Early Prediction of Severity in Acute Pancreatitis using the CRP/Albumin Ratio

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Abstract

Background: Acute pancreatitis (AP) is an inflammatory disease that can cause potentially lethal complications. Identifying patients at risk for (moderately) severe AP is crucial for appropriate triaging and intervention decisions.

Aim: This preliminary analysis aimed to determine the diagnostic value of the C-reactive protein (CRP)/albumin ratio in predicting (moderately) severe AP within 24 and 48 hours.

Methods: We performed a preliminary analysis of a multicentre retrospective cohort study. Patients were selected from studies conducted in 2008 until 2023 by the Dutch Pancreatitis Study Group and were included if data regarding their initial episode of AP was available. CRP and albumin were collected from the first three days of hospitalization and the highest ratios within 24 and 48 hours were calculated. Univariate and multivariate regressions identified predictors, and ROC analyses evaluated predictive accuracy.

Results: The study included 280 patients of whom 125 had (moderately) severe AP. Overall, CRP levels increased and albumin levels decreased during the disease course, leading to higher CRP/albumin ratios. The highest CRP/albumin ratios within 24 and 48 hours, leucocytes and creatinine were individual predictors of (moderately) severe AP. ROC analyses showed modest predictive values for the highest ratios within 24 and 48 hours, with AUCs of 0.582 and 0.607, respectively. High sensitivity cut offs (±80) showed low specificity.

Conclusion: The highest CRP/albumin ratios within 24 and 48 hours correlated significantly with (moderately) severe AP. However, overall predictive accuracy was modest. Small sample size, distribution of severity, and selection bias may have influenced the results. Future analysis with a larger and more representable population is needed to assess the clinical utility of the CRP/albumin ratio as a predictive marker for AP severity.

Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas characterized by sudden abdominal pain. Despite a decline in hospital admissions for overall abdominal pain, recent studies show a rising incidence and number of admissions for AP in Western countries. In 2018, a total of 288.220 admissions were reported in the United States, making it one of the most common gastrointestinal diseases requiring hospital admission. [1,2] Although AP has a mild and self-limiting course in most cases, approximately 15-25% of all patients develop (moderately) severe AP with local complications, such as (infected) necrosis, and/or organ failure.[3] Clinically, these complications can lead to long-term hospitalization, admission to intensive care units (ICU), invasive interventions and death. In essence, organ failure is the most common cause of death in patients with AP, transient organ failure (<48 hours) gives a mortality risk of 1.4-10% and overall persistent organ failure >40%.[4] It is essential to note that AP is a dynamic condition in which severity may rapidly progress. In an early stage of the disease, the systematic inflammatory response syndrome is the main cause of organ failure.[5] In a later stage, organ failure can be caused by infections such as infected necrosis. Although an early intervention does not exist, studies indicate that monitoring and support of pulmonary, renal, circulatory and hepatobiliary function on ICU can reduce systemic consequences in patients with severe AP.[6] To help improve the prognosis, an adequate and accessible prediction model to classify the (moderately) severe AP subgroup in an early stage of disease, is a necessity to assist clinicians in triaging patients to the appropriate level of care and making decisions regarding interventions. Furthermore, it can be useful in selecting predicted severe patients for interventional studies.

Currently, various scoring systems are being used to predict the severity of AP, for example, the Ranson's criteria[7], the Acute Physiology and Chronic Health Evaluation II (APACHE II)[8], the Bedside index of severity in acute pancreatitis (BISAP) score[9] and the Glasgow-Imrie criteria[10]. Research has shown that these scores have a relatively high sensitivity (±80%) and a reasonable specificity (±70%).[11] However, a disadvantage of these scores is that they consist of numerous physical parameters and blood test values, making them inconvenient to apply in clinical practice. Additionally, some scores may be completed up to 48 hours after admission, potentially causing a delay in appropriate care.

A more easy-to-use and reasonably valuable predictive value is serum C-reactive protein (CRP).[11] This acute phase protein is synthesized by the liver in response to inflammation and infection, resulting in elevated levels. On the contrary, albumin is a negative acute phase protein, which decreases during inflammation, resulting in lower values. Both reactions happen simultaneously in the acute moment. A recent meta-analysis of Wang et al.[11] showed that, in comparison to the APACHE II score, these individual values had a relative sensitivity of 0.95 (CRP) and 0.88 (albumin), and a relative specificity of respectively 1.18 and 1.22. Consequently, we presume that the ratio between CRP and albumin can be a sensitive and specific predictor for the severity of AP within 24 hours, which can help us improve disease outcomes and survival. In a systematic review, Tarar et al.[12] found few studies examining this hypothesis, of which none specifically evaluated the value of this ratio for moderately severe and severe AP. For that reason, this study determines to define the diagnostic value of the CRP/albumin ratio within 24-48 hours in predicting (moderately) severe AP within a multicentre retrospective cohort.

Methods

Study design & Data collection

This is a preliminary analysis of a multicentre retrospective cohort study that we are conducting in the Netherlands. Patients were collected from the following studies carried out by the Dutch Pancreatitis Study Group: PWN-Core (a registration cohort for prospective follow-up of the disease course and the use of medical data for scientific research), PYTHON[9], POEMA, APEC[10], POINTER[11] and the 639-cohort (PANTER[12] and PROPATRIA[13]). Patients were included if informed consent for registration of their medical files for research was given, and if data from their initial episode of AP was available. The diagnosis of AP was made based on the Atlanta criteria[6], requiring at least two of the following: 1) abdominal pain suggestive for AP; 2) serum amylase or lipase level greater than three times the upper normal value, or 3) characteristic findings on radiological imaging.

We used (electronic) health records to obtain data regarding patient and hospitalization characteristics, aetiology, laboratory and radiologic findings, APACHE II score and Glasgow-Imrie score (both highest <24 hours), severity, and the occurrence of organ failure or death. Laboratory results were collected from the day of admission and the following two days (referred to as day 0, day 1 and day 2). CRP and albumin are measured in g/dL, leucocytes in 10^9/L and creatinine in µmol/L. We calculated the highest CRP/albumin ratios within 24 and 48 hours to define the predictive value for the severity within the acute phase of the disease. The classification of severity was also made using the Atlanta criteria[6], defining patients without local complications or organ failure as mild, patients with local complications and/or transient organ failure as moderately severe and patients with persistent organ failure >48 hours as severe. Considering patients with moderately severe and severe AP both have a higher risk mortality and complications as mentioned before, these two groups were combined when comparing characteristics to the mild subgroup.

Statistical analysis

The statistical analyses were computed using SPSS for Windows, version 26. Categorical variables are presented as numbers and percentages, and were compared using the Chi-square test. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. Normally distributed variables are presented as a mean ± standard deviation and non-normally distributed are presented as a median (lower quartile, upper quartile). For comparison, we used the unpaired student T-test or the non-parametric equivalent, the Mann-Whitney U test. A univariate and multivariate logistic regression were utilized to determine which variables were individual prognostic factors for (moderately) severe AP. Variables were chosen based on presumed clinical significance and former research. The results are presented in odds ratios with corresponding 95% intervals. The diagnostic

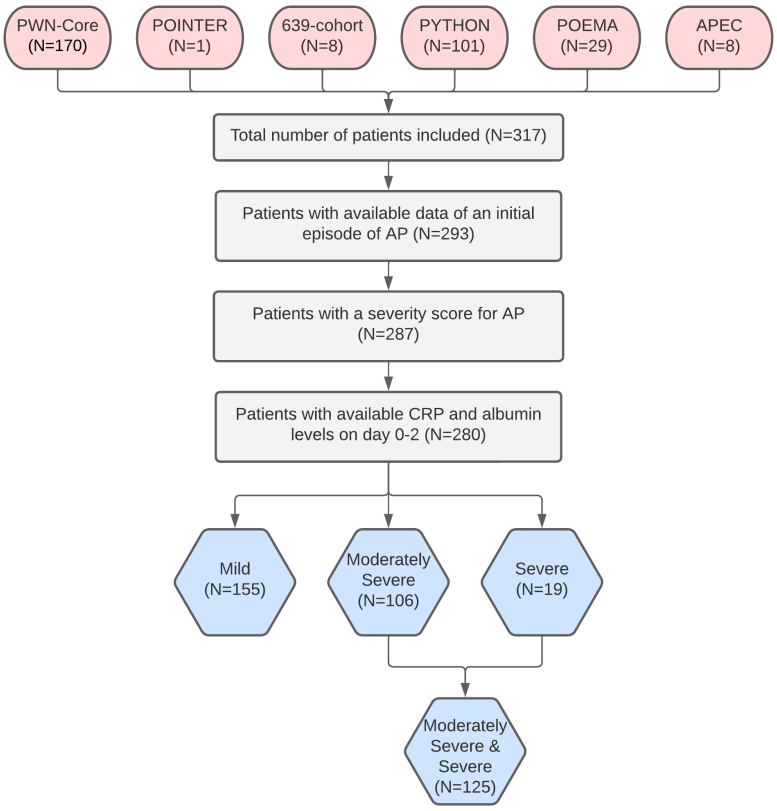

Figure 1. *Flowchart of patient selection*

values of the highest CRP/Albumin ratio within 24 and 48 hours in predicting the severity were examined with ROC curve analysis, with an area under the curve (AUC). A two-sided p-value of <0.05 was considered statistically significant.

Results

Study population

In total, 280 patients diagnosed with an initial episode of AP between September 2005 and February 2023 from seventeen different hospitals enrolled in the study. Figure 1 shows a flowchart of the patient selection. Overall, the population consisted of predominantly men (56.0%) at the age of 58 (45; 71). The most common aetiologies were biliary (49.0%), idiopathic (20.4%) and alcohol (15.7%). With regard to severity, 155 patients had mild AP, 106 moderately severe and 19 severe. Most severe patients were collected from older trials. Table 1 shows the demographic and clinical baseline characteristics, comparing mild AP to moderate severe and severe AP.

As suspected, the table also shows an increase of CRP and a decrease of albumin over the course of illness in both groups, resulting in an increase of the CRP/albumin ratio. For a total of 237 patients, we were able to calculate at least one CRP/albumin ratio within

Table 1. *Demographic and clinical characteristics sorted by severity subgroups*

Variables	*Mild AP (N=155)*		*Moderately Severe and Severe AP (N=125)*		*p-value*
Age (years)	58.0 (46.0; 71.0)		59.0 (45.0; 71.0)		0.994
Male	78 (50.3%)		79 (63.2%)		0.031
Medical history					
- Cardiovascular	62 (40.0%)	(N=151)	49 (40.2%)	(N=122)	0.881
- Pulmonary	29 (18.7%)	(N=149)	17 (13.6%)	(N=124)	0.206
- Chronic kidney disease	6 (3.9%)	(N=151)	6 (4.8%)	(N=123)	0.716
- Diabetes	22 (14.2%)	(N=153)	14 (11.2%)	(N=122)	0.478
Etiology					
- Biliary	79 (51.0%)		58 (46.4%)		0.447
- Alcohol	22 (14.2%)		22 (17.6%)		0.436
- Post-ERCP	4 (2.6%)		7 (5.6%)		0.196
- Autoimmune	3 (1.9%)		0 (0.0%)		0.118
- Hypertriglyceridemia	1 (0.6%)		5 (4.0%)		0.054
- Medicine induced	7 (4.5%)		0 (0.0%)		0.016
- Idiopathic	30 (19.4%)		27 (21.6%)		0.643
- Other	8 (5.2%)		4 (3.2%)		0.421
- Unknown	1 (0.6%)		2 (1.6%)		0.440
Highest leucocytes (day 0-2)	13.6 (10.2; 17.3)	(N=155)	17.6 (13.8; 22.4)	(N=122)	<0.001
Highest creatinine (day 0-2)	76 (63; 95)	(N=154)	88 (69; 117	(N=121)	0.004
Day 0 (admission)					
- CRP	13.0 (5.0; 39.3)	(N=150)	14.6 (4.0; 104.0)	(N=119)	0.367
- Albumin	43.0 (40.0; 45.6)	(N=118)	42.0 (37.0; 44.0)	(N=89)	0.006
- CRP/Alb ratio	0.264 (0.106; 0.876)	(N=117)	0.321 (0.078; 2.780)	(N=88)	0.305
Day 1					
- CRP	70.0 (23.0; 138.0)	(N=127)	167.0 (78.0; 273.0)	(N=103)	<0.001
- Albumin	36.0 (30.5; 38.3)	(N=37)	34.0 (28.3; 37.4)	(N=40)	0.102
- CRP/Alb ratio	2.496 (0.768; 5.191)	(N=36)	7.365 (1.733; 11.000)	(N=39)	0.001
Day 2					
- CRP	142.0 (74.0; 239.0)	(N=116)	309.0 (236.0; 388.0)	(N=95)	<0.001
- Albumin	34.1 ± 5.0	(N=24)	28.4 ± 4.1	(N=28)	<0.001
- CRP/Alb ratio	5.173 (2.706; 8.639)	(N=24)	11.954 (9.158; 14.549)	(N=25)	<0.001
Highest CRP/Alb ratio <24h	0.515 (0.134; 2.024)	(N=132)	0.900 (0.139; 6.493)	(N=101)	0.033
Highest CRP/Alb ratio <48h	0.705 (0.191; 3.107)	(N=133)	2.306 (0.174; 9.620)	(N=104)	0.005
Hospital stay (day)	6 (4; 9)	(N=153)	16 (10; 35)	(N=124)	<0.001
Intensive Care Unit					
- Admission to ICU	3 (9.7%)		24 (19.2%)		<0.001
- Duration (days)	2 (1; 3)		6 (3; 23)		0.070

Notes: If a variable has missings, the adjusted sample size is noted behind the variable. Normally distributed variables are presented as a mean ± standard deviation and non-normally distributed are presented as a median (lower quartile, upper quartile). CRP and albumin are measured in g/dL, leucocytes in 10^9/L and creatinine in µmol/L. Abbreviations: Alb = albumin, AP = acute pancreatitis, CRP = c-reactive protein, ERCP = endoscopic retrograde cholangiopancreatography.

the first 48 hours after admission. For the other 43 patients either CRP or albumin was determined on day 0-2 and a ratio could not be calculated. In percentage terms, CRP and albumin were determined more often in the (moderately) severe group. CRP/albumin ratio on day 1 and day 2, as well as for the highest ratio within 24 and 48 hours, were significantly higher in de (moderately) severe subgroup.

Table 2. *Occurrence of complications in patients with moderately severe and severe acute pancreatitis*

Variables	*MSAP + SAP (N=125)*
Fluid collections (total)	79 (63.2%)
(Peri)pancreatic necrosis (total)	83 (66.4%)
Location	
- Peripancreatic	26 (20.8%)
- Parenchymal	15 (12.0%)
- Peripancreatic & parenchymal	41 (32.8%)
- Unknown	1 (0.8%)
Organ failure (total)	35 (28.0%)
Per system	
- Respiratory	23 (18.4%)
- Renal	12 (9.6%)
- Cardiovascular	20 (16.0%)
Single or multiple	
- Single	20 (16.0%)
- Multiple	15 (12.0%)
Duration	
- Transient (<48h)	16 (12.8%)
- Persistent (>48h)	19 (15.2%)
Death caused by initial episode of AP	7 (5.6%)

Note: variables presented in number (percentage). Abbreviations: MSAP = moderately severe acute pancreatitis, SAP = severe acute pancreatitis.

Table 2 shows the occurrence of local complications, organ failure and death within the patients with moderately severe and severe AP. The (moderately) severe group has a statically significant longer hospital stay and are admitted to the ICU more frequently.

Univariate and multivariate regressions

Univariate logistic regressions showed a correlation between gender, highest creatinine and number of leucocytes within the first three days of hospitalization, highest CRP/Albumin ratio within 24 hours, and highest CRP/Albumin ratio within 48 hours and the severity of AP. Age, aetiology and medical history (cardiovascular, pulmonary, diabetes mellitus or chronic renal disease) were not associated with the severity of AP. The results of the multivariate logistic regressions with the statistically significant individual variables are shown in Table 3. With every increase of 1 point in the CRP/albumin ratio within 24 and 48 hours, the odds ratios of (moderately) severe pancreatitis increase by 13.4% and 13.7%, respectively. Additionally, the values of leucocytes and creatinine are individual predictors and give an increase in odds ratio of respectively 37.6% (per step of 3x109/L leucocytes) and 4.8% (per step of 5 µmol/L creatinine), respectively. In the multivariate regression, gender was not a statistically meaningful independent predictor.

ROC-analyses for CRP/albumin ratios

Figure 2 shows the ROC curves of the highest ratios within 24 and 48 hours in the prediction of (moderately) severe AP. The areas under the curve (AUC) with 95% confidence intervals are 0.582 (0.504-0.659) for the highest ratio within 24 hours and 0.607 (0.531-0.683) for the highest ratio within 48 hours. Both tests have discriminatory power, in which the highest ratio within 48 hours is slightly stronger. However, the overall accuracy is still relatively modest. In our view, a diagnostic test for (moderately) severe pancreatitis should especially be capable of identifying true positives. Therefore, we calculated the corresponding cut-off points with sensitivities similar

Table 3. *Multivariate regression*

	Sig.	**Odds ratio**	**95% C.I.**		**Sig.**	**Odds ratio**	**95% C.I.**
Highest CRP/Alb ratio <24 hours*	0.009	1.134	1.005 – 1.093	Highest CRP/Alb ratio <48 hours**	<0.001	1.137	1.059 – 1.220
Leucocytes[a]	<0.001	1.376	1.174 – 1.613	Leucocytes[a]	<0.001	1.369	1.168 – 1.605
Creatinine[b]	0.027	1.048	1.033 – 1.246	Creatinine[b]	0.029	1.047	1.005 – 1.092
Gender (male)	0.828	0.933	0.496 – 1.753	Gender (male)	0.960	0.984	0.523 – 1.853
Gender (female)	*Ref.*	-	-	Gender (female)	*Ref.*	-	-

**49 missings ** 45 missings*
[a]in steps of 3 [b]in steps of 5

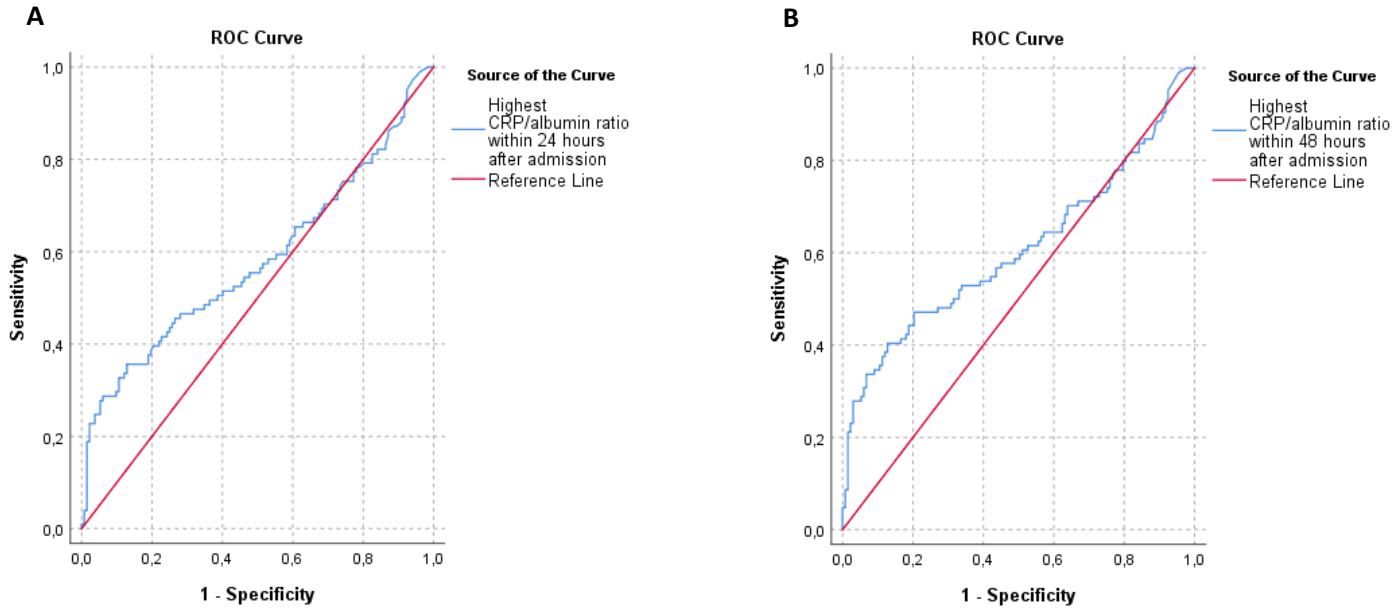

Figure 2. *ROC-analyses. A: Highest CRP/albumin ratio within 24 hours (AUC: 0.582, 0.504-0.659); B: Highest CRP/albumin ratio within 48 hours (AUC: 0.607 (0.531-0.638)*

to other diagnostic tests (±80%)[10]. For the ratios within 24 hours, we found a cut-off of 0.115 with a sensitivity of 78.2% and a specificity of 12.0%. For the ratios within 48 hours, we found a cut-off of 0.122 with a sensitivity of 79.8% and specificity of 20.3%. Both cut-off points show a low specificity for a sensitivity set at ±80%, meaning that they are likely to identify most true positives, but may also produce many false positives.

Discussion

In absence of an easy applicable and accurate prediction model, this study aimed to determine the predictive value of the CRP/albumin ratio for (moderately) severe AP within 24 and 48 hours.

Firstly, this preliminary analysis demonstrated that patients with (moderately) severe AP had significantly higher CRP/albumin ratios on day 1 and day 2, and higher ratios within 24 and 48 hours after admission than mild AP patients. To our knowledge, this is the first multicentre study in which this correlation is proven for the combined group of moderately severe and severe AP patients. This is an important finding, since both groups are at risk for poor disease outcomes and death. The ROC analyses showed that the highest ratios within 24 and 48 hours were of statistical diagnostic value, with the ratio within 48 hours being slightly more accurate. Nevertheless, with AUCs around 0.6 the clinical relevance is limited. When using cut-offs with a high sensitivity to prevent false negatives, the specificity for both scores is poor. Clinically, this could result in an overestimation of patients with moderate (severe) AP, potentially leading to unnecessary high care and costs. Nevertheless, we believe monitoring patients with potential mild outcomes is better than underestimating severe outcomes leading to emergency admissions to ICU, for example. Additionally, this study found that the level of leucocytes and creatinine are individual predictors for the severity. Creatinine is known to increase during inflammation as it is a breakdown product of muscle metabolism and it has been proven to be a predictor for severity of AP.[18-20] Leucocytes are activated as a result of the pancreas inflammation. The primary types of white blood cells involved in the immune response

are neutrophils and monocytes. Prior research has shown this marker can also be associated with the pancreatitis severity.[10, 21-23] Both of these variables are components of the APACHE II score.[8]

Prior studies have also highlighted the CRP/albumin ratio as a significant prognostic marker in acute pancreatitis. In their 2017 study, Kaplan et al.[24] found promising evidence supporting the use of the CRP/albumin ratio as a non-invasive, easily measurable, and repeatable inflammation-based predictor of overall survival for patients with AP. Zhao et al.[25] studied the relationship between the CRP/albumin ratio in predicting patients with severe AP and reported AUCs of almost 0.9 for the ratios on the first and second day after admission. However, the ratios were diagnostically not superior to the Ranson, MCTSI and BISAP score. A study from Kazmi et al.[26] examined the predictive value of CRP/albumin ratios at admission for severe AP and found an AUC of 0.827. Although not statistically proven, the overall sensitivity and specificity became more accurate when using the CRP/albumin ratio instead of only CRP.

When comparing these studies to our study, we believe strengths of our study are the multicentre design and the combinations of severity groups. Taking the other results into mind, we contend our results are an underestimation of the diagnostic value. Firstly, the sample size of this preliminary analysis is small and the distribution in severity is not in accordance with reality. In our study population the ratio between mild and (moderately) severe is about 55:45, where in reality this is around 80:20. This is most likely caused by collecting patients from older trials in which only predicted severe patients were included. However, in the future we will collect more patients from PWN-Core registry study in which all patients with an initial episode of AP can participate disregarding predicted severity. Secondly, in the present analysis data collection regarding concurrent infections was not complete. Concurrent infections could possibly declare outliers with high CRP/albumin ratios within the mild group, since CRP and albumin are not specific for pancreatitis. In future analyses, we expect that by enlarging the study population, making it more representable and correcting for concurrent infections, the diagnostic value of the CRP/albumin ratio will increase and the generalizability of our results will improve.

Conclusion

This preliminary analysis found that the CRP/albumin ratio within 24 and 48 hours is of statistically significant value in predicting (moderately) severe AP. To gain more insight on the clinical relevance, further analyses with a larger study population is needed.

References

1. Peery AF, Crockett SD, Murphy CC, Jensen ET, Kim HP, Egberg MD, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2021. Gastroenterology. 2022 Feb;162(2):621-644.
2. Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, Coward S, Forbes N, Heitman SJ, Shaheen AA, Swain M, Buie M, Underwood FE, Kaplan GG. Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. Gastroenterology. 2022 Jan;162(1):122-134.
3. Fagenholz PJ, Castillo CF, Harris NS, Pelletier AJ, Camargo CA Jr. Increasing United States hospital admissions for acute pancreatitis, 1988-2003. Ann Epidemiol. 2007 Jul;17(7):491-7.
4. Garg PK, Singh VP. Organ Failure Due to Systemic Injury in Acute Pancreatitis. Gastroenterology. 2019 May;156(7):2008-2023.
5. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al.; Acute Pancreatitis

Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013 Jan;62(1):102-11.
6. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013 Jul-Aug;13(4 Suppl 2):e1-15.
7. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet. 1974 Jul;139(1):69-81.
8. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.
9. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008 Dec;57(12):1698-703.
10. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. Gut. 1984 Dec; 25(12):1340-6.
11. Wang H, Lü M, Li W, Shi J, Peng L. Early Predictive Value of Different Indicators for Persistent Organ Failure in Acute Pancreatitis: A Systematic Review and Network Meta-Analysis. J Clin Gastroenterol. 2023 Mar 20.
12. Tarar MY, Khalid A, Choo XY, Khurshid S, Tumeh H, Muhammad K. Use of the C-Reactive Protein (CRP)/Albumin Ratio as a Severity Tool in Acute Pancreatitis: Systematic Review. Cureus. 2022 Sep 16;14(9):e29243.
13. Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al.; Dutch Pancreatitis Study Group. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med. 2014 Nov 20;371(21):1983-93.
14. Schepers NJ, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, et al.; Dutch Pancreatitis Study Group. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. Lancet. 2020 Jul 18;396(10245):167-176.
15. Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, et al.; Dutch Pancreatitis Study Group. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. N Engl J Med. 2021 Oct 7;385(15):1372-1381.
16. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al.; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010 Apr 22;362(16):1491-502.
17. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al.; Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Feb 23;371(9613):651-659.
18. Stirling AD, Moran NR, Kelly ME, Ridgway PF, Conlon KC. The predictive value of C-reactive protein (CRP) in acute pancreatitis - is interval change in CRP an additional indicator of severity? HPB (Oxford). 2017 Oct;19(10):874-880.
19. Zhao Z, Yu Y, Xie R, Yang K, Xu D, Li L, et al. Prognostic value of the creatinine-albumin ratio in acute pancreatitis debridement. BMC Surg. 2020 Dec 9;20(1):322.
20. Lipinski M, Rydzewski A, Rydzewska G. Early changes in serum creatinine level and estimated glomerular filtration rate predict pancreatic necrosis and mortality in acute pancreatitis: Creatinine and eGFR in acute pancreatitis. Pancreatology. 2013 May-Jun;13(3):207-11.
21. Muddana V, Whitcomb DC, Khalid A, Slivka A, Papachristou GI. Elevated serum creatinine as a marker of pancreatic necrosis in acute pancreatitis. Am J Gastroenterol. 2009 Jan;104(1):164-70.
22. Liu G, Tao J, Zhu Z, Wang W. The early prognostic value of inflammatory markers in patients with acute pancreatitis. Clin Res Hepatol Gastroenterol. 2019 Jun;43(3):330-337. doi: 10.

23. Karabuga B, Gemcioglu E, Konca Karabuga E, Baser S, Ersoy O. Comparison of the predictive values of CRP, CRP/albumin, RDW, neutrophil/lymphocyte, and platelet/lymphocyte levels in determining the severity of acute pancreatitis in patients with acute pancreatitis according to the BISAP score. Bratisl Lek Listy. 2022;123(2):129-135.
24. Kaplan M, Ates I, Akpinar MY, Yuksel M, Kuzu UB, Kacar S, et al. Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2017 Aug 15;16(4):424-430.
25. Zhao Y, Xia W, Lu Y, Chen W, Zhao Y, Zhuang Y. Predictive value of the C-reactive protein/albumin ratio in severity and prognosis of acute pancreatitis. Front Surg. 2023 Jan 10;9:1026604.
26. Haider Kazmi SJ, Zafar MT, Zia BF, Khalid SR, Kumar V, Tabassum S, et al. Role of serum C-reactive protein (CRP)/Albumin ratio in predicting the severity of acute pancreatitis: A retrospective cohort. Ann Med Surg (Lond). 2022 Sep 21;82:104715