

# Factors associated with thrombocytopenia in severe leptospirosis (Weil's disease)

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**OBJECTIVE:** This study was conducted to investigate factors associated with thrombocytopenia in a large cohort of patients with leptospirosis in an endemic area.

**METHODS:** This retrospective study included 374 consecutive patients with leptospirosis who were admitted to tertiary hospitals in Fortaleza, Brazil. All patients had a diagnosis of severe leptospirosis (Weil's disease). Acute kidney injury was defined according to the RIFLE criteria. Thrombocytopenia was defined as a platelet count <100,000/mm<sup>3</sup>.

**RESULTS:** A total of 374 patients were included, with a mean age of 36.1 ± 15.5 years, and 83.4% were male. Thrombocytopenia was present at the time of hospital admission in 200 cases (53.5%), and it developed during the hospital stay in 150 cases (40.3%). The patients with thrombocytopenia had higher frequencies of dehydration (53% vs. 35.3%, *p*=0.001), epistaxis (5.7% vs. 0.8%, *p*=0.033), hematemesis (13% vs. 4.6%, *p*=0.006), myalgia (91.5% vs. 84.5%, *p*=0.038), hematuria (54.8% vs. 37.6%, *p*=0.011), metabolic acidosis (18% vs. 9.2%, *p*=0.016) and hypoalbuminemia (17.8% vs. 7.5%, *p*=0.005). The independent risk factors associated with thrombocytopenia during the hospital stay were lengthy disease (OR: 1.2, *p*=0.001) and acute kidney injury (OR: 6.6, *p*=0.004). Mortality was not associated with thrombocytopenia at admission (12.5% vs. 12.6%, *p*=1.000) or during the hospital stay (12.6% vs. 11.3%, *p*=0.748).

**CONCLUSIONS:** Thrombocytopenia is a frequent complication in leptospirosis, and this condition was present in more than half of patients at the time of hospital admission. Lengthy disease and acute kidney injury are risk factors for thrombocytopenia. There was no significant association between thrombocytopenia and mortality.

**KEYWORDS:** Leptospirosis; Thrombocytopenia; Platelets; Acute Kidney Injury; Mortality.

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## INTRODUCTION

Leptospirosis is an infectious disease caused by the pathogenic spirochete *Leptospira interrogans*, which has a worldwide distribution (1-3). There is a large range of clinical manifestations in leptospirosis, and infected people can present with asymptomatic illness, self-limited systemic infection or severe and potentially fatal disease (1-5).

Symptomatic disease begins suddenly, with headache, fever, malaise, myalgia, conjunctival suffusion and transient rash (1). The severe form is characterized by jaundice, acute kidney injury (AKI) and hemorrhage, known as Weil's disease, and is mainly caused by the serovars *Icterohaemorrhagiae*, *Copenhageni* and *Lai*. There are also severe forms of the disease that occur without jaundice or renal failure, such as hemorrhagic pneumonitis (1,2).

Hematological manifestations are common in leptospirosis and are usually manifested as thrombocytopenia (6-8). Thrombocytopenia is often observed in connection with hemorrhagic pneumopathy and is a significant predictor of the development of acute respiratory failure, which is currently the main cause of death in this disease (6,7,9).

The aim of this study was to investigate the factors associated with thrombocytopenia in a large cohort of patients with severe leptospirosis in an endemic area.

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## PATIENTS AND METHODS

We examined a retrospective cohort of 374 consecutive patients admitted to tertiary hospitals in Fortaleza, northeastern Brazil. All patients had a diagnosis of leptospirosis confirmed by a microscopic agglutination test (MAT), with titers equal to or higher than 1:800. Serological testing was performed at least 7 days after admission, and patients with titers lower than 1:800 were excluded. Patients with negative serologies or other comorbidities, such as hypertension, diabetes and autoimmune diseases, were not included. The protocol of this study was approved by the ethics committees of both institutions.

Demographic characteristics, such as age, gender, the time between the onset of the initial symptoms and hospital admission and the length of hospital stay, were recorded. The clinical investigation included a record of all clinical signs and symptoms presented by each patient at hospital admission and during the hospital stay. Hemorrhagic phenomena, such as gastrointestinal hemorrhage, hemoptysis or blood-tinged sputum, hematuria and epistaxis, were recorded at admission and during hospitalization. Laboratory data collected during the hospital stay included an assessment of serum urea, creatinine, sodium, potassium, bilirubin, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), creatine kinase and lactate dehydrogenase levels; the total blood count; and the prothrombin time (PT).

Respiratory failure was defined as a need for mechanical ventilation. AKI was defined according to the RIFLE criteria (10). Thrombocytopenia was defined as a platelet count  $<100,000/\text{mm}^3$ , and severe thrombocytopenia was defined as a count  $<50,000/\text{mm}^3$ . The occurrence of metabolic acidosis was diagnosed at a pH  $<7.35$  and  $\text{HCO}_3^- <20$  mEq/L. Oliguria was defined as a urine volume  $<400$  mL/day after 24 h of effective hydration. Hypotension was defined as a mean arterial blood pressure (MAP)  $<60$  mmHg, and therapy with vasoactive drugs was initiated when the MAP remained  $<60$  mmHg. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission were also analyzed. Dialysis was indicated in those patients who remained oliguric after effective hydration, in those cases in which uremia was associated with hemorrhagic or severe respiratory failure and in those patients with hyperkalemia or metabolic acidosis that was refractory to clinical treatment. The use of antibiotic therapy in the later phase of leptospirosis is still controversial, but penicillin G was administered to several patients, at the discretion of the assistant, at a dosage of 8 million units/day in the first 7-10 days after the patients were admitted.

## RESULTS

The patients were divided into two groups according to their platelet levels (with thrombocytopenia vs. without thrombocytopenia). A comparison of clinical and laboratory characteristics was performed to investigate the differences between the two groups. All data were analyzed with the program SPSS ver. 10.0 (Chicago, IL, USA). The comparison of parameters was performed with a Student's *t*-test and Fisher's exact test. The Mann-Whitney *U*-test was used for the parameters with a non-normal distribution. A logistic regression model was used for the quantitative variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A

multivariate logistic regression was performed to analyze the possible risk factors associated with thrombocytopenia and death. The factors included in the multivariate model were those that showed significance ( $p < 0.05$ ) in the univariate analysis.

The patients' mean age was  $36.1 \pm 15.5$  years, and 312 (83.4%) were male. The time between the onset of symptoms and hospital admission was  $4.4 \pm 3.8$  days for patients with thrombocytopenia and  $5.9 \pm 4.8$  days for patients without thrombocytopenia ( $p = 0.001$ ). The average length of hospital stay was  $10.3 \pm 6.9$  days for patients with thrombocytopenia and  $9.3 \pm 6.2$  days for patients without thrombocytopenia ( $p = 0.190$ ).

The main signs and symptoms presented at admission were fever (96%), myalgia (88.2%), jaundice (78.9%), calf pain (74.2%), headache (72.2%), vomiting (68.2%), asthenia (55.8%), anorexia (50.7%), chills (49.2%), coluria (47.8%), hematuria (47.1%), abdominal pain (46.6%), dehydration (44.8%), diarrhea (41.2%), hepatomegaly (28.9%) and oliguria (21.2%).

Thrombocytopenia was present at hospital admission in 200 cases (53.5%), and 150 (40.3%) patients developed this condition during their hospital stay. Severe thrombocytopenia ( $<50,000/\text{mm}^3$ ) was found in 107 patients (29.3%). Patients with thrombocytopenia at admission had higher frequencies of dehydration (53% vs. 35.3%,  $p = 0.001$ ), epistaxis (5.7% vs. 0.8%,  $p = 0.033$ ), hematemesis (13% vs. 4.6%,  $p = 0.006$ ), myalgia (91.5% vs. 84.5%,  $p = 0.038$ ), hematuria (54.8% vs. 37.6%,  $p = 0.011$ ), metabolic acidosis (18% vs. 9.2%,  $p = 0.016$ ) and hypoalbuminemia (17.8% vs. 7.5%,  $p = 0.005$ ). The frequency of oliguria was not higher in patients with thrombocytopenia (23.1% vs. 19.0%,  $p = 0.374$ ). Penicillin use had a tendency to be more frequent in patients without thrombocytopenia at admission (42.6% vs. 32%,  $p = 0.07$ ). These data are summarized in Table 1.

Regarding the laboratory data, patients with thrombocytopenia at admission presented with hypokalemia ( $3.2 \pm 0.6$  vs.  $3.5 \pm 0.6$  mEq/L,  $p < 0.0001$ ), hypoalbuminemia ( $2.9 \pm 0.6$  vs.  $3.2 \pm 0.6$  g/dL,  $p = 0.067$ ), low hemoglobin levels ( $10.7 \pm 2.0$  vs.  $11.2 \pm 2.1$  g/dL,  $p = 0.021$ ) and high total bilirubin levels ( $12.3 \pm 11.0$  vs.  $7.5 \pm 9.1$  mg/dL,  $p = 0.001$ ) significantly more often than did patients with normal platelet levels (Table 2).

The multivariate analysis showed that hypokalemia (OR: 0.7,  $p = 0.02$ ), dehydration (OR: 2.1,  $p = 0.006$ ) and metabolic acidosis (OR: 2.3,  $p = 0.03$ ) were independent risk factors for thrombocytopenia at admission (Table 3). Lengthy disease (OR: 1.2,  $p = 0.001$ ) and the presence of AKI (OR: 6.6,  $p = 0.004$ ) were independent risk factors for thrombocytopenia during the hospital stay (Table 4).

Death occurred in 22 patients (12.5%) without thrombocytopenia and 25 patients (12.6%) with thrombocytopenia at admission. Mortality was not associated with the presence of thrombocytopenia at hospital admission (12.5% vs. 12.6%,  $p = 1.000$ ) or during the hospital stay (12.6% vs. 11.3%,  $p = 0.748$ ).

Low DBP (OR: 0.9,  $p = 0.02$ ), advanced age (OR: 1.0,  $p = 0.001$ ) and oliguria (OR: 5.4,  $p = 0.006$ ) were independent risk factors for death (Table 5).

## DISCUSSION

Hemorrhagic complications contribute to mortality in leptospirosis. Recent studies have shown a direct association



**Table 1** - Comparison of the demographics and clinical manifestations of leptospirosis patients with and without thrombocytopenia at admission.

	Thrombocytopenia	No thrombocytopenia	p-value
	(N = 200)	(N = 174)	
Age	36.4 ± 16.3 (9-82 years)	36.7 ± 15.0 (9-84 years)	0.624
Gender			
Male	168 (84.0%)	144 (82.8%)	0.781
Female	32 (16.0%)	30 (17.2%)	
Length of hospital stay	10.3 ± 6.9	9.3 ± 6.2	0.190
Signs and symptoms			
Crackles	33 (16.5%)	28 (16.1%)	1.000
Coluria	56 (45.5%)	64 (50%)	0.528
Dehydration	106 (53.0%)	61 (35.3%)	0.001
Diarrhea	79 (39.5%)	75 (43.1%)	0.528
Dyspnea	23 (11.7%)	16 (9.2%)	0.499
Epistaxis	7 (5.7%)	1 (0.8%)	0.033
Fever	194 (97.0%)	165 (94.8%)	0.304
Headache	147 (73.5%)	123 (70.7%)	0.565
Hematemesis	26 (13.0%)	8 (4.6%)	0.006
Hematuria	69 (54.8%)	38 (37.6%)	0.011
Hepatomegaly	65 (32.5%)	43 (24.7%)	0.110
Hypotension	13 (10.6%)	14 (10.9%)	1.000
Jaundice	164 (82.0%)	131 (75.3%)	0.128
Myalgia	183 (91.5%)	147 (84.5%)	0.038
Tachypnea	49 (24.5%)	32 (18.4%)	0.167
Vomiting	144 (72.0%)	111 (63.8%)	0.096
Anorexia	80 (53.7%)	65 (47.4%)	0.344
Asthenia	66 (53.7%)	74 (57.8%)	0.527
Oliguria	33 (19.0%)	46 (23.1%)	0.374
Calf pain	106 (78.5%)	78 (69.0%)	0.109
Abdominal pain	57 (46.3%)	60 (46.9%)	1.000
Metabolic acidosis	36 (18.0%)	16 (9.2%)	0.016
Hypoalbuminemia	35 (17.8%)	13 (7.5%)	0.005
AKI	167(83.9%)	134 (77.5%)	0.145
Need for dialysis	73 (36.5%)	51 (29.3%)	0.153
Penicillin G use	49 (32.0%)	52 (42.6%)	0.079
Death	25 (12.5%)	22 (12.6%)	1.000

The data are shown as the mean ±SD and range (minimum-maximum) or as numbers with percentages in parentheses. Significance,  $p < 0.05$ . Student's t-test and Fisher's exact test.

between thrombocytopenia and the occurrence of bleeding manifestations (7). In the present study, we evaluated a large number of patients with leptospirosis-associated thrombocytopenia.

Most studies on leptospirosis have focused on AKI and pulmonary complications. After several outbreaks of pulmonary hemorrhage in association with leptospirosis, attention has shifted to understanding the mechanism of bleeding diathesis in these patients. Initially, thrombocytopenia in leptospirosis was thought to be mild and rare. However, certain reviews have reported a higher prevalence (12,13). There are several hypotheses about the possible mechanism of this complication: 1) the presence of disseminated intravascular coagulation (12); 2) the participation of cytotoxins (13); and 3) the direct complication of vasculitis, triggered by the *Leptospira* (14). Further studies are needed to establish the actual pathophysiology of this complication.

The independent risk factors for thrombocytopenia were dehydration, metabolic acidosis and low potassium levels at admission. Low serum potassium was a protective factor against thrombocytopenia, i.e., hyperkalemia is associated with thrombocytopenia. This phenomenon may be due to oliguric AKI and metabolic acidosis because there is no cause-effect relationship between serum potassium and the

occurrence of thrombocytopenia. Dehydration and metabolic acidosis are systemic manifestations of leptospirosis that are associated with thrombocytopenia. Hemorrhagic manifestations were more frequent in patients in the thrombocytopenia group. Thrombocytopenia was also associated with poor laboratory findings, such as hypoalbuminemia, lower hemoglobin levels and higher AST and total bilirubin levels. However, this condition did not translate into a worse prognosis. In contrast to our study, Spichler et al. (14) reported that elevated creatinine ( $>3$  mg/dL; OR: 4.2) and total bilirubin ( $>6$  mg/dL; OR: 2.2) levels were associated with a lethal outcome. Turgut et al. (15) showed that there was an inverse correlation between ALT/AST levels and thrombocyte counts ( $r = -0.360$ ;  $p = 0.016$ ) and that, consistent with our data, there was no statistically significant correlation between bilirubin levels and thrombocytopenia. Certain researchers have reported that a high serum potassium level at hospital admission was an independent risk factor for mortality (16,17).

In our study, the overall mortality rate was 12.5%, which is comparable with the rate in other studies (17-23). This large range may be due to the variable severity of the clinical picture, which is partly due to differences between *Leptospira* strains and the absence of standards for the



**Table 2 - Comparison of laboratory data between leptospirosis patients with and without thrombocytopenia at admission.**

	Thrombocytopenia	No thrombocytopenia	p-value
	(N = 200)	(N = 174)	
Urea at admission (mg/dL)	134.9 ± 88.7 (19-578)	126.1 ± 94.7 (15-449)	0.169
Creatinine at admission (mg/dL)	4.1 ± 2.8 (0.3-15.2)	4.2 ± 3.0 (0.2-13.0)	0.953
Sodium at admission (mEq/L)	132.5 ± 6.5 (114-158)	133.8 ± 5.7 (118-149)	0.164
Potassium at admission(mEq/L)	3.8 ± 0.9 (2.0-8.2)	4.0 ± 1.0 (2.4-8.6)	0.098
Potassium min (mEq/L)	3.2 ± 0.6 (0.5-5.3)	3.5 ± 0.6 (2.0 - 4.8)	<0.0001
Creatine kinase at admission (UI/L)	976 ± 3032.1 (3-19692.0)	252.2 ± 511 (12.0-1978)	0.092
Total bilirubin at admission (g/dL)	12.3 ± 11.0 (0.6-49.5)	7.5 ± 9.1 (0.1-32.7)	0.001
Albumin at admission (g/dL)	2.9 ± 0.6 (1.7-4.4)	3.2 ± 0.6 (2.0-4.3)	0.067
AST at admission (UI/L)	123 ± 106 (23-604)	149.8 ± 420 (9-4215)	0.078
ALT at admission (UI/L)	77.2 ± 90.6 (11-956)	81.1 ± 85.1 (8-734)	0.871
Hb at admission (g/dL)	10.7 ± 2.0 (4.4-15.7)	11.2 ± 2.1 (6.8-11.2)	0.021
HCO <sub>3</sub> <sup>-</sup> at admission (mEq/L)	18.8 ± 4.7 (8.9-18.2)	19.5 ± 5.3 (9.0-20.2)	0.375
TAP (%)	74.6 ± 22.8 (17.3-100)	74.7 ± 18.9 (35.5-100)	0.284

The data are shown as the mean ± SD and range (minimum-maximum) or as numbers with percentages in parentheses. Significance, p<0.05. Student's t-test and Fisher's exact test.

diagnostic criteria. In the present study, mortality was not associated with the presence of thrombocytopenia. Other studies also showed that mortality was not associated with the presence of thrombocytopenia (16,17), but Spichler et al. (14) showed that it was associated with lethal outcomes, being an independent risk factor for mortality in leptospirosis.

Hemorrhagic manifestations are characteristic of Weil's disease and are potentially fatal. Patients can develop important hemodynamic abnormalities secondary to hypovolemia, which is caused by dehydration and the direct effects of *Leptospira* toxins that damage the vascular endothelium and increase permeability (6). Hemorrhage is recognized as the most important manifestation of human leptospirosis and is being increasingly reported around the world (24). The main hemorrhagic manifestations reported in this study were epistaxis, hemoptysis, hematemesis and hematuria, all of which were more frequent in the patients in the thrombocytopenia group.

AKI in leptospirosis is reported in 40-60% of severe cases (25) and is usually non-oliguric (26,27). However, the

present study found a higher prevalence (80.5%) according to the RIFLE criteria. There were no differences between the two groups regarding renal function or the need for dialysis.

This analysis found that lengthy disease and the presence of AKI were associated with thrombocytopenia during the hospital stay. Regarding antibiotic therapy in leptospirosis, in the present study, penicillin G was administered to 152 (41.6%) of the patients, and there was a tendency toward more frequent use of penicillin among those patients with thrombocytopenia.

Thrombocytopenia in leptospirosis is known to be associated with a worse prognosis (9). Tantitanawat and Tanjatham (28) found that platelet counts <100,000/mm<sup>3</sup> were an independent risk factor for death in leptospirosis. However, the present study found similar mortality rates in patients with and without thrombocytopenia. A low DBP, advanced age and oliguria were independent risk factors for death.

In summary, leptospirosis is a globally relevant disease with a potentially fatal outcome. Hemorrhagic complications are common and are reported as main causes of morbidity and mortality in this disease. Although thrombocytopenia

**Table 3 - Independent risk factors for thrombocytopenia in patients with leptospirosis at admission.**

	OR	95% CI	p-value
Low potassium level	0.7	0.5-0.9	0.02
Dehydration	2.1	1.2-3.5	0.006
Metabolic acidosis	2.3	1.0-5.4	0.03

OR: odds ratio; 95% CI: 95% confidence interval. Multivariate analysis; chi-square test. Significance, p<0.05.

**Table 4 - Independent risk factors for thrombocytopenia in patients with leptospirosis during their hospital stay.**

	OR	95% CI	p-value
Lengthy disease	1.2	1.0-1.4	0.001
AKI	6.6	1.8-23	0.004

OR: odds ratio; 95% CI: 95% confidence interval. Multivariate analysis; chi-square test. Significance, p<0.05.



**Table 5 - Independent risk factors for death in patients with leptospirosis.**

	OR	95% CI	p-value
Diastolic blood pressure	0.9	0.8-0.9	0.02
Advanced age	1.0	1.0-1.1	0.001
Oliguria	5.4	1.6-18	0.006

OR: odds ratio; 95% CI: 95% confidence interval. Multivariate analysis; chi-square test. Significance,  $p < 0.05$ .

was associated with mortality in previous studies, in the present study, this complication was not a risk factor for death. Advanced age and oliguria were independent risk factors for death.

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### AUTHOR CONTRIBUTIONS

All authors designed and performed the study. Daher EF, Mota JA and Silva Junior GB wrote the article. All authors have read and approved the final version of the manuscript.

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