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Epidemiological Predictors of Severe Leptospirosis in Adults: A Multicenter Retrospective Cohort Study in Northeastern Peninsular Malaysia

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Abstract

Leptospirosis is among the most widespread zoonotic infections globally and is particularly prevalent in tropical settings, where it remains endemic. In Malaysia, the disease burden has increased markedly over recent decades. Severe leptospirosis can result in multi-organ dysfunction and death; however, early identification of patients at risk of a severe clinical course remains a significant challenge. This study aimed to determine independent clinical and laboratory predictors of severe leptospirosis among adults admitted to hospitals in northeastern Malaysia. A multicenter retrospective cohort study was conducted at two tertiary referral hospitals in Kelantan, northeastern Peninsular Malaysia, over a seven-year period. Adults with confirmed leptospirosis were categorised as severe or non-severe according to established clinical criteria. Group comparisons were performed using appropriate statistical tests, followed by multivariable logistic regression with internal bootstrap validation to identify independent predictors of severe disease. Of 525 patients included in the final analysis (mean age 38.1 ± 16.8 years; 65.5% male), 303 (57.7%) met criteria for severe leptospirosis and overall, in-hospital mortality was 6.5%. Common presenting symptoms (>30% of patients) included fever, myalgia, nausea, vomiting, and arthralgia. Independent predictors of severe disease identified on multivariable analysis were; age > 40 years, delayed hospitalisation (presentation after four days of symptom onset), T-wave changes on electrocardiography, conjunctival suffusion, hyponatraemia, prolonged prothrombin time, and elevated alanine aminotransferase (all $p < 0.05$). The predictive model demonstrated good discriminatory ability (AUC 0.794, 95% CI: 0.747–0.841). Severe leptospirosis is associated with distinct clinical and laboratory features at presentation. Early recognition of key risk factors—particularly older age, delayed presentation, and electrocardiographic abnormalities—may enable clinicians to stratify risk, initiate timely targeted interventions, and potentially reduce morbidity and mortality in this endemic setting.

Keywords: leptospirosis; zoonosis; tropical infectious disease; mortality risk factors; prognostic factors; Malaysia

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Academic Editor: Georgia Vrioni

Received: 2 April 2026
Revised: 12 May 2026
Accepted: 23 May 2026
Published: 4 June 2026

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1. Introduction

Leptospirosis—colloquially referred to as rat-urine fever—is the most widespread anthropozoonotic infection worldwide [1]. The causative spirochete, belonging to the genus Leptospira, is transmitted principally through contact with the urine of infected animals, and survives for weeks in contaminated soil or water under humid, warm conditions [2]. The global burden of leptospirosis has grown substantially in recent decades, driven by geographical expansion, increasing contact with reservoir hosts, rising human population density, enhanced mobility, and rapid urbanisation, particularly in settings where neglected tropical diseases are endemic [3,4].

In Malaysia, leptospirosis is re-emerging as a significant public health concern. Conducive ecological conditions—including high humidity, warm ambient temperatures, large rodent populations, and extensive wildlife habitats—facilitate pathogen persistence and transmission [5]. Following its designation as a notifiable disease in 2010 [6], reported incidence rose from 6.99 per 100,000 population in 2010 to 30.2 per 100,000 in 2015 [7], with the sharpest single-year increase recorded in 2015, attributed to heavy rainfall, widespread flooding, and increased participation in recreational water activities [8,9]. Over 37 Leptospira serovars have been isolated in Malaysia, with *Leptospira interrogans*, *L. kirschneri*, and *L. wolffii* identified as the principal human-infecting species [10].

The clinical presentation of leptospirosis spans a wide spectrum. The majority of cases manifest as a self-limiting, asymptomatic or mild anicteric febrile illness [11], whilst the severe icteric form—accounting for approximately 5–10% of cases—typically causes serious end-organ complications and multi-organ failure [12]. Importantly, severe pulmonary complications, including pulmonary haemorrhagic syndrome, may also occur in anicteric cases and are associated with a higher case fatality rate [13]. Disease severity has been defined heterogeneously across the literature, and jaundice alone is an unreliable marker of clinical severity [14].

Leptospirosis follows a characteristic biphasic course. The initial septicaemic phase lasts two to nine days, followed by a brief remission period of one to three days with minimal fever. The second, immune-mediated phase is clinically critical and is associated with the development of major complications. In severe cases, the two phases may overlap, resulting in a continuous, undifferentiated illness [2,15]. The reported prevalence of severe leptospirosis among hospitalised patients varies widely—from 5% to over 60%—depending largely on the severity criteria applied and the clinical setting [16–18]. Clinical prediction of severity at the time of initial presentation is particularly challenging, as life-threatening complications typically emerge during the immune phase [13].

Early identification of predictors enables prompt treatment, including antibiotics, dialysis, or intensive care unit (ICU) admission, to reduce complications and improve clinical outcomes [19,20]. This study aimed to identify predictors of severe leptospirosis in Malaysia's endemic population, where it poses a major health problem. This will help clinicians, especially in rural areas, detect high-risk patients early and initiate proper management, including transfers to higher care levels and antibiotic therapy. This study is among the largest studies in this region using a dataset of this scale.

2. Materials and Methods

2.1. Study Location and Participants

This study was conducted at Hospital Universiti Sains Malaysia (HUSM) and Hospital Perempuan Raja Zainab II (HPRZII), two tertiary teaching hospitals located in Kelantan, northeastern Peninsular Malaysia. Kelantan is consistently reported to have among the highest leptospirosis incidence and mortality rates in Malaysia [21]. The state occupies

14,922 square kilometres on the East Coast of Peninsular Malaysia, with a population of approximately 1.8 million [22].

Medical records of adults with confirmed leptospirosis admitted between 2011 and 2017 were reviewed retrospectively. Inclusion criteria required confirmed adult cases with hospital stays exceeding two days and sufficient clinical and laboratory data for analysis. Patients with confirmed co-infections—including malaria, typhus, rickettsia, yellow fever, viral hepatitis, Rocky Mountain spotted fever, and arenavirus infection—were excluded to minimise diagnostic confounding.

2.2. Data Collection

A standardised data collection form was designed and approved by the relevant hospital ethics committees. Patient demographics and clinical data at hospital admission were recorded prospectively onto the form. Laboratory findings were recorded daily during hospitalisation until discharge or death; however, for the purposes of this analysis, baseline data were defined as values obtained on the day of admission or within the first 24 h of presentation, prior to the initiation of any therapeutic intervention. This definition was applied to minimise temporal ambiguity between predictor variables and the classification of disease severity.

Comorbidities were documented if recorded in the patient's medical file. Patient records and hospital database systems were used to extract clinical history, medication data, and laboratory results. Data were analysed anonymously using patient registration numbers, with unique study codes assigned prior to analysis.

2.3. Diagnosis and Severity Classification

A suspected leptospirosis case was defined as an acute febrile illness with exposure to contaminated water or a contaminated environment, accompanied by any one or more of the following features: headache, myalgia (particularly affecting calf muscles and the lumbar region), arthralgia, conjunctival suffusion, meningeal irritation, anuria or oliguria and/or proteinuria, jaundice, haemorrhagic manifestations (intestinal or pulmonary), cardiac arrhythmia or failure, skin rash, or gastrointestinal symptoms including nausea, vomiting, abdominal pain, or diarrhoea. Cases confirmed by IgM-specific ELISA were included in the analysis.

It is acknowledged that IgM ELISA carries well-established diagnostic limitations, including cross-reactivity with other febrile illnesses prevalent in the region—such as dengue and brucellosis—and the potential inability to reliably distinguish acute from convalescent or past infections in the absence of paired serology. In our setting, the Microscopic Agglutination Test (MAT), which is considered the reference standard for serological confirmation, was not routinely available as a point-of-care diagnostic during the study period, nor was polymerase chain reaction (PCR) universally performed. This reflects a real-world clinical constraint common to many endemic, resource-limited settings in Southeast Asia and represents an acknowledged limitation of this study that may result in a degree of diagnostic misclassification.

Confirmed cases were stratified into severe and non-severe leptospirosis according to previously published criteria [23,24]. To minimise circularity between the outcome definition and predictor variable selection, variables that directly formed part of the severity classification criteria—including serum creatinine thresholds used to define acute kidney injury (AKI) as a severity component—were excluded from the multivariable regression model. Only admission-point laboratory and clinical values were entered as predictors; progressive or peak in-hospital values that may reflect downstream disease evolution rather than baseline risk were not included.

2.4. Operational Definitions

Severe leptospirosis was defined by the presence of any of the following: jaundice (serum bilirubin > 51.3 μmol/L); renal insufficiency (oliguria with urine output <400 mL/day, or serum creatinine > 133 μmol/L, or blood urea > 25.5 mmol/L); ICU admission; initiation of dialysis; hospital stay exceeding ten days; or multi-organ dysfunction [24]. Additional definitions applied were: shock (systolic blood pressure < 90 mmHg or mean arterial pressure < 70 mmHg with requirement for vasopressor support); respiratory failure (respiratory insufficiency requiring mechanical ventilation); rhabdomyolysis (myalgia with creatine kinase elevation > 5 × upper limit of normal [ULN]); thrombocytopenia (platelet count < 100 × 10^9/L); leukocytosis (white blood cell count > 11.0 × 10^9/L); multi-organ dysfunction (dysfunction of two or more organ systems); delayed/late hospitalisation (hospital admission after four days of symptom onset); sepsis (systemic inflammatory response syndrome criteria in the presence of confirmed or suspected infection); hyponatraemia (serum sodium < 135 mmol/L); hypokalaemia (serum potassium < 3.5 mmol/L); elevated ALT (>2 × ULN); elevated AST (>2 × ULN); elevated ALP (>2 × ULN); prolonged PT (prothrombin time > 15 s); and prolonged aPTT (activated partial thromboplastin time > 40 s).

2.5. Statistical Analysis

Data were analysed using SPSS version 24 (SPSS Inc., Chicago, IL, USA). Patients were classified as severe or non-severe as described above. Categorical variables are presented as frequencies and percentages and were analysed using the Chi-square or Fisher's exact test as appropriate. Continuous variables are presented as mean ± standard deviation and were compared between groups using the independent samples *t*-test.

For the identification of independent predictors of severe disease, multivariable logistic regression was performed. Variable selection followed a purposeful approach informed by clinical plausibility, pathophysiological relevance, and statistical significance at univariate level. Variables attaining $p < 0.25$ on univariate analysis were considered for inclusion in the multivariable model, consistent with the recommendations of Hosmer and Lemeshow [25,26], which allow for the retention of potential confounders that may not reach conventional significance thresholds at the univariate stage. Variables directly incorporated into the severity outcome definition were excluded from the predictor set to prevent circular reasoning. After initial multivariable modelling, a stepwise backward elimination approach was applied. Multicollinearity among candidate predictors was assessed using the variance inflation factor (VIF); no variable pair demonstrated a VIF exceeding 5, indicating the absence of significant collinearity.

Internal validation of the final model was performed using bootstrap resampling with 1000 iterations; the optimism-corrected AUC is reported alongside the apparent AUC. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and a calibration plot. The sensitivity, specificity, and optimal cut-off threshold of the model were determined from receiver operating characteristic (ROC) curve analysis using the Youden Index. Odds ratios and 95% confidence intervals are reported. A *p*-value of <0.05 was considered statistically significant. Forest plots for univariate and multivariable analyses were generated using R (version 4.5.2) to visually represent effect sizes and confidence intervals.

3. Results

3.1. Patient Characteristics and Demographics

Of all patients admitted to the two hospitals during the study period, 525 met the inclusion and exclusion criteria and were included in the final analysis (see Figure 1). Severe leptospirosis was identified in 303 (57.7%) patients and non-severe disease in 222 (42.3%).

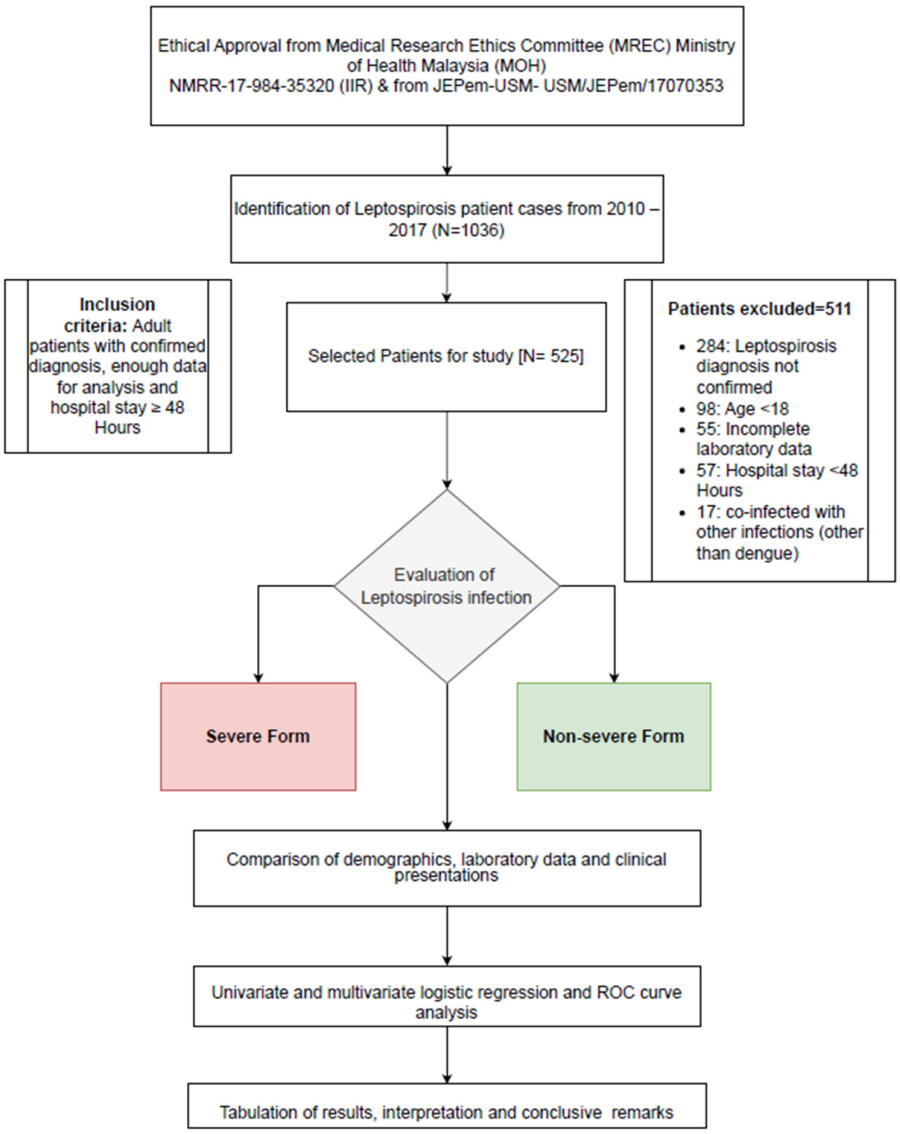


Figure 1. Study flow diagram.

The mean age was 38.1 ± 16.8 years. Male sex predominated, accounting for 65.5% of cases. The majority of patients resided in urban settings (74.1%), and 94.8% were of Malay ethnicity. Nine patients (1.7%) reported a previous episode of leptospirosis. Seventeen pregnant patients were included, of whom 11 had non-severe disease. The most common comorbidities were hypertension (16.4%) and diabetes mellitus (13.3%). Pre-existing chronic kidney disease (CKD) was significantly associated with severe disease ($p < 0.001$), as was the presence of multiple comorbidities (>2 comorbidities; $p = 0.002$).

Forty-eight percent of patients were classified as belonging to the leptospirosis risk group on the basis of occupational or environmental exposures, including direct contact with rodents (6.1%), contact with natural bodies of water (29.7%), contact with water or mud during work (5.1%), travel to an endemic area (7.6%), residence near an endemic area

(1.9%), presence of domestic animals at home or work (3.4%), and handling animal excreta with bare hands (0.2%). However, membership of the leptospirosis risk group was not significantly associated with the severe form of disease ($p = 0.543$), suggesting that severity is more likely determined by host immune response characteristics or the specific infecting serogroup than by the nature of the initial exposure.

Patients were hospitalised after a mean of 5.18 ± 4.2 days from symptom onset and commenced antibiotic therapy after a mean of 6.13 ± 5.2 days. Delayed hospitalisation (admission after day four of symptoms) occurred in 49.1% of cases, and antibiotic initiation beyond three days from symptom onset in 70.5%. Both were significantly associated with severe disease ($p = 0.021$ and $p = 0.010$, respectively). However, as discussed below, these associations should not be interpreted causally given the potential for confounding by illness severity at presentation and the possibility of reverse causality. Overall mortality was 6.5%; all but one death occurred within the severe disease group ($p < 0.001$). Full demographic and clinical data are presented in Table 1.

Table 1. Demographic and Clinical Features at Baseline for Leptospirosis Patients.

Variable	Overall (*N* = 525)	Non-Severe (*N* = 222)	Severe (*N* = 303)	*p*
Age (years), mean ± SD	38.1 ± 16.8	34.3 ± 16.2	40.9 ± 16.8	<0.001
Age > 40 years, *N* (%)	216 (41.1%)	66 (29.7%)	150 (49.5%)	<0.001
Male sex, *n* (%)	344 (65.5%)	132 (59.5%)	212 (70.0%)	0.012
Rural residence, *n* (%)	136 (25.9%)	49 (22.1%)	87 (28.7%)	0.082
Leptospirosis risk group, *n* (%)	252 (48.0%)	110 (49.5%)	142 (46.9%)	0.543
Smoking, *n* (%)	117 (22.3%)	39 (17.6%)	78 (25.7%)	0.026
Shock (requiring inotropes), *n* (%)	49 (9.3%)	4 (1.8%)	45 (14.9%)	<0.001
Pulmonary infiltrate, *n* (%)	112 (21.3%)	33 (14.9%)	79 (26.1%)	0.001
T-wave changes, *n* (%)	32 (6.1%)	4 (1.8%)	28 (9.2%)	<0.001
CKD, *n* (%)	23 (4.4%)	0 (0.0%)	23 (7.6%)	<0.001
Multiple comorbidities (>2), *n* (%)	17 (3.2%)	1 (0.5%)	16 (5.3%)	0.002
Delayed hospitalisation (>4 d), *n* (%)	258 (49.1%)	96 (43.2%)	162 (53.5%)	0.021
Delayed antibiotics (>3 d), *n* (%)	370 (70.5%)	142 (64.0%)	228 (75.2%)	0.010
Length of stay, days (mean ± SD)	6.77 ± 5.7	4.5 ± 1.8	8.41 ± 6.8	<0.001
Death, *n* (%)	34 (6.5%)	1 (0.5%)	33 (10.9%)	<0.001

CKD: chronic kidney disease. *p*-values indicate statistical significance ($p < 0.05$). Selected clinically significant variables shown; full dataset available in Supplementary Table S1.

3.2. Clinical Manifestations at Presentation

Clinical manifestations at hospital admission were categorised by prevalence into common (>30%), less common (10–30%), and rare (<10%) symptoms. Most patients presented with typical features of leptospirosis, including fever (93.7%), myalgia (65.7%), nausea and vomiting (61.1%), arthralgia (54.1%), and headache (48.2%). With the exception of abdominal pain and lethargy, symptoms occurring in more than 30% of patients were more frequently encountered in the non-severe group. Symptoms significantly associated with severe disease included lethargy, dehydration, hepatomegaly, dyspnoea, pulmonary rales, conjunctival suffusion, and any haemorrhagic manifestation (including haematemesis, haematuria, haemoptysis, gingivorrhagia, petechiae/purpura/ecchymosis, melaena, and pulmonary haemorrhage). Acute pancreatitis was documented in 13 patients, all of whom had severe disease. Full clinical manifestation data are summarised in Table 2.

Table 2. Selected Clinical Manifestations at Presentation by Disease Severity.

Symptom/Sign	Overall *N* = 525 (%)	Non-Severe *N* = 222 (%)	Severe *N* = 303 (%)	*p*
COMMON (≥30%)				
Fever	492 (93.7%)	215 (96.8%)	277 (91.4%)	0.011
Myalgia	345 (65.7%)	169 (76.1%)	176 (58.1%)	<0.001
Nausea and vomiting	321 (61.1%)	138 (62.2%)	183 (60.4%)	0.682
Arthralgia	284 (54.1%)	137 (61.7%)	147 (48.5%)	0.003
Lethargy	213 (40.6%)	73 (32.9%)	140 (46.2%)	0.002
LESS COMMON (10–30%)				
Dehydration	141 (26.9%)	45 (20.3%)	96 (31.7%)	0.004
Haemorrhagic diathesis	95 (18.1%)	16 (7.2%)	79 (26.1%)	<0.001
Hepatomegaly	89 (17.0%)	24 (10.8%)	65 (21.5%)	0.001
Dyspnoea	87 (16.6%)	22 (9.9%)	65 (21.5%)	<0.001
RARE (<10%)				
Conjunctival suffusion	42 (8.0%)	8 (3.6%)	34 (11.2%)	0.002
Pulmonary haemorrhage	18 (3.4%)	0 (0.0%)	18 (5.9%)	<0.001
Pancreatitis	13 (2.5%)	0 (0.0%)	13 (4.3%)	0.002

p-values indicate statistical significance ($p < 0.05$). Full symptom data available in Supplementary Table S2.

3.3. Clinico-Laboratory Characteristics of Study Participants (at Baseline)

Compared to non-severe form, mean values of uric acid, liver enzymes (ALT, AST, ALP), bleeding indicators (PT, aPTT, INR), inflammatory indicator (CRP) and creatine kinase (CK) were significantly higher in severe leptospirosis patients. These patients had significantly lower mean values of sodium (Na^{2+}), total protein, albumin, RBCs, platelets and hematocrit. Although they had lower hemoglobin and venous PH and higher pulse oximetry, the difference was statistically insignificant. A substantial number of patients had thrombocytopenia, leukocytosis and prolonged PT in the study cohort, significantly higher in severe cases. They also showed higher prevalence of hyponatremia, hypokalemia, hyperuricemia, deranged liver enzymes, hypoalbuminemia, rhabdomyolysis, anemia and prolonged aPTT. These findings indicate that severe leptospirosis patients present with marked variability in laboratory results compared to mild cases (See Supplementary Table S3).

3.4. Prevalence of Acute Kidney Injury (AKI) in Leptospirosis Patients

Of the 525 patients, 258 (49.1%) developed AKI according to the Acute Kidney Injury Network (AKIN) classification, based on serum creatinine criteria (urine output data were incomplete and therefore not used). AKIN stage I was documented in 92 patients (17.5%), stage II in 49 (9.3%), and stage III in 117 (22.3%). Given the substantial overlap between AKI and the clinical criteria used to define severe leptospirosis, AKI was excluded from the multivariable regression analysis to avoid circularity.

3.5. Multivariable Predictors of Severe Leptospirosis

Ten variables were included in the initial multivariable model based on clinical relevance, statistical significance in univariate analysis, and pathophysiological plausibility. Variables incorporated directly into the severity outcome definition were excluded. Male sex, lethargy, and dyspnoea were significantly associated with severe leptospirosis on univariate analysis but did not retain independent significance at the multivariable level.

Seven independent predictors of severe leptospirosis were identified (Figure 2, Table 3): age > 40 years (OR 3.06; 95% CI: 1.85–5.07), delayed hospitalisation after four days of symptom onset (OR 1.97; 95% CI: 1.28–3.03), T-wave changes on electrocardiography (OR 6.9; 95% CI: 2.28–20.9), conjunctival suffusion (OR 3.5; 95% CI: 1.23–9.95), hyponatraemia (OR 3.04; 95% CI: 1.74–5.31), prolonged PT (OR 2.15; 95% CI: 1.35–3.42), and elevated ALT (OR 2.87; 95% CI: 1.46–5.64).

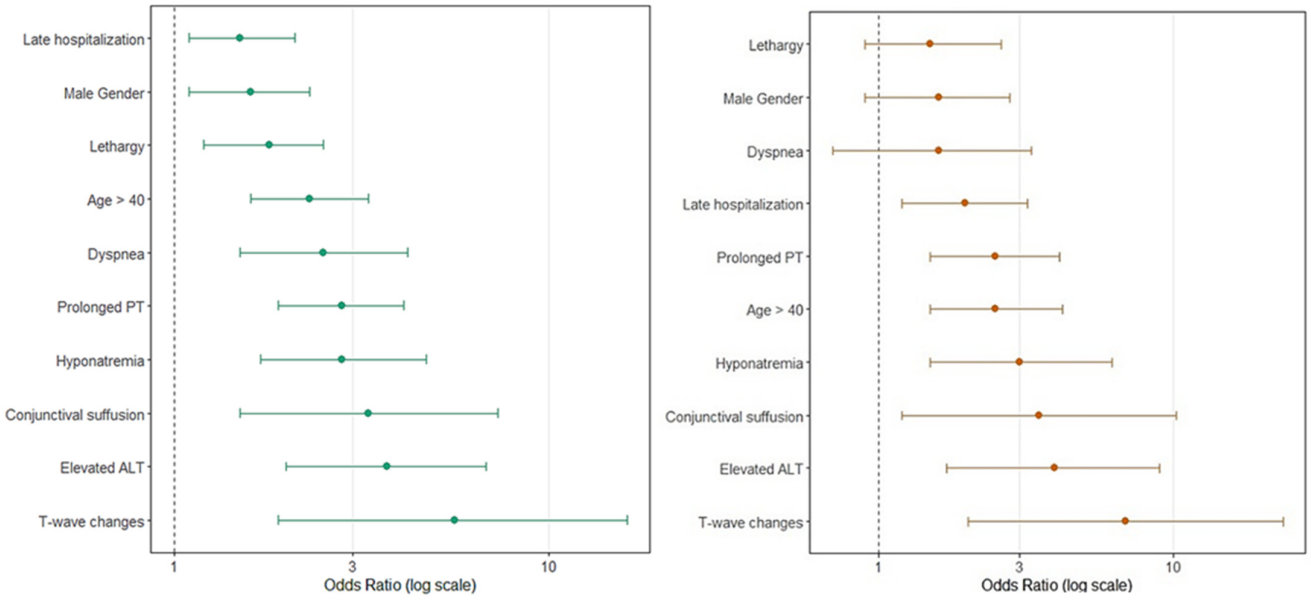


Figure 2. Forest plots for odds ratio of (**a**) Univariate and (**b**) Multivariate analysis for risk factors associated with severe form of leptospirosis. The vertical dotted line represents the line of no effect (odds ratio = 1).

Table 3. Independent Predictors of Severe Leptospirosis on Multivariable Logistic Regression.

Variable	Adjusted OR	95% Confidence Interval	*p*
T-wave changes (ECG)	6.90	2.28–20.90	<0.001
Age > 40 years	3.06	1.85–5.07	<0.001
Hyponatraemia	3.04	1.74–5.31	<0.001
Conjunctival suffusion	3.50	1.23–9.95	0.019
Elevated ALT (>2 × ULN)	2.87	1.46–5.64	0.002
Prolonged PT	2.15	1.35–3.42	0.001
Delayed hospitalisation (>4 d)	1.97	1.28–3.03	0.002

OR: odds ratio; ALT: alanine aminotransferase; PT: prothrombin time; ECG: electrocardiography; ULN: upper limit of normal. Overall model AUC: 0.794 (apparent); 0.778 (bootstrap-corrected). Hosmer–Lemeshow $p = 0.31$.

ROC curve analysis demonstrated good discriminatory ability for the multivariable model, with an apparent AUC of 0.794 (95% CI: 0.747–0.841; $p < 0.001$) and an optimism-corrected AUC of 0.778 following bootstrap internal validation. The Hosmer–Lemeshow goodness-of-fit test indicated adequate model calibration ($p = 0.31$). At the optimal cut-off derived using the Youden Index, the model achieved a sensitivity of 74.3% and specificity of 72.1% for predicting severe leptospirosis (Figure 3).

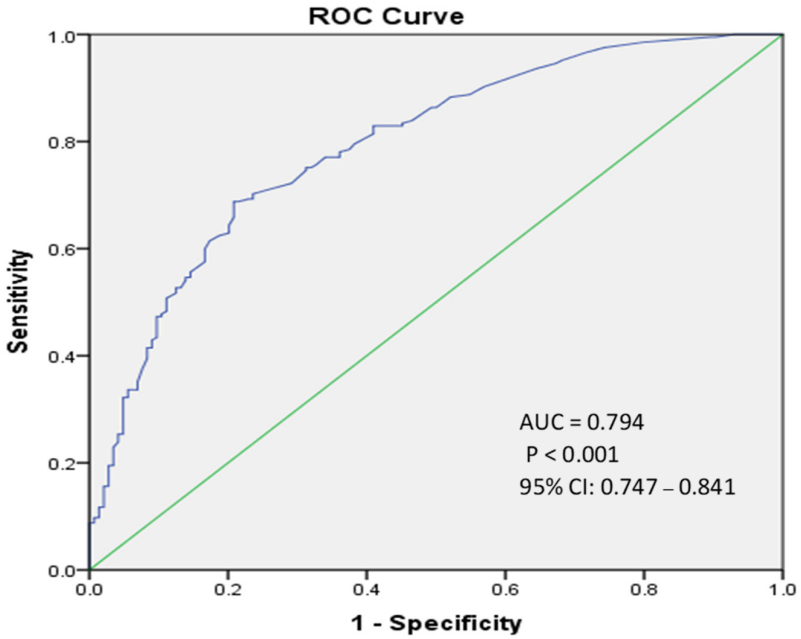


Figure 3. ROC curve analysis of logistic regression model to predict severe leptospirosis. The blue curve denotes the ROC curve of the predictive model. The green diagonal line represents the line of no discrimination (AUC = 0.5), serving as a reference for chance-level performance.

4. Discussion

This study provides a comprehensive analysis of predictors of severe leptospirosis in an endemic Malaysian population, representing one of the largest cohort studies to systematically evaluate this question in this setting. Seven independent predictors of severe disease were identified on multivariable logistic regression: age > 40 years, delayed hospitalisation, T-wave electrocardiographic changes, conjunctival suffusion, hyponatraemia, prolonged prothrombin time, and elevated ALT. These findings have practical clinical utility, as none requires specialist investigation; all can be assessed at the point of initial hospital presentation and may help clinicians—particularly in rural and resource-limited settings—stratify patients for escalated care.

The proportion of patients with severe leptospirosis in this cohort (57.7%) is broadly consistent with several previously published series from similar epidemiological settings [17,18]. Importantly, this elevated proportion likely reflects the tertiary referral nature of the study hospitals, which disproportionately admit more severely ill patients, and should not be extrapolated as representative of community-level disease severity. Male sex predominated (65.5%), and males with severe disease were more likely to present with pulmonary complications and shock, consistent with broader evidence suggesting that male sex is associated with both higher infection rates and more severe clinical outcomes [27–29]. Age > 40 years emerged as the strongest demographic predictor of severity (OR 3.06), consistent with studies from other high-incidence settings demonstrating that older age—typically defined at 45–46 years in those studies—is independently associated with severe disease and mortality [30–32]. The underlying mechanisms likely include age-related immune senescence, higher comorbidity burden, and delays in health-seeking behaviour.

T-wave changes on electrocardiography constituted the strongest independent predictor in the model (OR 6.9), occurring in 9.2% of severe cases in this cohort. This is consistent with a French retrospective study that identified ECG abnormalities as independent predictors of severity (OR 31.2) [33], though the magnitude of effect in that study was considerably larger, possibly reflecting differences in cardiac monitoring practices and patient selection.

Cardiac involvement in leptospirosis is well-recognised and associated with poor outcomes, though its pathophysiology remains incompletely understood [34,35]. The identification of T-wave changes as the most potent predictor in our model underscores the importance of routine electrocardiographic assessment in all hospitalised leptospirosis patients.

Conjunctival suffusion was identified as an independent predictor of severity (OR 3.5). This finding merits cautious interpretation: conjunctival suffusion is a classical diagnostic feature of leptospirosis and its association with severe disease may, in part, reflect clinical recognition bias or diagnostic intensity bias—clinicians with a high index of suspicion for leptospirosis may perform more thorough physical examinations and document this sign more consistently. An alternative, biological explanation is that the presence of conjunctival suffusion reflects a higher circulating bacterial burden or a more pronounced inflammatory response at presentation, which in turn predisposes to more severe systemic disease. This has been documented by others, who reported conjunctival suffusion in 56–60% of patients admitted to intensive care units with severe leptospirosis [36,37]. We recommend that this finding be interpreted with appropriate caution and validated in prospective cohorts with standardised clinical documentation.

Hyponatraemia (OR 3.04) was a significant independent predictor, consistent with published evidence demonstrating that electrolyte disturbances are a central feature of severe leptospirosis [38,39]. The pathophysiology of hyponatraemia in this context is multifactorial, involving inappropriate antidiuretic hormone secretion, renal sodium wasting, and fluid redistribution secondary to systemic inflammation. Prolonged PT (OR 2.15) reflects the coagulopathy associated with severe leptospirosis, mediated by leptospiral endothelial injury, thrombocytopenia, and hepatic dysfunction [40,41]. Elevated ALT (OR 2.87) corroborates published data demonstrating that hepatic dysfunction, whilst rarely directly life-threatening, is a consistent accompaniment of severe leptospirosis [42,43].

Delayed hospitalisation—defined as presentation beyond four days from symptom onset—was independently associated with severe disease (OR 1.97). This finding must be interpreted with particular caution, however, as the association is likely subject to confounding by illness severity at presentation and may reflect reverse causality: patients who develop the most severe clinical courses may simply do so by virtue of having a more aggressive infecting serogroup or less favourable host immune response, and these same biological factors may delay their recognition and health-seeking. Accordingly, this finding is presented as a hypothesis-generating observation and should not be interpreted as evidence that delayed presentation causes severe disease. Prospective studies with prespecified predictor capture and robust exposure characterisation are required to address this question.

Regarding antibiotic therapy, intravenous ceftriaxone was the most commonly used agent in this cohort, either alone or in combination with doxycycline or azithromycin. Although delayed antibiotic initiation beyond three days from symptom onset was significantly associated with severe disease on univariate analysis, the same caveat regarding reverse causality applies. Multiple published trials and a meta-analysis have not demonstrated a significant difference in outcome between antibiotic regimens [44,45], though early initiation has been associated with reduced rates of ICU admission in some series [46,47]. Based on the available evidence, presumptive antibiotic treatment during the diagnostic workup—particularly with low-cost β-lactam or cephalosporin regimens—remains a reasonable and clinically defensible practice in endemic settings.

Dengue co-infection was identified in 7% of patients and, whilst not associated with severe leptospirosis in this cohort [48,49], it contributed to diagnostic delay in a number of cases, highlighting the ongoing need for reliable, rapid diagnostic tools that can differentiate these conditions in endemic settings [50]. More than half of pregnant patients in the cohort

had non-severe disease; early diagnosis and antibiotic treatment appear to be effective in minimising feto-maternal complications [51].

The overall mortality in this cohort was 6.5%, with almost all deaths occurring in the severe disease group. This is broadly consistent with published case fatality rates for hospitalised leptospirosis patients in endemic Southeast Asian settings. The relatively low mortality likely reflects the predominance of the hepato-renal form of severe disease, with limited pulmonary haemorrhagic syndrome, the most lethal manifestation. However, severe pulmonary haemorrhagic syndrome (SPHS) has been reported elsewhere in Malaysia and its emergence in other states cannot be excluded, warranting ongoing epidemiological surveillance.

Several important emerging considerations warrant discussion. Whole-genome sequencing has enabled the identification of novel Leptospira strains in Malaysia, including *Leptospira yasudae* [52]. Although the virulence characteristics of this strain have yet to be fully elucidated, this finding underscores the need for continued research in the field. Additionally, host genetic factors—including polymorphisms in Toll like receptors (TLR1 and TRL2)—have been associated with dysregulated immune responses and an elevated risk of developing severe leptospirosis [53].

Regarding prognostic biomarkers, a recent review by Wickramasinghe and colleagues identified several novel candidates showing promise as early indicators of disease severity, including long pentraxin 3 (PTX3), classical pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), and circulating microRNAs (e.g., miR-601 and miR-630) [54]. Furthermore, a landmark study by Fanelli and colleagues examining the spatiotemporal dynamics of leptospirosis in Europe demonstrated that climate change is reshaping disease transmission patterns, further underscoring the need for adaptive surveillance strategies and targeted public health responses [55].

Limitations

This study has several limitations that should be considered when interpreting its findings. The retrospective design predisposes to incomplete data capture, documentation bias, and limited ability to control for unmeasured confounders. Selection bias arising from the study being conducted at two tertiary referral hospitals may limit generalisability to primary or community-level healthcare settings, where disease severity may differ. Diagnostic confirmation relied solely on IgM ELISA, which carries the limitations described in the Methods section. Data on infecting Leptospira serovars and leptospiral load were not available, precluding assessment of their contribution to disease severity. The temporal definition of 'baseline' was applied to reduce predictor–outcome ambiguity, but residual misclassification cannot be entirely eliminated in a retrospective design. Additionally, whilst internal bootstrap validation was performed, external validation in an independent cohort is necessary before this predictive model is used in clinical practice.

A predictive risk model for both severe and non-severe leptospirosis is demonstrated in Figure 4.

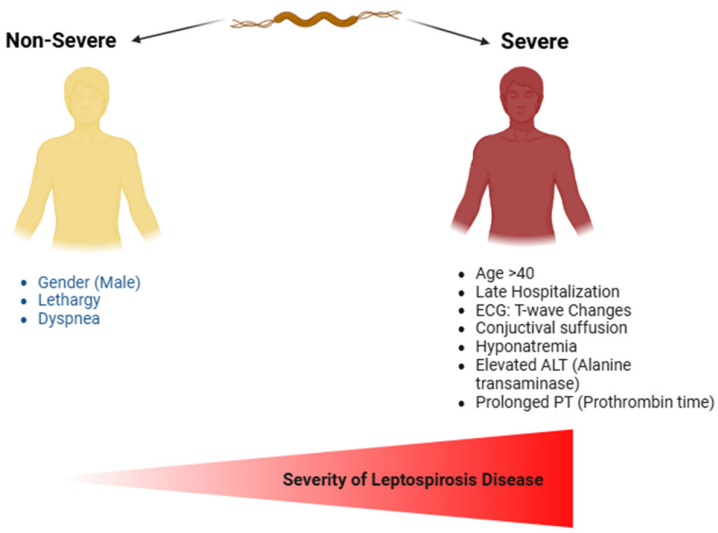


Figure 4. Predictive model for leptospirosis severity risk.

5. Conclusions

Severe leptospirosis is common among hospitalised adults in this endemic Malaysian setting, accounting for 57.7% of confirmed cases and carrying a mortality rate of 6.5%. Seven independent predictors of severe disease were identified—age > 40 years, delayed hospitalisation, T-wave ECG changes, conjunctival suffusion, hyponatraemia, prolonged PT, and elevated ALT—all of which are assessable at the bedside or from routine admission investigations. Early identification of these features may guide prompt risk stratification and targeted management, with the potential to reduce morbidity and mortality. Further prospective, multicentre studies—ideally incorporating serovar characterisation and host genetic profiling—are needed to confirm and extend these findings across different populations and healthcare settings.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/amh71020016/s1, Table S1: Demographic and Clinical Features (at baseline) for Leptospirosis Patients; Table S2: Comparison of Clinical manifestation (at baseline) between patients with severe and non-severe form of leptospirosis; Table S3: Clinico-Laboratory Findings at Baseline by Disease Severity, Grouped by Physiological System.

Author Contributions: Conceptualization, Y.K.A.H., S.A.S.S. and A.H.K.; methodology, S.A.S.S., A.H.K. and A.S.A.; investigation, Y.K.A.H. and A.S.A.; data curation, Y.K.A.H. and A.S.A.; formal analysis, S.Q.A.-E., Y.K.A.H. and N.H.; writing—original draft preparation, Y.K.A.H., A.H.K. and N.H.; writing—review and editing, N.H., Y.K.A.H., S.A.S.S., A.H.K., A.S.A., S.Q.A.-E. and A.A.; visualization, N.H. and Y.K.A.H.; supervision, S.A.S.S., A.H.K. and A.S.A.; project administration, Y.K.A.H., S.A.S.S., A.H.K., N.H. and A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was approved by the Ministry of Health Malaysia Research Ethics Committee (MREC) (NMRR-17-984-35320) (Approved Date: 18 July 2017) and Human Research Ethics Committee USM (JEPem) (USM/JEPeM/17070353) (Approved Date: 4 June 2018). All methods followed hospital guidelines and regulations.

Informed Consent Statement: Patients' informed consent was waived due to the retrospective design.

Data Availability Statement: The original contributions presented in this study are included in the article and Supplementary Materials. Further inquiries can be directed to the corresponding authors.

Acknowledgments: During the preparation of this manuscript, the author(s) used ChatGPT (https://chat.openai.com, OpenAI, GPT-4 and claud.ai, Anthropic Claude Sonnet 4.6) for the purposes of academic language polishing, citation audit and cross-referencing, and reference list renumbering and sequential realignment. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

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