

## ORIGINAL ARTICLE

# Integrative Analysis of GEO Datasets Identifies Key Genes in Chronic Hepatitis B and Chronic Kidney Disease

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## ABSTRACT

**Background:** The aim is to identify differentially expressed genes (DEGs) associated with both HBV and CKD and to elucidate their molecular mechanisms via bioinformatics analyses.

**Methods:** We analyzed two GEO datasets (GSE66494 and GSE83148) to identify DEGs. We conducted a series of bioinformatics analyses on these co-DEGs, encompassing Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment, protein-protein interaction (PPI) network analysis, as well as predictions of transcription factor-gene interactions and gene-miRNA regulatory networks.

**Results:** A total of 327 co-DEGs were identified. GO and KEGG pathway enrichment analyses revealed significant involvement of the mitogen-activated protein kinase (MAPK) and tumor necrosis factor (TNF) signaling pathways, highlighting their critical roles in the pathophysiology of HBV and CKD. The PPI network identified thirteen core genes, with three - MET proto-oncogene, receptor tyrosine kinase (MET), hypoxia inducible factor 1 subunit alpha (HIF1A), and matrix metalloproteinase 2 (MMP2) - demonstrating high diagnostic potential. Furthermore, interactions between transcription factors (e.g., GATA binding protein 2 [GATA2], nuclear factor kappa B subunit 1 (NFkB1) and miRNAs related to those core genes were explored, suggesting the regulatory roles of GATA2 and NFkB1 in core gene expression.

**Conclusions:** This study identifies potential biomarkers and molecular mechanisms linking HBV and CKD, providing a valuable foundation for early diagnosis and targeted therapeutic development.

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## KEYWORDS

chronic hepatitis B virus (HBV), chronic kidney disease (CKD), differentially expressed genes (DEGs), bioinformatics analysis

## INTRODUCTION

Chronic hepatitis B virus (HBV) is a globally prevalent viral liver disease, characterized by chronic hepatic inflammation and fibrosis. During the progress of HBV, severe complications often accompany it, including cirrhosis and hepatocellular carcinoma [1,2]. In recent years, the incidence of HBV infection has been reduced through the development of extensive vaccination programs and antiviral therapies. However, more than 200 million people globally remain infected. Its prevalence

is high in Asia and Africa, due to high population density, poor sanitation, and limited medical resources in those regions. This not only poses a significant health threat but also places a heavy economic burden on patients and society.

Chronic kidney disease (CKD) is another major global public health concern. The prevalence of this disease is steadily rising each year. The high incidence of CKD has been closely correlated to risk factors such as diabetes, hypertension, and aging [3,4]. Nowadays, an estimated 150 million people worldwide are diagnosed with CKD, and this number is projected to rise. Thus, there is an urgent need for effective intervention.

It has been reported that there is a significant correlation between HBV infection and CKD, suggesting the influence of HBV on renal function through various biological pathways, such as direct cytotoxicity caused by the virus and immune responses due to injuries of renal tubular, interstitial, and glomerular cells [5,6]. On the other hand, HBV infection may change the renal microenvironment, thereby promoting the progression of CKD [7]. The precise molecular mechanisms underlying the interaction between HBV and CKD are unclear. It is necessary to perform in-depth investigations to identify novel biomarkers and therapeutic targets for early diagnosis and personalized treatment of these diseases.

To this end, our study aimed to explore the molecular mechanisms underlying the interaction between HBV and CKD, using bioinformatics methods through the identification of differentially expressed genes (DEGs) associated with HBV and CKD. This study will provide new strategies for identifying new biomarkers associated with HBV and CKD, as well as effective therapeutic approaches.

## MATERIALS AND METHODS

### Gene expression profile data collection

Bioinformatics analyses were conducted using two datasets, GSE66494 and GSE83148, sourced from the GEO database (<http://www.ncbi.nlm.nih.gov/geo>). GSE66494 pertains to CKD and includes an experimental group of 54 samples and a validation group of eight samples. From this dataset, we selected 49 kidney tissue samples from CKD patients and five samples from healthy controls within the experimental group. GSE83148 is associated with HBV and contains data from the GPL570 microarray platform, comprising 122 liver tissue samples from HBV patients and six samples from healthy controls.

### Identification of DEGs

To identify DEGs, the expression data were secondarily normalized using the *normalizeBetweenArrays* function in the limma R package. Multiple testing correction was applied with the Benjamini-Hochberg method to control the false discovery rate, and genes with an adjusted  $p$ -value  $< 0.05$  and  $|\log_2(FC)| \geq 0.5$  were considered sig-

nificantly differentially expressed in each dataset. The overlap of DEGs among datasets was visualized with Venn diagrams generated using the ggplot2 (v3.4.4) and VennDiagram (v1.7.3) R packages to identify common DEGs (co-DEGs). Principal component analysis (PCA) of the common DEGs (co-DEGs) was then performed and visualized using ggplot2 (v3.4.4) to assess expression pattern separation across samples.

### Functional classification and pathway enrichment of co-DEGs

Functional enrichment analysis of the co-DEGs was conducted using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses implemented in the clusterProfiler R package, with a significance threshold of  $p < 0.05$ . Significant enrichment was observed only in the biological process (BP) category, suggesting that the co-DEGs are collectively involved in coordinated biological processes, whereas their molecular functions (MFs) and subcellular localizations are more diverse and thus did not reach statistical significance. The GO enrichment results were visualized using the ggplot2 package, highlighting the major BPs and signaling pathways associated with the co-DEGs.

### Interaction between proteins and key hub genes

A protein-protein interaction (PPI) network of the co-DEGs was constructed using the STRING database (<http://string-db.org>) with a minimum interaction confidence score  $> 0.4$ . The resulting network was visualized in Cytoscape software. Key hub genes were identified using the CytoHubba plugin by integrating the results of the Maximum Clique Centrality (MCC) and Maximum Neighborhood Component (MNC) algorithms.

### Profiles of hub gene expression

The analysis of hub gene expression profiles was conducted using the HBV validation set (GSE38941) and the CKD validation set (GSE30528). The expression profiles of the hub genes were illustrated through box plots created with the R package “ggplot2”. Additionally, the R package “pROC” was used to generate the receiver operating characteristic curve (ROC) and calculate the area under the curve (AUC) to assess the diagnostic value.

### Construction of the TF-miRNA co-regulatory network

To construct a regulatory network of transcription factors (TFs) and genes, we utilized both the NetworkAnalyst 3.0 platform (<https://www.networkanalyst.ca>) and the JASPAR database.

### Construction of the target miRNA regulatory network of co-DEGs

A regulatory network diagram illustrating co-expressed DEGs and miRNAs was created using the Cytoscape platform, based on data from the miRwalk database

(<http://mirwalk.umm.uni-heidelberg.de>).

## RESULTS

### Identification of DEGs in HBV and CKD

In this study, we identified 3,556 DEGs from the GSE-66494 dataset and 2,170 DEGs from the GSE83148 dataset. Intersection analysis of the two DEG sets, visualized by a Venn diagram, revealed 369 co-DEGs (Figure 1A). PCA based on the expression profiles of these co-DEGs demonstrated clear separation between disease and control samples, indicating that the observed variance was primarily driven by biological differences rather than batch effects (Figure 1B).

### Functional enrichment analysis of co-DEGs and KEGG signaling pathway assessment

Functional enrichment analysis of co-DEGs was performed using the clusterProfiler package in R, with a corrected p-value < 0.05 as the significance threshold. At the BP level, the co-DEGs were significantly enriched in pathways related to cellular responses to reactive oxygen species, chemical stress, hydrogen peroxide, epidermal growth factor, and oxidative stress (Figure 2A). No significantly enriched terms were identified in the cellular component or MF categories. The complete results of the GO enrichment analysis are provided in Supplementary Table S1.

In the KEGG pathway analysis, co-DEGs were significantly enriched in five pathways, including the MAPK signaling pathway, TNF signaling pathway, human T-cell leukemia virus type 1 infection, Kaposi's sarcoma-associated herpesvirus infection, and N-glycan biosynthesis (Figure 2D).

### Construction of PPI network for hub gene screening

A protein-protein interaction (PPI) network of the DEGs was constructed using the STRING database to identify hub genes potentially associated with HBV and CKD. The top 30 genes within this network were ranked using the CytoHubba plugin in Cytoscape software (Figure 3A). By integrating the top 20 key node genes identified through both the MCC and MNC algorithms in CytoHubba, 13 overlapping hub genes were obtained (Figures 3B - D). These included cyclin-dependent kinase 1 (CDK1), centromere protein E (CENPE), mitotic arrest deficient-like 1 (MAD2L1), non-SMC condensin I complex subunit G (NCAPG), centromere protein F (CENPF), ubiquitin conjugating enzyme E2C (UBE2C), AKT serine/threonine kinase 1 (AKT1), Fos proto-oncogene (FOS), HIF1A, Prostaglandin-endoperoxide synthase 2 (PTGS2), fibroblast growth factor 7 (FGF7), MMP2, and MET.

### Validation of thirteen hub genes and assessment of their diagnostic value

Data from GSE38941 and GSE30528 datasets were used to validate the thirteen core genes. Box plots were

created using the ggplot2 package in R, revealing significant differences in the expression of nine core genes: (*CDK1*, *CENPE*, *MAD2L1*, *NCAPG*, *UBE2C*, *AKT1*, *HIF1A*, *MMP2*, and *MET*) between HBV samples and the control group (Figures 4a, b). In CKD samples, four core genes (*FGF7*, *HIF1A*, *MMP2*, and *MET*) also exhibited significant differences compared to the control group (Figures 4c, d). The diagnostic performance of the thirteen core genes was evaluated using ROC curve analysis, and the corresponding AUC values are shown in Figure 5.

For HBV samples compared with normal controls, the AUC values were as follows: *CDK1* (0.882), *CENPE* (0.994), *MAD2L1* (0.765), *NCAPG* (0.918), *CENPF* (0.688), *UBE2C* (0.947), *AKT1* (0.941), *FOS* (0.559), *HIF1A* (0.900), *PTGS2* (0.671), *FGF7* (0.612), *MMP2* (0.759), and *MET* (0.976). For CKD samples compared with normal controls, the respective AUC values were *CDK1* (0.667), *CENPE* (0.547), *MAD2L1* (0.564), *NCAPG* (0.744), *CENPF* (0.684), *UBE2C* (0.752), *AKT1* (0.487), *FOS* (0.628), *HIF1A* (0.778), *PTGS2* (0.487), *FGF7* (0.769), *MMP2* (0.923), and *MET* (0.822).

Collectively, these findings suggest that *HIF1A*, *MMP2*, and *MET* exhibit strong diagnostic potential and may serve as candidate biomarkers for distinguishing between *HBV* and *HCV*.

### Interactions between TFs and hub genes

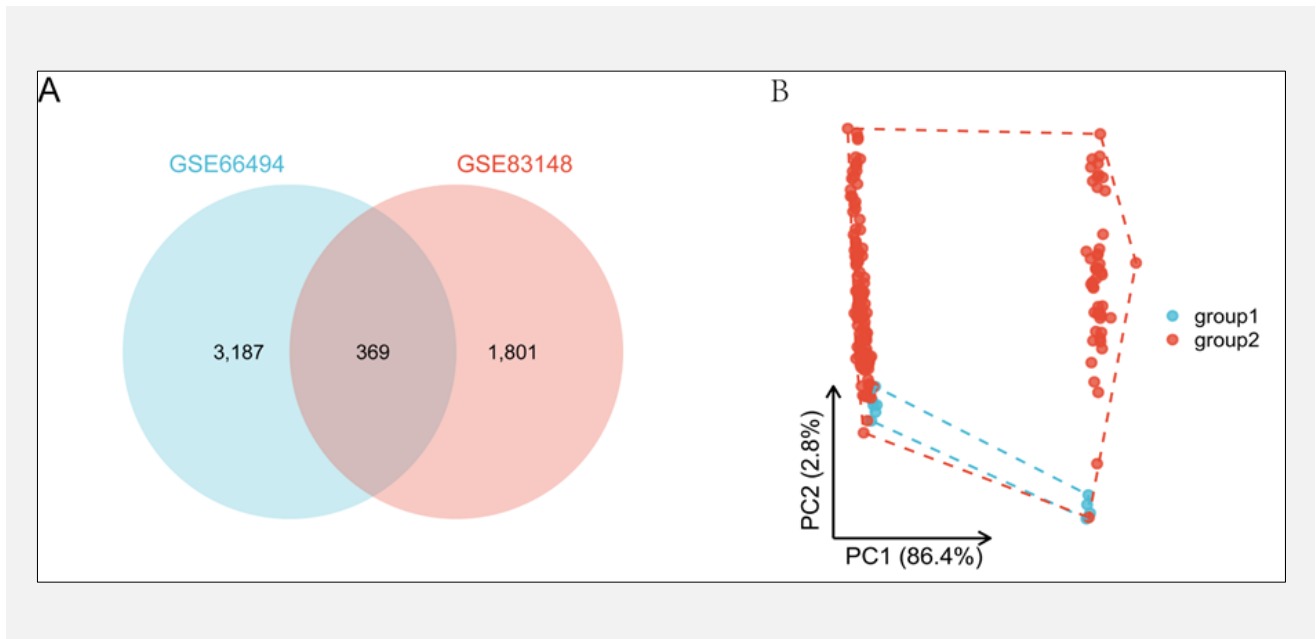
The TF-gene interaction network for the three core genes was predicted and visualized using the NetworkAnalyst database. As illustrated in Figure 6, this interaction network contains 22 nodes and 22 edges. Notably, GATA binding protein 2 (GATA2) interacts with all three core genes, while *NFKB1* only interact with the two core genes, *MET* and *HIF1A*. Further validation is needed to confirm the interactions between the TFs and core genes identified in this study.

### co-DEGs and the microRNA (miRNA) regulatory network

MicroRNAs (miRNAs) associated with the three hub genes were retrieved from the miRWalk database, and only entries with non-empty "validated" columns were retained for analysis. A co-regulatory network comprising the identified co-DEGs and their corresponding miRNAs was then constructed and visualized using the Cytoscape platform. The resulting network contained 24 nodes and 41 edges, highlighting key regulatory families, such as miR-143 and *miR-106* (Figure 7).

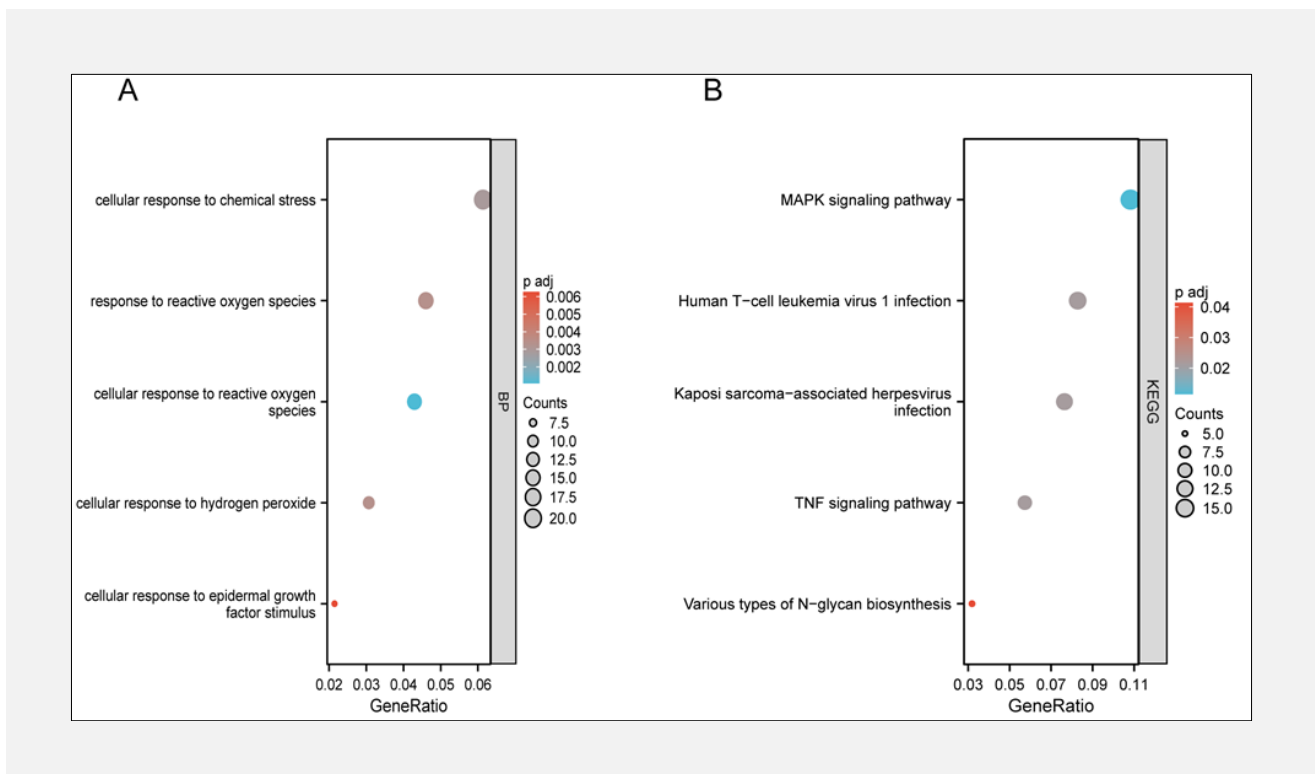
## DISCUSSION

In this research, we used bioinformatics analytical approaches to analyze GEO datasets related to either HBV or CKD. We identified a total of 369 co-DEGs shared by HBV and CKD. GO enrichment analysis revealed that these DEGs were significantly enriched in func-



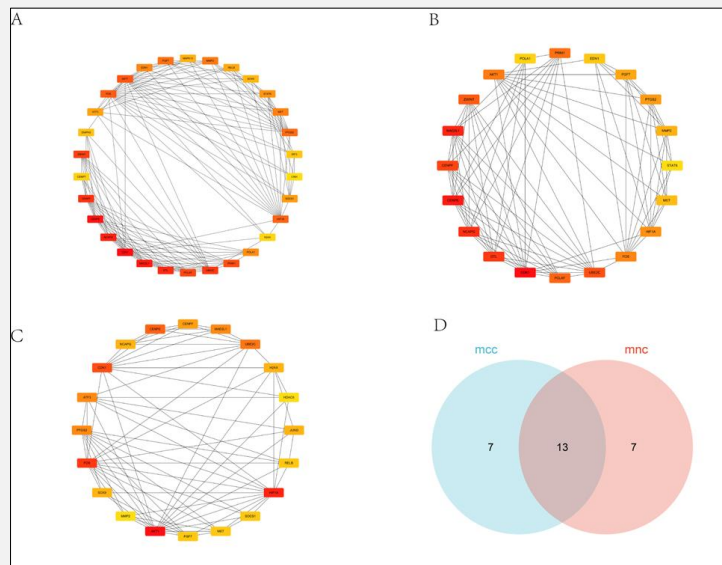
**Figure 1.** Identification of DEGs between HBV (GSE83148) and CKD (GSE66494), and PCA analysis of co-expressed differential genes.

**A:** Illustration of the intersection of the two datasets, **B:** PCA plot of the co-DEGs. CKD: chronic kidney disease, co-DEGs: co-differentially expressed genes, DEGs: differentially expressed genes, HBV: hepatitis B virus, PCA: principal component analysis.



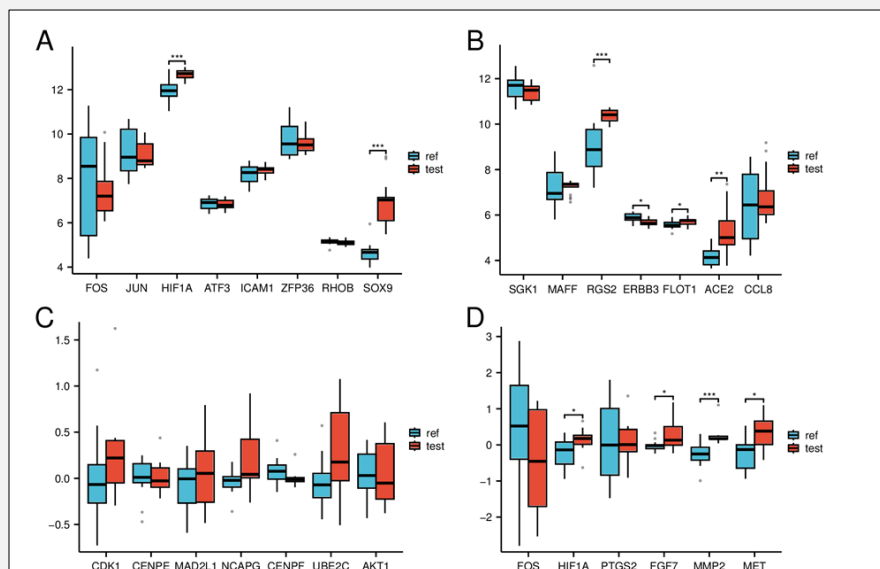
**Figure 2.** Enrichment analysis of GO and KEGG pathways related to the identified common DEGs.

**A:** Illustration of the enrichment analysis results for BPs in GO, **B:** Illustration of the pathways identified by KEGG. BPs, biological processes, GO: gene ontology, KEGG: Kyoto Encyclopedia of Genes and Genomes.



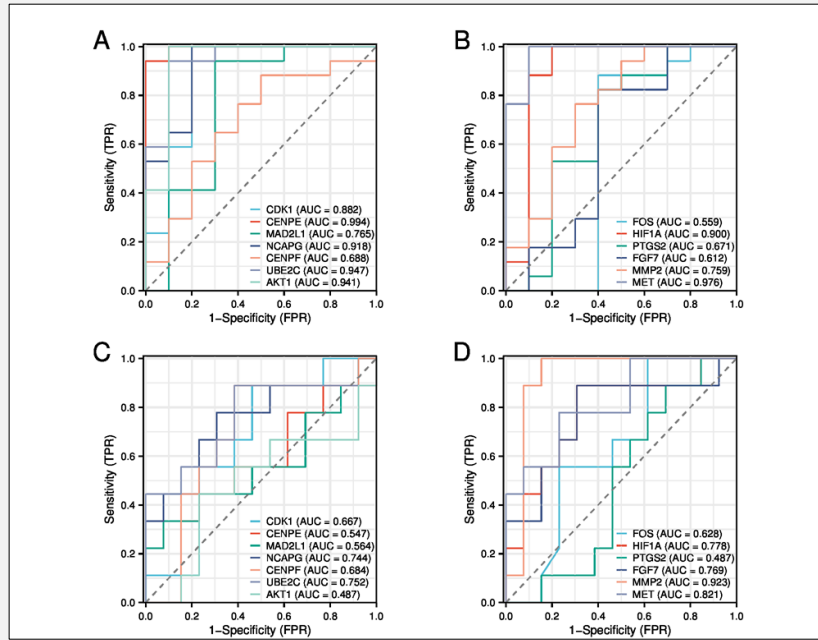
**Figure 3.** Analysis of the PPI network using the CytoHubba plugin in Cytoscape software.

**A:** Illustration of the PPI network among co-DEGs, **B:** Illustration of the top 20 core genes identified by the MCC algorithm of the CytoHubba plugin, and **C:** Illustration of the top 20 core genes identified by the MNC algorithm of the CytoHubba plugin, **D:** Venn diagram of the two sets of core genes, co-DEGs: co-differentially expressed genes, MCC: Maximum Clique Centrality, MNC: Maximum Neighborhood Component, PPI: protein-protein interaction.



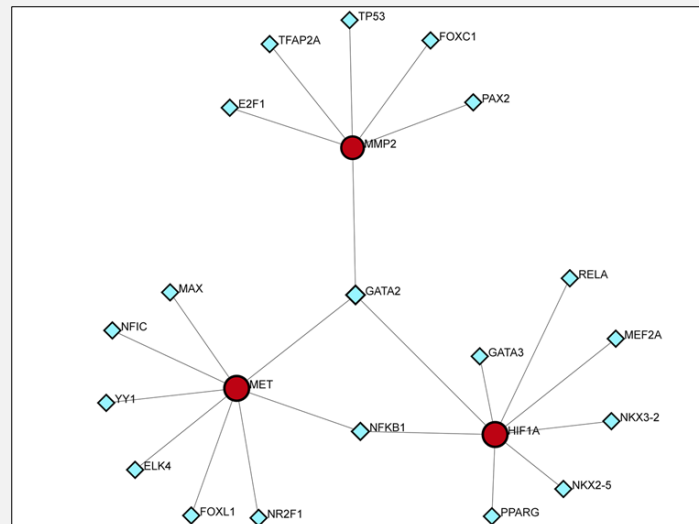
**Figure 4.** Comparison chart of the differences in thirteen core genes of the validation dataset.

**A:** Expression levels of the seven core genes in HBV based on the GSE38941 dataset, **B:** Evaluation of the expression levels of the six core genes in HBV based on the GSE38941 dataset, **C:** Expression levels of the seven core genes in CKD based on the GSE30528 dataset, **D:** Expression levels of the six core genes in CKD based on the GSE30528 dataset, \*\*\*  $p < 0.001$ , \*\*  $p < 0.01$ , \*  $p < 0.05$ . CKD: chronic kidney disease, HBV: chronic hepatitis B virus.



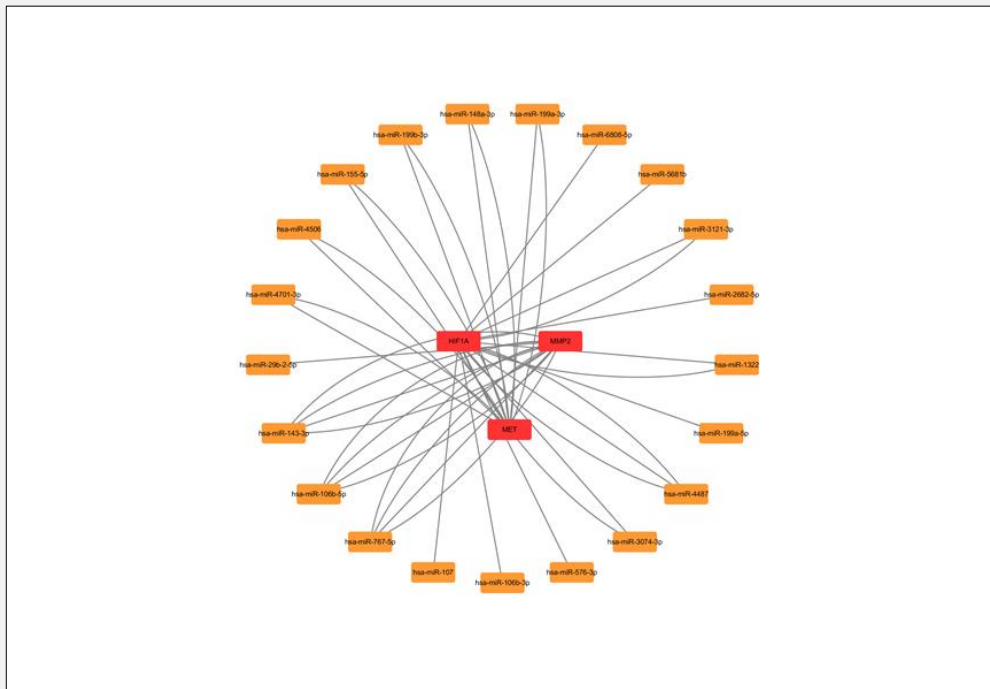
**Figure 5. Validation of the ROC curves for thirteen core genes in the dataset.**

**A:** Evaluation of the diagnostic value of the seven core genes in HBV through ROC curve analysis, **B:** Evaluation of the diagnostic value of the six core genes in HBV using ROC curve analysis, **C:** Evaluation of the diagnostic value of the seven core genes in CKD through ROC curve analysis, **D:** Evaluation of the diagnostic value of the six core genes in CKD using ROC curve analysis, and no significant difference is indicated, \*\*\*  $p < 0.001$ , \*\*  $p < 0.01$ , \*  $p < 0.05$ . AUC: area under the curve, CKD: chronic kidney disease, HBV: chronic hepatitis B virus, ROC: receiver operating characteristic.



**Figure 6. TF-gene interaction network for three hub genes.**

Red circles represent the three hub genes, blue diamonds represent TF-genes linked to these genes. TF: transcription factor.



**Figure 7. Interaction network involving miRNAs and three hub genes.**

Red symbols represent hub genes, orange symbols signify hub gene-related miRNAs.

tions related to cellular responses to reactive oxygen species, chemical stress, and hydrogen peroxide. Additionally, KEGG pathway enrichment analysis indicated involvement in the MAPK signaling pathway, TNF signaling pathway, human T-cell leukemia virus type 1 infection, Kaposi's sarcoma-associated herpesvirus infection, and various N-glycan biosynthesis pathways. These findings comprehensively illustrate the intricate relationships between co-DEGs and oxidative stress, signaling pathway transduction as well as viral infection.

In addition, a PPI network was constructed using the STRING online database and visualized in Cytoscape software. Thirteen key genes were subsequently identified by integrating the results of the MCC and MNC algorithms within the CytoHubba plugin.

Validation with additional GEO datasets revealed *HIF1A*, *MMP2* and *MET* as the three core genes with high diagnostic value. These genes play pivotal roles in the development of both HBV and CKD, holding great promise for clinical diagnosis and prognosis assessment.

*HIF1A*, a TF, regulates cellular functions such as metabolism and angiogenesis under low-oxygen conditions, promoting cell survival [8-10]. In HBV, *HIF1A*

affects the disease's pathological process by regulating viral replication and host immune responses [11]. In CKD, elevated *HIF1A* expression and its overactivation are intricately linked to renal hypoxia, fibrosis, and inflammatory responses [12]. Thus, *HIF1A* represents a potential therapeutic target, which is currently under pre-clinical trials, offering new insights into the mechanisms of renal fibrosis [13].

*MMP2*, a member of the matrix metalloproteinase family, is responsible for extracellular matrix remodeling and degradation [14,15]. Its expression significantly increases in HBV, promoting disease progress by enhancing liver fibrosis and inflammatory responses [16]. In CKD, abnormal *MMP2* expression is associated with renal tubular interstitial fibrosis and deterioration of renal function, indicating its critical role in kidney disease progression and repair [17]. Moreover, *MMP2* inhibitors have demonstrated their effectiveness in reducing renal tissue fibrosis and improving renal function, with similar efficacy observed in HBV treatment [15,18].

In summary, the three core genes identified in this study - *SRC*, *HIF1A*, and *MMP2* - play critical roles in the development of HBV and CKD through various mechanisms. These core genes are important players in both diseases, providing valuable insights for further re-

search into their pathogenic mechanisms and potential treatment strategies.

*MET*, encoding the hepatocyte growth factor (HGF) receptor c-MET, drives ERK/MAPK signaling that sustains HBV cccDNA and amplifies inflammatory injury [19]. In renal tubules, *MET* activation is reparative in acute injury but promotes fibrosis through TGF- $\beta$ /Smad signaling during chronic damage [20-22]. With dual hepatic and renal roles, *MET* serves as both a marker of HBV-related fibrosis and a therapeutic target in CKD, which is supported by emerging *MET*-inhibitor trials [23]. Along with HIF1A and MMP2, *MET* defines a core triad integrating hypoxia response, extracellular matrix remodeling, and fibrogenic signaling in hepatorenal disease.

Additional validated core genes included *CDK1*, *CENPE*, *MAD2L1*, *NCAPG*, *UBE2C*, *AKT1*, and *FGF7*. *CDK1* governs the G<sub>2</sub>/M transition and is upregulated in HBV-associated hepatocellular carcinoma and renal fibrosis [24,25]. *CENPE* regulates chromosome segregation and is aberrantly expressed in HBV-related liver disease [26]. *MAD2L1* maintains mitotic checkpoint integrity; its loss promotes genomic instability. *NCAPG* supports proliferation in liver and renal cancers [27]. *UBE2C* mediates oncogenic ubiquitination. *AKT1*, activated by HBx, drives survival and fibrosis [28,29]. *FGF7* regulates epithelial repair and phosphate metabolism in early CKD [30]. Collectively, these genes converge on cell-cycle, PI3K/AKT, and fibrotic pathways, underscoring shared oncogenic and inflammatory mechanisms between HBV infection and CKD.

To explore the intrinsic connection between these diseases, it is essential to understand the interaction network between TFs and genes involved in both HBV and CKD. Our identification of *HIF1A*, *MMP2* and *MET* as core DEGs revealed *GATA2*, a TF significantly associated with these genes, through the TF-gene interaction network. In HBV, *GATA2* can influence T-cell function by regulating related cytokines, facilitating viral persistence and the inflammatory response [31]. In CKD, *GATA2* regulates the expression of water-channel proteins, such as AQP2, AQP3, and AQP4, in renal tubular cells, maintaining renal water reabsorption balance. Disrupting this balance can lead to gradual renal function deterioration and promote CKD development [32]. Moreover, *GATA2* is involved in regulating the inflammation response through transcriptional control of relevant genes, such as C-X-C motif chemokine ligand 1 (CXCL1) and radical S-adenosyl methionine domain containing 2 (RSAD2). The abnormal activation of CXCL1 and RSAD2 drives CKD progression [33], indicating that *GATA2* plays a common regulatory role in the inflammatory and pathological development of both HBV and CKD.

We also investigated the correlation between miRNAs and the identified core genes, offering a novel perspective on the connection between HBV and CKD. Through analysis of the hub gene-miRNA interaction network, we identified three miRNAs - hsa-miR-106-

5p, hsa-miR-143-3p, and hsa-miR-767-5p - as core nodes. These miRNAs participate in regulating cell growth, differentiation, and apoptosis, influencing the development of both diseases. For instance, hsa-miR-143-3p expression is increased in hepatitis B-related acute liver failure and is also upregulated during CKD development, suggesting that HBV infection and CKD may share similar molecular mechanisms [34,35]. This provides valuable directions for exploring joint diagnostic and treatment strategies for these two diseases.

However, several key limitations exist in this study. First, our conclusions rely on bioinformatics analysis methods and the utilization of GEO datasets, lacking experimental validation. This deficiency may lead to insufficient functional validation of the selected biomarkers. Second, the small sample size of the data analyzed may affect the generalizability and reliability of the results. The lack of clinical validation could limit the application of our findings in real-world settings. Finally, potential batch effects between datasets may also impact on our analysis results. Therefore, future research should include experimental validation, increase the sample size, and perform multi-center clinical validation to strengthen our findings.

In this study, we identified potential biomarkers associated with HBV and CKD through bioinformatics analysis using publicly available GEO datasets. Despite the limitations mentioned, our findings, particularly the identified biomarkers (if validated in future research), hold promise for improving early diagnosis and personalized treatment strategies.

## CONCLUSION

In this study, we initially evaluated the potential connection between HBV and CKD by integrating multiple bioinformatics analysis methods using publicly available GEO datasets. This approach led to the identification of seven core genes, including *HIF1A*, *MMP2* and *MET*, which play key roles in the shared pathophysiology of HBV and CKD. Additionally, we identified potential biomarkers and investigated the regulatory interactions between TFs and miRNAs associated with these core genes. Our findings provide new insights that support the development of early diagnostic tools, prognostic markers, and targeted therapies for both HBV and CKD.

Nevertheless, several limitations in this study must be acknowledged. First, while we evaluated three core genes, further investigation is needed to elucidate the functional roles of the remaining genes. Second, the lack of extensive *in vitro* and *in vivo* experiments, as well as large-scale clinical trials, necessitates empirical validation of our findings in future studies. Third, the exclusive reliance on publicly available GEO datasets limits the generalizability and robustness of our results. Therefore, future studies should aim to validate our findings using multi-source data, particularly larger,

multicenter cohorts.

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#### Data Availability:

All GSE dataset files are available from the GEO database (accession numbers are GSE66494, GSE83148, GSE38941, and GSE30528).

#### Ethics Approval and Consent to Participate:

This study did not require institutional review board approval because it involved the use of publicly available data.

#### Declaration of Generative AI in Scientific Writing:

None.

#### Declaration of Interest:

The authors declare no competing interests.

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