Neutrophil-lymphocyte Ratio Predicts Clinical Response to Percutaneous Transhepatic Biliary Drainage in Acute Cholangitis

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Background: **Predicting response to biliary drainage is critical to stratify patients with acute cholangitis. Total leucocyte count (TLC) is one of the criteria for predicting the severity of cholangitis and is routinely performed. We aim to investigate the performance of neutrophil-lymphocyte ratio (NLR) in predicting clinical response to percutaneous transhepatic biliary drainage (PTBD) in acute cholangitis.** ***Patients and methods:*** **This retrospective study comprised consecutive patients with acute cholangitis who underwent PTBD and had serial (baseline, day 1, and day 3) TLC and NLR measurements. Technical success, complications of PTBD, and clinical response to PTBD (based on multiple outcomes) were recorded. Univariate and multivariate analysis was performed to identify factors significantly associated with clinical response to PTBD. The sensitivity, specificity, and area under the curve of serial TLC and NLR for predicting clinical response to PTBD were calculated.** ***Results:*** **Forty-five patients (mean age 51.5 years, range 22–84) met the inclusion criteria. PTBD was technically successful in all the patients. Eleven (24.4%) minor complications were recorded. Clinical response to PTBD was recorded in 22 (48.9%) patients. At univariate analysis, the clinical response to PTBD was significantly associated with baseline TLC ($P = 0.035$), baseline NLR ($P = 0.028$), and NLR at day 1 ($P=0.011$). There was no association with age, the presence of comorbidities, prior endoscopic retrograde cholangiopancreatography, admission to PTBD interval, diagnosis (benign vs. malignant), severity of cholangitis, organ failure at baseline, and blood culture positivity. At multivariate analysis, NLR-1 independently predicted the clinical response. Area under the curve of NLR at day 1 for predicting clinical response was 0.901. NLR-1 cut-off value of 3.95 was associated with sensitivity and specificity of 87% and 78%, respectively.** ***Conclusion:*** **TLC and NLR are simple tests that can predict clinical response to PTBD in acute cholangitis. NLR-1 cut-off value of 3.95 can be used in clinical practice to predict response.** **(J Clin Exp Hepatol 2023;13:390–396)**

Acute Cholangitis

Biliary obstruction is one of the common conditions presenting to the emergency department.[1] Acute cholangitis is one of the most life-threatening presentations of biliary obstruction and carries high morbidity and mortality.[2,3] The 2018 Tokyo Guidelines (TG-18) recommend urgent biliary drainage in patients with moderate to severe cholangitis.[4,5] Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred method for biliary drainage.[6–8] Percutaneous transhepatic biliary drainage (PTBD) is a well-established therapeutic alternative with a high level of technical and clinical success in unstable patients, those with higher level of biliary obstruction, hepaticojejunostomy, and failed ERCP.[9–11]

Predicting response to biliary drainage is critical to stratify patients and offer them an adequate level of care. Depending on the patient's response, additional procedures to treat the cholangitic abscess or drain the other bile ducts may be needed. Hypoalbuminemia, interleukin-7, and procalcitonin can predict mortality in cholangitis patients.[12,13] Total leucocyte count (TLC) is one of the criteria for predicting the severity of cholangitis (as per TG-18) and is routinely performed.

In previous studies, high baseline neutrophil-lymphocyte ratio (NLR) at admission has been shown to be an independent negative prognostic predictor in acute pancreatitis and corresponded with severe acute pancreatitis and organ failure.[14–17] In another study, higher baseline NLR was found to be an independent predictor of 28-day mortality in

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Abbreviations: AKI: Acute Kidney Injury; AUC: Area under curve; ERCP: Endoscopic retrograde cholangiopancreatography; Fr: French; ICU: Intensive care unit; NLR: Neutrophil-lymphocyte ratio; PTBD: percutaneous transhepatic biliary drainage; ROC: receiver operating characteristics; SIR: Society of Intervention radiology; TG: Tokyo guidelines; TLC: Total leukocyte count
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patients with severe fever and thrombocytopenia syndrome.[18] Similar results were reported in patients with bloodstream infection.[19] In a recent study, higher NLR had a significant correlation with the prediction of disease severity, shock, and positive blood cultures in patients with acute cholangitis who underwent biliary drainage.[20]

The use of TLC and NLR to predict response to biliary drainage seems attractive given that these tests are simple, inexpensive, and widely available. Therefore, the aim of this study was to evaluate the performance of TLC and NLR in predicting clinical response to PTBD.

MATERIALS AND METHODS

Study Design

Our institutional ethics committee approved this retrospective observational study (INT/IEC/2022/SPL-84). All patients or their kins provided written informed consent for performing the drainage procedure. In addition, we reviewed the records of consecutive patients with cholangitis who underwent PTBD between January 2019 and December 2021. The clinical data, intervention radiology notes, and follow-up for these patients were documented. Patients with insufficient baseline data, incomplete clinical records, missing laboratory information, or those lost to follow-up were excluded from the study.

Pre-PTBD Evaluation

Patients were evaluated before the procedure using ultrasound. The available imaging studies were thoroughly reviewed for the site and cause of biliary obstruction and resectability (in cases of malignant disease). In addition, the biliary drainage indications were recorded. Total serum bilirubin, serum creatinine, TLC, and NLR (within 24 h before PTBD [baseline, TLC-0, NLR-0]). An automated hematology analyzer (LH-780, Beckman coulter, USA) was used to perform TLC and differential leukocyte count measurements. The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes.

Cholangitis was classified as mild, moderate, or severe according to the TG-18 guidelines.[3,5] The presence of organ failure (TG-18 guidelines) and comorbidities was recorded.

Treatment Protocol

Following standard recommendations, all patients were initially managed with fluid resuscitation, oxygen support, organ system support, and broad-spectrum antibiotics based on the discretion of the treating clinicians.[3,5] Patients with mild cholangitis who did not respond to medical therapy and those with moderate and severe cholangitis underwent PTBD if they had a hilar block, failed ERCP, or were too unstable to undergo ERCP.

PTBD Procedure

As per Society of Interventional Radiology guidelines, the recommended threshold for platelet counts of more than 50000/μL and an international normalized ratio of less than 1.5 was followed. The procedure was carried out after the transfusion of fresh frozen plasma or platelets in cases of deranged coagulogram or low platelet count, respectively. Moderate to gross ascites was managed before PTBD with therapeutic paracentesis. Intravenous analgesia (injection Tramadol) and preprocedural antibiotics (injection piperacillin-Tazobactam) were given. The upper abdomen was scrubbed with povidone-iodine (10% w/v) and draped. Lignocaine was used for local anaesthesia at the access site. All procedures were performed under combined ultrasound and fluoroscopy guidance. Under ultrasound guidance, the puncture was performed either using an 18G or a 21G puncture needle (micropuncture access set) in case of a non-dilated system (peripheral ducts <2 mm). In patients with hilar block, we initially performed unilateral drainage. The resectability and liver area drained by the duct were considered while deciding whether to drain the left or right ductal system. Any duct having echogenic material within (indicating the presence of infected bile) or the duct draining the lobe with cholangitis abscesses was chosen. The contralateral system was drained in post-ERCP cholangitis with a functioning stent in one of the ductal systems. In patients who failed to respond to unilateral drainage, the contralateral duct was drained subsequently.

After aspirating a small amount of bile, 1–3 mL of diluted non-ionic iodinated contrast was gently administered through the puncture needle, followed by a hydrophilic guidewire. The entry tract was dilated using fascial dilators over a stiff guidewire. A 7 or 8 Fr drainage catheter was inserted, and external drainage was achieved. After an improvement in cholangitis, internalization procedure was performed. The hydrophilic guidewire was passed, and the stricture was negotiated using a 5Fr multipurpose catheter. After that, the hydrophilic guidewire was replaced with a stiff guidewire. Finally, an 8 Fr ring biliary catheter was placed across the stricture with its tip in the duodenum.

The first bile sample was cultured. The bile culture and antibiotics sensitivity results were then used to modify the empirical antibiotic regimen.

Recording of PTBD Outcomes and Complications

The technical success of the procedure was defined as the completion of the PTBD with the placement of a biliary catheter. Complications were recorded during the procedure and the days that followed in the hospital, as per Society of Interventional Radiology guidelines.[21]

Post-PTBD TLC and NLR

Post-PTBD TLC and NLR at 24 h (TLC-1/NLR-1) and 72 h (TLC-2/NLR-2) were recorded. Total bilirubin and creatinine were recorded on day 1, day 3, and day 7. Total Bilirubin on day 7 was recorded.

Outcomes

Outcomes including the duration of hospitalization, intensive care unit (ICU) admission at baseline, ICU admission after PTBD, duration of ICU stay, need for mechanical ventilation, bilirubin reduction> 50% at one week, resolution of organ failure, new-onset organ failure, new-onset cholangitis, and mortality were recorded. Clinical response to PTBD was assessed using multiple outcome parameters. Hospital stay ≤1 week, ICU stay ≤3 days (for patients already in ICU at the time of PTBD), resolution of organ failure at day 7, and bilirubin reduction ≥50% at day 7 defined clinical response. Lack of clinical response was defined by new ICU admission following PTBD, new onset organ failure following PTBD, need for mechanical ventilation following PTBD, and death.

Statistical Analysis

The continuous variables were recorded as mean with range. The categorical variables were recorded as percentages and proportions. The continuous variables were compared using Mann–Whitney U-test. The categorical variables were compared using the Chi-square test or Fischer's exact test. The receiver operating characteristics and area under the curve (AUC) were assessed. The cut-off values of TLC and NLR that led to the best combination of sensitivity and specificity were chosen. Multivariate logistic regression analysis was performed to identify factors associated with clinical response to PTBD. Parameters with *P*-value <0.2 at univariate were chosen for multivariate analysis. Statistical analysis was done using Statistical Package for Social Sciences (IBM SPSS 26.0). The results that showed *P*-values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics and Procedure Details

Forty-five patients with complete details were included in the study. The mean age was 51.5 years (range, 22–84). There were 17 (37.8%) males and 28 (62.2%) females. Fifteen (33.3%) patients had comorbidities (obesity [n = 12], diabetes mellitus [n = 11], hypertension [n = 9], hypothyroidism [n = 4]). Coagulopathy and thrombocytopenia needing correction was recorded in 7 (15.6%) and 4 (8.9%) patients, respectively. The mean PTBD requisition to procedure delay (due to the need for the correction of coagulopathy/thrombocytopenia) was 1 day (mean, 1–3 days). Therapeutic paracentesis was performed in 6 (13.3) patients and PTBD was performed the same day. Thirty-one (68.9%) patients had malignant biliary obstruction and 14 (31.1%) patients had benign strictures. Malignant biliary obstruction was due to carcinoma gallbladder (n = 18, 58.1%), cholangiocarcinoma (n = 6, 19.4%), carcinoma head of pancreas (n = 4, 12.9%), periampullary carcinoma (n = 2, 6.5%), and lymphoma (n = 1, 3.2%) (Table 1). Fourteen (45.2%) patients had resectable malignancy. As per Tokyo guidelines, 10 (22.2%) patients had mild, 19 (42.2%) patients had moderate, and 16 patients (35.6%) had severe cholangitis. Level of block was primary confluence in 22 (48.9%), secondary confluence in 13 (28.9%), proximal CBD in 2 (4.4%), distal CBD in 7 (15.6%), and hepaticojejunostomy site in 1 (2.2%). Mean baseline total bilirubin was 13.1 mg/dL (range, 0.5–34). Organ failure was present in 16 (35.6%) patients. Acute kidney injury was present in 14 (31.1%) patients. Blood culture was positive in 16 (35.6%) patients. Twelve (26.7%) patients were in the ICU at the time of PTBD. Table 1 shows the baseline characteristics of the included patients.

PTBD

Technical success was achieved in all cases. Right-sided PTBD was done in 14 (31.2%), left-sided in 20 (44.4%), and bilateral in 11 (24.4%) patients. The mean interval between right and left PTBD was 3.7 days ± 2.9 days. Thirteen (28.9%) patients previously underwent ERCP and had non-resolving or worsening cholangitis (mean interval to cholangitis 7.5 days ± 3.4 days). PTBD was done after failed ERCP in five patients. The mean admission to PTBD interval was 2 ± 0.9 days. There was no significant difference in the interval to PTBD between patients with prior ERCP (mean, 1.7 ± 0.8 days) and those with no history of ERCP (mean, 2.1 ± 0.9 days) (*P* = 0.131). PTBD was internalized in 24 (53.3%) patients.

Eleven (24%) procedure-related complications were encountered. There were no major complications. Three patients (6.6%) had haemobilia (immediately following the procedure) that resolved within 8 h without any active intervention. Five patients (11.1%) had PTBD slippage (2–4 days following the procedure) that was managed with catheter repositioning or reinsertion. Cholangitis worsened in three patients (6.6%), managed with the change/upgradation of intravenous antibiotics.

TLC and NLR Values and Association with Outcomes

The mean (±SD) TLC-0, TLC-1, and TLC-2 were 16.3 × 10^9/L (±8.11), 14.9 × 10^9/L (±6.09), and 13.7 × 10^9/L (±4.29), respectively. The mean (±SD) NLR-0, NLR-1, and NLR-2 were 8.6 (±3.24), 7.9 (±3.31), and 7.4 (±4.54), respectively. Table 2 shows the values of

Table 1 Baseline Demographic Details (n = 45).

Characteristics	Number (Percentage)
Male	17 (37.8%)
Female	28 (62.2%)
Mean Age	51.5 years (range, 22–84)
Comorbidities	15 (33.3%)
Benign	14 (31.1%)
Malignant	31 (68.9%)
Gallbladder Carcinoma	18
Cholangiocarcinoma	6
Carcinoma Pancreas	4
Periampullary Carcinoma	2
Lymphoma	1
Level of Block	
Primary confluence	22 (48.9%)
Secondary confluence	13 (28.9%)
Right secondary	5
Left secondary	4
Right and left secondary	4
Proximal CBD	2 (4.4%)
Distal CBD	7 (15.6%)
Anastomosis	1 (2.2%)
Severity of Cholangitis	
Mild	10 (22.2%)
Moderate	19 (42.2%)
Severe	16 (35.6%)
Site of PTBD	
Right	14 (31.1%)
Left	20 (44.4%)
Bilateral	11 (24.4%)
Mean bilirubin (mg/dL)	
Day 0	13.1 (0.5–34)
Day 7	6.4 (0.3–22.5)
Positive Blood Culture	16
Mean duration of hospitalization (days)	14 (4-29)
ICU admission	
Baseline	12 (26.7%)
After PTBD	2 (4.4%)
Mean duration of ICU admission (days)	9 (2-17)
Organ failure	
Baseline	16 (35.6%)
Day 7	6 (13.4%)
Resolution	10 (22.2)
New-onset	2
Death	7 (15.6%)

CBD, Common Bile duct; PTBD, Percutaneous Transhepatic Biliary Drainage; ICU, Intensive care unit.

serial TLC and NLR. Both TLC and NLR showed an overall decreasing trend (Figure 1).

Mean bilirubin at day 7 was 6.4 mg/dL (0.3–22.54). Bilirubin reduction ≥50% was achieved in 25 (55.5%) of the patients. Organ failure resolved in 10 patients. On day 7, six patients had organ failure, two of whom had new-onset organ failure. Cholangitis worsened in three patients. Two patients were admitted to the ICU after PTBD. The mean duration of ICU stay was 9 days (range, 2–17). Seven (15.6%) patients died during the 1st week.

Clinical response was recorded in 22 (48.9%) patients. At univariate analysis, the clinical response to PTBD was significantly associated with TLC-0 (P = 0.035), NLR-0 (P = 0.028), and NLR-1 (P=*0.011*). There was no association with age (P = 0.855), the presence of comorbidities (P = 0.099), prior ERCP (P = 0.239), admission to PTBD interval (P = 0.536), diagnosis (benign vs. malignant) (P = 0.885), severity of cholangitis (P = 0.575), level of block (P = 0.239), laterality of PTBD (P=*0.531*), organ failure at baseline (P = 0.113), and blood culture positivity (P = 0.944) (Table 3). At multivariate analysis, only NLR-1 independently predicted clinical response.

Table 2 Serial TLC and NLR.

Time	Total	Responders	Non-responders
Day 0			
Mean TLC × 10^9/L (±SD)	16.3 ± 8.11	14.11 ± 7.33	17.69 ± 9.81
Mean NLR (±SD)	8.6 ± 3.24	7.84 ± 4.63	9.23 ± 5.01
Day 1			
Mean TLC × 10^9/L (±SD)	14.9 ± 6.09	12.45 ± 5.99	14.64 ± 8.85
Mean NLR (±SD)	7.9 ± 3.31	6.54 ± 2.34	9.62 ± 5.93
Day 3			
Mean TLC × 10^9/L (±SD)	13.7 ± 4.29	12.41 ± 4.09	13.98 ± 6.31
Mean NLR (±SD)	7.4 ± 4.29	5.91 ± 3.42	7.42 ± 5.69

TLC, Total leucocyte count; NLR, Neutrophil lymphocyte ratio; SD, Standard deviation; day 0 within 24 h prior to PTBD.

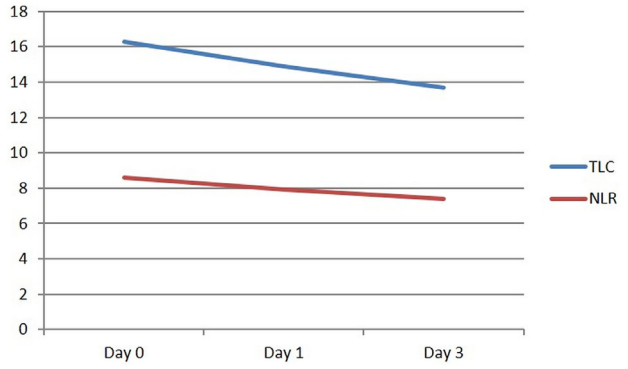

Figure 1 Trends in TLC and NLR. There is a decreasing trend for both TLC ($\times 10^9$/L) (blue) and NLR (red). NLR, neutrophil-lymphocyte ratio; TLC, total leukocyte count.

Receiver Operating Characteristics Analysis

AUCs for predicting clinical response was 0.786, 0.887, and 0.901, respectively. for TLC-0, NLR-0, and NLR-1. TLC-0 sensitivity and specificity were 74% and 65%, respectively, when a cut-off value of 12.75 $\times$ 10^9/L was used. Sensitivity and specificity were 82% and 75%, respectively, using a cut-off value of 4.05 for NLR-0 (Figure 2). NLR-1 sensitivity and specificity were 87% and 78%, respectively, with a cut-off value of 3.95.

Table 3 Univariate and Multivariate Analysis for Predicting Clinical Response to Percutaneous Transhepatic Biliary Drainage in Patients With Cholangitis.

Parameters	Univariate analysis (*P* value)	Multivariate analysis* (*P* value)
Age	0.855	–
Comorbidity	0.099	0.175
Prior ERCP	0.239	–
Admission to PTBD interval	0.536	–
Moderate to severe cholangitis	0.575	–
Level of block	0.239	–
Laterality of PTBD	0.531	–
No organ failure at baseline	0.113	0.238
Blood culture positivity at baseline	0.944	–
TLC0	0.035	0.064
NLR0	0.028	0.090
TLC1	0.121	0.896
NLR1	0.011	0.016
TLC2	0.180	0.152
NLR2	0.091	0.144

ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; TLC0/NLR0 baseline (within 24 h prior to PTBD), TLC1/NLR1 day 1; TLC2/NLR2 day3.
*Parameters with *P* value <0.20 were included in multivariate analysis.

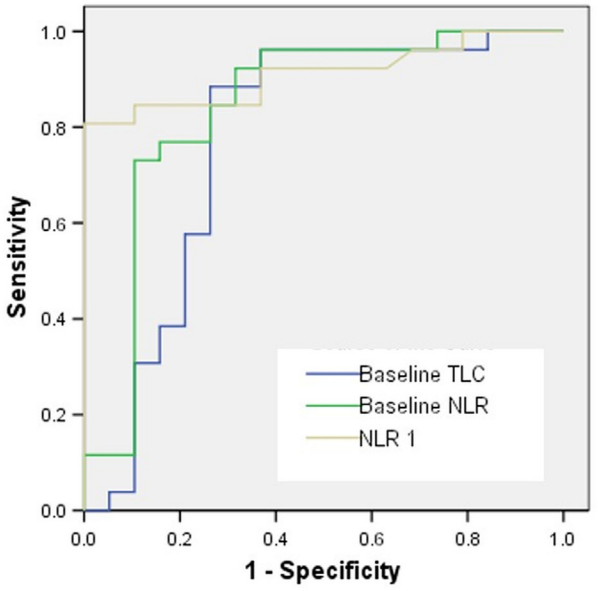

Figure 2 Receiver operating characteristic curves for TLC and NLR. Baseline (TLC-0 and NLR-0) and NLR-1 ROC curves for predicting clinical response are shown in A. Area under the curve are greater for NLR (0.887 and 0.901) than TLC (0.786). NLR, neutrophil-lymphocyte ratio; TLC, total leukocyte count; ROC, receiver operating characteristics.

DISCUSSION

In this study, evaluating the role of TLC and NLR in assessing response to PTBD in patients with cholangitis, NLR at day 1 was independently associated with clinical response. The AUC of NLR for predicting clinical response to PTBD was higher than that for TLC. NLR-1 cut-off value of 3.95 was associated with a sensitivity and specificity of 87% and 78%, respectively. These results suggest that TLC and NLR may be useful in managing patients with acute cholangitis who undergo PTBD.

Predicting response to PTBD is crucial for making appropriate decisions about additional interventions and developing a management strategy for patients with cholangitis. TLC is a simple and inexpensive test routinely performed on hospitalized cholangitis patients during their initial evaluation and follow-up. NLR can be easily calculated from differential leucocyte count. Previous studies evaluated prognostic factors in severe acute cholangitis.[22–27] A few published studies have evaluated factors predicting response to endoscopic biliary drainage in patients with acute cholangitis.[28,29] Schwed *et al.* reported higher baseline TLC and total bilirubin levels as independent prognostic factors for poor outcomes.[28] Another study found higher American Society of Anaesthesiology physical classification grades and delays in ERCP to be significantly associated with adverse outcomes.[29]

A few studies have evaluated factors associated with outcomes after PTBD in patients with malignant biliary obstruction.[30,31] In one of the studies, the presence of

ascites was significantly associated with mortality in multivariate analysis.[30] Another study reported hospital-acquired biliary sepsis being significantly associated with adverse outcomes in patients with malignant biliary obstruction undergoing PTBD.[31] To the best of our knowledge, there are no published reports of factors predicting outcomes in acute cholangitis patients undergoing PTBD.

NLR has been proven to predict the prognosis in both benign and malignant disorders.[32–36] In a few studies, NLR has been used to predict the severity of AP and response to percutaneous catheter drainage.[30–33] In critically ill patients, NLR has been demonstrated to be more accurate than TLC in predicting clinical outcomes.[14–17] Similarly, in diagnosing acute cholangitis and acute cholecystitis, NLR has proven to be more accurate than TLC.[37–41] However, none of the published studies have evaluated the role of NLR in predicting response to biliary drainage.

The advantage of NLR over TLC can be attributed to a variety of factors, including TLC's sensitivity to physiological and pathological conditions, including stress, pregnancy, and hydration state, and technical aspects like blood sample removal and handling.[17] Although NLR remains stable, white blood cell subtypes are vulnerable to these factors. NLR is a systemic inflammatory marker that reflects the balance of innate and adaptive immune responses. Inflammatory mediators such as myeloperoxidase, elastase, IL-1, and IL-6 activate neutrophils, causing non-specific inflammation and tissue destruction.[42] When these are severely activated, it can lead to multiple organ failure and even death. The lymphocyte immune response is intended to reduce non-specific inflammation by limiting the inflammatory response that follows the neutrophilic response.[42] As a result, a high NLR indicates an imbalance in the inflammatory response and could be used to predict disease severity.

There were a few limitations to our study. First, due to the retrospective nature of the data, it is prone to several biases. Second, our sample size was small because all patients did not have relevant investigations at selected time points. Third, the presence of a malignant biliary obstruction in many patients may be a confounding factor as TLC and NLR may be impacted by other underlying diseases, including malignancy. Finally, we did not compare TLC and NLR's performance to other inflammatory markers.

TLC and NLR are simple tests that can predict PTBD response in patients with acute cholangitis. NLR-1 cut-off value of 3.95 can be used in clinical practice to predict response to PTBD.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

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CONFLICTS OF INTEREST

All authors have none to declare.

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