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A Clinical Study to Determine Predictive Factors for Difficult Laparoscopic Cholecystectomy

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Abstract
Background: *Laparoscopic cholecystectomy is one of the most common surgeries performed and has replaced open cholecystectomy. Laparoscopic cholecystectomy is associated with better preservation of immune function and a reduction of the inflammatory response compared with open surgery.*
Objective: *To evaluate the predictive factors responsible for difficult laparoscopic cholecystectomy.*
Material and Methods: *The present prospective study was conducted in Department of Surgery from September 2016 to October 2018. A total sample size of 67 patients admitted in the department of various surgical wards in tertiary health center with diagnosis of cholelithiasis/ cholecystitis who were clinically evaluated and confirmed by USG included in the study population. Patients below 18 years of age, with CBD calculus, raised ALP, dilated, CBD, where CBD exploration was needed, obstructive jaundice ant not willing for laparoscopic cholecystectomy were excluded. The study was conducted after taking ethical clearance from the institute and informed consent from the patients. The data was collected and analysis done by SPSS version 22.*
Results: *The maximum numbers of cases were in the age group of 51-60 years (28.36%), with female dominance (68.66%) Chronic recurring pain was the main symptom seen in all 67 patients. The rate of conversion from laproscopic cholecystectomy to open cholecystectomy was 8.96%. BMI, H/O acute cholecystitis, thick wall, impacted stone and Pericholecystic collection showed statistical significant association with pre operative score.*
Conclusion: *The preoperative scoring is statistically and clinically a good test for predicting the operative outcome in laparoscopic cholecystectomy.*
Keywords: *Laproscopic cholecystectomy, predictive factors, preoperative scoring.*

Introduction

Cholelithiasis is a common ailment and affects about 10 to 15% of general population.[1] Laparoscopic cholecystectomy is one of the most common surgeries performed and has replaced open cholecystectomy. Since the introduction of laparoscopic cholecystectomy, the number of cholecystectomy perform in the United States has increased from 5 Lakh per year to 7 Lakh per year.[2]

Cholelithiasis is the most common biliary pathology. Gallstones are present in 10 to 15%

of the general population and asymptomatic in the majority (>80%). The prevalence of gallstone varies widely in different parts of the world. In India it is estimated to be around 4%. An epidemiological study restricted to rail road workers showed that north Indians have 7 times higher occurrence of gallstones as compared to south Indians.[3] It is estimated that at least 20 million people in the United States have gallstones and that approximately 1 million new cases of cholelithiasis develop each year. Changing incidence in India is mainly attributed to westernization and availability of investigation that is ultrasound in both rural and urban areas and due to change in socioeconomic structure. [4]

Approximately 1-2% of asymptomatic patients will develop symptoms requiring cholecystectomy per year, making cholecystectomy one of the most common operation performed by general surgeons. Cholelithiasis is rare in the first two decades. Incidence gradually increases after 21 years and reaches its peak in 5th and 6th decade. Women are more affected than men in the ratio of 4:1. [4]

In 1992, The National Institute of Health (NIH) consensus development conference stated that laparoscopic cholecystectomy "provides a safe and effective treatment for most patients with symptomatic gallstones." [3] Since the introduction of laparoscopic cholecystectomy, the number of cholecystectomy performed in the United States has increased from 5 lakh per year to 7 lakh per year. [5]

The advantages of laparoscopic cholecystectomy over open cholecystectomy are earlier return to bowel functions, less postoperative pain, informed cosmesis, shorter length of hospital stay, earlier return to full activity, and decreased overall cost. [6-8] Laparoscopic cholecystectomy is associated with better preservation of immune function and a reduction of the inflammatory response compared with open surgery. The rate of postoperative infections seems to be lower. [9]

Since the conversion rate from laparoscopic cholecystectomy to open cholecystectomy is 1.5 to 19%, there is a need to evaluate various factors responsible for difficult laparoscopic cholecystectomy.

Hence in the present study was done to evaluate the predictive factors responsible for difficult laparoscopic cholecystectomy.

Materials and Methods

Study Design

The present study was prospective analytical study carried out on patients diagnosed as cholelithiasis/ cholecystitis who are clinically evaluated and confirmed by ultrasonography in a tertiary care centre.

Study Period

The present study period was from December 2016 to June 2018.

Study Population

The study population was patients diagnosed as cholelithiasis/cholecystitis who are clinically evaluated and confirmed by ultrasonography in Krishna Institute of Medical Sciences.

Sample Size

A total sample size of 67 patients during study period diagnosed as cholelithiasis/ cholecystitis who are clinically evaluated and confirmed by ultrasonography was included in the study population.

Inclusive Criteria

- Patients aged between 18 to 60 years
- Symptoms and signs of Cholelithiasis / cholecystitis and diagnosed by USG examination.

Exclusion Criteria

- Patients below 18 years of age.
- Patients with CBD calcu1us, raised ALP, dilated
- CBD, where CBD exploration was needed.
- Patients with features of obstructive jaundice.
- Patients refusing surgery.
- Patients not willing for laparoscopic cholecystectomy.

Ethical Consideration

The study was approved by the Ethical Committee of the Medical College.

Data Collection

- All patients diagnosed as cholelithiasis/ cholecystitis were selected
- Informed consent was taken from the patients.
- The selected subjects were visited and the questionnaire was administered.
- The patients confirmed by USG examination was evaluated with following risk factors like age, sex, previous attack of cholecystitis , Abdominal scar-supraumbilical or infraumbilical, BMI, gallbladder wall thickening(>4mm), pericholecystic collection, impacted stone.
- Following evaluation the patient was subjected to laparoscopic cholecystectomy and time taken during surgery, biliary / stone spillage, injury to duct / artery and any probable need for open conversion was noted.
- All of the cases were operated by single laparoscopic surgeon.
- Post operatively cases were followed up for any complication.
- All patients were followed up for recurrent symptoms.

Statistical Analysis

- Data entered into Microsoft excel data sheet and analysed using SPSS 22 version software
- Categorical data represented in frequencies and proportions
- Fischer exact test was used as test of significance.

P value <0.05 considered statistically significant.

Observations and Results

Table 1: Age distribution among patients

Age group (years)	No of Patients	Percentage
<20	04	05.97
21-30	13	19.40
31-40	18	26.87
41-50	13	19.40
51-60	19	28.36
Total	67	100

The above table shows age distribution among patients. The maximum numbers of cases were in the age group of 51-60 years (28.36%), followed by in 41-40 years (26.87%).

Table 2: Sex distribution among patients

Sex	No of Patients	Percentage
Male	21	31.34
Female	46	68.66
Total	67	100

The above table shows sex distribution among patients. Out of 67 cases females (68.66%) were the most affected when compared to males (31.34%).

Table 3: Presenting complaints among patients

Complaints	No of Patients (n=67)	Percentage
Pain	67	100
Vomiting	33	49.25
Jaundice	04	05.97
Dyspepsia	13	19.41
Fever	06	08.96

The above table shows presenting complaints among patients. The mode of presentation in the present study was pain (100%), followed by vomiting (49.25%), dyspepsia (19.41%) and fever (8.96%).

Table 4: Presenting signs among patients

Signs	No of Patients (n=67)	Percentage
Tenderness In Right Hypochondrium	46	68.66
Guarding	04	05.97
Mass	04	05.97

The above table shows presenting signs among patients. The major sign in the present study was tenderness in right hypochondrium (68.66%), followed by guarding (5.97%) and abdominal mass (5.97%).

Table 5: BMI among patients

BMI (kg/m^2)	No of Patients	Percentage
Normal (18.5-24.9)	37	55.22
Overweight (25.0-29.9)	16	23.88
Obese (>30)	14	20.90
Total	67	100

The above table shows BMI among patients. It was observed that majority of patients with normal BMI (55.22%) followed by overweight (23.88%) and obese (20.09%)

Table 6: USG findings among patients

USG findings	No of Patients (n=67)	Percentage
Multiple calculi	43	64.18
Solitary calculi	13	19.40
Solitary impacted calculi	09	13.43
Wall thickening	18	26.87
Pericholecystic collection	07	10.45

The above table shows USG findings among patients. It was observed that majority of patients with multiple calculi (64.18%) followed by gall bladder wall thickening (26.87%), solitary calculi (19.40%), impacted calculi (13.43%) and pericholecystic collection (10.45%)

Table 7: Pre operative score among patients

Pre operative score	No of Patients	Percentage
0-5	49	73.13
6-10	17	25.38
11-15	01	01.49
Total	67	100

The above table shows pre operative score among patients. It was observed that majority of patients with score of 0-5 (73.13%) followed by 6-10 (25.38%) and 11-15 (1.49%)

Table 8: Outcome among patients

Outcome	No of Patients	Percentage
Easy	48	71.64
Difficult	13	19.40
Very difficult	06	08.96
Total	67	100

The above table shows outcome among patients. It was observed that majority of patients with easy outcome (71.64%) followed by difficult (19.40%) and very difficult (8.96%) Out of 67 patients, 6 patients were operated for open cholecystectomy. So, the rate of conversion from laproscopic cholecystectomy to open cholecystectomy was 8.96%.

Table 9: Frequency of intraoperative events leading to difficult procedure

Intra-operative events	No of patients (n=19)	Percentage
Dense adhesions at Calot's triangle	13	68.42
Visceral injury	01	05.26
Stone/biliary spillage	07	36.84
Vascular injury/significant bleeding	08	42.10

The above table shows intraoperative events leading to difficult procedure among patients. Out of 19 patients with difficult and very difficult procedure majority of patients had Dense adhesions at Calot's triangle (68.42%) followed by significant bleeding (42.10%), biliary spillage (36.84%) and visceral injury (5.26%)

Table 10: Correlation of Pre operative score and Outcome among patients

Pre operative score	Easy	Difficult	Very difficult	Total
0-5	47	02	00	49
6-10	01	11	05	17
11-15	00	00	01	01
Total	48	13	06	67

(X2=)

The above table shows Correlation of Pre operative score and Outcome among patients. There was a statistical significant positive correlation between pre operative score and outcome. ($P<0.05$) The positive predictive value for easy prediction was 94.7% and for difficult prediction was 100%.

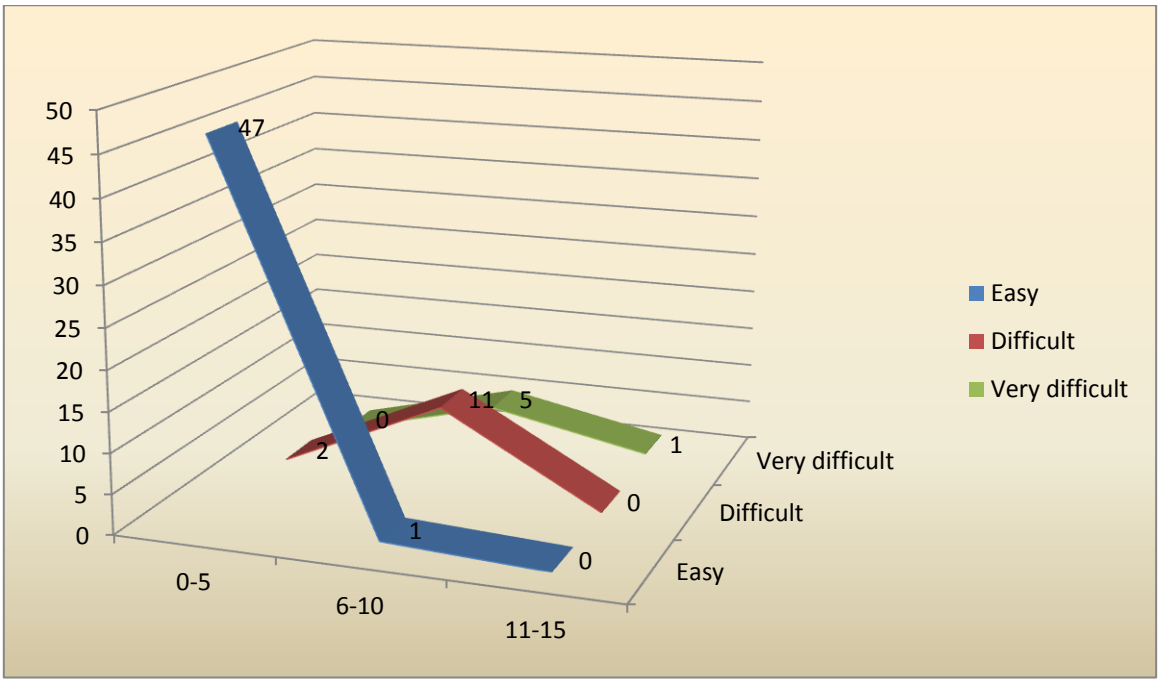

Figure 1: Correlation of Pre operative score and Outcome among patients

Table 11: Showing the analysis of Pre-operative Score with the risk factors

Risk Factors	Level	Pre-operative Score		P Value
		Difficult	Easy	
Age	≤50 Y	9	33	0.62
	>50 Y	4	15	
Sex	Female	10	31	0.51
	Male	03	17	
BMI wt(kg)/ht(m^2)	<25	01	34	<0.0001*
	25.0-29.9	02	12	
	≥30	10	02	
Previous Surg.	No	09	36	0.73
	Yes	04	12	
H/O acute cholecystitis	No	04	46	<0.0001*
	Yes	09	02	
USG- Wall Thickness	No	02	40	<0.0001*
	Yes	11	08	
Impacted Stone	No	07	46	<0.001*
	Yes	06	02	
Pericholecystic Collection	Nil	08	44	0.01*
	Yes	05	04	

The above table shows association of Pre operative score with risk factors among patients. It was observed that BMI, H/O acute cholecystitis, thick wall, impacted stone and Pericholecystic collection showed statistical significant association (P<0.05) while age, sex and previous surgery showed no statistical significant association. (P>0.05)

Discussion

The present prospective study was undertaken to determine the predictive factors for difficult laparoscopic cholecystectomy in a tertiary care centre.

The study was conducted in Department of Surgery from September 2016 to June 2018. A total sample size of 67 patients admitted in the department of various surgical wards in tertiary health center with diagnosis of cholelithiasis/ cholecystitis who were clinically evaluated and

confirmed by USG included in the study population. Patients below 18 years of age, with CBD calculus, raised ALP, dilated, CBD, where CBD exploration was needed, obstructive jaundice ant not willing for laparoscopic cholecystectomy were excluded.

The study was conducted after taking ethical clearance from the institute and informed consent from the patients. The data was collected from patients regarding demographic profile, clinical spectrum findings with outcome.

Age Distribution

In the present study, the maximum numbers of cases were in the age group of 51-60 years (28.36%), followed by in 41-40 years (26.87%).

The present study was in concordance with the study of Herman's et al[28]; and studies of Hanif et al[29] were the majority of patients were in the age group of 41-50 years.

Atul Kumar Gupta et al[30] studied various predictors of difficulty and their correlation with likely difficulty observed out of 50 adults undergoing laparoscopic cholecystectomy for symptomatic cholelithiasis majority of patients in the age group of 31-40 years (18 out of 50).

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed the mean age group of the study was 39.47 ± 12.08 years with the minimum age being 18 years and the maximum being 64 years. The majority of patients were in the age group of ≤50 years (25 patients) and only 16.7% (five cases) were >50 years.

Shiv K. Bunkar et al evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed majority were in the group 20-40 years of age (80 patients, 80%).

Sex Distribution

In the present study, out of 67 cases females (68.66%) were the most affected when compared to males (31.34%). Higher incidence of gallstone in females has been suggested due to the effect of estrogen and progesterone on biliary cholesterol level and gallbladder motility.

The findings were in concordance with the study of Battachary[33] and Hanif et al. [29] Both studies showed 71.4 % & 64% of the patients were females and 28.6% & 36% were males respectively.

Atul Kumar Gupta et al[30] studied various predictors of difficulty and their correlation with likely difficulty observed out of 50 adults there were 45 females and 5 males.

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed out of the 30 patients included in the study, 6 patients were male (20%) and 24 were females (80%).

Shiv K. Bunkar et al[32] evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed out of 100 cases 11 (11%) were males and 89 (89%) were females.

Presenting Complaints

Pain

Chronic recurring pain was the main symptom seen in all 67 patients. In 76.12% (51) of patients, pain was in the right hypochondrium. Of the 67 patients, 52.23% (35) patients had colicky type of pain. Radiation of pain to back was seen in14 (20.89%).

Pain was the most common symptom in both Ganey's series[34] and Alok sharma series.[35]

Vomiting

Vomiting was present in 33 (49.25%) of the patients. Vomiting was spontaneous and associated with the attack of pain. This was consistent with Ganey et al[34] and Alok Sharma et al[35] study.

Jaundice

Four (5.97%) patients had clinical jaundice, which was found to be obstructive type on further investigation. Later, patients underwent ERCP with CBD stenting, which was followed by Laparoscopic cholecystectomy after 6 weeks.

Dyspepsia

Dyspepsia was seen in 19.41% (13) of the patients. This is concordance with Ganey's series[34] and Alok Sharma series. [35]

Fever

Fever was observed in 8.96% (6) of the patients which was of moderate degree. This symptom is consistent with Ganey's series[34] and Alok Sharma series. [35]

Physical Examination Findings

In the present study, it revealed that majority of patients with normal BMI (55.22%) followed by overweight (23.88%) and obese (20.09%)

This was in concordance with the study of of J S Randhawa et al[36] and A K Pujahari et al.[37]

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed 6 patients with body mass index (BMI) >27.5 kg/m.

Shiv K. Bunkar et al[32] evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed BMI of patients were <25 in 26 (26%) patients; 25.1-30 in 60 (60%) patients and >30 in 14 (14%) patients.

Obese patients may have a difficult laparoscopic surgery due to various factors. Port placement in obese patient takes longer time due to the thick abdominal wall. Dissection at the Calot's triangle is also technically difficult due to the obscure anatomy because of excessive intraperitoneal fat and difficulty in the manipulation of instruments through an excessively thick abdominal wall.

Presenting Signs

Tenderness in right hypochondrium was seen in 46 (68.66%) patients. Tenderness was observed in more patients in the study of Hadfield et al. [38]

Guarding was found in 4(5.97%) patients in contrast to18.7% seen in the study of Hadfield et al. [38] Murphy's sign was positive in 19 (31%) patients.

Mass was palpable in 4 (5.97%) patients while in Hadfield's series[38] mass was palpable in 7% of the patients

Radiological Findings

In all the patients, ultrasonography was performed as a routine investigation all 67 patients had stones in gallbladder. Gall bladder wall thickening was present in 18 (26.87%) patients. Pericholecystic collection was seen in 7 (10.45%) patients. Out of total 67 patients, 43 (64.18%) cases had Multiple calculi, 13 (19.40%) had Solitary calculi and 9 (13.43%) had solitary impacted calculi.

In Alok Sharma et al[35] study, 98.3% had stones in Gall Bladder and 5.2 % had Gall Bladder wall thickening. Of the 98.3%, 73.7% had multiple stones, 26.3% had solitary stones and 5.2% had bile duct stones. Similar findings were observed in the study of Bunker SK et al. [32] the patients, ultrasonography was performed as a routine investigation.

Correlation of Pre-Operative Score and the Outcome

It was observed that majority of patients with score of 0-5 (73.13%) followed by 6-10 (25.38%) and 11-15 (1.49%) It was observed that majority of patients with easy outcome (71.64%) followed by difficult (19.40%) and very difficult (8.96%) Out of 67 patients, 6 patients were operated for open cholecystectomy. So, the rate of conversion from laproscopic cholecystectomy to open cholecystectomy was 8.96%.

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed 17 patients scored easy (56.7%) and 13 (43.3%) were difficult and nil in very difficult group.

Shiv K. Bunkar et al[32] evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed score between 0-5 had easy laparoscopic cholecystectomy in 88.4% patients, difficult laparoscopic cholecystectomy in 6.4% patients and very difficult in 5.2% patients. Patients who score between 6-10 have difficult laparoscopic cholecystectomy in 78.9% patients and very difficult in 21.1% patients. Patient who score between 11-15 have very difficult laparoscopic cholecystectomy in 100% patients.

In the present study the positive predictive value for easy prediction was 94.7% and for difficult prediction was 100%.

Shiv K. Bunkar et al[32] evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed scoring system had a

positive prediction value for easy prediction of 94% and for difficult prediction of 100%.

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed prediction came true in 76.4% for easy and 100% difficult cases.

In the studies of J S Randhawa et al[36] and A K Pujahari et al [37] of the 228 cases studied; cases with 0 to 5 pre-op score were 178 of which 158 were easy Laparoscopic Cholecystectomy, 14 were difficult Laparoscopic Cholecystectomy and 6 were very difficult LC. The positive prediction value for easy prediction was 88.8% and for difficult prediction was 92%. The conversion rate was 3/228 i.e. 1.315% and all were due to anomaly in the ducts. The positive predictive value for easy prediction was 94.7% and for difficult prediction was100%.

The conversion rate from laparoscopic cholecystectomy to open cholecystectomy was 8.96% which was in concordance with the of study of Kama et al. [39]

Atul Kumar Gupta et al[30] studied various predictors of difficulty and their correlation with likely difficulty observed conversion to open cholecystectomy was needed only in two patients (4%).

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed the proposed scoring system was reliable with a sensitivity of 76.47% and specificity of 100%.

Analysis of Pre-Operative Score with the Risk Factors

In the present study, it was observed that BMI, H/O acute cholecystitis, thick wall, impacted stone and Pericholecystic collection showed statistical significant association ($P<0.05$) while age, sex and previous surgery showed no statistical significant association. ($P>0.05$)

Nikhil Agrawal et al[31] studied preoperative prediction of difficult laparoscopic cholecystectomy by scoring method observed factors like previous history of hospitalization, clinically palpable gallbladder, impacted GB stone, pericholecystic collection, and abdominal scar due to previous abdominal surgery were found statistically significant in predicting difficult LC.

Shiv K. Bunkar et al[32] evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed BMI >30, previous medical disease like DM, palpable gall bladder, prior hospitalization pericholecystic collection and impacted stone are significant risk factors to predict difficult laparoscopic cholecystectomy.

Atul Kumar Gupta et al[30] studied various predictors of difficulty and their correlation with likely difficulty observed clinical predictors like duration of symptoms >1yr, history of acute cholecystitis and BMI >30 showed statistically significant association. Age >50yrs, Male gender, radiological predictors (Thickened gall bladder wall, small contracted gall bladder, Single large impacted stone) and deranged LFT did not show significant predictive value.

It is presumed that previous abdominal surgery; especially upper abdominal surgery may cause difficulty due to periumbilical and peri gallbladder adhesions. Nachnani et al[40] reported that previous abdominal surgery poses problems during creation of pneumoperitoneum and during adhesiolysis to gain adequate exposure to the operative field. But Kanaan et al[41] and Lipman et al[42] did not find prior abdominal surgery as a significant risk factor for conversion or prediction of difficult laparoscopic cholecystectomy.

In the present study, complications among patients showed out of 67 patients only 2 (2.98%) patients had wound infection.

Shiv K. Bunkar et al[32] evaluate pre-operative factors predicting difficult laparoscopic cholecystectomy observed postoperative complication was seen in four patients who developed an infection of the epigastric port site.

The preoperative scoring is statistically and clinically a good test for predicting the operative outcome in LC. In the present study, sample size was small but the predictors of difficult LC

correlated well with previous studies. Further randomized prospective trial with large sample size needed to validate the scoring system.

Summary

The present prospective study was undertaken to determine the predictive factors for difficult laparoscopic cholecystectomy in a tertiary care centre.

The study revealed following:

- The maximum numbers of cases were in the age group of 51-60 years (28.36%), followed by in 41-40 years (26.87%).
- Out of 67 cases females (68.66%) were the most affected when compared to males (31.34%).
- Chronic recurring pain was the main symptom seen in all 67 patients.
- In 76.12% (51) of patients, pain was in the right hypochondrium. Of the 67 patients, 52.23% (35) patients had colicky type of pain. Radiation of pain to back was seen in14 (20.89%).
- Vomiting was present in 33 (49.25%) of the patients. Vomiting was spontaneous and associated with the attack of pain.
- Four (5.97%) patients had clinical jaundice, which was found to be obstructive type on further investigation.
- Dyspepsia was seen in 19.41% (13) of the patients.
- Fever was observed in 8.96% (6) of the patients which was of moderate degree.
- The majority of patients with normal BMI (55.22%) followed by overweight (23.88%) and obese (20.09%)
- Tenderness in right hypochondrium was seen in 46 (68.66%) patients.
- Guarding was found in 4(5.97%) patients. Murphy's sign was positive in 19 (31%) patients.
- Mass was palpable in 4 (5.97%) patients .
- Gall bladder wall thickening was present in 18 (26.87%) patients.
- Pericholecystic collection was seen in 7 (10.45%) patients.
- Out of total 67 patients, 43 (64.18%) cases had Multiple calculi, 13 (19.40%) had Solitary calculi and 9 (13.43%) had solitary impacted calculi.
- It was observed that majority of patients with score of 0-5 (73.13%) followed by 6-10 (25.38%) and 11-15 (1.49%)
- It was observed that majority of patients with easy outcome (71.64%) followed by difficult (19.40%) and very difficult (8.96%)
- Out of 67 patients, 6 patients were operated for open cholecystectomy. So, the rate of conversion from laproscopic cholecystectomy to open cholecystectomy was 8.96%.
- In the present study the positive predictive value for easy prediction was 94.7% and for difficult prediction was 100%.
- The conversion rate from laparoscopic cholecystectomy to open cholecystectomy was 8.96%.
- It was observed that BMI, H/O acute cholecystitis, thick wall, impacted stone and Pericholecystic collection showed statistical significant association ($P<0.05$) while age, sex and previous surgery showed no statistical significant association. ($P>0.05$)
- Complications among patients showed out of 67 patients only 2 (2.98%) patients had wound infection.

Conclusion

The preoperative scoring is statistically and clinically a good test for predicting the operative outcome in LC.

The study concluded that history of previous abdominal surgery, tenderness in the right hypochondrium, and thickening of GB, whereas conversion to OP was significantly high in patients with thickening of GB and distended or contracted GB. Among demographic parameters,

BMI >30 kg/m was the significant predictor of difficult LC and conversion. This consequently increases the operating time of such patients. This can contribute to the quest for surgical excellence and better patient care for one of the most commonly performed surgical procedures in the world.

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