Section: General Surgery

Original Research Article

PRE OPERATIVE PREDICTORS OF DIFFICULT LAPAROSCOPIC CHOLECYSTECTOMY: A PROSPECTIVE STUDY

Krishna Rao[1], Prasad H Upase[2], C R Chhallani[3], Ashok Nayak[4]

[1]*Assistant Professor, Department of General Surgery, ESIC Medical College Kalaburagi, Karnataka, India.*
[2]*Senior Resident, Department of General Surgery, ESIC Medical College Kalaburagi, Karnataka, India.*
[3,4]*Senior Consultant General Surgery, BMJH Bengaluru, India.*

Received *: 14/07/2024*
Received in revised form *: 08/09/2024*
Accepted *: 23/09/2024*

Corresponding Author:
Dr. Krishna Rao,
Assistant Professor, Department of General Surgery, ESIC Medical College Kalaburagi, Karnataka India.
Email: raok4300@gmail.com.

DOI: 10.70034/ijmedph.2024.3.151

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (3); 846-851

ABSTRACT

Background: To identify the preoperative predictors of difficulty in laparoscopic cholecystectomy and to develop a scoring system on the basis of these observations that may be predictive of difficulty.

Materials and Methods: This study included 60 consecutive Laparoscopic cholecystectomies that were studied prospectively over a period of 19 months at Bhagwan Mahaveer Jain Hospital, Bengaluru from June 2015 to December 2016. Standard 4 port LC done in all the cases.

Results: A score of <=4 and >= 5 was found to be cut off point to predict easy and difficult LC with sensitivity and specificity, PPV, NPV and accuracy of 96%, 68.6%, 68.6%, 96% and 80% respectively. In our study we found that Age >50 years, H/o Acute cholecystitis, GB wall thickness >4mm, impacted stone in neck of GB, Diabetes Mellitus, total WBC count > 9000 cells/cumm and BMI >27.5 Kg/M2 statistically significant factors to predict difficult LC.

Conclusion: The scoring system evaluated in our study is a reliable and useful benchmark to predict difficult cases. However, the small sample size may be an impediment in attaining complete statistical validity. We propose large scale, multicentric studies to validate the scoring methodology and establish its efficacy.

Keywords: Pre-operative predictors, Difficult Laparoscopic Cholecystectomy.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most common laparoscopic procedures being performed by general surgeons all over the world. Preoperative prediction of the risk of conversion or difficulty of operation is an important aspect of planning laparoscopic surgery. The purpose of our prospective study is to analyze various risk factors and to predict difficulty preoperatively by the use of a scoring system.[1]

Laparoscopic cholecystectomy (LC) since its inception in 1987, has dramatically replaced conventional open cholecystectomy. LC has rapidly become the gold standard for routine gall bladder removal. Management of biliary tract disease has evolved from being a major procedure to a relatively safe and tolerable day care procedure today, offering early return to full activity.[2]

LC though safe and effective, yet can be difficult at times. Various problems faced are difficulty in creating pneumo peritoneum, accessing peritoneal cavity, releasing adhesions, identifying anatomy, anatomical variation, dissection of Calot's triangle, avoiding injury to surrounding structures and extracting the gall bladder. LC with these problems along with time taken more than normal we considered as difficult.[2]

LC is the most common difficult laparoscopic surgery performed by surgeons all over the world. This study is based on the assumption that difficulty can be predicted and its design is directed towards identification of these predictors.[2]

Gallstone disease is one of the most common problems affecting the digestive tract. Autopsy reports have shown a prevalence of gallstones from 11% to 36%.[3]

The prevalence of gallstones is related to many factors, including age, gender, and ethnic

background. Certain conditions predispose to the development of gallstones. Obesity, pregnancy, dietary factors, Crohn's disease, terminal ileal resection, gastric surgery, hereditary spherocytosis, sickle cell disease, and thalassemia are all associated with an increased risk of developing gallstones.[4]

Women are three times more likely to develop gallstones than men, and first-degree relatives of patients with gallstones have a twofold greater prevalence.[5]

Hence this study was conducted to identify the preoperative predictors of difficulty in laparoscopic cholecystectomy and to develop a scoring system on the basis of these observations that may be predictive of difficulty.

MATERIALS AND METHODS

This single Centre non randomized prospective, clinical observational study was conducted among in patients admitted in General Surgery Department, at Bhagwan Mahaveer Jain hospital Bengaluru, who underwent laparoscopic Cholecystectomy. Study period was June 2015 to December 2016 (1 year 7 months).

Inclusion Criteria: All the patients >12years of age who underwent laparoscopic cholecystectomy at Bhagwan Mahaveer Jain Hospital, Bengaluru.

Exclusion Criteria: Exclusion criteria included

1. Patients unfit for General Anesthesia due to severe cardio-pulmonary disease.
2. Patients who did not give consent to be included in the study.
3. Pregnant women.
4. Patients who were under 12 years of age.

Sample size = 60

Sample Size Calculation

$n = Z^2 \times (p) \times (1-p)/c^2$

Where:

Z = Z value (e.g. 1.96 for 95% confidence level)

p =sensitivity

c = absolute precession

(e.g., .05 = ±5)

A sample size of 60 will have 90% power to detect sensitivity is unlikely to exceed 96% (Based on published article by Gupta N, et al)[1]. In this calculation we used the following assumptions: We expect sensitivity estimated within 5 percentage points of the true value (965) with 95% confidence interval.

$N= (1.96)^2X (0.96) X (1-0.96)/ (0.05)^2=59$

Methodology: The study was conducted in Department of General surgery, Bhagwan Mahaveer Jain Hospital, Bengaluru. 60 consecutive patients who underwent Laparoscopic Cholecystectomy from 1st June 2015 to 31st December 2016 were included in the study.

All the patients were scored pre-operatively according to history, physical examination, laboratory parameters, and ultrasonography (USG) findings.

All the patients underwent standard 4 port laparoscopic cholecystectomy.

Patients were categorized as easy and difficult surgery according to following criteria at the end of surgery.

1. Easy

Time taken < 60 min, No bile/ calculus spillage, No injury to CBD/ cystic artery.

2. Difficult

Time taken >60 min, Bile/ calculus spillage /Injury to cystic artery, Injury to CBD, Conversion to open procedure.

Statistical Analysis: The results for each parameter (numbers and percentages) for discrete data and averaged (mean ± standard deviation) for each parameter were presented in tables and figures. Proportions were compared using Chi-square test of significance

In all above test P value less than 0.05 was taken to be statistically significant. The data was analyzed using SPSS package.

Proportions were compared by using Chi-square test, ROC was fitted to identify the cut off values of scoring system for difficult laparoscopic cholecystectomy. Logistic regression was fitted to identify independent risk factors. P value <0.05 was considered as statistically significant.

Patients were selected by applying the above mentioned inclusion and exclusion criteria. Written informed consent was taken, after explaining about the study, Patients who did not give consent were excluded from the study. A scoring system was devised for preoperative prediction of difficult laparoscopic cholecystectomy.

RESULTS

In this study out of 60 cases 25 were male patients and 35 were females, which constitutes 41.7% and 58.3% respectively. In our study there were 36 patients under 50 years and 24 patients were over 50 years. The minimum age of the patient was 14 years and maximum age 87 years. Maximum patients were in age group 40-49 years.

Age more than 50 years is statistically significant for difficult LC with p value 0.0325

In this study 36 patients were <50 years and 24 patients were >50 years. Mean age of the population studied is 45.57years with standard deviation of 16.219 years. Median age 45.00 years, minimum age 14 years and maximum age 87 years.

Out of 60 cases 41.7% (25) patients had difficult surgery and 58.3% (35) had easy surgery.

Out of 25 males 12 had easy surgery and 13 had difficulty. In 35 females 23 had easy surgery and 12 had difficulty. However male sex was not statistically significant for difficulty with p value 0.170.

Out of 60 patients, 44 patients had history of gall bladder disease symptoms. Of which 24 patients had easy surgery and 20 had difficult surgery.

History of gall bladder disease symptom was not statistically significant in our study with p value 0.324. [Table 1]

In this study out of 60 patients, 38 patients had acute cholecystitis, of 16 patients had easy surgery and 22 had difficult surgery. Admission with acute cholecystitis is statistical significant in our study with p value 0.001. [Table 2]

Out of 60 patients, 16 patients had previous abdominal surgeries. H/O previous abdominal surgery is not statistically significant for difficult surgery in our study with p value of 0.693. [Table 3]

Out of 60 patients, 1 patient had guarding/rigidity, that patient had difficult surgery, it is not statistically significant with p value 0.233.

Out of 60 patients, 2 patients had palpable gall bladder, both patients had difficult surgery, but palpable gall bladder is not statistically significant with p value 0.089. [Table 4]

Out of 60 patients, 10 patients had impacted stone in the neck of gall bladder, out of which 8 patients had difficult surgery. Impacted stone in gall bladder neck is statistically significant with p value 0.007. [Table 5]

Out of 60 patients 14 patients underwent pre-operative ERCP, of which 9 patients had difficult surgery. Pre-operative ERCP is not statistically significant with p value 0.050. [Table 6]

Out of 60 patients, 5 patients had gall stone induced pancreatitis. Among them 4 patients had difficult surgery. However gall stone induced pancreatitis is not statistically significant for difficult surgery with p value 0.069.

Out of 60 patients, 8 patients had Diabetes mellitus, of which 7 patients had difficult surgery. Diabetes mellitus is statistically significant for difficult surgery in our study with p value 0.005.

Out of 60 patients, 32 patients had increased WBC count >9000, of which 18 patients had difficult surgery. Out of 28 patients, who had normal counts <9000, in them 7 patients had difficult surgery. Increased WBC Count is statistically significant with p value 0.014.

Out of 60 patients, 36 patients had normal BMI, in them, 11 patients had difficult surgery. 8 patients had BMI >25-<27.5, among them 7 patients had difficult surgery and 16 patients had >27.5 BMI, in them 7 patients had difficult surgery. BMI is statistically significant with p value 0.012. [Table 7]

Out of 60 patients, 35 patients had normal gall bladder wall thickness and 25 had increased (>=4mm, thick and moderate) gall bladder wall thickness. In increased GB wall thickness group 18 patients had difficult surgery and in normal wall thickness group 7 patients had difficult surgery. Here increased GB wall thickness is statistically significant with p value <0.001.

Out of 60 patients, 8 patients underwent open conversion from LC.In that 5 were males and 3 were females.Conversion rate in 13.33%. OC seen in 20% of males and in 8.57 % in females. [Table 8]

The mean score in easy group is 3.51 with standard deviation 1.579 and in difficult group is 6.28 with standard deviation 1.400. The mean score is statistically significant with p value <0.001. [Table 9]

Out of 60 patients, 25 had total score <=4 and 35 patients had total score >=5.Out of 25 patients with score <=4, 24 patients had easy surgery and 1 had difficult surgery. Out 35 patients with score >=5, 11 had easy surgery and 24 had difficult surgery.This study has gotSensitivity=96.0%, Specificity=68.6%, PPV=68.6%, NPV=96.0%, Accuracy=80.0%. [Table 10]

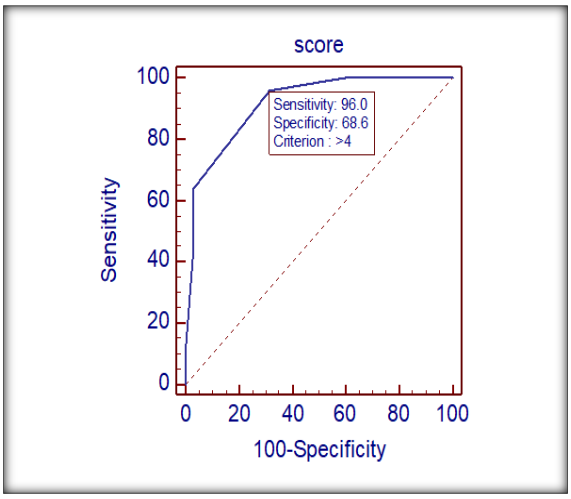

Figure 1: ROC curve and its area under curve for prediction of intraoperative outcome based on preoperative scores

In our study Area under the ROC curve (AUC) is 0.917. At score 4, the sensitivity is 96.00% and specificity 68.57%.

Table 1: Symptoms of Gall bladder stone disease in patients

	H/O Gb Symptoms		Total	P value*
	Yes	No		
Easy	24	11	35	***0.324***
	68.6%	31.4%	100.0%	
Difficulty	20	5	25	
	80.0%	20.0%	100.0%	
Total	44	16	60	
	73.3%	26.7%	100.0%	

Table 2: Patients who were admitted with acute cholecystitis

	Admission For Acute Cholecystitis		Total	P value*
	Yes	No		
Easy	16	19	35	***0.001***
	45.7%	54.3%	100.0%	
Difficulty	22	3	25	
	88.0%	12.0%	100.0%	
Total	38	22	60	
	63.3%	36.7%	100.0%	

Table 3: Past history of abdominal surgery

	Previous abdominal surgery		Total	P value*
	Yes	No		
Easy	10	25	35	0.693
	28.6%	71.4%	100.0%	
Difficulty	6	19	25	
	24.0%	76.0%	100.0%	
Total	16	44	60	
	26.7%	73.3%	100.0%	

Table 4: Patients who had guarding or rigidity

	Guarding/Rigidity		Total	P value*
	Yes	No		
Easy	0	35	35	0.233
	.0%	100.0%	100.0%	
Difficulty	1	24	25	
	4.0%	96.0%	100.0%	
Total	1	59	60	
	1.7%	98.3%	100.0%	

Table 5: the patients who had impacted stone in the neck

	Impacted Stone In Neck		Total	P value*
	Yes	No		
Easy	2	33	35	0.007
	5.7%	94.3%	100.0%	
Difficulty	8	17	25	
	32.0%	68.0%	100.0%	
Total	10	50	60	
	16.7%	83.3%	100.0%	

Table 6: patients who had pre-operative ERCP

	Pre Op ERCP		Total	P value*
	Yes	No		
Easy	5	30	35	0.050
	14.3%	85.7%	100.0%	
Difficulty	9	16	25	
	36.0%	64.0%	100.0%	
Total	14	46	60	
	23.3%	76.7%	100.0%	

Table 7: patients who had Gall stone induced pancreatitis

	Gs Indused Pancreatitis		Total	P value*
	Yes	No		
Easy	1	34	35	0.069
	2.9%	97.1%	100.0%	
Difficulty	4	21	25	
	16.0%	84.0%	100.0%	
Total	5	55	60	
	8.3%	91.7%	100.0%	

Table 8: patients who had gall bladder wall thickness

	Wall Thickness		Total	P value*
	Thick, Moderate(>=4mm)	Normal(<4mm)		
Easy	7	28	35	<0.001
	20.0%	80.0%	100.0%	
Difficulty	18	7	25	
	72.0%	28.0%	100.0%	
Total	25	35	60	
	41.7%	58.3%	100.0%	

Table 9: overall outcome of the surgery

	Outcome	N	Mean	SD	Mean Diff	SE of Diff	P value
Total Score	Easy	35	3.51	1.579	2.766	0.395	<0.001
	Difficulty	25	6.28	1.400			

Table 10: Scoring

	Score		Total
	<=4	>4	
Easy	24	11	35
	68.6%	31.4%	100.0%
	96.0%	31.4%	58.3%
Difficulty	1	24	25
	4.0%	96.0%	100.0%
	4.0%	68.6%	41.7%
Total	25	35	60
	41.7%	58.3%	100.0%
	100.0%	100.0%	100.0%

DISCUSSION

Majority of the patients in the present series were in the age group of 40 -49 years of age, the age of our patients ranged from 14 to 87 years and mean was 45.57 years. The similar age group has been mentioned in the study of Randhawa JS et al6as the mean age in their patients varied from 9 to 70 years and the mean was 44.37 years.

In our study >50 years age group had difficult surgery with significant p value 0.0325. Similar results were seen in studies done by Sultan AM et al,[7] Rosen M et al,[8] and age >50 years had difficult surgery but those studies had non-significant p values.

In our study there was no statistically significant difficulty between male and female patients with p value 0.170. Similar results were seen in studies done by Husain A et al,[9] (>0.05), Patil S et al,[10] (p value 0.5) and Nikhil Gupta et al,[1] p value 0.265).

In our study previous history of Gall bladder disease symptoms was not statistically significant to predict difficulty with p value 0.324. Similar results were seen in studies by Younis KK et al.,[11] (p value 0.720). But Studies done by Acharya A et al,[12] and Husain A et al,[9] showed statistically significant association for difficulty with p values 0.001 and <0.05 respectively. However in our study, out of 25 patients who had difficult surgery, 20 had GB symptoms (80%). It shows that surgery will be difficult in patients with previous history of GB disease symptoms.

In our study admission with acute cholecystitis was statistically significant to predict difficulty with p value 0.001. Similar results were seen in studies done by Acharya A et al,[12] (p value 0.001), and Sultan AM et al,[7] (p value 0.001).

In our study past abdominal surgery is not statistically significant to predict difficulty with p value 0.693. Similar results were seen in studies done by Randhawa JS et al,[6] with p value 0.882.

In our study palpable gall bladder was not statistically significant to predict difficulty with p value 0.089. In our study 2 patients had palpable gall bladder and both patients had difficult surgery. Studies done by Randhawa JS et al6 and Patil S et al,[10] showed statistically significant association between Palpable GB and difficulty with p value <0.001 and <0.001 respectively.

In our study impacted stone in neck of GB was statistically significant with p value 0.007. Similar results were seen in studies done by Acharya A et al,[12] and Randhawa JS et al,[6] with p values 0.001, 0.038 respectively.

In our study Pre-operative ERCP was not statistically significant to predict difficulty with p value 0.05. Similar results were seen in studies done by Sahu SK et al,[13] with p value >0.05. But study done by Vivek et al2showed statistically significant association of pre-operative ERCP to predict difficulty. However in our study, out of 14 patients who underwent Pre-op ERCP 9 had difficult surgery (64.28%). Which shows that pre-op ERCP is factor to predict difficulty.

In our study Gall stone induced pancreatitis was not statistically significant to predict difficulty with p value 0.069. Similar result was seen in study done by Sahu SK et al,[13] with p value >0.05. However in our study total 5 patients had GS induced pancreatitis, in them 4 had difficult surgery.

In our study DM was statistically significant to predict difficulty with p value 0.005. Similar results were seen in studies done by Husain Aet al,[9] and Stanisic V et al,[14] p values <0.05 <0.001 respectively. So DM is statistically significant to predict difficulty.

In our study WBC count >9000cells/cumm was statistically significant to predict difficulty with p value 0.014. Similar results were seen in studies done by Sultan A M7 with p value <0.01 and Rosen M8 et al with p value 0.006.

In our study BMI >27.5 showed statistically significant to predict difficulty with p value 0.012. Other studies which had similar result are J S Randhawa et al with p value 0.010. A study done by Husain A et al9 showed there is significant association between BMI >30 and difficult surgery. A study done by Patil S et al10 showed BMI >27.5 statistically significant to predict difficulty with p value <0.01.

In our study increased GB wall thickness (>4mm) showed statistically significant to predict difficulty with p value <0.01. Similar results were seen with

studies done by Acharya et al with p value <0.038, Husain A et al9 with p value <0.05, Patil S et al.[10] Nikhil Gupta et al study1 also showed statistically significant association between increased GB wall thickness and difficulty with p value <0.005.

Out of 60 patients, 8 patients underwent open conversion from LC. In them 4 patients had dense adhesion between GB and colon and duodenum. 2 patients had bleeding from cystic artery and 2 patients had gangrenous and friable GB. The OC % in our study is 13.33%. Similar results are seen in studies done by Patil S et al,[10] (OC 14%) and by Husain A et al,[8] (OC 17%).

In our study the results were Sensitivity=96.0%, Specificity=68.6%, PPV=68.6%, NPV=96.0%, Accuracy=80.0%. This is for the score <=4 and >=5 to predict easy and difficult respectively. Similar results were seen in studies done by Nikhil Gupta et al with Sensitivity and specificity of the scoring system at score 5 for prediction of easy or difficult laparoscopic cholecystectomy were 95.74% and 73.68% respectively. Area under ROC curve was 0.86. In our study Area under the ROC curve (AUC) was 0.917.

A study done by Joshi MR et al,[15] had Sensitivity and specificity of the preoperative scoring for difficult case was 53.8 % and 89.2% respectively with PPV of 63.64 % and NPV of 84.62%.

For easy case, sensitivity and specificity of pre-operative prediction was 89.2 % and 53.8 % respectively whereas positive and negative predictive value was 84.62 % and 63.64 % respectively. Area under ROC curve was 0.779. These results are comparable with our study.

CONCLUSION

The highest incidence of gallstone in present series is in the age group of 40-49 years, which is closely followed by 20-29 years and above 51 yrs. Ultrasound is the most accurate and sensitive investigation for diagnosis of Cholelithiasis. Of the 60 patients, all had stones in the gall bladder, 44 patients had GB disease symptoms. 38 were admitted with acute cholecystitis. 25 had GB wall thickening and 10 had impacted calculi in neck of GB.

In our study >50 years age group, admission with Acute cholecystitis , impacted stone in neck of GB, Diabetes Mellitus , WBC count >9000 cells/cumm, BMI >27.5 KG/M2, GB wall thickness >4mm were statistically significant to predict difficulty. However these factors were not is statistically significant to predict difficulty but surgery was more difficult in this groups- male sex, h/o GB disease symptoms, Pre-op ERCP, GS induced pancreatitis.

Knowledge of these factors for difficult laparoscopic cholecystectomy could help surgeons during pre-operative assessment and take necessary precautions during laparoscopic cholecystectomy.

The overall Sensitivity of our study is 96.0%, and Specificity=68.6%. PPV of our study is 68.6%, NPV=96.0%, Accuracy=80.0%. This is for the score <=4 and >=5 to predict easy and difficult respectively.

Proposed scoring system is reliable statistically with sensitivity of 96.0% and specificity 68.6%. This preoperative scoring system is statistically and clinically a good test for predicting the operative outcome in LC (area under ROC = 0.917).

We may conclude that the scoring system evaluated in our study is a reliable and useful benchmark to predict difficult cases. However, the small sample size may be an impediment in attaining complete statistical validity. We propose large scale, multicentric studies to validate the scoring methodology and establish its efficacy.

REFERENCES

1. Gupta N, Ranjan G, Arora MP, Goswami B, Chaudhary P, Kapur A, Kumar R, Chand T. Validation of a scoring system to predict difficult laparoscopic cholecystectomy. International Journal of Surgery. 2013 Nov 30;11(9):1002-6.
2. Vivek MA, Augustine AJ, Rao R. A comprehensive predictive scoring method for difficult laparoscopic cholecystectomy. Journal of minimal access surgery. 2014 Apr;10(2):62-67.
3. Brett M, Barker DJ. The world distribution of gallstones. International journal of epidemiology. 1976 Dec 1;5(4):335-41.
4. Al-Jiffry BO, Shaffer EA, Saccone GT, Downey P, Kow L, Toouli J. Changes in gallbladder motility and gallstone formation following laparoscopic gastric banding for morbid obesity. Canadian Journal of Gastroenterology and Hepatology. 2003;17(3):169-74.
5. Nakeeb A, Comuzzie AG, Martin L, Sonnenberg GE, Swartz-Basile D, Kissebah AH, Pitt HA. Gallstones: genetics versus environment. Annals of surgery. 2002 Jun;235(6):842-9.
6. Randhawa JS, Pujahari AK. Preoperative prediction of difficult lap chole: a scoring method. Indian Journal of Surgery. 2009 Aug 1;71(4):198-201
7. Sultan AM, El Nakeeb A, Elshehawy T, Elhemmaly M, Elhanafy E, Atef E. Risk factors for conversion during laparoscopic cholecystectomy: retrospective analysis of ten years' experience at a single tertiary referral centre. Digestive surgery. 2013;30(1):51-5.
8. Rosen M, Brody F, Ponsky J. Predictive factors for conversion of laparoscopic cholecystectomy. The American journal of surgery. 2002 Sep 30;184(3):254-8.
9. Husain A, Pathak S, Firdaus H. Assessment of operative predictors for difficulty in laparoscopic cholecystectomy. International Journal of Contemporary Medical Research. 2016; 3:1232-4.
10. Patil S, Inamdar PS. Evaluation of preoperative predictive factors that determine difficult laparoscopic cholecystectomy. International Surgery Journal. 2016 Dec 8;3(2):825-30
11. Younis KK, Al-Harbawi LQ, Ashoor OA. Evaluation of Clinical Parameters that Predict Difficulties during Laparoscopic Cholecystectomy. The Iraqi Postgraduate Medical Journal. 2013;12(2):175-80.
12. Adhikari SK, Acharya A. Preoperative Scoring System to Predict Difficult Laparoscopic Cholecystectomy. Post-Graduate Medical Journal of NAMS. 2012 Jan-Jul;12(1):45-50.
13. Sahu SK, Agrawal A, Sachan PK. Intraoperative difficulties in laparoscopic cholecystectomy. Jurnalul de chirurgie (Iaşi). 2013; 2:149-55.
14. Stanisic V, Milicevic M, Kocev N, Stojanovic M, Vlaovic D, Babic I, Vucetic N. Prediction of difficulties in laparoscopic cholecystectomy on the base of routinely available parameters in a smaller regional hospital. Eur Rev Med Pharmacol Sci. 2014 Apr 1;18(8):1204-1.
15. Joshi MR, Bohara TP, Rupakheti S, Parajuli A, Shrestha DK, Karki D, Laudari U. Pre-operative Prediction of Difficult Laparoscopic Cholecystectomy. Journal of Nepal Medical Association. 2015 Oct 7;53(200):221-6.