ORIGINAL RESEARCH

Assessment of HMGB1 and NLRP3 in Determining Efficacy and Prognosis in Hemodialysis Patients with Chronic Renal Failure

Xiaomin Huang, MM; Shuixian Wang, MM; Kai Yan, MM; Chang Liu, MM; Qi Zhang, MM; Nan Wu, MM

ABSTRACT

Background • In chronic renal failure (CRF), evaluating treatment efficacy and predicting prognosis is crucial. High Mobility Group Protein B1 (HMGB1) and Nod-like Receptor Protein 3 (NLRP3) were chosen as key markers in chronic renal failure to elucidate their roles in treatment response and prognosis, offering potential insights for enhancing patient care strategies.

Objective • This study aims to analyze the clinical impact of HMGB1 and NLRP3 in patients with CRF undergoing hemodialysis. We investigated the relationship between HMGB1 and NLRP3 levels, the efficacy of hemodialysis treatment, and the prognosis for one-year survival.

Methods • An observational study was conducted. The study included 62 CRF patients (Group A) admitted to our hospital from May 2020 to August 2022, and 40 healthy individuals undergoing routine medical check-ups during the same period (Group B). We compared the levels of HMGB1 and NLRP3 in the peripheral blood of Group A and Group B. Furthermore, we assessed changes in HMGB1 and NLRP3 before and after hemodialysis in CRF patients to evaluate treatment efficacy and prognostic indicators for one-year survival.

Results • Group A exhibited significantly lower HMGB1 expression and higher NLRP3 expression compared to Group B. ROC curve analysis demonstrated that the areas under the curve (AUCs) for HMGB1 and NLRP3 in predicting effective hemodialysis for CRF were 0.884 (95% CI: 0.800-0.968) and 0.721 (95% CI: 0.594-0.848), respectively. The AUCs for HMGB1 and NLRP3 in predicting death from CRF were 0.885 (95% CI: 0.804-0.967) and 0.935 (95% CI: 0.875-0.995), respectively.

Conclusions • Both HMGB1 and NLRP3 levels serve as valuable indicators for assessing the efficacy and prognosis of CRF patients undergoing hemodialysis. (*Altern Ther Health Med.* 2024;30(10):478-482).

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INTRODUCTION

Chronic renal failure (CRF) encompasses a gradual and persistent decline in renal function due to renal diseases.[1] As renal damage initiates, the deterioration of renal function occurs at varying rates, ultimately leading to end-stage renal failure, posing a serious threat to patients' lives.[2] Currently, there is no definitive cure for CRF. Therefore, multifaceted approaches, including kidney transplantation and hemodialysis, are commonly employed to mitigate disease progression.[3]

In recent years, advancements and widespread adoption of dialysis technology have moderately enhanced the quality of life for CRF patients undergoing hemodialysis. However, the mortality rate remains largely high.[4] Hence, a swift and precise assessment of hemodialysis effectiveness in CRF patients is paramount to safeguarding prognosis and overall health. While kidney diseases may originate from various etiologies, a majority progress to glomerulosclerosis or renal interstitial fibrosis.[5] Existing evidence associates glomerular sclerosis and renal interstitial fibrosis with inflammatory cytokines and oxidative stress (OS).[6]

As research progresses, the etiology of glomerular sclerosis and renal interstitial fibrosis has gained increased attention in the treatment of renal diseases. High mobility group protein B1 (HMGB1), a widely distributed binding protein in eukaryotic nuclei, participates in diverse inflammatory reactions through ligand binding to glycoylation end-product receptors.[7] Inflammatory responses and infections can impact glomerular and renal interstitial function. Furthermore, the downregulation of nod-like receptor protein 3 (NLRP3), a member of the pattern recognition receptor family, mitigates mitochondrial dysfunction, thereby alleviating renal fibrosis in CRF.[8]

A recent study by Liu Y, et al.[9] confirmed the close association between HMGB1 and disease progression in

hepatitis B patients with CRF, suggesting its potential as an evaluation indicator for prognosis and survival. NLRP3, given its mediating role in an inflammatory response, is considered pivotal in the diagnosis and treatment of multifactorial nephropathy, including CRF.[10] It indicates a close relationship between HMGB1, NLRP3, and the pathological progression of CRF, suggesting the potential for assessing the efficacy of hemodialysis treatment. However, there is a lack of comprehensive studies confirming these notions.

Therefore, the present study aims to evaluate the clinical outcomes and prognosis of CRF patients' post-hemodialysis treatment using HMGB1 and NLRP3, aiming to offer reference and guidance for future clinical re-administration of hemodialysis treatment. Our findings offer a potential avenue to assess hemodialysis efficacy. By providing valuable insights, it paves the way for informed clinical decisions and advancements in hemodialysis treatment strategies.

MATERIALS AND METHODS

Study Design

In this observational study, a total of 62 CRF patients admitted to our hospital from May 2020 to August 2022 were included which constitute Group A, alongside 40 healthy individuals undergoing routine medical check-ups during the same period constitute the Group B. The primary objective was to compare the levels of HMGB1 and NLRP3 in the peripheral blood of Group A and Group B, aiming to determine any significant differences that could contribute to the understanding of the relationship between these markers and CRF. All patients understood the study procedures and volunteered to participate. This study was conducted after approval by the Medical Ethics Committee.

Inclusion and Exclusion Criteria

Inclusion criteria for Group A were as follows: (1) Meeting the diagnostic criteria for CRF as stipulated by the National Kidney Foundation;[11] (2) Diagnosis of CRF confirmed through ultrasound, CT, and X-ray examination' (3) Absence of medication such as oxidant and lipid-lowering agents; (4) No signs of infection before enrollment. Exclusion criteria were as follows: (1) Renal artery stenosis; (2) Previous history of blood transfusion, surgery, or use of hormones and immunosuppressants.

Additionally, 40 concurrent healthy controls who underwent routine physical examinations in our hospital were selected as Group B. Inclusion criteria for Group B were as follows: (1) Absence of related organic diseases, immune, or systemic diseases; (2) No hepatorenal dysfunction. Exclusion criteria for Group B were as follows: (1) Presence of other malignant tumors; (2) Low compliance.

Patient Care Protocols in Chronic Renal Failure Management

Hemodialysis Methods. Water and salt management, along with blood pressure and blood sugar control, were administered to the enrolled CRF patients.[12] The metabolic environment of patients with acidosis was also corrected. Hemodialysis was conducted using maintenance hemodialysis equipment (IBP Hemodialysis M99XP), with a bicarbonate dialysate (Baxter International Co., Ltd.) concentration, dialysate volume, and blood flow set at 2.5%, 500 mL/min, and 200300 mL/min, respectively. Hemodialysis sessions were conducted 23 times per week, each lasting 4 hours.

Serum Index Detection. All participants observed an 8-hour overnight fast, after which 4 ml of cubital venous blood was drawn the next morning. The samples were allowed to naturally solidify at room temperature and were then centrifuged at 3000r/min for 15 minutes to obtain the supernatant. Some of these samples underwent testing using an automatic biochemical analyzer (manufacturer: Shandong Biobase Industry Co., Ltd., Registration number: Lu Machinery Registration No.: 20192220157, model specification: BK-1200) for HMGB1 and NLRP3 levels. Concurrently, another portion of the samples was refrigerated at -80°C for future analysis.

Outcome Measures

Comparative Analysis of General Data. General data for both cases and controls were carefully collected for a comprehensive comparison. Parameters such as sex ratio, age, disease duration, complications, triglyceride (TG) levels, total cholesterol (TCH), serum creatinine (Scr), and hemoglobin (HGB) levels were systematically assessed.

HMGB1 and NLRP3 Level Comparison. HMGB1 and NLRP3 levels were diligently measured and compared between groups A and B. This assessment aimed to detect any significant variations in these biomarkers between chronic renal failure patients and healthy controls.

Evaluation of HMGB1 and NLRP3 Dynamics in Group A. Alterations in HMGB1 and NLRP3 levels were carefully observed and recorded for all patients in Group A. This included a detailed examination of changes occurring both before and after hemodialysis treatment, providing valuable insights into the impact of the intervention on these key biomarkers.

Assessment of Efficacy. After hemodialysis treatment, patients were categorized into either the effective or ineffective group based on predefined criteria.[13] The assessment criteria were as follows: (1) marked response: disappearance or significant improvement of symptoms and signs, accompanied by a decrease in Scr ≥20%; (2) response: improved symptoms and signs, with a decrease in Scr by <20%; (3) stable disease: no progression of the disease or alleviation of symptoms and signs; and (4) ineffective: not meeting the aforementioned criteria.

ROC curves, derived from pre-treatment HMGB1 and NLRP3 levels, were employed to evaluate their predictive value in assessing efficacy among patients undergoing hemodialysis for CRF. The total number of cases with effective treatment was determined by calculating the sum of marked response, response, and stable disease cases, while the remaining cases were classified as ineffective.

Total Effective Cases=Marked Response Cases + Response Cases + Stable Disease Cases

Table 1. Comparison of Clinical Baseline Data between Two Groups

Variables	Group A (n = 62)	Group B (n = 40)	t/χ^2	*P value*
Sex			0.048	.827
Male	37(59.68%)	23(57.50%)		
Female	25(40.32%)	17(42.50%)		
Age	50.92±7.92	49.63±9.46	1.478	.143
Duration of Disease (Years)	3.80±1.40	3.79±1.36	0.938	.350
Comorbidity			0.310	.856
Coronary Heart Disease	19(30.65%)	13(32.50%)		
Hypertension	26(41.94%)	18(45.00%)		
Diabetes Mellitus	17(27.42%)	9(22.50%)		
TG (mmol/L)	3.42±0.97	3.43±0.98	1.479	.142
TCH (mmol/L)	1.13±0.53	1.13±0.49	0.000	>.999
Scr (mmol/L)	202.65±53.20	71.89±22.43	7.603	<.001
HGB (g/L)	77.40±11.60	123.72±18.04	14.640	<.001

Note: Data presented as mean ± standard deviation ($\bar{x} \pm s$) or [n (%)]. t/χ^2: Student's t test/Chi-square test; P-values in bold indicate statistical significance ($P < .05$).

Abbreviations: TG, Triglycerides; TCH, Total Cholesterol; Scr, Serum Creatinine; HGB, Hemoglobin.

One-Year Follow-up After Hemodialysis. All patients were diligently followed up for a duration of 1 year post-hemodialysis, and no cases were lost to follow-up. Subsequently, post-treatment HMGB1 and NLRP3 levels were further analyzed to construct ROC curves, aiming to ascertain their predictive value in determining mortality from CRF.

Statistical Analysis

For data analysis, SPSS version 21.0 was employed in this study. A χ^2 test was conducted to compare categorical variables, which were presented as the number of cases. The LSD-t test was applied for the comparison of continuous variables, presented as ($\bar{x} \pm s$) where $\bar{x}$ represents the mean and 's' represents the standard deviation. The significance of HMGB1 and NLRP3 in assessing treatment efficacy and prognosis among CRF patients was determined through the construction of receiver operating characteristic (ROC) curves. Statistically significant differences were identified when $P < .05$.

RESULTS

Comparison of Clinical Baseline Data

Groups A and B exhibited similarity in clinical baseline data, including sex, age, course of disease, complications, TG) level, and TCH level ($P > .05$). However, statistically significant differences were observed in Scr and HGB levels ($P < .05$). Refer to Table 1 for detailed information.

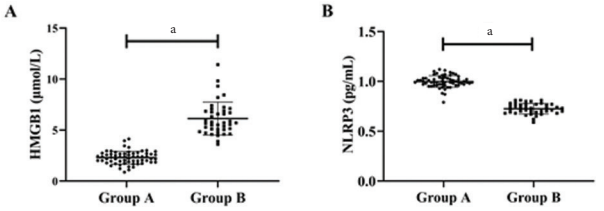
Comparison of HMGB1 and NLRP3 Detection Results

In Group A, HMGB1 expression was lower at 2.29±0.62 μmol/L, whereas NLRP3 expression was higher at 1.00±0.06 pg/mL compared to Group B, indicating a statistically significant difference ($P < .05$). Refer to Figure 1 for a visual representation of these findings.

HMGB1 and NLRP3 Alterations in CRF Patients Before and After Hemodialysis

In comparison with the baseline (before hemodialysis), CRF patients exhibited a significant reduction in HMGB1 levels and a statistically elevated NLRP3 expression after hemodialysis ($P < .05$). Please refer to Figure 2 for a graphical representation of these alterations.

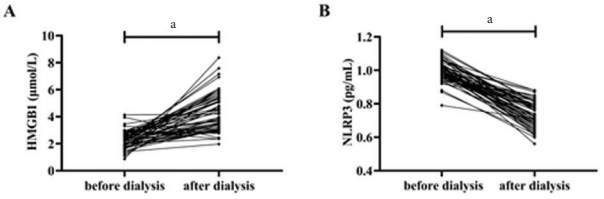
Figure 1. Comparison of HMGB1 and NLRP3



[a]indicates statistical significance ($P < .05$).

Note: (A) Comparison of HMGB1 in Groups A and B. (B) Comparison of NLRP3 in Groups A and B.

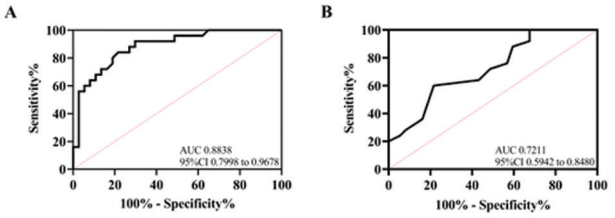
Figure 2. HMGB1 and NLRP3 Alterations in CRF Patients Before and After Hemodialysis



[a]indicates statistical significance ($P < .05$).

Note: (A) Comparison of HMGB1 Before and After Hemodialysis Treatment. (B) Comparison of NLRP3 Before and After Hemodialysis Treatment.

Figure 3. ROC Analysis of HMGB1 and NLRP3 for Evaluating Hemodialysis Treatment Efficacy in Chronic Renal Failure (CRF) Patients.



Note: Figure 3 depicts the value of HMGB1 and NLRP3 in assessing the efficacy of hemodialysis in chronic renal failure (CRF) patients. (A) Presents the ROC curve of HMGB1 for evaluating hemodialysis treatment effect, and (B) shows the ROC curve of NLRP3 for assessing hemodialysis treatment effect.

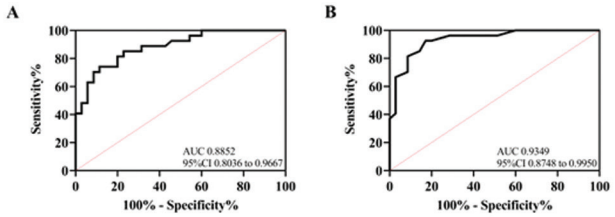
Value of HMGB1 and NLRP3 in Evaluating Efficacy of Hemodialysis in Patients with CRF

Through ROC curve analysis, the areas under the ROC curve (AUCs) for HMGB1 and NLRP3 in assessing the efficacy of hemodialysis for CRF were determined to be 0.884 (95% CI: 0.800-0.968) and 0.721 (95% CI: 0.594-0.848), respectively. Refer to Figure 3.

Value of HMGB1 and NLRP3 in Evaluating Prognosis of CRF Patients Treated by Hemodialysis

All patients successfully completed the 1-year follow-up. The results of ROC curve analysis demonstrated that the

Figure 4. ROC Analysis of HMGB1 and NLRP3 for Evaluating Prognosis in Chronic Renal Failure (CRF) Patients After Hemodialysis Treatment.



Note: ROC curves illustrate the diagnostic performance of HMGB1 and NLRP3 in predicting death within 1 year after hemodialysis treatment, providing valuable prognostic insights for CRF patients.

AUCs for HMGB1 and NLRP3 in predicting death from CRF in these patients were 0.885 (95% CI: 0.804-0.967) and 0.935 (95% CI: 0.875-0.995), respectively. Refer to Figure 4.

DISCUSSION

Chronic renal disease (CRD) is intricately linked to cellular energy dynamics, particularly in the context of adenosine triphosphate (ATP) utilization. As the disease gradually advances, the continual destruction of nephrons and increased apoptosis of renal intrinsic cells demand a sufficient supply of ATP to sustain normal bodily functions.[14] Mitochondria serve as the primary site for ATP synthesis within cells. When mitochondrial dysfunction occurs, there is an inadequate synthesis of ATP, leading to the release of excessive oxygen free radicals and inflammatory factors. These processes collectively contribute to the pathogenesis of CRF, fostering its progression toward end-stage renal disease (ESRD).[15]

Effectively regulating the mitochondrial function of CRF patients and managing inflammation and oxidative stress are important aspects of treatment. In contemporary clinical practice, hemodialysis has emerged as a crucial intervention for individuals with end-stage renal failure. It plays a significant role in efficiently removing excessive physiological metabolites and accumulated toxins from the patient's body, as well as in balancing water-electrolyte and acid-base levels, ultimately contributing to the control of systemic inflammation.[16]

The critical factor contributing to hemodialysis failure is the loss of vascular access function, primarily driven by thrombosis. Identifying monitoring factors that influence bodily changes, including thrombosis and inflammatory feedback, holds significant clinical importance. This identification process is crucial for evaluating the therapeutic efficacy of hemodialysis in CRF patients. Our motivation for undertaking this research stems from the need to address critical clinical challenges, specifically in identifying factors that impact hemodialysis outcomes for individuals with CRF.[17]

The analysis of HMGB1 and NLRP3 levels revealed significantly lower HMGB1 and noticeably higher NLRP3 in group A compared to group B. These findings suggest that the progression of CRF can induce alterations in the levels of these two indicators, and their judicious use may aid in monitoring the condition. After hemodialysis treatment, patients with CRF exhibit reduced HMGB1 and elevated NLRP3 levels. Notably, inhibiting the anticoagulant system, promoting platelet aggregation, and triggering the release of inflammatory factors are key influencing factors that contribute to thrombosis, directly impacting the efficacy of hemodialysis.[18,19]

Mitochondrial dysfunction results in the excessive generation of reactive oxygen species (ROS) surpassing the body's scavenging capacity. It leads to the accumulation of ROS, triggering related signal pathways that contribute to electrolyte and acid-base imbalances during hemodialysis.[20] HMGB1, a DNA-binding non-histone protein with diverse biological functions, plays a crucial role in this context.[21] Notably, high-dose HMGB1 has been demonstrated to amplify thrombin activity and promote platelet aggregation. It occurs through the inhibition of thrombin-thermoregulator activity and the activation of antithrombotic protein C, ultimately inducing the formation of microvascular thrombosis.[22,23]

Moreover, the activation of the NLRP3 inflammasome can exacerbate mitochondrial dysfunction in the renal tubules of proteinuria nephropathy, leading to oxidative stress and apoptosis. This inflammasome is triggered by mitochondrial damage and autophagy, inducing tissue inflammation and establishing a positive feedback loop between inflammation and mitochondrial dysfunction.[24] Consequently, the constrained increase in HMGB1 and the reduction of NLRP3 in humans may further potentiate thrombosis. This occurs through the anticoagulant effect of HMGB1, the promotion of platelet aggregation, and NLRP3 stimulation of mitochondrial metabolic function.

Furthermore, the results from ROC curve analysis revealed that the AUCs for HMGB1 and NLRP3 in assessing the efficacy of hemodialysis treatment for CRF were 0.884 (95% CI: 0.800-0.968) and 0.721 (95% CI: 0.594-0.848), respectively. These findings imply that, in the future, monitoring the expression levels of HMGB1 and NLRP3 in CRF patients can serve as a valuable tool for evaluating the effectiveness of hemodialysis treatment. This proactive approach allows for early intervention when necessary.

Our extended follow-up revealed that the AUCs for HMGB1 and NLRP3 expression in predicting mortality from CRF were 0.885 (95% CI: 0.804-0.967) and 0.935 (95% CI: 0.875-0.995), respectively. Existing evidence indicates that HMGB1 possesses the capacity to activate monocytes and macrophages, leading to the synthesis and release of pro-inflammatory cytokines in abundance. This, in turn, significantly increases inflammatory responses and establishes a positive feedback loop, ultimately contributing to the induction of thrombosis.[25]

Additionally, the activation of the NLRP3 inflammasome, induced by various stimulators, leads to its oligomerization. The subsequent polymerization of apoptosis-associated speck-like proteins, associated with the adaptor protein apoptosis, into the inflammasome further increases the release of pro-inflammatory factors. This exacerbates renal tissue inflammation, expediting the progression of the disease

in CRF patients.[26] Therefore, the limited improvement in outcomes for CRF patients may be attributed to the exacerbation of inflammation.

Our study uncovered insights into HMGB1 and NLRP3 dynamics during hemodialysis in chronic renal failure. Their distinct expression patterns, reflected in ROC AUCs signal hemodialysis efficacy and serve as potent prognostic indicators for CRF mortality, highlighting their enduring diagnostic relevance. These findings emphasize the multifaceted roles of HMGB1 and NLRP3 in influencing inflammatory responses, thrombosis, and disease progression in CRF patients. Consequently, integrating the monitoring of these biomarkers into clinical practice holds promising potential for early intervention, contributing to improved treatment outcomes and enhanced patient care.

Study Limitations

Despite the valuable findings, this study has inherent limitations. The relatively small sample size may impact the generalizability of results. Additionally, the observational nature of the study design limits the establishment of causal relationships. Variability in patient characteristics and treatments could introduce confounding factors, influencing the robustness of our conclusions. Future research with larger cohorts and interventional approaches is warranted to address these limitations and provide more definitive insights.

CONCLUSION

In conclusion, our study reveals that NLRP3 elevation and HMGB1 reduction are noteworthy biomarkers in CRF patients undergoing hemodialysis. Assessing the expression of both markers proves valuable in evaluating clinical outcomes and prognosticating post-hemodialysis outcomes for CRF patients. However, certain limitations in our research, such as inconsistent identification of influencing factors for NLRP3 and HMGB1 concerning hemodialysis efficacy, underscore the need for further exploration. Future investigations should explore additional factors like platelet aggregation, mitochondrial function, and thrombosis, enhancing the scientific rigor of clinical diagnosis and treatment strategies. Such efforts could pave the way for innovative approaches to timely intervention and complication reduction in patients undergoing hemodialysis for CRF.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

Nan Wu designed the study, Xiaomin Huang wrote the manuscript, Shuixian Wang and Kai Yan collected and analyzed data, Chang Liu and Qi Zhang revised the manuscript, and Xiaomin Huang and Shuixian Wang made equal contributions to this work. All authors read and approved the final submitted manuscript.

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None.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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