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Gallbladder perforation: morbidity, mortality and preoperative risk prediction

F. Ausania · S. Guzman Suarez · H. Alvarez Garcia · P. Senra del Rio · E. Casal Nuñez

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Abstract

Introduction Gallbladder perforation (GBP) is a life threatening complication of acute cholecystitis occurring in approximately 2–11 % of patients. The aim of this study is to analyse all factors associated with morbidity and mortality and assess the accuracy of preoperative risk prediction scores.

Methods Medical records of 1,033 patients who underwent cholecystectomy for acute cholecystitis in our centre between 2002 and 2012 were reviewed. Preoperative, intraoperative and postoperative relevant data were analysed with univariate and multivariate statistical methods to identify all factors associated with postoperative complications and mortality. Accuracy of ASA, POSSUM and APACHE II scores was also compared using receiver-operating characteristics methodology.

Results 137 (12.4 %) patients with gallbladder perforation were identified. Morbidity and mortality rates were 57.7 and 9.5 %, respectively. At multivariate analysis, preoperative albumin ($P = 0.007$, OR 0.175), open surgery ($P = 0.011$, OR 37.78) and preoperative sepsis ($P = 0.002$, OR 51.647) were associated with complications, and preoperative sepsis was the only factor independently associated with hospital mortality ($P = 0.007$, OR 9.127). Both POSSUM and APACHE II scores were superior to ASA score in risk prediction.

Conclusion Preoperative severe sepsis is the most important factor associated with postoperative morbidity and mortality following GBP, and it can be helpful to identify those patients needing the highest level of care possible.

Keywords Gallbladder perforation · Acute cholecystitis · Mortality

F. Ausania (✉) · S. Guzman Suarez · H. Alvarez Garcia · P. Senra del Rio · E. Casal Nuñez
HPB Unit, Department of Surgery, Hospital Xeral, Calle Pizarro 22, 36203, Vigo, PV, Spain
e-mail: f.ausania@googlemail.com

Gallbladder perforation (GBP) is an uncommon complication of acute cholecystitis, and previous large series have reported an incidence of approximately 2–11 %. It is associated with high morbidity and mortality rates, and unfortunately, its early detection can be difficult [1–3].

Delay in diagnosis seems to be the major cause of its high morbidity and mortality, and no studies have investigated whether or not risk prediction scores can be helpful in identifying high-risk patients [4].

The aim of this study is to analyse all factors associated with morbidity and mortality, and compare the accuracy of preoperative risk prediction scores.

Methods

From 2002 to 2012, 1,033 patients were submitted to cholecystectomy for acute cholecystitis at our Institution. Only patients with GBP were considered for this study.

GBP was defined as the presence of intraoperative breach of gallbladder wall, postoperatively confirmed by the pathologist.

Patients with previous percutaneous cholecystostomy were not considered for this study; however, our policy is to avoid percutaneous drainage for GBP, as we believe surgical approach is more indicated in these cases.

Preoperative data including demographics, BMI > 35, comorbidities, preoperative sepsis, preoperative albumin, clinical assessment, type and length of surgery, postoperative length of stay, morbidity and mortality were recorded.

Sepsis was divided in four different grades according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition: grade 1: systemic inflammatory response syndrome (SIRS); grade 2: sepsis; grade 3: severe sepsis and grade 4: septic shock [5].

Morbidity was defined as an unexpected event within 30 days after surgical intervention or during the same hospital admission which was harmful for the patient's health and required a change of therapeutic strategy. Mortality was defined as any death within 30 days after surgical intervention or during the same hospital admission.

American Society of Anaesthesiology (ASA) [6], physiological & operative severity score for the enumeration of mortality and morbidity (POSSUM) [7] and acute physiology and chronic health evaluation II (APACHE II) [8] scores were calculated.

Briefly, ASA score is a six-category physical status classification system based on patient's overall physical health; POSSUM has two parts, which include assessment of physiological parameters and operative scores; we decide to include physiological parameters only as part of the preoperative evaluation (age; cardiac status; pulse rate; systolic blood pressure; respiratory status; Glasgow Coma Scale score; serum concentrations of urea, potassium and sodium; haemoglobin concentration; white blood cell count and findings on electrocardiography). The physiological parameters are taken at the time of surgery. The APACHE II classification includes 12 physiological measures (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, haematocrit, white blood cell count and Glasgow Coma Scale score), age and severe chronic health problems.

Characteristics of patients and their outcomes were determined using statistical analysis. Discrete, categorical variables were analysed using Chi-squared or Fisher's exact test when necessary and appropriate. For means in case of continuous numeric data, we used the independent samples *t* test and the Mann–Whitney U test, respectively, for data normally and nonnormally distributed; the data were previously tested for normality by the Kolmogorov–Smirnov test. All statistical tests were 2-sided. A P value <0.05 was considered statistically significant.

Neimeier's classification was also used (Type I: acute free perforation into the peritoneal cavity; Type II: subacute perforation with pericholecystic abscess and Type III: chronic perforation with cholecystoenteric fistula) [9].

The threshold of statistical significance following univariate analysis was set at $P < 0.1$. Multivariate analysis of statistically significant variables was performed using binary logistic regression.

Receiver operator characteristic (ROC) curves were analysed to examine sensitivity and specificity of each ASA, POSSUM and APACHE II scores. The area under the curve (AUC) was compared to measure the ability of the scores.

All statistical analyses were done with the statistical software package SPSS (version 19; SPSS Inc., Chicago, IL, USA).

Results

From 2002 to 2012, 137 patients underwent emergency cholecystectomy for acute cholecystitis with GBP. Median age was 76 (36–99) years, median number of days from admission to surgery was 1.4 (0–22) days, 24.1 % of patients received laparoscopic surgery, and 65 (47 %) patients had grade 1–4 sepses at the time of the operation. Demographic and clinical factors are reported in Table 1. Seventy-nine (57.7 %) patients had at least one complication. Mortality rate was 9.5 %.

Morbidity

At univariate analysis, age, cardiac history, oral anticoagulation, preoperative sepsis and number of days between admission and surgery were associated with postoperative complications. Laparoscopic operation and preoperative albumin were also inversely associated with complications (Table 2). At multivariate analysis, low preoperative albumin, open surgery and preoperative sepsis were independently associated with complications (Table 3).

Mortality

At univariate analysis, age, interval to surgery and preoperative sepsis were significantly associated with mortality (Table 4). At multivariate analysis, preoperative sepsis was the only factor independently associated with hospital mortality (Table 5).

Scores

ASA, POSSUM and APACHE II scores were significantly associated with postoperative complications and mortality (Tables 3, 5).

APACHE II score showed the best accuracy in both predicting morbidity (Fig. 1, AUC: APACHE II = 0.729 vs. ASA = 0.635 and POSSUM = 0.721) and mortality (Fig. 2, AUC: APACHE II 0.799 vs. ASA 0.695 and POSSUM 0.782).

Table 1 Demographics and clinical characteristics

Factor	*N*
Age, median (range)	76.1 (36–99)
Gender (%)	
M	88 (64.2)
F	49 (35.8)
BMI > 35 (%)	11 (8)
Diabetes (%)	30 (21.9)
Smoking (%)	13 (9.5)
COPD (%)	23 (16.8)
Cardiac History (%)	39 (28.5)
Preoperative renal impairment (%)	14 (10.2)
Preoperative use of steroids (%)	3 (2.2)
Oral Anticoagulation (%)	23 (16.8)
Presence of tumour (%)	5 (3.6)
Preoperative sepsis (%)	65 (47.4)
1	14 (10.2)
2	37 (27)
3	14 (10.2)
Preoperative Albumin, median (range)	3.0 (1.2–4.7)
Days to surgery, median (range)	1.4 (0–22)
Laparoscopy (%)	33 (24.1)
Length of operation, minutes, median (range)	85.7 (45–180)
Intraop. transfusion (%)	11 (8)
Neimeyer classification (%)	
1	63 (46)
2	72 (52.6)
3	2 (1.4)
Reoperation (%)	3 (2.2)
Morbidity (%)	79 (57.7)
Mortality (%)	13 (9.5)
Postoperative stay, days, median (range)	9.5 (2-60)
ASA score (%)	
1	8 (5.8)
2	53 (38.7)
3	68 (49.6)
4	8 (5.8)
APACHE II score	9.1 (0–24)
POSSUM physiology score	28.8 (15–64)

BMI Body Mass Index, *COPD* chronic obstructive pulmonary disease

Table 2 Univariate analysis of factors associated with postoperative complications

	NO complication (58 pts)	Complication (79 pts)	*P*
Age, years, median (range)	69.2 (36–93)	77.2 (36–99)	<0.001
Gender (%)			
M	37	51	0.927
F	21	28	
BMI > 35 (%)	6	5	0.393
Diabetes (%)	11	19	0.477
Smoking (%)	6	7	0.770
COPD (%)	9	14	0.733
Cardiac history (%)	12	27	0.084
Preoperative renal impairment (%)	4	10	0.271
Preoperative use of steroids (%)	0	3	0.133
Oral anticoagulation (%)	5	18	0.028
Presence of tumour (%)	2	3	0.914
Preoperative sepsis (%)			
0	40	32	0.001
1	6	8	
2	12	25	
3	0	14	
4	0	0	
Preoperative albumin, median (range)	3.6 (2.6–4.7)	2.7 (1.2–4.4)	<0.001
Days to surgery, median (range)	0.75 (0–15)	1.99 (0–22)	0.026
Laparoscopy (%)	24	9	<0.001
Length of operation, minutes, median (range)	91 (45–180)	89.3 (50–180)	0.758
Intraoperative transfusion (%)	0	11	0.003
Neimeyer (%)			
1	25	38	0.570
2	33	39	
3	0	2	
ASA score (%)			
1	5	3	0.015
2	30	23	
3	20	48	
4	3	5	
APACHE II score	7.6 (0–16)	11.4 (0–24)	<0.001
POSSUM physiology score	25.9 (15–44)	32.8 (16–64)	<0.001

BMI Body Mass Index, *COPD* chronic obstructive pulmonary disease

Discussion

GBP is a life threatening complication of acute cholecystitis. Despite advances in early detection, the morbidity and mortality rates are still very high and have not dramatically changed over the years. Since the difficulties in diagnosis cause delay in treatment, higher morbidity and mortality rates are often encountered. Glenn and Moore originally reported a 42 % mortality rate following GBP [10], although more recent studies reported a 12–16 % rate [11].

Table 3 Multivariate analysis of factors independently associated with complications

	B	Wald	Sig.	OR	95 % CI	
					Lower	Higher
Age	−0.024	0.601	0.438	0.976	0.918	1.038
Laparoscopic surgery	3.632	6.524	0.011	37.780	2.328	613.108
Cardiac history	−0.013	0.000	0.990	0.987	0.136	7.161
Oral anticoagulation	−1.849	2.249	0.134	0.157	0.014	1.763
Interval to surgery	−0.122	1.355	0.244	0.885	0.721	1.087
Preoperative albumin	−1.745	7.330	0.007	0.175	0.049	0.618
Preoperative sepsis	3.944	9.717	0.002	51.647	4.325	616.781

In the present study, the morbidity and mortality rates were 57.7 and 9.5 %, respectively. Very little has been previously published about the outcome of these groups of patients [12]: we present the largest series ever published trying to detect those patients at risk of developing complications and dying during the hospital admission.

Three factors showed significant association with morbidity: preoperative albumin, laparoscopic surgery and preoperative sepsis/SIRS. Preoperative albumin is a very well-known factor associated with morbidity in most of abdominal operations, including elective surgery [13]. Low serum albumin has been historically linked to nutritional status; however, the relationship of albumin to inflammation was not initially recognized, and it is now known that inflammation is the most important variable that affects hepatic protein metabolism, and that inflammatory activity diminishes the ability of the patient to respond well to a second hit [14, 15]; however, correction of hypoalbuminemia to prevent postoperative complications is not recommended, making this finding not very useful [16].

The association between laparoscopic approach and lower morbidity could have been biased by several factors: firstly, laparoscopic cholecystectomy (LC) is associated with fewer complications when compared to open surgery [17], but there are no studies validating these results in GBP patients; secondly, laparoscopic approach was probably performed in easier cases and finally, some patients who would intuitively benefit the most from a minimally invasive approach did not undergo LC. The reasons might be that some of our general surgeons were not skilful laparoscopic surgeons. Many patients were operated as emergency open cholecystectomy during on-call hours by general surgeons, which explains our relatively low rate of laparoscopic cholecystectomies. It is obvious that hepatobiliary surgeons with good experience of laparoscopic technique are most skilled to remove perforated gallbladder using laparoscope, but they are not always available during on-call hours.

Unfortunately, these are limitations of our retrospective study, but this is what probably happens in most hospitals of the world.

Preoperative sepsis/SIRS was certainly the determinant factor associated with mortality and morbidity. Its role as a risk factor for postoperative complications and death has been already described in abdominal surgery, including hepatobiliary [18–21].

Differently than hypoalbuminemia and type of surgery, preoperative sepsis is the only factor that can change our therapeutic strategy, for instance administering broad spectrum antibiotics from the start and admitting these patients in a high-dependency unit. Most of the recent literature has been focusing on the importance of early surgery in acute cholecystitis patients [22], which is something we were expecting to be associated with good outcome in our series. However, interval to surgery lost its significancy into the multivariate analysis, probably due to the different population we evaluated: in case of GBP, the clinical presentation (sepsis) is more important than timing.

With regard to risk prediction of morbidity and mortality, APACHE II score was superior to ASA and POSSUM. However, the final accuracy of these tests was fair (AUC < 0.8) and we would not recommend using these tests to stratify patients' GBP at risk of postoperative complications; in our series more than 50 % of the patients had at least one complication, and using these scores is unlikely to change their management.

It could be argued that early identification of patients with GBP might improve the final outcome; unfortunately, preoperative diagnosis remains the most challenging problem [23]; abdominal ultrasound has fair sensitivity [24], and no clinical criteria can be used to differentiate GBP from acute cholecystitis. Some authors have demonstrated that CT scan can predict GBP in up to 81 % of patients thought the visualization of GB wall defects, gas and ascites, but these are retrospective findings and only when a CT was performed to confirm US findings [25, 26]. In our series, most of the patients were not submitted to abdominal CT scan and it would be very difficult to justify its routine use in patients with acute cholecystitis within a busy emergency department.

Previous studies have shown that age >60, male gender and systemic disorders are associated with GBP [27, 28], but they really are generic factors.

Table 4 Univariate analysis of factors associated with mortality

	No mortality (124 pts)	Mortality (13 pts)	*P*
Gender (%)			
M	82	6	0.223
F	42	7	
BMI > 35 (%)	11	0	0.599
Diabetes (%)	28	2	0.733
Smoking (%)	13	0	0.613
HOA (%)	7	0	1.000
COPD (%)	20	3	0.458
Cardiac history (%)	35	4	1.000
Preoperative renal impairment (%)	12	2	0.393
Preoperative use of teroids (%)	2	1	0.260
Oral anticoagulation (%)	20	3	0.458
Presence of tumour (%)	2	3	0.006
Preoperative sepsis (%)			
0	71	1	<0.001
1	13	1	
2	32	5	
3	8	6	
4	0	0	
Intraoperative transfusion (%)	8	3	0.071
Laparoscopy (%)	31	2	0.734
Neimeyer (%)			
1	54	9	0.363
2	68	4	
3	2	0	
ASA score (%)			
1	8	0	0.001
2	50	3	
3	62	6	
4	4	4	
Age, median (range)	73.2 (36–99)	79.6 (54–88)	0.083
Preoperative albumin, median (range)	3.1 (1.3–4.7)	2.7 (1.2–3.8)	0.179
Days to surgery, median (range)	1.2 (0–15)	4 (0–22)	0.003
APACHE II score, median (range)	9.3 (0–23)	14.8 (9–24)	<0.001
POSSUM physiology score, median (range)	28.9 (15–62)	39 (26–64)	<0.001
Lenght of operation, minutes, median (range)	89.1 (45–180)	98.4 (60–180)	0.308

The results of our study should not be misinterpreted concluding that sicker patients have worse outcome. In fact, comorbidities lost their significancy in multivariate analysis, meaning that sepsis is the main determinant regardless of patient's status prior to surgery and that is confirmed by the fair accuracy of risk scores that were tested.

Table 5 Multivariate analysis of factors independently associated with mortality

	B	Wald	Sig.	OR	95 % CI	
					Lower	Higher
Age	0.038	1.305	0.253	1.039	0.973	1.110
Interval to surgery	0.088	1.303	0.254	1.092	0.939	1.269
Intraoperative transfusion	1.281	1.860	0.173	3.601	0.571	22.711
Laparoscopic surgery	–					
0.213	0.054	0.815	0.808	0.135	4.827	
Preoperative sepsis	2.211	7.171	0.007	9.127	1.809	46.048

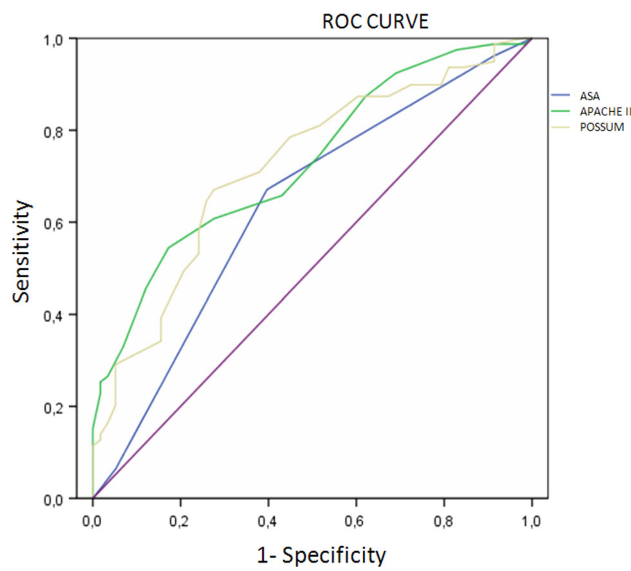

Fig. 1 ROC *curve* for postoperative complications

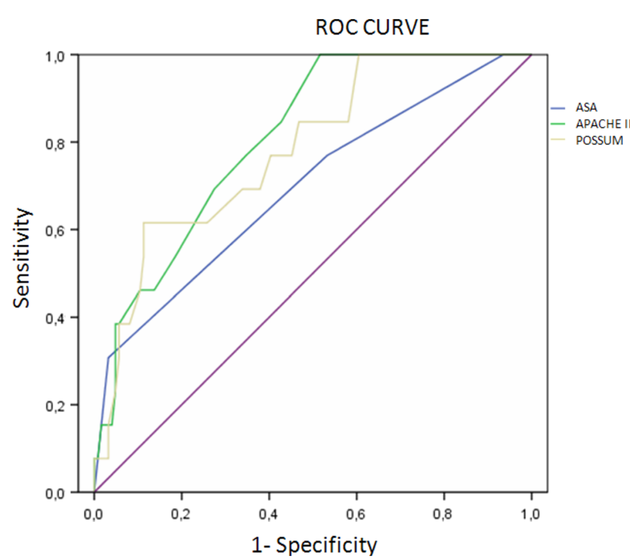

Fig. 2 ROC *curve* for postoperative mortality

Until preoperative detection of GBP will not be improved, whether or not percutaneous drainage should be preferred in patients with severe sepsis will remain matter of debate.

We can only recommend that those patients with intraoperative finding of GBP should be considered at very high risk for complications and mortality, and therefore broad spectrum antibiotics and monitoring in a high-dependency unit should be immediately started.

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References

1. Isch J, Finneran JC, Nahrwold DL (1971) Perforation of the gallbladder. Am J Gastroenterol 55:451–458
2. Bennet GL, Balthazar EJ (2003) Ultrasound and CT evaluation of emergent gallbladder pathology. Radiol Clin North Am 41: 1203–1216
3. Strohl EL, Diffenbaugh WG, Baker JH, Chemma MH (1962) Collective reviews: gangrene and perforation of the gallbladder. Int Abstr Surg 114:1–7
4. Doherty GM, Way LW (2003) Biliary Tract. In: Way LW, Doherty GM (eds) Current Surgical Diagnosis & Treatment, 11th edn. McGraw-Hill, New York, pp 595–624
5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (2009) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 136(5):e28
6. Saklad M (1941) Grading of patients for surgical procedures. Anesthesiology 2:281–284
7. Copeland GP, Jones D, Walters M (1991) POSSUM: a scoring system for surgical audit. Br J Surg 78:355–360
8. Knaus WA, Draper EA, Wagner DP (1985) APACHE II: a severity of disease classification system. Crit Care Med 13(10):818–829
9. Niemeier OW (1934) Acute free perforation of the gallbladder. Ann Surg 99:922–924
10. Glenn F, Moore SW (1942) Gangrene and perforation of the wall of the gallbladder. A sequele of acute cholecystitis. Arch Surg 44:677–686
11. Roslyn JJ, Thompson JE Jr, Darvin H, DenBesten L (1987) Risk factors for gallbladder perforation. Am J Gastroenterol 82: 636–640
12. Date RS, Thrumurthy SG, Whiteside S, Umer MA, Pursnani KG, Ward JB, Mughal MM (2012) Gallbladder perforation: case series and systematic review. Int J Surg 10(2):63–68
13. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF (1999) Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. Arch Surg 134(1):36–42
14. Fuhrman MP, Charney P, Mueller CM (2004) Hepatic proteins and nutrition assessment. J Am Diet Assoc 104:1258–1264
15. Carlson GL (2003) Surgical management of intestinal failure. Proc Nutr Soc 62(3):711–718
16. Boldt J (2010) Use of albumin: an update. Br J Anaesth 104(3):276–284
17. Suter M, Meyer A (2001) A 10-year experience with the use of laparoscopic cholecystectomy for acute cholecystitis: is it safe? Surg Endosc 15(10):1187–1192
18. Gupta H, Gupta PK, Schuller D, Fang X, Miller WJ, Modrykamien A, Wichman TO, Morrow LE (2013) Development and validation of a risk calculator for predicting postoperative pneumonia. Mayo Clin Proc 88(11):1241–1249
19. Tzeng CW, Katz MH, Fleming JB, Lee JE, Pisters PW, Holmes HM, Varadhachary GR, Wolff RA, Abbruzzese JL, Vauthey JN, Aloia TA (2014) Morbidity and mortality after pancreaticoduodenectomy in patients with borderline resectable type C clinical classification. J Gastrointest Surg 18(1):146–156
20. Cho SW, Tzeng CW, Johnston WC, Cassera MA, Newell PH, Hammill CW, Wolf RF, Aloia TA, Hansen PD (2014) Neoadjuvant radiation therapy and its impact on complications after pancreaticoduodenectomy for pancreatic cancer: analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). HPB (Oxford) 16(4): 350–356
21. Johnson RG, Arozullah AM, Neumayer L, Henderson WG, Hosokawa P, Khuri SF (2007) Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg 204(6):1188–1198
22. de Mestral C, Rotstein OD, Laupacis A, Hoch JS, Zagorski B, Alali AS, Nathens AB (2014) Comparative operative outcomes of early and delayed cholecystectomy for acute cholecystitis: a population-based propensity score analysis. Ann Surg 259(1): 10–15
23. Stefanidis D, Sirinek KR, Bingener J (2006) Gallbladder perforation: risk factors and outcome. J Surg Res 131(2):204–208
24. Kim PN, Lee KS, Kim IY, Bae WK, Lee BH (1994) Gallbladder perforation: comparison of US findings with CT. Abdom Imaging. 19(3):239–242
25. Tsai MJ, Chen JD, Tiu CM, Chou YH, Hu SC, Chang CY (2009) Can acute cholecystitis with gallbladder perforation be detected preoperatively by computed tomography in ED? Correlation with clinical data and computed tomography features. Am J Emerg Med 27(5):574–581
26. Morris BS, Balpande PR, Morani AC, Chaudhary RK, Maheshwari M, Raut AA (2007) The CT appearances of gallbladder perforation. Br J Radiol 80(959):898–901
27. Bedirli A, Sakrak O, Sözüer EM, Kerek M, Güler I (2001) Factors effecting the complications in the natural history of acute cholecystitis. Hepatogastroenterology. 48(41):1275–1278
28. Williams NF, Scobie TK (1976) Perforation of the gallbladder: analysis of 19 cases. Can Med Assoc J 115(12):1223–1225