



# Bioinformatics approach to identify common gene signatures of patients with coronavirus 2019 and lung adenocarcinoma

Xiao Liang<sup>1</sup> · Yali Chen<sup>1</sup> · Yuchao Fan<sup>2</sup>

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## Abstract

Coronavirus disease 2019 (COVID-19) continues as a global pandemic. Patients with lung cancer infected with COVID-19 may develop severe disease or die. Treating such patients severely burdens overwhelmed healthcare systems. Here, we identified potential pathological mechanisms shared between patients with COVID-19 and lung adenocarcinoma (LUAD). Co-expressed, differentially expressed genes (DEGs) in patients with COVID-19 and LUAD were identified and used to construct a protein–protein interaction (PPI) network and to perform enrichment analysis. We used the NetworkAnalyst platform to establish a co-regulatory of the co-expressed DEGs, and we used Spearman’s correlation to evaluate the significance of associations of hub genes with immune infiltration and immune checkpoints. Analysis of three datasets identified 112 shared DEGs, which were used to construct a protein–PPI network. Subsequent enrichment analysis revealed co-expressed genes related to biological process (BP), molecular function (MF), and cellular component (CC) as well as to pathways, specific organs, cells, and diseases. Ten co-expressed hub genes were employed to construct a gene–miRNA, transcription factor (TF)–gene, and TF–miRNA network. Hub genes were significantly associated with immune infiltration and immune checkpoints. Finally, methylation level of hub genes in LUAD was obtained via UALCAN database. The present multi-dimensional study reveals commonality in specific gene expression by patients with COVID-19 and LUAD. These findings provide insights into developing strategies for optimising the management and treatment of patients with LUAD with COVID-19.

**Keywords** COVID-19 · SARS-CoV-2 · Lung adenocarcinoma · Differentially expressed genes · Bioinformatics · Gene regulatory networks

## Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly worldwide since its outbreak in 2019. On 11 March 2020, the World Health Organization declared COVID-19 as a pandemic (Chan et al. 2020), requiring collaboration among healthcare systems across the

globe. Although approximately 80% of COVID-19 cases present as asymptomatic or mildly symptomatic, typically present as fever, cough, shortness of breath, gastrointestinal, musculoskeletal and neurological symptoms, severe and critically severe symptoms are experienced by approximately 15% and 5% of patients, respectively (Wu and McGoogan 2020). Severe cases rapidly progress to pneumonia and acute respiratory distress syndrome and may degenerate into a cytokine storm and multi-organ dysfunction, requiring intensive care and multi-dimensional life support, including oxygen therapy (Yang et al. 2020a). The high infection rate, which is associated with significant morbidity and mortality (Bakhribah et al. 2020), explains the devastation inflicted by COVID-19 that has overwhelmed healthcare systems worldwide.

Certain subgroups of patients are more susceptible to COVID-19. For example, people with reduced sperm quality are susceptible to infections, which may be due to environmental pollution in specific areas that are damaging to

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✉ Yuchao Fan  
yuchaofan\_pain@126.com

<sup>1</sup> Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

<sup>2</sup> Department of Anesthesiology, Sichuan Cancer Center, Sichuan Cancer Hospital & Institute, School of Medicine, University of Electronic Science and Technology of China, No.55, Section 4, Renmin South Road, Chengdu 610041, Sichuan Province, China

humans (Montano et al. 2021a, b). Cancer patients are particularly susceptible to COVID-19 because of their advanced age, immunosuppression, smoking, and frequent visits to healthcare facilities (Addeo and Friedlaender 2020). Further, patients with cancer with COVID-19 are more susceptible to rapid clinical deterioration (Bakouny et al. 2020). The mortality rates of patients with cancer with COVID-19 range between 25 and 30% (Saini et al. 2020; Zhang et al. 2021), and patients with cancer who have recently undergone chemotherapy or surgery are at higher risk of serious complications and death (Liang et al. 2020).

Patients with lung cancer are no exception, because they are more likely to develop severe illness or die after contracting COVID-19 through inherently associated pulmonary fragility and clinical or treatment-related risk factors (Passaro et al. 2021). Moreover, Liang et al. (Liang et al. 2020) found that lung cancer is the most common cancer among patients infected with COVID-19 (Liang et al. 2020), and the retrospective study by Yu et al. (Yu et al. 2020a) found that patients with non-small cell lung cancer (NSCLC) were the most likely among 1524 patients to contract COVID-19. Moreover, Dai et al. (Dai et al. 2020) found that compared with patients without cancer, those with lung cancer experience higher mortality, ICU admissions, and increased risk of developing critical symptoms and require invasive respiratory support. These factors pose a major challenge to effective management of patients with lung cancer, particularly during an epidemic.

The correlations between lung cancer and COVID-19 documented above suggest shared biological mechanisms (Bakouny et al. 2020). For example, certain types of anti-tumour hormone treatments may be effective for treating patients with COVID-19 (Stopsack et al. 2020). Therefore, the potential biological mechanisms and clinical interactions between COVID-19 and lung adenocarcinoma (LUAD) must be identified.

Protein–protein interactions (PPIs) between host and virus play a major role in viral infections and disease development. Viral infections interfere with human regulatory networks, leading to dysfunction of specific cellular processes. Bioinformatics analysis of gene expression identifies genes that contribute to pathogenesis, such as those of patients with COVID-19, as well as the components of specific pathways and their regulatory molecules. This information is typically acquired through analyses of differential expression and functional gene and pathway enrichment (Stopsack et al. 2020).

Bioinformatics studies of COVID-19 and cancer focus on the expression in cancers of key factors such as angiotensin-converting enzyme 2 (ACE2), transmembrane serine protease 2 (TMPRSS2), and neuropilin-1 (Chai et al. 2020; Ahmadi et al. 2021; Hoang et al. 2021; Hu et al. 2021a), although few studies report a common genetic signature of

COVID-19 and cancer, particularly of patients with LUAD, as well as potential underlying biological processes. Understanding the common genetic features between these two diseases and the underlying biological processes can help to explore the pathophysiological processes in patients with both diseases, improve the medical management of these patients, and allow the search for appropriate treatment modalities and medicines. Therefore, to fill these knowledge gaps, here we conducted bioinformatics analyses to identify genetic signatures common between patients with COVID-19 and LUAD. Our findings reported here on the regulatory networks and biological processes mediated by these genes illuminate the connections between the two diseases.

## Materials and methods

### Datasets

We employed the datasets as follows: COVID-19 genomics data were obtained from the Comparative Toxicogenomics Database (CTD) (<http://ctdbase.org>) and Dataset GSE147507 of the Gene Expression Omnibus database of the National Center for Biotechnology Information (NCBI) (Barrett et al. 2013). Dataset GSE147507 provides information on the transcriptional responses of lung epithelial and alveolar cells of patients with COVID-19. The genes collected from the CTD are associated with COVID-19 or its descendants. We obtained mRNA expression data for LUAD and clinical data of 594 samples from TCGA data (<https://cancergenome.nih.gov>).

### Identification of DEGs and genes co-expressed between patients with COVID-19 and LUAD

First, we analysed and screened for molecules that were significantly expressed in lung tissue of COVID-19 patients (GSE147507) as well as LUAD (TCGA) patients and normal lungs. These molecules may underlie the molecular occurrence of both diseases. This was done by comparing gene expression in the lungs of COVID-19 patients with gene expression in the lungs of normal subjects within the GSE147507 dataset, using the same approach for LUAD patients. This step was accomplished through an unpaired Student *t*-test via ‘DESeq2’ analysis implemented in the R environment (Love et al. 2014). Thresholds were defined as adjusted  $p < 0.05$  and log-fold change  $> |1|$ . The co-expressed genes among the CTD and DEGs of GSE147507 and LUAD data were identified using software included in the R environment. Data were visualised using the ‘ggplot2’ package in R.

## Protein–protein interaction (PPI) network analysis of co-expressed genes

To collect and integrate PPIs into a network of co-expressed genes, we searched the STRING database (<https://string-db.org/>) (Szklarczyk et al. 2019), and relevant data were imported into Cytoscape (v3.8.2) for visualisation and subsequent analysis. The cytoHubba plugins of Cytoscape were used to identify key modules; and the top 10 nodes, ranked using MCC of cytoHubba, are presented as hub genes. GeneMANIA (<http://www.genemania.org>) (Warde-Farley et al. 2010) uses extensive genomics and proteomics data to discover functionally similar genes. The GeneMANIA databases are further used to generate hypotheses about gene function, analyse gene lists, and prioritise genes for functional analysis as well as to construct PPI networks and predict gene functions.

## Enrichment analysis of co-expressed genes

The ‘clusterProfiler’ (Yu et al. 2012) and ‘org.Hs.eg.db’ packages of R were used to conduct Gene Ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of co-expressed genes. The cut-off threshold for GO and KEGG pathway enrichment analyses was  $p < 0.01$ . Further, we utilised Metascape tools (Zhou et al. 2019a) to identify MCODE components and completed enrichment analyses using integrated data of the biological information databases including STRING (Szklarczyk et al. 2019), BioGrid (Stark et al. 2006), OmniPath (Türei et al. 2016), InWeb\_IM (Li et al. 2017), COVID (<https://metascape.org/COVID>), DisGeNET (Piñero et al. 2017), and PaGenBase (Pan et al. 2013). The entirety of genes expressed by the human genome was used as the enrichment background. Terms with  $p < 0.01$ , minimum count = 3, and enrichment factor  $> 1.5$  were collected and grouped according to their membership similarities.

## Construction of a gene–miRNA, TF–gene interactions, and TF–miRNA co-regulatory network of hub genes

We predicted the correlations between hub genes and miRNA expression by constructing gene–miRNA interactions from TarBase v8.0 (Sethupathy et al. 2006). TF–gene interaction was built with the identified hub genes to evaluate the effect of TFs on functional pathways and the gene expression levels that encode their components (Taz et al. 2021). The network presents the TF–gene interaction via the ENCODE (<https://www.encodeproject.org/>) database. Further, we investigated miRNAs and regulatory TFs that modulate the expression of hub genes at the post-transcriptional

and transcriptional levels. Thus, a TF–miRNA co-regulatory network was established from the RegNetwork repository (Liu et al. 2015). These networks were built as minimum forms on the NetworkAnalyst platform (Zhou et al. 2019b) that generate comprehensive visual analyses of gene expression profiling data.

## Correlation between the expression of hub genes and immune infiltration in LUAD

We used the ‘gene set variation analysis’ package (Hänzelmann et al. 2013) to evaluate the correlation between the expression of hub genes and tumour-infiltrating immune cells in patients with LUAD. The immune cell subsets ( $n = 24$ ) included in the analysis were as follows: T cells, activated dendritic cells (aDCs), B cells, CD8 T cells, cytotoxic cells, DCs, eosinophils, immature DCs (iDCs), macrophages, mast cells, neutrophils, natural killer (NK) CD56 bright cells, NK CD56 dim cells, NK cells, plasmacytoid DCs (pDCs), T helper (Th) cells, central memory (Tcm) T cells, effector memory T (Tems) cells, T follicular helper (Tfh) cells, gamma delta T (Tgd) cells, Th1 cells, Th17 cells, Th2 cells, and regulatory T (Treg) cells. The associations of expression of hub genes were evaluated as well. Spearman’s correlation was used to evaluate the correlation of gene expression, and  $p < 0.05$  indicates a significant difference.

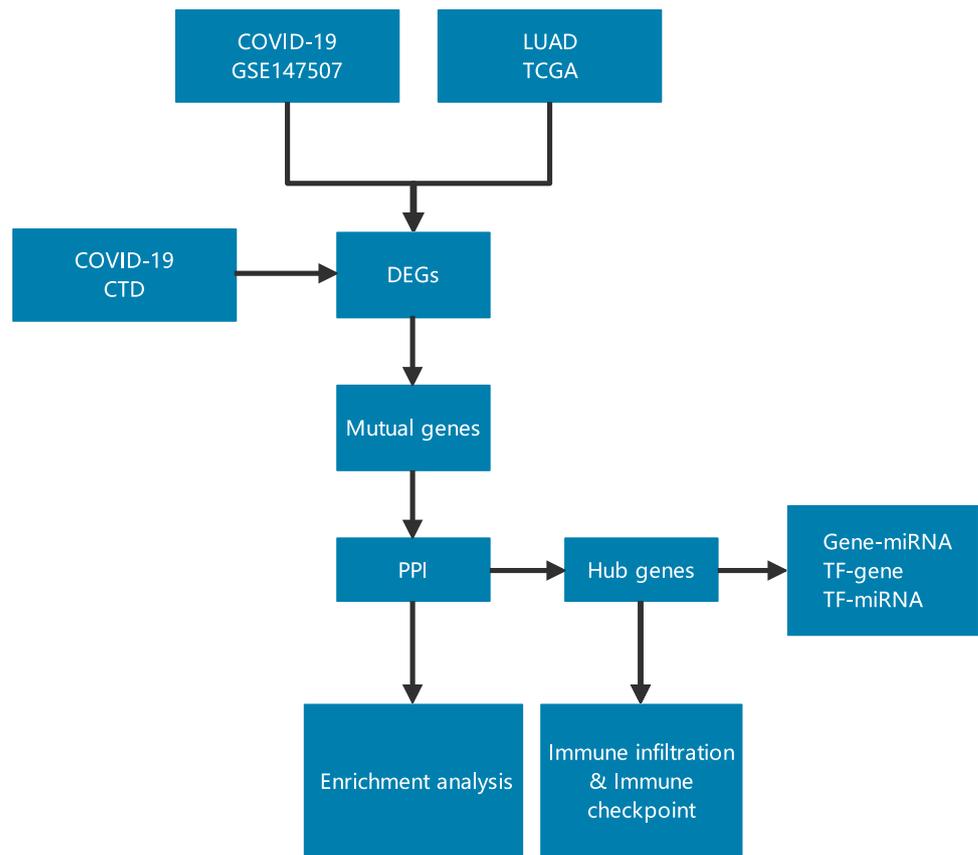
## Promoter methylation level of hub genes in LUAD

The methylation level of hub genes in LUAD and corresponding adjacent tissues were obtained from TCGA and present via the UALCAN database (<http://ualcan.path.uab.edu/analysis.html>). Student’s *t*-test was used to evaluate the significance of differences. Statistically significant was considered  $p < 0.05$ .

## Results

### Identification of DEGs co-expressed by patients with COVID-19 and LUAD

The design of our study is presented in Fig. 1. We identified 816 DEGs in the GSE147507 dataset between patients with COVID-19 and normal people, including 396 upregulated genes and 420 downregulated genes (Fig. 2A). Analysis of TCGA LUAD data revealed 13,874 DEGs, among which 10,635 were upregulated and 3,239 were downregulated (Fig. 2B). We identified 7703 genes among the CTD entries, which are associated with COVID-19 or its descendants. Venn analysis identified 112 genes in the CTD and DEGs in GSE147507 co-expressed by patients with COVID-19 and

**Fig. 1** Overall flow chart of this study

LUAD (Fig. 2C). These genes are listed in Supplemental Table 1 and were further analysed.

### PPI network analyses of co-expressed genes

PPI network analysis was conducted to identify potential interactions of the products of co-expressed genes. The PPI network with interaction nodes and edges was visualised using Cytoscape (Fig. 3A). The top 10 ranking hub genes were as follows: IL1B, CCL2, FOS, JUN, HBEGF, PDGFB, PGF, SPI1, MMP1, and CD34 (Fig. 3B) (Supplemental Table 2). The PPI network identified the functions of the co-expressed genes, which are primarily related to cell chemotaxis, leukocyte chemotaxis, negative regulation of viral process, response to type I interferon, cellular response to type I interferon, response to virus, and myeloid leukocyte migration (Fig. 3C).

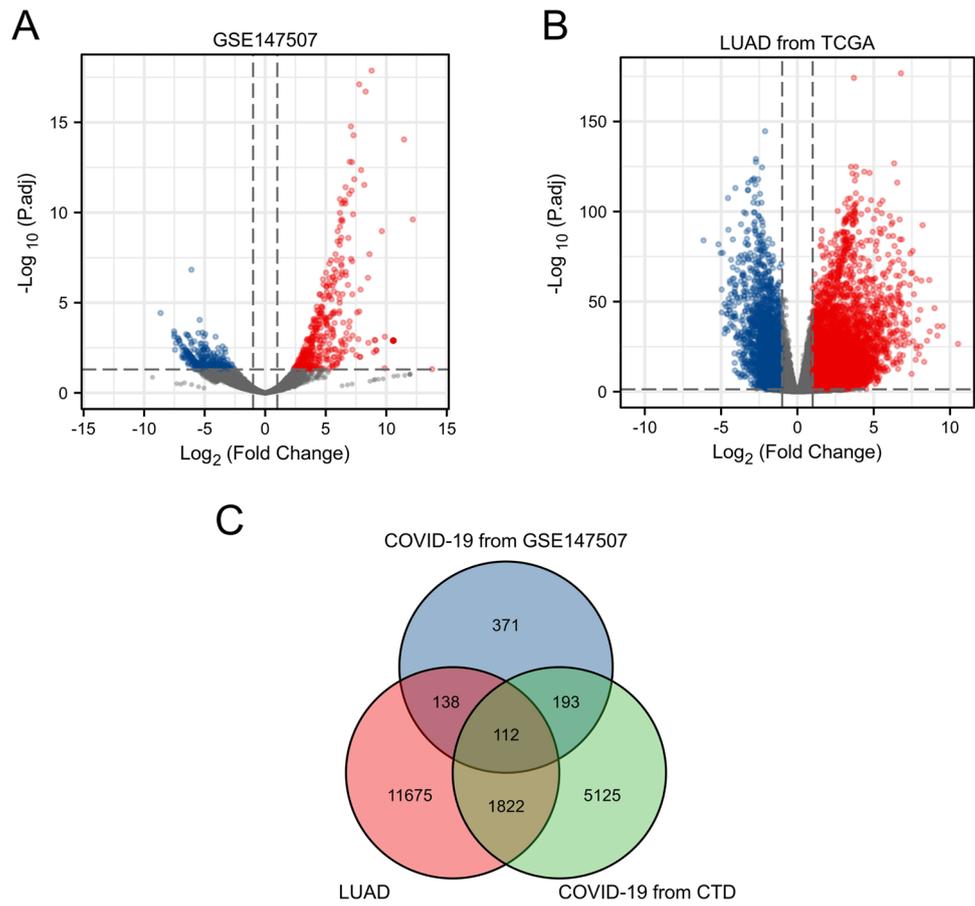
### Enrichment analysis of co-expressed genes between COVID-19 and LUAD

We first used the R environment to predict the functions of genes co-expressed by patients with COVID-19 and LUAD. The products of co-expressed genes were significantly associated with the functional categories as follows: biological

process (BP), molecular function (MF), and cellular component (CC) (Fig. 4A). The BP GO terms included leukocyte migration, cell chemotaxis, leukocyte chemotaxis, myeloid leukocyte migration, and response to organophosphorus. Most genes in CC ontology are associated with cytoplasmic vesicle lumen, vesicle lumen, tertiary granule membrane, and tertiary and specific granules. Further, receptor ligand activity, oxygen binding, haeme binding, antioxidant activity, and chemokine activity represented most MF ontology terms. Moreover, KEGG pathway analysis showed that the co-expressed genes most closely correlated with those of the IL-17 signalling pathway, MAPK signalling pathway, osteoclast differentiation, fluid shear stress, atherosclerosis, and Kaposi sarcoma-associated herpesvirus infection (Supplemental Table 3).

The co-expressed genes were subjected to pathway and process enrichment analysis using the databases as follows: KEGG pathway, GO Biological Processes, Reactome Gene Sets, Canonical Pathways, DisGeNET, PaGenBase, Wiki Pathways, and COVID. The top 20 clusters of co-expressed genes and their representative enriched terms are shown in Fig. 4B and listed in Supplemental Table 4. Five MCODE components were identified. Each component was independently subjected to pathway and process enrichment analysis, and the three highest scores with significant *p* values

**Fig. 2** Mutual genes among of CTD and DEGs of GSE147507 and LUAD. **A** DEGs of COVID-19 from GSE147507. **B** DEGs of LUAD from TCGA. **C** Common genes among of CTD and DEGs of GSE147507 and LUAD



items are shown in Fig. 5A, and co-expressed enriched genes were identified in the COVID (Fig. 5B), PaGenBase (Fig. 5C), and DisGeNET (Fig. 5D) ontology categories. The top few enriched clusters (one term per cluster) are listed in Supplemental Tables 5, 6, and 7.

### Gene-miRNA, TF-gene interactions and TF-miRNA co-regulatory network of hub genes and determination of regulatory signatures

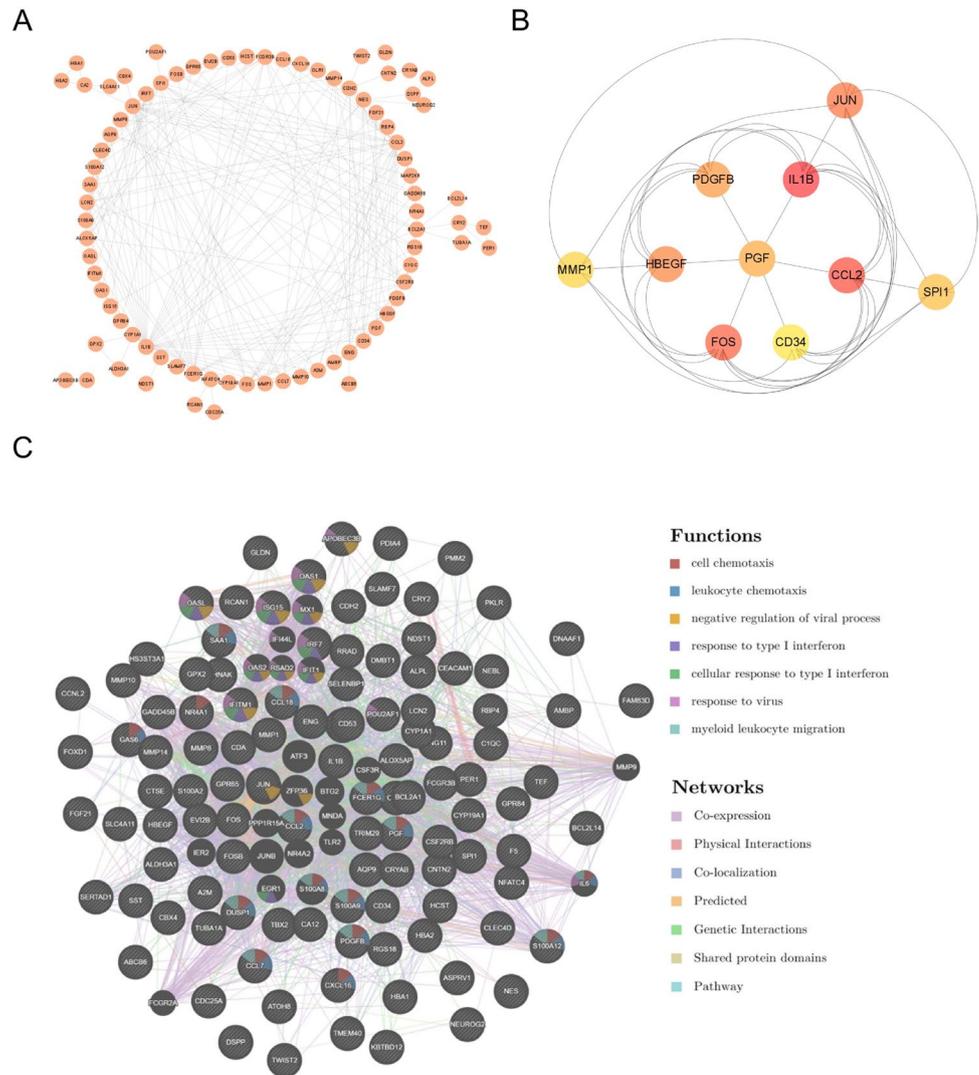
TarBase v8.0 was employed to predict specific miRNAs targeting hub genes and to identify gene-miRNA interactions. This analysis identified 16 miRNAs predicted to interact with 10 hub genes, and the gene-miRNA interaction network comprised 60 edges (Fig. 6A). These miRNAs potentially regulate the expression of hub genes. When we used NetworkAnalyst to predict regulatory interactions of 11 TF-genes with hub genes, we found that the network included 21 nodes and 33 edges (Fig. 6B). We next used NetworkAnalyst to construct a TF-miRNA regulatory network to identify significant differences at the transcriptional and post-transcriptional levels. The TF-miRNA co-regulatory network comprised 18 nodes and 37 edges, and one miRNA

and seven TF-genes were predicted to interact with the hub genes (Fig. 6C).

### Correlation between hub genes and immune infiltration in LUAD

Figure 7A illustrates the correlation between the expression of hub genes with immune infiltration, and Spearman's correlation of each gene with subsets of immune cells is presented in Table 1. We further evaluated the association of the expression of hub genes mainly with markers of infiltrating lymphocytes (Fig. 7B, Table 2) and immune checkpoints (Fig. 7C, Table 3). The results showed that hub genes were positively correlated with most immune cells, immune cell markers, and immune checkpoints, although the correlations were mostly weak or moderate. IL1B, CCL2, HBEGF, and SPI1 were positively correlated with most immune cells. CD34 was positively correlated with immune cells except Th2 and T helper. IL1B, CCL2, HBEGF, and SPI1 were positively correlated with most immune cell markers and immune checkpoints. Among them, SPI1 had the strongest correlation among all hub genes Figs. 8 and 9 (Supplemental Figs. 1, 2, and 3)

**Fig. 3** PPI network of mutual genes. **A** The PPI network of mutual genes built via STRING and present by Cytoscape. **B** The top 10 hub genes ranked by MCC of cytoHubba. **C** The PPI network of mutual genes built via GeneMANIA



**Methylation Level of hub genes in LUAD**

We compared the hub genes’ methylation levels of LUAD with normal tissue. The methylation level of HBEGF ( $p < 0.001$ ) and PDGFB ( $p < 0.001$ ) was significantly higher in LUAD compared with normal tissue. But IL1B ( $p < 0.001$ ), CCL2 ( $p < 0.001$ ), and MMP1 ( $p < 0.001$ ) in LUAD showed significantly lower methylation level compared with normal tissues. No differences were shown on FOS, JUN, PGF, and SPI1.

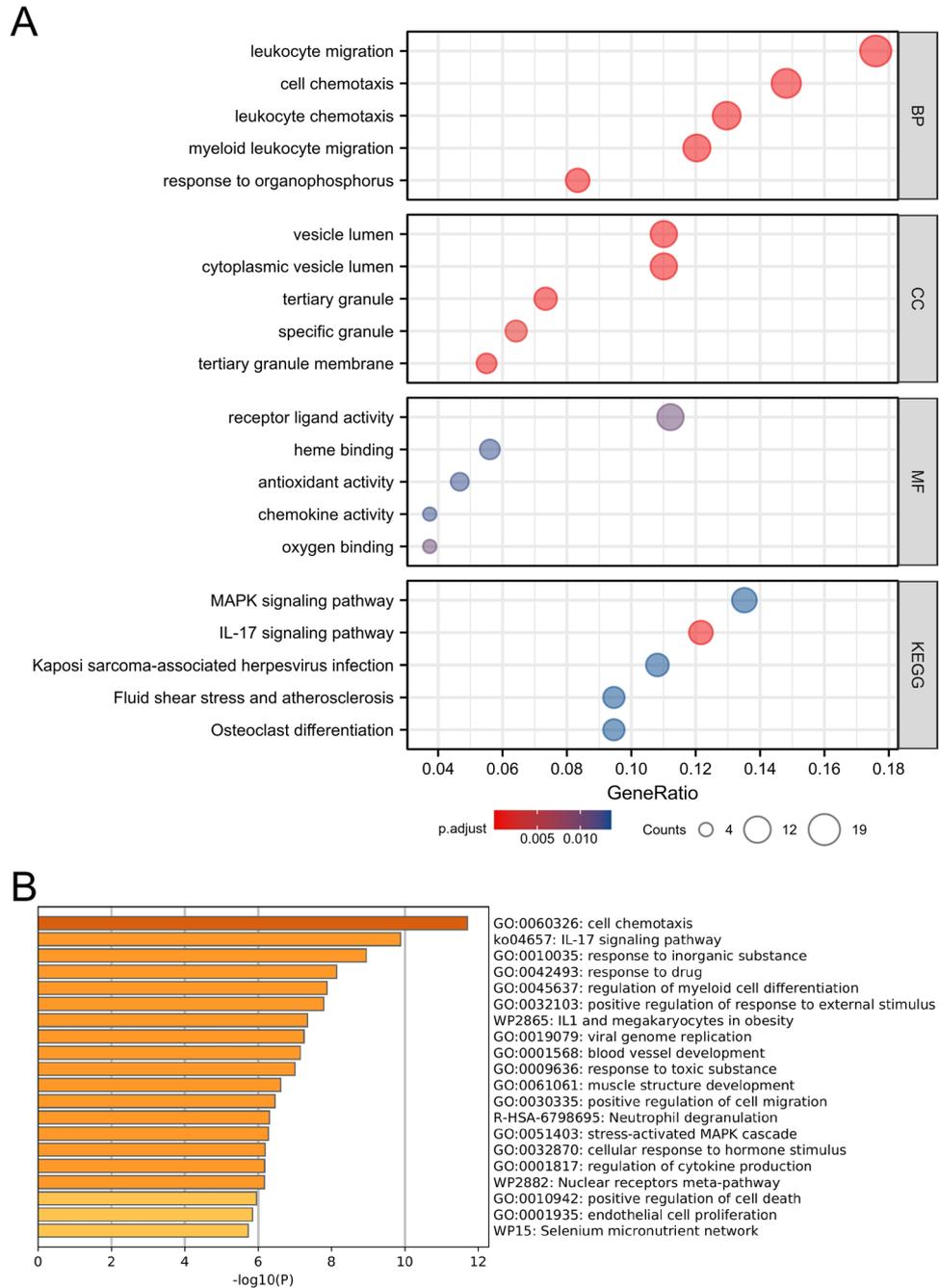
**Discussion**

COVID-19 damages numerous organs and systems in the human body, particularly the respiratory system. Patients with LUAD are therefore at high risk of contracting COVID-19. The combination of COVID-19 infection and LUAD predicts a higher mortality rate and more severe

clinical outcomes. The shared symptoms of the two diseases urgently require the identification of their common molecular genetic regulatory mechanisms.

To this end, here we conducted a comprehensive bioinformatics investigation to better understand how COVID-19 and LUAD affect the lung epithelium and alveolar tissues. First, we identified 112 shared genes with similar expression patterns extracted from three databases. Subsequently, the common genes were used to construct PPI networks, and the ensuing enrichment analysis revealed significant associations with the BP, CC, and MF pathways as well as with closely related research areas, specific organs, cells, and diseases. Ten hub genes representing the co-expressed genes were identified and used to construct gene-miRNA, TF-gene interactions, and TF-miRNA co-regulatory networks. Also, we analysed the association of hub genes with immune infiltration and immune checkpoints. Finally, methylation level of hub genes in LUAD was compared with normal tissues.

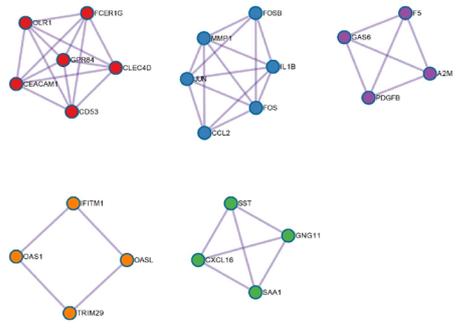
**Fig. 4** Functional enrichment of mutual genes between COVID-19 and LUAD. **A** GO and KEGG pathway enrichment analyses for mutual genes via R software. **B** Functional enrichment analysis for mutual genes via Metascape



The identification of co-expressed genes involved determining the intersection of COVID-19 and LUAD TCGA datasets as well as with COVID-19 expression data of the CTD database. This analysis identified co-expressed genes closely associated with COVID-19. Further, we considered the hub genes CCL2 and IL1B as phenotypic and mechanistic markers according to the direct data for COVID-19 in the CTD database. Moreover, we identified CCL2 as a potential biomarker of the severity of COVID-19 and the associated increased risk of mortality (Abers et al. 2021).

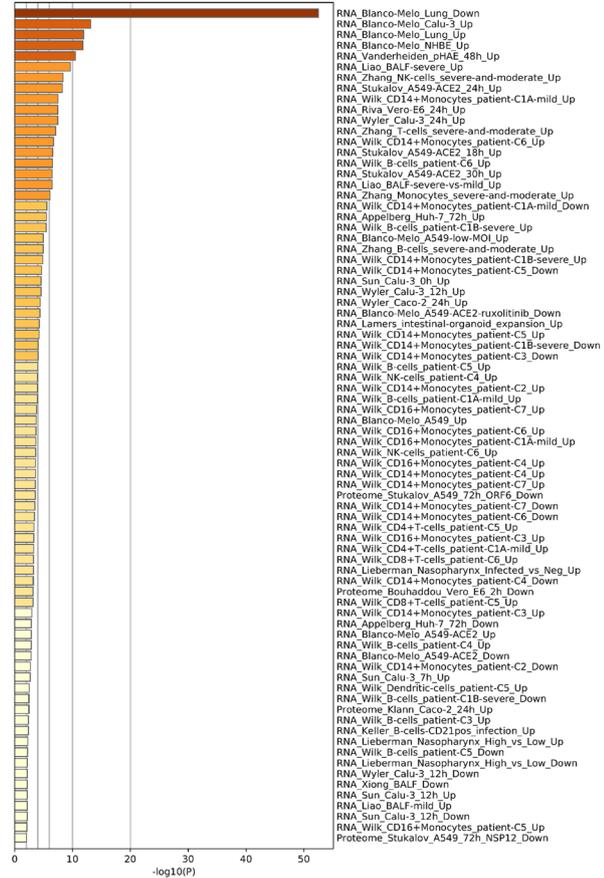
These hub genes are significantly associated with COVID-19 and play important roles in the tumorigenesis of LUAD. IL1B plays a crucial role in mediating acute and chronic inflammation and is associated with lung carcinogenesis (Li et al. 2015). IL1B antagonists reduce the requirement for administering oxygen to patients with COVID-1 as well as reducing fever, length of stay in the ICU, and mortality (Della-Torre et al. 2020; Cavalli et al. 2021). Further, CCL2 expression is elevated in the lungs of patients with NSCLC and promotes the growth of tumours (Hartwig et al.

**A**

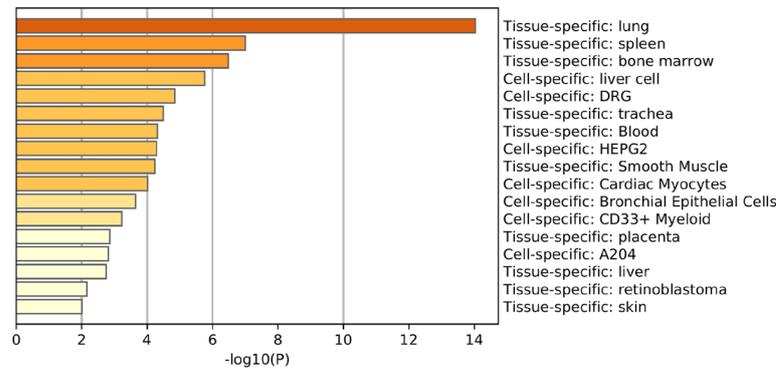


Color	MCODE	GO	Description	Log10(P)
Red	MCODE_1	R-HSA-6798695	Neutrophil degranulation	-10.6
Red	MCODE_1	R-HSA-202733	Cell surface interactions at the vascular wall	-5.7
Red	MCODE_1	R-HSA-109582	Hemostasis	-3.7
Blue	MCODE_2	ko04657	IL-17 signaling pathway	-15.0
Blue	MCODE_2	hsa04657	IL-17 signaling pathway	-14.9
Blue	MCODE_2	M167	PID AP1 PATHWAY	-12.3
Green	MCODE_3	R-HSA-418594	G alpha (i) signalling events	-7.8
Green	MCODE_3	R-HSA-500792	GPCR ligand binding	-7.1
Green	MCODE_3	R-HSA-388396	GPCR downstream signalling	-6.6
Purple	MCODE_4	R-HSA-114608	Platelet degranulation	-9.4
Purple	MCODE_4	R-HSA-76005	Response to elevated platelet cytosolic Ca <sup>2+</sup>	-9.3
Purple	MCODE_4	R-HSA-76002	Platelet activation, signaling and aggregation	-8.1
Orange	MCODE_5	R-HSA-913531	Interferon Signaling	-8.6
Orange	MCODE_5	GO:0045071	negative regulation of viral genome replication	-7.5
Orange	MCODE_5	R-HSA-909733	Interferon alpha/beta signaling	-7.2

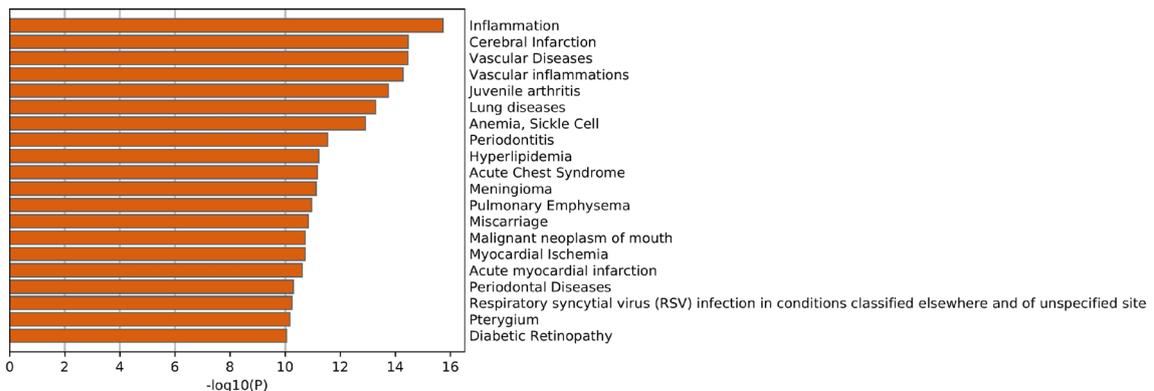
**B**



**C**



**D**



**Fig. 5** PPI enrichment and association analysis of mutual genes between COVID-19 and LUAD. **A** The MCODE networks identified for individual gene lists. Each MCODE component has performed pathway and process enrichment analysis independently, and the three best-scoring terms by p-value have been showed as the functional description of the corresponding components, shown in the tables underneath corresponding network plots. **B** Summary of enrichment analysis in COVID. **C** Summary of enrichment analysis in PaGenBase. **D** Summary of enrichment analysis in DisGeNET

2017). Moreover, patients with COVID-19 with LUAD, who express higher levels of CCL2, progress more rapidly and have a worse prognosis (Geraghty et al. 2020).

The transcription factors FOS and JUN to regulate gene expression through dimeric oncogenic complexes (Rorke et al. 2010; Kampen et al. 2019). The expression of several members of the JUN/FOS family, which are upregulated in tumour cells compared with their cells of origin (Latil et al. 2017), is involved in multiple cellular processes such as cell cycle progression, inhibition of apoptosis, and promoting tumorigenesis (Wang et al. 2019). Elevated activity of the JUN pathway in fibroblasts suggests its involvement in pulmonary fibrosis (Cui et al. 2020), which a serious complication of COVID-19 (Jiang et al. 2021) and is also closely related to the development of lung cancer (Arenberg et al. 2010).

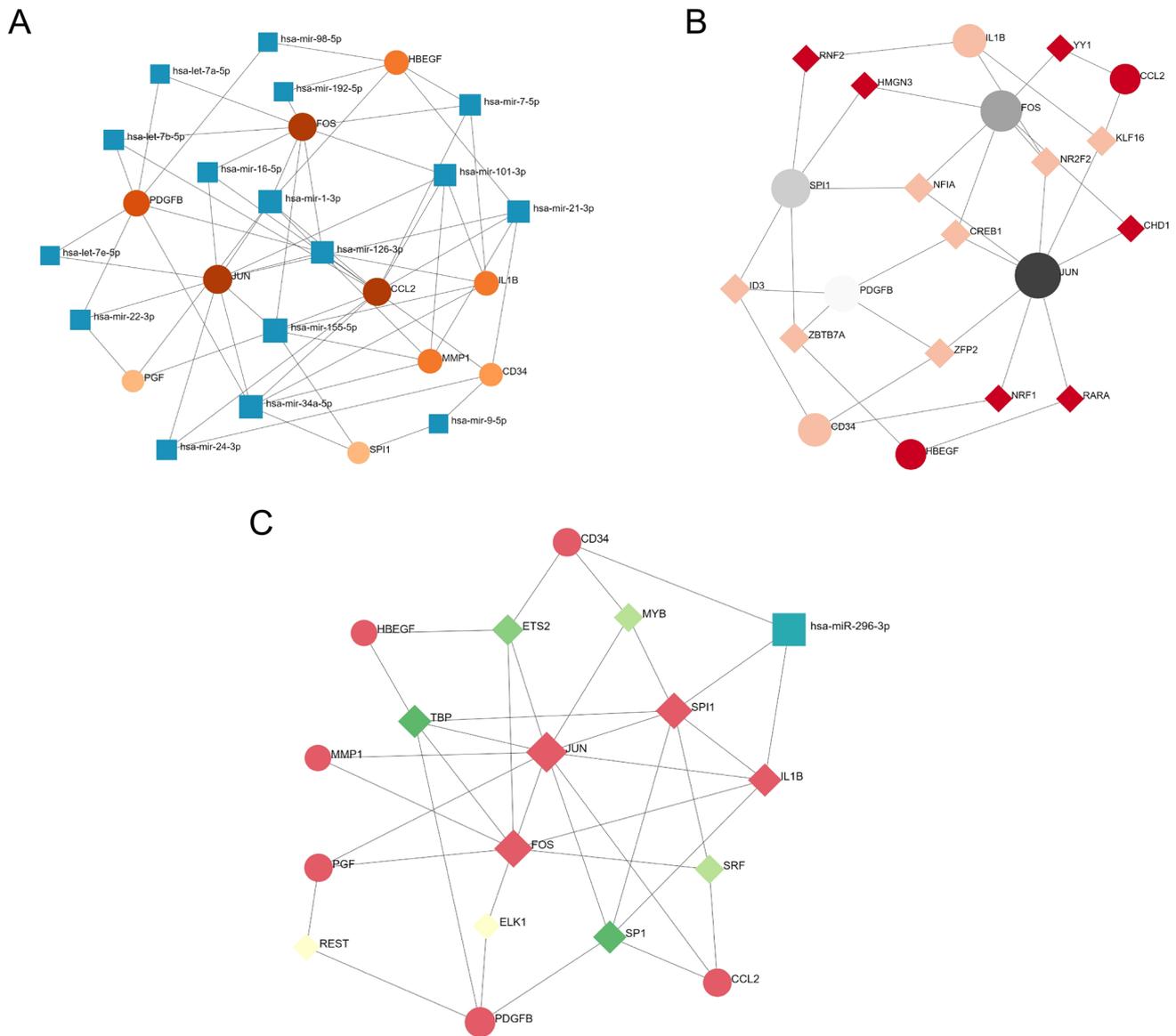
Airway epithelial reprogramming or the epithelial-mesenchymal transformation (EMT) contributes to the remodelling changes in lung fibrosis (Eapen et al. 2019), one of the main respiratory signs of COVID-19. HBEGF is a key driver of the EMT and influences the outcomes of treatment of lung cancer (Stawowczyk et al. 2017; Wu et al. 2021). The phenotypes of endothelial and lung cancer cells are influenced by the induction of paracrine signalling through interactions of the VEGF and PDGFB pathways (Wu et al. 2021). And the co-expression of these signalling ligands strongly correlates with lymph node metastasis and poor survival of patients with NSCLC (Donnem et al. 2010).

PGF is involved in LUAD cell metastasis (Chiang 2009), and SPI1 is a tumour-induced gene related to the peripheral immune system (Kossenkov et al. 2011), which induces upregulation of lncRNA SNHG6 to promote NSCLC (Gao and Ye 2020). High levels of MMP-1 expression are significantly associated with poor prognosis of patients with LUAD, as well as with smoking history and the aggressive mucinous adenocarcinoma subtype (Saito et al. 2018). Moreover, MMP-1 promotes the proliferation, migration, and invasion of NSCLC cells (Wang et al. 2020; Li et al. 2021). CD34, which is involved in diverse cellular processes including cell adhesion, signal transduction, and maintenance of progenitor cell phenotypes, is expressed by stem cells, including cancer stem cells (Kapoor et al. 2020). CD34 expression by cancer-associated fibroblasts

predicts the prognosis of patients with stages I–III NSCLC (Schulze et al. 2020). Thus, these hub genes are closely related to COVID-19 and contribute to tumour formation and the development of LUAD. Together, these findings suggest the genetic basis for high risk and poor prognosis of patients with LUAD with COVID-19.

Here, we performed enrichment analysis of 112 genes co-expressed by patients with COVID-19 and LUAD, to gain insight into the biological mechanisms of pathogenesis of each disease. For example, leukocyte migration and cell chemotaxis were the top 2 GO terms. In pulmonary inflammatory diseases and neoplasms, pathogenesis and progression are associated with the persistent presence of leukocyte migration that is required for the induction, maintenance, and regulation of the immune response (Kameritsch and Renkawitz 2020). Airway cell dysfunction and persistent leukocyte migration increase injury to the host and impair the host's ability to respond to microbial infection (Belchamber et al. 2021). Thus, COVID-19 involves the blood–brain barrier via leukocyte migration, and this neuro-invasion leads to numerous neurological complications such as loss of consciousness, amnesia, headache, or other disorders such as stroke, impaired consciousness, seizures, and encephalopathy (Zubair et al. 2020). Dysregulated inflammatory cell chemotaxis releases pro-inflammatory cytokines in the lung, leading to structural damage and impaired lung function (Domingo et al. 2018), and therefore plays a key role in cancer-related inflammation and cancer progression (Do et al. 2020).

The co-expressed genes were subjected to KEGG pathway analysis to investigate patients' responses to COVID-19 and LUAD. The top two KEGG pathways were IL-17 signalling and MAPK signalling. SARS-CoV-2 infection initiates an IL-17 transcriptional response in different cells of several organs, activating the IL-17 signalling pathway with greater intensity than other respiratory viruses (Hasan et al. 2021). This mechanism may explain why severe SARS-CoV-2 infection leads to the cytokine storm syndrome (Wu and Yang 2020; Lin et al. 2021). Viral infection activates the MAPK signalling pathway, which plays an important role in viral replication and facilitates viral infection (Cheng et al. 2020). Further, this pathway is activated in a wide spectrum of cancers, including LUAD. Activation of the MAPK pathway in patients with COVID-19 promotes viral replication and expression of pro-inflammatory cytokines, which leads to inflammation, thrombosis, and vasoconstriction (Burton et al. 2021). Uncontrolled activation of the MAPK pathway causes an extreme inflammatory response in patients with COVID-19 (Grimes and Grimes 2020). In contrast, the MAPK pathway regulates cell survival, and its activation promotes tumour cell survival and proliferation as well as tumour cell migration and invasion to promote



**Fig. 6** Network for Gene-miRNA interaction, TF-gene interaction, and TF-miRNA co-regulatory of common hub genes. **A** Network for gene-miRNA interaction. The blue rectangle nodes present miRNAs and hub genes connect with miRNAs as circle nodes. The shade of colour represents degree. The network consists of 26 nodes and 60 edges. **B** Network for TF-gene interaction. The circle nodes represent

the common genes and diamond nodes represent TF-genes. The network consists of 21 nodes and 33 edges. **C** The green diamond nodes indicate TF-genes, and the blue rectangle node presents miRNA. The rest of nodes represent the hub genes. The network consists of 18 nodes and 37 edges. The shade of colour represents degree

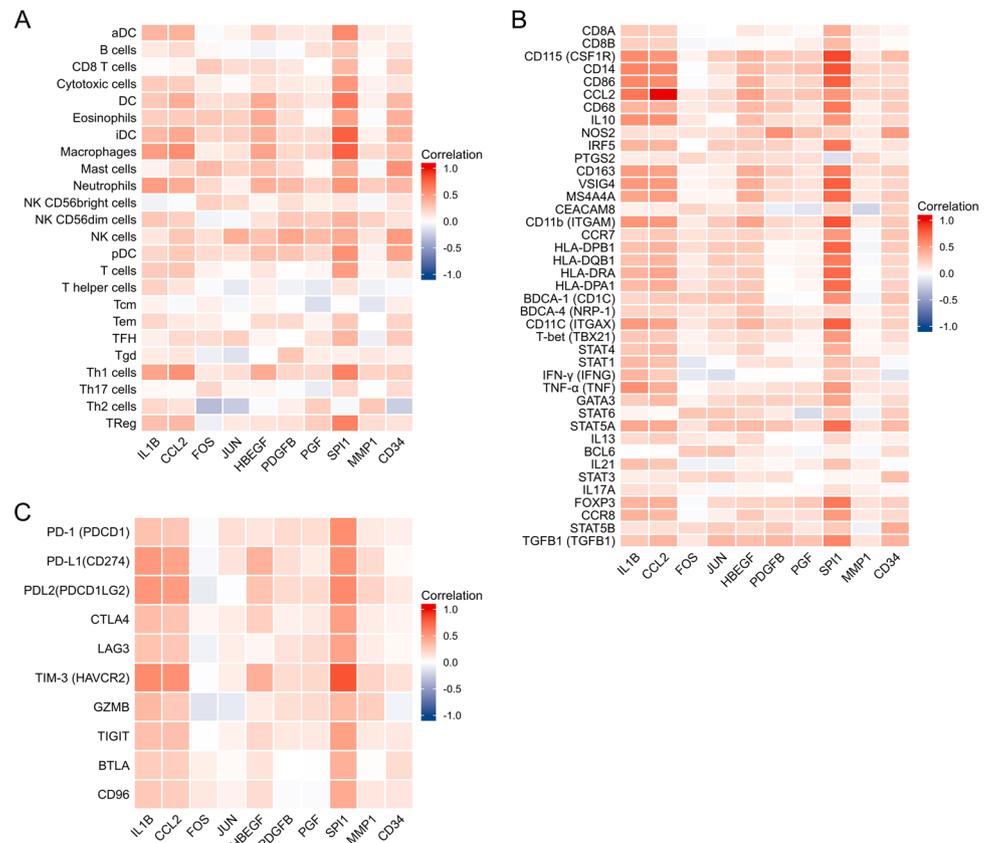
tumour progression and induce drug resistance in tumour cells (Koul et al. 2013).

The present KEGG analysis strongly suggests that common, important pathways participate in the development of COVID-19 and LUAD. For example, MCODE enrichment analysis revealed that co-expressed genes were strongly associated with haemostasis, platelet degranulation, response to elevated platelet cytosolic Ca<sup>2+</sup>, platelet activation, signalling, and aggregation. SARS-CoV-2 induces

platelet activation and endothelial dysfunction through activation of the complement pathway (Vinayagam and Sattu 2020; Zhang et al. 2020). The main manifestations of these events are thrombocytopenia, increased platelet destruction, reduced number of circulating platelets, elevated D-dimer levels, prolonged prothrombin time, and disseminated intravascular coagulation (Giannis et al. 2020).

Platelet activation is a pivotal cause of thrombosis, and the enhancement of platelet activation by SARS-CoV-2

**Fig. 7** Associations of hub genes expression and immune infiltration level in patients with LUAD. **A** Correlation of hub genes expression with immune infiltration level of 24 immune cell types in patients with LUAD by Spearman's analysis. **B** Correlation between hub genes and relate gene markers of immune cells in LUAD. **C** Correlation between hub genes and immune checkpoints in LUAD

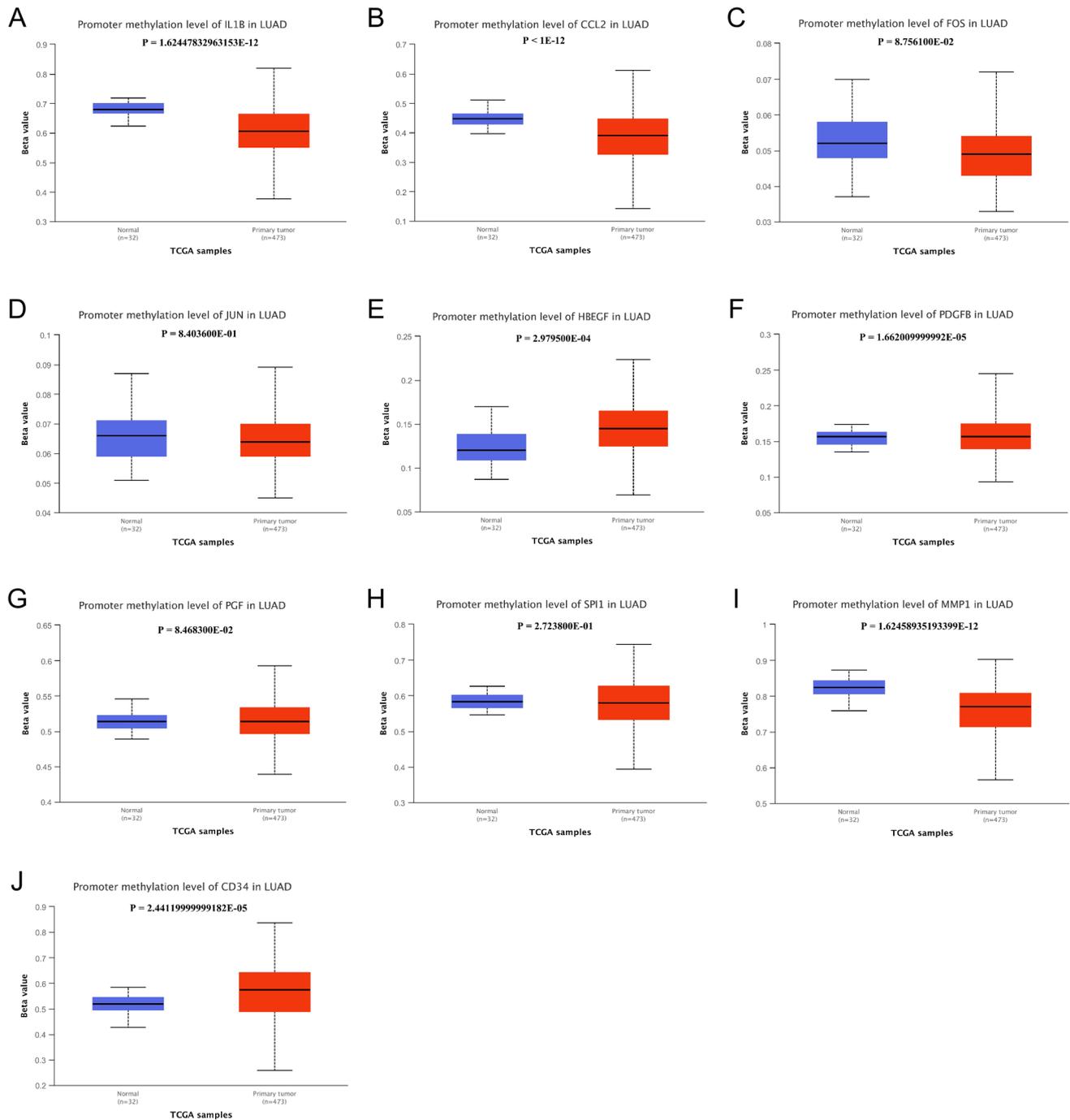


is mediated by components of the MAPK pathway acting downstream of ACE2 (Zhang et al. 2020). These events predispose patients with COVID-19 to thrombosis, may lead to coagulation in different tissues, and cause serious complications such as stroke, liver injury, heart attack, acute kidney injury, pulmonary embolism, and multi-organ failure (Iba et al. 2020). Moreover, PaGenBase and DisGeNET enrichment results show that these co-expressed genes are closely associated with specific tissues or cells such as lung, spleen, trachea, blood, liver, dorsal root ganglion, cardiac myocytes, and bronchial epithelial cells and are closely associated with inflammation, cerebral infarction, vascular inflammations, lung disease, myocardial ischaemia, and acute myocardial infarction. These pathologies correspond to the symptoms of patients with severe COVID-19, which causes catastrophic damage to all major organ system (Synowiec et al. 2021). We believe therefore that it is reasonable to conclude that the co-expressed genes identified here contribute to the greater likelihood of adverse outcomes of patients with LUAD.

Here, we identified 16 n miRNAs in the gene-miRNA network. miRNA regulates diverse oncological processes, including proliferation, cell survival, apoptosis, tumour metastasis, and growth. Among these miRNAs, 12 (Wang et al. 2017; Dong et al. 2018; Wu et al. 2019; Jin et al. 2020;

Li et al. 2020; Mokhlesi and Talkhabi 2020; Yu et al. 2020b; Zhou et al. 2020; Wei et al. 2021) are involved in the oncogenesis of NSCLC, and four (Chuang et al. 2015; Gao et al. 2019; Deng et al. 2021; Xu et al. 2021) contribute to the pathogenesis of other cancers. Eleven TF-genes are included in TF-gene interaction network. TFs regulate gene expression by recognising and utilising specific DNA sequences, which forms the basis of gene expression regulatory networks (Lambert et al. 2018) and plays a dominant role in biological processes shared by development and cancer (Huilgol et al. 2019). TFs are expressed at higher levels in cancer tissues compared with normal tissues, and specifically expressed TFs may serve tumour markers. Most TFs influence the survival of patients with one or more cancers (Hu et al. 2021b). The TF-miRNA co-regulatory network includes only one miRNA related to hypertension and coronary artery disease (Miao et al. 2019).

We explored the association between hub genes with immune infiltration and immune checkpoints in patients with LUAD. Immunosuppression caused by anti-cancer therapy increases the risk of COVID-19 infection and increases the susceptibility of cancer patients to severe COVID-19 (Seth et al. 2020). Cancers lead to inflammation and the formation of a tumour-associated immune microenvironment (Meng et al. 2020), which may interact with the inflammatory



**Fig. 8** Promoter methylation level of hub genes in LUAD and normal tissue. **A** IL1B, **B** CCL2, **C** FOS, **D** JUN, **E** HBEGF, **F** PDGFB, **G** PGF, **H** SPI1, **I** MMP1, **J** CD34

responses to COVID-19 (Amere Subbarao 2021). Such overlapping outcomes may affect the treatment of patients with LUAD with comorbid COVID-19 for inflammation-related complications caused by COVID-19 or anti-tumour therapy (Yang et al. 2020b; Mohamed Khosroshahi et al. 2021). A better understanding of the pathophysiological mechanisms

of immunity is required to optimise strategies for treating patients with LUAD with COVID-19.

Our present results strongly suggest that differential expression of IL1B, CCL2, and SPI1 was significantly associated with immune infiltration and immune checkpoints in patients with LUAD. For example, the cytokines

**Table 1** Associations of hub genes expression and immune infiltration level in patients with LUAD

Immune cell	IL1B		CCL2		FOS		JUN		HBEGF	
	<i>r</i>	<i>P</i>								
aDC	0.372	<0.001	0.393	<0.001	-0.021	0.634	0.060	0.165	0.212	<0.001
B cells	0.113	0.009	0.188	<0.001	0.033	0.452	-0.020	0.651	-0.052	0.229
CD8 T cells	0.018	0.674	0.058	0.182	0.269	<0.001	0.176	<0.001	0.184	<0.001
Cytotoxic cells	0.263	<0.001	0.255	<0.001	0.087	0.044	0.031	0.474	0.154	<0.001
DC	0.275	<0.001	0.410	<0.001	0.157	<0.001	0.187	<0.001	0.426	<0.001
Eosinophils	0.247	<0.001	0.259	<0.001	0.282	<0.001	0.243	<0.001	0.422	<0.001
iDC	0.354	<0.001	0.435	<0.001	0.211	<0.001	0.239	<0.001	0.395	<0.001
Macrophages	0.491	<0.001	0.562	<0.001	0.089	0.040	0.149	<0.001	0.454	<0.001
Mast cells	0.069	0.112	0.227	<0.001	0.355	<0.001	0.226	<0.001	0.312	<0.001
Neutrophils	0.495	<0.001	0.419	<0.001	0.192	<0.001	0.077	0.076	0.403	<0.001
NK CD56 bright cells	-0.062	0.154	-0.018	0.674	0.241	<0.001	0.189	<0.001	0.058	0.181
NK CD56 dim cells	0.285	<0.001	0.240	<0.001	-0.058	0.179	-0.033	0.440	0.144	<0.001
NK cells	0.121	0.005	0.288	<0.001	0.155	<0.001	0.413	<0.001	0.305	<0.001
pDC	0.202	<0.001	0.278	<0.001	0.188	<0.001	0.163	<0.001	0.317	<0.001
T cells	0.265	<0.001	0.294	<0.001	0.066	0.126	0.014	0.753	0.132	0.002
T helper cells	0.230	<0.001	0.138	0.001	-0.023	0.591	-0.104	0.016	0.084	0.053
Tcm	0.064	0.137	-0.030	0.491	0.084	0.053	-0.038	0.385	0.058	0.178
Tem	0.206	<0.001	0.113	0.009	0.086	0.046	0.011	0.800	0.186	<0.001
TFH	0.081	0.061	0.194	<0.001	0.175	<0.001	0.244	<0.001	0.054	0.211
Tgd	0.098	0.024	0.128	0.003	-0.083	0.054	-0.147	<0.001	-0.003	0.940
Th1 cells	0.453	<0.001	0.543	<0.001	0.116	0.007	0.167	<0.001	0.426	<0.001
Th17 cells	0.037	0.395	0.031	0.471	0.201	<0.001	0.055	0.201	0.055	0.202
Th2 cells	0.197	<0.001	0.141	0.001	-0.329	<0.001	-0.258	<0.001	-0.019	0.654
TReg	0.314	<0.001	0.356	<0.001	-0.076	0.080	0.113	0.009	0.143	<0.001
	PDGFB		PGF		SPI1		MMP1		CD34	
	<i>r</i>	<i>P</i>								
aDC	0.121	0.005	0.109	0.012	0.585	<0.001	0.107	0.013	0.08	0.065
B cells	-0.02	0.646	0.158	<0.001	0.279	<0.001	0.052	0.231	0.138	0.001
CD8 T cells	0.114	0.009	-0.002	0.955	0.358	<0.001	0.012	0.783	0.24	<0.001
Cytotoxic cells	0.105	0.015	0.087	0.043	0.521	<0.001	0.066	0.126	0.137	0.001
DC	0.182	<0.001	0.127	0.003	0.668	<0.001	0.075	0.084	0.359	<0.001
Eosinophils	0.172	<0.001	0.011	0.808	0.473	<0.001	-0.018	0.67	0.404	<0.001
iDC	0.187	<0.001	0.176	<0.001	0.770	<0.001	0.077	0.075	0.397	<0.001
Macrophages	0.194	<0.001	0.205	<0.001	0.763	<0.001	0.186	<0.001	0.304	<0.001
Mast cells	0.205	<0.001	0.022	0.614	0.409	<0.001	-0.03	0.487	0.551	<0.001
Neutrophils	0.346	<0.001	0.225	<0.001	0.525	<0.001	0.255	<0.001	0.363	<0.001
NK CD56 bright cells	0.169	<0.001	0.078	0.071	0.126	0.003	-0.038	0.377	0.148	<0.001
NK CD56 dim cells	0.275	<0.001	0.245	<0.001	0.385	<0.001	0.23	<0.001	0.143	<0.001
NK cells	0.444	<0.001	0.347	<0.001	0.426	<0.001	0.128	0.003	0.506	<0.001
pDC	0.292	<0.001	0.200	<0.001	0.552	<0.001	0.065	0.131	0.458	<0.001
T cells	0.008	0.861	0.048	0.269	0.496	<0.001	0.05	0.246	0.147	<0.001
T helper cells	-0.065	0.135	-0.105	0.016	0.145	<0.001	-0.07	0.106	-0.028	0.512
Tcm	-0.005	0.902	-0.165	<0.001	0.012	0.783	-0.127	0.003	0.089	0.039
Tem	0.191	<0.001	0.061	0.162	0.284	<0.001	0.002	0.962	0.217	<0.001
TFH	-0.002	0.956	0.154	<0.001	0.373	<0.001	-0.082	0.059	0.269	<0.001
Tgd	0.287	<0.001	0.093	0.031	0.080	0.063	0.119	0.006	0.08	0.066
Th1 cells	0.209	<0.001	0.195	<0.001	0.621	<0.001	0.221	<0.001	0.246	<0.001
Th17 cells	-0.021	0.635	-0.094	0.029	0.200	<0.001	-0.002	0.965	0.175	<0.001
Th2 cells	0.079	0.07	0.251	<0.001	-0.036	0.406	0.279	<0.001	-0.245	<0.001
TReg	0.154	<0.001	0.253	<0.001	0.626	<0.001	0.173	<0.001	0.141	0.001

Abbreviations: *LUAD* lung adenocarcinoma

**Table 2** Correlation analysis between hub genes and relate gene markers of immune cells in LUAD

Immune cell	Marker	IL1B		CCL2		FOS		JUN		HBEGF		
		<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	
CD8 + T cell	CD8A	0.272	<0.001	0.248	<0.001	-0.014	0.745	0.002	0.969	0.124	0.004	
	CD8B	0.238	<0.001	0.230	<0.001	-0.038	0.374	-0.030	0.485	0.028	0.511	
Monocyte	CD115 (CSF1R)	0.576	<0.001	0.530	<0.001	0.062	0.152	0.261	<0.001	0.381	<0.001	
	CD14	0.609	<0.001	0.593	<0.001	-0.008	0.854	0.158	<0.001	0.346	<0.001	
TAM	CD86	0.602	<0.001	0.582	<0.001	-0.015	0.736	0.087	0.045	0.399	<0.001	
	CCL2	0.675	<0.001	1.000	<0.001	0.128	0.003	0.205	<0.001	0.465	<0.001	
	CD68	0.365	<0.001	0.389	<0.001	0.109	0.012	0.164	<0.001	0.351	<0.001	
M1 macrophage	IL10	0.551	<0.001	0.551	<0.001	0.123	0.004	0.011	0.793	0.338	<0.001	
	NOS2	0.163	<0.001	0.135	0.002	0.141	0.001	0.156	<0.001	0.275	<0.001	
	IRF5	0.379	<0.001	0.376	<0.001	0.010	0.826	0.255	<0.001	0.252	<0.001	
M2 macrophage	PTGS2	0.096	0.027	0.130	0.003	0.203	<0.001	0.124	0.004	0.195	<0.001	
	CD163	0.498	<0.001	0.472	<0.001	0.055	0.201	0.090	0.038	0.410	<0.001	
	VSIG4	0.514	<0.001	0.509	<0.001	0.051	0.235	0.098	0.024	0.414	<0.001	
Neutrophils	MS4A4A	0.449	<0.001	0.497	<0.001	0.056	0.195	0.048	0.272	0.413	<0.001	
	CEACAM8	0.084	0.051	0.102	0.018	0.216	<0.001	0.134	0.002	0.194	<0.001	
	CD11b (ITGAM)	0.535	<0.001	0.521	<0.001	0.104	0.016	0.275	<0.001	0.462	<0.001	
Dendritic cell	CCR7	0.197	<0.001	0.280	<0.001	0.147	<0.001	0.185	<0.001	0.227	<0.001	
	HLA-DPB1	0.308	<0.001	0.381	<0.001	0.177	<0.001	0.268	<0.001	0.272	<0.001	
	HLA-DQB1	0.312	<0.001	0.378	<0.001	0.099	0.023	0.277	<0.001	0.226	<0.001	
	HLA-DRA	0.384	<0.001	0.451	<0.001	0.115	0.008	0.205	<0.001	0.272	<0.001	
	HLA-DPA1	0.352	<0.001	0.415	<0.001	0.145	<0.001	0.249	<0.001	0.284	<0.001	
	BDCA-1 (CD1C)	0.201	<0.001	0.277	<0.001	0.259	<0.001	0.297	<0.001	0.309	<0.001	
	BDCA-4 (NRP-1)	0.227	<0.001	0.226	<0.001	0.139	0.001	0.165	<0.001	0.299	<0.001	
Th1	CD11C (ITGAX)	0.514	<0.001	0.454	<0.001	0.120	0.005	0.239	<0.001	0.385	<0.001	
	T-bet (TBX21)	0.279	<0.001	0.271	<0.001	0.065	0.133	0.150	<0.001	0.189	<0.001	
	STAT4	0.289	<0.001	0.351	<0.001	0.076	0.077	0.118	0.006	0.231	<0.001	
	STAT1	0.357	<0.001	0.311	<0.001	-0.125	0.004	-0.015	0.734	0.141	0.001	
	IFN-γ (IFNG)	0.378	<0.001	0.257	<0.001	-0.112	0.010	-0.162	<0.001	0.015	0.737	
Th2	TNF-α (TNF)	0.559	<0.001	0.401	<0.001	0.014	0.738	0.115	0.008	0.109	0.012	
	GATA3	0.262	<0.001	0.352	<0.001	0.059	0.173	0.190	<0.001	0.243	<0.001	
	STAT6	0.060	0.164	0.026	0.543	0.292	<0.001	0.279	<0.001	0.207	<0.001	
	STAT5A	0.439	<0.001	0.425	<0.001	0.140	0.001	0.312	<0.001	0.345	<0.001	
Tfh	IL13	0.182	<0.001	0.255	<0.001	0.123	0.004	0.071	0.099	0.196	<0.001	
	BCL6	-0.002	0.955	0.016	0.715	0.268	<0.001	0.302	<0.001	0.136	0.002	
Th17	IL21	0.328	<0.001	0.282	<0.001	-0.067	0.122	-0.066	0.129	0.078	0.072	
	STAT3	0.088	0.042	0.120	0.005	0.193	<0.001	0.230	<0.001	0.138	0.001	
Treg	IL17A	0.165	<0.001	0.143	<0.001	0.045	0.297	-0.035	0.418	0.053	0.220	
	FOXP3	0.376	<0.001	0.403	<0.001	-0.021	0.634	0.197	<0.001	0.218	<0.001	
	CCR8	0.393	<0.001	0.359	<0.001	-0.018	0.670	0.080	0.066	0.271	<0.001	
	STAT5B	0.140	0.001	0.167	<0.001	0.194	<0.001	0.262	<0.001	0.191	<0.001	
CD8 + T cell	TGFB1 (TGFB1)	0.286	<0.001	0.375	<0.001	0.123	0.004	0.370	<0.001	0.329	<0.001	
	PDGFB			PGF		SPI1		MMP1		CD34		
	CD8A	0.071	0.101	0.028	0.514	0.406	<0.001	0.106	0.015	0.060	0.169	
	CD8B	0.019	0.653	0.089	0.041	0.345	<0.001	0.074	0.086	0.022	0.619	
	Monocyte	CD115 (CSF1R)	0.281	<0.001	0.236	<0.001	0.865	<0.001	0.145	<0.001	0.333	<0.001
		CD14	0.257	<0.001	0.312	<0.001	0.819	<0.001	0.213	<0.001	0.203	<0.001
		CD86	0.165	<0.001	0.222	<0.001	0.776	<0.001	0.186	<0.001	0.185	<0.001

**Table 2** (continued)

TAM	CCL2	0.259	<0.001	0.295	<0.001	0.528	<0.001	0.229	<0.001	0.252	<0.001
	CD68	0.282	<0.001	0.123	0.004	0.665	<0.001	0.087	0.043	0.256	<0.001
	IL10	0.180	<0.001	0.143	<0.001	0.522	<0.001	0.114	0.009	0.204	<0.001
M1 macrophage	NOS2	0.557	<0.001	0.306	<0.001	0.231	<0.001	0.121	0.005	0.499	<0.001
	IRF5	0.234	<0.001	0.126	0.004	0.667	<0.001	0.079	0.066	0.139	0.001
	PTGS2	0.166	<0.001	0.161	<0.001	−0.150	<0.001	0.212	<0.001	0.092	0.033
M2 macrophage	CD163	0.268	<0.001	0.137	0.001	0.652	<0.001	0.163	<0.001	0.256	<0.001
	VSIG4	0.193	<0.001	0.139	0.001	0.776	<0.001	0.115	0.008	0.210	<0.001
	MS4A4A	0.185	<0.001	0.149	<0.001	0.725	<0.001	0.132	0.002	0.270	<0.001
Neutrophils	CEACAM8	−0.084	0.052	−0.130	0.003	0.230	<0.001	−0.214	<0.001	0.229	<0.001
	CD11b (ITGAM)	0.208	<0.001	0.157	<0.001	0.817	<0.001	0.112	0.009	0.283	<0.001
	CCR7	0.131	0.002	0.107	0.013	0.512	<0.001	−0.030	0.494	0.293	<0.001
Dendritic cell	HLA-DPB1	0.025	0.571	0.055	0.203	0.747	<0.001	−0.049	0.255	0.268	<0.001
	HLA-DQB1	0.045	0.298	0.067	0.120	0.652	<0.001	−0.027	0.535	0.211	<0.001
	HLA-DRA	−0.013	0.772	0.068	0.115	0.736	<0.001	0.012	0.779	0.200	<0.001
	HLA-DPA1	0.017	0.701	0.043	0.315	0.719	<0.001	−0.023	0.594	0.238	<0.001
	BDCA-1 (CD1C)	−0.022	0.611	−0.009	0.832	0.551	<0.001	−0.057	0.186	0.308	<0.001
Th1	BDCA-4 (NRP-1)	0.145	<0.001	0.099	0.022	0.208	<0.001	0.057	0.186	0.220	<0.001
	CD11C (ITGAX)	0.233	<0.001	0.163	<0.001	0.769	<0.001	0.083	0.056	0.240	<0.001
	T-bet (TBX21)	0.163	<0.001	0.050	0.244	0.505	<0.001	0.037	0.388	0.176	<0.001
	STAT4	0.039	0.364	0.039	0.369	0.401	<0.001	0.050	0.248	0.102	0.018
	STAT1	0.168	<0.001	0.068	0.119	0.314	<0.001	0.201	<0.001	−0.028	0.516
	IFN- $\gamma$ (IFNG)	0.006	0.887	0.002	0.966	0.276	<0.001	0.144	<0.001	−0.127	0.003
	TNF- $\alpha$ (TNF)	0.161	<0.001	0.178	<0.001	0.510	<0.001	0.133	0.002	0.126	0.004
Th2	GATA3	0.239	<0.001	0.200	<0.001	0.454	<0.001	0.083	0.055	0.193	<0.001
	STAT6	0.111	0.011	−0.175	<0.001	0.262	<0.001	−0.070	0.106	0.257	<0.001
	STAT5A	0.299	<0.001	0.182	<0.001	0.706	<0.001	0.157	<0.001	0.351	<0.001
	IL13	0.005	0.899	−0.009	0.834	0.206	<0.001	0.034	0.438	0.080	0.064
Tfh	BCL6	0.079	0.070	−0.046	0.285	0.074	0.089	−0.035	0.422	0.186	<0.001
	IL21	0.038	0.384	0.096	0.026	0.302	<0.001	0.094	0.029	−0.014	0.753
Th17	STAT3	0.159	<0.001	0.001	0.983	0.043	0.321	0.053	0.222	0.329	<0.001
	IL17A	0.011	0.797	0.030	0.495	0.158	<0.001	0.085	0.049	0.034	0.435
Treg	FOXP3	0.228	<0.001	0.278	<0.001	0.663	<0.001	0.155	<0.001	0.239	<0.001
	CCR8	0.139	0.001	0.160	<0.001	0.505	<0.001	0.118	0.006	0.192	<0.001
	STAT5B	0.267	<0.001	0.126	0.004	0.273	<0.001	−0.063	0.146	0.422	<0.001
	TGFB1 (TGFB1)	0.371	<0.001	0.306	<0.001	0.605	<0.001	0.147	<0.001	0.390	<0.001

IL1B and CCL2 are released by activated immune cells in patients with COVID-19, which contributes to the induction of the catastrophic cytokine storm (Mohamed Khosroshahi et al. 2021). Specifically, the expression levels of IL1B, CCL2, and SPI1 correlated with those of the immune checkpoint TIM-3; and SPI1, in particular, is closely associated with TIM-3. TIM-3 induces depletion of T lymphocytes and serves as a surface marker of T cell depletion (Zhu et al. 2005). Compared with hospitalised patients with COVID-19 who do not require admission to the ICU, those admitted to the ICU show decreased

lymphocyte numbers and an increase in TIM-3 expression (Diao et al. 2020). Further, the cytokine storm is involved in the depletion of T lymphocytes, and high expression levels of TIM-3 in patients with COVID-19 are associated with higher expression levels of pro-inflammatory cytokines (Moon 2020). Therefore, treatment targeting immune alterations caused by the products of hub genes may provide new insights for the management of patients LUAD with COVID-19.

DNA methylation can cause changes in chromatin structure and DNA stability. Thus, it could control the expression of

**Table 3** Correlation analysis between significant hub genes and immune checkpoints in LUAD

Immune checkpoints	IL1B		CCL2		FOS		JUN		HBEGF	
	<i>r</i>	<i>P</i>								
PD-1 (PDCD1)	0.307	<0.001	0.286	<0.001	−0.020	0.647	0.161	<0.001	0.130	0.003
PD-L1 (CD274)	0.516	<0.001	0.461	<0.001	−0.033	0.441	0.140	0.001	0.392	<0.001
PDL2 (PDCD1LG2)	0.524	<0.001	0.498	<0.001	−0.099	0.023	−0.009	0.842	0.304	<0.001
CTLA4	0.337	<0.001	0.301	<0.001	0.043	0.317	0.097	0.025	0.237	<0.001
LAG3	0.304	<0.001	0.286	<0.001	−0.066	0.127	0.092	0.034	0.048	0.270
TIM-3 (HAVCR2)	0.582	<0.001	0.555	<0.001	−0.008	0.849	0.091	0.035	0.401	<0.001
GZMB	0.356	<0.001	0.275	<0.001	−0.137	0.001	−0.105	0.015	0.102	0.018
TIGIT	0.324	<0.001	0.321	<0.001	−0.005	0.901	0.068	0.114	0.197	<0.001
BTLA	0.252	<0.001	0.245	<0.001	0.083	0.054	0.026	0.549	0.135	0.002
CD96	0.277	<0.001	0.254	<0.001	0.117	0.007	0.064	0.138	0.176	<0.001
	PDGFB		PGF		SPI1		MMP1		CD34	
PD-1 (PDCD1)	0.185	<0.001	0.174	<0.001	0.564	<0.001	0.107	0.014	0.084	0.053
PD-L1 (CD274)	0.16	<0.001	0.097	0.024	0.543	<0.001	0.183	<0.001	0.03	0.482
PDL2 (PDCD1LG2)	0.185	<0.001	0.194	<0.001	0.588	<0.001	0.217	<0.001	0.113	0.009
CTLA4	0.075	0.085	0.110	0.011	0.479	<0.001	0.094	0.029	0.055	0.207
LAG3	0.141	0.001	0.186	<0.001	0.460	<0.001	0.096	0.026	0.036	0.407
TIM-3 (HAVCR2)	0.18	<0.001	0.196	<0.001	0.818	<0.001	0.217	<0.001	0.154	<0.001
GZMB	0.166	<0.001	0.182	<0.001	0.343	<0.001	0.248	<0.001	−0.058	0.181
TIGIT	0.112	0.01	0.109	0.012	0.472	<0.001	0.108	0.013	0.115	0.008
BTLA	0	0.997	−0.006	0.895	0.396	<0.001	0.01	0.815	0.179	<0.001
CD96	−0.019	0.667	−0.019	0.656	0.429	<0.001	0.119	0.006	0.13	0.003

genes in the organism. Abnormal methylation of genes is an important factor in the development of cancer (Mangelinck and Mann 2021). DNA methylation is also involved in the regulation of respiratory health. Studies (Lepeule et al. 2012) have shown that hypomethylation of the carnitine o-acetyltransferase gene promoter, Toll-like receptor-2, and coagulation factor-3 is associated with poor lung function. In contrast, hypomethylation of IFN- $\gamma$  and IL-6 was associated with improved lung function. We found higher methylation levels of HBEGF and PDGFB in LUAD than in normal tissues, whereas IL1B, CCL2, and MMP1 had lower methylation levels in LUAD, implying that abnormal methylation of these genes may be involved in the regulation of LUAD and COVID-19. Aberrant methylation due to IL1B-induced inflammation was shown to be strongly associated with the risk of gastric cancer (Maeda et al. 2017), suggesting that these hub genes may also be involved in tumorigenesis by interfering with methylation.

## Conclusions

The present bioinformatics study identified genes co-expressed in patients with COVID-19 and LUAD as well as the associated signal transduction pathways and

pathophysiological mechanisms. We further identified co-expressed hub genes, used them to construct regulatory networks, and investigated their contribution to immune alterations and DNA methylation. Thus, the present study provides new multi-dimensional insights that will contribute to efforts to optimise the treatment of patients with LUAD with COVID-19.

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**Availability of data and material** All data generated or analysed during this study are included in this published article [and its supplementary information files].

## Declarations

**Ethics approval and consent to participate** Not applicable.

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