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Original Article

Peak Serum Creatinine as a Biomarker of Pancreatic Necrosis in Acute Pancreatitis: A Cross-Sectional Study

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ABSTRACT

Pancreatitis is the inflammation of the pancreas. Pancreatitis can result in pancreatic necrosis which may lead to significant morbidity and mortality. It is possible to predict pancreatic necrosis and organ dysfunction using many biochemical indicators and markers. Peak serum creatinine has been identified as one of such useful markers to predict pancreatic necrosis. **Objective:** To find the diagnostic accuracy of elevated peak serum creatinine as a predictor of pancreatic necrosis in patients with acute pancreatitis taking the contrast-enhanced computed tomogram scan (CECT) as the gold standard and to establish the degree of agreement between the two clinical tests. **Methods:** A cross-sectional, analytical study that was carried out at the Department of Surgery, Benazir Bhutto Hospital, Rawalpindi from January 2020 to January 2023. 150 patients diagnosed as having pancreatitis were enrolled in the study. Peak serum creatinine at 48 hours > 1.8 mg/dl was labeled as a predictor of pancreatic necrosis. Contrast-enhanced computed tomogram scan was done within 96 hours of admission. The pancreatic necrosis suggested by raised serum creatinine was confirmed by CECT. The diagnostic accuracy of peak serum creatinine and the degree of agreement between the two modalities was calculated. The Kappa coefficient was used to calculate the strength of agreement. **Results:** The results show that Peak serum creatinine has a sensitivity of 45.5%, specificity of 97.35%, PPV of 85.0 %, NPV of 93.8 %, and accuracy of 84.6%. This study found that the degree of agreement between raised peak serum creatinine levels and CECT to predict pancreatic necrosis was 84.7% with a "Kappa coefficient" of 0.51. Consequently, the null hypothesis was rejected in light of these findings. **Conclusions:** It was concluded that elevated serum creatinine (SCr >1.8 mg/dl) at 48 h of admission can be used as a predictor of pancreatic necrosis in patients with acute pancreatitis.

INTRODUCTION

Acute pancreatitis is a sterile inflammation of parenchyma of the pancreas. The annual global incidence of acute pancreatitis ranges from 5-50/100000 [1]. Acute Pancreatitis can be classified into mild, moderately severe, or severe acute pancreatitis based on the revised Atlanta classification [2, 3]. In severe pancreatitis, mortality varies from 20- 50 %. Severe pancreatitis may lead to a systemic inflammatory response (SIRS), multiple organ failure, pseudocyst, and pancreatic necrosis (PNec). A diffuse or focused area of non-viable tissue in the pancreas associated with peripancreatic fat necrosis is known as pancreatic necrosis [1]. On a contrast-enhanced computed tomography (CECT) scan, necrotic areas can be identified by the lack of contrast enhancement. The revised 'Atlanta classification' recommends a CECT scan as the preferred method for diagnosing pancreatitis complications. A study showed that the Contrast-enhanced computed tomography scan's sensitivity was 71.4%, specificity 87%, positive predictive value 83.33%, negative predictive value 76.99%, and overall diagnostic accuracy was 79.5% [2, 3]. Several grading schemes and predictors have been developed to help determine and predict the severity of pancreatitis [4]. Early diagnosis of the severity of the illness can help change the way patients are treated. Serum

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creatinine assessment has been identified as one of the predictors of the severity of pancreatitis. It has been found that high serum creatinine levels in the initial 48 hours are associated with the development of pancreatic necrosis [4,5]. Many other serum markers such as C reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, albumin, serum creatinine, etc have been identified to be related to pancreatic necrosis [6]. Lipinski and colleagues found that elevated SCr and estimated glomerular filtration rate (EGFR) levels on admission in the initial 48 hours are associated with increased severity and PNec with a $p < 0.001$[4]. A study has found that the sensitivity, and specificity of SCr >1.8mg/dl within 48 hours to predict PNec was 41.2% and 98.9%, respectively with positive predictive value (PPV) of 93.3% and negative predictive value (NPV) of 82.1% [6]. But another study has shown that the sensitivity and specificity of SCr was 23% and 95%, respectively with PPV of 41% and NPV of 89% [7]. A study by Wiese *et al.*, demonstrated that a strong association with infected pancreatic necrosis was seen for creatinine (OR [95% CI] 1.019 [1.005–1.033], $p < 0.001$) [8]. Therefore, an elevated SCr concentration at any time during the first 48 hours of admission can be a marker for PNec in acute pancreatitis. To find the diagnostic accuracy of elevated peak serum creatinine as a predictor of pancreatic necrosis in patients with acute pancreatitis taking the CECT scan as the gold standard and to establish the degree of agreement between the two clinical tests. SCr is a very easily available and cost-effective test that can be of great help as a predictor of PNec[3,9].

This study aimed to gather local evidence to implement the use of Serum creatinine as a diagnostic tool for early prediction of pancreatic necrosis which may help in the prevention and management of pancreatic necrosis.

METHODS

A cross-sectional analytical study was undertaken at the Department of Surgery, Benazir Bhutto Hospital from January 2020 to January 2023, after receiving approval from the ethical review board of Rawalpindi Medical University (reference number: 13/55/RMU). The study was structured by the Standards for Reporting Diagnostic Accuracy Studies (STARD) checklist. The null hypothesis postulated that "Peak serum creatinine cannot accurately predict the PNec and there is no agreement between elevated peak serum creatinine and CECT for the prediction of pancreatic necrosis in acute pancreatitis". A sample size of 150 cases was calculated using the WHO calculator (95% confidence level), with a 6% margin of error and taking an expected percentage of the degree of agreement between serum creatinine > 1.8 mg/dl and CECT to be 83.5% in the prediction of pancreatic necrosis in acute pancreatitis [6]. Sampling was done using a non-probability consecutive sampling technique. Patients of the age group 20 years to 65 years presenting to surgical emergency with a diagnosis of acute pancreatitis as defined in the operational definition were included in the study. Patients with pancreatic malignancies and patients having previous renal compromise were excluded from the study. After informed consent, demographics (name, age, gender, address) were noted. Serum creatinine (SCr) levels were noted by obtaining blood samples on presentation and 48 hours after admission. Samples were sent to the Hematology lab of the Benazir Bhutto Hospital and reports were assessed. Patients having SCr > 1.8 mg/dl were labeled as positive. Then patients underwent a CECT scan from the hospital within 96 hours of admission to confirm the presence or absence of PNec. CECT scan was reported by consultant radiologists. All this information was collected with a specially designed proforma. Acute Pancreatitis was defined as upper abdominal pain often radiating to the back with serum amylase or lipase level >3 times than normal and inflammation of gland parenchyma of the pancreas on imaging [2]. For pancreatic necrosis (PNec), in terms of serum creatinine, if the value of SCr within 48 hours was > 1.8 mg/dl, PNec was labeled as positive but if the value was ≤ 1.8 mg/dl then PNec was labelled as negative. Confirmation of the PNec was done on a contrast-enhanced CT scan. A CECT scan was done within 96 hours of admission. The presence of a focal or diffuse area of non-viable parenchyma on CECT was labelled as PNec [6]. The diagnostic accuracy was defined as the ability of peak serum creatinine to correctly identify the patients of acute pancreatitis having pancreatic necrosis (PNec) as compared with the CECT scan as the gold standard test. Patients with PNec identified through elevated Peak Serum Creatinine (SCr) levels and subsequently confirmed by contrast-enhanced computed tomography (CECT) scan were categorized as true positive. Those labelled PNec solely based on elevated SCr levels but not detected on CECT scan were classified as false positive. Patients not demonstrating PNec on both peak SCr levels and CECT scan were designated as true negative, while those lacking elevated Peak Serum Creatinine levels but exhibiting PNec on the CECT scan were identified as false negative. Diagnostic accuracy was measured in terms of sensitivity (true positive rate), specificity (true negative rate), negative predictive value, positive predictive value, and accuracy. An agreement was labelled if both CECT and serum creatinine agreed upon the diagnosis of pancreatic necrosis, which can be either positive or negative. The strength of agreement was measured by Kappa statistics by Altman [10]. The data were entered and analyzed using SPSS version 22.0. Age and SCr level (quantitative variables) were calculated as mean and standard deviation. Gender, PNec (on SCr and CT) and agreement being qualitative variables were calculated as frequency and percentage. The normality of data was determined using the Q-Q plot analysis. Diagnostic accuracy in terms of sensitivity, specificity, positive predictive value, negative

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predictive value, and accuracy was calculated. The area under the curve (AUC) was calculated. This was done by constructing a contingency table between the PNec suggested by the peak serum creatinine and PNec confirmed by CECT. Kappa statistics (Altman, 1991) were calculated to determine the strength of agreement between serum creatinine > 1.8mg/dl and CECT findings for the absence or presence of pancreatic necrosis. Independent t-test was applied for discrete variables with a p-value ≤ 0.05 as significant.

RESULTS

There were a total of 150 patients with acute pancreatitis in this study. The mean age was found to be 43.27 ± 8.067yrs We found that the peak incidence of pancreatitis was in age group 40-49(Figure 1).

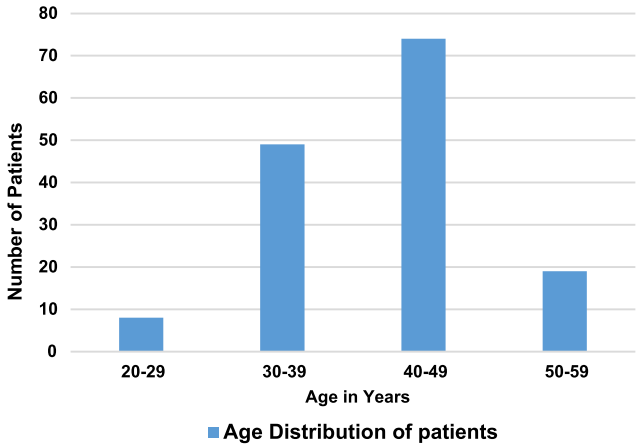

Figure 1: The Age Distribution of the Patients Presenting with Acute Pancreatitis

Total 66 patients were male while 84 patients were female with a male-to-female ratio of 1: 1.27(Figure 2).

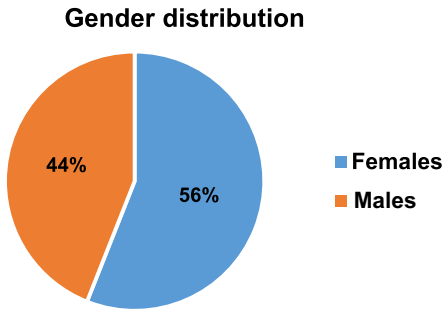

Figure 2: Gender Distribution of Patients(n=150)

Serum creatinine levels were assessed at admission and 48 hours' post-admission. The data exhibited a normal distribution based on Q-Q plot analysis. The mean creatinine level at 48 hours across the entire sample was 1.074 ± 0.64 mg/dl. A cohort of 20 patients was identified as potentially developing pancreatic necrosis, determined by a peak serum creatinine level exceeding 1.8 mg/dl. Calculation of the mean peak creatinine levels for patients diagnosed with pancreatic necrosis yielded 2.47 ± 0.68 mg/dl, while the corresponding value for patients without pancreatic necrosis stood at 0.85 ± 0.24 mg/dl (refer to Table 1). The resulting p-value of 0.001 signified a substantial disparity in peak creatinine levels between patients with and without pancreatic necrosis as determined by peak serum creatinine(Table 1).

Table 1: Mean Peak Creatinine in Patients with Pancreatic Necrosis on Creatinine(PNec on SCr)

Pancreatic Necrosis on Creatinine (Pnec on SCr)	Number of Patients n=150	Peak Creatinine at 48 Hours. Mean ± SD	*p value (95% CI)
Present	20	2.47± 0.68	0.001 (1.48-1.79)
Absent	130	0.85± 0.24	

CECT: Contrast Enhanced Computed Tomogram, SD: Standard Deviation, hours.: hours, CI: Confidence interval, *P value: independent samples T-test was applied

Among the 20 patients identified as having PNec based on SCr, 17 individuals were confirmed to have necrosis on CECT scan, categorizing them as true positive cases, while 3 patients did not exhibit any necrosis, constituting false positive results. Of the 110 patients anticipated to be free of pancreatic necrosis according to peak SCr levels, CECT scans corroborated the absence of necrosis, thus establishing them as true negative cases. Twenty patients initially not suspected to have PNec based on peak serum creatinine were subsequently found to have PNec upon undergoing a CECT scan 96 hours post-admission, representing false negative outcomes(Table 2).

Table 2: The number of patients having pancreatic necrosis on CECT scan and pancreatic necrosis on Peak Serum Creatinine (n:150)

Pancreatic Necrosis on Peak Serum Creatinine>1.8mg/dl	Pancreatic Necrosis on CECT Scan		Total
	Present	Absent	
Present	17	3	20
Absent	20	110	130
Total	37	113	150

The calculated sensitivity of serum creatinine as a predictor of pancreatic necrosis yielded 45.9%, with a specificity of 97.3%, a positive predictive value of 85.0%, and a negative predictive value of 93.8%. Notably, the overall accuracy of the method was ascertained to be 84.6%(Table 3).

Table 3: Measures of Diagnostic Accuracy for Pancreatic Necrosis on Peak Serum Creatinine

Variables	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	AUC, p-value (95% CI)
PNec on Peak SCr	45.5% (29.9%-63.08%)	97.35% (92.4%-99.45%)	85.0% (63.5%-94.81%)	93.8% (80.3%-88.1%)	84.6% (77.6%-90.0%)	0.825,0.001 (0.733-0.916)

PPV: positive predictive value, NPV: Negative predictive value, CI: Confidence interval, AUC: Area under curve

The ROC curve analysis was done which showed an area under the curve (AUC) of 0.825 with a p-value of 0.001, 95%

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CI 0.733-0.916. This also shows that peak serum creatinine levels have a high diagnostic predictive value for pancreatic necrosis (Figure 3).

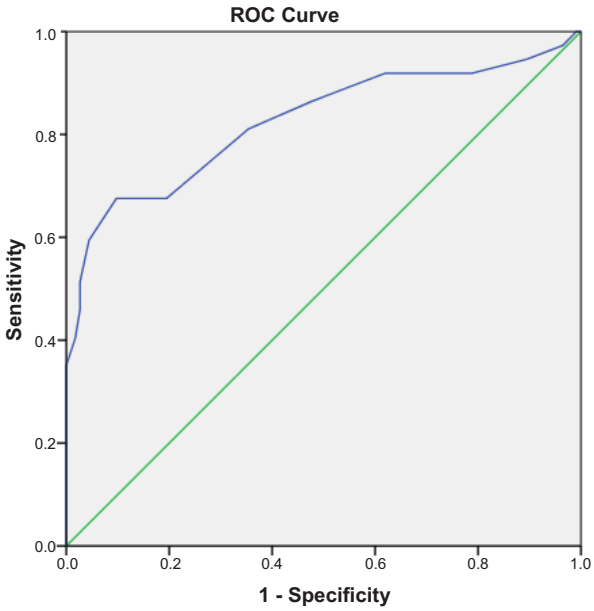

Figure 3: ROC Curve of Peak Serum Creatinine Levels by Pancreatic Necrosis

In the cohort of 150 patients, 127 exhibited concordant predictions for pancreatic necrosis (true positive and true negative) using both peak serum creatinine and CECT, while 23 patients displayed discordant predictions (false positive and false negative). The level of agreement between serum creatinine and CECT scan in predicting pancreatic necrosis was 84.7%. The computed kappa coefficient of 0.51 denotes a moderate level of agreement between the two modalities (Table 4).

Table 4: Degree of Agreement between Pancreatic Necrosis on Serum Creatinine and CECT scan (n:150)

Frequency (%)	Kappa Coefficient	p-value (95% CI)
127 (84.7)	0.51	0.001 (0.34-0.67)
23 (15.3)		

Kappa Coefficient: 0.51 means - strength of agreement (Altman, 1991)[10]

The overall results show that Peak serum creatinine has a specificity of 97.35%, PPV of 85.0 %, NPV of 93.8 %, and accuracy of 84.6%. and an agreement of 84.7% (kappa: 0.51). Consequently, the null hypothesis is rejected in light of these findings. Hence peak serum creatinine can be used as a predictor of pancreatic necrosis in patients with acute pancreatitis.

DISCUSSION

Acute pancreatitis is a disease with significant mortality and morbidity [1]. Pancreatic necrosis is associated with moderately severe and severe pancreatitis [2]. Early prediction and recognition of pancreatic necrosis and organ dysfunction can lead to a more tailored management which can improve the outcomes. Different biochemical markers such as are currently being investigated as predictors of pancreatic necrosis [11,12]. The mean age in current study was 43.27 ± 8.067yrs. One study found the mean age in acute pancreatitis patients to be 49.7 years [6]. However, another study found the mean age to be 52.5 years [13]. Yet another study has reported a mean age of 37 [14]. Hence the mean age of patients with acute pancreatitis in our study corresponds to that found in the international literature. Here 74 (49.3%) patients in the fourth decade of age that was age group 40-49 in present study. The mean ages in different international studies also show that acute pancreatitis is most common in the third and fourth decades of life. In our study, there are 66 (44%) males and 84 (56%) females with a male and female ratio of 1:1.27. Weis *et al.*, report that there was no significant gender difference in patients with acute pancreatitis developing pancreatic necrosis [8]. Walkowska *et al.*, also commented that gender distribution is dependent on etiology as alcoholic pancreatitis and gallstone pancreatitis are more common in male and female respectively [15]. In our study, acute pancreatitis was slightly more common in females and this can be because in our society alcohol intake is not as prevalent as in Western or other Asian societies and gallstones are the commonest etiology in our country. Serum creatinine was measured at admission and then at 48 hours. The highest value at 48 hours after admission was taken as peak creatinine. In current study mean peak creatinine at 48 hours in the whole sample was found to be 1.074 ± 0.64 mg/dl. This creatinine level is near the normal creatinine level of 1 mg/dl because only 37 (24.7%) out of 150 patients had pancreatic necrosis (confirmed on CT scan) and the rest had no necrosis and only mild acute pancreatitis. So mean creatinine levels in patients labelled as pancreatic necrosis on creatinine (Cr > 1.8 mg/dl) were calculated. It was found to be 2.47 ± 0.68 mg/dl (p-value = 0.001). In patients without pancreatic necrosis, it was 0.85 ± 0.24 mg/dl (p-value = 0.001). One study found the mean creatinine in patients with pancreatic necrosis to be 3.0 mg/dl [6]. In another study average concentrations of creatinine at baseline and 48 hours. after admission was 0.95 ± 0.75 mg/dl and 1.27 ± 0.81 mg/dl respectively (p-value = 0.001) [10]. This shows that serum creatinine is significantly raised in patients with pancreatic necrosis as compared to those without pancreatic necrosis. A peak serum creatinine level of > 1.8mg/dl at 48 hours was labelled pancreatic necrosis on creatinine (PNec on SCr). All the patients underwent a CT scan within 96 hours of admission to confirm the absence and presence of pancreatic necrosis being suggested on peak creatinine levels (PNec on CT scan). A total of 20 (13.3 %) patients had raised peak serum creatinine of more than 1.8 mg/dl and hence were predicted to have pancreatic necrosis. Among these 17 were confirmed to have PNec on CT scan. The sensitivity of

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serum creatinine as a predictor of pancreatic necrosis was calculated as 45.5%, specificity was 97.3%, positive predictive value was 85.0% and negative predictive value was 93.8%. The accuracy was 84.6%. The degree of agreement between PNec on SCr and PNec on CT scan was found to be 84.7 %. The AUC was 0.825. These results show that serum creatinine has a strong association with pancreatic necrosis and can be used as a predictor of pancreatic necrosis. Muddana *et al.*, studied the role of serum creatinine as a predictor of pancreatic necrosis. They studied a total of 129 patients. 15 patients had SCr > 1.8mg/dl predicting PNec and among these 14 were confirmed to have pancreatic necrosis on CT scan. 112 patients had SCr ≤1.8mg/dl suggesting the absence of PNec. On CT scan 92 patients were confirmed to have absence of necrosis. This showed that there was 83.5 % agreement between serum creatinine > 1.8mg/dl and CT scan on diagnosis of PNec. This study reported that SCr has a positive predictive value of 93%. Muddana *et al.*, concluded that an increase in SCr >1.8mg/dl within the first 48 h is strongly associated with the development of PNec [16]. One study has found that the sensitivity, and specificity of SCr in predicting pancreatic necrosis was 23% and 95%, respectively with PPV of 41% and NPV of 89%. According to this study, normal serum creatinine values at the time of presentation show that necrotizing pancreatitis is less likely and CECT is not needed unless complications occur [13]. A retrospective study of 2410 patients by Wiese *et al.*, demonstrated that a strong association with infected pancreatic necrosis was seen for creatinine (OR [95% CI] 1.019 [1.005–1.033], p < 0.001) [8]. The area under the curve (AUC) for serum creatinine in their study was 0.752. However, Wiese et showed that a predictive model has more diagnostic accuracy as compared to any of the serum markers alone. Another study by Papachristou *et al.*, concluded that early changes in serum creatinine can predict pancreatic necrosis and fatal outcomes [17]. Lipinski and colleagues found that elevated SCr and eGFR levels on admission in the initial 48 hours. are associated with increased severity and PNec with a p < 0.001 [18]. Hence this shows that findings in our study between PNec on SCr and CECT scan are comparable to that found in international literature. In our study Kappa statistics applied to determine the strength of agreement was found to be 0.51 with a p-value 0.001. Kappa coefficient of 0.51 shows a moderately strong degree of agreement [10]. A p-value of 0.001 shows that this agreement is highly significant statistically. Hence it shows that Peak serum creatinine >1.8 mg/l at 48 hours. is strongly correlated with pancreatic necrosis and may be used as a marker of pancreatic necrosis. The limitations of our study include that it was a single-center study. More such multicenter studies should be conducted to validate our results. In addition, in our study CECT scan was conducted within 96 hours. of admission, which could lead to missing the patients in whom pancreatic necrosis became evident after 96 hours. on CT scan. Also, we did not note the etiology and the severity of pancreatitis in this study and did not rule out their effect on the serum creatinine levels and pancreatic necrosis. Different scoring systems are used to estimate the severity of pancreatitis [19, 20] but the role individual biomarkers have not been studied yet. Also we did not differentiate infected pancreatic necrosis (IPN) from simple pancreatic necrosis in this study as some studies have shown association of biomarkers with IPN [5].

CONCLUSIONS

Severe acute pancreatitis (AP) presents a significant risk of mortality. Therefore, accurate prognostication of the disease's clinical trajectory at the time of admission is essential for formulating an effective treatment plan. Our study noted that elevated serum Cr >1.8 mg/dl within 48 h of admission can predict pancreatic necrosis with reasonable accuracy and hence can be used as a predictor of pancreatic necrosis.

Authors Contribution

Conceptualization: HSK

Methodology: HSK

Formal analysis: HSK

Writing-review and editing: HSK, MA, MH

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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