ORIGINAL RESEARCH

Effect of Hepatitis C Virus Infection on Liver Function, T Cell Immunity, and Mortality Risk in Maintenance Hemodialysis Patients

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Abstract

Objective

This retrospective study explored the clinical impact of hepatitis C virus (HCV) infection in maintenance hemodialysis (MHD) patients through comprehensive analysis of liver/renal function parameters, cellular immunity profiles, and long-term survival outcomes.

Methods

The study enrolled 28 HCV-infected MHD patients (MHD-HCV group), 28 HCV-negative MHD patients (MHD group), and 21 healthy controls (NC group) retrospectively. Liver and renal functions, lymphocyte subset analysis, and interleukin-10 (IL-10) levels were assessed. Overall survival at a median follow-up of 4 years was compared between the MHD-HCV and MHD groups.

Results

Biochemical analysis demonstrated significantly elevated liver enzymes in the MHD-HCV group compared to MHD group, with mean alanine aminotransferase (ALT) levels of 26.6 ± 18.6 vs. 10.1 ± 7.1U/L ($P < 0.001$) and aspartate aminotransferase (AST) levels of 20.0 ± 9.0 vs. 11.8 ± 5.5U/L ($P = 0.001$).Furthermore, the MHD-HCV group had elevated total bile acid (7.70 ± 7.17 vs. 3.44 ± 1.75, $P = 0.007$), total protein (67.9 ± 5.2 vs. 63.9 ± 5.6, $P = 0.012$), globulin (31.1 ± 5.9 vs. 26.5 ± 3.6, $P = 0.003$). Immunological profiling revealed significant upregulation of both regulatory T cells (Tregs: 4.48 ± 2.94 vs. 2.48 ± 1.81, $P < 0.001$) and interleukin-10 (IL-10: 78.7 ± 45.1 vs. 34.2 ± 15.2, $P < 0.001$).The patients in the MHD-HCV group had higher mortality risk compared with those in the MHD group ($\chi 2=4.383$, $P = 0.036$).

Conclusion

HCV infection in MHD patients leads to non-negligible liver dysfunction, elevated Tregs and IL-10, as well as higher mortality.

Keywords: Hepatitis C virus; maintenance hemodialysis; liver function; regulatory T cells; interleukin-10.

Introduction

Maintenance hemodialysis (MHD) is a crucial treatment modality for patients with advanced chronic kidney disease and end-stage renal disease (ESRD)[1]. Notably, the prevalence of HCV infection is higher in patients undergoing MHD than in those not undergoing renal hemodialysis[2]. Recent statistics indicate that the prevalence of HCV infection among patients undergoing MHD ranges from 3% to 75%, depending on various factors, including geographical region, ethnic background, and sex[1,3-5]. A large-scale meta-analysis revealed that chronic HCV infection acts not merely as a driver of hepatic disease progression, but also significantly elevates the risk of chronic kidney disease in the general population (adjusted hazard ratio [aHR] = 1.43) through promoting atherosclerosis and metabolic dysregulation. Moreover, it independently increases all-cause mortality (relative risk [RR] = 1.35) and cardiovascular mortality (aHR = 1.21) among maintenance dialysis patients[6]. HCV infection is associated with higher risks of mortality, hospitalization, and reduced quality of life, and serves as an unfavorable prognostic factor for patients undergoing renal hemodialysis and transplantation[7-9].

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are important markers of hepatocyte damage[10]. Patients infected with hepatitis C often suffer from varying degrees of liver damage, with notable elevations in liver function indicators like ALT and AST, which reflect inflammatory activities in the liver parenchyma[11,12]. However, studies have shown that the ALT and AST levels of hemodialysis patients infected with viral

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hepatitis are not different from those of the normal control group, both falling within the normal reference range (40 and 46 IU/L, respectively)[13]. Moreover, large sample analysis in the United States lasting five years showed that higher AST levels of >20 IU/L are incrementally associated with higher mortality in MHD patients. In contrast, AST levels in the 15–20 IU/L range are associated with the greatest survival[14]. Regrettably, few studies have explored the consequences of chronic HCV infections—characterized by unaltered ALT and AST levels—on renal function, immune status, and long-term outcomes in MHD patients.

HCV clearance is mediated by T cells and the innate immune response. ESRD patients show increased specific proinflammatory T cell and monocyte subsets, suggesting premature immunological aging[15]. Uremic toxins cause immune system disorder, resulting in a micro-inflammatory state, and hemodialysis can increase the inflammatory state[16]. Immunologically, ESRD involves disorders within the immune system, characterized by the coexistence of immune activation and suppression. The impact of hemodialysis, especially when HCV infection is present, on the immune function of patients, is complex and remains unclear.

This study aimed to investigate the impact of HCV infection on patients undergoing MHD by examining differences in liver, renal, and immune functions across three groups: MHD-HCV (MHD patients with HCV infection), MHD (MHD patients without HCV infection), and NC (normal controls). Additionally, we explored the potential long-term effects of HCV infection on survival outcomes in MHD patients, with a focus on understanding its broader clinical implications.

Methods

Study Design

This retrospective cross-sectional study was conducted at the First Affiliated Hospital of Xi'an Jiaotong University between September 2017 and November 2021. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University(XJTU1AF2018LSK-228). Due to the retrospective nature of the study, the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University waived the need of obtaining informed consent.

Population

The participants were divided into three groups: patients with and those without HCV infection undergoing MHD at the Department of Blood Purification at the First Affiliated Hospital of Xi'an Jiaotong University, and normal controls (NC group, n=21) from the Department of Health Medicine. MHD patients with HCV infection (MHD-HCV group, n=28) and MHD patients without HCV infection (MHD group, n=28) were matched by age, gender, and hemodialysis duration. The 4-year survival status of the MHD patients was investigated through medical records.

The inclusion criteria for MHD patients were as follows: (1) aged older than 18 years; (2) patients with or without HCV infection undergoing MHD. HCV infection in the study was defined as having a diagnosis of hepatitis C according to the current guidelines, anti-HCV positivity for more than 6 months, and a positive serum HCV RNA test result[17]. (3) MHD patients should have undergone MHD for at least 6 months, with a stable dialysis frequency and no interruption or major adjustments. MHD patients were excluded if they met any of the following criteria: (1) had a history of blood transfusion or surgeries in the past 3 months; (2) had any active or recent infection within the past 3 months; (3) had coexisting organic diseases, such as severe gastrointestinal or metabolic disorders; (4) had received antiviral treatment within one year before the study; (5) had a history of kidney transplantation; or (6) had severe malnutrition, liver disease (except for the MHD-HCV group with HCV infection), abnormal cardiopulmonary function, autoimmune disease, or malignant tumors.

Normal individuals who met the following criteria were included in the study: (1) were over 18 years of age; (2) had laboratory test results indicating normal liver and kidney function; (3) had normal ultrasonography of the liver, gallbladder, and kidneys; (4) had no HCV infection or other chronic or infectious diseases; (5) had no history of kidney disease; and (6) had no serious cardiovascular disease, blood disorders, or malignant tumors.

Data Collection

Baseline demographic, liver/renal function, and immunological data were retrieved from the Hospital Information System (HIS) and Laboratory Information System (LIS) of the First Affiliated Hospital of Xi'an Jiaotong University. Retrospective data collection spanned from September 2017 to May 2018.

Sample Analysis

Laboratory tests included red blood cell (RBC) count and hemoglobin (Hb), which were performed using the SYSMEX XN9000 fully automated hematology analyzer (Sysmex Corporation, Kobe, Japan).

The tests for AST, ALT, total protein (TP), albumin (ALB), globulin (GLO), albumin-globulin ratio (A/G), total bile acid (TBA), blood urea nitrogen (BUN), creatinine (CREA), uric acid (UA), and estimated glomerular filtration rate (eGFR) were conducted using the Hitachi LAbOSPECT 008AS automatic biochemical analyzer (Hitachi High-Tech Corporation, Tokyo, Japan). The ALT, AST, TBA, BUN, CREA, and UA kits were purchased from Fujifilm Wako Pure Chemical Co. (Tokyo, Japan), while the TP and ALB kits were obtained from Maccura Biotechnology Co., Ltd. (Sichuan, China). Per product specifications, ALT and AST assays did not contain supplemental pyridoxal 5'-phosphate (PLP).

The ratios of CD3+ T-cells (CD3+), CD4+ T-cells (CD3+CD4+), CD8+ T-cells (CD3+CD8+), and regulatory T-cells (Tregs, CD4+CD25+CD127-), were determined using a flow cytometer (FACSCanto™, BD Biosciences, San Jose, CA, USA) with fluorescent antibodies (BioLegend, Inc., San Diego, CA, USA). Additionally, serum interleukin-10 (IL-10) levels were measured using an enzyme-linked immunosorbent assay (R&D Systems, Inc., Minneapolis, MN, USA).

HCV RNA quantification was performed using the Applied Biosystems 7500 Real-Time PCR System (Thermo Fisher Scientific, USA) with DAAN Gene Co., Ltd. (Guangzhou, China) detection kits. A viral load >1,000 IU/mL was defined as positive.

To explore the effect of HCV infection on the survival status of MHD patients, we collected data on the 4-year survival of MHD patients.

Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as the mean ± standard deviation. Multigroup comparisons were performed using two-way ANOVA with a randomized block design. Differences between two unmatched groups were assessed using the independent-samples t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. For comparison between two matched groups, if the data were normally distributed, the paired samples t-test was used, and the Wilcoxon signed-rank test was applied when they were non-normally distributed. For the comparison of rates in categorical variables, we used McNemar's test or the chi-square test, depending on whether the two groups were matched or unmatched. Statistical significance was set at $P < 0.05$, and all tests were two-sided.

Results

Patient characteristics

The MHD-HCV group comprised 19 females and 9 males, with a mean age and dialysis duration of 53.86 ± 14.64 and 10.17 ± 6.06 years, respectively. HCV viral load in these patients was 4.144 ± 6.328×106 IU/mL. Similarly, the MHD group consisted of 19 females and 9 males, with a mean age and dialysis duration of 55.68 ± 15.07 and 8.10 ± 4.03 years, respectively. The two groups were successfully matched based on age, gender, and duration of hemodialysis. The patients in the two groups received erythropoietin regularly due to anemia, and showed no significant differences in red blood cell count (3.39 ± 0.65 vs. 3.55 ± 0.68, *P = 0.373*) and hemoglobin level (100.96 ± 16.41 vs. 108.46 ± 19.27, *P= 0.106*). The NC group included 13 females and 8 males, with a mean age of 53.19±10.53 years, and did not show significant differences in gender composition or age compared to the MHD and MHD-HCV groups (Table 1).

Differences in liver and kidney function indicators among the MHD-HCV, MHD, and NC groups

The levels of ALT and AST in the MHD group were significantly lower than those in the NC group (ALT: 10.14 ± 7.14 vs. 20.95 ± 8.82, P < 0.001; AST: 11.75 ± 5.45 vs. 19.33 ± 3.84, P < 0.001) and the MHD-HCV group (ALT: 10.14 ± 7.14 vs. 26.64 ± 18.64, *P < 0.001*; AST: 11.75 ± 5.45 vs. 20 ± 8.99, *P < 0.001)*. However, no significant differences in these parameters were observed between the MHD-HCV and NC groups (*P > 0.05*). The MHD-HCV group (7.70 ± 7.17 vs. 2.25 ± 1.03, *P < 0.001*) and the MHD group (3.44 ± 1.75 vs. 2.25 ± 1.03, *P = 0.006*) showed higher levels of TBA than the NC group, and there was a significant difference between the TBA levels in the MHD-HCV group and the MHD group (7.70 ± 7.17 vs. 3.44 ± 1.75, *P = 0.007*). Furthermore, both the MHD-HCV and MHD groups exhibited significantly lower levels of TP (67.86 ± 5.2 vs. 72.51 ± 3.15, *P = 0.001*; 63.92 ± 5.57 vs. 72.51 ± 3.15, *P < 0.001*), ALB (36.79 ± 3.18 vs. 44.57 ± 1.89, *P < 0.001*; 37.39 ± 3.24 vs. 44.57 ± 1.89, *P < 0.001*) and A/G (1.24 ± 0.28 vs. 1.6 ± 0.14, *P < 0.001*; 1.43 ± 0.19 vs. 1.6 ± 0.14, *P = 0.001*) than the NC group. Additionally, the MHD-HCV group showed higher levels of TP (67.86 ± 5.2 vs. 63.92 ± 5.57 *P=0.012*) and GLO (31.07 ± 5.91 vs. 26.53 ± 3.58, *P=0.003*) and a decreased A/G ratio (1.24 ± 0.28 vs. 1.43 ± 0.19, *P=0.013*) compared to the MHD group. Regarding renal function indicators, no significant differences were observed between the MHD-HCV and MHD groups (*P > 0.05*) (Table 2).

Serum immune markers in patients on MHD with HCV infection

The mean percentages of CD3+ T-cells (76.9 ± 13.68 vs. 63.43 ± 8.42, *P < 0.001*), CD4+ T-cells (46.55 ± 10.42 vs. 34.5 ± 9.11, *P < 0.001*), and CD4+/CD8+ T-cells (1.94 ± 0.83 vs. 1.53 ± 0.98, *P = 0.007*) were significantly elevated in the MHD-HCV group compared to the NC group. Similarly, the percentages of CD3+ T-cells (74.03 ± 12.49 vs. 63.43 ± 8.42, *P = 0.001*) and CD4+ T-cells (42.59 ± 10.7 vs. 34.5 ± 9.11, *P = 0.008*) were significantly increased in the MHD group compared to the NC group. However, no statistically significant differences were observed in the indicators mentioned above between the MHD-HCV and MHD groups (*P > 0.05*) (Figure 1a and 1b). The levels of Tregs (4.48 ± 2.94 vs. 2.48 ± 1.81, *P < 0.001*; 4.48 ± 2.94 vs. 1.73 ± 1.24, *P < 0.001*) and IL-10 (78.67 ± 45.05 vs. 34.19 ± 15.15, *P < 0.001*; 78.67 ± 45.05 vs. 30.64 ± 13.03. *P < 0.001*) were significantly higher in the MHD-HCV group than in the MHD and NC groups, and no significant differences in the levels of Tregs and IL-10 (P > 0.05) were detected between the MHD and NC groups (Figure 1c and 1d).

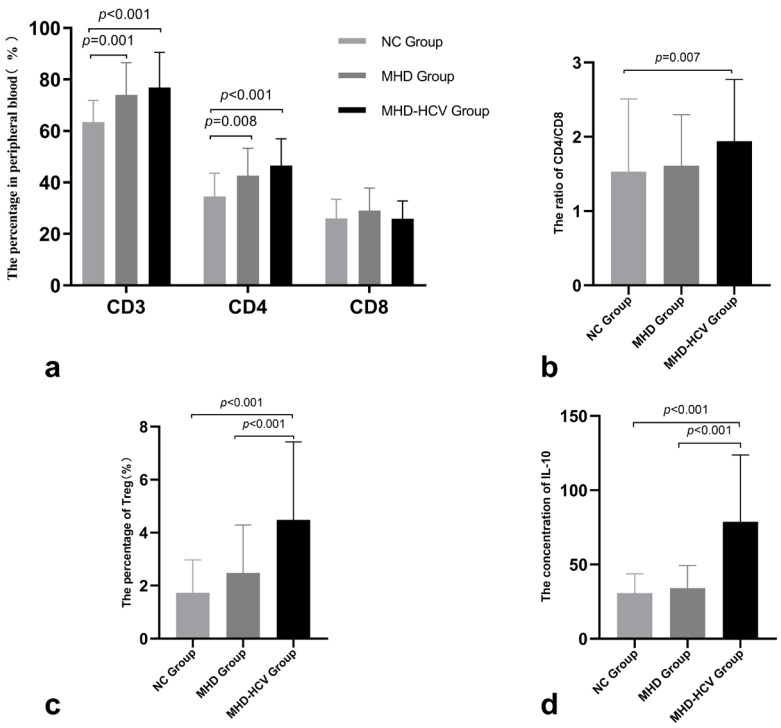

Figure 1. Comparison of serum immune markers among study groups. NC, normal controls (n=21); MHD, maintenance hemodialysis without HCV (n=28); MHD-HCV, maintenance hemodialysis with HCV (n=28). P-values are shown only for statistically significant pairwise comparisons (P < 0.05); all unmarked comparisons are non-significant.

Differences in survival status between the MHD and MHD-HCV groups

To investigate the effect of HCV infection on the survival status of MHD patients, all-cause mortality was compared between the MHD

Table 1. Demographics and baseline clinical characteristics across the three groups

Variables	NC group (N=21)	MHD group (N=28)	MHD-HCV group(N=28)	P value
Age	53.19±10.53	55.68±15.07	53.86±14.64	0.802
Gender composition （female：male）	13:8	19:9	19:9	0.765
RBC(×10^{12}/L)	4.8±0.61	3.55±0.68*	3.39±0.65*	< 0.001
Hb（g/L）	140.38±11.93	108.46±19.27*	100.96±16.41*	< 0.001
Dialysis duration		8.10±4.03	10.17±6.06	0.138
Type 2 diabetes		6(28)	4(28)	0.625
hypertension		20(28)	16(28)	0.180
Secondary hyperparathyroidism		16(28)	14(28)	0.791

NC, normal control; MHD, patients undergoing MHD without HCV infection; MHD-HCV, patients undergoing MHD with HCV infection; RBC, red blood cell count; Hb, hemoglobin . * $P < 0.05$, compared with NC group

Table 2. Comparison of liver and renal function markers in the serum of NC, MHD, and MHD-HCV groups

Variable	NC group (n=21)	MHD group (n=28)	MHD-HCV group (n=28)
ALT (U/L)	20.95 ± 8.82	10.14 ± 7.14*	26.64 ± 18.64#
AST (U/L)	19.33 ± 3.84	11.75 ± 5.45*	20 ± 8.99#
TBA (μmol/L)	2.25 ± 1.03	3.44 ± 1.75*	7.70±7.17*#
TP (g/L)	72.51 ± 3.15	63.92 ± 5.57*	67.86 ± 5.2*#
ALB (g/L)	44.57 ± 1.89	37.39 ± 3.24*	36.79 ± 3.18*
GLO (g/L)	27.95 ± 2.21	26.53 ± 3.58	31.07 ± 5.91*#
A/G	1.6 ± 0.14	1.43 ± 0.19*	1.24 ± 0.28*#
BUN (mmol/L)	5.56 ± 1.39	27 ± 6.86*	27.21 ± 6.62*
Creatinine (μmol/L)	60.62 ± 10.77	973.36 ± 319.03*	952.93 ± 255.55*
eGFR (mL/min/1.73m^2)	106.18 ± 8.8	10.94 ± 9.74*	13.74 ± 10.3*
UA (μmol/L)	299.1 ± 64.62	444.92 ± 130.97*	444.43 ± 91.38*

NC, normal control; MHD, patients undergoing MHD without HCV infection; MHD-HCV, patients undergoing MHD with HCV infection; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLO, globulin; A/G, albumin-to-globulin ratio; TBA, total bile acid; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UA, uric acid. * $P < 0.05$, compared with the NC group; # $P < 0.05$, compared with the MHD group.

Table 3. Comparison of survival status between the MHD-HCV group and MHD Group

Variable	MHD group (n=28)	MHD-HCV group (n=28)	χ^2	*p*
Mortality	7.14% (2/28)	28.57% (8/28)	4.383	0.036
Cause of death				
Gastrointestinal bleeding	1/28	2/28		
Pulmonary infection	/	2/28		
Multiple organ failure	1/28	2/28		
Cardiovascular events	/	1/28		
Others	/	1/28		

MHD, patients undergoing MHD without HCV infection; MHD-HCV, patients undergoing MHD with HCV infection.

and MHD-HCV groups. By May 2022, all patients in the MHD and MHD-HCV groups were successfully followed up. Eight of the 28 patients in the MHD-HCV group died from various causes, accounting for 28.57% of the total mortality. Comparatively, two patients died in the MHD group, resulting in a mortality of 7.14%. The mortality of the MHD-HCV group was much higher than that of the MHD group ($\chi2=4.383$, $P = 0.036$) (Table 3).

Discussion

HCV infection has been established as a risk factor for glomerulonephritis development and increases the progression of nephropathy to ESRD[18]. ALT and AST are important biomarkers of hepatitis, and their increased levels are significantly associated with an increased risk of progression in patients with chronic hepatitis C and liver cirrhosis[19,20]. Our results indicate that ALT and AST levels are higher in patients with HCV infection undergoing MHD than in those without HCV infection; however, we found no significant differences between patients in the MHD-HCV group and normal controls. Only the AST of one patient and the ALT of another patient in the MHD-HCV group exceeded the upper limit (40 U/L) of the normal reference range (AST=44 U/L, ALT=92 U/L) whereas the ALT and AST of the remaining MHD patients are within the normal reference range. Consistent with this finding, a study revealed that dialysis patients exhibited lower aminotransferase activity than predialysis patients with chronic renal failure[21]. Pyridoxal phosphate, a crucial coenzyme of transaminases, decreases to varying degrees during hemodialysis[22]. For patients undergoing renal dialysis, the measurement of transaminases with the addition of pyridoxal phosphate may improve the accuracy of assessing hepatocyte injury[23].Notably, most detection reagents lack pyridoxal phosphate, resulting in a false decrease in ALT and AST levels in MHD patients. Research also suggests that this reduction can be attributed to blood dilution, decreased pyridoxine levels, or elevated homocysteine levels in MHD patients. Additionally, dialysis-induced reductions in viremia, the production of hepatocyte growth factor and endogenous interferon-a, and lymphocyte activation all contribute to diminishing the impact of HCV on the hepatocytes of MHD patients[24]. Therefore, low levels of AST and ALT in MHD patients with HCV infection are not sufficient to rule out liver damage and other negative effects[14].

TBA is a sensitive indicator of liver injury, and increasing evidence has indicated a close relationship between TBA and cirrhosis[25]. Higher TBA levels are closely associated with high mortality in MHD patients[26].We observed that patients undergoing MHD, especially those with HCV infection, had significantly higher TBA levels than normal controls, and it was reported that elevated plasma bile acid levels in patients with chronic renal failure are due to decreased renal filtration[27,28]. We did not find any significant differences in the levels of BUN, creatinine, eGFR, or uric acid between the MHD and MHD-HCV groups. Therefore, the elevated TBA levels observed in the MHD-HCV group are more likely attributable to liver damage caused by HCV infection. This finding indicates that there is still non-negligible liver damage, although no significant difference in AST or ALT levels

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was observed between MHD patients with HCV infection and the general population. This finding is consistent with the results reported by Espinosa et al[29].

We observed significantly higher percentages of CD3+ T cells and CD4+ T cells in patients undergoing MHD than in normal controls. T-cell exhaustion typically arises in chronic HCV infection, with the expansion of Tregs serving as a pivotal mechanism underlying the compromised HCV-specific cytotoxic T-cell response observed in patients[30,31]. Therefore, CD8+ T-cells remained at normal levels in this study, despite HCV infection in the MHD population. T-cells, helper T-cells, and Tregs exert immunosuppressive functions through the secretion of IL-10, dampening inflammatory immune responses[32]. IL-10 can protect hosts from exaggerated immune reactions,[33] which can lead to immune escape during the acute phase of viral infection, resulting in chronic HCV infection34. High IL-10 levels are associated with an increased risk of cardiovascular events in patients[35,36]. A significant increase in the IL-10 level was observed, and the proportion of Tregs tended to increase in patients with HCV infection undergoing MHD. These can lead to relatively less severe liver and renal damage than that observed in the general population[37,38]. Our hypothesis posits that the increase in Treg cells and IL-10 levels represents a pivotal factor in the pathogenesis of chronic HCV infection in MHD patients. This immunosuppressive effect, orchestrated by these factors, is hypothesized to contribute to the relatively attenuated hepatic damage compared with the damage observed in HCV-infected individuals without renal impairment. Treg and IL-10 levels may have potential clinical value in monitoring the immune status and efficacy of antiviral therapy in patients with HCV infection undergoing MHD.

ALB and GLO are the two primary serum proteins in the human body and are indicative of nutritional and infection status. Elevated GLO levels, coupled with a diminished A/G ratio and TP levels, have been strongly linked to increased all-cause mortality in individuals with chronic kidney disease[39,40]. In our study, the level of TP in the MHD-HCV group was significantly higher than that in the MHD group, characterized by an increase in the GLO level and a significant reduction in the A/G ratio. Therefore, we speculate that patients undergoing MHD with HCV could have a more pronounced state of malnutrition and chronic infection and a higher risk of mortality. To verify this hypothesis, we followed up on the survival of these patients four years later and found that patients with HCV infection undergoing MHD exhibited a notable increase in mortality rates compared to those without HCV infection. The increased IL-10 level in this study may be one of the reasons for the increased mortality. This significant impact on clinical outcomes underscores the critical importance of prompt medical intervention for patients with HCV undergoing MHD. Therefore, timely diagnosis and treatment are essential to mitigate potential risks and improve the overall prognosis of these patients.

This study had some limitations. The number of cases included in this study was limited because of the relatively rare occurrence of HCV infection with RNA positivity among patients undergoing MHD. We recognize the potential clinical value of these immunological parameters in patients with MHD and HCV infection and plan to focus on immunological parameters such as Treg and IL-10 in future studies to improve the clinical understanding of HCV infection in MHD patients.

Conclusion

The MHD-HCV group had higher ALT and AST levels than the MHD group but did not significantly differ in ALT and AST levels compared to the NC group. MHD patients with HCV infection could have liver dysfunction with seemingly normal liver function test results; thus, it is necessary to explore population-specific AST and ALT reference ranges. Compared with the MHD group, the MHD-HCV group had increased Tregs and IL-10 levels and increased mortality. It is crucial for MHD patients infected with HCV to undergo antiviral intervention.

Statements and Declarations

Author Contributions

Ning Zhang: Writing – original draft, Supervision, Resources, Methodology, Formal analysis, Conceptualization. Hua Liu: Resources, Conceptualization. Syleenah Molebogeng Moloto: Data curation, Formal analysis, Investigation. Jian Hu:Resources, Visualization, Funding acquisition. Jie Zheng: Writing – review & editing. Yingli He: Writing – review & editing, Conceptualization. Xiaoqin Wang: Writing – review & editing, Funding acquisition, Conceptualization.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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