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IMPACT OF TOTAL SERUM BILIRUBIN ON HEMATOLOGICAL MARKERS, RENAL FUNCTION AND LIVER FUNCTION TESTS

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Abstract

Chronic kidney disease (CKD) is a significant health concern that can progress to end-stage renal disease (ESRD) and increase the risk of mortality. Studies have shown that lower levels of total bilirubin in the blood are associated with a higher risk of developing CKD. However, the relationships between serum bilirubin levels, renal function, and liver function remain unclear, and these associations have not been thoroughly explored in Peshawar, KP.

Aim and Objective: *This study aims to determine the prevalence of CKD in individuals of both genders with obstructive biliary diseases and to assess the impact of total bilirubin levels on various liver function markers. Additionally, the study seeks to analyze and compare differences in complete blood count (CBC) results and their effect on total serum bilirubin levels.*

Methodology: *A cross-sectional study was conducted at Abasyn University and Prime Teaching Hospital. Blood samples were collected in EDTA and gel-top tubes for the assessment of hematological and biochemical parameters.*

Results: *A total of 300 individuals were sampled from the Prime Teaching Hospital in Peshawar, comprising 54.3% males and 45.7% females. The study included participants from various age groups: 4.2% were 10-20 years old, 5.6% were 21-30, 13.9% were 31-40, 15.3% were 41-50, and 61.1% were over 50 years old. Age distribution by gender revealed varying proportions of males and females within each age group. The levels of hemoglobin, white blood cells, and platelets were found to be predictive of serum bilirubin (SBR) severity, as they were associated with different levels of these parameters. Distinct relationships were identified between hemoglobin (HB), total leukocyte count (TLC), platelet count (PLT), and SBR.*

Conclusion: *Abnormalities in several biochemical and hematological markers are associated with CKD. Regular evaluation of these markers in CKD patients is essential, as addressing these abnormalities can help reduce CKD-related morbidity and mortality.*

Keywords: *Alanine transaminase, Chronic kidney disease, Serum bilirubin level, Total leukocyte count*

INTRODUCTION

Chronic kidney disease (CKD) is a significant health concern that has the potential to result in end-stage renal disease (ESRD) and heightened mortality (1, 2). One of the most significant health conditions that leads to serious health difficulties like death, end-stage renal failure, and cardiovascular disease is chronic kidney disease (CKD) (3). A research was conducted in a tertiary care hospital to determine the prevalence and severity of chronic kidney disease (CKD). The study examined the hematology and biochemistry of 300 individuals with chronic kidney disease (CKD). Approximately 46% of the patients were diagnosed with stage 3 chronic kidney disease (CKD), whereas 29% were classified as stage 4. 42% of cases were attributed to hypertension. In comparison, 22% were attributed to diabetes, resulting in chronic kidney disease (CKD). A study discovered strong correlations among chronic kidney disease (CKD), age, gender, and body mass index (BMI) (4). Reduced levels of serum bilirubin could be used to forecast how chronic kidney disease will develop. An increased risk of chronic kidney disease (CKD) was linked to lower serum total bilirubin levels (1, 5). Patients receiving peritoneal dialysis (PD) have a 3-year death risk that is associated with their blood total bilirubin levels. Although somewhat increased amounts of blood total bilirubin might be advantageous, excessively high or low levels can be potentially risky (6). The study found a positive

correlation between total blood bilirubin and eGFR, and a negative correlation between total serum bilirubin and albuminuria in a sample of 633 Japanese type 2 diabetes patients from a hospital (7).

Assessed several hematological markers in individuals with chronic kidney disease (CKD) in Pakistan. The study comprised a cohort of 125 patients with chronic kidney disease (CKD) and a control group of 100 individuals who were in good health. The findings indicated that the patients with chronic kidney disease (CKD) had notably reduced levels of hemoglobin, hematocrit, and red blood cell count in comparison to the individuals in good health. Additionally, the research revealed a higher prevalence of anemia among those in the late stages of chronic kidney disease (CKD) (8, 9). Anemia and chronic renal disease commonly coexist in individuals with heart failure (HF) and are associated with a worse prognosis (10). A correlation has been found between elevated levels of uric acid in the blood and the occurrence of venous thromboembolism (VTE). This suggests that high serum uric acid levels may serve as a novel risk factor for the illness due to the antioxidant properties of uric acid (11, 12).

Total serum bilirubin, a yellow compound produced by the breakdown of red blood cells, serves as a significant marker for liver function and is widely used in clinical diagnostics to assess hepatic and hematological disorders (13). Bilirubin exists in two forms: unconjugated (indirect) and conjugated (direct). Elevated levels of total serum bilirubin can indicate various pathological conditions, including hemolytic anemia, liver cirrhosis, and bile duct obstruction (14). Understanding the impact of bilirubin on other hematological markers, renal function, and liver function tests (LFTs) is crucial for a comprehensive evaluation of patients' health status.

Several studies have demonstrated a correlation between bilirubin levels and hematological markers. For instance, high levels of bilirubin have been associated with increased reticulocyte counts and elevated lactate dehydrogenase (LDH) levels, both indicative of increased hemolysis (15). Additionally, elevated bilirubin levels have been linked to changes in hemoglobin and hematocrit values, reflecting the underlying red blood cell turnover and clearance rates (16). These changes underscore the significance of monitoring bilirubin in conjunction with other hematological parameters to accurately diagnose and manage hemolytic conditions.

Furthermore, total serum bilirubin has been shown to influence renal function, particularly in patients with liver disease. The accumulation of bilirubin can lead to the formation of bilirubin casts in renal tubules, potentially causing obstructive nephropathy and impairing kidney function [5]. Studies have also highlighted the relationship between serum bilirubin levels and serum creatinine, urea, and estimated glomerular filtration rate (eGFR), suggesting that elevated bilirubin may serve as a marker for renal impairment in certain clinical scenarios (17). This interplay between bilirubin and renal function emphasizes the need for a multidisciplinary approach in managing patients with concurrent liver and kidney disorders.

In addition to its role in hematological and renal function, bilirubin levels are crucial in assessing liver function tests (LFTs). LFTs, which include measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), provide insight into liver cell integrity and biliary tract function (18). Elevated bilirubin levels, particularly conjugated bilirubin, often correlate with abnormal LFTs, indicating liver dysfunction or biliary obstruction (19). Understanding the relationship between total serum bilirubin and LFTs is essential for the differential diagnosis of liver diseases and for monitoring disease progression and response to therapy.

High levels of uric acid in the blood have been found to be correlated with an increased probability of the onset of chronic kidney disease in male individuals The presence of heightened levels of uric acid in the blood was autonomously associated with a heightened likelihood of developing chronic kidney disease, a connection that remained significant even after accounting for various established risk elements like age, hypertension, and diabetes. Regular monitoring of serum uric acid levels can therefore play a vital role in the early detection and management of chronic kidney disease, potentially reducing the risk of further complications (20).

This study aims to evaluate and compare the influence of high bilirubin levels in the bloodstream on kidney and liver function deterioration while considering variations in hematological markers among the

people in District Peshawar, KP. In addition, our objective is to investigate the impact of serum total bilirubin levels on the progression of different liver function indicators. We also intend to evaluate and analyze the differences in complete blood count results and their influence on the overall level of serum bilirubin.

MATERIALS AND METHODS

The study was conducted using a cross-sectional observational design, and samples were analyzed at the Medical Laboratory Technology Department's Skill Lab at Abasyn University Peshawar and the Prime Teaching Hospital Peshawar. Ethical approval for the study was obtained from the Institutional Ethics Review Committee with reference number IERC-AUP 2023-018. The study included 300 patients, comprising both males and females, who had renal and liver diseases with abnormal hematological markers. Participants were selected based on their ability and willingness to undergo medical examinations and provide relevant information. Exclusion criteria included patients with hematological malignancies, bleeding disorders, pregnancy, chronic inflammatory diseases, and serum creatinine levels below 1.5 mg/dl.

A minimum of 2 milliliters of blood was collected in both EDTA and Gel tubes and transported to the Skill Lab of Abasyn University Peshawar for analysis. The analyzer was calibrated and maintained in strict accordance with the manufacturer's guidelines, including checking the expiration dates of reagents, calibration standards, and quality control samples. To ensure safety, personal protective equipment (PPE) such as gloves and lab coats were used throughout the process. The samples were analyzed following the research protocol (21).

For hematological marker evaluation, a complete blood count (CBC) test was performed to measure white blood cells, red blood cells, platelets, hemoglobin, and other blood cell components. Two milliliters of blood were placed in an EDTA tube, mixed gently for one to two minutes on a sample shaker, and then analyzed using a hematology analyzer. The printed results included all relevant indices (22).

The total bilirubin test was conducted to evaluate bilirubin levels, a chromatic compound produced from the breakdown of erythrocytes. Bilirubin is metabolized by the liver and excreted as bile (21). The test differentiates between two types of bilirubin: (i) unconjugated (indirect) bilirubin, an insoluble form produced during red blood cell breakdown, and (ii) conjugated (direct) bilirubin, a water-soluble form processed by the liver for elimination. The test procedure involved mixing the reagent and sample in the specified ratio (as outlined in Table I), allowing the mixture to incubate at room temperature for 5 minutes, and then aspirating the reaction mixture into the flow cell for absorbance measurement. The final color of the reaction remains stable for up to 8 minutes if protected from direct light.

Table I. Test Procedure (*R=Reagent)

	Bilirubin Total	Bilirubin Direct
R T1	500 µl	
R T2	10 µl	
R D1		500 µl
R D2		10 µl
Serum	25µl	25µl

Methodology for SGPT; Liver function tests, or LFTs, evaluate a number of liver health factors. The test producer fellow the literature of (21). i. Collect 2 milliliters of blood. ii. Use R1 400. iii. Use R2 100. iv. Use 50 micro liters. v. Place the serum in a water bath for 1 minute. vi. Outcome was document.

Evaluation of renal function; specifically for creatinine and urea analysis. Heat the reagent to a temperature of 37 °C. Proceed to label the test tube for each patient. Next, the blood is subjected to centrifugation, and the serum is extracted for testing purposes. Dispense 250µl of reagent R1. Next, include 250µl of reagent R2. Thoroughly combine the reagent and then introduce 50µl. Analyze the outcome with a biochemical analyzer (rayto RT 9200).

The data was analyzed using R version 4.3.3. Statistical analysis was performed on each dependent and independent variable.

RESULTS

Samples were collected from 300 individuals at Prime Teaching Hospital, Peshawar, encompassing both male and female participants as shown in Fig. 1(a). Males constituted 54% (n = 163) of the sample, while females made up 45% (n = 137). The study covered a wide range of age groups: 4% of participants were between 10–20 years, 5% were between 21–30 years, 13% were in the 31–40 age group, 15% were aged 41–50, and 61% were over 50 years, as illustrated in Fig. 1(b).

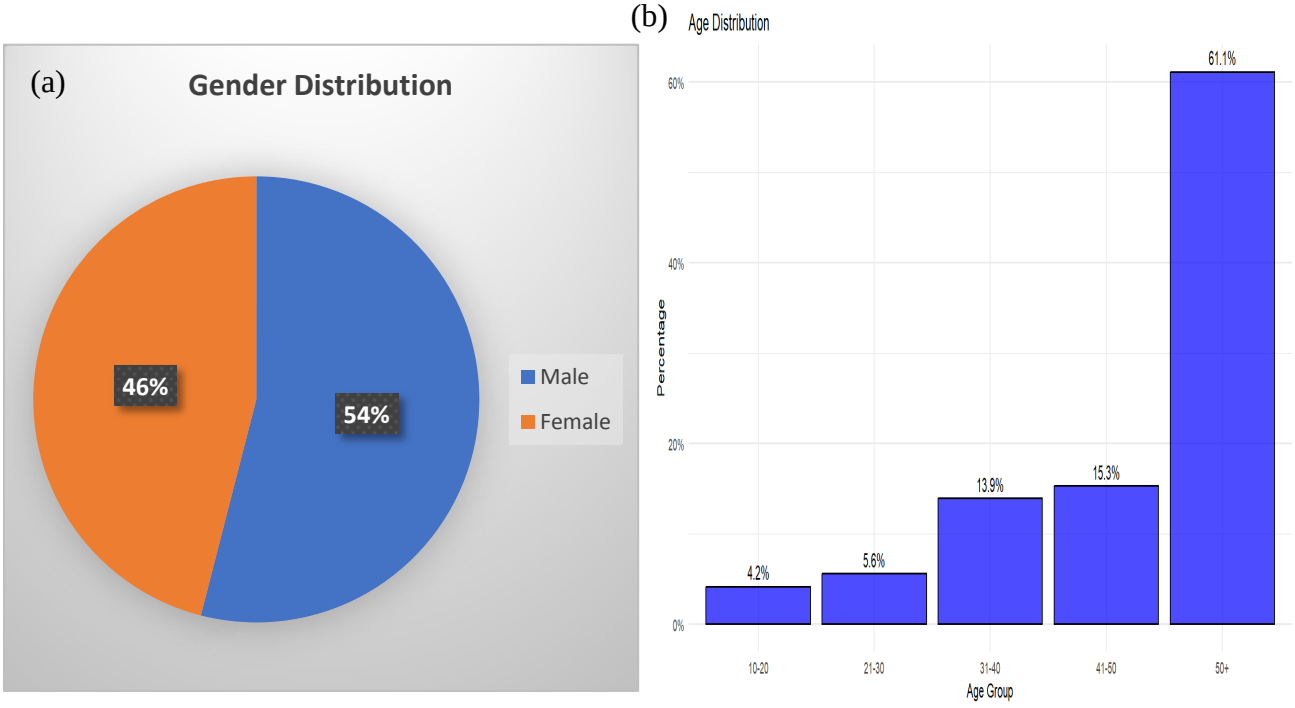
The gender-specific age distribution, as depicted in Fig. 1(c), shows that 25% of participants aged 10–20 were female and 75% male. In the 21–30 age group, there was an equal distribution of 50% male and 50% female. For the 31–40 group, 67.5% were female and 32.5% were male. The 41–50 age group had 31.8% female and 68.2% male, while in the group above 50 years, 43.2% were female and 56.8% male. The majority of participants were aged over 50.

CORRELATION OF RENAL FUNCTION WITH SBR

Renal function tests, including urea and creatinine, showed a negative correlation with serum bilirubin (SBR). Creatinine levels were decreased in 1.6% of patients, elevated in 43.8%, and within the normal range in 18.5% of patients, as illustrated in Fig. 1(d).

CORRELATION OF HEMATOLOGICAL MARKER WITH SBR

The hemoglobin levels were within the normal range for 111 patients (61%). A decrease of less than 5 mg/dl was observed in 62 patients (34%), while an increase of more than 17 mg/dl was observed in 7 patients (3.8%). The white blood cell count was normal for 5.5% of the patients, above 1100 for 35% of the patients, and decreased in 57.8% of the individuals. The platelet count was reported as normal for 16.5% of the patients, below the normal range for 78.7% of the patients, and above the normal range for 3.3% of the individuals. For 47% of individuals, the serum bilirubin (SBR) was below 5.1 µmol/l, whereas 53% had an SBR level over 5.1 µmol/l shown in the Figs. 2 (a) & (b). A substantial Spearman correlation was observed between hemoglobin level and SBR (Spearman's rho = 0.01, $p < 0.05$), indicating a meaningful relationship. The p-value for TLC is 0.03, and for PLT it is 0.05. This indicates that there is a substantial relationship between HB and PLT with SBR.



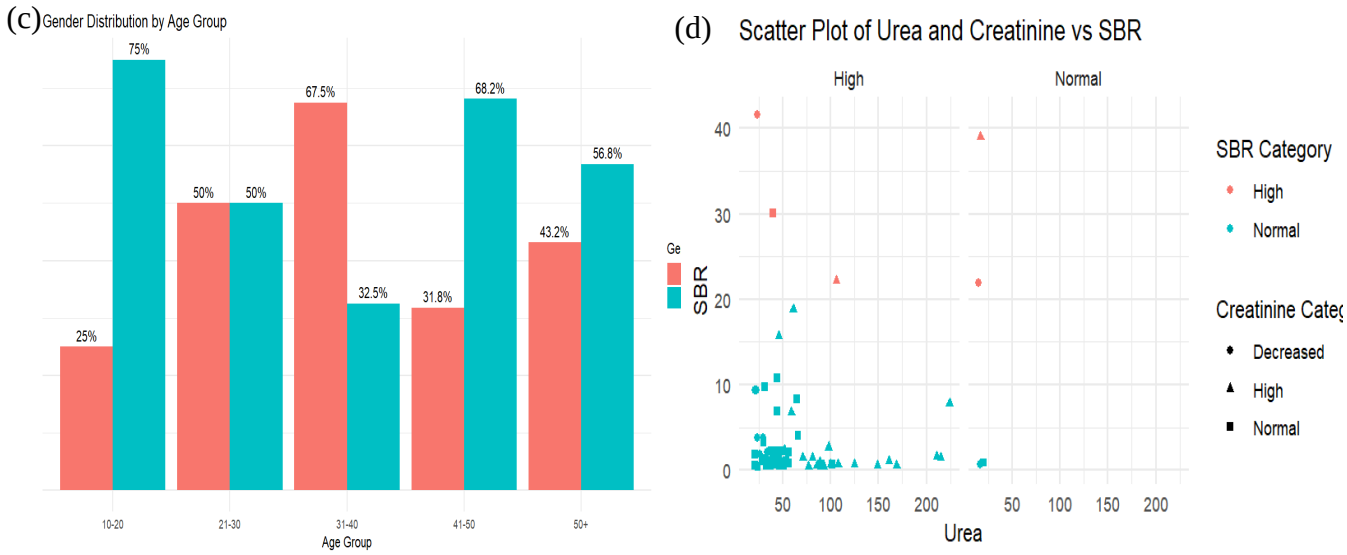


Fig.1 (a). Gender distribution of study samples, **(b).** Age distribution of study samples, **(c).** Age wise gender distribution of study samples, **(d).** Correlation of renal function test with serum biliburin (SBR)

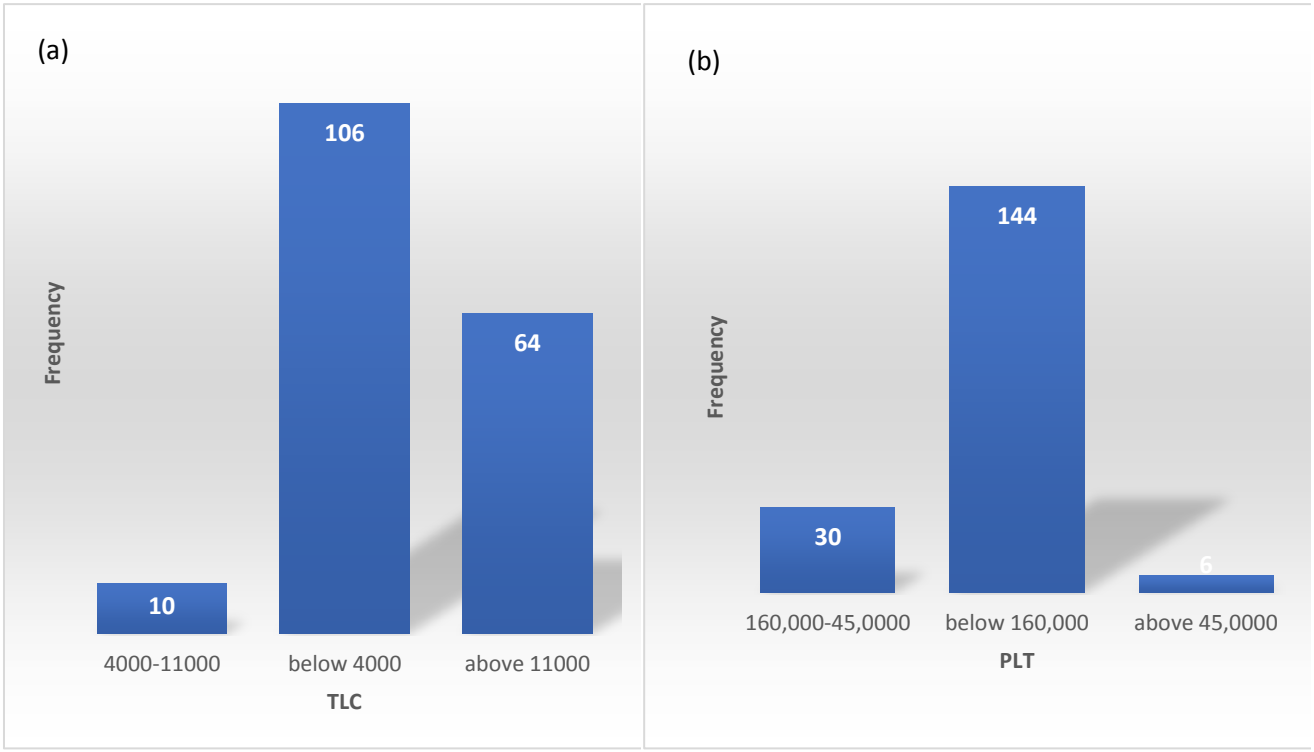


Fig. **2 (a).** The distribution of total leukocyte counts (TLC) across patients is shown, indicating the prevalence of people with counts below 4,000 (n=106), between 4,000 and 11,000 (n=10), and over 11,000 (n=64). (b) The findings demonstrate a notable occurrence of decreased leukocyte levels in the examined group. The distribution of platelet counts (PLT) among patients is as follows: 144 persons have counts below 160,000, 30 individuals have counts between 160,000 and 450,000, and 6 individuals have levels exceeding 450,000. The data reveals a prevalent prevalence of decreased platelet counts among the group under study.

Scatter plots depict the correlation between hemoglobin (HB), platelet counts (PLT), total leukocyte counts (TLC), and serum bilirubin (SBR). Every graphic exhibits distinct data points (colored blue) accompanied by fitted regression lines (colored red). The graphs indicate different levels of correlation, with TLC exhibiting a positive trend while HB and PLT seem to have weaker connections with SBR. Individual abnormal patients' ALPs were 89.3% and normal 10.7%, their ALTs were abnormal 88% and normal 12%, and their HBs were abnormal 73.7% and normal 26.3% (Figs. 3 a & b)

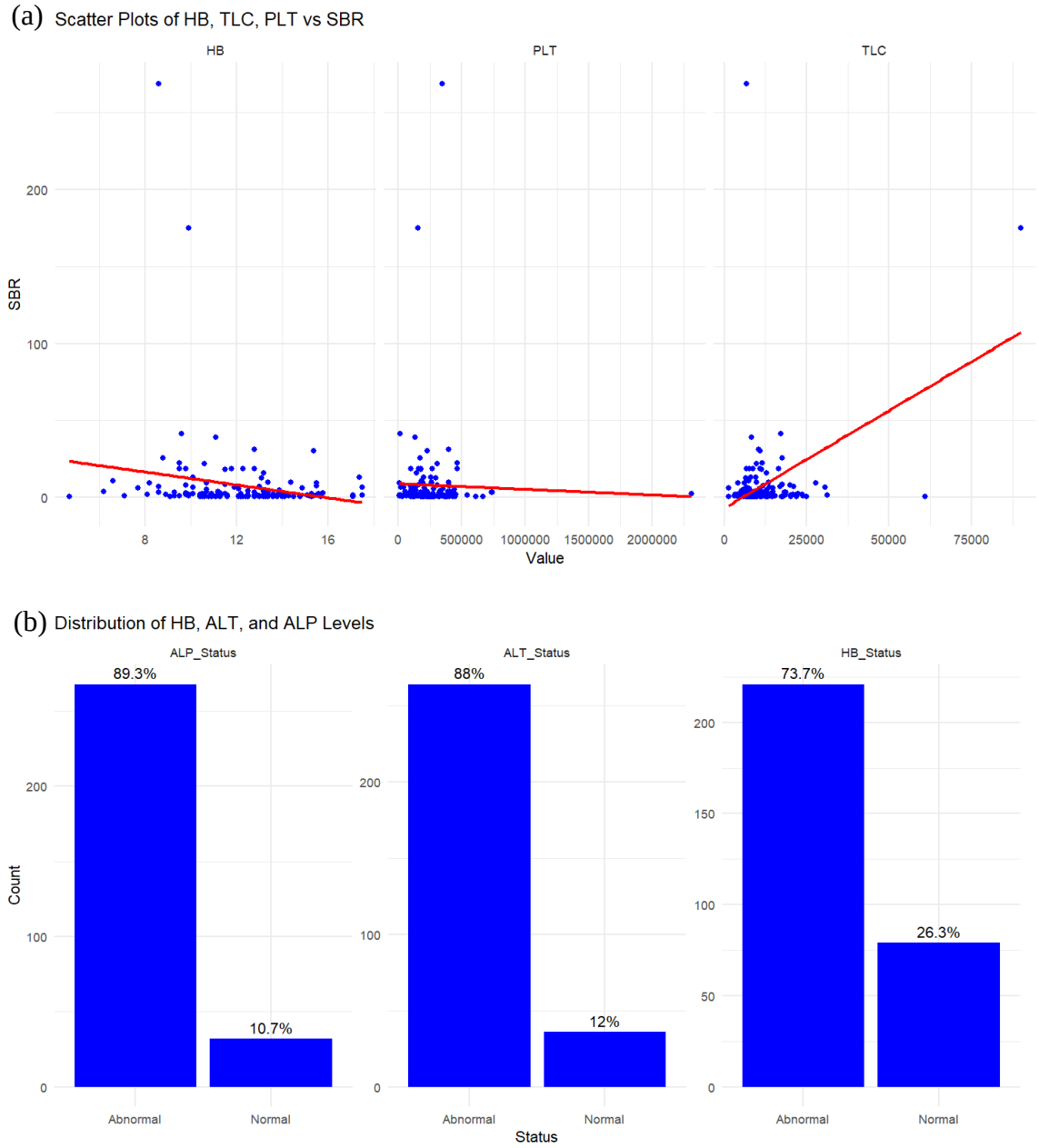


Fig. 3 (a). The distribution of hemoglobin (hb), alanine aminotransferase (alt), and alkaline phosphatase (alp) values within the population under study. **(b).** The bar graphs illustrate the percentage of persons with abnormal vs normal levels. The data reveals that 89.3% have aberrant alp levels, 88% have abnormal alt levels, and 73.7% have abnormal hemoglobin levels. These findings indicate a significant frequency of abnormalities in these biochemical indicators.

DISCUSSION

This research provides valuable insights into the renal function, hemoglobin, white blood cell, platelet, and serum bilirubin (SBR) levels of a diverse population from a Prime Teaching Hospital Peshawar. Our study highlights the intricate relationship between various hematological markers and renal function tests, which significantly influence patient health. The observed correlations between hemoglobin levels, total leukocyte count (TLC), platelet count (PLT), and SBR have important diagnostic and prognostic implications.

Previous studies have reported that mildly elevated serum bilirubin levels are associated with improved renal outcomes, suggesting a protective effect on kidney health. Furthermore, the therapeutic use of bilirubin has shown promise in reducing renal fibrosis, indicating its potential as a treatment target for slowing the progression of fibrosis-related kidney diseases. These findings suggest that bilirubin could play a vital role in preserving renal function and managing fibrosis in kidney disease patients (23).

In this study, a significant Spearman correlation (Spearman's rho = 0.01, $p < 0.05$) was observed between hemoglobin levels and SBR, indicating a meaningful association. The p-values for TLC and PLT were 0.03 and 0.05, respectively, demonstrating a strong relationship between hemoglobin, platelet count, and SBR.

One study has reported that relative hyperbilirubinemia, even within normal reference ranges, is associated with a slower progression of chronic renal function decline. Our findings further support these observations, as bilirubin administration was shown to reduce kidney fibrosis, a benefit demonstrated in both murine models and in vitro studies (24).

Several factors could account for the mild increase in serum bilirubin levels. In our investigation, male participants with elevated serum albumin levels also had higher SBR levels. Conversely, individuals with a history of diabetes mellitus or hypertension were found to have lower SBR levels. These associations have been well-documented in prior research and are consistent with the findings of our study (25, 26).

Hemoglobin (Hb) concentrations and red blood cell (RBC) counts were significantly reduced in patients with chronic renal failure compared to control subjects. This aligns with findings from other studies in the field (27). The primary cause of this reduction is impaired erythropoietin production, a hormone that stimulates red blood cell production in the bone marrow. In patients with renal failure, erythropoiesis is further inhibited by other factors, and the lifespan of RBCs is also significantly shortened, compounding the decline in red cell count and related parameters (28, 29).

Erythropoietin plays a critical role in regulating red blood cell production and prolonging cell viability by delaying DNA cleavage. In its absence, DNA breakage occurs more rapidly, leading to cell death. Even in patients with mild to moderate renal insufficiency, hemoglobin and hematocrit levels decline due to reduced erythropoietin production and increased red cell destruction in chronic kidney disease (CKD) (30).

Our study also found a statistically significant decrease in total leukocyte count ($p = 0.016$). This reduction in TLC among CKD patients undergoing dialysis is attributed to complement activation, which causes neutrophil aggregation and adhesion to endothelial surfaces. Similar to our findings, another study reported a decrease in TLC, although it was not statistically significant. In contrast, other research has shown that CKD patients have elevated leukocyte counts (31).

These results highlight the importance of comprehensive hematological and biochemical evaluations in managing CKD patients and suggest areas for further research to explore these associations in greater detail.

In addition to the aforementioned hematological and biochemical markers, liver enzymes such as alanine aminotransferase (ALT) and alkaline phosphatase (ALP) play a critical role in evaluating overall liver function and their potential association with kidney disease. ALT, an enzyme found primarily in the liver, is typically used as a marker of liver injury. Elevated ALT levels are often indicative of hepatocellular damage, which may indirectly impact renal function through shared metabolic pathways. Similarly, ALP, an enzyme found in the liver, bile ducts, and bones, can provide insight into liver or bone disorders. Elevated ALP levels are often associated with bile duct obstruction or bone disorders, but recent studies suggest a link between higher ALP levels and adverse renal outcomes. These associations are especially critical in the context of chronic kidney disease (CKD), where liver and renal functions are closely intertwined, and the presence of liver dysfunction may exacerbate the progression of CKD (32-34).

Hemoglobin (Hb) levels are another key factor to consider in CKD management. As the primary oxygen-carrying protein in red blood cells, hemoglobin levels are closely linked to erythropoietin production, which is often impaired in CKD patients. Low Hb levels, or anemia, are common in CKD and can lead to significant complications, including reduced oxygen delivery to tissues, fatigue, and an increased risk of cardiovascular events. Maintaining appropriate Hb levels in CKD patients is essential for preventing these complications and improving overall patient outcomes. In our study, hemoglobin showed a significant correlation with serum bilirubin (SBR), further emphasizing the intricate relationship between hematological markers and renal function. Future research should continue to explore these associations to improve

diagnostic and therapeutic approaches for CKD patients, with particular attention to liver enzyme markers, hemoglobin levels, and their role in disease progression (35-38).

CONCLUSION

Our investigation showed that the quantity of total bilirubin in the blood might be a new factor that increases the risk of chronic kidney disease development. Clinical observations have presented convincing evidence to substantiate the involvement of bilirubin in safeguarding against the onset and advancement of both chronic kidney disease (CKD) and renal failure. Reducing these anomalies contributes to a decrease in CKD-related morbidity and mortality.

Recommendations:

I. Establish a systematic protocol for regularly assessing renal function tests, hemoglobin levels, white blood cell counts, platelet counts, and serum bilirubin levels in patients, especially those who are susceptible to renal or hematological issues. This may facilitate prompt identification and quick action.

II. Target aberrant hematological and biochemical indicators with tailored therapies. For instance, individuals with increased serum bilirubin or aberrant hemoglobin levels may benefit from customized treatment strategies.

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Conflict of Interest:

Authors have no conflict of interest.

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