Can Ischemia Modified Albumin (IMA) Levels Be a Predictor of Acute Pancreatitis?

Hakan Yarkıcı[1], Gözde Derviş Hakim[2], Elif Merve Arı[3], Harun Akar[1], Ayfer Çolak[3]

[1]Department of Internal Medicine, Tepecik Training and Research Hospital, İzmir, Turkey
[2]Department of Gastroenterology, Tepecik Training and Research Hospital, İzmir, Turkey
[3]Department of Biochemistry, Tepecik Training and Research Hospital, İzmir, Turkey

Cite this article as: Yarkıcı H, Derviş Hakim G, Merve Arı EM,, Akar H, Çolak A. Can ischemia modified albumin (IMA) levels be a predictor of acute pancreatitis? *Turk J Gastroenterol.* 2021; 32(3): 327-335.

ABSTRACT

Background: *We aimed to evaluate the value of ischemia modified albumin (IMA) as a prognostic marker in acute pancreatitis (AP) patients, determine whether it is efficient in assessing the disease severity or not, and to estimate the correlation between IMA and the inflammatory markers, prognostic markers and scoring systems routinely used in clinical practice.*

Methods: *100 adult patients (18 years and older) who have been hospitalized and evaluated with AP diagnosis in Tepecik Training and Research Hospital,, Department of Gastroenterology, between April 1, 2017 and April 1, 2018 have been enrolled in the study. Patients have been stratified disease etiology (biliary or non-biliary). The non-biliary group has been divided into subgroups as alcoholic, lipemic, or idiopathic. Disease severity has been categorized as mild, moderate, or severe pancreatitis according to the Atlanta classification. Ranson, Harmless Acute Pancreatitis Score (HAPS), Bedside Severity Index for Acute Pancreatitis (BISAP) scores have been determined for each patient. Patients have been grouped as necrotizing or edematous according to the Atlanta classification.*

Results: *According to our findings, IMA has been found to be correlated with disease severity, Ranson and BISAP scores, and procalcitonin levels. We have observed that some laboratory parameters including blood urea nitrogen and hematocrit levels and HAPS scoring system are not correlated to IMA.*

Conclusion: *Our study is the first study to compare multiple prognostic factors with IMA in AP patients. In our study, the association between IMA and AP has been evaluated in the context of prognostic scoring and disease severity.*

Keywords: *Acute pancreatitis, ischemia modified albumin, IMA, scores*

INTRODUCTION

Acute pancreatitis (AP) is a non-bacterial inflammatory process resulting from the breaking down of pancreatic tissue via activation of digestive enzymes due to various reasons which are normally found in an inactive form.[1] While 80% of patients present with mild disease, 10-20% present as severe AP.[2] In order to determine the course and the severity of the disease, Ranson criteria, Harmless Acute Pancreatitis Score (HAPS), Bedside Severity Index for Acute Pancreatitis (BISAP) scoring systems as well as prognostic criteria such as hematocrit (HCT), blood urea nitrogen (BUN), age and procalcitonin can be used.[3] Recently, ischemic processes have been thought to be responsible for AP development and the use of ischemic markers is suggested to be beneficial in order to diagnose and determine the prognosis of the disease.[4] Ischemia-modified albumin (IMA) is 1 of the markers used in this context which is formed as a result of the changes in the N-terminal region triggered by the interaction between albumin protein produced in the liver and the free oxygen radicals which develop during ischemia. This newly formed albumin molecule is called IMA. The formation of IMA is the earliest sign of ischemia.[5] According to the previously published studies, IMA has been investigated mostly for its use in diagnosis in exploratory studies of AP. It has been shown to increase in AP however its validity in prognosis has been limited to exploratory studies.[6] The relationship between AP and IMA has not been sufficiently evaluated in clinical trials. In our study, we aimed to evaluate the value of IMA as a prognostic marker in AP patients, determine whether it is efficient in assessing the disease severity or not, and to estimate the correlation between IMA and the inflammatory markers, prognostic markers, and scoring systems routinely used in clinical practice.

MATERIALS AND METHODS

In this study, 100 adult patients (18 years and older) who have been hospitalized and evaluated with AP diagnosis

Corresponding author: ***Gözde Derviş Hakim****, e-mail:* ***gozdedervis@gmail.com***
Received: ***December 12, 2019*** *Accepted:* ***August 11, 2020*** *Available Online Date: X XX 2021*

DOI: ***10.5152/tjg.2021.191054***

in Tepecik Research and Training Hospital, Department of Gastroenterology, between April 1, 2017 and April 1, 2018 have been enrolled in the study. In our prospective study, inclusion criteria were as follows: being 18 years and older, presenting with the typical pain of AP, more than 3-fold increase in serum and/or urine amylase and lipase levels, presenting with the typical findings of AP in imaging studies and being diagnosed as AP by having at least 2 of these 3 criteria and having signed the informed consent form. Being younger than 18 years of age, and having conditions or diseases that may interfere with the IMA measurements such as chronic renal failure, hepatic failure, coronary artery disease, hypoalbuminemia (<2.5 g/dL), cerebrovascular disease, malignancy, connective tissue disease, acute inflammation, thyroid function disorders, and smoking have been set as exclusion criteria. Patients have been stratified according to their history of pancreatitis episodes (yes or no), how it ended (discharge or exitus), and disease etiology (biliary or non-biliary). The non-biliary group has been divided into subgroups as alcoholic, lipemic, or idiopathic. Disease severity has been categorized as mild, moderate, or severe pancreatitis according to the Atlanta classification. Ranson, HAPS, and BISAP scores have been determined for each patient. Patients have been grouped as necrotizing or edematous according to the Atlanta classification. While scoring for Ranson criteria, the first 5 parameters at baseline and 6 parameters 48 h following baseline have been used. For the Ranson criteria, patients were divided into 5 groups as 0 points, 1 point, 2 points, 3 points, and 4 points. For the HAPS, which was evaluated out of 3 points, the patients were divided into 2 groups as those who scored 0 and those who scored 1-2-3. For the BISAP score evaluated out of 5 points, patients were divided into 5 groups as 0 points, 1 point, 2 points, 3 points, and 4 points. Since no patients received 5 points or more for Ranson criteria and 5 points for BISAP scoring, these groups have been excluded. Consent was obtained from the Ethics Committee of Clinical and Laboratory Research of Tepecik Research and Training Hospital with the 7 March 2017/9 approval number.

Laboratory Analysis

The laboratory parameters, white blood cell (WBC), neutrophil (NEU), hemoglobin, HCT, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), *aspartate aminotransferase (AST), alanine aminotransferase (ALT), BUN, fasting blood glucose, and* lactate dehydrogenase have been enzymatically determined using OLYMPUS A05800 autoanalyzer (Japan). For IMA measurements, venous blood samples have been collected and transferred to normal biochemistry tubes containing gel, the serum has been separated from the blood samples within an hour and stored at –80°C as 2 aliquots. IMA test has been carried out monthly throughout the study period via Shimadzu UVmini-1240 spectrophotometry using cobalt chloride, dithiothreitol, and sodium chloride 0.9%, in line with the spectrophotometric method reported by Bar-Or et al.[5]

Statistical Analysis

Statistical analyses have been performed via The Statistical Package for the Social Sciences (SPSS) version 15 (SPSS Inc.; Chicago IL, USA) and R software. For descriptive continuous variables, arithmetic mean, standard deviation, range, and median values have been used meanwhile for categorical variables, frequency, and percentage distribution have been presented. For comparisons of more than 2 groups for dependent and independent variables, analysis of variance test, and post hoc Bonferroni test have been used. Correlation analysis has been performed in order to determine the association between 2 numerical variables and a P value of $< .05$ has been regarded as statistically significant.

RESULTS

In this study, 45% of the study population were female and 55% were male. Sociodemographic attributes and disease characteristics of these patients have been presented in Table 1. Fifteen percent ($n=15$) of the patients were ≤35 years old, 71% ($n=71$) were between 35 and 75 years old, and 14% ($n=14$) were ≥75 years old. According to the disease etiology, 48% ($n=48$) were biliary and 52% ($n=52$) were non-biliary. In this study, 36% ($n=36$) of the non-biliary group were idiopathic, 9% ($n=9$) were alcoholic, and 7% ($n=7$) were lipemic (Figure 1). Patients were also grouped according to their laboratory values such as HCT, BUN, CRP, and also according to the disease severity and Ranson, BISAP, HAPS, and Atlanta scores. These values have been presented in Table 2. Apart from the certain laboratory and classification characteristics patients have also been evaluated according to their age and minimum-maximum (min-max), median and arithmetic mean, and standard deviation of their laboratory values (Table 3). Individual mean IMA values of patients have been presented in Table 4. Accordingly, mean value was 0.46 ± 0.13 (min-max: 0.11-0.93) and median value was 0.45. The correlation between IMA levels, age, and laboratory values has been presented in Table 5. Accordingly, the correlation between IMA and age was weak ($r=0.198$, $P=.048$), with NEU it was weak

Table 1. Distribution of Study Group, According to Sociodemographic and Some Characteristics of Disease

	N (%)
Age (year)	
<35	15 (15)
35-75	71 (71)
>75	14 (14)
Gender	
Woman	45 (45)
Man	55 (55)
BMI	
Low or normal	45 (45)
Overweight or obese	55 (55)
Previous history of attack	
Yes	36 (36)
No	64 (64)
Termination status	
Exitus	2 (2)
Discharged	98 (98)
Total	100 (100)

BMI, body mass index.

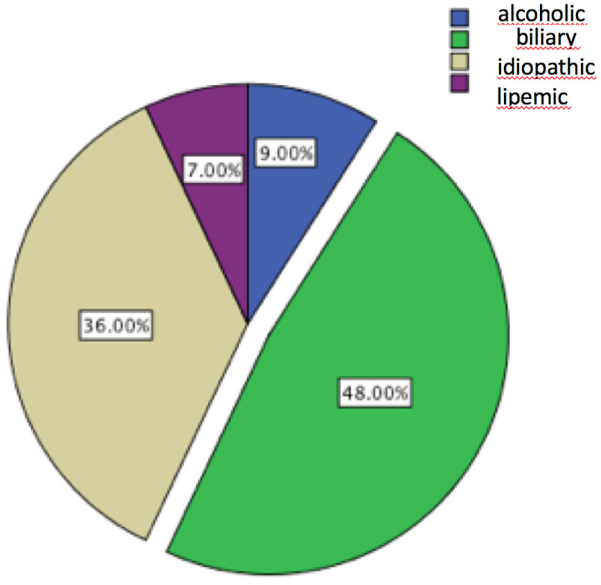

Figure 1. Classification of the patients according to the etiology.

($r=0.228$, $P=.022$), and with procalcitonin level it was moderate ($r=0.380$, $P < .001$) meanwhile, with albumin level it was negative moderate ($r=-0.396$, $P < .001$). The correlation between IMA levels and HCT was weak and

Table 2. Distribution of the Study Group, According to Some Laboratory Characteristics and Disease Prognosis Classifications

	N (%)
HCT	
Normal	78 (78)
High	22 (22)
CRP	
Normal	84 (84)
High	16 (16)
AST	
Normal	71 (71)
High	29 (29)
BUN	
Normal	21 (21)
High	79 (79)
Creatinine	
Normal	100 (100)
High	-
Severity of disease	
Mild	81 (81)
Moderate	14 (14)
Severe	5 (5)
Ranson score	
0	30 (30)
1	41 (41)
2	18 (18)
3	8 (8)
4	3 (3)
Bisap score	
0	25 (25)
1	32 (32)
2	33 (33)
3	8 (8)
4	2 (2)
Haps	
0	61 (61)
1-2-3	39 (39)
Atlanta score	
Necrotizing	2 (2)
Edematous	98 (98)
Total	100 (100)

HCT, hematocrit; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Bisap, Bedside Severity Index for Acute Pancreatitis; Haps, Harmless Acute Pancreatitis Score.

Table 3. The Mean Age and Laboratory Values of the Study Population

	Min-Max	Median	Mean ± SD
Age (year)	22-87	55	55 ± 17.21
BMI	22-32	26	26 ± 1.79
Hospitalization (Day)	2-30	5	5 ± 3.43
WBC (4.2-10.6 × 10^3 UL)	3500-23 000	10 900	11 615 ± 4122.77
NEU (2-6.9 × 10^3 Ul)	2600-22 000	8100	9015 ± 4180.68
HGB (12.2-16.2 g/dL)	9-18	13	13 ± 1.74
HCT (37.7-47.9%)	28-53	39.50	40 ± 5.15
ESR (0-20 mm/h)	2-122	19	27 ± 22.93
CRP (0-0.5 mg/dL)	0.2-39	3.1	7 ± 8.45
Procalcitonin (0.04-0.1 µg/L)	0.01-67	0.045	1 ± 7.07
AST (0-35 U/L)	11-1008	105	192 ± 205.01
ALT (0-35 U/L)	3-1020	94	171 ± 201.11
Amylase (28-100 U/L)	14-4782	203	533 ± 887.64
Lipase (3-67 U/L)	106-13 225	1661	2852 ± 2735.15
BUN (5-20 mg/dL)	3-94	29.50	32 ± 14.8
creatinine (0.6-1.1 mg/dL)	0.3-1.4	0.9	0.88 ± 0.21
Albumin (2.5-4 mg/dL)	2.7-4.4	3.9	3.8 ± 0.39
FBS (74-106 mg/dL)	66-123	102.5	101 ± 12.51
LDH (0-247 U/L)	18-2151	223	288 ± 253.81
Calcium (8-10.5 mg/dL)	7.5-11.5	9.25	9 ± 0.62

BMI, body mass ındex; WBC, white blood cell; NEU, neutrophil; HGB, hemoglobin; HCT, hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; FBS, fasting blood sugar; LDH, lactate dehydrogenase.

Table 4. The Mean of IMA Values

	Min-Max	Median	Mean ± SD
IMA	0.11-0.93	0.45	0.46 ± 0.13

IMA, ischemia modified albumin.

not statistically significant ($r=0.155$, $P=.122$). The correlation between IMA levels and CRP was weak and not statistically significant ($r=0.017$, $P=.865$). According to the correlation between IMA and renal enzymes; BUN has been found to be weak and not statistically significant ($r=0.124$, $P=.219$, respectively). Patients have been grouped as mild, moderate, and severe according to the disease severity and mean age and laboratory parameters have been evaluated between these groups (Table 6). Accordingly; a significant difference has been found between groups in terms of HCT values ($P=.015$), post hoc analysis showed the group making this significant difference to be the severe disease group. The mean values were, 40 ± 5.21 (95% CI: 38.66-40.97) for the mild disease group, 40 ± 360 (95% CI: 37.85-42.01) for the moderate disease group, and 47 ± 4.09 (41.51-51.69) for the severe disease group which was significantly higher than the other 2 groups. For CRP values, although statistically significant differences have been found between groups ($P < .001$), post hoc analysis showed no intergroup difference.

The difference between disease severity groups for procalcitonin levels was statistically significant ($P < .001$). Further analysis showed that the group creating the statistically significant difference was the severe disease group which had a procalcitonin level higher than

Table 5. Correlation of age and laboratory values with IMA

	r value	*P*
Age (year)	**0.198***	**.048**
WBC	0.127	.209
NEU	**0.228***	**.022**
HGB	−0.070	.486
HCT	0.155	.122
ESR	0.036	.722
CRP	0.017	.865
Procalcitonin	**0.380***	**<.001**
AST	0.039	.697
ALT	0.049	.626
Amylase	−0.111	.276
Lipase	−0.001	.991
BUN	0.124	.219
Creatinine	0.079	.432
Albumin	**−0.396***	**<.001**
FBS	−0.130	.199
LDH	0.104	.308
Calcium	−0.144	.153

WBC, white blood cell; NEU, neutrophil; HGB, hemoglobin; HCT, hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; FBS, fasting blood sugar; LDH, lactate dehydrogenase; IMA, ischemia modified albumin.
*Variables with statistically significant differences. Statistically significant values are in bold.

Table 6. The Relationship Between Age and Laboratory Values and Disease Severity

	Severity of disease									
	Mild			Moderate			Severe			
	N	Mean ± SD	CI (95%)	*N*	Mean ± SD	CI (95%)	*N*	Mean ± SD	CI (95%)	*P*
Age	81	54 ± 17.70	50.47-58.29	14	57 ± 14.54	48.96-65.75	5	63 ± 16.84	41.89	.507
WBC	81	10 965 ± 3590.69	10 171.47-11 759.40	14	13 314 ± 4752.47	10 570.29-16 058.28	5	17 380 ± 5405.73	10 667.89-24 092.11	**.001**
NEU	81	8330 ± 3381.07	7583.25-9078.48	14	10 692.86 ± 5344.22	7607.19-13 778.52	5	15 400 ± 6390.23	7465.49-23 334.51	**<.001**
HGB	81	13 ± 1.83	12.77-13.58	14	13 ± 1.26	12.65-14.11	5	14 ± 1.22	12.47-15.52	.569
HCT	81	40 ± 5.21	38.66-40.97	14	40 ± 360	37.85-42.01	**5**	47 ± 4.09	**41.51-51.69**	**.015**
ESR	80	22 ± 14.37	18.79-25.19	14	53 ± 40.35	29.49-76.08	5	44 ± 17.82	22.07-66.33	**<.001**
CRP	81	5 ± 6.86	3.87-6.90	14	16 ± 10.83	9.99-22.50	5	9 ± 9.38	–3.02-20.25	**<.001**
Procalcitonin	81	0.5 ± 2.26	0.36-1.04	14	1 ± 1.41	0.23-1.86	**5**	**17 ± 28.11***	**–17.46-52.36**	**<.001**
AST	81	189 ± 228.58	139.31-240.40	14	172 ± 146.40	87.33-256.38	5	290 ± 126.66	132.33-446.87	.564
ALT	81	169 ± 212.99	122.42-216.62	14	157 ± 160.64	64.46-249.97	5	234 ± 64.82	153.49-314.51	.759
Amylase	81	531 ± 922.0	327.73-735.47	14	594 ± 844.34	83.31-1103.77	5	397 ± 358.12	-47.46-841.86	.917
Lipase	81	2672 ± 2375.34	2147.76-3198.22	14	3954 ± 4490.62	1361.05-6546.67	5	2664 ± 1352.82	984.25-4343.75	.269
BUN	81	32 ± 13.56	28.79-34.79	14	35 ± 20.82	23.12-47.16	5	37 ± 16.59	16.80-58	.559
Creatinine	81	0.88 ± 0.19	0.84-0.93	14	0.9 ± 0.21	0.76-1	5	0.98 ± 0.40	0.48-1.48	.604
Albumin	81	3.78 ± 0.36	3.71-3.87	14	3.73 ± 0.38	3.51-3.96	5	3.4 ± 0.60	2.65-4.15	.091
FBS	81	100 ± 13.27	97.42-103.29	14	104 ± 9.63	98.37-109.49	5	103 ± 3.27	99.14-107.26	.572
LDH	81	276 ± 265.69	216.21-335.23	14	335 ± 213.23	212.10-458.33	5	359 ± 144.28	179.45-537.75	.595
Calcium	**81**	**9.38 ± 0.58**	**9.25-9.52**	14	8.81 ± 0.59	8.47-9.16	5	8.62 ± 0.43	8.09-9.15	**<.001**
IMA	81	0.45 ± 0.12	0.43-0.48	14	0.44 ± 0.13	0.36-0.52	**5**	**0.67 ± 0.16**	**0.48-0.86**	.001

WBC, white blood cell; NEU, neutrophil; HGB, hemoglobin; HCT, hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; FBS, fasting blood sugar; LDH, lactate dehydrogenase; IMA, ischemia modified albumin.
*The group that created significant results in post hoc analyzes. Statistically significant values are in bold.

Table 7. Correlation of Patient Values With Disease Severity, Ranson, Bisap, Haps, and Atlanta Scoring Systems With IMA

	IMA (Mean ± SD)	*P*
Severity of disease		
Mild	0.45 ± 0.12	**.001**
Moderate	0.44 ± 0.13	
Severe	**0.67 ± 0.16**	
Ranson score		
0	0.45 ± 0.13	**.016**
1	0.44 ± 0.11	
2	0.47 ± 0.12	
3	0.51 ± 0.16	
4	**0.7 ± 0.2**	
Bisap Score		
0	0.44 ± 0.12	**.002**
1	0.46 ± 0.13	
2	0.45 ± 0.12	
3	0.49 ± 0.08	
4	**0.81 ± 0.16**	
Haps		
0	0.46 ± 0.12	.648
1-2-3	0.47 ± 0.14	

Bisap, Bedside Severity Index for Acute Pancreatitis; Haps, Harmless Acute Pancreatitis Score; IMA, ischemia modified albumin. Statistically significant values are in bold.

the other 2 groups (17 ± 28.11 mg/dL). Table 7 shows mean IMA values and Ranson, HAPS, and BISAP scores per disease severity group. Mean IMA values were statistically different between disease severity groups and post hoc analysis showed that the group creating this difference was the severe disease group (Figure 2). IMA values were statistically higher in the severe disease group (0.67 ± 0.16), compared to the mild disease group (0.45 ± 0.12), and moderate disease group (0.44 ± 0.13) (*P*=.001). Similarly, Ranson scoring also showed a statistically significant difference (*P*=.016) and the difference was originating from category "4". Accordingly, the mean IMA level of category "4" (0.7 ± 0.2) was higher than category "3" (0.51 ± 0.16), category "2" (0.47 ± 0.12), category "1" (0.44 ± 0.11), and category "0" (0.45 ± 0.13). BISAP scoring also showed a statistically significant difference (*P*=.002) between groups and the difference was originating from category "4". Accordingly, the mean IMA level of category "4" (0.81 ± 0.16) was higher than category "3" (0.49 ± 0.08), category "2" (0.45 ± 0.12), category "1" (0.46 ± 0.13), and category "0" (0.44 ± 0.12). According to the re-categorized HAPS, IMA levels between category "0" and category "1-2-3" were not statistically significant (*P*=.648).

DISCUSSION

Today, the etiopathogenesis of AP remains partly unknown. The attempts of shedding light on the etiopathogenesis of AP in 1856 by Claude Bernard,

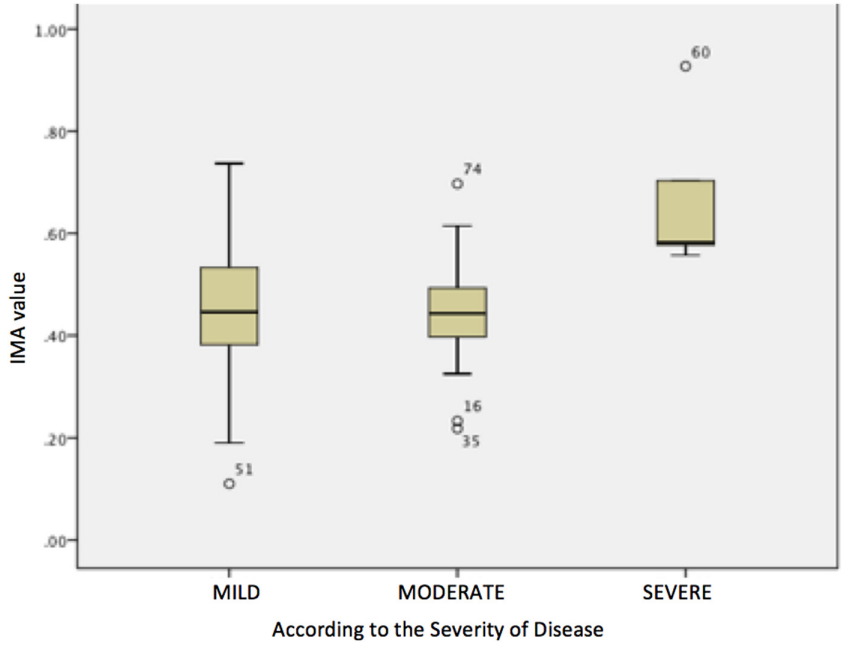

Figure 2. Classification of the patients according to the severity of the disease showing with the boxplot.

holding responsible the bile reflux to the pancreatic duct as the cause of pancreatitis, is still not considered fully clear.[2] Finding out the exact etiopathogenesis of AP and early categorization of patients according to the disease severity in terms of prognosis are important milestones for decreasing mortality and morbidity. The mortality rates of 10-20% in severe AP indicate that AP remains to be a seriously dangerous disorder.[7] In this case, current scoring systems and prognostic criteria and although still not in routine clinical use, the emerging markers being developed in studies are of high importance. Only in light of these parameters, AP patients can be rapidly categorized in terms of prognosis, treatment protocols, and relevant departments to apply them can be accurately determined and mortality rates can be decreased. Acute phase reactants such as CRP and procalcitonin are frequently being used for determining the AP severity. Procalcitonin has a sensitivity of 86% and a specificity of 95% in predicting AP severity.[8] According to a study, procalcitonin used as an early marker for predicting AP severity has a truth-value of 86%.[9] In our study, we have found a moderate-strong correlation between procalcitonin and IMA. No correlation has been found between disease severity and procalcitonin levels. In Europe, CRP is being widely used for severe AP. CRP level of >15 mg/dL in the first 48 h helps differentiate severe AP from mild AP. CRP level of >15 mg/dL in the first 48 h has been found to have a sensitivity of 80% and a specificity of 76%.[10] In our study, we did not observe a correlation between CRP levels, IMA, and disease severity. BUN is an important marker for early detection of hemoconcentration and provides substantial value for predicting necrosis or organ failure. According to a study conducted by Wu et al., investigating the relevant parameters for increased mortality in AP, a 5 mg/dL increase of BUN per day has been shown to increase mortality.[11] According to the other study of 1043 patients, investigating the association of serial BUN measurements in AP, also conducted by Wu, a BUN level of ≥20 mg/dL has been shown to significantly increase the risk of mortality.[12] Contrary to the previously published literature, in our study, no correlation has been found between BUN levels, IMA, and disease severity. HCT level of >44 has a 72% sensitivity in predicting organ failure, on 24th hour this rate increases to 94%. Serial measurements similar to BUN could be performed and the response to fluid replacement could be evaluated.[13] According to a retrospective study conducted by Baillargeon et al., an HCT level of ≥47% at admission or if the HCT level persists at the 24th hour, they claimed that the process might lead to pancreatic necrosis.[14] In a similar study conducted by Brown et al., a HCT level of ≥44% at admission and a persistent HCT level at the 24th hour have been found to have a sensitivity of 94% in predicting pancreatic necrosis.[15] In our study, similar to the published literature, the HCT level has been found to be parallel to disease severity and higher in case of severe AP. However, we did not observe a correlation between HCT and IMA. Although it is known that AP pathogenesis is multi-factorial, in recent studies its association between ischemia and oxidative stress is being highlighted.[4] Wang et al. reported that among the 2063 aortic dissection patients, 6 of them developed AP.[16] In this study, they have investigated the relationship between AP and ischemia. Cocota et al. reported that the patients who present with AP but have generalized atherosclerosis and abdominal aortic aneurysm may have underlying pancreatic ischemia.[17] In light of this literature data, ischemic markers came into use for diagnosis and prognostic follow-up of AP. In this context, IMA became a marker of investigation in clinical studies. These heavy metals are thought to have a lower capacity to bind to albumin N-terminal with a normal structure which results from ischemic events that take place in the body, acidosis that occurs during ischemia, hypoxia, and free radical damage. Although the mechanism is not clearly known, this new structurally changed molecule has been identified as "IMA" for the first time by Bar-Or et al.[5,18] The formation of IMA is directly associated with the production of free oxygen radicals.[19] Free oxygen radicals are related to pancreatic edema, necrosis, and cellular damage in AP.[20] Increased IMA levels are known to be secondary to tissue hypoxia, hypoperfusion, inflammation, and oxidative damage. The mechanism behind the increasing IMA value in AP is still not clearly known. The oxidative stress, increased inflammatory response, and microvascular damage are suggested to increase the IMA levels in AP. According to the previously published studies, IMA has been investigated mostly for its use in diagnosis in exploratory studies of AP. It has been shown to increase in AP, however, its validity in prognosis has been limited to animal studies.[6] According to an exploratory study conducted by Topaloglu et al., IMA increases in mice with AP.[6] Baser et al. showed IMA to be higher in mild AP compared to the control group.[21] Guldogan et al. investigated the prognostic value of IMA in AP and found out that IMA was not superior to Ranson scoring in AP.[22] Sahin et al. reported IMA to be correlated to AP severity and that it could be used as a predictor for determining AP severity.[23] Similar to other previously published literature, in our study, we found a correlation between IMA level and disease severity and the difference between groups was originating from severe AP group. Prognostic criteria, as well as scoring

systems, are of high importance in predicting the disease severity. The mortality rate of Ranson score in mild AP (score < 2) was 2.5% and 62% in severe AP (score > 3).[24] High Ranson scores are associated with systemic complications and necrotizing AP. According to the study of Guldogan et al., in which patients were classified as mild and severe AP and IMA levels were evaluated, no correlation between IMA and AP severity was found.[22] However, in our study, the IMA levels of patients who had 4 points among the Ranson groups were statistically significant in line with the ischemia mechanism in AP. HAPS scoring is another scoring system used to identify the AP severity. Sayrac et al.[25] indicated HAPS to be a useful predictor in detecting mild AP and claimed that aggressive treatment may not be necessary in the early phase for patients who have a HAPS score of 0 points. We were not able to find a literature reference showing a correlation between HAPS score and IMA, in our study no correlation was found between HAPS and IMA. Nowadays, the BISAP score is thought to be superior to Ranson in terms of its practical use and being able to evaluate it at admission. The AP patients with a BISAP score of 4-5, have a 7- to 12-fold increased risk of severe AP. Hagjer et al. stated that the BISAP score is instructive of disease severity and organ failure.[26] According to Hagjer et al., the Bisap scoring system is as good as Acute Physiology and Chronic Health Evaluation II (Apache-II) scoring and procalcitonin and superior to Ranson scoring, CRP, and HCT. A scoring system comparing IMA and BISAP score in AP patients still does not exist. In this context, our study represents a first. In our study, we have compared these 2 variables and the results have been found to be statistically significant. We think the difference is originating from the patients who got 4 points from the Bisap scoring. In line with the severe AP percentage in the literature, the scarcity of the severe pancreatitis cases in our study is 1 of the limitations of this study. We believe that the studies containing more cases of severe pancreatitis may highlight the correlation with the IMA level.

CONCLUSION

Our study is the first study to compare multiple prognostic factors with IMA in AP patients. In our study, the association between IMA and AP has been evaluated in the context of prognostic scoring and disease severity. According to our findings, IMA has been found to be correlated with disease severity, Ranson and BISAP scores, and procalcitonin levels. We have observed that some laboratory parameters including BUN and HCT levels and the HAPS scoring system are not correlated with IMA.

Ethics Committee Approval: Ethics committee approval was received from the Tepecik Research and Training Hospital Clinical and Laboratory Research Ethics Committee with the 7 March 2017/9 approval number.

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.H.G., Y.H., A.H.; Design – D.H.G., Y.H.; Supervision – D.H.G., Ç.A.; Resource – Y.H., A.E.M.; Materials – Y.H., D.H.G.; Data Collection and/or Processing – Y.H., A.E.M.; Analysis and/or Interpretation – Y.H., A.H.; Literature Search – D.H.G., Y.H.; Writing – Y.H., D.H.G.; Critical Reviews – D.H.G., Ç.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kumar V, Abbas AK, Fausto N, Mitchell RN. Robbins Basic Pathology. 8th ed. Philadelphia: Saunders Elsevier; 2007:675-685.
2. Stone HH, Fabian TC, Dunlop WE. Gallstone pancreatitis biliary tract pathology in relation to time of operation. Ann Surg. 1981;194(3):305-312. [CrossRef]
3. Cho JH, Kim TN, Chung HH, et al. Comparison of scoring systems in predicting the severity of acute pancreatitis. World J Gastroenterol. 2015;21(8):2387-2394. [CrossRef]
4. Winterbourn CC, Bonham MJD, Buss H, Abu-Zidan FM, Windsor JA. Elevated protein carbonyls as plasma markers of oxidative stres in acute pancreatitis. Pancreotology. 2003;3(5):375-382. [CrossRef]
5. Bar-Or D, Winkler JV, Vanbenthuysen K, Harris L, Lau E, Hetzel FW. Reduced albümin cobalt binding with transient myocardial ischemia after elective percutaneous transluminal coronary angioplasty: a preliminary comparison to creatine kinase-MB, myoglobin, and troponin I. Am Heart J. 2001;141(6):985-991. [CrossRef]
6. Topaloglu N, Kucuk A, Tekin M, et al. Serum ischemia-modified albumin levels in experimental model of acute pancreatitis. J Coll Phys Surg Pak. 2015;25(6):395-398. [CrossRef]
7. Maheshwari R, Subramanian RM. Severe acute pancreatitis and necrotizing pancreatitis. Crit Care Clin. 2016;32(2):279-290. [CrossRef]
8. Gross JB, Comfort MW, Mathieson DR, Power MH. Elevated values for serum amylase and lipase following the administration of opiates: a preliminary report. Proc Staff Meet Mayo Clin. 1951;26(5):81-87.
9. Kylänpää-Bäck ML, Takala A, Kemppainen E, Puolakkainen P, Haapiainen R, Repo H. Procalcitonin strip test in the early detection of severe acute pancreatitis. Br J Surg. 2001;88(2):222-227. [CrossRef]
10. Larvin M. Assessment of severity and prognosis in acute pancreatitis. Eur J Gastroenterol Hepatol. 1997;9(2):122-130. [CrossRef]
11. Wu BU, Johannes RS, Sun X, Conwell DL, Banks PA. Early changes in blood urea nitrogen predict mortality in acute pancreatitis. Gastroenterology. 2009;137(1):129-135. [CrossRef]

12. Wu BU, Bakker OJ, Papachristou GI, et al. Blood urea nitrogen in the early assessment of acute pancreatitis: an international validation study. Arch Intern Med. 2011;171(7):669-676. [CrossRef]
13. Tenner S. Initial management of acute pancreatitis: critical issues during the first hours. Am J Gastroenterol. 2004;99(12):2489-2494. [CrossRef]
14. Baillargeon JD, Orav J, Ramagopal V, Tenner SM, Banks PA. Hemoconcentration is an early riskfactor for necrotizing pancreatitis. Am J Gastroenterol. 1998;93(11):2130-2134. [CrossRef]
15. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. Pancreas. 2000;20(4):367-372. [CrossRef]
16. Wang R, Zhu JM, Qi RD, et al. Acute ischemic pancreatitis secondary to aortic dissection. Ann Vasc Surg. 2018;52:85-89. [CrossRef]
17. Cocota I, Badea R, Scridon T, Dumitrascu DL. Ischemic acute pancreatitis with pseudocyst in a patient with abdominal aortic aneurysm and generalized atheromatosis-case report. BMC Gastroenterol. 2015;15:35. [CrossRef]
18. Bar-Or D, Lau E, Winkler JV. A novel assay for cobaltalbumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 2000;19(4):311-315. [CrossRef]
19. Gidenne S, Ceppa F, Fontan E, Perrier F, Burnat P. Analytical performance of the albumin cobalt binding (ACB) test on the Cobas Mira Plus analyzer. Clin Chem Lab Med. 2004;42(4):455-461. [CrossRef]
20. Scott P, Bruce C, Schofield D, Shiel N, Braganza JM, McCloy RF. Vitamin C status in patients with acute pancreatitis. Br J Surg. 1993;80(6):750-754. [CrossRef]
21. Baser H, Can U, Karasoy D, et al. Evaluation of oxidant/antioxidants status in patients with mild acute pancreatitis. Acta Gastroenterolog Belg. 2016;79(1):23-28.
22. Güldoğan CE, Kılıc MÖ, Balamir İ, Tez M, Turhan T. Correlation between ischemia-modified albumin and Ranson score in acute pancreatitis. Turk J Trauma Emerg Surg. 2017;23(6):472-476. [CrossRef]
23. Sahin A, Turkoglu S, Tunc N, et al. Is ischemia-modified albumin a reliable tool for the assessment of acute pancreatitis? Ther Clin Risk Manag. 2018;14:627-635. [CrossRef]
24. Leese T, Shaw D, Holliday M. Prognostic markers in acute pancreatitis: can pancreatic necrosis be predicted? Ann R Coll Surg Engl. 1988;70(4):227-232.
25. Sayraç AV, Cete Y, Yiğit Ö, Aydın AG, Sayrac N. Utility of HAPS for predicting prognosis in acute pancreatitis. Turk J Trauma Emerg Surg. 2018;24(4):327-332. [CrossRef]
26. Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis—a prospective observational study. Int J Surg. 2018;54(A):76-81. [CrossRef]