A systems biology approach for investigating significantly expressed genes among COVID-19, hepatocellular carcinoma, and chronic hepatitis B

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Abstract

Background: Worldwide, COVID-19's death rate is about 2%, considering the incidence and mortality. However, the information on its complications in other organs, specifically the liver and its disorders, is limited in mild or severe cases. In this study, we aimed to computationally investigate the typical relationships between liver-related diseases [i.e., hepatocellular carcinoma (HCC), and chronic hepatitis B (CHB)] and COVID-19, considering the involved significant genes and their molecular mechanisms.

Methods: We investigated two GEO microarray datasets (GSE164805 and GSE58208) to identify differentially expressed genes (DEGs) among the generated four datasets for mild/severe COVID-19, HCC, and CHB. Then, the overlapping genes among them were identified for GO and KEGG enrichment analyses, protein–protein interaction network construction, hub genes determination, and their associations with immune cell infiltration.

Results: A total of 22 significant genes (i.e., ACTB, ATM, CDC42, DHX15, EPRS, GAPDH, HIF1A, HNRNPA1, HRAS, HSP90AB1, HSPA8, IL1B, JUN, POLR2B, PTPRC, RPS27A, SFRS1, SMARCA4, SRC, TNF, UBE2I, and VEGFA) were found to play essential roles among mild/severe COVID-19 associated with HCC and CHB. Moreover, the analysis of immune cell infiltration revealed that these genes are mostly positively correlated with tumor immune and inflammatory responses.

Conclusions: In summary, the current study demonstrated that 22 identified DEGs might play an essential role in understanding the associations between the mild/severe COVID-19 patients with HCC and CHB. So, the HCC and CHB patients involved in different types of COVID-19 can benefit from immune-based targets for therapeutic interventions.

Keywords: COVID-19, Hepatocellular carcinoma, Chronic hepatitis B, Immune cell infiltration, Viral infection, System biology analysis, Disease interconnection

Background

SARS-CoV-2 infection is a kind of coronavirus that infects the human respiratory system in China; this type of virus first appeared in December 2019. The World Health Organization (WHO) designated its related disease as a pandemic on March 11, 2020. Over 620 million cases and nearly 6.6 million fatalities were recorded by October 14, 2022 (i.e., https://covid19.who.int/). Elderly patients with significant health problems, including diabetes, obesity, and chronic renal disease, suffer from worse disease and higher death rates [1, 2, 3]. There is a considerable variation in clinical presentations of COVID-19, which may be anything from shortness of breath to kidney problems [4, 5].
Some researchers are very concerned about the effects of COVID-19 and those connected to patients with hepatitis C or B or both diseases. Such issues often strike those with liver problems, especially those with liver fibrosis, damage, or cancer [6, 7]. And, as the number of SARS-CoV-2 and HBV or HCV coinfected individuals increases, so does the risk of creating an outbreak [8, 9]. To provide better care for the significant population of patients at risk for having HCV or HBV, understanding the liver symptoms and conditions of COVID-19 that these patients experience is essential.

Two worldwide viral infections need scrutiny: COVID-19 and HBV. The studies have indicated that hepatitis B infection does not seem to increase one’s chance of developing SARS-CoV-2. Although there are few conflicting results on the effects of chronic hepatitis B (CHB) on COVID-19 patients, we know that it may cause certain complications. COVID-19 had a greater death rate in individuals with chronic liver disease, and it needs additional investigation for confirmation [10, 11].

A recent study reveals that SARS-CoV-2 has a specific receptor on host cells, ACE2, and a strong binding capacity to the virus [2, 12, 13]. Higher expression levels in various organs seem more easily infected by SARS-CoV-2. SARS-CoV-2 is highly contagious in cancer patients, and their prognosis is bleak [14]. Additionally, patients with HCC had a decreased ACE2 expression compared to normal samples, which correlated with a poor prognosis [14]. Nevertheless, many questions remain about the role that the SARS-CoV-2 proteins play in regulating human mRNA expression in cancer.

The fact that earlier research has shown that COVID-19 has a relationship to liver function in people with chronic hepatitis B has not deterred researchers from investigating its role in people with other liver disorders (e.g., CHB). Moreover, researchers published the findings on people with persistent HBV infections who had COVID-19. On the other hand, various biomarker signatures may serve as diagnostic information to enhance treatment plans for HCC and COVID-19 in specific personalized medicine.

Methods

Microarray datasets
Data from the NCBI-Gene Expression Omnibus (GEO) database, GSE164805 and GSE58208, were used in this study with a total sample size of 42. The 15 samples from GSE164805 come from five severe COVID-19 patients, five mild COVID-19 patients, and five healthy samples. There were ten individuals with HCC, twelve patients with CHB in GSE58208, and five control samples (i.e., GSE58208 has both CHB and HCC samples separately without in-common patients involved). The control groups, who were a reference in the datasets, had no inflammation, viral genome, or HCC/CHB histories. The GSE164805 samples were run on the Agilent-085982 Arraystar human IncRNA V5 microarray (GPL26963) to produce the expression profiling arrays, whereas the GSE58208 samples were run on the Affymetrix Human Genome U133 Plus 2.0 Array (GPL570).

Identification of DEGs
By comparing patients infected with mild and severe SARS-CoV-2, CHB, and HCC and their corresponding control samples, differentially expressed genes (DEGs) were identified using the GEO2R tool as well as “umap,” “GOquery,” and “limma” packages [15]. Next, we selected the statistically significant DEGs \( |\log_{2} (\text{FoldChange})| \geq 0.5 \) with a \( p \) value of less than 0.05 and Benjamini & Hochberg (False discovery rate) criterion for \( p \) value adjustment. Last, we used the Multiple List Comparator free publicly available tool in the Web site link (i.e., http://www.molbiotools.com/) to create Venn diagrams that show the overlapped DEGs obtained for the diseases mentioned above.

GO and KEGG enrichment analyses
Gene Ontology (GO) and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analyses were performed for the obtained significant DEGs. A major Knowledgebase upgrade, DAVID (Database for Annotation, Visualization, and Integrated Discovery) v6.8, comprises a complete collection of tools to interpret the meaning of genes with powerful annotation capabilities useful for scientists [16]. The GO analysis includes a biological process (BP), molecular functions (MF), and cellular components (CC). Additionally, the KEGG pathway analysis was carried out. The threshold of \( p \) value < 0.05 was used for both GO enrichment and KEGG pathway analyses.

Protein–protein interaction network construction and hub genes identification
The protein–protein interaction (PPI) network was generated, analyzed, and visualized using the Cytoscape 3.7.1 through STRING program (with default parameters) and included all the known interactions among the cell’s proteins [17, 18]. We employed the Cytoscape cytoHubba plugin to investigate the associations between the DEGs, including analyzing, clustering, and identifying hub genes. Using the plugin, the “Degree” criterion was selected for hub genes identification. Finally, the 10 top essential genes were picked from the PPI network analysis that can reveal the critical hub genes.
Assessment of immune cell infiltration

We utilized the TIMER (Tumour Immune Estimation Resource) database available through the R-based Web site link as a shiny app to estimate the correlations between the mRNA expression data for identified DEGs and tumor purity and the quantity of immunological infiltrates, as well as B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells. There were almost 10,000 samples from the TCGA representing 32 different kinds of cancer in this database [19, 20, 21]. All data were analyzed using the Spearman correlation technique where the categorization correlation criteria are as follows: low 0.00–0.19; moderate 0.20–0.39; high 0.40–0.59; very high 0.60–1.0.

Results

DEGs identification

In total, 19,336, 21,774, 4294, and 4663 DEGs were extracted from the GSE164805, GSE164805, GSE58208, and GSE58208 microarray datasets, respectively. And the results indicated that 2328, 2389, 2212, and 2487 DEGs were in common among different datasets: severe COVID-19 and CHB, mild COVID-19 and HCC, mild COVID-19 and CHB, and severe COVID-19 and HCC, respectively (Additional file 1: Fig S1).

Enrichment analyses of GO and KEGG

The DAVID Web site was used to run the GO and KEGG pathway enrichment investigation, from which the illustrated outcomes were then shown in terms of -log10 (p value). The DEGs were grouped according to their GO analysis into MF, BP, and CC. According to the BP analysis, the shared genes between the four datasets were primarily associated with protein transport and protein autophosphorylation. In contrast, the shared genes between mild COVID-19 and CHB and HCC were associated with protein transport, positive regulation of transcription DNA-templated, and transcription DNA-templated. Moreover, the shared genes between severe COVID-19 and CHB and HCC were related to protein phosphorylation, mRNA splicing via spliceosome, and transcription DNA template (Fig. 1). For the CC analysis, the shared DEGs among four datasets were mainly enriched in neoplasm, cytoplasm, and membrane, while the shared DEGs between mild COVID-19 and CHB as well as HCC were located in membrane and neoplasm.

Additionally, the shared genes between severe COVID-19 and CHB as well as HCC were positioned at the neoplasm, nucleus, and membrane (Fig. 2). In the MF, the shared gene among four datasets was primarily enriched in protein binding and poly(A) RNA binding. At the same time, common genes between mild/severe COVID-19 and CHB as well as HCC were also increased in protein binding and poly(A) RNA binding (Fig. 3). Genes

![Fig. 1 GO biological process enrichment analysis of overlapping DEGs: a mild COVID-19 versus CHB, b mild COVID-19 versus HCC, c severe COVID-19 versus CHB, d severe COVID-19 versus HCC datasets](image-url)
frequent in the KEGG signaling pathway analysis were also shown to be enriched in the insulin signaling pathway, endocytosis, RNA transport, carbon metabolism, and ubiquitin-mediated proteolysis (Fig. 4).

**Hub genes identification**

The PPI network of the determined DEGs for severe COVID-19 versus HCC (2389 nodes and 25,819 edges), severe COVID-19 versus CHB (2264 nodes and 24,656 edges), and severe COVID-19 versus CHB datasets.

**Figure 2** GO cellular component enrichment analysis of overlapping DEGs: a mild COVID-19 versus CHB, b mild COVID-19 versus HCC, c severe COVID-19 versus CHB, d severe COVID-19 versus HCC datasets.

**Figure 3** GO molecular function enrichment analysis of overlapping DEGs: a mild COVID-19 versus CHB, b mild COVID-19 versus HCC, c severe COVID-19 versus CHB, d severe COVID-19 versus HCC datasets.
edges), mild COVID-19 versus HCC (2292 nodes and 22,386 edges), and mild COVID-19 versus CHB (2139 nodes and 21,939 edges) was constructed. The top 10 genes were identified using the 11 techniques provided in cytoHubba and ranked using the degree method. The identified hub gene sets for severe COVID-19 versus HCC, severe COVID-19 versus CHB, mild COVID-19 versus HCC, and mild COVID-19 versus CHB are shown in Fig. 5.

**Significant DEGs associated with immune cell infiltration**

The statistically significant existence of either negative or positive correlations between identified unique DEGs from the previous section and immune cell infiltration was comprehensively explored based on the TIMER database. The results revealed that there was closely a positive correlation between the expression of all DEGs and the infiltration of B cells, CD8$^+$ T cells, CD4$^+$ T cells, macrophages, neutrophils, and dendritic cells ($p < 0.05$). The JUN, JUN, and GAPDH expressions were not significantly correlated for infiltration of B cells, CD8$^+$ T cells, and CD4$^+$ T cells, respectively. Moreover, no significant correlation was identified between the expression of all DEGs and the purity. However, some of the target DEGs identified negative (i.e., ACTB, IL1B, PTPRC, SRC, TNF) and positive (HNRNPA1, VEGFA) correlations. More details are depicted in Additional file 2: Fig S2.

**Discussion**

About 391 million persons globally are at risk of developing decompensated liver disease and hepatocellular cancer due to CHB [22]. Preexisting liver disease comorbidity may impact the results of COVID-19 in patients with chronic viral hepatitis [20]. Oncologists worldwide were affected by the COVID-19 epidemic. In this pandemic, CHB may be significant comorbidity of preexisting liver illnesses. A study suggests that HCC sufferers are more likely to develop severe COVID-19 because they have both cancer and chronic liver disease at the same time; however, there is no available clinical evidence [23]. Strengthening one’s immune system via regular physical activity is linked to a better response to viral infectious illnesses like COVID-19 [24].

Identifying undesirably expressed candidate genes, which may provide insight into how a process is regulated in response to a stimulus, may be of considerable assistance in determining the appropriate therapy targets and preventive measures to take. Accordingly, in this work, bioinformatics methods were employed to examine two microarray datasets (GSE164805 and GSE58208) to find probable drivers. Using the utilized criteria, we were able to narrow down the list of candidate hub genes to 22 (ACTB, ATM, CDC42, DHX15, EPRS, GAPDH, HIF1A, HNRNPA1, HRAS, HSP90AB1, HSPA8, IL1B, JUN, POLR2B, PTPRC, RPS27A, SFRS1,
SMARCA4, SRC, TNF, UBE2I, VEGFA) that will be discussed in detail as follows.

For comparisons across species and tissues, the researchers used the ACTB gene expression data from each of their RNA-seq experiments to normalize the expression of ACE2. Most cell types produced the housekeeping gene ACTB, which was an internal control for gene expression measurements. Additionally, all species investigated have the ACTB gene [25].

TLR7-ATM deficiency may cause two distinct immunodeficiency phenotypes. The potential that the ATM deficit influenced the progression of COVID-19 in the TLR7-deficient case cannot be ruled out. Furthermore, the death of B cells due to ATM deficiency reduced germinal center frequency and size after vaccination. Patients with COVID-19 pneumonia who have X-linked TLR7 and ATM pathogenic mutations, along with their clinical and molecular characterizations, have also been studied elsewhere [26].

Various signaling pathways could target CDC42, which was downregulated in HCC515 cells with COL-3 treatment [27]. CDC42 could also be affected by the Coronaviridae family neurotropic virus (i.e., porcine hemagglutinating encephalomyelitis virus) [28]. Additionally, CDC42 is one of the many genes downregulated in lung cells when COL-3 functions as a protective mechanism. So, such genes (CDC42) are required for a chemokine, TNF, and MAPK signaling pathways [27].

It is crucial to note that SARS-CoV-2 is an RNA virus that is the source of the current global coronavirus epidemic [29, 30]. SARS-CoV-2 may readily infect human intestinal epithelial cells in individuals with COVID-19 who have gastrointestinal symptoms and fecal RNA excretion of the virus [31, 32]. RNA helicase DHX15 may be targeted to regulate SARS-CoV-2 and the inflammation of the gastrointestinal tract produced by SARS-CoV-2, based on the findings on its involvement in regulating enteric RNA virus-induced intestinal inflammation [33].

The mRNA vaccine vesicles must enter cells and hijack the host cell machinery to create a viral protein antigen, which will then be processed and presented by MHC molecules to stimulate B and T cell responses. All are necessary to translate mRNA, the ribosome, translation initiation factors, aminoacyl-tRNA synthetases,
and elongation factors. EPRS seems to control pro-
fibrotic protein production [34].

The ACE2 mRNA transcript level was determined to
be comparable to GAPDH and beta-actin. Overall, the
data show that the mRNA encoding for the ACE2 gene
is expressed similarly across patients. Patients with
COVID-19 will need to be investigated in the future to
learn more about how SARS-CoV-2 infection affects the
thyroid [35].

ACE2 expression was lowered by HIF1A knock-
down under hypoxic circumstances, alone or combined
[36]. Patients with severe COVID-19 may also see an
increase in the degradation of FOXP3 proteins because
the hypoxic lung environment activates HIF1A, which is
involved in aerobic glycolysis [37]. Furthermore, it was
shown that overexpression of HIF1A in human embry-
onic kidney cells strongly decreases the production of
ACE2 [38].

HNRNPA1 was downregulated in Calu-3 cells, indicat-
ing a human cell’s reaction to inhibit viral replication
in contrast to the prior instances of upregulated genes.
Human RNA-binding proteins such as HNRNPA1, which
was recently identified as the “hub protein” with the most
significant functional ties to the human SARS-CoV-2
genome, were shown to have conserved connections to
the SARS-CoV-2 genome in this research [39, 40].

In addition to playing a significant part in cancer devel-
opment, the signaling of growth factor receptors (GFR) is
also essential for the progression of some viral infections
[41–43]. Recent investigations have shown that infec-
tion with SARS-CoV-2 significantly alters the expression
of numerous genes involved in cellular signaling path-
ways essential in cancer development. One of these is the
RAS-RAF/MEK/ERK signaling pathway [44]. Those with
COVID-19 and more severe symptoms have been shown
to have more significant H-Ras gene overexpression in
their peripheral blood mononuclear cells (PBMC).

The SARS-CoV-2 infection triggers such overexpres-
sion in immune cells, a molecular process. This finding
can highlight the importance of the Ras family of genes
in the host immune response, not just to COVID-19 but to
other viral infectious diseases as well [45].

Viruses may activate Hsps, particularly Hsp70 and
Hsp90, which increase viral replication. For example,
the Hsp90 inhibitor geldanamycin inhibits coronavirus
replication in cell culture systems [46]. HSP90AB1 over-
expression also suggests that increased inflammation
triggered extrapulmonary tissue remodeling. The estro-
gen signaling pathway connected with the HSP90AB1
target was identified as the primary COVID-19 signaling
mechanism [47].

The HSPA8 protein involved in antigen processing and
presentation was changed in six COVID-19 individuals
[48]. HSPA8 was one of the most downregulated COVID-
19 genes [49]. The results demonstrated that HSPA8
was connected to other genes involved with heat shock
response and ER stress, suggesting that cellular stress
response is vital in SARS-CoV2-related coronavirus
pathogenesis [46]. Also, in SARS-CoV-2-infected NHBE
cells, many interleukin genes were elevated, includ-
ing IL1B [50]. SARS-CoV-2-infected NHBE cells exhib-
ted a significant increase in lung fibrosis-related genes
e.g., IL1B). For COVID-19 individuals suffering from an
inflammatory storm, an integrated analysis suggested
that new target genes such as IL-1 may be beneficial [51].

Cardiac myocyte hypertrophy is linked to an increase
in c-Jun expression level, according to research. As part
of the activator protein-1 complex, c-Jun regulates cell
death and survival [52]. Viral infections are connected
with inflammation, and JUN is crucial in this pro-
cess [40]. In individuals with COVID-19, CD4+ T cells
expressed significant amounts of inflammatory genes,
including JUN [53].

A topological study of the gain component was carried
out, and the POLR2B gene, which was shown to have a
higher network degree, was discovered [54]. The POLR2B
gene was shown to be ubiquitinated, and its protein levels
dropped in other studies [55].

As a critical antigen, T cell activation in atherosclerosis
relies on PTPRC, previously known as CD45. Vaccination
may activate naive B cells, as shown by the upregulation of
many genes (such as PTPRC) implicated in GO pathways
for B cell activation. Severely affected COVID-19 patients
have lower levels of the PTPRC gene, indicating that activa-
tion of naive B cells may be hampered in these people
[56, 57].

The housekeeping Rps27a gene encodes a 40S subunit
of the ribosomes. There are two protein-coding tran-
scripts for the mouse Rps27a gene (named S27a-44 and
S27a-45). It was discovered that the levels of two of the
four ribosomal fusion proteins encoded by human ubiqui-
tuins, RPS27A and UBA52, were elevated in patients
with Alzheimer’s disease and COVID-19 with Alzhei-
mer’s disease, respectively [28, 58].

A genome-wide CRISPR investigation has identified
SMARCA4 as a SARS-CoV-2-specific gene. SMARCA4
and SMAD3 may be involved in SARS-CoV-2 entrance,
and virus-induced cell death is possible. The provi-
ral activity of SMARCA4, a protein expressed by the
SMAD3 gene, has been described by Wei’s group [59].

However, ABL kinases are combined with SRC
family kinases to enhance vaccinia virus actin-based motil-
ity. Patients infected with SARS-CoV-2 may benefit from
SRC’s anti-inflammatory and antifibrotic action and
cytokine inhibition. RPS3 was found to be an essen-
tial player in viral replication, while SRC non-receptor
protein kinase was found to be a hub gene in the inflammatory response. It has been observed that proteins like SRC, which control the cytokine secretion network, were crucial in the ACE2-related inflammatory responses to the cytokine secretion-associated proteins [60, 61].

In the COVID-19 cohort with Alzheimer’s disease, the serine- and arginine-rich splicing factor 1 is encoded by the downregulation of SRSF1. SRSF1 activity becomes uncontrolled due to neurodegeneration-related hypoxia, resulting in increased splicing, which is then detected in Alzheimer’s patients [28].

High levels of TNF-α are caused, according to Tsukamoto et al. [62], by genetic changes at the TNF-α locus. Increased TNF-α production is linked to two biallelic polymorphisms in TNF-α, one associated with severe infectious diseases [63]. Consequently, anti-TNF medicine is being considered a possible treatment for COVID-19 [57]. Inflammatory cytokines like TNF and IFNG have been linked to low vitamin D levels. In contrast, vitamin D has been shown to suppress these cytokines and boost anti-inflammatory cytokines generated by macrophages [51].

UBE2I is a ubiquitin-conjugating enzyme involved in protein breakdown, although it may also promote transcription [64].

Due to the removal of ACE2’s antagonistic effect on VEGFA production, SARS-CoV-2 elevates levels of VEGFA in the body. Heart problems are also significantly linked to the rise in VEGFA expression, which causes cardiac hypertrophy to proceed. For example, ACE2 suppresses cell invasion and migration in NSCLC cells by suppressing VEGFA/VEGFR2/ERK pathway in breast cancer. Antagonizing VEGFA has also been caused by SARS-CoV-2 downregulation of ACE2, an essential factor. VEGFA is a crucial gene in COVID-19 cancer high-risk patients, according to a comprehensive gene–disease association analysis [52, 65, 66].

When the livers of COVID-19 patients who had passed away were examined histologically, it was discovered that there were extensive vascular abnormalities, steatosis, and mitochondrial abnormalities. These conditions were assumed to be brought on by SARS-CoV-2 [10]. According to the findings of several studies, the results for patients with COVID-19 infections was poorer when the patients also had an associated chronic liver illness, which reduced the patients’ liver function [66–68]. Extremely high levels of angiotensin-converting enzyme 2 (ACE2) have been seen in many different kinds of cancer cells, including lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC), suggesting a link between COVID-19 and the progression of cancer and the mortality rate [70]. It is possible to indicate that the likelihood of direct liver damage of the HCC patient by SARS-CoV-2 would be unlikely owing to the low expression of ACE2. Still, HCC patients with obesity are more likely to be affected by COVID-19-linked severe pathogenesis and poor prognosis [71].

Twenty percent of cirrhotic patients with COVID-19 had acute-on-chronic liver failure or acute decompensation, according to a global study that included cohorts from 13 Asian countries [69]. This is a significant result because it indicates that persons with cirrhosis are at increased risk of experiencing severe liver damage from the SARS-CoV-2 virus. Patients infected with COVID-19 who already have liver disease have a more significant risk of severe complications and mortality than healthy patients [72]. According to the findings of a research that included 15 patients with chronic hepatitis B and COVID-19, those patients had a more severe illness and a higher death rate when compared to patients who did not have HBV infection, which suggests that HBV coinfection may increase the development of liver damage, which is linked with unfavorable outcomes [73, 74].

Moreover, many researchers have investigated potential relationships between COVID-19 and chronic liver disease. However, the roles of these 22 genes are important while being related to the clinical manifestations.

To understand the pathophysiological and clinical features of SARS-CoV-2 infection, one may need to have an in-depth comprehension on cytokine storm because of inappropriate recognition of the pathogen with an improper response of the immune system involving different genes and signaling pathways [75]. Furthermore, the immune response at the liver may result in immunodeficiency in patients with liver disease by distorting the liver architecture and hence disarrange the cellular organization and functions resulting in a hepatic inability to synthesize proteins. By taking into account that inflammatory cytokine signaling in the immune system and IL signaling (VEGFA, TNF, SMARCA4, IL1B, JUN, HSP90AB1, HIF1A) and B cell/T cell receptor signaling pathway (JUN, PTPRC) play important roles through the cytokine storm. As, patients with COVID-19 often have multi-organ failure, which may include liver damage due to the hypoxia and cytokine storm that accompanies SARS-CoV-2 infection [75, 76]. As also seen in COVID-19, cytokine storm has the potential to be engaged in disseminated intravascular coagulation (DIC) and thrombocytopenia, both of which have the potential to aggravate the effects of DIC [77].

On the other hand, multiple signaling pathways may be involved in both diseases such as MAPK (CDC42, HRAS, HSP90AB1, HSPA8, RPS27A, SRC), PI3K-Akt-mTOR (HRAS, HSP90AB1), hypoxia (ACTB, JUN, VEGFA, HIF1A, GAPDH), JAK/STAT (PTPRC, SRC, UBE2I), and NF-kB signaling pathways (ATM, HRAS, IL1B, JUN,
PTPRC, SFRS1, TNF) that are the key factors in these patients with hypercoagulation, infection, and inflammation [11, 78].

Last but not least, apoptosis pathway (ACTB, ATM, HSPA8, SFRS1, TNF, UBE2I), DNA damage and metabolism of RNA (CDC42, JUN, POLR2B, SMARCA4, DHX15, EPRS, HNRNPA1), and cell cycle process (ATM, POLR2B, UBE2I, VEGFA) can play roles in hepatocellular necrosis and cellular infiltration in the liver organ of patients with COVID-19, resulting in liver apoptosis [79].

Gene expression analysis has contributed to personalized medicine advancements in cancer and transplantation. This has given us a reason to apply similar methods to other diseases, such as those related to prototypical inflammatory autoimmune diseases with unknown causes. Increased understanding of disease biology, better patient care, and more tailored therapy approaches are only some of the potential benefits of gene expression profiling’s clinical and translational use. Once a novel biomarker or combination of biomarkers has been discovered in fundamental research, it may take some time until they are used in clinical practice.

This is due to the time and effort needed to validate biomarkers, establish their practical efficacy, develop a manufacturing method, and get regulatory approval. When taken together, these results highlight gene expression’s worth as a novel tool with the potential to provide unique data to each person [80, 81].

Conclusions
A total of 22 hub genes were identified among HCC, CHB, and mild/severe COVID-19 after evaluating two GEO datasets utilizing existing methods for GO and KEGG enrichment approaches, construction of a PPI network for hub gene identification, and immune cell infiltration. These genes may have the highest potential role in signaling pathways, biological processes, cellular components, molecular functions, and immunological and inflammatory processes. Considering the outcomes obtained from the above-mentioned approach among HCC, CHB, and mild/severe COVID-19, it is vital to study the disease interconnections in-depth soon. And more immune-based therapeutic targets can be developed to cover the potential gaps specifically in terms of their molecular mechanisms among these illnesses.

Supplementary Information
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