Section: General Surgery

Systematic Review

C REACTIVE PROTEIN ANALYSIS IN PREDICTING THE SEVERITY OF ACUTE PANCREATITIS - SYSTEMATIC REVIEW

S. Subramanian[1]

[1]Assistant Professor, Department of General Surgery, Palakkad Institute of Medical Sciences, Palakkad, India

Received : 20/12/2023
Received in revised form : 20/02/2024
Accepted : 02/03/2024

Keywords:
Acute pancreatitis, C-reactive protein, Procalcitonin, Interleukin, Severity.

Corresponding Author:
Dr. S. Subramanian,
Email: abinand.hospital@gmail.com

DOI: 10.47009/jamp.2024.6.2.234

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (2); 1172-1175

Abstract

Background: Acute pancreatitis (AP) is one of the most common conditions associated with high morbidity and mortality rates. As a result of ongoing multiple organ failure (MOF), pancreatic necrosis, and/or sepsis, the current death rate from AP ranges between 5 and 10%. C-reactive protein (CRP) is a widely used biomarker to assess the prognosis and severity of acute pancreatitis. This study aimed to assess the efficacy of C-reactive protein (CRP) levels in assessing the severity of acute pancreatitis (AP). **Materials and Methods:** A systematic database search was conducted using PUBMED and Google Scholar databases. Studies reporting the diagnostic accuracy of CRP for acute pancreatitis in patients were included. The article's evaluation and data extraction were conducted according to PRISMA guidelines. The overall quality of evidence for each outcome was assessed using the GRADE methodology. **Result:** The literature search yielded 985 articles from designated online databases for this study. After eliminating duplicate articles from the automation tools and for other reasons, such as improper citations and articles in other languages, 104 records were considered. Fifty-nine articles were excluded because they were irrelevant to the studies; after a detailed review of the titles and abstracts, only 45 were selected. After a more detailed eligibility assessment, 11 articles were considered for qualitative and quantitative synthesis. **Conclusion:** Currently available evidence suggests an absolute correlation between CRP level and the prognosis of pancreatitis. Thus, it can be used as an effective tool for predicting the severity of pancreatitis.

INTRODUCTION

Acute pancreatitis (AP) is a potentially fatal condition that affects 13–45 per 100,000 people annually. As a result of ongoing multiple organ failure (MOF), pancreatic necrosis, and/or sepsis, the current death rate from AP ranges between 5 and 10%.[1] Since Alexander the Great (356-323 BC) died at the age of 33 from acute necrotising pancreatitis as a result of his chronic alcoholism, acute pancreatitis has been known to man since the pre-Christ period. Organ and disease conditions were extensively studied by Wirsung in the 17th century and Halsted in the early 19th century.[2] Acute pancreatitis is divided into two categories according to the commonly used Atlanta classification: mild and severe.

The term "interstitial" or "edematous" refers to pancreatitis that lacks parenchymal necrosis and is typically mild. Patients with pancreatitis must meet the following four criteria for the diagnosis of severe acute pancreatitis (SAP): (1) Failure of an organ with one or more of the following: shock (systolic blood pressure of 90 mm Hg), pulmonary insufficiency (PaO2 of 60 mm Hg), renal failure (serum creatinine level of 2 mg/dL [176.8µmol/L] following rehydration), and bleeding from the gastrointestinal tract (500 mL in 24 hours); (2) local complications like necrosis, pseudocyst, or abscess; (3) at least three of Ranson's criteria; or (4) at least eight of the Acute Physiology and Chronic Health Evaluation II (APACHE II) criteria.[3]

The most prevalent and widely accepted theory for the development of pancreatitis states that pancreatic enzymes (chymotrypsin, elastase, and trypsin) can leak into the pancreatic tissue when pancreatic acini are damaged or disrupted. The tissue is exposed to leaked enzymes, which causes autodigestion and acute pancreatitis. Oedema, vascular damage, bleeding, and necrosis result from the breakdown of tissue and cell membranes by activated proteases (lipase, elastase, and trypsin).[4] Hepatocytes produce C-reactive protein or CRP. The normal level of CRP in healthy individuals is less than 10 mg/L; however, in disease states, this level can increase in the first 6 to 8 hours and reach a peak of approximately 350±400 mg/L after 48 hours.[5]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

CRP's primary function of CRP is to identify potentially hazardous autogenous materials in the plasma expelled from injured tissues, bind and detoxify them, and/or assist in their elimination.[6] There is a strong correlation between CRP and pancreatic and peripancreatic necrosis from the perspective of differential diagnosis. This enables an overall accuracy rate of 86% in the detection of pancreatic necrosis and allows for the differentiation between edematous and necrotizing disease with a sensitivity and specificity above 80%.[7] There was a notable rise in CRP levels during the initial stages of severe acute pancreatitis, indicating that CRP may function as a precursor to the development of acute pancreatitis into a more severe condition.[8]

This systematic literature review and meta-analysis investigated the efficiency of C-reactive protein in detecting the severity of acute pancreatitis.

MATERIALS AND METHODS

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, we followed the PRISMA 2009 guidelines for systematic literature review, data reporting, and discussion. The article's evaluation and data extraction were conducted according to the established guidelines.

The overall quality of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

Search strategy: A systematic literature review was performed using PubMed (MedLine database). The search methodology was aligned with the PICOS strategy, integrating Medical Subject Headings (MeSH) as search terms whenever feasible. Filters were applied to include studies with designs such as randomised controlled trials (RCTs) and observational studies as well as articles encompassing systematic reviews and meta-analyses. The selected studies were limited to those conducted between 2014 and February 2024. No additional filters were used and the search terms used in the literature review are outlined below.

Keywords employed in the search strategy include "pancreatitis" or "acute pancreatitis" and "C-reactive protein" in conjugation with terms such as "efficacy," "diagnosis," and "treatment efficacy." Boolean operators (AND, OR) were used to refine the search and capture the intersection of these terms.

Study Selection: The eligibility of all abstracts was assessed, and articles were incorporated into the qualitative synthesis if they fulfilled the following criteria.

Inclusion Criteria

We included studies that involved human subjects, those published from January 2014 to March 2024, those using C-reactive protein to diagnose pancreatitis, and peer-reviewed articles published in English.

Exclusion Criteria

We excluded studies that lacked relevant outcome measures, had insufficient data, and were not published in English.

Data Extraction: The assessment of search results relied on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

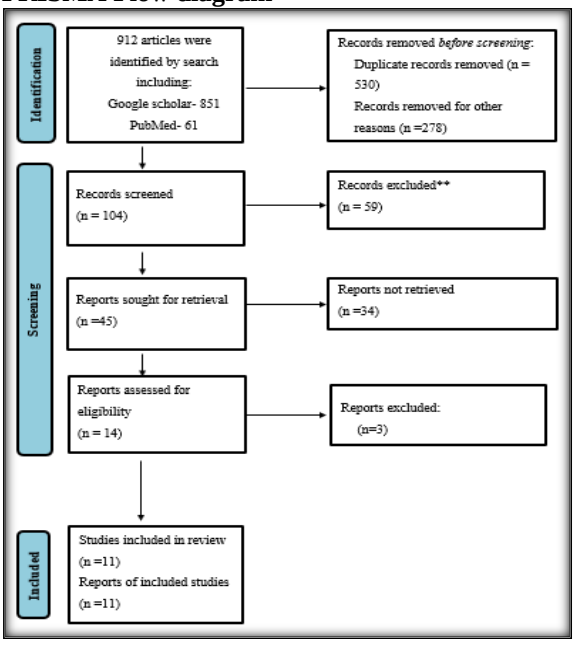
Participants, interventions, comparators, and outcomes (PICO) criteria were used to determine the eligibility of articles for inclusion in the meta-analysis. Individuals who met the study enrolment criteria were included. Articles meeting the following criteria were included: C-reactive protein [MeSH Terms]) and acute pancreatitis [MeSH Terms]).

Synthesis of Findings: Data synthesis involved a narrative summary of pertinent study characteristics, methodologies employed, and key findings related to the efficacy of C-reactive protein in diagnosing acute pancreatitis. Owing to the anticipated heterogeneity in study designs, a qualitative approach was adopted, emphasising the unique contributions of each study to the overarching understanding of the effectiveness of CRP in predicting the severity of pancreatitis.

Ethical Considerations: As this review was based on an analysis of previously published studies, ethical approval was not required. All the included studies adhered to ethical standards, as outlined in their respective publications.

RESULTS

PRISMA Flow diagram



The literature search outlined above yielded 985 articles from designated online databases for this study. After eliminating duplicate articles from the automation tools and for other reasons, such as improper citations and articles in other languages, 104 records were considered. Fifty-nine articles were excluded because they were irrelevant to the studies;

ISSN (O): 2687-5365; ISSN (P): 2753-6556

after a detailed review of the titles and abstracts, only 45 were selected. The excluded articles covered various topics, including review articles; studies involving medical conditions unrelated to pancreatitis; studies that did not report relevant outcomes related to the accuracy, comparison, or laboratory-based investigations that lack direct applicability to pancreatitis patients; studies with insufficient data quality, including those with missing or unreliable data necessary for accurate assessment of the efficacy of C-reactive proteins in diagnosing acute pancreatitis prognosis; and those that did not meet the inclusion criteria. After a more detailed eligibility assessment, 11 articles were considered for qualitative and quantitative synthesis.

Table 1: Characteristics of included studies

Name of the author	Study type	Number of patients	Study findings
Kalpan M et al.,	Retrospective study	192	This study showed that the CRP/albumin ratio is an independent predictor of overall survival in patients with AP and is a low-cost, repeatable, and non-invasive systemic inflammation-based marker. In patients with AP, the CRP/albumin ratio, along with other prognostic scores and laboratory parameters, can potentially be used to predict the prognosis.[9]
Stirling AD et al.,	Retrospective study	337	When predicting the severity of AP, the interval change in CRP level is comparable to absolute CRP level. Based on this study, the most accurate way to predict severe pancreatitis is either an absolute value of >190 mg/dL at 48 h or an increase of >90 mg/dL from admission.[10]
Yılmaz EM et al.,	Retrospective study	264	The study proved that CRP is far better than RDW in predicting the prognosis of acute pancreatitis, drawing attention to CRP, which is already a well-known indicator of inflammation, as a potential marker that shows promise for use in assessing the prognosis in cases of AP.[11]
Zhao Y et al.,	Cohort study	284	A potential supplementary tool for assessing the prognosis and degree of severe acute pancreatitis (SAP) in patients with AP is CRP, which has the potential to predict death, pancreatic necrosis, organ failure, and SAP.[12]
Wang Y et al.,	Retrospective study	260	This study discovered that serum CRP levels directly reflect the gastrointestinal function of patients with SAP and are positively correlated with APACHE II, CTSI, and gastrointestinal failure scores.[13]
Liang Y et al.,	Cohort study	104	Tracking changes in CRP levels in peripheral blood for seven days to identify AP severity revealed that PCT in the deaths was substantially higher than that in the survivors at various time points, suggesting that tracking changes in CRP in peripheral blood was useful in tracking the prognosis of SAP patients.[14]
Xu XY et al.,	Cohort study	217	The study found that, due to its high accuracy, affordability, and ease of detection, CRP exhibits significant promise as a straightforward and dependable indicator of disease progression and as a screening tool for ICU admission, and can be used as a potential diagnostic biomarker to assess AP patients.[15]
Bouassida M et al.,	Cohort study	556	The study discovered that CRP was the only significant independent predictor of conversion in patients with AP and that it also possessed superior discriminative power in predicting pancreatitis prognosis when compared to WBC and NLR.[16]
Mitsunaga S et al.,	Cohort study	418	In terms of prognosis, systemic weakness, tumour burden, IL-6 levels, and CRP levels stratified the aggressiveness of advanced pancreatitis. The aggressiveness of advanced pancreatitis can be determined by measuring C-reactive protein levels.[17]
Bhatia M et al.,	Prospective study	50	The study findings indicate that patients with milder diseases and fewer complications had lower CRP levels, whereas those with more complications had higher values. Fifty hours after the stimulus, or two–three days after peaking, C-reactive protein typically increases. Between 67 and 100% of pancreatic necrosis was detected at values higher than 120 mg/l.[18]
Dogra V et al.,	Prospective observational study	50	Acute pancreatitis (AP) is a potentially fatal condition that exhibits a broad range of clinical manifestations. Diagnostic markers, such as pancreatic enzymes like lipase and amylase, have not performed well as prognostic indicators. Promising results have been observed in previous studies that have used CRP as a prognostic marker. CRP readings can provide early information about ongoing inflammatory processes.[19]

DISCUSSION

According to the evidence we collected, an increase in CRP level can be used as a major diagnostic predictor for the prognosis of pancreatitis.

Acute pancreatitis (AP) is an inflammatory disease with widely variable severity, ranging from mild cases with low mortality to severe cases with high mortality. Some biomarkers, such as procalcitonin (PCT) and interleukin 6 (IL-6), have been studied as possible early predictors of disease severity; however, they are not routinely used in hospitals. The gold standard remains C-reactive protein, which has a cut-off value of 150 mg/mL 48 hours after the disease onset.[20]

During the acute phase response, the release of pro-inflammatory cytokines such as TNFα, IL-6, and IL-8 triggers the production of CRP by the liver. A CRP level greater than 150 mg/dL within 48 h of admission is the threshold that is widely recognised as a predictor of severe acute pancreatitis. However, it should be mentioned that this number was determined in cases where severe pancreatitis would have resulted from local complications and temporary (< 48 h) organ failure. Stirling et al. reported that >190 mg/dL was the ideal absolute CRP level to predict severe disease.[10]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Among these biomarkers, CRP is the most representative and widely used marker that accurately represents the systemic inflammatory cascade reactions and protective immune responses of the body in clinical settings. Lower CRP levels can be a sign of enhanced systemic inflammatory response or weakened host immune status. Variations in CRP levels can serve as useful indicators of immunological-inflammatory dynamics. According to a study by Xu XY et al., CRP at hospitalization and other scoring methods like SOFA, BISAP, and modified Marshall scores showed similar efficacy in predicting the course of AP disease.[15]

An increased CRP concentration of > 100 mg/l, as a stand-alone prognostic marker, suggests that the course of acute pancreatitis is complicated. While elevated CRP levels are sensitive to acute pancreatitis, other inflammatory conditions must be ruled out because they are non-specific. According to Bhatia et al., patients with higher CRP levels at admission had higher rates of complications. This led the researchers to the conclusion that patients with milder diseases typically have lower CRP levels and fewer complications, while patients with more severe diseases typically have higher values.[18]

From the results we obtained, it is evident that C-reactive protein is an effective biomarker for identifying the prognosis of acute pancreatitis even at earlier stages, which will be very useful in assessing and treating the disease.

CONCLUSION

Our systematic review showed an absolute correlation between CRP level and the prognosis of pancreatitis. From the available data, we found C-reactive protein (CRP) levels above 150 mg/mL within 48 h of admission, which indicated severe pancreatitis. However, these CRP values cannot be used as valuable tools within the initial 24 h. This phenomenon should be accurately evaluated to fix standard values and ascertain intermediate- and long-term outcomes.

REFERENCES

1. Gomatos IP, Xiaodong X, Ghaneh P, Halloran C, Raraty M, Lane B, et al. Prognostic markers in acute pancreatitis. Expert Rev Mol Diagn 2014;14:333–46. https://doi.org/10.1586/14737159.2014.897608.
2. Deherkar JA, Pandey A, Deshmukh S. C-reactive protein levels in acute pancreatitis and its clinical significance. Int Surg J 2019;6:3328. https://doi.org/10.18203/2349-2902.isj20194074.
3. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. JAMA 2004;291:2865–8. https://doi.org/10.1001/jama.291.23.2865.
4. Bhatia M, Wong FL, Cao Y, Lau HY, Huang J, Puneet P, et al. Pathophysiology of acute pancreatitis. Pancreatology 2005;5:132–44. https://doi.org/10.1159/000085265.
5. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med 1999;17:1019–25. https://doi.org/10.1016/s0736-4679(99)00135-3.
6. Puolakkainen P, Valtonen V, Paananen A, Schröder T. C-reactive protein (CRP) and serum phospholipase A2 in the assessment of the severity of acute pancreatitis. Gut 1987;28:764–71. https://doi.org/10.1136/gut.28.6.764.
7. Werner J, Hartwig W, Uhl W, Müller C, Büchler MW. Useful markers for predicting severity and monitoring progression of acute pancreatitis. Pancreatology 2003;3:115–27. https://doi.org/10.1159/000070079.
8. Imamura T, Tanaka S, Yoshida H, Kitamura K, Ikegami A, Takahashi A, et al. Significance of measurement of high-sensitivity C-reactive protein in acute pancreatitis. J Gastroenterol 2002;37:935–8. https://doi.org/10.1007/s005350200157.
9. 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;16:424–30. https://doi.org/10.1016/s1499-3872(17)60007-9.
10. 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 2017;19:874–80. https://doi.org/10.1016/j.hpb.2017.06.001
11. Yılmaz EM, Kandemir A. Significance of red blood cell distribution width and C-reactive protein/albumin levels in predicting prognosis of acute pancreatitis. Ulus Travma Acil Cerrahi Derg 2018;24:528–31. https://doi.org/10.5505/tjtes.2018.98583.
12. 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 2022;9:1026604. https://doi.org/10.3389/fsurg.2022.1026604.
13. Wang Y, Li L. Predicative values of C-reactive protein for the therapeutic effects of ulinastatin combined with somatostatin in severe acute pancreatitis and for the severity of gastrointestinal failure. Exp Ther Med 2018;16:3165–71. https://doi.org/10.3892/etm.2018.6577
14. Liang Y, Zhao X, Meng F. Procalcitonin, C-reactive protein, and neutrophil ratio contribute to the diagnosis and prognosis of severe acute pancreatitis. Iran J Public Health 2019;48:2177–86. https://doi.org/10.18502/ijph.v48i12.3548.
15. Xu XY, Gao Y, Yue CS, Tang YJ, Zhang ZJ, Xie FJ, et al. Predictive and Prognostic Potentials of Lymphocyte-C-Reactive Protein Ratio Upon Hospitalization in Adult Patients with Acute Pancreatitis. J Inflamm Res 2024:1659–69. https://doi.org/10.2147/JIR.S450587
16. Bouassida M, Zribi S, Krimi B, Laamiri G, Mroua B, Slama H, et al. C-reactive protein is the best biomarker to predict advanced acute cholecystitis and conversion to open surgery. A prospective cohort study of 556 cases. J Gastrointest Surg 2020;24:2766–72. https://doi.org/10.1007/s11605-019-04459-8.
17. Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Okuyama H, et al. C-reactive protein level is an indicator of the aggressiveness of advanced pancreatic cancer. Pancreas 2016;45:110–6. https://doi.org/10.1097/MPA.0000000000000465.
18. Bhatia M, Nirhale D, Athavale V, Calcuttawala M, Kale A, Sankhe M. C-reactive protein with sequential organ failure assessment score: Valuable parameters in managing acute pancreatitis. Trop J Med Res 2014;17:86. https://doi.org/10.4103/1119-0388.140423.
19. Dogra V, Peer JA, Gilkar IA, Mushtaq U. Role of C-reactive protein in acute pancreatitis: an observational study in a tertiary care centre. Int Surg J 2022;9:559. https://doi.org/10.18203/2349-2902.isj20220372.
20. Staubli SM, Oertli D, Nebiker CA. Laboratory markers predicting severity of acute pancreatitis. Crit Rev Clin Lab Sci 2015;52:273–83. https://doi.org/10.3109/10408363.2015.1051659.

ISSN (O): 2687-5365; ISSN (P): 2753-6556