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Original Research Article

Impact of etiology on course and outcomes of severe acute pancreatitis

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ARTICLE INFO

Article history:
Received 23 April 2014
Accepted 24 April 2015
Available online 2 July 2015

Keywords:
Severe acute pancreatitis
Etiology
Outcome

ABSTRACT

Background and objective: Since the influence of etiological factors on the course and outcomes of acute pancreatitis (AP) is not fully understood yet, the aim of the study was to compare the outcomes of alcoholic and biliary severe acute pancreatitis (SAP).

Materials and methods: We investigated 81 patients with alcoholic and biliary SAP. Demographic data, etiologic factors, severity scores, intra-abdominal pressure, imaging studies, interventions, and treatment outcomes were prospectively entered into specially maintained database and subsequently analyzed.

Results: No statistically significant difference was observed in the prevalence of SAP in biliary and alcoholic AP groups ($P = 0.429$). Although, in the biliary SAP group patients were predominantly elderly women ($P = 0.003$), the total in-hospital stay was longer in alcoholic SAP patients ($P = 0.021$). The abdominal compartment syndrome developed more frequently ($P = 0.041$) and necrosectomy was more frequently performed in alcoholic SAP group (not statistically significant). Although not statistically significant, a lower mortality rate among biliary SAP patients (25.0% vs. 13.5%) was observed.

Conclusions: We defined a trend toward decreased incidence of infected necrosis in larger volume (≥30%) pancreatic necrosis, absence of abdominal compartment syndrome, lower rate of necrosectomies, shorter in-hospital stay, and an insignificantly reduced mortality rate in biliary SAP patients, indicating more favorable course of biliary SAP.

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Peer review under the responsibility of the Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2015.04.002

1. Introduction

Throughout the last decades, acute pancreatitis (AP) remains one of the most extensively investigated therapeutic problems with a hardly improvable course. The incidence of the first attack of AP has increased in past decades and varies from 4.9 to 200 cases per million inhabitants [1,2]. In 80% of AP patients, pancreatic injury is mild or moderate and self-limiting, requiring only brief hospitalization to recover without complications. About 25% of the patients with AP develop severe acute pancreatitis (SAP), which is strongly associated with organ failure and local complications such as pancreatic or peripancreatic necrosis, formation of walled-off necrosis or pseudocyst; infected pancreatic necrosis is observed in 30%–70% of SAP patients [3]. The extent and infection of pancreatic necrosis directly correlates with morbidity and mortality [4,5]. Due to considerable improvements in the diagnosis and management of these patients, overall mortality of the disease has decreased, but still ranges between 15% and 25% [6]. The extent of pancreatic necrosis as well as the presence of secondary bacterial infection have been identified as major determinants of lethal outcomes after the third week, representing the most common cause of late mortality [6]. Secondary infection of pancreatic necrosis increases the mortality up to 25% in young or middle-aged patients and even up to 50% in the aged patients [5].

The influence of etiological factors on the course and outcomes of AP is not fully understood yet [7,8]. The dominant (>80%) etiological factors of AP are gallstones and alcohol consumption [1,9]. Prevalence of these two main etiologic factors in AP varies considerably among different countries, reflecting differences in culture, tradition and lifestyle. Predominance of biliary pancreatitis has been reported in southern countries, on the contrary a similar frequency or predominance of alcoholic pancreatitis has been observed in northern ones [10].

The aim of this single center study was to compare the clinical course and outcomes of biliary and alcohol induced SAP. The primary endpoints in this study were development of pancreatic necrosis ≥30% and infected pancreatic necrosis, as well as the need for minimally invasive and/or surgical interventions. Secondary endpoints of the study were duration of intensive care unit (ICU) and overall hospital stay, prevalence of multidrug resistant microorganisms, occurrence of high intra-abdominal pressure and abdominal compartment syndrome, overall morbidity and mortality of alcoholic and biliary SAP patients.

2. Materials and methods

2.1. Patients

The study population comprised 81 patients with alcoholic or biliary SAP admitted to the Department of Surgery, Hospital of Lithuanian University of Health Sciences, from January 1, 2007, to December 31, 2009. Biliary SAP was diagnosed in 37 cases; SAP of an alcoholic origin was diagnosed in 44 cases ($P = 0.429$). The Regional Ethical Committee approved the study (protocols Nos. BE-2-47 and P1-113/2005), and all the patients provided written informed consent. All analyzed demographic and clinical data was prospectively entered into a specially designed database. Inclusion criteria were defined as follows: (1) a time interval from the onset of abdominal symptoms and admission was ≤72 h; (2) at least 3-fold elevated levels of serum amylase or lipase; (3) no previous history of acute or chronic pancreatitis; (4) SAP established by multifactorial clinical scores (APACHE II > 7; Glasgow-Imrie > 2; MODS > 2); and peak C-reactive protein value of >150 mg/L; and/or pancreatic necrosis of ≥30% as defined by contrast enhanced computed tomography (CECT) scan; and (5) alcoholic or biliary SAP. Patients reporting alcohol consumption shortly before the onset of symptoms, having no gallstones in the gallbladder or bile ducts as defined by abdominal ultrasound (US) and/or CT scan were included in the alcohol induced SAP group, whereas patients with gallbladder and/or bile duct stones on abdominal US and/or CT scan, elevated serum bilirubin and/or liver enzymes, and no history of recent alcohol intake were included in the biliary SAP group.

The severity of the disease and clinical status were assessed on the day of admission and reassessed using the same prognostic tools every week and when the clinical condition deteriorated. Prognostic scores (APACHE II, MODS) were assessed on the day of admission. The CECT scan was performed on day 4–7 after the onset of disease to demonstrate the presence of pancreatic necrosis. According to CT scan results patients in whom peri-/pancreatic necrosis exceeding 30% was determined were allocated to subgroups (alcoholic SAP vs. biliary SAP, peri-/pancreatic necrosis ≥30%).

All patients were managed according to our standard AP treatment protocol (based on the recent international guidelines) [11–17]. Early antibiotic treatment (ciprofloxacin 800 mg/day, metronidazole 1500 mg/day for 14 days) was initiated, if at least one of the following indications was present within first 72 h from the onset of the disease: CRP value exceeded 150 mg/L, APACHE II score was >7 and/or necrosis >30% was demonstrated on CECT.

Patients with SAP referred to our hospital from other institutions later than 72 h from the onset of the disease, recurrent AP (more than one episode) and chronic pancreatitis were excluded from this study.

2.2. Interventions

The minimally invasive ultrasound-guided drainage (UGD) and/or open necrosectomy were performed when the patient's condition deteriorated despite intensive conservative treatment with progression of inflammation and/or organ dysfunction [15,18]. UGD was employed to evacuate the fluid collections and to postpone or to obviate the need of open necrosectomy. The latter was performed in patients with fine needle aspiration (FNA) proven infected necrosis and/or clinical signs of generalized sepsis. Decompressing fasciotomy or UGD of intraperitoneal fluid collections was performed to alleviate high intra-abdominal pressure (IAP ≥ 20 mm Hg) in case of abdominal compartment syndrome (ACS) [17,19].

Table 1 – Patients' characteristics and comparison of primary endpoints in alcoholic and biliary SAP groups.

	Alcoholic SAP $n = 44$	Biliary SAP $n = 37$	P
Gender			
Male	42 (95.4)	10 (27)	0.003
Age, mean ± SD (range), years	40.9 ± 12.5 (21–82)	61.4 ± 16.3 (20–82)	0.001
Severity at admission, mean ± SD (range), score			
APACHE II	6.19 ± 4.4 (0–15)	7.64 ± 2.9 (1–14)	0.112
MODS	1.62 ± 2.5 (0–10)	1 ± 1.3 (0–5)	0.202
Patients at ICU	27 (61.4)	18 (48.7)	0.578
Length of stay, median (range), days			
In-hospital	48 (16–240)	34 (8–110)	0.021
[ICU	8.4 (1–59)	14 (1–68)	0.512
Complications			
MODS	12 (27.3)	4 (10.8)	0.169
Pulmonary dysfunction	8 (18.2)	4 (10.8)	0.539
Renal dysfunction	4 (9.1)	2 (5.4)	0.687
Cardiac dysfunction	1 (2.3)	6 (16.2)	0.055
Pneumonia	6 (13.6)	3 (8.1)	0.726
Sepsis	3 (6.8)	3 (8.1)	1.000
Mortality	11 (25.0)	5 (13.5)	0.409

Values are number (percentage) unless otherwise indicated.
ICU, intensive care unit; MODS, multiple organ dysfunction syndrome.

2.3. *Microbiology*

In total, 136 specimens from 44 alcoholic and 37 biliary SAP patients were investigated for presence and susceptibility of bacteria: 116 samples from peri-/pancreatic fluid collections, 11 samples of intraperitoneal fluid, 7 blood and 2 necrotic tissue samples. Isolates were identified with the Phoenix ID system (Becton Dickinson, USA). Antimicrobial susceptibility of all the isolates was tested by the Kirby–Bauer disk diffusion method on Mueller–Hinton agar following recommendations of the Clinical Laboratory Standards Institute. Prospectively maintained database of microbiology laboratory was used to analyze the incidence of infection and isolated pathogens.

2.4. *Statistical analysis*

Statistical analysis was performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, USA). Results shown in the text, tables, and graphs are expressed as median (range) or mean ± standard deviation. The independent Student, Mann–Whitney *U*, and Pearson linear regression tests were used as appropriate. Significance was accepted at $P < 0.05$.

3. Results

The majority of patients in this study were younger men in the alcohol-induced SAP group, whereas in the biliary SAP group, elderly women predominated ($P = 0.003$). There was no significant difference between the alcohol-induced and biliary SAP groups when comparing APACHE II (6.19 ± 4.4 vs. 7.64 ± 2.9) and MODS (1.62 ± 2.5 vs. 1 ± 1.3) prognostic scores (Table 1).

There was no significant difference between alcohol induced and biliary SAP groups in terms of frequency and timing of FNA, UGD and open necrosectomy. Patients were also monitored for the high IAP and ACS. There were no patients suffering from this severe complication in the biliary SAP group, whereas 5 patients in the alcoholic SAP group were diagnosed with elevated IAP and ACS, requiring surgical intervention. Decompressing subcutaneous fasciotomy of the anterior m. rectus abdominis sheath was performed, when high (23.5 mm Hg; range, 20–27.2 mm Hg) IAP has been recorded. Fasciotomy was effective in all cases and resulted in significant decrease of IAP (14.2 mm Hg; range, 12–16 mm Hg, $P < 0.001$). However, 3 of the 5 patients had subsequently died (mortality rate, 60%) (Table 2).

Within the first 7 (median 5; range 4–7) days from the onset of symptoms, CECT was performed in 41 patients (93.2%) with alcoholic SAP and in 31 patients (83.8%) with biliary SAP (Figure). According to CT scan results, 24 patients (58.5%) with alcoholic SAP and 16 patients (51.6%) with biliary SAP developed pancreatic necrosis exceeding 30%. Subgroup analysis (peri-/pancreatic necrosis ≥30%) revealed that patients with alcoholic SAP were more frequently diagnosed with secondary infection of peri-/pancreatic necrosis with subsequent open necrosectomy, their in-hospital stay was longer and mortality rate was

Table 2 – Performed interventional procedures.

	Alcoholic SAP	Biliary SAP	P
FNA, *n* (%)	17 (38.6)	16 (43.2)	0.838
Day, median (range)	16 (6–25)	16 (8–29)	1.000
UGD, *n* (%)	8 (18.2)	5 (13.5)	0.767
Day, median (range)	20 (3–47)	21 (3–37)	0.898
Necrosectomy, *n* (%)	22 (50.0)	9 (24.3)	0.135
Day, median (range)	42 (15–210)	29 (3–55)	0.654
Fasciotomy, *n* (%)	5 (11.4)	0 (0)	0.067

FNA, ultrasound-guided fine needle aspiration; UGD, ultrasound-guided drainage.

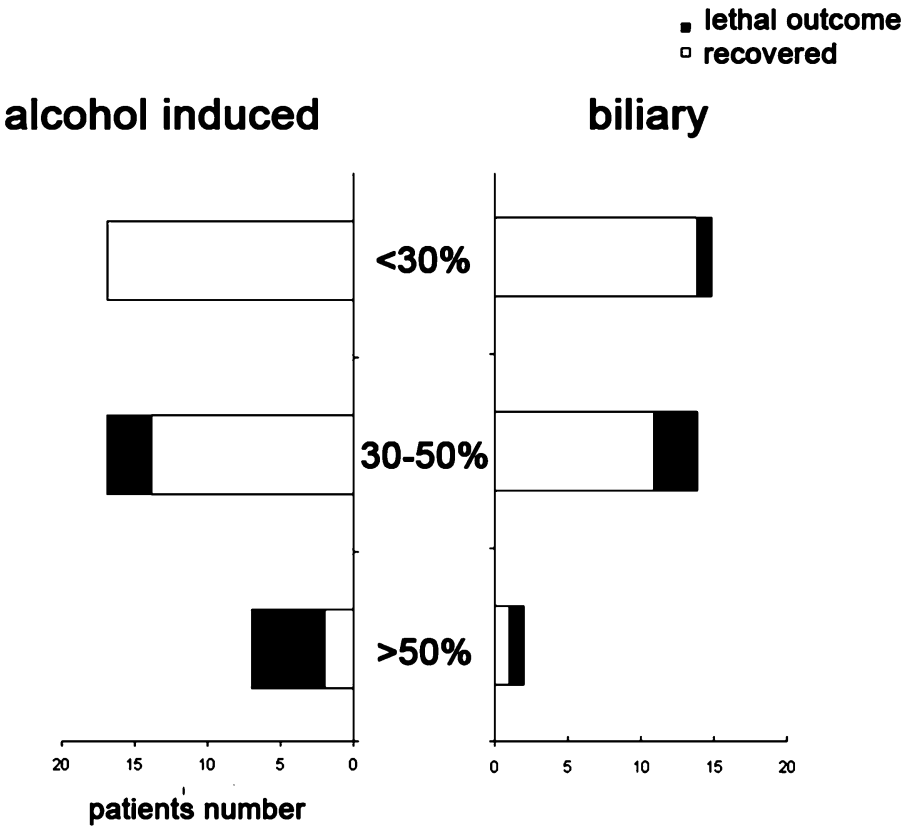

Figure – The extent of pancreatic necrosis and lethal outcomes. The extent of pancreatic necrosis by contrast enhanced computed tomography and number of lethal outcomes and recovered patients in the alcoholic (n = 44) and biliary (n = 37) SAP groups are demonstrated (%). The extent of pancreatic necrosis directly correlated with the mortality rate in the alcoholic SAP group (R = 0.5; P = 0.01).

higher. A direct positive correlation between the extent of pancreatic necrosis and the mortality rate in the alcoholic SAP group ($R > 0.5$, $P = 0.01$) was documented. However, analysis revealed no statistically significant differences between the subgroups (Table 3, Figure).

Analysis of secondary endpoints revealed that total in-hospital stay was longer in the alcohol-induced SAP group when compared to the biliary SAP group ($P = 0.021$). However, there was no difference in the length of stay at ICU between the groups. The rate of multiple organ dysfunction syndrome (MODS), pulmonary, renal dysfunction or cardiac dysfunction was similar between both groups. There was no significant difference in the mortality rate between the groups (Table 1).

A total of 36 (81.8%) and 30 (81.1%) patients were investigated for secondary infected peri-/pancreatic necrosis (IPN) in the alcoholic and biliary SAP groups, respectively. Infected necrosis was diagnosed more frequently in patients with alcoholic SAP (n = 24, 66.7%) than in patients with biliary SAP (n = 14, 46.6%); however, there was no significant difference between the groups (Table 4).

Bacterial culture analysis revealed that the overall number of bacterial strands isolated from the alcoholic SAP patients was higher when compared with that from biliary SAP patients (168 vs. 68). Patients with alcoholic SAP had a higher prevalence of bacteria from the Enterobacteriaceae, Staphylococcaceae, Streptococcaceae, Corynebacteriaceae, and Pseudomonadaceae families and the *Acinetobacter* genus. *Proteus* spp. genus of Enterobacteriaceae family was more frequently isolated from patients with alcoholic SAP (13.1% vs. 2.9%, $P = 0.03$). In contrast, *Candida* spp. was more frequently isolated from the biliary SAP patients (4.2% vs. 19.1%, $P = 0.002$) (Table 4). However, there was no statistically significant difference in the prevalence of antibiotic resistant strands of bacteria in either of the treatment groups.

Table 3 – Comparison of primary endpoints when pancreatic necrosis exceeds 30%.

	Alcoholic SAP	Biliary SAP	P
CT	41 (93.2)	31 (83.8)	0.871
Pancreatic necrosis ≥30%	24 (58.5)	16 (51.6)	0.843
Mortality	8 (33.3)	3 (18.75)	0.505
IPN	15 (62.5)	5 (31.3)	0.389
In-hospital stay, median (range), days	89 (20–240)	29.5 (16–110)	0.564
Necrosectomy	13 (54.2)	4 (25.0)	0.364
Pancreatic necrosis <30%	17 (41.5)	15 (48.4)	0.831

Values are number (percentage) unless otherwise indicated.
CT, computed tomography; IPN, infected peri-/pancreatic necrosis.

Table 4 – Analysis of bacterial strands isolated from 136 specimens of patients with alcoholic and biliary severe acute pancreatitis.

	Alcoholic SAP	Biliary SAP	P
Investigated for infection (patients)	36 (81.8)	30 (81.1)	1.000
IPN	24 (66.7)	14 (46.6)	0.428
Microorganisms	*n* = 168	*n* = 68	
Enterobacteriaceae	80 (47.6)	24 (35.3)	0.292
E. coli	29 (17.3)	11 (16.2)	1.000
Citrobacter spp.	9 (5.4)	3 (4.4)	1.000
Proteus spp.	22 (13.1)	2 (2.9)	0.03
Klebsiella spp.	7 (4.2)	6 (8.8)	0.215
Enterobacter spp.	4 (2.4)	2 (2.9)	1.000
Other	9 (5.4)	0 (0)	0.066
Enterococcaceae	29 (17.2)	13 (19.1)	0.854
Staphylococcaceae	20 (11.9)	7 (10.3)	0.826
S. aureus	9 (5.4)	0 (0)	0.066
Coagulase-negative staphylococci	11 (6.6)	7 (10.3)	0.423
Streptococcaceae	8 (4.8)	6 (8.8)	0.365
Candida	7 (4.2)	13 (19.1)	0.002
Corynebacterium spp.	8 (4.8)	2 (2.9)	0.729
Pseudomonas + *Acinetobacter*	16 (9.5)	3 (4.4)	0.293

Values are number (percentage).
IPN, infected peri-/pancreatic necrosis.

4. Discussion

We have identified some differences between alcoholic and biliary SAP groups in terms of demographic characteristics, course, and outcomes of severe acute pancreatitis.

In the present study majority of patients with alcoholic SAP were males, whereas significantly older females dominated in the biliary SAP group. These results are consistent with data from the other studies showing biliary and alcoholic AP is common in elderly women and in middle-aged men, respectively [1,2].

A similar mortality rate has been reported in patients with AP of different etiologies [20]. However, it is still no unequivocal data on the influence of etiology on the course and outcome of SAP. De Beaux et al. demonstrated an impeded course of disease in biliary AP patients [21]. Agreeably we have disclosed an increased rate of cardiac dysfunction in biliary SAP patients; however, it may not be directly linked with the etiology of the disease, rather than with the increased age of the patients. Other investigators have disclosed an increased risk of infection and a tendency toward higher mortality in biliary pancreatitis [13]. On the contrary we have revealed a direct positive correlation between the extent of pancreatic necrosis and mortality in alcoholic SAP group ($R > 0.5$; $P = 0.01$), which was not the case with the biliary SAP patients. These results are consistent with data from several previous reports [13,22]. Our data support the implication showing no differences in the extent of pancreatic necrosis and the rate of secondary infection between the investigated patient groups. Differences emerged in the subgroup of patients with pancreatic necrosis of ≥30%: a trend toward a lower rate of secondary infection (62% vs. 31%, $P = 0.389$) and a presumably lower mortality rate (33.3% vs. 18.75%; $P = 0.505$) in favor of biliary SAP patients.

Some studies have found no significant differences in terms of outcomes and prognosis between these groups [13], while others have reported better early and late outcomes for biliary AP in terms of lower incidence of pancreatic necrosis and lower risk of lethal outcomes [10,16–18,20,21]. Similarly to the latter, our data revealed a shorter in-hospital stay and an insignificantly reduced mortality rate in biliary SAP patients when compared with alcoholic SAP patients (25.0% vs. 13.5%). Although not statistically significant, probably due to relatively low patient numbers, an almost twofold lower mortality rate seems to be of some relevance.

In case of SAP, an early diagnosis of intra-abdominal hypertension and abdominal compartment syndrome, as well as its adequate management is crucial to the outcome. We have demonstrated earlier that measurements of intra-abdominal pressure are of importance in early phase of SAP [19], while subcutaneous fasciotomy or ultrasound-guided drainage of intra-abdominal/peripancreatic fluid collections were safe and effective alleviating increased intra-abdominal pressure [17]. Development of ACS was observed in 5 (11.4%) patients with alcoholic SAP in whom subsequent subcutaneous fasciotomy was performed. In contrast, there were no either signs of increased IAP or a need for fasciotomy/drainage in biliary SAP patients ($P = 0.04$). In the present study, open necrosectomy was required more frequently in alcoholic SAP patients compared with biliary SAP (50.0% vs. 24.3%). However, there was no significant difference between the groups. It has been reported that open necrosectomy was performed in 10%–70% of SAP patients with repeated laparotomies in 25%–40% of cases [4,23,24]. In contrast, we have performed the only re-laparotomy with repeated necrosectomy in the biliary SAP patient. A low incidence of repeated necrosectomies in our study may be attributed to an extensive use of step-up approach-utilizing image guided drainage of abdominal collections, thus postponing surgical debridement until complete demarcation of necrotic tissues. The rational for this particular strategy is endorsed by others [25] and is further supported by data from the randomized controlled PANTER trial [15].

Microorganisms most frequently isolated from pancreatic necrosis or peripancreatic collections were gram-negative bacteria of enteric origin. Raty et al. have found the differences in the microbiology of infected pancreatic necrosis in alcoholic and biliary pancreatitis with predominant gram-positive bacteria in alcohol induced AP and gram-negative bacteria in biliary AP [26]. On the contrary, we identified a very similar distribution of gram-negative and gram-positive bacteria between the groups. The main difference was predominance of *Proteus* spp. in the alcoholic SAP group (13.1% vs. 2.9%; $P = 0.03$) and predominance of *Candida* in the biliary SAP group (19.1% vs. 4.2%, $P = 0.002$). The predominance of fungi in biliary pancreatitis may be attributed to the prophylactic use of wide-range antibiotics and advanced age of these patients. Similarly to other reports, fungal infection has not influenced the in-hospital mortality rate [27]. Importantly, we found no differences in antibiotic resistant strands between the investigated groups. Therefore, we speculate that the type of pathogenic as

well as nosocomial micro-organisms present in peri-/pancreatic necrosis were not directly related to the etiology of SAP.

5. Conclusions

Evaluating the presented study we need to admit the main shortcoming, i.e., an insufficient number of patients within the groups, which seems precluded demonstrating more profound differences in course and outcomes between biliary and alcoholic SAP patients. Our data revealed a trend toward a lower rate of secondary infection in patients with ≥30% pancreatic necrosis, absence of ACS, lower rate of open necrosectomies, and shorter in-hospital stay indicating a more favorable course of disease in biliary SAP. These results, however, may be specific for the geographical region and the specific ethnic group. Further larger-scale studies are needed to evaluate the influence of etiology on the outcomes of SAP.

Conflict of interest

The authors state no conflict of interest.

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