Research Article

Interleukin-6: An Early Predictive Marker for Severity of Acute Pancreatitis

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Abstract

Background and Aims: Interleukin (IL)-6, IL-8, IL-10, and C-reactive protein (CRP) have been evaluated for predicting outcomes of acute pancreatitis. However, there is considerable variation in their performance among different studies. We evaluate their accuracy in predicting progression to severe pancreatitis. **Materials and Methods:** Serum IL-6, IL-8, IL-10, and CRP levels were measured within 24 h of admission in forty patients of clinically predicted severe acute pancreatitis (SAP). Persistent organ failure (>48 h) defined SAP. The performance of inflammatory markers was evaluated in predicting the progression of pancreatitis. **Results:** IL-6 ≥28.90 pg/mL had a sensitivity of 62.86%, specificity of 80%, positive predictive value (PPV) of 95.65%, LR+ of 3.1429, LR− of 0.4643, and diagnostic odds ratio (DOR) of 6.7692; IL-8 ≥88.70 pg/mL had a sensitivity of 60%, specificity of 80%, PPV of 95.45%, LR+ of 3.000, LR− of 0.5000, and DOR of 6.000; IL-10 ≤5.70 pg/mL had DOR of 0.2647, sensitivity of 51.43%, specificity of 20%, PPV of 81.82%, LR+ of 0.6429, and LR− of 2.4286. CRP ≥110.00 mg/L had DOR of 2.3636, sensitivity of 37.14%, specificity of 80%, PPV of 92.86%, LR+ of 1.8571, and LR of 0.7857. **Conclusions:** IL-6 ≥28.90 pg/mL, measured within 48 h of onset is the best among the tested biomarkers in this study for predicting the progression to severe pancreatitis.

Keywords: Inflammatory cytokines, interleukins, predictive markers, severe acute pancreatitis

Introduction

According to the Atlanta guidelines, a case of severe acute pancreatitis (SAP) is defined as one with features of acute pancreatitis and with persistent organ failure lasting beyond 48 h.[1] This essentially makes the diagnosis of SAP a retrospective one, by which time a critical window for early intervention may be lost. To enable the early prediction of clinical outcomes of pancreatitis, multiple scoring systems such as Ranson,[2-4] Glasgow,[5] and APACHE II,[6] in addition to novel biochemical markers such as Interleukin (IL)-6, IL-8 and C-reactive protein (CRP), and IL-10 have been described. The Ranson score uses 11 variables, collected at admission and 48 h after admission. The Glasgow score includes nine variables. Both have predictive values of 71%–88%.[7,8] The APACHE score is derived from 12 variables and can be repeated at any time during the clinical course of the patient.[9]

The existing scoring systems require a large number of clinical and biochemical parameters, making them cumbersome to perform. Hence, a search for a single marker which might allow for earlier, easier, and more accurate prediction of SAP still continues, especially in the face of emerging treatment modalities whose efficacy hinges on the early intervention. Few randomized studies have shown that patients with SAP benefit from early, aggressive prophylactic antibiotic therapy, as opposed to mild pancreatitis which is usually self-limited and resolves with basic fluid and supportive management.[10,11] Early endoscopic sphincterotomy (within 24–48 h of admission) is indicated in patients with severe acute gallstone-induced pancreatitis.[12] Early treatment with protease inhibitors has been shown to be of value in a meta-analysis[13] and also as a prophylactic treatment to prevent endoscopic retrograde cholangiopancreatography-induced acute pancreatitis. If the development of SAP can be predicted before the development of the multiple organ dysfunction syndrome, the early initiation of aggressive therapy might prevent its development. Emerging therapies such as cytokine inhibitors are targeting mediators of

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inflammation and hence studying the crucial factors involved in the progression of SAP has become imperative.

This study aims to evaluate the accuracy of early measurement of inflammatory markers, IL-6, IL-8, IL-10, and CRP in predicting outcomes in patients clinically suspected to have SAP.

Materials and Methods

Study design

This was a cohort study where the efficacy of early measurement of serum IL-6, IL-8, and IL-10 and CRP levels for predicting the progression to SAP was calculated.

Study participants

Study population

All in-patients of acute pancreatitis admitted to our hospital.

Sample size calculation

A purposive method of sampling was used.

Inclusion criteria

1. An 18–60-year-old patients of either sex, diagnosed with acute pancreatitis. The diagnosis of acute pancreatitis was established by the criteria set by the Atlanta guidelines,[1] namely, any two of the following three criteria to be fulfilled:
   a. Clinical features suggestive of acute pancreatitis
   b. Serum amylase or lipase levels elevated to more than three times the upper limit of normal
   c. Ultrasonography (USG) or computed tomography showing features of acute pancreatitis.
2. Onset of pain to be within 24 h before admission to the hospital
3. Patients predicted to develop SAP by the following criteria on admission:[1]
   Patients fulfilling the diagnostic criteria for a systemic inflammatory response syndrome (SIRS), defined by the presence of two or more of the following:[1]
   i. Rectal temperature >38°C (100.4F) or <36°C (96.8F)
   ii. Heart rate >90 beats/min
   iii. Respiratory rate >20/min or $PaCO_2$ <32 mmHg
   iv. White blood cell count >12,000/mm^3, <4000/mm^3, or >10% bands.

Exclusion criteria

1. Patients with known immunodeficient status
2. Primary hypertriglyceridemia
3. On long-term cyclooxygenase inhibitors (more than 3 months)
4. Severe cardiac disease
5. Preexisting hepatic disorders (total bilirubin >1.5 times the upper limit of normal)
6. Psychiatric disorders
7. Preexisting renal compromise (serum creatinine >2.0 mg/dl)
8. Received parenteral nutrition within 2 weeks of the study.

Patient screening and selection

At initial screening, the diagnosis of acute pancreatitis and presence of SIRS was confirmed on clinical, biochemical (serum lipase, renal function tests, liver function tests, serum electrolytes, complete hemogram, arterial blood gas analyses), and radiological investigations (USG, contrast-enhanced computed tomography abdomen). After verifying the absence of any exclusion criteria, such patients, with predicted severe acute pancreatitis (PSAP) were inducted into the trial after obtaining a written, informed consent.

Study duration

This study was conducted over a period of 17 months.

Laboratory protocol

Venous blood samples were collected within 24 h of admission from all patients for estimation of serum levels of IL-6, IL-8, IL-10, and CRP. Samples for IL-6, IL-8, and IL-10 were transported to the laboratory in an ice-box. Estimation of levels of cytokines was done in a laboratory having run more than 100 tests of inflammatory cytokines and thus with established internal controls. IL-6, IL-8, and IL-10 levels were measured on the Siemens IMMULITE 1000, by solid phase, enzyme labeled chemiluminescent sequential immunometric assay.

Patient monitoring and standard of care

Marshall Scores of all patients were calculated on day 0 and day 3 to assess for organ failure. Patients having a Marshall score of 2 or more on day 0 as well as day 3 were diagnosed to have persistent organ failure for >48 h, thereby confirming the progression to SAP. Marshall score was assessed by the following parameters:[14]

a. PaO_2/FiO_2
b. Serum creatinine (mg/dL)
c. Systolic blood pressure
d. Arterial pH.

All patients received antibiotic and supportive therapy as per standard protocols for the management of SAP.

Study end points

Primary outcome variables

The percentage of patients progressing from PSAP to SAP, defined by persistent organ failure, i.e., organ failure for >48 h after admission; organ failure defined by the modified Marshall score, measured on day 0 and day 3 of admission. Patients with a modified Marshall score of 2 or more on day 0 and on day 3 were considered to have persistent organ failure and thus progressed to SAP.

Secondary outcome variables

Secondary outcome variables were sensitivity, specificity, positive predictive value (PPV), accuracy, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) of levels of IL-6, IL-8, IL-10, and CRP for progression to SAP.

Statistical analysis

Receiver operating characteristic (ROC) curve and cutoff analysis were performed on the data to calculate cutoff levels

of the inflammatory markers with the highest sensitivity, specificity, PPV, accuracy, positive likelihood ratio, negative likelihood ratio, and DOR for progression to SAP. All the statistical analyses were done using the Number Cruncher Statistical System (NCSS)[11] data analysis software (Copyright 2016 NCSS, LLC All Rights Reserved).

Statement of ethics

The study was conducted over a period of 17 months in a publicly funded tertiary care center in Mumbai as per the International Conference on Harmonization good clinical practice standards. Approval was obtained from the Institutional Ethics Committee.

Results

Forty consecutive patients of PSAP were included in the study.

Mean age of patients in the study was 40.1 (13.28) years. 35 (87.5%) were males and 5 (12.5%) were females.

Of the forty patients included in the study, 35 (87.5%) had persistent organ failure beyond 48 h after admission and were classified as having progressed to SAP.

Interleukin-6 [Table 1 and Figure 1]

IL-6 levels ranged from 2 to 452 pg/mL with median levels of 30.3 pg/mL (95% confidence interval [CI]: 21.8–54.2 pg/mL).

ROC curve analysis revealed a cutoff level of ≥28.90 pg/mL to have the highest DOR of 6.7692 for predicting the progression to SAP.

Sensitivity of IL-6 level ≥28.90 pg/mL was 62.86%, specificity was 80%, PPV was 95.65%, and accuracy was 65% for predicting progression to SAP. Positive likelihood ratio was 3.1429 and negative likelihood ratio was 0.4643.

Interleukin-8 [Table 1 and Figure 1]

IL-8 levels ranged from 5 to 7500 pg/mL with median levels of 95.75 pg/mL (95% CI: 59.9–165 pg/mL).

ROC curve analysis revealed a cutoff level of ≥88.70 pg/mL to have the highest DOR of 6.000 for predicting the progression to SAP.

Sensitivity of IL-6 level ≥88.70 pg/mL was 60%, specificity was 80%, PPV was 95.45%, and accuracy was 62.5% for predicting progression to SAP. Positive likelihood ratio was 3.000 and negative likelihood ratio was 0.5000.

Interleukin-10 [Table 1 and Figure 2]

IL-10 levels ranged from 5 to 393 pg/mL with median levels of 5.2 pg/mL (95% CI: 5–8.9 pg/mL).

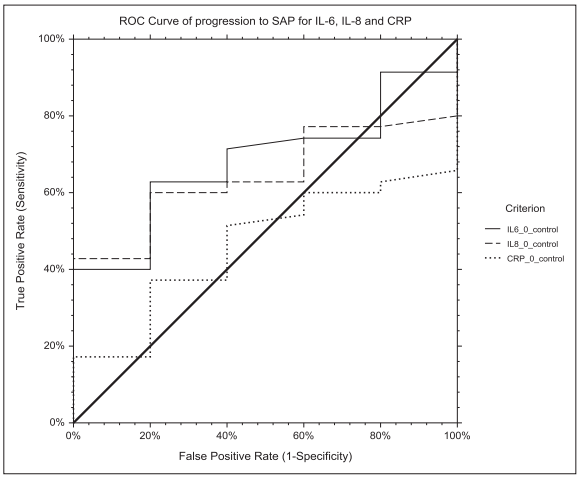

Figure 1: Receiver operating characteristic curve of progression to severe acute pancreatitis for interleukin-6, interleukin-8 and C-reactive protein

Table 1: Evaluation of interleukin-6, interleukin-8, interleukin-10 and C-reactive protein as predictors of progression to severe acute pancreatitis

Marker with cut-off level	True positives	False positives	False negatives	True negatives	Sensitivity	Specificity	Positive Predictive value	Accuracy	LR+	LR-	DOR (LR+/LR-)
IL-6 ≥ 4.80pg/mL	32	4	3	1	91.43%	20.00%	88.89%	82.50%	1.1429	0.4286	2.6667
IL-6 ≥ 21.80pg/mL	25	2	10	3	71.43%	60.00%	92.59%	70%	1.7857	0.4762	3.7500
IL-6 ≥ 28.90pg/mL	22	1	13	4	62.86%	80.00%	95.65%	65%	3.1429	0.4643	6.7692
IL-6 ≥ 36.10pg/mL	18	1	17	4	51.43%	80.00%	94.74%	55%	2.5714	0.6071	4.2353
IL-8 ≥ 40.40pg/mL	27	3	8	2	77.14%	40.00%	90.00%	72.50%	1.2857	0.5714	2.2500
IL-8 ≥ 67.60pg/mL	22	2	13	3	62.86%	60.00%	91.67%	62.50%	1.5714	0.6190	2.5385
IL-8 ≥ 88.70pg/mL	21	1	14	4	60.00%	80.00%	95.45%	62.50%	3.000	0.5000	6.0000
IL-8 ≥ 97.80pg/mL	19	1	16	4	54.29%	80.00%	95.00%	57.50%	2.7143	0.5714	4.7500
IL-10 ≤ 5.00pg/mL	16	4	19	1	45.71%	20.00%	80.00%	42.50%	0.5714	2.7143	0.2105
IL-10 ≤ 5.70pg/mL	18	4	17	1	51.43%	20.00%	81.82%	47.50%	0.6429	2.4286	0.2647
IL-10 ≤ 6.40pg/mL	18	5	17	0	51.43%	-	78.26%	45%	0.5143	-	-
CRP ≥ 38.00mg/L	34	5	1	0	97.14%	-	87.18%	85%	0.9714	-	-
CRP ≥ 78.00mg/L	18	2	17	3	51.43%	60.00%	90.00%	52.50%	1.2857	0.8095	1.5882
CRP ≥ 110.00mg/L	13	1	22	4	37.14%	80.00%	92.86%	42.50%	1.8571	0.7857	2.3636
CRP ≥ 121.00mg/L	10	1	25	4	28.57%	80.00%	90.91%	35.00%	1.4286	0.8929	1.6000

LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; DOR-: Diagnostic Odds Ratio

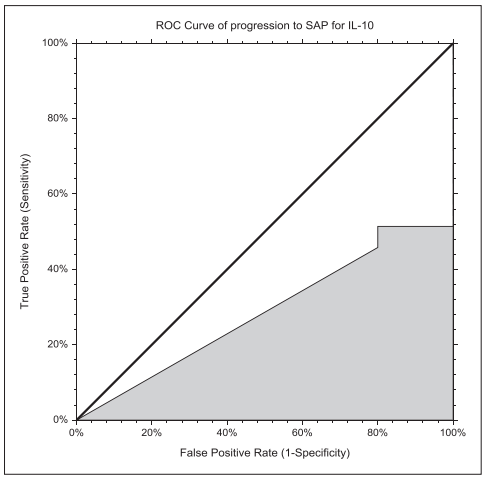

Figure 2: Receiver operating characteristic curve of progression to severe acute pancreatitis for interleukin-10

ROC curve analysis revealed a cutoff level of ≤5.70 pg/mL to have the highest DOR of 0.2647 for predicting the progression to SAP.

Sensitivity of IL-6 level ≤5.70 pg/mL was 51.43%, specificity was 20%, PPV was 81.82%, and accuracy was 47.50% for predicting progression to SAP. Positive likelihood ratio was 0.6429 and negative likelihood ratio was 2.4286.

C-reactive protein [Table 1 and Figure 1]

CRP levels ranged from 28 to 182 mg/L with a median level of 76 mg/L (95% CI: 56–110 mg/L).

ROC curve analysis revealed a cutoff level of ≥110.00 mg/L to have the highest DOR of 2.3636 for predicting the progression to SAP.

Sensitivity of CRP level ≥110.00 mg/L was 37.14%, specificity was 80%, PPV was 92.86%, and accuracy was 42.50% for predicting progression to SAP. Positive likelihood ratio was 1.8571 and negative likelihood ratio was 0.7857.

Discussion

In our study, IL-6 with cutoff at a level of ≥28.90 pg/mL proved to be the marker with the highest DOR (6.7692), positive likelihood ratio (3.1429), PPV (96.65%) for predicting the progression of pancreatitis from simple to severe form sensitivity for predicting the progression to SAP, however, is slightly lower at 62.86%, at this cutoff. Over the years, several studies have demonstrated elevated levels of IL-6 to be an excellent predictor of severity of acute pancreatitis,[15-18] however, there has been considerable variability between the cutoff levels reported in various studies. Cutoff levels of >130 U/mL showed a sensitivity and specificity of 100% and 71% respectively as reported by Heath *et al*.,[19] whereas Pezzilli *et al*. found the sensitivity, specificity, and PPV of IL-6 at a cutoff value of 2.7 pg/mL to be 100%, 86%, and 91% respectively.[20]

IL-8 was the next best marker after IL-6 in predicting the progression of patients to SAP, with a DOR of 6.000, a positive likelihood ratio of 3.000, a negative likelihood ratio of 0.5000, sensitivity of 60%, specificity of 80%, and PPV of 95.45% for a cutoff of ≥88.70 pg/mL when measured on the day of admission, however, in light of the efficacy of IL-6 as a predictive marker, the use for IL-8 as a predictor for severity is limited.

Our study showed IL-10 on day 0 to be an extremely poor marker for predicting the progression to SAP. IL-10 is an anti-inflammatory cytokine which inhibits the release of pro-inflammatory cytokines (i.e., IL-1 β, IL-6, and tumor necrosis factor-α) from monocytes/macrophages thus preventing subsequent tissue damage.[21-26] Studies have correlated lower levels of IL-10 with a higher severity of pancreatitis,[18,27,28] however, our study failed to reproduce these findings.

A widely accepted marker for severity of acute pancreatitis is CRP level of >150 mg/L,[19] however we found a cutoff level of even 110 mg/L to have a very low sensitivity for predicting severe pancreatitis, albeit having a PPV of over 90%. We would, therefore, be wary of using CRP as a marker for predicting the severity of acute pancreatitis. Fisic *et al*. demonstrated that CRP levels on admission did not reliably differentiate between severe and mild cases of acute pancreatitis, but reached statistical significance when measured on the 3rd day after onset.[29] This could be one of the reasons why CRP was not found to be an effective marker for severe pancreatitis in our study, since it was measured within 24 h of admission, without further repeat measurements. However, given our goal to identify a serological marker which would help predict severe pancreatitis as early as possible, CRP does not seem an attractive option.

Drawing on this experience, a study aiming to accurately assess the performance of inflammatory cytokines as predictive markers for SAP would need to have a large sample size with daily measurements of concentrations of inflammatory cytokines since disease onset, comparison with radiological scoring systems and correlation with mortality.

Conclusions

From this study, we conclude that IL-6 measured within 24–36 h of onset of pancreatitis, with a cutoff at a level of ≥28.90 pg/ml is the best inflammatory cytokine among those tested in this study for predicting the progression of acute pancreatitis from simple to severe form. On the other hand, IL-10 and CRP are not as effective in predicting severity of pancreatitis early in the course of the disease as they have often been reported to be.

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Conflicts of interest

There are no conflicts of interest.

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