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SU91-MSAHW-S23-046

FAHS

**Sonographic Evaluation of Liver Disease Severity and Renal Stone
Presence in Different Chronic Liver Diseases**



SUPERIOR UNIVERSITY

Thesis Submitted to

The Superior University Lahore

In Partial Fulfillment of the

Requirement for the Degree of

Master of Science in Allied Health Sciences

By

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No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Faculty of Allied Health Sciences, The Superior University, Lahore in partial fulfillment of the requirements for the degree of Master of Philosophy in the field of **“Mention your research area”** in Faculty of Allied Health Sciences at The Superior University, Lahore.

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DEDICATION

To:

My parents who believed in me and instilled me with love of learning

My brothers who have inspired me to reach excellence and supported me to pursue my dreams.

My husband who stood by me through every hurdle and every moment of doubt, who has always been my biggest cheerleader and source of strength.

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Your contributions are gratefully acknowledged.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
CLD	Chronic Liver Disease
Hep B	Hepatitis B
Hep C	Hepatitis C
NAFLD	Non-Alcoholic Fatty Liver Disease
US	Ultrasound
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
FIB4 Index	Fibrosis 4 index
APRI	AST to Platelet Ratio Index

ABSTRACT

Objectives:

To evaluate the prevalence of CLD causes and investigate the relationship between different CLD etiologies as well as severity of liver disease with renal stone presence.

Material and Methods:

A cross-sectional study was conducted on 385 patients at District Headquarter Hospital Nankana Sahib, Punjab. Data were collected after approval from research ethical committee and hospital administration. Participants underwent trans-abdominal ultrasound using a GE Logic P7 machine. Data were scrutinized for liver disease causes, renal stone prevalence and demographic factors using chi-square tests and logistic regression models.

Results:

Among others, most common etiology of CLD was NAFLD (55.6%), followed by hepatitis C (25.7%) and hepatitis B (14.3%). Renal stones were observed in 32.7% of NAFLD patients, 42.4% of hepatitis C patients, and 48.1% of hepatitis B patients. Ultrasound imaging revealed that increased liver echogenicity, liver nodularity with ascites and increase in portal vein diameter were key markers of disease progression and renal complications. Advanced liver disease stages correlated with increased renal stone prevalence in patients without history of urinary tract stone ($p < 0.05$).

Conclusion:

The findings also underscore the metabolic syndrome as a central driver of hepatic and renal dysfunction and emphasize the necessity for multidisciplinary approaches in managing CLD patients. NAFLD and viral hepatitis are major contributors to CLD, with significant renal complications. Ultrasound proved to be a valuable diagnostic tool, emphasizing the need for integrated hepatic and renal health assessments. Preventive strategies targeting metabolic syndrome could mitigate these systemic complications.

Keywords: CLD, nephrolithiasis, ultrasonography.

Chapter 1

INTRODUCTION

Liver diseases take 2 million lives worldwide each year. Complicated Liver Disease is the reason for death in half of population affected with liver diseases. The other half of the decompensated liver disease patients linked to high morbidity and extremely impact the economics. Patients with Chronic Liver Disease (CLD) shows low quality of life indices and are the reason for major strain on the nation's economic resources. Chronic liver disease (CLD) in Pakistan is the leading factor and ranked as 8th reason for the loss of life-year. And also, high ratio of hospital admissions and morbidity are due to CLD (1).

In Pakistan and other developing countries, Chronic liver disease onset is at considerably younger age than developed countries. Among other developing countries around the globe, the highest burden of decompensated liver disease is assumed by Pakistan (2). Chronic liver disease is common clinical problem in our country and is a growing national concern. Chronic liver disease involves the mechanism of advanced damage to liver cell and then restoration of these liver tissue cells which is the reason for scarring called fibrosis and then leads to cirrhosis (3). When normal functions of liver, which includes synthesis of proteins like clotting factor protein, detoxification mechanism for harmful by-products of metabolism, and bile excretion, all deteriorates for more than six months, causes chronic liver diseases. The disease fall in broad spectrum of etiologies. The most common are alcohol associated liver disease, non-alcohol allied fatty liver disease (NAFLD) which worsens to non-alcoholic steatohepatitis (NASH), viral induced chronic hepatitis, genetically susceptible causes, vascular malformation, drugs and idiopathic / cryptogenic around 15% (4).

In Pakistan, risk factors of CLD and its etiologies are different from those in other countries and include viral induced hepatitis (Hepatitis B and C), non-alcoholic related fatty liver disease (NAFLD), non-alcoholic linked steatohepatitis (NASH), ailment such as diabetes mellitus, obesity and ingestion of herbal and dietary supplements are also significant risk factors for CLD, while the rare causes are alcoholic fatty liver condition, autoimmune hepatitis, Wilson's disease and haemochromatosis. Among these causes, globally the prevalence of hepatitis C is 2nd highest in Pakistan following China (1). The traditional Herbal remedies also cause development of CLD, its wide

spread use is considered a standard and routinely practiced in our county as well as others (5).

Chronic Liver diseases leads to liver cirrhosis, it's a final stage, when the normal liver tissue becomes scar tissue, liver parenchyma is damaged irreversibly, wide spread nodules are formed, vascularity is reorganized, occurrence of neo angiogenesis and deposition of extra cellular matrix. At cellular level there is appearance of stellate cells and fibroblasts, underline the mechanism of fibrosis and cirrhosis (4). Due to very high prevalence of CLD, Pakistan was categorized as a cirrhotic state (1). Cirrhosis ratio due to non-viral causes has significantly increased over the last decade and these causes are reported in numerous recent studies as the major etiology of cirrhosis (6). Chronic Liver Disease (CLD) is also a prime factor in the onset of liver cancer, or other extra hepatic complications including acute or chronic renal insufficiency and renal stones (7).

Nephrolithiasis, or kidney stones, has increasing prevalence and incidence worldwide and considered as another significant problem with substantial health impacts and economic affliction. The manifestation of nephrolithiasis is not only expensive due to medical treatment but also has a lot of time away from work and low productivity (8). From extra dietary minerals in the urine, solid concretions or crystal aggregations form in the kidneys (9). The crystals accumulate in the renal medulla and are sometime dislodged and appear anywhere in urinary tract (ureter and urinary bladder) (10).

Around 10–12% of the population at some phase of their lives might experience kidney stones (11). Globally, Kidney stone disease is a typical complaint among health issues. A symptomatic kidney stone developed in the lifetime has an incidence of 5-10%. Multiple factors affect the formation of the kidney stone and are suggested in many epidemiological studies, factors include gender, age, environmental factors, ethnicity, livelihood and high BMI (12). Furthermore, kidney stones can also form as a consequence of various explicit changes in the kidney tissue due to numerous maladies such as type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver disease. In the recent years, Asian countries reported increased occurrence of renal stone, it is perhaps due to westernization of their culture, a sedentary lifestyle and an unhealthy or irregular diet, among other causative factors (13). It is also suggested in few previous studies that patients with family history of hypertension are more

susceptible to conditions like hypercalciuria and hyperuricosuria, which are the risk factors for nephrolithiasis (14).

Recurrent kidney stone development is also a grave issue with the literature suggesting high incidence of stone reappearance within 10 years to be high as 50% (15). The risk of developing chronic kidney diseases, end-stage renal disease, cardiovascular disease, diabetes and hypertension has increased due to renal stone presence, it also decreases the quality of life (16, 17). Kidney stones sometimes lead to ureteral blockage, consequential to life-threatening conditions like septic shock (14).

Although, hepatobiliary and renal system are distinct, metabolic and physiological changes in cirrhotic patients may predispose to nephrolithiasis. Liver and kidney shared some metabolic disease causes in their functional insufficiency. Fluctuations in the process of urine concentration and dilution with altered urine components, low urinary pH, reduced excretion of citrate and augmented excretion of uric acid and calcium are due to metabolic syndrome which causes an increased risk of renal stone formations likely of uric acid or calcium oxalate in nature (13). Renal tubular epithelial cell damage is also a major contributor to stone formation in patients with chronic viral associated CLD (18).

In liver Oxalate is produced but is not metabolized, it is eliminated predominantly through kidneys. With metabolic liver function disease, the excretion of urinary oxalates is considerably high (typically $> 0.8-1 \text{ mmol}/1.73\text{m}^2/24 \text{ h}$, normal < 0.5), resulting in deposition of calcium-oxalate (CaOx) within the parenchyma of kidneys called as nephrocalcinosis/oxalosis or formation of urinary tract stone (urolithiasis). In this way the urogenital tract shows the impact of primary liver disease (19).

The diagnosis of liver cirrhosis and renal stones involves a combination of clinical assessment, laboratory investigations, imaging studies and in some cases biopsy is mainly done for evaluation of liver disease. In assessment of liver disease the physician physically examines the patient and look for the clinical signs of cirrhosis which include jaundice, spider angiomas, palmar erythema, and signs of portal hypertension such as splenomegaly and ascites (20). Laboratory tests often reveal abnormalities such as elevated liver enzymes, hypoalbuminemia, and coagulopathy. Imaging studies show internal anatomy/pathology, ultrasound, CT scan, and MRI, can

detect liver nodularity, splenomegaly, and other features of cirrhosis. With advancement of imaging technology the liver stiffness and fat content are determined by transient elastography, a specialized ultrasound procedure. Child-Pugh scoring system based on combination of laboratory and clinical assessment is widely used. However, a liver biopsy remains the gold standard for a definitive diagnosis, allowing for the assessment of fibrosis and nodular regeneration (21, 22, 23, 24).

Non-contrast spiral computed tomography (CT) scan is the imaging examination of choice for the diagnosis of nephrolithiasis due to its high sensitivity and specificity in detecting kidney stones, as well as its ability to determine the size, location, and stones density. Also the supportive information can be taken from the urine analysis, as the presence of hematuria, crystals and pH of urine, while the underlying metabolic disorders contributing to stone formation can be evaluated by the serum biochemical test (21).

Liver disease advancement in patients causes renal dysfunction and have deranged laboratory results such as serum creatinine, which misleads the diagnosis of renal dysfunction or stone presence (25). Abdominal or renal ultrasound is initially and routinely done for investigation of renal stones in liver disease and is ideal in this population to avoid radiation exposure, but for accurate diagnosis computed tomography is considered as gold standard. Moreover, patients with primary liver disease, risk of bleeding and other complications like ascites and hepatic hydrothorax should be carefully assessed (22, 26).

Among all the imaging modalities used in modern medicine ultrasound is primary (27). Its characteristics also include easy availability, providing real-time and quick dynamic images, non-invasive evaluation of disease and patient health. Other than x-rays, Ultrasound is the only modality with non-ionizing radiation nature that can be escorted to the patient's bedside for prompt evaluation (28, 29). Hepatorenal syndrome often remains undiagnosed until there is significant disease progression and portal hypotension linked to altered renal function and ascites (30). Abdominal Doppler ultrasound helps in better and earlier diagnosis (31).

With abdominal ultrasound, manifestations of chronic liver disease from fat deposition in liver parenchyma (fatty liver disease, steatosis), viral induced liver cell damage expressed as inflammation (hepatitis) and multiple long term cell damages cause scarred

tissue appeared as fibrosis/cirrhosis can be diagnosed. The scan may also show liver lesions, abnormal spots or growths on liver (29, 32). In cirrhotic patient ultrasound scan features suggestive of the disease include shrunken liver, fine nodular margins of liver, altered echotexture, coarse liver parenchyma, splenomegaly, ascites, and distended portal and splenic veins (33). Ultrasound has greater sensitivity in detecting liver parenchymal changes (91% vs. 72%) but lower specificity (85% vs. 95%) compared with CT (34). The better specificity of ultrasound for the liver surface changes provides assurance to clinician, the appearance of chronic disease signs confirm the corresponding disease condition. The moderate results in sensitivity urge the use of liver biopsy to confirm the presence of CLD in the setting when ultrasound show no signs of CLD (35). Performing high frequency ultrasound with advance techniques in high risk patients potentially reduce the practice of liver biopsy for CLD diagnosis (29).

Kidney stones appears on ultrasound as hyperechoic (white) focal area with posterior shadowing. To distinguish stones from normal kidney anatomy which may also appear bright white, the posterior acoustic shadowing is a helpful sonographic sign. With color Doppler, Twinkling artifact is a useful finding and valuable in diagnosing smaller stone which may not have been visualized with B-mode ultrasound. However, ultrasound sensitivity and specificity for renal stone detection are 45% and 88%, respectively, while for ureteric calculi, sensitivity is 45% and specificity is 94%. The sensitivity of US decreased with size of stone <3 mm or presence in a non-dilated system, moreover, the larger stone size improves the sensitivity of ultrasound for its detection (36).

The frequency of Chronic liver disease with concomitant nephrolithiasis is significantly greater than the general population. Although, there are limited fact and figures in its support. Literature is reviewed by using Pub med and google scholar. Review articles demonstrate only few accomplished studies to explore the connotation of chronic liver disease with renal stone disease or association of specific cause of CLD like non-alcoholic fatty liver disease, Hepatitis B and Hepatitis C with renal stone. Furthermore, nephrolithiasis frequency in CLD patients diagnosed by ultrasonography is unknown. This gap in evidence highlights the importance to:

- Determine the prevalence of CLD etiologies, assess their association with nephrolithiasis, and explore how disease severity impacts the development of renal stones.

AIM AND OBJECTIVES

The study was conducted with following objectives:

- To determine the prevalence of Chronic Liver Disease causes.
- To evaluate the association of different cause of Chronic Liver Disease and presence of renal stone.
- To investigate the severity of liver disease association with the presence of renal stone.

Chapter 2

LITERATURE REVIEW

Liver is a major and largest internal organ in the body, performing multiple function including detoxification of waste material, storage of glucose, formation and excretion of bile and by products, synthesis of multiple proteins required in multiple function in our body. Any injury to this hard worker and major organ of the body due to exogenous and endogenous factors cause its malfunction, when it unable to recover for more than 6months, the liver dysfunction is called as chronic liver disease (CLD). Multiple factors and agents causes this persistent injury to liver, which changes it morphological and functional ability leading to cirrhosis. In Pakistan recent prevalence of liver cirrhosis was 13.5% (37). Malfunction of liver also causes other extrahepatic and systematic problems. Nephrolithiasis (kidney stones) is among major and emerging one. Recent literature demonstrated the higher prevalence of kidney stones in CLD patients. This literature review will highlight the prevalence of CLD, renal stones in CLD, risk factor and mechanism suggesting the association between these two different organs, various diagnostic tools for evaluation of hepatic and renal abnormalities and severity stratification techniques suggested in many.

2.1 Chronic Liver Disease Epidemiology and Related Conditions

Worldwide among other leading health issues chronic liver disease is foremost with numerous etiologies and contributing risk factors in its development. Cheemerla *et al.*, (38) noted that now a day's pattern of CLD causes varies and includes NAFLD as the leading and globally renowned cause, approximately acknowledged in 59% of cases. The increasing NAFLD prevalence rather than viral mediated causes are driven by factors like increase in sedentary life style and co morbidities like obesity and diabetes, liver disease progress to condition including fibrosis and cirrhosis which are related to hepatocellular carcinoma. The ratio of obesity-related liver disease are increasing globally. It is also suggested the NAFLD caused by metabolic problems subsidize the formation of renal stones.

Table 2.1: Liver cirrhosis caused by etiologies of Chronic Liver Disease, Dar *et al.*, (23)

Etiologies	Percentage (n)
Hepatitis C	47.6% (39)
Alcoholic Liver Disease	20.7% (17)
Hepatitis B	17.1% (14)
Fatty Liver Disease	12.2% (10)
Other rare causes	2.4% (2)

In developing countries of Asia and Africa, viral caused hepatitis remains leading etiologies of CLD, especially hepatitis B (HBV) and hepatitis C (HCV). Significant proportion of chronic liver disease cases in Pakistan are due to viral hepatitis as demonstrated in study conducted by Ali *et al.*, (33) . In progressive stage HBV and HCV infections causes liver cirrhosis can lead to development of hepatocellular carcinoma.

Alcohol intake also contribute to development of chronic liver disease which is common in western culture and some Asian countries like India. Gracio *et al.*, (22) defined alcohol abuse as another major caused of CLD, even in small amount and daily intake causes increased portal vein pressure persistent increase pressure leads to portal hypertension which is major contributor to liver cirrhosis. Patient with portal hypertension develops renal dysfunction and ascites, complicating the patient's condition and leads to poor prognosis. In patients with ALD related cirrhosis, complications like variceal bleeding, encephalopathy, and kidney dysfunction appears. Liver dysfunction with renal damage increases the probability of kidney stones formation.

2.2 Metabolic Risk Factors for Chronic Liver Disease

Metabolic disorders include a long list but diabetes, insulin resistance, hypertension, obesity and dyslipidemia are common major risk factors for the development of chronic liver disease. Majid *et al.*, (5) studied the knowledge of patients about risk factors for CLD in admitted patients of civil hospital Karachi, Pakistan. They highlighted the rise in diabetes and obesity has fueled the increasing incidence of NAFLD and other liver diseases. The risk of nephrolithiasis was also influenced by

the increase in metabolic conditions that damaged liver. Similarly, Chang *et al.*, (14) discussed that patients with metabolic syndrome were older with higher blood pressure, serum total cholesterol, triglycerides, blood sugar, uric acid, low density lipoproteins, and larger waist circumference than those without any metabolic syndrome. The pro-inflammatory and pro-thrombotic environment was the contributing risk to both liver and kidney dysfunction. A study on 298 patients from Lahore General Hospital performed by Ahsan *et al.*, (39) showed factors like age over 40 years, hypertension, and obesity (BMI > 30) were strongly correlated with a higher prevalence of kidney stones in NAFLD patients suggesting underlying metabolic factors. Interestingly, no significant correlation between diabetes and nephrolithiasis was observed in their study and suggests insulin resistance drives the disease mechanism in patients with NAFLD. Study conducted by Kim *et al.*, (8) on a cohort including over 200,000 Korean adults also showed elevated BMI, higher glucose levels, and dyslipidemia as the major factor contributing to nephrolithiasis in NAFLD patients and suggested the stronger association between these two disorders more in men than women. Moreover, the common use of herbal medications in many countries, including Pakistan, as part of traditional medicine is also the emerging cause of CLD. Majid *et al.*, (5) in their study found that liver damage could be aggravated by the use of certain herbs and contribute to the progression of CLD. This also affects renal function, increasing the risk of nephrolithiasis. Thus, during assessment of patients with CLD, it is important to consider the potential impact of these substances on liver and kidney health. Khan *et al.*, (2) highlighted the endemic causes like viral hepatitis like Hepatitis B and C, also the electrolyte imbalance was observed in the study population suggesting progressive liver disease and predispose to other illness.

2.3 Prevalence of Renal Stones in CLD Patients

Higher prevalence of renal stones in patients with CLD are suggested in multiple research compositions. Several studies mention this concomitant prevalence compared to the general population while other shows its variation with underlying liver disease etiology. Few of them mentioned the increased prevalence of renal stones especially among patients with advance CLD condition.

A two-fold increase in nephrolithiasis occurrence was demonstrated in study by Porter *et al.*, (7) in CLD patients compared to controls, an incidence rate of 26% was noted in the liver disease group whereas 14% in the control group. They also concluded that

the risk of developing kidney stones was significantly exaggerated by cirrhosis and progressive disease state especially in hepatitis C. Several factors which are common in patients with chronic liver conditions, such as altered metabolic profiles, fluid imbalances, and impaired kidney function contribute to renal stone development. Chen *et al.*, (17), included data of 13262 women with hepatitis C infection from National Health and Nutrition Examination Survey (NHANES) and explored the prevalence of nephrolithiasis in them. HCV infection with the presence of kidney stones had positive association in their study population (OR = 1.70, 95% CI: 1.13–2.56). The study also showed statistically significant difference among specific subgroups, such as those with obesity, BMI in the range of 25-29.9kg/m²(OR = 2.45, 95% CI: 1.24–4.83) and other races (OR = 8.17, 95% CI: 1.62–41.22). However, no causal relationship was established from the study findings due to cross-sectional study design, further investigation to explore the mechanisms linking the two maladies, would be needed. Similarly, a higher frequency of nephrolithiasis in patients with NAFLD and hepatitis C was reported in Khan *et al.*, (2) research. The prevalence of kidney stones was found higher in their patient population compared to their control group, 42.4%, of HCV was with renal stone while 32.7% NAFLD patients had renal stone. Liver disease etiology was observed to be significantly associated with presence of kidney stones and relationship was emphasized in their study. In the same way, Reddy *et al.*, (40) had studied the contribution of chronic viral hepatitis to develop renal stones in compromised patients and observed higher prevalence of kidney stones in HCV patients.

Viral Hepatitis B (HBV) infected patients discharged from Urology department at Affiliated Hospital of Anhui Medical University, China were retrospectively studied by Hou *et al.*, (11) and explored the relationship between upper urinary calculi and HBV positive individuals. Observation from 1,062 patients included in the study advocated higher prevalence of urinary calculi in chronic HBV infected patient, proposing renal stone formation was directly contribute by viral infection presence. The study also observed pH greater than 6 in HBV-positive patients with kidney stones and highlighted urinary pH as a risk factor, also the role of metabolic abnormalities with altered urinary pH was suggested for renal stones formation in CLD patient.

In a study by Einollahi *et al.*, (41) a significant association between NAFLD and urolithiasis were observed. The study revealed NAFLD patients had a 2.4 times higher risk of developing kidney stones compared to healthy individuals. This suggests that individuals with NAFLD were predisposed to renal complications as fatty liver is not only a liver disorder but also a metabolic disease. The association between NAFLD and renal stones was also explored in study of Kauvar *et al.*, (42) and found higher prevalence of nephrolithiasis in patients with fatty liver compared to the healthy population. Among 250 patients, 80% of study population were men, indicated a particularly higher risk for kidney stones in men with NAFLD than women with same disease. Correspondingly, Sametzadeh *et al.*, (43) indicated that NAFLD patients with renal stones had a significantly higher frequency (82.1%) compared to those without renal stones (17.9%) ($P < 0.0001$). The study further suggested that the likelihood of renal stone formation is positively correlated and increased with severity of NAFLD, with the highest frequency of renal stones (100% vs. 78.8%, $p = 0.008$) was shown in severe NAFLD patients. Renal stone formation in NAFLD patients was significantly associated to age as risk factor while no vulnerability was appeared to any specific gender.

Chang *et al.*, (14) in their cross sectional and longitudinal cohort study, demonstrated the major risk factor for renal stone in patients with metabolic syndrome compared to non-diseased. Metabolic syndrome included risk factors such as hypertension, obesity, and dyslipidemia. The findings from the study suggested the strong association between metabolic syndrome and kidney stone formation and significant likelihood of renal stone formation in diseased compared to individual having no metabolic disturbance. They concluded the pathogenesis of nephrolithiasis was mediated by metabolic alteration in CLD patients having non-viral causes.

Table 2.2: Associated risk factors for renal stone development mentioned in previous studies

Study by	Year	Risk Factors
Gracio <i>et al.</i> , (22)	2016	Portal hypertension, alcohol abuse
Porter <i>et al.</i> , (7)	2018	High BMI, dehydration, family history of liver and renal disease
Kauvar <i>et al.</i> , (42)	2018	Men with fatty liver
Kim <i>et al.</i> , (44)	2019	Gall stones
Wei <i>et al.</i> , (45)	2019	Older age, high BMI, high blood sugar levels, elevated triglycerides, cholesterol, and LDL levels, lower or higher physical movement, low educational background
Khalil <i>et al.</i> , (46)	2020	Urinary pH
Hou <i>et al.</i> , (11)	2022	
Chang <i>et al.</i> , (14)	2021	Hypertension, obesity, and dyslipidemia
Cheemerla <i>et al.</i> , (38)	2021	Obesity related metabolic disturbances
Chen <i>et al.</i> , (17)	2022	BMI (25-29.9) Other races
Moftakhar <i>et al.</i> , (16)	2022	Fatty liver, diabetes, and hypertension as well as age, male sex, overweight, and high social economic status

While Gracio *et al.*, (22) discussed the severity of liver disease and complications of cirrhosis in addition to the metabolic factors that linked to kidney dysfunction. The increased pressure in the portal venous system in progressive CLD condition, highlights the relationship between portal hypertension (a major complication of cirrhosis) and renal malfunction and also suggests renal tubular damage. Cirrhotic patient with worsening in systemic malfunction could develop kidney stone, which not only further complicate the clinical management but also a factor for increasing financial burden on the resources. Consistently, Khalil *et al.*, (46) in their case control study by grouping the patient with non-alcoholic fatty liver disease and without disease, also the NAFLD group was further subdivided to diabetic and non-diabetic

group. The study aimed to explore the urinary pH as indicator of fatty liver disease ongoing in the patient. The findings suggest strong association between the simple markers for the disease assessment, which can be utilized for screening a large population. Besides, Kim *et al.*, (44) emphasized the metabolic interplay between liver dysfunction and kidney health through their study demonstrating the bidirectional relationship between gallstones and renal stones, as the presence of gallstones significantly increasing the risk of renal stones.

In southern Iran Moftakhar *et al.*, (16) conducted a large cohort study and indicated significant association between kidney stones, various risk factors and disease conditions, including higher financial prestige, male gender, high BMI, fatty liver, diabetes, and hypertension. The study findings revealed the shared pathophysiological mechanisms that contribute to both kidney stones and liver diseases, as kidney stones were more common in individuals with metabolic abnormalities, such as fatty liver. The economic burden associated with CLD was discussed by Qazi *et al.*, (1). Another malady, kidney stone with CLD exacerbate the financial strain on individuals and healthcare systems.

2.4 Mechanisms Underlying Renal Stone Formation in CLD

The association between CLD and nephrolithiasis is driven by combination of several underlying mechanisms like metabolic, hormonal and physiological. However metabolic disruptions is primary contributor in liver diseases. Conditions like NAFLD and metabolic syndrome, hallmarks the presence of Insulin resistance, all these contribute to renal stone formation. Li *et al.*, (15) examined the relationship between gallstones and increased risk of renal stones development and noted metabolic disturbances like diabetes, hypertension, hyperlipidemia, hyperparathyroidism, urinary tract infection, gout, Crohn's disease, liver cirrhosis and obesity in the study population. These metabolic disturbances are common in CLD patients and are contributor to renal stone development. The risk of kidney stones was found to be significantly higher in individuals with gallstones, 1.79-fold higher compared to individuals without gallstones. The associated liver dysfunction or advance liver cirrhosis was found to had interaction with gallstone ($P = 0.0253$).

Other than insulin resistance, oxidative stress, and altered urinary composition are also linking liver disease with nephrolithiasis. NAFLD, is not only associated with

metabolic syndrome, insulin resistance, and dyslipidemia, it can also cause imbalance in kidney function leading to altered urinary profile.

Ergani *et al.*, (13) defined the insulin resistance affecting the renal tubules and ability of the kidney to regulate ammonia production. Ammonia synthesis is affected in this condition causes lowering of urine pH and favors uric acid crystallization in acidic environment result in renal stones. Insulin resistance worsens the morbidity of obesity and intensifies malfunction of both liver and kidneys. Moreover, accumulation of fatty acids in the liver is demonstrated by Nguyen *et al.*, (34) which results in cellular damage and renal dysfunction due to oxidative stress. The study noted mismanagement in calcium and ammonia levels are also seen with higher levels of urinary calcium and oxalate in patients with fatty liver disease, further increasing their risk of kidney stones. Similarly, Ahsan *et al.*, (39) noted the increasing risk of kidney stones, in a study conducted with 298 NAFLD patients who underwent CT abdomen pelvis at Radiology Department of Lahore general Hospital.

The underlying pathophysiology for increased risk of kidney stones in CLD patients is multifactorial. Altered lipid metabolism and dyslipidemia also contribute to stone formation in addition to metabolic disturbances. Badillo *et al.*, (47) found abnormal lipid profiles (high levels of triglycerides and cholesterol) in NAFLD patients which alter the urinary composition by excessive excretion of cholesterol and other precursor substances, promoting stone formation. Furthermore, progressive renal damage due to oxidative stress in NAFLD patients also increases the likelihood of stone development. Chronic kidney disease development due to non-alcoholic fatty liver disease was explored by Lonardo *et al.*, (30) . The study found NAFLD-induced hepatic dysfunction as leading cause of CLD and metabolic abnormalities such as insulin resistance, alters the kidney function. They suggest mechanisms underlying both liver and kidney dysfunction are deeply interconnected with insulin resistance. Also in progressive NAFLD, vasoregulatory changes occur in hepatic and systemic circulation provoke hepatorenal reflex and renal function impairment.

Another critical factor, Lipotoxicity also called as fat deposition reaching above threshold level contributes the development of nephrolithiasis in CLD patients. Higher serum creatinine levels are also found in CLD patients with progressive disease course. Khalil *et al.*, (46) found liver injury markers like ALT and AST not to be

significant in NAFLD diagnosis. Additionally, dehydration increasing the concentration of urine with stone-forming solutes in patients with cirrhosis.

2.5 Diagnostic Tools and Clinical Implications

Routinely assessment and accurate diagnosis of both CLD and nephrolithiasis is crucial for better prognosis in interventions and management. Saksena *et al.*, (48) highlighted the importance of using tools like the Child-Pugh classification in monitoring renal function of CLD patients and assessment of liver disease severity. Renal dysfunction was found in 36.9% of patients, with higher prevalence in patients with alcoholic liver disease in their study population. Allan *et al.*, (29) reviewed the diagnostic accuracy of ultrasound in identifying chronic liver disease and noted its effectiveness as a tool in early detection. Among non-invasive tools for liver disease diagnosis, Ultrasound is readily available (49), cost-effective imaging technique and identify both liver abnormalities and kidney stones, making it as an essential tool in the diagnostic workup of patients with CLD. Kim *et al.*, (44) also emphasized the ultrasound role in screening high-risk patients for presence of both gallstones and kidney stones, due to its non-invasive and non-ionizing characteristics. Analysis of, how evaluation performed with ultrasound as imaging tool help in diagnosing chronic liver diseases and assessing liver fibrosis was done by Afzal *et al.*, (50) while also being useful for detecting renal stones. To evaluate liver pathology in cirrhotic patient such as portal hypertension, advance ultrasound techniques like Color Doppler ultrasound and contrast-enhanced ultrasound can also be applied. Other non-invasive scoring systems (such as FIB-4 and APRI) with Ultrasound also give valuable for both liver and kidney diseases diagnosing and managing. Qin *et al.*, (51) conducted the cross sectional study on 2058 NAFLD patients in china to evaluate a marker for hepatic fibrosis, FIB-4 score and assess the associated increased risk of urolithiasis in NAFLD patients. The finding from study suggests FIB-4 score as a screening tool in identification of high risk patient for both liver disease progression and kidney stone development, allowing more targeted interventions for better outcomes. In addition to ultrasound, other imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are valuable in diagnosing liver pathologies, to evaluate the degree of severity and kidney stones. Nam *et al.*, (10) Zeina *et al.*, (52) and Kauvar *et al.*, (42) demonstrated that computed tomography (CT) scans in providing valuable information especially in detecting both liver and renal

abnormalities and useful for clinicians in managing patients with CLD.. Role of MRI-derived proton density fat fraction (PDFF) was suggested as gold standard for liver steatosis assessment, in Ferraioli *et al.*, (53) study. Its potential application also useful in assessing patients at risk of kidney stones due to liver damage.

For more comprehensive assessment of both liver and renal health, these imaging modalities can be utilized, enabling clinicians to more effectively manage CLD and nephrolithiasis. However, as the first-line diagnostic tool, Ultrasound is commonly used in emergency departments and in triage for scrutinizing the patients. Qazi *et al.*, (1) demonstrated liver echogenicity and nodularity as reliable markers for liver disease severity, shows the efficacy of ultrasonography. Moreover, these ultrasound markers have been linked to both liver disease severity and renal stone formation. Riaz *et al.*, (54) found overall diagnostic accuracy of ultrasound as 86.67%, sensitivity of 92.98 %, and specificity of 66.67 % in comparison with gold standard of liver biopsy. The study underlined the role of ultrasound in screening process while in some cases, it cannot be a replacement for more invasive diagnostic techniques like liver biopsy.



Figure 2.1: Gray scale abdominal ultrasound. Showing excessive homogenous fatty infiltration in liver and increased liver parenchymal echogenicity relative to right kidney cortex. Siddiqui *et al.*, (55).

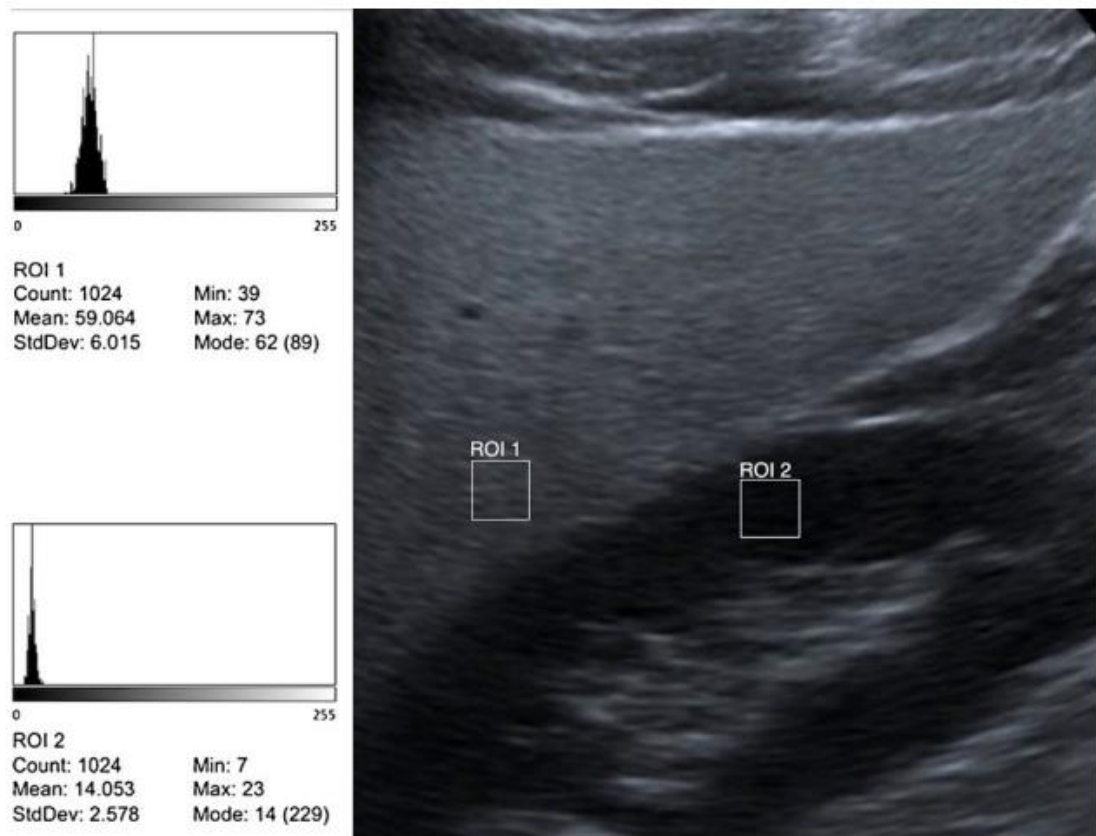


Figure 2.2: Mean Echo intensity quantification. Sonographic Hepatorenal index (SHRI) evaluated by placing two ROI at same depth over liver and kidney cortex, in this example, mean liver brightness (59) divided by mean renal cortex brightness (14) give result of 4.21 (severe fatty infiltration in liver). Freeware ImageJ, National Institutes of Health, Bethesda, MD, USA) (55, 56).



Figure 2.3: B-mode conventional ultrasound showing liver surface and edge nodularity (55).

2.6 Management Strategies and Future Directions

Multidisciplinary approach can address the management of CLD patients at risk of nephrolithiasis. In focus of managing metabolic syndrome interventions such as weight loss, dietary modifications, and increased physical activity should be imparted in the **lifestyle** which may help to reduce the risk of both liver and kidney disease. The importance of controlling blood pressure, glucose levels, and lipid profiles are highlighted in many studies like Kim *et al.*, (8) suggested these modification to prevent the progression of both liver disease and kidney stone formation. Ahsan *et al.*, (39) through study findings suggest the association between hypertension and diabetes in patients with both CLD and nephrolithiasis and signify the importance of managing metabolic conditions to reduce the risk of complication.

In addition to lifestyle changes, managing metabolic abnormalities require pharmacological interventions such as insulin sensitizers, lipid-lowering agents (statins) and antioxidants which may be beneficial for management CLD patients and reducing the risk of nephrolithiasis and other complications. Lee *et al.*, (57) emphasized the use of medication in controlling metabolic risk factors, particularly in with NAFLD and hepatitis C patients. Risnandar *et al.*, (21) defined medications, such as diuretics and ACE inhibitors, can reduce proteinuria and improve kidney function, although hypotension and electrolyte imbalances sometime occur as adverse effect and careful consideration is necessary when managing cirrhotic patients with these medications. However, advance research is needed to explore the effectiveness of these treatments in CLD patients and preventing kidney stones and other complications.

Liver function tests and imaging studies in patients with NAFLD and other forms of CLD should be regularly performed to assess the progression of both liver and kidney disease. As recommended by Poter *et al.*, (7), the chronic kidney disease (CKD) or end-stage renal disease (ESRD) can be prevented through early detection of kidney stones in CLD patients which is critical and can significantly impact the patient's quality of life.

Surgical interventions may be required in patients with advanced liver disease. Some minimally invasive approaches such as extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PNL) have lower risk of complications and are preferred in patients with compromised liver functions.

2.7 Previous Studies

Porter *et al.*, (7) in 2018 uses the cross sectional case control study techniques to evaluate the incidence of nephrolithiasis in patients with chronic liver disease. In their survey of 198 patients and 322 controls which was matched by age, sex and state of residence, they had their health record reviews for confirmed diagnosis of liver disease as primary cause. Aiming to study the cases of CLD as it is a prominent national health concern and could be lead to cirrhosis, liver cancer and renal stones with other chronic conditions. In United States 7-8% of adults had renal stone as painful cause of their unhealthy state. It is also related to several systemic diseases like chronic kidney disease and renal failure. In their study the liver disease group of 128 males with median age 63yrs had BMI of 27.8 which is higher than their 199 male controls of 63yrs having BMI 26.7 ($P < .01$). The most common liver disease was hepatitis C 30% followed by alcoholic cirrhosis 21.2%. They demonstrated the 2 times higher prevalence of nephrolithiasis in chronic liver disease patients and a significant association even after adjusting the confounding variables as age, sex, BMI, family history of kidney stone or liver disease.

Renal dysfunction in chronic liver disease with different etiologies were evaluated by Saksena *et al.*, (48) through prospective cross sectional study during November 2016 to August 2018 in Department of Medicine, Shri. B. M. Patil Medical College, Hospital and Research center, Vijayapur, India; with 65 cases of chronic liver disease fulfilling their inclusion criteria. The alteration of renal function test with gradation of liver disease (Child-Pugh criteria) and with different chronic liver disease (CLD) etiologies are associated due to multi-organ involvement in acute conditions or secondary to advance liver disease. The studied subject were majority of male (90.8%) with mean age of 45.78 $\pm$ 13.19 years. they used predesigned Performa for data collection and patient were interviewed according to its scheme. Renal dysfunction were seen in 36.9% patients, 72.2% were suffered from alcoholic liver disease, 13.9% patients had Hep B and 10.8% had Hep C. They concluded that emphasis and care should be given to the patients in treating CLD regarding their renal function alteration. The morbidity and mortality can be decreased by proper screening, prevention and cautious treatment of CLD and associated renal dysfunction.

Qudsieh *et al.*, (58) aimed to report increased liver echogenicity as important sonographic sign which was unacknowledged before. And also its impact on different

factors like HbA1c, ALT, AST, BMI, serum cholesterol and triglyceride levels etc. They conducted a cross sectional study in the department of Radiology and Gastroenterology of a major public hospital between October 2020 to June 2021. They had taken the patients referred for ultrasound department unknown of having CLD, dyslipidemia or DM. These patients showed the sonographic sign of increased liver echogenicity were then referred to department of gastroenterology for further evaluation and confirmation of fatty liver disease also by excluding any undiagnosed CLD. From the 60 patients out of 320 patients fulfilling the inclusion criteria, lipid profile, HbA1c, and LFT results were taken along with their demographics. The study participants showed mean SD for age and BMI of 45 and 32.5kg/m² respectively. Moreover, 57 patients were obese and had grade II and III liver echogenicity. They concluded a statistically significant relation of liver echogenicity grading (degree of fatty infiltration) and HbA1c (P 0.001), triglycerides (P 0.004), ALT (P 0.03), AST (0.079). In logistic regression analysis HbA1c, AST, age, gender, cholesterol, bilirubin levels and liver size were noted significantly related to liver echogenicity. They also concluded that obesity followed by triglyceridemia were on the top of the leading causes of NAFLD and mentioned that reporting the increased liver echogenicity were found to be essential in early detection and controlling metabolic risk factors (like dyslipidemia and insulin resistance) of NAFLD.

Ahsan *et al.*, (39) conducted the cross sectional study to investigate the association of NAFLD with development of renal calculi in Pakistani women and men of all ages. They had taken a total of 298 patients who underwent CT abdomen pelvis in Radiology department of Lahore General Hospital from October 2022 to January 2023. patients with NAFLD, viral liver disease, liver cirrhosis, splenectomy, liver metastasis, chronic renal failure, transplanted kidney and of both genders were included in the study. They used chi square test to assess the statistical significance of renal calculi and NAFLD which was stronger in men than women. The cases with age more than 40 had more prevalence of renal calculi and NAFLD while cases of age less than 20 had small number (P for intercept 0.001). Ratio of renal calculi and NAFLD were strongly correlated with hypertension (P 0.06), while diabetes mellitus had no significant correlation (P 0.23). They concluded that nephrolithiasis was more prevalent in NAFLD patients as compared to healthy subjects.

Kiran Ahsan *et al.*, (49) in 2021 studied the 381 reports of non-alcoholic fatty liver

disease patients who underwent Trans-abdominal ultrasound to investigate the presence of kidney stones in them. All the participants were independent of Cardio Vascular disease. They demonstrated the higher incidence of nephrolithiasis in female than male (13.2% vs 7.9%) and a total of 10.2% in overall study population suffering from non-alcoholic fatty liver disease.

Hou *et al.*, (11) in 2022 investigated the relationship between HBV infection and upper urinary calculi (UUC). They retrospectively evaluate the data of 1062 patients in 2017-2018 matching the inclusion criteria of study and were discharged from urology department. Ultrasonography or Computed Tomography was done to diagnose the Upper Urinary Calculi and HBV infection was confirmed by hepatitis B surface antigen (HBsAg). The chronic HBV infection was prevalent in UUC patients (8.0%) (OR 2.175, 95% CI 1.267-3.734; P=0.004) than non UUC patients (3.8%). The high urinary PH >6 and stag horn calculus was more incident in HBV stratified UUC patients. The association between UUC and(11) HBV was also statistically significant in men (OR 2.156 95% CI 1.162-4.003; P=0.015) than women (P=0.099).

In 2022 Chen *et al.*, (17) explored the prevalence rate of nephrolithiasis in hepatitis C infected US women. Data was mined from National Health and Nutrition Examination Survey database. Cross sectional survey data from 2007 to 2018 was used six times in a row. It contain total of 13262 participants ≥ 20 yrs. and women, including 201 infected with HCV. They demonstrated the positive association between HCV infection and kidney stone presence (OR=1.70, 95% CI: 1.13-2.56).due to their cross sectional design they did not establish the casual relationship between HCV and renal stones. At the same time they also conducted subgroup analysis to find the sensitive population. Which they found as other races (OR=8.17, 95% CI: 1.62-41.22) and BMI within 25-29.9 kg/m² (OR=2.45, 95 % CI: 1.24-4.83).

Sametzadeh *et al.*, (43) in 2023 studied the non-contrast CT Abdomen-Pelvis to investigate the association of renal stone formation in Non-Alcoholic Liver Disease patients based on age and sex. From the study population of 907 individuals, the frequency of NAFLD with renal stone is higher than NAFLD without stone (82.1%vs17.9% p <0.0001) suggesting of NAFLD as independent risk factor for renal stone formation and a higher frequency of renal stones seen in severe NAFLD patients than the mild (100% vs 78.8%; p=0.008) strengthens the association, but the

association was independent of sex ($p=0.487$). The susceptibility of NAFLD patients for renal stone development is higher with increasing age ($p<0.009$).

2.8 Conclusion and Future Directions

Comprehensive overview of the growing body of evidence is mentioned in this literature review linking chronic liver disease, particularly NAFLD and hepatitis with an increased risk of nephrolithiasis. The complex interplay between liver and kidney health and underlying pathophysiology in their association, including insulin resistance, Lipotoxicity, and metabolic dysfunction are highlighted here. CLD patients especially with severe NAFLD are suggested in numerous studies, are at higher risk of developing kidney stones. Besides, there is still a lack of comprehensive data that clearly establishes the prevalence and severity of renal stones in CLD patients.

In the light of higher prevalence of nephrolithiasis in CLD patients, and epidemiological increase in CLD patients ratio demands early detection and monitoring of both systems. Among all diagnostic tools, ultrasound and the FIB-4 score are the cheaper ones and non-invasive and proven to be useful in identifying high-risk patients, facilitating early intervention. However, causal relationship between CLD and nephrolithiasis is needed to establish in further research, particularly through longitudinal studies. Also developing the targeted treatments to address the metabolic disruptions seen in CLD patients should be focused. To reduce the risk of both liver and kidney disease management of insulin resistance, dyslipidemia, and obesity could be helpful. Additionally, the role of liver echogenicity and other advance non-invasive imaging techniques needs to be address in further investigations could provide valuable insights into early risk identification and prevention strategies.

Chapter 3

METHODOLOGY

3.1 Research Design

This was cross-sectional type of study design.

3.2 Clinical Settings

It was conducted at Radiology Department of District Headquarter Hospital Nankana Sahib.

3.3 Sample Size

Through Cochran formula, at 95% confidence level and 5% confidence interval, in RAO sample size calculator it was calculated as 385.

3.4 Sampling Technique

Data was collected through consecutive sampling (non-probability) technique.

3.5 Study Duration

4 months.

3.6 Selection Criteria

3 6.1 Inclusion Criteria:

- Patients advised for trans-abdominal ultrasound and have right upper quadrant pain, nausea vomiting and other symptoms for more than 6months.
- Those already diagnosed with CLD on the basis of history, physical examination(presence of ascites, varices, splenomegaly), laboratory findings (decreased serum albumin, increased prothrombin time, altered liver function tests), and ultrasound findings (portal hypertension, splenomegaly, varices, ascites), presenting to the hospital with signs and symptoms of decompensated CLD.
- Those having chronic liver disease due to chronic hepatitis and alcoholism.
- Those patients giving informed consent.
- Age >18years.
- Patients from both genders are included in it.

3.6.2 Exclusion Criteria:

- All other patients who were not fulfilling the above mentioned criteria and patients having age less than 18year.
- Had tuberculosis, malignancy and central nervous system diseases.

3.7 Ethical Consideration

Data collection was conducted after approval from research ethical committee with reference # IRB/FASH/Allied-HS/10/24/MS/RS-3591 and from DHQ Nankana Sahib Hospital administration. Also, the patients will be assured of confidentiality. He/she would be certain that no information regarding the interviews and test results will be shared to any one and that this information will be used only for research purpose. Informed consent was duly signed from all participants.

3.8 Data Collection Procedure

Data was collected from all patients referred to Radiology Department of District Headquarter Hospital Nankana Sahib for trans-abdominal ultrasound, fulfill the inclusion criteria. Trans-abdominal ultrasound done by consultant radiologist using GE logic P7 with curvilinear probe of frequency 3-5 MHz and linear probe of 9-12 MHz for further evaluation, had reveals the pathological detail of abdominal viscera.

The diagnosis of fatty liver was based on comparison of echogenicity difference between liver and right kidney and divided into mild, moderate and severe on the basis of slightly brighter, brighter and significantly bright liver than kidney cortex. The severity of liver disease was graded by assessment and presence of five features (liver surface nodularity, liver edge nodularity, ascites, splenomegaly and portal vein diameter) taken by trans-abdominal ultrasound. In normal liver no feature of liver disease is present while in mild cases one or two features, in moderate cases two or three features and severe cases three or more than four features were present and suggestive of liver disease severity. Renal stone was diagnosed as echogenic focus of more than 3mm with posterior acoustic shadowing. Obstructing stones in the ureter are detected by following the dilated ureter till to the point of obstruction. Color Doppler wills produce twinkling sign within or just distal to urinary tract calculi. Its location in the urinary system from the renal calyces, the ureteral segments and the bladder was also described.

The results were compiled by the attached Performa. The questionnaire had been

developed, containing all relevant questions and modified with the help of previous studies. Questionnaires were marked with an identification number.

3.9. Data Analysis

Continuous variable was expressed as the mean $\pm$ SD and categorical variables as frequencies with percentages. Comparisons will be performed using the χ^2 test for categorical variables while ANOVA and logistic regression analysis for liver disease severity and the presence of renal stones.

Chapter 4

RESULTS

The study comprised of 385 patients with known and unknown causes of CLD and had disease duration of ≥ 6 months. Majority of the participants were female (n=228) 60%, while 40% were male (n=157). The mean age of the study population was 43.71 (± 12.82) year, 61.3% were aged 30-50 years, over 50 years were 28.1% and 10.6% were under 30 years. Regarding their BMI, 63.6% were fall in 25-30 category, 19.5% had BMI greater than 30 while 19.5% had less than 25 BMI. The study sample include 62.9% urban residents and 37.1% participants were from rural areas. The study recorded co-morbidities, history of smoking in 28.6%, diabetes in 28.8% and hypertension in 29.6%, also history of urinary tract calculi in (n=57) 14.8% , family history of liver and renal disease were recorded in 19% and 12.5% of participants.

Table # 4.1: Frequency of Chronic Liver Disease across multiple etiologies

Causes of Chronic Liver Disease	Frequency (n)	Percentage (%)
Autoimmune Disease	12	3.1
Alcohol Intake	10	2.6
Hepatitis B (HBV)	55	14.3
Hepatitis C (HCV)	99	25.7
Non-alcoholic Fatty Liver Disease (NAFLD)	214	55.6

Of the participants 55.6% were affected from NAFLD, 25.7% had Hep C, 14.3% of patients had Hep B and 3.1% accounted for autoimmune related CLD while 2.6% of patients had history of alcohol intake causing the liver dysfunction leading to chronic liver disease.

Table # 4.2: Distribution of CLD etiologies across gender.

Cause of CLD	Male (%)	Female (%)
Autoimmune Disease	50.0	50.0
Alcohol Intake	100.0	0.0
Hepatitis B (HBV)	38.2	61.8
Hepatitis C (HCV)	30.3	69.7
Non-alcoholic Fatty Liver Disease (NAFLD)	43.0	57.0

Autoimmune diseases were equally distributed between genders. All alcohol-related CLD cases were male. NAFLD, Hepatitis B and C showed higher prevalence in females.

Table # 4.3: Prevalence of CLD causes with renal stone

Cause of CLD	Patients without the history of renal stone	Patients with Renal Stones	Prevalence (%)
Alcohol Intake	9	3	33.3
Autoimmune Disease	9	2	22.2
Hepatitis B (HBV)	52	25	48.1
Hepatitis C (HCV)	92	39	42.4
Non-Alcoholic Fatty Liver Disease (NAFLD)	171	56	32.7

In patients without the history of renal stone, higher prevalence of renal stones was observed among patients with chronic viral hepatitis, particularly Hepatitis B. NAFLD accounts for a substantial percentage of renal stones as it is the most prevalent cause of CLD in the population, but with a moderate prevalence rate. Autoimmune and Alcohol Intake showed relatively lower prevalence of renal stones, likely due to smaller sample sizes or differing pathophysiological mechanisms.

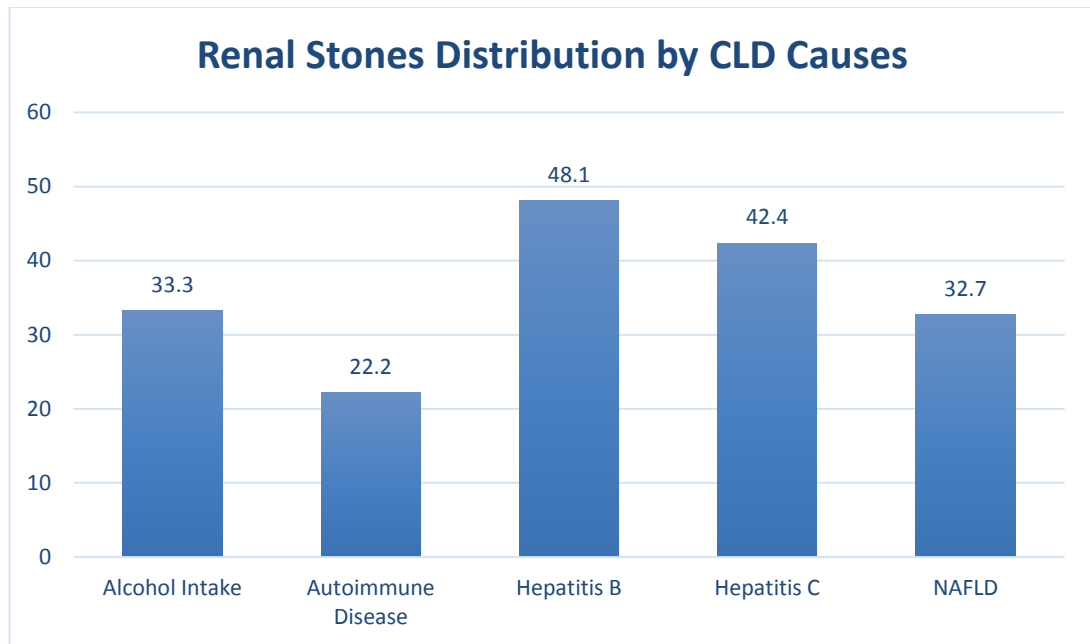


Figure # 4.1: Bar graph showing renal stone prevalence in different CLD causes

Table # 4.4: Chi square test analysis of different causes of CLD

Cause of CLD	Pearson Chi-Square Value	p-value
Non-Alcoholic Fatty Liver Disease (NAFLD)	4.578	0.032*
Hepatitis B (HBV)	3.236	0.072**
Hepatitis C (HCV)	1.532	0.216***
Autoimmune Disease	0.922	0.337***
Alcohol Intake	0.069	0.793***

* Significant, **borderline, ***not significant.

After restricting the analysis to patients without a history of urinary tract stones and applying weights on three top causes, NAFLD shows a statistically significant association with renal calculi. This highlights the importance of metabolic factors in renal stone formation among CLD patients. A borderline significance, $\chi^2 = 3.236$ and p-value = **0.072**, suggesting a potential but weak association between Hepatitis B and renal calculi, while hepatitis C, autoimmune disease and alcohol causing liver disease showed no significant association with renal calculi presence in the studied cohort. Other factors that appeared to have significant association with renal calculi were liver size, ascites, portal vein diameter and intrahepatic vessel obliterations (p values < 0.001).

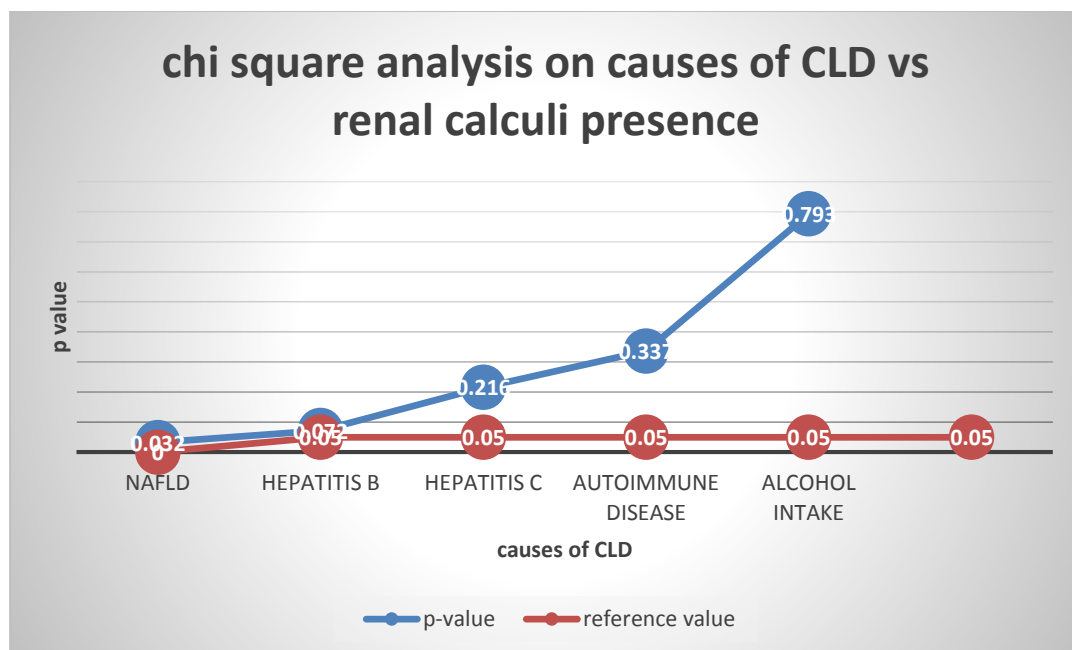


Figure # 4.2: Line graph representing P values of chi square

Table # 4.5: Binary Logistic regression analysis model with confounders affecting CLD causes

Variable	Model Adjustment	p-value	Exp(B)	Interpretation
History of Alcohol Intake	Without Confounders	0.793(not significant)	0.762	No association observed before adjusting for confounders.
	With Confounders	0.028	0.000	Significant protective effect; reduced odds of renal calculi, likely mediated by disease severity.
Viral Serology (Hep B)	Without Confounders	0.086	>1	Weak positive association.
	With Confounders	<0.05	8.941	Strong positive association; Hepatitis B increases odds of renal calculi, mediated by liver dysfunction.
NAFLD	Without Confounders	0.857	1.380	No significant association; potential confounding by severity of liver disease.
	With Confounders	0.802	0.778	Remains not significant; no independent contribution to renal calculi risk.
Hepatitis C	Without Confounders	0.931	1.154	No significant association.
	With Confounders	0.876	1.166	Remains not significant; minimal contribution to renal calculi risk.
Autoimmune Disease	Without Confounders	0.527	0.467	No significant association.
	With Confounders	0.527	0.467	Remains not significant; weak protective effect

Binary logistic regression was employed to predict the factors affecting presence of renal calculi in patients with chronic liver disease. Independent variables included clinical, biochemical, and demographic characteristics of study population. The logistic regression model fits the data well (Hosmer-Lemeshow $p = 0.633$), with a high explanatory power (Nagelkerke $R^2 = 0.775$). The key predictor's, History of Alcohol Intake (after adjustment, $\text{Exp}(B) = 0.000$; $p = 0.028$) reflects protective effect, while Viral Serology (Hepatitis B) ($\text{Exp}(B) = 8.941$; $p < 0.05$) showed strong positive association.

Table # 4.6: Predictors for renal stone presence across different causes of CLD

Variable	Model Adjustment	p-value	Exp(B)	Interpretation
Severity of Disease	Confounder	<0.001	Varies	Strong predictor of renal calculi; interacts with other variables like Viral Serology (Hep B).
Liver Echogenicity	Confounder	0.007	Strongest	Significant association across categories; reflects liver texture changes.
Urine pH	Confounder	0.002	Categories	Significant effects at pH <6 and >7; mediates predictors like alcohol intake.
Liver Size	Confounder	<0.001	Positive	Larger liver size associated with increased renal calculi risk, indicating systemic liver effects.
Spleen Size	Confounder	<0.001	Strong	Moderate-severe splenomegaly predicts renal calculi, interacting with portal hypertension markers.
Serum Creatinine	Confounder	<0.001	High	Indicates renal dysfunction strongly predicts renal calculi.
Serum Urea	Confounder	0.002	High	Elevated levels predict renal calculi and mediate liver disease effects.

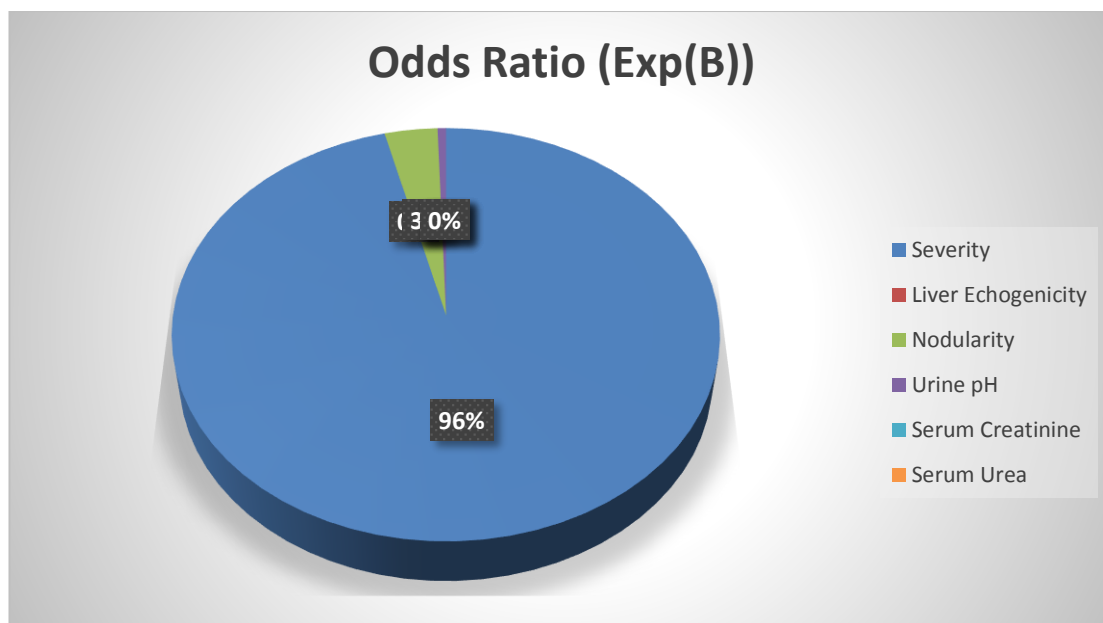


Figure # 4.3: Pie chart representing odds ratio of confounders across CLD causes

Confounders like Severity of Disease, Liver Echogenicity, and Liver Size significantly influence outcomes and mediate relationships with predictors as well as Renal dysfunction markers (Creatinine, Urea) and Urine pH (<6, >7) strongly predict renal calculi, supporting their physiological relevance.

Table # 4.7: Frequency of renal stone presence and absence across severity of disease categories

Severity of Disease	Renal Calculi Present	Renal Calculi Absent	Total Cases
Mild	29	60	89
Mild to Moderate	72	108	180
Moderate to Severe	63	38	101
Severe	13	2	15
Total	177	208	385

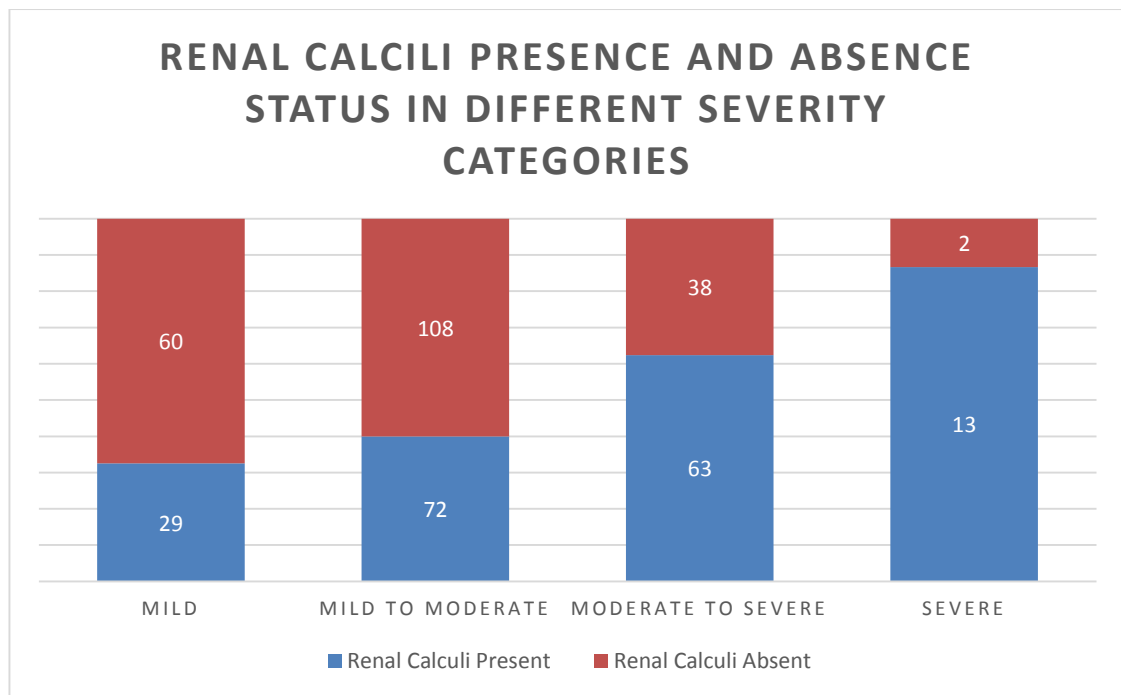


Figure # 4.4: Severity of disease distributed with renal calculi

Renal calculi prevalence increases significantly with the severity of disease, mild diseased cases had 32.6% renal calculi while severe diseased cases had 86.7% renal calculi. The proportion of renal calculi absent decreases as severity increases, 67.4% without renal calculi were of mild category and 13.3% severe cases were without renal calculi.

When the severity of liver disease was evaluated against the presence of renal calculi **ANOVA** ($F(1, 384) = 29.073, p < 0.001$), indicating a significant difference in mean severity scores between patients with and without renal calculi. Patients with renal calculi have higher severity scores (Mean=2.34, SD=0.83) compared to those without renal calculi (Mean=1.91, SD=0.71) indicating a potential clinical association. **Welch's ANOVA:** $F(1, 346.734) = 28.313, p < 0.001$, confirming robustness despite unequal variances. Chi-square test results also indicate a significant association ($\chi^2=29.073, p < 0.001$). The proportion of patients with renal calculi increases with disease severity, peaking at 66.7% in the severe category. Both ANOVA and chi square analyses highlights an association between renal calculi and disease severity. With logistic regression analysis, Nagelkerke R-Square and Hosmer-Lemeshow Test emphasize the strong predictive power of the model ($\chi^2=9.902, p=0.272, R^2=47.4\%$) and the significance of severity of disease as a key predictor for renal calculi presence ($p < 0.001$) and highlights the increasing trend in odds ratios with disease severity.

Overall prediction accuracy: 76.4%, Sensitivity (Correct prediction of "Present"): 69.5%, Specificity (Correct prediction of "Absent"): 82.2%.

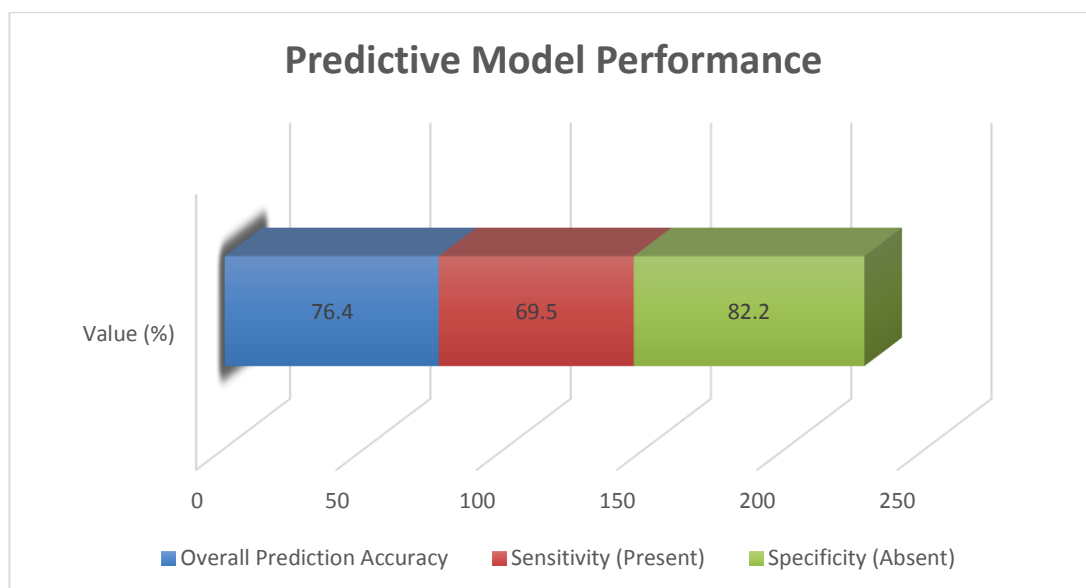


Figure # 4.5: Accurate prediction of renal stone presence with severity of disease

Patients in the **Mild to Moderate** and **Moderate to Severe** categories have much higher odds of renal calculi presence compared to those in the "Mild" category. Even in the "Severe" category, the odds remain significantly elevated, although lower than in the less severe categories, likely reflecting other confounding factors.

Table # 4.8: Logistic regression analysis of renal stone presence with severity of disease and other covariates

Step	Nagelkerke R-Square	Significant Predictors	Interpretation
Step 1 (Severity Alone)	Moderate	Severity of Disease	Severity is a strong independent predictor.
Step 2 (With Covariates)	High	Severity, Echogenicity, Nodularity Urine pH, Creatinine	Severity remains significant, but additional variables refine the prediction.

The logistic regression model further supported these associations, Variables such as **liver echogenicity, liver size, and nodularity, urine pH, serum urea, serum creatinine** significantly contributed to predicting the presence of renal calculi. Patients with advanced CLD indicators (e.g., liver nodularity or echogenicity) demonstrated higher odds of developing renal calculi.

Chapter 5

DISCUSSION

Chronic liver disease is a broad spectrum of etiological and multi-organ involving disease. The insight into the association between chronic liver diseases (CLD) and the presence of renal stones is significantly evaluated through findings in this study. The higher occurrence of CLD among females, predominantly residing in urban areas, was revealed through demographic data, which suggests lifestyle and environmental factors as significant contributors in the development of liver diseases, similar to former studies. Furthermore, the impending role of metabolic syndromes in aggravating liver pathology was also highlighted by the higher portion of participants in BMI range between 25 and 30 emulate with findings from a case control study having higher BMI in liver disease patients than control group (27.8 vs 26.7, $P < 0.01$) (7). The distinct distribution of CLD etiologies by gender-specific analysis align with global patterns and cultural differences, particularly in regions where alcohol consumption is principally a male-associated behavior as alcohol-related liver diseases were exclusively observed in males while Autoimmune diseases and NAFLD displayed nearly equal gender distribution.

This research aimed in the perspective of various causes of CLD due to its global impact, approximately 1.5 billion cases worldwide, predominantly arises from non-alcoholic linked fatty liver disease (NAFLD, 59%) followed by viral associated hepatitis B (HBV, 29%) and hepatitis C (HCV, 9%) (38). These statistics resonate with this study's findings, where NAFLD emerged as the most prevalent etiology (55.6%), validating its close association with metabolic syndrome and obesity.

Regarding Hepatitis B and C, Ali *et al.*, and Tasneem *et al.*, described these as enduring contributors to CLD in Pakistan, with HCV being the chief cause in a majority of cases (59, 60). This aligns with findings in this study, which highlight the high prevalence of HCV-related CLD (25.7%). Higher ratio of female study population were infected with these viral associated CLD which is similar to another Pakistani study demonstrating larger ratio of female with HCV compared to males (61). A study at Jinnah Postgraduate Medical Center by Khan *et al.*, further revealed that HCV patients commonly present with symptoms of decompensation like anemia and thrombocytopenia. Other studies also demonstrated the HCV's role in promoting

renal dysfunction and exacerbating chronic kidney disease with advance progression in HCV-positive patients (2), it also aligns with the findings from observed data. Alcohol related liver disease and autoimmune disease causing liver malady are less common than others. Alcohol consumption in Pakistan is restricted rather than other neighboring and western countries which have high ratio of young adults and major cause of cirrhosis in these regions (38).

Ahsan *et al.* and Moftakhar *et al.*, in their studies reported individuals with NAFLD, caused by metabolic syndrome components such as obesity, diabetes, and dyslipidemia were at an increased risk of kidney stones, aligns with this study acknowledging a significant correlation between NAFLD and the prevalence of renal stones (16, 39), additionally, Sametzadeh *et al.*, determined the higher ratio of renal stones in NAFLD patients with than without renal stones (82.1% vs 17.9%, $P < 0.0001$) (43), it also mirror with Taylor *et al.*, findings which underscored the role of obesity and weight gain with higher incidence of renal formation (62). Similarly, Badillo *et al.*, demonstrated a higher incidence of NAFLD patients with renal stones presence compared to individuals with healthy livers and noted significant association between fatty liver and urolithiasis. Consistent to Badillo *et al.*, Einollahi *et al.*, also recommended insulin resistance, oxidative stress, and alterations in urinary composition, such as reduced urinary pH and increased calcium oxalate levels in the underlying mechanism for stone production in liver disease patients (41, 47). Correspondingly, altered urinary profiles in NAFLD patients, including reduced ammonium excretion and acid-base disturbances was observed by Bargagli *et al.*, which contribute to urolithiasis (63). Likewise in this study altered urine pH is the key contributing factor in CLD patients for renal stone presence exhibiting larger NAFLD cohort compared to other CLD causes. Additionally, that finding is more supported by Miyake *et al.*, study who reported a significant association between low urinary pH and NAFLD (64). Numerous studies further substantiated NAFLD's association with renal stones. Qin *et al.*, described a significant risk of urolithiasis in NAFLD patients (OR 1.73), accrediting this to mutual metabolic factors disturbing hepatic and renal health (51). Moreover, the role of hepatic fibrosis in aggravating renal complication, with progressive NAFLD stages correlating with higher urolithiasis prevalence was defined by Venkatesh *et al.*, (65).

The higher prevalence of Hep C and correspondingly ratio of renal calculi in female

patients align with survey based study from Chen *et al.*, signifying positive relationship (OR = 1.70, 95%CI: 1.13– 2.56) (17). Hou *et al.*, in their study access the risk of urinary calculi in chronic hepatitis B virus infected patients, demonstrated higher prevalence of HBsAg positivity (OR=2.175 at 95% CI: 1.267–3.734 and P=0.004) in patients with upper urinary tract calculi (41/514) than patients having no upper urinary tract calculi (21/548). Also, the relative odds of HBsAg positivity were significant in men (OR=2.156 at 95% CI: 1.162–4.003 and P=0.015) but not in women (OR=2.947 at 95% CI: 0.816–10.643 and P=0.099) after stratifying by sex (11), however after adjustment of confounding variables in this study, Viral Serology (Hepatitis B) (Exp (B) = 8.941; p < 0.05) exhibited strong positive association with renal calculi.

Conferring from the study by Ergani *et al.*, the mechanism and risk factors affecting the formation of kidney stones are independent like insulin resistance and dyslipidemia. In renal tubules insulin act as the contributing factor in ammonia production, with obesity insulin resistance develops in the body and correspondingly affect ammonia production causes low urine pH, also dyslipidemia causes low urine pH, both these factors enhances the uric acid crystal summation in this acidic urine environment and results in deposition of stones in kidneys. Additionally, hypoammoniogenesis is linked to mechanism of excess fatty acid deposition called Lipotoxicity which is due to altered kidney function and cellular damage in kidney stone patient (13).

A significant association between the severity of liver disease and the prevalence of renal calculi is established from this study. Highest prevalence of renal calculi (70.0%) is appeared in patient with severe liver disease, representing the impact of advanced hepatic dysfunction on renal health and stone formation. Sametzadeh *et al.*, demonstrated that frequency of renal stones in severe NAFLD was significantly higher than in patients with mild NAFLD (100% vs 78.8%; P=0.008). This correlation could be attributed to metabolic and physiological changes in severe CLD, such as altered calcium and oxalate metabolism, increased urinary calcium excretion, and decreased urinary pH (43). These findings align with previous literature suggesting shared metabolic risk factors between hepatic and renal systems. Nguyen *et al.*, signifies higher BMI and history of smoking as the predictors of hepatic steatosis and severity of liver disease in patients with nephrolithiasis (34),

whereas in this study the severity of liver disease liver can be predicted by liver echogenicity and nodularity with higher odds.

A two way relationship between gallstone and renal stone was highlighted in recent studies like Ahmad *et al.*, and Kim *et al.*, defined the increasing risk of renal stones with gallbladder stones and vice versa (HR=1.93 after adjustment) (44, 66). These findings align with the observed systemic interconnectedness of hepatobiliary and renal system in this study.

Use of Ultrasound and early detection of renal and hepatic health is underscored in this study. Other imaging modalities like CT and MRI for evaluating CLD and concurrent renal abnormalities are also undeniable. A recent study has confirmed the validity of ultrasound scoring system for diagnosis of CLD, conducted by Shaista *et al.*, in Rawalpindi, Pakistan and showed diagnostic accuracy of 92.98% (54). Vardar *et al.*, also emphasize the importance of ultrasound markers in early prediction of hepatic malfunction, like increased echogenicity with more ultrasound beam attenuation and poor penetration suggesting coarsening and heterogeneity of liver parenchyma also called as liver parenchymal nodularity all signifies the progression of liver disease. Only liver enzymes like AST and ALT levels are raised in initial disease stage while bilirubin levels elevated later with advance disease. Furthermore, the study demonstrated the role of ultrasound in diagnosis increase in portal vein diameter which develop in progressive liver disease (27). It corroborated with observation from this study, combination of laboratory and imaging technique to define severity of disease and comprehensive assessment of liver and kidneys. Likewise moderate diagnostic accuracy of ultrasound was highlighted by Allan *et al.*, and Shaista Afzal *et al.*, in gauging liver parenchymal and other structural changes that accompanying CLD (29, 35, 50). Outcomes from this study align with Memon *et al.*, who demonstrated liver echotexture and nodularity had closely associated with CLD severity and can predict complications like portal hypertension, ascites and renal dysfunction (32). The role of liver echogenicity by Shen *et al.*, ($P < 0.009$) in predicting fibrosis in HBV patients (67) is also aligns with this study as increased renal stone prevalence in patients with advanced liver disease, indicated by ultrasound imaging markers such as liver echogenicity ($p = 0.007$). Qudsieh *et al.*, also support these findings and emphasized the factor of increased liver echogenicity in early detection of metabolic complications (58).

Ultrasound is less sensitive in mild disease stage especially in evaluation of mild fat deposition in the liver, it is also affected by the other confounder like obesity and other co-morbid diseases while advance techniques/ modalities should be combined with general gray scale ultrasound including Doppler and other semi-quantitative and quantitative ultrasound techniques, to accurately diagnose and precisely evaluate the disease severity as recommended by Wang *et al.*, and Ferraioli *et al.*, (53, 68).

CONCLUSIONS

The evaluation of our findings with existing literature underscores the relationship between liver and renal health, particularly in the context of metabolic syndrome and NAFLD, affecting 55.6% of study population. Metabolic disturbances in progressive liver disease like moderate to severe (62%) and severe category (86%) are grave contributors to renal stone formation. It also imparts significant clue for the association between CLD severity and renal calculi as severity of disease subsidizes to the increased frequency of renal calculi with high predictive accuracy. Particularly, the ability to correctly predict the renal stone presence in chronic liver disease patients had reached the sensitivity of 69.5%, with a strong overall classification accuracy. The demographic and cross-tabulation scrutinizes the gender-specific distribution of CLD causes, like alcohol-related liver diseases being utterly male-dominated. The need for multidisciplinary approaches and incorporating advanced diagnostic techniques and focusing on early intervention of liver disease, can help clinicians in better management of patient and alleviate the systemic impacts of chronic liver disease especially renal complications. Imminent research should be aimed to disentangle the core mechanisms linking hepatobiliary and renal diseases and integrating renal assessments into CLD management protocols and addressing metabolic risk factors carefully.

LIMITATIONS AND STRENGTHS

Limitations

1. **Sample Size:** While the study included 385 participants, larger sample sizes may provide more robust and generalizable results.
2. **Single-Center Design:** The study was conducted at a single center, potentially limiting the generalizability to other populations or regions.
3. **Cross-Sectional Nature:** The study design limits the ability to establish causality between CLD severity and renal calculi.
4. **Lack of Dietary and Lifestyle Data:** Factors such as diet, physical activity, and medication use, which may influence renal calculi formation, were not assessed.

Strengths

1. **Comprehensive Analysis:** The study utilized both demographic and clinical data to provide a holistic understanding of the relationship between CLD and renal calculi.
2. **Advanced Statistical Methods:** The use of Welch's ANOVA and Spearman correlations ensured robust analysis of data.
3. **Focused Population:** The inclusion criteria ensured a homogenous population, enhancing the internal validity of the findings.

RECOMMENDATIONS

This study lays the groundwork for further research aimed at improving the clinical management of patients with CLD and coexisting renal conditions.

1. **Longitudinal Studies:** Conducting prospective, long-term research studies to explore the causal relationship between CLD progression and renal calculi development. Particularly, the some severe liver disease cases without renal stone needs further probing of protective factors and other overlooked mechanisms.
2. **Multicenter Trials with Larger Sample Size:** Expanding the study to multiple centers for including larger cohorts will enhance the generalizability of the findings. Through various population and geographical settings, the statistical robustness allow better conformation of the findings.
3. **Interventional Research:** Investigating the impact of specific metabolic interventions on the incidence of renal calculi in CLD patients.
4. **Exploration of Molecular Pathways:** Understanding the underlying metabolic and molecular mechanisms linking CLD and renal calculi. Disturbances in calcium, oxalate, uric acid, and bile acid metabolism are favorable areas of inquiry that may reveal shared mechanisms of liver-kidney dysfunction.
5. **Dietary and Lifestyle Interventions:** Evaluating the role of dietary modifications and lifestyle changes like weight management, improved glycemic control and hydration focused regimens, helps in mitigating the risk for both renal calculi and hepatic diseases.
6. **Biomarker Based Models:** Inquiring the effectiveness of model combining ultrasound findings with laboratory findings (e.g., liver function tests, liver enzymes, urinary calcium/oxalate levels, renal function tests) to screen the patients which are at risk of developing dual organ dysfunction.
7. **Integration into Clinical Protocols:** Routine renal ultrasound screenings should be incorporated into the standard diagnostic workflow for CLD patients, particularly those with metabolic comorbidities (e.g., diabetes, obesity, or hyperlipidemia), to ensure early detection and management.

8. **Patient Education & Lifestyle Programs:** Structured patient education modules should be develop with focusing on diet, hydration, and lifestyle changes to prevent renal stone development and overall metabolic deterioration in CLD patients.

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APPENDICES

APPENDIX - 1

ENGLISH CONSENT FORM

The study you are about to participate is a randomized control trial survey titled as;

“Sonographic Evaluation of Liver Disease Severity and
Renal Stone Presence in Different Chronic Liver Diseases”

The study has no potential harm to participants. All data collected from you will be coded in order to protect your identity, and should not be disclosed to anyone. Following the study there will be no way to connect your name with your data. Your answers to the questions will not affect the quality of education given to you. Any additional information about the study results will be provided to you at its conclusion, upon your request.

You are free to withdraw from the study at any time. You agree to participate, indicating that you have read and understood the nature of the study, and that all your inquiries concerning the activities have been answered to your satisfaction.

NAME _____

SIGNATURE _____

DATE _____

APPENDIX - 2

URDU CONSENT FORM

میں _____ تصدیق کرتا / کرتی ہوں کہ محترمہ فرواسیماب ظفر نے اپنی اس تحقیق
"جگر کی بیماری کی شدت اور جگر کی مختلف دائمی بیماریوں میں گردے کی پتھری کی موجودگی کا سونوگرافک جائزہ"

“Sonographic Evaluation of Liver Disease Severity and Renal Stone Presence in Different Chronic Liver Diseases”

زیر نگرانی سعدیہ صابر کے متعلق بتادیا ہے۔ مجھے اس تحقیق کی نوعیت، مقاصد، احداث، توقعات، فوائد اور خطرات کے متعلق
ساری معلومات فراہم کر دی گئی ہیں۔

اس تحقیق کے دوران ساری معلومات صیغہ راز میں رہیں گی اور مریض کا نام اور دیگر معلومات صرف تحقیق کے لیے استعمال ہوں
گی۔ مجھے یہ بھی بتادیا گیا ہے کہ میں اس تحقیق سے متعلق ہر قسم کے سوال پوچھنے کا مجاز ہوں اور یہ تحقیق صرف ایک شخص ک
مفاد میں نہیں ہے بلکہ بحیثیت مجموعی انسانیت کا مفاد اس سے واسطہ ہے۔ تمام تفصیلات جاننے کے بعد میں اس تحقیق میں شامل
ہونے یا نہ ہونے پر کسی کا قائل نہیں ہوں۔ اس تحقیق سے کسی بھی وقت علیحدہ ہونے پر مجھ پر کوئی پابندی نہیں ہوگی۔ میں بذات
خود بقائمی حوش و حواس اور رضامندی سے اس تحقیقاتی عمل میں شامل ہوتی / ہوتا ہوں۔

دستخط محقق: _____

دستخط شرکت کار: _____

تاریخ: _____

APPENDIX – 3

Demographics Form & Questionnaires

PROFORMA FOR DATA COLLECTION

Topic: Sonographic Evaluation of Liver Disease Severity and Renal Stone Presence in Different Chronic Liver Diseases

Ref No.: _____ MR #: _____
 Age/ sex: _____ Height: _____
 Weight: _____ Date: _____

Disease history, abdominal ultrasound findings and lab values:

Geographical residence	Rural [] Urban []
H/O Smoking	Positive [] Negatives []
H/O Diabetes	Positive [] Negatives []
H/O Hypertension	Positive [] Negatives []
Family History Of Liver Disease	Positive [] Negatives []
Family History Of Renal Disease	Positive [] Negatives []
H/O Urinary Tract Calculi	Positive [] Negatives []
Auto-Immune Disease	Positive [] Negatives []
H/O Alcohol Intake	Positive [] Negatives []
Viral Serology Hep B	Positive [] Negatives []
Viral Serology Hep C	Positive [] Negatives []
Duration Of Disease	6-12 months, >12 months
Liver size (measured at mid clavicular line)	≤11cm, 12-17cm, >18cm
Liver echogenicity compared to kidney	Isoechoic [], slightly echogenic [], echogenic [], significantly echogenic [], hypoechoic []
Liver Surface Nodularity	Normal [], Mild [], Moderate [], Severe []
Liver Edge Nodularity	Normal [], Mild [], Moderate [], Severe []
Focal Liver Lesions	Present [] Absent []

Ascites	Not Present [], Mild [], Moderate [], Severe []
Portal Vein Diameter	Normal(≤ 12 cm), Mild(12-15cm), Moderate(15-17cm), Severe(>17 cm)
Intrahepatic vessels obliteration	Not present [], mild [], moderate [], severe []
Spleen size/Splenomegaly	Normal(≤ 12 cm), Mild(12-15cm), Moderate(15-17cm), Severe(>17 cm)
Renal Calculi/Calculus	Present [] Absent [],
Location and size of Calculi/Calculus	Right kidney[] _____ Left kidney[] _____ Number _____
Hydronephrosis	Present [] Absent []
Vesicle Calculi	Present [] Absent []
Serum AST (IU/L)	5-35, 40-200, >200
Serum ALT (IU/L)	5-40, 40-200, >200
Serum alkaline phosphatase (IU/L)	30-120, ≥ 140
Total bilirubin	0.1-1.5, 2-3, >3
Urea (mg/dl)	Normal (10-50), high (>51)
Creatinine (mg/dl)s	Normal (0.55-1.02), high (>1.02)
Urine PH	<6 , 6-6.5, >7
Platelet Count ($\times 10^9/L$)	Normal (150-400), abnormal (<150)
Hb Level (g/dl)	Normal (11.5-16), abnormal (≤ 11.5)
BMI	<25 , 25-30, >30
Disease severity	Mild (), mild to moderate (), Moderate to severe (), severe ().
Others	
Suggestive findings	

PERMISSION LETTER



OFFICE OF THE
MEDICAL SUPERINTENDENT
DHQ HOSPITAL NANKANA SAHIB



NO. 8503 MS/DHQ/NNS

Dated 05-07-2024

PERMISSION FOR DATA COLLECTION (Research Purposes Only)

Miss Farwa Seemab Zafar, We acknowledge the receipt of your request dated 20th July 2024 to collect data for your research study titled "*Sonographic Evaluation of Liver Disease Severity and Renal Stone Presence in Different Chronic Liver Diseases*".

We appreciate your initiative in conducting research on this important subject, which holds significant relevance in enhancing clinical understanding and improving patient outcomes. Your outlined objectives, particularly the evaluation of liver disease severity and its association with renal stone presence, are commendable.

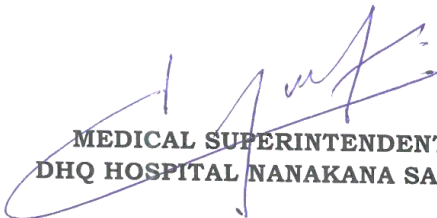
In adherence to ethical restrictions set forth by the hospital administration and in strict compliance with data protection regulations, we confirm that patient data will not be made available for distribution outside DHQ Hospital Nankana Sahib. Additionally, access to patient identification numbers and sonographic images is strictly prohibited as part of your research study.

However, the data that may be permitted for your research, subject to appropriate verification and supervision, includes:

- Findings from diagnostic tests
- Patient medical history
- Presenting complaints
- A formal interview with the patient, where feasible and subject to availability

All collected data will be duly verified and supervised by Dr. Madiha Rasool to ensure compliance with ethical and administrative protocols.

We appreciate your commitment to upholding ethical standards during the data collection process and commend your professionalism in maintaining patient confidentiality. We trust that your research will contribute meaningfully to the advancement of medical knowledge while ensuring strict adherence to all regulatory and ethical guidelines.


MEDICAL SUPERINTENDENT
DHQ HOSPITAL NANKANA SAHIB

ETHICS COMMITTEE LETTER



OFFICE OF THE DEAN-FAHS

SUPERIOR UNIVERSITY

Ref.: IRB /FAHS/Allied-HS/10/24/MS/RS-3591

Date: 29th October 2024

Name: Farwa Zafar (MS Allied Health Sciences)

Registration: SU91-MAHSW-S23-046

Subject: Ethical Approval Letter

The Research Ethical Committee convened on Dated: **17th October, 2024** to discuss your protocol titled **"Sonographic evaluation of liver disease severity and renal stone presence in different chronic liver diseases"**

No further corrections and recommendations were suggested. The above-mentioned protocol has been approved after considering various research issues including ethical concerns with condition that the researcher will submit completion report at the end of his/her research.

Prof. Dr. Muhammad Naveed Babur
Dean/Convener REC
Faculty of Allied Health Sciences
Superior University, Lahore

17-KM, Main Raiwind Road, Lahore.
UAN: 042 111 00 00 78 | www.superior.edu.pk

PLAGIARISM CERTIFICATE

February 20, 2025



PLAGIARISM CERTIFICATE

For MPhil and PhD

This is certified that the thesis entitled: Sonographic Evaluation Of Liver Disease Severity And Renal Stone Presence In Different Chronic Liver Diseases.

Student Name: Farwa Seemab Zafar

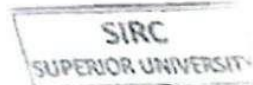
Reg /Roll No: SU91-MSAHW-S23-046

Submitted on date: 19.02.2025

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Supervisor Signature

Research Project / Thesis



Librarian

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20-02-2025

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PLAGIARISM REPORT

Reports:Sonographic Evaluation of Liver Disease Severity and Renal Stone Presence in Different Chronic Liver Diseases (FARWA SEEMAB ZAFAR)

1

by Tayyab khan

Submission date: 20-Feb-2025 10:05AM (UTC+0500)
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