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Gallbladder perforation. A case series and review of the literature

INTRODUCTION: *Gallbladder perforation (GBP) is an uncommon life-threatening and almost exclusive complication of cholecystitis. It is often associated with relatively high morbidity and mortality rates due to delay in diagnosis. GBP still continues to be a challenging issue for the surgeons. Most cases can only be diagnosed during surgery. The aim of this retrospective, case series was to present our clinical experience with gallbladder perforation and to provide an overview of promoting factors, clinical manifestations, diagnostic workup and management of GBP on the basis of recent literature review.*
PATIENTS AND METHODS: *This study involved four patients with gallbladder perforation (three males and one female), who were treated in our department from May 2019 to November 2019. We made a retrospective analysis of these patients and a review of the related literature.*
RESULTS: *According to Niemeier's classification, all patients had type II gallbladder perforation. Mean age was 70 years (range 50-85 years). They had also significant comorbidities, of which diabetes mellitus was the most common (three patients). Ultrasonography was the initial mode of investigation in these four patients. Out of the four cases, three patients underwent immediate intervention and only one patient was initially managed conservatively with intravenous antibiotics.*
CONCLUSIONS: *Early diagnosis of gallbladder perforation and immediate intervention are of crucial importance. Clinical examination, diagnostic imaging and high index of suspicion of this severe condition would be significant in establishing an early diagnosis of the perforation.*

KEY WORDS: Cholecystitis, Gallbladder perforation, Niemeier

Introduction

Gallbladder perforation (GBP) is considered a rare life-threatening and almost exclusive complication of cholecystitis. Sometimes GBP may not differ clinically from uncomplicated acute cholecystitis with high morbidity and mortality rates due to delayed diagnosis [1-3].

Therefore, GBP still continues to be a challenging issue for the surgeons. According to several authors, most of the cases are identified and confirmed intraoperatively [1,4]. Undoubtedly, in cases with high index of clinical suspicion for perforation, diagnostic procedures such as ultrasound scan and especially cross-sectional imaging modalities may help to establish an early diagnosis of GBP. Male acute cholecystitis cases with high fever, high white blood cell (WBC) count, and associated systemic diseases should be thoroughly investigated, as well [1,5,6]. In 1934, Niemeier [7] classified free gallbladder perforation and generalized biliary peritonitis as acute or type I GBP, pericholecystic abscess and localized peritonitis as subacute or type II GBP and cholecystoenteric fistu-

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la as chronic or type III GBP. This classification is still in use. Main aim of this study is to present our clinical experience with GBP and to provide an overview of the pathogenic and promoting factors of gallbladder perforation, clinical manifestations, diagnostic workup and management of this severe complication on the basis of recent literature review.

Patients and Methods

We report four cases of patients with gallbladder perforation with a review of the related literature. The original classification of Niemeier was used to identify the patients [7]. Parameters such as age, gender, time from the onset of symptoms to the time of surgery, diagnostic procedures, surgical treatment, postoperative morbidity and mortality were also being analyzed and evaluated.
The literature review involved an extensive online search of the MEDLINE and Semantic Scholar databases applying the search terms 'gallbladder perforation', 'Niemeier' and 'cholecystitis'. Perforations due to trauma, iatrogenic causes or gallbladder carcinoma were excluded. The reference lists of articles obtained were also searched comprehensively in order to identify additional relevant citations. Case series including small number of patients (less than five patients) and those that did not specify accurately the type of gallbladder perforation according to the original classification of Niemeier were excluded from this study.

Results

Four patients with gallbladder perforation (three males and one female) were treated in our department from May 2019 to November 2019. Their mean age was 70 years (range 50-85 years). According to Niemeier's classification, they had type II gallbladder perforation. They had also significant comorbidities, of which diabetes mellitus was the most common (three patients).
Cholelithiasis was unknown prior to gallbladder perforation in two patients. Surgical confirmation of the perforation was obtained for all patients.

Case N. 1

An 85-years-old man was presented to the emergency department with four days history of pain in right hypochondrium. There were no history of nausea, vomiting, diarrhea or burning micturition, gallbladder disease and no history of trauma. His vitals at admission were BP: 155/65 mm Hg, Pulse rate: 76 bpm, Temp: 37,5 °C, Resp. rate: 22/min. Abdominal examination revealed tenderness in the right hypochondrium and bowel sounds were present. Rest of the systemic examination was unremarkable. Laboratory studies showed a white cell count of 12340/mm^3, random blood sugar of 226 mg/dl, blood urea of 71 mg/dl, serum creatinine of 1,2 mg/dl and C-reactive protein (CRP) of 2,69 mg/dl. Serum amylase and electrolytes were normal. Coagulation

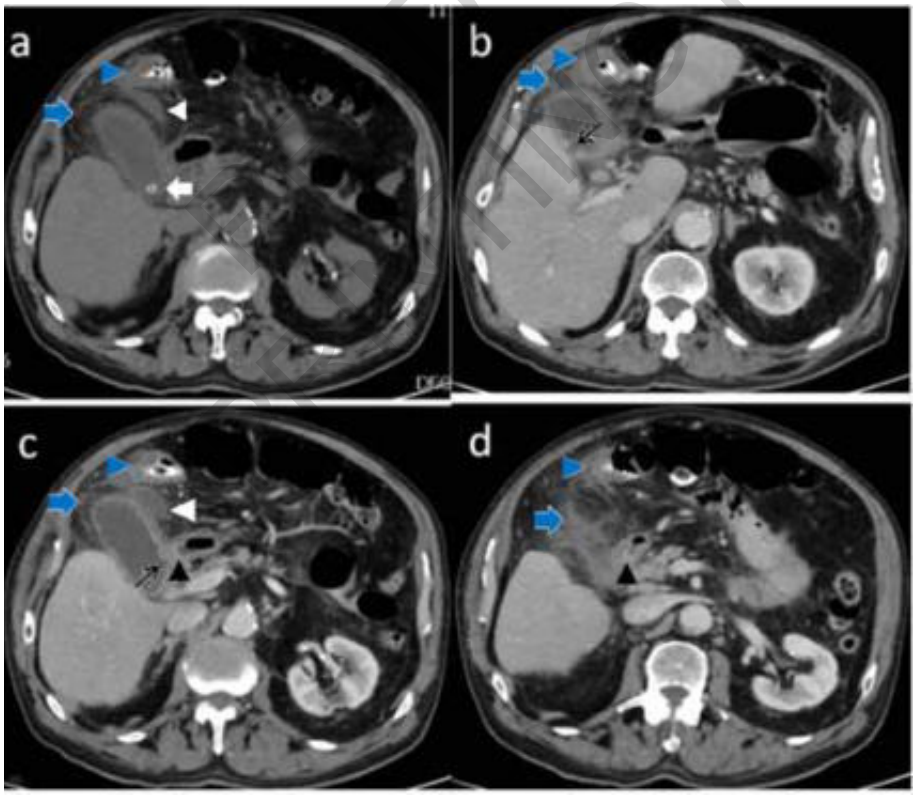

Fig. 1: Axial CT images [A,B,C,D] of the patient diagnosed with type II GBP. CT illustrates gallbladder distention with thickened wall, pericholecystic abscess formation (white arrowhead), focal wall defects (black arrow), intraperitoneal fat stranding (blue arrow), thickening of the adjacent wall of duodenum (black arrowhead) and the hepatic flexure of colon (blue arrowhead) and the presence of a calculus (white arrow) in the neck of gallbladder.

profile and liver function tests were also within normal limits.

Chest X-ray revealed no gas under diaphragm whereas X-ray abdomen showed multiple dilated gut loops without air fluid levels. During the next 2 days laboratory findings revealed a white cell count of 20970/mm^3, C-reactive protein of 25,84 mg/dl and patient's surface temperature was raised (38,2 °C). On abdominal examination, generalized tenderness was present mainly at the right upper quadrant region. The ultrasonography (USG) of the abdomen revealed distended gallbladder with thickened wall (5mm) and internal echoes with a single calculus in the neck of gallbladder. US findings also revealed pericholecystic and perihepatic free fluid, thickened wall of the duodenum (descending and horizontal part) and hepatic flexure of the colon and positive sonographic Murphy sign.

Common bile duct (CBD) measured 1cm. CT of the abdomen showed gallbladder distention, thickened gallbladder wall, pericholecystic abscess formation (3,1 cm x 1,6 cm), intraperitoneal fat stranding, thickening of the adjacent wall of the descending part of duodenum and hepatic flexure of the colon and the presence of a calculus in the neck of gallbladder (Fig. 1). The patient, who had significant comorbidities including diabetes mellitus and hypertension, was kept successfully under conservative treatment. After initial resuscitation with fluid and broad spectrum antibiotics, the patient underwent laparoscopic cholecystectomy on an elective basis about three weeks after hospital discharge. The patient was discharged symptom free on 2nd post-operative day. In the follow up, patient was asymptomatic and was doing well.

Case N. 2

A 50-year-old male was admitted with complaints of severe pain in the abdomen for one day. The pain was located mainly in the epigastrium and right hypochondrium region without any vomiting. His vitals at admission were BP: 140/70 mm Hg, Pulse Rate: 94 bpm, Temp: 37 °C, Resp. rate: 26/min. Tenderness was present in the right hypochondrium region on physical examination without any rigidity or guarding. Rest of the systemic examination was unremarkable. Bowel sounds were present. Laboratory studies showed a white cell count of 22720/mm^3 and C-reactive protein of 9,13 mg/dl. Bilirubin, liver enzymes and renal function tests were within normal limits. An erect X-ray of the abdomen was suggestive of gaseous distention of bowel loops without air fluid levels. Chest X-ray revealed no gas under diaphragm. During the next 2 days patient's surface temperature was raised (37,7 °C) and his abdominal pain worsened with newly developed rigidity and rebound tenderness on abdominal palpation in the right hypochondrium.

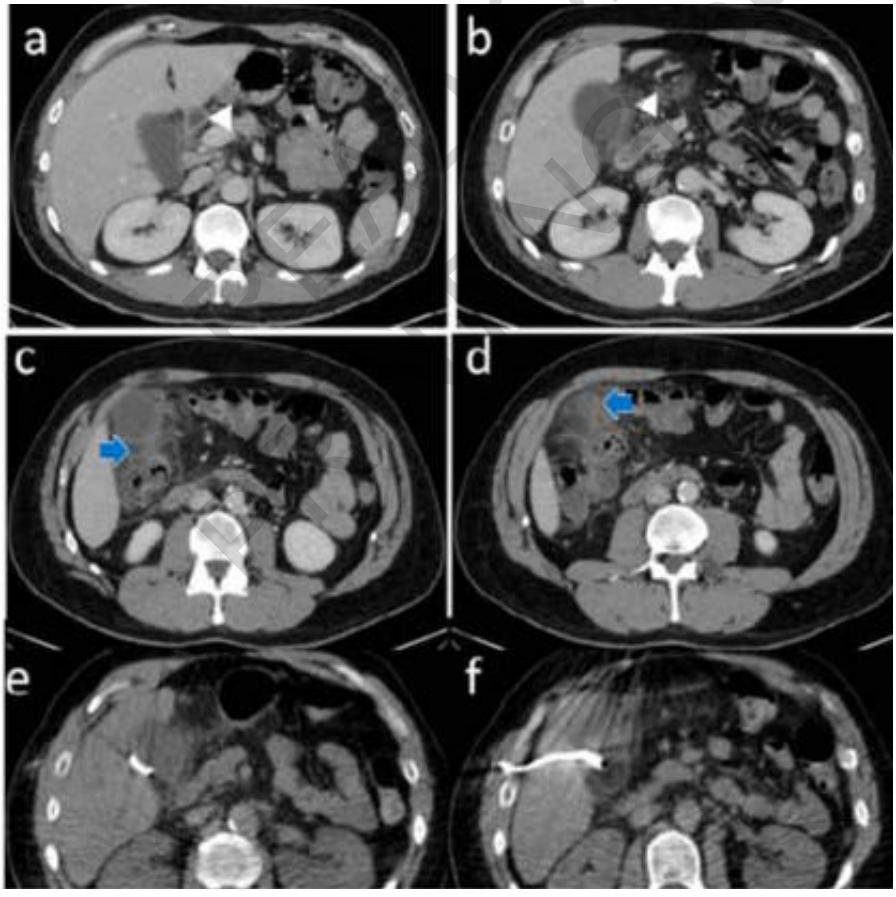

Fig. 2: Axial CT images of the patient with type II GBP showing gallbladder mural thickening with intraperitoneal fat stranding (blue arrow), pericholecystic abscess (white arrowhead) [A,B,C,D] and CT guided percutaneous transhepatic cholecystostomy [E,F].

The USG of the abdomen on admission was suggestive of a slightly distended gallbladder without any wall thickening and cholelithiasis. The sonographic examination of abdomen also revealed the presence of three gallbladder polyps characterized as small (maxd~6,3mm) echogenic but non-shadowing and immobile elevations of the gallbladder wall that project into the lumen. With these findings the patient underwent a contrast-enhanced computed tomography (CT) scan of the abdomen which showed gallbladder distention with wall thickening, focal wall defect in the neck of gallbladder, pericholecystic abscess formation and fat stranding (Fig. 2).
CT guided percutaneous transhepatic cholecystostomy using an 8-Fr pigtail catheter was done. Daily bile output through the cholecystostomy tube was around 400 to 600 ml. There was improvement in the patient's general condition with resolution of abdominal pain. The patient was discharged symptom free 8 days after the procedure. He underwent laparoscopic cholecystectomy on an elective basis about eight weeks after hospital discharge. In the follow up, he was found in a fair state.

Case N. 3

A 79-year-old female reported to emergency with painful abdomen. Pain had been dominant in the right hypochondrium region for almost 20 days. At examination, the blood pressure was of 130/70 mm of Hg and the pulse rate was of 100 bpm. On local examination, tenderness was found in the right hypochondrium and bowel sounds were present. Laboratory studies revealed a white cell count of 7660/mm^3, C-reactive protein of 11,6 mg/dl, ALP of 246 U/L, SGOT of 113 U/L, SGPT of 144 U/L, direct bilirubin of 0,4 mg/dl and total bilirubin of 1,2 mg/dl. During the next few days laboratory findings revealed a white cell count of 10380/mm^3 and C-reactive protein of 27,84mg/dl. There were no history of nausea, vomiting and fever.
Chest X-ray revealed no gas under diaphragm. Initial sonographic examination of abdomen revealed gallbladder wall thickening and distention, pericholecystic abscess and free fluid, positive sonographic Murphy sign and cholelithiasis. An urgent computerized tomography of abdomen revealed gallbladder distention, thickened gallbladder wall, post-contrast enhancement of gallbladder wall, pericholecystic abscess formation, pericholecystic fat stranding and thickening of the adjacent bowel wall (hepatic flexure of colon) (Fig. 3).
Suspicion of gallbladder empyema and perforation were confirmed intraoperatively (Fig. 4). The patient, who had significant comorbidities including diabetes mellitus, hypertension and heart disease, underwent emergency cholecystostomy. Although the gallbladder seemed to be enlarged, bile leaked on a localized focus of the gallbladder with gentle squeezing. The bile was seen to be oozing from a small perforation in the gallbladder near the fundus. The patient remained stable and was discharged with full recovery on 9th post-operative day. She was followed up for 3 months post operatively and found in a fair state.

Case N. 4

A 66 year old male with type 2 diabetes was presented to the emergency department with complaints of sudden onset of severe abdominal pain. The pain was mainly located in the epigastrium and right hypochondrium region. There were no history of nausea, vomiting and fever. The blood pressure of the patient was of 140/60 mm of Hg and his pulse rate was of 84 bpm. Abdominal

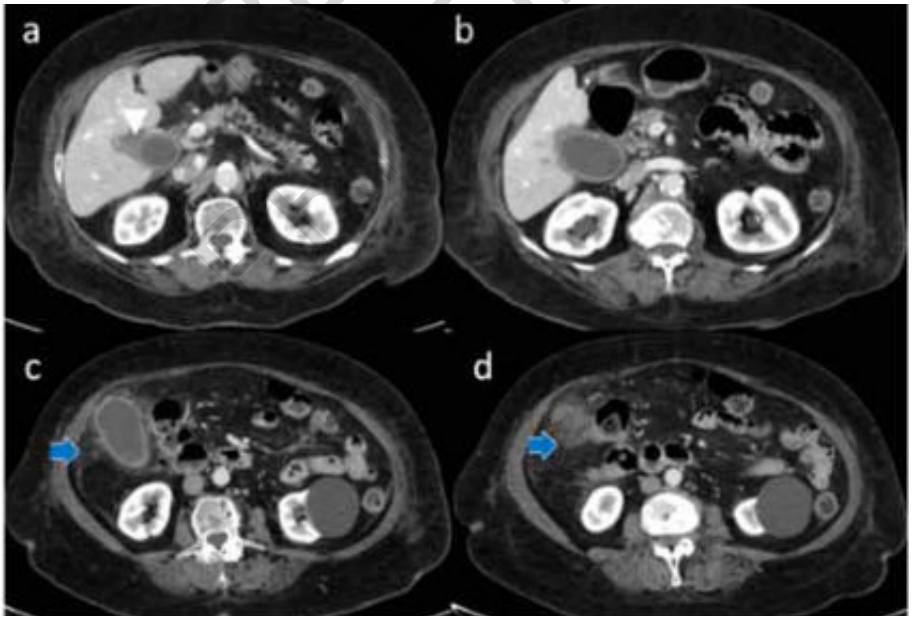

Fig. 3: Axial post contrast CT scan images [a,b,c,d] show distention of the gallbladder with wall thickening and enhancement, pericholecystic abscess (white arrowhead) and intraperitoneal fat stranding (blue arrow).

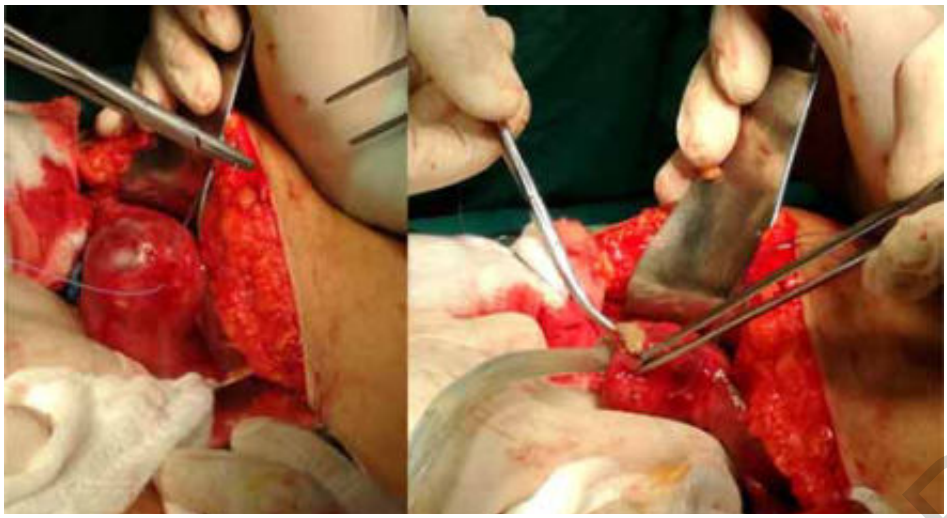

Fig. 4: Intraoperative pictures showing empyema of the distended gallbladder.

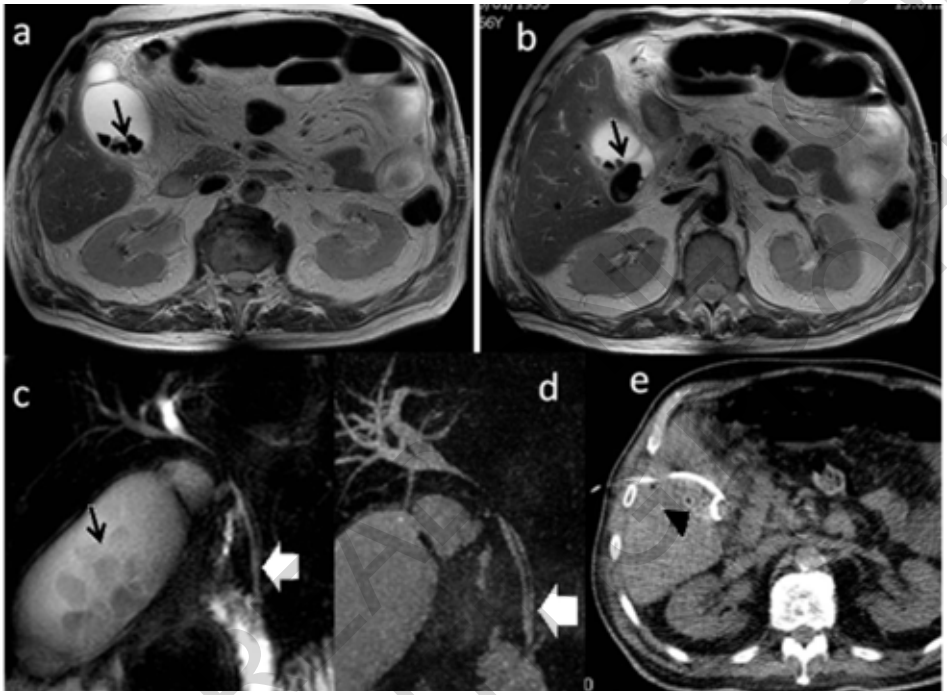

Fig. 5: Axial T2W MRI images [A,B] and magnetic resonance cholangiopancreatic images [C,D] showing the presence of a long cystic duct (anatomical variation of cystic duct, white arrow) and also the calculi in the gallbladder (black arrow). Axial CT scan image [e] shows transhepatic CT guided cholecystostomy and nitrogen gas within gallstones (black arrowhead).

examination revealed rigidity, guarding and rebound tenderness and bowel sounds were sluggish. Laboratory studies at admission revealed a white cell count of 14080/mm^3, CRP of 11,53 mg/dl, direct bilirubin of 1,4 mg/dl and total bilirubin of 4,1 mg/dl. Renal function tests were within normal limits. During the next few days laboratory test results were as follows: white blood cells 22210 cells/mm^3, CRP 65,29mg/dl, random blood sugar 230 mg/dl, serum amylase 84 U/L, ALP 246 U/L, γ-GT 356 U/L, SGOT 106 U/L, SGPT 93 U/L, direct bilirubin 1,2 mg/dl and total bilirubin 3,5 mg/dl. On local examination, generalized tenderness was found in the whole abdomen and rigidity was present. Medical treatment was initiated. Chest X-ray revealed pleural effusions on both sides and a slight elevation of the right hemidiaphragm. Ultrasonography was performed, which showed a slightly distended gallbladder with thickened wall, the presence of cholelithiasis and the impaction of a gallstone in the Hartmann's pouch. There was also biliary sludge in the biliary lumen and free intraperitoneal fluid. To further evaluate the biliopancreatic tree, an urgent Magnetic resonance cholangiopancreatography (MRCP) was ordered, which revealed the distention of the gallbladder with the presence of cholelithiasis, pericholecystic and intraperitoneal free fluid, and the dilatation of small bowel loops (Fig. 5).
CT guided transhepatic percutaneous cholecystostomy using an 8-Fr pigtail catheter was done (Fig. 5). Daily bile output through the cholecystostomy tube was around 40 to 100 ml. After the procedure, he recovered and was discharged symptom free 10 days later. The patient underwent laparoscopic cholecystectomy about two weeks

after hospital discharge. Suspicion of gallbladder perforation was confirmed intraoperatively. Findings were of an enlarged and ruptured gallbladder with necrotic patches.Then, the patient was discharged on the 2nd post-operative day in a stable condition. He was followed up for 2 months post operatively and was doing well.

Discussion

Duncan first reported gallbladder perforation (GBP) in 1844. Mortality of 15-30% along with significant morbidity has been reported by several authors [7,8]. GBP is an almost exclusive and uncommon complication following cholecystitis, which accompanies severe inflammation of the gallbladder with or without cholelithiasis. The incidence of GBP has been reported to range from 2 to 18% of all cases of acute cholecystitis [9]. In addition, the overall incidence of GBP owing to acalculous cholecystitis is higher between calculous and acalculous cholecystitis, reaching approximately 10 to 20% [10,11].
Despite the differences in the etiology, progression, treatment and prognosis between the two forms of cholecystitis, the clinical manifestations of gallbladder perforation are similar regardless of the underlying cause [12-14].
Based on the causes of the perforation, Estevao-Costa J [15] proposes a classification of GBP as follows (Table I). The most plausible mechanisms for gallbladder perforation complicating acute cholecystitis are: i) bile stasis owing to cystic duct obstruction, fasting, dehydration, total parenteral nutrition, which causes changes in both the bile content and concentration, ii) gallbladder's vascular impairment owing to distention of the viscus, underlying systemic illness like sepsis, shock, atherosclerosis and iii) ischemic necrosis and perforation of the gallbladder wall. GBP occurs most commonly at the fundus, which is the most distal part and therefore poorly vascularized [9,12,13]. The mechanisms of spontaneous or idiopathic GBP in an otherwise normal gallbladder have not been reported yet [4,16,17].
In the majority of the patients diagnosed with acute calculous cholecystitis, an impacted stone in the cystic duct slips back in the gallbladder and thus enables the cholecystitis to resolve. In the case that cholecystitis does not resolve because of persistent impaction of stone, there may be a progress in inflammation along with the development of an empyema. Ischemia, necrotic damage of the gallbladder wall and perforation can be caused by persistent inflammation and distention of the gallbladder due to impacted stone. Increased intraluminal pressure prevents lymphatic and venous drainage, leading to vascular compromise [18].The ischemic part necrotizes and eventually ruptures, usually precipitated by infection [19-22].
Perforation may also follow acalculous cholecystitis, although rarely. Non obstructive cholecystitis with intense inflammation, with virulent infection and existence of immune-compromised state could lead to thrombosis of blood vessels, transluminal necrosis and perforation [23,24].
In chronic diseases, bile stasis triggers release of inflammatory enzymes, such as phospholipase A. More fluid is secreted into the gallbladder lumen by the damaged mucosa, when compared to the quantity absorbed. The resulting distention further activates the release of inflammatory mediators (e.g., prostaglandins), worsening mucosal damage and leading to ischemia, all of which precipitate the perforation of the gallbladder. Moreover, certain gallbladder diseases, such as emphysematous and gangrenous cholecystitis, malignancy and trauma, are significantly associated with increased risk of perforation [25].
According to the revised Niemeier's classification [7], gallbladder perforation is classified into three types (Table II). Depending on the site of perforation, differences in the clinical course may be noticed. When the perforation occurs at the fundus, the bile is more likely to drain

Table I - *Proposed classification of GBP according to the causes of the perforation*

Spontaneous	Traumatic	Iatrogenic
a. Idiopathic	Penetrating	
b. Secondary	Blunt	
Lithiasis		
Inflammation/ infection (predisposing factor – diabetes, atherosclerosis, malignant, pregnancy)		
Other(congenital obstruction, salmonella typhi, anticoagulants)		

Table II - *Revised Niemeier's classification of GBP*

Type I – Acute	Type II – Subacute	Type III - Chronic
Free gallbladder perforation and generalized biliary peritonitis	Pericholecystic abscess and localized peritonitis	Internal fistula, mostly to the duodenum or common bile duct

TABLE III - *Summary data from the update of literature*

	n	Age (years)	Type I (%)	Type II (%)	Type III (%)	Cholelithiasis (%)	Mortality (%)
Lennon et al.[3]	32	67	37,5	53,1	9,4	84,4	12,5
Wig et al.[34]	27	50	44,4	7,4	48,1	88,9	11,1
Ong et al.[4]	6	47	16,7	83,3	0	83,3	0
Menakuru et al.[35]	31	68	29	45,2	25,8	93,5	9,7
Stefanidis et al.[30]	30	60	70	30	0	-	-
Morris et al.[36]	17	48	5,9	94,1	0	-	-
Ergul et al.[37]	37	64	32,4	56,8	10,8	89,2	10,8
Derici et al.[38]	46	68,5	37	45,6	17,4	-	15,2
Date et al.[24]	19	72	47,4	47,4	5,3	78,9	0
Boruah et al.[39]	17	56	5,9	70,6	23,5	-	17,6
Tubachi et al.[40]	11	60	63,6	27,3	9,1	-	0

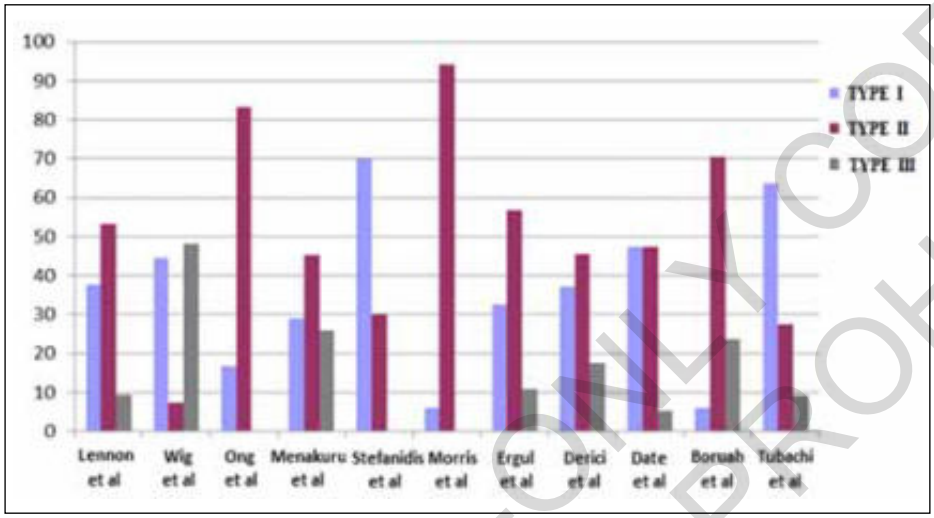

Fig. 6: Frequency association between type I, II, and III of GBP based on recent literature review [3,34,4,35,30,36-38,24,39,40].

into the peritoneal space (type I) causing diffuse peritonitis, since the fundus is not always covered by the omentum. Perforation at other sites of the gallbladder wall is often covered by the omentum or intestinal loops and the condition remains limited in the right upper quadrant with formation of a plastrone and pericholecystic fluid collections (type II) [19-22].

Systemic diseases, such as diabetes mellitus and atherosclerotic heart disease, infections, traumas, malignancies and corticosteroids are known as predisposing factors for GBP [26]. Elderly patients are also at an increased risk for gallbladder perforation [27]. The incidence of perforation appears to increase fourfold with a delay in surgical treatment of more than 2 days from the onset of abdominal symptoms [28]. In an early study, Glenn et al. [18] reported an incidence of gallbladder perforation five times higher among those patients being treated conservatively, than to those who underwent cholecystectomy.

Although acute uncomplicated cholecystitis is more common among females, with a two to one female to male ratio [29], GBP appears more frequently among males [1,6,20,30]. Roslyn et al. [1] reported that there were a greater number of men than women with type I and type II perforations, as compared to those with type III perforations and also that type I and II GBP tend to occur in younger patients, especially more or less at the age of 50 years, whereas type III gallbladder perforations are more common in the elderly.

The clinical presentation of gallbladder perforation can vary between an acute generalized peritonitis (if fundus is involved) and benign non-specific abdominal symptoms (if fundus is not involved). It is considerably difficult and challenging to differentiate gallbladder perforation from uncomplicated acute cholecystitis likely because bile leak from a ruptured gallbladder might be contained in the extra peritoneal gallbladder fossa, and hence might not produce symptoms of peritonitis immediately [31].

The predictive value of clinical findings or laboratory studies in the diagnosis of acute cholecystitis has been questioned in a systematic literature review [32]. According to Parker et al. [33], high fever, right upper quadrant pain and leukocytosis are not diagnostic features for GBP. High fever was only found in 56% and similarly high WBC count in 59% of the cases with acute cholecystitis [33].

The extensive search of the related literature revealed 11 studies, based on a representative number of articles that met the review criteria [3,34,4,35,30,36-38,24,39,40] (Table III, Fig. 6).

Symptoms of type I and type II resemble to a large extent acute uncomplicated cholecystitis. Type III may cause gastrointestinal obstruction (gallstone ileus). While type I and II are usually accompanied by fever and leukocytosis, type III rarely causes fever and shows only a mild increase in WBC count [20]. Contents of a perforated gallbladder might be contained in the extraperitoneal gallbladder fossa, resulting in a delayed onset of symptoms of peritonitis [36]. In some cases, a sudden decrease in pain owing to decompression may be a sign of perforation. Also, perforation should be suspected in patients with acute cholecystitis who suddenly become toxic and whose clinical status starts to deteriorate rapidly [41]. Type I perforation is often associated with systemic diseases (such as atherosclerosis, diabetes mellitus, malignancy and immunosuppression) that may induce ischemia of gallbladder wall causing necrosis and perforation, without a history of chronic gallstone disease, while most of patients with type III GBP have a previous long time history of gallstones [20]. Jayasinghe et al. [42] reported an unusual presentation of spontaneous gallbladder perforation and pointed out the importance to conduct a full body inspection in the septic patient, even when a source has been identified. Percutaneous abscesses arising from the gallbladder are a rare but potentially severe complication of acute cholecystitis and may present in a wide variety of locations [42].

Bedirli et al. [6] reported that the interval between the onset of symptoms and operation was significantly longer in patients with GBP than in those without perforation. Complications of GBP include bile leak and peritonitis, abscesses around the gallbladder fossa (intraperitoneal or intrahepatic), intraperitoneal air, sepsis or septic shock, fistulae and bowel obstruction [29].

Gallbladder perforation (GBP) diagnosis is rarely made preoperatively. In one review, a correct diagnosis was established preoperatively in only one out of the nine (11.1%) patients [43]. Some authors claim that US could not specifically detect perforations, but it was useful and contributed significantly in determining the need for surgical intervention, as it could identify the presence of pericholecystic free fluid [20,35]. Sood et al. [2] noted that the sonographic hole sign, in which the defect in the gallbladder wall is visualized, is the only reliable sign of GBP. However, in Kim et al.'s study [44], the site of the defect was not detected by ultrasonography in any of the 13 patients. CT scan seems to improve the diagnostic accuracy [44].

Ultrasound is often the initial imaging method in radiological evaluation of gallbladder perforation and it yields excellent outcomes. Nevertheless, the presence of increased intestinal gas and pain may limit its possibilities. CT is a sensitive tool in establishing the diagnosis of gallbladder perforation and usually follows ultrasound examinations. In gallbladder perforation there are three groups of findings: those that focus on the gallbladder itself, the structures adjacent to the gallbladder (pericholecystic changes) and other organs, as well [45].

The radiological findings for GBP may be direct or indirect. Direct GBP signs are: defect of gallbladder wall ("hole sign") and gallstones outside the gallbladder, such as in the bowel lumen or even in the peritoneal cavity. Additionally, non-specific signs are: gallbladder distention, gallbladder collapse, intraluminal membranes, coarse intraluminal echogenic debris, thickened, irregular, bulging and/or absent gallbladder wall, post-contrast enhancement of gallbladder wall, as assessed by computed tomography, positive sonographic Murphy sign, gas in gallbladder wall or lumen, pericholecystic fluid collections, pericholecystic abscess, pericholecystic fat stranding, biloma, fistulae, bile duct dilatation, free intraperitoneal fluid, inflammation of pericholecystic liver parenchyma, liver abscess, pneumobilia, portal vein thrombosis, thickening of the adjacent bowel wall and ileus. The "hole sign" is more frequently detected on CT rather than on US. When the resolution of the ultrasound probe is better, the chance of visualising the hole gets higher [45]. Konno et al. [46] reported two cases where bile leakage through the perforated gallbladder wall was clearly demonstrated by color Doppler US. CT is more accurate in the visualization of free intraperitoneal fluid, pericholecystic fluid and abscess [20].

All non-specific signs listed above are more or less frequently found in other diseases of the gallbladder. However, sudden change in clinical condition (relief or worsening of symptoms) of acute cholecystitis when followed by changes in radiological findings such as decrease in the distention of the gallbladder, more thickened and/or more irregular gallbladder wall and formation of pericholecystic or intraperitoneal fluid collections are highly suggestive of perforation, even when the perforation site cannot be visualized [45]. Gallbladder distention accompanied with oedema of its walls may constitute the earliest signs of impeding perforation [47]. Signs such as pericholecystic fluid collections and free intaperitoneal fluid are hardly ever found in uncomplicated acute cholecystitis and therefore should raise suspicion of perforation in the absence of direct signs. Furthermore, signs of emphysematous or gangrenous cholecystitis increase the risk of perforation. The crumpled wall of a decompressed gallbladder floating within fluid of the gallbladder fossa has a distinctive appearance and can be seen in some cases of type I perforation [36].

Pericholecystic abscesses are classified into three types: i) Type I - adjacent to the gallbladder, ii) Type II – intramural, iii) Type III - intraperitoneal inflammation of pericholecystic liver parenchyma and/or liver abscess may possibly be suggestive of an intrahepatic perforation, particularly when there is direct continuity with the gallbladder, if the abscess contains stones and there is no pericholecystic fluid [48]. Besides, abscess of the liver with no discernible gallbladder is also highly suggestive of an intrahepatic perforation [49]. An extended long period of time between the onset of symptoms and the diagnosis

is typical of GBP accompanied with liver abscess formation. Signs of a fistula include gas in the gallbladder, bile ducts and/or gall stones in the bowel, often with signs of bowel obstruction, mostly in the ileum. If the stone obstructs the duodenum, it is called Bouveret syndrome. Fistulae may form between the gallbladder and the duodenum, transverse colon or common bile duct, and sometimes they may be complex.

As mentioned above, certain gallbladder diseases, such as emphysematous and gangrenous cholecystitis carry high risk of perforation and should therefore be meticulously investigated. Despite the fact that it may look very similar to acute uncomplicated cholecystitis, gangrenous cholecystitis usually presents with floating intraluminal membranes (sloughed mucosa), gas within the gallbladder wall or lumen (echogenic foci on US), absence of gallbladder wall enhancement (on CT), mural striation, disruption of the gallbladder wall and/or pericholecystic abscess formation [50]. On US, probably the most specific sign of gangrenous cholecystitis is gallbladder wall striation [51]. Emphysematous cholecystitis usually affects elderly men with diabetes. Typical US signs include punctate hyperechoic foci within the wall or lumen of the gallbladder, frequently with reverberation artifact, because of gas collections [52]. CT is considered to be the most sensitive and specific imaging technique for the diagnosis of emphysematous cholecystitis. Characteristic CT findings are low-attenuation foci that represent gas in the gallbladder wall or lumen.

Cholecystectomy, drainage of abscess if present, and abdominal lavage are mostly sufficient to treat GBP [1,4]. Cholecystectomy may be difficult and challenging in type III gallbladder perforations. If a cholecystectomy is performed, further surgical procedures like repair of the fistula may be required [53,54]. Cholecystectomy can be performed after the infection is relieved by US guided percutaneous drainage in type II gallbladder perforations [20,55]. Laparoscopic cholecystectomy can be performed for acute, gangrenous, and/or perforated cholecystitis as well as uncomplicated cholecystitis, but a conversion may be necessary in case of difficulties like an unclear anatomy [35,54]. Urgent cholecystectomy for patients with acute cholecystitis can be regarded safe, cost-effective and leads to less time off work in comparison with delayed surgery [6,30]. However, percutaneous cholecystostomy by US or CT is gaining ground as an alternative to the surgical procedure particularly in clinically critical patients [35,56]. This treatment option does not require general anesthesia and can be performed in a patient population that is considered to be critically ill with high rates of clinical and technical success and low reported complications [56]. The ideal timing of the PC indwell tube removal is argued since the data available are mainly controversial.

Type I perforation is a clinical diagnosis assisted by radiology, and its treatment is relatively straightforward in the form of urgent laparotomy (or laparoscopy) and cholecystectomy, or cholecystostomy. On the other hand, the decision to treat type II perforations is considered to be far more complicated because of the perforation's chronic nature and lack of consensus within the published literature about the most appropriate investigative or treatment modality [24].

Furthermore, type II perforations are more likely to occur in older patients with greater co-morbidities, and their questionable fitness for surgery often limits treatment options and poses challenges to the overall process of care. Advances in radiological imaging have allowed for more efficient preoperative diagnosis of type II perforation, assisting the timely planning of treatment. Yet, the evidence remains divided regarding the indications and efficacy of open cholecystectomy (OC) over percutaneous drainage (PD) for type II GBP. Felice et al. [57] in 1985, reported mortality rates after OC and PD as 8.6% and 22% respectively. The higher mortality in the latter cohort was attributed to the fact that PD was offered only to those patients who were unsuitable or unfit for OC. According to Huang et al. in 2007, mortality rates following OC and PD appear to be 50% and 0% respectively but no explanation was provided for the higher mortality following OC in this study [58]. The advancement of interventional radiological techniques since 1985 has undeniably improved the mortality rates in patients undergoing PD for type II perforations.

Additionally to the treatment modalities described above, it is of the utmost importance for surgeons to take into consideration a number of novel alternatives in patients who are unsuitable for cholecystectomy. These include ultrasound-guided transduodenal (or transgastric) drainage of the gallbladder with stenting [59] and endoscopic transpapillary gallbladder stenting [60]. Despite the fact that these procedures are conceptually similar to percutaneous cholecystostomy, they differ in the technical aspects of tube design, tube diameter, and the ability to apply suction.

Percutaneous cholecystostomy, which was first described in 1980s, is a technique that involves puncture of the gallbladder under imaging guidance (ultrasonographic or computed tomographic), followed by wire-guided placement of a drainage catheter [61]. External drainage allows time for resolution of both the systemic illness and local inflammation, resolution of local inflammation also reduces the probability that conversion to open cholecystectomy will be needed at subsequent surgery [62].

Following the procedure, elective removal of the catheter can be considered once the tract is mature (usually 4 to 6 weeks) and local inflammation has resolved, especially if the cystic duct is patent, few gallbladder stones remain, and there are no bile-duct stones [63-64].

Transmural EUS-guided gallbladder drainage, which was described in 2007, is a newly introduced alternative to percutaneous cholecystostomy [65]. The gallbladder is often closely opposed to the gastrointestinal tract and is conspicuous on endosonography. Then, a guidewire is positioned within the gallbladder, which allows for the deploy-

ment of transnasal drainage catheters or internal stents. Long-term data for the use of transmural EUS-guided gallbladder drainage as definitive therapy are limited.
As mentioned previously, transpapillary route is considered to be an alternative way to percutaneous methods of endoscopic drainage of the gallbladder. Endoscopic transpapillary gallbladder drainage, which was firstly reported more than 25 years ago, can be divided into two different methods: endoscopic naso-gallbladder drainage (ENGBD) and endoscopic gallbladder stenting (EGBS). These transpapillary procedures are used to place a drainage tube in the gallbladder via the cystic duct in the same manner as with endoscopic retrograde cholangiopancreatography (ERCP). Transpapillary drainage can also be used to facilitate removal of a percutaneous cholecystostomy tube.
These techniques have been successfully used in the case of percutaneous transhepatic drainage or aspiration being contraindicated, such as in patients with ascites and coagulopathy or anatomically challenging [66].
However, although these techniques have demonstrated favorable mortality and morbidity rates, they are currently not provided in most tertiary centers, whereas high quality evidence in the form of randomized outcome data are lacking.

Conclusion

Perforation of the gallbladder is considered to be a rare, but potentially life-threatening complication of acute cholecystitis, which poses a huge diagnostic challenge. GBP diagnosis can be made preoperatively with a high index of suspicion of the condition facilitated by imaging findings. Early diagnosis of gallbladder perforation and immediate surgical intervention are of crucial importance and remain the gold standard for decreasing the morbidity and mortality related to the perforation. We suggest that in any elderly male patient with symptoms of acute cholecystitis who has predisposing factors perforation should be suspected. The significant heterogeneity in data suggests the demand for greater clarity in reporting standards to facilitate future outcomes research and the new modalities formulation.

Riassunto

La perforazione della cistifellea (GBP) è una complicanza non comune, potenzialmente letale, e quasi esclusiva della colecistite. È spesso associata a tassi di morbilità e mortalità relativamente elevati a causa del ritardo nella diagnosi. La GBP continua a essere un problema impegnativo per i chirurghi. La maggior parte dei casi può essere diagnosticata solo durante l'intervento chirurgico. Lo scopo di questa retrospettiva, serie di casi è quella di presentare la nostra esperienza clinica con la perforazione acuta della cistifellea e fornire una panoramica dei fattori patogenetici, manifestazioni cliniche, analisi diagnostica e gestione della GBP sulla base della recente revisione della letteratura.
Questo studio ha coinvolto quattro pazienti con perforazione della cistifellea (tre maschi e una femmina), che sono stati trattati nel nostro reparto da maggio 2019 a novembre 2019. Abbiamo effettuato un'analisi retrospettiva di questi pazienti e una revisione della letteratura correlata.
Secondo la classificazione di Niemeier, tutti i pazienti presentavano perforazione della cistifellea di tipo II. L'età media era di 70 anni (range 50-85 anni). Avevano anche significative comorbilità, di cui il diabete mellito era il più comune (tre pazienti). L'ecografia è stata la modalità iniziale di indagine in questi quattro pazienti. Dei quattro casi, tre pazienti hanno subito un intervento immediato e solo un paziente è stato inizialmente gestito in modo conservativo con antibiotici per via endovenosa.
Conclusioni: La diagnosi precoce della perforazione della cistifellea e l'intervento immediato sono di importanza cruciale. L'esame clinico, l'imaging diagnostico e l'alto indice di sospetto di questa grave condizione sono significativi per realizzare una diagnosi precoce della perforazione.

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