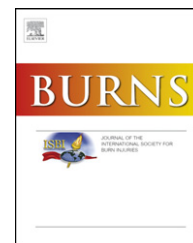


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Acalculous cholecystitis in severely burned patients: Incidence and predisposing factors

P. Theodorou^{a,d,*}, C.A. Maurer^b, T.A. Spanholtz^{a,d}, T.Q.V. Phan^a, P. Amini^a, W. Perbix^a, M. Maegele^{c,d}, R. Lefering^d, G. Spilker^a

^aDepartment of Plastic and Reconstructive Surgery, University of Witten-Herdecke, Cologne City Hospitals (Merheim), Ostmerheimerstr. 200, 51109 Cologne, Germany

^bDepartment of General, Visceral, Vascular and Thoracic Surgery, Hospital of Liestal, 4410 Liestal, Switzerland

^cDepartment of Traumatology and Orthopedic Surgery, Merheim-Hospital University of Witten-Herdecke, 51109 Cologne, Germany

^dInstitute for Research in Operative Medicine (IFOM), University of Witten-Herdecke, 51109 Cologne, Germany

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ABSTRACT

Objective: To investigate the incidence and predisposing factors of acalculous cholecystitis (AAC) in severely burned patients.

Background data: Although some studies report on AAC in critically ill patients, very little is known about AAC after severe burns.

Methods: We conducted a retrospective cohort study involving patients with burns admitted to the burn intensive care unit (BICU) of a university hospital. The patient cohort was divided into two groups (AAC group: burned patients with histological proven acalculous cholecystitis, $n = 15$; Control group: population of all other burned patients admitted to the BICU, $n = 1225$). Univariate and multivariate analyses were used to identify predisposing factors for the development of AAC.

Results: Fifteen patients with acalculous cholecystitis were identified in the study period. This represents 1.2% of all significant burns admitted. Comparing the AAC group with the Control population the following patients' characteristics, therapeutic measures and outcome parameters were significantly different in the univariate analysis: mean age (54.0 years vs. 42.0 years), BMI (28.9 kg/m² vs. 25.6 kg/m²), abbreviated burn severity index (8.3 vs. 6.4), total body surface area burn deep partial thickness (12.0% vs. 6.2%) and full thickness (10.2% vs. 6.8%), concomitant inhalation injury (80.0% vs. 28.9%), sepsis (46.7% vs. 14.9%), catecholamine (100% vs. 30.4%) and antibiotic requirement (100% vs. 58.2%), non-biliary tract operations (4.9 vs. 1.5), BICU length of stay (63.4 days vs. 21.0 days), ventilator days (50.3 vs. 11.9), packed red blood cells (PRBCs) administration (70.0 units vs. 13.0 units) and mortality (53.3% vs. 19.7%). In the multivariate analysis however, only age, the number of administered units of PRBCs and the duration of mechanical ventilation turned out to be independent predictors for the occurrence of AAC.

Conclusion: AAC is a rare complication of severely burned patients and may reflect the severity of the patient's general conditions. Predisposing factors for AAC are advanced age, the need of blood transfusions and prolonged mechanical ventilation. In the presence of these predisposing factors, early monitoring may help to detect AAC earlier and to initiate appropriate intervention.

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* Corresponding author at: Department of Plastic and Reconstructive Surgery, University of Witten-Herdecke, Cologne City Hospitals (Merheim), Ostmerheimerstr. 200, 51109 Cologne, Germany. Tel.: +49 221 89073817; fax: +49 221 89073878.

E-mail address: Panos.Theodorou@yahoo.de (P. Theodorou).

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1. Introduction

Acute acalculous cholecystitis (AAC) is an acute inflammation of the gallbladder in the absence of gallstones and accounts for 2–14% of all cases of acute cholecystitis [1,2]. Its incidence varies with the group of patients considered, being much higher in critically ill patients, after major trauma and in paediatric and burned patients, than in the general population [3–5]. In burn intensive care units (BICUs) AAC complicates between 0.4% and 3.5% of all burns [6,7] and tends to have a more fulminant course, frequently associated with gangrene, perforation and empyema, compared with acute calculous cholecystitis [8–10].

Although aetiology is uncertain, AAC has been associated with biliary stasis, dehydration, multiple transfusions, narcotic analgesics, duration of ventilatory support, positive end-expiratory pressure (PEEP), total parenteral nutrition (TPN), activation of factor XII, sepsis and shock [6,7,11].

The non-specific nature of signs and laboratory findings [12] often results in delay of treatment and contributes to its high morbidity and mortality. Although symptoms in burned patients are similar to those in other patients (right upper quadrant pain, tenderness, fever), the clinical picture can be obscured by overlying burn, sedation, analgesics, or endotracheal intubation. Laboratory values are difficult to interpret, because elevated liver enzymes and hyperbilirubinaemia are found in various degrees of liver dysfunction and multiple organ failure in critically ill patients. Leucocytosis ($WBC > 10,000/mm^3$) is present in nearly 90% of AAC patients, but is a non-specific finding in patients with severe burns.

The diagnosis of acute acalculous cholecystitis can be aided by ultrasonic examination, computed tomography and radio-nuclide cholescintigraphy.

AAC is an emergency. Without immediate treatment there may be rapid progression to perforation or gangrenous cholecystitis, with a mortality rate as high as 65% [13]. With timely diagnosis and intervention the mortality drops to 7% [14]. Therefore, it is important to be aware of predisposing factors that may assist in making an early diagnosis of this condition. The aim of the present retrospective study was to identify such risk factors for AAC development in patients with burns. To address this aim, we compared demographics, burn characteristics and clinical data between AAC patients and non-AAC burn patient cohort and performed a multivariate logistic regression analysis, to define independent predictors of AAC for patients in a burn intensive care unit.

2. Methods

2.1. Patient sample and AAC criteria

We retrospectively reviewed the charts of patients treated in the BICU of the University of Witten-Herdecke, Cologne-Merheim from January 1989 to December 2004 ($n = 1461$). Exclusion criteria included age < 14 years (74 patients), admission diagnosis of toxic epidermal necrolysis (TEN) (26 patients), electrical injuries (65 patients) and a stay in the

BICU < 3 days (120 patients), leaving 1240 patients for analysis.

Findings suggesting acute cholecystitis on physical examination included right upper quadrant pain or a palpable gallbladder with localized tenderness. Ultrasonographic signs suggesting acute cholecystitis included gallbladder distension (longitudinal diameter > 12 cm or transverse diameter > 5 cm), pericholecystic fluid, thickened gallbladder wall (4 mm or more in thickness) and sonographic Murphy's sign. AAC was clinically diagnosed, if one or more physical findings together with two or more sonographic signs were present in the absence of gallstones. The definitive diagnosis of clinically suspected AAC was made by histological confirmation of acute inflammation of the gallbladder without perioperative evidence of gallstones.

The patient cohort meeting the inclusion criteria ($n = 1240$) was divided into two groups: AAC group: patients undergoing cholecystectomy due to acalculous cholecystitis, and Control group: all other burned patients admitted to the BICU.

2.2. Data collection

Clinical data potentially relevant for further analyses were prospectively collected by the attending surgeon and entered into a web-based data collection platform specifically adapted for this program. The data set was completed for each patient after transfer from the BICU or death. Data integrity was evaluated through an assessment of missing values, range checks, evaluation for implausible values and internal consistency.

To ensure that all patients with AAC were identified, the database was cross-checked for "cholecystectomy" as surgical intervention and additionally for "gallbladder" as pathological specimen. The herewith identified patient files were then further analyzed, if the criteria of AAC were met. The therapeutic options of cholecystostomy or conservative medical treatment alone have never been used for patients with cholecystitis in our unit.

Burn size and depth were assessed by completion of a Lund-Browder diagram by the attending surgeon, documenting the extent of injury in each body region. Inhalation injury was defined as a history consistent with inhaled toxic fumes and bronchoscopic verification of tracheal and bronchial damage. Abbreviated burn severity index (ABSI) was calculated from the medical records. Demographics (age, gender, BMI), BICU length of stay, intubation status on admission, acute renal failure with consecutive haemodialysis and antibiotic treatment including prophylactic antibiotics on admission day were recorded from the medical notes. The number of non-biliary tract surgical procedures, units of packed red blood cells (PRBCs) received, duration of ventilatory support, catecholamine requirement and sepsis were documented for the period prior to cholecystectomy for the AAC patients and throughout the whole stay in the BICU for the Control population. Through documentation of these factors for the period prior to cholecystectomy for the AAC group and comparison to the equivalent factors during the entire BICU stay for the Control group, we were able to investigate the causative connection of these variables to the development of AAC. Sepsis was diagnosed based on the

criteria set by the Society of Critical Care Medicine [15], in conjunction with blood culture growth or presence of organisms in the organs at autopsy. In our burn unit we administer red blood cells when haemoglobin levels are <8 mg/dL or haematocrit <28%. We usually transfuse to a target level of 10 mg/dL.

Institutional permission to develop the study was obtained and confidentiality of the information was maintained.

In addition, a Medline search of the English-language literature using the key words "acalculous cholecystitis" produced 809 references. We reviewed the abstracts of all these articles and further reviewed the full text of articles that suggested possible causes of acalculous cholecystitis. The review was expedited by the targeting of phrases such as "thermal injury", "major trauma", "burns", "induced by", "caused by" and "associated with".

Table 1 – Baseline characteristics and clinical data.

Baseline and injury variables	AAC group Mean (S.D.)	Control group Mean (S.D.)	p
N	15	1225	
Age (year)	54.0 (11.1)	42.0 (18.1)	0.001 [†]
BMI (kg/m ²)	28.9 (6.8)	25.6 (4.7)	0.031 [†]
ABSI-score	8.3 (1.9)	6.4 (3.0)	0.002 [†]
%TBSA burn	33.4 (21.6)	23.5 (22.2)	0.160 [†]
%2a Degree	11.3 (13.2)	10.6 (10.8)	0.752 [†]
%2b Degree	12.0 (10.0)	6.2 (10.0)	0.034 [†]
%3 Degree	10.2 (10.2)	6.8 (15.7)	0.012 [†]
	n (%)	n (%)	p
Gender			0.573 [*]
Women	3 (20.0)	371 (30.3)	
Men	12 (80.0)	854 (69.7)	
Inhalation injury	12 (80.0)	354 (28.9)	<0.001 [*]
Admitted on ventilator	10 (66.7)	489 (39.9)	0.060 [*]
Clinical data	n (%)	n (%)	p
Antibiotics on admission	10 (66.7)	298 (24.3)	0.001 [*]
BT requirement [#]	15 (100)	545 (44.5)	<0.001 [*]
Antibiotic requirement [#]	15 (100)	713 (58.2)	<0.001 [*]
Catecholamine requirement [#]	15 (100)	372 (30.4)	<0.001 [*]
PEEP ventilation	15 (100)	628 (51.3)	<0.001 [*]
Mechanical ventilation >21 days [#]	15 (100)	257 (21.0)	<0.001 [*]
Sepsis [#]	7 (46.7)	183 (14.9)	0.004 [*]
Haemofiltration	6 (40.0)	92 (7.5)	0.001 [*]
	Mean (S.D.)	Mean (S.D.)	p
BICU length of stay (days)	63.4 (36.5)	21.0 (26.8)	<0.001 [†]
Ventilator days [#]	50.3 (18.4)	11.9 (21.6)	<0.001 [†]
Non-BT operations [#]	4.9 (4.0)	1.5 (2.4)	0.006 [†]
Units PRBCs [#]	70.0 (47.5)	13.0 (26.9)	<0.001 [†]
PRBCs per %burned area [#]	2.5 (1.3)	0.5 (1.1)	<0.001 [†]
Catecholamine infusion rate ($\mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$)			
Dobutamine	1.84 (2.47)	0.59 (1.91)	
Dopamine	3.53 (2.60)	1.17 (2.53)	
Norepinephrine	0.10 (0.09)	0.04 (0.14)	
Epinephrine	0.15 (0.32)	0.04 (0.18)	
Outcome	n (%)	n (%)	p
Mortality	8 (53.3)	241 (19.7)	0.004 [*]

AAC group: acalculous cholecystitis group; Control group: rest burn patient cohort; BMI = body-mass index; ABSI = abbreviated burn severity index; TBSA burn = total body surface area burn; BT = blood transfusion; PEEP ventilation = positive end-expiratory-pressure ventilation; BICU = burn intensive care unit; Non-BT operations = number of non-biliary tract surgical procedures; PRBCs = units of packed red blood cells.

^{*} Fisher exact test.

[†] Mann-Whitney U test.

[#] Parameters were considered for the period prior to cholecystectomy for the AAC group and throughout the whole stay in the BICU for the Control group.

2.3. Statistical analysis

An exploratory analysis strategy was used for this study. Comprehensive descriptive statistics including number, mean, standard deviation (S.D.), minimum and maximum were used for quantitative data. A univariate comparison between the two groups – patients with acalculous cholecystitis and Control group – was performed, using Fisher's exact test for counts and Mann-Whitney *U* test for continuous variables. Absolute counts and percentages were given for nominal and ordinal data. In a second step, multivariate analysis, in which development of AAC was the dependent outcome variable was performed by logistic regression employing stepwise forward selection. Independent variables with a *p* value <0.05 for an association with AAC by univariate statistics were included in the multivariate analysis. Estimated coefficients for independent variables, standard errors, and odds ratios (OR) with 95% confidence intervals (CI) were described. All *p* values are two-tailed, and *p* < 0.05 was considered to indicate statistical significance. Statistical calculations were performed with SPSS® for windows (Vers. 14.0, SPSS Inc. 2005).

3. Results

3.1. Incidence of AAC in severely burned patients

From 1989 to 2004 a total of 1240 patients with severe burns were enrolled in this study. During this 16-year period 20 patients had a cholecystectomy for suspected AAC, but finally, only 15 cases fulfilled the criteria of AAC, representing 1.2% of the study population. Five patients with cholecystitis were intraoperatively found to have gallstones.

3.2. Results of diagnostic investigations in AAC patients

Diagnostic investigation in the AAC population included ultrasound in 15 (100%), computed tomography in 13 (86.7%), and radionuclide cholescintigraphy in 2 (13.3%) patients. All patients affected had highly pathologic ultrasound changes, together with major clinical symptoms (pain and/or abdominal distension, haemodynamic instability requiring increasing amounts of catecholamines and/or fluids, organ failure).

At the time of diagnosis, all AAC patients were hospitalized in the BICU, 14 (93.3%) had prolonged fasting (>7 days) and 11 (73.3%) were receiving total parenteral nutrition. One day prior to cholecystectomy WBC count was outside the normal range ($4.0\text{--}10.0 \times 10^{-9} \text{ L}^{-1}$) in 14 patients (93.3%), of whom 8 had values $>20 \times 10^{-9} \text{ L}^{-1}$. Alanine aminotransferase was elevated ($>50 \text{ IU L}^{-1}$) in 11 (73.3%), aspartate aminotransferase ($>50 \text{ IU L}^{-1}$) in 5 (33.3%), total bilirubin ($>1.1 \text{ mg/dL}$) in 11 (73.3%) and alkaline phosphatase ($>150 \text{ IU L}^{-1}$) in 12 patients (80.0%). Five patients (33.3%) developed bilirubin levels greater than 3 mg/dL.

3.3. Baseline patients' and injury characteristics

Baseline patients' and injury characteristics of both groups are summarized in Table 1. Significances in Table 1 were calculated as univariate analyses.

3.4. Therapeutic modalities and outcomes

Treatment of acalculous cholecystitis included open and laparoscopic cholecystectomy (10 open and 5 laparoscopic). Mortality was 60% in the open and 40% in the laparoscopic procedure. The evidence of advanced disease with gangrene, abscess or perforation was noted in eight patients (53.3%). Four specimens showed gangrenous cholecystitis, one showed abscess and three others showed perforation of the gallbladder.

Overall, all-cause mortality for the 1240 analyzed patients in the BICU was 20.1%. The causes of death in the AAC group included multiple organ failure in three patients and ARDS, liver failure, renal failure, fungal sepsis and biliary pancreatitis in one patient each.

3.5. Multivariate analysis

Predisposing factors for AAC according to the univariate analysis (*p* value < 0.05) were selected for stepwise logistic regression analysis. Table 2 shows the significant results from this multivariate analysis. Age, number of administered units of PRBCs and length of ventilatory support were calculated to be independent predictive factors for the development of AAC (Fig. 1).

4. Discussion

The frequency of AAC in our study population of more than 1200 patients with severe burns was 1.2%. The limited data on this topic goes back for 20 or more years, referring an incidence rate of up to 3.5% [5–7,11]. A total of 30 cases with AAC after thermal injury have been reported in the literature since 1960, with a small patient sample analyzed each time. Acalculous cholecystitis was present in 3 (0.8%) among 380 burned patients reported by Ross et al. [6]. McDermot and associates reported acalculous disease in 4 (3.5%) of 113 patients with burns to more than 30% of the total body surface area [7]. Alawneh [5] and Munster et al. [11] reported AAC in all their burned patients who suffered acute cholecystitis (7 and 10 cases, respectively), while case reports complete the rest AAC study population after thermal injury in the last 4 decades. None of the studies above completed a multivariate analysis to define independent risk factors for the occurrence of AAC, and

Table 2 – Logistic regression analysis main effects model for AAC occurrence.

Risk factor	β	S.E.	OR	CI	<i>p</i>
Age (year)	0.40	0.016	1.040	1.009–1.073	0.011
Ventilator days	0.14	0.009	1.014	0.996–1.033	0.012
Units PRBCs	0.19	0.007	1.020	1.007–1.033	0.003
Constant	–7.327	0.989			

β = estimated coefficient for independent variables; S.E. = standard error; PRBCs: units of packed red blood cells. Predicted probabilities for AAC occurrence can be determined from the equation $\text{Pr}(\text{AAC}) = e^z / (1 + e^z)$, where $z = \text{constant} + \sum \beta_i X_i$, where β_i is the corresponding coefficient for variable X_i .

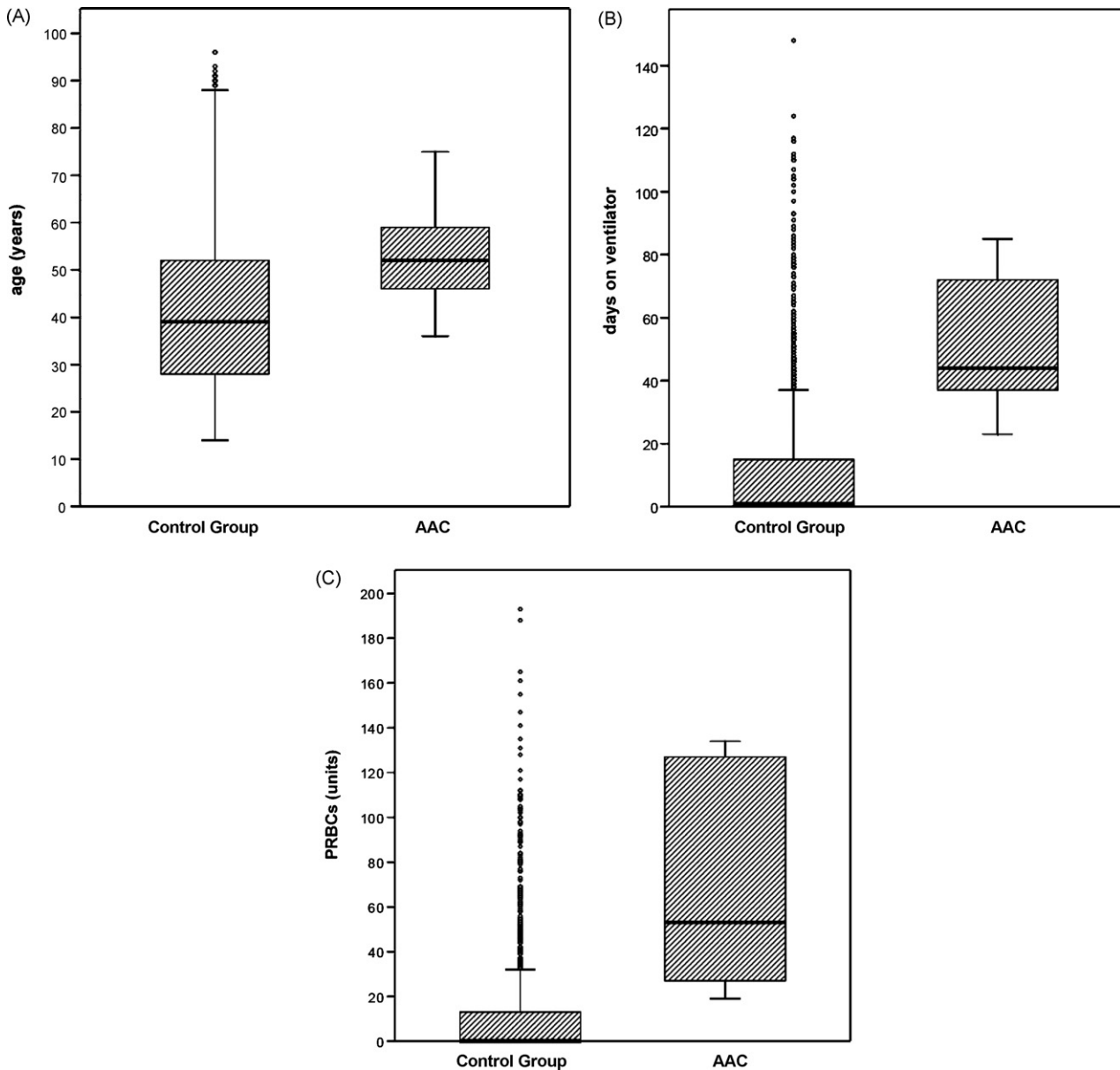


Fig. 1 – (A–C) Independent predictors of AAC: box plots of patient age (A), days on ventilator (B) and administration of packed red blood cells PRBCs (C) in the AAC and Control group population. AAC: acalculous cholecystitis group; Control group: rest burn patient cohort; PRBCs = units of packed red blood cells.

only one of them employed a burn patient population greater than 400 patients [11].

Severely burned patients have multiple conditions predisposing them to acalculous cholecystitis. By multivariate analysis we were able to identify three independent predictors for the occurrence of AAC in our burn population, including units of PRBCs administration, age and length of ventilatory support.

Administration of numerous blood transfusions has already been associated with AAC [5,6], producing stasis as the result of an increase in the bile pigment. In the present study all AAC patients received considerably more PRBCs, than the Control group. This was not a surprise, regarding that all of them required significantly more burn wound excisions,

extensive debridements and skin grafting, than the rest burn patient cohort.

Mechanical ventilation with positive end-expiratory pressure is also known to induce bile stasis as shown in the dog model [16,17]. Duration of mechanical ventilation was another independent predictor of AAC occurrence in our burn unit, as 80% of our AAC patients experienced inhalation injury and all of them were receiving PEEP ventilation >21 days prior to cholecystectomy.

The role of fasting and bile stasis in the pathogenesis of AAC has also focused attention on total parenteral nutrition [18–20], causing bile stasis due to the lack of neural and hormonal stimuli to the biliary tract. In the present study 14 patients (93.3%) had prolonged fasting (>7 days) and 11

(73.3%) were receiving total parenteral nutrition prior to AAC.

Whereas calculous disease is associated with arterial dilatation and extensive venous filling, AAC is associated with multiple arterial occlusions and minimal-to-absent venous filling, suggesting that vascular occlusion and gallbladder ischemia is central to the pathogenesis of AAC. According to this hypothesis, bacterial invasion of ischemic tissue as a result of bacteraemia is a secondary phenomenon [21], which is supported by observations from other clinical series [19,20]. Although seven of our patients had sepsis antecedent to AAC, sepsis was not found to be an independent predictor for the occurrence of acalculous cholecystitis.

In our multivariable analysis, we also identified age as an independent predictor of AAC. Our data do not delineate the pathophysiology of this relationship, but one could theorize the contribution of multimorbidity and immunodeficiency and therefore increased risk of bacterial infection and sepsis related to elderly patients. The result that the number of non-biliary tract surgical procedures was not found to be a significant predictor of AAC was surprising, since multiple surgical procedures have been repeatedly found to be associated with acalculous cholecystitis [3,22,23]. The inclusion of both PRBCs received and number of non-biliary tract surgical procedures (consisting mostly of burn wound excisions and skin grafting) in the AAC occurrence regression model is the most likely explanation, as there is a strong interaction between those two variables.

Numerous radiographic modalities have been utilized to confirm the diagnosis of AAC. Those used most commonly are ultrasonography (US), computed tomography (CT) and radio-nuclide cholescintigraphy (RC). The ultrasonographic examination is non-invasive, can be done at bedside and may be easily repeated day by day, as needed. Its sensitivity in the diagnosis of AAC varies from 25% to 100% [24]. CT scan is as accurate as ultrasound in the diagnosis of AAC [25] and it has been especially helpful in documenting the presence of pericholecystic inflammation and fluid, gross abnormalities of the gallbladder wall and other signs of intra-abdominal pathology [25,26]. RC is almost 100% sensitive in detecting AAC, but it is associated with a false positive rate of up to 40% in patients with atypical symptoms, hepatocellular dysfunction, prolonged fasting, or severe intercurrent illness [27,28].

The high incidence of gangrene and perforation in acalculous cholecystitis [8-10] dictates the need for immediate surgical intervention. The three treatment options include cholecystectomy, cholecystostomy and percutaneous cholecystostomy. Antibiotic therapy does not substitute for removal or drainage of AAC, but remains an important adjunct. The mainstay of therapy for AAC has been cholecystectomy [1]. Pericholecystic fluid collections may be drained if necessary and other acute problems that could mimic acute cholecystitis may be identified and managed, if AAC is not present. Cholecystostomy can be a lifesaving alternative in the patient considered too unstable to undergo general anaesthesia [18,29]. Percutaneous cholecystostomy (PC) has been introduced as an alternative method to treat acute cholecystitis in patients with significant comorbid diseases [30,31] and has low morbidity and mortality rates. In our study laparoscopic cholecystectomy was performed in 5 and open procedure in 10 AAC patients.

The independent predictors for AAC identified in our study show indirectly an interrelation of acalculous cholecystitis with the burn trauma itself, as both clinical predictors determined (duration of ventilatory support and number of blood transfusions administered) correlate with the severity of thermal injury. The morbidity and mortality of patients with AAC is much higher, than for those with calculous disease [1,3,10], with a mortality rate of the AAC population in our series of 53.3%. The reasons therefore are the co-existing poor clinical conditions, together with a delay in therapy of acalculous cholecystitis. Thus, early and aggressive diagnostics should be performed in the presence of one or several predisposing factors of AAC.

There are some study limitations that require further discussion. The significant problem all databases face is that of incomplete data. Risk models can only adjust for data that has been collected. Our study did not examine in the multivariate analysis some previously reported risk factors for the occurrence of AAC, such as total parenteral nutrition and narcotic analgesics. Furthermore the results of this study must be interpreted with caution because of the limited number of AAC patients and its retrospective character. Despite these limitations, we suggest that the present study accurately portrays the rate of AAC and its predictors in the burn patient population.

5. Conclusion

The patient age, length of ventilatory support and units of PRBCs administration were found to independently predict AAC occurrence after thermal injury. Finally, in addition to the patient and injury characteristics analyzed in this study, one must consider the potential contribution of diagnostic delay in the development of advanced degree of gallbladder pathology and mortality. Evaluating the time component may better elucidate the subsequent risk for rapid progression of AAC and the benefit of early aggressive diagnostic in the presence of one or several predisposing factors for AAC.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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