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Original Article

Various Patterns of the Derangement of Liver Function Tests in End-Stage Renal Disease Patients on Maintenance Hemodialysis-a Single Centered Study from Pakistan

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ABSTRACT

Background: Chronic kidney disease (CKD) patients on maintenance hemodialysis often present with various comorbidities, among which liver dysfunction is not uncommon. The prevalence of hepatitis B and C among this population suggests a multifaceted interaction between liver health and renal impairment. Studies have indicated that serum aminotransferase levels are inversely related to the severity of CKD and may be affected by hemodialysis.

Objective: This study aimed to delineate the patterns and etiologies of liver function test derangements in an end-stage renal disease (ESRD) cohort on maintenance hemodialysis, assessing the association between dialysis duration and liver enzyme levels.

Methods: In this cross-sectional observational study, 91 ESRD patients undergoing hemodialysis at a single center were evaluated. Liver function patterns were classified as hepatocellular, cholestatic, or mixed based on serum levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALKP), and gamma-glutamyl transferase (GGT). Statistical analysis was performed using SPSS version 25, with a significant p-value set at ≤ 0.05.

Results: The average age of patients was 44 ± 15 years. The majority had been on dialysis for one (41.8%) or two years (33%). Hepatitis C (20.9%) was the predominant cause of viral hepatitis, followed by Hepatitis B (13.2%). Sepsis was identified as a major contributor to liver enzyme derangement (58.2%). The most common pattern of deranged liver enzymes was mixed (49.5%), followed by cholestatic (27.5%) and hepatocellular (23%). Elevated transaminases were noted, with AST at 227.8 ± 264.1 IU/mL and ALT at 237.1 ± 281.8 IU/mL.

Conclusion: In the studied ESRD population, sepsis was the leading cause of liver dysfunction, with a higher incidence of mixed liver enzyme pattern derangements. The elevated aminotransferase levels contrast with previous studies, suggesting the need for enhanced infection control and consistent monitoring of liver health in the hemodialysis setting.

Keywords: End-Stage Renal Disease, Hemodialysis, Liver Function Tests, Hepatitis C, Aminotransferases, Sepsis, Liver Enzyme Derangement, Chronic Kidney Disease.

INTRODUCTION

End-stage renal disease (ESRD) is characterized by a severe, irreversible decline in kidney function, defined by an estimated glomerular filtration rate below 15 mL per minute per 1.73 m2 of body surface area, or the necessity for dialysis regardless of the glomerular filtration rate (1). Derangements in liver function tests (LFTs) typically suggest hepatocyte damage (2); however, in ESRD patients, these abnormalities are not only indicators of liver health but are also associated with increased mortality, particularly in

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the presence of sepsis (3). Elevated levels of aspartate aminotransferase (AST) in hemodialysis patients have been linked to an increased risk of all-cause mortality (4). Interestingly, ESRD patients without apparent liver injury often exhibit lower transaminase levels compared to the general population, irrespective of their viral serology status (5, 6). Yet, serum aminotransferase levels can increase by 15 – 35% following dialysis, suggesting hemo-concentration as a potential cause (7). Furthermore, elevated serum gamma glutamyl transferase (GGT) levels in hepatitis C infected ESRD patients have been identified as an indirect marker of liver disease (8).

The spectrum of LFT abnormalities in ESRD patients can vary depending on the underlying cause of liver damage and may present as hepatocellular, cholestatic, mixed hepatocellular-cholestatic patterns, isolated hyperbilirubinemia, or isolated hypertransaminasemia. A hepatocellular pattern, commonly resulting from viral hepatitis, can also occur due to ischemic injury, hepatotoxic drugs, autoimmune hepatitis, or vascular liver diseases. Cholestatic patterns are typically observed in conditions like choledocholithiasis or biliary stricture, which involve intraluminal, intramural, or extrinsic compression of the biliary system. However, similar patterns can also arise from non-obstructive causes such as sepsis or drug-induced liver injury. Moreover, liver injuries may manifest a mixed pattern when there is a confluence of these etiologies. Other specific patterns include isolated hyperbilirubinemia due to defects in bilirubin conjugation or ongoing hemolysis, or predominant increases in ALT or AST, depending on the specific etiological factor involved.

Previous studies have highlighted specific aspects of liver enzyme derangement in hemodialysis patients. For instance, Ravel et al. reported that 5.03% of maintenance dialysis patients had elevated AST levels (4). Idrees and colleagues, focusing on hepatitis B-infected individuals in a hemodialysis setting, noted higher GGT levels compared to transaminase levels (9). Comparisons of transaminase and GGT levels between patients on dialysis and those with chronic kidney disease, as well as between hemodialysis and peritoneal dialysis patients, have been documented, though these studies often did not delineate the causes of LFT derangements or their specific patterns (10). Local studies previously conducted primarily focused on renal transplant recipients, with little emphasis on the hemodialysis population. This gap highlights the necessity for research in this area, particularly in understanding the etiologies and patterns of liver enzyme derangement in hemodialysis patients in this region.

This study aims to explore the various patterns and causes of liver function test derangements in patients undergoing maintenance hemodialysis, building a foundation for future research that can enhance the management and prognostic assessment of these patients.

MATERIAL AND METHODS

Following the approval from the Ethical Review Committee at the Sindh Institute of Urology and Transplantation (SIUT), a cross-sectional observational study was conducted at the Department of Hepato-gastroenterology and Nephrology from June 14, 2022, to December 13, 2022. The study employed a non-probability consecutive sampling technique to enroll participants. Based on a 5.03% prevalence of elevated aspartate aminotransferase (AST) levels in the hemodialysis population (4), with a margin of error of 4.5% and a 95% confidence level, the calculated sample size required was 91 participants.

Eligible participants included males and females aged 18 to 70 years who had been undergoing maintenance hemodialysis for at least one year and presented with deranged liver function tests persisting for at least one week. Exclusion criteria were patients with acute kidney injury, as defined by KDIGO guidelines; pregnancy; recent history of acute myocardial infarction; muscular disorders such as myositis or muscular dystrophy; drug-induced liver injury from substances including herbal medication, cimetidine, halothane, antituberculosis drugs (e.g., isoniazid), or statins; previous diagnosis of chronic Hepatitis B or C; liver cirrhosis characterized by specific sonographic criteria; or significant alcohol consumption.

Data collection involved obtaining informed consent followed by recording the patient's age, gender, comorbidities (diabetes mellitus, hypertension, and ischemic heart disease), and duration of dialysis. Laboratory evaluations were performed on the day of assessment, including tests for total bilirubin, direct bilirubin, alkaline phosphatase (ALKP), AST, alanine transaminase (ALT), gamma-glutamyl transferase (GGT), hepatitis B surface antigen (HbsAg), and anti-HCV antibodies. Patients were categorized into hepatocellular, cholestatic, or mixed liver function test derangement patterns based on operational definitions.

Data analysis was conducted using SPSS version 25. Descriptive statistics, including mean and standard deviation, were calculated for continuous variables such as age, duration of hemodialysis, and laboratory parameters. Categorical variables, such as gender, liver function test patterns, and comorbidities, were presented as frequencies and percentages. The primary outcome was the pattern of liver function test derangements. Stratification by factors such as duration of hemodialysis, age, gender, and comorbidities was performed to assess the influence of these variables. The chi-square test was utilized for categorical data, and a p-value of ≤0.05 was considered statistically significant. The study adhered to the ethical guidelines of the Declaration of Helsinki to ensure the rights,

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safety, and well-being of all participants were protected throughout the research process. This adherence to ethical standards ensured the integrity and reliability of the research findings.

RESULTS

Table 1: Baseline Characteristics of the Study Population (n = 91)

Characteristic	Mean ± SD
Age (years)	44 ± 15
Hemoglobin (Hb) (g/dL)	8.8 ± 1.9
Hematocrit (HCT) (%)	29.3 ± 5
Total Leukocyte Count (TLC) (10^9/L)	13.7 ± 9.1
Neutrophils (N) (%)	75.2 ± 9.1
Lymphocytes (L) (%)	16.6 ± 7.9
Platelets (10^9/L)	213.6 ± 121.2
Urea (mg/dL)	137 ± 69.8
Creatinine (mg/dL)	5.3 ± 2.5
Sodium (mEq/L)	136.8 ± 14.4
Potassium (mEq/dL)	5.4 ± 7.1
Chloride (mEq/dL)	102 ± 5.9
Bicarbonate (mEq/L)	18.5 ± 4.9
Total Bilirubin (T. Bilirubin) (mg/dL)	7.5 ± 9.6
Direct Bilirubin (D. bilirubin) (mg/dL)	3.8 ± 5.0
Aspartate Transaminase (AST) (IU/mL)	227.8 ± 264.1
Alanine Transaminase (ALT) (IU/mL)	237.1 ± 281.8
Alkaline Phosphatase (IU/mL)	311.8 ± 285.3
Gamma Glutamyl Transpeptidase (IU/mL)	214.8 ± 238.3
Albumin (mg/dL)	3.1 ± 3.5

Table 2: Frequency of Different Categorical Variables in the Study (n = 91)

Variable	Category	Frequency (%)
Pattern of Liver Enzymes	Hepatocellular	21 (23%)
	Cholestatic	25 (27.5%)
	Mixed	45 (49.5%)
Duration of Hemodialysis	1-2 years	68 (74.7%)
	3-4 years	16 (17.6%)
	>4 years	7 (7.7%)
Co-morbidity with CKD	Hypertension	17 (18.7%)
	Diabetes	15 (16.5%)
	Ischemic Heart Disease	7 (7.7%)
	Others	52 (57.1%)
Cause of Deranged Liver Enzymes	Viral Hepatitis	
	Hepatitis B	12 (13.2%)
	Hepatitis C	19 (20.9%)
	Acute Hepatitis A	3 (3.3%)
	Hepatitis E	4 (4.4%)
	Non-viral hepatitis	Sepsis

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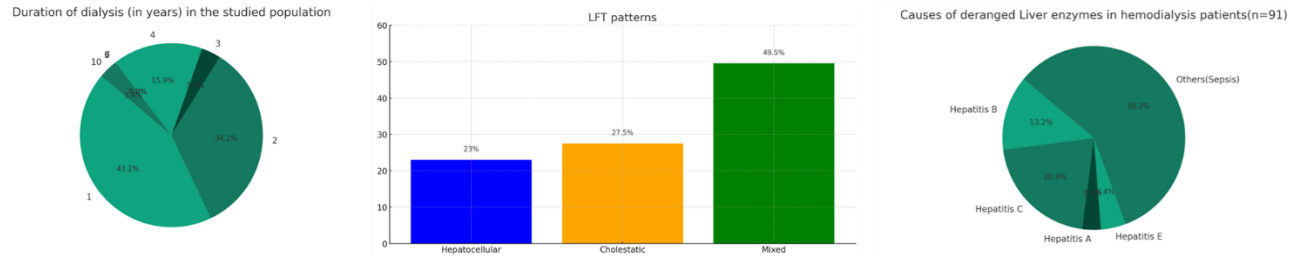

Figure 1 Study Characteristics

The study encompassed 91 patients undergoing maintenance hemodialysis, with their ages ranging broadly but averaging at 44 years, demonstrating a standard deviation of 15 years. The distribution of dialysis duration, a key parameter, revealed that a significant plurality, 38 patients (41.8%), had been receiving treatment for one year, closely followed by 30 patients (33%) for two years. The prevalence of longer-term dialysis was markedly less, with 3 (3.3%) at three years and 14 (15.4%) at four years. Notably, a marginal number, 3 (3.3%), had been on dialysis for a decade, underscoring a trend towards relatively shorter dialysis durations in this cohort (Figure 1).

The liver function test patterns exhibited noteworthy variations. The hepatocellular pattern was identified in 21 patients (23%), while the cholestatic pattern was observed in 25 patients (27.5%). A significant finding was that nearly half of the studied population, 45 individuals (49.5%), exhibited a mixed pattern, indicating a combination of liver function test derangements (Figure 2).

When delving into the etiologies behind the liver enzyme disturbances, viral hepatitis emerged as a significant contributor. Hepatitis C was the most prevalent viral cause, affecting 19 patients (20.9%), whereas Hepatitis B was documented in 12 patients (13.2%). Less frequent were Hepatitis A and E, found in 3 (3.3%) and 4 (4.4%) of the cases, respectively. Remarkably, the largest single cause identified was sepsis, which accounted for over half of the non-viral cases, affecting 53 patients (58.2%) (Figure 3). This indicates that sepsis is a critical factor in liver function aberrations among patients with end-stage renal disease on hemodialysis.

Comorbid conditions were also well-represented in this population, with hypertension noted in 17 patients (18.7%), diabetes in 15 (16.5%), and ischemic heart disease in 7 (7.7%). The prevalence of other comorbidities was substantial, observed in 52 patients (57.1%), demonstrating the complex medical profiles often associated with individuals undergoing long-term dialysis (Table 2).

DISCUSSION

In the cohort of patients with chronic kidney disease (CKD) on maintenance hemodialysis, the presence of comorbid liver diseases was a significant concern, with hepatitis B and C being particularly prevalent among these individuals (10). The interrelation between serum aminotransferase levels and the severity of renal impairment, especially that stemming from glomerular lesions, has been suggested by numerous studies. One study from Iraq indicated that CKD patients, regardless of their dialysis status, presented with lower serum aminotransferases compared to the healthy population, noting particularly diminished AST levels in hemodialysis patients compared to non-dialysis CKD patients (13). Complementing this, Ray et al. noted in 2015 that serum aminotransferases decreased with the advancing severity of CKD (5). Concurrently, Sette et al. observed a negative correlation between serum ALT and AST levels with creatinine, and a positive one with the glomerular filtration rate, suggesting a consistent decrease in these enzymes with the progression of CKD (14). This notion was further supported by a Brazilian study, which documented a reduction in serum aminotransferases in the CKD patients on hemodialysis, positing a multifactorial etiology for this decline (15).

The notion that serum aminotransferase levels may be diminished during conservative CKD treatment and further reduced during dialysis was observed, which was in line with the findings of Fabrizi and colleagues, who posited that reduced aminotransferase activity could obscure the detection of viral hepatitis in the hemodialysis population (16). Nevertheless, the current study found increased transaminase levels among patients, likely attributable to underlying conditions affecting liver enzyme derangements.

The research further determined that the most frequent liver enzyme derangement pattern in the ESRD population on dialysis was mixed, followed by cholestatic and hepatocellular. This could be related to gram-negative sepsis, which was identified as a significant cause of liver enzyme abnormalities, manifesting primarily in the form of raised ALKP and GGT levels (17). The prominence of hepatitis C virus (HCV) infection was noted as the leading viral hepatitis cause of liver enzyme abnormalities in the hemodialysis cohort, aligning with previous findings that indicate a high seroprevalence of HCV in patients dependent on hemodialysis (18-21). Such vulnerability to HCV was ascribed to the increased risk of nosocomial transmission within hemodialysis units and the substantial exposure to blood products, with the duration of dialysis also playing a crucial role in HCV transmission (22, 23).

One of the limitations acknowledged in this study was the small sample size. Despite being pioneering work from this region to evaluate the etiologies and patterns of elevated liver enzymes in hemodialysis patients, larger multi-centered studies are needed for broader validation of these findings.

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CONCLUSION

In conclusion, sepsis emerged as the primary cause of liver dysfunction within the study's hemodialysis population. Contrary to previous research, serum aminotransferase levels were slightly higher in this cohort. Such insights underscore the necessity of stringent infection control measures within the hemodialysis setting, as the association between infection and increased morbidity and mortality in this patient group cannot be overstated. The findings emphasize the critical need for consistent monitoring to preempt and manage liver-related comorbidities effectively, thereby enhancing patient care and outcomes for those with CKD on hemodialysis.

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