was set as the filter criterion.

3. Results

3.1. Identification of common host factors between COVID-19 and asthma

BALF samples were selected for subsequent analysis to obtain the common host factors between COVID-19 and asthma. According to the screening criteria of adjusted P -value < 0.05 and $\log_2 |FC| > 1$, 588 (18327), 5 (19287) and 10 (19563) DEGs in asthma were obtained from GSE74986, GSE130499 and GSE67940 datasets, respectively (Supplementary Table 1-3). 1547 (56476) and 4943 (9610) DEGs between

Table 2
The clinical information of GSE152418 dataset.

		Healthy (N = 17)	Moderate (N = 5)	Severe (N = 8)	ICU (N = 4)	F-value	p
Gender	Male	8	0	5	2	$\chi^2 = 4.322$	0.229
	Female	9	4	3	2		

Table 3
The clinical information of GSE164805 dataset.

		Healthy (N = 5)	Mild (N = 5)	Severe (N = 5)	F-value	p-value
Age (X ± M)		59.80 ± 6.943	51.40 ± 4.393	58.00 ± 9.083	2	0.184
Gender	Male	4	4	5	$\chi^2 = 1.154$	0.562
	Female	1	1	0		

COVID-19 and healthy people were respectively obtained from GSE155249 and CRA002390 datasets (Supplementary Table 4-5). 192 common host factors of COVID-19/asthma comorbidity were received by taking the DEGs intersection between COVID-19 and asthma. These genes may be potential host factors for the SARS-CoV-2 virus to cause asthma and COVID-19 infection.

3.2. GO, KEGG and WIKI enrichment analyses highlighted the mechanisms for COVID-19/asthma comorbidity

BPs results showed that common host genes were involved in the

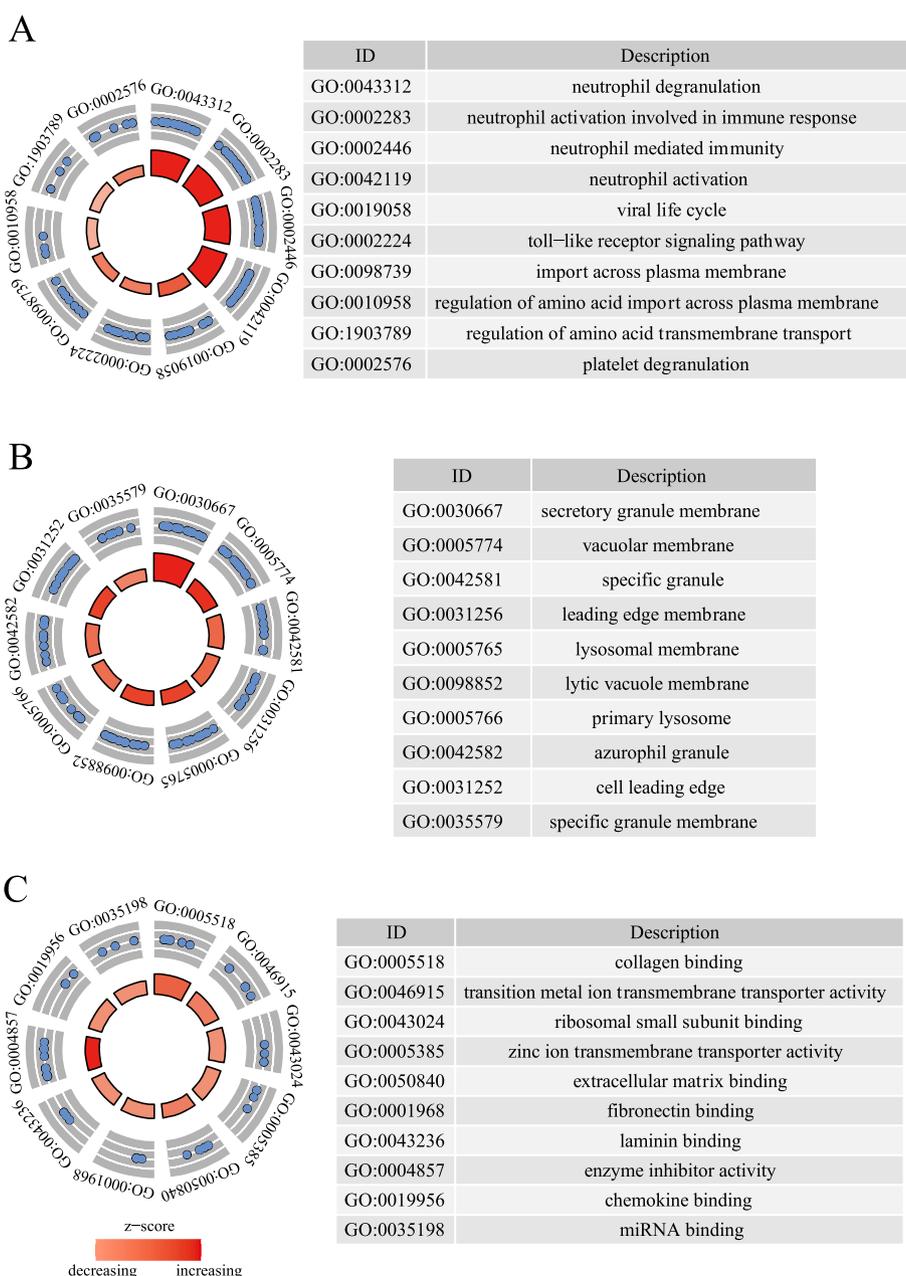


Fig. 2. Enrichment analysis of common host factors. (A): biological process analysis. (B): cellular component analysis. (C): molecular function enrichment analysis.

occurrence and development of two diseases, including neutrophil degranulation and neutrophil activation involved in immune response, neutrophil-mediated immunity, neutrophil activation, viral life cycle and other immune and virus-related signal pathways (Fig. 2A and Supplementary Table 6). According to KEGG pathway enrichment analysis, metabolic pathways, PI3K/AKT signaling pathway, pathways in cancer, lysosome, human T-cell leukemia virus 1 infection, proteoglycans in cancer, cytokine-cytokine receptor interaction, chemokine signaling pathway, phagosome and human papillomavirus infection played important roles in COVID-19/asthma comorbidity (Table 4). The top 10 pathways in WIKI enrichment analysis were the VEGFA-VEGFR2 signaling pathway, nuclear receptors meta-pathway, insulin signaling, angiotensin-like protein 8 regulatory pathway, focal adhesion-PI3K/AKT/mTOR-signaling pathway, PI3K/AKT signaling Pathway, Nrf2 pathway and circadian rhythm related genes (Table 5).

3.3. Protein-protein interaction network construction

The interaction network of the 192 common host factors of COVID-19/asthma comorbidity was generated by the STRING database and visualized by the Cytoscape software. The connectivity of 192 genes were sorted according to the degree values. The top genes were FN1, UBA52, EEF1A1, ITGB1, XPO1, NPM1, EGR1, EIF4E, SRSF1, CCR5, PXN, IRF8 and DDX5 (Fig. 3).

3.4. MCODE analysis revealed the critical common host factors for COVID-19 and asthma

MCODE analysis of 192 genes were performed and the five modules with the closest connection were obtained. In module 1, EEF1A1 and DDX5 with the highest degree values were significantly enriched in “nucleic acid transport” and “nucleocytoplasmic transport”. In Module 2, EGR1, IFITM2, IRF8, IFITM1 and ISG20 with the same difference were mainly involved in the “type I interferon signaling pathway”. In Module 3, HIST2H2AC and THBS1 were the most critical host factors, and were significantly enriched in “extracellular matrix organization” and “ECM-receptor interaction”. In module 4, UBE2D3, UBA52 and RNF146 had the same degree of connectivity, and were most prominent in “protein polyubiquitination” and “ubiquitin mediated proteolysis”. In module 5, SEC23A, MCFD2 and CTSC had the same degree values, and were most prominent in “vesicle targeting, rough ER to cis-Golgi” and “apoptosis”. EEF1A1, EGR1, UBA52, DDX5 and IRF8 were finally identified as the key co-host factors in COVID-19 and asthma based on the degree values ranking in the PPI network and MCODE analysis (Fig. 4 and Table 6).

3.5. SPEED2 inferred the upstream pathway activity of common host factors in COVID-19 and asthma

The activities of the upstream pathways of 192 host factors between COVID-19 and asthma were predicted by using the SPEED2 database. Fig. 5A ranked the important pathways and showed the average rank of

the genome provided in each entry. H₂O₂, VEGF, IL-1 and Wnt signaling pathways had the strongest activities in the upstream pathways.

3.6. Tissue-specific enrichment analysis revealed the expression of critical host factors in COVID-19 and asthma

The results of the tissue-specific analysis in the GETx database showed that EEF1A1 had a higher expression level in many tissues, and IRF8 had a lower expression level in many tissues. Most of the host factors between asthma and COVID-19 were distributed in tissues such as the lung, stomach, vagina, breast, liver, ovary, small intestine, spleen, whole blood and so on (Fig. 5B).

3.7. Gene-drug interactions networks indicated the potential drugs for COVID-19 and asthma

The 192 key host factors were searched in the STITCH database to identify known drugs that interact with host factors co-expressed between asthma and COVID-19. The host factor interaction networks were identified to probe candidate drugs that may be effective in the treatment of COVID-19/asthma comorbidity. Among all host factors, FN1 has the largest degree value. Ultimately, LY294002, wortmannin, PD98059 and heparin would be identified as the most potent drugs for COVID-19/asthma comorbidity (Table 7 and Fig. 6).

3.8. Verification of the expression levels of key host factors in COVID-19 related datasets

The heatmaps, boxplots and PCA diagrams in Fig. 7 showed the differences between COVID-19 and healthy groups in the GSE152418 and GSE164805 datasets. The expression levels of the hub host factors between asthma and COVID-19 were further verified in these two datasets (Fig. 8 and Fig. 9). Notably, DDX5 was lowly expressed in the COVID-19 group in the CRA002390 dataset. However, DDX5 showed an opposite trend against severity in both validation sets, which needs to be confirmed by further experiments. Although there was no statistical difference in the expression of EGR1 between the two groups in the GSE152418 dataset; the mRNA expression of EGR1 gradually increased with the severity of COVID-19 and showed the same trend in both validation datasets. UBA52 was lowly expressed in the healthy group, but there was no correlation between its increased expression and the severity of COVID-19. IRF8 and EEF1A1 were only validated in the GSE152418 dataset, and both were lowly expressed in COVID-19. As the severity of COVID-19 increased, the mRNA expressions of IRF8 and EEF1A1 showed a decreasing trend.

4. Discussion

The initial diagnosis and subsequent monitoring of asthma largely depend on lung function tests, and lung function tests will produce droplets or aerosols that may cause virus diffusion. Thus, the restrictions

Table 4
KEGG enrichment analysis.

Gene Set	Description	Size	Expect	Ratio	P-Value	FDR
hsa01100	Metabolic pathways	16	8	2	0.0000030122	0.000030122
hsa04151	PI3K-Akt signaling pathway	8	4	2	0.0027808	0.013904
hsa05200	Pathways in cancer	7	3.5	2	0.0060738	0.020246
hsa04142	Lysosome	6	3	2	0.013082	0.021803
hsa05166	Human T-cell leukemia virus 1 infection	6	3	2	0.013082	0.021803
hsa05205	Proteoglycans in cancer	6	3	2	0.013082	0.021803
hsa04060	Cytokine-cytokine receptor interaction	5	2.5	2	0.027799	0.027799
hsa04062	Chemokine signaling pathway	5	2.5	2	0.027799	0.027799
hsa04145	Phagosome	5	2.5	2	0.027799	0.027799
hsa05165	Human papillomavirus infection	5	2.5	2	0.027799	0.027799

KEGG: Kyoto Encyclopedia of Genes and Genomes.

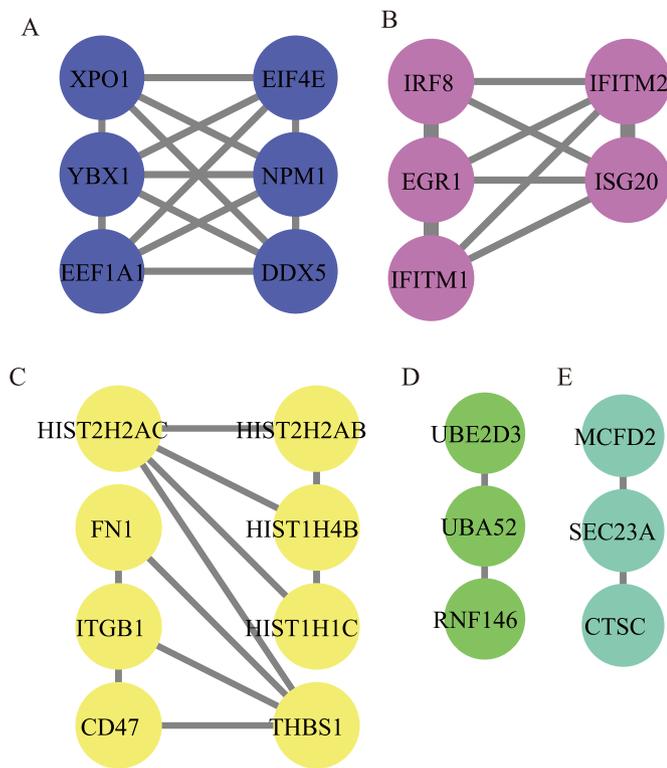


Fig. 4. Module analysis (A–E) of 192 common host factors between asthma and COVID-19. The dot represents the host factor, and the line represents the interaction of each host factor. Different color represents different modules.

4.1. Enrichment analysis highlights the bioinformatics mechanisms of host factors and significant shared signaling pathways

Several important terms of BP, CC and MF of COVID-19 in asthma patients’ co-pathogenic mechanisms were obtained through GO analysis. The BP was mainly related to the immune response that neutrophils participate in. Neutrophilic asthma (NA) is a clinically important asthma phenotype and characterized by neutrophil infiltration, which is different from allergic asthma [35]. External stimulus induces the migration of neutrophils to inflamed sites and activates immune response [36]. In addition, the increased levels of neutrophils are associated with severe COVID-19 [37], indicating that neutrophil-mediated immuno-inflammatory response is crucial in the pathological process of asthma and COVID-19. The CC involved in the immune response mainly included secretory granule membrane, vacuolar membrane, cell leading edge, lysosomal membrane and lytic vacuole membrane. Enzyme inhibitor activity is the most important molecular function. p38 MAPK upregulation promotes the expression of various proinflammatory cytokines and chemokines leading to

bronchial inflammation and airway remodeling, thus some enzyme inhibitors (such as MAPK inhibitors) are considered to be a protector for asthma patients [38]. Similarly, MAPK inhibitors can reduce COVID-19 infection by inhibiting inflammatory response and thus are regarded as a promising treatment [39].

KEGG analysis revealed that PI3K/AKT signaling pathway was one of the important pathways for comorbidity. PI3K/AKT pathway may play a key role in asthma by regulating airway remodeling [40]. PI3K/AKT pathway can promote T-helper 2 cytokine expression, eosinophil infiltration and mucus production, thus aggravating airway inflammation and hyperresponsiveness [41]. PI3K inhibitors can significantly reduce the number of eosinophils in the lungs, the level of eosinophil chemokine, and the expression of IL-5 and IL-13 in BALF of asthmatic mice [42]. Inhibition of PI3K/AKT/mTOR pathway with targeted molecules or natural compounds can attenuate peri-bronchial and peri-vascular inflammation to protect airways, such as LY294002 and Bixin [43,44]. On the other hand, the mTOR inhibitor rapamycin is identified as a potential medication for COVID-19 patients by constructing the drug-target network for the human coronavirus–host interactome via various bioinformatics approaches [45]. Mortality of diabetic patients hospitalized with COVID-19 is significantly reduced in the metformin-treated group, which may be related to the mTOR-inhibiting effect of metformin [46]. SARS-CoV-2 spikes can promote COVID-19-related inflammation and apoptosis through the PI3K/AKT/mTOR signaling pathway [47]. In the late stage of lung injury in mice, AKT inhibitors can promote the recovery of lung injury by increasing the number of regulatory T cells [48], which can inhibit lung fiber proliferation and inflammation [49,50]. Therefore, inhibition of AKT may increase the number of regulatory T cells in the lungs of COVID-19 patients, thereby reducing lung inflammation and promoting repair [51]. Thrombosis of microvessels and large vessels is one of the characteristics of COVID-19, which significantly increases the possibility of COVID-19 patients complicated by disseminated intravascular coagulation (DIC) [52]. Coincidentally, PI3K/AKT signaling pathway can activate platelets and promote coagulation [53]. The blocking of the PI3K/AKT signaling pathway is accompanied by a significant inhibitory with thrombosis [54]. Therefore, PI3K/AKT signaling pathway has great potential to reduce thrombosis and prevent DIC in COVID-19 patients [55]. The significance of PI3K/AKT in COVID-19 comorbidity was also determined in the WIKI enrichment analysis. Furthermore, MAPK and PI3K/AKT pathways are involved in inflammation. It is well known that COVID-19 is characterized by an overwhelming inflammation, and asthma is a chronic airway inflammatory disease. It is found that lung inflammation may promote the expression of ACE2 and TMPRSS2 and increase the risk of COVID-19 [56]. Our research revealed that the inflammatory process exists in COVID-19 and asthma. Therefore, it is of great value to find inflammatory pathways acting on COVID-19 and asthma comorbidity. And MAPK inhibitors that block inflammation are the drug candidate, which is consistent with the predicted results of pathway enrichment analysis.

Although human T-cell leukemia virus 1 infection does not increase

Table 6

Top items of enrichment analysis of genes in five modules.

Module	ONTOLOGY	ID	Description	P value	P.adjust	geneID	Count
1	BP	GO:0050657	Nucleic acid transport	1.74E-07	1.43E-05	EIF4E/XPO1/YBX1/NPM1	4
1	KEGG	hsa03013	Nucleocytoplasmic transport	1.04E-03	1.56E-02	EEF1A1/XPO1	2
2	BP	GO:0060337	Type I interferon signaling pathway	2.91E-12	2.43E-10	EGR1/IFITM2/IRF8/IFITM1/ISG20	5
2	KEGG	hsa05133	Pertussis	2.79E-02	6.19E-02	IRF8	1
3	BP	GO:0043062	Extracellular structure organization	1.88E-07	3.44E-05	THBS1/ITGB1/FN1/CD47	4
3	KEGG	hsa04512	ECM-receptor interaction	1.30E-08	4.02E-07	THBS1/ITGB1/FN1/CD47	4
4	BP	GO:0000209	Protein polyubiquitination	5.65E-06	4.40E-04	UBE2D3/UBA52/RNF146	3
4	KEGG	hsa04120	Ubiquitin mediated proteolysis	3.05 E-04	2.74E-03	UBE2D3/UBA52	2
5	BP	GO:0048207	Vesicle targeting, rough ER to cis-Golgi	4.09E-08	9.04E-07	SEC23A/MCFD2/CTSC	3
5	KEGG	hsa04210	Apoptosis	3.33E-05	4.17E-02	CTSC	1

BP: biological process; KEGG: Kyoto Encyclopedia of Genes and Genomes.

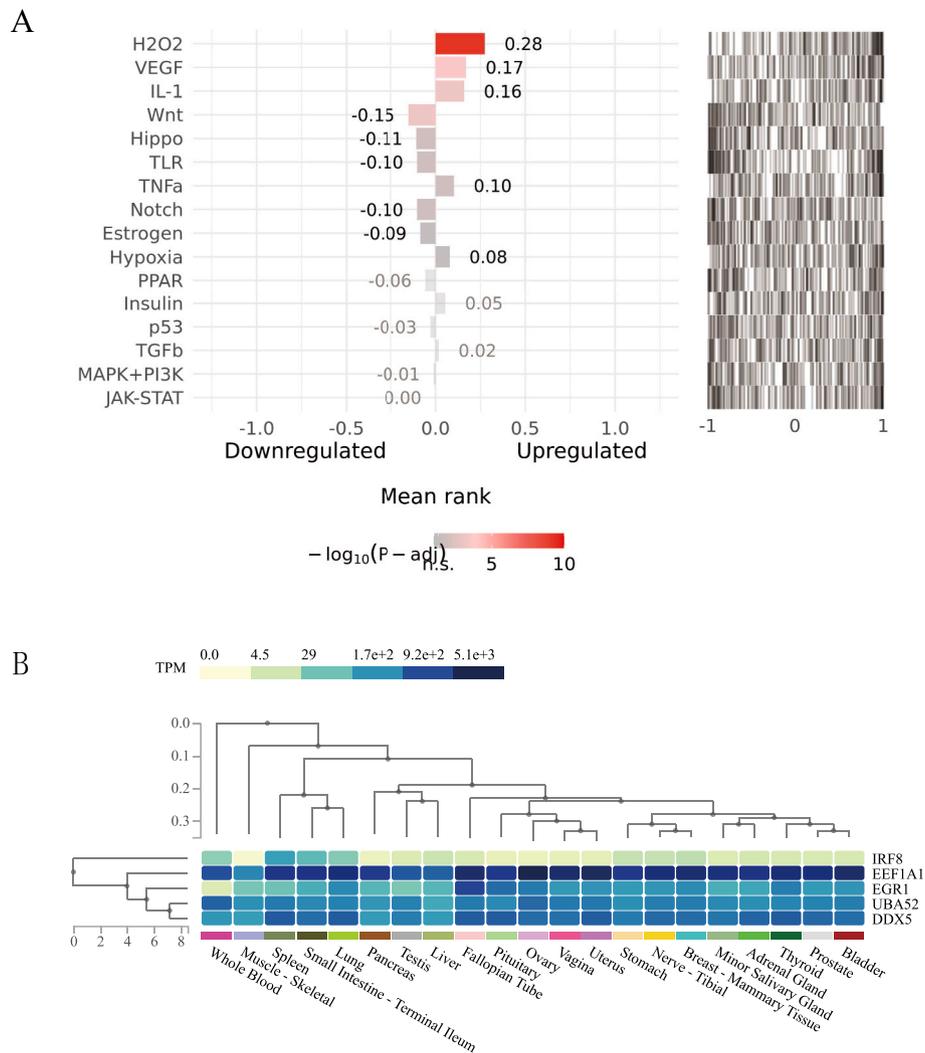


Fig. 5. (A): SPEED2 signaling pathway enrichment analysis of common targets between COVID-19 and asthma. (B): Tissue-specific expression analysis of the critical host factors (The vertical axis represents different tissues, and the horizontal axis represents the expression levels of 13 key host factors in each tissue. The expression levels of genes are measured by Transcripts Per Million (TPM). The darker the color, the higher the distribution of the corresponding host factor in a specific tissue).

the severity of COVID-19, it can cause immunosuppression [57]. A Genome-wide Association Study of Asthma shows that Wnt and cytokine-cytokine receptor interaction play key roles in the progress of asthma [58]. Immune effector cells can precipitate abnormal systemic inflammatory responses by releasing large amounts of pro-inflammatory cytokines and chemokines during SARS-CoV infection [59]. Besides, the common host factors between asthma and COVID-19 were significantly related to metabolic pathways, tumors, lysosome, phagosome and human papillomavirus infections.

In addition, WIKI enrichment analysis revealed that host-pathogen interaction of human coronaviruses-PI3K/AKT signaling pathway was closely related to the host factor interaction network. Nrf2 exerts an anti-inflammatory effect by inhibiting the expression of pro-inflammatory factors, such as IL-6 and IL-1 β [60]. Nrf2 also induces the expression of several macrophage-specific genes that involve in the virus surveillance, including macrophage receptors, scavenger receptors for oxidized low-density lipoprotein, CD36, and receptors required for bacterial phagocytosis and IL-17D [61–63]. Nrf2 in macrophages and epithelial cells can effectively inhibit the pro-inflammatory and oxidative effects of particulate pollutants in allergic inflammation and asthma [64]. In fact, Nrf2 deficient mice are more likely to develop severe airway inflammation and asthma [65]. Abnormal proliferation and hypertrophy of airway smooth muscle cells are one of the pathological

characteristics of asthma [66]. Nrf2 can activate antioxidant capacity and inhibit abnormal proliferation in airway smooth muscle cells [67]. In addition, Nrf2 can enhance the integrity of the airway epithelial barrier [68], which contributes to reducing air pollution and respiratory virus infection [69]. The above researches indicate that the Nrf2 pathway may be a potential and important target against asthma and COVID-19 comorbidity. SARS-CoV2 can interact with the Nrf2 pathway, indicating that targeting the Nrf2 pathway may help to inhibit the replication of SARS-CoV2 in cell lines [70].

4.2. PPIs and MCODE analyses reveal essential host genes for comorbidity

PPI network analysis was conducted to identify the key genes of COVID-19 and asthma, the top genes were FN1, UBA52, EEF1A1, ITGB1, XPO1, NPM1, EGR1, EIF4E, SRSF1, CCR5, PXN, IRF8 and DDX5. Cellular FN, a protein produced by human bronchial epithelial cells as a marker of vascular injury, is demonstrated to be positively associated with asthma severity and prothrombotic blood alterations [71]. FN drives airway remodeling and chronic inflammation when deposited into the asthmatic airways [72]. Research has shown that the high-resolution profile of immunoglobulin regions exhibits an upward trend of FN1 during COVID-19 [73]. Therefore, we can speculate that

Table 7
List of recommended medications for COVID-19 and asthma comorbidities.

Enrichment FDR	Genes	Pathway Genes	Fold Enrichment	Pathway
1.47E-05	13	200	8.1864088	STITCH LY294002 (CID00003973)
1.51E-04	11	175	7.9165272	STITCH LY294002 (CID100003973)
9.41E-04	10	176	7.1559518	STITCH wortmannin (CID000312145)
2.25E-03	13	350	4.6779479	SIDER Mood swings
2.41E-03	9	163	6.9540047	STITCH wortmannin (CID100005691)
3.85E-03	10	223	5.6477467	STITCH PD98059 (CID000004713)
8.81E-03	9	200	5.6675138	STITCH PD98059 (CID100004713)
1.43E-02	11	325	4.2627454	SIDER Febrile neutropenia
2.13E-02	10	313	4.0237940	SIDER Abdominal bloating
2.13E-02	10	314	4.0109793	SIDER Breast enlargement
2.13E-02	10	312	4.0366907	SIDER Injection site reaction
2.13E-02	10	316	3.9855934	SIDER Nocturia
2.13E-02	10	313	4.0237940	SIDER Perineal pain
2.13E-02	10	313	4.0237940	SIDER Perineal pain female
2.13E-02	12	412	3.6682937	SIDER Vaginal discharge
2.13E-02	10	313	4.0237940	SIDER Vaginal dryness
2.13E-02	8	188	5.3593511	STITCH Ang II (CID100025476)
2.13E-02	4	34	14.817030	STITCH cytochalasin B (CID100002919)
2.13E-02	10	310	4.0627339	STITCH progesterone (CID000005994)
2.13E-02	3	13	29.064173	STITCH sulindac sulfide (CID100091605)
2.45E-02	11	386	3.5890991	SIDER Night sweats
2.50E-02	4	41	12.287293	STITCH cytochalasin B (CID006433621)
2.50E-02	7	161	5.4758588	STITCH heparin (CID100008784)
2.50E-02	7	162	5.4420572	STITCH hydride acetate (CID020274032)
2.55E-02	11	396	3.4984653	SIDER Hypertrophy
2.55E-02	3	18	20.990792	STITCH dacarbazine (CID005353562)
2.55E-02	3	18	20.990792	STITCH dacarbazine (CID105281007)
2.90E-02	3	19	19.886013	STITCH sulindac sulfide (CID000091605)
3.66E-02	8	233	4.3242833	STITCH cycloheximide (CID000006197)
3.68E-02	3	21	17.992107	STITCH Arg-Gly-Asp (CID100104802)

the expression of FN1 may increase in asthma patients infected with SARS-CoV-2. ITGB1 is involved in cytoskeletal pathways and increased in myofibroblasts by regulating the TGF- β signaling pathway [74]. ITGB1 is an essential host factor for selected adenoviruses-associated variants that facilitate cell attachment and entry [75]. These studies demonstrate that the high expression of ITGB1 in asthma patients may contribute to cell adsorption and invasion after SARS-CoV-2 infection. XPO1 is a fraction of the karyopherin- β superfamily of nuclear transport proteins. Selective XPO1 inhibitors can exert anti-inflammatory, antiviral and anti-oxidant effects on COVID-19 patients [76]. Therefore, XPO1 may be a potential host factor for asthma and COVID-19 co-occurrence by mediating airway inflammation and virus replication. EIF4E is involved in the process of protein translation and its upstream molecule is MAPK-activated protein kinase (MNK)-1. Inhibition of MNK-1 can reduce inflammation and airway remodeling [77]. In addition, the phosphorylation and release of 4EBP (the corresponding downstream

binding protein of EIF4E) are required for hypertrophy of human airway smooth muscle cells [78]. The SARS-CoV-2 replication depends on the interaction between viral mRNA and EIF4E, and blocking this interaction is one of the targets for the treatment of COVID-19 [79]. COVID-19 patients have been proved to be at increased risk of stroke, pulmonary embolism and other thromboembolism [80]. Elevated expression of CCL5, a chemokine that binds to CCR5, has been demonstrated in patients with COVID-19 [81,82]. Platelet activation leads to the initiation of the coagulation cascade, which can be triggered by the CCL5/CCR5 axis [83]. Moreover, CCR5 inhibitors can reduce inflammatory cytokines in critically ill COVID-19 patients, increase CD8 T cells and reduce SARS-CoV-2 in plasma [84]. Therefore, the blocking of the CCL5/CCR5 axis may reduce the risk of complications caused by thrombosis in COVID-19 patients. Other targets related to virus infection and replication mainly included NPM1, EGR1, DDX5, SRSF1 and HIST2H2AC.

PPI networks were divided into different areas by module analysis according to different biological functions and showed the core targets in each module. EEF1A1 and DDX5 were the core targets with higher degree values in module 1. EEF1A1, a translation regulator, is involved in the protein translation process of eukaryotes as a plasmid vector for cell transfection. DDX5, a prototypical member of the RNA helicases family, is known to participate in RNA metabolism involving transcription and translation. EEF1A1 and DDX5 are confirmed to interact with several viral proteins to promote virus replication [85,86]. The host factors in module 2 were mainly enriched in the “type I interferon signaling pathway”, of which EGR1 was the most significant. EGR1 directly binds to the IRV promoter and upregulates the expression of IFN-regulated antiviral targets to suppress the replication of PEDV (a globally distributed alphacoronavirus) [87]. In Module 3, HIST2H2AC and THBS1 were the most critical host factors and significantly enriched in “extracellular matrix organization” and “ECM-receptor interaction”. In addition, UBE2D3, UBA52 and RNF146 had been regarded as the core targets in module 4. UBE2D3 plays an essential role in RIG-I-mediated virus infection as activators, and RIG-I senses viral RNA and initiates an innate immune response for type I interferon production [88]. UBA52 was identified as a host factor that interacts with the RNA polymerase acidic protein for virus replication in influenza [89] and relates to ubiquitination [90]. SEC23 has the function of transporting newly synthesized proteins and lipids from the endoplasmic reticulum to the Golgi apparatus for further processing and secretion. SEC23A, the most important target in module 5 involved in vitamin D synthesis, may affect the level of vitamin D synthesis [91]. Vitamin D deficiency increases the risk of COVID-19 and worsens the severity of asthma [92,93]. IRF8 was revealed as another key co-host factor for COVID-19 and asthma co-occurrence. The dysregulated immune response in COVID-19 may be related to decreased autophagy-related genes expression and the expansion of myeloid-derived suppressor cell subsets via suppressing IRF8-mediated mechanisms [94].

4.3. Inferring upstream pathway activity and tissue-specific enrichment analysis of hub genes

We tried to infer the upstream pathway activity via SPEED2 and upregulated genes were found, including H₂O₂, VEGF, IL-1 and so on. H₂O₂-mediated oxidative stress plays an important role in airway inflammation in asthma [95] and predicts COVID-19-associated mortality [96]. VEGF enhances disintegrin and metalloproteinase-33 expression and airway smooth muscle cell proliferation, which may be implicated in inflammation and airway vascular remodeling in asthma [97]. Inflammatory cytokines can activate the VEGF signaling pathway in COVID-19 patients [98], which may increase vascular permeability related to endothelial dysfunction to promote endothelial inflammation [98,99]. Severe vascular endothelial dysfunction predisposes to cause endodermatitis, vascular leakage and thrombosis [100,101]. Besides, VEGF participates in the cytokine storm exacerbation and thus anti-VEGF compounds are supposed to be helpful candidates for

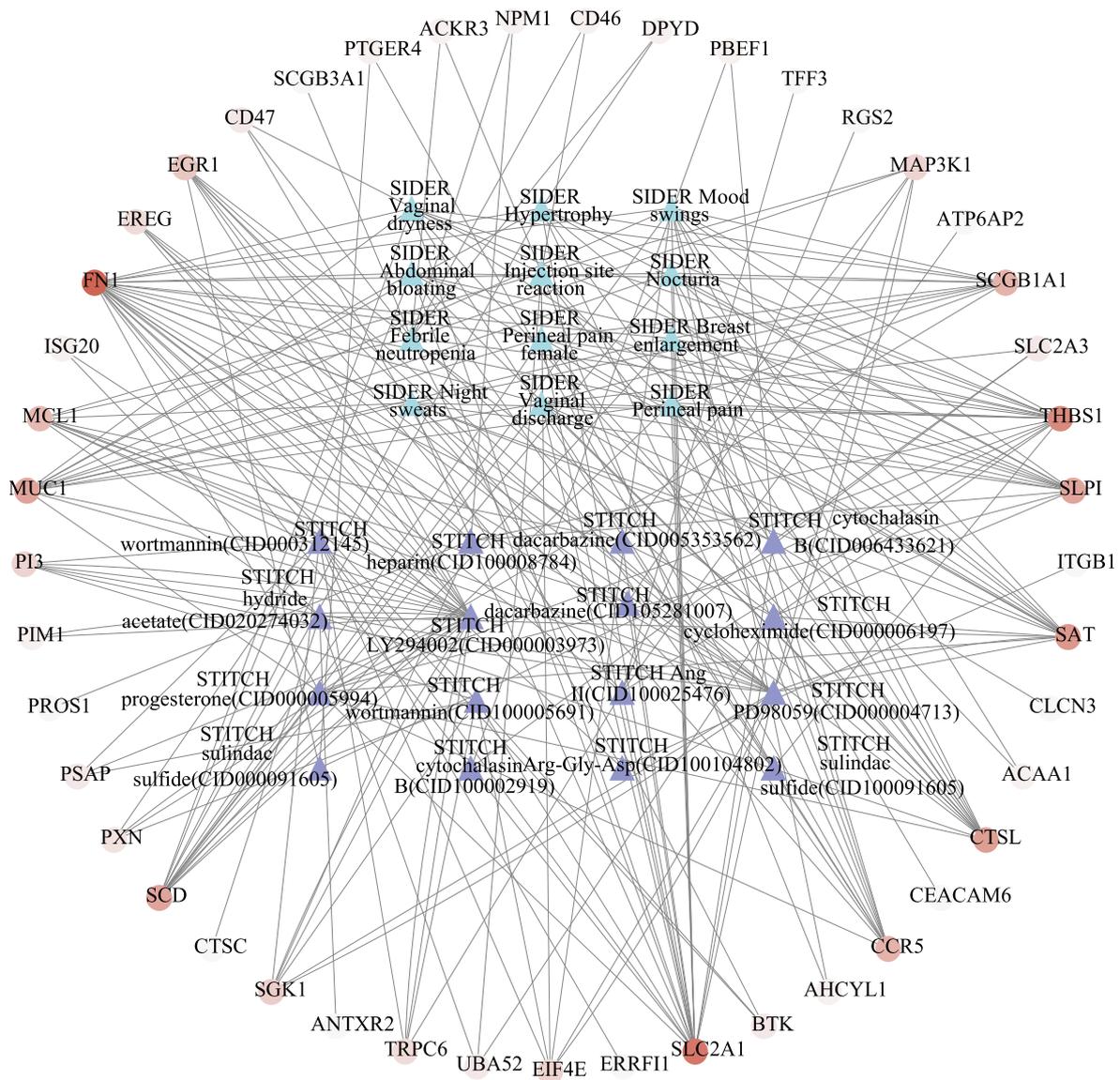


Fig. 6. Drug-gene interaction network. The circle represents the common host factor between asthma and COVID-19, the darker the color, the higher the degree value; the triangle represents the drug and side effect resource (SIDER) enriched by the host factors, blue represents SIDER and purple represents different drugs; the line represents the interaction between host factors and drugs or SIDER.

COVID-19 [102]. IL-1 is a potential therapeutic target in patients with neutrophilic asthma [103] and severe inflammatory ARDS complicated by COVID-19 [104].

Tissue-specific enrichment analysis was carried out to explore the novel association of tissue with genes in interaction networks, and we found that the expression of EEF1A1 was highly enriched in the lung. EEF1A1 is a translation regulator involved in protein synthesis in line with the result that EEF1A1 had a higher distribution density in other tissues and whole blood. Thus, EEF1A1 may be an important regulator in the pathophysiological response of patients with asthma and COVID-19.

4.4. Identification of candidate drugs for COVID-19/asthma comorbidity and corresponding biological functions

The host factors interaction network between COVID-19 and asthma was constructed to probe candidate drugs that may be effective for comorbidity. Ultimately, LY294002, wortmannin, PD98059 and heparin were identified as the most potent drugs.

LY294002, a PI3K/AKT pathway inhibitor, reduces PI3K and AKT expression and suppresses chronic inflammation [105]. Moreover,

LY294002 ameliorates glucocorticoid insensitivity in severe asthma by restoring histone deacetylase 2 activity and inhibiting the phosphorylation of nuclear signaling transcription factors [106]. LY294002 can inhibit the expression of MCP-1, IL-6 and IL-8 released by bronchial epithelial cells, promote pulmonary neutrophil apoptosis and reduce the inflammatory response [107]. LY294002 can inhibit the proliferation, migration and secretion of proinflammatory factors of airway smooth muscle cells to reduce airway hyperresponsiveness and airway inflammation [108]. Wortmannin selectively inhibits PI3K and affects the signal pathway transduction, leading to reduced iNOS expression and NO production in bronchiole epithelial cells to alleviate airway inflammation and hyperresponsiveness in asthma patients [109]. The PI3K/AKT pathway-specific inhibitors are supposed to ameliorate COVID-19 by inhibiting excessive inflammation, protecting cells and antiviral effect [110]. As mentioned, KEGG analysis revealed that PI3K/AKT signaling pathway was one of the important pathways for comorbidity. Considering the context of important scientific literature, the specific PI3K/AKT pathway inhibitors are recommended as the treatment for COVID-19/asthma comorbidity. LY294002 and Wortmannin with a function of selectively inhibiting PI3K and affecting the

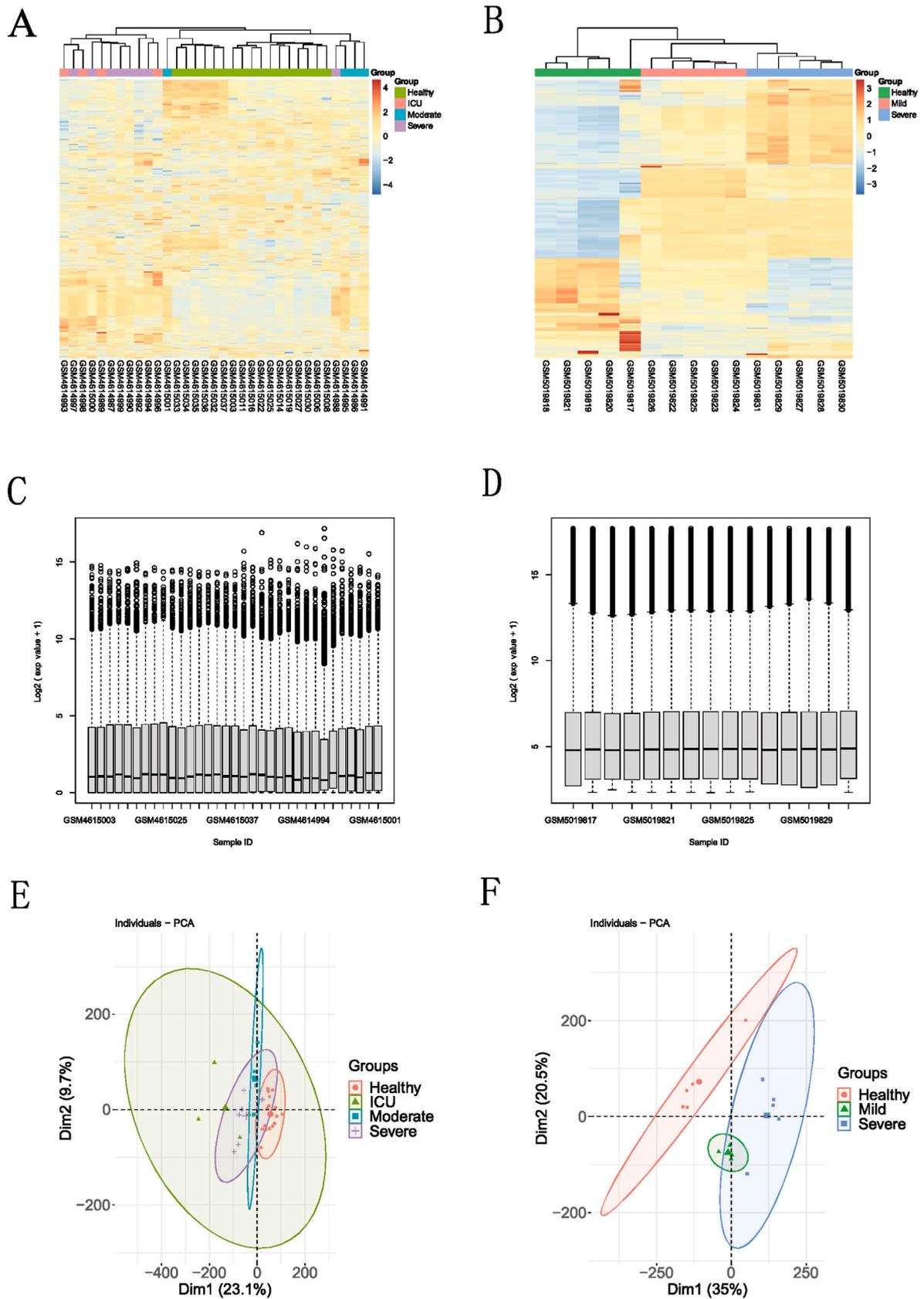


Fig. 7. (A, B): Heatmap between different severity of COVID-19 and healthy group in the GSE152418 and GSE164805 dataset; the blue box represents the healthy group, the gray box represents the moderate COVID-19 group, the orange box represents the severe COVID-19 group, and the red box represents living in ICU of the COVID-19 group. (C, D) Boxplot for viewing the distribution of sample values in the GSE152418 and GSE164805 datasets. A value centered on the median indicates that the data is normalized and cross-comparable; (E, F): Principal Component Analysis between different severity of COVID-19 and healthy group in the GSE152418 and GSE164805 dataset.

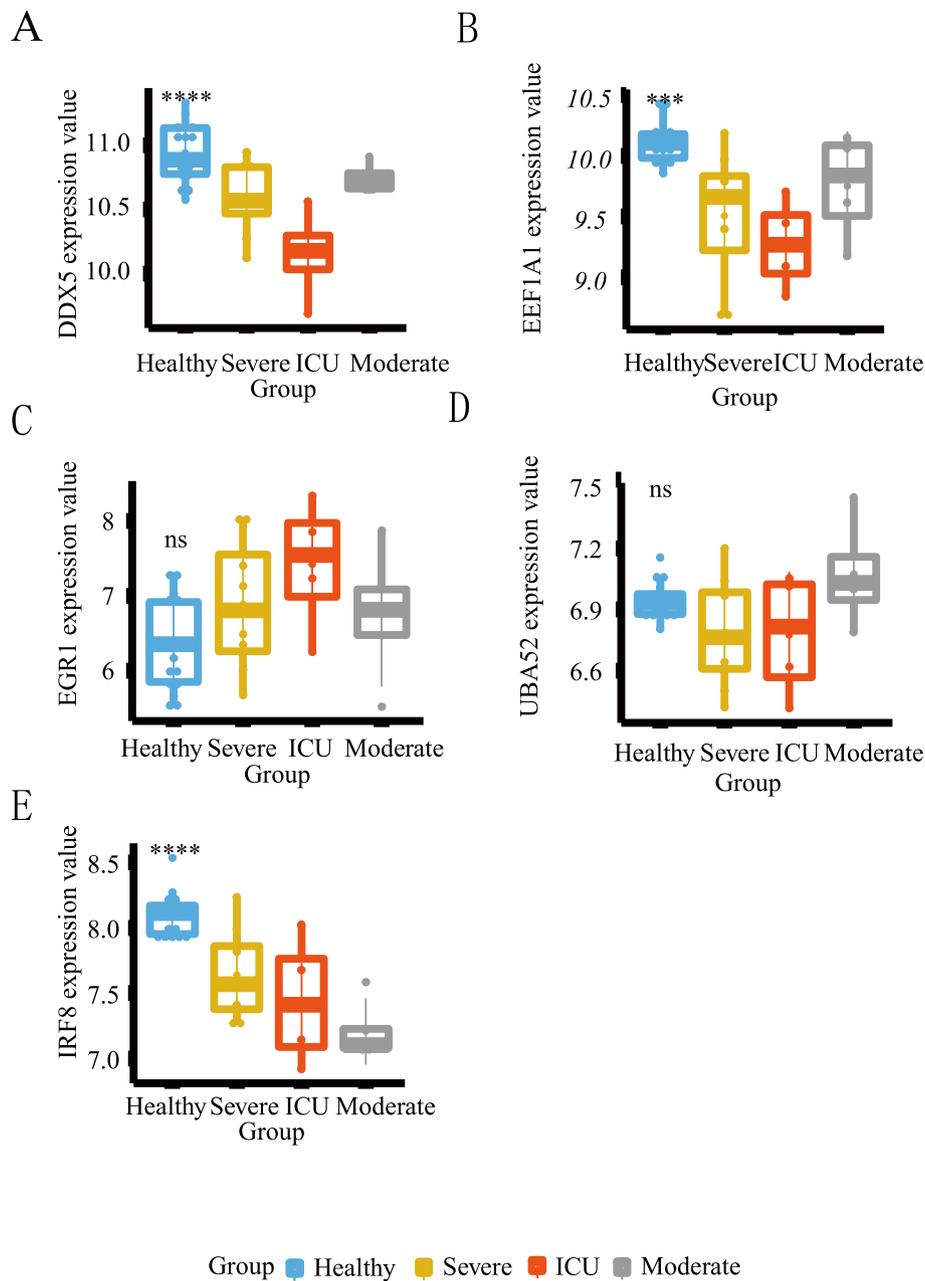


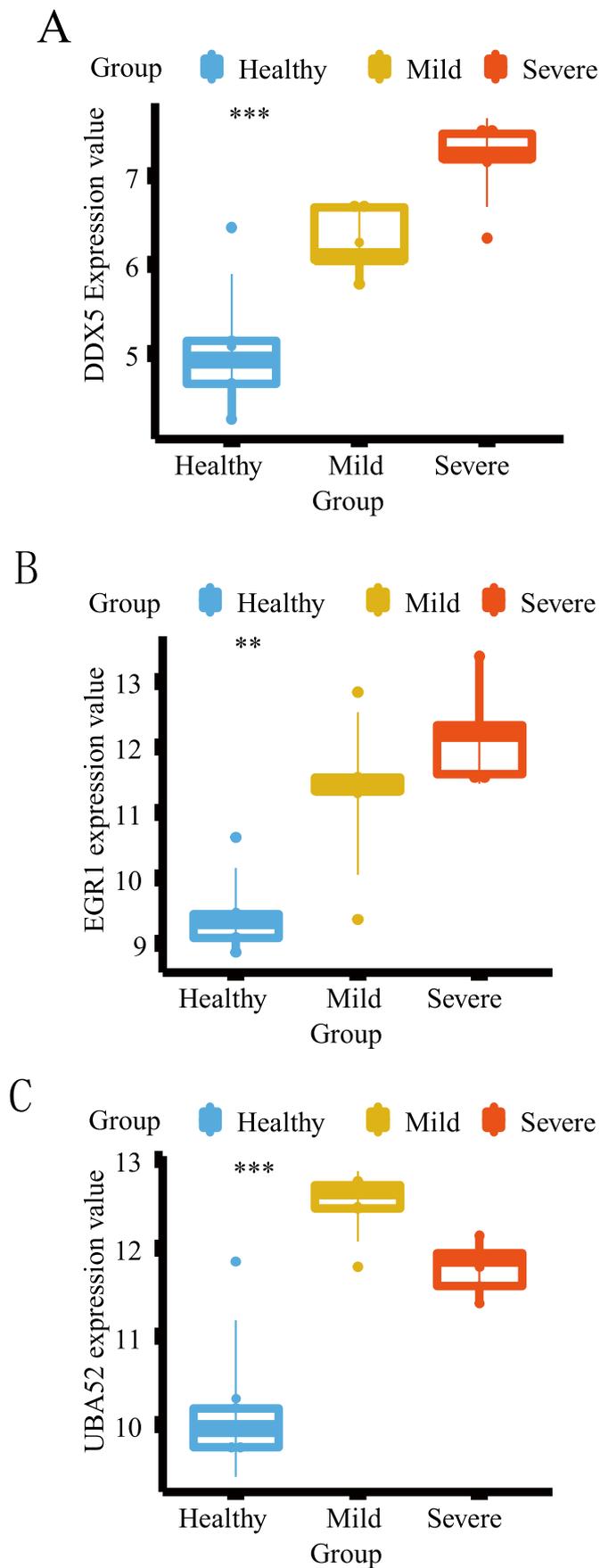
Fig. 8. Differential expression analysis of the hub common host factors in the GSE152418 dataset. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$. The horizontal axis represents the different groups, and the vertical axis represents the gene expression level. The blue box represents the healthy group, the gray box represents the moderate COVID-19 group, the orange box represents the severe COVID-19 group, and the red box represents the living in ICU of the COVID-19 group.

signal pathway transduction are potential therapeutic drugs for COVID-19/asthma comorbidity predicted by the STITCH database. Therefore, LY294002 and wortmannin are both considered to be potential pharmacological targets for COVID-19/asthma comorbidity. EGR1, a transcription factor related to vascular dysfunction, was highly expressed in COVID-19 patients compared with healthy people in this study. The study has shown that EGR1 is inhibited by pharmacological blockade of the PI3K/AKT pathway via wortmannin [111].

PD98059, an inhibitor of ERK, has an effect on regulating the imbalance of Th1/Th2 and Treg/Th17 for neutrophilic asthma [112] and was predicted to be a druggable target. We also revealed that the MAPK signaling pathway was related to the host factor interaction network, but it was not clear which specific way will be affected.

Exogenous heparin can inhibit the adhesion of SARS-CoV-2 to target cells to reduce virus infection [113]. Heparin and its chemical

derivatives have been proved to be effective heparanase (HPSE) inhibitors [114,115]. HPSE can cause vascular endothelial barrier dysfunction and vascular leakage, leading to pulmonary edema and proteinuria nephropathy [116–118]. Coincidentally, the expression of HPSE is increased in the plasma of COVID-19 patients [119]. Therefore, heparin may reduce the severe clinical manifestations of COVID-19 patients by inhibiting HPSE activity. Heparin has been shown to have a variety of anti-inflammatory properties [120–122]. In addition, heparin can also inhibit the NF- κ B signaling pathway and reduce the production of TNF- α , IFN- γ , IL-6 and IL-8 [122,123]. The excessive inflammatory response in severe COVID-19 patients is closely related to cytokine storm [124], suggesting that heparin may contribute to inhibiting the cytokine storm in severe COVID-19. A randomized clinical trial finds that the nebulized low molecular weight heparin (LMWH) can be used as an adjunctive treatment for an acute mild-moderate asthma



(caption on next column)

Fig. 9. Differential expression analysis of the hub common host factors in the GSE164805 dataset. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$. The horizontal axis represents the different groups, and the vertical axis represents the gene expression level. The blue box represents the healthy group, the gray box represents the moderate COVID-19 group, the orange box represents the severe COVID-19 group, and the red box represents the living in ICU of the COVID-19 group.

attack [125]. In addition, LMWH administered by inhalation can significantly improve the symptoms of ARDS and dyspnea to treat hypoxemia caused by COVID-19 [126]. Therefore, aerosol inhalation of heparin may be effective in the treatment of COVID and asthma comorbidity.

4.5. The expressions of the five key host factors in COVID-19 patients

EGR1 and UBA52 were proved to be highly expressed in COVID-19 patients compared with healthy people, indicating the above core genes may play an important role in the pathogenesis of COVID-19. EEFEA1, DDX5 and IRF8 showed an upward trend in the healthy group, suggesting that these genes might be decreased in COVID-19 patients. The key host factors that were highly expressed in COVID-19 patients may be the major pathogenic factors, while those that were highly expressed in healthy people and reduced in COVID-19 patients may be protective factors.

EGR1, a transcription factor that regulates antiviral genes, is reported to be restricted at the post-transcriptional level by SARS-CoV-2 infection [127]. This existing research result seems to be inconsistent with ours. UBA52 is a conserved host factor that interacts with H5N1 avian influenza virus proteins and plays an important role in viral amplification [89]. According to the results of this study, we speculate that the increased expression of UBA52 promotes ubiquitination of modified proteins, participates in SARS-CoV-2 replication and inhibits the innate immune response of the host.

EEFEA1 regulates the enzymatic delivery of aminoacyl tRNAs to the ribosome. The EEFEA1-based vector is applied for the expression of receptor-binding domain protein of SARS-CoV-2 to regulate the correct exposure of antigenic determinants, which has a significant impact on the accuracy of serological tests [128]. Furthermore, siRNA silencing of EEFEA1 induces a decrease in viral N protein levels during SARS-CoV-2 infection, indicating that the reduced EEFEA1 is a drug target for the inhibition of SARS-CoV-2 replication [129]. DDX5 enhances virus replication via interaction with several viral proteins as mentioned earlier. Although EEFEA1 and DDX5 are related to SARS-CoV-2 replication, there is no definite evidence to show the changes in EEFEA1 and DDX5 during SARS-CoV-2 infection. IRF8 is a transcription factor that belongs to the interferon regulatory factor family. In line with the results of this study is that the mRNA levels of IRF8 in mild and severe COVID-19 patients are significantly reduced compared with the healthy population [94].

5. Conclusion

To explore the mechanisms of COVID-19/asthma comorbidity, we screened the COVID-19 and asthma datasets derived from BALF samples and strictly processed the core common host factors. Successively, we conducted a series of bioinformatics analyses, such as the PPI network, enrichment analysis, inferring of upstream pathway activity, tissue-specific enrichment analysis and the expressions of key host factors in COVID-19. Our research reveals the immune response that neutrophils participate in is the most important biological process of COVID-19/asthma comorbidity. The PI3K/AKT signaling pathway may involve in allergic reactions in asthma patients and enhance the SARS-CoV-2 infection through mediating inflammation and apoptosis. And the WIKI enrichment analysis revealed that the Nrf2 signaling pathway may be the key signaling pathway to mediate the host-pathogen interaction.

We also identified EEF1A1, EGR1, UBA52, DDX5 and IRF8 as the key co-host factors for COVID-19/asthma comorbidity. Finally, we confirmed that LY294002, wortmannin, PD98059 and heparin may develop as druggable targets against COVID-19/asthma comorbidity.

6. Limitation

Datasets of this study were obtained from BALF samples, although we selected 2 PBMC-related datasets to verify the predicted targets, whole blood and lung tissue samples of COVID-19 patients were inevitably excluded to ensure the homogeneity resulting in the loss of some DEGs, which is a limitation in choosing asthma samples. In the future, further research needs to be carried out to compare the commonalities and differences by recruiting more samples of asthma patients complicated by COVID-19. It is worth noting that the combination of complete clinical information and transcriptome analysis will bring breakthroughs to the mechanism of COVID-19/asthma comorbidity. Finally, we have theoretically found some evidence to support the therapeutic values of potential drugs, but more clinical evidence is still needed.

Data availability statements

The data and R code of this article are available at Gene Expression Omnibus public repository and supplementary file.

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Authors' contributions

Xiu-Fang Huang, Shao-Feng Zhan and Xiao-Hong Liu participated in the guidance and revision of the entire article. Yong Jiang, Qian Yan and Cheng-Xin Liu conducted the writing and data analysis. Chen-Wen Peng participated in data analysis in the revision process. Hong-Fa Zhuang, Qiong Liu, Hui-Li Liao and Wen-Jiang Zheng performed the literature searches and data analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Liu Xiaohong reports article publishing charges was provided by Shenzhen Hospital of Integrated Traditional Chinese and Western Medicine.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.compbimed.2022.105601>.

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