

GASTROENTEROLOGY

Clinical significance of presence and extent of extrapancreatic necrosis in acute pancreatitisSurinder S Rana,* Vishal Sharma,* Ravi K Sharma,* Puneet Chhabra,* Rajesh Gupta[†] and Deepak K Bhasin*Departments of *Gastroenterology and [†]Surgery, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India**Key words**

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Author's contribution

- 1 Surinder S Rana: analysis and interpretation of the data, drafting of the article, and collection and assembly of data.
- 2 Vishal Sharma: drafting of the article, collection and assembly of data.
- 3 Ravi K Sharma: collection and assembly of data.
- 4 Puneet Chhabra: collection and assembly of data.
- 5 Rajesh Gupta: provision of study materials or patients.
- 6 Deepak K Bhasin: analysis and interpretation of the data, drafting of the article, and critical revision of the article for important intellectual content.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disorder of the pancreas and surrounding tissues that has varying severity.¹ It is usually mild in majority of the patients, but in up to 20% of the patients the attack may be severe leading on to a variety of local and systemic complications and significant morbidity and mortality.¹⁻³ The factors that determine the severity of AP have not been completely understood. Pancreatic necrosis (PN) has been shown to be one of the important determinants of poor prognosis.³⁻⁵ Studies have shown that majority of the patients who

Abstract

Background and Aim: Extrapancreatic necrosis (EPN) alone represents a subgroup of pancreatitis with better outcome than patients with pancreatic parenchymal necrosis (PN). However, data on clinical significance of EPN is limited, and significance of the extent of EPN is not known.

Methods: Two hundred thirteen patients (136 [63.8%] males; mean age: 39.8 ± 13.2 years) with acute pancreatitis were prospectively enrolled and followed up till recovery or death. Contrast-enhanced computed tomography of each patient was retrospectively evaluated for presence of PN and EPN, pleural effusion and ascites. EPN was termed extensive if it extended to paracolic gutters or pelvis.

Results: Twenty-one (9.9%) patients had interstitial pancreatitis, seven (3.3%) patients had PN alone, 48 (22.5%) patients had EPN alone, and 137 (64.3%) patients had combined PN and EPN. Patients with EPN alone had significantly higher frequency of organ failure than patients with interstitial pancreatitis. Compared with patients with EPN alone, the patients with combined necrosis had significantly higher frequency of pleural effusion (88.2% vs 75%), ascites (41% vs 20.8%), and need for intervention (32.6% vs 14.6%). Patients with extensive EPN (*n* = 57) had significantly higher frequency of pleural effusion, ascites, and multi-organ failure than those with limited EPN.

Conclusion: EPN alone should be considered as a separate category of acute pancreatitis as it has less severe course than PN but has more severe course than interstitial pancreatitis. Patients with extensive EPN in spite of having increased frequency of ascites, pleural effusion, and multi-organ failure had similar outcome as compared to patients with limited EPN.

develop organ failure as well as life threatening complications of AP have necrotizing pancreatitis.³⁻⁵

Necrotizing pancreatitis usually leads on to necrosis of both the pancreatic parenchyma as well as peripancreatic tissue.¹ PN is usually recognized on the computed tomography (CT) as a non-enhancing region in the pancreas, and it is commonly associated with varying amounts of extrapancreatic necrosis (EPN).⁵ EPN alone in the absence of PN has been recognized as a distinct entity by Howard and Wagner in 1989 and is usually defined as the necrosis of the peripancreatic tissue with a normally enhancing pancreatic gland on contrast-enhanced imaging studies.⁶⁻¹⁰

The prognostic significance of EPN is not clear as there is limited published literature on this entity.^{6–11} Available studies have suggested that patients with non-infected EPN alone have better prognosis than patients with non-infected PN, but worse prognosis than patients with mild interstitial pancreatitis.^{6–11} The EPN also varies in the extent with some patients having EPN limited to the peripancreatic area whereas others having extensive EPN involving the paracolic gutters and pelvis. To the best of our literature search, there is no information on the clinical significance of extent of EPN. We therefore conducted this prospective study to determine the clinical significance of presence and extent of EPN in patients with AP.

Methods

The present study was done at a large tertiary care teaching hospital in North India. The data of all the patients with AP seen in our unit during January 2012–December 2013 were prospectively collected. The diagnosis of AP was made on the basis of presence of two of the following three findings: abdominal pain consistent with AP, elevation in serum amylase, and/or lipase more than three times the upper limit of normal value and radiological evidence of AP.¹ The study was approved by the institutional ethics committee, and an informed written consent was obtained from the patients or relatives prior to inclusion in the study. We excluded patients who had underlying chronic pancreatitis, malignancy, or underwent contrast-enhanced CT (CECT) prior to 3 days or later than 10 days of onset of symptoms and patients in whom CECT was contraindicated (like pregnancy or renal failure).

Following inclusion in the study, the demographic, clinical, laboratory, and radiological data for all patients were collected, and the patients were followed up till recovery or death. The CECT of the abdomen was performed 72 h after the onset of symptoms. The CT films of the included patients were retrospectively evaluated for the presence of PN as well as EPN (see definitions later). The data collected included age, gender, etiology of pancreatitis, hematocrit, results of other laboratory investigations including liver and kidney function tests, electrolytes, serum amylase, lipase, and lipids. The details of outcomes vis-à-vis occurrence of local complications, organ failure (including multi-organ failure [MOF] and persistent organ failure [POF]), need for percutaneous, or endoscopic or surgical interventions for local complications and mortality. We compared various groups for outcomes, that is, occurrence of mortality, surgery, intervention, or organ failure.

Definitions. Interstitial and necrotizing pancreatitis as well as local complications were defined according to revised Atlanta classification.¹ PN was defined as focal or diffuse non-enhancement of pancreas on CECT whereas EPN was defined as extrapancreatic changes more than simple fat stranding (Fig 1).⁹ EPN alone was diagnosed when there were extrapancreatic changes as defined above with complete enhancement of the pancreatic parenchyma (Fig 1). PN alone was diagnosed when there was focal or diffuse non-enhancement of pancreas on CECT with no or minimal peripancreatic changes (Fig 1).⁵ Patients having both PN as well as EPN were diagnosed as having combined necrosis (Fig 1). The patients with no evidence of both pancreatic as well as EPN were diagnosed with interstitial pancreatitis. The

EPN was subclassified as limited and extensive: If the EPN was limited to peripancreatic tissue it was defined as limited EPN, whereas if it was extending along the paracolic gutters or into the pelvis it was termed as extensive EPN (Fig 1). Organ failure was described as presence of respiratory failure (partial pressure of oxygen in arterial blood (PaO₂)/Fraction of inspired oxygen (FiO₂) < 300), renal failure (serum creatinine > 1.8 mg/dL), or cardiovascular failure (blood pressure less than 90 mmHg and non-responsive to fluids).¹ Presence of involvement of more than one organ system was termed as MOF while if the organ failure persisted for > 48 h, it was labeled as POF.

Statistical analysis. The descriptive data were presented as percentages for categorical variables and mean ± SD for quantitative variables. The continuous variables were compared using Student's *t*-test whereas the categorical variables were compared using the chi-squared test. A *P*-value of < 0.05 was considered as significant.

Results

During the study period, 287 patients of AP were prospectively assessed for possible inclusion in the study, and 74 patients were excluded for various reasons (10 patients had an early CT, 53 patients underwent CT later than 10 days of onset of symptoms, and in 11 patients CT was not done). In the final analysis, 213 patients (136 [63.8%] males; mean age 39.81 ± 13.19 years) were included. The etiology of AP was alcohol in 100 (46.9%) patients, gallstone disease in 65 (30.6%), and others in 48 (22.5%) patients.

PN and EPN. Of the 213 patients, 21 (9.9%) patients had interstitial pancreatitis and 192 (90.1%) patients had necrotizing pancreatitis. Seven patients (3.3%) had PN alone, 48 patients (22.5%) had EPN alone, and 137 (64.3%) patients had both intra and EPN. Overall, 185 (86.8%) patients had EPN, and of these 30.8% (57/185) patients had extensive EPN and 69.2% (128/185) patients had limited EPN.

Clinical outcomes. Organ failure developed in 141 patients (66.2%). Of these 109 (51.2%) developed POF and 40 (18.8%) developed MOF. Thirty-three (15.5%) patients died whereas surgery and radiological percutaneous/endoscopic intervention was needed in 14 (6.6%) and 56 (26.3%) patients, respectively.

In comparison of patients with EPN alone (*n* = 48) with the patients having no pancreatic or EPN (*n* = 21) (interstitial pancreatitis), the patients with EPN alone had significantly higher frequency of organ failure (72.9% vs 23.8%, *P* < 0.001). The POF was higher in the EPN alone group (52.1% vs 14.3%) while the two groups were similar for MOF. The differences in mortality and need for intervention, although higher in the EPN alone group, did not achieve statistical significance (Table 1).

The comparison between the patients having combined necrosis with those having EPN necrosis alone suggested an increased frequency of pleural effusions (88.2% vs 75%, *P* = 0.036) and ascites (41% vs 20.8%, *P* = 0.015) in the former group. However, the two groups did not differ vis-à-vis the occurrence of organ failure, POF, or MOF, but the need for percutaneous interventions

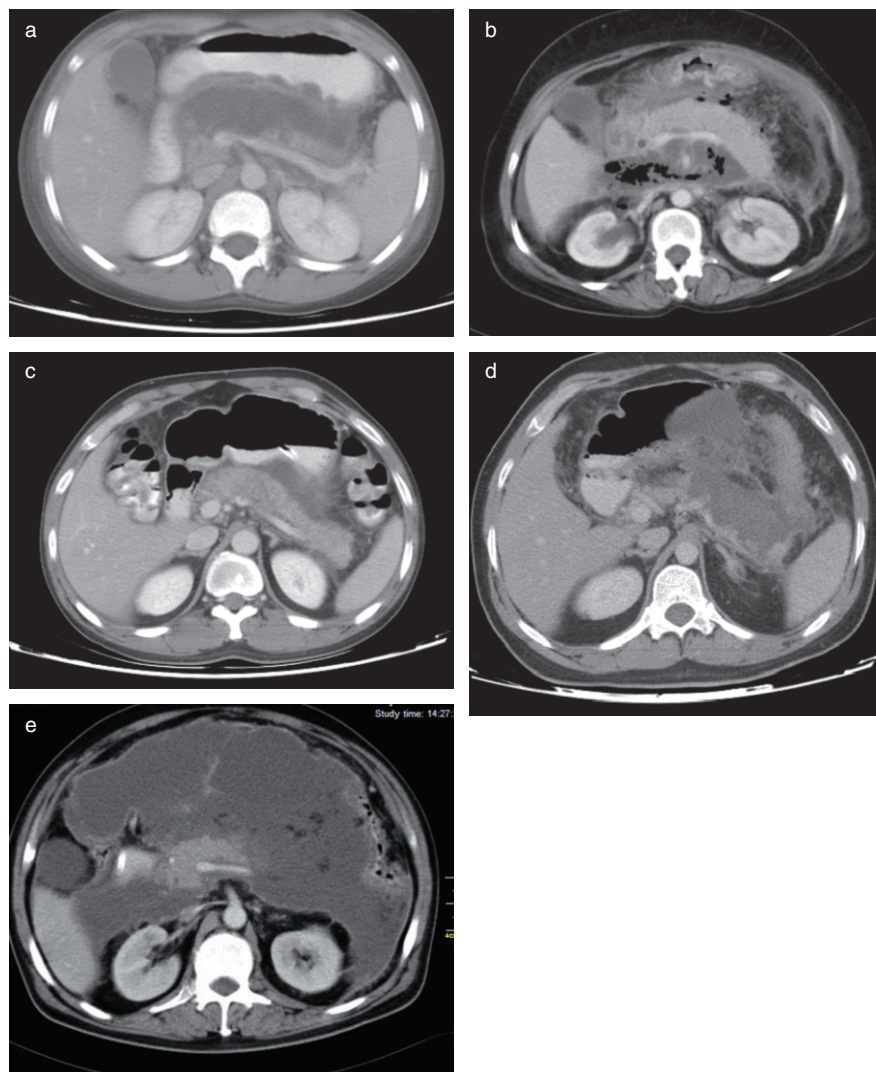


Figure 1 (a) Non-enhancing pancreas suggestive of pancreatic necrosis alone. (b) Normally enhancing pancreas with emphysematous extrapancreatic necrosis (EPN) alone. (c) Normally enhancing pancreas with EPN alone. (d) Combined pancreatic necrosis (PN) and EPN. (e) Extensive EPN.

Table 1 Comparison of outcome in patients with acute interstitial pancreatitis with patients having EPN alone

	Interstitial pancreatitis (<i>n</i> = 21) <i>n</i> (%)	EPN alone (<i>n</i> = 48) <i>n</i> (%)	<i>P</i> -value
Pleural effusion	12 (57.1%)	36 (75%)	0.163
Ascites	3 (14.3%)	10 (20.8%)	0.740
Organ failure	5 (23.8%)	35 (72.9%)	0.000
MOF	1 (4.8%)	6 (12.5%)	0.427
POF	3 (14.3%)	25 (52.1%)	0.004
Intervention	2 (9.5%)	7 (14.6%)	0.712
Surgery	0	2 (4.2%)	1.00
Mortality	0	4 (8.3%)	0.225

EPN, extrapancreatic necrosis; MOF, multi-organ failure; POF, persistent organ failure.

The bold values denote significant *p* values (*p* < 0.05)

was higher in the parenchymal necrosis group (32.6% vs 14.6%, *P* = 0.016). The mortality was higher in those with parenchymal necrosis (20.1% vs 8.3%, *P* = 0.077) but did not reach statistical significance (Table 2).

When patients with extensive EPN (*n* = 57) were compared with the patients who had limited EPN (*n* = 128), the frequency of pleural effusion (94.7% vs 82%) and ascites (50.9% vs 30.5%) were higher in the former group. The frequency of MOF (31.6 vs 15.6%) was significantly higher in the extensive PPN group. The frequency of organ failure (77.2% vs 68%), need for intervention (33.3% vs 25.8%), surgery (10.5% vs 6.2%), and mortality (22.8% vs 14.8%) were higher in the extensive EPN group, but the difference did not achieve statistical significance (Table 3). The frequency of pancreatic parenchymal necrosis was similar in these two groups (93 patients, i.e. 72.7% in limited EPN, and 44 patients, i.e. 77.2% in extensive EPN group, *P* = 0.588)

Discussion

EPN alone is being increasingly recognized as separate entity in AP, which may have a different course and outcome than patients

Table 2 Comparison of outcome in patients with combined necrosis with patients having extrapancreatic necrosis alone

	Combined necrosis (n = 144) n (%)	Extrapancreatic necrosis alone (n = 48) n (%)	P-value
Pleural effusion	127 (88.2%)	36 (75%)	0.036
Ascites	59 (41.0%)	10 (20.8%)	0.015
Organ failure	101 (70.1%)	35 (72.9%)	0.855
MOF	33 (22.9%)	6 (12.5%)	0.149
POF	81 (56.2%)	25 (52.1%)	0.620
Intervention	47 (32.6%)	7 (14.6%)	0.016
Surgery	12 (8.3%)	2 (4.2%)	0.524
Mortality	29 (20.1%)	4 (8.3%)	0.077

MOF, multi-organ failure; POF, persistent organ failure.

Table 3 Comparison of outcome in patients with extensive EPN with those having limited EPN

	Extensive EPN (n = 57) n (%)	Limited EPN (n = 128) n (%)	P-value
Pleural effusion	54 (94.7)	105 (82.0)	0.022
Ascites	29 (50.9)	39 (30.4)	0.013
Organ failure	44 (77.2)	87 (67.9)	0.224
MOF	18 (31.6)	20 (15.6%)	0.018
POF	37 (64.9%)	67 (52.3%)	0.148
Intervention	19 (33.3)	33 (25.8)	0.294
Surgery	6 (10.5)	8 (6.2)	0.369
Mortality	13 (22.8)	19 (14.8)	0.209

EPN, extrapancreatic necrosis; MOF, multi-organ failure; POF, persistent organ failure.

with PN.^{7–11} In our study, out of 192 patients with necrotizing pancreatitis, majority of patients (71.3%) had both intra and EPN. It was followed by EPN alone (25%), and PN alone was the least common (3.7%). Also, among patients with EPN, majority had limited EPN (69.2%) whereas extensive EPN was observed in 30.8% patients. This is similar to revised Atlanta classification wherein it has also reported that of all the necrotizing pancreatitis combined parenchymal and EPN is the commonest followed by EPN alone, and PN is the least common.¹ Previously, Sakorafas *et al.* in a cohort of 62 patients noted EPN alone in 12 (19%) patients.⁷ Another report including 152 patients with acute pancreatic reported presence of peripancreatic necrosis alone in 8 of the 185 patients (4.3%) in whom imaging was done.¹¹ Lankisch *et al.* reported extrapancreatic fluid collections in 39% and only EPN in 20% of their patients in a series of 228 patients.⁸ The report from 21 Dutch centers, in contrast, has reported a very high number (49%) of patients to have EPN alone among the patients with necrotizing AP.⁹

Previously, few studies have evaluated the clinical significance of EPN alone and have suggested that it should be considered as a separate disease entity from PN and interstitial pancreatitis.^{7–11} Sakorafas *et al.* in a cohort of 62 patients noted that patients with

EPN alone had lower Acute physiology and chronic health evaluation (APACHE) II scores on admission, required fewer surgeries, did not develop postoperative fistulae or hemorrhage, had shorter hospital stay, and had lower mortality in comparison with patients with PN.⁷ Bakker *et al.* also reported that patients with EPN had lesser frequency of POF (21% vs 45%, $P < 0.001$), infected necrosis (16% vs 47%, $P < 0.001$), need of intervention (18% vs 57%, $P < 0.001$), and mortality (9% vs 20%, $P < 0.001$) as compared with patients with combined necrosis.⁹ Lankisch *et al.*, in contrast, indicated that the presence of extrapancreatic fluid collections significantly correlated with need for dialysis and mechanical ventilation and also increased pseudocyst formation, need for surgery, and mortality.⁸ In the current study, we also found that patients with EPN alone had lesser frequency of pleural effusions (75% vs 88.2%, $P = 0.036$) and ascites (20.8% vs 41%, $P = 0.015$) as well as required fewer interventions (14.6% vs 32.6%, $P = 0.016$) in comparison with patients with combined necrosis. However, the two groups did not differ vis-à-vis the occurrence of organ failure, and although the mortality was higher in those with parenchymal necrosis (20.1% vs 8.3%, $P = 0.077$), it did not reach statistical significance.

The occurrence of similar frequency of organ failure in both groups contrasts with the results of Dutch multicenter study that reported lesser frequency of organ failure in patients with EPN. The Dutch study had much higher frequency of EPN (49%) in contrast to our study where only 25% patients had EPN. The correlation of organ failure with PN has been addressed by a number of previous studies, but the results are contradictory.^{12–15} However, recent studies have concluded that PN is associated with increased frequency of organ failure.^{10,16} We also found significantly higher frequency of organ failure in patients with EPN alone as well as patients with combined necrosis in comparison with patients with non-necrotizing interstitial pancreatitis. The occurrence of organ failure in AP is multifactorial and is possibly caused by the release and production of various cytokines and vasoactive substances, and activation of pro-inflammatory pathways by the injury of the pancreatic and peripancreatic tissue.^{17,18} Because the tissue injury, a triggering event for inflammatory cascade, is common to both PN and EPN, we believe that this could be the reason for similar frequency of organ failure in both groups. However, this needs to be confirmed by further larger sample size studies.

On comparing patients with EPN alone with that of interstitial non-necrotizing pancreatitis, we found that patients with EPN alone had significantly higher frequency of organ failure (72.9% vs 23.8%, $P < 0.001$). And although the mortality and need for intervention were higher in the EPN alone group, the differences did not achieve a statistical significance. In a previous report comparing interstitial pancreatitis and EPN, an increased rate of organ failure, Intensive care unit (ICU) admission, a higher need for vasopressors as well as interventions, and longer stay was noted amongst patients with EPN alone.¹¹ Our data suggest that the EPN alone group is different from the interstitial pancreatitis as well as the group with parenchymal necrosis, and it is appropriate to classify AP into three groups: interstitial, EPN alone, and pancreatic parenchymal necrosis group.

We further evaluated the clinical significance of extensive EPN (necrosis extending into paracolic gutters or the pelvis) by comparing the outcome parameters between patients with limited and extensive EPN. In comparison with patients with limited EPN,

patients with extensive EPN had a significantly increased frequency of pleural effusion, ascites, and MOF, but similar frequency of organ failure, mortality, and need for intervention. This concept of extensive EPN has not been evaluated previously, although studies have reported that extent of pancreatic parenchymal necrosis correlates with the development of organ failure.^{12,16} The increased frequency of ascites, pleural effusion, and MOF could be a manifestation of wide spread injury in extensive EPN. However, similar frequency of mortality and need for intervention suggests that extent of EPN may not determine the clinical outcome.

Our study has a few limitations. Ours is an apex tertiary referral hospital in North India that caters to a large population of all the northern states of India, and therefore majority of patients referred and admitted at our centre are sick patients. Therefore, we had a higher frequency of patients with severe necrotizing pancreatitis, and the number of patients with interstitial pancreatitis was small. Also, 74 patients in this study were excluded as they did not undergo CT or CT was done very early or later than 10 days, but the outcome of these excluded patients was similar to the included 213 patients. Although such a high frequency of severe AP is different from population data, these data are similar to our previous reports.^{3,19} Also, the number of patients in the EPN alone group was less as compared with patients with combined necrosis group.

In conclusion, EPN alone needs to be considered as a distinct group with clinical course and outcomes different from patients with interstitial or pancreatic parenchymal necrosis groups. Moreover, patients with extensive EPN, although having increased frequency of ascites, pleural effusion, and MOF, have similar outcome as compared with patients with limited EPN.

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