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Clinical Correlation of Systemic Iron Status and Quantitative Biochemical Composition of Gallstones: A Cross-Sectional Study in Northern India

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ABSTRACT

Background: Cholelithiasis is a major global health concern, with emerging evidence suggesting that iron deficiency may modulate biliary cholesterol saturation and gallbladder motility. This study investigates the overlap between systemic iron status and gallstone composition in a North Indian population.

Methods: This cross-sectional study evaluated 60 patients (45 females, 15 males) undergoing cholecystectomy at a tertiary hospital in Amritsar. Systemic iron status was assessed via haemoglobin (Hb), serum iron, and ferritin. Surgically retrieved stones underwent quantitative chemical analysis for cholesterol, bilirubin, and calcium using FTIR spectroscopy. Data were analysed using Python, employing Kruskal-Wallis tests and Spearman's rank correlation.

Results: Anaemia was highly prevalent, affecting 100% of male and 88.9% of female participants. Cholesterol stones were the most frequent morphology (females: 51.1%; males: 60.0%). Quantitative analysis showed cholesterol stones were dominant in cholesterol (137.68±28.41 mg/dL), while pigmented stones had significantly higher bilirubin (5.25±0.55 mg/dL) and calcium (13.41±3.46 mg/dL). A statistically significant positive correlation was identified between haemoglobin levels and stone calcium content ($\rho=0.36$, $p=0.004$). However, serum iron and ferritin did not significantly correlate with stone types or primary chemical constituents.

Conclusion: Although iron deficiency is highly prevalent in patients with cholelithiasis, systemic iron markers are not independent predictors of gallstone chemical subtypes. The significant association between haemoglobin and calcium content suggests a role for haematological parameters in biliary mineralization, necessitating further longitudinal research into the biochemical mechanisms of stone nucleation.

Keywords: Cholelithiasis, Anaemia, Ferritins, Gallstones, Gallbladder

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INTRODUCTION

Cholelithiasis remains a cornerstone of gastroenterological morbidity globally, affecting an estimated 10% to 20% of the adult population.[1] In Westernized and rapidly urbanizing societies, the healthcare burden is particularly acute, with nearly one-third of cases progressing from asymptomatic biliary sludge to clinical complications, including acute cholecystitis, choledocholithiasis, and gallstone pancreatitis.[2] While the classical "five Fs" (fat, female, fertile, forty, and fair) risk profile remains clinically relevant, the multifactorial pathogenesis of stone formation characterized by bile supersaturation, gallbladder hypomotility, and accelerated crystal nucleation suggests a more complex biochemical interplay than lipid metabolism alone.[3]

Traditional lithogenic models focus predominantly on cholesterol-to-bile acid ratios and hormonal influences on gallbladder contractility.[4] However, emerging evidence suggests that the trace element microenvironment, particularly systemic iron status, may serve as a critical modulator of biliary physiology. Iron serves as an essential cofactor for hepatic enzymes involved in bile acid synthesis, most notably cholesterol 7α-hydroxylase[5]. A deficiency in systemic iron may therefore impair the conversion of cholesterol to bile acids, leading to a pro-lithogenic state of biliary cholesterol supersaturation.[6-7]

Furthermore, iron deficiency has been implicated in altered gallbladder kinetics. Theoretical models suggest that myoglobin-dependent smooth muscle function within the gallbladder wall may be compromised in iron-deficient states, promoting bile stasis a primary prerequisite for the aggregation of cholesterol monohydrate crystals and bilirubin salts.[7] While the link between hemolysis-induced iron turnover and pigment stones is well-documented,[8] the specific association between iron deficiency anaemia and the broader spectrum of gallstone types, including cholesterol and mixed stones, remains a subject of active debate.[9]

In the Indian subcontinent, there exists a unique epidemiological paradox where a high prevalence of cholelithiasis coexists with a widespread burden of nutritional iron deficiency anaemia.[10,11] Despite this overlap, clinical investigations into the association between serum iron, ferritin levels, and the quantitative chemical composition of gallstones are sparse and often contradictory. Understanding whether iron status is a modifiable risk factor or a coincidental biomarker is essential for developing comprehensive preventive strategies.

The present study aimed to evaluate the serum iron and ferritin profiles in patients with cholelithiasis and correlate these systemic markers with the quantitative chemical analysis of surgically retrieved gallstones. By investigating the intersection of micronutrient status and biliary lithogenesis, the study seeks to elucidate the role of nutritional deficiencies in gallstone pathogenesis.

MATERIALS AND METHODS

Study Design and Site: This cross-sectional observational study was conducted at the Department of Surgery, Sri Guru Ram Das Charitable Hospital, Amritsar, between July 2024 and December 2025. The study received approval from the Institutional Ethics Committee (SGRD/IEC/2024-310) following written informed consent taken from the participants before enrolment.

Patient Recruitment and Eligibility: This study utilized a convenience sample of 60 consecutive patients diagnosed with symptomatic cholelithiasis. These diagnoses were determined via clinical assessment and verified through high-resolution ultrasonography of the hepatobiliary tract. All individuals scheduled for elective cholecystectomy with ultrasound-confirmed gallstones were eligible for inclusion, with no restrictions on age or sex. To ensure data integrity and patient safety, specific exclusion criteria were applied. Patients were omitted from the study if they had underlying coagulation disorders, were critically ill, or suffered from systemic sepsis or acute inflammation. Additionally, anyone with a history of long-term NSAID use (more than six months), patients with known chronic kidney disease (CKD), haematological malignancies, hemoglobinopathies (such as Thalassemia), and those currently receiving iron supplementation was excluded, as these medications can significantly alter gallbladder motility and kinetics.

To minimize selection bias, all eligible patients during the study period were recruited consecutively. To reduce measurement bias, all biochemical analyses of blood and gallstones were performed by laboratory personnel who were blinded to the clinical status and demographic data of the participants.

Study Size: A sample size of 60 participants was determined based on the volume of elective cholecystectomies performed at our hospital during the study period, aiming for a representative cross-section of the local population presenting with symptomatic cholelithiasis

Clinical and Diagnostic Assessment: For every study participant, a thorough clinical history was recorded alongside a detailed physical examination. Initial screening included a complete blood count (CBC), fasting blood sugar levels, and standard urinalysis.

Haematological and Iron Metrics: Venous blood samples were drawn under sterile conditions following a preoperative fast. Participants were categorized into two distinct groups according to World Health Organization (WHO) criteria: anaemic individuals (Haemoglobin <13g/dL for males and <12g/dL for non-pregnant females) and non-anaemic individuals (Hb levels at or above these respective thresholds).[12] Ferritins concentration was measured utilizing the Chemiluminescence Immunoassay (CLIA, ortho-clinical diagnostics) technique. Reference intervals were established as 15-300 ng/ml for males and 15-150 ng/ml for females. Serum iron was concurrently analysed to evaluate circulating iron status.[13]

Surgical Intervention and Stone Analysis: All patients underwent either laparoscopic or open cholecystectomy. Following surgical retrieval, gallstones were meticulously collected, washed with deionized water to remove biliary debris, and dried. These stones were then subjected to quantitative chemical analysis to determine the concentrations of Total Cholesterol, Bilirubin and Calcium by FTIR spectroscopy. Based on the predominant chemical constituent and morphological features, the stones were classified into cholesterol, pigmented, or mixed varieties.[14]

Primary Outcome Definition: The primary outcome was evaluated in two ways to align with the research objectives: Categorical Outcome: Gallstones were classified into three distinct types (Cholesterol, Mixed, and Pigmented) to assess prevalence across age and gender groups. Continuous Outcome: The absolute concentrations of cholesterol, bilirubin, and calcium within the stones were treated as continuous variables to determine their correlation with serum markers (Iron, Ferritin, and Haemoglobin).

Statistical Analysis: Data were analyzed using Python programming language (version 3.10). Descriptive statistics and data curation were performed using the Pandasv (1.5.3) and NumPy libraries. For inferential statistics, the SciPy (stats module v0.13.5) was utilized to perform the Kruskal-Wallis test for non-parametric comparison of continuous variables across stone types and Spearman's rank correlation to evaluate relationships between serum markers and stone constituents. Multivariate Binary Logistic Regression analysis was conducted using the Stats models library to identify independent predictors of cholesterol stone formation. All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

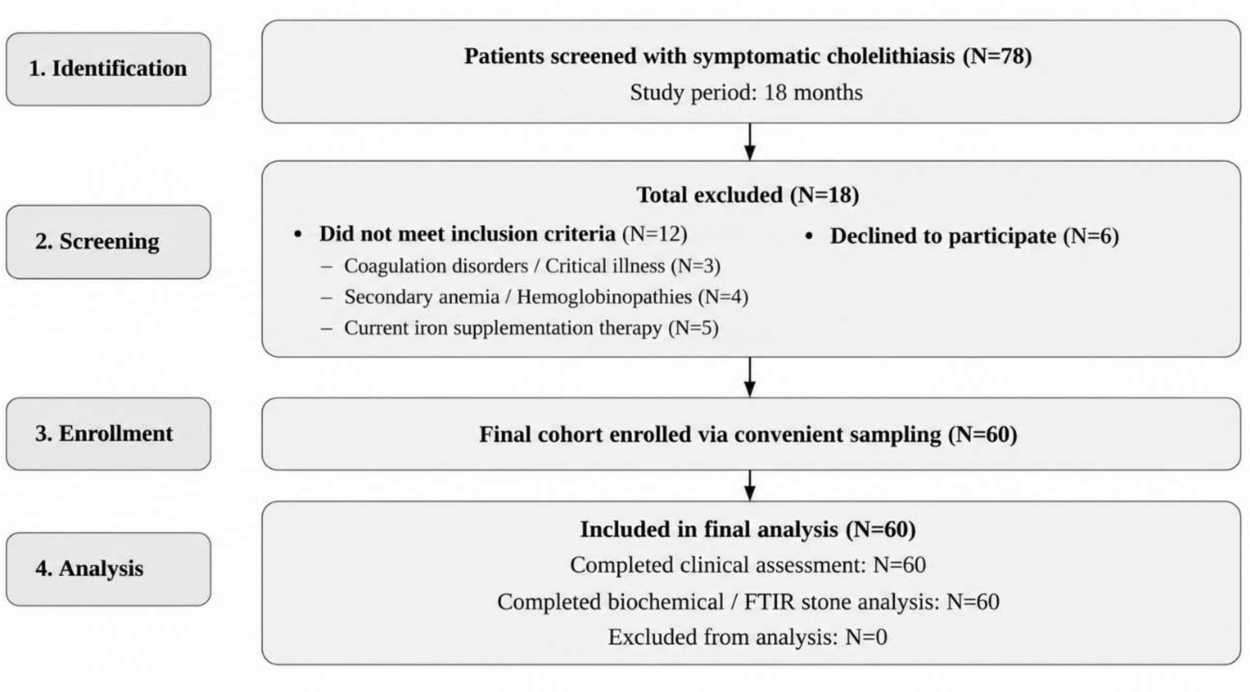


Figure 1: STROBE flow diagram of participant selection and progress

RESULTS

The diagram shows the screening, exclusion, enrollment, and final analysis of patients with symptomatic cholelithiasis over an 18-month study period

The present study of 60 individuals (45 females and 15 males) reveals a high prevalence of poor iron status across both genders, with a mean age of 48.2 years (Table 1). While haemoglobin levels were nearly identical between groups (approximately 10.67 g/dL), 100% of the male subjects met the WHO criteria for anaemia and iron deficiency, compared to 88.9% and 77.8% of females, respectively. Despite these high deficiency rates, the mean serum ferritin levels remained relatively high at 70.66 ng/mL, suggesting a complex clinical picture where iron stores may be present but unavailable for effective red blood cell production.

The table 2 illustrates the distribution of gallstone types cholesterol, mixed, and pigmented among 60 patients based on gender and age. Cholesterol stones emerged as the most frequent type across both sexes, accounting for over half of the cases in females (51.1%) and males (60.0%). Notably, mixed stones were found only in female patients, while male patients showed a higher proportional tendency toward pigmented stones (40.0%). From a statistical standpoint, the p-values for gender (0.052) and age group (0.655) exceed the standard 0.05 threshold, suggesting that neither demographic factor significantly influences the specific type of gallstone formed in this study group.

Table 1: Demographic and Baseline Haematological Profile (n=60)

Parameter	Female (n=45)	Male (n=15)	Total (n=60)
Age (years), Mean ± SD	47.1±14.8	51.5±15.3	48.2±15.0
Haemoglobin (g/dL), Mean ± SD	10.68±1.38	10.65 ± 0.84	10.67±1.27
Anaemia (WHO Criteria), n (%)	40 (88.9%)	15 (100%)	55 (91.7%)
Serum Iron (µg/dL), Mean ± SD	36.97±25.30	28.25±8.83	34.79±22.51
Iron Deficiency, n (%)	35 (77.8%)	15 (100%)	50 (83.3%)
Serum Ferritin (ng/mL), Mean ± SD	69.32±37.09	74.68±42.04	70.66±38.07

Note: Anaemia defined as Hb <12 g/dL (F) and <13 g/dL (M). Iron Deficiency defined as Serum Iron <50 µg/dL (F) and <60 µg/dL (M).

Table 2: Distribution of Gallstone Types by Gender and Age Group

Variable	Cholesterol Stone (n=32)	Mixed Stone (n=12)	Pigmented Stone (n=16)	p-value
Gender				0.052
Female	23 (51.1%)	12 (26.7%)	10 (22.2%)	
Male	9 (60.0%)	0 (0.0%)	6 (40.0%)	
Age Group				0.655
<40 years	7	3	6	
40-60 years	11	6	7	
>60 years	14	3	3	

Table 3: Comparison of Serum Biochemical Parameters across Gallstone Types

Serum Parameter	Cholesterol Stone (n=32)	Mixed Stone (n=12)	Pigmented Stone (n=16)	p-value*
Hb (g/dL)	10.47 ± 1.23	11.44 ± 1.75	10.50 ± 0.55	0.101
Serum Iron (µg/dL)	32.12 ± 18.74	41.48 ± 30.52	35.11 ± 23.40	0.627
Serum Ferritin (ng/mL)	77.72 ± 41.18	56.14 ± 14.46	67.45 ± 41.99	0.273

*p-values determined via Kruskal-Wallis test.

Table 4: Quantitative Chemical Composition of Gallstone Types

Constituent (mg/dL)	Cholesterol Stone	Mixed Stone	Pigmented Stone
Cholesterol Amount	137.68 ± 28.41	68.56 ± 8.53	51.40 ± 17.80
Bilirubin	0.62 ± 0.25	2.39 ± 0.57	5.25 ± 0.55
Calcium	10.89 ± 2.57	11.61 ± 4.37	13.41 ± 3.46

Table 5: Correlation and Risk Predictors for Cholesterol Stone Formation

Title			
Spearman Rank Correlation (ρ) between Serum Markers and Stone Constituents			
Variable	**Stone Cholesterol**	**Stone Bilirubin**	**Stone Calcium**
Hemoglobin	-0.09 (p=0.475)	0.01 (p=0.958)	**0.36 (p=0.004)**
Serum Iron	-0.03 (p=0.796)	0.03 (p=0.819)	0.15 (p=0.252)
Multivariate Logistic Regression for Cholesterol Stone Prediction			
Variable	**Odds Ratio (OR)**	**95% Confidence Interval**	**p-value**
Serum Iron Level	0.985	0.96 – 1.01	0.239
Age	1.032	0.99 – 1.07	0.095
Gender (Male)	1.171	0.34 – 4.03	0.803

The table 3 represents the relationship between various blood serum parameters haemoglobin, serum iron, and serum ferritin and the specific composition of gallstones. While patients with mixed stones exhibited slightly higher mean haemoglobin (11.44±1.75 g/dL) and serum iron (41.48±30.52 µg/dL) compared to those with cholesterol or pigmented stones, these differences are not statistically significant. The p-values for all three parameters (0.101, 0.627, and 0.273) remain above the 0.05 significance threshold, indicating that serum iron levels and red blood cell markers do not vary substantially based on the type of gallstone a patient develops.

The table 4 shows the chemical composition of three distinct gallstone types, showing significant variations in their primary constituents. Cholesterol stones are characterized by a dominant cholesterol content (137.68 ±28.41 mg/dL) with minimal bilirubin, whereas pigmented stones contain the highest levels of bilirubin (5.25±0.55 mg/dL) and calcium (13.41±3.46 mg/dL). Mixed stones occupy a middle ground, featuring moderate amounts of both cholesterol and bilirubin. Overall, concentration of calcium remains relatively stable across all types, though it progressively increases as the composition shifts from cholesterol-dominant to pigmented.

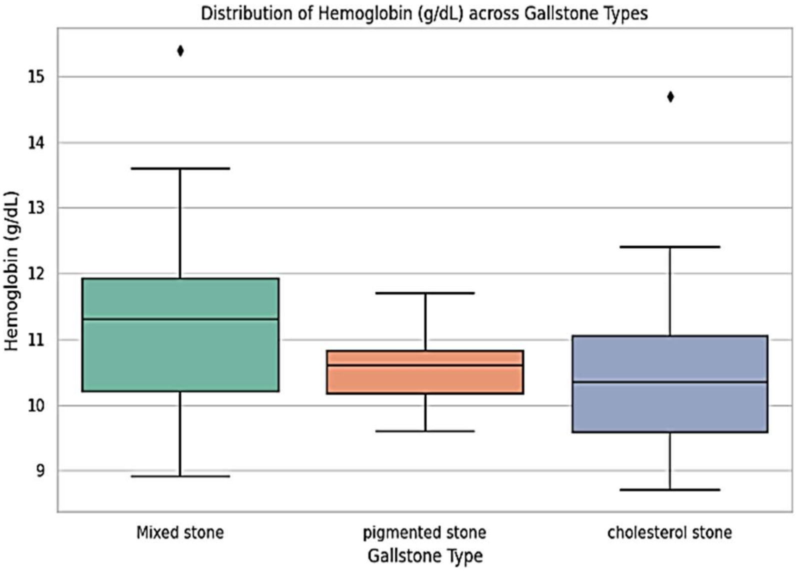
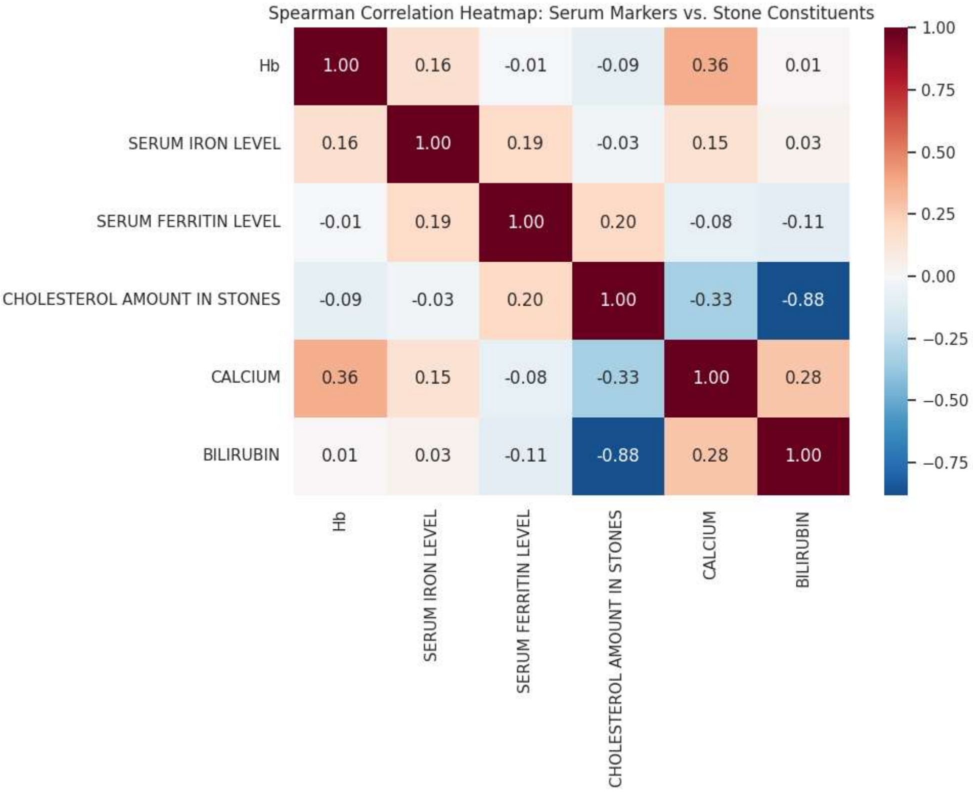


Figure 2: Distribution of Haemoglobin (g/dL) across Gallstone Types

Legend: Box-and-whisker plot illustrating the distribution of systemic haemoglobin levels stratified by gallstone chemical composition. The horizontal line within each box represents the median value, while the box boundaries denote the interquartile range (IQR; 25th to 75th percentiles). The whiskers extend to the minimum and maximum values within 1.5 times the IQR. Categories include Cholesterol stones (n=32), Mixed stones (n=12), and Pigmented stones (n=16). Differences across groups were evaluated using the Kruskal-Wallis test (p=0.101).



	Hb	SERUM IRON LEVEL	SERUM FERRITIN LEVEL	CHOLESTEROL AMOUNT IN STONES	CALCIUM	BILIRUBIN
Hb	1.00	0.16	-0.01	-0.09	0.36	0.01
SERUM IRON LEVEL	0.16	1.00	0.19	-0.03	0.15	0.03
SERUM FERRITIN LEVEL	-0.01	0.19	1.00	0.20	-0.08	-0.11
CHOLESTEROL AMOUNT IN STONES	-0.09	-0.03	0.20	1.00	-0.33	-0.88
CALCIUM	0.36	0.15	-0.08	-0.33	1.00	0.28
BILIRUBIN	0.01	0.03	-0.11	-0.88	0.28	1.00

Figure 3: Spearman Correlation Heatmap of Serum Markers and Stone Constituents

Legend: Matrix representing the non-parametric Spearman rank correlation coefficients (ρ) between systemic haematological markers (Haemoglobin, Serum Iron, Serum Ferritin) and quantitative gallstone constituents (Cholesterol, Calcium, Bilirubin). The color scale indicates the direction and strength of the correlation, ranging from dark blue (strong negative correlation, -1.0) to dark red (strong positive correlation, +1.0). Numerical values within each cell represent the correlation coefficient (). Note the significant positive correlation between systemic haemoglobin and gallstone calcium content (r=0.36, p<0.05).

The provided analysis uses Spearman Rank Correlation and Multivariate Logistic Regression to examine relationships between blood markers and gallstone composition. The correlation data reveals a statistically significant, positive link between haemoglobin levels and stone calcium (ρ=0.36, p=0.004), though no significant correlations were found for serum iron or other stone constituents. Furthermore, the regression model indicates that serum iron, age, and gender are not significant independent predictors for the formation of cholesterol stones, as all p-values exceeded the 0.05 threshold and the odds ratios remained close to 1.0. Overall, the findings suggest that while haemoglobin may relate to calcium content, these systemic markers generally do not serve as strong predictors for specific stone types.

The boxplot illustrates (Figure 2) the distribution of haemoglobin levels across three gallstone types, showing that patients with mixed stones generally possess higher median levels and a wider range of values compared to those with pigmented or cholesterol stones. High-value outliers are present in both the mixed and cholesterol stone groups, while the pigmented stone group demonstrates the most compact distribution. Overall, the visual data suggests that while median haemoglobin stays mostly between 10 and 11.5 g/dL, individual variance is greatest in the mixed stone category.

The Spearman Correlation Heatmap (Figure 3) shows the relationship between serum markers and stone constituents, highlighting a strong negative correlation (-0.88) between cholesterol amount and bilirubin in stones. While most serum markers show negligible links to stone composition, hemoglobin (Hb) displays a moderate positive correlation (0.36) with calcium levels. Other variables, such as serum iron and ferritin, demonstrate very weak associations with the chemical makeup of the gallstones.

DISCUSSION

The present study's most striking finding that 83.3% of patients were iron deficient and 91.7% were anaemic is strongly supported by the work of Prasad PC et al.[15] Their data indicated that 78% of gallstone patients had subnormal serum iron levels, with a significant majority being anaemic females. This reinforces the "iron deficiency-lithogenesis" hypothesis, which suggests that low iron levels decrease the activity of iron-dependent hepatic enzymes, thereby altering bile composition and favouring cholesterol crystal precipitation.

This is further validated on a larger epidemiological scale by Wen SH et al. [9]. In their cross-sectional study of over 7,800 participants, they identified a clear inverse relationship: higher serum iron levels were protective against gallstone formation (OR = 0.979). Specifically, they found that individuals in the highest iron tertile had a 23.7% lower risk of developing stones compared to those in the lowest tertile. The present study's high anaemia rates in the case group (Table 1) serve as a clinical reflection of this statistical risk.

While the present study found that serum iron did not significantly differ between stone types (Table 3), the chemical analysis in Table 4 showed that pigmented stones hold the highest calcium and bilirubin concentrations. This mirrors the findings of Khan M et al.[16] who reported that calcium, iron, and copper concentrations in stones follow the order: Pigmented>Mixed>Cholesterol. Khan's work emphasizes that biliary calcium is significantly higher in pigmented stone patients, which provides a physiological basis for the significant positive correlation (ρ=0.36) found between haemoglobin and stone calcium in the present results.

The present study identified cholesterol stones as the most prevalent (53.3%). Sharma R et al. [17] provides a structural explanation for this, using scanning electron microscopy to show that cholesterol stones form distinct crystals, whereas pigmented stones are more compact and thermally stable due to the presence of calcium palmitate and bilirubin. This structural compactness of pigmented stones likely explains why they showed the most consistent haemoglobin distribution in the present study's boxplot analysis (Figure 2).

Historically, gallstones were viewed through the lens of gender and age. However, the present study found that gender and age were not significant independent predictors (Table 5). This shifting trend is supported by Liu X et al.[18] who suggested moving beyond traditional demographics to look at markers like the Monocyte-to-HDL Ratio (MHR). Similarly, Sharma B and Sharma SR[19] highlight that modern diagnostics are moving toward "serum parameters" (like RDW-CV and MPV) as efficient tools for early prediction. The present study's focus on the haemoglobin-calcium link aligns with this modern push to find serum-based biochemical "clues" for stone etiology. The present study contributes to a growing body of evidence suggesting that gallstone disease is not merely a localized gallbladder issue but a systemic metabolic and haematological disorder. While Wen SH et al. [9] and Prasad PC et al. [15] establish iron as a risk factor, the present study's unique correlation between haemoglobin and stone calcium suggests that the intensity of erythropoiesis and iron turnover may directly influence how stones mineralize.

Despite the high prevalence of iron deficiency within the cohort, multivariate logistic regression revealed that serum iron levels were not a significant independent predictor of cholesterol stone formation (OR = 0.985, 95% CI [0.96, 1.01], p = 0.239). This suggests that while iron deficiency is a frequent comorbidity in cholelithiasis, its role may be more related to overall biliary stasis or metabolic dysfunction rather than dictating the specific chemical crystallization of cholesterol.

LIMITATION

The study's generalizability is primarily constrained by its small sample size (n=60) and the use of a convenience sampling method within a single-center setting in Northern India, which may reflect specific regional dietary and genetic influences. Furthermore, the cross-sectional design captures only a temporal snapshot of the disease process, preventing the establishment of a definitive causal link between iron deficiency and initial stone nucleation. Finally, by focusing exclusively on symptomatic patients scheduled for elective surgery, the findings may not account for the biochemical variations present in the broader population of individuals with asymptomatic cholelithiasis.

FUTURE DIRECTIONS

Future research should prioritize longitudinal cohort studies to establish a definitive causal link between iron correction and the prevention of stone nucleation. Expanding the scope to include molecular markers like hepcidin and dynamic gallbladder motility assessments would further elucidate the biochemical mechanisms of stasis. Furthermore, multicentric studies across diverse geographical regions are necessary to account for dietary and genetic variations. Given the significant association between haemoglobin and calcium, targeted investigations into the role of erythropoiesis in biliary mineralization are recommended to identify if iron-related haematological parameters serve as modifiable risk factors in gallstone pathogenesis.

CONCLUSION

The study demonstrates a high coexistence of nutritional iron deficiency and cholelithiasis within the North Indian population. Quantitative chemical analysis confirms that while cholesterol is the primary constituent in the majority of surgically retrieved stones, pigmented and mixed varieties present distinct biochemical profiles. The data indicates that systemic haemoglobin levels significantly correlate with the calcium concentration in gallstones, suggesting a potential approach for investigating biliary crystal nucleation. However, serum iron and ferritin do not appear to be primary determinants of stone morphology or chemical subtype. Consequently, while addressing iron deficiency is vital for general patient health, it may not serve as a direct modifiable risk factor for altering gallstone composition in symptomatic patients.

Individual Author's Contribution: **PS** contributed to study design, data collection, analysis, and manuscript preparation. **RRS** and **MSU** assisted in study conception, study design, data collection. **PKG** assisted in study design, data analysis and manuscript preparation.

Availability of data: The data that support the findings of this study are available from the corresponding author on reasonable request.

Declaration of Non-use of generative AI Tools: This article was prepared without the use of generative AI tools for content creation, analysis, or data generation. All findings and interpretations are based solely on the authors' independent work and expertise.

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