Observational Study

Medicine

OPEN

Association of abnormal NDUFB2 and UQCRH expression with venous thromboembolism in patients with liver cirrhosis

Yixuan Tan, MD[a], Yanhong Ma, MD[b], Suzhi Guo, MD[b], Yaoting Lin, MD[c,*]

Abstract

Venous thromboembolism (VTE) refers to abnormal coagulation of blood in veins, resulting in complete or incomplete occlusion of the blood vessels. Patients with liver cirrhosis are prone to blood clots. However, relationship between NDUFB2 and UQCRH and VTE is not clear. GSE19151 and GSE48000 profiles for venous thromboembolism were downloaded from gene expression omnibus (GEO) generated using GPL571 and GPL10558. Multiple datasets were merged and batched. The differentially expressed genes (DEGs) were screened and weighted gene co-expression network analysis (WGCNA) was performed. The construction and analysis of protein–protein interaction (PPI) network, functional enrichment analysis, Gene Set Enrichment Analysis (GSEA) were conducted. Gene expression heat map was drawn. Comparative toxicogenomics database (CTD) analysis were performed to find disease most related to the core genes. Western blotting (WB) experiments were further verified. TargetScan screened miRNAs that regulated central DEGs. 129 DEGs were identified. According to gene ontology (GO), DEGs were mainly enriched in mRNA metabolism, oxidative phosphorylation, nucleic acid binding and enzyme binding. The Kyoto Encyclopedia of Gene and Genome (KEGG) analysis showed that target cells were mainly enriched in ribosomes and oxidative phosphorylation. The intersection of enrichment items and GOKEGG enrichment items of DEGs is mainly enriched in oxidative phosphorylation, myocardial contraction and ribosome. In the metascape enrichment project, dna template transcription, cell stress response regulation and proton transport across the membrane can be seen in the GO enrichment project. The PPI network obtained 10 core genes (COX7C, NDUFB2, ATP5O, NDUFA4, NDUFAB1, ATP5C1, ATP5L, NDUFA7, NDUFA6, UQCRH). Gene expression heat map showed that 5 core genes (NDUFAB1, NDUFB2, UQCRH, COX7C, NDUFA4) were highly expressed in venous thromboembolism samples, and lowly expression in normal tissue samples, and 2 core genes (NDUFA7, NDUFA6) were lowly expressed in venous thromboembolism samples. CTD analysis showed that 5 genes (NDUFAB1, NDUFB2, UQCRH, COX7C, NDUFA4) were found to be associated with obesity, necrosis, inflammation and hepatomegaly. The result of WB showed that expression level of NDUFB2 and UQCR in venous thromboembolism was higher than that in control group. NDUFB2 and UQCRH are highly expressed in venous thromboembolism with liver cirrhosis, making them potential molecular targets for early diagnosis and precise treatment.

Abbreviations: ATP = adenosine triphosphate, CTD = comparative toxicogenomics database, DEGs = differentially expressed genes, DVT = deep venous thrombosis, ETS = electron transfer system, FC = fold change, FDR = false discovery rate, GEO = gene expression omnibus, GO = gene ontology, GSEA = Gene set enrichment analysis, HCC = hepatocellular carcinoma, KEGG = Kyoto Encyclopedia of Gene and Genome, MCODE = molecular complex detection, OXPHOS = oxidative phosphorylation, PPI = protein–protein interaction, PTE = pulmonary thromboembolism, TOM = topological overlap matrix, VTE = venous thromboembolism, WB = western blotting, WGCNA = weighted gene co-expression network analysis.

Keywords: liver cirrhosis, molecular targets, NDUFB2, UQCRH, venous thromboembolism

1. Introduction

Venous thromboembolism (VTE) is a dangerous chronic disease that includes deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). According to statistics, about 90% of the emboli in PTE come from the deep venous system of the lower extremities, while thrombosis from other parts is rare. Therefore, effective prevention of lower limb DVT can effectively prevent PTE.[1–3] Venous thromboembolism is a common disease with multiple factors and high mortality. First of all,

SG and YL contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the Fourth Hospital of Hebei Medical University.

[a]Hepatobiliary Surgery, Danzhou People's Hospital, Nada Town, Danzhou City, Hainan Province, China, [b]Department of ICU, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [c]Gastrointestinal surgery, Danzhou People's Hospital, Nada Town, Danzhou City, Hainan Province, China.

**Correspondence: Yaoting Lin, Gastrointestinal surgery, Danzhou People's Hospital, No. 21-1, Datong Road, Nada Town, Danzhou City, 571700, Hainan Province (e-mail: linyaoting23821@163.com).*

How to cite this article: Tan Y, Ma Y, Guo S, Lin Y. Association of abnormal NDUFB2 and UQCRH expression with venous thromboembolism in patients with liver cirrhosis. Medicine 2024;103:1(e36868).

Received: 22 September 2023 / Received in final form: 12 December 2023 / Accepted: 14 December 2023

http://dx.doi.org/10.1097/MD.0000000000036868

the abnormal increase of coagulation factors is easy to induce thrombosis. Secondly, intimal injury will lead to the release of a large number of procoagulant factors, leading to formation of intravascular thrombus. Third, there is hypercoagulable state, especially in patients with tumor or nephrotic syndrome.[4,5] The incidence of VTE is increasing in China.[6–8] Although the mortality of DVT and PTE is declining, VTE is still third leading cause of death worldwide. The disease has become a major global health problem and has aroused widespread concern in the international academic community and society. However, the cause of venous thromboembolism is unclear. Therefore, it is important to study molecular mechanism of venous thromboembolism.

Liver cirrhosis is a common clinical chronic progressive liver disease, which is caused by one or more causes of long-term or repeated effects of diffuse liver damage.[9] In the early stage, there may be no obvious symptoms due to the strong compensatory function of the liver. In the later stage, liver function damage and portal hypertension are the main manifestations, and there are multiple system involvement and complications.[10] Cirrhosis is an end-stage liver disease that can lead to changes in any component of the hemostatic system. Studies have shown that patients with cirrhosis are not only at increased risk of bleeding, but also at risk of venous thromboembolism (VTE).[11]

As a vital component of life science development, bioinformatics has been at the forefront of research in life science and technology. In recent years, China biotechnology has experienced remarkable progress, leading to an explosive growth in bioinformatics resources. Bioinformatics unveils the biological significance represented by big data, acting as a bridge between data and clinic. It plays a crucial role in tumor treatment, particularly in the analysis and reporting of gene detection data.[12,13]

This paper intends to employ bioinformatics technology to identity the core genes associated with venous thromboembolism and normal tissue, followed by conducting enrichment analysis and pathway analysis. Public datasets will be used to verify the significant role of NDUFB2 and UQCRH genes in venous thromboembolism. Furthermore, the findings will be validated through basic cell experiment.

2. Methods

2.1. Processing and design of data samples

We obtained sample information for venous thromboembolism from the NCBI public database and identified 2 datasets, GSE19151 and GSE48000. They were divided into venous thromboembolism group (n = 284) and control group (n = 113). With the help of R software limma package (version3.42.2), the merging and difference analysis of the 2 datasets were realized. For the setting of thresholds, $P < .05$ and FC > 1.5 were considered to be significantly different.

2.2. Weighted gene coexpression network analysis (WGCNA)

Using de-batch and post-merge matrix of GSE19151 and GSE48000 to calculate median absolute deviation of each gene. The good samples genes method of R package WGCNA was used to remove the outlier genes and samples, construct scale-free co-expression network. We calculated characteristic gene differences of the modules, and selected tangent line for module tree view, incorporated part of modules. The gray module cannot be assigned to any module collection.

2.3. Bioinformatics analysis is used to screen and identify genes

The resulting significantly differentiated genes were identified and annotated by GO analysis using the DAVID database, including molecular function (MF), cellular component (CC), and biological process (BP). Pathway condensation analysis was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database and David. The inclusion of 3 types of inclusion criteria in the row pre-concentration and KGEG pathways was statistically significant ($P < .05$).

In addition, Metascape[14] (http://metascape.org/) was used to perform functional annotation and complementary analysis of genes. PPI analysis (confidence = 0.400) was established using the Search Tool for the Retrieval of Interacting Genes online tool and visualized by cytoscape.

2.4. In-depth analysis of the core genes for venous thromboembolism

Visualize the expression status of core genes between disease and health samples, use the CTD database to discover disease information related to core genes, and further analyze the potential risk relationship between venous thromboembolism and core genes. Retrieve miRNA information that regulates core genes on https://www.targetscan.org to deepen your understanding of core genes.

2.5. Western blotting (WB)

Western blotting, also known as immunoblotting, is a method to detect the expression of a certain protein in complex samples according to the specific binding of antigens and antibodies, and can qualitatively and semi-quantitatively analyze proteins. Total protein was extracted and the protein content was determined. After SDS-PAGE electrophoresis and membrane transfer, the protein samples were blocked with 5% skim milk for 1 hour at room temperature, shaken with Tris Buffered Saline Tween at high speed on a shaker, washed for 5 minutes, and repeated 3 times. The primary antibody was added and incubated overnight at 4°C, followed by TBST shaking 3 times (5 minutes each time) and TBST shaking 3 times (5 minutes each time). The results were analyzed after chemiluminescence development.

3. Results

3.1. Analysis of differentially expressed genes

According to set cutoff value and the de batching merge matrix of GSE19151 and GSE48000, 129 DEGs were identified (Fig. 1). We sorted them according to P value from small to large, and selected first 500 for follow-up analysis.

3.2. Functional enrichment analysis

3.2.1. DEGs. We analyzed DEGs by GO and KEGG. According to GO, they were mainly enriched in mRNA metabolism, oxidative phosphorylation, nucleic acid binding and enzyme binding (Fig. 2A,C,E).

KEGG showed that target cells were mainly enriched in ribosomes and oxidative phosphorylation (Fig. 2G).

3.2.2. GSEA. The intersection of GSEA and GOKEGG enrichment project is used to verify the enrichment results of GOKEGG. The results showed that the intersecting enrichment items were mainly oxidative phosphorylation, myocardial contraction and ribosome (Fig. 2B,D,F,H).

3.3. Metascape enrichment analysis

In the metascape enrichment project, dna template transcription, cell stress response regulation and proton transport across the membrane can be seen in the GO enrichment project (Fig. 3A). At the same time, we also output the enrichment

network colored by enrichment term and *P* value (Fig. 3B,C and Fig. 4), which visually shows the correlation and confidence of each enrichment project.

3.3.1. WGCNA. The network topology is analyzed and soft threshold power of WGCNA is set to 20 (Fig. 5A,B). A hierarchical clustering tree of all genes is constructed and important modules are generated (Fig. 5D). The interaction between these modules was analyzed (Fig. 5C). The module-phenotypic correlation heat map (Fig. 6A) and the GS-MM correlation scatter map of related hub genes were generated (Fig. 6B–E and Fig. 7).

The wayne diagram was drawn for differential genes screened by WGCNA and DEGs, and the intersection was taken to create and analyze the protein–protein interaction network (Fig. 8).

3.4. Identification of core genes

The DEGs PPI network was constructed from the Search Tool for the Retrieval of Interacting Genes online database and analyzed by the Cytoscape software (Fig. 9A). The core gene cluster (Fig. 9B) was obtained. Identification of hub genes by 2 different algorithms (Fig. 9C,D), and Wayne diagram was used to obtain the intersection (Fig. 10). Core genes (COX7C, NDUFB2, ATP5O, NDUFA4, NDUFAB1, ATP5C1, ATP5L, NDUFA7, NDUFA6, UQCRH) were obtained.

The PPI network and the core genes identified (NDUFS3, NDUFC1, NDUFA6, UQCRC2) were corroborated by the results of the PPI.

3.5. Gene expression heat map

We visualized heat map of core gene expression in sample (Fig. 11). It was found that 5 core genes (NDUFAB1, NDUFB2, UQCRH, COX7C, NDUFA4) were highly expressed in venous thromboembolism samples, low expression in normal tissue samples, which may play a regulatory role in venous thromboembolism.

3.6. In-depth understanding of core genes

We searched on CTD for diseases associated with core genes, and we found that core genes (NDUFAB1, NDUFB2, UQCRH, COX7C, NDUFA4) were associated with obesity, necrosis, inflammation, and hepatomegaly (Fig. 12).

Then we searched for miRNAs related to the core gene in targetscan (Table 1), and we found that the miRNA related to COX7C gene was hsa-miR-144-3p, the miRNA related to ATP5O gene was hsa-miR-325-3p, the miRNA related to NDUFA4 gene was hsa-miR-205-5p, and the miRNA related to NDUFAB1 gene was hsa-miR-300, The miRNA associated with the HSA-miR-381-3p and ATP5C1 gene is hsa-miR-382-5p, and the miRNA associated with the NDUFA7 gene is hsa-miR-24-3p.

3.7. WB

This was further confirmed by WB experiment results. The expression levels of NDUFB2, UQCRH, ND1, Ndufs1, Ndufs2, Ndufs3, Ndufs4, Ndufs5, Ndufv1, Ndufa1, Ndufa2, Ndufb1, Ndufc1, Ndufc2, SDHC, SDHD, SDHA, ISP, Cytb, Cyt1, CyoE, COR1, CCR2, COX1, COX2, COX8, IL-6, IL-8, IL-1B, and TNF-a in VTE were higher than those in normal control group, higher than those in VTE group in VTE-OE and lower than those in VTE group in VTE-KO (Fig. 13).

4. Discussion

Venous thromboembolism (VTE) is a common disease with multiple factors and high mortality caused by venous blood stasis syndrome, vascular endothelial cell injury, hypercoagulable state and so on.[15,16] Severe venous thromboembolism in the acute stage can lead to lower limb gangrene and even fatal pulmonary embolism, which is a direct threat to the safety of patients. Anticoagulant therapy is the main treatment, and surgical thrombectomy is feasible in severe cases.[17–19] Clinically, patients with liver cirrhosis are prone to venous thrombosis.[20] In patients with liver cirrhosis, the hepatic portal vein reflux is blocked due to the destruction of the hepatic lobular structure, which leads to slow blood flow in the portal vein, local vortex formation, and local platelet aggregation, thereby forming portal vein thrombosis. Thrombosis due to coagulopathy in cirrhosis is a real risk.[21] The main result of this study is that NDUFB2 and UQCRH genes are highly expressed in venous thromboembolism. The higher the NDUFB2 the worse the prognosis.

The protein encoded by NDUFB2 is a subunit of the ubiquinone oxidoreductase (complex I). This protein has NADH dehydrogenase activity and oxidoreductase activity, and it plays an important role in the transferring electrons from the NADH to respiratory chain. Studies have shown

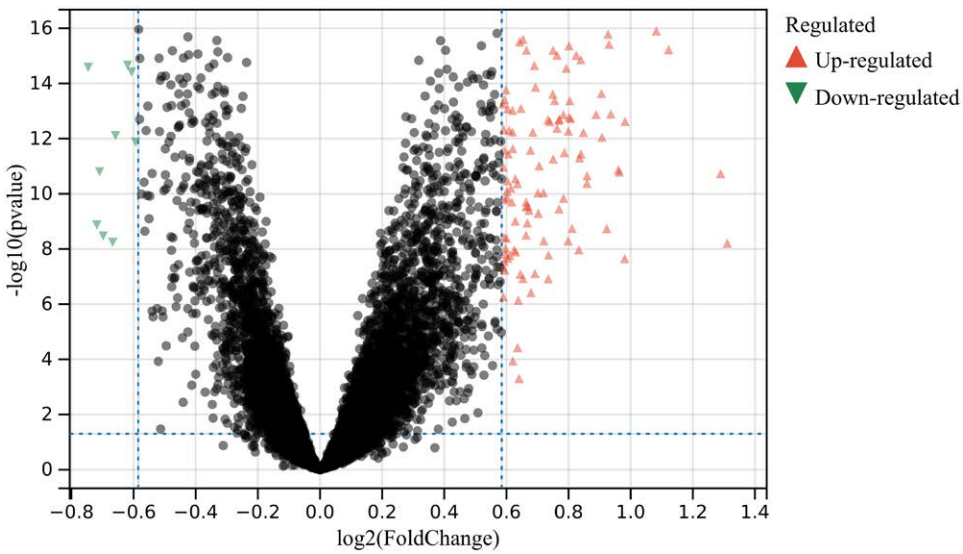

Figure 1. Analysis of differentially expressed genes. 129 DEGs were identified.

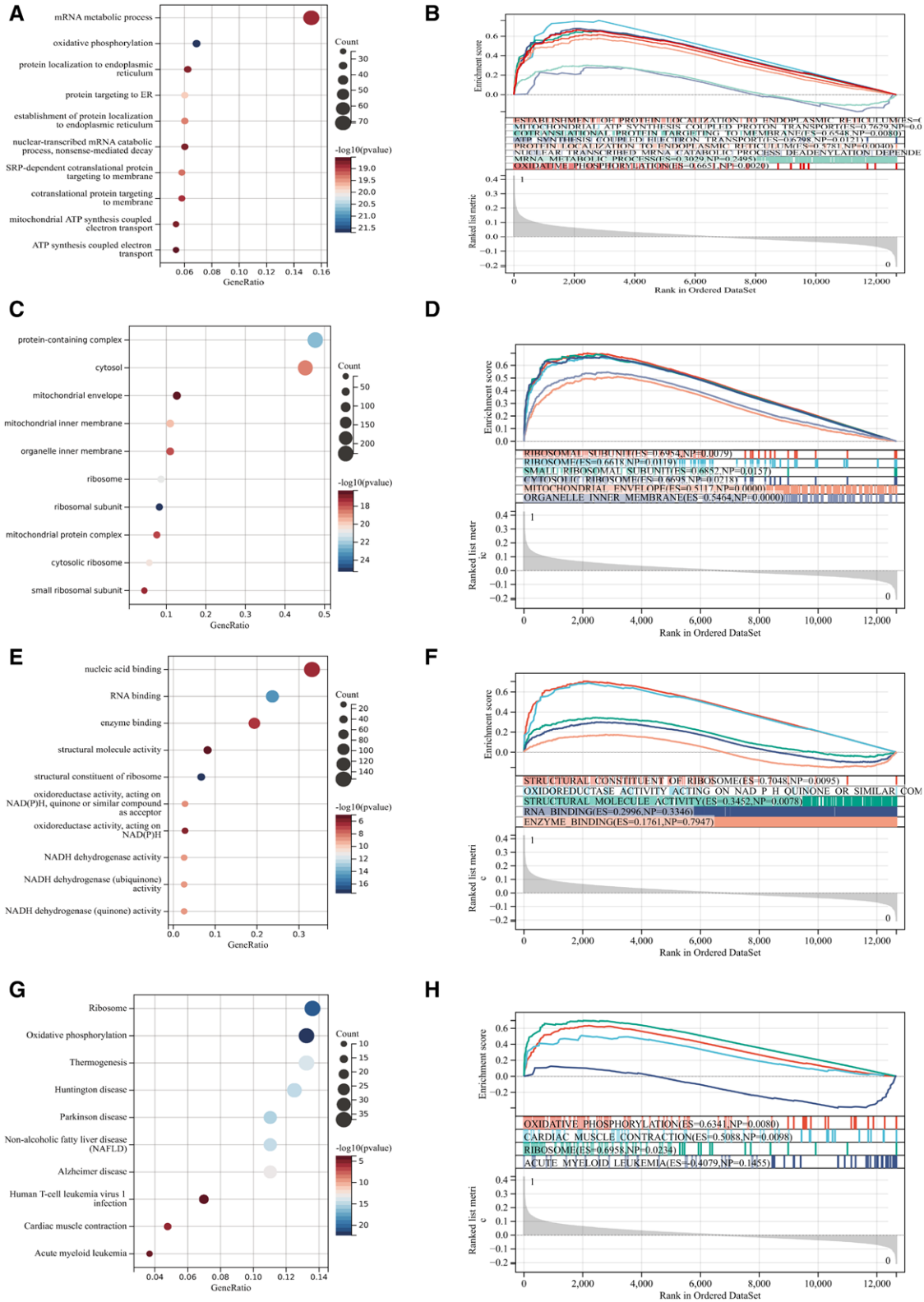

Figure 2. Functional enrichment analysis. (A, C, E) GO analysis. (G) KEGG analysis (B, D, F, H) GSEA. KEGG = Kyoto Encyclopedia of Gene and Genome.

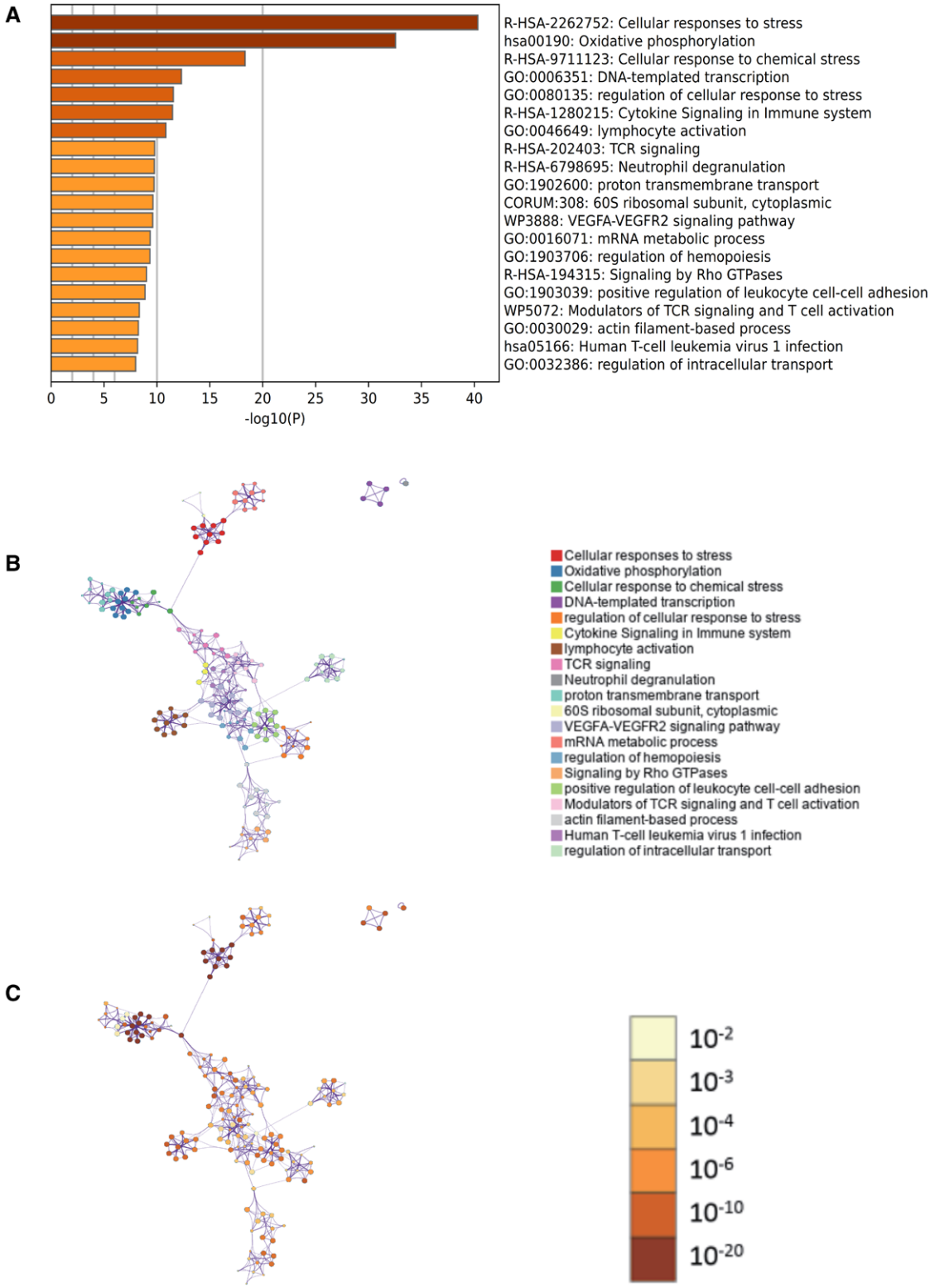

Figure 3. Metascape enrichment analysis. (A) In the metascape enrichment project, dna template transcription, cell stress response regulation and proton transport across the membrane can be seen in the GO enrichment project (B) enrichment networks colored by enrichment terms (C) enrichment networks colored by *P* values.

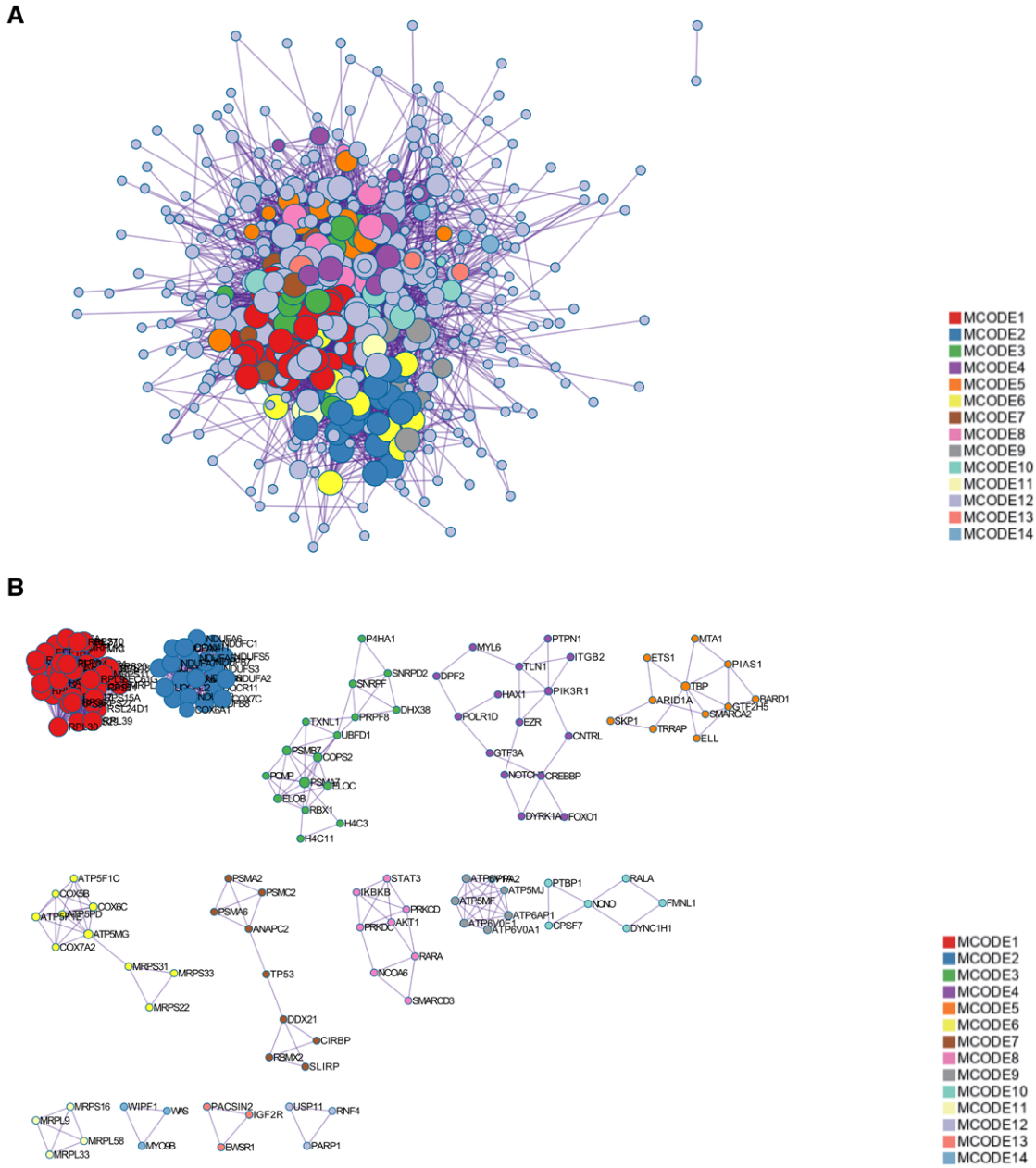

Figure 4. Metascape enrichment analysis.

that NDUFB2 is related to the DNA repair, dryness and cell cycle regulation. In addition, the expression of NDUFB2 promotes tumorigenesis. It was found that among the 10 necrotic apoptosis genes related to prognosis, NDUFB2 was highly elevated in gliomas, and was associated with overall survival in GBM.[22] In the study of Zheng Hope et al, NDUFB2 is a copper death-related gene. Functionally, copper death-related genes may be associated with a variety of cancers.[23] Studies by Hashime Sawai et al have shown that NDUFB2 is the key gene of mitochondrial oxidative phosphorylation and participates in the occurrence and development of bipolar disorder through mitochondrial oxidative phosphorylation.[24] Oxidative phosphorylation plays a key role in regulation of cell and tissue metabolism, some studies have shown that the regulation of oxidative phosphorylation can inhibit in flammation.[25] Based on the above studies and our results, we speculate that NDUFB2 gene may play a role in occurrence and development of venous thromboembolism in patients with cirrhosis.

UQCRH serves as the hinge protein of the mitochondrial electron transport chain, playing a crucial role in the electron transfer reaction within the oxidative phosphorylation (OXPHOS) pathway. UQCRH is the core gene in OXPHOS. The OXPHOS metabolic pathway is an indispensable basic process in most cells, which produces adenosine triphosphate (ATP) by transferring electrons to a transmembrane protein complex in the mitochondrial membrane and then providing energy for the metabolic process.[26] The OXPHOS metabolic pathway is a fundamental process in most cells, and it significantly contributes to ATP production, particularly in the adult mammalian heart, where oxidative phosphorylation is the primary ATP generation mechanism, promoted by the mitochondrial electron transfer system (ETS). The ETS complexes combine with the redox reaction of oxygen as the terminal electron acceptor to produce the electrochemical potential, which is driving force for F1FO-ATP synthetase to produce ATP. The function of CIII, in which UQCRH plays a regulatory role in electron transfer between

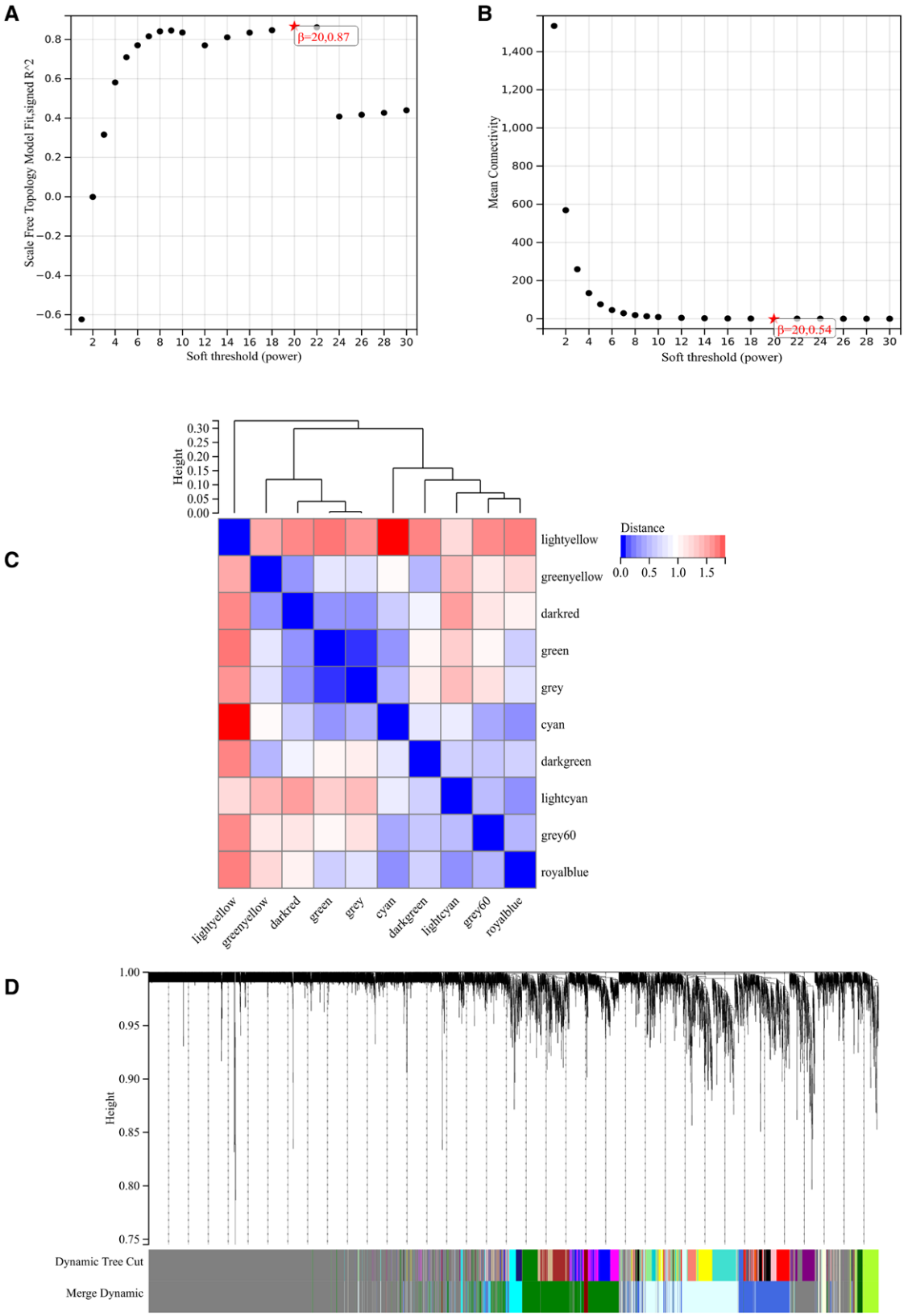

Figure 5. WGCNA (A) β = 20, 0.87 (B) β = 20, 0.54 (C) The interaction between these modules (D) A hierarchical clustering tree of all genes is constructed and important modules are generated. WGCNA = weighted gene co-expression network analysis.

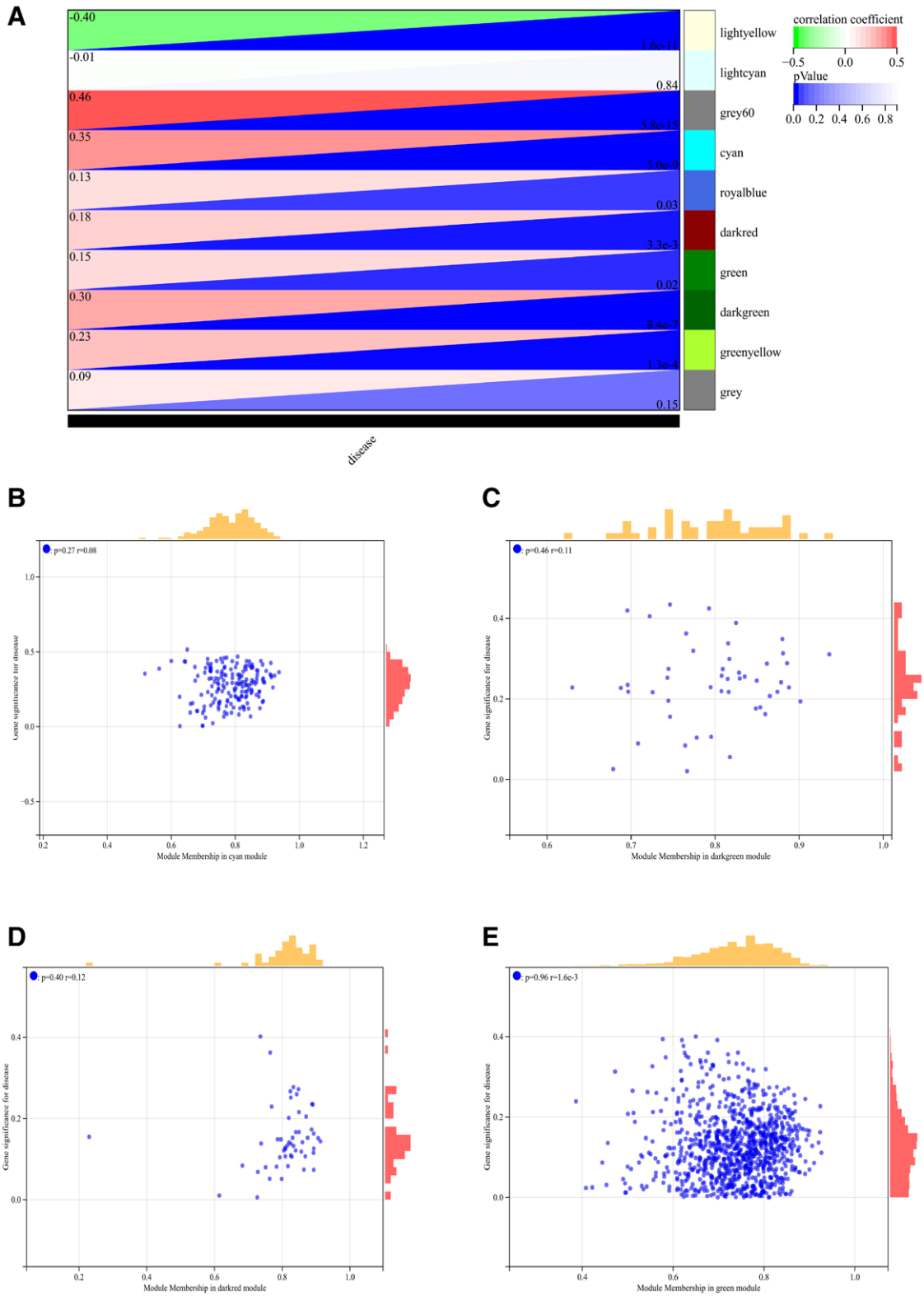

Figure 6. WGCNA. (A) The module-phenotypic correlation heat map (B–E) GS-MM correlation scatter map of related hub genes. WGCNA = weighted gene co-expression network analysis.

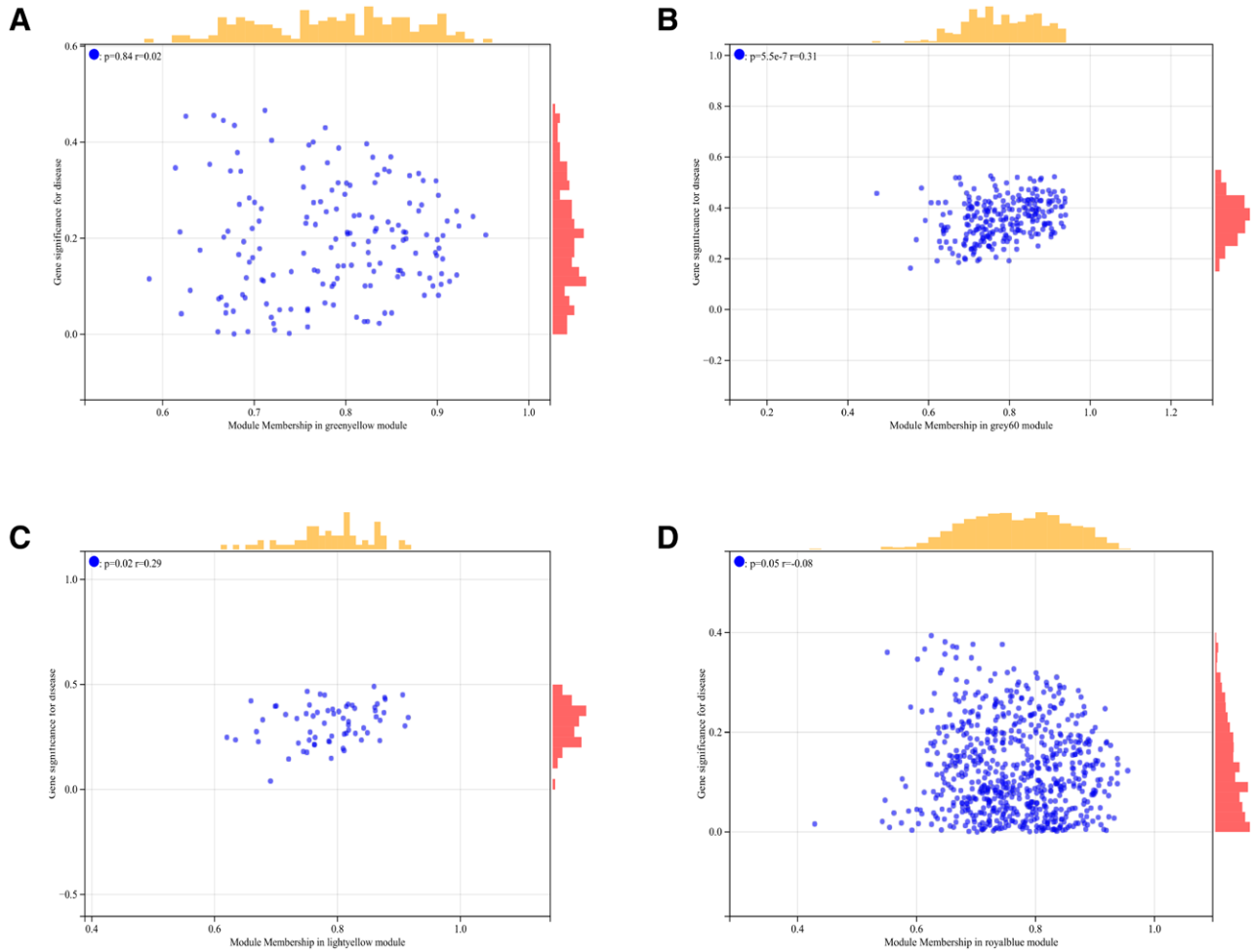

Figure 7. WGCNA. GS-MM correlation scatter map of related hub genes. WGCNA = weighted gene co-expression network analysis.

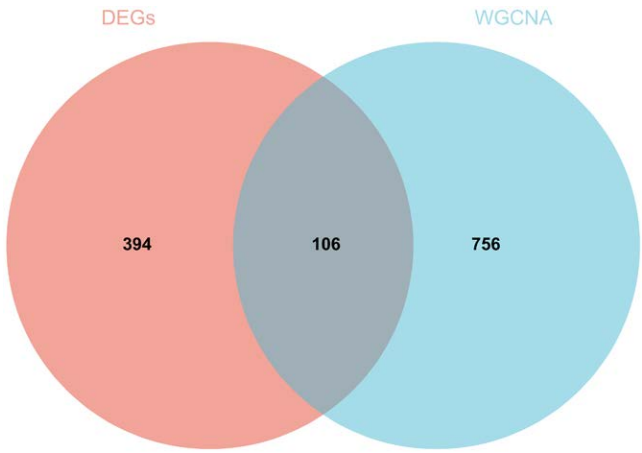

Figure 8. WGCNA. Draw the Wayne diagram of the differential genes screened by WGCNA and DEGs and take the intersection to create and analyze the protein–protein interaction network. WGCNA = weighted gene co-expression network analysis.

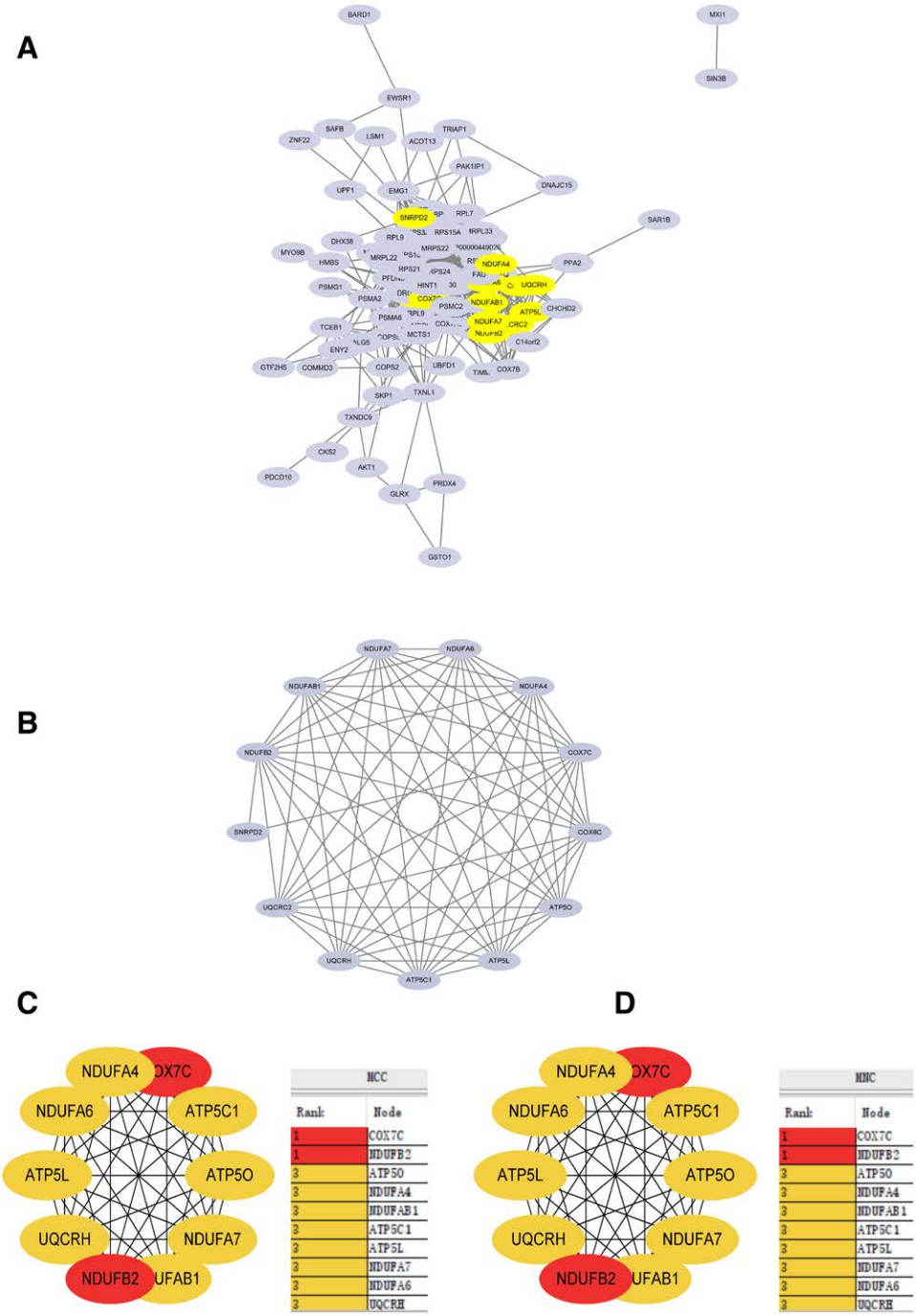

Figure 9. Construction and Analysis of protein–protein interaction (PPI) Network. (A) DEGs PPI network. (B) The core gene cluster. (C) MCC was used to identify central genes (D) MNC was used to identify central genes. MCC = maximal clique centrality. MNC = maximum neighborhood component.

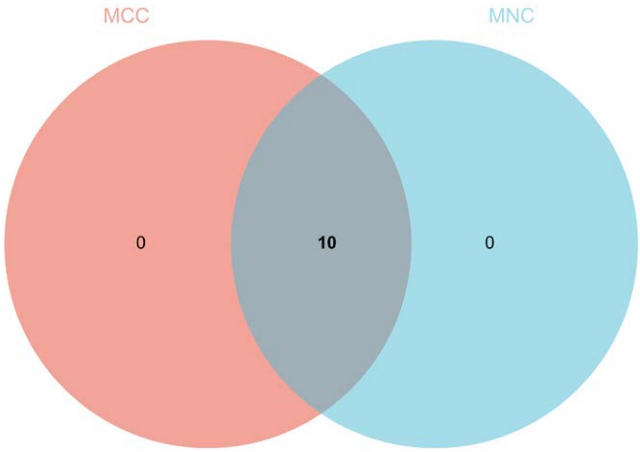

Figure 10. Construction and Analysis of protein–protein interaction (PPI) Network. Wayne diagram was used to obtain the intersection.

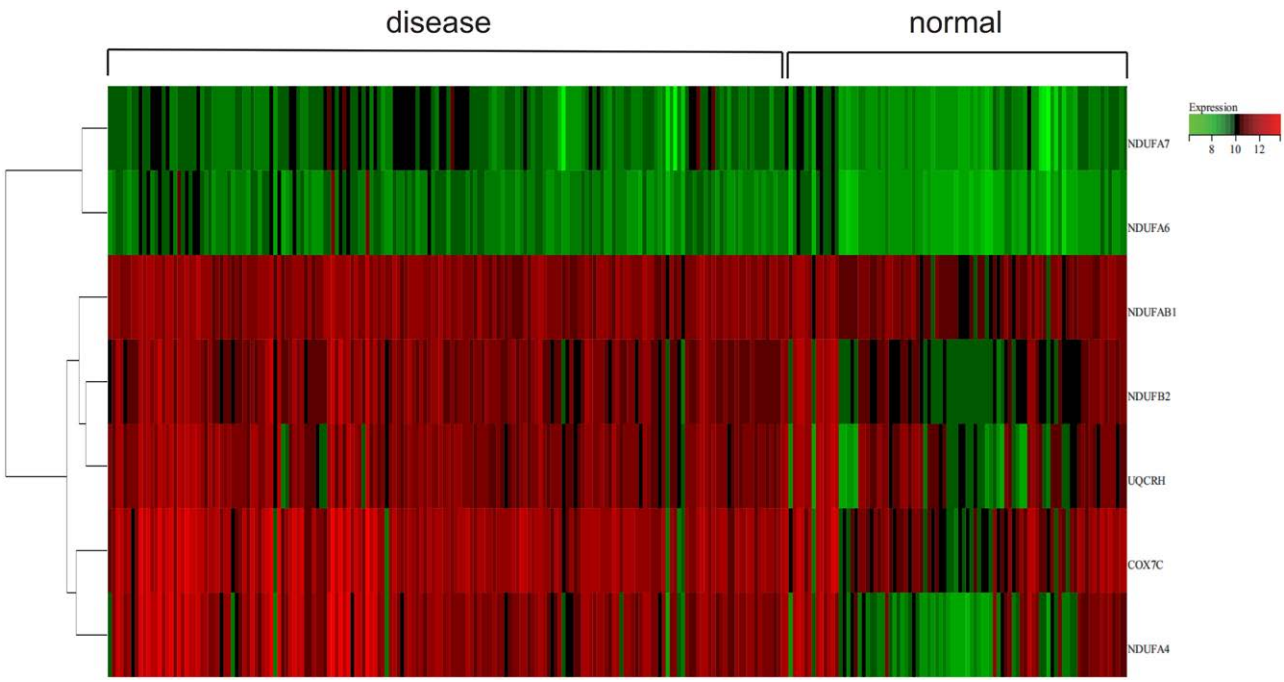

Figure 11. Gene expression heat map. Visualized the heat map of core gene expression in the sample.

cytochrome c of CIII and c of CIII, appears to hold special pathogenic significance.[27–29] Although UQCRH is widely expressed in the tissues, its function is important for the organs with the high energy metabolism.[30] UQCRH expression has been linked to certain types of cancer. One study suggests that UQCRH expression is positively correlated with the survival of patients with renal cell carcinoma, indicating its potential as a tumor suppressor gene in this context.[31] However, another study found increased UQCRH expression in patients with hepatocellular carcinoma, and its overexpression was associated with poor prognosis in hepatocellular carcinoma patients.[32] Moreover, UQCRH has been identified as a prognostic indicator for lung adenocarcinoma.[33] The study of Chen Weigang et al showed that UQCRH was up-regulated in hepatocellular carcinoma (HCC) tumor samples, and the overexpression of UQCRH was negatively correlated with OS deterioration in HCC patients. As an OXPHOS-related gene, UQCRH is significantly associated with mitosis and cell cycle pathway, and it partly participates to immune cell infiltration and immune function in HCC.[34] Our study found that high expression of the UQCRH gene in venous thromboembolism, and a higher expression of UQCRH was associated with worse prognosis. Based on the aforementioned research and our results, we speculate that UQCRH may play a critical role in occurrence and development of venous thromboembolism in patients with cirrhosis.

NDUFB2 and UQCRH are 2 subunits of the mitochondrial respiratory chain complexes, playing crucial roles in the electron transport chain within the mitochondria.[35] These 2 subunits operate in different complexes along the electron transport chain, collectively participating in the transfer of electrons from NADH through the intricate respiratory chain, ultimately driving the reduction of cytochrome c. This process is essential for maintaining mitochondrial membrane potential and generating energy through ATP synthesis. The collaborative action of NDUFB2 and UQCRH is vital for sustaining the normal function of the mitochondrial respiratory chain, which is paramount for cellular energy metabolism and survival.[36] Any abnormalities in either of these subunits may lead to mitochondrial

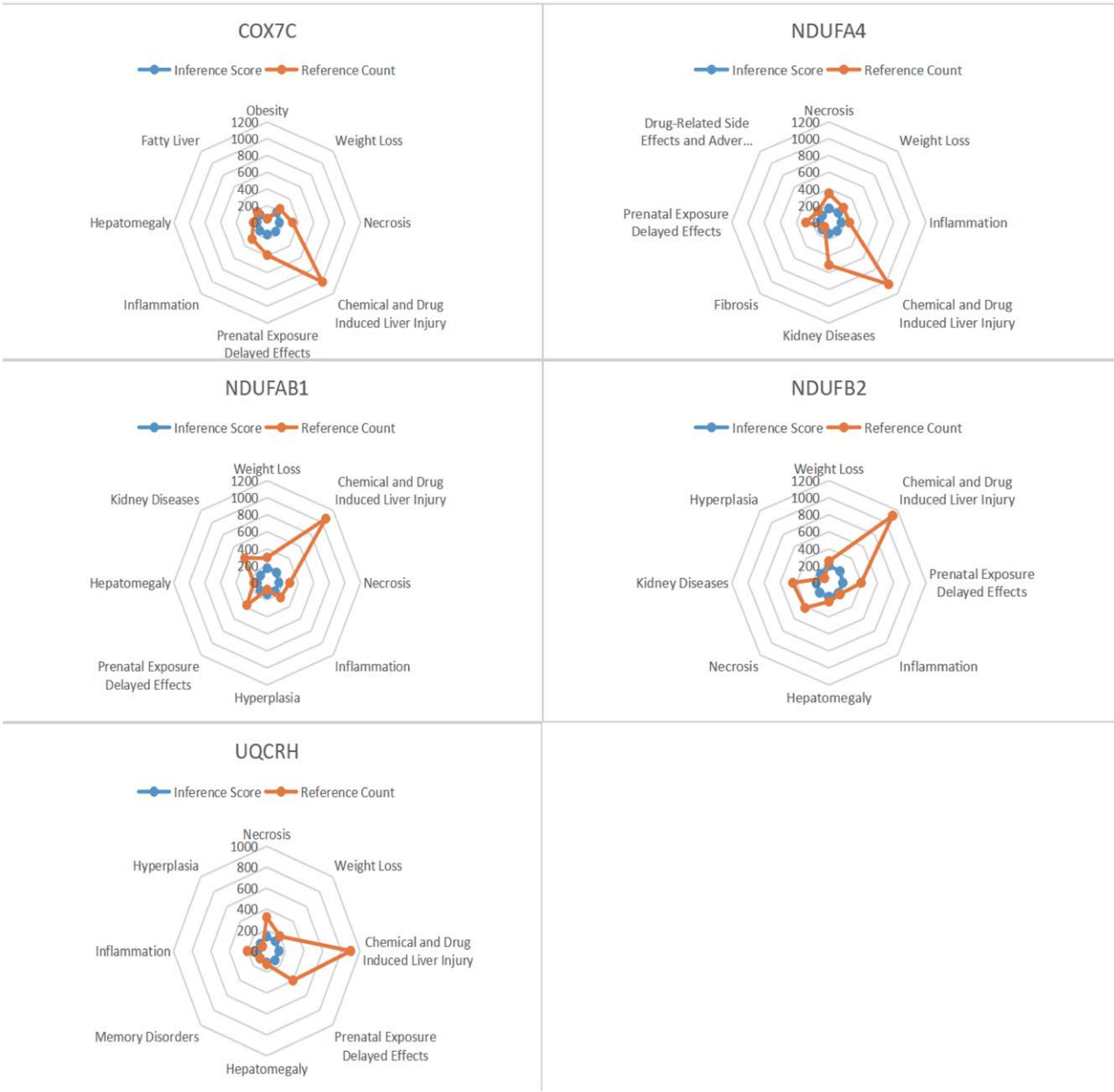

Figure 12. CTD analysis. Five genes (NDUFAB1, NDUFB2, UQCRH, COX7C, NDUFA4) were found to be associated with obesity, necrosis, inflammation and hepatomegaly.

Table 1

A summary of miRNAs that regulate hub genes.

	Gene	MIRNA	
1	COX7C	hsa-miR-144-3p	
2	NDUFB2	none	
3	ATP5O	hsa-miR-325-3p	
4	NDUFA4	hsa-miR-205-5p	
5	NDUFAB1	hsa-miR-300	hsa-miR-381-3p
6	ATP5C1	hsa-miR-382-5p	
7	ATP5L	none	
8	NDUFA7	hsa-miR-24-3p	
9	NDUFA6	none	
10	UQCRH	none	

dysfunction, subsequently affecting cellular energy production and other biological processes.

Although this paper has carried out rigorous bioinformatics analysis, there are still some shortcomings. Animal experiments with overexpression or knockdown of the gene were not performed in this study to further verify its function. Therefore, this aspect should be explored in depth in future studies.

To sum up, NDUFB2 and UQCRH are highly expressed in cirrhotic patients with venous thromboembolism, and may play a significant role in the development of venous thromboembolism through oxidative phosphorylation. NDUFB2 and UQCRH may be molecular targets of venous thromboembolism in patients with liver cirrhosis, and provide a basis for the study of the mechanism of venous thromboembolism.

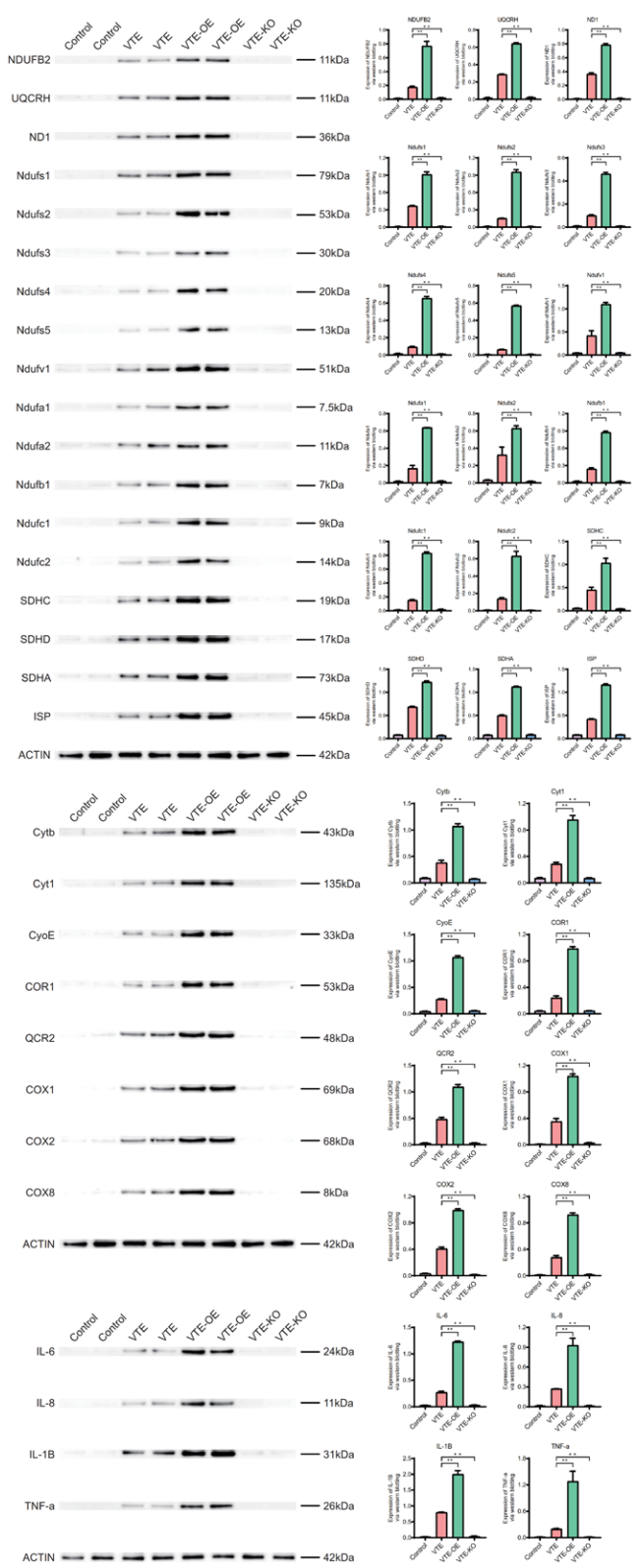

Figure 13. WB. NDUFB2 and UQCR in venous thromboembolism was higher than that in control group.

Author contributions

Conceptualization: Yanhong Ma, Suzhi Guo.
Data curation: Yanhong Ma, Yixuan Tan, Suzhi Guo, Yaoting Lin.
Formal analysis: Yanhong Ma, Yixuan Tan, Suzhi Guo, Yaoting Lin.
Methodology: Yanhong Ma, Yixuan Tan, Suzhi Guo, Yaoting Lin.
Software: Suzhi Guo, Yaoting Lin.
Writing – original draft: Yanhong Ma, Yixuan Tan, Suzhi Guo, Yaoting Lin.
Writing – review & editing: Yanhong Ma, Yixuan Tan, Suzhi Guo, Yaoting Lin.

References

[1] Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2020;38:496–520.
[2] Bartholomew JR. Update on the management of venous thromboembolism. Cleve Clin J Med. 2017;84(12 Suppl 3):39–46.
[3] Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism--international consensus statement. Int Angiol. 2013;32:111–260.
[4] Kacimi S, Moeinafshar A, Haghighi SS, et al. Venous thromboembolism in cancer and cancer immunotherapy. Crit Rev Oncol Hematol. 2022;178:103782.
[5] Battinelli EM, Murphy DL, Connors JM. Venous thromboembolism overview. Hematol Oncol Clin North Am. 2012;26:345–67, ix.
[6] Jaffer AK. Venous thromboembolism (VTE). Cleve Clin J Med. 2008;75:S2.
[7] Mount HR, Rich M, Putnam MS. Recurrent venous thromboembolism. Am Fam Physician. 2022;105:377–85.
[8] Bruni-Fitzgerald KR. Venous thromboembolism: an overview. J Vasc Nurs. 2015;33:95–9.
[9] Baumgartner K, Cooper J, Smith A, et al. Liver disease: cirrhosis. FP Essent. 2021;511:36–43.
[10] Ginès P, Krag A, Abraldes JG, et al. Liver cirrhosis. Lancet. 2021;398:1359–76.
[11] Bikdeli B, Jiménez D, Garcia-Tsao G, et al. Venous thromboembolism in patients with liver cirrhosis: findings from the RIETE (Registro Informatizado de la Enfermedad TromboEmbolica) registry. Semin Thromb Hemost. 2019;45:793–801.
[12] Goh J, Goh C, Lim QW, et al. Transcriptomics indicate nuclear division and cell adhesion not recapitulated in MCF7 and MCF10A compared to luminal A breast tumours. Sci Rep. 2022;12:20902.
[13] Hartsough EJ, Weiss MB, Heilman SA, et al. CADM1 is a TWIST1-regulated suppressor of invasion and survival. Cell Death Dis. 2019;10:281.
[14] Zhou Y, Zhou B, Pache L, et al. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. Nat Commun. 2019;10:1523.
[15] Wang Q, Ding J, Yang R. The venous thromboembolism prophylaxis in patients receiving thoracic surgery: a systematic review. Asia Pac J Clin Oncol. 2021;17:e142–52.
[16] Shoag J, Davis JA, Corrales-Medina FF. Venous thromboembolism in pediatrics. Pediatr Rev. 2021;42:78–89.
[17] Stansby G, Berridge D. Venous thromboembolism. Br J Surg. 2013;100:989–90.
[18] Skeik N, Smith JE, Patel L, et al. Risk and management of venous thromboembolism in patients with COVID-19. Ann Vasc Surg. 2021;73:78–85.
[19] Friedman AM. Introduction: obstetric venous thromboembolism. Semin Perinatol. 2019;43:187–8.
[20] Pasta A, Calabrese F, Labanca S, et al. Safety and efficacy of venous thromboembolism prophylaxis in patients with cirrhosis: a systematic review and meta-analysis. Liver Int. 2023;43:1399–406.
[21] Ambrosino P, Tarantino L, Di Minno G, et al. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. Thromb Haemost. 2017;117:139–48.
[22] Zheng P, Ren D, Cong Y, et al. Single-cell sequencing reveals necroptosis-related prognostic genes of glioblastoma. Oxid Med Cell Longev. 2023;2023:2926655.
[23] Zheng X, Zhang C, Zheng D, et al. An original cuproptosis-related genes signature effectively influences the prognosis and immune status of head and neck squamous cell carcinoma. Front Genet. 2022;13:1084206.
[24] Sawai H, Takai-Igarashi T, Tanaka H. Identification of collaborative activities with oxidative phosphorylation in bipolar disorder. Bioinformation. 2015;11:207–16.

[25] Xu Y, Xue D, Bankhead A, 3rd, et al. Why all the fuss about oxidative phosphorylation (OXPHOS). J Med Chem. 2020;63:14276–307.
[26] Wilson DF. Oxidative phosphorylation: regulation and role in cellular and tissue metabolism. J Physiol. 2017;595:7023–38.
[27] Tang JX, Thompson K, Taylor RW, et al. Mitochondrial OXPHOS biogenesis: co-regulation of protein synthesis, import, and assembly pathways. Int J Mol Sci. 2020;21:3820.
[28] Greene J, Segaran A, Lord S. Targeting OXPHOS and the electron transport chain in cancer; molecular and therapeutic implications. Semin Cancer Biol. 2022;86(Pt 2):851–9.
[29] Ashton TM, McKenna WG, Kunz-Schughart LA, et al. Oxidative phosphorylation as an emerging target in cancer therapy. Clin Cancer Res. 2018;24:2482–90.
[30] Spielmann N, Schenkl C, Komlódi T, et al. Knockout of the Complex III subunit Uqcrh causes bioenergetic impairment and cardiac contractile dysfunction. Mamm Genome. 2022;243:229–43.
[31] Luo Y, Medina Bengtsson L, Wang X, et al. UQCRH downregulation promotes Warburg effect in renal cell carcinoma cells. Sci Rep. 2020;10:15021.
[32] Park ER, Kim SB, Lee JS, et al. The mitochondrial hinge protein, UQCRH, is a novel prognostic factor for hepatocellular carcinoma. Cancer Med. 2017;6:749–60.
[33] Gao F, Liu Q, Li G, et al. Identification of ubiquinol cytochrome c reductase hinge (UQCRH) as a potential diagnostic biomarker for lung adenocarcinoma. Open Biol. 2016;6:150256.
[34] Chen W, Yang Z, Chen Y. A novel oxidative phosphorylation-associated gene signature for prognosis prediction in patients with hepatocellular carcinoma. Dis Markers. 2022;2022:3594901.
[35] Menail HA, Cormier SB, Léger A, et al. Age-related flexibility of energetic metabolism in the honey bee Apis mellifera. FASEB J. 2023;37:e23222.
[36] Li Z, Zhang Y, Liu Y, et al. Identification of key genes in Gram-positive and Gram-negative sepsis using stochastic perturbation. Mol Med Rep. 2017;16:3133–46.