The Neutrophil-Lymphocyte Ratio as an Early Predictor of Severity and outcome of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Background and study aim: The post-ERCP pancreatitis (PEP) incidence is 3.5%, making it the most frequent complication following ERCP. Pancreatitis is mild-to-moderate in severity in 90% of cases. The current study aims to evaluate the neutrophil-lymphocyte ratio (NLR) as an early predictor of the severity and outcome of post-endoscopic retrograde Cholangiopancreatography pancreatitis.

Patients and Methods: The study was conducted on 90 patients who underwent ERCP. 67 with mild/moderate pancreatitis and 23 with severe pancreatitis. Clinical and laboratory evaluation performed including NLR measurement at day 0 & day 1,2 after ERCP.

Results: The mean value of NLR on days 1 and 2 was significantly associated with a severe form of acute pancreatitis. Roc curve analysis revealed that, at cut-off point 6.05, NLR at day 1 can predict severe pancreatitis with a sensitivity of 91.3% and specificity of 89.6%. Furthermore, NLR day 2 at cut-off point 5.42 can predict severe pancreatitis with a sensitivity of 91.3% and specificity of 94%. BMI ≥30, history of previous pancreatitis, history of previous PEP, NLR day 1, NLR day 2, a malignant indication of ERCP, duration of the procedure, difficult cannulation, and pancreatic duct contrast were significant risk factors for severe pancreatitis. Multiple logistic regression analysis revealed that NLR day 1 and day 2 were significant independent risk factors for severe pancreatitis.

Conclusion: The NLR offers beneficial clinical guidance to better assess the severity of AP. It is also inexpensive, readily available, and has a moderately high prognostic power in predicting the severity, outcome, and overall survival of AP patients.

INTRODUCTION

Acute pancreatitis is a particularly serious adverse event linked to endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post-ERCP pancreatitis (PEP) varies between 4% and 15% [1-3]. Though the incidence of severe form of PEP is low (0.3-0.6%) [4], it has been linked with substantial morbidity, prolonged hospital admission, and, occasionally, death. The PEP mortality rate is increasing. This requires an early and prompt prediction of severity [5]

PEP has been described as the occurrence of the following: acute abdominal pain that is characteristic and lasts for at least twenty-four hours after the ERCP procedure with ≥ 3-fold higher than the upper limit of the normal values of serum amylase and/or lipase levels; and/or abdominal computed tomography (CT) that is consistent with acute pancreatitis. Furthermore, PEP was classified as mild, moderate, or severe based on the revised Atlanta classification [6]. Mild PEP cases (patients with PEP that demands being hospitalized for 2-3 days); moderate PEP cases (PEP patients who require hospitalization for 4-10 days); and severe ones (PEP patients requiring hospital admission for more than 10 days and/or the occurrence of any of these conditions: persistent organ failure, pancreatic necrosis, acute fluid collections, surgical or percutaneous intervention, or death) [7]. Even though the risk factors for PEP occurrence have been extensively

researched, few studies have looked into indicators or predictors of PEP severity. Systemic inflammatory response syndrome (SIRS) and serum phosphate have been suggested as prognostic markers for PEP [8,9]. Therefore, a need for novel, simple, and early indicators of severe PEP so that patients can be stratified for vigorous hydration, close monitoring, and particular transferring to the intensive care unit (ICU) [10].

The neutrophil-lymphocyte ratio (NLR) has been shown to predict adverse complications of acute pancreatitis unrelated to ERCP [11-14]. Compared to the total white blood cell (WBC) count, the NLR more accurately depicts the inflammatory and immunological response [11]. In patients with acute pancreatitis, the NLR could predict the severity of the disease, local complications, organ failure, as well as the need for ICU admission [11,13]. Nevertheless, the association between severe PEP and the NLR has not been thoroughly studied [10].

The current study aimed to evaluate the prognostic role of the Neutrophil-Lymphocyte Ratio in Post-ERCP Pancreatitis and to investigate its role in predicting severity, and outcome of the patients and identify the risk factors of PEP.

METHODS

This cohort prospective study was conducted on 90 patients who underwent ERCP and developed pancreatitis. Patients were selected from the inpatient and outpatient clinic of the Tropical Medicine Department at Menoufia University Hospital, and the Hepatogastroenterology Department at National Liver Institute, Menoufia University between February 2023 and February 2024. They were 51 males (56.7%) and 39 females (43.3%); their ages ranged between 20 and 80 years with a mean value of (56.8±13.1) years and they were classified according to revised Atlanta classification [6] into two groups: mild/moderate pancreatitis group included 67 patients and severe pancreatitis group included 23 patients calculated NLR at day 0 & day 1, 2 post ERCP.

Inclusion criteria: Patients subsequently diagnosed with PEP after ERCP whatever the cause (including benign or malignant biliary obstruction).

Exclusion Criteria: Patients who had concurrent acute inflammatory conditions (such as pneumonia, liver abscess, acute cholangitis, and cholecystitis) at admission, patients <18 years of age, and incomplete medical records were excluded from the study.

All patients were subjected to the following: full history taking (age, sex, DM, HTN, abdominal pain, weight loss, jaundice, previous pancreatitis, previous ERCP, and previous PEP), full clinical assessment: general examination (BP, temperature, pulse, jaundice, lower limb edema) and local examination(abdominal tenderness, liver, spleen, ascites). Sample collection and laboratory tests were as follows: Aseptic withdrawal of 6 ml of venous blood after overnight fasting was done from each patient and was divided into three tubes: Tube 1: Two ml of blood was allowed to clot at 37 °C, centrifugated & separated serum used for assaying fasting blood sugar, liver enzymes (ALT & AST) & liver function tests (serum bilirubin, albumin), renal function test, serum calcium, pancreatic enzymes(amylase &lipase) (AU480, Beckman colter, USA), CRP by turbidmetry USA). Tube 2: Two ml of blood was collected on the EDTA tube for assaying CBC, calculating NLR at day 0, 1,2 post-ERCP (Sysmex XN 1000, USA). Tube 3: Two ml of blood was collected on a citrate blue tube for assaying prothrombin time, (Stago, USA). Imaging (abdominal ultrasonography, CT Abdomen (pancreatic protocol), MRCP, and ERCP). Patients' outcome was assessed regarding hospital stay in day, ICU admission, and mortality.

Statistics

An IBM personal computer executing the Statistical Package of Social Science (SPSS) version 20 (IBM Corporations, 2011), Armonk, NY, and Epi Info 2000 software was used to gather, tabulate, and statistically analyze the data. The subsequent statistics were used. To investigate the relationship between two qualitative variables, the chi-squared test ($\chi 2$) was employed. When comparing two groups with quantitative variables that are not normally distributed, the Mann-Whitney test is a test of significance. When comparing more than two groups with quantitative non-parametric variables, the Kruskal Wallis test (K) is utilized. A test of significance for examining the relationship between non-parametric quantitative

variables was the Spearman correlation coefficient. Positive (+) or negative (-) correlations are typically found in the results of the correlation coefficient test (r-test). It is employed to measure how strongly two variables have a linear relationship. For multivariate analysis with a binary dependent variable, binary logistic regression was employed. To assess biomarker performance, receiver operator characteristics (ROC) were created, along with the corresponding sites of maximal accuracy for sensitivity and specificity. The test's accuracy is measured by the area under the ROC curve (AUROC). A test is considered flawless if its area is 1, and useless if its area is 0.5. [0.90-1 = excellent (A) ,0.80-0.90 = good (B) ,0.70-0.80 = fair, (C) 0.60-0.70 = poor, (D) 0.50-0.60 = fail (F)]

A P-value of (>0.05) was considered not statistically significant. A P-value of (≤0.05) was considered statistically significant. A P-value of (≤0.001) was considered statistically highly significant

Sample size estimation Based on a review of past literature (Lee, S et al.,2021), found that NLR on day 2 post-ERCP has a high discriminatory ability for severe PEP. NLR on day 2 > 8.17 (OR 18.29). The least sample size calculated using Statistics and Sample Size Pro Program Version 6 is 32 participants. The power of the study is 80% and the confidence level is 95%.

RESULTS

Table 1 demonstrates the demographic data among studied patients. 67(74.4%) out of 90 patients with acute pancreatitis exhibit mild to moderate pancreatitis, while 23(25.6%) patients show evidence of severe pancreatitis. There was statistically non-significant difference between the two groups regarding gender, age, history of diabetes mellitus or hypertension.

Regarding the baseline investigation (Pre-ERCP) CBC findings showed that there was a statistically significant difference between the two patients' groups regarding TLC, being lower in the severe pancreatitis group, while Hb concentration, HCT, platelet count, or NLR didn't differ. Additionally, Statistical analysis revealed that there was a significant difference between the two groups regarding baseline bilirubin, direct bilirubin, and ALT values. Where patients with severe pancreatitis show high values compared to Mild/Moderate cases. However, other baseline laboratory investigations didn't differ as shown in Supplementary Table 1.

According to the indication of ERCP in studied patients, cases with malignant etiology are significantly frequent in patients with severe pancreatitis compared to those with mild to moderate presentation. However, there is a statistically non-significant difference between the two patient groups regarding the purpose of ERCP (Figure 1).

Statistical analysis revealed that previous pancreatitis, previous PEP, and higher BMI are significantly more frequent in severe cases compared to mild to moderate ones. Longer duration of ERCP, difficult cannulation, total Sphincterotomy, papillotomy, and pancreatic duct contrast are frequently associated with severe pancreatitis (Figure 2)

Table 2 shows Post-ERCP assessment. There was a statistically significant difference between the two patient groups regarding Urea, creatinine, BUN and CRP day 2 while, TLC, CRP day 1, Glucose day 1&2, Amylase and lipase didn't differ. Also, there was a statistically significant different between the two patient groups regarding hospital stay in days.

Roc curve analysis revealed that, at the cut of point 6.05, NLR at day 1 can predict severe pancreatitis with a sensitivity of 91.3% and specificity of 89.6%. Furthermore, NLR day 2 at the cut-off point of 5.42 can predict severe pancreatitis with a sensitivity of 91.3% and specificity of 94%. (Table 3 and Figure 3)

Statistical analysis showed that the mean value of NLR day 1, and day 2 are significantly higher in pancreatitis patients requiring ICU admission (9.1±1.96& 11.7±3.74) compared to those who don't (3.71±13.8&3.3±1.9). Additionally, within the severe group, NLR day 2 showed significantly higher values in ICU-admitted patients (11.7±3.74) (Table 4 and Figure 4 A). Regarding the relation between NLR values and mortality in pancreatitis patients, these tables showed that the mean value of NLR day 1and 2 are significantly higher in dead (9.8±2.29& 13.4±3.93) compared to survived patients (4.03±2.39& 3.72±2.40). Within the severe pancreatitis group, NLR days 1 and 2 were significantly higher in dead patients (9.8±2.29&

13.4±3.93) (Table 4 and Figure 4 B). There were significant positive correlations between NLR days 1 and 2 and the duration of hospital stay (0.606 &.0.755). In addition, NLR day 2 shows a significant positive correlation with hospital stay within the severe group (0.439), while NLR day 1 doesn't (Table 4 and Figure 4 C & D).

BMI ≥30, history of previous pancreatitis, history of previous PEP, NLR day 1(≥6.05), NLR day 2(≥5.42), a malignant indication of ERCP, duration of the procedure, difficult cannulation, and pancreatic duct contrast were significant risk factors for severe pancreatitis (Table 5). Multiple logistic regression analysis revealed that NLR day 1 and day 2 are significant independent risk factors for severe pancreatitis (Table 6).

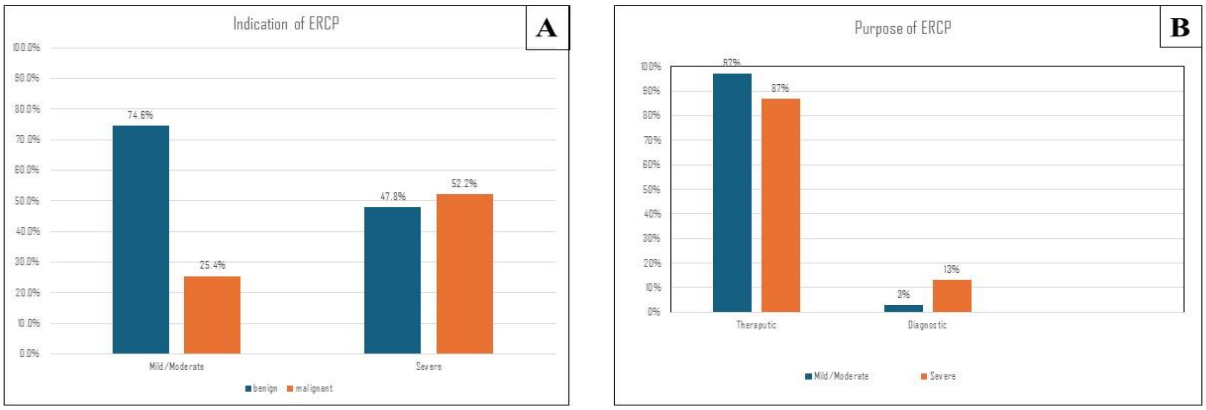

Figure (1).

Table (1). Demographic data among studied patients

Item	Mild /Moderate		Severe		Total		Test of significance and P-value
	no (67)	%	no (23)	%	no (90)	%	
Gender							
- Males	40	59.7	11	47.8	51	56.7	X^2 =0.983
- Females	27	40.3	12	52.2	39	43.3	P=0.321
Age							
- Mean ± SD	56.5±14.3		57.7±9.2		56.8±13.1		U=0.088
- range	20-80		36-75		20-80		P=0.930
- Median (IQ)	60(51-63)		59(53-61)		59.5(52-62)		
Diabetes Mellitus							
- Yes	29	43.3	7	30.4	36	60	X^2 =1.18
- No	38	56.7	16	69.6	54	40	P=0.278
Hypertension							
- Yes	19	28.4	6	26.1	25	27.8	X^2 =0.044
- No	48	71.6	17	73.9	65	72.2	P=0.834

χ^2: Chi-square test, SD: Standard deviation, IQ: Inter quartile

Table (2). Post ERCP Investigation

Item	Mild /moderate (no=67)	Severe (no=23)	Total (no=90)	Test of significance and P-value
Total leucocytic count				
- Mean ± SD	14.6±6.8	31.7±30.4	18.9±17.8	U=1.90
- range	8-44	9-108	8-108	P=0.057
- Median (IQ)	12(11-16)	12(11-58)	12(11-17.8)	
CRP post-ERCP day 1				
- Mean ± SD	53.3±53.2	92.4±98.9	63.3±69.4	U=1.37
- range	5.8-284	10.9-339.6	5.8-339.6	P=0.172
- Median (IQ)	40(24-68)	48.8(18-125)	40(24-71)	
CRP post-ERCP day 2				
- Mean ± SD	38.5±31.6	108.6±119.3	56.5±72.1	**U=2.67**
- range	3.3-162.5	8.4-415	3.3-415	**P=0.008***
- Median (IQ)	27.5 (18-56)	47(24-175)	30.2(18-62)	
Urea post-ERCP				
- Mean ± SD	29.3±13.8	99.8±44.5	47.3±39.8	**U=6.51**
- range	15-88	30-216	15-216	**P=0.00****
- Median (IQ)	24(21-33)	98(77-118)	30(21.8-65)	
Creatinine post-ERCP				
- Mean ± SD	0.95±0.30	2.66±1.15	1.38±0.98	**U=6.41**
- range	0.6-1.8	0.8-5.6	0.6-5.6	**P=0.00****
- Median (IQ)	0.8(0.7-1.1)	2.4(21-3.1)	0.9(0.8-1.8)	
BUN post ERCP				
- Mean ± SD	9.01±2.4	11.2±5.9	9.6±3.7	**U=2.09**
- range	5.2-17.8	3.1-23	3.1-23	**P=0.036***
- Median (IQ)	8.9 (7.5-10.6)	11.5(5.5-16.7)	9.2(7.4-11.2)	
Glucose post-ERCP day 1				
- Mean ± SD	174.9±69.6	166±50.6	173.3±65.1	U=0.292
- range	103-380	113-274	103-380	P=0.770
- Median (IQ)	180(110-220)	140(124-210)	160(113-212.5)	
Glucose post-ERCP day 2				
- Mean ± SD	168.1±55.9	162.7±32.1	166.7±50.8	U=0.181
- range	96-3.5	105-217	96-305	P=0.857
- Median (IQ)	153(119-201)	165(153-188)	159.5(122-200)	
Amylase post-ERCP				
- Mean ± SD	859.2±656.1	1034.9±777.05	904.1±688.8	U=1.38
- range	210-2832	103-3281	103-3281	P=0.167
- Median (IQ)	514(350-1349)	980(576-1055)	730(386.3-1219.3)	
Lipase post-ERCP				
- Mean ± SD	2007.2±2280.5	2007±1187.1	2007.1±2050	U=1.64
- range	218-7723	260-4444	218-7723	P=0.101
- Median (IQ)	580(366-3656)	1847(1221-2564)	1341(389.8-2869)	
Hospital Stay (days)				

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-	Mean ± SD	6.8±2.5	17.4±4.7	9.5±5.6	**U=6.92**
-	range	3-15	10-23	3-23	**P=0.00****
-	Median (IQ)	6(5-8)	17(13-21.5)	7.5(5-12)	

Item	**Mild / Moderate N (67)**	**Severe N (23)**	**Test of significance and P-value**
NLR day 1			
- Mean ± SD	3.3±1.7	8.4±2.5	**U=6.5**
- range	1.4-7.01	3-13.7	**P=0.00****
- Median (IQ)	2.8(2.1-3.9)	8.3 (7.8-9.5)	
NLR day 2			
- Mean ± SD	2.8±1.04	10.2±3.8	**U=7.03**
- range	0.7-5.7	4.5-19.7	**P=0.00****
- Median (IQ)	2.7(2.7-3.3)	9.1(8.2-10.8)	

IQ: Inter quartile, SD: Standard deviation, NLR: neutrophil lymphocytic ratio, CRP: C reactive protein, BUN: blood urea nitrogen

Table (3). Roc curve analysis
Cut of point 6.05 day 1
Cut of point 5.42 day 2

NLR day 1	**Pancreatitis**		**Total**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**	**P value**
	Severe	Mild/moderate							
Severe	21	7	28						
Mild/moderate	2	60	62	91.3%	89.6%	75%	96.8%	0.953	**0.00****

NLR day 2	**Pancreatitis**		**Total**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**	**P value**
	Severe	Mild/moderate							
Severe	21	4	25						
Mild/moderate	2	63	65	91.3%	94%	84%	96.9%	0.995	**0.00****

Table (4). Relation between NLR and ICU admission, Mortality, and hospital stay in days

Item	**ICU admission**		**Not Admitted**		**Test of significance and P-value**
	no (15)	**%**	**no (75)**	**%**	
NLR day 1					
- Mean ± SD	9.1±1.96		3.71±13.8		**U=5.59**
- range	7.8-13.7		1.4-10.5		**P=0.00****
- Median (IQ)	8.3(7.9-9.5)		3(2.1-5.3)		
NLR day 2					
- Mean ± SD	11.7±3.74		3.3±1.9		**U=5.97**
- range	7.9-19.7		0.7-9.1		**P=0.00****
- Median (IQ)	10.5(9.3-13.6)		2.8(2.3-3.7)		
Item	**ICU admission**		**Not Admitted**		**Test of significance and P-value**
	no(15)	**%**	**no (8)**	**%**	
NLR day 1					
- Mean ± SD	9.1±1.96		7.2±3.01		U=0.364
- range	7.8-13.7		3-10.5		P=0.392
- Median (IQ)	8.3(7.9-9.5)		7.6(4.7-9.7)		
NLR day 2					

- Mean ± SD - range - Median (IQ)	11.7±3.74 7.9-19.7 10.5(9.3-13.6)		7.5±1.9 4.5-9.1 8.1(6.2-8.8)		**U=3.25** **P=0.001****
Item	**Death**		**Alive**		**Test of significance and P-value**
	no(9)	**%**	**no(79)**	**%**	
NLR day 1					
- Mean ± SD - range - Median (IQ)	9.8±2.29 7.8-13.7 9.5(8.5-9.5)		4.03±2.39 1.4-10.5 3(2.2-5.7)		**U=4.48** **P=0.00****
NLR day 2					
- Mean ± SD - range - Median (IQ)	13.4±3.93 9.5-19.7 13.6(10.8-13.6)		3.72±2.40 0.7-10.5 2.8(2.4-4)		**U=4.85** **P=0.00****
Item	**Death**		**Alive**		**Test of significance and P-value**
	no (9)	**%**	**no (14)**	**%**	
NLR day 1					
- Mean ± SD - range - Median (IQ)	9.8±2.29 7.8-13.7 9.5(8.5-9.5)		7.6±2.3 310.5 8.06(6.4-8.8)		**U=1.96** **P=0.050***
NLR day 2					
- Mean ± SD - range - Median (IQ)	13.4±3.93 9.5-19.7 13.6(10.8-13.6)		8.2±1.8 4.5-10.5 8.4(7.8-9.1)		**U=3.74** **P=0.00****
Item	**Hospital stay**				
	R		**P value**		
NLR day 1	**0.606**		**0.00****		
NLR day 2	**0.755**		**0.00****		
Item	**Hospital stay**				
	R		**P value**		
NLR day 1	0.078		0.723		
NLR day 2	**0.439**		**0.036***		

Table (5). Univariate analysis for risk factors for severe pancreatitis

Item	Odds ratio (CI 95%)	P Value
Gender (female)	1.62(0.623-4.2)	0.323
Age (≥60)	0.703(0.271-1.83)	0.469
BMI (≥30)	3.41(1.05-11.1)	0.042*
Previous Pancreatitis(+ve)	3.71(1.30-10.6)	0.014*
Previous ERCP(+ve)	2.97(1.11-7.92)	0.030*
WBCs (≥10000)	2.774(0.580-13.3)	0.202
BUN (≥20)	5151413(0-…)	0.999
Glucose day 1(≥126)	1.12(0.414-3.01)	0.828

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Glucose day 2 (≥126)	2.02(0.61-6.7)	0.250
CRP day 1(≥8)	571629(0-……)	0.999
CRP day 2(≥8)	589776(0-…)	0.999
NLR day 1 (≥6.05)	90(17.3-467.8)	0.00**
NLR day 2 (≥5.42)	28.2(165.4-968)	0.00**
Purpose of ERCP (Therapeutic)	0.205(0.032-1.32)	0.095
Indication of ERCP (malignancy)	3.2(1.19-8.6)	0.020*
Duration of procedure	1.04(1.01-1.075)	0.008*
Cannulation (difficult)	2.96(1.1-7.95)	0.032*
Pancreatic duct contrast (yes)	5.42(1.63-17.99)	0.006*

Table (6). Multivariate analysis for risk factors for severe pancreatitis

Item	Odds ratio (CI 95%)	P Value
BMI (≥30)	6.29(0.312-127.02)	0.230
Previous Pancreatitis(+ve)	1.81(0.179-1.84)	0.614
Previous ERCP(+ve)	12.1(0.533-275.2)	0.118
NLR day 1 (≥6.05)	23.01(1.42-372.3)	0.027*
NLR day 2 (≥5.42)	159.4(8.16-3113.7)	0.00**

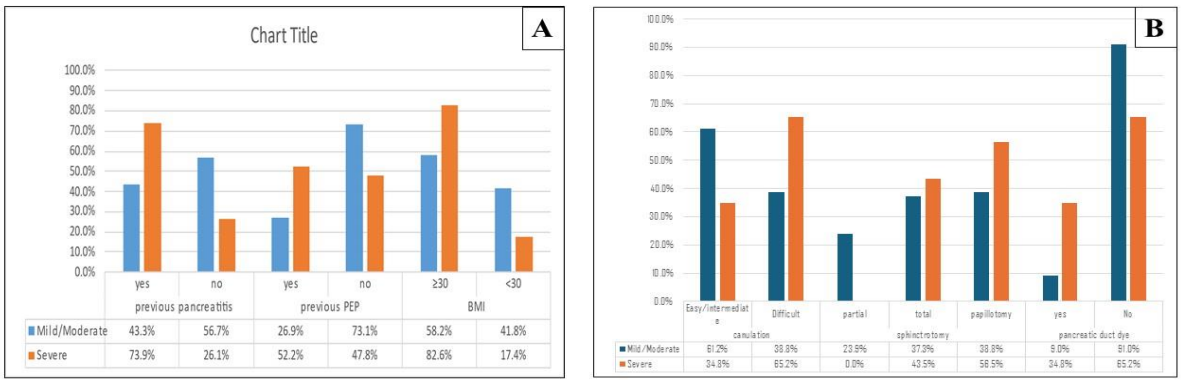
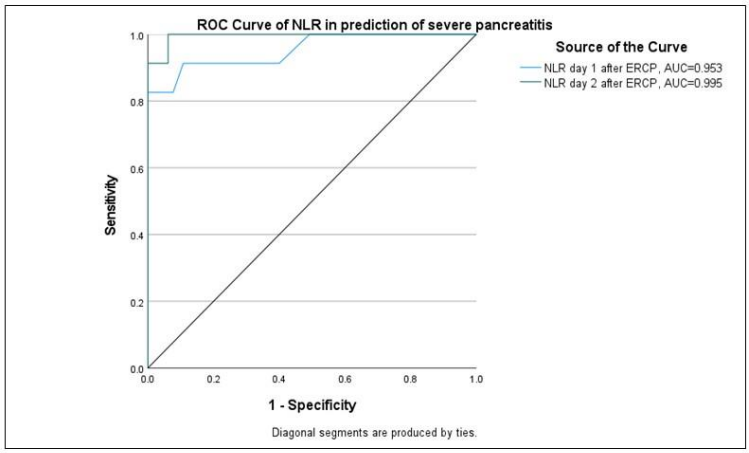


Figure (2).



ROC curve

Figure (3).

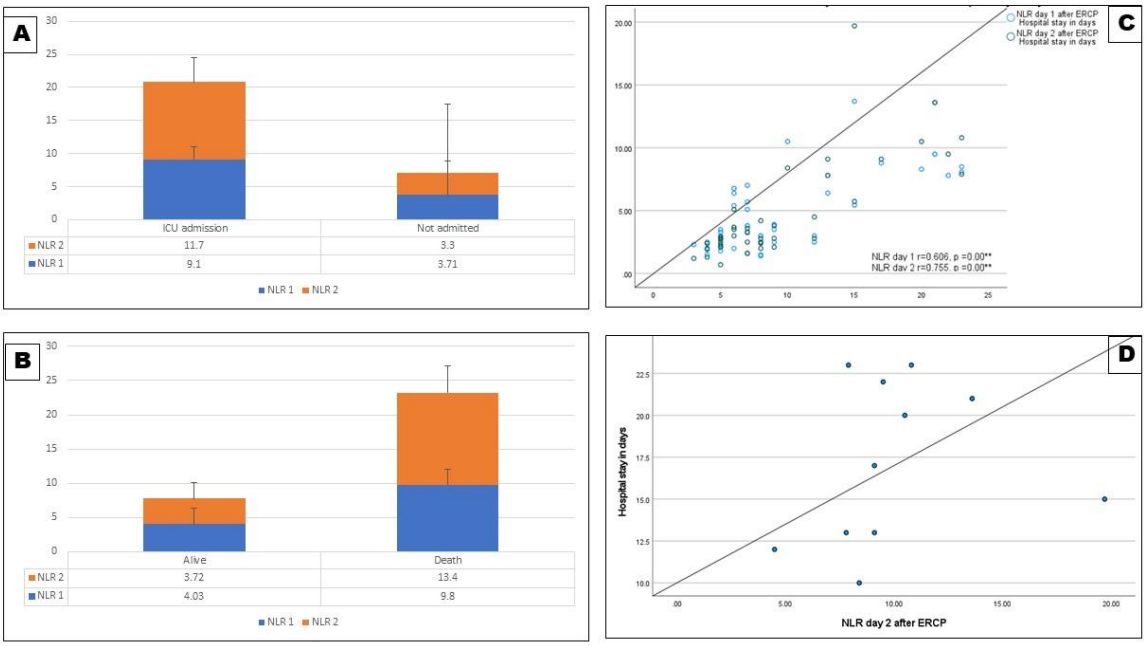


Figure (4).

DISCUSSION

The most frequent adverse consequence of ERCP is post-ERCP pancreatitis, which is iatrogenic in contrast to simple acute pancreatitis. PEP is still an imperative ERCP consequence that can negatively affect patient quality of life, morbidity, and death [15]. Although the larger part of acute pancreatitis is mild and resolves on its own, about 25% of people may experience

severe cases with complications including organ failure or necrosis. There have been reports of significant death rates of up to 50% in cases with severe acute pancreatitis (SAP) [12].

Stratification by severity and early beginning of suitable treatment may be hindered by the inability to anticipate PEP's severity at an early stage [10]. Procedural features, post-procedural variables, and patient physiological characteristics and co-morbidities all have a role in the pathophysiology of PEP and can be utilized to predict the likelihood that it will manifest. In assessing the occurrence and severity of post-ERCP pancreatitis, procedure-related risk variables are just as significant as patient-related factors [16]. It's critical to understand the PEP risk variables. As research has progressed, a growing number of contributing factors have been identified, such as patient individual differences, endoscopists' expertise levels, and several clinical aspects [17].

The current study aimed to evaluate the neutrophil-lymphocyte ratio as an early predictor of the severity and outcome of post-endoscopic retrograde cholangiopancreatography pancreatitis and identify risk factors for severe pancreatitis.

In the present study, we noticed that 90 patients developed PEP, of whom 67(74.4%) exhibited mild to moderate pancreatitis, while 23(25.6%) patients showed evidence of severe pancreatitis. There were 51 males (56.7%) and 39 females (43.3%) with no discernible gender difference between patients with mild/moderate and severe pancreatitis. According to **Chi et al.,** female sex was an independent risk factor for PEP, with 60% of the patients being female and 40% being male [18]. Furthermore, it was reported that gender differences can result in differing body structures, functions, and hormone production values, causing a higher probability of PEP in women than in men [19]. The gender-based discrepancy in the results can be explained by the different population samples used in the study, where 61.3% of the patients included in their study had evidence of choledocholithiasis, a condition that is more common in females. In this study, malignancy was detected in 32.2% of PEP patients.

Regarding the age, the current study found that the mean age of PEP patients was 56.8 ±13.1 years with a non-significant difference between patients with mild/moderate and severe pancreatitis. **Lin and his colleagues** in their study on the Chinese population reported that age less than 60 was an independent risk factor for PEP [20]. Studies have shown that the prevalence of PEP is significantly higher in patients younger than 60 years of age than in elderly patients, possibly due to the decrease in the exocrine function of the pancreas with increasing age. When the pancreas is mildly injured, the body is stressed, leading to a sudden increase in pancreatic juice and further aggravating pancreatic injury [20,21].

Patients with PEP were 36 (60%) diabetic patients and 25 (27.8%) hypertensive patients with a statistically non-significant difference between the two patient groups. Similarly, **Chi et al.** in their study have reported that DM and HTN are not significant risk factors for PEP [18].

Regarding the BMI, we noticed that 58 (64.4%) patients had a BMI ≥ 30, and 32 (35.6%) had a BMI <30. Furthermore, patients with severe PEP frequently showed a BMI equal to or higher than 30 compared to those with mild to moderate cases. Come online with these findings, previous studies stated that SAP is strongly correlated with visceral fat-to-muscle ratio, peripancreatic visceral adipose tissue, and abdominal obesity (waist circumference) [22-24].

In the current study, statistical analysis revealed that there was a significant difference between the two patient groups regarding the baseline (pre-ERCP) TLC where the TLC was considerably higher in patients who develop mild/moderate compared to those with severe PEP. However, NLR did not differ. Post-ERCP laboratory investigations showed that TLC was higher in a severe group than mild/moderate ones but statistically non-significant, while the mean value of NLR on days 1 and 2 was significantly higher in a severe form of acute pancreatitis.

In addition to how the blood samples are handled, several physiological and pathological factors, such as pregnancy, stress, and hydration state, might affect the total WBC count [25]. When compared to the WBC count, the neutrophil-lymphocyte ratio (NLR) is a more accurate indicator of unfavorable outcomes in several benign, malignant conditions, or infections including hepatocellular carcinoma (HCC), colorectal cancer (CRC), esophageal cancer, and coronary heart disease (CHD) [26, 27]. The immunological response is more

accurately reflected by neutrophils and lymphocytes than by the total WBC count. Specifically, research has shown that the severity of acute pancreatitis is correlated with peripheral lymphocytopenia [11].

Cumulative evidence indicates that both the innate immune system (which includes neutrophils, monocytes, and macrophages) and adaptive immune system (which is primarily made up of lymphocytes) play crucial roles in the development of the disease, though the exact pathophysiology by which local pancreatic injury triggers the systemic inflammatory response is still unclear [28, 29].

The greater the NLR value, the more unbalanced the inflammatory state is, since it represents a balance between inflammatory regulator lymphocytes and inflammatory activator neutrophils [30, 31]. According to a study, patients with HCC who have higher pretreatment NLR may have worse outcomes. [32]. NLR is linked to AP and is more accurate than other serum indicators at predicting the severity and prognosis of AP [33]. In assessing the severity of AP, Huang et al. have shown that NLR is more sensitive and accurate than WBC [30].

In the present study, the mean value of NLR on days 1 and 2 post-ERCP significantly differed between the 2 patient groups with considerably higher values in patients with severe form of acute pancreatitis. Roc curve analysis reveals that, at cutoff point 6.05, NLR on day 1 post-ERCP can predict severe pancreatitis with sensitivity 91.3, specificity 89.6%, AUC 0.953and P value 0.00. Furthermore, NLR at cutoff point 5.42 on day 2 post-ERCP can predict severe pancreatitis with a higher AUC of 0.995 and specificity of 94%, sensitivity of 91.3%, and a P value of 0.00

The study findings are supported by **Lee et al.'s** documentation that the NLR can distinguish between patients with mild/moderate PEP and those who develop severe PEP. Additionally, they observed that, out of all the variables examined, NLR on day 2 post-ERCP had the strongest predictive power (AUC = 0.89) for severe PEP [10]. Additionally, **Han et al.** and **Kong et al.** reported that the NLR is associated with acute pancreatitis severity [34,35].

Given that the NLR measures the balance between neutrophilia, which indicates systemic inflammation, and lymphopenia, which represents the stress-induced cortisol response, the more elevated the NLR, the more significantly unbalanced the inflammatory status [34].

In the current study, the univariate analysis revealed BMI ≥30, history of previous pancreatitis, history of previous PEP, NLR day 1, NLR day 2, a malignant indication of ERCP, duration of procedure, difficult cannulation and pancreatic duct contrast are significant risk factors for sever pancreatitis.

Consistent with our results, Chi, et al. reported that a history of pancreatitis, pancreatic duct imaging pancreatic sphincterotomy, and difficult cannulation were significantly associated with PEP [18]. Dalma Dobszai et al found a clear correlation between overweight or obesity and the development of SAP [36]. Likewise, it was believed that fewer injections, cannulations, and minimal amount of contrast medium cause less papillary trauma making them crucial in avoiding PEP [16].

We found that univariate and multivariate analysis that NLR days 1 and 2 are significant independent risk factors for severe pancreatitis. This finding was consistent with that of Suppiah et al., who observed that the NLR within the first 48 hours is a reliable indicator of severe acute pancreatitis [12]. Likewise, a Korean study involving 490 patients found that the NLR is linked to both organ failure and severe acute pancreatitis [37].

Patients who require close observation, vigorous hydration, abdominal imaging, and potential transfer to the intensive care unit can be identified using NLR on the second day following ERCP. We observed in our study that the mean value of NLR days 1, and day 2 were significantly higher in pancreatitis patients requiring ICU admission with a p-value (0.00), and NLR day 2 with higher significant values in the severe pancreatitis group admitted to ICU with p-value (0.001) which consisted with **Lee et al.** and **O'connell et al.** studies [10] [38].

We noticed that the mean value of NLR days 1 and 2 was significantly higher in dead patients with p-values (0.00) and NLR days 1 and 2 were higher significant in dead patients of severe pancreatitis with p-values (0.050) & (0.00) respectively. According to earlier reports, the

NLR has the highest prognostic value and is the most potent predictor of overall survival in AP patients [33]. Additionally, **Suppiah et al.** discovered a significant correlation between the risk of developing a severe form of AP and adverse outcomes and the higher NLR measured during the first 48 hours of hospitalization [12].

The prediction and early identification of PEP is challenging. PEP has the potential to dramatically raise patient mortality risk as well as healthcare-related costs [39]. Thus, a straightforward indicator that can accurately forecast the patient's prognosis within 24 hours of the disease's onset is required. The treatment of SAP patients greatly depends on early detection and prediction. The NLR's reasonably high prognostic power in predicting the severity of AP patients, along with its affordability and ease of use, gave us helpful clinical guidance that improved our ability to assess the severity of AP.

CONCLUSION

The NLR offers beneficial clinical guidance to better assess the severity of AP. It is also inexpensive, readily available, and has a moderately high prognostic power in predicting the severity, outcome, and overall survival of AP patients. Early modification of risk factors may reduce the likelihood of developing severe pancreatitis and decrease its morbidity and mortality.

Ethical approval: Each participant was informed about the study and given the chance to submit their informed consent before enrolment. The Menoufia University of Egypt's Faculty of Medicine's ethical committee gave its approval to the study (IRB: 4/2022 TROP 22).

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HIGHLIGHTS

- The NLR having moderately high prognostic power in predicting the severity and outcome of PEP patients.
- At cutoff point 6.05, NLR on day 1 post-ERCP can predict sever pancreatitis with sensitivity 91.3, specificity89.6% .
- NLR at cutoff point 5.42 on day 2 post-ERCP can predict sever pancreatitis with specificity94% , sensitivity 91.3%.

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