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Serum Level of Galectin-3 in Early Detection of Acute Pancreatitis

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ABSTRACT

BACKGROUND

Acute pancreatitis (AP) is a common cause of hospital admissions. Diagnosing AP in patients presenting to emergency departments remains a challenge for physicians. Thus, we aimed to evaluate the diagnostic accuracy of galectin-3 to find a new and effective method for detecting AP.

METHODS

In this prospective cross-sectional study, 43 patients with a manifestation of AP were enrolled. The serum levels of galectin-3 were measured at admission and 48 hours later and compared between the groups of patients with and without AP.

RESULTS

Serum levels of galectin-3 at admission and after 48 hours were significantly higher in AP cases compared with non-AP individuals. The area under the curve (AUC) for galectin-3 was 73.1%, which revealed a good accuracy in predicting the AP diagnosis.

CONCLUSION

Serum levels of galectin-3 at admission and after 48 hours were significantly higher in AP cases, and their diagnostic value was acceptable in the detection of AP.

KEYWORDS:
Acute pancreatitis, Galectin-3, Diagnostic accuracy

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INTRODUCTION

Acute pancreatitis (AP), as the acute inflammation of pancreatic tissue, is a common cause of hospital admissions among gastrointestinal disorders globally. Activation of intra-acinar proteolytic enzymes in a calcium-dependent and cathepsin-B-dependent manner is the primary pathophysiological mecha-

nism recommended for AP.[1,2] Proteolytic enzyme activation destroys acinar cells and releases inflammatory cytokines and intracellular content into the extracellular space, which attracts inflammatory cells and other causes for pancreas damage.[3, 4] Serum total amylase and lipase individually or in combination remain the most widely used biomarkers for clinical diagnosis of AP. Lipase assay has an advantage over amylase in clinical diagnosis of AP compared with chronic pancreatitis and appears to have greater specificity. However, both biomarkers have low diagnostic accuracy in some cases.[3]

Galectin-3 (GAL-3) is a feature of the β-galactoside-binding protein family that identifies the N-acetyllactosamine construction of multiple glycoconjugates. Galectin-3 has a unique chimeric structure and plays an essential role in inflammatory and autoimmune diseases.[5-7] GAL-3 is involved in many intra and extracellular physiological functions. After releasing from damaged cells, extracellular GAL-3 can cross-link specific ligands on cell surfaces, influence cell signaling, and change immune responses.[8-10]

Variation in the levels of GAL-3 is recognized in different types of diseases, including cardiac, renal, and liver disorders, cancers, and infections. It may be applied in the diagnosis and prognosis of various types of conditions, and hence may similarly help as a therapeutic point for attending diseases.[11,12] Since the prevalence of pancreatitis is very high in this geographical area, we aimed to evaluate the GAL-3 biomarker level immediately after admission and 48 hours afterward in patients with suspected AP symptoms.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted in the emergency department of two major hospitals in the southwest of Iran from November 2019 to May 2020. Our research team measured the serum levels of GAL-3 in patients suspected of AP. Inclusion criteria were patients referred to the emergency department with increased serum amylase, trypsin, and lipase levels, the elevation of alanine aminotransferase to >150 IU/L, computerized tomography findings, signing a consent form to participate in the study, with the onset of symptoms in less than 72 hours, and age over 18 years.[13,14] Exclusion criteria were patients with a history of inflammatory diseases, active cancer, developed organ failure, surgery, or invasive abdominal procedure in the last 7 days, use of corticosteroids in the previous 14 days, receiving chemotherapy or immunosuppressive drugs during the previous 29 days, endoscopic retrograde cholangiopancreatography (ERCP) or trauma-induced pancreatitis, symptoms of sepsis or inflammatory diseases such as ulcerative colitis or collagen and vascular diseases, cancers or infectious diseases such as brucellosis, hepatitis B, vaccine history in the last trimester, viral illness and radiation in the previous trimester, chronic pancreatitis, metabolic disorders, pregnancy and lactation, unconfirmed abdominal pain caused by AP, and abdominal tenderness suspected of peritonitis. We also excluded patients with uncompleted data.

The study flowchart is shown in figure 1. 50 patients with suspected AP diagnosis, who had been diagnosed by emergency medicine specialists based on the clinical and para-clinical findings, were investigated. Finally, 43 patients participated in this study. A blood sample was obtained, and the serum level of GAL-3 was measured. The serum was separated by centrifugation and stored at −80°C until use. All samples were coded for blind analysis. The concentration of GAL-3 was measured twice (at admission and 48 hours after entering the study) using a quantitative immunoassay technique by commercially available ELISA kits (IBL Co., Ltd., Gunma, Japan) according to the manufacturer's protocols. The samples were analyzed in duplicates, and mean serum levels of GAL-3 were reported in ng/mL in each group.

Statistics

The normal distribution of all quantitative variables was studied tests using the Kolmogorov-Smirnov test. The Chi-square test was used to compare qualitative variables between the groups. Student t test and paired t test were used for variables with normal distribution. On the other hand, Mann-Whitney and Wilcoxon tests were used for variables without normal distribution. To evaluate the differences between the groups during different periods, repeated measure ANOVA was used, and a P values less than 0.05 were considered statistically significant.

RESULTS

The present study aimed to evaluate the serum level

of GAL-3 in the early determination of AP prognosis. It was found that the age range of patients was between 18 and 80 years, with a mean of 51.69± 13.66 years. Of the 43 people included in the study, 24 (55.8%) were men, and 19 (44.2%) were women. This study also found that out of 43 patients, 28 (65.1%) were diagnosed with pancreatitis. There was no statistically significant difference in the frequency of sex in the studied patients in other demographic features in terms of age (p=0.796) and gender (p =0.548) in both groups with and without AP.

Further serum levels of GAL-3 at admission and after 48 hours were significantly higher in AP cases compared with non-AP individuals (Table 1). Serum levels of GAL-3 at the time of entry and 48 hours later in patients under 50 years of age with AP were significantly higher than those without pancreatitis. However, in people older than 50 years, the differences were not significant (Table 2). Further, by grouping all patients based on sex, we found that in men, the serum levels of GAL-3 were significantly higher in the AP group (Table 3).

Of 43 patients, 28 patients had a positive AP diagnosis, and 15 had a negative AP diagnosis. Also, the ROC curve was used to determine the diagnostic value of GAL-3 in AP diagnosis. In this regard, the area under the ROC curve represents the GAL-3 serum level's diagnostic accuracy. Besides, it shows that the AUC at admission was 73.1% (95% CI:57%-89.2%), which means that this test's accuracy is acceptable in the determination of AP. According to the results, GAL-3 serum level of 5.3 ng/mL with 96.42% sensitivity and 40% specificity is the optimal cut-point for detecting AP. Further, the AUC after 48 hours is 70.7% (95% CI: 53.7%-87.7%), which means that this test's accuracy is acceptable in AP determination. According to the results, after 48 hours, GAL-3 serum level of 11.8 ng/mL with 67.85% sensitivity and 73.3% specificity is the optimal cut-point for detecting AP (high accuracy of 90% is excellent, the accuracy of 70-90% is good, the accuracy of 50-70% is acceptable, and the accuracy of less than 50% is unacceptable figure 2).

DISCUSSION

Our study's purpose was to determine whether elevated serum levels of GAL-3 are a useful diagnostic screening tool for AP. By applying this screening tool, we may be able to reduce unnecessary radiographs in patients with AP. In this investigation, of 43 patients, the mean serum level of galactin-3 at the time of admission in patients with proven pancreatitis was significantly higher than those without pancreatitis. This difference remained significant in men and people under 50 years, while in women, there are no different levels of GAL-3 at admission compared with 48 hours later. However, it should be noted that in this study, GAL-3 levels were similar in men and women with pancreatitis. A comprehensive study by Bohme revealed that serum levels of GAL-3 were significantly higher in patients with chronic pancreatitis than controls. In addition, in contrast with the current results, the notable elevated GAL-3 serum levels persevered in women compared with men. The study also found that age range did not correlate with serum GAL-3 levels.[15] In a 2017 study by Shimura and colleagues, in agreement with our results, in patients diagnosed with pancreatic cancer, there was no significant difference between the mean of age and sex of individuals with elevated and non-elevated serum GAL-3 levels.[16] Boer and others, in 2011, suggested a strong association between GAL-3 and age and sex. In comparison, GAL-3 was higher in women than men and was elevated with increasing age.[17]

The study conducted by Zhao and co-workers is based on the rationale that pancreatic ductal adenocarcinoma has a higher level of GAL-3; hence, GAL-3, secreted by pancreatic ductal adenocarcinoma cells, might have an effect on tumor residing pancreatic stellate cells.[18] Furthermore, Henderson and colleagues have shown the expression of GAL-3 by human and murine hepatic stellate cells.[19] GAL-3 is also known to have both paracrine and autocrine effects on macrophages. These studies revealed that GAL-3 might have an essential role in the pathogenicity of pancreas disease.[20] Moreover, a study found that deletion of GAL-3 reduced the expression of pro-inflammatory biomarkers such as TNF-α and IL-1β in F4/80-CD11c- and CD11c-F4/80- cells.[21] Thus, deletion of GAL-3 ameliorates AP by attenuating the early influx of neutrophils and inflammatory mononuclear cells of innate immunity, provides the basis to consider GAL-3 as a therapeutic target in AP.[22] Another characteristic of enhanced expression of GAL-3 is the in-

Table 1: Patients' demographics and para-clinical characteristics

		Negative AP (n=15)	Positive AP (n=28)	*p* value
Age (mean±SD year)		51.6 ± 13.11	51.75 ±14.18	0.973
Sex	Female 44.2%	5 (26.3%)	14 (73.7%)	0.548
	Male 55.8%	10 (41.6%)	14 (58.3%)	
Galectin-3 (mean± SD ng/ml)	At admission	9.52 ± 7.69	17.46 ±11.38	0.013
	After 48 hours	9.93 ± 8.58	16.76 ±11.47	0.027

P value ≤ 0.05 is considered significant, AP: Acute pancreatitis

Table 2: Comparison of galectin-3 based on the diagnosis of pancreatitis and age group

Age			TGalectin-3 ng/mL mean± SD	*p*-value
≤ 50 years	At admission	Negative AP	4.56±4.16	0.002
		Positive AP	15.66±7.65	
	After 48 h	Negative AP	5.14±4.7	0.012
		Positive AP	14.19±7.42	
> 50 years	At admission	Negative AP	13.86±7.58	0. 429
		Positive AP	18.47±8.11	
	After 48 h	Negative AP	14.12±7.23	0.567
		Positive AP	18.18±8.19	

P value ≤ 0.05 is considered significant. AP: Acute pancreatitis

Table 3: Comparison of galectin-3 based on the diagnosis of pancreatitis and sex

Sex			TGalectin-3 ng/mL mean± SD	*p*-value
Male	**At admission**	Negative AP	6.71±5.85	0.006
		Positive AP	17.46±11.3	
	After 48 h	Negative AP	7.13±6.12	0.005
		Positive AP	18.97±13.8	
Female	**At admission**	Negative AP	15.14±8.43	0. 964
		Positive AP	17.47±11.92	
	After 48 h	Negative AP	15.54±10.7	0.835
		Positive AP	14.54±8.45	

P value ≤ 0.05 is considered significant. AP: Acute pancreatitis

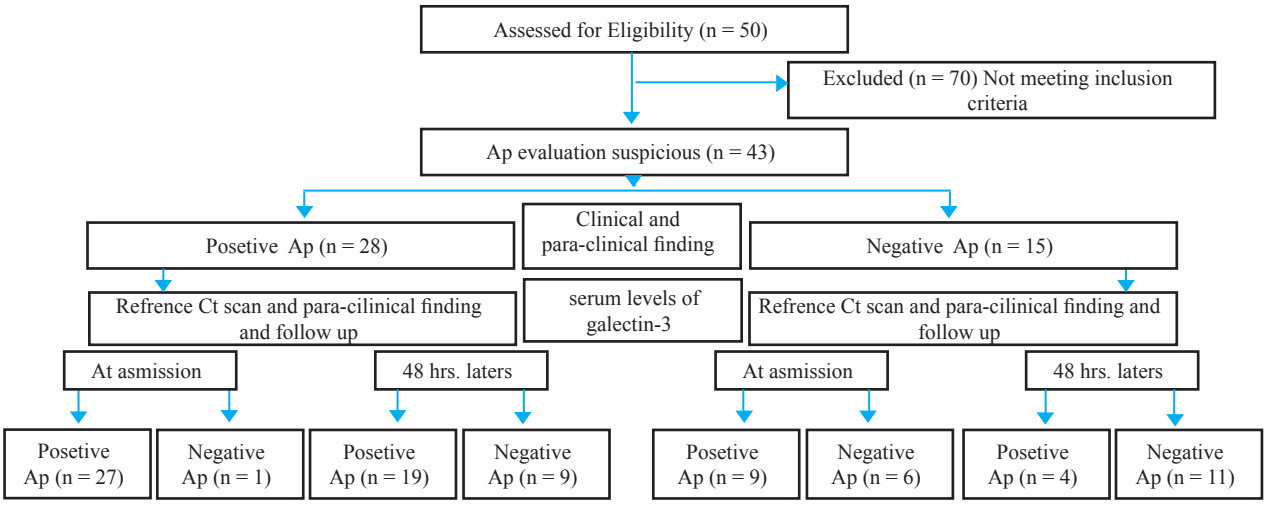

Fig. 1: Study flowchart

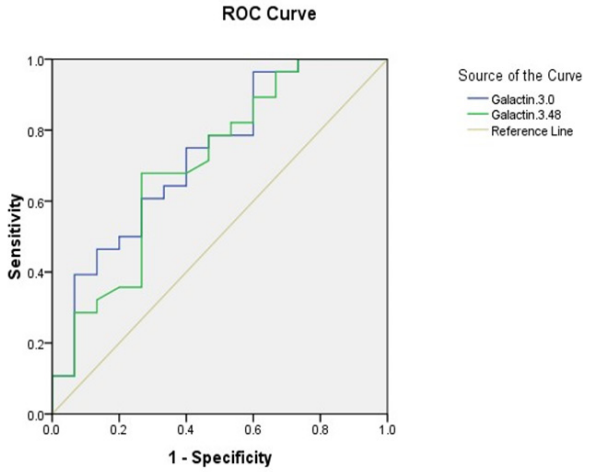

Fig.2: ROC curve of galectin-3 at admission (blue line) and after 48 hrs (green line) in detecting acute pancreatitis

creased risk of apoptosis in pancreatic acinar cells during pancreatitis.[23] Fu-Tong Liu and colleagues showed that GAL-3 could influence intracellular signaling pathways and exert various functions due to its location in the cytosol and nucleus. GAL-3 is expressed by virtually all immune and inflammatory cell types and has an essential role in regulating these cells' functions and contributes to the inflammatory response. Thus, GAL-3 may be a therapeutic target for various inflammatory diseases.[24] Our study also found that GAL-3 was significantly higher in patients with AP than in those without pancreatitis. It was also found that the measurement of this serum biomarker was susceptible upon arrival and, over time, is likely to change. Another study performed by Li Wang and co-workers showed that galectin-1 and GAL-3 protein increase 3.2-fold and 3.0-fold, respectively, in chronic pancreatitis compared with normal controls. Moreover, the researchers found a significant correlation between GAL-3 and fibrosis and the ductular complex's density. Furthermore, up-regulation of GAL-3 in ductular complexes suggests a role of this lectin in tissue remodeling in chronic pancreatitis. Finally, they concluded that GAL-3 seemed to be involved in extracellular matrix changes and ductular complex formation.[25] A systematic review and meta-analysis concluded that GAL-3 exhibited some diagnostic value in patients with pancreatic cancer, which may reveal that GAL-3 might have better diagnostic value in other diseases of the pancreas.[26]

CONCLUSION

Overall, our results show that the serum level of GAL-3 at admission was significantly higher in cases with AP. The diagnostic value was acceptable in detecting AP but still does not confirm AP through GAL-3 serum levels as a safe alternative in the preliminary evaluation in suspected cases. In particular, elevated GAL-3 at admission and after 48 hours could be a strong indicator for detection of AP in the future. These findings suggest that we can use GAL-3 in addition to increased serum amylase and lipase levels. However, further studies are warranted to confirm and strengthen these findings.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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