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Cathepsin B is a potential therapeutic target for coronavirus disease 2019 patients with lung adenocarcinoma

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was declared a serious global public health emergency. Hospitalization and mortality rates of lung cancer patients diagnosed with COVID-19 are higher than those of patients presenting with other cancers. However, the reasons for the outcomes being disproportionately severe in lung adenocarcinoma (LUAD) patients with COVID-19 remain elusive. The present study aimed to identify the possible causes for disproportionately severe COVID-19 outcomes in LUAD patients and determine a therapeutic target for COVID-19 patients with LUAD. We used publicly available data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases and various bioinformatics tools to identify and analyze the genes implicated in SARS-CoV-2 infection in LUAD patients. Upregulation of the SARS-CoV-2 infection-related molecules dipeptidyl peptidase 4, basigin, cathepsin B (CTSB), methylenetetrahydrofolate dehydrogenase, and peptidylprolyl isomerase B rather than angiotensin-converting enzyme 2 may explain the relatively high susceptibility of LUAD patients to SARS-CoV-2 infection. CTSB was highly expressed in the LUAD tissues after SARS-CoV-2 infection, and its expression was positively correlated with immune cell infiltration and proinflammatory cytokine expression. These findings suggest that CTSB plays a vital role in the hyperinflammatory response in COVID-19 patients with LUAD and is a promising target for the development of a novel drug therapy for COVID-19 patients.

1. Introduction

Coronavirus disease 2019 (COVID-19) was declared a serious global public health emergency in January 30, 2020. According to the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (https://coronavirus.jhu.edu/map.html), as of September 1, 2021, there were 218,435,582 confirmed COVID-19 cases and 4,543,213 deaths attributed to it. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection triggers a unique inflammatory response. It attenuates innate antiviral defenses and induces the production of high levels of proinflammatory cytokines [1]. Aberrant and excessive immune cells such as monocytes and macrophages might be implicated in COVID-19 pathology [2]. An excessive inflammatory response to SARS-CoV-2 is associated with mononuclear cell infiltration in the lungs [3]. Hyperactivated pulmonary macrophages derived from infiltrating inflammatory monocytes promote pro-inflammatory cytokine release and recruitment of cytotoxic effector cells, exacerbating tissue damage at the site of infection [4]. Overwhelming inflammation and cytokine-related lung injury may be instrumental in COVID-19 progression [2–5].

Cancer patients exhibit apparent immune cell dysfunction [6]. Attenuated immunocompetence in cancer patients may increase their susceptibility to SARS-CoV-2 [7]. Moreover, cancer is strongly associated with chronic inflammation. The tumor microenvironment is infiltrated by various immunocytes and their composition and relative abundance are key factors affecting cancer progression [8]. Hence, COVID-19 progression may differ between cancer patients and otherwise healthy individuals. Based on an analysis of 411 patients in Brazilian Cancer Center, 51(12.4%) died due to COVID-19. Lung (0.333) and hematological (0.213) cancers have higher fatality rate [9]. A single-center retrospective cohort study showed that non-small cell lung cancer patients with COVID-19 exhibit 40.7% mortality, which is much higher than the 2.2% mortality in the general population [10]. Lung cancer patients are comparatively more susceptible to COVID-19

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complications, and have relatively higher COVID-19-associated hospitalization rates and deaths than patients with other cancers [11–13]. A meta-analysis including 3442 patients from 11 studies showed that chemotherapy administered to cancer patients with COVID-19 is not associated with the severe outcomes of COVID-19 [14]. The mechanism by which the outcome of COVID-19 becomes disproportionately severe in lung cancer patients remains to be elucidated.

Receptors and receptor helper molecules play an important role in virus invasion and disease progression. Angiotensin-converting enzyme 2 (ACE2) is a key SARS-CoV-2 receptor and is implicated in COVID-19 pathophysiology [15]. Basigin (BSG) is a SARS-CoV-2 receptor found in T cell and epithelial cell lines [16,17]. The homologous receptors C-type lectin domain family 4 member L (CD209) and C-type lectin domain family 4 member M (CLEC4M) are potential receptors for SARS-CoV-2 invasion [18]. Dipeptidyl peptidase 4 (DPP4) is a primary receptor for Middle East respiratory syndrome coronavirus and plays a vital role in SARS-CoV-2 penetration. The SARS-CoV-2 spike glycoprotein (S) might interact with DPP4 [19]. C-C motif chemokine receptor 5 (CCR5) is a co-receptor facilitating the entry of macrophage-tropic virus into host cells. It is also a potential blockade target in COVID-19-induced cytokine release syndrome [20]. Transmembrane serine proteases 2 and 4 (TMPRSS2/4) along with paired basic amino acid cleaving enzyme (FURIN) and the cysteine proteases cathepsin B/L (CTSB/L) activate S, and form two independent pathways by which SARS-CoV-2 may enter host cells [21–23]. Solute carrier family 6 member 20 (SLC6A20), methylenetetrahydrofolate dehydrogenase (MTHFD1), peptidylprolyl isomerase A (*PPIA*), and peptidylprolyl isomerase B (*PPIB*) *are* essential for viral replication [24–26]. These host genes are all vital for SARS-CoV-2 infection. A few SARS-CoV-2 receptors and regulating factors such as ACE2, TMPRSS2, and CTSL have been analyzed in patients with lung cancer to determine the association between COVID-19 and cancer [27–29]. Nevertheless, the disproportionately severe COVID-19 outcomes in lung cancer patients remain to be explained.

In the present study, we systematically analyzed and compared the expression patterns of the aforementioned host genes in LUAD and adjacent normal tissues and evaluated the correlation between SARS-CoV-2 infection and the expression levels of these genes. The aim of this study was to identify the possible causes for disproportionately severe COVID-19 outcomes in cancer patients.

2. Methods

2.1. Gene expression analysis

The LUAD-related microarray datasets analyzed here were acquired from the Gene Expression Omnibus (GEO) and included GSE31210 [30] (246 samples), GSE27262 [31] (50 samples), GSE7670 [32] (54 samples), GSE19804 [33] (120 samples), GSE118370 [34] (12 samples), GSE43767 [35] (69 samples), GSE32863 [36] (116 samples), GSE68465 [37] (462 samples), GSE12667 [38] (75 samples), GSE63459 [39] (65 samples), GSE72094 [40] (442 samples), GSE43458 [41] (110 samples), GSE10072 [42] (107 samples), and GSE19188 [43] (110 samples). All datasets were merged after data filtering and normalization. The ComBat method was used to reduce the batch effect in each dataset [44]. Group data were statistically analyzed with *t*-tests, and $P < 0.05$ was considered statistically significant. Gene expression tests and visualisation were performed using the "ggplot2" package in R v. 3.6.1 (R Core Team, Vienna, Austria). The UALCAN database [45] (http://ualcan.path.uab.edu/analysis.html) was used to determine the protein and promoter methylation levels of the foregoing host genes in LUAD tissue. Protein expression was validated in LUAD and normal tissue using the immunohistochemical (IHC) analyses in the Human Protein Atlas (HPA, https://www.proteinatlas.org/) database [46].

2.2. CTSB expression analysis after SARS-COV-2 infection

To explore the expression changes of *CTSB* after SARS-COV-2 infection, *CTSB* expression was evaluated using the publicly available transcriptomic datasets GSE152586 [47], GSE177027 [48], GSE152418 [49], and GSE171110 [50]. Analysis of *CTSB* expression in lungs was based on the GSE152586 dataset comprising transcriptomic analyses of human alveolar type II cell organoids 48 h following SARS-CoV-2 infection. For an animal model, CTSB expression analysis in hamster lung samples was based on the GSE177027 dataset comprising transcriptomic analyses of Syrian hamsters 4 d after SARS-CoV-2 infection. CTSB expression analysis of patients with severe COVID-19 was based on the GSE152418 and GSE171110 datasets. The raw read counts of GSE152418 were normalized by the transcripts per million (TPM) method while those of GSE171110 were normalized by log counts per million reads. Patients in intensive care units (ICU) were considered to have severe COVID-19. *CTSB* expression was graphically visualized using Graph Prism v. 6.0 (GraphPad Software, La Jolla, CA, USA). Group means were compared by *t*-tests, and $P < 0.05$ was considered statistically significant. *CTSB* expression levels in COVID-19 patients were analyzed using http://covid19.cancer-pku.cn, which visualized the GSE158055 dataset [51]. The Blood Atlas database (https://www.proteinatlas.org/humanproteome/blood) was used to examine *CTSB* expression in blood immune cells, including B cells, T cells, dendritic cells (DCs), monocytes, and granulocytes.

2.3. Protein-protein interaction (PPI) network construction

PPI network data were obtained using the Search Tool for the Retrieval of Interacting Genes (STRING) database [52] (http://string-db.org) and visualized using Cytoscape v. 3.6.1 (https://cytoscape.org/download.html) [53]. All data are available online.

2.4. Gene expression correlation analysis

R v. 4.0.5 (R Core Team, Vienna, Austria) was used to calculate the correlation between the expression level of *CTSB* and that of other genes in peripheral blood mononuclear cells (PBMCs) of patients with severe COVID-19. To this end, Spearman's correlation coefficients were determined for the GSE152418 dataset. Tumor Immune Estimation Resource [54] (TIMER, https://cistrome.shinyapps.io/timer/) was used to predict the abundance of tumor-infiltrating immune cells based on the gene expression profiles. Correlations of *CTSB* expression with the abundance of immune infiltrates including B cells, $CD4^+$ T cells, $CD8^+$ T cells, DCs, neutrophils, and macrophages were analyzed using TIMER.

2.5. Gene functional enrichment analysis

To identify significantly enriched functional pathways, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and Gene Ontology (GO) categories positively associated with *CTSB* expression in patients with severe COVID-19 were visualized using Metascape (https://metascape.org/gp/index.html#/main/step1) [55]. Genes positively associated with *CTSB* expression were identified in TRRUST [56] (Transcriptional Regulatory Relationships Unraveled by Sentence-based Text mining) (https://www.grnpedia.org/trrust/), which detected the most highly enriched TF-target pairs.

2.6. Cell proportion analysis and differential CTSB expression among cell types

Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia2.cancer-pku.cn/) was used to analyze cell type proportions and differential *CTSB* expression among cell types based on RNA-Seq expression data for LUAD and normal lung tissue samples in The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx)

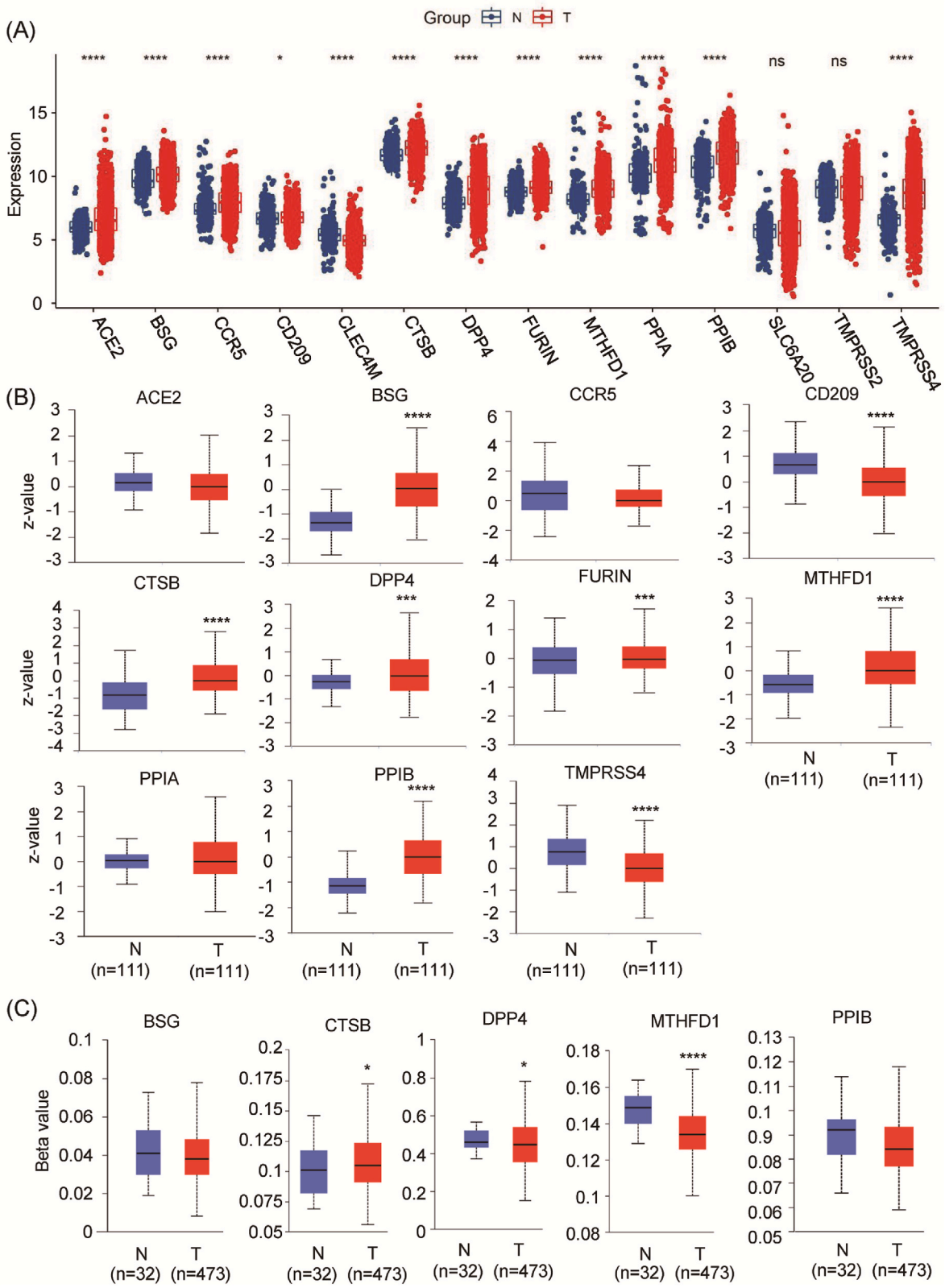

Fig. 1. Expression levels of genes involved in SARS-CoV-2 infection. (A) Box plot comparing transcription levels of genes involved in SARS-CoV-2 infection between normal and LUAD tissues based on GEO datasets. (B) Verification of upregulated genes at translational level using UALCAN database. (C) Methylation levels of BSG, CTSB, PPIB, DPP4, and MTHFD1 promoters in LUAD. N, normal tissues; T, LUAD tissues; ns, not significant. Asterisks indicate significant differences *, $P < 0.05$, ***, $P < 0.001$, ****, $P < 0.0001$. ACE2, angiotensin-converting enzyme 2; BSG, basigin; CCR5, C-C motif chemokine receptor 5; CD209, C-type lectin domain family 4 member L; CLEC4M, C-type lectin domain family 4 member M; CTSB, cathepsin B; DPP4, dipeptidyl peptidase 4; FURIN, paired basic amino acid cleaving enzyme; MTHFD1, methylenetetrahydrofolate dehydrogenase; PPIA, peptidylprolyl isomerase A; PPIB, peptidylprolyl isomerase B; SLC6A20, solute carrier family 6 member 20; TMPRSS2, transmembrane serine protease 2; TMPRSS4, transmembrane serine protease 4.

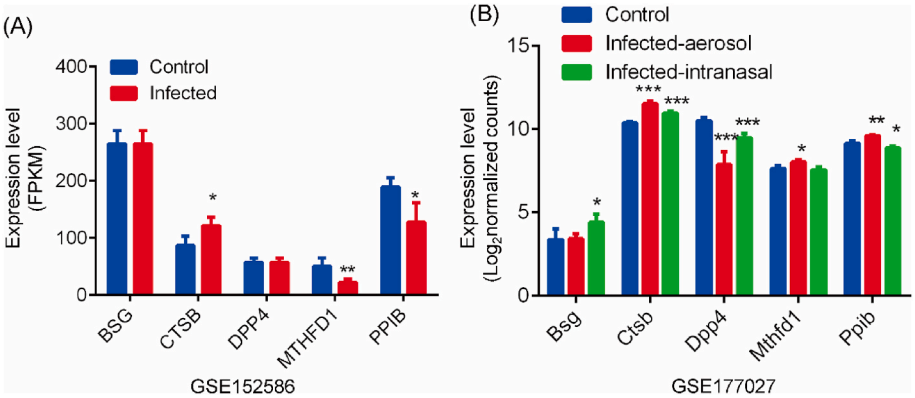

Fig. 2. *BSG*, *CTSB*, *DPP4*, *MTHFD1*, and *PPIB* expression analysis in lungs following SARS-COV-2 infection.
(A) *BSG*, *CTSB*, *DPP4*, *MTHFD1*, and *PPIB* expression in human alveolar type II cell organoids at 48 h after SARS-CoV-2 infection. (B) *BSG*, *CTSB*, *DPP4*, *MTHFD1*, and *PPIB* expression in hamster lung samples 4 d after SARS-CoV-2 infection. *Bsg*, *Ctsb*, *Dpp4*, *Mthfd1*, *Ppib* are homologs to human *BSG*, *CTSB*, *DPP4*, *MTHFD1*, and *PPIB*. Differences between group means were analyzed by Student's *t*-test. Asterisks indicate significant differences: *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$.

datasets. CIBERSORT was used as the deconvolution tool, and there was no normalization. ANOVA was used to analyze differential *CTSB* expression.

2.7. Prognostic value analysis

The relationships among *CTSB* expression level, overall survival (OS), and relapse-free survival (RFS) in lung cancer patients were analyzed using the PrognoScan database (http://www.abren.net/PrognoScan/) [57]. Log-rank tests with Cox proportional hazard ratio (HR) and 95% confidence intervals (CIs) were performed.

2.8. Statistical analysis

The results of the survival analysis are presented as hazard ratios (HRs) and log-rank test P-values according to PrognoScan database. Correlations between two variables were evaluated by Spearman's rank correlation coefficient (r) using R v. 3.6.1 (R Core Team, Vienna, Austria) software. Student's *t*-test was used to compare two independent samples with Graph Prism v. 6.0 (GraphPad Software, La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. mRNAs and proteins of other SARS-CoV-2 infection-related molecules besides ACE2 were upregulated in LUAD compared to normal lung tissues

SARS-CoV-2 infection involves various infection-related molecules, and we analyzed their transcription profiles in 391 adjacent normal tissue and 1,647 LUAD tissue samples based on the microarray data in the GEO database. *ACE2*, *BSG*, *CD209*, *CCR5*, *CTSB*, *DPP4*, *FURIN*, *MTHFD1*, *TMPRSS4*, *PPIA*, and *PPIB* were upregulated in LUAD tissues compared to normal tissues (Fig. 1A). This differential expression might contribute to the observed increase in susceptibility to SARS-CoV-2 infection in LUAD patients. Further analysis revealed that the protein levels of DPP4, BSG, CTSB, FURIN, MTHFD1, and PPIB were higher, whereas those of CD209 and TMPRSS4 were lower in LUAD tissues than in normal tissues. In contrast, the expression levels of the major SARS-CoV-2 receptor ACE2 did not significantly differ ($P > 0.05$) between normal lung and LUAD tissues (Fig. 1B). Moreover, IHC staining confirmed that the DPP4, BSG, CTSB, MTHFD1, and PPIB levels were relatively elevated in LUAD tissues (Supplementary Fig. S1). Disease severity and mortality were higher in male than female patients infected with SARS-CoV-2 [58,59]. To determine the associations between the aforementioned genes and the observed clinical characteristics, we measured the protein levels of the former in both male and female patients with LUAD. Except for DPP4 expression, the expression levels of most proteins, especially CTSB ($P < 0.001$) and PPIB ($P < 0.05$), were significantly higher in male patients than in female patients (Supplementary Fig. S2). DNA methylation is an important event in gene activation. We investigated the factors contributing to *BSG*, *CTSB*, *PPIB*, *DPP4*, and *MTHFD1* upregulation in LUAD. Elevated *BSG*, *PPIB*, *DPP4*, and *MTHFD1* expression was linked to lower DNA methylation levels, especially for the latter two genes, which exhibited a statistically significant change ($P < 0.05$ and $P < 0.0001$) (Fig. 1C). This finding suggests that hypomethylation of the *BSG*, *PPIB*, *DPP4*, and *MTHFD1* promoters might induce the expression of these genes in LUAD. However, *CTSB* upregulation was accompanied by elevated DNA methylation (Fig. 1C). Hence, DNA methylation might not contribute to abnormal *CTSB* expression.

3.2. CTSB was significantly upregulated after SARS-CoV-2 infection and might be associated with hyperinflammatory response in COVID-19 patients

To explore SARS-CoV-2 infection-related gene expression in the lungs, we analyzed the publicly available GSE152586 and GSE177027 transcriptomic datasets recently uploaded to the GEO database repository. *CTSB* was significantly upregulated ($P < 0.05$) whereas *MTHFD1* and *PPIB* were significantly downregulated in human alveolar type II cell organoids 48 h after SARS-CoV-2 infection (Fig. 2A). However, BSG and DPP4 were unaltered. CTSB was consistently notably upregulated in hamster lung samples 4 d after SARS-CoV-2 infection ($P < 0.001$). In contrast, other genes in these tissues were differently expressed compared with those in human organs (Fig. 2B).

We used the STRING database to identify the proteins that interact with CTSB and elucidate the molecular mechanisms of *CTSB* in COVID-19 progression. The PPI network showed that CTSB interacted with proteins involved in antigen processing and presentation, and inflammatory response including major histocompatibility complex (MHC) class II DR alpha (HLA-DRA), MHC class II DR beta 1 (HLA-DRB1), MHC class II DQ beta 1 (HLA-DQB1), CD74, NLR family pyrin domain-containing 3 (NLRP3), PYD and CARD domain-containing (PYCARD), caspase 1 (CASP1), cystatin-A (CSTA), cathepsin D (CTSD), and CTSL (Fig. 3A). In macrophages, the NLRP3 inflammasome was activated by interacting with CTSB [60]. NLRP3 inflammasome dysregulation resulted in severe COVID-19 symptoms, tissue damage, and cytokine storm (CS) [61]. To explore whether the release of abnormal cytokines was associated with CTSB, we determined *CTSB* expression in various immunocytes in the blood. *CTSB* was relatively upregulated in classical, intermediate, and non-classical monocytes, plasmacytoid cells, myeloid DCs, and basophils (Fig. 3B and Supplementary Fig. S3). Memory and naive $CD4^+$ T cells and regulatory T (Treg) cells also expressed appreciable CTSB levels. Hence, *CTSB* was expressed in various innate and adaptive immunocytes, especially in classical monocyte cells.

We then analyzed the correlations between *CTSB* expression and immune cell marker sets in the PBMCs of patients with severe COVID-19.

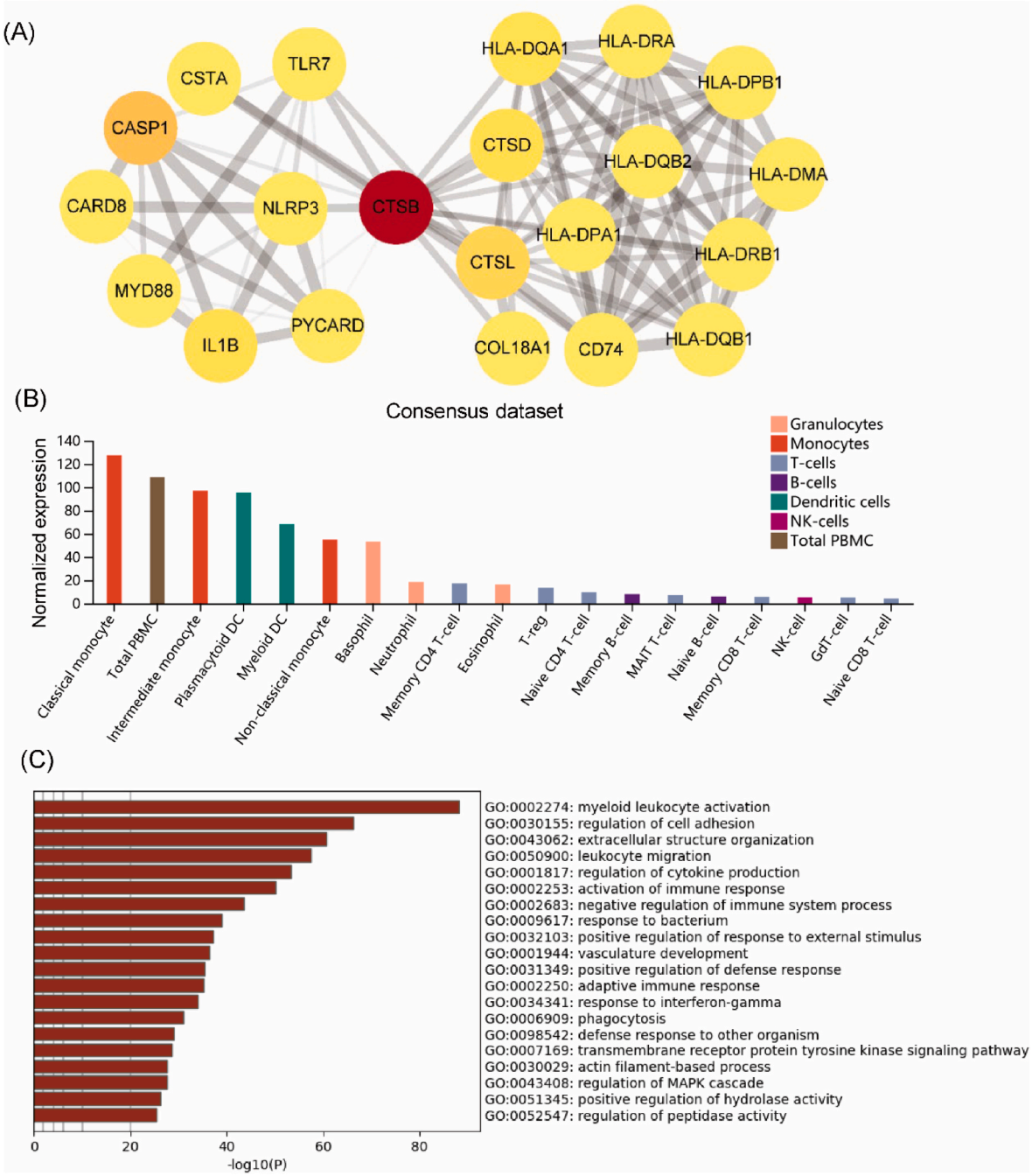

Fig. 3. Analysis of correlation between *CTSB* and proinflammatory cytokine release in COVID-19 patients. (A) Proteins interacting with CTSB were analyzed by STRING database. Line thickness is proportional to data support strength. (B) CTSB expression in human blood cells was analyzed using a consensus dataset. (C) Functional enrichment analysis of genes positively correlated with CTSB in PBMCs of patients with severe COVID-19. Heatmap showing top 20 gene ontology (GO) biological processes. Discrete color scale represents statistical significance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

CTSB was positively associated with most immune cell marker sets including monocytes, M1/M2 macrophages, $CD8^+$ T, general T, B, T-helper 1 (Th1), T-helper 2 (Th2), follicular helper T (Tfh), T-helper 17 (Th17), and exhausted T cells as well as DCs (Table 1).

We analyzed the correlations between *CTSB* expression and the genes in the PBMCs of patients with severe COVID-19 (Supplementary Table S1). GO and KEGG enriched term analyses showed that the genes positively correlated with *CTSB* were enriched in GO biological processes associated with myeloid leukocyte activation and regulation of cytokine production (Fig. 3C and Supplementary Fig. S4A). These were closely related to the inflammatory response. Most of these genes were regulated by RELA and NF-κB1 transcription factors (TFs), which play a crucial role in proinflammatory cytokine biosynthesis (Supplementary Fig. S4B).

The hyperinflammatory response in patients with COVID-19 is directly associated with disease severity and mortality [62]. To establish the correlation between *CTSB* expression and patients with severe COVID-19, we evaluated the former using the publicly available transcriptomic datasets GSE171110, GSE152418, and GSE158055. In all cases, *CTSB* was upregulated in patients with severe COVID-19 (Fig. 4A and B). In dataset GSE171110 and GSE152418, *CTSB* expression exhibited a statistically significant increase in COVID-19 patients ($P <$

Table 1
Analysis of correlations between *CTSB* and gene markers of immune cells in PBMCs of patients with severe COVID-19.

Description	Gene markers	*Cor*	*p*
Monocyte	*CD86*	0.75	***
	CD115 (CSF1R)	0.70	***
M1 macrophage	*INOS (NOS2)*	−0.04	0.76
	IRF5	0.30	*
	COX2 (PTGS2)	0.33	**
M2 macrophage	*CD163*	0.68	***
	VSIG4	0.58	***
	MS4A4A	0.73	***
$CD8^+$ T cell	*CD8A*	0.55	***
T cell (general)	*CD3D*	0.74	***
	CD3E	0.61	***
	CD2	0.65	***
B cell	*CD19*	0.21	0.09
	CD79A	0.34	**
Neutrophil	*CD66b (CEACAM8)*	0.10	0.44
	CD11b (ITGAM)	0.65	***
	CCR7	0.50	***
Natural killer cell	*KIR2DL1*	−0.05	0.69
	KIR2DL3	0.03	0.79
	KIR2DL4	0.24	0.05
	KIR3DL1	0.05	0.68
	KIR3DL3	−0.12	0.35
	KIR2DS4	−0.16	0.19
Dendritic cell	*HLA-DPB1*	0.68	***
	HLA-DQB1	0.59	***
	HLA-DRA	0.69	***
	HLA-DPA1	0.65	***
	BDCA-1 (CD1C)	0.35	**
	BDCA-4 (NRP1)	0.31	*
	CD11c (ITGAX)	0.47	***
Th1	*T-bet (TBX21)*	0.47	***
	STAT4	0.52	***
	STAT1	0.52	***
	IFN-g (IFNG)	0.13	0.31
	TNF-a (TNF)	0.02	0.86
Th2	*GATA3*	0.07	0.60
	STAT6	0.39	**
	STAT5A	0.64	***
	IL13	0.05	0.67
Tfh	*BCL6*	0.38	**
	IL21	−0.25	*
Th17	*STAT3*	0.44	***
	IL17A	−0.09	0.50
Treg	*FOXP3*	−0.15	0.23
	CCR8	−0.05	0.67
	STAT5B	0.13	0.30
	TGFb (TGFB1)	−0.11	0.36
T cell exhaustion	*PD-1 (PDCD1)*	0.10	0.45
	CTLA4	0.30	*
	LAG3	−0.02	0.86
	GZMB	0.41	***

PBMCs, peripheral blood mononuclear cells; *Cor*, R value of Spearman's correlation; Th1, T-helper 1 cell; Th2, T-helper 2 cell; Tfh, follicular helper T cell; Th17, T-helper 17 cell; Treg, regulatory T cell. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

0.01 and $P < 0.05$). Furthermore, *CTSB* expression was higher in elderly and male patients with COVID-19 than in younger patients and the female population (Fig. 4C and D). This finding was consistent with the fact that elderly persons and males are more likely to develop severe COVID-19 than other subpopulations [58,59].

3.3. Elevated CTSB expression promoted immune cell infiltration and was associated with poor prognosis in patients with LUAD

CS induced by SARS-CoV-2 is a leading cause of death in patients with severe COVID-19. There is greater T- and B-lymphocyte accumulation in LUAD tissues than in normal lung tissues [63]. We used the GEPIA database to compare the proportions of immunocytes in normal lung and LUAD tissues. Activated NK, dendritic, B, plasma, $CD8^+$ T, follicular helper T, and regulatory T cells, especially M0, M1, and M2 macrophages were more abundant in LUAD than in normal lung tissues (Fig. 5A). We also compared relative *CTSB* expression among the various cell types in LUAD and normal lung tissues. In LUAD tissues, *CTSB* expression was positively correlated with the proportion of immune cells. *CTSB* was overexpressed in the immune cells of LUAD tissues compared with normal lung tissues (Fig. 5B). M0, M1, and M2 macrophages showed higher *CTSB* expression levels and occurred in greater proportions in LUAD than in normal lung tissues (Fig. 5). Therefore, we speculated that *CTSB* is associated with immune infiltration in LUAD.

We calculated correlations between *CTSB* expression and immune cell infiltration in LUAD patients with COVID-19. In LUAD tissue, *CTSB* expression was significantly positively correlated with infiltration of $CD8^+$ T cells ($r = 0.303$, $P = 7.86e\text{-}12$), $CD4^+$ T cells ($r = 0.222$, $P = 7.83e\text{-}07$), macrophages ($r = 0.563$, $P = 7.70e\text{-}42$), neutrophils ($r = 0.623$, $P = 2.29e\text{-}53$), and DCs ($r = 0.601$, $P = 2.53e\text{-}49$) (Fig. 6A).

Proinflammatory cytokines including interleukin (IL) 2 (IL-2), IL-6, IL-7, IL-10, C-X-C motif chemokine ligand 10 (CXCL-10), C-C motif chemokine ligand 2 (CCL-2), and tumor necrosis factor alpha (TNF-α) were upregulated in patients with severe COVID-19 [64,65]. We investigated the correlations between *CTSB* expression and several critical proinflammatory cytokines in LUAD (Fig. 6B). *CTSB* expression was significantly positively correlated with the proinflammatory cytokine levels in LUAD including CCL-2 ($r = 0.366$, $P = 4.67e\text{-}17$), CXCL-10 ($r = 0.38$, $P = 2.33e\text{-}18$), C-X-C motif chemokine ligand 12 (CXCL-12) ($r = 0.326$, $P = 1.23e\text{-}13$), IL-6 ($r = 0.28$, $P = 2.51e\text{-}10$), IL-7 ($r = 0.214$, $P = 1.65e\text{-}06$), IL-10 ($r = 0.528$, $P = 1.04e\text{-}36$), and TNF-α ($r = 0.278$, $P = 3.23e\text{-}10$). Hence, *CTSB* is closely linked to immune infiltration and proinflammatory cytokine levels in LUAD.

Cancer patients with COVID-19 have poor prognosis [66]. We used PrognoScan to assess the effects of *CTSB* on LUAD patient survival. *CTSB* upregulation was significantly associated with poor prognosis in the OS (HR [95% CI] = 5.42 [2.53–11.58], Cox P = 0.000013) and RFS (HR [95% CI] = 4.04 [2.34–6.99], Cox P = 0.000001) of LUAD patients (Fig. 6C).

4. Discussion

It was previously proposed that *ACE2* upregulation at the transcriptional level renders LUAD patients relatively more susceptible to SARS-CoV-2 infection [28,67–69]. Our results showed that besides ACE2, the potential virus receptors *CD209*, *DPP4*, *BSG*, and *CCR5* and the host factors *TMPRSS4*, *CTSB*, *FURIN*, *MTHFD1*, and *PPIA/PPIB* were also significantly upregulated at the transcriptional level (Fig. 1A). However, only *DPP4, BSG, CTSB, MTHFD1,* and *PPIB* exhibited higher transcription- and translation-level expression in LUAD tissues (Fig. 1B and Supplementary Fig. S1). At the protein level, *ACE2* expression did not significantly differ between LUAD and normal tissues (Fig. 1B). Previous studies only analyzed the expression of ACE2 in LUAD and normal tissues at the mRNA level. We further determined the protein level of ACE2 by using HPA database and UALCAN database. The spike protein of SARS-CoV-2 primarily binds to ACE2 protein and thus invades host cells. The unaltered protein level of ACE2 in LUAD indicated that ACE2 may not be the key molecule determining LUAD patients' susceptibility to SARS-CoV-2 infection. Thus, LUAD patients' susceptibility to COVID-19 may be related to other molecules. PPIA/PPIB intracellularly binds and activates BSG, interacts with non-structural protein 1 (nsp1) in SARS-CoV, enables the virus to bind BSG, and subsequently infects cells that express it [70]. PPIB and BSG upregulation in LUAD may promote SARS-COV-2 penetration into LUAD tissue via the PPIA/PPIB-BSG receptor pathway. Therefore, BSG and PPIB inhibitors could effectively prevent SARS-CoV-2 from entering the lung tissue of LUAD patients. Consistent with previous study, our results also found that DPP4 expression was elevated in LUAD patients, which may be another reason for LUAD patients' susceptibility to COVID-19 [71]. Therefore, drug inhibition of DPP4 may be beneficial for LUAD patients

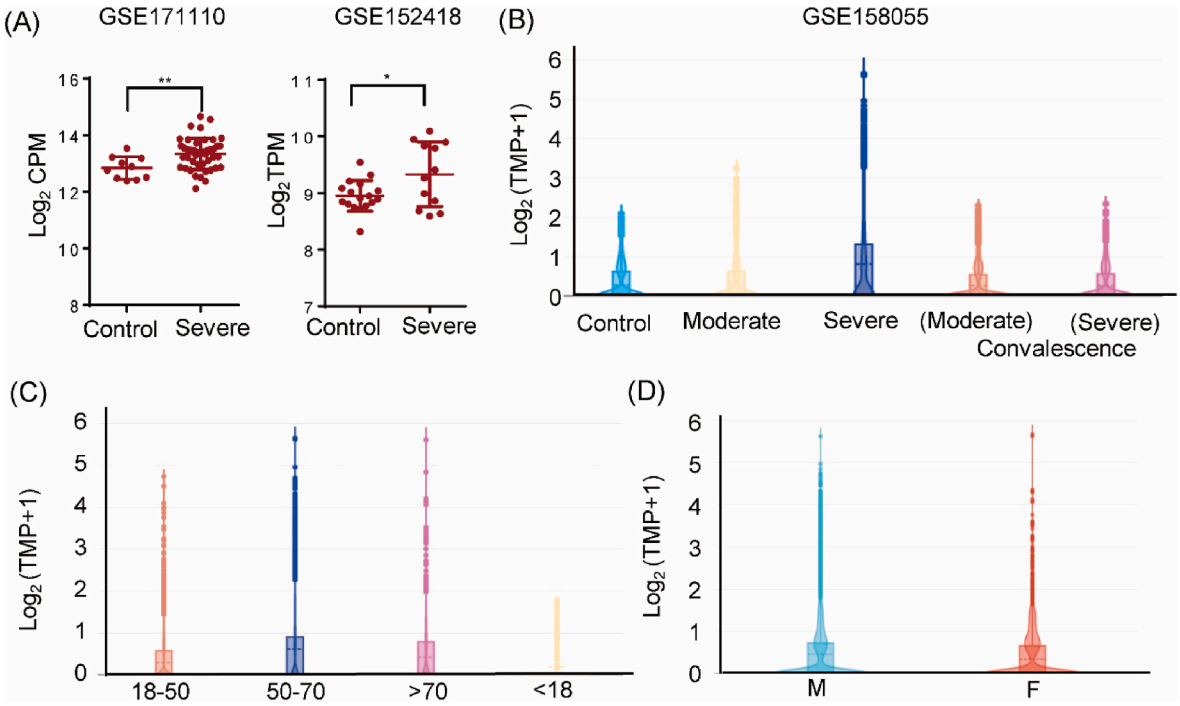

Fig. 4. Analysis of *CTSB* expression in patients with COVID-19. (A) *CTSB* expression in healthy individuals and in patients with severe COVID-19. Differences between group means were analyzed by Student's *t*-test. Asterisks indicate significant differences: *, $P < 0.05$, **, $P < 0.01$. (B) *CTSB* expression in COVID-19 patients with different disease progression (C), age, and (D) gender. F, female, M, male. Data were analyzed and visualized using http://covid19.cancer-pku.cn.

with COVID-19 [71]. However, a recent study showed that administration of DPP4 inhibitors in patients with diabetes did not alter the outcomes of COVID-19 [72]. Thus, the efficacy of DPP4 in LUAD patients with COVID-19 is questionable.

DPP4, *BSG*, *CTSB*, *MTHFD1*, and *PPIB* upregulation in LUAD tissues indicated that these genes might play fundamental roles in COVID-19 progression in patients with LUAD. However, only *CTSB* was upregulated in both human alveolar type II cell organoids and hamster lung tissue samples infected with SARS-CoV-2 (Fig. 2). Thus, we hypothesize that *CTSB* plays a critical role in SARS-CoV-2 infection. A recent study suggested that it was *CTSL* rather than *CTSB* that was upregulated in response to SARS-CoV-2 infection and positively correlated with the course and severity of COVID-19 [73]. However, other studies showed that *CTSB* was also significantly upregulated in lung tissues following SARS-CoV-2 infection [74,75]. This finding was consistent with the results of the present study. Our analysis showed that *CTSB* was upregulated in patients with severe COVID-19 (Fig. 4). These observations imply that both *CTSL* and *CTSB* play vital roles in COVID-19 progression. *CTSB* interacted with NLRP3 and was upregulated in immune cells (Fig. 3A and B; Supplementary Fig. S3). NLRP3 inflammasome is activated through the interaction of CTSB with NLRP3 [60]. The activated NLRP3 inflammasome induces secretion of proinflammatory cytokines, including IL-6 and IL-1β [76]. These results suggest that *CTSB* expression is closely related to proinflammatory cytokine release in patients with COVID-19. *CTSB* was positively correlated with the immune cell marker sets in the PBMCs of patients with severe COVID-19 (Table 1). Most of the genes positively correlated with *CTSB* expression participated in cytokine production (Fig. 3C and Supplementary Fig. S4). Thus, we assumed that *CTSB* upregulation following SARS-CoV-2 infection could dysregulate NLRP3 inflammasome activity and eventually lead to a hyperinflammatory response in COVID-19 patients.

COVID-19 patients with LUAD are relatively more likely to develop severe disease and exhibit comparatively higher mortality rates than those of patients presenting with other cancers [11–13]. More immune cells accumulated in LUAD than normal lung tissue and the proportion of immune cells in LUAD tissue was positively correlated with *CTSB* expression (Fig. 5). The latter was also positively correlated with immune cell infiltration and proinflammatory cytokine levels in LUAD patients (Fig. 6A and B). Thus, *CTSB* upregulation after SARS-CoV-2 infection might promote immune cell infiltration and increase proinflammatory cytokine levels in LUAD patients. Elevated *CTSB* expression in LUAD patients was associated with poor prognosis (Fig. 6C). Lysosome-encapsulated cellular proteases are critical risk factors for cancer progression. *CTSB* controls tumor growth, migration, invasion, angiogenesis, and metastasis [77]. The release of CTSB from myeloid-derived suppressor cells activates the NLRP3 inflammasome and promotes tumor growth [78]. Both earlier research and the present study confirmed that *CTSB* plays a principal role in tumor development and viral infection. Hence, we postulate that it has great potential in the diagnosis and treatment of COVID-19 patients with cancers. *CTSB* may activate hyperinflammatory responses following SARS-CoV-2 infection. Therefore, *CTSB* inhibitors could mitigate inflammation [79]. The *CTSB* inhibitor CA-074 methyl ester (Me) reduces inflammation and apoptosis in polymyositis and lung interstitial inflammation [80,81]. *CTSB* also plays a vital role in cancer progression. Several studies have reported that *CTSB* inhibitors suppress metastasis in several cancers [82–85]. Therefore, they may also have therapeutic efficacy against severe cases of COVID-19 infection as well as certain tumors.

The present study demonstrated that *DPP4, BSG, CTSB, MTHFD1*, and *PPIB* rather than *ACE2* may be responsible for the high susceptibility of LUAD patients to SARS-CoV-2 infection. Among them, *CTSB* expression was strongly correlated with the hyperinflammatory response in COVID-19 patients and with immune cell infiltration in LUAD. Thus, *CTSB* upregulation may be related to increased COVID-19 severity and mortality in LUAD patients. Our study suggests that *CTSB* is a promising drug development target in COVID-19 patients with lung cancers. However, the therapeutic potential of CTSB inhibitors in patients with severe COVID-19 must be validated by animal experiments and clinical trials. Moreover, it is uncommon that disease progression is determined by a single gene alone. Therefore, future research should investigate other factors controlling COVID-19 development and progression.

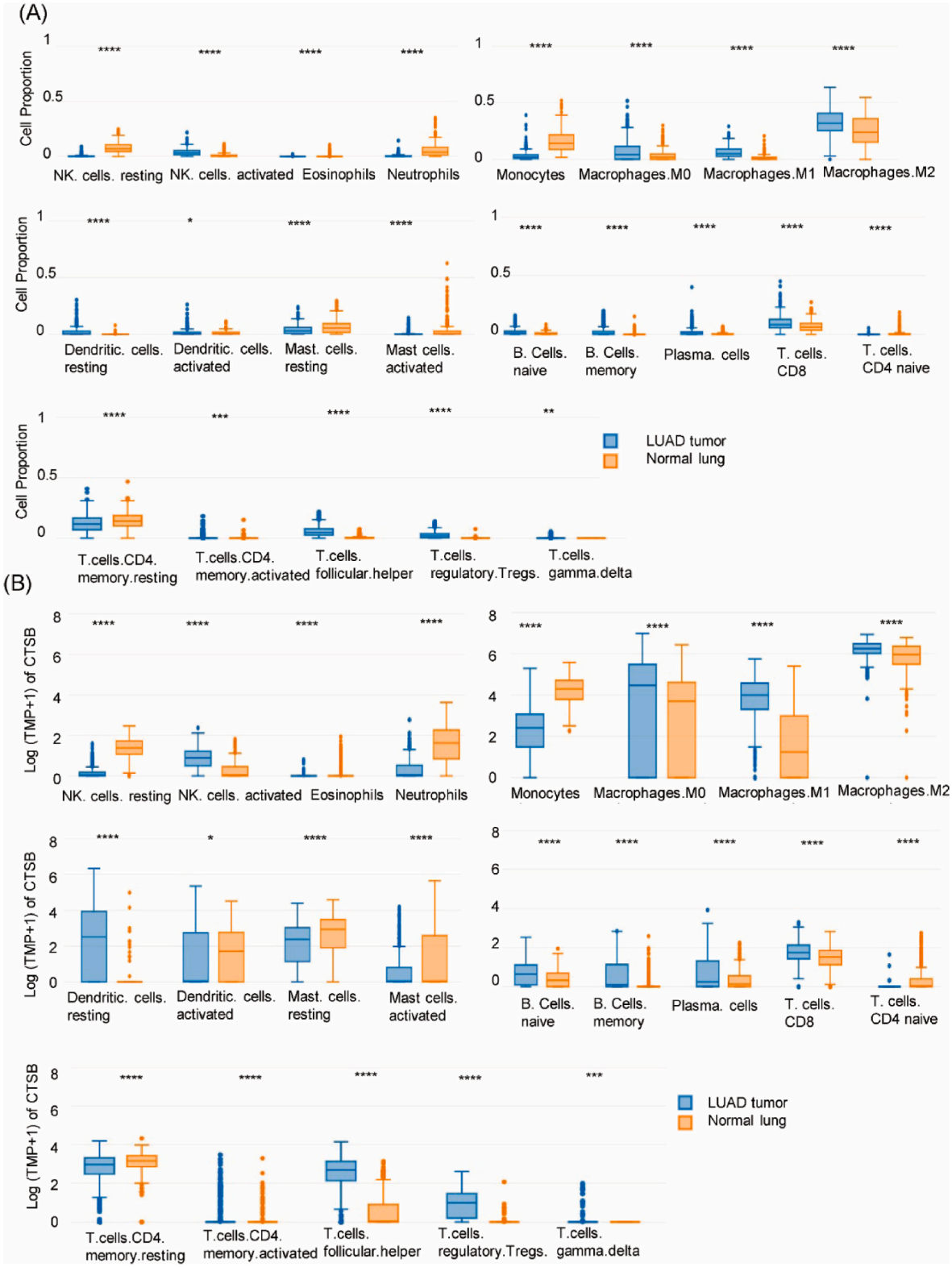

Fig. 5. GEPIA-based cell proportion analysis and differential *CTSB* expression in normal lung and LUAD tissues. (A) Cell type proportion analysis based on LUAD and normal lung tissue samples from TCGA and GTEx databases. (B) *CTSB* expression by cell type based on LUAD and normal lung tissue samples from TCGA and GTEx databases. Group means compared by ANOVA. Asterisks indicate significant differences: *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$, ****, $P < 0.0001$.

Data availability statement

Data supporting the findings of the present study are available in the article itself and the Supplementary Material. They are also available from the corresponding author upon reasonable request.

Author contributions

Conceptualization, X.D. and J.L.; methodology, X.D.; software, X.D.; validation, X.D.; investigation, X.D., N.Y., M.Y., H.G., Y.G., J.L. and Y.L.; resources, X.D., N.Y., M.Y., H.G., Y.G., J.L. and Y.L.; data curation, X.D.;

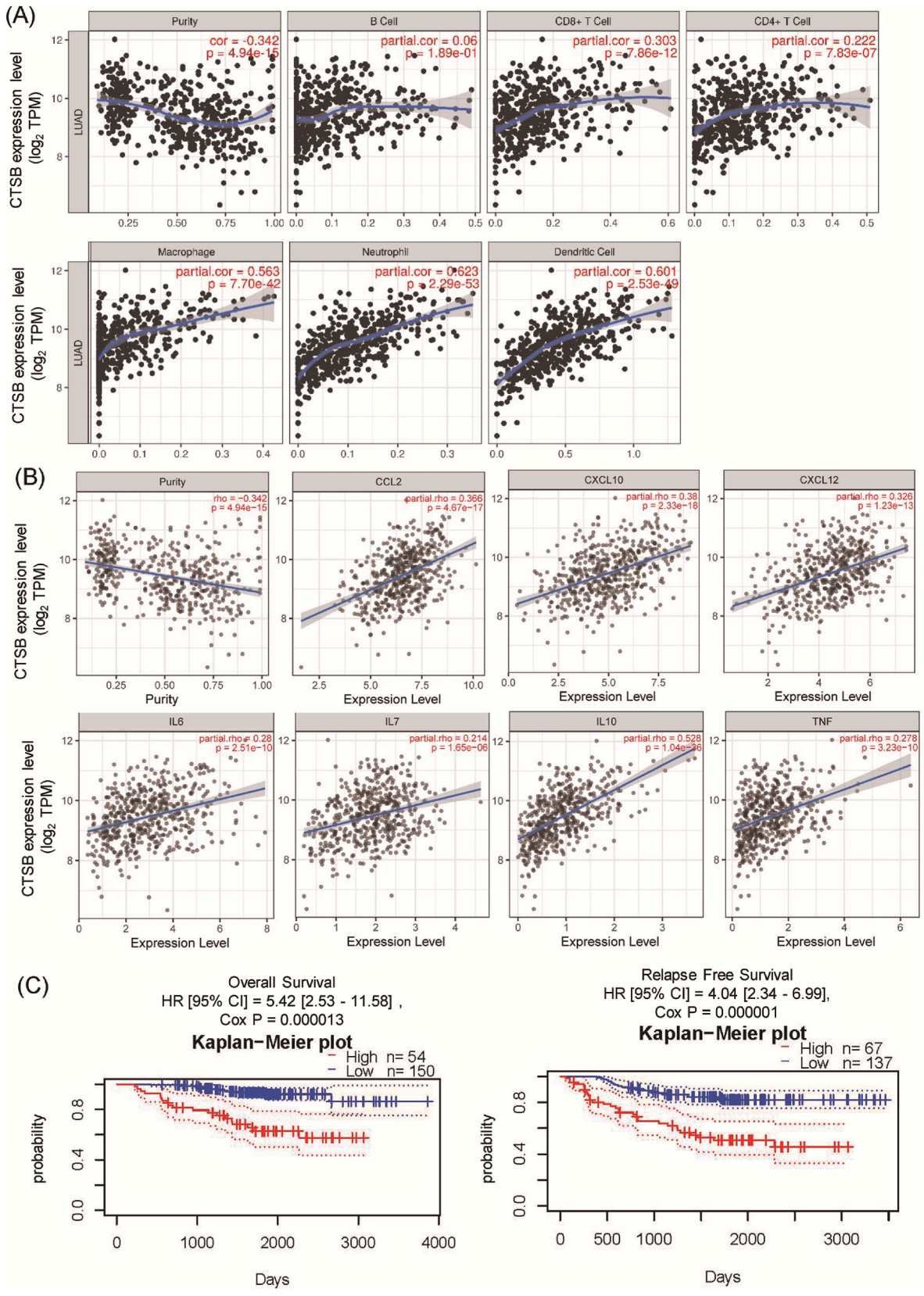

Fig. 6. Elevated CTSB levels promoted immune cell infiltration and cytokine release and was associated with poor prognosis in lung adenocarcinoma (LUAD). (A) Correlations between CTSB expression and infiltration levels of B, CD8+T, CD4+T, and dendritic cells, macrophages, and neutrophils in LUAD were analyzed with TIMER. (B) Correlations between CTSB and cytokine expression in LUAD. CTSB is on y-axis and related marker genes are on x-axis. Log2 TPM normalization used for indicated gene expression levels. $P < 0.05$ was considered statistically significant. (C) Prognostic value of *CTSB* in patients with LUAD.

writing—original draft preparation, X.D.; writing—review and editing, X.D., H.G., M.Q., J.X., X.Z. and J.L; visualization, X.D.; supervision, X.D. and J.L.; project administration, X.D. and J.L.; funding acquisition, X.D. and J.L. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

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Appendix A. Supplementary data

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