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Spontaneous bacterial peritonitis and soft tissue healing after tooth extraction in liver cirrhosis patients

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Objective. The objective of this study was to identify the association between tooth extraction and occurrence of spontaneous bacterial peritonitis (SBP) and to assess delayed soft tissue healing of extraction sockets in patients with cirrhosis.

Study Design. One hundred nineteen participants awaiting liver transplantation who required tooth extraction were included. Seven days before the surgery, the patients underwent panoramic radiography and laboratory examinations. Soft tissue healing was evaluated 7 days after the tooth extraction and medical records were checked after 21 days for development of SBP. The relationship between predictive factors and outcomes was assessed by using multiple binomial logistic regression.

Results. One hundred ninety-five teeth were extracted, resulting in 146 alveolar wounds, in which the majority (47%) consisted of alveolar sockets of multirooted teeth. One participant was diagnosed with SBP (*Escherichia coli* [*E. coli*]) and another diagnosed with bacterascites (*Streptococcus viridans* [*S. viridans*] group), occurring 11 and 6 days after tooth extraction. Poor soft tissue healing was observed in 20 (13.7%) patients, which was correlated to 2 risk factors, that is, jaundice (P = .007, adjusted odds ratio [OR] = 4.91, 95% confidence interval [CI] = 1.56-15.47) and moderate neutropenia (P = .048, adjusted OR = 13.99, 95% CI = 1.02-192.07).

Conclusions. No association was found between tooth extraction and SBP in patients with cirrhosis. The delayed soft tissue healing was related to jaundice (hyperbilirubinemia) and moderate neutropenia. (Oral Surg Oral Med Oral Pathol Oral Radiol 2024;000:1−11)

Liver dysfunction leads to impairment of the hepatic reticuloendothelial system, reduced number and compromised function of neutrophils, monocytes, lymphocytes (B, T, and NK), exacerbation of pro-inflammatory response, and deficiency of the complement system.[1] Such a change in the immune response is termed as cirrhosis-associated immune dysfunction (CAID) and the patients presenting with acute-or-chronic liver failure (ACLF) are those with the highest level of systemic inflammation and severe immunodeficiency.[1] As a result, the incidence of bacterial infections is 4 to 5 times higher in these patients than in the general population, which increases their mortality rate by 3.75 times in a short period.[2]

Spontaneous bacterial peritonitis (SBP) is an infectious complication affecting approximately 30% of the cirrhotic individuals with ascites, which results in high mortality rate as well (i.e., 40%).[3,4]

Although the pathophysiology of the SBP is not fully understood, it is thought that it may occur by the translocation of intestinal bacteria through transmural migration, as cirrhotic individuals have slow intestinal transit, increased bacterial colonization, and permeability of the intestinal wall, including an association with immunosuppression. However, there is a hypothesis that microorganisms from infectious processes far from the gastrointestinal tract, such as pneumonia, dermatitis, urinary tract infections, and odontogenic infections, might infect the ascitic fluid through hematogenous route.[3,5]

The possibility that oral pathogens can translocate from their sites and cause peritonitis has been discussed since 1985,[6] in which several species of the *Streptococ-*

Statement of Clinical Relevance

Dental treatment of patients with liver cirrhosis can present various concerns for complications. This study demonstrates that dental extractions are not associated with development of postoperative spontaneous bacterial peritonitis, and that delayed healing is associated with hyperbilirubinemia and neutropenia.

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cus viridans group were isolated and identified (i.e., *S. oralis, S. mitis, S. salivarius, S. gordonii, S. sanguis*, and *S. vestibularis*).[7–9]

In fact, the possibility of oral cavity infections reaching distant organs has been described in the literature, as is the case of infective endocarditis (IE).[10] In individuals who are on the transplant waiting list, it is necessary to eliminate these foci efficiently and rapidly and, in many cases, tooth extraction is the chosen treatment.[11] However, complicating factors are usually observed in patients with chronic liver disease, such as malnutrition, poor oral hygiene, impaired immune response, and hemorrhagic diathesis, which can impair the process of tissue healing,[11,12] increasing the risk of post-surgery infection[13] and consequently favoring the development of SBP.

The aim of the present study was to identify the association between tooth extraction and occurrence of SBP, as well as to assess delayed soft tissue healing of extraction sockets, in patients with cirrhosis on the transplant waiting list.

MATERIALS AND METHODS

Ethical consideration

This study was approved by the local research ethics committee according to protocol number 52421321.7.0000.0068 and conducted based on recommendations set by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). All the participants signed an informed consent form.

Study design and cases

A cross-sectional study of patients with cirrhosis on the liver transplant waiting list was carried from May 2018 to September 2023.

Sample calculation

Sample calculation was performed by using the Epi Info software, version 7.2.0.1, and based on data reported by Santoiemma et al.,[14] who assessed the prevalence of SBP in patients with cirrhosis (14.5%). As there are approximately 150 individuals on the liver transplant waiting list at the Clinics Hospital of the University of São Paulo School of Medicine (HCFMUSP), an ideal sample of 84 participants was determined for the present study considering the sample size of 80%, significance level of 5%, and study design effect of 1.0.

Eligibility criteria

Individuals with cirrhosis, older than 18 years, enrolled on the transplant waiting list and with indication of extraction of erupted teeth were included from this study.

Patients who underwent liver transplantation within 21 days following tooth extraction were excluded from this study. Because the timeframe for the onset of SBP after tooth extraction is unknown, this period was established by using IE as a reference. According to Martin et al. (2007),[15] symptoms of bacteremia associated with IE can appear up to 21 days after a dental procedure.

Clinical examination

In the medical history, the following data were obtained: gender, age, co-morbidities, continuous-use medications, etiology of cirrhosis, current model of end-stage liver disease with sodium (MELD-Na), signs of cirrhosis decompensation, prior episode of SBP, and harmful habits. Criteria defined by Garcia-Tsao et al.[16] were used to determine the signs of cirrhosis decompensation (i.e., the presence of hepatic encephalopathy, recurrent variceal hemorrhage, refractory ascites, and hepatorenal syndrome).

Intraoral physical examination was aimed to identify the presence of infectious foci, defined as teeth exhibiting: (I) extensive carious lesions extending beyond the alveolar bone; (II) irreversible pulpitis; (III) pulp necrosis; (IV) dentoalveolar abscess; (V) fistula; and (VI) periodontal disease with periodontal attachment loss greater than 4 mm, furcation involvement, or grade II or III tooth mobility.[17,18]

Along with the intraoral examination, the following indexes were applied: decayed, missing, and filled teeth (DMFT),[19] simplified oral hygiene index (SOHI),[20] and gingival index (GI).[21]

Some parameters were dichotomized for statistical analysis. GI was graded into “no gingivitis” (grades 0 and 1) and “marked gingivitis” (grades 2 and 3), as well as SOHI into “satisfactory” (grades < 3) and “unsatisfactory” (grades ≥ 3).

Information on the reason for tooth extraction and type of alveolar wound (i.e., alveolar socket of single-rooted teeth, multirooted teeth, and 2 or more contiguous teeth) was also collected.

Complementary examinations

Seven days before the tooth extraction, the patients underwent digital panoramic radiography and laboratory examinations, such as complete blood count, platelet count, international normalized ratio (INR), activated partial thromboplastin time (aPTT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. The degree of severity of the hematological alterations of interest for the present study was ranked according to definitions set by the Chinese Society of Clinical Oncology[22] (i.e., anemia), Morales et al.[23] (i.e., lymphocytopenia), Fillmore et al.[24] (i.e., neutropenia), Temel et al.[25] (i.e.,

thrombocytopenia), Wang et al.[26] (i.e., INR), and Gondal and Aronsohn[27] and Br and Sarin[28] (i.e., hyperbilirubinemia). Bilirubin below 3 mg/dL was defined as severe hyperbilirubinemia.

Procedures

Teeth extraction was performed according to procedures described by Buhatem Medeiros[29] et al. Due to increased risk of bleeding, all patients had additional hemostatic measures applied to include tranexamic acid tablets mixed in with saline solution applied to extraction sockets,[30] which did not create any bias related to the healing process.

Soft tissue healing assessment

After 7 days from the procedure, the soft tissue healing of extraction sockets was assessed according to the healing index of Alissa et al.[31] as follows: very poor (1), poor (2), good (3), very good (4), and excellent (5). Grades of soft tissue healing ≤ 2 were characterized as a delayed repair and grades > 2 as adequate repair.

Development of SBP

The patients were followed up for 21 days after tooth extraction in order to verify the occurrence of SBP. This time interval was defined according to the period usually necessary for a complete epithelization of the alveolar socket[32] and for occurrence of IE,[15] which is the most studied model of distant infection associated with bacteremia resulting from dental procedures.[33]

The diagnosis of SBP was performed by testing the ascitic fluid collected after abdominal paracentesis, in which polymorphonuclear cells (PMNs) count ($\geq$ 250/mm^3) was used and microorganisms were identified by means of culture and bacterioscopy (i.e., Gram staining). Positive bacterial culture and PMN count $<$ 250/mm^3 characterize bacterascites episodes.[3,4]

Statistical analysis

The association between predictive factors and outcomes of interest (i.e., delayed soft tissue healing of extraction sockets and development of SBP) was investigated by means of binary multivariate logistic regression and selection of relevant variables by using univariate analysis ($P < .20$), with results expressed by odds ratio (OR) at confidence interval of 95% (95% CI) and significance level of 5%. All statistical analyses were performed by using the Jamovi software, version 2.3.24.0 (The Jamovi Project, Sidney, Australia).

RESULTS

A total of 119 patients were included in the study, the majority being male patients (76%) with mean age of 56.09 years old and mean value of MELD-Na score of 19.37. The major etiologies of cirrhosis were alcohol-associated liver disease (32%), hepatitis C virus (28%), and non-alcoholic steatohepatitis (11%). Decompensated cirrhosis was observed in 97 (82%) patients, with 13 (11%) presenting previous episodes of SBP and 1 (1%) presenting a previous episode of bacterascites. The main co-morbidities identified were cardiovascular diseases (34%), kidney diseases (13%), and diabetes mellitus (29%).

Regarding the continuous-use medications, 53 (49%) patients were using proton pump inhibitors and 23 (19%) were on antibiotic prophylaxis with neomycin, norfloxacin, levofloxacin, ciprofloxacin, and sulfamethoxazole associated with trimethoprim for the prevention of hepatic encephalopathy (HE) and SBP.

Analysis of laboratory tests showed that 74% of the patients presented with anemia, 82% with lymphocytopenia and/or neutropenia, 101 (85%) with thrombocytopenia, 61.34% with elevated INR, and 72% with hyperbilirubinemia (Table I).

The mean DMFT was 18.66. The results of SOHI demonstrated that 52% of the patients had unsatisfactory oral hygiene and 24% had marked gingivitis.

A total of 195 teeth were extracted (mean = 1.64 teeth/patient, median = 1, range = 5), resulting in 146 alveolar wounds, of which most part (47%) consisted of alveolar sockets of multirooted teeth. Seven days after the tooth extraction, 20 (13.7%) patients had a poor soft tissue healing of the extraction sockets (Table II).

Development of SBP

Only 2 (1.7%) patients presented with infection of ascitic fluid, 1 was diagnosed with SBP (patient #1) and another with bacterascites (patient #2).

Patient #1 was a 61-year-old man who had alcohol-associated liver disease, presenting an MELD-Na score of 24 and decompensated cirrhosis (i.e., ascites and jaundice), but without previous episodes of SBP. He did not make use of antibiotic prophylaxis, nor presented with anemia, lymphocytopenia, neutropenia, or thrombocytopenia. Elevated levels of INR (1.67), aPTT (34.80 seconds), AST (55 U/L), and bilirubin (4.41 mg/dL) were observed. The 4 lower incisors were extracted due to advanced periodontal disease. The alveolar wound was satisfactorily healed after 7 days. On the 11th day after tooth extraction, the patient reported diffuse abdominal pain. On the 18th day, the patient was hospitalized reporting fever, chills, and hypotension. The ascitic fluid showed presence of PMN cells (6680/mm^3) and positive culture for *Escherichia coli* (*E. coli*). Once diagnosed with SBP, the patient was treated for 15 days with intravenous ceftriaxone 1 g every 12 hours and metronidazole 1 plastic bag of 100 mL (500 mg of metronidazole) for

Table I. Baseline preoperative laboratory examinations of patients undergoing tooth extractions (n = 119)

		No. of patients (%)
Anemia	No	31 (26)
	Yes	88 (74)
Anemia grading		
Mild - grade 1 (Hb between 10 and 13.40 g/dL)		68 (57)
Moderate - grade 2 (Hb between 8 and 9.99 g/dL)		18 (15)
Severe - grade 3 (Hb between 6.50 and 7.99 g/dL)		2 (2)
Lymphocytopenia	No	23 (19)
	Yes	96 (81)
Lymphocytopenia grading		
Grade 1 (lymphocytes between 0.80 and 1.49 $\times$ 10^3/mm^3)		54 (45)
Grade 2 (lymphocytes between 0.50 and 0.79 $\times$ 10^3/mm^3)		22 (18)
Grade 3 (lymphocytes between 0.20 and 0.49 $\times$ 10^3/mm^3)		17 (14)
Grade 4 (lymphocytes below 0.20 $\times$ 10^3/mm^3)		3 (3)
Neutropenia	No	66 (55)
	Yes	53 (45)
Neutropenia grading		
Mild (neutrophils between 1 and 2.49 $\times$ 10^3/mm^3)		49 (41)
Moderate (neutrophils between 0.50 and 0.99 $\times$ 10^3/mm^3)		3 (3)
Severe (neutrophils between 0 and 0.49 $\times$ 10^3/mm^3)		1 (1)
Thrombocytopenia	No	18 (15)
	Yes	101 (85)
Platelets $<$ 50 $\times$ 10^3/mm^3 (Biolato et al., 2023)		29 (24)
Platelets $<$ 30 $\times$ 10^3/mm^3 (Biolato et al., 2023)		6 (5)
Prolonged INR ($>$ 1.20)	No	46 (39)
	Yes	73 (61)
INR $>$ 1.20 $<$ 1.50		56 (50)
INR from 1.50 to 2		12 (10)
INR $>$ 2		5 (4)
Prolonged aPTT ($>$ 33.20 seconds)	No	60 (50)
	Yes	59 (50)
High AST ($>$ 37 U/L)	No	43 (36)
	Yes	76 (64)
High ALT ($>$ 41 U/L)	No	86 (72)
	Yes	33 (28)
Hyperbilirubinemia ($>$ 1 mg/dL)	No	33 (28)
	Yes	86 (72)
Bilirubin above 3 mg/dL		30 (25)
Bilirubin above 5 mg/dL		15 (12)

Hb, hemoglobin; PT, prothrombin time; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Values of reference: erythrocytes = 4.50 to 6.50 million/mm^3; hemoglobin = 13.50 to 17.50 g/dL; lymphocytes = 1.50 to 3.50 $\times$ 103/mm^3; neutrophils = 2.50 to 7.50 $\times$ 103/mm^3; platelets = 150 to 400 $\times$ 103/mm^3; INR = 0.95 to 1.20; aPTT = 25 to 33.2 seconds; AST = below 37 U/L; ALT = below 41 U/L; bilirubin = 0.20 to 1 mg/dL.

intravenous infusion every 8 hours. The patient remained in critical condition, developing hyponatremia and hyperphosphatemia and progressing to death on the 33rd day after tooth extraction.

Patient #2 was a 54-year-old woman who had alcohol-associated liver disease, presenting an MELD-Na score of 18, decompensated cirrhosis (i.e., ascites and HE), and previous episode of SBP 2 months prior to tooth extraction. She made use of antibiotic prophylaxis for SBP with norfloxacin. Pre-operative laboratory investigations showed moderate anemia (Hb = 8.60 g/dL), grade 1 lymphocytopenia (960/mm^3), mild thrombocytopenia (97,000/mm^3), and slightly elevated levels of INR (1.32), serum AST (46 U/L), and total serum bilirubin (1.12 ml/dL). The patient underwent an upper incisor extraction due to periapical lesion, developing satisfactory healing after 7 days. On the 6th day after tooth extraction, the patient was hospitalized presenting cognitive dysfunction (i.e., HE). Paracentesis performed on the 10th day showed white blood cells count of 70 cells/mm^3 (2% of PMN cells) and positive bacterial culture for *Streptococcus viridans* (*S. viridans*) group, thus leading to a diagnosis of bacterascites. The medical staff opted to maintain the use of norfloxacin 400 mg tablets, once a day, as long as the patient remains with ascites or until transplantation. After 4 days, no microorganism

Table II. Characterization of the extracted teeth: reason for tooth extraction, type of surgical wound and type of soft tissue healing of the extraction sockets (n = 160)

	No. of patients (%)	*Total*
Reason of tooth extraction*		160
Periapical lesion	60 (37.5)	
Periodontal disease	49 (30.6)	
Presence of extensive caries	29 (18.1)	
Residual root	21 (13.1)	
Root fracture	1 (0.62)	
Type of alveolar wound		146
Alveolus of single-rooted tooth	41 (28.0)	
Alveolus of multi-rooted tooth	68 (46.6)	
Alveolus of 2 or more contiguous teeth	37 (25.3)	
Criteria for soft tissue healing assessment		146
Poor	20 (13.7)	
Good	15 (10.2)	
Very good	42 (28.8)	
Excellent	69 (47.2)	

*Some patients presented more than one reason for tooth extraction.

was isolated and no white blood cells were counted in the ascitic fluid.

Soft tissue healing assessment

The association between the outcome of interest and clinically relevant variables were analyzed to determine the potential risk factors involved (Table III). Severe hyperbilirubinemia (total serum bilirubin values above 3 mg/dL) were defined for this model, as clinical features of an increase in this metabolite (i.e., jaundice)[27] and impaired wound healing[34] can be observed from this level.

Univariate logistic regression was used to assess the association between risk factors and delayed soft tissue healing (Table IV).

Variables with $P < .20$, that is, jaundice, HE, upper gastrointestinal bleeding (UGIB), diabetes mellitus, cardiovascular disease, anemia, neutropenia, severe hyperbilirubinemia, and SOHI were selected for multivariate analysis.

Two variables were excluded from the final model because they had a high degree of multicollinearity with a variance inflation factor above 5, namely: cardiovascular disease because it mostly represented patients diagnosed with metabolic syndrome, diabetes mellitus and systemic arterial hypertension; and severe hyperbilirubinemia because the patients represented with jaundice. The other variables were maintained because they adjusted the model for the necessary presumptions, with the coefficient of determination (pseudo R^2 of Nagelkerke) equal to 0.30.

Multiple logistic regression analysis showed that jaundice (adjusted OR = 4.91, 95% CI = 1.56-15.47) and neutropenia (adjusted OR = 13.99, 95% CI = 1.02-192.07) were moderate risk factors for a delayed soft tissue healing (Table V).

DISCUSSION

The oral and dental features of patients with cirrhosis on the liver transplant waiting list have been studied by several authors.[35–44] Most of the studies evaluated the risk of post-extraction bleeding.[45–48] Some authors have also assessed the occurrence of local and distant infections[11] and the need for antibiotic therapy.[12] So far, however, no study has been performed to verify alveolar socket healing and occurrence of SBP.

The population selected for the present study had demographic and clinical characteristics very similar to those described in previous studies.[11,12,45–47] The clinical aspects of the patients studied reveal a high prevalence of severe cirrhosis complications, indicating decompensation and hematological abnormalities. On the other hand, in most patients, these hematological abnormalities were mild and did not require medical intervention. In fact, some of these abnormalities are expected in the clinical course of cirrhosis, particularly due to hypersplenic sequestration[49] and decreased thrombopoietin production.[45]

Elevated INR and severe hyperbilirubinemia, which are directly related to liver failure, are notable because they can indicate a condition called ACLF, particularly when bilirubin levels exceed 5 mg/dL[27] and INR levels exceed 1.50.[28] ACLF is a sudden clinical worsening of liver function characterized by acute decompensation leading to a functional deterioration of other organs and high 28-day mortality rate.[27] Patients with ACLF are more likely to develop SBP more easily and with greater severity.[50]

In the present study, only 2 patients with decompensated cirrhosis had infection of the ascitic fluid. Bacterascites is considered a variation of SBP, but is recognized as a distinct clinical entity.[51,52] SBP and bacterascites share similarities in terms of etiology, morbidity, mortality, and treatment,[4] and considering that they occurred 11 and 6 days after tooth extraction, causality might be a possibility. However, the identified microorganisms (i.e., *E. coli* and *S. viridans* group) are part of the normal gastrointestinal tract microflora and may infect the ascitic fluid through intestinal bacterial translocation.[53,54] Specifically regarding the *S. viridans* group, it is important to remember that due to its low virulence, it is associated with few infections in humans. However, when isolated from ascitic fluid, *S. viridans* cannot be dismissed as a contaminant because it can be found in approximately two-thirds of the patients with SBP and symptomatic bacterascites. On

Table III. Clinical characteristics of the patients according to type of soft tissue healing of the extraction sockets (n = 146)

	Adequate soft tissue healing (n = 126)	*Delayed soft tissue healing (n = 20)*
Characteristics of cirrhosis		
History of SBP	14 (11.1%)	3 (15%)
Jaundice	23 (18.3%)	12 (60%)
Ascites	82 (65.1%)	15 (75%)
Esophageal varices	119 (94.4%)	20 (100%)
Hepatic encephalopathy	62 (49.2%)	13 (65%)
Upper gastrointestinal bleeding	35 (27.8%)	9 (45%)
Hepatorenal syndrome	11 (8.7%)	0 (0%)
Mean MELD-Na	19.50	20.40
Co-morbidities		
Diabetes mellitus	34 (27%)	9 (45%)
Cardiovascular disease	45 (35.7%)	4 (20%)
Nephropathy	19 (15.1%)	4 (20%)
Hematological parameters		
Anemia		
Normal - grade 0 (Hb above 13.40 g/dL)	30 (23.8%)	8 (40%)
Mild - grade 1 (Hb from 10 to 13.40 g/dL)	72 (57.1%)	9 (45%)
Moderate - grade 2 (Hb from 8 to 9.99 g/dL)	23 (18.3%)	2 (10%)
Severe − grade 3 (Hb from 6.5 to 7.99 g/dL)	1 (0.8%)	1 (5%)
Lymphocytopenia		
Grade 0 (lymphocytes above $1.50 \times 10^3/mm^3$)	26 (20.6%)	4 (20%)
Grade 1 (lymphocytes between 0.80 and $1.49 \times 10^3/mm^3$)	64 (50.8%)	8 (40%)
Grade 2 (lymphocytes between 0.50 and $0.79 \times 10^3/mm^3$)	18 (14.3%)	5 (25%)
Grade 3 (lymphocytes between 0.20 and $0.49 \times 10^3/mm^3$)	15 (11.9%)	3 (15%)
Grade 4 (lymphocytes below $0.20 \times 10^3/mm^3$)	3 (2.4%)	0 (0%)
Neutropenia		
Normal - grade 0 (neutrophils above $2.50 \times 10^3/mm^3$)	76 (60.3%)	8 (40%)
Mild - grade 1 (neutrophils from 1 to $2.49 \times 10^3/mm^3$)	47 (37.3%)	9 (45%)
Moderate - grade 2 (neutrophils from 0.50 to $0.99 \times 10^3/mm^3$)	2 (1.6%)	3 (15%)
Severe - grade 3 (neutrophils below $0.49 \times 10^3/mm^3$)	1 (0.8%)	0 (0%)
Thrombocytopenia		
Platelets below $50 \times 10^3/mm^3$	27 (21.4%)	4 (20%)
Hyperbilirubinemia		
Bilirubin above 1 mg/dL	86 (68.3%)	16 (80%)
Bilirubin above 3 mg/dL	23 (18.3%)	12 (60%)
Medications in use		
Antibiotic prophylaxis for HE and SBP	28 (22.2%)	6 (30%)
Harmful habits		
Smoking	17 (13.5%)	2 (10%)
Oral conditions		
With periodontal disease	43 (34.1%)	6 (30%)
Without periodontal disease	83 (65.9%)	14 (70%)
SOHI - Satisfactory (scores < 3)	58 (46%)	6 (30%)
SOHI - Unsatisfactory (scores ≥ 3)	68 (54%)	14 (70%)
GI − With gingivitis (scores 0-1)	89 (70.6%)	14 (70%)
GI - Without gingivitis (scores 2-3)	37 (29.4%)	6 (30%)
Type of alveolar wound		
Alveolus of single-rooted tooth	37 (29.4%)	4 (20%)
Alveolus of multi-rooted tooth	56 (44.4%)	12 (60%)
Alveolus of 2 or more contiguous teeth	33 (26.2%)	4 (20%)

SBP, spontaneous bacterial peritonitis; *HE*, hepatic encephalopathy; *Hb*, hemoglobin; *SOHI*, simplified oral hygiene index; *GI*, gingival index; *MELD-Na*, model of end- stage liver disease with sodium.

the other hand, in cases of asymptomatic bacterascites, this may only represent a transient colonization of ascitic fluid by the bacteria.[7] Once the clinical outcomes had been very different for the 2 patients, it was important to assess the clinical context. The first patient who developed SBP did not use antibiotic prophylaxis for SBP and had a 76% probability of 3-month mortality (MELD-Na score = 24), with severe hyperbilirubinemia and prolonged INR indicating presence of ACLF. The second patient was on antibiotic prophylaxis, had a 25% probability of 3-month mortality (MELD-Na score = 18), and laboratory investigations

Table IV. Univariate binomial logistic regression of delayed soft tissue healing of extraction sockets (n = 20) in relation to risk factor

	Unadjusted OR	*95% CI*	*P value*
Characteristics of cirrhosis			
History of SBP			
No	1.0	-	.473
Yes	1.65	0.42-6.45	
Jaundice			
No	1.0	-	< .001
Yes	6.72	6.72-18.30	
Ascites			
No	1.0	-	.386
Yes	1.61	0.55-4.72	
Esophageal varices			
No	1.0	-	.992
Yes	7.15/+6	0.00-infinite	
Hepatic encephalopathy			
No	1.0	-	.194
Yes	1.92	0.72-5.12	
Upper gastrointestinal bleeding			
No	1.0	-	.125
Yes	2.13	0.81-5.57	
Hepatorenal syndrome			
No	1.0	-	.989
Yes	1.35/-7	0.00-infinite	
MELD-Na	1.03	0.95-1.11	.543
Co-morbidities			
Diabetes mellitus			
No	1.0	-	.106
Yes	2.21	0.84-5.81	
Cardiovascular disease			
No	1.0	-	.175
Yes	0.45	0.14-1.43	
Nephropathy			
No	1.0	-	.576
Yes	1.41	0.2-4.67	
Hematological parameters			
Anemia			
Normal - grade 0 (Hb above 13.40 g/dL)	1.0	-	
Mild - grade 1 (Hb from 10 to 13.40 g/dL)	0.47	0.16-1.33	.155
Moderate - grade 2 (Hb from 8 to 9.99 g/dL)	0.37	0.06-1.68	.181
Severe - grade 3 (Hb from 6.5 to 7.99 g/dL)	3.75	0.21-66.76	.368
Lymphocytopenia			
Grade 0 (lymphocytes above $1.50 \times 10^3/mm^3$)	1.0	-	
Grade 1 (lymphocytes from 0.80 to $1.49 \times 10^3/mm^3$)	0.81	0.23-2.93	.751
Grade 2 (lymphocytes from 0.50 to $0.79 \times 10^3/mm^3$)	1.81	0.43-7.66	.423
Grade 3 (lymphocytes from 0.20 to $0.49 \times 10^3/mm^3$)	1.30	0.26-6.61	.752
Grade 4 (lymphocytes below $0.20 \times 10^3/mm^3$)	4.15/-7	0.00-infinite	.992
Neutropenia	1.0	-	
Normal - grade 0 (neutrophils above $2.50 \times 10^3/mm^3$)	1.82	0.66-5.04	.250
Mild - grade 1 (neutrophils from 1 to $2.49 \times 10^3/mm^3$)			
Moderate - grade 2 (neutrophils from 0.50 to $0.99 \times 10^3/mm^3$)	14.25	2.06-98.36	.007
Severe - grade 3 (neutrophils below $0.49 \times 10^3/mm^3$)	1.65/-6	0.00-infinite	.993
Thrombocytopenia			
Above $50 \times 10^3/mm^3$	1.0	-	
Below $5.1 \times 10^3/mm^3$	0.92	0.28-2.97	.885
Hyperbilirubinemia			
Above 1 mg/dL	1.0	-	
Below 0.90 mg/dL	0.92	0.58-5.92	.293
Hyperbilirubinemia		-	
Above 2.90 mg/dL	1.0	6.72-18.30	< .001
Below 3 mg/dL	6.72		
Medications in use			
Antibiotic prophylaxis for HE and SBP			
No	1.0	-	
Yes	1.57	0.55-4.48	.397
Harmful habits			
Smoking			
No	1.0	-	
Yes	0.71	0.15-3.35	.668
Gingivitis (GI)			
Without gingivitis	1.0	-	
With gingivitis	1.03	0.37-2.89	.954
Periodontal disease			
Without periodontal disease	1.0	-	
With periodontal disease	0.75	0.27-2.07	.573
Simplified oral hygiene index			.185
Unsatisfactory (scores < 3)	1.0	-	
Satisfactory (scores ≥ 3)	1.99	0.72-5.51	
Type of alveolar wound			
Alveolus of single-rooted tooth	1.0	-	
Alveolus of multi-rooted tooth	1.98	0.59-6.62	.266
Alveolus of 2 or more contiguous teeth	1.12	0.26-4.84	.78

SBP, spontaneous bacterial peritonitis; *HE*, hepatic encephalopathy; *Hb*, hemoglobin; *MELD-Na*, model of end- stage liver disease with sodium; *SOHI*, Simplified oral hygiene index; *GI*, gingival index; *OR*, odds ratio; *95% CI*, 95% confidence interval.

showed the absence of neutropenia, hyperbilirubinemia, or signs of ACFL. As the worst outcome (death) occurred in the patient who had severe periodontal

Table V. Multiple binomial logistic regression analysis of poor soft tissue healing of the extraction sockets in relation to risk factors selected for inclusion in the final model (n = 20)

	Adjusted OR	*95% CI*	*P value*
Jaundice			
No	1.0	-	.007
Yes	4.91	1.56-15.47	
Upper gastrointestinal bleeding			
No	1.0	-	.112
Yes	2.66	0.79-8.93	
Hepatic encephalopathy			
No	1.0	-	.732
Yes	1.24	0.36-4.27	
Anemia			
Normal - grade 0 (Hb above 13.40 g/dL)	1.0	-	.766
Mild - grade 1 (Hb from 10 to 13.40 g/dL)	0.82	0.22-3.07	.171
Moderate - grade 2 (Hb from 8 to 9.99 g/dL)	0.26	0.04-1.78	.295
Severe - grade 3 (Hb from 6.50 to 7.99 g/dL)	6.8	0.21-178.59	
Neutropenia			
Normal − grade 0 (neutrophils above 2.50 × 10^3/mm^3)	1.0	-	.563
Mild - grade 1 (neutrophils from 1 to 2.49 × 10^3/mm^3)	1.39	0.45-4.26	.048
Moderate - grade 2 (neutrophils from 0.50 to 0.99 × 10^3/mm^3)	13.99	1.02-192.07	.994
Severe - grade 3 (neutrophils below 0.49 × 10^3/mm^3)	1.38/-5	0.00-infinite	
Diabetes mellitus			
No	1.0	-	.755
Yes	1.22	0.35-4.19	
Simplified oral hygiene index			
Unsatisfactory	1.0	-	.553
Satisfactory	1.46	0.42-5.08	

OR, odds ratio; *95% CI*, 95% confidence interval.

disease (acute infection), it is important for the dentist to be prepared to perform a comprehensive evaluation of the patient. This can help identify patients who are most likely to develop severe conditions, preventing the professional from linking these outcomes solely to the oral condition.

The small number of patients with infection of ascitic fluid does not allow a proper assessment of the association between tooth extraction and development of SBP.

On the other hand, the delayed soft tissue healing was observed in a greater number of cases of patients with cirrhosis (around 13%). As it accounts for a minority of cases, this setting indicates that cirrhosis itself is not a risk factor for a delayed soft tissue healing. Once again, it is important to highlight the role of very unfavorable clinical conditions for the general health of the patient. Two variables were found to be statistically associated with delayed healing, namely, moderate neutropenia and jaundice.

Neutropenia has been recognized in several situations as an important marker of risk of infection in many diseases.[55] But more severe and frequent infections tend to occur when the absolute neutrophil count falls below 500 cells/mm^3 for more than 10 days.[56]

In the present study, severe neutropenia was not associated with a delayed soft tissue healing, probably because only 1 patient had this condition. In contrast, moderate neutropenia (i.e., 500 to 999 cells/mm^3) was observed in 5 patients, with the majority presenting poor tissue healing. It is important to highlight that, although neutropenia has been considered as one of the risk factors for a delayed wound healing in the model used, its statistical significance was marginal ($P <$ .048). The small number of patients with neutropenia and its statistically marginal significance mean that further studies should be performed in order to confirm such a finding.

Jaundice (serum bilirubin levels above 3 mg/dL) was observed in 24% of the patients, of whom 60% presented with poor soft tissue healing ($P = .007$). In this case, it seems that the data are more robust than those in the previous situation. The biological plausibility behind this result also seems to be more grounded. Expressive elevation of the serum bilirubin levels points to acuteness of liver cirrhosis and it is associated with a greater severity of the disease, which can also indicate the presence of ACLF. This, in turn, might also be correlated to a higher risk of CAID.[27,50]

Hyperbilirubinemia could also impair the wound healing through the reduced cell multiplication capacity in fibroblasts and endothelial cells,[57] decreased synthesis of types I and III collagens,[34] impairment in the action of prolyl hydroxylases (enzyme essential for incorporation of proline into the collagen and its consequent synthesis),[58] exacerbated TNF-alpha, IL-2, IL-6,

and oxidized low-density-lipoprotein accumulation in alveolar wounds, possibly extending the inflammatory phase of the tissue healing and promoting the activation of intracellular proteases and oxidative stress through the release of oxygen free radicals.[57]

In any case, we believe that further studies should be carried out in order to confirm the findings of the present study.

Although sample calculation was performed, we believe that our sample should be larger, meaning that this was a drawback of the present study.

CONCLUSION

In this cohort of patients with cirrhosis requiring teeth extractions, there was minimal incidence of SBP. Incidences of delayed soft tissue healing were associated with jaundice and moderate neutropenia. These findings indicate that SBP as a result of dental extractions in patients with liver disease is of lesser concern.

DECLARATION OF COMPETING INTEREST

The authors have no conflicts of interest to declare.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Gustavo Souza Galvão: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Juliana Bertoldi Franco:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maria Paula Siqueira de Melo Peres:** Writing – original draft, Methodology, Conceptualization. **Gabriela Bănacu Melo:** Writing – original draft, Methodology, Conceptualization. **Jefferson R. Tenório:** Writing – original draft, Methodology, Conceptualization. **Janaina B. Medina:** Writing – original draft, Methodology, Conceptualization. **Camila de Barros Gallo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Karem L. Ortega:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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STATEMENT OF INSTITUTIONAL REVIEW BOARD APPROVAL

This study was approved by the local research ethics committee according to protocol number CAAE 52421321.7.0000.0068.

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