RESEARCH

Evaluation of the prognostic value of the neutrophil to lymphocyte ratio, lactate dehydrogenase enzyme, and proteinuria in patients with acute pancreatitis admitted at Assiut University Hospitals and its correlation with Ranson's criteria scoring system

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Abstract

Background: Acute pancreatitis is a relatively common acute medical presentation that may progress beyond the pancreas to cause multi-organ failure or death. It is associated with high morbidity and mortality with mortality rates changing little in the past few decades despite advances in intensive care and surgical management. Early evaluation of acute pancreatitis severity is essential to allow the clinician to predict the patient's clinical course, estimate the prognosis, determine the need for intensive care unit admission, and prevent complications. So, the purpose of our study is to evaluate the prognostic value of the neutrophil to lymphocyte ratio, lactate dehydrogenase enzyme, and proteinuria in patients with acute pancreatitis and its correlation with Ranson's criteria scoring system as new, rapid, and easy parameters to predict severity of acute pancreatitis.

Results: The mean age of patients in years was 47.97, and the median was 52 with a range of ages between 18 and 87; 38% of the patients included were males, and 61% were females. The mean Ranson's score was 2.77 ± 1.4 , and the median was 3 with a range of 0–6; 44.5% of patients included have low severity, 42.4% have mild severity, and 13.1% of patients have high severity. Neutrophil to lymphocyte ratio both at the time of admission and after 48 h of admission was significantly increasing with an increase in disease severity with a *P* value of < 0.001 that was statistically significant. Lactate dehydrogenase enzyme at the time of admission was also significantly increasing with diseased severity with a *P* value of 0.001 that was statistically significant and the same for lactate dehydrogenase enzyme level after 48 h of admission with a *P* value of 0.002 that was also statistically significant. Proteinuria is positive only in 15.2% of patients and with the same result after 48 h of admission.

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Conclusion: The neutrophil to lymphocyte ratio gives a rapid impression of the extent of the inflammatory process, and it can effectively predict severity at the time of admission and even after 48 h of admission and can also differentiate between patients with mild and severe acute pancreatitis in both calcular and non-calcular cause-dependent acute pancreatitis patients. Lactate dehydrogenase can be used to predict severity in calcular cause-dependent acute pancreatitis patients only at the time of admission and after 48 h of admission. Proteinuria in urine analysis on admission and after 48 h does not seem to be a reliable predictor for disease severity in acute pancreatitis.

Background

Acute pancreatitis is a disease characterized by the devastation and irritation of pancreas tissue through the activation of pancreatic acinar cells as a result of being activated by different causes such as biliary disease, alcohol use, and hyperlipidemia [1]. The rate of events of each etiology of acute pancreatitis changes over geographic districts and socio-economic states.

Other causes which will cause acute pancreatitis include idiopathic, drug-induced pancreatitis; post-ERCP pancreatitis; any benign or malignant mass that obstructs the main pancreatic duct; autoimmune pancreatitis; bacterial and viral infection; trauma to the pancreas; congenital or acquired anatomical abnormalities as choledochal cysts, duodenal duplication, and secondary fibrosis of the pancreatic duct; hypercalcemia; and vasculitis (polyarteritis nodosa and systemic lupus erythematosus) [2–4].

According to the American College of Gastroenterology, a patient must have at least two of the following three features present to make the diagnosis of acute pancreatitis: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), (2) serum amylase and/or lipase level at least 3 times greater than the upper limit of the normal value, and (3) characteristic manifestation of acute pancreatitis on contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography [5].

Acute pancreatitis can be mild, moderate, or severe. While mild pancreatitis is commonly self-limited, severe pancreatitis can be associated with the development of many local and systemic complications such as fluid collections and necrosis. Severe acute pancreatitis is associated with single or multiple organ failure with a mortality rate as high as 25% [6].

Forming risk-defining systems and determining the severity of acute pancreatitis are of great importance in predicting the prognosis and how successful the treatment is [7]. Several scoring systems, such as Ranson's score, the Glasgow criteria, APACHE-II score, BISAP, and computed tomography severity index, have been developed. These scoring systems incorporate physiologic, laboratory, and radiographic parameters using cutoff values and converting continuous variables into binary values to evaluate and determine the severity of acute pancreatitis. Given that the multiple factors scoring systems are complex and sometimes difficult to use, there has been continued interest in identifying simpler or less expensive methods to predict severity [8].

Over the past years, multiple research groups have investigated the value of the hematological components of the systemic inflammatory response specifically for use in predicting the severity of the disease, as well as the outcome, and have reported that the individual components of the differential leukocyte count may have clinically predictive utility. Neutrophil to lymphocyte ratio (NLR) is a straightforward and effectively calculated systemic inflammation-based score that has been widely investigated in the assessment of a variety of disease states, including inflammatory, cardiovascular, and neoplastic conditions [9, 10].

Methods

A prospective study was performed in the period between May 2018 and May 2019.

Inclusion criteria

This study was carried out on 99 patients with acute pancreatitis, all of them fulfilling the 3 American College of Gastroenterology criteria for the diagnosis of acute pancreatitis: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), (2) serum amylase and/or lipase level at least 3 times greater than the upper limit of the normal value, and (3) characteristic manifestation of acute pancreatitis on contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography.

Exclusion criteria

The following are the exclusion criteria:

- 1. Patients are excluded from the study if they do not meet the criteria for acute pancreatitis.
- 2. Patients who are under the age of 18.
- 3. Patients with chronic pancreatitis.

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All patients in the study were subjected to the following:

- Full history and examination.
- Full laboratory investigation such as liver function test, coagulation profile, kidney function test, complete blood count, serum calcium level, serum sodium and potassium level, and albumin level, and assessment of the patient according to Ranson's score.
- Neutrophil to lymphocyte ratio, lactate dehydrogenase, and proteinuria in urine analysis.
- The parameters will be compared between cases of different etiologies in relation to Ranson's criteria as two groups, acute gallstone pancreatitis and acute pancreatitis not due to gallstones as shown below, and the patients were categorized according to their Ranson's score into low, mild, and high severity groups.

Ranson's Criteria

Criteria for acute pancreatitis not due to gallstones

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At admission	During the initial 48 h
Age >55 y	Hematocrit fall >10 points
$WBC > 16,000/mm^3$	BUN elevation >5 mg/dL
Blood glucose >200 mg/dL	Serum calcium <8 mg/dL
Serum LDH >350 IU/L	Arterial Po ₂ <60 mm Hg
Serum AST >250 U/dL	Base deficit >4 mEq/L
	Estimated fluid sequestration >6 L
Criteria for acute gallstone panc	reatitis
At admission	During the initial 48 h
Age >70 y	Hematocrit fall >10 points
$WBC > 18,000/mm^3$	BUN elevation $>2 \text{ mg/dL}$
Blood glucose $>$ 220 mg/dL	Serum calcium <8 mg/dL
Serum LDH >400 IU/L	Base deficit $>5 \text{ mEq/L}$
Serum AST >250 U/dL	Estimated fluid sequestration >4 L

Ranson's score interpretation

One point is given for each positive parameter:

- 0 to 2 points: low severity
- 3 to 4 points: low severity
- 5 to 6 points: mild severity
- 7 to 11 points: high severity [11]

The NLR, LDH, and proteinuria in urine analysis were assessed at the time of admission and after 48 h of admission in addition to the assessment of the patient according to Ranson's score at the time of admission and after 48 h of admission.

Statistical analysis

Data were verified, coded by a researcher, and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics such as means, standard deviations, medians, ranges, and percentages were calculated. Test of significances—for continuous variables with more than two categories, ANOVA test was calculated to test the mean differences of the data that follow a normal distribution and independent sample Kruskal-Wallis was used to compare the median difference between the groups that do not follow a normal distribution, and post hoc test was calculated using Bonferroni corrections [12]. A significant P value was considered when it is equal to or less than 0.05.

Results

Ninety-nine patients diagnosed with acute pancreatitis were included in the study fulfilling the 3 American College of Gastroenterology criteria for the diagnosis of acute pancreatitis (38 of them were males and 61 females) as shown in Fig. 1. The mean age of patients in years was 47.97, and the median was 52 with a range of ages between 18 and 87 as shown in Fig. 2.

Seventy-six of the patients diagnosed with acute pancreatitis were due to calcular cause, and 23 were due to non-calcular cause including hypertriglyceridemia, idiopathic, and malignancy as shown in Fig. 3. The main presenting symptom of patients diagnosed with acute pancreatitis was epigastric pain radiating to the back with a range of 90.9% as shown in Fig. 4.

It was found that the mean \pm SD of WBCs was 14.42 ± 5.8 with a median (range) of 14.7 (4–34), Hgb level mean \pm SD was 12.01 ± 2.0 with a median (range) of 11.5 (8–17), and platelet level mean \pm SD was 249.60 ± 88.1 with a median (range) of 234 (74–521) as shown in Table 1.

It was found that neutrophil to lymphocyte ratio at the time of admission mean \pm SD was 8.15 ± 6.8 and the median was 5.5 with a range of 0.4-43 and that neutrophil to lymphocyte ratio after 48 h mean \pm SD was 4.59 ± 3.1 and the median was 3 with a range of 0.8-27 as shown in Table 2. It was found that the mean LDH level at the time of admission was 562.21 ± 179.2 and the median was 541 with a range of 100-971) and that the mean LDH after 48 h of admission was 288.86 ± 125.1 and the median was 269 with a range of 75-843 as shown in Table 3.

It was found that the mean amylase level at the time of admission was 658.36 ± 319.1 and the median was 596 with a range of (37-2460) and that the mean amylase level after 48 h of admission was 250.16 ± 111.8 and the median was 189 with a range of 23-1069) as shown in Table 4.

Ranson's criteria scoring system is calculated and interpreted for all patients and divided based on different etiologies in relation to Ranson's criteria into two groups: acute gallstone (calcular)-dependent pancreatitis and acute non-gallstone (non-calcular)-dependent pancreatitis. It was found that the mean Ranson's score was 2.77 ± 1.4 , and the median was 3 with a range of 0–6.



Regarding the severity of acute pancreatitis (totally), it was found that 44.5% of patients have low severity, 42.4% have mild severity, and 13.1% of patients have high severity. Regarding the severity in case of noncalcular cause of acute pancreatitis (hypertriglyceridemia, idiopathic, and malignancy), it was found that 26.1% of patients have low severity, 56.5% have mild severity, and 17.4% of patients have high severity. Regarding the severity in case of calcular cause of acute pancreatitis, it was found that 50% of patients have low severity, 38.2% have mild severity, and 11.8% of patients have high severity as shown in Table 5 and Figs. 5 and 6.

After categorization of the patients according to Ranson's criteria scoring system into low, mild, and high severity, analysis of data revealed that NLR both at the time of admission and after 48 h of admission was significantly increased with an increase in disease severity with a P value of < 0.001 that was statistically significant. Analysis of data also revealed that LDH at the time of admission was also significantly increasing with disease severity with a P value of 0.001 that was statistically significant and revealed the same for LDH level after 48 h of admission with a P value of 0.002 that was also statistically significant as shown in Table 6.

Analysis of the data in case of patients diagnosed with acute pancreatitis due to non-calcular cause revealed that NLR both at the time of admission and after 48 h of admission was increasing with an increase in disease severity according to Ranson's scoring system with a P value of 0.023 at admission and a P value of 0.003 after 48 h of admission that was statistically significant. About LDH, it was found that both levels at the time of admission and after 48 h of admission were statistically





insignificant with a *P* value of 0.079 and 0.083, respectively, as shown in Table 7.

Analysis of the data in case of patients diagnosed with acute pancreatitis due to calcular cause revealed that NLR both at the time of admission and after 48 h of admission was increasing with an increase in disease severity according to Ranson's scoring system with a P value of < 0.001 at admission and a P value of < 0.001 after 48 h of admission that was statistically significant. About LDH, it was found that both levels at the time of admission and after 48 h of admission were increasing with an increase in disease severity with a P value of 0.010 at admission and a P value of 0.020 48 h after admission that was statistically significant as shown in Table 8.

Discussion

The current study included 99 patients who were diagnosed to have acute pancreatitis; the mean age of those patients was 47.97 ± 8.11 years with a range between 18 and 87 years. Thirty-eight (38.4%) patients were males, and 61 (61.6%) patients were females with female predominance 2:1 ratio, agreeing with data obtained by Gülen et al. [1] which stated that the median age of the patients was 53.1 (IQR = 36–64) years, and 63.8% (n = 212) of the total patients (332) were female and this may be attributed to the increased incidence of gallstones in females [1].

Acute pancreatitis is an inflammatory disease of the pancreas. The etiology and pathogenesis of acute pancreatitis have been intensively investigated for many years worldwide. There are multiple causes of acute pancreatitis which can be easily recognized. In developed countries, obstruction of the common bile duct by stones (38%) and alcohol consumption (36%) are the most frequent causes of acute pancreatitis. Gallstone-induced pancreatitis is caused by duct obstruction by



Table 1 CBC findings of the studied sample

Variable	Category	n = 99
• WBCs	• Mean \pm SD	14.42 ± 5.8
	• Median (range)	14.7 (4–34)
• Hgb	• Mean \pm SD	12.01 ± 2.0
	• Median (range)	11.5 (8–17)
 Platelet 	\cdot Mean ± SD	249.60 ± 88.1
	• Median (range)	234 (74–521)

gallstone migration. Obstruction is localized in the bile duct and pancreatic duct, or both [13]. The most frequent etiology in the current study is gallstones (76.8%).

In this study, we focused on the prognostic value of the neutrophil to lymphocyte ratio, LDH, and proteinuria in urine analysis to predict the severity of acute pancreatitis based on the classification by Ranson's criteria scoring system; with respect to the relationbetween NLR and systemic inflammatory ship response, multiple studies have recently investigated the relationships between NLR and outcome in a population of patients with acute pancreatitis. The utility of the NLR in acute pancreatitis was first investigated by Azab et al. [14]. They noticed that the NLR was a more sensitive parameter than total leukocyte counts in predicting ICU admission and longer hospitalization. Suppiah et al. [15] later revealed that NLR measured during the first 48 h of hospitalization was significantly associated with the risk of developing a severe form of acute pancreatitis (classified by 1992 Atlanta Criteria).

In the current study, after categorization of the patients according to Ranson's criteria scoring system into low, mild, and high severity, we evaluate the prognostic value of the NLR both at the time of admission and 48 h after admission in the total population of the patients and calcular cause and noncalcular cause patients, and the *P* value at the time of admission was < 0.001 in total patients, 0.023 in noncalcular cause patients, and < 0.001 in calcular cause patients, while the *P* value of the NLR after 48 h of admission was < 0.001 in total patients, 0.003 in noncalcular cause patients, and < 0.001 in calcular cause

Γa	ble	3	LDH	findings	of	the	studied	sample
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Variable	Category	n = 99
· LDH	\cdot Mean ± SD	562.21 ± 179.2
	• Median (range)	541 (100–971)
• LDH 48 h	\cdot Mean ± SD	288.86 ± 125.1
	• Median (range)	269 (75–843)

patients that was statistically significant and consistent with other studies.

Interpretation of the data revealed that NLR both at the time of admission and after 48 h of admission can predict severity and also can effectively differentiate patients with mild and severe acute pancreatitis in both calcular and non-calcular cause-dependent acute pancreatitis patients.

Multivariate investigation showed that LDH and lipase at the time of admission had a great ability in predicting the outcome in patients with acute pancreatitis [16, 17].

In the current study, after categorization of the patients according to Ranson's criteria scoring system into low, mild, and high severity, we evaluate the prognostic value of the LDH both at the time of admission and 48 h after admission in the total population of the patients, calcular cause- and non-calcular cause-dependent patients, and the P value at the time of admission was 0.001 in total patients, 0.079 in non-calcular cause patients, and 0.010 in calcular cause patients, while the P value of the LDH after 48 h of admission was 0.002 in total patients, 0.083 in non-calcular cause patients, and 0.020 in calcular cause patients. The interpretation of the data revealed that LDH results were statistically significant and can predict severity in calcular cause-dependent acute pancreatitis patients. However, it was statistically insignificant in non-calcular cause-dependent patients, and this is similar to the data obtained by Sharif et al. which stated that LDH and lipase at the time of admission could be paramount prognostic markers for predicting morbidity and mortality in patients with acute pancreatitis. However, the previously mentioned study did not divide patients into calcular and noncalcular cause-dependent pancreatitis [17].

Table 2 Neutrophil/lymphocytic ratio of the studied sample

Variable	Category	n = 99
• NLR	• Mean \pm SD	8.15 ± 6.8
	• Median (range)	5.5 (0.4–43)
• NLR 48 h	• Mean \pm SD	4.59 ± 3.1
	• Median (range)	3 (0.8–27)

Table 4	Amylase	level	of the	studied	sample

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Variable	Category	n = 99
Amylase level	• Mean \pm SD	658.36 ± 319.1
	• Median (range)	596 (37–2460)
 Amylase 48 h level 	• Mean \pm SD	250.16 ± 111.8
	• Median (range)	189 (23–1069)

Table 5 Severity of acute pancreatitis according to Ranson's score

Variable	Category	n = 99
Ranson's criteria	• Mean ± SD	2.77 ± 1.4
	• Median (range)	3 (0–6)
Severity of acute pancreatitis (total)*	Low (0–3% mortality)	44 (44.5%)
	Mild (15% mortality)	42 (42.4%)
	• High (40% mortality)	13 (13.1%)
Severity of acute pancreatitis (non-calcular)*	・Low (0–3% mortality)	6 (26.1%)
	Mild (15% mortality)	13 (56.5%)
	• High (40% mortality)	4 (17.4%)
Severity of acute pancreatitis (calcular)*	Low (0–3% mortality)	38 (50%)
	Mild (15% mortality)	29 (38.2%)
	· High (40% mortality)	9 (11.8%)

*Low severity = Ranson 0-3%, mild severity = Ranson 15%, and high severity = Ranson 40% mortality

Proteinuria in urine analysis was positive only in 15.2% of patients and the same result after 48 h of admission. There was no difference in the incidence of severe acute pancreatitis between patients with or without proteinuria and was similar to the results found by Zuidema et al. [18].

Conclusion

• The neutrophil to lymphocyte ratio (NLR) is a simple, easily calculated systemic inflammation-based score which is calculated from the white cell differential count, gives a rapid impression of the

extent of the inflammatory process, and can effectively predict severity at the time of admission and even after 48 h of admission and can also differentiate between patients with mild and severe acute pancreatitis in both calcular and non-calcular causedependent pancreatitis patients.

- Lactate dehydrogenase (LDH) can be used to predict severity in calcular cause-dependent acute pancreatitis patients only at the time of admission and after 48 h of admission.
- Proteinuria in urine analysis on admission and after 48 h does not seem to be a reliable predictor for disease severity in acute pancreatitis.





Table 6 NLR and LDH comparison regarding disease severity (tota

Parameter	Acute pancreatitis severity			
	Low (1) (n = 44)	Mild (2) (n = 42)	High (3) (n = 13)	
NLR	4.29 ± 2.8	10.59 ± 9.1	13.31 ± 9.2	< 0.001*
P value**	1 vs 2 < 0.001	2 vs 3 = 0.264	1 vs 3 < 0.001	
NLR 48 h	2.62 ± 2.5	5.55 ± 2.4	8.17 ± 4.9	< 0.001*
P value**	1 vs 2 < 0.001	2 vs 3 = 0.028	1 vs 3 < 0.001	
LDH	499.73 ± 175.9	587.57 ± 163.1	691.77 ± 165.3	= 0.001*
P value**	1 vs 2 = 0.018	2 vs 3 = 0.054	1 vs 3 < 0.001	
LDH 48 h	231.48 ± 97.2	323.00 ± 137.2	371.38 ± 167.4	= 0.002*
P value**	1 vs 2 = 0.004	2 vs 3 = 0.292	1 vs 3 = 0.003	

*ANOVA test was used to compare the mean difference between the groups

Parameter	Acute pancreatitis severity			
	Low (1) (n = 6)	Mild (2) (n = 13)	High (3) (n = 4)	
NLR	2.88 ± 1.7	13.47 ± 9.5	10.71 ± 3.2	= 0.023*
P value**	1 vs 2 = 0.016	2 vs 3 = 0.246	1 vs 3 = 0.046	
NLR 48 h	2.28 ± 0.6	7.72 ± 5.1	6.21 ± 2.5	= 0.003*
P value**	1 vs 2 = 0.002	2 vs 3 = 0.145	1 vs 3 = 0.006	
LDH	411.67 ± 89.6	622.38 ± 54.9	693.00 ± 85.1	= 0.079*
P value**	1 vs 2 = 0.051	2 vs 3 = 0.555	1 vs 3 = 0.047	
LDH 48 h	215.00 ± 50.7	370.00 ± 57.3	394.25 ± 84.9	= 0.083*
P value**	1 vs 2 = 0.084	2 vs 3 = 0.608	1 vs 3 = 0.064	

Table 7 NLR and LDH comparison regarding disease severity (non-calcular)

*Kruskal-Wallis test was used to compare the mean difference between the groups

Parameter	Acute pancreatitis severity				
	Low (1) (n = 38)	Mild (2) (n = 29)	High (3) (n = 9)		
NLR	4.52 ± 2.7	9.30 ± 6.7	14.47 ± 9.9	< 0.001*	
P value**	1 vs 2 = 0.002	2 vs 3 = 0.031	1 vs 3 < 0.001		
NLR 48 h	2.68 ± 0.9	4.58 ± 1.9	9.04 ± 7.5	< 0.001*	
P value**	1 vs 2 = 0.030	2 vs 3 = 0.001	1 vs 3 < 0.001		
LDH	513.63 ± 162.6	571.97 ± 144.1	691.22 ± 98.8	= 0.010*	
P value**	1 vs 2=0.137	2 vs 3 = 0.051	1 vs 3 = 0.003		
LDH 48 h	234.08 ± 93.7	301.93 ± 105.6	361.22 ± 142.9	= 0.020*	
P value**	1 vs 2 = 0.046	2 vs 3 = 0.255	1 vs 3 = 0.014		

Table 8 NLR and LDH comparison regarding disease severity (calcular)

*Kruskal-Wallis test was used to compare the mean difference between the groups

Recommendations

- Early diagnosis, assessment of severity, and treatment of acute pancreatitis patients are a cornerstone in determining the overall morbidity and mortality.
- All patients diagnosed with acute pancreatitis should be subjected to full history and examination; full laboratory investigation such as liver function test, coagulation profile, kidney function test, complete blood count, serum calcium level, serum sodium and potassium level, and albumin level; and assessment of the patient according to Ranson's criteria scoring system.
- All patients diagnosed with acute pancreatitis should be subjected to neutrophil to lymphocyte ratio (NLR) and lactate dehydrogenase (LDH) level as they provide an easy, early, and rapid prediction of the severity and adverse outcomes in patients with acute pancreatitis.

Abbreviations

WBCs: White blood cells; APACHE-II: Acute Physiology and Chronic Health Evaluation-II; BISAP: Bedside Index for Severity in Acute Pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; LDH: Lactate dehydrogenase; NLR: Neutrophil to lymphocyte ratio; SD: Standard deviation; Hgb: Hemoglobin

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Authors' contributions

LA made substantial contributions to the design of the work and the acquisition, analysis, interpretation of the data, and was a major contributor in revising the manuscript.

Alk made substantial contributions to the design of the work and supervising the work.

FRE is the corresponding author, has a major role in collecting the data and laboratory investigations of the patients in the study, had a major role in writing the manuscript, and had a major role in doing the statistical analysis of the data.

All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Board of Faculty of Medicine, Assiut University, and informed written consent was obtained from all participants according to the Declaration of Helsinki. The committee's reference number is not available.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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