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Early Serum Biomarkers for Severity Stratification in Patients with Acute Pancreatitis: A Review

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Abstract

Roughly one patient in five with acute pancreatitis develops severe disease, and mortality in that group approaches thirty per cent. Identifying them on the first day is the point of severity stratification. Decades of biomarker work have produced a large literature and, on the evidence reviewed here, no marker that clearly outperforms a routine blood urea nitrogen measurement.

Objectives: *To review the published evidence on early serum biomarkers for severity stratification in acute pancreatitis: what C-reactive protein, procalcitonin and the cytokines achieve, how they compare with routine laboratory values and with established multifactor scores, and why the timing of measurement determines the answer.*

Material and Methods: *Narrative review of prospective cohorts, comparative accuracy studies, pooled analyses and consensus classifications indexed in PubMed and the major gastroenterology and critical care journals. Studies were eligible if they reported the accuracy of a serum marker or clinical score for predicting severity, organ failure, infected necrosis or mortality in a defined population with acute pancreatitis. No new patient data were generated; every estimate quoted is one published by the original investigators.*

Results: *In 410 prospectively enrolled patients, the rise in blood urea nitrogen at 24 hours predicted mortality with an area under the curve of 0.842 and persistent multiorgan failure at 0.828, comparable to the BISAP score (0.836 and 0.850) and better than APACHE-II (0.756 and 0.741). For severe pancreatitis specifically, BISAP outperformed both, at 0.873 against 0.756 for the urea rise and 0.761 for APACHE-II. Rise in urea was the only variable independently associated with mortality on multivariable analysis, with an odds ratio of 12.7 (95% CI 4.2-16.6). C-reactive protein has a conventional threshold of 150 mg/L at 48 hours, but its discrimination is poor before 72 hours and improves substantially only afterwards, by which time the clinical question has usually answered itself.*

Conclusion: *The constraint in this field is timing rather than the choice of analyte. The inflammatory markers with the best reported accuracy become informative at 48 to 72 hours, while the decision they are meant to inform is made on admission. Routine values available within the first day perform as well as more elaborate alternatives and should be used in preference to waiting.*

Abbreviations: *AP – Acute Pancreatitis, SAP – Severe Acute Pancreatitis, BUN – Blood Urea Nitrogen, CRP – C-Reactive Protein, PCT – Procalcitonin, IL-6 – Interleukin 6, BISAP – Bedside Index of Severity in Acute Pancreatitis, APACHE-II – Acute Physiology and Chronic Health Evaluation II, CTSI – Computed Tomography Severity Index, PASS – Pancreatitis Activity Scoring System, HAPS – Harmless Acute Pancreatitis Score, AUC – Area Under the Receiver Operating Characteristic Curve, POF – Persistent Organ Failure.*

Keywords: *Acute Pancreatitis; Severity Stratification; C-Reactive Protein; Blood Urea Nitrogen; BISAP*

Introduction

Acute pancreatitis is among the most common gastrointestinal reasons for emergency admission, and its course is bimodal. Most patients recover without incident; a minority develop organ failure, necrosis and death [1,2]. Severe disease occurs in close to twenty per cent of cases and carries mortality in the region of thirty per cent (Figure 2) [3].

Severity is defined retrospectively. The revised Atlanta classification grades an episode as mild, moderately severe or severe according to whether organ failure occurs and whether it persists beyond 48 hours [4], which is a sound definition for research and useless for the decision a clinician faces on admission. Its predecessor had the same structure [5].

The practical need is therefore for something measurable in the first hours that predicts what the Atlanta criteria will show two days later. Multifactor scores were built for this purpose, from APACHE-II borrowed from intensive care [6] through pancreatitis-specific instruments [7,8,9,10], and a parallel literature has pursued single serum markers [11,12].

This review examines what those markers achieve, and argues that the field's central difficulty is not which analyte is measured but when it becomes informative.

Material and Methods

Search strategy: PubMed and the archives of the major gastroenterology, surgical and critical care journals were searched for studies of severity prediction in acute pancreatitis. Search terms combined acute pancreatitis with severity prediction, C-reactive protein, procalcitonin, interleukin-6, blood urea nitrogen, haematocrit, albumin, BISAP, APACHE-II, Ranson and revised Atlanta classification. Reference lists of retrieved cohorts and reviews were screened by hand.

Eligibility: Studies were included if they reported the accuracy of a serum marker or clinical score for predicting severity, persistent organ failure, infected necrosis or mortality in a defined population with acute pancreatitis, or if they defined the severity classification in current use. Studies reporting markers of established infection rather than early severity are cited separately and identified as such.

Data extraction and handling: Design, sample size, timing of measurement, outcome predicted, cutoff and reported accuracy estimates were extracted as published. Timing is reported alongside every accuracy figure, because in this field a marker's apparent performance depends primarily on how late it is measured. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 and 2 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

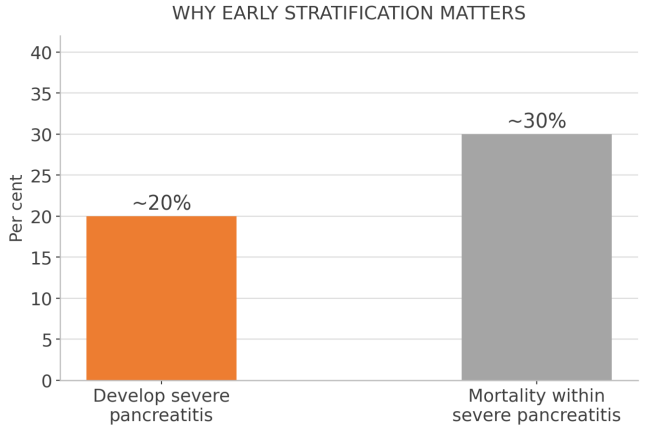

Figure 2: Proportion of patients with acute pancreatitis developing severe disease, and mortality within that group [3]

Results

A routine value performs as well as the scores: The most direct comparison prospectively enrolled 410 patients and compared the change in blood urea nitrogen over 24 hours against BISAP, APACHE-II, haematocrit and its variation, and C-reactive protein. For predicting mortality, the rise in urea achieved an area under the curve of 0.842, against 0.836 for BISAP and 0.756 for APACHE-II. For persistent multiorgan failure the figures were 0.828, 0.850 and 0.741 respectively (Figure 1) [3].

On multivariable analysis, the rise in urea was the only variable independently related to mortality, with an odds ratio of 12.7 (95% CI 4.2-16.6) [3]. The optimal thresholds were modest and clinically unremarkable: a rise in urea greater than 1.87 mg/dL over 24 hours, a haematocrit rise above 0.6 per cent, an admission haematocrit above 45 per cent and a BISAP score of two or more [3]. Earlier population-level work had already shown that serial urea measurement predicts in-hospital mortality, and that it does so better than serial haemoglobin [11].

For severe pancreatitis as an endpoint rather than death, the ordering changed: BISAP achieved 0.873, ahead of APACHE-II at 0.761 and the urea rise at 0.756 [3]. Which test is best therefore depends on which outcome is being predicted, and studies reporting a single headline figure obscure that.

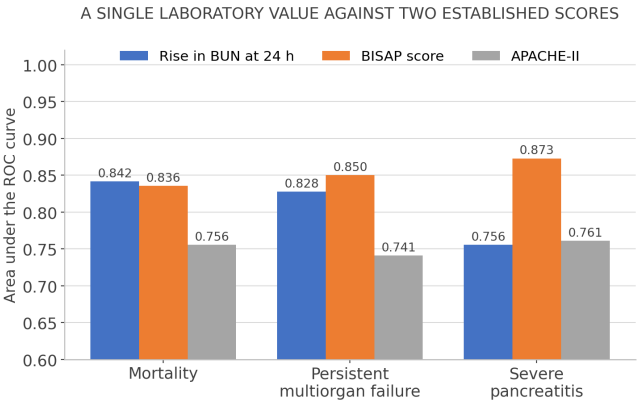

Figure 1: Discrimination of a 24-hour urea rise against two established scores, by outcome predicted, in 410 prospectively enrolled patients [3]

Study	n	Focus	Principal reported finding
Bradley 1993 [5]	—	Classification	First consensus severity classification
Brivet et al. 1999 [12]	—	Cytokines	Early sustained cytokine response, unpredictive of death
Wu et al. 2009 [11]	69 hospitals	Urea	Serial urea predicts in-hospital mortality
Banks et al. 2013 [4]	—	Classification	Revised Atlanta definitions in current use
Buxbaum et al. 2018 [10]	—	Activity score	PASS predicts clinical outcomes prospectively
Pando et al. 2021 [3]	410	Comparison	Urea rise AUC 0.842 for mortality; OR 12.7

Table 1: Principal studies reviewed, with focus and the finding as reported by the original investigators

C-reactive protein and the timing problem: C-reactive protein is the marker most often described as the standard, with a conventional threshold of 150 mg/L measured 48 hours after symptom onset [13]. The difficulty is structural rather than analytical. It is an acute-phase protein that takes more than 72 hours to peak, so a value drawn on admission carries little information and the threshold only becomes meaningful once the clinical course has largely declared itself.

The same timing effect appears when infection rather than severity is the endpoint. Within the first 72 hours after admission, pooled discrimination for infected necrosis was modest for C-reactive protein and for procalcitonin alike, improving markedly only after that point. Persistently high values of both are therefore informative about established infection, and neither is useful for the early triage decision [14]. Procalcitonin behaves similarly, rising faster than C-reactive protein but reflecting bacterial burden rather

than pancreatic injury.

When the question becomes infection: Once necrosis is established, the clinical question changes from how severe this will be to whether the necrosis is infected, and that determines whether intervention is needed. Treatment strategy has long been stratified by infection status [18], and operative series distinguish sterile from infected necrosis explicitly [19]. This is the setting in which persistently raised C-reactive protein and procalcitonin do carry information, and it is a later and different decision from the one severity scores address [14].

Cytokines measure the process but not the outcome: Interleukin 6 and related cytokines rise early and are mechanistically closer to the pathology than any acute-phase protein. Reported accuracy for distinguishing moderately severe and severe disease is high in pooled series. But the honest finding in this literature is an old one: a study characterising the pro- and anti-inflammatory cytokine response in severe disease found it early and sustained, and nonetheless unpredictive of death [12].

That result has not been overturned so much as bypassed. Cytokine assays remain outside routine practice in most hospitals, turnaround is slow relative to the decision window, and the marker that correlates best with the biology is not necessarily the one that best predicts the outcome [12,13].

Other routine values: Several inexpensive measurements carry independent information, and hypoalbuminaemia carries prognostic weight across acute illness generally [20]. Serum albumin is independently associated with persistent organ failure [15], and haematocrit and its change over 24 hours reflect the intravascular depletion that precedes organ failure [3,11]. Fluid management interacts with these measures, since the choice of resuscitation fluid itself alters systemic inflammation [16], which means a marker drawn after resuscitation reports partly on the treatment rather than the disease.

The scoring systems built from such variables have been compared repeatedly, with BISAP, APACHE-II and Ranson-type indices performing broadly similarly and no instrument emerging as clearly superior across outcomes [7,8,9]. Simple algorithms designed to identify patients who will not become severe, rather than those who will, take the opposite and arguably more tractable approach [17].

Marker	Informative from	Principal limitation
Rise in blood urea nitrogen	24 hours	Better for mortality than for severity grade [3,11]
Haematocrit and its change	24 hours	Confounded by fluid resuscitation [3,16]
Serum albumin	Admission	Reflects baseline state as well as disease [15]
C-reactive protein	48-72 hours	Too slow for the admission decision [13,14]
Procalcitonin	After 72 hours	Reports infection rather than severity [14]
Interleukin 6	Admission	Not routinely available; unpredictive of death [12]

Table 2: When each marker becomes informative, and the limitation reported for it

Discussion

The evidence supports a conclusion that is unglamorous and reasonably firm. A change in blood urea nitrogen over the first 24 hours predicts death and persistent organ failure about as well as a purpose-built pancreatitis score and better than a general intensive care score, and it requires no additional test [3,11]. For a marker that is already measured in every patient, that is a strong result, and it sets the bar any new biomarker must clear.

The reason the more sophisticated markers have not cleared it is timing. C-reactive protein is described as the standard at a 48-hour threshold [13], and pooled data show that both it and procalcitonin discriminate poorly before 72 hours and well afterwards [14]. A test that becomes accurate at 72 hours is not a triage test. By then the patient has either developed organ failure or has not, and the Atlanta classification can be applied directly [4].

Which outcome is being predicted

A recurring source of confusion is that severity, persistent organ failure and death are treated as interchangeable endpoints when the same test ranks differently against each. In the comparison reviewed here, the urea rise was the best predictor of mortality and among the worst of the severity grade, while BISAP showed the reverse pattern [3]. A study reporting that one test outperformed another is uninterpretable without knowing which endpoint was used.

There is also a case for reversing the question. Identifying patients who will not develop severe disease, and can therefore be managed on a general ward, is a different and easier prediction than identifying those who will, and algorithms built for that purpose exist [17].

Study limitations

The limitations belong to the underlying literature. The principal comparative cohort was single-centre and included 410 patients, with cutoffs derived within the same dataset by the Youden index, which inflates apparent accuracy [3]. Severity classification changed between 1993 and 2012, so studies published on either side of that boundary are not directly comparable [4,5]. Timing of sampling is inconsistently reported, and a marker's apparent accuracy depends heavily on it [13,14]. Fluid resuscitation, which alters both haematocrit and inflammatory markers, differs between centres and eras [16]. Studies of infected necrosis use different reference standards for infection, from gas on imaging to culture, which are not equivalent [14].

Two gaps deserve naming. No study reviewed here tested whether acting on an early severity prediction, rather than simply making it, changes any patient outcome. And no comparative study reports accuracy stratified by aetiology, although biliary, alcoholic and hypertriglyceridaemic pancreatitis differ in tempo and in the baseline value of several of the markers concerned [1,2].

Conclusion

Severity stratification in acute pancreatitis is a timing problem disguised as a biomarker problem. The inflammatory markers with the best reported discrimination, C-reactive protein and procalcitonin, become informative at 48 to 72 hours, after the clinical course has largely declared itself. Cytokines rise early but were shown a quarter of a century ago to be unpredictive of death, and remain outside routine practice. What performs is mundane: the change in blood urea nitrogen over the first 24 hours matched a purpose-built score for predicting mortality and persistent organ failure and beat a general critical care score, at no extra cost. Reporting which endpoint a prediction refers to, and when the sample was drawn, would do more for this literature than another candidate analyte.

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Conflict of Interest

No author has any competing interest arising from this work.

Ethics Statement

Nothing here rests on new data. The article draws solely on studies that are already published, involved no recruitment, and so required no ethical review.

References

1. Whitcomb DC. "Acute pancreatitis". N Engl J Med 354(2006):2142-2150.
2. Forsmark CE, Baillie J. "AGA Institute technical review on acute pancreatitis". Gastroenterology 132(2007):2022-2044.
3. Pando E, Alberti P, Mata R, Gomez MJ, Vidal L, Cirera A, Dopazo C, Blanco L, Gomez C, Caralt M, Balsells J, Charco R. "Early changes in blood urea nitrogen (BUN) can predict mortality in acute pancreatitis: comparative study between BISAP score, APACHE-II, and other laboratory markers: a prospective observational study". Can J Gastroenterol Hepatol (2021):6643595.
4. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. "Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus". Gut 62(2013):102-111.
5. Bradley EL 3rd. "A clinically based classification system for acute pancreatitis". Arch Surg 128(1993):586-590.
6. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. "APACHE II: a severity of disease classification system". Crit Care Med 13(1985):818-829.
7. 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 57(2008):1698-1703.
8. Wang AJ, Xu S, Hong JB, Liu P, Xia L, Zhu Y, He WH, Chen YX, Lü NH. "The comparison of different clinical scoring systems for predicting prognosis in acute pancreatitis based on the revised Atlanta classification". Zhonghua Nei Ke Za Zhi 52(2013):668-671.
9. Luo X, Wang J, Wu Q, Peng L, Yang G, Li X, et al. "A modified Ranson score to predict disease severity, organ failure, pancreatic necrosis, and pancreatic infection in patients with acute pancreatitis". Front Med (Lausanne) 10(2023):1145471.
10. Buxbaum J, Quezada M, Chong B, Gupta N, Yu CY, Lane C, et al. "The Pancreatitis Activity Scoring System predicts clinical outcomes in acute pancreatitis: findings from a prospective cohort study". Am J Gastroenterol 113(2018):755-764.
11. Wu BU, Johannes RS, Sun X, Conwell DL, Banks PA. "Early changes in blood urea nitrogen predict mortality in acute pancreatitis". Gastroenterology 137(2009):129-135.
12. Brivet FG, Emilie D, Galanaud P. "Pro- and anti-inflammatory cytokines during acute severe pancreatitis: an early and sustained response, although unpredictable of death. Parisian Study Group on Acute Pancreatitis". Crit Care Med 27(1999):749-755.
13. Sternby H, Hartman H, Johansen D, Thorlacius H, Regnér S. "Laboratory markers predicting severity of acute pancreatitis". Scand J Gastroenterol 50(2015):1230-1237.
14. Pápai M, Benczúr B, Farkas N, Er■ss B, Hegyi P, et al. "Persistently high procalcitonin and C-reactive protein are good predictors of infection in acute necrotizing pancreatitis: a systematic review and meta-analysis". Int J Mol Sci 25(2024):1273.
15. Hong W, Lin S, Zippi M, Geng W, Stock S, et al. "Serum albumin is independently associated with persistent organ failure in acute pancreatitis". Can J Gastroenterol Hepatol (2017):5297143.
16. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. "Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis". Clin Gastroenterol Hepatol 9(2011):710-717.
17. Lankisch PG, Weber-Dany B, Hebel K, Maisonneuve P, Lowenfels AB. "The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease". Clin Gastroenterol Hepatol 7(2009):702-705.
18. Büchler MW, Gloor B, Müller CA, Friess H, Seiler CA, Uhl W. "Acute necrotizing pancreatitis: treatment strategy according to the status of infection". Ann Surg 232(2000):619-626.
19. Rodriguez JR, Razo AO, Targarona J, Thayer SP, Rattner DW, Warshaw AL, Fernandez-del Castillo C. "Debridement and closed packing for sterile or infected necrotizing pancreatitis". Ann Surg 247(2008):294-299.
20. Allison SP, Lobo DN. "The clinical significance of hypoalbuminaemia". Clin Nutr 43(2024):909-914.

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