# Determination of Liver Function Tests and Liver Ultrasonographic Findings in Patients with Leptospirosis in a Tertiary Hospital

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## ABSTRACT

**Introduction.** Leptospirosis is an important zoonotic disease commonly found in tropical or sub-tropical countries. The most severe form is Weil's syndrome which presents with jaundice, renal failure, and bleeding diatheses. Although jaundice occurs in 38% of patients with leptospirosis, no studies in Asia have focused on the liver biochemical profile of these patients. Characterization of liver biochemical profile and ultrasonographic findings may shed more light on the disease process. Identification of liver biochemical parameters that portend a poor prognosis may also allow for early aggressive intervention.

**Objective.** To describe the liver biochemical profile and liver ultrasonographic findings in adult patients with laboratory-confirmed leptospirosis, admitted at a tertiary hospital in Manila, Philippines. The association of clinical and laboratory features with clinical outcomes (i.e., severe liver injury, Weil's syndrome, and mortality) was also investigated.

**Methods.** This retrospective cross-sectional study reviewed all available cases of adult patients with laboratory-confirmed leptospirosis admitted in the Philippine General Hospital from January 2009 to August 2018. The clinical features, liver biochemical profiles, and ultrasound findings were recorded and analyzed. Comparison between the means of each group based on clinical outcome (i.e., mortality, Weil's syndrome) was done via Students' t-test for continuous variables, and calculation of the Odds Ratio for categorical variables.

**Results.** Total and direct bilirubin levels were elevated in patients with leptospirosis compared to serum amino-transferases and alkaline phosphatase levels which were only mildly elevated. Abdominal ultrasound showed typically un-enlarged livers with normal parenchymal echogenicity, normal spleens, and non-dilated biliary trees. Dyspnea was associated with an increased odds for mortality. Although jaundice was present in 39.5% of patients and significantly associated with severe liver injury, this was not associated with mortality. Liver biochemical test values did not differ among patients who expired and those who survived to discharge. The presence of myalgia and abdominal pain increased the odds for Weil's syndrome.

**Conclusion.** To date, no local studies have fully described the liver biochemical profile of patients with leptospirosis. Our findings are compatible with previous studies showing that leptospirosis typically presents with predominantly elevated direct bilirubin from cholestasis and systemic infection. Contrary to previous literature, however, our study found no association between jaundice and mortality.

*Keywords: leptospirosis, liver profile, liver ultrasound*



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## INTRODUCTION

Leptospirosis is an important zoonotic disease worldwide. It was first described in 1886 by Adolf Weil with a presentation consisting of splenomegaly, jaundice, and nephritis.[1] Leptospirosis can present with great clinical variability, from a mild flu-like illness to life threatening shock and hemorrhage.[1] Weil's syndrome, at the extreme end of this spectrum, is classically defined as a triad of jaundice, renal failure, and hemorrhage (i.e., pulmonary, gastrointestinal, etc.).[1]

In developed countries, infection is through exposure to contaminated water (via agriculture, outdoor recreational activities, and travel to endemic areas).[2] Whereas, in developing countries, outbreaks are related to poor sanitation, overcrowding, climatic conditions, and normal daily activities.[3]

This disease is endemic to many countries in the Asia Pacific region such as Bangladesh, Cambodia, India, Indonesia, Laos, Nepal, Sri Lanka, Thailand, Vietnam, and the Philippines.[3] Acute epidemics have been documented after flooding in Indonesia, India, and the Philippines.[3,4]

In the Philippines, there were a total of 5,232 cases reported in 2018, showing an increase of 70.59% compared to 2017. Most cases were from the National Capital Region (37.98%), with males comprising a majority of the cases (84%), and with most (14%) belonging to the 20-24-year- old age group. The case fatality rate for this year was at 9.65%.[5]

There have been no previous local studies describing at length the liver biochemical profile and ultrasonographic picture of patients with leptospirosis. The characterization of liver biochemical profile and ultrasonographic findings that portend a poorer prognosis, may allow for earlier recognition, and may identify those patients who will benefit from ICU admission and more aggressive treatment. This study aims to describe the liver biochemical profile and ultrasonographic findings commonly seen among in-patient Filipino adults diagnosed with leptospirosis, as well as to determine if there is a correlation between these features and clinical outcomes (i.e., mortality). This study also aims to determine the association between clinical features (demographics and clinical presentation), liver biochemical tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubins, alkaline phosphatase, and international normalized ratio [PT-INR]) and the occurrence of severe liver injury, Weil's syndrome, and mortality.

## METHODS

### Study Design

This was a retrospective cross-sectional study. Adults who were at least 18 years old, diagnosed with laboratory-confirmed leptospirosis, and admitted at the Philippine General Hospital, a tertiary hospital in Manila, Philippines, from January 2009 to August 2018 were included in this study. Leptospirosis was confirmed via one of the following methods: Leptospira micro-agglutination test (lepto-MAT), rapid Leptospirosis IgM test, or culture. Patients whose charts could not be accessed, or whose records were not available for review were excluded from this study. Likewise, patients with known liver disease (i.e., acute and chronic viral hepatitis, alcoholic liver disease, chronic liver disease, etc.) were excluded.

### Ethical Considerations

This study was approved by the Ethics Review Board of the Philippine General Hospital (UPMREB code 2020-211-01). Utmost care was dedicated to ensuring the confidentiality of identifiable patient information: patient identifiers (i.e., names, addresses, telephone numbers) were not included. Informed consent was waived as this was a retrospective study, which utilized data available in the medical records of the institution.

### Data Collection and Analysis

The demographics of each patient (i.e., age, sex, known exposure to contaminated water sources), presenting symptoms (e.g., fever, myalgia, jaundice etc.), and clinical outcomes (i.e., survival to discharge vs. mortality) were collected. Age was stratified into patients 40 years and above and patients younger than 40. This is because a previous case control study showed that age 40 and above was a predictor of mortality.[6] For each patient, available baseline laboratory tests (aminotransferases, bilirubin, alkaline phosphatases, PT-INR, and ultrasonographic findings) were also encoded in the password-protected Excel file used by the authors. Patients who presented with Weil's syndrome (as determined by their respective physicians during their admission) were also taken note of. Classification of severe liver injury is based on the definition by the Philippine College of Physicians Leptospirosis Guidelines 2010, where severe leptospirosis is defined as an AST/ALT ratio of >4, or bilirubin levels >190 umol/L (Appendix). Those whose liver biochemical tests did not fall within these cut-off values were classified as having no severe liver injury.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. Categorical data (e.g., signs and symptoms) were summarized using frequencies and percentages. Continuous data (e.g., AST, ALT levels, AST:ALT ratios, bilirubin levels etc.), were described in means ± standard deviation. To compare means between groups (e.g., survivors vs. non-survivors), the Student's t-test was used. A range of values for the 95% confidence interval (CI) that did not cross the line of 1 was considered to be statistically significant. Associations between categorical variables (e.g., jaundice and mortality) were analyzed by calculating for the Odds Ratios (95% CI).

## RESULTS

A total of 120 patients with laboratory-confirmed leptospirosis, admitted from January 2009 to August 2018 were

initially included. One patient who had an incidental left liver lobe mass was excluded from the final analysis resulting to a total of 119 patients. Due to missing entries for some of the variables considered in the study, some of the summary statistics and statistical tests done used subsets of the 119 patients. Missing data on variables needed to classify severity of liver disease resulted in an analysis base of 64 patients. Likewise, results of liver biochemical tests also have varying bases due to missing entries. To maximize the available data, listwise deletion of patients where a case is omitted in the presence of missing entry in at least one variable was not done. Subjects with valid data on a variable or on a set of variables were included in the analyses. The baseline characteristics of the analyzed patients are outlined in Table 1.

The mean values of each liver biochemical test are presented in Table 2, however only 64 patients had baseline levels of AST, ALT, and bilirubins determined at admission. The mean AST and ALT levels showed only a modest increase at 2.8 and 1.9 times higher than the upper limit of normal, respectively. On the other hand, the bilirubins were significantly elevated at 9.8 times for total bilirubin and 24.9 times for direct bilirubin. However, the elevation was more modest at 2.2 times the upper limit of normal for mean indirect bilirubin, and at 1.3 times from the upper limit of normal for alkaline phosphatase. The coagulation profile as measured by PT-INR was within acceptable limits.

Only eight patients had an abdominal ultrasound done: all had non-dilated biliary trees and normal spleens. Five had normal livers and no gallstones. Another had hepatomegaly, fatty liver changes, and nonspecific gallbladder wall thickening. One had hepatomegaly and a normal gallbladder. One had fatty liver changes, and gallbladder stones.

**Table 1.** Baseline Characteristics and Clinical Profile

| Characteristics (Median Range) | Number of patients, n (%) |
|---|---|
| ***Age*** | |
| ≥40 years old | 58 (48.7) |
| <40 years old | 61 (51.2) |
| ***Male*** | 102 (85.7) |
| ***Exposure to contaminated water*** | 87 (73.1) |
| ***Duration of symptoms prior to admission*** *(mean days ± SD)* | 6.9 ± 4.4 |
| ***Weil's syndrome*** | 36 (30.2) |
| ***Need for hemodialysis*** | 62 (52.1) |
| ***Mortality*** | 5 (4.2) |
| ***Symptoms reported*** | |
| Fever | 112 (94.1) |
| Myalgia/Calf tenderness | 75 (83.0) |
| Nausea/vomiting | 59 (49.6) |
| Abdominal pain | 56 (47.1) |
| Oliguria | 54 (45.4) |
| Conjunctival suffusion | 47 (39.5) |
| Jaundice | 47 (39.5) |
| Diarrhea | 45 (37.8) |
| Cough | 25 (21.0) |
| Dyspnea | 17 (14.3) |
| Mental status changes | 13 (10.9) |
| Chest pain | 9 (7.6) |
| Hemoptysis | 9 (7.6) |

**Table 2.** Liver Biochemical Tests of Admitted Patients with Leptospirosis

| Liver biochemical test (normal values) [a] | n | Mean ± SD |
|---|---|---|
| ***AST*** *(14-36 IU/L)* | 106 | 102.30 ± 230.94 |
| ***ALT*** *(<35 IU/L)* | 110 | 65.80 ± 43.05 |
| ***AST/ALT Ratio*** | 105 | 1.40 ± 1.23 |
| ***Total Bilirubin*** *(3-22 umol/L)* | 68 | 214.70 ± 195.22 |
| ***Direct Bilirubin*** *(0-7 umol/L)* | 68 | 174.23 ± 172.25 |
| ***Indirect Bilirubin*** *(0-19 umol/L)* | 67 | 41.08 ± 48.63 |
| ***ALP*** *(38-126 IU/L)* | 10 | 162.30 ± 67.87 |
| ***PT-INR*** | 104 | 1.27 ± 0.36 |

[a] *Normal range of values are institution-based*

## Association of Clinical Characteristics to Clinical Outcomes

### *Severe Liver Injury*

Table 3 summarizes the proportion of patients who had severe liver injury, based on the criteria outlined by the Philippine College of Physicians Leptospirosis Guidelines of 2010, along with their clinical profile. Out of the 119 patients in the study, 56.3% ($n$ = 64) had complete data (AST, ALT, bilirubins) to apply these criteria for severe liver injury. From this group of patients, thirty-six were diagnosed with severe liver injury, while 28 were not. Given this, Table 3 only explores the association of severe liver injury with the other listed characteristics among the 64 patients with severe liver injury status. Results revealed that only jaundice was significantly associated with severe liver injury at the 0.05 level (OR = 5.49, 95% CI: 1.87, 16.10).

### *Mortality*

Of the 119 patients with laboratory confirmed leptospirosis, five expired (4.2%) and 114 survived to discharge (95.8%). Table 4A summarizes the distribution of patients per clinical characteristics and clinical outcomes (i.e., survival to discharge vs. mortality). Clinical characteristics were similar for both survivors and non-survivors, except for dyspnea (OR = 10.70, 95% CI: 1.64, 69.80), which was associated with higher odds of mortality. Severe liver injury (AST/ALT >4 or TB>190) was not found to be associated with mortality (OR = 3.38, 95% CI: 0.36, 32). No evidence of association was also seen between jaundice and mortality (OR = 2.39, 95% CI: 0.38, 14.90) as the 95% CI straddles the line of 1.

Table 4B also summarizes the results of the independent samples t-test to determine differences in mean liver biochemical test values between patients who survived and those

**Table 3.** Distribution of Patients according to Individual Characteristics and Severe Liver Injury

| Characteristics | | Severe Liver Disease | | | | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Yes | | No | | |
| | | n | % | n | % | |
| ***Age greater than or equal to 40*** | No | 18 | 60.0 | 12 | 40.0 | 0.75 (0.28, 2.03) |
| | Yes | 18 | 52.9 | 16 | 47.1 | |
| ***Sex*** | Female | 2 | 50.0 | 2 | 50.0 | 1.31 (0.17, 9.91) |
| | Male | 34 | 56.7 | 26 | 43.3 | |
| ***Exposure to contaminated water*** | No | 13 | 59.1 | 9 | 40.9 | 0.84 (0.30, 2.38) |
| | Yes | 23 | 54.8 | 19 | 45.2 | |
| ***Weil's syndrome*** | No | 4 | 36.4 | 7 | 63.6 | 2.67 (0.69, 10.20) |
| | Yes | 32 | 60.4 | 21 | 39.6 | |
| ***Need for hemodialysis*** | No | 14 | 60.9 | 9 | 39.1 | 0.75 (0.26, 2.10) |
| | Yes | 22 | 53.7 | 19 | 46.3 | |
| ***Mortality*** | No | 32 | 54.2 | 27 | 45.8 | 3.38 (0.36, 32.0) |
| | Yes | 4 | 80.0 | 1 | 20.0 | |
| ***Symptoms reported*** | | | | | | |
| Fever | No | 3 | 60.0 | 2 | 40.0 | 0.85 (0.13, 5.44) |
| | Yes | 33 | 55.9 | 26 | 44.1 | |
| Myalgia/Calf tenderness | No | 11 | 47.8 | 12 | 52.2 | 1.70 (0.61, 4.78) |
| | Yes | 25 | 61.0 | 16 | 39.0 | |
| Nausea/vomiting | No | 21 | 63.6 | 12 | 36.4 | 0.54 (0.20, 1.46) |
| | Yes | 15 | 48.4 | 16 | 51.6 | |
| Abdominal pain | No | 13 | 44.8 | 16 | 55.2 | 2.36 (0.86, 6.49) |
| | Yes | 23 | 65.7 | 12 | 34.3 | |
| Oliguria | No | 17 | 56.7 | 13 | 43.3 | 0.97 (0.36, 2.61) |
| | Yes | 19 | 55.9 | 15 | 44.1 | |
| Conjunctival suffusion | No | 22 | 59.5 | 15 | 40.5 | 0.73 (0.27, 2.00) |
| | Yes | 14 | 51.9 | 13 | 48.1 | |
| Jaundice | No | 10 | 34.5 | 19 | 65.5 | 5.49 (1.87, 16.10) |
| | Yes | 26 | 74.3 | 9 | 25.7 | |
| Diarrhea | No | 25 | 59.5 | 17 | 40.5 | 0.68 (0.24, 1.92) |
| | Yes | 11 | 50.0 | 11 | 50.0 | |
| Cough | No | 32 | 61.5 | 20 | 38.5 | 0.31 (0.08, 1.17) |
| | Yes | 4 | 33.3 | 8 | 66.7 | |
| Dyspnea | No | 30 | 55.6 | 24 | 44.4 | 1.20 (0.30, 4.74) |
| | Yes | 6 | 60.0 | 4 | 40.0 | |
| Mental status changes | No | 32 | 56.1 | 25 | 43.9 | 1.04 (0.21, 5.09) |
| | Yes | 4 | 57.1 | 3 | 42.9 | |
| Chest pain | No | 33 | 55.0 | 27 | 45.0 | 2.45 (0.24, 25.00) |
| | Yes | 3 | 75.0 | 1 | 25.0 | |
| Hemoptysis | No | 31 | 52.5 | 28 | 47.5 | 9.95 (0.53, 188.00) |
| | Yes | 5 | 100.0 | 0 | 0.0 | |

*Note: % are row percentages*

who expired (unequal variances assumed). Different bases (n) for survivors were observed for each liver biochemical test due to missing values. None of the available tests differed significantly between both groups of patients (95% CI across all variables straddling the line of 1). Therefore, association between the baseline liver biochemical tests and mortality could not be concluded.

### *Weil's Syndrome*

Table 5A summarizes the distribution of patients per clinical characteristics and the occurrence of Weil's syndrome. Myalgia or calf tenderness (OR = 3.07, 95% CI: 1.37, 6.91), and abdominal pain (OR = 2.69, 95% CI: 1.17, 6.17), as well as need for hemodialysis (OR = 200, 95% CI: 12.40, 3610.10), oliguria (OR = 5.41, 95% CI: 2.13, 13.7), and jaundice (OR = 43.50, 95% CI: 5.69, 333.00) were found to be significantly

**Table 4A.** Distribution of Patients according to Individual Characteristics and Mortality

| Characteristics | | Mortality | | | | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Non-Survivors | | Survivors | | |
| | | n | % | n | % | |
| ***Age greater than or equal to 40*** | No | 59 | 96.7 | 2 | 3.3 | 1.61 (0.30, 10.00) |
| | Yes | 55 | 94.8 | 3 | 5.2 | |
| ***Sex*** | Female | 16 | 94.1 | 1 | 5.9 | 0.65 (0.07, 6.22) |
| | Male | 98 | 96.1 | 4 | 3.9 | |
| ***Exposure to contaminated water*** | No | 28 | 87.5 | 4 | 12.5 | 0.08 (0.01, 0.76) |
| | Yes | 86 | 98.9 | 1 | 1.1 | |
| ***Weil's syndrome*** | No | 35 | 97.2 | 1 | 2.8 | 1.77 (0.19, 16.40) |
| | Yes | 79 | 95.2 | 4 | 4.8 | |
| ***Need for hemodialysis*** | No | 56 | 98.2 | 1 | 1.8 | 3.86 (0.42, 35.59) |
| | Yes | 58 | 93.5 | 4 | 6.5 | |
| ***Symptoms Reported*** | | | | | | |
| Fever | No | 7 | 100.0 | 0 | 0.0 | 0.77 (0.03, 15.20) |
| | Yes | 107 | 95.5 | 5 | 4.5 | |
| Myalgia/Calf tenderness | No | 41 | 93.2 | 3 | 6.8 | 0.37 (0.06, 2.33) |
| | Yes | 73 | 97.3 | 2 | 2.7 | |
| Nausea/vomiting | No | 57 | 95.0 | 3 | 5.0 | 0.67 (0.11, 4.14) |
| | Yes | 57 | 96.6 | 2 | 3.4 | |
| Abdominal pain | No | 62 | 98.4 | 1 | 1.6 | 4.77 (0.52, 44.00) |
| | Yes | 52 | 92.9 | 4 | 7.1 | |
| Oliguria | No | 62 | 95.4 | 3 | 4.6 | 0.80 (0.13, 4.94) |
| | Yes | 52 | 96.3 | 2 | 3.7 | |
| Conjunctival suffusion | No | 68 | 94.4 | 4 | 5.6 | 0.37 (0.04, 3.41) |
| | Yes | 46 | 97.9 | 1 | 2.1 | |
| Jaundice | No | 70 | 97.2 | 2 | 2.8 | 2.39 (0.38, 14.90) |
| | Yes | 44 | 93.6 | 3 | 6.4 | |
| Diarrhea | No | 72 | 97.3 | 2 | 2.7 | 2.57 (0.41, 16.00) |
| | Yes | 42 | 93.3 | 3 | 6.7 | |
| Cough | No | 90 | 95.7 | 4 | 4.3 | 0.94 (0.10, 8.78) |
| | Yes | 24 | 96.0 | 1 | 4.0 | |
| Dyspnea | No | 100 | 98.0 | 2 | 2.0 | 10.70 (1.64, 69.80) |
| | Yes | 14 | 82.4 | 3 | 17.6 | |
| Mental status changes | No | 101 | 95.3 | 5 | 4.7 | 0.68 (0.04, 13.10) |
| | Yes | 13 | 100.0 | 0 | 0.0 | |
| Chest pain | No | 106 | 96.4 | 4 | 3.6 | 3.31 (0.33, 33.20) |
| | Yes | 8 | 88.9 | 1 | 11.1 | |
| Hemoptysis | No | 105 | 95.5 | 5 | 4.5 | 1.01 (0.05, 19.70) |
| | Yes | 9 | 100.0 | 0 | 0.0 | |

**Table 4B.** Mean, Standard Deviation and Results of Independent Samples t-test in Comparing Liver Biochemical Test Results by Mortality

| Liver Biochemical Tests | Survivors [Mean ± SD] | Non-survivors [Mean ± SD] | T-test for Equality of Means t (95% CI for Mean Difference) |
|---|---|---|---|
| ***AST** (U/L)* | 5 [92.40±30.83] | 101 [102.79±236.55] | -0.38 (-65.31, 44.52) |
| ***ALT** (U/L)* | 5 [62.20±7.29] | 105 [65.97±44.04] | -0.70 (-14.84, 7.31) |
| ***TB** (umol/L)* | 5 [318.66±164.59] | 114 [206.45±196.21] | 1.45 (-312.42, 88.02) |
| ***DB** (umol/L)* | 5 [246.29±141.14] | 63 [168.51±174.14] | 1.16 (-93.79, 249.36) |
| ***IB** (umol/L)* | 5 [72.36±57.76] | 62 [38.56±47.4] | 1.27 (-37.02, 104.63) |
| ***AST/ALT ratio*** | 5 [1.51±0.56] | 100 [1.39±1.26] | -0.43 (-0.80, 0.55) |

*AST: aspartate aminotransferase; ALT: alanine aminotransferase; TB: total bilirubin; DB: direct bilirubin; IB: indirect bilirubin*

**Table 5A.** Distribution of Patients according to Individual Characteristics and Weil's Syndrome

| Characteristics | | Weil's Syndrome | | | | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Yes | | No | | |
| | | n | % | n | % | |
| ***Age greater than or equal to 40*** | No | 41 | 67.2 | 20 | 32.8 | 1.28 (0.58, 2.81) |
| | Yes | 42 | 72.4 | 16 | 27.6 | |
| ***Sex*** | Female | 8 | 47.1 | 9 | 52.9 | 3.13 (1.09, 8.92) |
| | Male | 75 | 73.5 | 27 | 26.5 | |
| ***Exposure to contaminated water*** | No | 19 | 59.4 | 13 | 40.6 | 1.90 (0.81, 4.46) |
| | Yes | 64 | 73.6 | 23 | 26.4 | |
| ***Need for hemodialysis*** | No | 21 | 36.8 | 36 | 63.2 | 200 (12.40, 3610.10) |
| | Yes | 62 | 100.0 | 0 | 0.0 | |
| ***Symptoms Reported*** | | | | | | |
| Fever | No | 4 | 57.1 | 3 | 42.9 | 1.80 (0.38, 8.47) |
| | Yes | 79 | 70.5 | 33 | 29.5 | |
| Myalgia/Calf tenderness | No | 24 | 54.5 | 20 | 45.5 | 3.07 (1.37, 6.91) |
| | Yes | 59 | 78.7 | 16 | 21.3 | |
| Nausea/vomiting | No | 40 | 66.7 | 20 | 33.3 | 1.34 (0.61, 2.95) |
| | Yes | 43 | 72.9 | 16 | 27.1 | |
| Abdominal pain | No | 38 | 60.3 | 25 | 39.7 | 2.69 (1.17, 6.17) |
| | Yes | 45 | 80.4 | 11 | 19.6 | |
| Oliguria | No | 36 | 55.4 | 29 | 44.6 | 5.41 (2.13, 13.7) |
| | Yes | 47 | 87.0 | 7 | 13.0 | |
| Conjunctival suffusion | No | 46 | 63.9 | 26 | 36.1 | 2.09 (0.90, 4.88) |
| | Yes | 37 | 78.7 | 10 | 21.3 | |
| Jaundice | No | 37 | 51.4 | 35 | 48.6 | 43.50 (5.69, 333.00) |
| | Yes | 46 | 97.9 | 1 | 2.1 | |
| Diarrhea | No | 48 | 64.9 | 26 | 35.1 | 1.90 (0.81, 4.43) |
| | Yes | 35 | 77.8 | 10 | 22.2 | |
| Cough | No | 69 | 73.4 | 25 | 26.6 | 0.46 (0.19, 1.15) |
| | Yes | 14 | 56.0 | 11 | 44.0 | |
| Dyspnea | No | 70 | 68.6 | 32 | 31.4 | 1.49 (0.45, 4.91) |
| | Yes | 13 | 76.5 | 4 | 23.5 | |
| Mental status changes | No | 75 | 70.8 | 31 | 29.2 | 0.66 (0.20, 2.18) |
| | Yes | 8 | 61.5 | 5 | 38.5 | |
| Chest pain | No | 78 | 70.9 | 32 | 29.1 | 0.51 (0.13, 2.03) |
| | Yes | 5 | 55.6 | 4 | 44.4 | |
| Hemoptysis | No | 74 | 67.3 | 36 | 32.7 | 9.31 (0.53, 164.00) |
| | Yes | 9 | 100.0 | 0 | 0.0 | |

**Table 5B.** Mean, Standard Deviation and Results of Independent Samples t-test in Comparing Liver Biochemical Test Results by Weil's Syndrome Status

| Liver Biochemical Tests | Weil's Syndrome [Mean ± SD] | Non-Weil's Syndrome [Mean ± SD] | T-test for Equality of Means t (95% CI) |
|---|---|---|---|
| ***AST*** *(U/L)* | 75 [86.03±79.74] | 31 [141.68±410.75] | -0.75 (-207.29, 95.99) |
| ***ALT*** *(U/L)* | 77 [62.30±30.56] | 33 [73.96±63.22] | -1.01 (-35.02, 11.70) |
| ***TB*** *(umol/L)* | 56 [233.74±200.09] | 12 [125.84±146.62] | 2.16 (3.75, 212.06) |
| ***DB*** *(umol/L)* | 56 [190.26±177.72] | 12 [99.39±123.96] | 2.12 (1.79, 179.95) |
| ***IB*** *(umol/L)* | 55 [44.27±51.34] | 12 [26.45±31.08] | 1.57 (-5.46, 41.12) |

*AST: aspartate aminotransferase; ALT: alanine aminotransferase; TB: total bilirubin; DB: direct bilirubin; IB: indirect bilirubin*

associated with Weil's syndrome. Male sex was also found to be associated with the occurrence of Weil's syndrome (OR = 3.13, 95% CI: 1.09, 8.92).

A comparison between the mean values of liver biochemical tests using the independent samples t-test (unequal variances assumed) revealed that the mean TB (t = 2.16, 95% CI: 3.75, 212.06) and the mean DB values (t = 2.12, 95% CI: 1.79, 179.95) of those with Weil's syndrome differ significantly from individuals who do not present with these symptoms (Table 5B).

## DISCUSSION

The clinical presentation of leptospirosis ranges from a subclinical infection to fulminant and fatal disease. The most common causes of death from leptospirosis are septic shock with multiorgan failure, and severe bleeding complications commonly involving the lungs, gastrointestinal tract, urogenital tract, skin, and bleeding from venipuncture sites.[1]

The majority of the patients were males (85.7%), and had a history of exposure to contaminated water (73.1%). This is consistent with the global epidemiology.[1] They were symptomatic for an average of seven days prior to consulting at our institution. The most common clinical presentations were fever (94.1%), myalgia or calf tenderness (83%), nausea and vomiting (49.6%), and abdominal pain (47.1%). Five patients (4.2%) succumbed to the disease. In our study, 87 (73.1%) participants were exposed to flood water. This emphasizes the need for social control measures such as health education campaigns, proper sewage and sanitation systems, and flood management, as well as rodent control.

Similar to previous studies,[7] among the patients who had baseline liver biochemical tests, the serum aminotransferases and alkaline phosphatase levels documented in our patients at baseline were only mildly elevated. In contrast, the total and direct bilirubin fraction were markedly elevated from normal, which may be explained by the infiltration of leptospires into Disse's space. Migration between hepatocytes by this organism causes detachment of the intercellular junctions and disruption of the bile canaliculi, leading to the leakage of bile, and histopathology of the liver has shown plugging of bile canaliculi,[1] hence the markedly elevated bilirubin levels. Coagulation parameters (measured by INR) were within normal limits, hence the hemoptysis seen in 7.6% of patients at baseline may be from other reasons such as low platelets or due to direct effect by the leptospires, rather than an acquired coagulopathy from hepatic dysfunction. This is compatible with the theory that pulmonary hemorrhage is caused by leptospirosis toxin-mediated capillary vasculitis.[8] It is notable that of the 64 patients with complete baseline liver biochemical tests, 60 were male. This can be explained by the predominantly male (85.7%) study population.

Our study revealed no apparent pathologic radiologic features associated with leptospirosis. The majority of patients (63%) with available ultrasound results had normal findings in the liver and biliary tree, and normal, unenlarged spleens. This is contrary to a study done by Shastri et al. in India where 69.8% presented with hepatomegaly with coarse echotexture, and 24.7% presented with hepatosplenomegaly.[9] Similar to our results, they did not note any biliary tree dilatation. The apparent absence of pathologic radiologic features may reflect the acute process that underlies leptospirosis. After an incubation period of 1-2 weeks, an acute leptospiremic phase occurs, lasting for an average of 3-10 days. Milder cases resolve spontaneously in 7-10 days; more severe cases present with fulminant organ failure or bleeding.[10] The patients with more severe manifestations succumb rapidly, which may explain the lack of specific ultrasonographic findings. However, the absence of particular ultrasound findings may be also explained by the small sample size. Since our study was retrospective, and none of our patients had available ultrasound records before they contracted leptospirosis, it is difficult to correlate the findings of hepatomegaly to leptospirosis as these may have been pre-existing conditions. Hence, a study with a larger population and ultrasound done before and after the disease may yet reveal a particular identifying feature.

In our study, jaundice occurred in 39.5% of admitted patients with confirmed leptospirosis, consistent with the local study by Mendoza et al., where 38% of the patients experienced jaundice.[4] This is also similar to the findings in France by Abgueguen et al. where jaundice was present in 39% of patients.[11] Among the analyzed clinical parameters, only jaundice was found to increase the odds of severe liver injury. This is consistent with the pathophysiology of jaundice, whereby damage to the hepatocytes and bile ducts impairs bilirubin metabolism, resulting in the clinical picture of icterus. Similarly, liver injury may also present with jaundice. However, jaundice does not seem to be predictive of mortality in our study.

Of the presenting symptoms, only dyspnea was found to have a higher association with mortality. This finding is consistent with previous findings of pulmonary involvement as being a predictive marker of mortality.[6,12] It emphasizes that clinicians should always look out for dyspnea in patients with leptospirosis and monitor dyspneic patients closely. This is important especially in resource limited settings without readily available access to chest x-rays and other imaging modalities. Additionally, in a case control study conducted in Brazil, predictors of mortality included age >40.[6] This association was not seen in the patients included in this study.

Among our subjects, liver biochemical tests were comparable between survivors and non-survivors. Of note, in contrast to the study by Chang et al.[13] where an AST/ALT ratio of >3 predicted a poorer prognosis, the mean values for AST/ALT ratio for both survivors and non-survivors in this study were not statistically different.

The presence of myalgia or calf tenderness and abdominal pain at baseline increased the odds for Weil's syndrome. While oliguria, the need for hemodialysis, and jaundice were

found to be significantly associated with this syndrome as well, this finding is expected as these are classically the components of Weil's syndrome, and their clinical utility beyond this is moot.

For patients that have developed Weil's syndrome, only mean TB and DB levels were significantly elevated. This finding could alter patient management since bilirubins are not routinely ordered in patients who are not grossly jaundiced. Early detection of elevated TB and DB may serve as a warning to physicians that these patients may deteriorate rapidly by developing Weil's syndrome.

### Limitations of the Study

Only 119 patients with laboratory-confirmed leptospirosis were included in the analysis. As this is a retrospective chart review, not all patients had the necessary liver biochemical tests extracted at baseline and among these, only 64 patients had the necessary baseline laboratories to analyze for severe liver injury. This small sample-size may limit the generalizability of the data, but nevertheless acts as a stepping stone to characterize the liver biochemical profile of Filipino patients with leptospirosis. Lastly, multivariate analysis was not possible due to the small number of events (mortality), hence the independent predictive value of the individual patient variables could not be assessed.

## CONCLUSION

To date, no local studies yet have fully described the liver biochemical profile of patients with leptospirosis. Leptospirosis presents with markedly elevated bilirubins, and only mildly elevated alkaline phosphatase and aminotransferase levels. The liver ultrasound results showed mostly normal findings.

No clinical characteristics (aside from dyspnea) and liver biochemical tests were significantly associated with mortality. The presence of myalgia and abdominal pain increased the odds for Weil's syndrome.

### Statement of Authorship

CRGC and PMGMC contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising of manuscript, and final approval of version to be published. JPO contributed in the conceptualization of work, revising of manuscript, and final approval of version to be published. MABB contributed in the statistical analysis, data management, and presentation of data. JMKT contributed in the conceptualization of work, acquisition and analysis of data, and final approval of version to be published. ARBH and AVCJ contributed in the conceptualization of work, acquisition of data, and final approval of version to be published.

### Author Disclosure

The authors claim no conflict of interest in any form. The authors also certified that they have no affiliations with or involvement in any organization which would benefit from the research study.

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## REFERENCES

1. Wagenaar JP, Goris MA. Leptospirosis. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 20th ed. McGraw Hill; 2018. pp. 1290-295.
2. Faine S, Adler B, Bolin C, Perolat P. Clinical leptospirosis in humans. Leptospira and leptospirosis, 2nd ed. MedSci, Melbourne; 1999.
3. Victoriano AFB, Smythe LD, Gloriani-Barzaga N, Cavinta LL, Kasai T, Limpakarnjanarat K, et al. Leptospirosis in the Asia Pacific region. BMC Infect Dis. 2009 Sep; 9:147. doi: 10.1186/1471-2334-9-147.
4. Mendoza MT, Roxas EA, Ginete JK, Alejandria MM, Roman ADE, Leyritana KT, et al. Clinical profile of patients diagnosed with leptospirosis after a typhoon: a multicenter study. Southeast Asian J Trop Med Public Health. 2013 Nov;44(6):1021–35.
5. Republic of the Philippines Department of Health. Disease surveillance report: leptospirosis morbidity week 48. 2018.
6. Spichler AS, Villaca PJ, Athanazio DA, Albuquerque JOM, Buzzar M, Castro B, et al. Predictors of lethality in severe leptospirosis in urban Brazil. Am J Trop Med Hyg 2008 Dec;79(6):911-4.
7. Vinetz JM, Glass GE, Flexner CE, Mueller P, Kaslow DC. Sporadic urban leptospirosis. Ann Intern Med. 1996 Nov;125:794–8. doi: 10.7326/0003-4819-125-10-199611150-00002.
8. Luks AM, Lakshminarayanan S, Hirschmann JV. Leptospirosis presenting as diffuse alveolar hemorrhage: case report and literature review. Chest. 2003 Feb(2):639-43. doi: 10.1378/chest.123.2.639.
9. Shastri M, Diwanji N, Desai E, Chitara M, Bhatt A. Spectrum of radiological findings in leptospirosis on chest radiograph and ultrasonography-study during epidemics in South Gujarat region of India. Int J Anat Radiol Surg. 2017 Oct;6(4): RO07-RO12. doi: 10.7860/IJARS/2017/26056:2306
10. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 20th ed.New York: McGraw-Hill Education; 2018.
11. Abgueguen P, Delbos V, Blanvillain J, Chennebault JM, Cottin J, Fanello S, et al. Clinical aspects and prognostic factors of leptospirosis in adults. Retrospective study in France. J Infect. 2008 Sep;57(3): 171–8. doi: 10.1016/j.jinf.2008.06.010.
12. Dupont H, Dupont-Perdrizet D, Perie JL, Zehner-Hansen S, Jarrige B, Daijardin JB. Leptospirosis: prognostic factors associated with mortality. Clin Infect Dis. 1997 Sep;25(3):720-4. doi: 10.1086/513767.
13. Chang ML, Yang CW, Chen JC, Ho YP, Pan MJ, Lin CH, et al. Disproportional exaggerated aspartate transaminase is a useful prognostic parameter in late leptospirosis. World J Gastroenterol. 2005 Sep;11(35):5553–6. doi: 10.3748/wjg.v11.i35.5553.
14. Philippine College of Physicians. Philippine clinical practice guidelines on the diagnosis, management, and prevention of leptospirosis. 2010.
15. Haake DA, Levett PN. Leptospira species (Leptospirosis). In: Bennett JE, Dolin R, Blaser MJ, eds. MandellDouglas and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Philadelphia: Churchill Livingston Elsevier; 2020. pp. 2898-2905.

# APPENDIX

## Definition and diagnosis of leptospirosis

**Suspected Leptospirosis** is defined as a history of exposure to floodwaters plus any of the following signs and symptoms: fever, headache, myalgia, conjunctival suffusion, diarrhea and abdominal pain, jaundice, decreased urine output and changes in sensorium or meningismus.

**Confirmed Leptospirosis** is defined as laboratory confirmation of the diagnosis via any of the following tests (WHO, 2003): a) positive leptospiral culture of the blood and/or urine; b) high positive single micro-agglutination test (MAT) titer of greater than or equal to 1:1,600; c) seroconversion from an initial negative to a positive antibody titer by MAT; d) fourfold rise in antibody titers by MAT from the acute to convalescent phase.

**Severe Leptosirosis**, according to the 2010 Philippine College of Physicians Clinical Practice Guidelines, is indicated by any of the following laboratory tests: leukocytosis (WBC >12,000 cells/$mm^3$) with neutrophilia, thrombocytopenia (platelets <100,000 cells/$mm^3$), elevated serum creatinine (>3 mg/dl), elevated liver biochemical tests (AST/ALT ratio >4, bilirubin >190 umol/L), prolonged prothrombin time (PT %<85%), serum potassium >4 mmol/L, severe metabolic acidosis (ph <7.2, serum bicarbonate <10), hypoxemia ($Pao_2$ <60 mmhg), chest radiograph with extensive alveolar infiltrates, and ECG findings of myocarditis, repolarization abnormalities, and heart block.[14] Aside from this, patients presenting with hemodynamic instability, an altered mental status, renal failure, oliguria, abdominal pain, frank jaundice, meningismus, dyspnea, and pulmonary hemorrhage are classified as having severe leptospirosis.[15]