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Hypocalcemic tetany: a simple bedside marker of poor outcome in acute pancreatitis

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Abstract

Background Hypocalcemia is a marker of poor prognosis in acute pancreatitis (AP) but the prognostic significance of hypocalcemic tetany in patients with AP has not been studied. We aimed to determine the prognostic significance of hypocalcemic tetany in patients with AP.

Methods Consecutive patients of AP who presented within 7 days of symptoms were included. Serum calcium levels were measured on admission and the patients were divided into two groups based on the presence (group 1) or absence of hypocalcemia (group 2). Chvostek and Trousseau signs were sought in all patients with hypocalcemia and the outcome measures were compared between patients with normocalcemia, asymptomatic and symptomatic hypocalcemia (tetany). The outcome parameters assessed were persistent organ failure (POF), need for intervention, and mortality.

Results Of 105 patients (53 male; mean age 37.34±12.62 years), 37 (35.2%) had hypocalcemia (group 1) and 68 (64.8%) had normal corrected serum calcium levels (group 2). Patients with hypocalcemia had significantly higher frequency of POF, mortality and need for intervention (P<0.05). Twelve of 37 (32.4%) patients with hypocalcemia had tetany. Patients with tetany had significantly lower serum corrected calcium and ionized calcium levels compared with patients with asymptomatic hypocalcemia (P<0.05). Patients with tetany had significantly higher mortality rates compared with patients with asymptomatic hypocalcemia (100% vs. 8%; P=0.00001) as well as POF (100% vs. 32%; P=0.000006).

Conclusion Presence of hypocalcemic tetany in AP patients bears a poor prognosis and is associated with increased mortality.

Keywords Hypocalcemia, tetany, acute pancreatitis

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Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas resulting from autodigestion of the pancreatic tissue due to premature activation of the enzymes within the acini leading to various local and systemic complications. The majority of the patients have "self-limiting disease" while around 20% of the patients have severe disease with mortality ranging from 5-20% [1]. The factors that determine the severity of AP have not been completely understood, and hence it is difficult to predict the clinical course of patients with AP [2].

Hypocalcemia in AP has long been described but its pathogenesis is still debatable. The first clue to the puzzle came from Langerhans in 1890 when he described the formation of calcium soaps in the necrosed fat in AP [3]. Fifty four years later Edmondson ascribed hypocalcemia to the formation of these soaps [4]. Although it seemed plausible that extraskeletal sequestration due to formation of soaps was the mechanism responsible for hypocalcemia in AP. In AP, resistance of hypocalcemia to parenteral calcium supplementation remains unexplainable in view of the abundant calcium stores. Various experiments and studies in 1990's showed that hypocalcemia was due to the raised glucagon levels in AP and hypocalcemia occurred due to decreased release of calcium from the skeleton

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as a result of calcitonin release stimulated by glucagon [5,6]. Another explanation given for hypocalcemia was the low magnesium levels which render the target organs resistant to the actions of parathyroid hormone. Magnesium levels have been found to be high in the necrosed pancreatic tissue [7]. Ryzen *et al* showed in his study that magnesium deficiency may play a role in hypocalcemia in AP despite normal serum magnesium levels. The authors showed that patients with normal serum magnesium had a low magnesium concentration in the peripheral blood mononuclear cells and this concentration correlated with the serum calcium values in hypocalcemic patients [8]. Magnesium deficiency was more pronounced in patients with alcoholic AP. Various authors have also proposed the role of relative deficiency of parathyroid hormone in hypocalcemia of AP [9-11]. Hypoalbuminemia has also been described as the cause for hypocalcemia in AP [12]. More recently, the role of free fatty acids in sequestration of calcium has been described in two animal studies [13,14].

Hypocalcemia has been demonstrated to be a useful marker predicting severity in AP and is part of several scoring systems predicting severity in AP [15-18]. There are few case reports of hypocalcemic tetany in AP but the prognostic significance of hypocalcemic tetany has not been studied in patients with AP [7,19,20]. The present study aimed to determine the prognostic significance of hypocalcemic tetany in patients with AP.

Patients and methods

Study design and participants

We conducted this prospective observational study at a large tertiary care referral center in North India between October 2013 and July 2014. The study was approved by the Institute Ethics Committee and all participants gave informed consent for participation in the study. All consecutive patients of AP presenting within 7 days of onset of symptoms to the hospital were enrolled.

AP was defined as per revised Atlanta classification [2] i.e., presence of two or more of the following: characteristic abdominal pain; serum amylase and/or lipase raised three times above the upper limit of normal; or imaging consistent with AP. Biliary etiology was defined by the detection of gallstones on imaging and exclusion of other causes. In a patient with recent history of alcohol consumption and absence of other causative factors, AP was ascribed to alcohol. Post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis was defined as presence of significant pain requiring hospitalization for at least 48 h of admission after ERCP with elevated amylase and lipase (>3 times above the upper limit of normal measured after 24 h) [21]. Patients who gave no history of recent alcohol consumption, had no gallstones on imaging and work up for other causes was inconclusive, were labeled as having idiopathic pancreatitis.

Age above 18 years, hospital admission within 7 days of onset of symptoms, and willingness to participate in the study were the inclusion criteria. Patients younger than 18 years of age, hospitalized after 7 days of onset of symptoms, pregnant patients, patients not willing to participate in the study, patients with recurrent AP and patients with imaging suggestive of chronic pancreatitis were excluded from the study. Conditions associated with hypocalcemia like chronic kidney disease or hypoparathyroidism, steroids, patients with hematological malignancies, burns or crush injuries were also part of the exclusion criteria. Patients who met the inclusion criteria were included and followed until recovery or death.

Procedures

On admission all patients underwent routine investigations including hemogram with hematocrit, renal function tests, liver function tests, fasting serum triglycerides, serum calcium, ionized calcium levels, phosphorus, magnesium, arterial blood gas analyses, iPTH and vitamin D levels. Contrast enhanced computed tomography (CECT) of abdomen was done between days 5 and 7 of onset of symptoms. CT severity index (CTSI) score was calculated based on the sum of the Balthazar and pancreatitis necrosis score on a CECT done with pancreatic protocol. Bedside index of severity in AP (BISAP), systemic inflammatory response syndrome (SIRS), and acute physiological and chronic health evaluation (APACHE) II were recorded in all patients within 24 h of admission. Severity was defined as per revised Atlanta criteria [2].

Tetany was defined as presence of either Trousseau or Chvostek sign in a patient with hypocalcemia [22]. Chvostek sign was elicited by tapping on the face at a point just anterior to the ear and just below the zygomatic bone. Twitching of the ipsilateral facial muscles was taken as the positive response. For Trousseau sign, if not present spontaneously, a sphygmomanometer cuff was inflated at 20 mmHg above the patient systolic pressure for 3 min and carpopedal spasm was taken as the positive response. The clinical signs of tetany were sought for in the first 24 h from admission and their demonstration at any time during these 24 h was considered as presence of tetany.

All patients were given standard medical care throughout the study period. In addition, all patients with hypocalcemia received 10 mL of 10% w/v calcium gluconate intravenously given in 5% dextrose or 0.9% saline slowly over 5 min followed by a continuous infusion of 10 ampoules of calcium gluconate dissolved in 5% dextrose or 0.9% sodium chloride over 24 h until the resolution of hypocalcemia. All patients who had tetany were given intramuscular 6 lakhs IU of vitamin D. Vitamin D was also given to other patients who were vitamin D deficient. Patients who had hypomagnesemia also received intravenous magnesium bolus followed by infusion. Clinical findings were periodically recorded and investigations were repeated on as and when required basis. Patients were subjected to intervention (surgery, percutaneous drainage or endoscopy) as and when required according to the patients clinical condition. The patients were followed up until clinical recovery or death.

Statistical analysis

We used IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY, USA). The descriptive data were presented as percentages for categorical variables and mean±SD or median (IQR) for quantitative variables. Continuous data were tested for normal distribution prior to stastistical analysis using Kolmogrov Smirnov test. The chi square test was used to compare the categorical variables, Mann-Whitney test was used to compare the continuous variables in case of skewed data, and Student's *t*-test for normally distributed data. We used area under the receptor operative curve (AUROC) for univariate analysis. The cut-off value for calcium was derived using the coordinate points on ROC with optimal sensitivity and specificity. The threshold values of 7.5 for APACHE II and 2.5 for BISAP were used as coordinate points on ROC curve because these were the nearest values to APACHE ≥ 8.0 and BISAP >2 which have already been described in literature to have a significant impact on outcome in AP. We calculated the sensitivity and specificity for mortality using tetany as a variable with the help of a 2x2 contingency table. A 2-tailed P-value ≤0.05 was considered statistically significant.

Results

One hundred and fifty three patients were assessed for possible inclusion in the study and 48 patients were excluded. Finally, 105 patients (53 male; mean age 37.34±12.62 years) were included in the study. The etiology of AP was gallstones in 47 (44.8%), alcohol in 30 (28.6%), idiopathic in 17 (16.2%), both alcohol and gallstones in 6 (5.7%) and post ERCP in 5 (4.7%) patients. Of 105 patients, 37 (35.2%) patients had hypocalcemia and 68 (64.8%) patients had normal calcium levels.

Comparison of clinical and demographical profile of patients between group 1 (hypocalcemia) and group 2 (normal corrected serum calcium group) (Table 1)

The two groups were similar in age, sex, etiology and mean CTSI scores. Compared with group 2, patients in group 1 had higher SIRS score (2.43 vs. 2.04; P=0.03), APACHE II score (7.54 vs. 4.02; P=0.002) and BISAP score (BISAP score of 4 in 13.5% patients vs. 1.5% patients; P=0.004). The majority of the patients (54.1%) in group 1 had severe pancreatitis compared with 26.5% patients in group 2 (P=0.003). Tetany was observed in 32.4% of patients with biochemical hypocalcemia.

Comparison of biochemical parameters of calcium and magnesium between group 1 and 2 (Table 2)

Levels of corrected serum calcium were significantly lower in group 1 (7.35 mg/dL) compared with group 2 patients (9.2 mg/dL) (P<0.001). Serum ionized calcium levels were also lower in group 1 compared with group 2 (0.67 mmol/L vs. 0.78 mmol/L; P=0.002). Vitamin D3 levels were similar between the two groups (7.0 ng/mL vs. 8.36 ng/mL; P=0.11). Levels of serum iPTH were significantly higher in group 1 compared with group 2 (120.52 IU/L vs. 108.68 IU/L, P=0.002). Mean serum magnesium levels were lower in group 1 compared with

Table 1 Comparison of clinical profile of hypocalcemic and normocalcemic groups

Characteristic	Group 1 (Hypocalcemia)	Group 2 (Normocalcemia)	P-value
Number n (%)	37 (35.2)	68 (64.8)	
Age (years)	37.86±11.93	37.05±13.06	0.68
Sex (M:F)	20:17	33:35	0.58
Etiology n (%)			
Alcohol	13 (35.2)	17 (25)	0.16
Gallstones	17 (45.9)	30 (44.1)	
Idiopathic	7 (18.9)	10 (14.7)	
Post ERCP	0	5 (7.4)	
Mixed	0	6 (8.8)	
After CTSI - mean±SD*	5.83±3.95	5.32±3.40	0.49
SIRS	2.43±0.86	2.04±1.05	0.03
BISAP			
0	5 (13.5)	9 (13.2)	0.004
1	1 (2.7)	19 (27.9)	
2	19 (51.4)	31 (45.6)	
3	7 (18.9)	8 (11.8)	
4	5 (13.5)	1 (1.5)	
APACHE II	7.54±5.76	4.02±3.57	0.002
Severity			
Mild	5 (13.5)	29 (42.6)	0.003
Moderately severe	12 (32.4)	21 (30.9)	
Severe	20 (54.1)	18 (26.5)	
Serum Mg (mg/dL)	1.62±0.45	1.93±0.21	0.055
Tetany	12 (32.4%)	0	0.000001

ERCP, endoscopic retrograde cholangiopancreatography; CTSI, computed tomography severity index; SIRS, systemic inflammatory response syndrome; BISAP, bedside index of severity in acute pancreatitis; APACHE II, acute physiological and chronic health evaluation

Table 2 Comparison of biochemical parameters between hypocalcemic and normo-calcemic groups

Characteristic	Group 1 (hypocalcemia)	Group 2 (normocalcemia)	P-value
Serum corrected Ca (mg/dL)	7.35±0.79	9.20±0.53	0.000003
Phosphorus (mg/dL)	2.58±1.21	2.94±1.04	0.06
Ionized Ca (mmol/L)	0.67±0.29	0.78±0.20	0.02
25 OH Vit D3 (ng/mL)	7.00±4.53	8.36±4.82	0.11
iPTH (IU/L)	120.52±86.83	108.68±367.85	0.002
Serum Mg (mg/dL)	1.62±0.45	1.93±0.21	0.055

Ca, calcium; Vit D3, vitamin D3; iPTH, intact parathyroid hormone; Mg, magnesium

group 2 but the difference did not reach statistical significance (P=0.055).

Comparison of outcome parameters between group 1 and group 2

The frequency of persistent organ failure (POF) was significantly higher in group 1 compared with group 2 [n=20 (54.1%) vs. n=18 (26.5%); P=0.005]. Patients in group 1 required intervention more frequently compared with group 2 [n=13 (35.1%) vs. n=11 (16.1%); P=0.04]. Of the 105 patients, 16 (15.2%) succumbed to their illness with 14 (37.8%) deaths in group 1 and 2 (2.9%) in group 2 (P<0.001).

Comparison of clinical and demographical profile of patients with tetany and asymptomatic hypocalcemia (Table 3)

Patients who had tetany were similar to patients with asymptomatic hypocalcemia in age (P=0.25), sex (P=0.73), etiology (P=0.80), BISAP (P=0.14) and mean CTSI scores (P=0.07). However, SIRS and APACHE II scores were significantly higher in patients with tetany compared with patients with asymptomatic hypocalcemia (2.91 vs. 2.2; P=0.02) and (10.6 vs. 6.04; P=0.009) respectively. All patients (100%) in the tetany group had severe pancreatitis while only 8 (32%) in the asymptomatic hypocalcemia group had severe pancreatitis (P=0.001).

Comparison of biochemical parameters of calcium and magnesium patients with tetany and asymptomatic hypocalcemia (Table 4)

Corrected serum calcium and ionized calcium levels were significantly lower in patients with tetany (6.75 vs. 7.63; P=0.003) and (0.44 vs. 0.77; P=0.001) respectively. Vitamin D3 levels were insignificantly different, lower in the tetany group as compared to the patients in asymptomatic hypocalcemia group (4.99 ng/mL vs. 7.97 ng/mL; P=0.059). Parathyroid hormone levels were insignificantly higher in patients with tetany as compared to patients with asymptomatic hypocalcemia (155 IU/L vs. 104 IU/L, P=0.16). Mean serum magnesium levels were similar in the two groups (1.48 mg/dL vs. 1.74 mg/dL, P=0.42).

Comparison of outcome parameters in patients with tetany and asymptomatic hypocalcemia

All patients in the tetany group had POF (100%) compared with 8 (32%) patients in patients with asymptomatic hypocalcemia. Six patients (50%) in the tetany group required intervention compared with 7 (28%) patients in the asymptomatic hypocalcemia group, but the difference did not

Table 3 Comparison of clinical profile between group of patients having hypocalcemic tetany and patients having asymptomatic hypocalcemia

Characteristic	Tetany	Asymptomatic hypocalcemia	P-value
Number	12	25	
Age (years)	36.08±9.20	38.72±13.12	0.53
Sex M:F	6:6	14:11	0.73
Etiology			
Alcohol	4 (33.3)	9 (36)	0.80
Gall stones	5 (41.7)	12 (48)	
Idiopathic	3 (25.0)	4 (16)	
Post ERCP	0	0	
Mixed	0	0	
Comorbidities			
Diabetes	0 (0%)	2 (8%)	0.89
Hypertension	0 (0%)	1 (4%)	
CAD	1 (8.3%)	0 (0%)	
Hypothyroidism	1 (8.3%)	0 (0%)	
Mean CTSI score[$]	4.5±4.75	6.48±3.42	0.22
SIRS	2.91±0.29	2.2±0.95	0.02
BISAP			
0	0	5 (20)	0.14
1	0	1 (4.0)	
2	5 (41.7)	14 (56)	
3	4 (33.3)	3 (12)	
4	3 (25)	2 (8)	
APACHE II	10.66±5.26	6.04±5.46	0.009
Severity			
Mild	0	5 (20)	0.001
Moderately severe	0	12 (48)	
Severe	12 (100)	8 (32)	

ERCP, endoscopic retrograde cholangiopancreatography; CAD, coronary artery disease; CTSI, computed tomography severity index; SIRS, systemic inflammatory response syndrome; BISAP, bedside index of severity in acute pancreatitis; APACHE II, acute physiology and chronic health evaluation

Table 4 Comparison of biochemical parameters between patients with tetany and asymptomatic hypocalcemia

Characteristic	Tetany	Asymptomatic hypocalcemia	P-value
Serum corrected Ca (mg/dL)	6.75±0.897	7.63±0.56	0.003
Phosphorus (mg/dL)	2.78±1.52	2.48±1.04	0.66
Serum potassium (mEq/L)	3.48±1.76	4.01±0.88	0.78
Ionized Ca (mmol/L)	0.44±0.18	0.77±0.27	0.001
Vit D3 (ng/mL)	4.99±3.31	7.97±4.78	0.059
iPTH (IU/L)	155.28±102.98	103.83±74.52	0.16
Serum Mg (mg/dL)	1.48±0.59	1.74±0.30	0.42
pH	7.334±0.10	7.35±0.071	0.78
HCO_3 (mmol/L)	16.88±3.41	18.42±3.73	0.60

Ca, calcium; Vit D3, vitamin D3; iPTH, intact parathyroid hormone; Mg, magnesium; HCO_3, bicarbonate

reach statistical significance (P=0.189). Interventions in these patients (6 in the tetany group and 7 in the asymptomatic hypocalcemia group) included percutaneous drainage in all of them and surgical necrosectomy in 2 additional patients in the tetany group. Thirty day (early) mortality was observed in 10 (83.3%) patients in the tetany group compared with 2 (8%) patients in the asymptomatic hypocalcemia group. Two more patients in the tetany group succumbed to the illness on days 41 and 81 from the onset of illness and thus all patients in the tetany group died.

Clinical profile of patients with tetany

Tetany was observed in 12 (32.4%) of patients (6 male) with biochemical hypocalcemia. All patients with tetany had severe pancreatitis. CECT could be done in 6 patients with tetany and 3 patients had CTSI score of 8 and the other 3 patients had CTSI of 10. Trousseau sign (Fig. 1A,B,C) could be elicited in all patients, whereas Chvostek sign could be elicited in only 3 (25%) patients. None of the patients with tetany had metabolic alkalosis. Ionized calcium less than 0.652 mmol/L predicted tetany with a sensitivity of 91.2% and specificity of 74.8% (optimal sensitivity and specificity as derived from ROC). Ionized calcium less than 0.652 mmol/L predicted severe pancreatitis with a sensitivity of 60.5% and specificity of 82.1% (optimal sensitivity and specificity as derived from ROC).

Predictors of mortality

On univariate analysis, APACHE II, BISAP, low corrected serum calcium levels and low ionized serum calcium levels were significant predictors of mortality (Table 5). For prediction of mortality, APACHE II ≥7.5 had a sensitivity of 81.3% and specificity of 84.3% whereas BISAP ≥2.5 had a sensitivity of 56.3% and specificity of 86.5%. The lower corrected serum calcium levels had a sensitivity of 81.3% and specificity of 87.6 % whereas lower ionized serum calcium levels had a sensitivity of 81.3% and specificity of 77.5% for prediction of mortality. Tetany predicted mortality with a sensitivity of 75% and specificity of 100%.

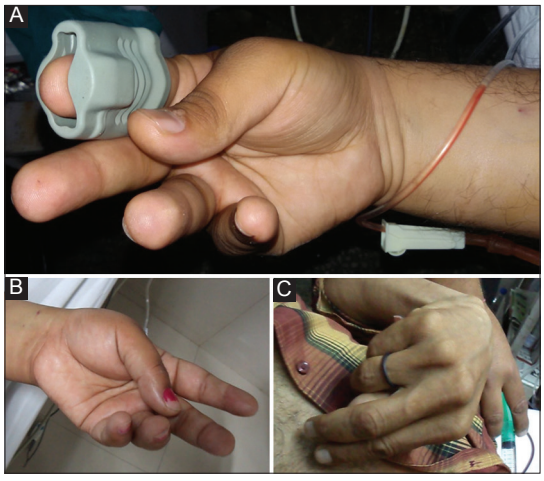

Figure 1 (A) Trousseau sign in a patient with acute pancreatitis. This patient had tetany on the day of admission in emergency and succumbed to respiratory failure within 24 h. (B) Trousseau sign in a 30/f who developed tetany on day 5 of onset of symptoms. (C) Carpal spasm in a patient who developed tetany within 72 h of onset of symptoms

Discussion

The prognostic significance of hypocalcemic tetany had not been previously studied in patients with AP. We have shown that presence of tetany predicted a very poor prognosis in all our AP patients with tetany at presentation leading to high mortality. Tetany in AP was described for the first time by Hayes *et al* [23] in 1955. He described 2 cases of tetany in AP where the patients developed tetany within 24 h from AP onset. The authors showed that the only biochemical abnormality in these patients which could explain tetany was lower ionized serum calcium. The authors ascribed this to binding of ionized calcium to the increased concentration of free fatty acids in plasma. The authors also described that this part of early symptomatic hypocalcemia was not responsive to intravenous calcium but it responded to parathyroid hormone supplementation. In contrast, when the tetany recurred in these patients late in the disease, it responded to intravenous calcium gluconate and by this time the serum fatty acids level came down to normal limits. Hypomagnesemia has also been described as cause of tetany in AP. In our study only 2 of the 12 patients who developed tetany had lower serum magnesium levels. The mechanism of hypomagnesemia in AP has been shown by multiple experiments in animals to be related to accumulation of magnesium in the necrosed pancreatic tissue [24,25].

Impairment of calcium metabolism ensues in AP and serum calcium below 8 mg/dL within 48 h of admission is one of the Ranson's criteria predicting severity in AP, and significantly higher mortality rates have been reported in patients with hypocalcemia [26,27]. We also found that patients with hypocalcemia had significantly a higher frequency of POF, need for intervention as well as mortality compared with patients with normal serum calcium levels. The low corrected serum calcium levels had a sensitivity of 81.3% and specificity of 87.6% whereas lower ionized serum calcium levels had a

Table 5 Univariate analysis for prediction of mortality in acute pancreatitis using area under the receptor operative curve (AUROC)

Variable	AUROC	95% CI
APACHE II	0.882	0.793-0.970
BISAP	0.815	0.709-0.921
Corrected serum calcium	0.902	0.825-0.979
Ionised serum calcium	0.859	0.786-0.931

APACHE II, acute physiology and chronic health evaluation; BISAP, bedside index of severity in acute pancreatitis

Summary Box

What is already known:

- Hypocalcemia is one of the predictors for severity in acute pancreatitis
- Acute pancreatitis patients with hypocalcemia have a poor prognosis
- There is paucity of studies linking tetany with an adverse outcome in acute pancreatitis

What the new findings are:

- Tetany could be a marker for predicting the poor outcome in patients with acute pancreatitis
- Tetany predicted mortality in acute pancreatitis with a specificity of 100%
- Acute pancreatitis patients with hypocalcemic tetany should be managed aggressively and preferably in the intensive care unit

sensitivity of 81.3% and specificity of 77.5% for prediction of mortality.

Tetany due to AP is very rare and such patients have extremely poor prognosis [28,29]. There are few case reports of hypocalcemic tetany in AP but the prognostic significance of hypocalcemic tetany has not been studied [7,20]. Most of the cases of tetany with AP reported in the literature succumbed to their illness thereby implying a grave prognosis of tetany. We also found that tetany had the highest specificity for prediction of mortality i.e. 100% compared with 84.3% for APACHE II (>7.5), 85.6% for BISAP (>2.5) and 86.7% for corrected serum calcium (<7.72 mg/dL).

Mortality in AP is initially determined by the heightened inflammatory response and POF. Later in the course of the disease, mortality is determined by complex events like development of infection, sepsis, need for surgery and consequent perioperative mortality. There are numerous prognostic models and markers to predict severe disease, prolonged hospital stay, infectious complications etc., but very few of them predict mortality, the final outcome in AP. In the current study, we found that presence of tetany had the highest specificity for prediction of mortality. Although the percentage of deaths in patients with severe pancreatitis (42.1%) was high compared with what has been described in literature, but this can be explained by the fact that our center is a tertiary care referral center, and, by the time patients are referred to us, they are morbidly sick.

The limitations of the current study include data from a single center and consequently the small number of patients with tetany. Moreover, we did not compare tetany/corrected serum calcium levels with other biochemical markers of severity and prognosis such as C-reactive protein. Finally, we did not test for serum calcitonin or urinary levels of variables of calcium metabolism and levels of free fatty acids which could have given more insight into the pathophysiology of hypocalcemia in AP. Although tetany carries a 100% specificity for prediction of poor outcome in AP, its absence does not rule out the existence of a severe disease with poor outcome.

In conclusion, AP patients with tetany have a very poor prognosis and presence of hypocalcemic tetany could be used as a simple bedside marker of increased mortality. Further studies with large sample size are required to confirm these results and also to study the pathophysiology of hypocalcemia and tetany in AP in order to treat these patients with poor prognosis more effectively.

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