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Original article

Reduction in mortality in severe acute pancreatitis: A time trend analysis over 16 years

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ABSTRACT

Background: The trend in the outcome of patients with acute pancreatitis (AP) as a result of evolving management practices is not known.
Objective: To study and compare the outcomes of patients with AP at a tertiary care academic center over a period of 16 years.
Methods: In a retrospective study on a prospectively acquired database of patients with AP, we analyzed time trends of severity and mortality of AP. The influence of determinants of severity [APACHE II score, organ failure (OF), infected pancreatic necrosis (IPN)], and management strategy on the actual and predicted mortality was assessed. The actual mortality was adjusted for severity to analyze the severity-adjusted mortality at different times as a reflection of management practices over time.
Results: A total of 1333 patients were studied. The number of patients hospitalized with AP has been increasing over time. The proportion of patients with severe AP also increased from 1997 to 2013 as shown by increasing incidence of organ failure and IPN (Spearman's rank correlation coefficient (ρ): OF $\rho(17) = 0.797$, $p < 0.01$; IPN $\rho(17) = 0.739$, $p < 0.001$), indicating an increasing referral of sicker patients. Consequently, the overall mortality has been increasing ($\rho(17) = 0.584$; $p = 0.014$). However, despite increasing severity of AP, the mortality adjusted for OF has decreased significantly ($\rho(17) = -0.55$, $p = 0.02$).
Conclusion: Even with increasing proportion of patients with severe AP, there has been a significant decrease in organ failure adjusted mortality due to AP suggesting improved management over years.

Acute pancreatitis (AP) is a potentially lethal disease associated with substantial morbidity and mortality [1]. The severity of AP ranges from mild pancreatic inflammation and edema (interstitial edematous pancreatitis) to severe necrotizing pancreatitis [2]. Superadded infection of the necrotic tissue worsens the course of acute necrotizing pancreatitis with increased mortality [3]. Even more ominous is the systemic complication in the form of organ failure, which has serious adverse impact on survival [4]. The major determinants of survival are organ failure (OF) and infected pancreatic necrosis (IPN) [5]. The revised Atlanta classification has defined severe AP based on the presence of organ failure [6]. With increasing understanding of the pathophysiology of AP over time, the management protocols have also evolved [7,8]. Early recognition of organ dysfunction during the course of AP, prompt transfer of patients to a specialized center, optimal allocation of resources, and management in an intensive care are important steps to reduce mortality due to AP. Similarly, a high index of suspicion for IPN allows its early detection and protocolized management including minimally invasive interventions. The incidence of acute pancreatitis is reported to be increasing but the data regarding change in its outcome are scarce. A recent study has shown that acute pancreatitis related mortality has decreased marginally but not at the population level [9]. The overall decrease in mortality might be due to a relative increase in mild cases as the mortality is higher in transferred patients [10]. The data from tertiary care centers are limited to deduce if there is any real decrease in mortality due to severe pancreatitis [11]. As the hospital admission rate and cost of management are increasing [12], it is important to analyze the time trends with regard to the outcome of AP particularly to assess if our current standard of care that has evolved over time has translated into an improved outcome.

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The objective of the present study was to analyze trends in patients with AP hospitalized over the past 16 years with regard to referral pattern, severity of disease, and outcome.

Methods

Patient population and data collection

The present study was conducted at the All India Institute of Medical Sciences, New Delhi, a tertiary care academic center. We included all consecutive patients with AP admitted under the Gastroenterology services of our center from February 1997 to May 2013 through retrospective analysis of a prospectively acquired and maintained database as part of many prospectively conducted studies [2–4,7,13].

Characterization of AP

The diagnosis of AP was based on the presence of acute onset of abdominal pain, increased serum amylase/lipase levels (>3 times the upper limit of our laboratory reference standards) and evidence of AP on imaging studies, i.e. abdominal ultrasonography (USG) and/or contrast enhanced computed tomography (CECT) scan of the abdomen. The records of individual patients thus identified were then characterized based on their age, sex, delay in presentation, clinical course, worst APACHE II score, severity of AP, development of organ failure (OF), infected pancreatic necrosis (IPN) and final outcome i.e. survival/death. Delay in presentation, measured in days, was the time from the onset of abdominal pain to first contact with our center. For calculation of worst APACHE II score during hospitalization, records of investigations for individual patients were assessed and scored during the course of in-hospital treatment. If any patient had had even worse APACHE II score before presentation and reliable documentation of that was available, that value was taken as the worst APACHE II score.

Organ Failure was defined according to the original Atlanta classification as follows: respiratory failure (partial pressure of arterial oxygen [paO2], <60 mm), acute renal failure (serum creatinine, 2.0 mg/dL), cardiovascular failure (systolic blood pressure, 90 mm Hg any time during the course of acute pancreatitis which was fluid non-responsive), or severe gastrointestinal bleeding (500 mL/24 h) [14]. A patient was said to have had organ failure if one or more organ systems had failed anytime during the course of the illness. As for the worst APACHE II assessment, the documentation of referring hospitals was taken into due consideration for this variable as well.

Pancreatic necrosis

Acute pancreatitis was categorized as either interstitial or necrotizing. Pancreatic necrosis was diagnosed on a CECT scan as non-enhancing areas of the pancreas. Pancreatic necrosis was classified either as sterile or infected. Infected pancreatic necrosis (IPN) was suspected if there was evidence of sepsis in the form of fever and leukocytosis with deterioration or no improvement of their clinical condition. The diagnosis of IPN was confirmed when pancreatic necrotic tissue/fluid showed presence of bacteria on Gram's stain or when it grew an organism on culture as described previously [3]. We have included all patients with suspected and bacteriologically proven IPN in this analysis.

Management of acute pancreatitis

Patients were managed according to a standard protocol as has been reported previously. Some of the changes in the management over years include more emphasis on early enteral nutrition, selective use of antibiotics, and care of sick patients in ICU under gastroenterology services since the year 2005 rather than central ICU. One notable change has been primarily conservative treatment of patients with infected pancreatic necrosis since 2003 as reported previously [7].

Time trends analysis

For the purpose of analysis of trends in admission, clinical course and outcome, the records of patients were grouped year-wise based on the date of admission.

The proposed determinants of severity were variable for patients hospitalized during different times, and it was not deemed appropriate to use average values alone as determining factors for mortality. Therefore, the actual mortality was assumed to be a composite of 2 broad categories of determinants: the severity of AP and the management at different time points.

Three predictor variables were taken into consideration: APACHE II score, OF, and IPN. For estimating the role of changing severity of pancreatitis in contributing to mortality, the risk of mortality associated with every value of the predictor variables (APACHE II, OF, IPN) was calculated. The weighted average was then plotted to show predicted mortality based on each of the components. For obtaining the mortality risk associated with APACHE II scores, the regression equation published by Knaus et al. [15] was used. Since no similar equations were available for OF and IPN, previously published data showing risk of mortality associated with each of the parameters was used [16]. There was substantial similarity between the reference population and our patient population particularly with regard to single and multi-organ failure [16]. The mortality predicted by these components (*Predicted Mortality*) was then compared with the actual mortality observed. The predicted mortality calculated in this manner automatically assumes that the management of patients has been similar for a given severity, and thus correlates with changes in severity over time.

To assess the impact of changing management practices, the *Adjusted Mortality* was calculated by averaging the severity at presentation for a given predictor variable over the years. This allowed an assessment of what the mortality would have been had a similar patient population presented every year. This therefore serves as a proxy for impact of management practices in that year. By ensuring that variations in the disease severity over the years were statistically nullified, changes in outcome could be better correlated with the overall management of the patient.

In essence thus, the composite mortality curve for each predictor variable could be separated into 2 components: Predicted Mortality, the mortality rate assuming no change in risk of mortality for a given severity, and Adjusted Mortality, the mortality rate assuming no change in severity at presentation over the years.

The mathematical equations used can be summarized as follows:

$$\text{Predicted mortality (for a given predictive factor k for a given year)} = \sum_{k=0}^{n} (\text{proportion of patients in our study with k for that year}) \times (\text{overall mortality for k in reference population})$$

$$\text{Adjusted mortality (for a given predictive factor k for a given year)} = \sum_{k=0}^{n} (\text{Overall proportion of patients in our study with k}) \times (\text{mortality for k in our population for that year}).$$

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