Journal of Infection and Public Health 12 (2019) 751–759

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Mortality of leptospirosis associated acute kidney injury (LAKI) & predictors for its development in adults: A systematic review

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ARTICLE INFO

Article history:
Received 6 March 2019
Received in revised form 23 May 2019
Accepted 11 June 2019

Keywords:
Leptospirosis associated acute kidney injury
Predictors
Mortality
Clinical characters
Adults
Systematic review

ABSTRACT

Leptospirosis is the most widely spread zoonosis and Leptospirosis Associated Acute Kidney Injury (LAKI) is common and fatal if not properly and swiftly treated. The aim of this review is to evaluate the mortality of LAKI and to identify the risk factors for its development. An electronic search was performed to identify the studies included LAKI patients series. Only studies which investigated mortality or risk factors for LAKI development in adults were included. Twenty-three studies with 24 patients series were included in the final analysis and included 1698 patients. The median series mortality was 10.05% (range 0–33.3%) with a total of 223 death. Only four studies identified the independent risk factors for LAKI development which were oliguria, jaundice, arrhythmia, crackles, elevated direct bilirubin level, elevated activated prothrombin time, hyperbilirubinemia and leukocytosis. Although the mortality of LAKI is high, its predictors are not studied enough in literature.

Contents

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https://doi.org/10.1016/j.jiph.2019.06.014
1876-0341/

Introduction

Leptospirosis is a major public health problem in many regions of the globe particularly in tropical countries and it is underrecognized and underreported [1]. Nowadays the disease is not only restricted to the rural setting but also the urban areas particularly the outbreaks after the rainy season [2]. The disease is commonly misdiagnosed with other frequently available tropical diseases which causes the tropical febrile illness particularly dengue [3,4] and this may be attributed to the similarity of the clinical manifestations in these diseases [5]. In western countries, there is no enough clinical experience with the disease in most health care centers [6,7].

The febrile illnesses particularly leptospirosis are a major cause of acute kidney injury (AKI) in tropical and sub-tropical regions of the world [8,9] and a growing body of evidence supports the development of leptospirosis associated acute kidney injury (LAKI) not only in severe icteric form but also in the anicteric form of the disease [9–13]. The clinical manifestations of leptospirosis range from mild anicteric self-limiting flue like symptoms in 90% of patients to severe icteric Weil's disease in 10% of the cases with a mortality rate of 10% [14].

The incidence of AKI in leptospirosis varies from 10% to 60% or more depending on the definition used and it is suggested that AKI of leptospirosis to be more severe than AKI from other causes as the percent of RIFLE F or AKIN 3 was higher in LAKI comparing to other diseases [15]. Multiple organ failure is frequently encountered in LAKI patients and associated with higher mortality [13,14,16].

Although clinical features of leptospirosis are well studied in the literature, however, few large series studied the clinico-laboratory features of LAKI and less number of studies investigated the risk factors for this potentially fatal complication [11,17–21] and its mortality predictors [9,11,15,21–24]. LAKI mortality rate is estimated at around 19% with increasing mortality with multiple organ failure involvement particularly pulmonary involvement or intensive care unit (ICU) admission [14].

There is no systematic review summarizing the evidence for the LAKI mortality in adults with confirmed leptospirosis and the+ predictors for development of LAKI in adult patients. The current review aims to evaluate the mortality of LAKI and to determine the risk factors for the development of AKI in adults with confirmed leptospirosis based on the previously published literature.

Method

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used to conduct and report this systematic review [25].

Eligibility criteria

This review included all studies contained human adults with a confirmed diagnosis of leptospirosis who developed LAKI. Suspected or probable cases and other age groups were excluded. All study designs were included. The review used no restriction to the definition of AKI and it included all the definitions and classification systems of AKI available in the literature. There was no restriction to the date or geographical region. Studies were excluded if they only reported elevation of serum creatinine in leptospirosis patients without further investigation for mortality or risk factors for LAKI developments. Studies included less than 10 patients were also excluded to reduce patient selection bias. The primary outcomes of the review were the mortality of LAKI in leptospirosis adults patients and the risk factors for the development of LAKI in those patients. The secondary outcomes were the clinical features for LAKI patients when available.

Information sources and search strategy

We searched PubMed, Scopus, and ScienceDirect databases at the end of October 2018 to identify eligible studies to be included in the review. The different keywords used for different databases are provided in Appendix 1. Google scholar (first 500 results) was also searched using the same keywords to identify more studies for inclusion. Furthermore, the reference lists of the identified studies were screened for additional eligible studies. The last search was done at the end of November 2018. Only articles in English were included in the review.

Study selection

One author screened the titles and abstracts of the studies identified from the different searched databases and resources after duplication was removed by the reference management system "EndNnote" software version X7. The eligibility criteria were applied for the shortlisted full-text studies to select the studies for inclusion in the review.

Summary measures & data extraction process

We designed a data extraction form to summarize the most related data for the scope of the review. The form was piloted on five randomly selected studies and was refined accordingly. An independent reviewer extracted the data from the included studies which included the first author's name, year of publication, study designs, setting and periods, number of participants, mean age, male percentage and AKI definition used. The outcomes needed for the review were also extracted as in the metric (Table 1). The second reviewer checked the extracted data to confirm the completeness and correctness of the data collected from each study. Any conflict between the two reviewers was resolved by dialogue.

Scope of the study

The scope of the review was limited to mortality and predictors for the development of AKI in adults with confirmed leptospirosis. The clinical features of LAKI patients were also included in the review as a secondary outcome.

Results

The search for PubMed, Scopus, ScienceDirect and Google scholar (first 500 results) identified 1148 studies. After screening and assessing for eligibility only 23 studies were included for the final analysis. Three studies were excluded as 2 were in Russian and one was in Korean. Another four articles were excluded as the full

Table 1
Characteristics of the included studies arranged by the year of publication.

First author, year of publication [reference number]	Country (year of study)	Study design, setting	Number of leptospirosis patients, mean (unless stated) age, Male %	AKI definition used in the study	Proportion of patients with LAKI (%)	Proportion of LAKI patients needed RRT %	LAKI mortality (%) (deaths/ number of LAKI patients)	Risk factors for LAKI development	Risk factors for mortality in LAKI patients
Seguro et al., 1990 [28]	Brazil (1 year)	PS, SC	56, 11–46 (range), 98%	SrCr > 2.0 mg/dl.	100(56/56)	38% (21/56)	18% (10/56)	NR	NR
Lombardi, 1997 [29]	Uruguay (1993)	RS, NR	20, 35, 100%	NR	100% (20/20)	30% (6/20)	5% (1/20)	NR	NR
Yang et al., 2001 [30]	Taiwan (May 1996–August 1999)	RS, SC	12, 56.3, 75%	NR	100% (12/12)	41.7% (5/12)	33.3% (4/12)	NR	NR
Niwattayakul et al., 2002 [31]	Thailand (January 1999 - August 31, 2000)	PS, SC	148, 36, 72.3%	SrCr > 1.5 mg/dL	26.4% (39/148)	NR	10.2% (4/39)	low BP	NR
Sion et al., 2002 [6]	Greece (1985 -19 98)	RS, SC	17, 47, 100%	NR	100% (17/17)	11.8% (2/17)	23.5% (4/17)	NR	NR
Cengiz et al. 2002 [32]	Turkey (June 1991–September 1998)	PS, SC	36, 42 (for LAKI patients), 72% (of LAKI patients)	SrCr level > 2 mg/dl.	75% (27/36)	48.1% (17/36)	7% (2/27)	NR	NR
Covic et al., 2003 [13]	Romania (1997 – 2001)	RS, SC	58, 43.9, 60.3%	SrCr > 150 mmol/L	100% (58/58)	74.1% (43/58)	25.9% (15/58)	NR	NR
Peces, 2003 [33]	Spain (14 years)	RS, SC	24, 44.3 (16-72) (median), 96%	NR	100% (24/24)	46% (11/24)	8% (2/24)	NR	NR
Markum, 2004 [20]	Indonesia (January 1993–December 1996)	RS, Bicentric	68, 38.3, 75%	Inc in SrCr to 1.5 mg/dl or more	88.2% (60/68)	NR	2 (2.9%)	leukocytosis	NR
Daher et al., 2004 [34]	Brazil (May 1996–June1998)	PS, SC	35, 34.6, 86%	plasma creatinine $\geq$133 μmol/l	35(100%)	17(49%)	1(3%)	NR	NR
Daher et al., 2009 [17]	Brazil (May 1985–December 2006)	RS, Bicentric	196, 40, 80%	RIFLE criteria	196(100%)	52% (103/196)	14% (27/196)	For Oliguric AKI: crackles & direct bilirubin level. For non-oliguric AKI: elevated activated prothrombin time	NR
Hurst et al., 2009 [10]	Hawaii (1992–2004)	RS, SC	18, 27.1, 89%	SrCr > 1.5 mg/dl	12/18 (66.7%)	25% (3/12)	0	NR	NR
Silva Júnior et al., 2011 [15]	Brazil (from May 1985 to August 2008)	RS, Bicentric	287, 37, 80.8%	RIFLE & AKIN	237(82.6%) as RIFLE OR 242(84.3%) as AKIN	43.4% (105/242)	15.5% (37/142)	NO	RIFLE F, AKIN 3, need of dialysis, urinary vol <400 ml/d
Basu et al., 2011 [35]	India (January 2007–January 2008)	PS, SC	12, 39.7, 59.7%	RIFLE	50% (6/12)	0	0	NR	NR
Daher et al., 2011 [26]	Brazil (85–96)	RS, Bicentric	94, 36, 77%	RIFLE	100% (94/94)	75% (70/94)	20.2% (19/94)	NR	Oliguria, lower DBP, arrhythmia, and advanced age

Table 1 (*Continued*)

First author, year of publication [reference number]	Country (year of study)	Study design, setting	Number of leptospirosis patients, mean (unless stated) age, Male %	AKI definition used in the study	Proportion of patients with LAKI (%)	Proportion of LAKI patients needed RRT %	LAKI mortality (%) (deaths/ number of LAKI patients)	Risk factors for LAKI development	Risk factors for mortality in LAKI patients
Daher et al., 2011 [26]	Brazil (97–2010)	RS, Bicentric	224, 41, 84.8%	RIFLE	100% (224/224)	24.1% (54/224)	12.1% (27/224)	NR	Oliguria, lower DBP, arrhythmia, and advanced age
Dassanayake et al., 2012 [18]	Sri Lanka (July 2007–July 2008)	PS, SC	62, 39, 75%	Increase in SrCr of > 0.5 mg/dl. OR increase in SrCr of > 50% from baseline. OR reduction in calculated CLcr of > 50% OR need for dialysis	16% (10/62)	NR	0	Oliguria, Jaundice, arrhythmia	NR
Teles et al., 2016 [11]	Brazil (Jan 2007–Dec 2011)	RS, SC	205, 35.4, 81.9%	KDIGO Criteria	88.7% (182/205)	25.8% (47/182)	9.9% (18/182)	Hyperbilirubinemia and leukocytosis	KDIGO 3 And Need For Mechanical Ventilation
Gupta et al., 2016 [36]	India (1-1-2008–30-6-2009)	PS, SC	25, 50.6, 84%	SrCr ≥ 2 mg/dl	100% (25/25)	16% (4/25)	4% (1/25)	NR	NR
Nair et al., 2016 [24]	India (September 2012–September 2014)	PS, SC	151, 40.34, 75%	KDIGO	98.7% (149/151)	19.5% (29/149)	10.7% (16/149)	fever duration, decreased urine output, swelling of lower limbs, breathlessness, vomiting, yellow discoloration of urine, altered sensorium. Edema, pallor, icterus	AKI stage 3, RRT initiation, number of hemodialysis sessions, altered sensorium, smoking, alcoholism, baseline and repeat creatinine, level of creatinine >4 mg/dl, absolute and percentage creatinine increase, baseline and repeat urea, urine output, arterial gases
Ghasemian et al., 2016 [23]	Iran (2007–2012)	PS, SC	51, 53.5, 82.4%	SrCr > 1.5 mg/dl	51(100%)	29.4% (15/51)	13.7% (7/51)	NR	Leukocytosis
Saravanan et al., 2017 [8]	India (NR)	PS, SC	18, 39.8, 61.1%	SrCr > 1.5 mg/dL	100% (18/18)	11.1% (2/18)	0	NR	NR
Vijayan, 2017 [9]	India (1-1-13 till 31-12-13)	PS, SC	46, 40.07, 78.2%	SCr ≥ 0.3 mg/dl or ≥150–200% from baseline or urine output < 0.5 ml/kg per hour for more than 6 h	100% (46/46)	NR	6.5% (3/46)	NR	Pulmonary involvement either in the form of cough with expectoration, lung crepitations or dyspnea.
Abidi et al., 2017 [22]	Morocco (NR)	PS, SC	100, 36, 92%	NR	100% (100/100)	4% (4/100)	23% (23/100)	NR	Glasgow Coma Scale, a respiratory rate greater than 30, lung infiltrate

RS: retrospective study, PS: prospective study, SC: single centre, SrCr: serum creatinine, AKI: acute kidney injury, RRT: renal replacement therapy, CLcr: creatinine clearance, DBP: diastolic blood pressure, bp: blood pressure, LAKI: leptospirosis associated AKI, RIFLE: risk; injury; failure; loss; end stage kidney disease, AKIN: acute kidney injury network, KDIGO: kidney disease improving global outcomes, NR: not reported.

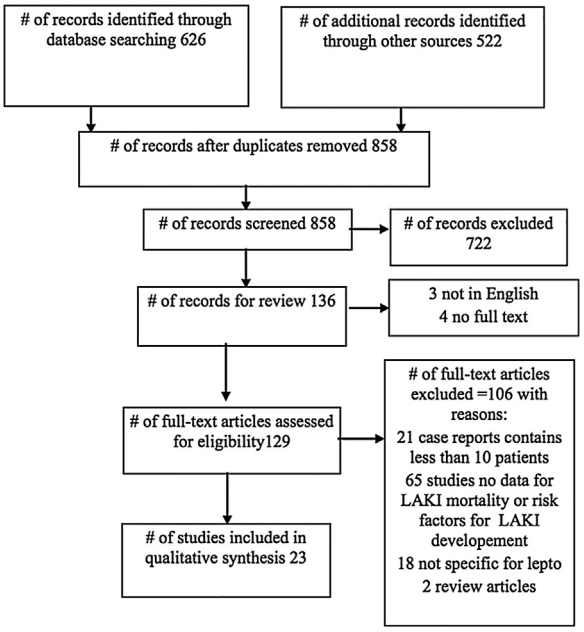

Fig. 1. Flow diagram for selection of studies included in the review.

text cannot be obtained. Details of screening and eligibility assessment are provided in Fig. 1. One study retrospectively investigated two series of patients with LAKI in two different periods [26] making 24 patient series in the review. The total number of patients included in the review was 1963. Of them, 1698 had AKI (86.5%) secondary to leptospirosis. Among total participants in reviewed studies, 1576 (80.3%) were male. The median number of patients in each series was 54 (range 12–287). The review included 12 retrospectively studied series and the other 12 were prospectively studied, and the studies included in the review were published between 1990 and 2017 in different regions of the world; six were published in Brazil, five in India and one for each of Thailand, Taiwan, Sir Lanka, Indonesia, Hawaii, Greece, Iran, Turkey, Romania, Uruguay, Spain, Morocco.

LAKI mortality

Data of LAKI mortality was present in all patient series (24/24), including 1698 patients. The median series mortality was 10.05% (range 0–33.3%) with a total of 223 deaths. There was no death reported in 4/24 series but there was more than 20% mortality reported in 5/24 series. LAKI Mortality was found to vary according to the study design, study date, geographical location, the incidence of LAKI, mean age of the included patients in the series, and the need for renal replacement therapy (RRT).

There were 12/24 series which were prospectively studied with 562 patients and median series mortality 6.75% (range 0–23%) and the other12/24 series were retrospective with 1136 patients and had the median series mortality 13.05% (range 0–33.3%).

We compared the median series mortality for the patients series before 2010 with those after 2010, and we got 12/24 series with 556 patients and median series mortality 9.1% (range 0–33.3%) for those before 2010 and 12/24 series with 1142 patients and median series mortality 10.3 (range 0–23%) for those after 2010.

The review included 11/24 series from Asia with 443 patients and with median series mortality 6.5% (range 0–33.3%), while from South America it included 8/24 series; seven of them from Brazil and one from Uruguay with a total of 1044 patients and median series mortality 13.05% (range 3–20.3%). There were three series from Europe and one from America with a median series mortality of 15.75% (range 0–25.9). Only one series was found from Africa (Morocco) and it investigated the mortality of LAKI in ICU for 100 patients and showed a mortality rate of 23%.

The review included 15/24 series with LAKI incidence of 100% with 976 patients and the median series mortality of 13.7% (range 0–33.3%), while in the remaining 9/24 series with median series AKI incidence of 75% (range 16–98.7%) including 722 patients the median series mortality was 7% (range 0–15.5%).

We compared the series which included patients with mean age of ≥40 years with those series included patients with mean age of <40 years and we had 13/24 series which included patients with mean age of ≥40 years with total number of 853 patients and median series mortality 10.7% (range 0–33.3%), compared to 11/24 series of patients with mean age of <40 years with total number of 845 patients and median series mortality of 9.9% (range 0–23%).

Data of LAKI mortality regarding the use of renal replacement therapy was studied by comparing the series where RRT was used by >50% compared to series where RRT used <50%. Data were available from 20 series, with a total of 554/1543 patients needed to use this modality, and in 1/20 series RRT was not used. In 4/19 series used RRT > 50% and included 321 patients, the median series mortality was 17.83% (range 14–25.9%), compared to 15/19 series used RRT < 50% and included 233 patients where median series mortality was 9.9% (range 0–33.3%).

Predictors of mortality in LAKI

Our review identified six studies which investigated the predictors of mortality in LAKI patients. All of them were obtained after the year 2010 [9,15,22–24,26]. One of the studies investigated the ICU mortality and identified Glasgow Coma Scale, a respiratory rate greater than 30 and lung infiltrate as independent risk factors for ICU mortality [22]. Another study identified the positive predictors of mortality in AKI in tropical acute febrile illness (TAFI) where leptospirosis was considered the most common cause for in-hospital mortality among all other causes with16/18 death due to leptospirosis in the study and identified more than 10 positive predictors [24]. Table 1 shows the different LAKI mortality predictors identified in the included studies.

LAKI development predictors

Only four studies investigated the independent risk factors of LAKI, the first study was from Indonesia (2004). The predominant serovar in that study was *Leptospira bataviae* which accounted for 95.6% of all leptospirosis cases and for 96.7% of acute renal failure (ARF) cases. Among all the clinical presentations and laboratory data studied, only leukocytosis was found to have a significant correlation with ARF [20]. The second study was from Brazil (2009). The predominant serovars were *Leptospira icterohaemorrhagiae* 100% and *Leptospira copenhageni* 59%. That study identified elevated activated prothrombin time as the only marker for nonoliguric LAKI. However, multivariate logistic regression showed crackles and elevated direct bilirubin level as the only independent risk factors for oliguric LAKI [17]. The third study was from Sri Lanka (2012). No serovars data was available in that study. The logistic regression model showed oliguria, jaundice, and arrhythmia as independent risk factors for ARF or myocarditis [18]. The fourth study was from Brazil (2016) and data regarding serovars were not included. The logistic regression identified hyperbilirubinemia and leukocytosis as independent risk factors for LAKI [11]. Another two studies who were not incorporated (as the full text was not obtainable), one of them showed independent risk factors for LAKI were indirect bilirubin, albumin, hemoglobin, and platelets [21] and the second one identified old age and association with leptospirosis risk groups as independent risk factors for LAKI development. The

same study identified the age >40 years as the only risk factor for severe LAKI [19].

In a different study, a good association has existed between hypotension and AKI and pulmonary complications in leptospirosis patients [27] and in another study for AKI in tropical acute febrile illness (TAFI), leptospirosis was found as the most common cause of AKI, its severe stages, need for RRT use, and mortality, and was considered the most nephrotoxic among other TAFI causes [24]. Table 1 shows the different LAKI development predictors in the included studies.

LAKI clinical features

Information on secondary outcomes was not available in all series included in the review and sometimes had heterogenous definitions between different studies and in some of them were not specified by numbers or percent which did not allow further investigation for those clinical features. Moreover, higher mortality was reported with a higher frequency of some clinical features. Table 2 shows the reported clinical characters of LAKI patients in the included series.

Data on oliguria was reported in 13/24 series. In six series with 442 patients where 24.4% (10–42%) patients had oliguria, median series mortality was 8.6% (0–20.2%), while in seven patient series with a total of 217 patients where 58.3% (50–95%) patients had oliguria, the median series mortality was 18% (0–33.3%).

Mortality data on hepatomegaly was available from 9/24 series; in five series included 520 patients and around 38% (25–38.9%) of them had hepatomegaly, median series mortality was 7.5% (0–33.3%), while in 4 series included 225 patients and around 60% (40–100%) of patients had hepatomegaly, the median series mortality was 13.6% (6.5–25.9%). Splenomegaly was reported in 7/24 series. In four Series with 574 patients where 2.2% (0–3.1%) patients had splenomegaly, median series mortality was 13.1% (range 2.9–20.2%), while in three series included 116 patients with 45.7% (41.4–50%) patients had splenomegaly, median series mortality was 25.9% (6.5–33.3%).

Mortality data on pulmonary hemorrhage was available in 3/24 series included 86 patients with five deaths reported overall. Median series mortality in patients with pulmonary hemorrhage was 3% (0–10.2%). Data on respiratory symptoms (dyspnea, cough, and crackles on pulmonary auscultation) were available in 12/24 series. In seven series with a total of 451 patients, where 24% (6.7–29.1%) of patients had these symptoms, median series mortality was 14% (0–25.9%), while in five series with a total of 417 patients where 45% (34–59.1%) of patients had these symptoms, median series mortality was 6.5% (0–23%).

Mortality data on altered consciousness were available from 9/24 series. In five series with 486 patients where 10% (3.6–24%) of patients had altered consciousness, the median series mortality was 13.7% (5–23%), while in four series with 112 patients where 50% (32–100%) of patients had altered consciousness, median series mortality was 24.7% (4–33.3%). Mortality data on headache was available from10/24 series. In five series which included 269 patients; of them 54.2% (27.8–65%) had headache, the median series mortality was 6.5% (0–20%), while in another five series with 507 patients and 72.2% (76.0–100%) of them had headache, their median series mortality was 14% (0–25.9%)

Mortality data on bleeding was available from 15/24 series, where in eight series with 495 patients when 16% (5.6–28.4%) of patients had bleeding diathesis, the median series mortality was 5.6% (0–20.2%), while in seven series with 447 patients with 47% (33–80%) of them had bleeding diathesis, median series mortality was 23% (0–33.3%).

Mortality data on jaundice was available from 17/24 series. In 11 series with 614 patients and 94.4% (76.1–100%) of them had jaundice, their median series mortality was 13.7% (3–33.3%), while in six series which included 153 patients and 54.2% (27.8%–71.3%) of them had jaundice, the median series mortality was 1.5% (0–23.5%).

Discussion

This is the first review to comprehensively investigate and summarize the available evidence of LAKI mortality in adults and to evaluate the predictors of LAKI development in literature. In the first stage of preparing for the review we identified many studies (more than 70 studies) reported the development of AKI in their series as a common feature for leptospirosis, but no further investigation for this complication was performed. These studies were excluded from our review as they did not meet the eligibility criteria for the review. In less number of studies (26 studies), the AKI was investigated for its clinical profile and mortality but risk factors for the development of LAKI in positively diagnosed adults were only investigated in six studies. These results indicate that there is paucity in the literature investigating the predictors of LAKI in adults with a confirmed diagnosis. Investigation of LAKI was noted in the last two decades comparing to most of the previous studies which addressed the AKI in leptospirosis as a common feature without further investigation. The review showed 22/24 studies were after 2000 which indicates the increasing interest in investigating the complications of the disease and its burden in the last two decades and our result of the higher median series mortality for the series published after 2010 [10.3% (range 0–23%)] supports this claim.

The median mortality of all series in the current review was 10.05% [(range 0–33.3%)] with 223 deaths was considered lower than 19.05% reported in the systematic review for LAKI among all age groups and which cited series with higher mortality like those summarizing case reports [14]. The mortality range (0–33.3%) may reflect the broad spectrum of the severity of the disease and the heterogeneity in inclusion criteria.

The high mortality in the series studied from Europe and US [15.75% [(range 0–25.9%)], although being less reliable as they included small sample size series (12–58 patients) with a total of 111 patients, but this may also be attributed to the fact that Clinical experience with the disease is limited in Europe in most health care centers [6,7] and the evidence that the mortality is higher in populations without previous exposure compared to pre exposed populations in the endemic regions [37]. Depending on the local epidemiology of leptospirosis serovars in these regions to justify the higher mortality may be less reliable; although serovar *Icterohaemorrhagiae* which is known to have higher mortality than other serovars is predominant in these regions, evidence supports that a specific type of disease is not caused by a specific serovar [38].

It is not uncommon to find LAKI mortality increased with age as our results showed that mortality in the series with mean age >40 years was higher [10.7% (range 0–33.3%)] than series included patients with mean age <40 years [9.9% (range (0–23%)] and this is consistent with other studies which considered advanced age as an independent risk factor for LAKI mortality [26] and for the worst criterion of LAKI [19] or for the oliguric LAKI with worse prognosis [17]. This may be attributed to the higher incidence of other comorbidities in the advanced age like diabetes, hypertension in addition to the normal physiological changes in the old age [39]. Data on LAKI mortality by gender and pregnancy were not available in the current review, however as the majority of the patients were male, this may not allow trusted results in the mortality difference between the two genders. The high percentage of the male is very common in leptospirosis patients and this may be due to the risk factors associated with some occupations particularly the farming and military work [40–42].

Table 2
Clinical symptoms and laboratory data in the included LAKI patient series.

Criteria	Number of patient series (of 24)	Number/total number of patients	Median value across patient series (range)	Mean series value	Median series mortality across patient series (range)
Fever	14	817/870	99% (61–100%)	93.70%	9.6% (0–33.3%)
Myalgia	15	767/880	92% (46.7–100%)	83.40%	7% (0–33.3%)
Dehydration	5	380/607	62% (43–91%)	64.40%	14% (3–25.9%)
Headache	10	543/776	70.5% (27.8–100%)	67.40%	12.9% (0–25.9%)
Disturbed consciousness	9	115/601	24% (3.6–100%)	33.50%	20.2% (4–33.3%)
Convulsion	3	5/514	1% (0–1.3%)	0.80%	14% (12.1–20.2%)
Bleeding	15	351/942	28.3% (5.6–80%)	33.30%	12.2% (0–33.3%)
Conjunctional suffusion	8	131/315	47.4% (12.1–93.5%)	49.70%	5.8% (0–25.9%)
Leukocytosis	6	270/390	73.2% (47–90%)	71.30%	11.8% (2.9–33.3%)
Leucopenia	3	5/121	3.4% (2–16.7%)	7.40%	25.9% (13.7–33.3%)
Thrombocytopenia	11	291/523	58% (5.6–94%)	56.90%	9.9% (0–33.3%)
Anemia	3	76/258	55.6% (13.2–72.4%)	47.10%	9.9% (0–25.9%)
Respiratory symptoms	12	323/868	28.6% (6.7–59%)	31.30%	12.9% (0–25.9%)
Pulmonary Hemorrhage	3	12/86	20.5% (2.8–30%)	17.80%	3% (0–10.2%)
Arrhythmia	5	85/582	20% (10.7–33.3%)	19.90%	14% (0–25.9%)
Nausea and vomiting	9	564/813	69.4% (27.8–95%)	69.70%	13.7% (0–25.9%)
Abdominal pain	4	76/190	47.5% (5–75%)	43.80%	24.5% (5–33.3%)
Diarrhea	5	141/330	42.9% (11.0–70%)	43.50%	6.5% (0–25.9%)
Hepatomegaly	11	326/745	38.95 (25–100%)	46.50%	9.6% (0–33.3%)
Splenomegaly	7	64/690	3.1% (0–50%)	20.60%	14.1% (2.9–33.3%)
Acute pancreatitis	4	14/388	12.7% (0–25%)	12.60%	13.1% (12.1–25.9%)
Respiratory failure	7	78/584	30% (5.5–75%)	30.90%	14% (0–33.3%)
Rhabdomyolysis	3	33/121	25% (5.2–53%)	27.70%	25.9% (13.7–33.3%)
Jaundice	17	909/1024	93% (40–100%	78%	10.2 % (0–33.3%)
Raised bilirubin	5	232/356	71% (51.3–92%)	71.70%	9.9% (2.9–13.7%)
Increased transaminases	6	251/304	94.5% (47.2–100%	81%	18.3% (0–25.9%)
Hypokalemia	8	94/243	36.5% (7.4–75%)	34.80%	12.5% (0–33.3)
Hyperkalemia	5	7/312	5% (0–12%)	5%	9.9% (3–25.9%)
Hyponatremia	4	101/275	28.4% (24.7–79.3%)	40.20%	16.7% (0–25.9%)
Proteinuria	8	130/287	40% (17.2–77%)	44.70%	5.3% (0–25.9%)
Hematuria	4	57/138	57.9% (20.7–71%)	51.90%	18.6% (0–25.9%)
Oliguria	13	298/659	50% (10–95%)	47.50%	12.1% (0–33.3%)

AKI in leptospirosis is very common and one of the most serious complications and a compiled evidence indicates that it is not only restricted to severe form of the disease but also mild anicteric, uncomplicated cases may develop this fatal complication [9–11,13]. This may be of particular importance in tropics where leptospirosis is endemic in many tropical countries in addition to late or misdiagnosis of the disease, the weather conditions and low public health standards [36]. It was not surprising to identify higher mortality of LAKI in the worse criterion of AKI class [11,15,21] and in oliguria which was found to be associated with worse prognosis of LAKI in different studies [15,17,18,28,43–45] and with higher frequency of the use of RRT [15,24,26] as these factors were considered as mortality predictors in LAKI patients.

The higher number of LAKI studies from Brazil may indicate the high burden of the disease in that country compared to other countries in the same region and reflects the active role for the Brazilian researchers in identifying and resolving this fatal complication. This clue was compatible with the previous systematic review result regarding the alarming picture of LAKI world widely which identified Brazil as the country of the greatest interest in LAKI research [14].

Predictors LAKI mortality and LAKI development

Predictors of LAKI mortality from different studies showed an increase in mortality if LAKI is combined with worse renal outcomes like the higher criterion of AKI in different staging systems KDIGO3, AKIN3, RIFLE F, or oliguria, or need for dialysis [11,15,24,26]. Pulmonary involvement was found as an independent risk factor for mortality in LAKI patients. This was not only strict for the severe form of pulmonary complication which required the mechanical ventilation [11], but also when the pulmonary involvement included cough with expectoration, lung crepitation or dyspnea [9], or tachypnea with RR > 30/min, or lung infiltrate [22]. Central nervous system (CNS) involvement in the form of altered consciousness or sensorium considered as a predictor for mortality and this should draw the attention to evaluate the neurological functions in those patients and avoid delaying the ICU admission [22,24]. Cardiac involvement in form of arrhythmia or hypotension has been found as a significant risk factor not only for the development of LAKI [18,21,26,27] which is an independent risk factor for mortality but also as a predictor for LAKI mortality itself [21,26]. This result should draw the attention for the critical importance of early evaluation of these features in leptospirosis patients.

Very common laboratory data which were considered as predictors for LAKI development and as mortality predictors for LAKI and should be measured in those patients included indirect bilirubin, WBCs, and platelets [11,17,18,20,21,23,24]. Thrombocytopenia is commonly encountered in LAKI patients and has worse renal outcomes. Triglyceride level was found to be higher in thrombocytopenic patients comparing to non-thrombocytopenic and was considered as a marker for the worse morbidity in LAKI patients [33].

Clinical features

The available mortality data related to clinical features which could be studied from different series in the review showed increased mortality with higher frequency of some specific features. Jaundice which was not uncommon to be associated with higher mortality in LAKI as it was a well-known predictor for development of LAKI itself [17,18,24] and compiled results showed that the icteric severe form of leptospirosis is the serious form with higher mortality [2,46–49]. Altered consciousness which was associated with higher mortality in our review was also considered as

a predictor for ICU mortality [22]. Hemorrhagic diathesis was not surprisingly associated with higher mortality as this is consistent with other studies which concluded the worse outcomes including mortality with increased bleeding tendencies in leptospirosis patients [17,50].

Interestingly, the higher frequency of hepatomegaly or splenomegaly in our review was found to have higher median series mortality, however, none of these two features was investigated as a predictor for LAKI development or for increasing of its mortality in the univariable or multivariable investigation in the included studies. This may draw the attention for including these two organomegalies in the prediction research for LAKI development and its mortality which may further highlights the crucial role not only for nephrologists as it is well established but also for gastroenterologists whom their role in managing and monitoring of the disease is not studied enough in the literature.

Several limitations can be identified in this review including bias in study selection due to electronic search limitation in the old studies and exclusion of studies when full text can't be obtained or when the study is published in other languages than English. The data of clinical profile in some series was not numerically reported and many of these data were missed. This prevented further investigation for these clinical features regarding its association with mortality. The higher percentage of male in the studies included although not uncommon feature in leptospirosis studies but limits the generalization of the results to female patients. The definition of AKI was inconsistent among the included studies, which may lead to less reliability in the overall conclusion from the included series.

Conclusion & recommendations

This review supports that LAKI is a severe disease and associated with high mortality. Although well-known complication of the severe form of leptospirosis, AKI in its severe stages was also identified in the mild anicteric form. Further studies to investigate risk factors for AKI development in leptospirosis is needed particularly in the regions where the disease is endemic. Moreover, particular attention for investigating these factors in mild form of the disease should be considered to avoid or reduce the hidden burden of this reemerging disease.

Clinical features and lab data which have been found as predictors for LAKI development: oliguria, jaundice, arrhythmia, crackles, elevated direct bilirubin level, elevated activated prothrombin time, hyperbilirubinemia and leukocytosis, or for its mortality: KDIGO 3, RIFLE F, AKIN 3, need of dialysis, urinary vol <400 ml/d, need for mechanical ventilation, pulmonary involvement, Glasgow Coma Scale, respiratory rate greater than 30, lower DBP, arrhythmia, Leukocytosis, and advanced age should be critically observed when diagnosing or monitoring leptospirosis patients and those detected patients should not be delayed to be evaluated by nephrologist or to be admitted to the ICU. The early and aggressive treatment by antibiotics and by RRT should be immediately initiated in those patients to avoid the worse outcomes and to prevent further burdening of the patients and the overwhelmed health care systems as well.

Funding

No funding sources.

Competing interest

None declared.

Ethical approval

Not required.

Acknowledgment

We are thankful for Hamdan Tahir Library staff, USM, particularly Madam Nurul Azurah Mohd Roni and Madam Noraida Hassan for their urgent providing of the needed articles for the review and for their continuous technical support.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2019.06.014.

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