DOI: 10.53469/jcmp.2025.07(09).45

Bioinformatics Analysis of Comorbidity Genes in Chronic Kidney Disease and Heart Failure and the Application of Traditional Chinese Medicine

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Abstract: ***Objective:*** *To identify and validate the overlapping genes between Chronic Kidney Disease (CKD) and Heart Failure (HF) using bioinformatics techniques, predict Chinese herbs targeting these genes, and explore the findings in the context of the traditional Chinese medicine theory of "Yang Wei Yin Xian".* ***Methods:*** *The datasets of CKD and HF were obtained from the GEO database. Differential analysis was performed in R 4.4.1, and Venn diagrams were used to select overlapping differentially expressed genes. Enrichment analysis was conducted to investigate the main pathways and biological significance. Three machine learning methods were applied to further screen the genes, and the pROC package was used to plot the receiver operating characteristic curves and calculate the area under the curve. The correlation between characteristic genes and immune cells was studied through immune infiltration analysis. The GeneMANIA database was used to find homologous genes, and the COREMINE Medical database was used to predict Chinese herbs targeting the key genes.* ***Results:*** *A total of 75 overlapping genes between CKD and HF were identified. Gene Ontology (GO) analysis showed enrichment mainly in positive regulation of transferase activity, positive regulation of inflammatory response, etc. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis showed enrichment mainly in the HIF-1 signaling pathway, ferroptosis, etc. Three machine learning methods were used to screen the overlapping genes, and 11 core target genes were obtained by taking the intersection. Five genes (CYBB, MME, IFIT3, FCGR1B, C4orf29) with an AUC>0.7 were identified using the "pROC" package. These five genes were uploaded to the GeneMANIA database, and 25 homologous and functionally related target genes were obtained. Finally, 84 Chinese herbs, including Scutellaria baicalensis, soft-shelled turtle carapace, Polyporus umbellatus, and Gnaphalium affine, were predicted using the COREMINE Medical database. These herbs are mainly heat - clearing and detoxifying herbs, tonics, blood - activating and stasis - resolving herbs, and diuretic and dampness - draining herbs. The conclusions were also explored in the context of the traditional Chinese medicine theory of "Yang Wei Yin Xian".* ***Conclusion:*** *This study found that the five genes FCGR1B, CYBB, C4orf29, MME, and IFIT3 are of great significance in the research and treatment of CKD combined with HF in both traditional Chinese and Western medicine. Chinese herbs with the effects of clearing heat and detoxifying, nourishing Yin and enriching marrow, and inducing diuresis to reduce edema can be helpful in treatment. The screening results were also found to be closely related to the traditional Chinese medicine theory of "Yang Wei Yin Xian".*

Keywords: Bioinformatics, Chronic kidney disease, Heart failure, Traditional Chinese medicine and herbs, Yang Wei Yin Xian.

1. Introduction

In the progression of chronic kidney disease (CKD), heart failure (HF) has emerged as one of its primary fatal complications, garnering increasing attention from researchers [1]. The bidirectional interaction between the kidneys and heart involves complex pathways including overactivation of the renin-angiotensin-aldosterone system (RAAS), chronic inflammation, and oxidative stress [2]. CKD leads to the accumulation of uremic toxins, inflammation, anemia, and increased preload and afterload, thereby exacerbating heart failure. Conversely, conventional treatments for heart failure often contribute to CKD progression, creating a bidirectional relationship between the two conditions [3]. The pathophysiological mechanisms of cardiac remodeling in CKD are multifactorial, encompassing neurohormonal stimulation, cardiac steroid activation, mitochondrial dysfunction, inflammation, innate immune activation, and oxidative stress. Additionally, cardiac metabolic and calcium homeostasis disturbances, macro- and microvascular dysfunction, increased cellular pro-fibrotic responses, accumulation of uremic solutes, and mineral and bone disorders contribute to cardiovascular diseases like HF in CKD [4]. These complex pathophysiological mechanisms limit the efficacy of existing treatment regimens for CKD-associated HF [5]. Traditional Chinese medicine (TCM) offers multiple advantages in managing this condition, including multi-targeted therapy, reduced side effects, and improved quality of life, alongside classical pathomechanism theories such as "yang deficiency and yin tension." Research indicates that Linggui Zhugan Decoction may improve cell pyroptosis by activating the TLR4/NF-κB/IRE1α pathway, thereby alleviating CKD with HF [6]. Moreover, the advancement and widespread application of bioinformatics — including techniques such as screening differentially expressed genes across diseases via gene expression profiling and investigating their mechanisms—can effectively integrate with the multi-targeted action mechanisms of TCM. This holds significant implications both for novel drug development and for providing microscopic-level evidence supporting TCM formulae in treating related diseases. Therefore, this study employs bioinformatics techniques to investigate CKD with HF and explores its relationship with the TCM theory of "Yang deficiency and Yin tension," contributing to the understanding of its mechanisms and the research on integrated Chinese and Western medicine treatments.

2. Materials and Methods

2.1 Differentially Expressed Gene Screening

Searching the GEO database with the keyword "CKD" yielded the dataset "GSE37171," containing 63 CKD samples and 20 healthy control samples, with the detection platform being GPL570. Using "HF" as the keyword, the dataset 'GSE57338' was identified, containing 54 HF samples and 95 healthy control samples, with the GPL11532 platform. After downloading, data cleaning was performed in RStudio 4.4.1, followed by differential analysis using the "limma" package. The criteria for selecting differentially expressed genes were: $|\log2FC| \geq 0.5$ and $P < 0.05$.

2.2 Enrichment Analysis

n RStudio 4.4.1, differentially expressed genes were analyzed using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways via packages such as "org.Hs.eg.db" and "clusterProfiler".

2.3 Machine Learning Algorithms Further Screen for Important Genes

Using packages such as "glmnet", "e1071", and "randomForest", configure the Least Absolute Shrinkage and Selection Operator (LASSO) with alpha=1, family = "binomial", Support Vector Machine (SVM) feature selection with k=10 and halve. above=100 to select 75 variables for model building, Random Forest (RF) with n_trees=500, and display the top 20 genes. Core differentially expressed genes were screened using these three machine learning methods. The intersection of the results from the three machine learning approaches was then calculated.

2.4 Validating the Correlation Between Genes and Diseases Through Diagnostic Efficacy

In RStudio 4.4.1, the validation set was designated as "GSE142153," comprising 7 CKD samples and 10 healthy control samples, with the detection platform being GPL6480. The "pROC" package was used to analyze the intersection genes from machine learning models. Key genes were plotted on receiver operating characteristic (ROC) curves, and the area under the curve (AUC) values were calculated. Genes with AUC > 0.7 were selected. Additionally, correlation analysis was performed between the core differentially expressed genes and the CKD dataset.

2.5 Analyze the Functional Pathways of Core Genes

Perform gene set enrichment analysis (GSEA) on core differentially expressed genes using packages such as "limma." Investigate the high-frequency pathways of core differentially expressed genes and their relationships with CKD and HF.

2.6 Investigating the Characteristics of Immune Cell Infiltration in Diseases and Its Relationship with Core Genes

Immune infiltration analysis was performed using the "CIBERSORT" package to investigate the relationship between disease and 22 immune cell types. Correlation analysis was then conducted with core genes identified through machine learning screening.

2.7 Identify Core Genes and Associated Genes for Traditional Chinese Medicine Prediction

Upload genes screened by machine learning with AUC > 0.7 to the GeneMANIA database to obtain core target genes with homogeneity and functional relevance. Upload all genes to the COREMINE medical database to predict Chinese herbal medicines capable of treating CKD with HF, using a screening criterion of $P < 0.05$.

3. Result

3.1 Differentially Expressed Genes in the Co-morbidity of CKD and HF

Through differential analysis, we identified 4, 490 CKD-specific differentially expressed genes (Figure 1a) and 453 HF-specific differentially expressed genes (Figure 1b). The intersection of these sets yielded 75 co-occurring CKD-HF differentially expressed genes (Figure 1c).

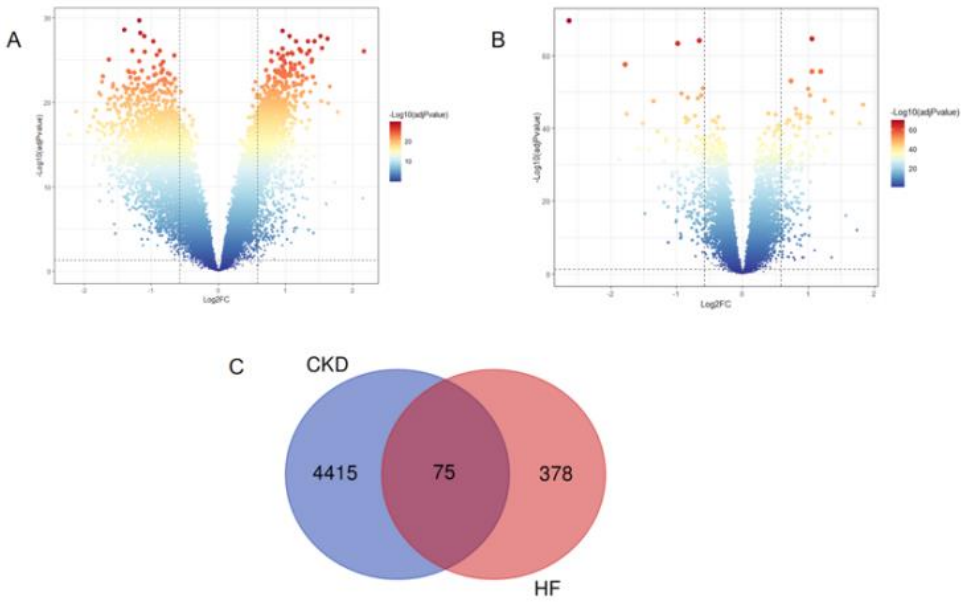


Figure 1: Volcano Plot of Differential Genes in CKD and HF and Venn Diagram of Comorbid Genes

3.2 Co-morbidity Differential Gene GO and KEGG Enrichment Analysis

GO enrichment analysis revealed that these differentially expressed genes primarily participated in biological processes (BP) such as upregulation of inflammatory response and upregulation of transferase activity. In cellular components (CC), they were mainly associated with immune response and inflammation, intracellular material transport, immune receptor activity, and secretion. In molecular function (MF), enrichment was observed in late glycation end-product receptor binding, interleukin-1 receptor activity, and immune receptor activity (Figure 2). KEGG enrichment analysis revealed that these differentially expressed genes were primarily enriched in pathways such as HIF-1 signaling and ferroptosis (Figure 3).

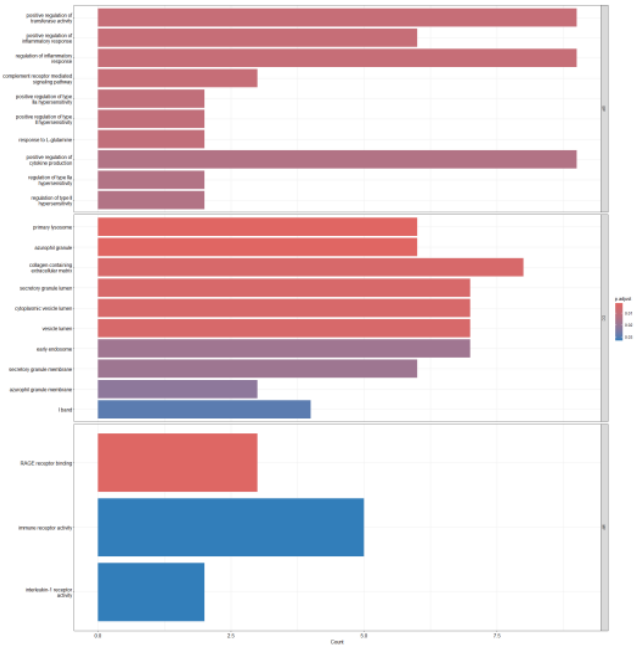


Figure 2: GO Enrichment Analysis

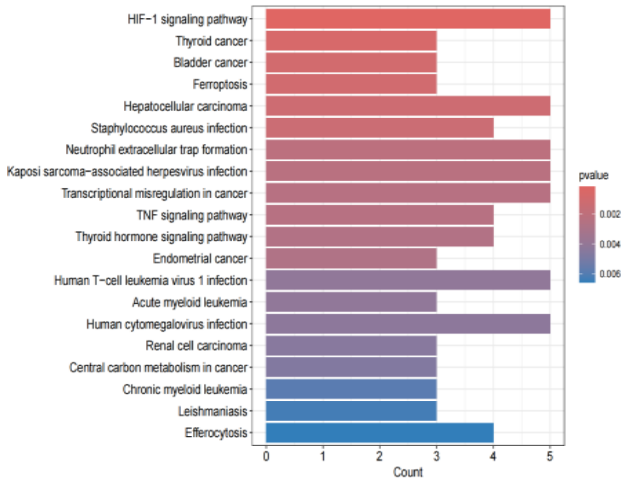


Figure 3: KEGG Enrichment Analysis

3.3 Machine Learning and Core Differentiating Genes

LASSO screening identified 14 core genes among comorbid differential genes (Figure 4), while SVM screening identified 71 (Figure 5A, B) and RF screening identified 40 (Figure 5C, D). The intersection of these sets yielded 11 core comorbid differential genes (Figure 6).

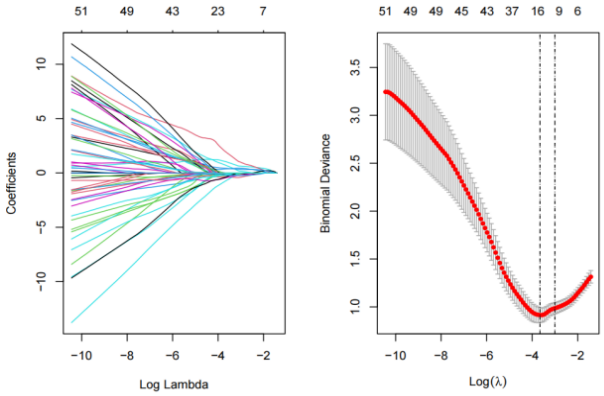


Figure 4: LASSO Coefficient Path Plot and Comparison Plot of Predicted vs. Actual Values

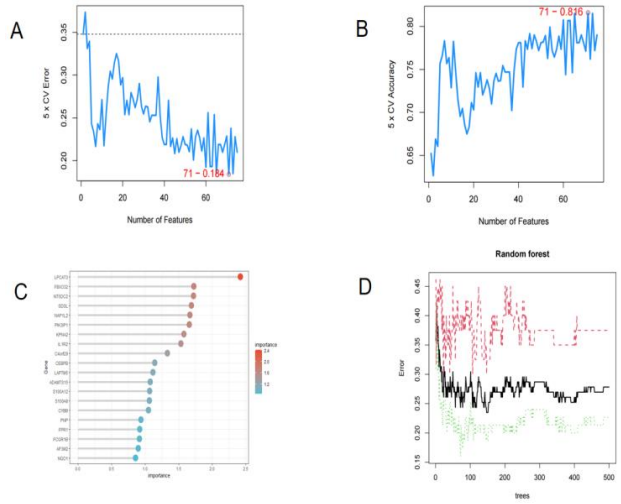


Figure 5: SVM Decision Boundary Plot and Support Vector Plot (A, B), RF Feature Importance Plot and Prediction Error Plot (C, D)

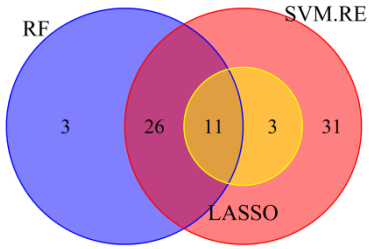


Figure 6: Venn Diagram of Core Differential Genes

3.4 ROC Validation and Correlation Analysis

Using the "pROC" package to calculate 11 co-disease genes yielded 5 genes with AUC > 0.7 (Figure 7). These were FCGR1B, CYBB, C4orf29, MME, and IFIT3. Expression difference box plots were generated (Figure 8), indicating that FCGR1B, CYBB, and IFIT3 were highly expressed in the disease group. CYBB and C4orf29 showed high expression in the control group.

3.5 Conduct GSEA Enrichment Analysis on Core Genes to Investigate Their Primary Functional Pathways.

GSEA enrichment analysis revealed (Figure 9) that the five core genes were enriched in pathways including the Polycomb repressive complex, the citrate cycle, and apoptosis in multiple species (Figure 9).

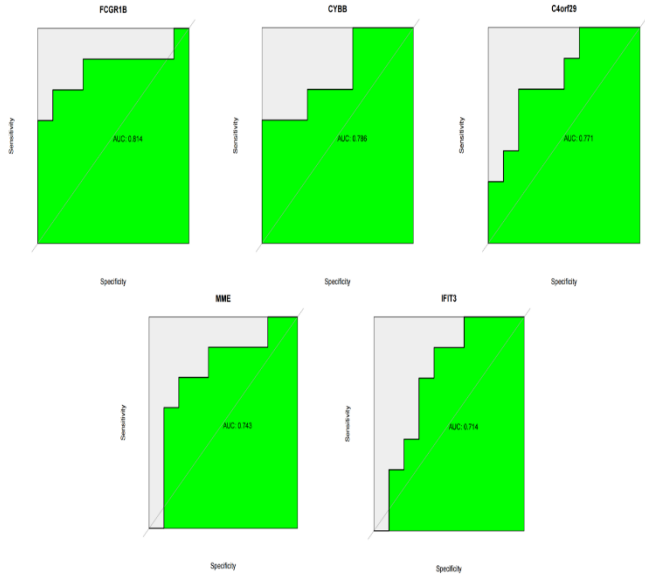


Figure 7: AUC Curve Plot

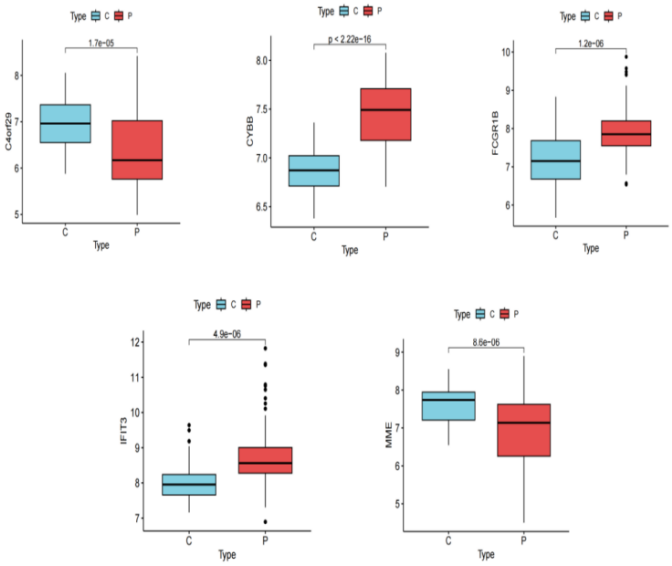


Figure 8: Comparative Boxplot of Core Differential Genes

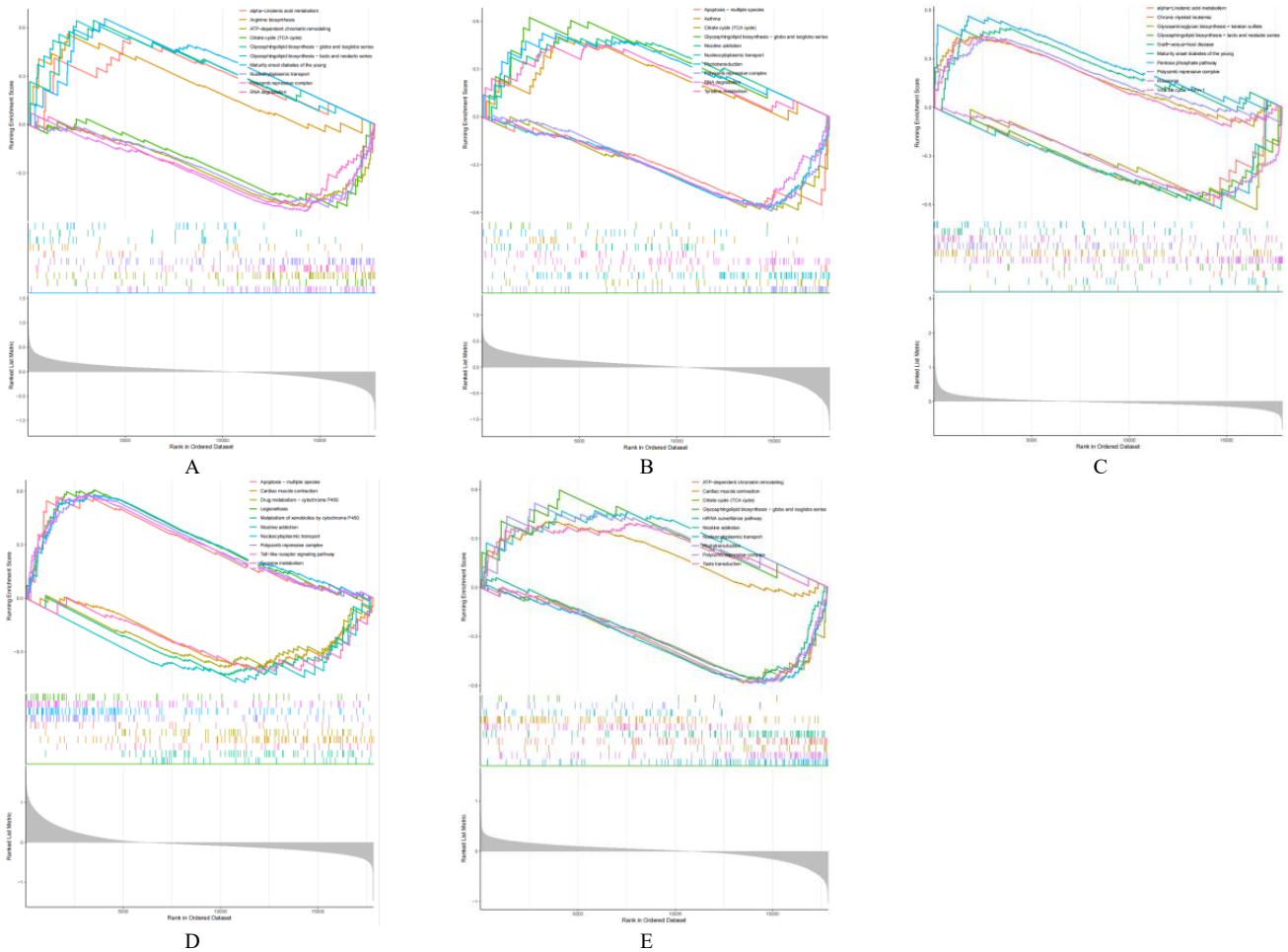
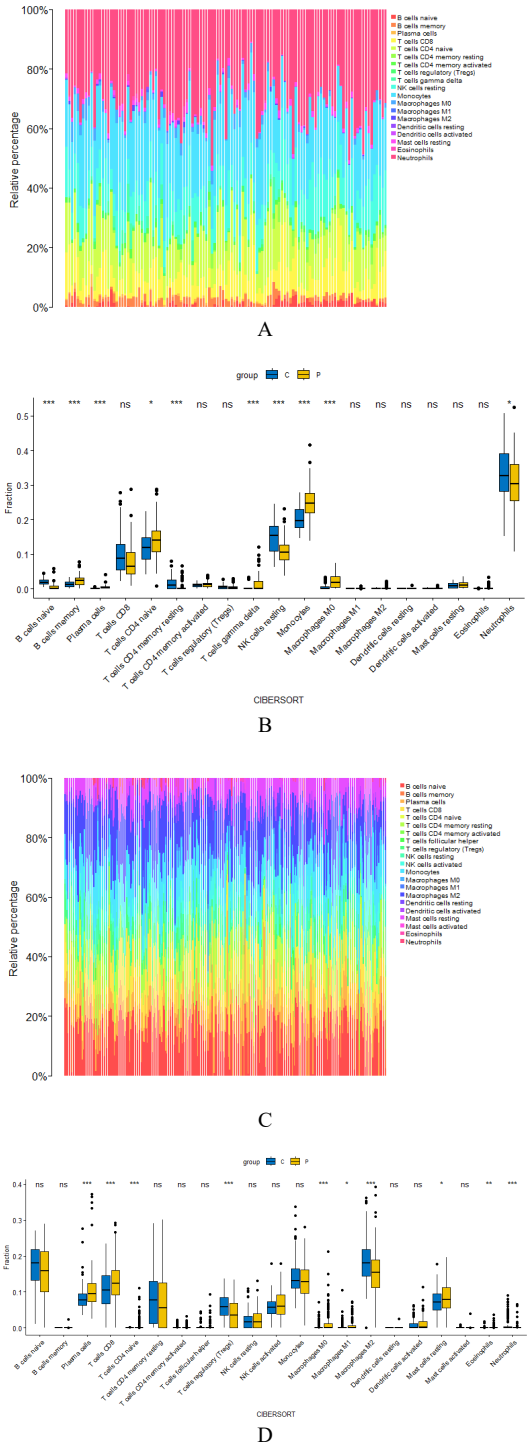


Figure 9: GSEA Enrichment Landscape Plot

Note: Figure A represents (FCGR1B), Figure B represents (CYBB), Figure C represents (C4orf29), Figure D represents (MME), Figure E represents (IFIT3).

3.6 Differential Analysis of CIBERSORT-Based Immune Infiltration in CKD and HF

In CIBERSORT analysis, we observed increased infiltration of neutrophils and resting natural killer cells in CKD samples (Figure 10A, B). Furthermore, memory B cells and plasma cells were highly expressed in the disease group within the CKD dataset. In the CKD samples (Figure 10C, D), infiltrates of resting dendritic cells and activated dendritic cells were elevated. Within the CKD dataset, plasma cells and CD8+ T cells showed high expression in the disease group, while resting memory CD4+ T cells and regulatory T cells exhibited high expression in the control group.

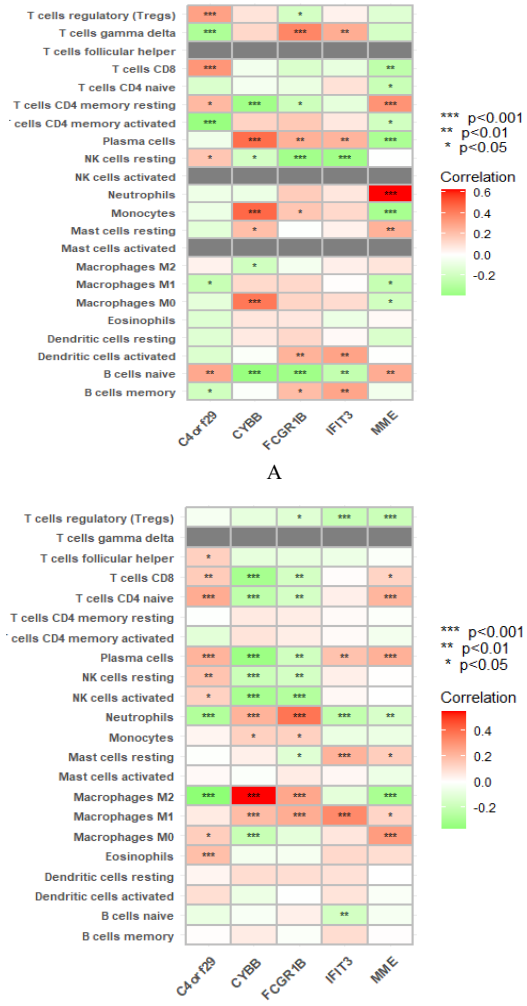


A
B
C
D

Figure 10: CKD Stacked Plot and Comparative Boxplot (A, B), HF Stacked Plot and Comparative Boxplot (C, D)

3.7 Correlation Analysis Between Immunohistochemical Findings and Core Genes

Through correlation analysis between CIBERSORT and five core genes, we found strong associations in CKD samples (Figure 11A): FCGR1B with γδ T cells, CYBB with monocytes, C4orf29 with regulatory T cells, MME with neutrophils, and IFIT3 with resting natural killer cells. In HF samples (Figure 11B), FCGR1B showed significant correlation with neutrophils, CYBB with M2 macrophages, C4orf29 with naive CD4+ T cells, MME with M2 macrophages, and IFIT3 with M1 macrophages.



A
B

Figure 11: Heatmap of Core Differential Genes and CIBERSORT Correlation in CKD (Panel A) and HF (Panel B)

3.8 Screening Genes Highly Correlated with Core Genes Via the GeneMANIA Database and Predicting Traditional Chinese Medicine Effects

After performing correlation analysis on the five identified genes (Figure 12A), they were uploaded to the GeneMANIA database, yielding a total of 25 genes with correlations and connections (Figure 12B). Submitting these 25 genes to the coremine medical database screened out 84 traditional Chinese medicinal herbs. These primarily included heat-clearing and toxin-eliminating herbs, tonifying herbs, blood-activating and stasis-resolving herbs, and diuretic and dampness-draining herbs (Table 1).

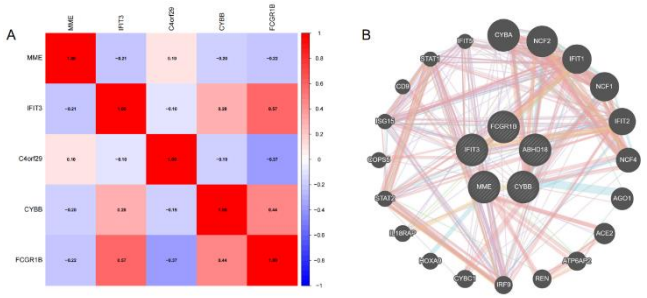


Figure 13: Heatmap of Core Differential Genes Correlation (A), GeneMANIA Gene Interaction Network (B)

Table 1: Co-expressed Genes and Predicted Traditional Chinese Medicines

Co-expressed Genes	Predicted Traditional Chinese Medicines
CYBB	*Euphorbia hirta L., Hemerocallis citrina Baroni, Scutellaria baicalensis Georgi, Syringa oblata Lindl.*
MME	*Hydrocotyle sibthorpioides Lam., Gelidium amansii, Oreoseris delavayi, Asini Corii Colla, Dendrobium nobile Lindl.*
IFIT3	*Dolomiaea souliei, Hyriopsis cumingii, Scutellaria baicalensis Georgi, Cha Shu Gen, Phytolacca acinosa Roxb.*
ABHD18	*BieJia, BieJiaJiao, Porphyra, Vernicia fordii*
CYBA	*Dioscorea polystachya Turcz., Glycyrrhiza uralensis Fisch., Lycium chinense Mill., Corylus heterophylla Fisch.*
NCF2	*Pseudognaphalium affine, Moschus, Polyporus umbellatus, Leonurus japonicus Houtt., Cuscutachinensis Lam.*
IFIT1	*BieJiaJiao, YuBiao, Pseudosciaena crocea*
NCF1	*Pseudognaphalium affine, Inula japonica Thunb., Polyporus umbellatus, Hemerocallis citrina Baroni, JinFeiCao*
IFIT2	*Aesculus chinensis Bunge*
NCF4	*Oenothera biennis L., Sinomenium acuturn, Sesamum indicum L., ChaShuGen*
AGO1	*Brassica rapa L., Plantago asiatica L., Setaria italica, BombyxmoriL.*
ACE2	*Viverra zibetha Linnaeus, Ephedra sinica Stapf, Ephedrae Herba, Cremastra appendiculata, CAULISPOLYGONIMULTIFLORI*
ATP6AP2	*Bombyx mori Linnaeus, Ganoderma lucidum, raisin, Triticum aestivum L*
REN	*Astragalus complanatus R．Br., Jasminum grandiflorum L., Euphorbia kansui T. N. Liou ex S. B. Ho, XuanSheng, ChaShuGen*
IRF9	*Houttuynia cordata Thunb., Carthamus tinctorius L., Panax ginseng C. A. Mey.*
HOXA9	*CanSha, Senna alexandrina Mill., Scolopendridae, Buthus martensii Karsch*
IL18RAP	*ShuiNiuJiao*
STAT2	*MuDanPi, ChiShao, MianHuaGen, Centella asiatica (L.) Urban, Panax notoginseng*
COPS5	*Scutellaria barbata D. Don, Senna alexandrina Mill., JuBai, Citrus reticulata Blanco, JuYe*
ISG15	*Pseudosciaena crocea, jcthyocolla, Celosia cristata L., Semiliquidambar cathayensis Chang*
CD9	*Marsdenia tenacissima, Isodon rubescens, Coffee, DaQingYe, IsatisindigoticaFort.*
STAT1	*BaiYaoZi, Patrinia scabiosaefolia, Abrus pulchellus subsp., Illicium verum, BanMao*
IFIT5	*BieJiaJiao, BieJia, Citrus aurantium L., Citrus reticulata Blanco*

4. Discussion

In traditional Chinese medicine, CKD with HF does not have a corresponding disease name. Based on its symptoms, it falls under the categories of “Guange” (obstruction of the orifices), “edema,” and “palpitations.” Chronic kidney disease progresses over an extended period, often presenting with underlying deficiency and superficial excess. Deficiencies in spleen and kidney qi, blood, yin, and yang lead to pathological products like dampness, blood stasis, and turbid toxins. Treatment typically centers on tonifying deficiency with herbs, supplemented by formulas that activate blood circulation to resolve stasis, drain dampness, and clear turbidity [7]. During heart failure, insufficient heart qi and deficient heart yang result in inadequate blood circulation, further exacerbating pathological products like blood stasis and fluid retention. Traditional Chinese medicine treatment for heart failure primarily employs herbs that benefit qi and warm yang, activate blood circulation and resolve stasis, and promote diuresis and drain dampness [8].

Bioinformatics analysis identified 75 co-occurring genes between CKD and HF, with GO and KEGG enrichment studies revealing that pathways regulating inflammatory responses, ferroptosis, and hypoxia-inducible factor-1 (HIF-1) signaling play critical roles in the progression of CKD with HF.

Regulatory and pro-inflammatory pathways of the inflammatory response promote the activation of inflammatory cells and the release of inflammatory mediators, exacerbating inflammatory damage to the glomeruli and renal interstitium, and inducing renal cell apoptosis and fibrosis [9]. For instance, excessive production of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) promotes inflammatory cell infiltration and the release of inflammatory mediators, exacerbating renal injury [10]. Excessive cytokine production also accelerates cardiomyocyte apoptosis, myocardial remodeling, and deterioration of cardiac function [11]. For instance, cytokines like IL-1β and TNF-α activate apoptotic pathways within cardiomyocytes, leading to reduced myocardial cell numbers and impaired cardiac contractility [12].

Ferroptosis plays a pivotal role in the progression from acute kidney injury (AKI) to CKD. Dysadaptive renal repair following AKI can lead to CKD, with ferroptosis participating in this process through multiple molecular mechanisms and cellular metabolic pathways, including System Xc-, GPx4, and iron homeostasis. Furthermore, ferroptosis can cause pathological changes such as tubular epithelial cell injury and interstitial fibrosis, thereby promoting CKD progression [11]. Research also indicates that ferroptosis can affect cardiomyocyte function and survival through multiple pathways, leading to cardiomyocyte apoptosis, myocardial remodeling, and deterioration of cardiac function [13].

Activation of the HIF-1 signaling pathway promotes renal repair and regeneration, mitigating kidney injury. Furthermore, HIF-1 influences the progression of chronic kidney disease by regulating pathways such as iron metabolism and inflammatory responses [14]. During heart failure, HIF-1 activates a series of downstream target genes, such as VEGF and glucose transporter 1 (GLUT1), to enhance myocardial energy metabolism and oxygen utilization efficiency. It also improves cardiac function in heart failure by inhibiting cardiomyocyte apoptosis and reducing myocardial fibrosis [15].

After screening for co-morbidity-associated genes using three machine learning approaches, we identified five genes: FCGR1B, CYBB, C4orf29, MME, and IFIT3. FCGR1B plays a role in regulating immune responses. In chronic kidney disease, abnormal immune responses may contribute to renal injury, and FCGR1B may influence the progression of renal lesions by modulating inflammatory responses [16]. CYBB also primarily functions in immune regulation, with studies indicating its association with the development of diabetic nephropathy [17]. MME participates in multiple biological processes, including peptide hormone degradation, nervous

system functional regulation, and immune responses. Research has shown that MME exhibits significant differences in the kidneys of lupus mice and can influence BnP metabolism [18, 19]. IFIT3 regulates apoptosis and survival while participating in the innate immune response of glomerular endothelial cells [20, 21]. Furthermore, IFIT3 is crucial in mitochondrial structural alterations during myocardial infarction [22].

GSEA enrichment analysis revealed polycomb repressive complex co-occurrence four times. The polycomb repressive complex pathway influences cell survival and death by regulating apoptosis-related gene expression [23]. The citric acid cycle appeared three times. Disruption of the citric acid cycle may increase renal energy expenditure while impairing substrate metabolism, leading to intracellular accumulation of lipids and glucose intermediates. This, in turn, affects AMPK and mTORC1 activity. Long-term, it may impair citric acid cycle turnover and oxidative phosphorylation, ultimately causing renal injury [24].

CIBERSORT immune infiltration analysis revealed that both initial CD4+ T cells and M0 macrophages were highly expressed in the disease groups across both CKD and HF datasets. Resting memory CD4+ T cells were highly expressed in the control group. Related studies indicate that mechanisms underlying renal macrophage heterogeneity—whether through recruitment of monocyte subsets, regulation of macrophage polarization, or modulation of unique macrophage functions—may aid in developing macrophage-targeted therapies for kidney diseases [25]. A study investigating T cell roles in chronic stress-induced heart failure suggested that CD4+ T cell activation may be inappropriately triggered through mechanisms like neoantigen generation or self-tolerance disruption, thereby mediating adverse remodeling and heart failure progression [26]. This highlights the significant research value of immune cells in treating CKD with HF.

Finally, the GeneMANIA database yielded 25 co-expressed genes highly correlated with the diagnosis and progression of CKD with HF. The Coremine Medical database screened 84 traditional Chinese medicinal herbs. Nine herbs—Daylily, Scutellaria baicalensis, Turtle Shell, Polygonum aviculare, Poria cocos, Fish Brain Stone, Silkworm Sand, Tea Tree Root, and Senna Leaf—appeared twice in the prediction, while Turtle Shell Gel appeared three times. Studies indicate Turtle Shell Gel reduces myocardial hypertrophy, inhibits fibrosis, and improves blood rheology parameters [27]. Daylily possesses antioxidant, antidepressant, anti-inflammatory, and lipid/glucose-lowering effects [28]. Mugwort contains abundant flavonoids that inhibit cellular and humoral immunity, influencing immune organs, specific immunity, and nonspecific immunity [29]. The CYBB gene encodes the β-chain of cytochrome b-245, a component of the NADPH oxidase complex. Within the NADPH family, NOX4 can form an amplification loop via the ROS/PKCα/MAPK/STAT3 cascade, promoting further NOX4 induction and facilitating fibroblast activation and renal fibrosis [30]. Daylily (Hemerocallis fulva) may protect cardiac and renal function in CKD-HF patients by inhibiting NADPH oxidase activity, thereby reducing CYBB-related oxidative stress. These findings demonstrate significant research value for developing novel therapeutics targeting CKD-HF using traditional Chinese medicine. Clinically, they also hold importance for precision medicine approaches in formulating herbal prescriptions from a microscopic perspective. Among the predicted herbs, we observed a predominance of those possessing functions such as nourishing yin and subduing yang, clearing heat and detoxifying, and promoting diuresis to reduce edema. This suggests that replenishing yin deficiency, clearing heat toxins, and eliminating edema may constitute an effective therapeutic approach for treating CKD with HF.

Traditional Chinese medicine posits the theory of “weak yang and taut yin,” originally describing the pulse pattern and pathogenesis of chest pain due to chest obstruction. Subsequent research suggests its initial triggering factors are closely related to heart yang deficiency and kidney yang deficiency failing to ascend and nourish heart yang [31]. Concurrently, the “weak yang” of heart-kidney yang deficiency represents the root cause, while the “string-like yin” manifestations of qi stagnation, blood stasis, phlegm-dampness, and fluid retention constitute the secondary symptoms. These two factors mutually reinforce each other, forming a vicious cycle that constitutes the primary pathogenesis of heart failure [32]. “Yang deficiency” manifests as heart-kidney yang deficiency. Studies indicate that the classical warming formula Fuzi Lizhong Decoction influences energy metabolism by acting on mitochondrial respiratory chain complexes I and IV, regulating Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase activity, thereby treating spleen yang deficiency in rat models [33]. This demonstrates the close relationship between yang deficiency and mitochondrial/energy metabolism, aligning with our analysis screening of IFIT3 and enrichment of the HIF-1 signaling pathway and citric acid cycle. This suggests that in the progression of CKD with HF from a TCM perspective, the sequence from heart-kidney yang deficiency to spleen yang deficiency may represent a key disease pathway. This deficiency disrupts the spleen’s physiological functions — transporting and transforming food and fluids, ascending the clear and descending the turbid, and controlling blood — leading to systemic dysfunction. Concurrently, TCM emphasizes the interdependent relationship between yin and yang—prolonged yang deficiency inevitably triggers yin deficiency, reflecting the complementary principle of “seeking yang within yin and yin within yang.” Research indicates a close association between heart yin deficiency and the development of myocardial fibrosis. Medicinal herbs that nourish yin, invigorate blood circulation, and promote diuresis have demonstrated significant advantages in combating cardiac fibrosis by reducing myocardial cell apoptosis, inhibiting fibroblast activation, and lowering inflammatory response levels [34]. Among the predicted drugs, turtle shell gelatin and turtle shell—traditional Chinese medicines known for nourishing yin, subduing yang, and replenishing essence and marrow—may serve as novel research targets distinct from mainstream yin-nourishing agents like raw rehmannia root and ophiopogon tuber.

“Yin String” primarily manifests as chronic CKD complicated by HF progressing to deficiency of both qi and yang, with concomitant deficiency of qi, blood, yin, and yang. This disrupts the body’s internal environment, causing yin-yang imbalance. Consequently, impaired propulsive warmth leads

to qi stagnation and blood stasis, phlegm-fluid retention, and turbid toxins—symptoms of excess. The emergence of these excess patterns further exacerbates renal failure. The kidneys fail to metabolize and eliminate phlegm, fluid retention, and toxic substances, which accumulate within the body, subsequently impairing the functions of various organs and disrupting the body's yin-yang equilibrium. Numerous existing studies have demonstrated that qi-yin deficiency, blood stasis obstruction, and phlegm-fluid retention with toxic accumulation all play significant roles in exacerbating inflammatory responses [35]. Our aforementioned data clearly indicate that CKD with HF is closely associated with immune cell infiltration and the release of inflammatory mediators. Moreover, the predicted blood-activating and stasis-resolving, heat-clearing and toxin-eliminating herbs have long been widely applied in the clinical treatment of CKD with or without HF. For instance, Professor Zhao Yuyong achieved favorable clinical outcomes by employing methods such as heat-clearing and toxin-eliminating to unblock kidney collaterals, blood-activating and stasis-resolving to unblock kidney collaterals, and dampness-expelling and turbidity-draining to unblock kidney collaterals [36]. Research indicates that Chinese herbal medicines with heat-clearing, toxin-eliminating, stasis-resolving, and collaterals-unblocking properties can modulate inflammatory responses in cardiovascular diseases and intervene in oxidative stress mechanisms of chronic kidney disease [37, 38]. This validates the reliability of our TCM prediction results. Simultaneously, the predicted uncommon TCM herbs provide insights for formulating prescriptions and conducting further pharmacological research on treating CKD with HF. Additionally, studies reveal a close relationship between CKD with HF and ferroptosis. Research indicates that herbs such as Scutellaria baicalensis, Rheum palmatum, and Ligusticum chuanxiong can treat CKD and HF by regulating ferroptosis-related signaling pathways [39, 40].

5. Summary

In summary, this study identified five genes—FCGR1B, CYBB, C4orf29, MME, and IFIT3—as being of significant importance in both Chinese and Western medical research and treatment for CKD with HF. These genes were used to predict Chinese herbal medicines that could guide clinical application, with the findings closely related to the theory of "yang pulse being faint and yin pulse being taut." Pathway analysis of comorbidities in CKD with HF reveals that energy metabolism pathways align with the TCM therapeutic principle of "tonifying qi and warming yang." Furthermore, relevant inflammatory pathways, immune infiltration studies, and the predicted therapeutic effects of Chinese herbal medicines—including anti-inflammatory, antioxidant, and anti-fibrotic actions—are closely related to TCM treatment methods such as "promoting blood circulation and removing blood stasis" and "draining dampness and reducing turbidity." This demonstrates that the TCM treatment approach for CKD with HF complements modern medical research. However, this study is limited to bioinformatics analysis and lacks further clinical, cellular, or animal experimental validation. Additionally, the restricted sample size of the dataset may lead to potential flaws such as overfitting and bias in the analytical results. In summary, this study employed bioinformatics techniques to investigate the co-morbidity mechanisms of CKD with HF, predict potential biomarkers, prognostic markers, and therapeutic targets, and identify TCM formulations with potential clinical efficacy. These findings were discussed in light of TCM theory, contributing to future research in this field.

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