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Case Study

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The laboratory examination results: platelet, creatinine, and urea as predictors of mortality in Leptospirosis patients

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Abstract: Leptospirosis is a priority zoonotic disease in Indonesia and has the potential to cause outbreaks. The mortality rate of leptospirosis cases ranges from 5-20%. Predictors of mortality in leptospirosis include advanced age, oliguria, shortness of breath, icterus, thrombocytopenia, and elevated levels of potassium, creatinine, bilirubin, and urea. The purpose of this study was to analyze mortality predictor factors based on laboratory results in leptospirosis patients in Demak Regency, Indonesia. Data were obtained from 51 leptospirosis patients based on hospital medical record data in Demak Regency for 2018-2023. The study design used was a retrospective cohort. Predictors of mortality were analyzed with Cox regression. The results showed causes of death include: thrombocytopenia <100,000 cells/mm³ (53.33%), creatinine >3 mg/dL (58.33%), and urea >90 mg/dL (61.54%). Laboratory results shown to be associated with mortality have been identified, including platelets <100,000 cells/mm³ (HR: 5.39; CI 95%: 1.23-23.59; p-value: 0.0063), creatinine >3 mg/dL (HR: 4.37; CI 95%: 1.43-13.3; p-value: 0.0040), and urea >90 mg/dL (HR: 7.44; 95% CI: 1.70-32.44; p-value: 0.0008). Research concludes, platelets, creatinine, and urea are predictors of leptospirosis mortality. This study presents significant clinical implications for the management of leptospirosis in improving the treatment of patients. Detection of these predictors will help to quickly identify patient severity, thereby enabling decision making regarding early use of intensive care.

Keywords: leptospirosis; predictor; mortality; platelets; creatinine; urea; cox regression.

INTRODUCTION

The world is facing a growing threat from emerging infectious diseases (EIDs), 60% of which are zoonotic.[1] Leptospirosis is a zoonotic disease that has the potential to become an outbreak.[2,3] In Indonesia, leptospirosis is categorized as a priority zoonosis, reflecting the urgency of controlling this disease at the national level.[4]

Leptospirosis causes a variety of symptoms, ranging from mild infection to severe potentially fatal illness. In general, the mortality rate of leptospirosis cases ranges from 5-20%.[5] Leptospira bacteria, which are causative agents, mainly

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attack main organs such as the kidneys, liver, and lungs, often causing multisystem complications.[6,7]

Humans can become infected with Leptospirosis due to direct or indirect contact with the urine of animals infected with Leptospira.[8,9,10] Leptospirosis transmission is influenced by agent factors (such as the quantity, virulence, and pathogenicity of Leptospira), host factors (such as occupation and socioeconomic status), and environmental factors (including standing water and rodent populations). [8, 11,12,13]

In Indonesia, one high-risk area for leptospirosis is Demak Regency, Central Java, known as an endemic region for this disease. Based on preliminary study data at the Demak Regency Health Office, cases of human leptospirosis have been reported annually from 2008 to 2023, with a CFR value consistently exceeding 11%.[14] This high risk indicates the need for more effective management strategies to prevent and reduce leptospirosis-related mortality in this region.

Several factors have been identified as predictors of mortality in leptospirosis cases, including socio-demographic conditions, laboratory test results, clinical symptoms, treatment management, and the presence of complications or comorbidities.[5,15,16,17,18]

Studies in various countries indicate that laboratory parameters, such as thrombocytopenia (<100,000 cells/mm³), elevated total bilirubin (>300 mcmol/L), high creatinine (>200 mcmol/L), and urea levels, are predictors of leptospirosis mortality.[17] Based on references, patients who experience thrombocytopenia (<100,000 cells/mm³), have a four times greater risk of death compared to patients who do not have thrombocytopenia.[15] Research conducted in Ukraine in 2022 that states platelets <50,000/µL as a significant risk factor for leptospirosis mortality (OR: 3.95; 95% CI: 1.45-10.73). Additionally, creatinine levels of >200 mcmol/L were one of the main predictors of leptospirosis mortality (OR: 1.95; 95% CI: 1.47-2.60).[17] Blood urea levels also been associated with severe leptospirosis which increases the risk of death. (p=0.028; 35.82 ± 31.10).[19]

Although previous studies have identified platelets, creatinine, and urea as important predictors of mortality in leptospirosis, focused research in Demak District is needed to validate these findings in the local geographic context. This localized study could help develop more comprehensive and accurate predictive models for leptospirosis mortality, potentially improving clinical management and reducing mortality rates in affected patients.

Based on the literature search reveals a lack of research using Cox regression analysis to assess predictors of mortality in leptospirosis patients based on laboratory variables in Indonesia, especially in Demak Regency. This study aims to address this gap, providing insights for more effective and efficient management of leptospirosis to reduce the associated mortality rate.

MATERIAL AND METHOD

Study Design

This study is an analytical study using a retrospective cohort design to analyze mortality predictors based on laboratory results in leptospirosis patients in Demak Regency.

Sampling and Data Collection

The sample size was determined using the Lemeshow formula for unknown populations. The study included 51 patients who met all criteria through total sampling. Total sampling was used to ensure all eligible patients from the study period and facilities were included.

The samples in this study were all leptospirosis patients who are confirmed and recorded in medical records at Sunan Kalijaga Hospital, Sultan Fatah Demak Hospital, or NU Islamic Hospital in 2018-2023, with clear inclusion and exclusion criteria. Patients were included if they were confirmed to have leptospirosis by

hospitals in Demak Regency and had documented final outcomes of treatment (alive or dead). Exclusion criteria included patients who were lost to follow-up (e.g., transferred to facilities outside Demak Regency) and those whose medical records lacked complete data on the study's independent variables (platelets, creatinine, and urea).

Variables and Measures

The independent variables platelet count, creatinine, and urea levels were measured through laboratory tests. These variables were categorized based on standard cutoff values relevant to the severity of leptospirosis based on previous studies: platelet count (<100,000 cells/mm³), creatinine (>3 mg/dL) and urea >90 mg/dL). Data on these variables were collected at the time of patient admission to provide baseline values. Outcome data were based on the final documented status (alive or dead) in the medical records.

Statistical Analysis

Continuous data were presented as median and mean ± SD. Cox regression analysis was applied to evaluate mortality predictors among leptospirosis patients. Univariable Cox regression was conducted to assess the effect of each laboratory variable separately on time to death, generating hazard ratios (HR) and p-values without adjustment for other variables. The proportional hazards (PH) assumption was examined through visual inspection of log–log survival plots and was deemed to be satisfied.

RESULTS AND DISCUSSION

The results of the study are presented in a table of characteristics of leptospirosis patients based on laboratory results (Table 1) and analysis of the relationship between laboratory examination results and mortality of leptospirosis patients (Table 2). Bivariate analysis was performed to determine the relationship of platelets, creatinine, and urea with the mortality of leptospirosis patients. The statistical test used is the cox regression test and the strength of the relationship is expressed in the form of a hazard ratio. Here are the results of the analysis:

Table 1. Distribution of Characteristics of Leptospirosis Patients

Variable	Status	n	Range	Median	Mean ± SD
Platelets(cells/mm³)	Dead	18	11-167	32.50	47.94 ± 40.09
	Alive	33	13-373	105.00	131.91±98.06
Creatinine (mg/dL)	Dead	18	1.5-10.6	4.65	4.77 ± 2.32
	Alive	33	0.6-11.9	1.80	2.73±2.45
Urea (mg/dL)	Dead	18	69.9-480.2	180.40	219.29 ± 120.37
	Alive	33	14.1-480.3	52.43	94.82±100.23

The analysis of laboratory characteristics among leptospirosis patients revealed striking differences between those who survived and those who died. In terms of platelet count, deceased patients had a median of 32.50 ×10³ cells/mm³ and a mean ± SD of 47.94 ± 40.09, significantly lower than survivors who had a median of 105.00 ×10³ cells/mm³ and a mean ± SD of 131.91 ± 98.06 (Table 1). This severe thrombocytopenia serves as a key clinical marker of severe leptospirosis and is often associated with bleeding complications, coagulopathy, or disseminated intravascular coagulation, worsening the patient's prognosis.

Furthermore, creatinine levels among deceased patients had a median of 4.65 mg/dL and a mean ± SD of 4.77 ± 2.32, which were considerably higher than those in survivors (median 1.80 mg/dL; mean ± SD 2.73 ± 2.45). Elevated creatinine levels reflect acute kidney injury, one of the most common and fatal complications in severe leptospirosis. Similarly, blood urea levels in deceased patients (median 180.40 mg/dL; mean ± SD 219.29 ± 120.37) were substantially higher than in survivors (median 52.43 mg/dL; mean ± SD 94.82 ± 100.23),

indicating severe uremia due to nitrogenous waste accumulation secondary to renal failure.

Table 2. The Relationship of Platelets, Creatinine, and Urea with Mortality of Leptospirosis Patients

Variable		Survival Status of Leptospirosis Patients		HR	95% CI	*P value*
		Dead	Alive			
Platelets(cells/mm³)	<100.000	16 (53.33%)	14 (46.67%)	5.39	1.23-23.59	0.0063
	=>100.000	2 (9.52%)	19 (90.48%)			
Creatinine (mg/dL)	> 3	14 (58.33%)	10 (41.67%)	4.37	1.43-13.31	0.0040
	<=3	4 (14.81%)	23 (85.19%)			
Urea (mg/dL)	>90	16 (61.54%)	10 (38.46%)	7.44	1.70-32.44	0.0008
	<=90	2 (8.00%)	23 (92.00%)			

Based on table 2, platelets, creatinine, and urea have a significant relationship with the survival status of leptospirosis patients with variable p-values of platelets (p-value: 0.0063), creatinine (p-value: 0.0040), and urea (p-value: 0.0008). Cox regression analysis shows that these three variables have an independent effect on the patient's risk of death, as reflected in the hazard ratio (HR) value of each.

Patients with platelet <100,000 cells/mm³ had a 5.39-fold higher risk of death (HR: 5.39; 95% CI: 1.23–23.59) compared to patients with platelets ≥100,000 cells/mm³. The confidence interval does not include 1.0, indicating that the result is statistically significant. This suggests that severe thrombocytopenia is a strong risk factor for mortality in leptospirosis, which is most likely related to a tendency to severe bleeding or uncontrolled complications of coagulopathy.

Furthermore, creatinine >3 mg/dL were associated with a 4.37-fold increased risk of death (HR: 4.37; 95% CI: 1.43–13.31) compared to patients with creatinine ≤3 mg/dL. The 95% confidence range excludes 1.0, indicating that the association is statistically meaningful. Elevated creatinine reflects severe acute kidney dysfunction, which can physiologically lead to fluid and electrolyte balance disorders as well as the accumulation of metabolic toxins that worsen the patient's condition.

Meanwhile, urea >90 mg/dL had the strongest association with mortality, with a 7.44-fold higher risk of death (HR: 7.44; 95% CI: 1.70–32.44) compared to patients with urea ≤90 mg/dL. The confidence limits lie entirely above 1.0, reinforcing the statistical significance of this association. Significant uremia indicates the severity of kidney damage and plays an important role in worsening hemodynamic status as well as triggering severe metabolic complications, which contribute to the high mortality rate.

Platelet

Patients with leptospirosis often have a decrease in platelet count in the blood, known as thrombocytopenia. Low platelet levels can be a poor indicator in the prognosis of leptospirosis patients. Prolonged illness and acute kidney injury are risk factors for thrombocytopenia.[20] Patients with severe thrombocytopenia tend to have a higher risk of death.[19] This is due to the possibility of serious bleeding due to blood clotting disorders caused by a decrease in platelet count.[21]

The proportion of deaths among leptospirosis patients was higher in the group with platelet examination results <100,000 cells/mm³ than the platelet group =>100,000 cells/mm³ (53.33% vs 9.52%). In addition, an HR score of 5.39 was obtained. This means that leptospirosis patients in the group with platelet examination results <100,000 cells/mm³ have a 5.39 times higher risk of death compared to the group with platelet results =>100,000 cells/mm³. The p-value is 0.0063. This value is less than α so it can be concluded that there is a significant relationship between platelet examination results and leptospirosis patient survival (Table 2).

The relationship between platelet levels and leptospirosis mortality can be explained by several studies such as reference, patients who experience thrombocytopenia (<100,000 cells/mm³), have a 4 times greater risk of death compared to patients who do not experience thrombocytopenia.[15] These results are in line with research conducted in Ukraine in 2022 that stated platelets less than 50,000 cells/mm³ to be a risk factor for leptospirosis mortality (OR: 3.95; 95% confidence interval [CI]: 1.45-10.73).[17]

Platelets are the dominant predictor associated with leptospirosis mortality. Thrombocytopenia, which often occurs in leptospirosis, is a major risk factor that causes the disease to become severe and deadly. One potential explanation for thrombocytopenia in leptospirosis is that certain strains of Leptospira activate platelets directly.[17] Thrombocytopenia in the acute phase of the disease may play a role in hemorrhagic disorders. In many studies, thrombocytopenia has been identified as one of the most common causes of severe disease course and death.[18,22,23]

Studies have shown that patients with low platelet levels at the time of hospital admission have a worse prognosis in terms of survival compared to patients who have normal platelet levels.[15] This indicates that platelet levels can serve as an important predictive factor for assessing the risk and clinical outlook of leptospirosis patients. Individuals presenting with significant thrombocytopenia often require intensive medical care, including platelet transfusions, to mitigate the heightened risk of bleeding. Consistent monitoring of platelet levels is therefore a crucial component of clinical management, enabling the early detection of deterioration and the timely administration of therapeutic interventions.

Given the strong association between thrombocytopenia and mortality in leptospirosis patients, there is a clear need to explore potential clinical interventions aimed at mitigating this risk. Early identification of thrombocytopenia upon hospital admission should prompt immediate risk stratification and consideration for supportive measures such as platelet transfusion, fluid resuscitation, and correction of coagulation abnormalities. In severe cases, early admission to intensive care units (ICU) may improve outcomes by enabling close hemodynamic monitoring and rapid response to bleeding complications.

Additionally, the development of early warning systems that incorporate laboratory thresholds such as platelet count <100,000 cells/mm³ could serve as an effective clinical decision-support tool. Such systems could flag high-risk patients in real time, enabling clinicians to initiate prompt interventions before clinical deterioration occurs. These laboratory-based alerts could be integrated into hospital information systems to enhance early detection and guide resource allocation in endemic regions with limited access to advanced care.

Future studies are needed to evaluate the effectiveness of specific interventions, such as prophylactic platelet transfusions or immunomodulatory therapies, in reducing morbidity and mortality in thrombocytopenic leptospirosis patients. Moreover, incorporating laboratory markers into standardized clinical pathways may help optimize treatment protocols and improve the overall prognosis of leptospirosis, especially in resource-constrained settings.

Creatinine

Leptospirosis can cause varying degrees of damage to the kidneys, especially in more severe cases. When the body is infected with Leptospira bacteria, the immune system response can cause inflammation that damages kidney tissue. As a result, kidney function may be impaired, which can be reflected in elevated levels of creatinine in the blood. [24]

The proportion of leptospirosis patients who experienced the dead was higher in the group with creatinine test results >3 mg/dL compared to <= 3 mg/dL (58.33% vs 14.81%). The analysis produced an HR of 4.37, indicating that individuals with elevated creatinine had a substantially greater risk of mortality. With a p-value of 0.0040 below the predetermined α threshold, the association

between increased creatinine levels and mortality was statistically significant. These findings highlight that impaired renal function, reflected by creatinine >3 mg/dL, plays an important role in worsening the clinical prognosis of leptospirosis patients.

The relationship of creatinine levels with leptospirosis mortality can be explained by several studies such as research on leptospirosis mortality predictors in Ukraine showed that creatinine >200 mcmol/L became one of the main predictors in leptospirosis mortality after bilirubin and platelet levels (OR: 1.95; 95% confidence interval [CI]: 1.47-2.60).[17]. This finding is in line with Al Hariri Research (2019) which states that an increase in creatinine levels that exceed normal limits indicates the involvement of kidney organs so that it can cause clinical one of which is acute kidney failure.[25] Elevated creatinine levels were also found in patients dying of renal failure in leptospirosis patients.[26]

Creatinine was the dominant predictor associated with leptospirosis mortality. High creatinine levels are often an estimate of kidney function and an indicator of the severity of kidney damage in leptospirosis patients.[27] Patients with significant kidney damage tend to have a poorer prognosis in terms of survival. Elevated creatinine levels can also be a sign of serious complications, such as acute kidney failure, which is a life-threatening condition.[28] Acute renal failure can worsen a patient's prognosis and increase the risk of death.

Elevated creatinine levels in leptospirosis patients indicate kidney damage that significantly increases mortality risk. Early interventions such as routine creatinine monitoring, adequate fluid management, and avoidance of nephrotoxic drugs are crucial to mitigate this risk. Furthermore, developing an early warning system based on creatinine laboratory values can assist healthcare teams in prompt and accurate decision-making to prevent severe complications like acute renal failure. Implementing such systems is expected to improve patient prognosis and reduce leptospirosis mortality rates.

Urea

Urea levels in the blood are also a biomarker for evaluating kidney function in cases of leptospirosis. Leptospirosis infection can cause kidney damage, which can affect the body's ability to excrete waste products such as urea. As a result, urea levels in the blood may increase in response to kidney disorders that occur during infection.[29]

The proportion of leptospirosis patients who died was substantially higher among those with urea levels >90 mg/dL compared with individuals whose levels were ≤90 mg/dL (61.54% vs 8.00%). The analysis yielded an HR of 7.44, reflecting a markedly elevated mortality risk in patients presenting with severe uremia. A p-value of 0.0008 well below the α threshold, confirms that this association is statistically significant. These results highlight the crucial role of elevated urea as a marker of severe physiological derangement and a strong predictor of mortality in leptospirosis.

The relationship between urea levels and leptospirosis mortality can be explained by several studies such as the results of research by Virgil (2023) in Indonesia with a p value of 0.044.[30] Different findings in Bantul found that urea was not associated with leptospirosis mortality (OR: 2.82; p-value: 0.291; 95% CI: 0.35-129.0).[15]

Urea is the dominant predictor associated with leptospirosis mortality, because urea contributes to bleeding in the acute phase of leptospirosis. Elevated levels of urea in the blood are often a sign of the severity of kidney damage in leptospirosis patients. Patients with high urea levels tend to have a poorer prognosis in terms of survival, and are indicators of serious complications that increase the risk of death. Elevated blood creatinine and urea levels indicate kidney damage and the potential for acute renal failure, one of the most common and important predictors of mortality in leptospirosis.[18]

Measuring and monitoring urea levels provide essential insights in the clinical management of leptospirosis patients, assisting in early detection of possible complications and guiding appropriate treatment to enhance survival and patient safety. Elevated blood urea levels reflect impaired nitrogen metabolism due to kidney dysfunction and tissue damage. Risk mitigation strategies may include targeted nutritional therapy to reduce nitrogen load and close monitoring of protein intake to optimize kidney function. Moreover, early warning systems employing algorithms that integrate urea levels with other clinical parameters can offer more accurate complication risk predictions, enabling proactive interventions such as fluid and medication adjustments, thereby improving clinical outcomes in leptospirosis patients.

CONCLUSION

Laboratory parameters such as platelet count, creatinine, and urea levels have been identified as the strongest risk factors associated with mortality in leptospirosis patients. This study statistically confirmed that these indicators are significant predictors of leptospirosis-related death. Accordingly, routine measurement and monitoring of these laboratory values can provide critical insights for clinical management, facilitate early detection of potential complications, and guide timely therapeutic interventions to improve patient safety and survival outcomes.

Nonetheless, these findings should be interpreted with caution, considering several limitations. The retrospective study design and reliance on secondary data from medical records may introduce potential biases, such as incomplete data or variability in clinical documentation. Additionally, the relatively small sample size may limit the statistical power and robustness of the findings. Generalization to other regions in Indonesia or internationally should also be approached carefully, given potential differences in population characteristics, healthcare infrastructure, and the epidemiology of leptospirosis.

To enhance the clinical applicability of these findings, it is recommended that healthcare providers implement routine laboratory monitoring for leptospirosis patients, particularly those presenting early signs of renal dysfunction or hemorrhagic manifestations. The development of early warning systems based on platelet, creatinine, and urea values should also be considered to support faster and more precise clinical decision-making.

Future research should involve prospective studies with larger sample sizes to validate these results and strengthen their inferential power. Furthermore, exploring additional predictors and developing multifactorial risk prediction models would be valuable for improving early detection systems and optimizing mortality risk management in leptospirosis patients.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

There is no conflict of interest.

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