

Mortality Risk Factors in Patients with Pyogenic Liver Abscess

dos Santos-Rosa OM^{1*}, dos Santos RLC², Favaro ML³, Fonseca AZ⁴ and Junior MAFR⁵

¹Assistant Professor and Master, Federal University of Maranhão, Pinheiro, MA, Brazil

²Medical Doctor, Federal University of Pará, Belém, PA, Brazil

³Assistant Professor and Ph.D. in Health Sciences, Surgical Clinic Center of the University of Santo Amaro - UNISA, São Paulo, SP, Brazil

⁴Ph.D. in Health Sciences, Institute of Medical Assistance to the State Public Servant IAMSPE

⁵Full Professor and Faculty Member, Institute of Medical Assistance to the State Public Servant IAMSPE

*Corresponding author:

Otto Mauro dos Santos Rosa,
Assistant Professor and Master,
Federal University of Maranhão, Pinheiro,
MA, Brazil,
E-mail: ottomsrosa@yahoo.com.br

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1. Summary

1.1. Rationale: Pyogenic liver abscess is a severe and universally fatal disease without a cure. It has a non-specific clinical and laboratory pattern and a slow evolution. The incidence of pyogenic liver abscess is variable, ranging from 1.1 to 17 cases per 1000 inhabitants. It has nonspecific clinical signs and symptoms such as abdominal pain, fever, and jaundice. Pyogenic liver abscess may be treated using isolated antibiotic therapy or surgical procedures (open surgery, video-laparoscopic surgery, and ultrasound-guided puncture). It has a mortality rate that ranges from 5.6 to 80%.

1.2. Objective: To identify mortality risk factors of patients with pyogenic liver abscess who underwent ultrasound-guided puncture and drainage in combination with antibiotic therapy.

1.3. Method: A total of 25 patients with pyogenic liver abscess were treated in the general surgery and trauma department of the Grajaú General Hospital. They underwent ultrasound-guided percutaneous drainage for the treatment of a liver abscess. Epidemiological characteristics, laboratory markers, and imaging examinations (ultrasonography and tomography) were evaluated.

1.4. Results: The patients in this study were predominantly males, with a mean age of 50 years. Cholelithiasis, hepatopathy, and alcoholism were the most frequent conditions in their medical history.

Abdominal pain (84%), fever (56%), and inappetence (36%) were the most common clinical manifestations. We observed a 20% mortality rate in our study. In our study, hypoalbuminemia was identified as an important isolated risk factor, positively associated with death. It increases the likelihood of death by eleven times (RR=11 CI 95% 2.9-4.2).

1.5. Conclusion: In this study, which involved 25 patients with pyogenic liver abscess who were treated using ultrasound-guided puncture and drainage and antibiotic therapy, we can conclude that patients with less than 1.2 g/dl serum albumin are at a higher risk of death.

2. Introduction

Pyogenic liver abscess is the presence of a purulent collection inside the liver. This collection is formed due to the contamination of the liver parenchyma by bacteria, leading to a local inflammatory reaction with a subsequent cellular inflammatory response [1, 2].

Pyogenic liver abscess is a rare disease, with incidence ranging from 1.1 to 2.3 per 100,000 inhabitants, according to population-based studies in Canada and Denmark. The incidences of pyogenic liver abscess in the USA and Taiwan are 3.6 per 100,000 and 17.6 per 100,000, respectively [3]. In Brazil, no population-based study has been conducted to determine the incidence of pyogenic liver abscess.

It has high a morbidity and mortality rate. According to some authors, this is due to the delay in diagnosis and the initiation of the appropriate therapy [4].

There has been a significant increase in the incidence of pyogenic liver abscesses, notably in Asia and especially in Taiwan, the region of the world with the highest prevalence. This increase is mainly due to a hyper virulent strain of *Klebsiella pneumoniae* (CA-KLA) that causes pyogenic hepatic abscess syndrome [5].

The clinical manifestations are diverse and non-specific. They range from inappetence and diarrhea to the most common such as abdominal pain, jaundice, and fever. Pyogenic hepatic abscess has a slow evolution, which is why patients do not seek medical attention immediately. This has resulted in mixed results regarding the onset of symptoms (range: 3 to 120 days) [6].

The etiology may vary according to the region. In Central Europe, bile etiologies are the most common, followed by cryptogenic abscesses caused by *Staphylococcus aureus*, *Streptococcus*, and *E. coli*, while in Southeast Asia the most common microorganism is *Klebsiella pneumoniae*. These differences in the microbiological spectrum have implications on risk factors and the disease course [7].

Pang et al (2011) [8] reported that in most patients, pyogenic hepatic abscess was associated with cryptogenic causes, followed by bile causes and portal causes (appendicitis and diverticulitis). They also found an association between the microbiology and etiology. *E. coli* is associated with bile duct disease, *Klebsiella* is associated with cryptogenic causes, and *Streptococcus milleri* is associated with portal causes.

The pyogenic liver abscess is an extremely serious, uniformly fatal disease without cure. Mortality may vary drastically from 5.6 to 80%, depending on several factors such as etiology, size of abscesses, presence of gas in the collection, pre-existing conditions, type of therapeutic approach, and time of treatment initiation [9, 10]. A number of US studies published in 1938 reported a high mortality rate of approximately 60-80%, with surgical treatment as the sole therapy, while other studies reported that the mortality rate was approximately 10% [8, 11, 12].

A significant decrease in mortality to 13-18% occurred as a result of the effective use of antibiotics, starting in the 1980s [13]. Another sharp decrease was observed in studies with the advent of ultrasonography and computed tomography. Mortality in studies, during and after 1990, was between 4 and 10% [14]. The development of interventional radiology with percutaneous image-guided drainage and minimally invasive surgery in recent decades have contributed to the decrease in mortality and increased the survival of patients [7, 13].

The therapy to be administered must take into account the cause, the experience of the service, and availability of a means of diagnosis and treatment. Antibiotic therapy in addition to radiological

intervention or surgical therapy or both may be used for treatment [8, 12, 15].

Broad-spectrum parenteral antibiotic therapy is the basis of treatment and should be initiated as early as possible, in addition to drainage of the collection and the collection of material for culture [5, 12, 16].

Culture-guided antibiotic therapy is the gold standard for treatment. However, the initial antibiotic therapy varies in the literature. Associations such as metronidazole with gentamicin, amoxicillin with clavulanate, metronidazole with gentamicin and cefoxitin, ampicillin with gentamicin and metronidazole or ceftriaxone with metronidazole. Associations were found in the literature. The duration of antibiotic therapy ranged from 14 days to six months, with the most common being approximately four to six weeks [4, 6, 8, 17-19].

However, the combination of radiological intervention (aspiration or drainage) with antibiotic therapy has shown better results regarding the number of days hospitalized, morbidity, mortality, and complications [10, 13, 19, 20].

The rarity of pyogenic liver abscess, its association with high morbidity, long hospital stay, and high mortality, as well as the great diversity of symptoms described in the literature, demonstrate a lack of consensus and, therefore, the need for better studies. Currently, questions regarding the appropriate initial antibiotic approach, the appropriate surgical procedure for each case, and the length of treatment have not been addressed. The absence of a prospective national study with a good level of evidence is a strong argument for the conduction of studies to identify factors that may interfere with the care and outcome of these patients.

3. Patients and Methods

All patients included in the study were treated at the Grajaú General Hospital - São Paulo/SP for pyogenic liver abscess. The patients were treated in the General Surgery and Emergency Room Trauma sectors. A total of 25 patients were included in the study from April 2015 to June 2017.

The diagnosis of liver abscess was made based on clinical, laboratory and imaging data (ultrasound and/or tomography). Clinical characteristics, presence of medical history, signs, symptoms, results of laboratory tests, characteristics of imaging examinations, interventions, complications, and evolution were recorded in a standardized form.

The presence of fever was defined as temperature greater than 37.5 °C, recorded within the first 24 h of presentation. All other vital signs were defined by the first set of observations after the presentation. Tachycardia was defined as a heart rate greater than or equal to 100 beats per minute and hypotension as a systolic blood pressure less than 90 mmHg. For the blood test results, the admission exam was used for analysis. Reference values for labo-

ratory tests were defined by reference values provided by the local laboratory.

The size of the abscess was defined as the largest diameter found, and in the case of multiple abscesses, it was defined as the largest diameter of the largest abscess.

Patients with suspected pyogenic abscess underwent a broad spectrum of empirical antibiotic therapy. According to a protocol instituted by CCIH, based on local bacterial flora, quinolone (ciprofloxacin) and nitro imidazole (metronidazole) were used. The antibiotics were administered for four to six weeks.

The patients were separated into two groups based on the outcome. The survival group comprised of patients who were discharged. The death group comprised of patients who died. Patients who had undergone surgery were excluded from the study.

Statistical analyses were performed using Epi Info 7 software. Numerical data were presented as mean ± standard deviation or median with an interquartile range, when appropriate, and categorical data were presented as a percentage. The comparison between two groups of numerical data was done using either the unpaired t-test or Mann-Whitney test, when appropriate. Categorical data were compared using the chi-square test and Fisher's exact test (if more than 20% of the expected frequencies were less than 5). A p<0.05 was considered to be significant. For variables with statistically significant associations, a Receiver Operating Characteristic curve (ROC curve) was plotted to identify their cutoff points, which was the cross of the highest sensitivity and specificity value.

The data were collected after approval of the project by the ethics and research committee with registration number 58601216.1.0000.5447.

4. Results

In our study cohort, there was a slight predominance of the male sex (56%). The mean age was 57.3 years and the peak incidence was around 57-years old. Patients were hospitalized for an average

Table 1: Association between demographic characteristics, history of the disease, and death

	Death	Discharge	p
Age	55.4 (16.56)	57.68 (16.24)	0.78
Gender (M-F)	(1-4)	(13-6)	0.07
History (days)	7 (7-13)	9.5 (1-15)	0.83
Evolution	38 (15.5-60)	23 (18-33)	0.28

of 28 days. Both variables were not statistically significant.

Over half of the patients had a history of cholelithiasis, 28% had a history of hepatopathy, and 20% had a history of alcoholism. In addition to dysentery and Crohn's disease.

The mean duration of symptoms before medical attention was sought for 25 days. The most common symptoms at entry were abdominal pain (84%), fever (56%), inappetence (36%), vomiting

(28%), and weight loss (24%). The differences, however, may be

Table 2: Association between clinical signs, symptoms, and death

Clinical signs	Death	Discharge	p
Fever	2	12	0.37
Abdominal pain	5	17	0.49
Jaundice	2	9	0.62

due to chance.

Most patients presented changes in the markers of inflammation (leukocytes and C-reactive protein). About one-third of the patients had elevated urea and creatinine serum levels. Almost half of the patients had hepatic enzyme changes and hyperbilirubin-

Table 3: Association between serum markers and death

Laboratory	Death	Discharge	p
Leukocytes	14.45 (11.4-18.3)	18.6 (13-24.2)	0.49
Hemoglobin	8.8 (8.4-9.1)	10 (9.2-10.2)	0.11
Platelets	441 (189-460)	309 (202-392)	0.51
PCR	96.3 (49.5-275.7)	180 (80-262.7)	0.6
Urea	20 (12-42)	42 (18.5-79)	0.23
Creatinine	0.75 (0.6-2.15)	1.1 (0.8-1.7)	0.39
Albumin	1.4 (1.1-3)	2.82 (1.7-3.9)	0.005
TGO	14 (5-22)	91.5 (25.5-254)	0.12
TGP	12 (6-25)	89.5 (16.5-228)	0.06
Alkaline Phosphatase	236 (136-404)	228 (211-249)	0.7
GGT	394.4 (137-1121)	113.5 (90-137)	0.22
Bilirubin	5.1 (0.3-28.45)	1.48 (97-3.42)	0.48
INR	1.48 (1.45-1.68)	1.44 (1.2-1.72)	0.69

emia, while 90% had canalicular enzyme changes and 75% enlarged INR.

The mean levels of serum albumin in the survival and death groups were 2.8 g/dl and 1.4 g/dl, respectively. Hypoalbuminemia was significantly associated with death. Patients with albumin levels less than or equal to 1.2 g/dl had an 11-fold increased risk of death (RR=11 CI 95% 2.9-4.2 p=0.0059).

Binary logistic regression was performed using all variables with a level of significance less than 0.20. This was to determine if these variables were predictors of death, as shown in Table 4. The

Table 4: Multivariate analysis of risk factors for death

Variables	Multivariate analysis	p
	OR (IC 95%)	
Albumin	1.37 (0.085-22.24)	0.03
Jaundice	1.2(0.17-9.01)	0.84
Hemoglobin	0.87(0.62-1.21)	0.41
TGO	0.96(0.91-1.02)	0.2
TGP	0.99(0.98-1.01)	0.48
Gender	0.13 (0.01-1.44)	0.09

model containing albumin was significant [$X^2(1)=11.102$; $p=0.03$, R^2 Negelkerke=0.567. OR: 0.09; 95% CI (0.009-0.825)].

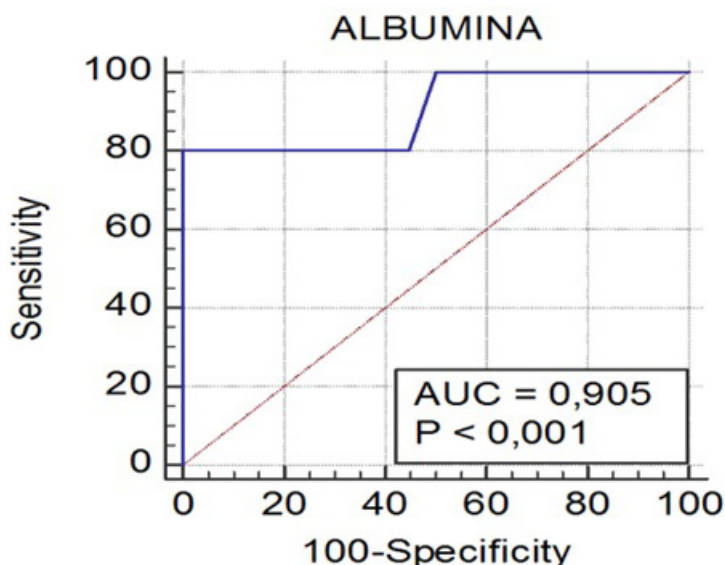


Figure 1: Albumin ROC curve

During the analysis of the ROC curve, we used a cutoff value of 1.2 g/dl with 80% sensitivity and 100% specificity for death. The area below the curve (AUC) was 0.905 (95% CI 0.720 - 0.985).

All patients underwent ultrasonography and tomography. Fifty percent had multiple abscesses. The mean maximum diameter was 12.54 cm. The right hepatic lobe was affected in 90% of patients,

Table 5: Topographical association of size of abscesses with death

	Death	Discharge	p
Diameter	8.9 (4-9.6)	9.8 (7.8-12.7)	0.19
Diameter > 5 cm (%)	2 (9.52)	19 (90.48)	0.13
Right liver lobe (%)	3(16.5)	14 (82.35)	0.52
Left hepatic lobe (%)	2 (25)	6 (75)	0.52

and segments VI, VII, and VIII were affected in 75% of patients. However, one cannot rule out the possibility that these differences were due to chance.

Table 6: Association between culture result and death

Microbiology	Death	Discharge	p
Positive culture (%)	2 (16.67)	10 (83.33)	0.54

The culture was positive in 52% of the patients. The most prevalent isolated microorganism was Escherichia coli (24%), followed by Enterobacter (8%).

Initially, all patients underwent broad-spectrum intravenous antibiotic therapy and ultrasound-guided percutaneous drainage. One patient had a pneumothorax as a complication. No patient underwent isolated clinical treatment or surgery. Five (20%) patients died.

5. Discussion

The mean age of the patients included in the study was 57.3 years, clinicofsurgery.com

with a peak incidence around 57 years and a slight predominance of males (56%). In the study by Kuo et al (2013) [17], which involved 431 patients (males: 61%), they reported a mean age of 56.9 ± 15.0 years (range: 19 to 89 years old). Sohn et al (2016) [19] reported male predominance and a mean age of 64 years, which is slightly higher than the mean age of our patients. A cross-sectional study performed in Taiwan involving 134 patients reported a difference in gender (male: female, 3:1). However, the mean age was 59.4 years, similar to the mean age of patients in our study [21].

The main etiology found in our study was biliary, followed by cryptogenic and portal. The most commonly isolated microorganism was Escherichia coli. Cerwenka et al (2010) [22] reported that in Asia cryptogenic causes of pyogenic liver abscess were mostly associated with K. pneumonia, while in Europe, biliary causes of pyogenic liver abscess were mostly associated with Staphylococcus, Streptococcus, and E. coli. A similar result was reported by Chen (2014) [21] in their cross-sectional study, which involved 134 individuals. In the study by Rismiller (2017) [15], cryptogenic causes predominated. However, the most predominant microorganism was E. coli.

The most frequent history was cholelithiasis, hepatopathy, alcoholism, dysentery, Crohn's disease, and appendectomy. In a retrospective study by Liao et al (2016) [4], they reported that the most frequent history associated with pyogenic liver abscess included alcoholism, biliary disease, chronic renal disease, chronic liver disease, and diabetes mellitus.

Kuo et al (2013) [17] reported that most of the patients with pyogenic liver abscess had diabetes mellitus (44%), followed by those who had biliary diseases (35%). Our findings were different from those of the aforementioned study. However, in studies involving Asian patients, pyogenic liver abscess syndrome caused by Klebsiella Pneumoniae is more common among diabetic patients [5].

In our study, patients were hospitalized for a mean duration of 28 days. The mean time that elapsed before patients sought medical attention was 25 days. Similar results (21.2 days of hospital stay) were reported in a study involving Taiwanese patients [17]. A few studies reported lower mean durations (14.26 and 17.51 days) [19, 21].

Abdominal pain, fever, in appetite, vomiting, and weight loss were the most observed symptoms among patients in our study. Liao et al (2016) [4], in a retrospective study involving 1,062,629 individuals, investigated whether appendectomy increased the chance of hepatic abscess and found that abdominal pain and fever were the most common symptoms. They also found a positive association between appendectomy and pyogenic hepatic abscess with an HR of 1.77 (95% CI 1.59, 1.97). Pang et al (2011) [8], in a retrospective study involving 63 patients that lasted for 10 years, found that fever, tachycardia, and abdominal pain were the most common symptoms. In this study, surgery was reserved for cases

involving drainage failure.

Although about one in three patients had changes in the laboratory test results, only hypoalbuminemia was statistically associated with death. An albumin level less than 1.2 mg/dl was statistically associated with mortality (RR=11 CI 95% 2.9-4.2). Czerwonko et al (2016) [11], when studying predictive factors for recurrence and mortality in the first episode, observed that bilirubin > 5 [OR 60.11 95% CI (4,49-804.68); p=0.02] and bilateral involvement [OR 9.95 95% CI (1.61-62.1); p=0.014] are associated with mortality. Other factors associated with mortality in the literature were the presence of malignancy, multiple abscesses, anaerobic infection, hyperbilirubinemia, increased creatinine level, MEDS score [17], thrombocytopenia, and anemia [19].

Yang et al (2008) [23] associated thrombocytopenia, increased alkaline phosphatase, gas formation in the abscess, APACHE III score > 40, use of cefazolin (instead of prolonged spectrum cephalosporin), and delayed drainage with mortality. Their findings were different from our findings.

Half of the patients evaluated in our study had multiple abscesses. In the literature, single abscesses are prevalent. The sizes of the abscesses found in our study (mean: 12.54 cm) were also larger than those found by Chen et al [21] and Sohn et al [19]. The topography of the abscesses in the right hepatic lobe was affected in 90% of the patients. This finding is consistent with those of previous studies [17, 21].

Fifty-two percent of the patients evaluated in our work had positive cultures. *Escherichia coli* was the most common microorganism. In the literature, *K. pneumoniae* is the most common microorganism (mean: 70%) in patients with pyogenic liver abscess [17, 19, 21]. However, negative cultures, according to Yang et al [23], may be associated with low levels of bacteremia.

The combination of antibiotic therapy and puncture with drainage yields better outcomes, in terms of morbidity and mortality, compared to antibiotic therapy and puncture or antibiotic therapy and open surgery. Meddings et al (2010) [9], in a population-based study (n=17, 787), found that patients who underwent percutaneous drainage (OR 0.45 0.39-0.42) had lower mortality compared to those who underwent open surgery (OR 0.87 0.68-1.1). Liu et al (2016) [24], in a Chinese retrospective study involving 105 individuals, observed that mortality decreases by 0.9% with early diagnosis, antibiotic therapy, and drainage. In a systematic review with meta-analysis of five randomized controlled trials that compared puncture and drainage, Yu et al (2004) [2] concluded that the success rate of drainage was higher than that of puncture [RR: 0.81, 95% CI, (0.66-0.99); p= 0.04].

Five (20%) patients in our study died. Our results are similar to those reported in the literature [17], although studies involving larger cohorts reported better results in terms of mortality (4.5% [22] and 6.9% [19]). Hypoalbuminemia was significantly associat-

ed with mortality, a result similar to that found in the literature [8, 12, 17, 19]. Other mortality risk factors described in the literature in patients with pyogenic liver abscess include the male gender, malignancy, jaundice, organ failure, abscess rupture, endophthalmitis, diabetes mellitus, and presence of gas [21].

6. Conclusion

In this study, which involved 25 patients with pyogenic liver abscess treated using ultrasound-guided puncture and drainage in

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