


Delayed referral increases the need for surgery and intervention in patients with acute pancreatitis

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Introduction

Acute pancreatitis (AP) is a life-threatening disease, outcomes of which depend upon timely and effective management strategies adopted. Evidence-based standard guidelines have been put forth by multiple societies.^{1–4} However, despite the availability of evidence-based recommendations, it has been shown that they are rarely adopted in the community practice.^{5,6}

It is recommended that all patients of AP should be admitted. Moreover, patients with severe AP (SAP) need management in an intensive care unit setting.⁴ However, whether management at a tertiary care centre is likely to yield additional benefits, especially early in disease course in terms of outcomes of AP is yet unknown. A nationwide inpatient data from USA depicted that mortality and length of hospital stay in AP patients were much lower in high-volume centres (defined as ≥ 118 patients/year) compared to low-volume centres.⁷ Similar data from a large Taiwan national health insurance database revealed lower mortality rates amongst SAP patients managed at high-volume centres compared to low-volume centres.⁸

Abstract

Background: The aim was to study the outcomes of acute pancreatitis (AP) patients who were referred from other facilities to a tertiary care centre.

Methods: Patients with AP who were referred from other hospitals to a tertiary care centre between April 2013 and September 2019 were studied and their outcomes were analysed. Comparison was made between patients referred early (≤ 7 days) versus those referred late (> 7 days).

Results: Of the 838 patients seen by us, 650 patients (77.6%) were referred from other centres. Median (interquartile range) onset to admission interval was 5 (4–7) days for those who were referred ≤ 7 days and was 16 (11–30) for those who were referred > 7 days. Patients referred beyond 7 days of pain onset had higher rates of development of organ failure ($P = 0.007$), including acute lung injury ($P = 0.008$) and acute kidney injury ($P = 0.026$), infected necrosis ($P < 0.0001$), requirement of endoscopic/percutaneous drainage ($P < 0.001$) and need for surgery ($P < 0.02$) compared to patients who were referred ≤ 7 days of pain onset. Mortality was however similar in the two groups.

Conclusion: Patients with AP referred to a specialized centre with AP early (≤ 7 days) have better outcomes than those referred late (> 7 days) from other facilities.

However, there is sparse data on the outcomes of patients who are referred to a tertiary care centre after initial management at primary/secondary level centres. Also, it would be prudent to know whether early referral at tertiary care centres is likely to improve outcomes of AP patients or treatment at primary and secondary health centres with subsequent referrals as need may arise may suffice.

Unfortunately, despite it being a pertinent issue, there are no studies available on this. Hence, we planned this study to at our centre which is a large tertiary care academic institute to study the outcomes of patients who were referred from other centres. We further wanted to study and to see whether early referral to a tertiary care centre (≤ 7 days after onset) yields better outcomes as compared to delayed (> 7 days after onset) referrals.

Methods

This prospective observational study was conducted in the department of Gastroenterology at a tertiary care centre in North India from April 2013 to September 2019. The diagnosis of AP was

made by (any two of the three): (i) acute abdominal pain; (ii) elevated serum amylase or lipase (more than thrice upper limit of normal range); and (iii) typical appearance on ultrasound and/or contrast-enhanced computed tomography. Informed consent was taken from all patients. Ethical clearance was obtained from institutional ethical committee and the study was performed in accordance with the ethical standards laid down in Declaration of Helsinki.

At the time of hospitalization, a note was made whether the patient had been treated initially at another facility and referred to our centre or had come directly to us. A detailed clinical examination was undertaken in all the patients. A contrast-enhanced CT scan of abdomen was done on or after 5–7 days of onset of pain. Revised Atlanta classification was used to grade the severity of AP into mild AP, moderately SAP and SAP.⁹ Severity assessment was also done with the help of the different scoring systems; systemic inflammatory response syndrome (SIRS) score, Bedside Index of Severity in Acute Pancreatitis (BISAP) score and Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score at admission. Organ failure (acute lung injury, acute kidney injury and cardiovascular failure) was defined as per modified Marshall scoring system.⁹ Transient and persistent organ failure was defined using a cut off of 48 h. Complete blood counts, renal function tests, liver function tests, serum electrolytes and arterial blood gas analysis were done in all patients at baseline.

The management of all patients was according to American Gastroenterology Association guidelines.¹ Initial management included fluid resuscitation, analgesics, oxygen support and nutritional management. Antibiotics were administered only when there was a documented focus of infection as per the culture and sensitivity reports. In patients where there was clinical evidence of sepsis and/or persistent/worsening organ failure beyond the first week of onset of pain, empirical antibiotics were administered. Infected necrosis (IPN) was diagnosed on the basis of positive drain cultures or the presence of gas within the necrosis on contrast-enhanced computed tomography. A step up approach was adopted for the management of all AP patients.¹⁰ Percutaneous pigtail catheter drainage(PCD) or endoscopic drainage was undertaken in patients with symptomatic fluid collections, infected collections and worsening organ failure despite medical management. Patients not responding to above measures were considered for surgical necrosectomy(minimally invasive), preferably beyond 4 weeks of onset of pain.

The course in the hospital was monitored for development of organ failure, development of fluid collections, need for intensive care unit stay, requirement of organ support, need for intervention such as PCD endoscopic drainage or surgery and final outcome. The patients were divided into two groups; early referrals, ≤ 7 days of disease onset and >7 days of disease onset. These two groups were compared for disease course and outcome parameters.

Statistical analysis

The data were analysed using SPSS software (version 20.0; IBM Corp, Armonk, NY, USA). When the data was normally distributed, continuous variables were compared using the Student's *t*-test (in case of two groups) and for more than two groups one-way

analysis of variance was used. For skewed data Mann–Whitney test was used. Dichotomous variables were compared using chi-squared test. Quantitative data were described as mean and standard deviation or median, interquartile range and range. A *P*-value of <0.05 was taken as statistically significant.

Results

A total of 838 patients of AP were admitted between April 2013 and September 2019. Of these, 650 (77.6%) patients were referred from other hospitals whereas 188 patients (22.4%) had presented directly to our hospital. Among the 650 patients referred to us, 221 (34%) were admitted ≤ 7 days of disease onset and 429 (66%) after 7 days of disease onset. The mean age of referred patients was 40.21 ± 13.2 years and 471 (75%) patients were males. Median (interquartile range) duration of pain prior to admission was 5 (4–7) days for those who were referred ≤ 7 days and was 16 (11–30) days for those who were referred >7 days after pain onset. The most common aetiology of pancreatitis was alcohol(48.6%) followed by gallstone disease (16.4%).

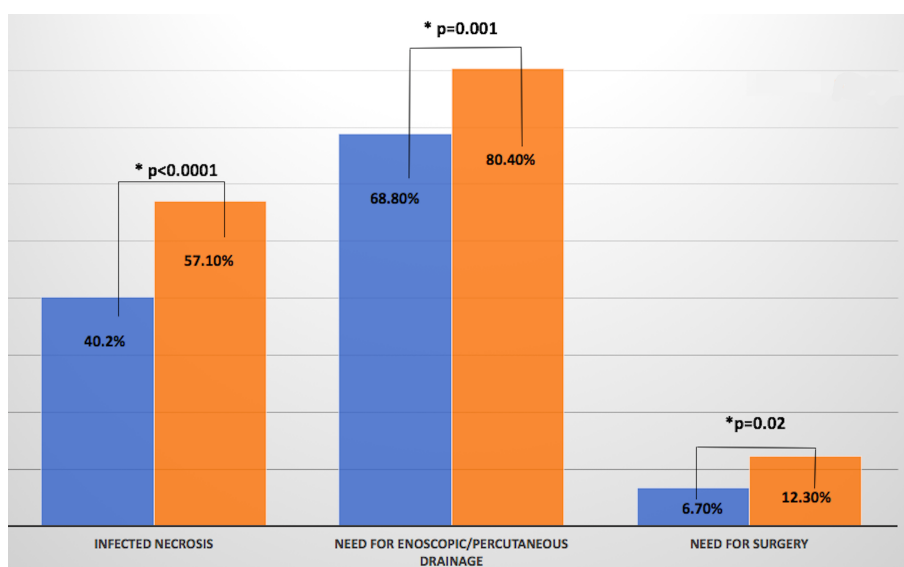
Comparison of patients who were referred ≤ 7 days and those who were referred >7 days revealed that rates of development of organ failure ($P = 0.007$), including acute lung injury ($P = 0.008$) and acute kidney injury ($P = 0.026$) were significantly higher in those referred ≤ 7 days. The group of patients who were referred within 7 days of pain onset also had higher SIRS scores ($P = 0.05$) and BISAP scores($P < 0.001$) which are surrogate markers of disease severity (Table 1). The common organisms grown amongst the early referred and late referred groups were *Escherichia coli*, *Acenobacter* species, *Klebsiella* species and *Pseudomonas* species. There was no difference in the organisms grown in these two groups. Although the rates of development of fluid collections were similar in both early referral and late referral groups ($P = 0.735$), the rates of infected necrosis were significantly higher in those referred >7 days ($P < 0.0001$) (Fig. 1, Table 2). Requirement of PCD/endoscopic drainage($P < 0.001$) and need for surgery ($P < 0.02$) were also significantly higher in patients who were

Table 1 Comparison of disease course between patients referred ≤ 7 days with those referred >7 days after disease onset

	≤ 7 days (<i>n</i> = 221)	>7 days (<i>n</i> = 429)	<i>P</i> -value
SIRS score, <i>n</i> (%)	168/221 (76.0)	294/429 (68.5)	0.05*
BISAP score	2.03 ± 1.0	1.69 ± 0.99	<0.001*
APACHE II score (admission)	8.88 ± 4.9	8.44 ± 4.6	0.28
Atlanta classification, <i>n</i> (%)			
Mild	31 (14.0)	33 (7.7)	0.617
Moderate	79 (35.7)	196 (45.7)	
Severe	111 (50.2)	200 (46.6)	
Organ failure, <i>n</i> (%)	147/221 (66.5)	237/429 (55.2)	0.007*
Acute lung injury, <i>n</i> (%)	127/221 (57.4)	198/429 (46.1)	0.008*
Acute kidney injury, <i>n</i> (%)	66/221 (29.9)	92/429 (21.4)	0.026*
Shock, <i>n</i> (%)	28/221 (12.6)	50/429 (11.6)	0.799

* $P \leq 0.05$. APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; BISAP, Bedside Index for Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome.

Fig 1. Comparison of clinical course and outcome parameters between patients referred ≤ 7 days with those referred >7 days after disease onset. (■), ≤ 7 days; (■), >7 days. *indicates $P < 0.05$ between two groups.



referred late (Fig. 1, Table 2). However, the mortality was similar in the two groups.

Discussion

We studied the outcomes of patients of AP referred to our tertiary care centre from other facilities. We found that patients who were referred beyond 7 days after onset of disease had more infected necrosis and greater need for intervention/surgery as compared to those referred earlier than 7 days. This could be due to suboptimal treatment at the primary and secondary care facilities before the referral. Management guidelines of AP suggest that early initiation of fluids and enteral nutrition are the key elements in improving outcomes of these patients.^{1,3,4,11} Early fluid resuscitation helps in attenuating inflammatory response and limiting the extent of necrosis which in turn could improve outcomes.^{4,12} Fischer *et al.*¹³ showed that delayed resuscitation was associated with higher mortality and a trend towards greater persistent organ failure compared to early resuscitation. Another study by Brown *et al.*¹⁴ noted that

none of the patients whose haematocrit decreased at 24 h developed necrotizing pancreatitis while 12/28 patients whose haematocrit remained $>44\%$ developed necrotizing pancreatitis.

A greater proportion of patients in the delayed presentation had infected necrosis (57.1% versus 40.2%). Higher rates of infected necrosis in the late referral group could also be due to a delay in initiating enteral feeding at primary/ secondary level health care centres. Early initiation of enteral nutrition prevents transmigration of gut microbiota which is often found to be the source of infection in pancreatic necrosis.¹⁵ Hence various guidelines highlight the role of starting early enteral nutrition irrespective of the severity of AP.^{1,4,11,16,17} Zou *et al.* showed that AP patients receiving early enteral nutrition had significantly lower rates of pancreatic infection and lower median hospital stays.¹⁸ Various studies in the past have noted that the rates of infected necrosis increase beyond the first week of illness.^{19,20} In fact, we have also earlier shown that risk of infection in AP increases with every week of illness.²¹

The delayed referral group despite having lesser severity scores and lesser organ failure at onset had more requirement of percutaneous or endoscopic drainage ($P = 0.001$) and surgery ($P = 0.02$). This can be attributed to higher rates of infected necrosis. In an earlier study, we divided all patients presenting to our centre on the basis of timing of presentation into three groups; <7 days, 8–21 days and >21 days. That study had included all patients, those coming directly to our centre as well as those who were referred from other hospitals. The occurrence of infected necrosis, duration of hospitalization, need for surgery and mortality were least in those presenting ≤ 7 days of illness.²² Similar results were observed by Beaux *et al.*²³ who reported that 75% of their 279 patients were admitted directly to their specialized unit whereas the rest were transferred from other units.²³ In the latter group, those who were referred beyond the first week had worse clinical outcomes. In another study, by Wu *et al.*, of the 339 consecutive AP patients, 84% were direct admissions whereas the rest were hospital transfers.²⁴ Transferred patients had higher hemoconcentration ($P < 0.0001$) and increased necrosis ($P < 0.0001$) as compared to

Table 2 Comparison of clinical course and outcome parameters between patients referred ≤ 7 days with those referred >7 days after disease onset

	≤ 7 days ($n = 221$)	>7 days ($n = 429$)	P-value
Need for ICU care, n (%)	102 (46.1)	189 (44.0)	0.93
Need for ventilator, n (%)	41 (18.5)	92 (21.4)	0.26
Need for dialysis, n (%)	16 (7.2)	21 (4.9)	0.29
Pancreatic/peripancreatic collections, n (%)	184 (83.2)	362 (84.4)	0.735
Infected necrosis, n (%)	89 (40.2)	245 (57.1)	<0.0001*
Need for percutaneous and/or endoscopic drainage, n (%)	152 (68.8)	345 (80.4)	0.001*
Need for surgery, n (%)	15 (6.7)	53 (12.3)	0.02*
Hospital stay (days)	23.24 \pm 17.8	26.19 \pm 18.7	0.06
Mortality, n (%)	39 (17.6)	87 (20.2)	0.29

* $P \leq 0.05$. ICU, intensive care unit.

directly presenting patients, both factors associated with worse outcome.

In our study, the late referral group also had longer hospital stay, though it did not reach statistical significance. The likely reasons for worse outcomes such as higher infected necrosis and need for intervention, and a trend towards greater hospital stay in patients referred late may not just be delay in initiation of early target based fluid resuscitation, and enteral nutrition but could also be irrational prescription of broad spectrum antibiotics within the first week of onset at referring facilities. Administering broad spectrum antibiotics at primary/secondary care centres in the first few days may result in growth of drug-resistant organisms which can further worsen outcome and prolong hospital stay. The irrational use of antibiotics is highlighted by a study from USA which noted prophylactic use of antibiotics in 53% of patients of AP.⁶ Enteral nutrition was considered first in only 23% of patients.⁶ In the same study, authors concluded that adherence to best clinical guidelines is poor even in developed countries.⁶ We expect adherence to guidelines and best clinical practices to be even poorer in developing Southeast Asian countries.

The patient volume of the treating centre has an impact on outcomes in AP patients. It has been noted that treatment at high volume units ($118 \geq$ patients/year) is associated with lower length of hospitalization and lower mortality.⁷ The number of specialized/high-volume centres in developing countries is small, and there is a lack of uniformity in management practices at primary and secondary level facilities. Hence, it is important that knowledge regarding evidence-based practises is widely disseminated, guidelines adhered to and patients with AP are referred early to large tertiary care centres for early appropriate management.

We did not find any difference in mortality rates amongst early referral vs. delayed referral groups in our study. This may be explained by effective multidisciplinary management of infected pancreatic necrosis at our tertiary care centre. Our results are in concurrence with those of a large multicentric study by the Dutch pancreatitis group which found no significant impact of infected pancreatic necrosis on mortality.²⁵ They attributed this to efficient multidisciplinary management and minimally invasive treatment options at tertiary care centres.²⁵

Our study has some limitations. Details of treatment received (fluid resuscitation, organ support provided, antibiotics administered) at primary/secondary care centres were not available. The severity of disease at onset in patients who were referred to us beyond 7 days of pain onset was not known. The duration of hospital stay in our study included only the stay in our hospital (where the patients were referred). This might have underestimated the actual hospital stay, especially in patients who were referred beyond 7 days. However, despite that, a higher duration of hospital stay (in our hospital) in patients referred beyond 7 days remains a significant finding indicating worse outcome in the delayed referral group.

Our data, thus, gives us an opportunity to analyse the importance of management in a specialized unit in a developing country. AP just like other medical emergencies such as myocardial infarction and stroke needs early aggressive management at specialized centres. Since the median timing of presentation of referred patients >7 days was 16 (11–30) days, the outcomes might be affected by the natural disease course of AP (infectious complications beyond

2 weeks warranting higher interventions/drainages). Data on treatment received by patients managed at referring centres could have helped us do propensity matching to gauge the impact of referral.

Ours is the first study with a large sample size which has prospectively studied the outcome of referred patients presenting to a large high-volume tertiary care centre. Our hospital is a tertiary care centre in a city with 1.5 million population, and gets referrals from three north Indian states. We propose that patients with high disease severity scores (BISAP score, SIRS, APACHE II), patients having organ failure (including those having transient organ failure), and those having signs of infected necrosis should be referred early. In addition, there is a need to disseminate knowledge to general physicians and surgeons who form the first interface for such patients.

In conclusion, this study shows that delayed referrals of patients with AP is associated with higher infected necrosis and more need for endoscopic/percutaneous or surgical interventions. Early referrals are due to higher organ failure and disease severity at onset. There is need for increasing awareness at primary and secondary health-care centres regarding need for adherence to standard guidelines in managing AP patients and also to sensitize them regarding early referrals to higher tertiary care large-volume centres. Our findings can have implications in further policy-making regarding management of AP patients.

Conflicts of interest

None declared.

References

1. Crockett SD, Wani S, Gardner TB *et al.* American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. *Gastroenterology* 2018; **154**: 1096–101.
2. Banks PA, Freeman ML, Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am. J. Gastroenterol.* 2006; **101**: 2379–400.
3. Leppäniemi A, Tolonen M, Tarasconi A *et al.* 2019 WSES guidelines for the management of severe acute pancreatitis. *World J. Emerg. Surg.* 2019; **14**: 27.
4. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol.* 2013; **13**(4 Suppl. 2): e1–15.
5. Dua MM, Worhunsy DJ, Tran TB *et al.* Severe acute pancreatitis in the community: confusion reigns. *J. Surg. Res.* 2015; **199**: 44–50.
6. Vlada AC, Schmit B, Perry A, Trevino JG, Behrns KE, Hughes SJ. Failure to follow evidence-based best practice guidelines in the treatment of severe acute pancreatitis. *HPB* 2013; **15**: 822–7.
7. Singla A, Simons J, Li Y *et al.* Admission volume determines outcome for patients with acute pancreatitis. *Gastroenterology* 2009; **137**: 1995–2001.
8. Shen H-N, Lu C-L, Li C-Y. The effect of hospital volume on patient outcomes in severe acute pancreatitis. *BMC Gastroenterol.* 2012; **12**: 112.
9. Banks PA, Bollen TL, Dervenis C *et al.* Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102–11.
10. van Santvoort HC, Besselink MG, Bakker OJ *et al.* A step-up approach or open necrosectomy for necrotizing pancreatitis. *N. Engl. J. Med.* 2010; **362**: 1491–502.

11. Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association clinical practice update: management of pancreatic necrosis. *Gastroenterology* 2020; **158**: 67–75.e1.
12. Aggarwal A, Manrai M, Kochhar R. Fluid resuscitation in acute pancreatitis. *World J. Gastroenterol.* 2014; **20**: 18092–103.
13. Fisher JM, Gardner TB. The “golden hours” of management in acute pancreatitis. *Am. J. Gastroenterol.* 2012; **107**: 1146–50.
14. Brown A, Baillargeon J-D, Hughes MD, Banks PA. Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? *Pancreatology* 2002; **2**: 104–7.
15. Dervenis C, Smailis D, Hatzitheoklitos E. Bacterial translocation and its prevention in acute pancreatitis. *J. Hepatobiliary Pancreat. Surg.* 2003; **10**: 415–8.
16. Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005; **54**(Suppl. 3): iii1–9.
17. Trikudanathan G, Wolbrink DRJ, van Santvoort HC, Mallery S, Freeman M, Besselink MG. Current concepts in severe acute and necrotizing pancreatitis: an evidence-based approach. *Gastroenterology* 2019; **156**: 1994–2007.e3.
18. Zou L, Ke L, Li W *et al.* Enteral nutrition within 72 h after onset of acute pancreatitis vs delayed initiation. *Eur. J. Clin. Nutr.* 2014; **68**: 1288–93.
19. Besselink MG, van Santvoort HC, Boermeester MA *et al.* Timing and impact of infections in acute pancreatitis. *Br. J. Surg.* 2009; **96**: 267–73.
20. Dellinger EP, Tellado JM, Soto NE *et al.* Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Ann. Surg.* 2007; **245**: 674–83.
21. Noor MT, Radhakrishna Y, Kochhar R *et al.* Bacteriology of infection in severe acute pancreatitis. *JOP* 2011; **12**: 19–25.
22. Mallick B, Dhaka N, Sharma V *et al.* Impact of timing of presentation of acute pancreatitis to a tertiary care centre on the outcome. *Pancreatology* 2019; **19**: 143–8.
23. de Beaux AC, Palmer KR, Carter DC. Factors influencing morbidity and mortality in acute pancreatitis; an analysis of 279 cases. *Gut* 1995; **37**: 121–6.
24. Wu BU, Conwell DL, Singh VK *et al.* Early hemoconcentration is associated with pancreatic necrosis only among transferred patients. *Pancreas* 2010; **39**: 572–6.
25. Schepers NJ, Bakker OJ, Besselink MG *et al.* Impact of characteristics of organ failure and infected necrosis on mortality in necrotizing pancreatitis. *Gut* 2019; **68**: 1044–51.