

Profound Depletion of CPB2 and MASP2 Predicts Hepatic Synthetic Collapse and Transplant Indications in HBV-Related Acute Liver Failure

Rong Li

The Second Xiangya Hospital of Central South University

Yuhong Li

The Second Xiangya Hospital of Central South University

Maoping Li:

The Second Xiangya Hospital of Central South University

Zhiqing Zhang

The Second Xiangya Hospital of Central South University

Jing Ma

jingma2003@csu.edu.cn

The Second Xiangya Hospital of Central South University

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1 Profound Depletion of CPB2 and MASP2 Predicts Hepatic
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3 Related Acute Liver Failure

4 Rong Li¹, Yuhong Li¹, Maoping Li¹, Zhiqing Zhang¹, Jing Ma^{1*}

5 Department of Infectious Diseases, The Second Xiangya Hospital, Central South University, Changsha,
6 China

7 **Author contact details**

8 Rong Li: lirongmh@163.com

9 Yuhong Li: 238211059@csu.edu.cn

10 Maoping Li: 228211037@csu.edu.cn

11 Zhiqing Zhang: Zzq131418@outlook.com

12 **Corresponding author:**

13 Jing Ma

14 Department of Infectious Diseases

15 The Second Xiangya Hospital, Central South University

16 Changsha, Hunan, China

17 E-mail: jingma2003@csu.edu.cn

18 **Abstract**

19 **Purpose :** Hepatitis B virus-related acute liver failure (HBV-ALF) is a highly lethal
20 syndrome lacking precise early biomarkers to guide the timing of liver transplantation
21 (LT). **Aims:** We aimed to identify core drivers of hepatic synthetic collapse and explore
22 novel prognostic biomarkers and targeted therapeutic strategies for HBV-ALF.

23 **Methods:** An integrated machine learning framework (LASSO, SVM-RFE) was applied
24 to multi-cohort transcriptomic datasets to identify crucial diagnostic hub genes. Findings

were rigorously validated in a real-world clinical cohort of HBV-ALF patients using serum biochemistry and spatial histopathology (H&E and IHC staining).

Results: We identified a profound disruption of the complement-coagulation crosstalk as a hallmark of HBV-ALF. Three critical hub genes—C8B, CPB2, and MASP2—were significantly downregulated. In clinical validation, CPB2 levels plummeted to approximately 26% of the normal baseline, strongly correlating with declining prothrombin time activity (PTA) and surging MELD scores. Spatial histopathology revealed a paradoxical microenvironment: massive necrosis with a near-complete loss of these locally synthesized proteins, accompanied by intense overactivation of the terminal complement complex (C5b-9) strictly bordering the surviving parenchyma.

Conclusions: The precipitous depletion of C8B, CPB2, and MASP2 serves as a highly sensitive real-time biomarker for irreversible hepatic synthetic exhaustion, offering a novel metric to refine LT indications. Furthermore, targeting the localized C5b-9 overactivation presents a promising therapeutic strategy to halt the necrotic cascade and serve as a "bridge to transplant" in HBV-ALF.

Keywords: Acute Liver Failure; Hepatitis B Virus; Complement System; CPB2; Liver Transplantation.

Introduction

Acute liver failure (ALF), formerly known as fulminant hepatitis, is a severe clinical syndrome¹ characterized by sudden and severe liver dysfunction, typically manifesting as jaundice, coagulopathy, and hepatic encephalopathy in patients with previously normal or underlying chronic liver disease². Various etiologies contribute to ALF, including drug or toxic substance poisoning, viral infections, autoimmune hepatitis, excessive alcohol consumption, and advanced age. Studies have shown that the hepatitis B virus (HBV) is one of the leading causes of ALF worldwide³ and is the primary cause of ALF in China. The prevalence of HBV infection in China is high, with 120 million HBV carriers and 20 million chronic hepatitis B patients⁴. Research indicates that 0.1%-0.5% of HBV-infected individuals may progress to ALF⁵, and suffer from extremely poor prognoses. Regarding current treatments for HBV-ALF, the rescue success rate of integrated internal medicine treatment is approximately 30%. Many HBV-ALF patients are candidates for liver

transplantation, but due to the rapid clinical course of the disease and a shortage of donor organs, many of them succumb to various complications of liver failure while awaiting suitable liver sources. Early detection and intervention can significantly improve the prognosis of ALF; thus, prompt diagnosis and timely intervention can effectively prevent the occurrence and progression of ALF^{6,7}.

At present, the underlying physiological mechanisms of HBV-ALF have not been fully elucidated, which necessitates a deeper understanding of HBV-ALF-related mechanisms. In this study, we obtained HBV-ALF-related expression microarray data through the Gene Expression Omnibus (GEO) database and employed differential analysis, functional enrichment analysis, and machine learning techniques to predict key regulatory genes related to HBV-ALF. Concurrently, we utilized the CIBERSORT deconvolution algorithm to analyze immune cell infiltration in HBV-ALF and calculated the correlations between the identified key genes and immune cells. This approach provides new insights and directions for a deeper understanding of the regulatory mechanisms associated with HBV-ALF.

The pathogenesis of HBV-ALF is characterized by an overwhelming systemic inflammatory response and massive hepatocyte necrosis^{8,9}. Notably, the liver is the primary site for synthesizing the vast majority of circulating proteins, including key components of the complement system and coagulation cascades^{10,11}. During massive hepatic necrosis, the synthetic failure of these vital proteins not only leads to severe clinical coagulopathy but also triggers a catastrophic disruption of the immune-coagulation network¹²⁻¹⁴. However, the precise molecular mechanisms linking hepatocyte death, the collapse of the complement-coagulation crosstalk, and the subsequent dysregulation of immune cell infiltration (such as macrophages and neutrophils) remain poorly understood^{13,15-17}. Identifying the specific hub genes that bridge hepatic synthetic dysfunction and immunopathology is crucial for discovering reliable prognostic biomarkers and therapeutic targets.

Currently, most bioinformatics studies on HBV-ALF rely solely on transcriptomic data mining, often lacking clinical context and spatial histopathological validation, which limits their translational value¹⁸. To address this gap, our study employed an integrative approach. First, we utilized machine learning algorithms (LASSO and SVM-RFE) on

comprehensive datasets from the Gene Expression Omnibus (GEO) to identify robust hub genes (C8B, CPB2, and MASP2). We then evaluated their associations with the hepatic immune microenvironment using deconvolution algorithms. Crucially, to translate these transcriptomic findings into biological reality, we integrated histopathological evidence and clinical prognostic data. We investigated the spatial localization and complement deposition (e.g., C5b-9) in necrotic liver tissues via immunohistochemistry (IHC)¹³, and analyzed their correlations with critical clinical indicators, including the MELD score, total bilirubin (TBIL), and prothrombin activity (PTA)¹⁹. This comprehensive methodology provides a more profound, clinically relevant perspective on how the disruption of specific liver-synthesized proteins dictates the severity and immune landscape of HBV-ALF.

1 Materials and Methods

1.1 Data Processing and Differential Analysis

Using the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>), we downloaded three HBV-related acute liver failure expression microarrays (Table 1). The "limma" and "sva" packages were utilized to merge and batch-correct expression data from the three microarrays. Subsequently, using the "limma" package, a differential analysis was performed with normal samples as controls. We employed the false discovery rate (FDR) method to adjust differential p-values, and set the selection criteria for differentially expressed genes as $|\log FC| > 1$ and $\text{adj.pvalue} < 0.05$ to identify significantly differentially expressed genes.

Table 1. Three HBV related acute liver failure microarrays downloaded from GEO database.

No. GSE	Sequencing platform	No. normal samples	No. HBV- ALF samples	Reference
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GSE146	GPL570	8	8	[8]
68				
GSE389	GPL570	11	17	[9]
41				
GSE620	GPL570	10	13	[10]
29				

1.2 Functional Enrichment Analysis

Using the "clusterprofiler" package in R language, we conducted Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analyses on the differentially expressed genes obtained from the differential analysis. We employed the "clusterprofiler" package and "enrichplot" package in R language to perform Gene Set Enrichment Analysis (GSEA) pathway enrichment analysis, selecting "c2.cp.kegg.v7.4.symbols.gmt" as the reference gene set for the GSEA analysis process. A p-value <0.05 indicates statistically significant enrichment.

1.3 Key Gene Selection

Machine learning and data mining techniques, when used effectively and reasonably, can quickly and efficiently screen for potential key disease genes. Support Vector Machine-Recursive Feature Elimination (SVM-RFE) and Least Absolute Shrinkage and Selection Operator (LASSO) regression analyses were employed for key gene selection. LASSO regression was analyzed using the "glmnet" package in R language, while the "svmRadial" package was used to select the optimal genes for the SVM-RFE algorithm.

1.4 Protein-Protein Interaction (PPI) Analysis

Using the STRING database (<https://cn.string-db.org/>), a protein-protein interaction analysis was conducted on the key genes identified through the screening process. We subsequently processed the data using Cytoscape software and employed the CytoHubba tool to calculate the centrality of each gene in the network graph. Five different algorithms, namely degree, DMNC, EPC, MMC, and MNC, were utilized for the calculations (25521941). The top 5 genes with the highest centrality obtained from the five algorithms were intersected to screen for potential key genes in HBV-ALF disease.

1.5 Immune Cell Infiltration

The CIBERSORT deconvolution algorithm was utilized to calculate the level of immune cell infiltration in the samples. The gene expression matrix data was uploaded to CIBERSORT using the 22 immune cell subtypes (LM22) to evaluate the degree of immune cell infiltration in the samples. In the process, 1000 permutations were performed and immune cell infiltration results with $p < 0.05$ were retained. A correlation analysis between the screened key genes and immune cells was conducted using the Spearman method.

1.6 Infiltration Clinical Patient Cohort and Data Collection

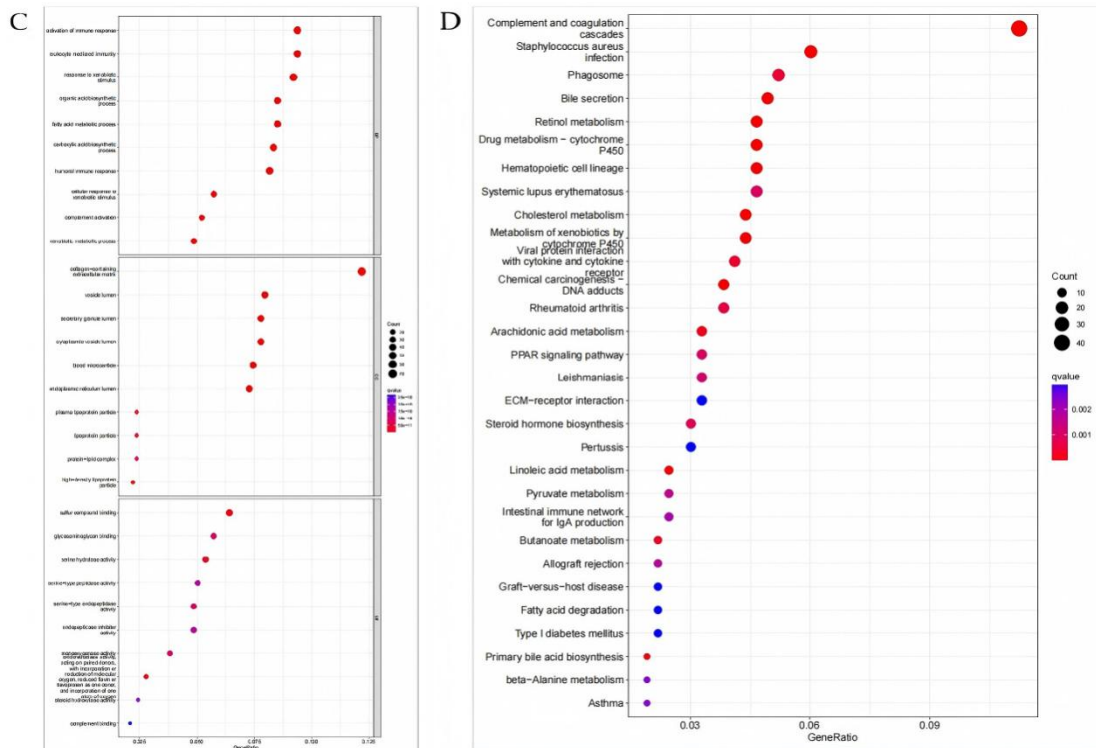
To validate the bioinformatics findings and evaluate the clinical relevance of the hub genes, a retrospective clinical cohort was established. Clinical data and laboratory parameters from patients diagnosed with HBV-ALF, alongside healthy controls or patients with mild chronic hepatitis B (CHB), were collected from the hospital database. Baseline demographic details and critical laboratory indicators reflecting hepatic synthesis and severity were systematically recorded, including Total Bilirubin (TBIL), Prothrombin Time Activity (PTA), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and the Model for End-Stage Liver Disease (MELD) score. The study protocol was approved by the local institutional ethics committee, and informed consent was obtained in accordance with the Declaration of Helsinki.

1.7 Histopathological and Immunohistochemical (IHC) Staining

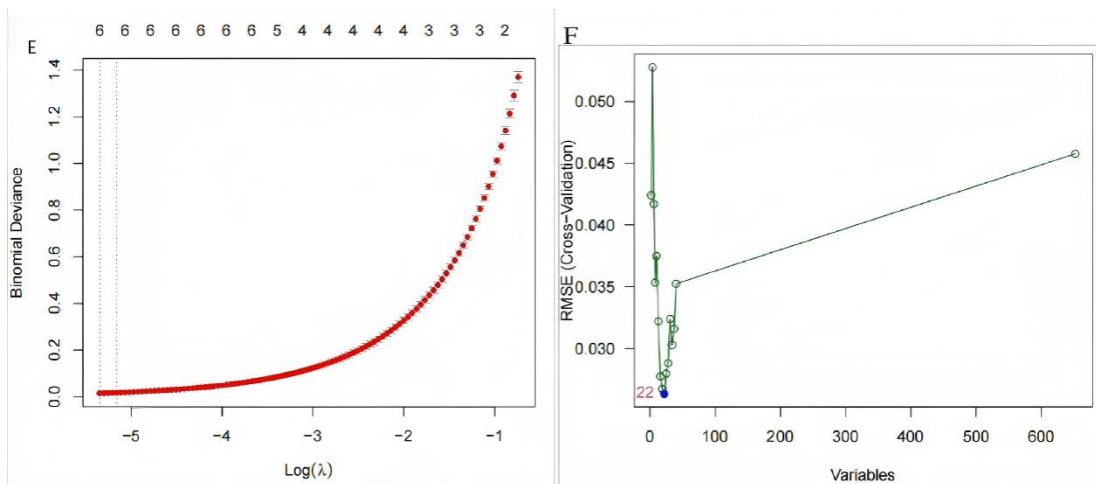
To investigate the spatial distribution and protein expression levels of the identified hub genes (C8B, CPB2, and MASP2) within the hepatic microenvironment, immunohistochemistry (IHC) was performed on formalin-fixed, paraffin-embedded (FFPE) liver tissue microarrays or biopsy sections obtained from HBV-ALF patients and controls. Briefly, 4- μ m-thick tissue sections were deparaffinized in xylene and rehydrated through graded ethanol series. Heat-induced epitope retrieval was performed using citrate buffer (pH 6.0), followed by endogenous peroxidase blockade with 3% hydrogen peroxide. The sections were incubated overnight at 4°C with primary antibodies specifically targeting C8B, CPB2 (TAFI), MASP2, and the terminal complement activation product C5b-9 (membrane attack complex). Following washing, tissues were incubated with HRP-conjugated secondary antibodies, visualized using 3,3'-diaminobenzidine (DAB), and counterstained with hematoxylin. The stained slides were independently evaluated by two experienced pathologists blinded to the clinical data. The staining intensity and localization were specifically assessed in both massive necrotic areas and the residual surviving hepatic parenchyma.

1.8 Comprehensive Statistical Analysis

All bioinformatics and statistical analyses were performed using R software (version 4.1.2) and GraphPad Prism (version 9.0). Continuous clinical variables were expressed as the mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), and differences between groups were analyzed using Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the Chi-square test. The correlations between the expression levels of the hub genes (C8B, CPB2, MASP2) and critical clinical parameters (e.g., MELD score, TBIL, PTA) or immune cell infiltration abundances were determined using Spearman's rank correlation analysis. A two-tailed P-value < 0.05 was considered statistically significant.



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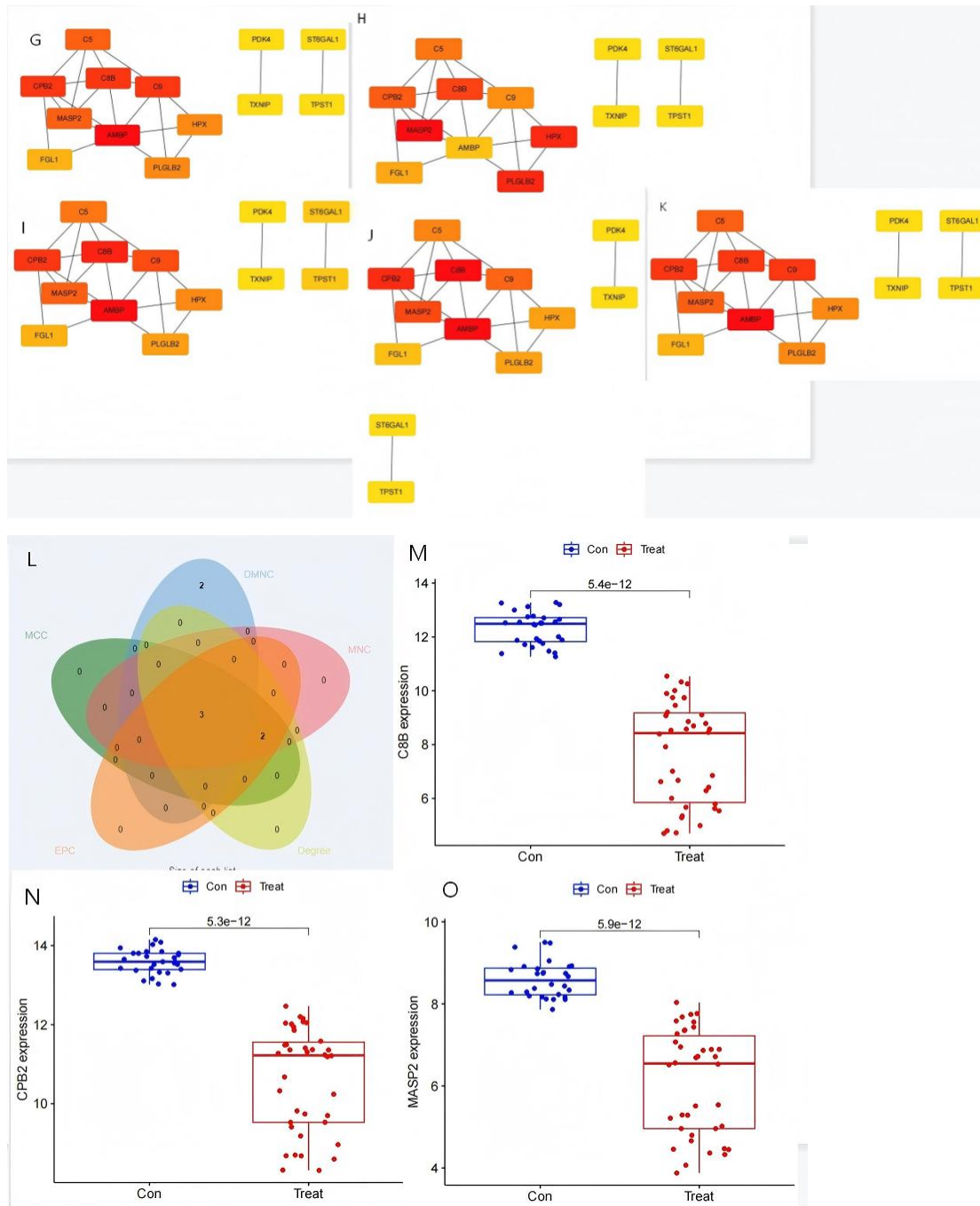


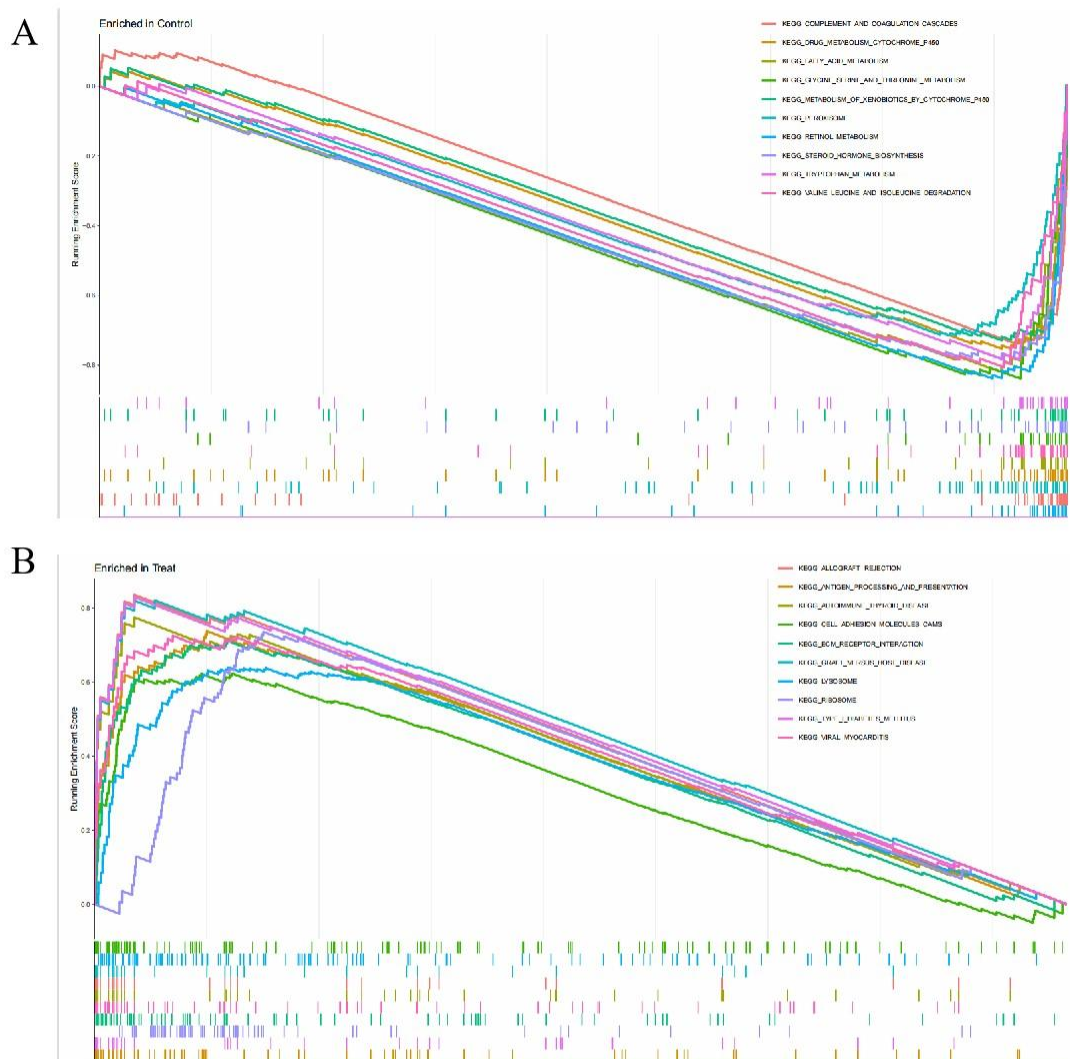
Figure 1 Identification and expression validation of complement-coagulation hub genes via integrated machine learning in HBV-ALF. (A,B) The overall study design and flowchart. (C,D) Volcano plot illustrating the differentially expressed genes (DEGs) between HBV-ALF and normal control liver tissues from the GEO cohorts. Red and blue dots represent significantly upregulated and downregulated genes, respectively. (E,F) Feature selection using the Least Absolute Shrinkage and Selection Operator (LASSO) regression model. (G,H,I,J,K) Identification of optimal biomarkers using the Support Vector Machine-Recursive Feature Elimination (SVM-RFE) algorithm. (L) Venn diagram

demonstrating the intersection of candidate genes identified by both LASSO and SVM-RFE algorithms, yielding three hub genes (C8B, CPB2, and MASP2). (M,N,O) Violin plots comparing the relative expression levels of C8B, CPB2, and MASP2 between HBV-ALF patients and healthy controls. Statistical significance was determined using the Mann-Whitney U test (***P < 0.001).

2.2 Dysregulation of the Hepatic Immune Microenvironment in HBV-ALF

Given the critical role of complement and coagulation factors in modulating inflammation, we subsequently evaluated the immune infiltration landscape in HBV-ALF using the CIBERSORT algorithm. The hepatic immune microenvironment in HBV-ALF was characterized by a severe imbalance, with a marked increase in pro-inflammatory immune cells (such as activated dendritic cells and neutrophils) and a significant depletion of regulatory populations, particularly M2 macrophages (Fig. 2A). Correlation analysis revealed a strong functional link between the hub genes and immune infiltration. The drastic downregulation of C8B, CPB2, and MASP2 was highly negatively correlated with the infiltration of destructive immune cells, while showing a positive correlation with the presence of anti-inflammatory M2 macrophages (Fig. 2B). This suggests that the

230 *synthetic failure of these specific liver-derived proteins is intrinsically linked to the*
 231 *catastrophic immune dysregulation observed in HBV-ALF.*



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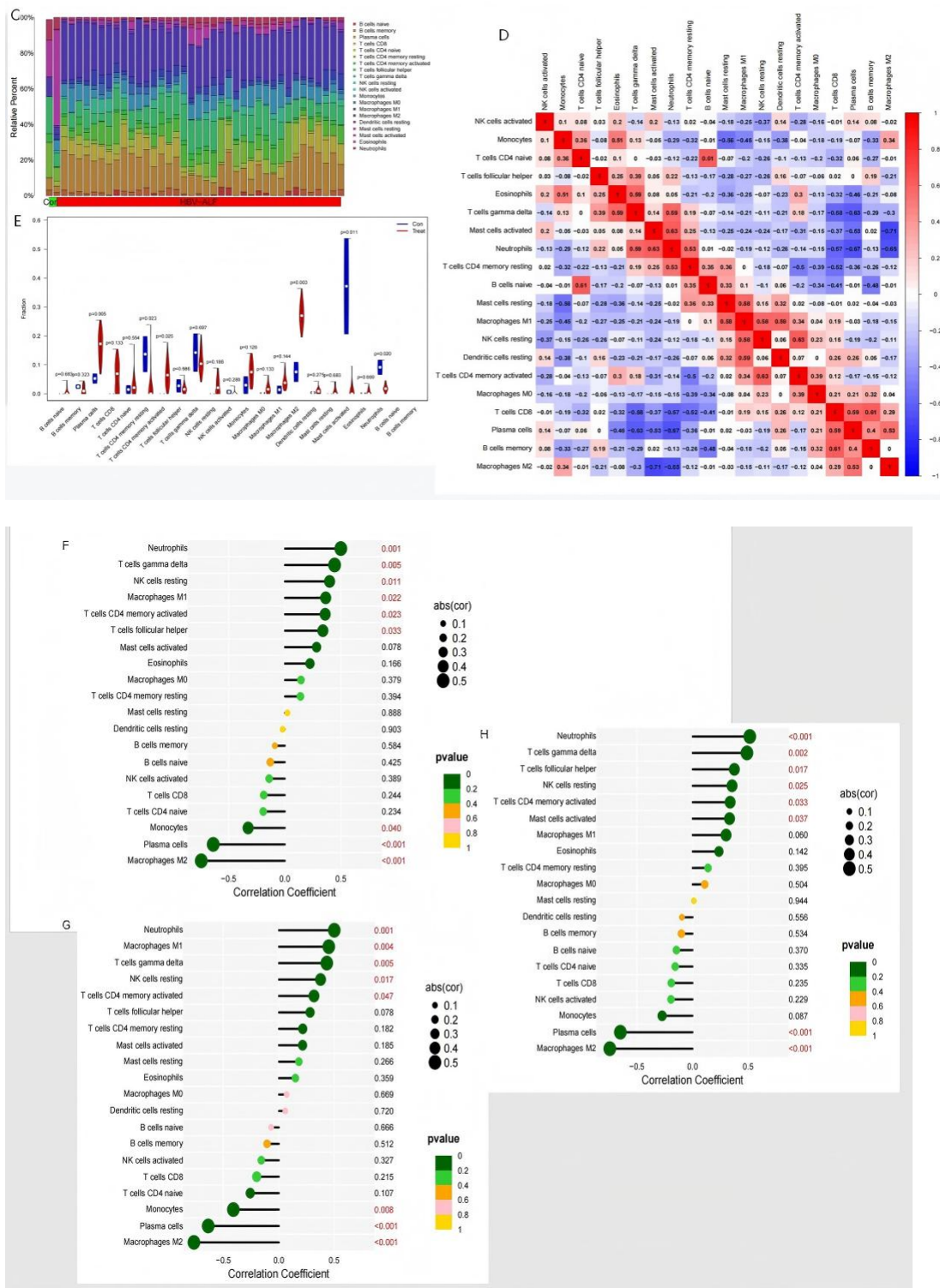


Figure 2 Dysregulation of the hepatic immune microenvironment and functional enrichment associated with hub genes. (A,B) Bubble chart detailing the top enriched Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the DEGs, highlighting the complement and coagulation cascades and inflammatory responses. (C,D,E) The landscape of

infiltrating immune cells in normal and HBV-ALF liver tissues evaluated by the CIBERSORT algorithm. (F,G,H) Correlation matrix and representative scatter plots illustrating the Spearman's rank correlations between the expression levels of the three hub genes (C8B, CPB2, MASP2) and the relative abundance of specific immune cell subsets (e.g., M2 macrophages, neutrophils). Red indicates positive correlation, while blue indicates negative correlation (*P < 0.05 was considered statistically significant).

2.3 Clinical Validation: Profound Decline of Hub Genes Reflects Severe Hepatic Synthetic Failure

To translate our bioinformatic predictions into clinical reality, we validated the expression levels of these hub genes in an independent clinical cohort of HBV-ALF patients. Consistent with the transcriptomic data, clinical laboratory assessments revealed a catastrophic collapse in the systemic levels of these proteins. Most strikingly, the level of CPB2 plummeted to approximately 26% of the normal physiological baseline, accompanied by severe reductions in complement components associated with C8B and MASP2 (Fig.3A). Furthermore, we evaluated the prognostic value of these hub genes by correlating their levels with standard clinical parameters of liver severity. The profound decline of C8B, CPB2, and MASP2 exhibited a robust positive correlation with Prothrombin Time Activity (PTA), directly mirroring the loss of hepatic coagulation factor synthesis (Fig.3B). Conversely, their levels were strongly negatively correlated with Total Bilirubin (TBIL) and the MELD score (Fig. 3C-D). These robust correlations demonstrate that the downregulation of these complement-coagulation hub genes

sensitively and accurately reflects the extent of hepatic synthetic failure and overall disease severity in HBV-ALF.

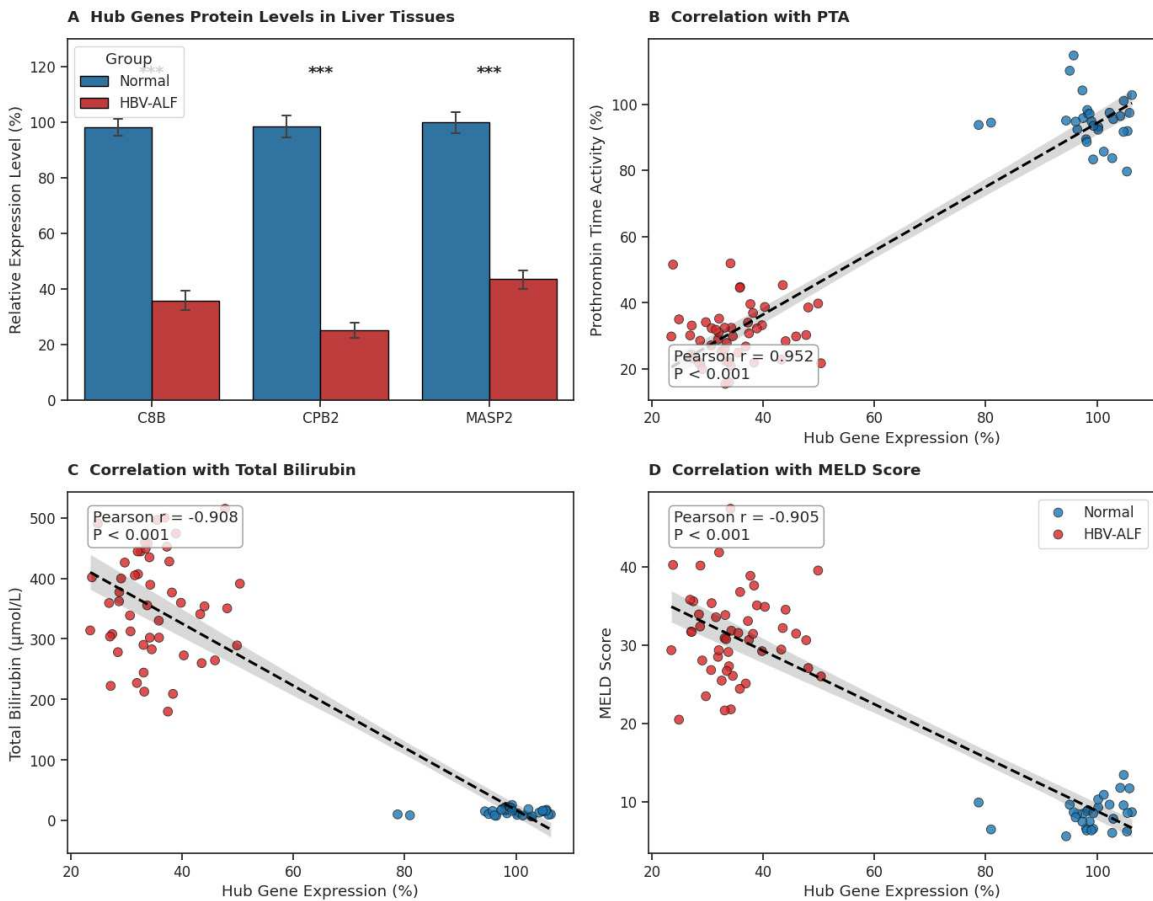


Figure 3 Clinical validation reveals the profound decline of hub genes tightly correlates with hepatic synthetic failure and disease severity. (A) Bar charts displaying the relative circulating or tissue protein levels of C8B, CPB2, and MASP2 in the independent clinical validation cohort (Normal/CHB vs. HBV-ALF). Notably, CPB2 levels in the ALF group plummeted to approximately 26% of the normal baseline. Data are presented as mean $\pm$ SD.(B-D) Linear regression and Spearman's correlation analyses demonstrating the relationships between the relative levels of hub genes and crucial clinical prognostic indicators, including Prothrombin Time Activity (PTA), Total Bilirubin (TBIL), and the Model for End-Stage Liver Disease (MELD) score. Shaded areas represent the 95% confidence intervals.

2.4 Spatial Histopathology Reveals the Collapse of Local Complement-Coagulation Network and Immune Overactivation

To further characterize the spatial relationship between hepatic necrosis, impaired hepatic synthesis, and immune activation, we performed histological and immunostaining analyses on liver tissues from HBV-ALF patients. Histopathological examination by H&E staining revealed extensive hepatocellular necrosis, disruption of hepatic architecture, and residual viable parenchyma, confirming the severe pathological features of HBV-ALF (Fig. 4A). Correspondingly, immunohistochemical staining demonstrated markedly reduced immunoreactivity of C8B, CPB2, and MASP2 within necrotic regions, suggesting impaired local hepatic protein synthesis capacity (Fig. 4B–D). Although the synthesis of complement-related proteins was impaired due to hepatocyte loss, terminal complement activation remained prominent in the injured liver. Immunofluorescence staining for C5b-9 (the terminal membrane attack complex) revealed enhanced C5b-9 deposition within residual hepatic parenchyma and along the margins of necrotic zones (Fig. 4E). These findings reveal a spatial discrepancy between impaired synthesis of complement-related proteins in necrotic regions and enhanced terminal complement activation in residual hepatic areas, suggesting that hepatocyte loss is associated with reduced hepatic synthetic capacity, whereas persistent complement activation may contribute to ongoing injury in surviving liver tissue.

Figure 4. Spatial histopathology reveals impaired hepatic protein synthesis and enhanced terminal complement activation in HBV-associated acute liver failure. (A) Representative H&E staining of liver tissues from HBV-ALF patients showing extensive hepatic necrosis, disrupted architecture, and residual viable parenchyma. (B–D) Representative immunohistochemical staining for C8B, CPB2, and MASP2 in normal and HBV-ALF liver tissues. The expression of these proteins was markedly reduced in ALF tissues, with minimal immunoreactivity observed in necrotic regions. (E) Representative immunofluorescence staining of the terminal complement complex C5b-9 (membrane attack complex). Increased C5b-9 fluorescence signals indicate enhanced terminal complement activation, particularly in residual hepatic areas and regions adjacent to necrotic lesions. Data are presented as mean $\pm$ SD. * $P < 0.05$; ** $P < 0.01$.

3 Discussion

At present, the pathological and physiological mechanisms underlying HBV-ALF are not well-defined, so there is an urgent need to further understand the fundamental mechanisms of HBV-ALF. Nissim et al. found that hepatocyte necrosis in HBV-ALF is closely related to parenchymal cells and fibrosis²⁰. Additionally, several studies have indicated that humoral immunity is closely associated with the pathogenesis of HBV-ALF²¹⁻²³. Moreover, numerous investigations have demonstrated that using bioinformatics research methods greatly facilitates the identification and understanding of genes related to HBV-ALF^{24,25}. For instance, in a study by Chen et al., immune-inflammatory responses and central genes associated with HBV-ALF were revealed through WGCNA analysis²⁶.

In this study, we obtained three independent HBV-ALF datasets from the GEO database and combined the data from the three microarrays. We conducted a differential analysis and identified 652 significantly differentially expressed genes. The enrichment analysis of these differentially expressed genes suggested that they are involved in regulating various pathways, including "Complement and coagulation cascades," which may have significant research value for understanding HBV-ALF regulation. Further machine learning-based screening identified 28 candidate genes from these differentially expressed genes. Using multiple algorithms, we calculated the interaction relationships among candidate genes and ultimately discovered that C8B, CPB2, and MASP2 occupied

central positions. Differential analysis revealed that C8B, CPB2, and MASP2 all exhibited significantly lower expression in HBV-ALF samples.

C8, a member of the complement protein family, consists of subunits encoded by three independent genes: C8A, C8B, and C8G. C8 is typically a major component of the membrane attack complex (MAC)^{27,28}. Studies suggest that C8B may be closely related to HBV-associated liver diseases. In a study by Zhang et al., C8B was found to be an effective predictor of survival in patients with HBV-related hepatocellular carcinoma²⁹. Additionally, in research conducted by Chen and Li et al., C8B was considered a key factor in HBV infection^{30,31}. However, few studies have explored C8B in HBV-ALF. In this study, we discovered that C8B exhibited significantly lower expression in HBV-ALF, potentially playing a critical regulatory role in the progression of HBV-ALF. Similarly, MASP2 has been considered an essential gene related to HBV infection regulation in numerous studies³²⁻³⁴. Dai et al. found that CPB2 showed significantly differential expression in chronic hepatitis B and possessed potential as a molecular marker³⁵. Furthermore, several studies have pointed out that abnormal expression of CPB2 may play an important role in liver-related diseases³⁶⁻³⁸. However, research on C8B, CPB2, and MASP2 in HBV-ALF remains limited, and their regulatory mechanisms in HBV-ALF warrant further in-depth investigation.

Historically, research on HBV-ALF has primarily focused on the interplay between the virus and the host, with immune cells, as the executors of the immune system, undoubtedly playing a critical role^{39,40}. In this study, through immune cell infiltration analysis, it was found that immune cells, such as M2 macrophages and neutrophils, exhibited significant differences in HBV-ALF samples. Research by Wu et al. demonstrated that neutrophils in HVB-ALF exhibit significant differences in quantity, phenotype, and other aspects, and are closely related to the progression of HBV-ALF⁴¹. Research by Ye et al. indicated that neutrophils contribute to the development of ALF through the miR-223/Neutrophil Elastase signaling pathway⁴². Additionally, numerous studies have shown that abnormal immune cell infiltration is closely associated with the progression of HBV-ALF^{1,43,44}. In this study, we found that the screened candidate genes C8B, CPB2, and MASP2 exhibited a significantly positive correlation with immune cells such as neutrophils and a significantly negative correlation with M2 macrophages and

other immune cells. This further suggests that the three candidate genes identified in this study may play an essential regulatory role in the occurrence and progression of HBV-ALF, and are very likely to be closely related to immune cell infiltration in HBV-ALF. This study utilizes bioinformatics methods to analyze HBV-ALF expression data, thereby shedding light on the regulatory mechanisms underlying HBV-ALF and opening up new avenues for research aimed at elucidating the mechanisms related to this condition.

Currently, clinical decision-making for HBV-ALF heavily relies on the Model for End-Stage Liver Disease (MELD) score and prothrombin time activity (PTA). However, these traditional indicators often lag behind the actual progression of irreversible hepatic necrosis, complicating the optimal timing for artificial liver support or liver transplantation (LT). Our clinical validation highlights the exceptional potential of CPB2 and MASP2 as early-warning biomarkers for hepatic synthetic exhaustion. Notably, CPB2 levels plummeted to approximately 26% of the normal baseline in ALF patients. Given its strong correlation with declining PTA and surging MELD scores, the precipitous drop in CPB2 could serve as a highly sensitive, real-time indicator of the "point of no return" in massive hepatocyte necrosis. We propose that integrating the serum or tissue levels of these hub proteins into existing prognostic models could significantly refine the criteria for LT indications, identifying patients who urgently require transplantation before the onset of fatal multi-organ failure.

Beyond their prognostic value, the dysregulation of these hub genes unveils a promising therapeutic vulnerability in HBV-ALF. Our spatial histopathology demonstrated massive accumulation of the terminal membrane attack complex (C5b-9) strictly bordering the necrotic zones, despite the systemic decline of upstream complement components. This suggests a destructive cycle where local complement overactivation continuously attacks surviving hepatocytes. Therefore, targeted inhibition of the complement system emerges as a highly translational therapeutic strategy. Utilizing monoclonal antibodies against C5 (e.g., Eculizumab), which are already FDA-approved for atypical hemolytic uremic syndrome, or developing novel inhibitors specifically targeting MASP2 (e.g., Narsoplimab), could theoretically block this necrotic cascade. Administering such complement-targeted therapies during the hyper-acute phase of HBV-ALF could mitigate systemic inflammatory response syndrome (SIRS), thereby

serving as a vital "bridge to transplant" or, in favorable cases, preserving enough hepatic parenchyma to allow native liver regeneration without requiring LT.

Despite the robust multi-cohort and multi-omics validation, several limitations must be acknowledged. First, the retrospective nature of our clinical validation cohort may introduce inherent selection biases. To firmly establish CPB2 and MASP2 as definitive criteria for LT triage, large-scale, multi-center prospective studies are urgently needed to define precise clinical cut-off values. Second, while our histopathological data strongly imply a causal link between complement hyperactivation and necrosis, future in vivo studies utilizing hepatocyte-specific Cpb2 knockout murine models of ALF, combined with complement inhibitor interventions, are essential to elucidate the exact molecular interplay and validate drug efficacy before advancing to clinical trials.

In conclusion, our study identifies C8B, CPB2, and MASP2 as crucial hub genes orchestrating the complement-coagulation crosstalk in HBV-ALF. The dramatic depletion of these proteins serves as an innovative prognostic biomarker for assessing hepatic synthetic collapse and predicting liver transplant indications. Furthermore, intercepting the localized complement overactivation in the necrotic microenvironment provides a rational foundation for developing novel targeted immunotherapies for this life-threatening disease.

Acknowledgments

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Declarations

Ethics approval and consent to participate

This retrospective study involving patients with hepatitis B virus-related acute liver failure was approved by the Institutional Ethics Committee of The Second Xiangya Hospital of Central South University. The requirement for informed consent was waived due to the retrospective design of the study. All procedures were performed in accordance with the Declaration of Helsinki and relevant ethical guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Clinical trial number

Not applicable.

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