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Leptospirosis in India: a systematic review and meta-analysis of clinical profile, treatment and outcomes

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SUMMARY

Introduction: Leptospirosis is a zoonotic bacterial infection with significant mortality and morbidity, especially in resource-limited settings. This systematic review aimed to study the clinical profile and outcome of patients with leptospirosis in India.
Methodology: All articles up to 02.08.2022 were searched using the two databases, PubMed and Scopus. A total of 542 articles were found using the search terms related to 'leptospirosis' and 'India'. After two rounds of screening, 55 articles were included. The data were collected on epidemiology, clinical features, laboratory features and treatment of patients with leptospirosis.
Results: Most cases of leptospirosis were reported from the coastal belt. A large percentage of patients were identified as farmers, and exposure to rainfall was identified as an important risk factor. Fever was present in 97%, and conjunctival suffusion was present in 35% of cases. Haemoptysis, gastrointestinal bleeding, and haematuria were present in 5%, 5% and 12% of patients, respectively. Liver and kidney were involved in 34% and 35% of the patients, respectively. The average haemoglobin, leucocyte count and platelet count across various studies ranged from 9.6-12.5 grams/dl, 8.8-11.3 thousand/µl and 20-130 thousand/µl, respectively. Treatment details were sparsely available in some studies, with penicillin, ceftriaxone, and doxycycline used commonly. The pooled mortality across various studies was calculated as 11% [95% CI-8-15%, I^2=93%, P<0.001].
Conclusions: Leptospirosis is associated with significant mortality in Indian settings. There is a need for studies focussing on treatment modalities.

Keywords: Leptospira, Weil's disease, acute febrile illness.

INTRODUCTION

Leptospirosis is a zoonotic bacterial infection associated with significant morbidity and mortality. It is one of the most widespread yet neglected zoonoses, with most reports from South America, the Caribbean, and South Asia [1]. An estimate suggests that a total of 58,900 deaths are reported every year [2]. More than three-fourths of cases occur between the tropics of Cancer and the tropic of Capricorn [3]. In a systematic review (1970-2012), 13% of all the outbreaks were reported from South Asia [4]. An evidence gap map on leptospirosis in India suggested a paucity of evidence on management and control [5]. This systematic review aimed to study the epidemiological features, clinical profile, laboratory parameters, diagnostics, treatment and outcome of patients with leptospirosis in India.

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METHODOLOGY

A systematic review of the literature was performed in two databases (PubMed and Scopus) to identify leptospirosis studies reported up to 02.08.2022. Studies (randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and case series) with clinical, laboratory and treatment details of diagnosed leptospirosis cases from India were included. In-vitro studies, case reports or studies with non-human subjects were excluded. In addition, those studies that did not have sufficient clinical data were also excluded. The following search string was used:

leptospirosis OR leptospira OR Weil's AND disease) AND (clinical OR epidemiology OR symptoms OR sign OR haemorrhagic OR neurological OR laboratory OR treatment OR penicillin OR doxycycline OR azithromycin) AND (India).

The title-abstract and full-text screening were done by two authors (PR and WW). Wherever there was a lack of consensus, the third author (NG) was consulted to arrive at a consensus. The included studies' data (epidemiology, clinical features, laboratory parameters, treatment and outcome) were entered into a pre-defined workbook. NG did the data analysis. The pooled proportion was calculated for all the included variables. A pooled mortality was calculated using the Revman software (version 5.3, Cochrane Nordic, Copenhagen, Denmark). A random effects model was used to generate the forest plot.

RESULTS AND DISCUSSION

A total of 318 articles from PubMed and 375 articles from Scopus were found using the search term. Four articles were added from other sources (references of screened articles). After deleting 155 duplicates, 542 articles were included in the title-abstract screening. The full text could not be retrieved for one article. A total of 55 articles with 11,303 cases were included

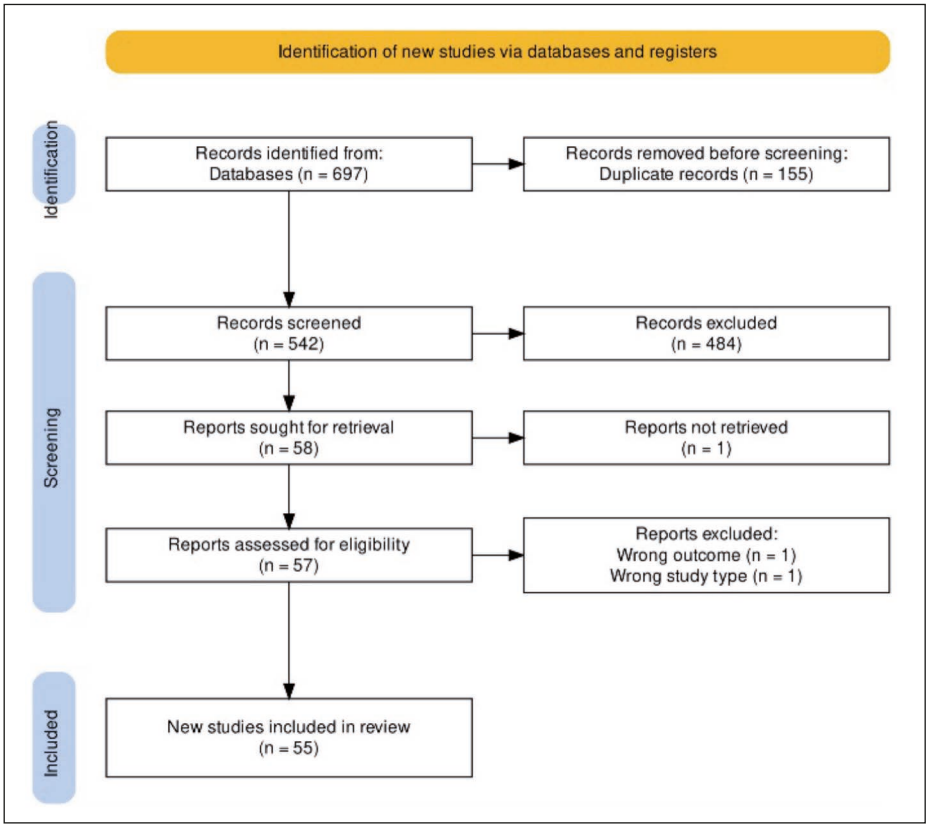

Figure 1
PRISMA chart showing the screening and final inclusion of studies used in this Systematic review.

in the final analysis (Figure 1) [6-61]. Two articles were excluded because they did not meet the inclusion criteria.
Considering the vastness and the heterogeneity of the collected data, the results and discussion section have been organized into sub-headings.

Biology
Leptospira spp is a spirochaete traditionally divided into the pathogenic *L. interrogans* and the saprophytic *L. biflexa* [1]. In the present day, *Leptospira* spp. is divided into multiple serovars. The most common serovar identified in the various Indian sites were icterohaemorrhagiae, australis, autumnalis, grippotyphosa, canicola, pomona and pyrogenes (Table 1) [9, 11, 24, 30, 33, 40, 51, 55]. Their distribution varies across geographical regions [1, 40]. For example, icterohaemorrhagiae is significantly more frequent in rural regions [40]. The association between serovars and clinical manifestations has not been clear-cut, but icterohaemorrhagiae has been associated with severe manifestations in some reports [1].

Epidemiology
Leptospirosis is a zoonotic disease with the infection maintained in the kidney of reservoir animals like rodents, cattle, goats, pigs etc. [6]. Humans acquire the infection when they come in contact with water contaminated with the urine of an affected animal. In a study by Padmakumar et al., more than half of the leptospirosis cases had a history of positive contact with animals [10]. In our review, exposure to rats was found in 67% of the leptospirosis cases. In a study by Narayanan et al., stagnant water and rat infestation in the house were independently associated with leptospirosis infection [11]. In a study by Vimala et al., 42% of trapped rats (*Rattus rattus* and *Rattus norvegicus*) were positive for leptospirosis [25]. Exposure to stagnant water was found in 45% of the patients.
Chakurkar et al. divided the pattern of leptospirosis in India into rural and urban patterns [12]. Cases in rural regions were primarily associated with farming, while urban cases were primarily related to poor sewage disposal and rodent infestation. Farming is associated with higher exposure to contaminated water, especially in the case of farming crops (paddy, sugarcane, banana, etc.) requiring substantial water irrigation [6]. The percentage of patients identified as farmers in our review was 41%. Other occupations at risk of leptospirosis include sewage workers and veterinarians [7]. Water exposure can also occur during recreational sports such as rafting, kayaking or canoeing [7]. In a study by Balasundaram et al., 55% of the cases had a history of recreational water sports [8].
A significant increase in the number of leptospirosis cases has been observed after rainfall-related flooding. Contaminated animal urine on soil mix easily with surface water during floods, making a large population, especially those living in low-lying areas, susceptible to leptospirosis [14]. This explains the higher frequency of the included cases in the rainy season (July to October) (Figure 2). Of the included studies, 18 were directly linked to rainfall. This also included 12 studies where flood-related events were described. In the study by Karande et al., all children diagnosed with leptospirosis had either played in or waded in the water-logged areas [14]. In another study by Sehgal et al., the patient's residence near a river was a risk factor for infection [9].

Table 1 - Infective serovars/serogroups identified across different studies in India.

Sn	*Author*	*Icterohaemorrhagiae*	*Australis*	*Autumnalis*	*Grippotyphosa*	*Louisiana*	*Canicola*	*Pomona*
1	Jeyakumar 2008 [51]	3%	6%	8%	3%	*11%*		
2	Kuriakose 1996 [30]	12%	20%	*27%*	7%	10%	5%	1%
3	Manocha 2004 [24]				50%			50%
4	Murhekar 1998 [55]	38%	*73%*		65%		38%	
5	Muthusethupathi 1995 [33]	4%	2%	*74%*			2%	
6	Narayanan 2016 [11]	*37%*	27%	5%	16%	1%	5%	8%
7	Prabhakaran 2014 [40]	10%	6%	9%	8%		*37%*	18%
8	Sehgal 2002 [9]	11%					*89%*	

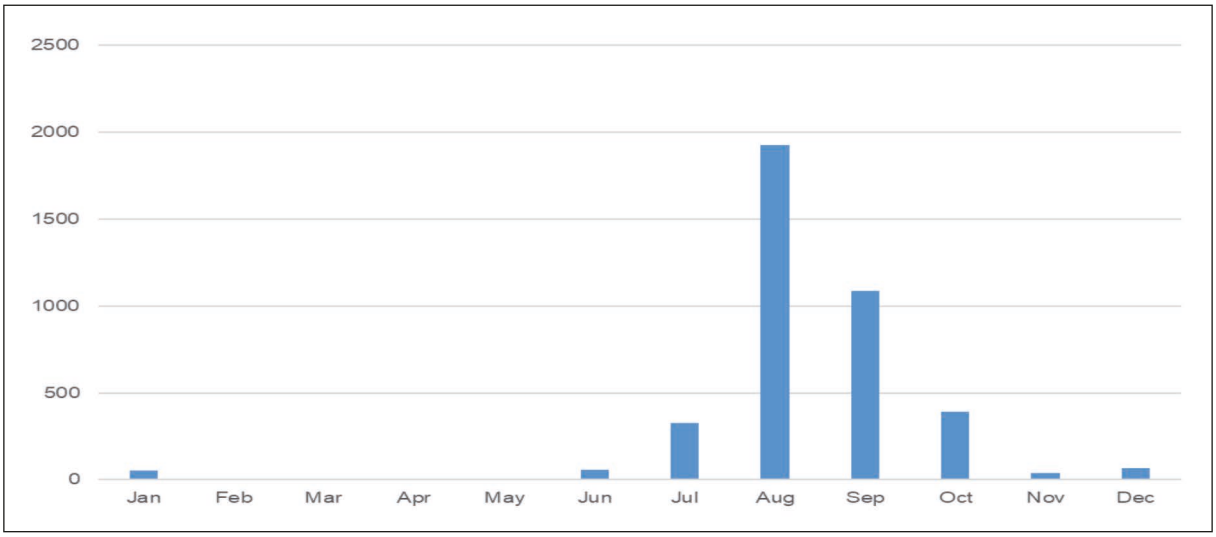

Figure 2 - Seasonal distribution of leptospirosis cases across studies from India.
Abbreviations: Jan: January, Feb: February, Mar: March, Apr: April, Jun: June, Jul: July, Aug- August, Sep: September, Oct- October, Nov- November, Dec- December.

Most cases were reported from the coastal belt (Gujarat, Tamil Nadu, Maharashtra, Kerala, Karnataka, Andaman and Nicobar Islands) (Figure 3). Since most of these regions have deltas of large rivers, there are prone to frequent flooding. The population density next to the rivers might have contributed to the outbreaks as well. Also, the coastal areas have a higher amount of rainfall. This situation increases the probability of human exposure to contaminated waters. Another reason for the increased incidence in the southern coastal areas could be the increased survival of leptospires in warm and humid environments [1].

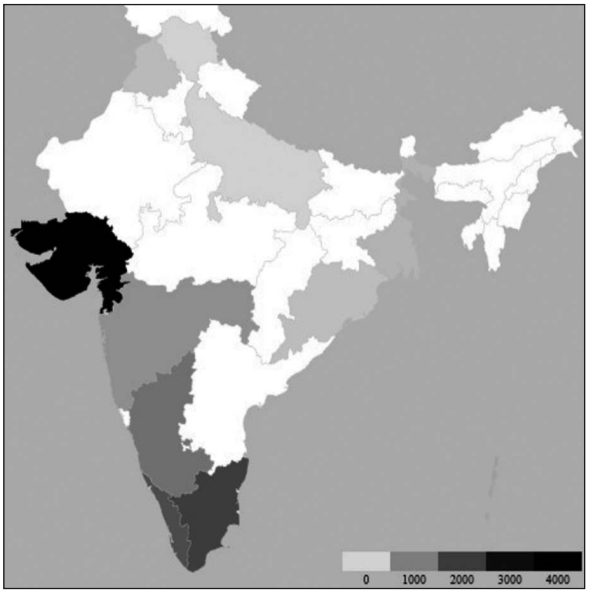

Figure 3 - State-wise distribution of cases of leptospirosis across India*.
*The colour scale at the bottom represents the number of leptospirosis cases. As the number of cases increases, the shade becomes darker.

Clinical features

Acute febrile illness

The most common manifestation of leptospirosis is an undifferentiated acute febrile illness. Fever at presentation has been reported in 97% of the included cases and lasted usually for 4-5 days (Table 2). Headache (43%), myalgia (51%) and arthralgia (18%) were common constitutional features. Some studies suggested that muscle tenderness (localized or general) was significantly more common in cases of leptospirosis when compared to other causes of febrile illnesses (Table 2) [8, 10, 14]. Lymphadenopathy (5%) and rash (6%) were relatively uncommon. Gastrointestinal manifestations such as diarrhoea (18%) and abdominal pain (24%) were also seen (Table 2). Hepatomegaly (31%) and splenomegaly (29%) were not uncommon.

Table 2 - Clinical features of adult patients with leptospirosis presenting as Acute Febrile illness.

Sn	*Author/Year*	*N*	*Fever*	*Head*	*Msl*	*LN*	*Rash*	*Drrh*	*Abd pain*	*Liver*	*Spleen*
1	Narayanan 2016 [11]	118	98.3%	36%	32%					15%	
2	Mathur 2019 [15]	237	100%		39%			8%	4%		
3	Padmakumar 2016 [10]	45	–	–		–	2%	22%	27%	33%	–
4	Sethi 2003 [16]	20	100%	95%	90%	30%	–	25%	25%		–
5	Sehgal 2002 [9]	569	100%	26%	83%	–	–	27%			–
6	Mathew Thomas et al. 2006 [17]	31	97%	71%		–	–			23%	13%
7	Chaudhry 2017 [18]	107	90%	31%	39%	–				43%	27%
8	Salkade 2005 [19]	62	79%	–	13%	–	–	29%	29%		–
9	Holla 2018 [21]	202	92%	18%	36%				19%		
10	Shah Kinjal 2009 [13]	24	100%	–		–	–				–
11	Chakurkar 2008 [12]	44	100%	4%	36%		7%	30%	16%		
12	Somasundaram Aravindh 2014 [22]	122	97%	87%	54%	–	–				–
13	Patil 2017 [7]	193	81%	52%	51%	–	–				–
14	Chawla 2004 [23]	60	97%	–		–	–				–
15	Manocha 2004 [24]	25	100%	24%	16%	–	–	8%	40%		–
16	Vimala 2014 [25]	10	100%	70%	60%	–	–				–
17	Madhusudhana 2015 [26]	42	100%	–		–	–				–
18	Trivedi 2010 [27]	144	100%	76%	97%	–	–				–
19	George Thomas 2012 [28]	467	89%	19%	8%	–	–	15%	26%		–
20	Adiga Deepa 2017 [29]	130	89%	41%	29%	–	–	26%	9%		–
21	Balasundaram Padmakumar 2020 [8]	110	–	–	83%	–	2%		37%	39%	–
22	Kuriakose 1997 [30]	978	–	–		–	–			11%	–
23	DebMandal 2011 [31]	214	100%	100%		0.5%	–			87%	87%
24	Saravanan 2014 [32]	894	100%	–		–	–				–
25	Muthusethupathi 1995 [33]	57	100%	25%	82%	–	–	26%	18%		–
26	Majumdar 2013 [34]	77	100%	–		–	12%			9%	
27	Patel 2011 [35]	44	100%	89%	95%	20%	4%			25%	23%
28	Bhardwaj Pankaj 2008 [36]	62	–	–	50%	–	–				–
29	Sethi 2010 [37]	232	97%	14%	11%	2%	2%		13%	20%	10%
30	Chauhan 2010 [38]	13	100%	92%	77%	–	–				–
31	Pappachan 2002 [39]	282	100%	78%	93%	7%	6%		28%	58%	2%
32	Prabhakaran 2014 [40]	410	100%	45%	52%	–	–	6%	26%		–
33	Zala/ 2018 [41]	154	100%	38%	29%	–	14%		38%		–
34	Gupta 2021 [42]	63	100%	22%	54%	–	5%	21%	40%	29%	17%
35	Varma/ 2013 [43]	100	100%	49%	69%	–	–	29%	43%	50%	17%
36	Jagadishchandra 2003 [44]	84	100%	64%	30%	–	–	24%	30%		–
37	Datta 2011 [45]	51	100%	41%	78%	–	–			73%	72%

Abbreviation: S.n- Serial number, N- Sample size, Msl- Muscle involvement, LN- Lymphadenopathy, Drrh- Diarrhoea, Abd pain- Abdominal pain, Liver- Hepatomegaly, Spleen- Splenomegalya.

An important feature that helps differentiate leptospirosis from other viral causes of Acute febrile illness is the presence of leucocytosis (Table 3) [42, 43]. In our review, leukocytosis was seen in 54% of the patients. Leucopenia was uncommonly reported in 8% of the patients. Raised Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and procalcitonin have also been shown to help differentiate leptospirosis from other viral causes [42, 43].

Haemorrhagic fever

Conjunctival suffusion has been reported to be more common in leptospirosis cases when compared to other causes of acute febrile illnesses [8]. According to an estimate, conjunctival suffusion has been seen in less than 10% of the cases of febrile illnesses due to causes other than leptospirosis [8]. Our review showed it in 35% of leptospirosis cases (Table 4). Conjunctival congestion, especially in combination with icterus, is considered virtually pathognomonic for leptospirosis [1, 8]. Haemoptysis, gastrointestinal bleeding, and haematuria were present in 5%, 5% and 12% of patients, respectively (Table 4). Bleeding manifestations in leptospirosis could be attributed to thrombocytopenia, coagulation abnormalities and uraemia [62]. Thrombocytopenia is commonly seen in many causes of acute febrile illnesses, including leptospirosis.

Table 3 - Laboratory parameters of adult patients with leptospirosis.

Sn	*Author/Year*	*N*	*↑TLC*	*↓TLC*	*↓Plt*	*↑Bil*	*↑AST*	*↑ALT*	*↑ALP*	*↑Cr*
1	Mathur 2019 [15]	237			14%					
2	Padmakumar 2016 [10]	45	78%	2%		56%	89%	87%	87%	53%
3	Mathew Thomas 2006 [17]	31	55%			74%				
4	Chaudhry 2017 [18]	107	42%		27%					32%
5	Mathew Anoop 2018 [20]	113								
6	Holla 2018 [21]	202	81%		78%	80%	78%	79%	73%	53%
7	Shah 2009 [13]	24	54%		58%	100%	80%	80%		
8	Chakurkar 2008 [12]	44	20%	9%	57%	25%	14%		14%	
9	Trivedi 2010 [27]	144		10%	77%					
10	George Thomas 2020 [28]	467								
11	Adiga Deepa 2017 [29]	130								
12	Balasundaram 2020 [8]	110	83%		63%	53%	93%	91%	84%	49%
13	DebManda 2011 [31]	214					92%	81%		64%
14	Muthusethupathi 1995 [33]	57			23%		44%	47%		
15	Patel 2011 [35]	44	50%		75%	98%				73%
16	Sethi 2010 [37]	232	23%		7%		30%			60%
17	Chauhan 2010 [38]	13	100%		62%	77%				
18	Ittyachen 2007 [49]	53			74%					74%
19	Pappachan 2002 [39]	282			51%	18%	46%		16%	47%
20	Unnikrishnan 2005 [48]	92								50%
21	Zala 2018 [41]	154	52%		88%	79%	88%	86%		41%
22	Gupta 2021 [42]	63	63%	8%	78%					76%
23	Varma 2013 [43]	100			47%	71%				80%
24	Datta 2011 [45]	51	55%		73%	78%	78%	78%	71%	41%

Abbreviation: S.n- Serial number, N- Sample size, ↑TLC- Leucocytosis, ↓TLC- Leucopenia, ↓Plt- Thrombocytopenia, ↑Bil- Increased bilirubin, ↑AST- Increased Aspartate transaminase, ↑ALT- Increased Alanine Transaminase, ↑ALP- Increased Alkaline phosphatase, ↑Cr- Increased Creatinine.

The average platelet count across various studies ranged from 20 to 130 thousand/µl. Thrombocytopenia was seen in 50% of the patients in this review (Table 3). It is hypothesized to be a result of the direct effect of the organism, bone marrow suppression and increased destruction of the platelets [29]. In a study by Adiga et al., the severity of the disease was found to be proportional to the severity of thrombocytopenia [29].

Table 4 - Bleeding manifestations in adult patients with leptospirosis.

Sn	*Author/Year*	*N*	*Bleeding [NOS]*	*Hematuria*	*GI bleeding*	*Hemoptysis*	*Conjunctival suffusion*
1	Narayanan 2016 [11]	118					5%
2	Mathur 2019 [15]	237	15%				24%
3	Padmakumar 2016 [10]	45	–	–			53%
4	Sethi 2003 [16]	20	–	5%			50%
5	Sehgal/2002 [9]	569	–	20%		2%	25%
6	Mathew Thomas/2006 [17]	31	–	–	–		23%
7	Chaudhry 2017 [18]	107	6%	4%	1%	4%	30%
8	Salkade 2005 [19]	62	29%	–	–	29%	15%
9	Holla 2018 [21]	202					4%
10	Shah 2009 [13]	24	–	–	–	13%	
11	Chakurkar 2008 [12]	44	7%	4%	4%	20%	14%
12	Somasundaram 2014 [22]	122	–	–	–		16%
13	Clerke 2002 [46]	38	–	–	–	26%	
14	Chawla 2004 [23]	60	7%	–	–		40%
15	Manocha 2004 [24]	25	–	4%	4%		
16	Trivedi 2010 [27]	144	–	–	–	25%	
17	Balasundaram 2020 [8]	110	–	–	–		58%
18	Kuriakose 1997 [30]	978	–	–	–		49%
19	Debmandal 2011 [31]	214	–	5%	5%		
20	Muthusethupathi 1995 [33]	57	–	–	26%	9%	58%
21	Panicker/ 2001 [47]	40	5%	–	–		
22	Patel 2011 [35]	44	23%	–	–		23%
23	Bhardwaj 2008 [36]	62	–	–	–		3%
24	Sethi 2010 [37]	232	–	2%	2%		7%
25	Chauhan 2010 [38]	13	–	–	–		54%
26	Pappachan 2002 [39]	282	–	–	–	5%	81%
27	Prabhakaran 2014 [40]	410	–	–	–		41%
28	Zala 2018 [41]	154	–	–	–	9%	22%
29	Gupta 2021 [42]	63	3%	–	–		29%
30	Varma/ 2013 [43]	100	25%	–	–		35%
31	Jagadishchandra 2003 [44]	84	–	27%	2%		30%
32	Datt 2011 [45]	51	35%	–	–		

Abbreviation: S.n- Serial number, N- Sample size, NOS- Not otherwise specified, GI- Gastrointestinal.

Weil's disease

Concurrent icterus and Acute Kidney Injury has been classically described under the heading of Weil's disease. Icterus results from intracellular cholestasis and was seen in 34% of the patients (Table 5). Intracellular cholestasis as the primary mechanism of liver involvement can also be extrapolated from the increased bilirubin, increased alkaline phosphate and relatively normal transaminase levels (Table 3) [22]. The average bilirubin, AST and ALT were 2.7-14.6 grams/ dl, 58-524 IU/l and 58-503 IU/l, respectively. In contrast, yellow fever has a marked increase in transaminase levels owing to hepatocellular injury. Acute kidney injury resulting from tubulointerstitial nephritis was seen in 35% of the patients (Table 5). The average creatinine at presentation ranged from 1.8-5.4 mg/dl (Table 3).

Pulmonary leptospirosis

Pulmonary involvement in the form of dyspnoea was noticed in 17% of the patients (Table 5). It can result from pneumonitis, pulmonary haemorrhage or acute respiratory distress syndrome (ARDS) [28]. Pneumonitis presents as a consolidation on imaging. Pulmonary haemorrhage has been suggested to be one of the most important causes of mortality in Indian leptospirosis patients [27]. Pulmonary haemorrhage in leptospirosis is considered an immune-mediated phenomenon and presents most commonly as haemoptysis with diffuse small round opacities on imaging [27].

Cardiac leptospirosis

Heart involvement in the form of myocarditis is reported in 30% of the patients (Table 5). This myocarditis in leptospirosis has been described to be similar to septic cardiomyopathy [20]. Sinus bradycardia and first-degree atrioventricular block were found to be common in those with cardiac involvement [46]. In an autopsy study, inflammation and haemorrhages were noticed in all three layers of the heart [13]. It must be noted that cardiac involvement may be masked by pulmonary or hepatorenal involvement [13].

Neuroleptospirosis

The neurological manifestation of leptospirosis has been linked to both direct invasions by leptospires and immune complexes formed in the second week of illness [47]. The direct invasion leads to altered sensorium but aseptic meningitis is related to vasculitis resulting from the immune-mediated reaction [47]. Altered sensorium could also be explained partly by metabolic encephalopathy secondary to hepatorenal dysfunction [17]. Neck stiffness and altered sensorium were seen in 10% and 18% of leptospirosis patients, respectively in this review (Table 5).

Table 5 - Organ Involvement in adult patients with Leptospirosis.

Sn	*Author/Year*	*N*	*Liver*	*Kidney*	*Lungs*	*Heart*	*CNS*	
			Icterus	*Oliguria*	*Dyspnoea*	*Myocarditis*	*Neck stiffness*	*Altered sensorium*
1	Narayanan 2016 [11]	118	6%				3%	
2	Mathur 2019 [15]	237	81%	37%				2%
3	Padmakumar 2016 [10]	45	20%		38%			
4	Sethi 2003 [16]	20	80%	45%	5%		20%	20%
5	Sehgal 2002 [9]	569	25%	39%	21%		2%	
6	Mathew Thomas 2006 [17]	31	45%				65%	81%
7	Chaudhry 2017 [18]	107			19%			14%
8	Salkade 2005 [19]	62	40%	29%	44%	39%		
9	Mathew Anoop 2018 [20]	113	50%		27%			
10	Holla 2018 [21]	202	22%	26%				
11	Shah 2009 [13]	24	71%	13%	46%	96%		
12	Chakurkar 2008 [12]	44	27%	32%	100%	93%		11%

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Sn	Author/Year	N	Liver	Kidney	Lungs	Heart	CNS	
			Icterus	Oliguria	Dyspnoea	Myocarditis	Neck stiffness	Altered sensorium
13	Somasundram 2014 [22]	122	34%	25%				10%
14	Clerke/ 2002 [46]	38	71%					
15	Patil 2017 [7]	193	18%		22%			
16	Chawla 2004 [23]	60	67%	55%				
17	Manocha 2004 [24]	25	68%	24%	12%			
18	Trivedi 2010 [27]	144						
19	George Thomas 2020 [28]	467	21%	13%	6%			4%
20	Adiga Deepa 2017 [29]	130	14%	18%				
21	Balasundaram 2020 [8]	110	36%	11%	71%			
22	Kuriakose 1997 [30]	978	14%				17%	
23	Debmandal 2011 [31]	214	94%					
24	Sarvanan 2014 [32]	894	15%					
25	Muthusethupathi 1995 [33]	57	84%	72%			7%	42%
26	Majumdar 2013 [34]	77	40%					
27	Panicker 2001 [47]	40					33%	
28	Patel 2011 [35]	44	86%	39%				5%
29	Bhardwaj 2008 [36]	62	15%					
30	Sethi 2010 [37]	232	27%	11%	12%		3%	14%
31	Chauhan 2010 [38]	13	77%				54%	
32	Ittyachen 2007 [49]	53						
33	Pappachan 2002 [39]	282	70%	24%	9%		4%	10%
34	Prabhakaran 2014 [40]	410	37%		25%			
35	Unnikrishnan 2005 [48]	92		67%		10%		
36	Zala 2018 [41]	154	55%					18%
37	Gupta/2021 [42]	63	59%	63%	8%	32%		
38	Varma 2013 [43]	100	63%	56%	33%			12%
39	Jagadishchandra 2003 [44]	84	35%	27%	13%		2%	14%
40	Datta 2011 [45]	51	75%	29%	25%		6%	22%

Abbreviation: S.n- Serial number, N- Sample size.

Paediatric patients

A total of 346 children diagnosed with leptospirosis were included in the review. The presence of fever was seen in 95% of the children (Table 6). Headache, myalgia and conjunctival suffusion were present in 54%, 47% and 33% of the patients, respectively (Table 6). In a study by Karande et al., tenderness of the abdominal muscles was significantly associated with the diagnosis of leptospirosis in children [53]. In another study, a straight leg raising test to demonstrate myalgia helped differentiate leptospirosis from other causes [58]. Bleeding manifestations were present in 6% of the patients (Table 6). Jaundice and acute kidney injury was seen in 13% and 6% of the patients, respectively (Table 6). In a study by Narayanan et al., no significant difference in pulmonary, cardiac or neurological involvement was seen between adult and paediatric cases of leptospirosis [11].

Table 6 - Clinical features in paediatric patients diagnosed with leptospirosis.

Sn	*Author/Year*	*N*	*Fever*	*Headache*	*Myalgia*	*Bleeding*	*Conjunctival suffusion*	*Jaundice*	*Renal involvement*
1	Narayanan 2016 [11]	35	100%	83%	63%		26%	31%	
2	Mathur 2019 [15]	86	100%	–	76%	12%	55%	2%	5%
3	Karande 2005 [54]	15		60%		47%	40%	13%	13%
4	Karande 2002 [14]	26	77%	54%	–	15%	15%	8%	8%
5	Rajajee 2002 [58]	139	96%	–	24%	–	19%	18%	1%
6	Karande 2003 [53]	18	100%	50%	61%	–	28%	0%	–
7	Zaki 2010 [61]	27	81%	18%	44%	4%	63%	15%	26%

Abbreviation: S.n- Serial number, N- Sample size.

Diagnostics

Leptospirosis needs to be differentiated from other Acute Febrile illnesses that are frequent in Indian settings during the monsoons. The most common differentials are dengue, scrub typhus, enteric fever and chikungunya. The diffuse erythematous rash seen in dengue, pathognomonic eschar of scrub typhus, gastrointestinal involvement in enteric fever and the small joint arthralgia of chikungunya is rarely seen in leptospirosis. Icterus and conjunctival suffusion seen in leptospirosis are very uncommon in any of the other differentials. Despite these differences, it is difficult to differentiate leptospirosis from these febrile illnesses without the use of microbiological methods.

The diagnosis of leptospirosis can be achieved by many methods. In the first week, the diagnostic modality of choice is polymerization chain reaction assay (PCR) or culture of the blood [1]. The sensitivity and specificity of PCR for the diagnosis of scrub typhus in a study were 97 and 96%, respectively [11]. After the first week, the sensitivity of these tests on blood decreases substantially. PCR or culture in the urine samples is useful in the second week. These tests are, however, limited by availability, cost and resource intensiveness [1]. In the included studies, PCR was done in two studies, whereas culture was done in three studies (Table 7) [11, 30, 50].

After the first week, serology is the preferred method. Microagglutination test [MAT] is the gold standard serological method of choice, but it requires maintenance of live cultures of leptospires and is usually available at reference centres

Table 7 - Details of methods used for diagnosis of leptospirosis in the included studies.

Sn	*Author/Year*	*MFC*	*DGM*	*IgM ELISA*	*Rapid*	*MAT*	*PCR*	*Culture*
1	Narayanan 2016 [9]			Yes	Yes	Yes	Yes	Yes
2	Mathur 2019 [16]			Yes	Yes	Yes		
3	Padmakumar 2016 [10]			Yes				
4	Sethi 2003 [16]				Yes	Yes		
5	Sehgal 2002[13]			Yes	Yes	Yes		
7	Chaudhry 2017 [19]	Yes		Yes				
8	Salkade 2005 [20]				Yes			
9	Mathew Anoop 2018 [21]			Yes		Yes		
10	Holla 2018 [22]			Yes				
11	Shah Kinjal 2009 [14]				Yes			
12	Somasundaram Aravindh 2014 [23]	Yes			Yes	Yes		
13	Chawla 2004 [24]			Yes				

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Sn	*Author/Year*	*MFC*	*DGM*	*IgM ELISA*	*Rapid*	*MAT*	*PCR*	*Culture*
14	Manocha 2004 [25]	Yes			Yes	Yes		
15	Vimala 2014 [26]				Yes			
16	Madhusudhana 2015 [27]				Yes	Yes		
17	Trivedi 2010 [28]			Yes	Yes			
18	George Thomas 2012 [29]			Yes				
19	Adiga Deepa 2017 [30]			Yes				
20	Balasundaram Padmakumar 2020 [12]	Yes		Yes				
21	Kuriakose 1997 [31]			Yes		Yes		Yes
22	DebMandal 2011 [32]			Yes				
23	Saravanan 2014 [33]	Yes						
24	Muthusethupathi 1995 [34]			Yes		Yes		
25	Majumdar 2013 [35]			Yes				
26	Patel 2011 [36]			Yes		Yes		
27	Bhardwaj Pankaj 2008 [37]			Yes				
28	Sethi 2010 [38]	Yes		Yes		Yes		
29	Chauhan 2010 [39]			Yes				
30	Pappachan 2002 [40]					Yes		
31	Prabhakaran/ 2014 [41]			Yes		Yes		
32	Zala 2018 [42]			Yes				
33	Gupta2021 [43]	Yes		Yes				
34	Varma 2013 [44]			Yes				
35	Jagadishchandra 2003 [44]			Yes				
36	Datta 2011 [46]	Yes		Yes				
37	Ittyachen 2007 [47]			Yes				
38	Jena 2004 [50]			Yes			Yes	Yes
39	Jeyakumar 2008 [51]					Yes		
40	Kamath 2014 [52]			Yes				
41	Karande 2002 [14]			Yes				
42	Karande 2003 [53]			Yes				
43	Karande 2005 [54]		Yes	Yes		Yes		
44	Murhekar 1998 [55]					Yes		
45	Panicker 2001 [47]			Yes				
46	Pappachan 2007 [56]			Yes		Yes		
47	Patel 2006 [57]			Yes		Yes		
48	Rajajee 2002 [58]	Yes		Yes		Yes		
49	Sehgal 2003 [59]				Yes	Yes		
50	Sugunan 2009 [60]					Yes		
51	Unnikrishnan 2005 [48]			Yes				
52	Zaki 2010 [61]		Yes		Yes			

* Abbreviation: S.n- Serial number, N- Sample size, MFC- Modified Faine's criteria, DGM- Dark ground microscopy, ELISA-Enzyme linked immunosorbent assay, Rapid- Rapid diagnostic test, MAT- Microagglutination test, PCR- Polymerase chain reaction assay.

[1]. A total of 24 studies used MAT to diagnose leptospirosis [Table 7]. In the absence of MAT, IgM Enzyme-linked immunosorbent assay (IgM ELISA) is the most commonly used serological method for diagnosing leptospirosis. A total of 38 studies used IgM ELISA in this review (Table 7). In a study by Narayanan et al., the sensitivity and specificity of IgM ELISA were found to be 100 and 93%, respectively [11]. Conventional serological methods like ELISA and MAT are limited by laboratory requirements, expertise and considerable turn-around time. For this reason, there has been increasing use of rapid tests for making a diagnosis of leptospirosis. Sensitivity issues limit darkfield microscopy for direct observation of leptospires in blood or urine sample. Nevertheless, it was used in two studies (Table 7) [54,61]. Rapid tests of different formats were used across 13 of the included studies (Table 7). Most commonly used rapid tests were based on lateral flow assay-based immunochromatography (ICT). In a diagnostic randomized controlled trial, rapid ICT-based tests had high agreement with the conventional tests. They had a significantly less turn-around time but did not have an impact on days of hospitalisation or antimicrobial consumption [63].

It should be noted here that serological tests are associated with their inherent fallacies. In endemic areas, false positives are not uncommon. Therefore, they must be interpreted carefully, especially in those patients presenting with atypical symptoms. Some studies used paired sampling two weeks apart to increase the specificity of serological tests [46]. A validated scoring system called Modified Faine's criteria uses a combination of epidemiological features, clinical findings and diagnostic tests to diagnose leptospirosis. This criterion was used for diagnosis in nine studies (Table 7).

Treatment details and outcome

Treatment details were sparsely available in some studies. Nine studies used penicillin, while ceftriaxone was used in three studies (Table 8). In one recent study by Gupta et al., piperacillin-tazobactam and meropenem were used empirically as the patient presented with severe manifestations, and other Gram-negative bacterial infections were in the differentials [42]. Doxycycline was used in three studies, while azithromycin was used in one study (Table 8) [31, 37, 42]. The most common duration of intravenous penicillin or doxycycline in the included studies was seven days. Two studies used corticosteroids, especially in patients with pulmonary involvement [27, 37]. Dialysis is often required in patients with severe renal involvement.

Mortality outcomes were reported in 23 studies. In a study by Chawla et al., male gender, alcohol dependence, higher age, multi-organ dysfunction,

Table 8 - Drugs used in different studies used in patients with leptospirosis.

Authors	*Penicillin*	*Ampicillin*	*Doxycycline*	*Azithromycin*	*Ceftriaxone*	*Piperacillin-tazobactam*	*Meropenem*	*Ciprofloxacin*
Chakurkar 2017 [12]	Yes	Yes						
Gupta 2021 [42]	Yes		Yes	Yes	Yes	Yes	Yes	
Karande 2003 [53]	Yes							
Karande 2005 [54]	Yes							
Patel 2006 [57]	Yes							
Sethi 2010 [37]			Yes		Yes			
Somasundaram 2014 [22]	Yes							
Trivedi 2010 [27]	Yes							
Zaki 2010 [61]	Yes							Yes
Debmandal 2011 [31]	Yes		Yes		Yes			

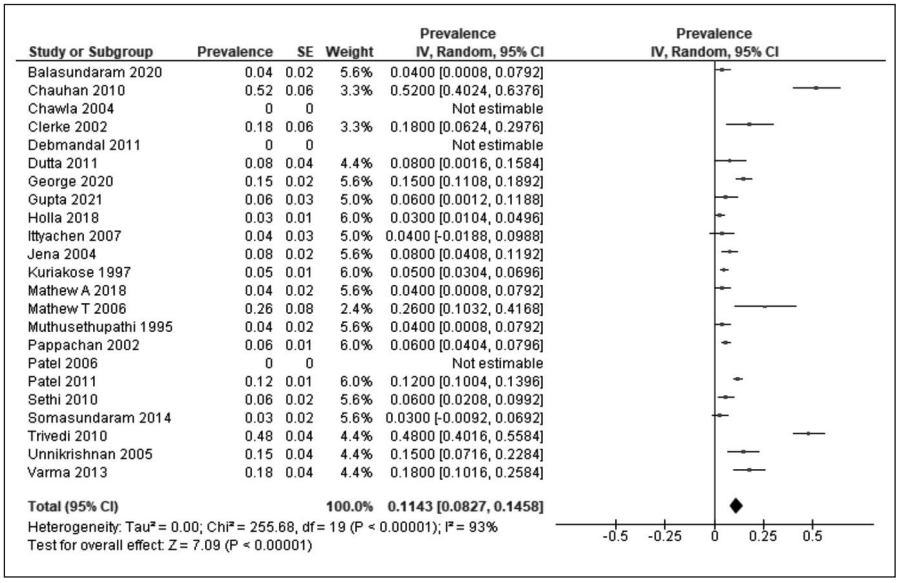

Figure 4
Meta-analysis of mortality using random-effects model in leptospirosis cases reported in studies from India.
Abbreviations: SE: Standard error, CI-Confidence interval.

acidosis and ARDS were identified as poor prognostic factors [23]. In a study by Somasundaram et al., mortality and organ dysfunction outcomes were poorer in leptospirosis patients with pre-existing decompensated liver disease [23]. In a study by Pappachan et al., pulmonary and neurological involvement were independently associated with mortality [39]. In another study by Unnikrishnan et al., cardiac involvement and bleeding manifestations were also associated with mortality [48]. In another study by Varma et al., liver/ kidney involvement, thrombocytopenia, and creatine kinase elevation were predictors of death. The mortality rates ranged from 0-52% in various studies. The mortality outcomes in children were reported in two studies, ranging from 6-13% [54,58]. In a study that compared paediatric and adult cases of leptospirosis, worse outcomes were more commonly seen in adult cases of leptospirosis [11]. Using the random effect model, the pooled mortality across various studies was calculated as 11% [Figure 4] [95% CI-8-15%, I^2=93%, P<0.001].

Chemoprophylaxis

Chemoprophylaxis for individuals at high risk of exposure (sewage workers, paddy farmers) during the peak transmission season (monsoon) has shown to be effective. Mass chemoprophylaxis in regions with heavy floods has also been advocated. Doxycycline has been used in most studies with a dose of 200 mg weekly for a maximum period of 6 months [6]. In a randomized controlled trial, weekly doxycycline did not decrease the infection rates but reduced the incidence of clinical disease significantly [64]. In a case-control study by Desai et al., leptospirosis cases received doxycycline chemoprophylaxis for significantly less duration than similarly exposed controls [6].

LIMITATIONS OF THE STUDY

This review had several limitations. Most of the studies were retrospective observational studies with their inherent biases. The mapping of the disease burden was limited to published cases with available clinical details. The presence of leptospirosis in regions without published cases cannot be ruled out. Treatment details were missing in most of the cases. The studies included for the calculation of pooled mortality had considerable heterogeneity.

CONCLUSIONS

Leptospirosis is reported across India, with most reports coming from the coastal belt. It is primarily reported in farmers, with a definite seasonal distribution. Most outbreaks follow heavy rainfalls, especially when they are associated with floods. Liver and Kidney involvement are

amongst the most common complications. The disease is associated with a high mortality rate in hospital settings.

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