Microbes and Infectious Diseases 2022; 3(3): 578-587

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Original article

Liver morbidity among haemodialysis patients negative for manifest HBV and HCV : A hospital-based study in an endemic area

Abdulrahman Alduraywish [1], Mostafa Ragheb [2], Rania Kishk [3], Ibrahim Taher [4], Hamdy Omar [5], Nageh Louis [2], Wafaa Omar*[2]

1- *Department of Internal Medicine, Faculty of Medicine, Jouf University, Saudi Arabia.*
2- *Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt*
3- *Department of Microbiology and Immunology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt*
4- *Department of Pathology, Faculty of Medicine, Jouf University, Saudi Arabia.*
5- *Department of Internal Medicine, Faculty of Medicine, Suez Canal University; Ismailia, Egypt*

ARTICLE INFO

Article history:
Received 10 April 2022
Received in revised form 30 April 2022
Accepted 5 May 2022

Keywords:
End-stage kidney disease
Chronic liver disease
Ultrasonography
Alanine aminotransferase
Aspartate aminotransferase
Fatty liver

ABSTRACT

Background: End-stage renal disease (ESRD) is an increasing health problem worldwide. Older age, diabetes mellitus and hypertension, acute kidney damage are among some of the factors that play a role in ESRD. This study aims at exploring liver morbidity (LM) among Egyptian hemodialysis (HD) patients. **Methods:** The study included 142 patients free from overt hepatitis B virus (HBV) or hepatitis C virus (HCV); their data were retrieved from files and all were clinically assessed and tested for liver functions, serological markers and viremia of HCV and HBV. **Results:** Of 142 eligible HD patients, two seroconverted to overt HCV, and five showed occult HCV. According to the laboratory and ultrasonography (US) data, three patterns of LM were found in 62 (43.7%), non-alcoholic fatty liver disease (NAFLD) in 30 (48.4%), liver fibrosis in 19 (30.6%), and hepatitis in 13 (21%). The mean durations of renal impairment (7.6 ± 5.91), hemodialysis (9 ± 6.1269), and total dialysis sessions (976.26 ± 683.69) were significantly higher in patients with LM compared to others (6.78 ± 4.82, 5.38 ± 3.69, and 699.4 ± 467.1). Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels were elevated in 14 (22.6%) and 13 (21%) of patients with LM. However, the ROC curve revealed ALT and AST cut-off points of 16.5 and 25.5 IU/L to discriminate LM. **Conclusion:** LM is common among EDRD patients undergoing hemodialysis despite the low levels of ALT and AST. The use of the US and the new lower levels of ALT and AST could improve the screening approach of LM.

Introduction

Worldwide, end-stage renal disease (ESRD) is an increasing health problem. The main etiology of chronic kidney disease (CKD) may differ in different countries. Common risk factors are aging, diabetes mellitus and hypertension, and chronic use of non-steroidal anti-inflammatory drugs, and acute kidney damage. Polycystic kidney disease is an example of a hereditary cause of CKD [1-3]. In many Arab countries, obstructive uropathy constitutes a major cause of ESRD (40%) mostly due to renal calculi and schistosomiasis. In areas endemic for hepatitis viruses B (HBV) and C (HCV),infection-related chronic glomerulonephritis is a leading cause of CKD [4]. Other unhealthy lifestyle factors; such as smoking, alcohol, and obesity are also associated with CKD and ESRD [5-7]. The association of liver disease with chronic kidney injury is common and blood-borne hepatitis

DOI: 10.21608/MID.2022.132560.1274
* *Corresponding author:* Wafaa Hassan Omar
E-mail address: drwafaaomar@yahoo.com

viruses as HBV; HCV is commonly encountered in patients on hemodialysis. Several types of renal diseases have been associated with HBV and HCV [4,8]. Hepatitis B and C remain prevalent particularly within haemodialysis (HD) populations globally despite improvements in infection control, uptake of hepatitis B vaccines and the emergence of novel therapeutic options for hepatitis C [9]. The prevalence of combined advanced liver and kidney impairment is increasing, as evidenced by increasing numbers of simultaneous liver–kidney transplant referrals over the past 2 decades [10].

The association between CKD and non-alcoholic fatty liver disease (NAFLD) is of major concern. Renal impairment is more prevalent in patients with NAFLD while untreated non-alcoholic steatohepatitis (NASH) could progress to cirrhosis and hepatocellular carcinoma (HCC) and increased risk of cardiovascular mortality. Early diagnosis and treatment of NAFLD in CKD patients could ameliorate the cardiovascular risk and delay renal impairment [11].

This study is aimed to explore the type of liver morbidity (LM) among patients on regular chronic hemodialysis using commonly used diagnostic tools (liver function test)

Patients, Materials and Methods

The study included 142 patients with ESRD undergoing maintenance haemodialysis. They were selected according to the following criteria; regular hemodialysis, HBsAg negative, HCV Ab negative, and not suffering from other types of liver diseases as autoimmune, drug induced or metabolic as haemochromatosis or Wilson's disease at the time of enrollment. The studied population was selected by a non-random convenience sampling, from two hemodialysis centers (Suez Canal University Hospitals and Ismailia General Hospital) in Ismailia City, Egypt during the period from July 2018 to January 2019.

Ethical consideration

An informed consent was obtained from all participants, and the approved patients were enrolled. The study has also been approved by the ethics committee of the Faculty of Medicine, Suez Canal University, Egypt (Ref. #3680).

Clinical and laboratory assessment

Data collected included sociodemographic, clinical, laboratory, as well as the risk factors for blood-borne infections and co-morbid illnesses. Examination with US was conducted for the measurement of the morphological parameters (liver size, morphology, surface and echogenicity, and spleen volume, check for ascites) and the hemodynamic parameters (portal vein diameter and mean flow velocity) [12]. All ultrasound examinations were performed by a single experienced operator, who was blind to the clinical and laboratory data of the studied participants. The machine used was Sonoace R3 (Samsung Medison, Seoul, Korea) with a curvilinear 2.5 - 5 MHz transducer.

Sampling and investigations

Two 5-mL peripheral venous blood samples were taken; serum was separated and stored at -80 °C for testing markers (HCV Ab, HBsAg, HBcAb, and HBsAb) and real-time PCR. Peripheral mononuclear cells (PMNCs) were separated from the other sample and stored immediately at -80 °C. Repeated testing for serological markers of HBV and HCV was also done for all patients to check for seroconversion. In patients with positive HCV Ab, RT-PCR for HCV RNA was performed in the sera to check for overt HCV infection (OCI). If no viremia, the test was performed in peripheral mononuclear cells (PMNCs) to check for occult HCV infection (OCI). Similarly, RT-PCR for HBV DNA was carried out on the sera of positive HBcAb patients to check for occult HBV infection (OBI). Occult hepatitis B infection (OBI) is defined as the existence of low-level HBV DNA in the serum (<200 IU/mL), cells of the lymphatic (immune) system, and/or hepatic tissue in patients with serological markers of previous infection (anti-HBc and/or anti-HBs positive) and the absence of serum HBsAg [13]. Occult HCV infection (OCI) is defined as the presence of HCV RNA in hepatocytes or peripheral blood mononuclear cells (PBMCs) with no detectable HCV RNA in the serum [14].

Study outcomes

According to the interpretation of the clinical, imaging, and laboratory findings, the liver was considered possibly morbid if there were changes in the liver echogenicity and/or its size, associated with splenic enlargement, dilated portal, or splenic veins. Also, the liver is morbid if there is evidence of necro-inflammation of the liver cells (elevated ALT and/or AST) or altered synthetic function (prolonged INR, low serum albumin). The pattern of LM was described as fatty or fibrous by the pattern of the liver texture as shown by ultrasonography. Hepatitis-like pattern was described when ALT

and/or AST were elevated. There are multiple scoring systems for assessment for liver morbidity, the most important of which are the Child-Pugh score and MELD score. The Child-Pugh score is a system for assessing the prognosis — including the required strength of treatment and necessity of liver transplant — of chronic liver disease, primarily cirrhosis [15,16].

The etiology of liver morbidity was described [4,8,11] as: a) viral-related (according to results of HBV or HCV serological markers and viremia by RT-PCR for HCV RNA or HBV DNA), b) NAFLD, diagnosed as fatty liver (if there was bright liver by US in the absence of other pathogens and normal liver enzymes) or NASH (if there was steatosis associated with high ALT) [17], or c) Unclassified in absence of the previous two causes. Interpretation of hepatitis B markers was done according to the criteria of the Center of Disease Control and Prevention. USA [18].

Statistical analysis

The collected data were managed by the SPSS-version 20 program of statistical analysis. Continuous data were described as mean and standard deviation, and qualitative data were summarized by frequencies and percentages. For the analytic data, the Chi-square test was used to detect the differences between qualitative data, while the Student's t-test was used to detect the difference between continuous data. A p value <0.05 was considered statistically significant. To find out the cut-off values of liver enzymes (ALT and AST) to assess ongoing liver pathology in HD patients, a Receiver Operating Characteristic curve (ROC curve) was constructed and analyzed.

Results

This study included 142 participants, aged from 12 - 75 years, 76 (53.5%) were males, 12 (8.5%) were current smokers and 81 (57%) were living in urban areas. Liver morbidity (LM) was evident in 62 (43.7%), and three patterns were seen namely; NAFLD followed by fibrous and hepatitis. Of the 30 patients with NAFLD, 25 showed fatty liver, mostly with hepatomegaly and normal ALT. All had no evidence of overt or occult HCV or HBV despite sero-reactivity to HBcAb in 6 (24%) participants. History of previous surgery, dental procedure, and blood transfusion was recalled by 115 (81.0%), 120 (84.5%), and 103 (72.5%) patients respectively. Comorbid hypertension, diabetes mellitus, and renal stones were present in 62 (43.7%) and 11 (7.7%), and 22 (15.5%) patients, while a family history of liver disease was recorded in 21 (14.8%). The mean duration of impaired kidney function (IKF) and the duration of hemodialysis were 7.75 ± 5.52 and 6.35 ± 4.89 years respectively. The mean duration of dialysis sessions were 820.28 ± 586 hours along the course of replacement therapy. History of blood transfusion before and after HD was reported by 23.9% and 10.6% of patients, respectively. Anemia was managed by regular erythropoietin in 90.1% of patients and by iron therapy in 70.4% **(Table 1).**

Abdominal US revealed hepatomegaly in 55 (38.7%) patients. The liver echogenicity was normal in 89 (62.7%), fibrous in 22 (15.5%) and fatty in 31 (21.8%) patients. None had ascites and 10 (7.0%) patients had splenomegaly. Laboratory workup revealed that mean values of ALT and AST, serum albumin, and total serum bilirubin were 22.3 ± 14.6 IU/L , 22.74 ± 12.77 IU/L, 3.89 ± 0.4 gm/dL, and 0.55 ± 0.24 mg/dl respectively. Elevated ALT and/or AST were found in 18 (12.67%), high total serum bilirubin in 3 (2.1%), and low serum albumin in 21 (14.8%). Of all, anemia, leukopenia, and thrombocytopenia were recorded in 95.1%, 7 %, and 7.7 % of patients. HCV Ab was positive in 15 (10.6%) patients, for the first time in two (1.4% seroconversion). RT-PCR testing for sera of HCV Ab positive patients revealed HCV RNA in the two naïve seroconverted cases, and in the remaining 13, viremia was only evident in PMNCs of 5 cases. Overall, 44 (31.0%) patients were sero-reactive to HBcAb, all proved negative for HBV DNA by RT-PCR. According to the constellation of clinical, imaging, and laboratory data, LM was evident in 62 (43.67%) patients **(Table 2).** The pattern of LM was described as fatty, fibrous, or hepatitis patterns.

In this study, the mean number of dialysis sessions throughout the replacement therapy was significantly higher in patients with LM (p = 0.007). Similarly, the mean duration of HD and the duration of IKF function were higher in patients with morbid liver. However, the difference between patients with and without LM showed no statistically significant differences regarding age, residence, risk factors, comorbid illnesses, and family history of liver disease **(Table 1).**

Comparison of manifestations of liver disease between patients with and without LM:

Using US, 28 (45.1%) patients with LM showed hepatomegaly compared to 27 (40.0%) without LM (p >0.05). Among patients with LM, fibrous and fatty echo-patterns were present in 19

(30.6%) and 30 (48.39%) compared to none in patients without respectively (p = 0.11). Eight (12.9%) patients with LM had splenomegaly compared to 2 (2.5%) without, (p = 0.02). The mean ALT values were significantly higher in patients with LM (p = 0.01) while the mean of AST was significantly higher in patients without LM (p= 0.001). All the 14 patients with high ALT showed evidence of LM, while only 4 of 13 patients with elevated AST had evidence of LM. However, the difference between both groups showed no significant differences regarding serum albumin, total serum bilirubin, INR, anemia, leukopenia, and thrombocytopenia **(Table 2).**

The Receiver Operating Characteristic curve analysis (ROC curve) revealed that the ALT and AST cut-off values, of 16.5 and 25.5 IU/L respectively, could discriminate between patients with and without LM with the diagnostic criteria as shown in **figure (1)** and **table (3)**. The new cut-off point of ALT has a higher sensitivity and lower specificity (67.7 and 48.75%) compared to AST (50 and 67.5%). However, the two cut-off values have a comparable area under the curve, PPV, NPV, and accuracy.

Out of the 142 participants, 44 (31%) were found to be HBcAb positive; but no HBV DNA viremia was present. HBsAb titer (≥10 mIU/mL) was found in 131 (92.25%); including 43 (30.3%) related to infection and 88 (62%) as a result of vaccination. The remaining 11 patients were non-immune; one (0.7%) had isolated HBcAb and 10 (7%) were non-reactive to hepatitis B markers (susceptible group). The frequency of HBcAb was significantly higher in patients with LM (40.3%) compared to patients without (23.75%), p = 0.044. HCV Ab was positive in 15 (10.6%) patients, 11 (17.7%) with LM and 4 (5%) without, p = 0.025. Of 15 HCV Ab positive patients, five with occult HCV had evidence of LM.

The results of HBV markers revealed that liver morbid patients had an insignificantly higher frequency of infection-related immunity (p>0.05), lower vaccination-related immunity (p<0.005), and insignificantly higher frequency of susceptible patients (p >0.05) compared to patients without LM **(Table 4)**.

Table 1. Socio-demographics and risk factors stratified for liver morbidity among the study hemodialysis patients.

Characteristic		**n = 142**	**With liver morbidity (n = 62)**	**Without liver morbidity (n = 80)**	***p***
Age mean (years)		44.05 ± 16.78	45.42 ± 16.39	42.99 ± 16.2	0.970
Gender	Male	76 (53.5)	32 (51.6)	44 (55)	0.250
	Female	66 (46.5)	30 (48.4)	36 (45)	
Housing area	Urban	81 (57)	32 (51.6)	49 (61.25)	0.095
	Rural	61 (43)	30 (48.4)	41 (48.75)	
Previous surgery		115 (81)	49 (79)	66 (82.5)	0.490
Previous dental procedure		120 (84.5)	52 (81.8)	68 (86.2)	0.320
Previous blood transfusion		103 (72.5)	48 (76.4)	55 (70.1)	0.270
Previous Schistosomiasis		6 (4.2)	3 (5.5)	3 (3.4)	0.43
Tartar emetic injection		5 (3.5)	2 (3.6)	3 (3.9)	0.640
Previous renal stones		22 (15.5)	7(12.7)	15 (17.2)	0.320
Hypertension		62 (43.7)	31 (47.3)	31(41.4)	0.300
Diabetes mellitus		11 (7.7)	6 (4.2)	5 (5.7)	0.210
Family history of viral liver disease		21 (14.8)	9 (12.7)	12 (16.1)	0.580
Duration of IKF		7.75 ± 5.52	9 ± 6.12	6.78 ± 4.82	0.020
Duration of hemodialysis		6.35 ± 4.89	7.6 ± 5.91	5.38 ± 3.69	0.011
Number of dialysis sessions		820.28 ± 586	976.26 ± 683.69	699.4 ± 467.1	0.007

Data shown are frequency, n (%), mean ± SD and P values. IKF = Impaired kidney function.

Table 2. Analysis of liver morbidity manifestations among 142 studied subjects on regular hemodialysis.

Finding		Total (n = 142)	With liver morbidity (n = 62)	Without liver morbidity (n = 80)	*p*
Enlarged liver		55 (38.7)	28 (45.1)	27 (40.0)	>0.05
Liver echogenicity	Normal	93 (62.7)	13 (21)	80 (100)	NA
	Fibrous	19 (15.5)	19 (30.6)	0 (0.0)	
	Fatty	30 (21.8)	30 (48.39)	0 (0.0)	
Splenomegaly		10 (7.0)	8 (12.9)	2 (2.5)	0.02
ALT (IU/L), mean		22.30 ± 14.600	26.05 ± 17.544	19.33 ± 11.147	0.01
High ALT (>40 IU/L)		14 (9.9)	14 (22.58)	0 (10)	0.017
AST (IU/L), mean		22.74 ± 12.770	19.58 ± 15.438	23.30 ± 9.158	0.001
High AST (>40 IU/L)		13 (9.2)	4 (6.45)	9 (11.25)	<0.001
Serum albumin (gm/dL), mean		3.890 ± 0.400	3.837 ± 0.401	3.938 ± 0.400	0.59
Low S. albumin (<3.5 gm/dL)		21 (14.8)	12 (19.35)	9 (11.25)	>0.05
S. bilirubin mean		0.55 ± 0.240	0.583 ± 0.264	0.529 ± 0.217	0.48
High S. bilirubin (>1.1 mg/dL)		3 (2.1)	2 (3.22)	1 (1.25)	>0.05
INR, mean		1.05 ± 0.080	1.0460 ± 0.066	1.0581 ± 0.085	1.0
Prolonged INR (>1.3)		1 (0.7)	1 (1.6)	0 (0)	NA
HB content (g/dL), mean		9.78 ± 1.340	9.518 ± 1.165	9.978 ± 1.444	0.38
Anemia		135 (95.1)	61 (98.38)	74 (92.5)	>0.05
WBC (/μL), mean		6663 ± 15300	6512 ± 1886	6781 ± 1894	0.49
Leukopenia		10 (7.0)	6 (9.7)	4 (5)	>0.05
Platelet count (/μL), mean		227542 ± 65635	225822 ± 62426	228875 ± 6838	0.68
Thrombocytopenia		11 (7.7)	(9.7)	5 (3.75)	>0.05

Data shown are frequency, n (%), mean ± SD and P values. There were elevated ALT and/or AST levels in 18 (12.67%) patients. NA = Not applicable

Table 3. The diagnostic performance of the cut-off values of ALT and AST as assessed by ROC curves. Data shown are cut-off level (IU/L), *p* values, Area Under the receiver operating characteristic Curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive (NPP) and accuracy.

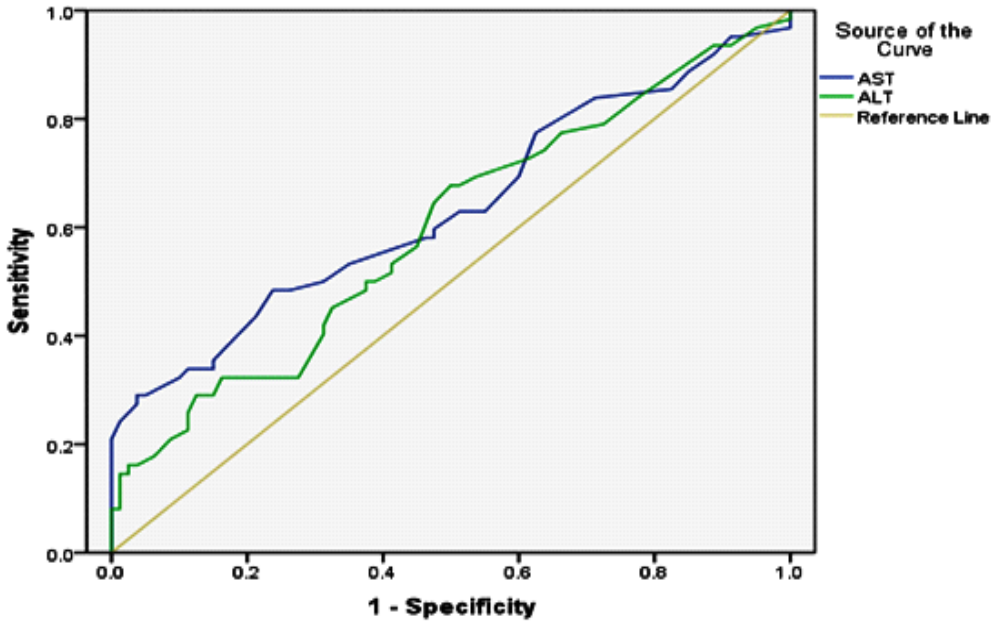
	Cut-off	*p*	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
ALT	16.5	0.047	0.6	67.70%	48.75%	50.60%	66.10%	57%
AST	25.5	0.006	0.63	50%	67.50%	54.40%	63.50%	60%

Table 4. Hepatitis markers among the studied hemodialysis patients.

	Total (n = 142)	**With liver morbidity (n = 62)**	**Without liver morbidity (n = 80)**	**P**
Infection related immunity	43 (30.3)	25 (40.3)	18 (22.5)	>0.05
Vaccination related immunity	88 (62.0)	33 (53.2)	55 (68.75)	<0.005
Isolated HBcAb	1 (0.7)	0 (0)	1 (1.25)	NA
Susceptible	10 (7.0)	4 (6.45)	6 (3.4)	>0.05
HBcAb positive	44 (31.0)	25(40.3)	19 (23.75)	0.044
HCV Ab positive	15 (10.6)	11(17.7)	4 (5)	0.025
HCV RNA in PMNCs among the 15 HCV Ab-positive patients	5	5	0	-

Data shown are frequency, n (%) and P values. NA = Not applicable, Susceptible = negative for all hepatitis B markers, PMNCs = peripheral mononuclear cells.

Figure 1. Receiver operating characteristic (ROC) curve of the levels of ALT (Alanine aminotransferase) and AST (Aspartate aminotransferase) in 142 hemodialysis patients. At cut-off points of 16.5 and 25.5 IU/L, ALT and AST could, respectively differentiate between patients with and without liver morbidity better than the conventional Upper Limit of Normal used in the study.



Discussion

Patients with ESRD are liable to infection with hepatitis viruses due to repeated hospitalization, exposure to invasive procedures, and blood transfusion [19-21]. For a long time, HD was reported as one of many predictors for infection with HCV and HBV. Currently, the prevalence of viral hepatitis is declining in HD units in Egypt and many other countries, this was in agreement with **Ozer et al,** 2015 [22].

In the current study settings, new infection with HCV was infrequently discovered despite the segregation of patients according to their infection status, which is compatible with a study by **Bernieh** [23] . Unfortunately, many of such patients did not recall manifestation of acute hepatitis and their liver enzymes were mostly below the conventional Upper Limit of Normal (ULN; 40 IU/L).

Our results showed 62 (43.7%) of that patients were diagnosed with LM; NAFLD, fibrous

and hepatitis being the most revealed patterns which was consistent with renew bariatrics. Report: Obesity Rates by Country, 2017 which reveals that, Worldwide, NAFLD represents the most common cause of (chronic liver disease) CLD particularly after the increasing prevalence of obesity and sedentary life [24]. Early diagnosis and treatment of NAFLD in CKD patients could ameliorate the cardiovascular risk and delay renal impairment [11,25].

The second most frequent pattern of LM was the fibrous liver diagnosed in 19 patients. They included two cases of overt HCV, five had occult HCV and four were positive for HBcAb without viremia. The third category was the hepatitis pattern affecting 18 patients, 5 with NASH previously discussed, and 13 with normal liver texture. All had no evidence of overt or occult HCV and the majority has been exposed to hepatitis B infection with no residual viremia.

During this study, the US was of great help to evaluate the presence and type of liver morbidity. The diagnosis of liver cirrhosis and fatty liver by the US has been reported to correlate with liver tissue elastography. Furthermore, the US reliably documents moderate to severe fatty liver compared to histopathology, this was in consistent with **Zheng et al.** which reveals that ultrasonography is still the imaging technique of choice for diagnosis of fatty liver in clinical settings and screening of population [26-28].

We found the diagnostic performance of ALT was more consistent with LM compared to AST. All the 14 patients with elevated ALT had evidence of LM compared to only 4 of 13 with elevated AST. This was not in agreement with **Cohen et al,** 1976 which reveals that In the latter cases, the rise in AST could be due to injury in other organs [29]. But in agreement with **Liberato et al.** which shows that the low levels of liver enzymes were also reported by many studies in patients with CKD and/or hemodialysis [30]. Moreover, a ROC curve showed ALT and AST cut-off values of 16.5 and 25.5 IU/L respectively to discriminate against patients with LM. According to the new values, 58.5% and 40.1% of the studied participants had high ALT and AST values compared to 9.9% and 9.2% when the conventional ULN was used. While the cut-off values of ALT have a higher sensitivity and lower specificity (67.7 and 48.75%) compared to AST (50 and 67.5%), both have a comparable PPV and NPV. Unfortunately, the accuracy of the AUC of either enzyme is considered low. The cut-off values of ALT and AST, shown in this study were in agreement with **Gouveia et al.** which that the results were very close to 17 and 24 IU/L reported in 90 patients on continuous ambulatory peritoneal dialysis with viral hepatitis [31].

Presently, the study patients with LM and low serum albumin showed no evidence of decompensation which was in agreement with **Aghakhani et al.** which indicates that, Hypoalbuminemia in the ESRD patients has been attributed to many factors such as low dietary protein, decreased synthesis, or inflammation [32].

Liver morbidity among our HD patients was significantly associated with the duration of renal impairment (p=0.02), the duration of maintenance hemodialysis (p = 0.011) as well as the total number of dialysis sessions (p = 0.007). The association between these factors with LM has not been previously reported. In addition, none of the classical risk factors was associated with LM; namely blood transfusion, surgery, or dental procedures. This changing pattern could be attributed to the inclusion of participants who were intended to be free from overt infection with hepatitis viruses. Other factors include the use of sensitive tools for screening of hepatitis markers and better management of anemia which was consistent by a study by **Jadoul et al.** [33,34]. The frequency of HBcAb and HCV Ab were significantly higher in patients with LM (40.3% and 17.7%) compared to patients without (23.75% and 5%). Furthermore, sera of 44 HBcAb positive patients proved non-viremic when tested by RT-PCR for HBV DNA. However, to exclude OBI in the study cohort, sera, and liver tissues of all patients should be tested regardless of their HBcAb status [35].

The study limitation

Testing for occult HCV and HBV was only carried out for patients exposed to HCV and HBV and did not include others who were negative for HCV Ab or HBcAb.

Conclusion

Liver morbidity of different causes has been shown in a considerable proportion of patients undergoing hemodialysis. The most common type was NAFLD, followed by fibrous liver and hepatitis. Among the studied population who were proposed to be free from active HBV and HCV, new overt HCV and occult HCV was diagnosed with no evidence of occult HBV infection present. The

limited role of liver enzymes in the detection of liver morbidity in hemodialysis patients was contradicted by the usefulness of US by delineating any change in the echo-pattern of the liver.

Competing interest

There are no conflicts of interest.

Data availability

We have presented almost all the data in the study; however, raw and individual data are available upon request after permission from the Bioethical committee of the hospital.

Recommendations

A further validation study is recommended to assess the diagnostic values of ALT and AST among hemodialysis patients. Efforts should be directed to improve the lifestyle of HD patients to prevent and treat fatty liver disease. Meanwhile, occult infection with HBV and/or HCV among patients and health care workers is recommended to track the source of new infections.

Financial disclosures: This study was funded by a grant from the Deanship for Research, Jouf University, Sakaka, Saudi Arabia (37/440).

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