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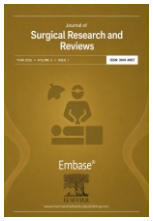

Research Article

Section: General Surgery

Impact of Glycemic Control on Intraoperative Difficulty in Diabetic Patients Undergoing Cholecystectomy: A Comparative Cross-Sectional Study

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HIGHLIGHTS

- HbA1c increased operative difficulty
- FBS showed no association
- Difficulty prolonged operative time
- Increased conversion risk
- Poor control worsened outcomes

Key Words:
Diabetes mellitus
HbA1c
Cholecystectomy
Nassar grade
Intraoperative difficulty

ABSTRACT

Introduction: Gallstone disease is a common surgical condition, and cholecystectomy is the standard treatment for symptomatic gallbladder disease. In diabetic patients, chronic hyperglycemia may impair gallbladder motility and promote inflammation, fibrosis, and adhesions, thereby increasing operative difficulty. **Aim & Objective:** To evaluate the impact of glycemic control on intraoperative difficulty in diabetic patients undergoing cholecystectomy and to assess the association of fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) with the Nassar intraoperative difficulty grade, operative duration, and conversion to open surgery. **Materials & Methods:** This comparative cross-sectional subgroup analysis was conducted from June 2024 to November 2025 at the Department of Surgery, Hamdard Institute of Medical Sciences and Research and Hakeem Abdul Hameed Centenary Hospital, New Delhi. A total of 186 diabetic patients undergoing cholecystectomy were enrolled. Glycemic status was assessed using FBS and HbA1c, and intraoperative difficulty was graded according to the Nassar classification. Associations were analyzed using the Chi-square test or Fisher's exact test. **Results:** Of the 186 patients, 59.7% had FBS ≥126 mg/dL and 39.8% had HbA1c ≥8%. Laparoscopic cholecystectomy was completed in 91.4% of cases, while 8.6% required conversion to open surgery. High intraoperative difficulty occurred in 27.5% of patients. HbA1c ≥8% was significantly associated with increased operative difficulty (33.8% vs 23.2%; p=0.048), whereas FBS and duration of diabetes were not. Difficult surgery was strongly associated with operative time >60 minutes, conversion to open surgery, and xanthogranulomatous cholecystitis (all p<0.001). **Conclusion:** Poor long-term glycemic control, reflected by HbA1c ≥8%, was significantly associated with increased intraoperative difficulty in diabetic patients undergoing cholecystectomy.

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INTRODUCTION

Gallstone disease is one of the most frequent benign biliary disorders requiring surgical intervention, and cholecystectomy remains the standard treatment for symptomatic gallstones, recurrent biliary colic, acute or chronic cholecystitis, empyema, mucocele and other gallbladder-related complications [1]. Laparoscopic cholecystectomy has become the preferred approach because it offers less postoperative pain, shorter hospital stay, faster mobilization and earlier return to routine activity compared with open surgery [2]. However, even though the operation is commonly performed, it is not always technically simple. In some patients, dense adhesions, contracted gallbladder, thickened wall, impacted stones, edematous tissues, bleeding, bile spillage and distorted Calot's triangle anatomy can make dissection difficult. Such operative difficulty is important because it may prolong operative time, increase conversion risk, raise the chance of bile duct or vascular injury and affect postoperative recovery [1].

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Uncontrolled hyperglycemia produces long-term damage to nerves, blood vessels and several organ systems, and therefore diabetes has direct relevance in surgical patients [3]. The World Health Organization describes hyperglycemia as a common effect of uncontrolled diabetes that may gradually damage many body systems, particularly nerves and blood vessels. In patients undergoing cholecystectomy, diabetes is important not only as a systemic comorbidity but also as a factor that may influence the natural history of gallbladder disease. Diabetic patients frequently have obesity, dyslipidemia, autonomic neuropathy and altered gallbladder motility, all of which can promote bile stasis & gallstone formation. Recurrent inflammation & delayed presentation may further contribute to difficult operative findings [4]. Hyperglycaemia also promotes systemic inflammation, endo-thequate preoperative preparation, clear anatomical identification and the surgeon's ability to manage difficult intraoperative findings [8].

The relationship between diabetes and gallbladder disease is biologically plausible. Autonomic neuropathy may reduce gallbladder contraction, leading to poor emptying and prolonged bile retention. Bile stasis favors cholesterol crystal formation and stone development. In addition, insulin resistance and associated lipid abnormalities may alter bile composition, increasing the tendency for gallstone formation [5]. Once gallstones develop, repeated episodes of subclinical or clinical inflammation can result in a fibrotic, thick-walled or contracted gallbladder. During surgery, these changes may present as difficult grasping, dense omental adhesions, unclear tissue planes, friability and difficult identification of cystic duct and cystic artery. Therefore, diabetic patients may have a higher likelihood of operative complexity, especially when diabetes is long-standing or poorly controlled [6]. The quality of glycemic control may be more clinically meaningful than the simple presence of diabetes. Glycemic control is commonly assessed using fasting blood sugar and glycated hemoglobin (HbA1c) [7]. Fasting blood sugar reflects current glucose status, whereas HbA1c reflects average glycemic exposure over the previous 2 to 3 months. Poor control is associated with impaired immunity, reduced neutrophil function, endothelial dysfunction, microvascular compromise, delayed healing and increased inflammatory activity. These systemic effects may influence local gallbladder pathology by allowing recurrent inflammation, edema and tissue fibrosis to progress. Intra-operatively, this may translate into difficult traction, obscured anatomy, troublesome adhesiolysis, increased bleeding from inflamed tissues, prolonged dissection and higher operative difficulty grade [8].

Preoperative HbA1c is increasingly used as a risk marker in surgical practice because it provides an objective estimate of chronic glycemic burden. Evidence from abdominal surgery suggests that elevated HbA1c may be associated with higher postoperative morbidity, including wound infection, major complications and overall adverse outcomes. A systematic review and meta-analysis on elective major abdominal surgery reported that raised HbA1c was linked with increased risks of postoperative complications, although the strength of association and threshold values varied across studies [9]. Another systematic review concluded that available evidence was heterogeneous and that better-quality studies were needed to define the relationship between HbA1c and surgical outcomes [10]. These findings show that glycemic control has surgical relevance, but they also highlight the need for procedure-specific evaluation, particularly for cholecystectomy where operative difficulty is strongly affected by local inflammation and anatomy.

Difficult cholecystectomy is now recognized as an important operative concept because it allows surgeons to describe and predict technical complexity in a structured manner. Difficulty may arise from patient-related, disease-related, and anatomy-related factors. Patient-related factors include obesity, diabetes, advanced age, and associated comorbidities. Disease-related factors include acute cholecystitis, recurrent attacks, empyema, gangrene, mucocele, an impacted Hartmann's pouch stone, chronic fibrosis, and dense adhesions around Calot's triangle. Anatomy-related factors include a short or wide cystic duct, low or abnormal insertion of the cystic duct, an intrahepatic or buried gallbladder, an aberrant right hepatic artery, accessory hepatic ducts, and unclear biliary anatomy. Grading systems such as the Nassar operative difficulty scale are useful because they classify intraoperative findings according to adhesions, cystic pedicle difficulty, gallbladder condition, and complexity of dissection. Such grading helps convert subjective surgical experience into measurable data [11].

In diabetic patients, operative grading is especially valuable because all patients with diabetes do not carry the same surgical risk. A patient with short-duration, well-controlled diabetes may have relatively mild gallbladder inflammation, whereas a patient with poor glycemic control, longer disease duration and repeated attacks may have dense adhesions and severe distortion of anatomy. Therefore, comparing intra-operative difficulty

according to fasting blood sugar, HbA1c and duration of diabetes can provide more useful information than merely comparing diabetic and non-diabetic groups. It may identify whether uncontrolled diabetes is associated with prolonged surgery, higher difficulty grade, conversion, or more severe inflammatory pathology [12].

This issue is clinically important in both elective and emergency cholecystectomy. In elective cases, preoperative recognition of poor glycemic control may allow optimization, better counseling, planning of senior surgical assistance and anticipation of technical difficulty. In emergency cases, uncontrolled diabetes may coexist with acute inflammation, sepsis, dehydration or metabolic instability, making operative management more challenging.

Perioperative diabetes guidance emphasizes glucose monitoring and optimization because poor glycemic control can increase infection risk and adverse surgical outcomes [13]. Thus, evaluation of glycemic status before cholecystectomy has practical value beyond routine biochemical documentation.

Figure 1. Impact of preoperative glycemic control on intra-operative difficulty during laparoscopic cholecystectomy. Good glycemic control (HbA1c <7%) reduces inflammation, improves microvascular perfusion, and minimizes fibrosis and adhesions, resulting in easier surgery and fewer complications. In contrast, poor glycemic control (HbA1c ≥7%) promotes chronic hyperglycemia, inflammation, and dense adhesions, leading to increased operative difficulty and complications.

The aim of the study is to evaluate the impact of glycemic control on intra-operative difficulty among diabetic patients undergoing cholecystectomy.

The objectives are to assess the association of preoperative fasting blood sugar and HbA1c levels with intra-operative difficulty graded by the Nassar classification, and to correlate intraoperative difficulty with operative outcomes, including duration of surgery and conversion to open cholecyst-ectomy.

MATERIALS & METHODS

This comparative cross-sectional subgroup analysis was conducted from June 2024 to November 2025 in the Department of Surgery, Hamdard Institute of Medical Sciences and Research and its associated Hakeem Abdul Hameed Centenary Hospital, New Delhi. New Delhi. A total of 186 diabetic patients undergoing elective or emergency cholecystectomy were included as per convenience sampling, excluding cases with incomplete biochemical, operative or histo-pathological data.

Data were retrieved from hospital records and the master database. Glycemic status was assessed using FBS and HbA1c, categorized as <126/≥126 mg/dL & <8%/≥8%, respectively. For statistical analysis,

Nassar Grades I and II were categorized as the low-difficulty group, while Grades III and IV were categorized as the high-difficulty group. Associations were tested using Chi-square/ Fisher's exact test.

Table 1: Pre-operative Variables – Glycemic Profile and Duration of Diabetes

Variable	Category	n	%
FBS (Binary)	<126	75	40.3
	≥126	111	59.7
HbA1c (Binary)	<8%	112	60.2
	≥8%	74	39.8
Duration of Diabetes	≤5 years	100	53.8
	>5 years	86	46.2

Table 2: Intra-op Variables – Surgical

Parameter	Category	n	%
Procedure	Laparoscopic	170	91.4
	Conversion to open	16	8.6
Surgery Duration	≤60 min	118	63.4
	>60 min	68	36.6

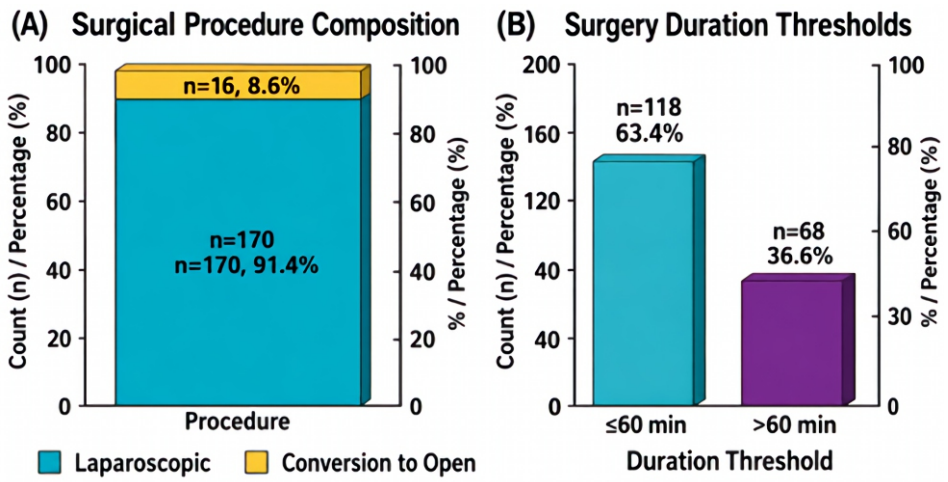

Figure 2: Intra-operative Variables and Surgical Approach Analysis

Table 3: Post-op Variables – Intraoperative Difficulty and Histopathological Findings

Parameter	Category	n	%
Intraoperative Difficulty (Nassar Grade)	Grade I	107	57.5
	Grade II	28	15.1
	Grade III	28	15.1
	Grade IV	23	12.4
Histopathological Findings	Chronic cholecystitis ± cholelithiasis	148	79.6
	Xanthogranulomatous cholecystitis	31	16.7
	Chronic cholecystitis with cholesterosis	7	3.7

Table 4: Association of Pre-op Variables, Intra-op Variables, and Post-op Variables with Intraoperative Difficulty

Variable Category	Variable	Subcategory	High Difficulty n (%)	Low Difficulty n (%)	p-value
Pre-op Variables	FBS	<126	20 (26.7)	55 (73.3)	0.87
		≥126	31 (27.9)	80 (72.1)	
	HbA1c	<8%	26 (23.2)	86 (76.8)	**0.048**
		≥8%	25 (33.8)	49 (66.2)	
	Duration of Diabetes	≤5 yrs	25 (25.0)	75 (75.0)	0.52
		>5 yrs	26 (30.2)	60 (69.8)	
Intra-op Variables	Surgery Duration	≤60 min	15 (12.7)	103 (87.3)	**<0.001**
		>60 min	48 (70.6)	20 (29.4)	
	Conversion to Open Surgery	Yes	14 (87.5)	2 (12.5)	**<0.001**
		No	39 (22.9)	131 (87.1)	
Post-op Variables	Histopathological Findings (HPE)	Chronic cholecystitis ± cholelithiasis	30 (20.3)	118 (79.7)	**<0.001**
		Xanthogranulomatous cholecystitis	19 (61.3)	12 (38.7)	
		Chronic cholecystitis with cholesterosis	2 (28.6)	5 (71.40)	

RESULTS

A total of 186 patients with diabetes mellitus who underwent cholecystectomy were included in the study. The baseline clinical and biochemical characteristics, intraoperative findings, and histopathological outcomes were analyzed. We assessed glycemic status using fasting blood sugar and HbA1c levels, and recorded operative details including procedure type, duration, & intraop-erative difficulty graded by the Nassar classification. Histopath-ological examination of the gallbladder specimens was also performed. The distribution of these variables and their associa-tion with intraoperative difficulty are presented in the following tables and figures.

Among the 186 diabetic patients, the **pre-operative variables** demonstrated that 59.7% had fasting blood sugar (FBS) ≥126 mg/dL, indicating suboptimal short-term glycemic control. In terms of long-term glycemic status, 39.8% patients had HbA1c ≥8%, while 60.2% had HbA1c <8%. Regarding duration of diabetes, 46.2% patients had diabetes for more than 5 years **(Table 1)**.

These **pre-operative variables** indicate a mixed distribution of glycemic control and chronic diabetic exposure, allowing assessment of their impact on intraoperative difficulty and surgical outcomes. The **intra-op variables** showed that laparoscopic cholecystectomy was successfully performed in the majority of patients (91.4%), while 8.6% required conversion to open surgery. Regarding operative duration, 63.4% of surgeries were completed within 60 minutes, whereas 36.6% lasted more than 60 minutes, indicating varying levels of intraoperative complexity **(Table 2)**.

These **intra-op variables** suggest that although minimally invasive surgery was feasible in most patients, a substantial proportion experienced prolonged operative time and technically challenging procedures **(Figure 2)**.

The post-op variables demonstrated that the majority of patients had lower intraoperative difficulty grades, with Grade I accounting for 57.5% of cases, while 27.5% belonged to higher difficulty grades (Grade III–IV), indicating moderate to severe operative complexity. Histopathological evaluation revealed that chronic cholecystitis with cholelithiasis was the predominant finding (79.6%), followed by xanthogranulomatous cholecystitis (16.7%) and chronic cholecystitis with cholesterosis (3.7%). These post-op variables suggest that although most patients had uncomplicated operative and histopathological outcomes, a considerable subset demonstrated advanced inflammatory pathology and increased surgical difficulty **(Table 3)**. Correlation analysis of the **pre-op variables, intra-op variables, and post-op variables** demonstrated that poor long-term glycemic control was significantly associated with increased intraoperative difficulty. Patients with HbA1c ≥8% showed a higher proportion of difficult surgeries (33.8%) compared to those with HbA1c <8% (23.2%), and this association was statistically significant ($p = 0.048$). In contrast, fasting blood sugar levels and duration of diabetes did not demonstrate a statistically significant relationship with operative difficulty ($p > 0.05$), suggesting that chronic glycemic burden may contribute more substantially to operative complexity **(Table 4)**.

Among the **intra-op variables**, surgery duration showed a highly significant association with intra-operative difficulty. Procedures lasting >60 minutes demonstrated markedly higher rates of difficult surgery (70.6%) compared to surgeries completed within 60 minutes (12.7%) ($p < 0.001$).

However, a small proportion of high-difficulty cases were still completed within 60 minutes, likely reflecting better operative planning and greater surgical expertise, allowing efficient management of technically challenging cases. Similarly, conversion to open surgery demons-trated a highly significant association with operative difficulty ($p < 0.001$). The majority of converted cases belonged to the high-difficulty group (87.5%), supporting the concept that severe adhesions, distorted anatomy, and dense fibrosis increase the likelihood of conversion. Nevertheless, a very small proportion of low-difficulty cases also required conversion, suggesting that conversion may occasionally occur despite relatively lower operative difficulty. Importantly, not all high-difficulty cases required conversion to open surgery. A considerable proportion of difficult surgeries were completed laparoscopically, possibly due to surgeon experience, meticulous dissection techniques, and effective intra-operative decision-making. Among the post-operative variables, histo-pathological findings demonstrated a significant association with intra-operative difficulty ($\chi^2 = 16.14$, $p < 0.001$). Xanthogranulomatous cholecystitis showed the highest proportion of difficult surgeries, with 61.3% of patients belonging to the high-difficulty group compared to 38.7% in the low-difficulty group.

In contrast, chronic cholecystitis with cholelithiasis demonstrated a lower proportion of difficult surgeries (20.3%), while chronic cholecystitis with cholesterosis showed difficult surgery in 28.6% of cases. These findings indicate that advanced inflammatory pathology, particularly xanthogranulomatous cholecystitis, is strongly associated with increased operative complexity, likely due to dense fibrosis, adhesions, and distortion of normal biliary anatomy.

DISCUSSION

In our study of 186 diabetic patients undergoing cholecystectomy, the findings indicate that long-term glycemic control was more closely related to operative difficulty than isolated fasting glucose or duration of diabetes. Although 59.7% patients had FBS ≥126 mg/dL and 46.2% had diabetes duration >5 years, neither FBS nor duration showed significant association with high intraoperative difficulty. In contrast, HbA1c ≥8% was significantly associated with higher operative difficulty, with difficult surgery observed in 33.8% patients compared with 23.2% among those with HbA1c <8% ($p = 0.048$). This suggests that chronic hyperglycemic exposure, rather than isolated preoperative glucose elevation, contributes to recurrent inflammation, fibrosis, adhesions and difficult dissection. Similar observations were reported by Shirol VV and Motimath PS [14], who demonstrated a significant association between elevated HbA1c and gallstone disease among

diabetic patients. Almobarak AO et al. [15] also identified HbA1c and metabolic factors as important predictors of gallstone disease, reinforcing the relationship between chronic poor glycemic control and biliary pathology.

Operative findings in our study demonstrated that laparoscopic cholecystectomy was feasible in most patients, with 91.4% completed laparoscopically and only 8.6% requiring conversion to open surgery. High intraoperative difficulty was present in a substantial subset of patients, reflecting dense adhesions, chronic inflammatory changes, and distorted Calot's triangle anatomy. This finding indicates that, although laparoscopic completion was possible in most patients, a clinically important subgroup experienced technically demanding surgery associated with prolonged operative duration and an increased likelihood of conversion to open surgery. Nassar et al. [16] emphasized that operative grading based on adhesions, gallbladder condition and difficulty of dissection provides an objective assessment of technical complexity and correlates with operative duration and conversion risk.

In the present study, surgeries lasting >60 minutes demonstrated significantly higher intraoperative difficulty compared with surgeries completed within 60 minutes (70.6% vs 12.7%, p <0.001). These findings are consistent with Luthra A et al. [17], who observed increased operative difficulty, dense adhesions & prolonged operative duration among diabetic patients undergoing laparoscopic cholecystectomy. However, a small proportion of high-difficulty cases were still completed within shorter operative duration. This may reflect greater surgical expertise, efficient adhesiolysis, accurate identification of anatomy and improved laparoscopic handling by experienced surgeons, allowing difficult procedures to be completed safely within shorter operative time.

Conversely, a minority of low-difficulty cases required operative duration >60 minutes despite relatively lower Nassar grades. This prolonged duration may not necessarily indicate severe inflammatory difficulty alone & can occasionally occur because of intraoperative events such as gallbladder perforation with bile spillage requiring irrigation, minor bleeding from the liver bed, transient technical difficulties during pneumoperitoneum creation, equipment related adjustments, or anesthetic & operative coordination delays. Similar operative variations have been acknowledged in studies evaluating laparoscopic cholecystectomy outcomes & intraoperative complexity. Conversion to open surgery demonstrated a highly significant association with operative difficulty (p <0.001). Most converted cases belonged to the high-difficulty group, supporting the concept that severe adhesions, dense fibrosis, contracted gallb-ladder & distorted anatomy increase the likelihood of conversion. Malik M et al. [18] and Bedirli A et al. [19] similarly reported higher conversion rates among diabetic patients undergoing laparoscopic cholecystectomy because of difficult operative anatomy and chronic inflammatory changes. However, despite high intraoperative difficulty, a considerable proportion of difficult cases in our study were still completed laparoscopically without conversion. This observation may be attributed to increasing surgical experience, better laparoscopic expertise, improved intraoperative decision-making and meticulous dissection techniques, enabling safe laparoscopic completion even in technically demanding cases. At the same time, a very small proportion of low-difficulty cases required conversion to open surgery, likely as a precautionary measure following intraoperative events such as iatrogenic injury or bleeding, where conversion was undertaken to maintain operative safety rather than because of severe anatomical difficulty alone.

Histopathological examination revealed that chronic cholecystitis with cholelithiasis was the predominant finding, accounting for 79.6% of cases, while xanthogranulomatous cholecystitis and chronic cholecystitis with cholesterosis were observed in 16.7% and 3.7% of patients, respectively. A significant association was observed between histopathological findings and intraoperative difficulty ($\chi^2 = 16.14$, $p < 0.001$). Xanthogranulomatous cholecystitis demonstrated the highest proportion of difficult surgeries, with 61.3% of patients belonging to the high-difficulty group, compared with 20.3% among those with chronic cholecystitis with cholelithiasis and 28.6% among those with cholesterosis. These findings suggest that severe chronic inflammatory changes, extensive fibrosis, dense adhesions, and distortion of Calot's triangle associated with xanthogranulomatous cholecystitis substantially increase operative complexity. Similar observations have been reported by Agarwal et al. [20], who identified chronic cholecystitis with cholelithiasis as the most common histopathological diagnosis, while Giudicelli et al. [21] highlighted the challenging surgical nature of xanthogranulomatous cholecystitis because of marked fibrosis, difficult adhesiolysis, and increased operative difficulty.

Overall, our findings suggest that poor long-term glycemic control, prolonged operative duration, conversion requirement and advanced inflammatory histopathological changes together contribute to increased intraoperative difficulty in diabetic patients undergoing cholecystectomy.

CONCLUSION

In conclusion, poor long-term glycemic control, particularly HbA1c ≥8%, was significantly associated with increased intraoperative difficulty among diabetic patients undergoing cholecystectomy, whereas fasting blood sugar and duration of diabetes were not significant predictors. Although laparoscopic cholecystectomy was completed in most patients, a considerable proportion had higher Nassar grades, prolonged operative duration, and conversion to open surgery. Xanthogranulomatous cholecystitis was significantly associated with increased intraoperative difficulty and represented the histopathological finding most strongly linked to challenging cholecystectomy. Therefore, preoperative HbA1c assessment may help anticipate difficult cholecystectomy and improve surgical planning.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the

broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical healthcare, diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

FBS: Fasting Blood Sugar
HbA1c: Glycated Hemoglobin
LC: Laparoscopic Cholecystectomy
Nassar: Nassar Operative Difficulty Classification
XGC: Xanthogranulomatous Cholecystitis

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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None

ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research directions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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