Performance of Tokyo Guidelines 2018 and Predictors of Mortality in Acute Cholangitis Patients in Indonesia

Vesri Yoga[1,2*], Achmad Fauzi[3], Hasan Maulahela[3], Hamzah Shatri[4,5], Em Yunir[6], Bradley J. Waleleng[3], Dadang Makmun[3], Kaka Renaldi[3], Cleopas Martin Rumende[7], Sukamto[8]

[1]Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas - Dr. M. Djamil General Hospital, Padang, Indonesia.
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Division of Gastroenterology, Pancreato-biliary and Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Division of Psychosomatic and Palliative, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[5]Clinical Epidemiology and Evidence-Based Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[6]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[7]Division of Psychosomatic and Palliative, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[8]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

*__Corresponding Author__:
Vesri Yoga, MD. Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas - Dr. M. Djamil General Hospital. Jl. Perintis Kemerdekaan, Padang, Indonesia.
Email: vesriyoga@gmail.com.

ABSTRACT

Background: *Acute cholangitis is associated with high mortality, necessitating prompt diagnosis and intervention. The Tokyo Guidelines 2018 (TG18) are a crucial diagnostic tool, but their sensitivity and specificity require evaluation. Moreover, factors influencing acute cholangitis mortality in Indonesia remain unidentified. This study evaluates the diagnostic accuracy of TG18 and identifies mortality predictors in adult patients with acute cholangitis in Indonesia.* ***Methods:*** *A retrospective cohort study was conducted using the medical records of acute cholangitis patients at Cipto Mangunkusumo Hospital from 2019 to 2022. TG18 was compared with endoscopic retrograde cholangiopancreatography (ERCP). Bivariate and multivariate analyses were employed to identify mortality predictors.* ***Results:*** *The study involved 163 individuals (male: 51.5%; mean age: 51.0 ± 12.81 years). The in-hospital mortality rate was 11.6%. TG18 demonstrated a sensitivity and specificity of 84.05% (95% confidence interval (CI):77.51%–89.31%) and 95.65% (95%CI: 78.05%–99.89%), respectively, compared with ERCP. Significant mortality predictors in univariate analysis included TG18 grade III (risk ratio (RR): 13.85; 95%CI: 3.31–57.89; p<0.001), history of malignancy (RR: 4.40; 95%CI: 1.52–12.68; p=0.006), noncompliance with antibiotic guidelines (RR: 3.27; 95%CI: 1.36–7.85; p=0.008), and procalcitonin levels ≥ 2.0 ng/dL (RR: 2.44; 95%CI: 1.056–5.63; p=0.037). Multivariate analysis revealed that significant predictors included TG18 grade III (RR: 10.67; 95%CI: 2.50–45.56; p<0.001), non-compliance with antibiotic guidelines (RR: 2.92; 95%CI: 1.34–6.36; p=0.007), and procalcitonin levels ≥ 2.0 ng/dL (RR: 2.37; 95%CI: 1.18–4.75; p=0.015).* ***Conclusion:*** *TG18 demonstrates favorable sensitivity*

for diagnosing acute cholangitis. Independent predictors of acute cholangitis mortality include TG18 grade III, noncompliance with antibiotic guidelines, and procalcitonin levels ≥ 2.0 ng/dL.

Keywords: *acute cholangitis, mortality, Tokyo Guidelines 2018.*

INTRODUCTION

Acute cholangitis is primarily a bacterial infection affecting the biliary system. It usually results from the partial or complete blockage of the bile or hepatic ducts.[1] The primary cause of obstruction is usually a stone or a malignancy. This leads to stasis of bile flow, reduced immune response, and bacterial colonization of bile. Bile flowing back into the circulation can cause bacteremia, leading to sepsis and potential death.[2] Acute cholangitis is a serious global health issue. It affects roughly 0.3% to 1.6% of the population, with severe cases making up about 12.3%.[3] Each year, the United States records more than 200,000 cases of acute cholangitis. In contrast, the frequency of this condition in Indonesia remains inadequately documented.[4]

Cholangitis affects individuals across all racial and ethnic backgrounds. In Southeast Asia, a concerning form known as Asian cholangitis, or recurrent pyogenic cholangitis (RPC), has increased alarmingly and is approaching epidemic levels. This variant is characterized by repeated biliary infections. It is often associated with chronic biliary problems and intestinal parasites.[5] A retrospective case-control study in Qatar found that the prevalence of cholangitis was higher among Asians (57.4%) than Middle Easterners (35.7%) and Africans (33.3%). Although the results did not reach statistical significance, they highlight potential issues that need further investigation.[6]

The mortality rate in severe cholangitis remains significantly high without proper management. Despite advancements in drainage technology and antibiotic selection, the mortality rate for acute cholangitis is still considerable, ranging from 10.6% to 12%.[7] Identifying predictors of mortality is essential for enhancing patient outcomes and lowering mortality rates. Although several studies have explored factors contributing to mortality in acute cholangitis, comprehensive research on this topic is still insufficient.[8] Schneider et al.[9] study analyzed prediction models for in-hospital mortality in acute cholangitis, found that patients with malignant diseases had a higher risk of mortality compared to those with benign conditions (odds ratio [OR]: 3.0). Furthermore, certain laboratory indicators are also associated with increased mortality risk. These include elevated serum creatinine levels (>2 mg/dl), low platelet counts (<100,000/mm^3), and high bilirubin levels.

However, acute cholangitis is traditionally diagnosed by meeting Charcot's triad, which includes fever, right upper quadrant abdominal pain, and jaundice. In 2018, the Tokyo Guidelines 2018 (TG18) introduced new criteria for diagnosing acute cholangitis through clinical and laboratory parameters.[10] This study compares the effectiveness of TG18 against Charcot's triad in diagnosing acute cholangitis while also identifying clinical and laboratory predictors of mortality. Notably, this is the first investigation in Indonesia utilizing TG18 criteria as predictors of mortality in acute cholangitis cases. Our research focuses on key data regarding demographics, comorbidities, and clinical outcomes for acute cholangitis in Indonesia. The findings will help clinicians better identify and manage high-risk patients. This study lays a vital foundation for future research on acute cholangitis in the region.

METHODS

The study population was all acute cholangitis patients who were treated at Cipto Mangunkusumo Hospital (RSCM). ERCP was used for all patients as the diagnostic gold standard. The inclusion criteria for this study were patients over 18 years old, hospitalized at RSCM between 2019 and 2022, and diagnosed with acute cholangitis via ERCP results. Patients with incomplete medical records were excluded from the study. The subjects were selected utilizing a consecutive sampling method. Data

were collected by digitally tracing medical records using the International Classification of Diseases 10 (ICD-10) code, which includes K80.0, K80.1, K80.2, K80.3, K80.4, K80.8, K81.1, K83.0, and K83.1.

Research data were collected from medical records and subsequently validated through electronic medical records to mitigate the potential for bias in this study. The patient recruitment and selection processes were carried out comprehensively, with a particular emphasis on standardized laboratory results to ensure the reliability and validity of the findings. The data encompass characteristics of the research subjects, mortality outcomes, and signs and symptoms classified by TG18 and Charcot's triad. ERCP results indicating acute cholangitis were assessed based on bile duct obstruction, dilation, or the presence of pus or pus fluid during the procedure. This study also evaluated the risk factors that predict mortality related to acute cholangitis. The evaluated predictors included: a history of malignancy, diabetes, antibiotic according to TG18 guidelines, delayed biliary drainage (ERCP)? 48 hours, severity of acute cholangitis per TG18 criteria, and procalcitonin levels. In this study, a procalcitonin level of 2 ng/mL was utilized as a marker, indicating the presence of severe cholangitis.

Research Ethics

This study obtained ethical approval from the Health Research Ethics Committee, Faculty of Medicine, University of Indonesia (approval number: KET-485/UN2.F1/ETIK/PPM 00.02/2002). All data used during the research will be kept confidential.

Statistical Analysis

Statistical analysis was conducted using SPSS 20.0 software from the International Business Machine Corporation, New York. Categorical data were presented in terms of amounts and percentages, while numerical data were presented with mean ± standard deviation or median with ranges. The univariate analysis involved comparing clinical parameters as the predictors of mortality. Output was provided as a risk ratio (RR), and significance was determined using Fisher's exact test. Predictors with a p-value of <0.25 underwent further multivariate analysis through backward logistic regression. The performance was evaluated by comparing TG18 and Charcot's triad with ERCP, including sensitivity, positive predictive value (PPV), and negative predictive value (NPV).

RESULTS

In the period from 2019 to 2022, the records of 328 individuals diagnosed with acute cholangitis were reviewed. Following a thorough screening of the inclusion and exclusion criteria, a total of 163 subjects were selected for the research. Among the research subjects, 84 (51.5%) were female with an mean age of 51.0 ± 12.81 years. Accordingly, 46% of the patients had a history of malignancy; 41.7% had a history of gallstones; 18.4% were obese; and 17.2% had diabetes mellitus (DM). Furthermore, the TG18 criteria were met by 84.0% of the subjects, and 48.5% presented with Charcot's triad. The distribution of TG18 grades 1, 2, and 3 was 14.1%, 47.9%, and 38.0%, respectively. The median duration for the ERCP performance was 4 days, with 46.0% of the procedures taking place within 48 h. The in-hospital mortality rate was recorded as 11.6%, with a total of 19 patients affected (**Table 1**).

Performance of TG18 and Charcot's Triad

The study involved 163 patients with acute cholangitis confirmed by ERCP. Of these, 137 were diagnosed according to TG18 criteria, while only 79 (48.5%) met Charcot's triad criteria. TG18 demonstrated a sensitivity of 84% (95%CI: 76.42-88.42%), in contrast to Charcot's triad sensitivity of 48.5% (95%CI: 40.58-56.41%). Specificity was not evaluated as the study did not include patients with ERCP results inconsistent with acute cholangitis. A comparison of the performance between Charcot's triad and TG18 is presented in **Table 2**.

Utilizing TG18 as a diagnostic criterion, the sensitivity of Charcot's triad was found to be 56.93% (95%CI: 48.20-65.36%), while its specificity reached 96.15% (95%CI: 80.36-99.9%). The positive predictive value (PPV) was 98.73% (95%CI: 91.90-99.81%), and the negative predictive value (NPV) stood at 29.76% (95%CI: 25.62-34.27%). Overall accuracy was

Table 1. Characteristics of the Subjects

Characteristics	Results
Age	51.0 ± 12.81 years
Gender	
Man	79 (48.5%)
Woman	84 (51.5%)
Comorbidity	
Malignancy of the liver and biliary tract	74 (46%)
Cholelithiasis	68 (41.7%)
Obesity	30 (18.4%)
Hypertension	29 (17.8%)
Diabetes mellitus	28 (17.2%)
Chronic liver disease	15 (9.2%)
Heart disease	11 (6.7%)
Chronic Kidney Disease Stage V	5 (3.1%)
Viral hepatitis	5 (3.1%)
Tuberculosis	4 (2.5%)
Autoimmune	1(0.6%)
HIV/AIDS	2 (1.2%)
Habit	
Smoke	36 (22.1%)
Alcohol	14 (8.6%)
Diagnosis	
According to Charcot's triad*	79 (48.5%)
TG 18* compatible	137 (84.0%)
Grade TG 18	
Grade 1	23 (14.1%)
Grade 2	78 (47.9%)
Grade 3	62 (38.0%)
Therapy history	
Antibiotics as directed	107 (65.6%)
ERCP in 48 h	76 (46.3%)
Prior history of ERCP	37 (22.6%)
In-hospital mortality	19 (11.6%)

*Compared to the Endoscopic Retrograde Cholangiopancreatography (ERCP) gold standard.

Table 2. Comparison of TG18 and Charcot's Criteria

	Charcot's +	Charcot's -	Total
TG18 +	78 (98.7%)	59 (70.2%	137 (84%)
TG18 -	1 (1.3%)	25 (29.8%)	26 (16%)
Total	79 (48.5%)	84 (51.5%)	163 (100%)

assessed at 63.19% (95%CI: 55.29-70.6%). The low sensitivity indicates that the Charcot triad is inadequate for ruling out acute cholangitis when a negative result is observed. Conversely, a positive Charcot triad indicates a 96.15% likelihood of acute cholangitis, demonstrating its effectiveness in confirming the diagnosis.

Predictive Factors for In-Hospital Mortality in Acute Cholangitis

Evaluation of predictive factors was conducted to identify factors predicting mortality in patients with acute cholangitis. This evaluation focused on several key aspects: the severity of the condition based on TG18, the presence of liver and biliary tract malignancies, comorbid diabetes mellitus, delayed ERCP ≥ 48 hours after admission, inappropriate antibiotic choices, and procalcitonin levels. The bivariate analysis results are presented in **Table 3**. Following this, a multivariate analysis was performed to further stratify risk factors associated with mortality in acute cholangitis. The multivariate analysis included risk factors identified in the bivariate analysis with a p-value of less than 0.250. Four key variables were assessed: the severity of TG18, liver and biliary malignancies, diabetes mellitus, antibiotics not according to guidelines, and procalcitonin levels with a value limit of ≥ 2.0.

Variables with $p<0.250$ were included in the initial multivariate logistic regression model. The analysis utilized a backward logistic

Table 3. Bivariate Analysis of the Mortality Predictor Factors

Characteristics	Dead	Not dead	p-value	Risk Ratio (95% CI)
TG18 grade of severity				
Grade III	17 (27.4%)	45 (72.6%)	<0.001	13.846 (3.311–57.897)
Grades I and II	2 (2%)	99 (98.0%)		
Malignancy				
Yes	15 (20%)	60 (80%)	0.006	4.4 (1.525–12.687)
Not	4 (4.5%)	84 (95.5%)		
Diabetes mellitus				
Yes	4 (14.3%)	24 (85.7%)	0.631	1.285 (0.461–3.584)
Not	15 (11.1%)	120 (88.9%)		
ERCP time				
≥48 h	18 (13.3%)	117 (86.7%)	0.945	1.030 (0.442–2.402)
<48 h	1 (3.6%)	27 (96.4%)		
Antibiotics				
Not according to guidelines	12 (21.4%)	44 (78.6%)	0.008	3.275 (1.366–7.851)
According to the guidelines	7 (6.5%)	100 (93.5%)		
Procalcitonin levels				
≥2.0 ng/dL	10 (19.6%)	41 (80.4%)	0.037	2.440 (1.056–5.638)
<2.0 ng/dL	9 (8%)	103 (92%)		

regression technique, which systematically removed variables with the highest p-values. The final results indicated that grade III according to TG18, antibiotics not according to guidelines, and procalcitonin levels of ≥ 2.0 ng/mL were independent predictors of mortality in patients with acute cholangitis, as shown in **Table 4**.

DISCUSSION

In this study, the sensitivity of the TG18 relative to the ERCP gold standard was found to be 84.05% (95%CI: 77.51%–89.31%). This level of sensitivity is considered clinically acceptable for aiding clinicians in diagnosing acute cholangitis without relying on a gold standard diagnostic tool. Previous studies have also reported similar sensitivities for the TG18. Mohan et al. found that the TG18 detects 80% of cases of acute cholangitis[11], while Kiriyama et al. reported a sensitivity of 84.2% and up to 90%, respectively.[12] Given these findings, the TG18 is recommended for use in assisting the diagnosis of acute cholangitis in healthcare settings with limited support modalities.

The sensitivity of Charcot's triad was found to be 48.47% (95%CI: 40.58%–56.41%), with a specificity of 86.96% (95%CI: 66.41%–97.22%). Studies have consistently shown that the sensitivity of Charcot's triad ranges from 50% to 70%, with Kiriyama et al. diagnosing only 21.2% of cases.[10,12] When considering the TG18 as the gold standard, Charcot's triad exhibits a high specificity of 96.15% (95%CI: 80.36%–99.9%). Similarly, based on ERCP as the gold standard, Charcot's triad demonstrates a specificity of 93.2% in agreement with the systematic review study of Rumsey et al.[13] Furthermore, the use of TG18 has been shown to increase the sensitivity of diagnosis from 82.6% to 92.3% in comparison to the 2007 Tokyo Guidelines.[14] Although Charcot's triad is simpler and easier to memorize than the TG18, the latter should still be utilized if

Table 4. Multivariate Analysis of the Predictor Factors of Mortality

Characteristics	Risk Ratio (95% CI)	p-value
Stage 1		
Severity grade III	8.277 (1.796–38.149)	0.007
Antibiotics not according to guidelines	2.584 (1.178–5.668)	0.018
Procalcitonin level ≥ 2.0 ng/dL	2.198 (1.091–4.427)	0.027
Liver and biliary malignancy	1.755 (0.636–4.839)	0.277
Stage 2		
Severity grade III	10.679 (2.502–45.565)	0.001
Antibiotics not according to guidelines	2.923 (1.342–6.367)	0.007
Procalcitonin level ≥ 2.0 ng/dL	2.371 (1.183–4.753)	0.015

suspicion of cholangitis is high, especially when Charcot's triad yields a negative result due to its low sensitivity.

In this study, the in-hospital mortality rate was determined to be 11.6%. This finding aligns with Tan et al.'s study, which documented a mortality rate of 12% during a 25-year observation period for acute cholangitis. Notably, Tan et al.[7] study revealed no reduction in mortality over the observation period. This trend may be attributed to the rising incidence of acute cholangitis caused by malignancy, contributing to increased mortality rates despite advancements in healthcare quality. Additionally, Yildiz et al.'s [15] study also reported a comparable mortality rate of 10.6%. The variations observed in the mortality rates may be influenced by differences in country settings and healthcare systems, which affect the treatment outcomes for cholangitis patients.

Similar to this study and in line with this investigation, Ghali et al.[16] noted a significantly elevated occurrence of Grade III severity as per TG18, with a higher fatality rate compared to Grades I and II (6.89% vs. 0.4%; p<0.05). This finding was mirrored by Mohan et al.[11] who reported a mortality rate of 21.1% for TG18 Grade III patients compared to only 4.5% for Grades I and II (p<0.05). Severe acute cholangitis not only increases mortality but also extends hospital stay and the likelihood of intensive care unit admission.[17] Our multivariate analysis affirmed severe cholangitis as an independent predictor of mortality (RR: 10.679; 95%CI: 2.502–45.565, p=0.001). This observation may be attributed to the indirect use of the Sequential Organ Failure Assessment (SOFA) score in the TG18 severity categorization. Notably, the criteria for cardiovascular dysfunction using ≥5 μg/kg dopamine align with a SOFA cardiovascular score of 3. Likewise, the criteria for respiratory, renal, and hematological disorders each correlate with a SOFA score of 2, as established in previous studies.[10,18] The strong correlation of the SOFA score with the mortality risk is evident in the hospital mortality rates for patients with SOFA scores of 0–1, 2–3, 4–5, and >5, which reached 2.4%, 6.5%, 19.2%, and 41.9%, respectively.[19] Applying the TG18 criteria implies a minimum score of 2 for every patient, which results in a mortality risk of 6.5%. Consequently, patients with TG18 Grade III face a greater mortality risk compared to those with Grades I and II.

The procalcitonin levels emerged as a significant independent predictor of mortality in acute cholangitis (RR: 2.371; 95%CI: 1.183–4.753; p=0.015). Notably, procalcitonin levels of ≥2.0 present a similar risk of increased mortality in alignment with the findings of Umefune et al.[20] who indicated that procalcitonin levels exceeding 2.2 ng/mL exhibit high sensitivity and specificity in predicting the occurrence of Grade III acute cholangitis. Grade III cholangitis patients face a greater mortality risk compared to Grade I and II patients.[11,16] Moreover, patients with positive blood cultures had notably higher procalcitonin levels than those with negative cultures (8.6 ng/mL vs. 0.7 ng/mL), indicating a potential risk of bacteremia and sepsis for patients with elevated procalcitonin levels.[21] Notably, the changes in the procalcitonin levels before and after ERCP were not found to impact mortality.[22]

In this study, the etiology of malignancy in cholangitis cases emerged as a significant predictor of mortality. Tan et al.[7] also observed a similar trend (OR: 1.11; 95%CI: 1.04–1.18; p=0.01). The research conducted by Schneider et al.[9] indicated that patients with malignancy exhibited a higher mortality rate compared to those with non-malignant etiologies (OR: 3.0; 95%CI: 1.4–6.4; p=0.001). Furthermore, Tagashira et al.[23] highlighted a higher risk of death in patients with biliary obstruction caused by hepatobiliary malignancy (OR: 8.00; 95%CI: 2.92–21.97; p<0.001). This elevated risk of mortality associated with malignancy may be attributed to recurrent hyperbilirubinemia, as evidenced by the significant disparity in the mortality rate between patients with Grade II acute cholangitis with and without hyperbilirubinemia in our study (14.8% vs. 0%, p=0.015). In addition, patients who died were found to have higher bilirubin levels compared to the survivors (total bilirubin level: 22.45 vs. 13.90; p=0.014).[24] Comparable studies have also shown that hyperbilirubinemia escalates the risk of mortality. For instance, the study of Tagashira et al.[23] revealed that patients with bilirubin > 2.5

mg/dL had an increased risk of mortality (OR: 3.39; 95%CI: 1.46–7.89; p=0.005).

In cancer patients, inflammation leads to increased liver synthesis of the C-reactive protein, which subsequently reduces the serum albumin levels.[25] Hypoalbuminemia is an independent risk factor for mortality in acute cholangitis patients (OR: 1.355; 95%CI: 1.098-1.613; p<0.01).[24] This study revealed a higher mortality rate in patients with hypoalbuminemia compared to those without it (30% vs. 5.7%, p<0.001).[26] Albumin demonstrates anti-inflammatory, anti-oxidant, anti-coagulant, and anti-platelet aggregation properties.[26] Moreover, hypoalbuminemia affects drug binding, leading to increased drug bioavailability and consequent adverse effects.[25] The correction of hypoalbuminemia in acute cholangitis patients is crucial for improving the prognosis.

In this study, the use of antibiotics that did not comply with the guidelines was an independent predictor of mortality (RR: 2.923; 95%CI: 1.342–6.367; p<0.05). A retrospective cohort study of 573 patients in Japan defined inadequate antibiotic use as using empiric antibiotics that were inactive against an isolated organism or delaying the administration of antibiotics until culture results showed an increased mortality (OR: 2.78; 95%CI: 1.27–6.11; p=0.01) compared to patients who were given adequate antibiotics.[23] Patients who receive antibiotics not according to guidelines may face higher mortality due to the risk of developing bacteremia from organisms with extended-spectrum beta-lactamase (ESBL). Moreover, inappropriate antibiotic prescription can lead to increased adverse effects, including organ toxicity.[27] Therefore, administering and initiating antibiotics according to guidelines will prevent ESBL colonization, reduce the risk of organ toxicity, and reduce mortality.

In this study, delaying the implementation of ERCP for ≥48 h increased the risk of mortality (RR: 1.030; 95%CI: 0.442–2.402), but it was not statistically significant (p=0.945). This is in line with the results of a meta-analysis of eight studies conducted by Du et al.[28] which found that performing ERCP for <48 h compared to ≥48 h reduced the death rate (OR: 0.57; 95%CI: 0.51–0.63; I^2=0%). The reduction in mortality also occurred, even if we used a 24-h or 72-h threshold. In addition, delays in implementing ERCP increased the length of stay (LOS) (6.9 days *vs. 4.5* days, p<0.0001*;* OR: 0.58; 95%CI: 0.49–0.7; *p*<0.0001).[29] Drainage of pus from the bile duct using ERCP is the definitive treatment for acute cholangitis. Unnecessary delays in the implementation of ERCP should not occur, so that mortality rates, LOS, and costs can be reduced.

In this study, diabetes was determined to be a statistically insignificant predictor of mortality (RR: 1.285; 95%CI: 0.461–3.584; p=0.631). However, in a study conducted by Jimenez-Castillo et al.[30] it was established that diabetes was the only statistically significant predictor of mortality in cases of acute cholangitis (OR: 6.933; 95%CI: 1.119–355.028; p=0.042). Type 2 diabetes mellitus is known to generally diminish the immune response due to impaired cytokine production, inhibition of leukocyte recruitment, defects in pathogen recognition, and other associated mechanisms.[31] According to a retrospective study by Weissman et al., [32] comorbid DM is associated with a 31% higher risk of inpatient mortality (adjusted odds ratio [aOR]: 1.31; p=0.004) and a 53% increased risk of developing sepsis (aOR: 1.53; p=0.002). It also correlates with longer hospital LOS (4.5 days vs. 3.7 days; p<0.001) and higher hospital costs ($9934 vs. $8486; p<0.001).

CONCLUSION

In this study, the Tokyo Guidelines 2018 criteria were strongly validated and demonstrated an improved performance in the diagnosis of acute cholangitis when compared to Charcot's triad. The severity assessment based on TG18, antibiotic selection non-compliant with TG guidelines, and procalcitonin levels ≥ 2.0 ng/dL were identified as independent predictors of mortality in acute cholangitis.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES

1. Ahmed M. Acute cholangitis - an update. World J Gastrointest Pathophysiol. 2018;9(1):1–7. doi:10.4291/wjgp.v9.i1.1.
2. An Z, Braseth AL, Sahar N. Acute cholangitis: Causes, diagnosis, and management. Gastroenterol Clin North Am. 2021;50(2):403-14. doi: 10.1016/j.gtc.2021.02.005.
3. Tringali A. Endoscopic management of acute cholangitis. Gastroenterol Hepatol Open Access. 2016;5(2):208–213. doi:10.15406/ghoa.2016.05.00133.
4. Christeven R, Frandy F, Andersen A. Acute cholangitis: An update in management based on severity assessment. The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy. 2018;19(3):170-7. doi:10.24871/1932018170-177.
5. Yasuda H, Takada T, Kawarada Y, et al. Unusual cases of acute cholecystitis and cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:98–113. doi:10.1007/s00534-006-1162-9.
6. Allam H, Al Dosouky M, Abdelaziem S, et al. Acute calculous cholangitis in a diverse multi-ethnic population. International Journal of Surgery Open. 2016;2:22–5. doi:10.1016/j.ijso.2016.02.006.
7. Tan M, Schaffalitzky de Muckadell OB, Laursen SB. Unchanged mortality in patients with acute cholangitis despite an increase in malignant etiologies – a 25-year epidemiological study. Scand J Gastroenterol. 2019;54(3):335–41. doi:10.1080/00365521.2019.1585568.
8. Touzani S, El Bouazzaoui A, Bouyarmane F, et al. Factors associated with mortality in severe acute cholangitis in a Moroccan intensive care unit: A retrospective analysis of 140 cases. Gastroenterol Res Pract. 2021;1:1-7. doi:10.1155/2021/4583493.
9. Schneider J, Hapfelmeier A, Thöres S, et al. Mortality risk for acute cholangitis (MAC): a risk prediction model for in-hospital mortality in patients with acute cholangitis. BMC Gastroenterol. 2016;16:15. doi:10.1186/s12876-016-0428-1.
10. Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). J Hepato-Biliary-Pancreat Sci. 2018;25(1):41–54. doi: 10.1002/jhbp 515.
11. Mohan R, Goh SWL, Tan G, et al. Validation of TG07 and TG13/TG18 criteria for acute cholangitis and predictors of in-hospital mortality in patients over 80 years of age. Clin Exp Hepatol. 2021;7(4):396–405. doi:10.5114/ceh. 2021.110996.
12. Kiriyama S, Takada T, Hwang TL, et al. Clinical application and verification of the TG13 diagnostic and severity grading criteria for acute cholangitis: an international multicenter observational study. J Hepato-Biliary-Pancreat Sci. 2017;24(6):329–37. doi:10.1002/jhbp.458.
13. Rumsey S, Winders J, MacCormick AD. Diagnostic accuracy of Charcot's triad: a systematic review. ANZ J Surg. 2017;87(4):232–8. doi:10.1111/ans.13907.
14. Hudgi A, Cartelle AL, Ahmed A, et al. Tokyo guidelines (TG18) for acute cholangitis provide improved specificity and accuracy compared to fellow assessment. Cureus. 2022;14(7);1-6. doi:10.7759/cureus 27527.
15. Yıldız BD, Özden S, Saylam B, et al. Simplified scoring system for prediction of mortality in acute suppurative cholangitis. Kaohsiung J Med Sci. 2018;34(7):415–9. doi:10.1016/j.kjms.2017.12.016.
16. Ghali MS, Al-Yahri O, Dhaheri MA, et al. Retrospective application and validation of Tokyo 18 guidelines for diagnosis and stratification of acute cholangitis in Qatar. J Emerg Med Trauma Acute Care. 2022;2022(4):1-9. doi:10.5339/jemtac.2022.17.
17. Raghhupatruni P, Gopalakrishna R, Ankarath V, et al. Profile and outcome of patients with acute cholangitis in a tertiary center in South India. J Dig Endosc. 2021;12(03):127–32. doi:10.1055/s-0041-1739561.
18. Gyawali B, Ramakrishna K, Dhamoon A. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;7:1-13. doi:10.1177/2050312119835043.
19. Elias A, Agbarieh R, Saliba W, et al. SOFA score and short-term mortality in acute decompensated heart failure. Sci Rep. 2020;10(1):20802. doi:10.1038/s41598-020-77967-2.
20. Umefune G, Kogure H, Hamada T, et al. Procalcitonin is a useful biomarker to predict severe acute cholangitis: a single-center prospective study. J Gastroenterol. 2017;52(6):734–45. doi:10.1007/s00535-016-1278-x.
21. Shinya S, Sasaki T, Yamashita Y, et al. Procalcitonin is a useful biomarker for determining the need to perform emergency biliary drainage in cases of acute cholangitis. J Hepato-Biliary-Pancreat Sci. 2014;21(10):777–85. doi:10.1002/jhbp.132.
22. Jain A, Jena A, Gautam V, et al. Role of change in the levels of inflammatory markers post-drainage in predicting outcome in acute cholangitis. Arq Gastroenterol. 2022;59:212–8. doi:10.1590/S0004-2803.202202000-39.
23. Tagashira Y, Sakamoto N, Isogai T, et al. Impact of inadequate initial antimicrobial therapy on mortality in patients with bacteraemic cholangitis: a retrospective cohort study. Clin Microbiol Infect. 2017;23(10):740–7. doi:10.1016/j.cmi.2017.02.027.
24. Aboelsoud M, Siddique O, Morales A, et al. Early biliary drainage is associated with favourable outcomes in critically ill patients with acute cholangitis. Przegląd Gastroenterol. 2018;13(1):16–21. doi:10.5114/pg.2018.74557.
25. Nazha B, Moussaly E, Zaarour M, et al. Hypoalbuminemia in colorectal cancer prognosis: Nutritional marker or inflammatory surrogate? World J Gastrointest Surg. 2015;7(12):370–7. doi:10.4240/wjgs.v7.i12.370.

26. Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8–12. doi:10.1016/j.ejim.2018.04.014.
27. Cabral S, Adediran T, Harris A, et al. Factors associated with inappropriate antibiotic use in hospitalized patients. Infection Control & Hospital Epidemiology. 2020;41(S1):s233–s234. doi:10.1017/ice 2020.785.
28. Du L, Cen M, Zheng X, et al. Timing of performing endoscopic retrograde cholangiopancreatography and inpatient mortality in acute cholangitis: A systematic review and meta-analysis. Clin Transl Gastroenterol. 2020;11(3):e00158. doi:10.14309/ctg.0000000000000158.
29. Mulki R, Shah R, Qayed E. Early vs late endoscopic retrograde cholangiopancreatography in patients with acute cholangitis: A nationwide analysis. World J Gastrointest Endosc. 2019;11(1):41–53. doi:10.4253/wjge.v11.i1.41.
30. Jiménez Castillo RA, Jaquez-Quintana JO, Reyna-Arechiga AI, et al. Risk factors for mortality in patients with acute bacterial cholangitis - Type 2 diabetes is a significant clinical predictor. Rev Espanola Diseases Dig Organ Of Soc Espanola Patol Dig. 2022;114(1):59–61. doi:10.17235/reed. 2021.8251/2021.
31. Berbudi A, Rahmadika N, Tjahjadi AI, et al. Type 2 diabetes and its impact on the immune system. Curr Diabetes Rev. 2020;16(5):442–9. doi:10.2174/1573399815666191024085838.
32. Weissman SDO, Allen MBS, Tangella AV MBBS, et al. S126 comorbid diabetes on hospitalization outcomes in acute pancreatitis. The American Journal of Gastroenterology. 2022;117(10S):p e90. doi:10.14309/01.ajg.0000857144.80477.bb.