Leptospirosis in the elderly: the role of age as a predictor of poor outcomes in hospitalized patients

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ABSTRACT

Background: The aim of this study was to investigate factors associated with poor outcomes among elderly hospitalized patients with leptospirosis.

Methods: This is a retrospective cohort study with leptospirosis patients admitted to three tertiary hospitals in Fortaleza, Brazil, from January 1985 to July 2017. Patients were divided into two groups: elderly (age ≥ 60 years) and young (age < 60 years). A comparison of demographical, clinical and laboratory data, treatment and outcomes was executed in order to investigate differences between groups.

Results: A total of 507 hospitalized patients were included, with mean age 38 ± 15 years. Elderly group presented lower incidence of myalgia, vomiting, and dyspnea, as well as, higher medium systolic blood pressure. Elderly also manifested higher frequency of AKI (85.9 vs. 74.7%, $p = 0.05$), hemodialysis requirement (54.7 vs. 37.0%, $p = 0.007$) and death (32.8 vs. 12.2%, $p < 0.001$). In multivariate analysis, age ≥ 60 years was a predictor of hemodialysis requirement ($p = 0.008$, OR = 2.049, 95% CI = 1.207–3.477) and death ($p < 0.001$, OR = 3.520, 95% CI = 1.940–6.386).

Conclusion: Leptospirosis in the elderly is associated with less hemodynamic impairment and higher frequency of AKI. Advanced age was also a predictor of poor outcomes, such as hemodialysis requirement and death, mostly due to kidney involvement.

KEYWORDS

Leptospirosis; elderly; acute kidney injury; prognosis; mortality

Introduction

Leptospirosis is a widespread bacterial disease caused by pathogenic spirochetes from the genus *Leptospira*. This global zoonosis is transmitted by exposure of human skin to water contaminated with infected mammals' urine, predominantly rodents [1]. This condition is characterized by the occurrence of outbreaks during rainy seasons, and it has been historically linked to poverty, lack of basic sanitary conditions, presence of vectors and flooding as well as touristic activities in the wildlife, military expeditions and agriculture [2]. Its clinical presentation may vary from a mild non-specific influenza-like infection to a severe disease with life-threatening complications, such as acute kidney injury (AKI), jaundice, pulmonary hemorrhage (Weil's disease), myocarditis, and liver failure [3].

According to previous studies, age plays an important role in leptospirosis prognosis and outcomes. It has been reported that leptospirosis epidemiology changed significantly in the last decades. The incidence has augmented while mortality has decreased, mostly due to early diagnosis and treatment [2,4]. However, when analyzing the elderly population, mortality rates have

not decreased in this period, and they are still remarkably higher than that of younger patients [5].

Additionally, the impact of this disease in the elderly is a result of their susceptibility and frequent comorbidities. A large epidemiologic study demonstrated that the hospitalization rate due to leptospirosis in the USA was higher for elderly patients when compared to younger individuals, especially those < 20 years [6]. Another study evidenced that leptospirosis in elderly patients is associated with severe manifestations, including cardiac and renal involvement, poor prognosis and a higher risk of death [7].

The aim of this study was to compare epidemiological, clinical and laboratory data of elderly and young patients with leptospirosis as well as to determine the role of age as a predictor of poor outcomes in this population.

Materials and methods

Study population

The present study included all adult patients with a confirmed diagnosis of leptospirosis consecutively

admitted to the São José Infectious Diseases Hospital, Walter Cantídio University Hospital and Fortaleza General Hospital, in Fortaleza, northeast of Brazil, from January 1985 to July 2017.

Study design

This is a retrospective cohort study. All data were collected from medical records of patients with confirmed leptospirosis admitted to those three hospitals, which are the main tertiary hospitals in our region. Therefore, the sample is representative of severe leptospirosis cases in our region. Patients were divided into two groups according to age on admission: elderly (age ≥ 60 years) and young (age < 60 years). A comparison of demographical, clinical and laboratory data, as well as treatments and outcomes during hospital stay was performed in order to investigate differences between these two groups. A multivariate analysis was also carried out in order to identify the role of age as a predictor of poor outcomes in leptospirosis.

Case definition

Leptospirosis cases were defined as the presence of positive serology through microscopic agglutination test (MAT) higher than 1:800, associated with epidemiological and clinical history compatible with leptospirosis.

Studied parameters

Demographic characteristics such as age, gender, time between initial symptoms and hospital admission as well as the length of hospital stay were recorded. The clinical investigation included a record of all clinical signs and symptoms as well as vital signs (systolic and diastolic blood pressures, temperature, heart and respiratory rate) presented by each patient on hospital admission. An analysis of treatment and outcomes during hospital stay was also carried out, including death, acute kidney injury (AKI) development and dialysis requirement. All types of treatments used by the patients during hospitalization were recorded. Laboratory data on hospital admission included serum urea, creatinine, sodium, potassium, total, direct and indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), serum albumin, hemoglobin, hematocrit, leukocytes count, platelets count and arterial blood gas analysis.

Definitions

AKI was defined according to the 'Kidney Diseases Improving Global Outcomes' (KDIGO) criteria, which is the currently most accepted definition and classification for AKI [8]. The occurrence of metabolic acidosis was

evidenced when pH < 7.35 and serum bicarbonate < 20 mEq/L, and severe metabolic acidosis when pH < 7.10 . Tachypnea was defined as a respiratory rate higher than 25 per minute. Oliguria was defined as urine output < 0.5 ml/kg/day after 24 h of effective hydration. Hypotension was defined as mean arterial blood pressure (MAP) < 60 mmHg. Therapy with vasoactive drugs was initiated when MAP remained lower than 60 mmHg despite the use of endovenous fluids. Azotemia was defined as serum urea > 120 mg/dL, which represents an elevation three times higher than the normal range. Hyponatremia was defined as serum sodium < 135 mEq/L.

Statistical analysis

Statistical analysis was executed using the SPSS program for Windows version 20.0 (IBM, USA), and its results were expressed through tables. Kolmogorov–Smirnov test was used for numeric variables, in order to assess variable distribution. Variables with normal distribution were expressed through mean $\pm$ standard deviation (SD). Variables with non-normal distribution were expressed through median values + range. Patients were divided into two groups: elderly (age ≥ 60 years) and young (age < 60 years). Comparison of categorical variables was executed using Pearson's Chi-square while numerical variables were compared using Student's T-test (for variables with normal distribution) or Mann–Whitney test (for variables with non-normal distribution). P values ≤ 0.05 were considered statistically significant. In order to evaluate the role of age as a predictor of poor outcomes, a logistic regression model was used for categorical variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All outcomes which presented statistical significance ($p \leq 0.05$) in the univariate analysis were included in the logistic regression.

Ethics

This study has followed the international ethical recommendations for research with human beings, based on the 7th version of the Declaration of Helsinki. The protocol of this study was reviewed and approved by the Ethics Committee of São José Infectious Diseases Hospital, Walter Cantídio University Hospital and Fortaleza General Hospital, Fortaleza, Ceará, Brazil.

Results

A total of 507 patients were included in the study, with 82.6% males. Sixty-four patients were included in the elderly group (≥ 60 years) while 443 were included in the young group (< 60 years). Mean age was 66 ± 6 years in the elderly group and 34 ± 12 years in the young group. When comparing demographic data, both groups presented similar time between onset

of symptoms and admission (7.8 ± 4.2 vs. 7.3 ± 4.0 days, $p = 0.515$) and hospitalization time (10 ± 8 vs. 11 ± 7 days, $p = 0.595$), as summarized in [Table 1](#).

Regarding clinical data, elderly group presented a significantly lower prevalence of myalgia (65.6 vs. 81.3%, $p = 0.004$), vomiting (43.8 vs. 59.7%, $p = 0.016$) and dyspnea (17.2 vs. 30.9%, $p = 0.024$) than the young group. On the other hand, there was no difference between groups regarding the prevalence of dehydration (35.9 vs. 35.4%, $p = 0.938$) and oliguria (23.4 vs. 25.7%, $p = 0.692$) on admission. Elderly patients presented significantly higher medium systolic blood pressure (122 ± 26 vs. 111 ± 20 mmHg, $p = 0.001$) than young patients, as evidenced in [Table 2](#).

There was no significant difference between groups regarding treatment ([Table 1](#)). However, elderly group manifested significantly higher incidence of poor outcomes than the young group, including AKI (85.9 vs. 74.7%, $p = 0.05$), hemodialysis requirement (54.7 vs. 37.0%, $p = 0.007$) and death (32.8 vs. 12.2%, $p < 0.001$), as summarized in [Table 1](#). When classifying AKI according to KDIGO criteria, the majority of patients (54.8%) presented severe AKI (stage 3), but there was no difference between groups in AKI severity ('stage 3' – 70.9 vs. 69.3%, $p = 0.883$). Despite its significant levels in univariate analysis, age ≥ 60 years was not a risk factor for AKI development in our cohort.

Regarding laboratory data, elderly group manifested significantly higher levels of leukocytes count (15.4 ± 6.5 vs. $13.6 \pm 10.3 \times 10^3/\text{mm}^3$, $p = 0.003$) and serum urea (176 ± 100 vs. 133 ± 89 mg/dL, $p = 0.002$) as well as lower levels of serum sodium (134.6 ± 7.2 vs. 136.5 ± 14.9 mEq/L, $p = 0.005$) and potassium (3.8 ± 1.0 vs. 4.1 ± 0.9 mEq/L, $p = 0.029$), as presented in [Table 3](#).

According to multivariate analysis, age ≥ 60 years was a predictor of different poor outcomes, including hemodialysis requirement ($p = 0.008$, OR = 2.049, 95%

CI = 1.207–3.477) and death ($p < 0.001$, OR = 3.520, 95%CI = 1.940–6.386), as evidenced in [Table 4](#).

Discussion

Leptospirosis is probably the most important zoonosis in the world, with worldwide distribution and potentially fatal outcomes [9]. Due to its impact and importance, several studies have evaluated its pathophysiology, clinical characteristics and treatment options, but just a few have specifically investigated elderly patients. To our knowledge, this is the first study in our region to evaluate the role of age as a predictor of poor outcomes in leptospirosis.

When analyzing leptospirosis' epidemiology, we can observe that it is endemic in tropical areas due to flooding and lack of basic sanitation in several parts of these countries, especially urban slums [10]. It has been associated with certain professional activities, traditionally executed by young men, such as military expeditions and agriculture [11]. This classical epidemiologic distribution might explain the male predominance among the patients of the present study, both young and old. Due to developments in sanitation and hygiene, especially in developed countries, this tendency of young male preponderance has decreased in the last decade, and leptospirosis is now more associated to recreational activities, tourism and sporting events [10,12,13]. Hormonal differences between sexes may also justify a higher prevalence of leptospirosis among young men. Interactions between female hormones and immune system seem to protect this group from infection, and this effect is more intense in young women during reproductive age than in the elderly [14].

According to past studies, leptospirosis presentation may vary from a mild and non-threatening form

Table 1. Comparison of demographic, clinical data, treatment and outcomes between elderly and young patients with leptospirosis.

	≥60 years (N = 64)	<60 years (N = 443)	p
<i>Demographic data</i>			
Time between symptoms and admission (days)	7.8 ± 4.2	7.3 ± 4.0	0.515
Hospitalization time (days)	10 ± 8	11 ± 7	0.595
Age (years)	66 ± 6	34 ± 12	< 0.001
<i>Gender</i>			
Males	44 (66.8%)	375 (84.7%)	0.002
Females	20 (31.2%)	68 (15.3%)	
<i>Treatment</i>			
Platelets transfusion	10 (15.6%)	54 (12.2%)	0.500
RBC transfusion	10 (15.6%)	52 (11.7%)	0.575
Antibiotics	61 (95.4%)	426 (96.1%)	0.202
Vasoconstrictors	13 (20.3%)	69 (15.5%)	0.449
Diuretics	13 (20.3%)	98 (22.1%)	0.835
<i>Outcomes</i>			
AKI	55 (85.9%)	331 (74.7%)	0.05
Hemodialysis	35 (54.7%)	164 (37.0%)	0.007
Death	21 (32.8%)	54 (12.2%)	< 0.001

RBC – red blood cells; AKI – Acute kidney injury. Chi-squared and Student *t*-tests were used. $P < 0.05$ was considered statistically significant.

Table 2. Comparison of symptoms and signs between elderly and young patients with leptospirosis on admission.

	≥60 years (N = 64)	<60 years (N = 443)	p
Fever	52 (81.2%)	394 (88.9%)	0.077
Myalgia	42 (65.6%)	360 (81.3%)	0.004
Calf pain	29 (45.3%)	210 (47.4%)	0.753
Jaundice	43 (67.2%)	312 (70.4%)	0.597
Dehydration	23 (35.9%)	157 (35.4%)	0.938
Vomiting	28 (43.8%)	264 (59.7%)	0.016
Diarrhea	17 (26.6%)	170 (38.5%)	0.065
Pulmonary crackles	9 (14.3%)	60 (13.5%)	0.910
Dyspnea	11 (17.2%)	137 (30.9%)	0.024
Oliguria	15 (23.4%)	112(25.7%)	0.692
Heart Rate (bpm)	96 ± 15	96 ± 19	0.433
Respiratory rate (/min)	26 ± 8	24 ± 8	0.907
Systolic BP (mmHg)	122 ± 26	111 ± 20	0.001
Diastolic BP (mmHg)	71 ± 15	69 ± 15	0.155
Temperature (°C)	37.4 ± 1.0	37.2 ± 1.6	0.673

BP – blood pressure. Chi-squared and Student t tests were used. P < 0.05 was considered statistically significant.

Table 3. Comparison of laboratory data between elderly and young patients with leptospirosis.

	≥60 years (N = 64)	<60 years (N = 443)	p
Hemoglobin (g/dL)	10.6 ± 2.5	11.1 ± 2.1	0.081
Hematocrit (%)	31.6 ± 7.2	33.0 ± 6.6	0.141
Leukocytes (10 ³ /mm ³)	15.4 ± 6.5	13.6 ± 10.3	0.003
Platelets (10 ³ /mm ³)	103.3 ± 94.6	112.6 ± 107.7	0.432
Urea (mg/dL)	176 ± 100	133 ± 89	0.002
Creatinine (mg/dL)	3.83 ± 2.35	3.81 ± 2.86	0.498
Sodium (mEq/L)	134.6 ± 7.2	136.5 ± 14.9	0.005
Potassium (mEq/L)	3.8 ± 1.0	4.1 ± 0.9	0.029
AST (U/L)	105 (12–422)	149 (9–1832)	0.383
ALT (U/L)	66 (8–734)	75 (12–1770)	0.759
Albumin (g/dL)	3.02 ± 0.55	3.18 ± 0.62	0.239
Total Bilirubin (mg/dL)	11.3 (0.22–33.8)	9.7 (0.13–60.78)	0.463
Direct Bilirubin (mg/dL)	10.1 (0.19–30.0)	9.4 (0.05–46.0)	0.257
Indirect Bilirubin (mg/dL)	3.7 (0.03–16.9)	4.0 (0.02–24.65)	0.852
LDH (U/L)	854 ± 576	777 ± 547	0.655
CPK (U/L)	930 (31–7,515)	942 (3–19,690)	1.000
pH	7.38 ± 0.09	7.36 ± 0.09	0.143
HCO ₃ (mEq/L)	17.9 ± 4.4	19.0 ± 4.8	0.168

AST – aspartate aminotransferase; ALT – alanine aminotransferase; LDH – lactate dehydrogenase; CPK – creatine phosphokinase; HCO₃ – serum bicarbonate. Mann Whitney U and Student t tests were used. P < 0.05 was considered statistically significant. Data were presented as mean ± SD for variables with normal distribution and median (range) for variables with non-normal distribution.

Table 4. Factors associated with age ≥ 60 years in leptospirosis (multivariate analysis).

	OR	95% CI	p
Hemodialysis	2.049	1.207–3.477	0.008
Death	3.520	1.940–6.386	< 0.001

OR – odds ratio; CI – confidence interval. Logistic regression was used. P < 0.05 was considered statistically significant.

to a severe multisystemic disease. It may affect multiple organs and lead to serious consequences, such as renal, hepatic, pulmonary, cardiac, hemodynamic and vascular dysfunction. In its severe form, known as Weil's disease, patients may manifest acute kidney injury (AKI), acute hepatic insufficiency, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), circulatory shock and sepsis [15].

The elderly patients in our cohort also manifested fewer symptoms such as dyspnea, myalgia and vomiting, as well as less clinical evident dehydration and oliguria. Regarding vital signs, the patients aged ≥60 years presented a significantly better clinical and hemodynamic

status on admission than young patients, evidenced by higher systolic blood pressure which can be explained by the arterial stiffness that is happening with aging [16]. Also, physicians in our region tend to admit elderly patients with a potential fatal infectious disease (which is the case of leptospirosis) more frequently than they do with young patients. As a result, elderly leptospirosis patients with milder presentations tend to be admitted to hospitals while young patients are frequently hospitalized only when presenting more severe forms of the disease or complications.

Leptospirosis' pathophysiology includes the release of toxins produced by the spirochetes, direct infiltration of *Leptospira* into the cells as well as systemic inflammation and cytokine production by the host's immune response [17–19]. Some investigators demonstrated that *Leptospira* infection triggers cytokine production by the host's immune system and that higher levels of circulating cytokines, especially IL-10, IL-6 and IL-8, were directly associated with death. These studies evidenced

that patients with severe leptospirosis overproduce these cytokines, in a phenomenon called ‘cytokine storm’, which may be linked to poor prognosis [20,21].

In the present study, elderly patients presented milder clinical presentations on admission, but had a higher incidence of AKI and mortality. Renal involvement is one of the most important and life-threatening complications of leptospirosis and AKI incidence may vary from 40% to 87%. Electrolyte disorders like hypokalemia and hyponatremia are also very common and may lead to severe consequences such as arrhythmias, especially in the elderly population [22,23].

Leptospira species may affect the kidneys in several different ways [15]. It may infiltrate renal tissue and cause mononuclear cell invasion, leading to an inflammatory response. In fact, interstitial nephritis has been observed in kidneys of leptospirosis patients, even when there is no AKI or tubular dysfunction [24]. Additionally, tubular invasion is another important mechanism of leptospirosis renal dysfunction. It mainly affects proximal tubules, leading to reduced reabsorption of sodium (Na) and elevated Na excretion fraction (FENa) [25]. Considering that distal segments are relatively preserved by *Leptospira* sp, Na-K exchange in the collecting duct is increased, leading to hypokalemia in early stages of the disease. Furthermore, studies have shown that collecting ducts present a relative vasopressin resistance and less water reabsorption, which may lead to the characteristic non-oliguric presentation of leptospirosis-associated AKI [26].

On the other hand, hemodynamic alterations also play an important role in leptospirosis pathophysiology. Dehydration, secondary to vomiting, diarrhea and fever, as well as decreased sodium reabsorption, and hemorrhagic phenomena may lead to hypotension and decrease renal blood flow [27]. In these cases, when there is a predominance of hemodynamic factors and poor renal perfusion, renal involvement tends to manifest more frequently as a pre-renal AKI, with oliguria and hyperkalemia [15]. Considering that older patients in the present study manifested less hemodynamic alterations, the higher incidence of AKI in this group is better explained by direct infiltration of *Leptospira* in the kidneys, leading to tubular dysfunction and non-oliguric AKI.

Due to renal involvement, elderly patients also presented higher hemodialysis requirement. Dialysis should be started as early as possible in leptospirosis-associated AKI. Past studies have evidenced the benefits of early initiation of renal replacement therapy (RRT) in leptospirosis, as well as the superiority of some types, such as daily hemodialysis, in reducing mortality [28,29]. However, a recent study with severe leptospirosis patients demonstrated that the mode of dialysis clearance did not affect mortality in this group of patients,

despite reducing the serum levels of certain cytokines [30]. Considering that elderly group presented less oliguria and signs of congestion than the young group, we hypothesize that the higher incidence of dialysis requirement in this group happened due to elevated levels of urea and uremic syndrome.

On the other hand, the association of advanced age and higher mortality is consensual when it comes to leptospirosis patients, like many other diseases. In a review, Taylor et al. demonstrated that mortality rates of untreated leptospirosis were higher in patients aged ≥ 60 years than in younger age groups [5]. Others evidenced that leptospirosis in the elderly population is linked to severe disease and elevated risk of death [7]. What we highlight as novelty is the fact that elderly patients with leptospirosis frequently develop severe complications during the hospital stay, even when they do not present signs of severity on admission, which is peculiar to this infection.

Multiple factors have been presented as possible causes of death in leptospirosis. Gancheva et al. stated that co-morbidities contributed significantly to death in elderly patients⁷. Others evidenced that cardiac involvement, including arrhythmias, heart failure and myocardial infarction were linked to death, especially in severe cases [31–33]. However, the most frequently cited cause of death in leptospirosis is AKI. Some previous studies have demonstrated that AKI was more prevalent in adults and elderly people than in children and that mortality increases with age [34,35]. Considering these factors, we believe that renal failure was the most important cause of death among our patients, especially the elderly, who presented higher AKI incidence.

In summary, elderly patients with leptospirosis presented less hemodynamic impairment on admission, higher incidence of AKI and higher frequency of death during hospital stay than younger patients. Age ≥ 60 years was an independent predictor of poor outcomes, such as hemodialysis requirement and death. These poor outcomes were more frequent in the elderly group despite manifesting less symptoms on admission. Therefore, earlier hospitalization might be considered for this group of patients in order to provide better management of these life-threatening complications.

Study limitations

The main limitations of this study derive from its retrospective nature. Some data from patient's records were not available on admission. The difference of patient number in each group may also be considered a limitation, since it interferes with statistical analysis, but we have chosen to keep this study design in order to compare age groups and investigate the role of age as a risk factor for poor outcomes,

as we have a large group of patients followed in our region, which is a representative sample. Additionally, the study was conducted in only one region of Brazil, so disease patterns may be different in other regions of the globe, mainly due to leptospirosis serovars variations and other epidemiological factors that vary across the world.

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