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Site and size of extrapancreatic necrosis are associated with clinical outcomes in patients with acute necrotizing pancreatitis

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ABSTRACT

Background: The site and size of extrapancreatic necrosis (EPN) as assessed on computed tomography may influence the severity of acute necrotizing pancreatitis (ANP). The objective of the study was to evaluate the impact of site and size of EPN on the clinical outcomes in patients with acute necrotizing pancreatitis (ANP).

Method and materials: This retrospective study comprised of consecutive patients with ANP who were admitted between January 2017 and March 2019. Patients in whom the initial contrast enhanced CT showed EPN were eligible for inclusion. The site, volume and maximum dimension of EPN were recorded. The severity of AP and modified CT severity index (MCTSI) was calculated. Clinical outcomes were recorded.

Results: A total of 119 patients (mean age, 37.56 years, 91 males) were included. There was a significant association between the location of EPN and the outcome parameters. The left posterior pararenal collections were significantly associated with mortality ($P = 0.041$), left paracolic gutter collections with the length of hospitalisation (LOH) ($P = 0.014$), and right paracolic gutter and mesenteric collections with the intensive care unit (ICU) stay ($P = 0.024$, and $P = 0.021$, respectively). There was a significant correlation between the volume and the maximum dimension of collection with LOH and ICU stay. The area under the receiver operating characteristic curve for volume, maximum dimension and MCTSI for predicting death was 0.724 (95% CI, 0.612–0.837), 0.644 (95% CI, 0.516–0.772) and 0.574 (95% CI, 0.452–0.696), respectively.

Conclusion: The site and size of EPN provide reliable and objective information for assessing clinical outcomes in patients with ANP.

Introduction

Acute pancreatitis (AP) is one of the most common conditions presenting to emergency department [1]. Mild acute pancreatitis is a self-limiting condition [2]. On the other hand, moderately severe AP and severe AP have significant morbidity and mortality [3]. Computed tomography (CT) plays an important role in evaluation of patients with AP. CT has an important role in detection of local complications, mainly the detection and characterization of fluid collections and planning their management [4]. The use of CT for prognostication is also desirable. Several CT based scoring systems have been proposed for predicting the clinical outcome in AP. The initial Balthazar score gave way to the CT severity index (CTSI) and modified CTSI (MCTSI) [4–6]. These earlier scoring systems gave a lot of weightage to the detection of pancreatic necrosis (PN) [4–6]. However, studies have shown that the detection of PN may not be mandatory. Patients may die within 48 h of systemic complications before the PN has set in while others may tolerate PN without organ failure [7,8]. Additionally, isolated extrapancreatic necrosis (EPN), a distinct clinical entity has been reported to constitute around 20–40% of the case of necrotizing AP [9,10]. These patients have no PN. Finally, a proportion of patients with acute kidney injury may not undergo contrast-enhanced CT, thus precluding the detection of PN [11]. Extrapancreatic inflammation on CT is an alternate CT scoring system that is based on the detection of pleural effusion,

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ascites and retroperitoneal fluid collection [12]. In a study comparing the various CT scoring systems, extrapancreatic inflammation on CT score was a slightly better predictor of the outcome including persistent organ failure (OF), intervention and mortality [13]. A recent study showed that the volume of EPN can be used as a simple grading system for predicting the severity of AP [14]. However, none of the published studies have evaluated the impact of the site and size of EPN on the clinical outcomes in patients with AP. In the present study, we assessed whether the site and size of EPN affect the clinical outcomes of patients with acute necrotizing pancreatitis.

Material and methods

This was a retrospective evaluation of a prospectively acquired database of patients with AP admitted in the gastroenterology unit of a tertiary care referral hospital between January 2017 and March 2019. The study was approved by the institutional ethics committee. The diagnosis of AP was based on the revised Atlanta classification [15]. Patients in whom the initial CECT performed between 5 and 7 days after onset of pain showed EPN were eligible for inclusion. Patients with acute on chronic pancreatitis were excluded. Baseline parameters including age, sex, etiology and severity of AP were recorded.

CT technique and evaluation

CECT scans were acquired on multidetector-row CT scanners (64-, 128- or 256-detector row scanners, ACT, GE Healthcare; Somatom Definition Flash, Siemens Healthcare; Philips iCT, respectively). CT scans were performed 65 s following intravenous injection of 80–100 ml of non-ionic contrast (Omnipaque ® 300 mg/mL, GE Healthcare). The scan parameters were tube current-300 mAs; voltage-120 kVp; pich-0.993; field of view-350 mm and slice thickness-1 mm. The entire abdomen was scanned from domes of diaphragm to pubic symphysis.

The images were assessed independently by two radiologists (PG and PR with 6 years and 3 years of experience in abdominal imaging, respectively) on Oxirix® viewer (Pixmeo, Geneva, Switzerland) or RadiAnt DICOM viewer (Medixant ®, Poznan, Poland). The disagreement regarding the site of EPN was resolved in consensus. Mean of the dimensions and volume measured by the two radiologists was considered for analysis. The radiologists were blinded to the clinical data and the outcome parameters. The MCTSI was calculated for all patients. Pancreatic necrosis was defined as a non-enhancing area or a hypoenhancing area with attenuation of <30 HU within the pancreatic parenchyma. The EPN was defined as a collection of fluid with or without solid component. The location of EPN was recorded (Fig. 1). The definition of various locations is given in Table 1. The craniocaudal, transverse and anteroposterior dimensions (in centimeters) of the largest EPN were measured. The volume of EPN (in milliliters) was calculated based on the three dimensions using the ellipsoid formula.

Management of fluid collections

A step-up approach was adopted for the management of fluid collections which involved initial conservative treatment followed by percutaneous catheter drainage (PCD) or endoscopic drainage. The indications of drainage of collection were suspected or proven infection, sepsis, persistent organ failure, and symptoms due compression of adjacent organs. Patients who failed to improve underwent upgradation (up to 24 Fr) or additional PCD placement. Patients who were not improving with above treatment were considered for percutaneous endoscopic necrosectomy or surgical necrosectomy depending on the clinical indication.

Outcome parameters

The clinical outcomes were collected from the patient case files. The following clinical outcomes were evaluated: length of hospitalization (LOH, in days), length of intensive care unit (ICU) stay (in days), need for necrosectomy, drainage (percutaneous or endoscopic), readmission (up to 12 weeks after discharge from hospital following first admission), and death (up to 12 weeks following discharge from the hospital).

Statistical analysis

Statistical analysis was carried out using commercially available software (IBM Statistical Package for the Social Sciences Statistics, release 23; SPSS, Chicago, Ill). The categorical variables were presented as frequencies and percentages. The continuous variables were expressed as mean with range. Categorical variables were compared using Chi-square test or Fischer's exact test based on the distribution in 2 × 2 table. Quantitative variables were compared using the Student *t*-test or Mann-Whitney *U* test, as appropriate. The normality of volume of EPN, maximum dimension of the EPN, hospital stay, and ICU stay distributions were analyzed using a Shapiro-Wilk test. The correlations between the volume of EPN/largest dimension of the EPN and hospital stay/ICU stay was analyzed using the Spearman rank correlation coefficient. All statistical analysis was carried out at a P value < 0.05 and was considered significant. A receiver operating characteristic (ROC) curve was constructed to determine the optimal threshold values of the EPN volume and maximum dimension for predicting the clinical outcomes. For the same clinical outcomes, ROC curves were also constructed for MCTSI. The area under the ROC curve (AUC) was calculated. Sensitivity and specificity were calculated for volume, maximum dimension and MCTSI.

Results

Patients characteristics

A total of 180 patients with AP were evaluated during the study period. Sixty-one patients had no fluid collections (n = 37) or had only pancreatic necrosis (n = 34). Finally, 119 patients with EPN were included in the study. Baseline characteristics are shown in Table 2.

Site and size of EPN

The sites of the EPN are shown in Table 3. Single EPN was present in 25 (21%) patients and multiple EPNs were recorded in 94 (79%) patients. The most common location was lesser sac (n = 96, 80.6%), followed by left anterior pararenal (n = 60, 50.4%), and left paracolic gutter (n = 44, 36.9%), with right posterior pararenal being the least common (n = 8, 6.7%).

The mean volume of EPN was 603.19 mL (range, 45–4853 mL). The mean of maximum dimension of EPN was 13.64 cm (2.5–30.5 cm).

Association between site and clinical outcome

There was no significant difference in the clinical outcomes in patients with single EPN compared with those having two or more EPNs ($P = 0.90$). There was a significant association between mortality and the left posterior pararenal collections ($P = 0.041$). A significant association was found between the need for PCD and

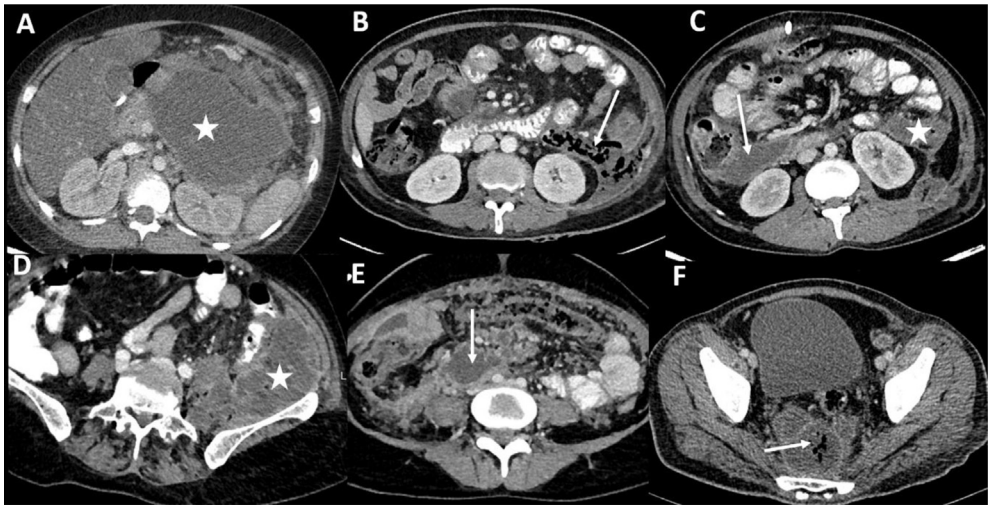

Fig. 1. Sites of EPN on contrast enhanced CT scan in different patients. A. A large collection is seen in the lesser sac (star). B. There is a collection in the left anterior and posterior pararenal space (arrow). C. A collection is seen in the right anterior pararenal space (arrow). Also note a collection in left anterior pararenal space (star). D. A large left paracolic gutter collection is seen (star). E. There is a collection in the mesentery (arrow). F. A collection is seen in the pelvis (arrow).

Table 1
Definition of locations of extrapancreatic necrotic collections.

Location	Definition
Lesser sac	Collections in lesser sac with/without extension to the perihepatic/subhepatic/gastrosplenic or perisplenic locations
Anterior pararenal	Collections located anterior to kidneys
Posterior pararenal	Collections located posterior to kidneys
Paracolic gutter	Collections located lateral to the colon
	Right PCG: lateral to the caecum and ascending colon
	Left PCG: lateral to the descending colon
Pelvic	Collections in pelvis
Mesenteric	Collections in small bowel mesentery/transverse mesocolon/sigmoid mesocolon/omentum

Table 2
Baseline characteristics of 119 patients with AP.

Parameters	Results
Age (years)	37.56 (range, 14-66)
Male to female ratio	3.25 (91/28)
Etiology of pancreatitis	
• Alcohol	64 (53.7%)
• Gallstones	29 (24.3%)
• Both alcohol and gallstones	7 (6%)
• Post-ERCP	16 (13.5%)
• Idiopathic	3 (2.5%)
Severity of AP	
• Moderately severe	24 (20.2%)
• Severe	95 (79.8%)
MCTSI	8.69 (range, 4-10)
Length of hospitalization (days)	29.22 (4-83)
Length of ICU stay (days)	6.18 (0-45)
Readmission	12 (10.1%)
Need for intervention	
• PCD	88 (73.9%)
• Endoscopic drainage	25 (21%)
• Necrosectomy	15 (12.6%)
Death	24 (20.2%)

AP: acute pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography; ICU: intensive care unit; MCTSI: modified CT severity index; PCD: percutaneous drainage.

lesser sac collections ($P = 0.007$) and right posterior pararenal space collections ($P = 0.028$). Right posterior pararenal space collections were also found to have a significant association with readmission ($P = 0.042$). The left paracolic gutter collections had significant association with length of hospitalization ($P = 0.014$) while right paracolic gutter collections and mesenteric collections had significant association with length of ICU stay ($P = 0.024$ and $P = 0.021$, respectively). There was no significant association between the location of collection and surgery.

Association between size and clinical outcome

Volume

There was a significant correlation between the volume of EPN and the length of hospitalization (Spearman's correlation coefficient 0.253, $P = 0.006$) and length of ICU stay (Spearman's correlation coefficient 0.271, $P = 0.003$). The volume of EPN also had a significant association with mortality ($P = 0.044$). However, there was no significant association with the need for surgery ($P = 0.907$), PCD ($P = 0.617$) or readmission ($P = 0.571$). Fig. 2 shows the association of the volume of EPN with the clinical outcomes.

Maximum dimension

The maximum dimension of EPN had significant correlation with length of hospitalization (Spearman's correlation coefficient 0.296, $P = 0.001$) and ICU stay (Spearman's correlation coefficient 0.285, $P = 0.002$). The maximum dimension of EPN also had a significant association with mortality ($P = 0.020$). There was no significant association with the need for surgery ($P = 0.655$), PCD ($P = 0.227$) or readmission ($P = 0.364$).

Fig. 3 shows the correlation between the size of collection and length of hospital and ICU stay.

Table 3
Site of EPN in 119 patients with AP.

Site of EPN	Number
Lesser sac	96 (80.6%)
Anterior pararenal	
• Right	27 (22.6%)
• left	60 (50.4%)
Posterior pararenal	
• Right	8 (6.7%)
• Left	26 (21.8%)
Paracolic gutter	
• Right	31 (26%)
• Left	44 (36.9%)
Pelvic	16 (13.4)
Mesenteric	42 (35.3%)

ROC curves

The AUROC for volume of EPN, maximum dimension of EPN and MCTSI for predicting the severity of AP was 0.605 (95% CI, 0.475–0.754), 0.633 (95% CI, 0.500–0.766), and 0.627 (95% CI, 497–758), respectively. The sensitivity, and specificity of volume (cut-off of 385 mL), maximum dimension (cut-off of 12.9 cm), and MCTSI (cut-off of 8) were 70.8% and 66.3%, 66.7% and 52.6%, and 80% and 35%, respectively.

The AUROC for volume of EPN, maximum dimension of EPN and MCTSI for predicting death was 0.724 (95% CI, 0.612–0.837), 0.644 (95% CI, 0.516–0.772), and 0.574 (95% CI, 0.452–0.696), respectively. The sensitivity, and specificity of volume (cut-off of 261 mL), maximum dimension (cut-off of 12.4 cm), and MCTSI (cut-off of 8) were 64.9% and 59.3%, 62.8% and 62.5%, and 68% and 48%, respectively.

The ROC values for other clinical outcomes are given in Table 4 and ROC curves are shown in Fig. 4.

Discussion

In this study, we found that the site and size of EPN are associated with severity as well as various clinical outcomes of patients with AP. We found that the left posterior pararenal space EPNs had a significant association with mortality. Lesser sac and right posterior pararenal space EPNs had a significant association with the need for percutaneous drainage. Patients with EPNs in left paracolic gutter had a significant longer hospitalization while those having EPNs in right paracolic gutter and the mesentery had a significant longer ICU stay. We also found that the size of EPN (volume as well as the largest dimension) had a significant correlation with the length of hospitalization and ICU stay. The AUROC for the size of collection was better than MCTSI for predicting severity, mortality as well need for PCD.

CT scoring systems have a variable accuracy in predicting the clinical outcomes of patients with AP [4–6,12]. CTSI and MCTSI are the most commonly used CT indices in clinical practice [5,6]. However, these scoring systems that give significant weightage to the PN have certain limitations including the need for contrast administration, inability to predict prognosis early in the course of the disease when PN is not visible, and moderate interobserver agreement [8,11]. Additionally, correlation between PN and OF in AP is controversial [11]. Investigators have shown that CT scoring systems that do not include PN have a comparable or better performance [12]. A recent study showed that volume of EPN could be

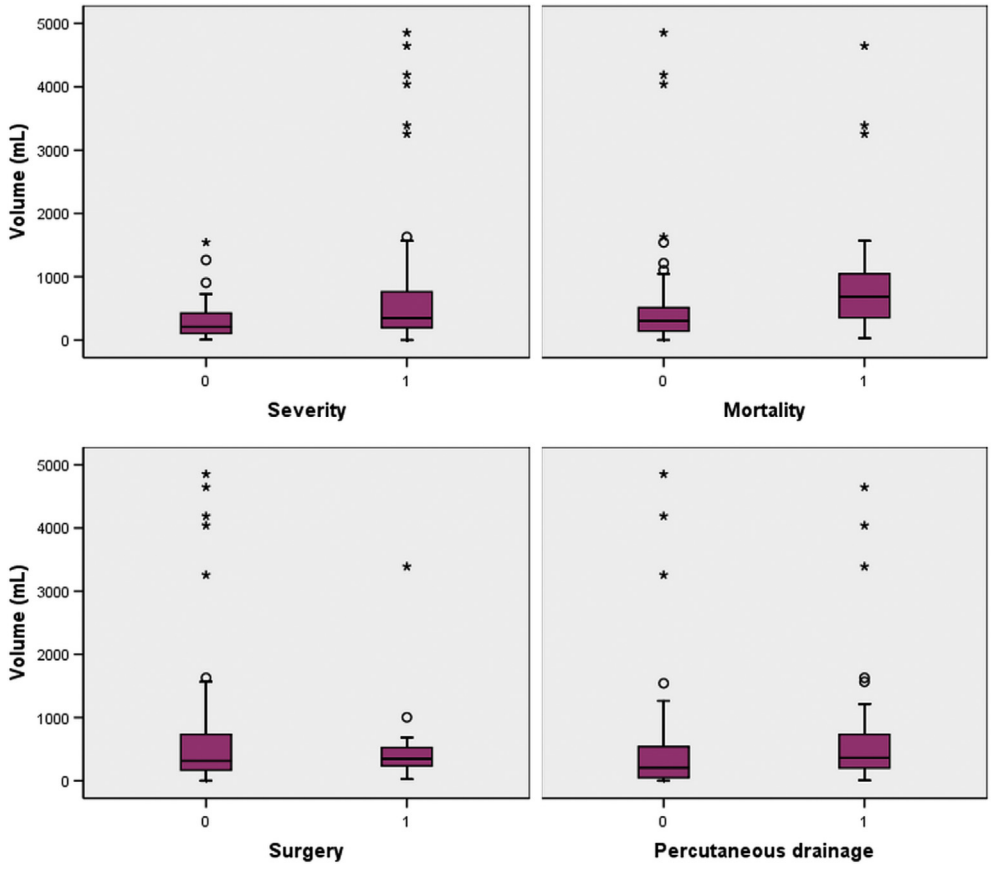

Fig. 2. Box plots show significant association between the volume of EPN and mortality. No significant difference is seen for the rest of the parameters.

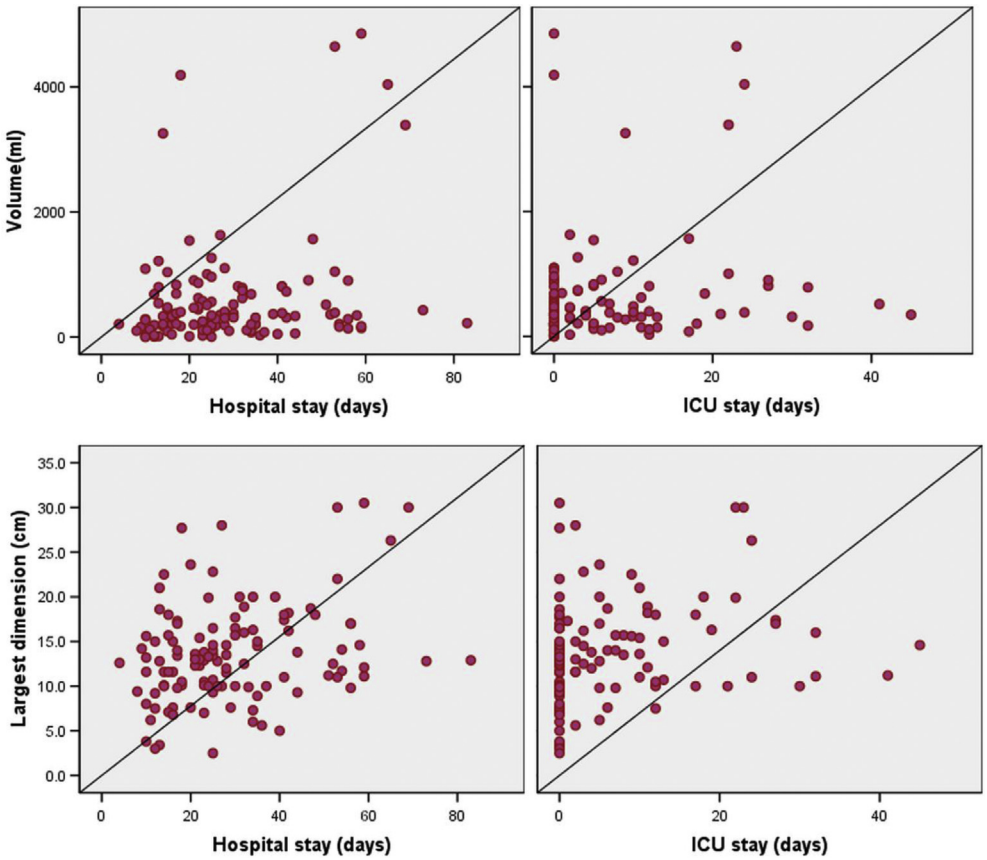

Fig. 3. Upper panel of scatter plots show the correlation between the volume of EPN and the length of hospital stay and ICU stay. Lower panel shows the correlation between the largest dimension and the length of hospital stay and ICU stay.

Table 4
Association between site and size of collection with various clinical outcomes.

EPN feature	*P*-value			
	Mortality	Surgery	PCD	Length of hospital stay
Site				
LS	0.712	0.184	**0.008**	0.326
RAPR	0.396	0.087	0.330	0.871
LAPR	0.185	0.594	0.567	0.803
RPPR	1	0.594	**0.028**	0.608
LPPR	**0.041**	0.316	0.675	0.871
RPCG	0.153	0.954	0.609	0.099
LPCG	0.139	0.755	0.287	**0.014**
Pelvis	0.054	0.753	0.207	0.755
Mesentery	0.800	0.455	0.479	0.767
Size				
Volume	**0.044**	0.907	0.617	**0.253**[a]
Maximum dimension	0.020	0.655	0.227	**0.296**[a]

[a] Spearman's correlation coefficient, LS-lesser sac, RAPR-right anterior pararenal, LAPR-left anterior pararenal, RPPR-right posterior pararenal, LPPR-left posterior pararenal, RPCG-right paracolic gutter, LPCG-left paracolic gutter.

used as an independent predictor of severity [14]. However, none of the published studies have evaluated the impact of the site of EPN on the clinical outcomes. In a study by Rana et al. extensive EPN was defined as one extending to the paracolic gutters and/or pelvis [16]. It was reported that patients with extensive EPN have increased frequency of pleural effusion, ascites and multiple OF. However, there was no significant association between the extent of EPN and mortality/need for intervention. However, this study or any other published study, to the best of our knowledge has not evaluated the impact of the location of EPN on the clinical outcome. The significant association between the lesser sac and right posterior pararenal space EPN and need for PCD could be explained by the fact that lesser sac is the most common site of EPN due to its contiguity with pancreatic parenchyma. In addition, there is usually a communication between lesser sac EPN and EPN in the left pararenal space and left paracolic gutter. Both left pararenal and left paracolic gutter collections were seen in 32 (33.3%) patients with lesser sac EPN. Hence, draining the lesser sac EPN achieves a dual purpose of draining the native EPN as well as its extension into the left retroperitoneal spaces. Additionally, lesser sac EPN drainage may prevent the further extension of the pancreatic juices.

The significant association between the need for drainage and right posterior pararenal space EPN is not clear. The significant association between the left posterior pararenal space EPN and mortality may signify a greater extent of retroperitoneal inflammation. Paracolic EPNs were found to have significant association with the length of hospitalization and length of ICU stay. Rana et al. found a higher frequency of multiple OF for EPN extending to paracolic gutter; however, they did not report association with the length of hospitalization/ICU stay [16]. The association with multiple OF may explain a longer hospital and ICU stay. Patients with mesenteric collections were also found to have a significantly longer ICU stay. Mesenteric collections are difficult to drain by percutaneous as well as endoscopic methods and may be the manifestation of bowel fistulisation, hence may explain the longer ICU stay.

The volume of EPN has been reported as an early predictor of severity of AP [14]. In their study, Meyrignac et al. found that the volume of EPN is a simple grading method to predict severity, OF,

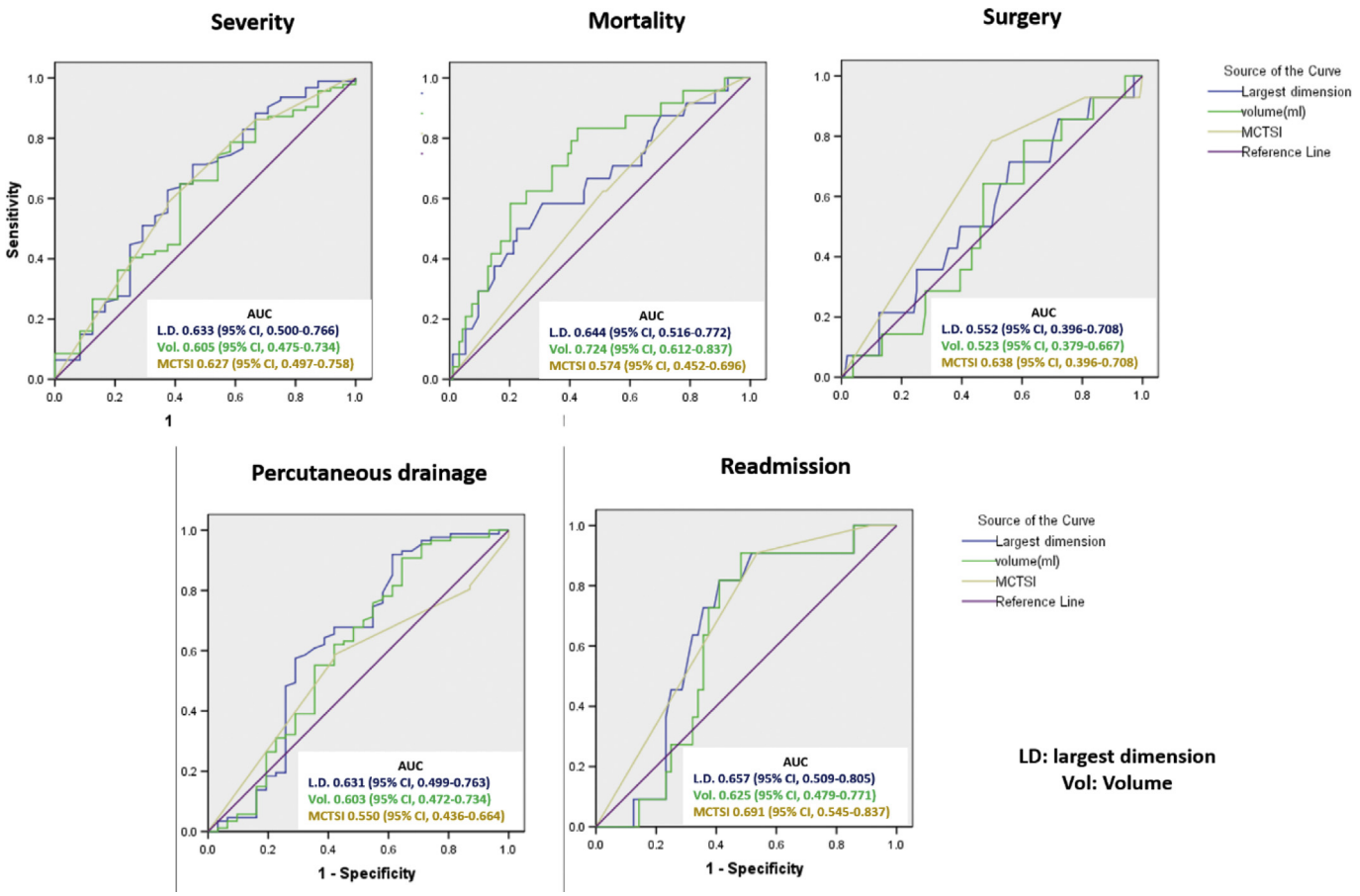

Fig. 4. Receiver operating characteristic curves for largest dimension of EPN, volume of EPN and modified CT severity index (MCTSI) in predicting severity, mortality, surgery, percutaneous drainage and re-admission.

infection, length of hospitalization, need for intervention and mortality [14]. They suggested a cut-off of 100 mL for predicting severity. In another study, Koutroumpakis et al. classified EPN based on the size [17]. Using a cut-off of 5 cm, they classified EPN into limited and extensive. They found significant association between extensive necrosis and need for surgical intervention, OF and length of hospitalization. A recent study by Çakar et al. found moderate positive correlation with the length of hospital stay [18]. Our study shows similar results with volume as well as the maximum dimension of EPN showing significant correlation with clinical outcome. However, unlike the study by Meyrignac et al. we found larger cut-offs for predicting the various clinical outcomes [14]. Additionally, the diagnostic performance of volume was less compared to the study by Meyrignac et al. [14]. These differences are probably due to the larger baseline volume of EPN in our study. The mean volume of EPN in our study was 603.19 mL compared to 114 mL in the study by Meyrignac et al. [14]. Additionally, all the patients in our study had necrotizing pancreatitis with clinically moderately severe and severe disease. In the study by Meyrignac et al. 60% patients had mild AP [14]. Despite these differences, like previous study by Meyrignac et al. we found that the volume of EPN had a larger AUROC compared to MCTSI for predicting mortality and need for PCD [14].

Similar to results of the study by Koutroumpakis et al. the dimension of collection predicted the clinical outcomes [17]. We found a larger optimal cut-off for predicting the clinical outcomes. This variation may be explained by the differences in the study groups. While Koutroumpakis et al. studied patients with isolated EPN, we had patients with combined PN and EPN as well as isolated EPN [17].

There were a few limitations to our study. Although, the overall sample size was large, there were relatively few patients with EPNs in certain locations. This may have affected the significance of certain results. The volume was calculated using the three dimensions of the EPN rather than the manual segmentation technique used by Meyrignac et al. [14]. The volume derived by taking three dimensions of EPN is more practical, although the limitation is over-estimation or under-estimation as the EPNs are not perfect ellipsoids. While more accurate, manual segmentation is time-consuming, especially for radiologists not routinely using this technique. Moreover, volumetry using manual segmentation may not be available on all workstations. However, as this method is more accurate, further studies employing this method will yield more reliable results.

In conclusion, the site and size of EPN is highly correlated with the clinical outcomes in patients with AP with a performance better than MCTSI for certain outcomes. A scoring system incorporating these objective measures may be more useful that the currently utilized CT-based scoring systems.

Financial disclosure

None.

Declaration of competing interest

None.

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