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Original Research Article

Ultrasonography based imaging criterion to ascertain pancreatic enlargement in pediatric acute pancreatitis

Dhanraj S Raut[1,*], Shubhangi A Desai[2], Dhananjay V Raje[2], Dinesh Singh[3], Vithalrao P Dandge[1]

[1] *Dept. of Paediatrics, NKP Salve Institute of Medical Sciences, Nagpur, Maharashtra, India*
[2] *MDS Bio-Analytics Pvt. Ltd., Mumbai, Maharashtra, India*
[3] *Spiral CT Sacan and Diagnostic Centre, Nagpur, Maharashtra, India*

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ABSTRACT

Introduction: Imaging studies have shown enlargement of pancreatic parts in children diagnosed with acute pancreatitis. The purpose here is to develop imaging based diagnostic evaluation criterion for acute pancreatitis in children.
Materials and Methods: This study included 62 children of acute pancreatitis in the age range of 0.33 to 13 years, as reported in a single hospital center (1994-2019). A study was planned including 1116 normal healthy children in the age range of 0.16 to 18 years for pancreatic evaluation during 2016-17. Ultrasonography based measurement of three pancreatic parts were obtained for each individual in disease and normal groups. Age-adjusted receiver operating characteristics curve analysis was performed on each pancreatic part independently to derive respective cut-offs using a training set. These cut-offs were further referred to dichotomize the measurement data for each individual and was subjected to multiple logistic regression with presence/absence of acute pancreatitis as dependent variable. A probability score and accordingly the cut-off were obtained indicating a collective impression of enlargement of pancreas in disease condition independently for males and females.
Result: On test data, the accuracy of age-adjusted cut-offs for three parts was near 80% for males, while it ranged between 81-85% for females. ROC analysis of probability score resulted into threshold value of 0.024 for males and 0.044 for females, with sensitivity of 94.11% and 90.91% respectively. The classification accuracy of score derived for males and females was nearly same (83%).
Conclusion: The extent of enlargement of pancreas in acute pancreatitis in children can be determined using the MLR method along with hypoechogenicity.

1. Introduction

Acute pancreatitis (AP) is an emerging problem in pediatrics with most cases resolving spontaneously.[1] In the year 1935, Dobbs first drew attention to the occurrence of AP in children.[2] Pediatric onset of AP is labeled when the first episode of AP occurs before the patient's 19^{th} birthday.[3,4] The disorder spans across pediatric age range, with either focal or diffuse process, and may occur as a single episode, recur or become chronic.[5,6] Recent studies Estimate the incidence of AP between 3.6 and 13.2 cases per 100,000 children per year.[7] The INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) consortium meeting in December 2010 and May 2011 operationally defined the diagnosis of AP as requiring two of the following three criteria:(a) abdominal pain

* *Corresponding author*.
E-mail address: 147dsr@gmail.com (D. S. Raut).

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compatible with acute pancreatitis (b) serum amylase or lipase levels greater or equal to three times the upper limits of normal, and (c) imaging findings consistent with AP.[3,4,8,9] As per the first INSPPIRE criterion, acute onset of persistent upper abdominal pain, along with nausea and vomiting is the hallmark symptom of AP.[10] Measurements of serum lipase had a sensitivity and specificity of 96.6% and 99.4% respectively, whereas serum amylase had a sensitivity and specificity of 78.6% and 99.1% respectively.[11] The urinary amylase excretion is highly sensitive indicator of presence of AP.[12]

Currently, ultrasonography (USG), Computed Tomography (CT) and magnetic resonance imaging are the three widely used imaging modalities for evaluating pancreatitis in the pediatric population.[13] Abdominal USG is used as the radiologic procedure of choice with symptoms referable to the pancreas.[1,3,7,14–16] USG findings in AP often result in a hypoechoic gland that is focally or diffusely enlarged.[9,15,17] Nearly 20% or more with AP initially had normal imaging findings especially in early stages or mild cases.[5] The sensitivity of trans-abdominal ultrasound in detecting pancreatitis was reported as 79.4%.while the sensitivity of CT was reported as 47- 81%.[1,13] Referring to the imaging criterion of INSPPIRE as on date, there are no specific guidelines to decide the enlargement of pancreas in AP. Therefore, this study aims at determining the extent of enlargement of head, body, and tail of pancreas in AP cases, already diagnosed with clinically and biochemically documented criteria. Till date, no study has focused on the entire three parts together and derived criterion for enlargement of pancreas in the disease condition.

2. Materials and Methods

This is a retrospective study in which we reviewed the medical records of total 69 children diagnosed with acute pancreatitis from a single hospital (Children) located in a mega town of Central India. The age of children ranged between 3.5 months to 13 years as reported during the period of September 1994-July 2019. The completed demographic, clinical, biochemical and radiological details were retrieved from medical records for the children. Out of these 69 cases, 63 satisfied two of the three INSPPIRE criteria and were considered for downstream analysis. Amongst these: a) 61 patients presented with severe epigastric abdominal pain with persistent vomiting b) serum amylase level was more than 375 IU /L (Normal: 25 to 125 IU/L by kinetic method) in 41 cases and the urinary amylase was raised more than 48.1 IU/ hr (normal 6 to 48.1 IU/hr by kinetic method) in 25 cases with c) abdominal USG finding with enlarged, bulky and hypoechoic pancreas in 37cases reported by the radiologist. According to INSPPIRE criteria 2 out of 3 are required for diagnosis of AP in children, accordingly in present study pain in abdomen was observed in 61 patients and with raised serum amylase in 39 cases, which fulfill the criteria to be labeled as AP in 39 cases. In remaining 22 cases having pain in abdomen with positive abdominal USG and raised urinary amylase constitute the criteria for diagnosis of AP in 22 cases. Hence total 61 cases were diagnosed and in remaining 2 cases the pain in abdomen was not presenting feature. Out of these two cases, in one case, infant was 3.5-month old had extreme irritability with positive abdominal USG along with raised serum amylase. In other case presented with painless pancreatitis and the diagnosis was made on the basis of two criteria as raised serum amylase and positive abdominal USG. Thus, above 63 cases fulfilled the INSPPIRE criteria for diagnosing AP. It was observed that the lipase study was not done. From the record it was observed that the urinary amylase was tested in 28 patients and in 25 showed raised levels. Urinary amylase testing was done, when the patient presented after 4 days of pain in abdomen (After 4 days, serum amylase level may become normal in AP patients[5]). All the patients received medical treatment and were followed up for the entire hospital course until clinical recovery. The clinical recovery was judged by disappearance of epigastric tenderness. Upon clinical recovery, every patient was subjected to second abdominal USG, and accordingly the scans were available. A sample sonogram at diagnosis and after recovery is shown in Figure 1. To establish the imaging-based criterion for enlargement of pancreas in AP, a study to generate normative data on pancreatic dimensions was planned during June 2016-December 2017, in which normal children were enrolled for abdominal USG evaluation. The aim was to establish the age and gender-specific pancreatic dimensions in normal children, so as to ascertain the pancreatic enlargement in the disease condition. Till December 2017, at total of 1116 children in the age range of 2 months to 18 years were included in the control group, upon proper consent from parents. The inclusion criteria in control group were: (a) normal healthy siblings of patients attending outpatient department and those visiting for vaccination, and (b) those children without any clinical or laboratory evidence of pancreatic disorder. Exclusion criteria from the pancreatitis group were children having protein energy malnutrition (according to Indian Academy of pediatrics classification), type I diabetes mellitus, cystic fibrosis, premature infants & neonates and clinical or laboratory evidence of hepatic diseases and obesity where echogenicity gets altered, were excluded from the acute pancreatitis category.[16,18–24] The demographic and anthropometric details of these children were obtained using standard protocols. The Institutional Ethics Committee‘s approval was sought before the study.

2.1. Abdominal Ultrasonography

A radiological center with the qualified radiologist performing the ultrasonography remained the same

throughout this study. During the course of study, two duly calibrated machines with 3.5, 5.0, 7.5, MHz sector electronic probes were used.

1. Period 1994 to Jan 2007, Toshiba Capasee – Japan [SSA-220A] machine was used and 19 cases of AP were studied.
2. Period Feb 2007 to July 2019, Sonoacc X8 Medison-Korean [SAX8] was used and 44 cases of AP and all the control group children (1116) were studied.

2.2. Anatomical landmarks

2.2.1. Pancreatic head

For measuring head of pancreas, duodenum, which envelops the lateral and caudal contour of the head, was taken as a landmark for measurements,where the pancreatic head was usually directly ventral to the inferior vena cava.[16,25,26]

2.2.2. Pancreatic body

The superior mesenteric artery and splenic vein served as an important landmark for localization of the body of pancreas.[16,25]Compression scanning with a "large footprint" curved linear transducer was the key technique in visualizing the body of pancreas.[26]

2.2.3. Pancreatic tail

The splenic artery and vein, facilitated identification of tail of pancreas with the scanning through the spleen and left kidney, as the tail was opposite to the medial margin of left kidney.[16,26]

The sonographic examination of pancreas involved assessment of the greatest anteroposterior dimension of head, body and tail regions, as well as the overall texture, when compared with that of liver at a similar depth. The maximum anteroposterior diameter of head, body and tail were measured perpendicular to the long axis of the organ on transverse/oblique images. If pancreas was oriented transversely across the abdomen, the entire gland could be seen in single image. However, the pancreas often had varying degree of obliquity, with the tail lying more cranial than the head and body. In these cases, several images were necessary to demonstrate the entire gland.[16]Pancreatic echogenicity was determined by comparison with the adjacent liver at a similar depth on both transverse and longitudinal views, and categorized as less than, equal to, or greater than liver echogenicity.[16,21]

2.3. Statistical analysis

The descriptive statistics for demographic and anthropometric parameters were obtained for normal and AP groups. Subjects were classified according to gender and all analyses related to pancreatic parts were performed separately for each gender. A schematic representation of the analysis flow is given in Figure 2. In each group, data were partitioned into training and test set. In the normal group, the partitioning ratio was 80:20%, while in the disease group; it was 66:33%. Thus, the training set comprised of 894 normal and 40 disease cases, while the test set had 212 normal and 22 disease cases. Since age has direct relevance to the size of the pancreas, it was considered as a covariate in the analysis. Accordingly, age-adjusted receiver operating characteristics (ROC) analysis was performed on each perusing the training data set. The threshold value for each part was determined using Youden's index, and the diagnostic criteria like area under curve (AUC), sensitivity, specificity, and accuracy were obtained for the threshold value of each part. The thresholds were used on the test data set to determine their diagnostic strength. The age-adjusted pancreatic dimensions on three parts were dichotomized with 0 indicating value below threshold (no enlargement) and 1 indicating above threshold (enlargement) for each subject. This categorical transformation on three parts was treated as independent variable space, while the AP status was referred as an outcome. To obtain a unified diagnostic criterion based on three parts, a multiple logistic regression (MLR) was performed, which resulted in a probability score for each subject. ROC analysis was performed on probability scores to obtain a threshold score and its diagnostic ability was evaluated on the test data set. All the analyses were performed using R-3.4.3 (R Core Team, Vienna, Austria).

3. Results

A total of 1178 children, 1116 control and 62 out of 63 diagnosed with AP, were considered in the study. One patient died during the hospital stay. Out of 62 cases, 32 (51.6%) had mild AP, 7 (11.29%) had moderately severe AP, while 23 (37.0%) had severe AP.[1]The summary statistics like mean and standard deviation were obtained for demographic and anthropometric characteristics of individuals in both the groups, as shown in Table 1. The overall characteristics of the two groups were comparable. The median time between onset of symptoms and admission to hospital was 4 days with a mean of 5.43 (SD: 8.25 days); and about 92% of the cases required hospitalization. The median hospital stay was 8 days and the median duration of illness of patients was 12 days. The mean age-adjusted dimension of each pancreatic part in the disease group was significantly higher than that of the normal group (P value < 0.0001), indicating the tendency of enlargement in AP condition.

3.1. Age-adjusted ROC analysis on pancreatic measurements

To derive thresholds for each part, age-adjusted ROC analysis was performed on the training set according to gender. For males, the thresholds for head, body, and tail were 1.26 cm, 1.10 cm, and 1.20 cm respectively (Table 2), with the corresponding AUCs 91.8%, 92.7% and 84.2% (Figure 4). On similar lines, for females, the thresholds for head, body, and tail were 1.30 cm, 1.10 cm, and 1.26 cm respectively, with the corresponding AUCs 89.9%, 92.4% and 89.8%. The sensitivity and specificity corresponding to these thresholds showed inconsistency in both gender types. For example, in males, the sensitivity of head was maximum (92.4%), while specificity was maximum for tail (84.2%). Similarly, in females, sensitivity was maximum for body (92.12%), while specificity was maximum for head (86%). Therefore, for each gender type, an integrated approach involving all three parts was adopted using MLR to obtain probability scores and thereby a classifier.

3.2. ROC analysis of probability scores

ROC analysis on these scores resulted in a threshold value of 0.024 for males and 0.044 for females, such that a value above these thresholds is indicative of pancreatic enlargement with the possible disease condition. The sensitivities were 94.11% for males and 90.91% for females (Figure 3). The diagnostic strength of various thresholds was evaluated on the test data set as shown in Table 2. As regards individual age-adjusted ROC thresholds, the classification accuracy for males was near 80%, while for females, it ranged between 81 to 85%. The classification accuracy of the probability score derived from MLR for males and females was nearly the same (83%).

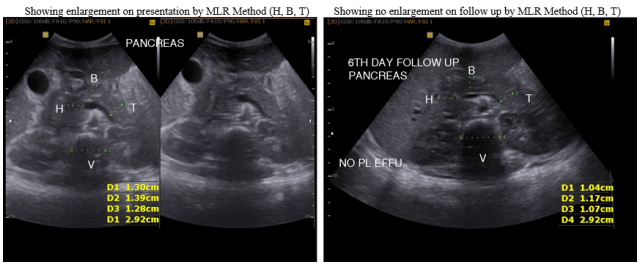

Fig. 1: Ultrasosnography images showing pancreas at diagnosis and after 6 days upon clinical recovery for a sample patient - in 4.5 years male.

4. Discussion

USG is widely recommended as it can detect the hypoehoic gland that is diffusely or patchily enlarged in such disease condition. The present study targeted the imaging modality to assess pancreatic enlargement, which is one

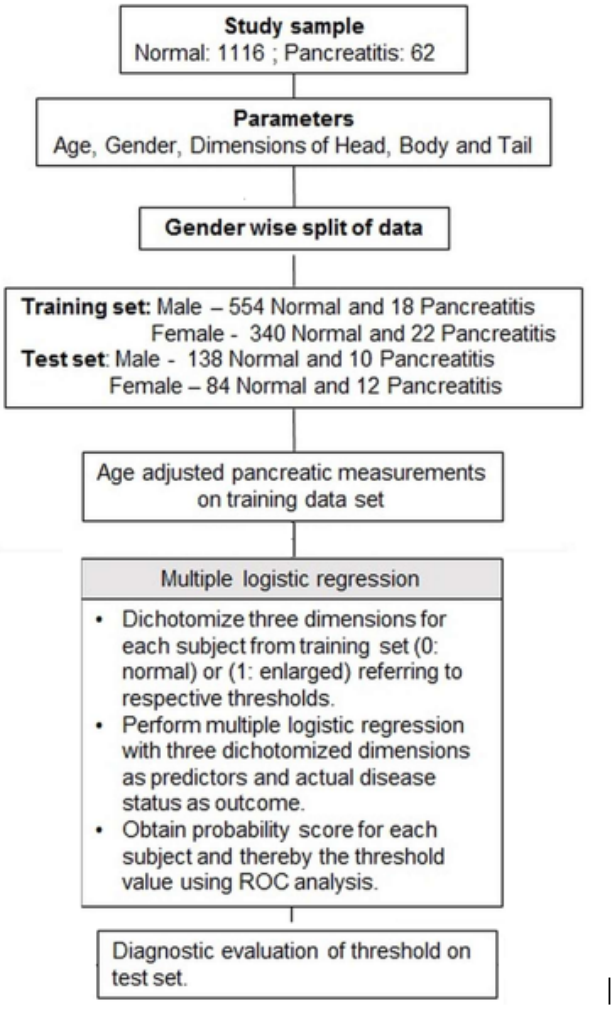

Fig. 2: Analysis flow to obtain imaging-based diagnostic criterion for acute pancreatitis

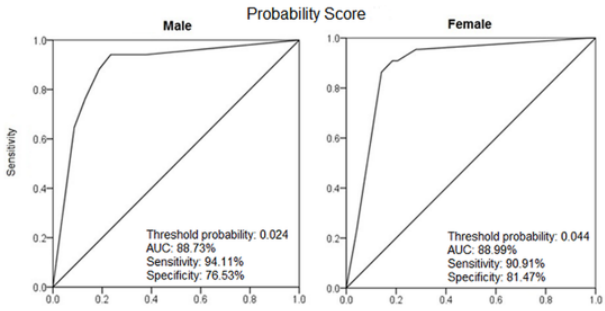

Fig. 3: Receiver operating characteristic (ROC) curves according to gender for training data using multiple logistic regression (MLR) approach

Table 1: Descriptive statistics for individual characteristics in two groups

Characteristics	Normal (n=1116)	Pancreatitis (n=62)	P-value
Age in years [Mean ± SD]	6.71±4.42	7.78±2.78	0.064[a]
Gender [No. (%)]			
Male	626 (56.1)	28 (45.2)	0.120[b]
Female	490 (43.9)	34 (54.8)	
Height(cm)[Mean ± SD]	113.03±27.28	119.21±14.11	0.082[a]
Weight(kg) [Mean ± SD]	19.18±11.37	20.05±7.19	0.567[a]
Pancreas dimension (age-adjusted)			
Head (cm) [Mean ± SD]	0.995±0.333	1.873±0.636	< 0 .0001[a] (S)
Body (cm) [Mean ± SD]	0.910±0.253	1.702±0.533	< 0.0001[a] (S)
Tail (cm) [Mean ± SD]	0.972±0.277	1.643±0.554	< 0.0001[a] (S)

[a] Obtained using independentt-test; [b] Obtained using Chi Square test; S: Significant

Table 2: Diagnostic evaluation of different methods on test data set for both gender types

Method - Pancreatic part (cut-off)	Classification accuracy	
	Male	Female
Age-adjusted ROC		
Head (Male:1.26 cm; Female:1.30 cm)	80.41%	82.11%
Body (Male:1.10 cm; Female:1.10 cm)	81.76%	81.05%
Tail (Male:1.20 cm; Female: 1.26 cm)	80.01%	85.26%
Multiple Logistic Regression (MLR)		
Probability score (Male: 0.024; Female: 0.044)	83.78%	83.15%

Table 3: Enlargement of pancreas in acute pancreatitis cases at 1^{st} presentation and after clinical recovery using different methods (N=62)

Method	1^{st} abdominal USG AP [a]	2^{nd} abdominal USG:After clinical recovery [b]
Body > 1.5 cm (Khanna et al.)	36 (58.1)	4 (6.5)
Mean ± 2SD (Siegel et al.)		
Head	32 (51.6)	3 (4.8)
Body	41 (66.1)	5 (8.1)
Tail	33 (53.2)	12 (19.3)
Percentile curves (Raut et al.)		
Head	33 (53.2)	4 (6.5)
Body	44 (70.9)	4 (6.5)
Tail	30 (48.4)	10 (16.1)
MLR	55 (88.7)	20 (32.2)

aHypo-echogenicity was observed in 61 patients and Hyper echogenicity in 1 patient; [b] All 62 patients showed iso-echogenicity

of the INSPPIRE diagnostic criterion. Earlier, Khanna et al.proposed a criterion of body dimension more than 1.5 cm as indicative of enlargement. Later, Siegel et al.suggested a criterion: dimension of any part exceeding 2SD above the mean as indicative of AP.[16,17] Recently, Raut et al.developed percentile curves for each part based on data of normal children.[27] In the present study, the threshold measurements were obtained for each part using the age-adjusted ROC analysis. Subsequently, the probability score based classifier, as indicator of enlargement, was obtained using MLR. Table 3 provides the number of cases showing enlargement at presentation and after clinical recovery. As per the criterion by Khanna et al.' 36(58.1%) had enlargement on day 1, while 4(6.5%) showed enlargement even after clinical recovery.[17] The criterion by Siegel et al. detected 41(66.1%) cases based on body dimension, followed by 33(53.2%) using tail and 32(51.6%) using head. After clinical recovery, tail showed maximum i.e. 12(19.3%) cases as still enlarged. The percentile curves proposed by Raut et al. detected 44(70.9%) cases with body dimension above 95% percentile, followed by 33(53.2%) on head and 30(48.4%) on tail.[27] A visual representation of the shift in dimensions on percentile plots is shown in Figure S2. The multiple regression models detected 55(88.7%) cases with enlargement at first presentation, while 20(32.2%) cases continued to show enlargement after clinical recovery.

The severity of AP in children as defined by the consensus committee was referred.[1] The maximum i.e. 32 (51.6%) cases had mild, 7(11.29%) moderate, while

Table 4: Description of various parameter according to severity of pancreatitis

	Mild AP	Moderate AP	Severe AP	Total
Total number of cases	32 (51.6%)	7 (11.29%)	23 (37%)	62
Time interval between pain in abdomen and admission in Days[a] [Mean±SD] (Median)	3.35±2.48 (3)	3.71±2.43 (3)	6.35±6.22 (5)	-
Time interval between pain in abdomen and 1^{st} abdomen USG in Days[b] [Mean±SD](Median)	4.35±2.81(4)	4.14±2.48(3)	7.17±6.51(5)	-
First abdominal USG				
Within 48 hours	14 (73.7%)	2 (10.5%)	3 (15.8%)	19
After 48 hours	18 (41.9%)	5 (11.6%)	20 (46.5%)	43
Enlargement by MLR	25 (45.5%)	7 (12.7%)	23 (41.8%)	55
Enlargement type: Global	18 (43.9%)	5 (12.1%)	18 (43.9%)	41
Enlargement type: Patchy	7 (50 %) [H & B: 5; B & T:2]	2 (14.3%) [H & B:2]	5 (35.7%) [H & B:4 & B:1]	14
No enlargement by MLR	7 (USG within 48 hr)	0	0	7
Second abdominal USG on clinical recovery				
Enlargement by MLR	0	5 (25%) [H&B: 2; H&T: 3]	15 (75%) [Gobal: 8; H&T: 3; H&B:2; H:2]	20
Echogenicity				
On 1^{st} abdominal USG	Hypoechogenicity- 32 (51.6%)	Hypoechogenicity- 7 (11.29%)	Hypoechogenicity- 22 (35.5%) Hyperechogenicity- 1 (1.6%)	62
On 2^{nd} abdominal USG	Iso-echogenicity 32 (51.16%)	Iso-echogenicity 7 (11.29%)	Iso-echogenicity 23 (37%)	

H: Head; B: Body and T: Tail; [a] Significant P-value: 0.042; [b] Insignificant P-value: 0.068 obtained using one-way ANOVA.

23(37%) had severe AP (Table 4). The time interval between pain in abdomen and hospital admission showed statistically significant difference of mean days across three severity categories (P value 0.042), while the mean time interval between pain in abdomen and first abdominal USG was insignificantly different across categories (P value 0.068). For 19(30.6%) cases, the first abdominal USG was performed within 48 hours of pain in abdomen, in which 14(73.8%) had mild and 2(3.2%) cases had moderate and 3(4.8%) had severe AP. In 43, the first USG was done after 48 hours, out of which 18 (29.0%) had mild, 5(11.6%) had moderate and 20(46.5%) had severe AP. The enlargement in pancreatic size was detected by MLR method in 55 cases, out of which 25(45.5%) were mild AP, 7(12.7%) were moderately severe and 23(41.8%) were severe. No enlargement by MLR was seen in 7 mild cases with first USG done within 48 hr. However, the cases had hypoechogenicity. Similar observation was made by previous workers stating that nearly 20% or more of the children in early or mild AP stage had normal imaging.[5] The sensitivity of transabdominal ultrasound in detecting pancreatitis was reported as 79.4%.[13] In such cases, it is proposed that further USG study may be undertaken after 24 to 48 hours to demonstrate the enlargement of pancreas.

This method also revealed that global enlargement of pancreas was observed in 41(66.1%) and patchy enlargement in 14(22.5%) cases. Patchy enlargement predominantly involved head and body parts of pancreas. MLR method further demonstrated that 20(32.2%) cases continued to show enlargement after clinical recovery in moderately severe and severe AP groups and none in mild AP group. Fleischer AC et al. stated that this may be due to residual effects of edema, hemorrhage and fibrosis that occur as a result of pancreatic inflammation.[24] This study also demonstrates that all cases of AP do not have enlargement on presentation and may remain within normal limits with hypoechogenicity. However, on clinical recovery, there could be a marginal change in size with iso-echogenicity. Similar observation was made by Siegel et al. and showed that in 54% of the cases pancreatic measurements were normal.[16] In the present study, it was observed that the mean measurements of normal children and diagnosed cases on clinical recovery

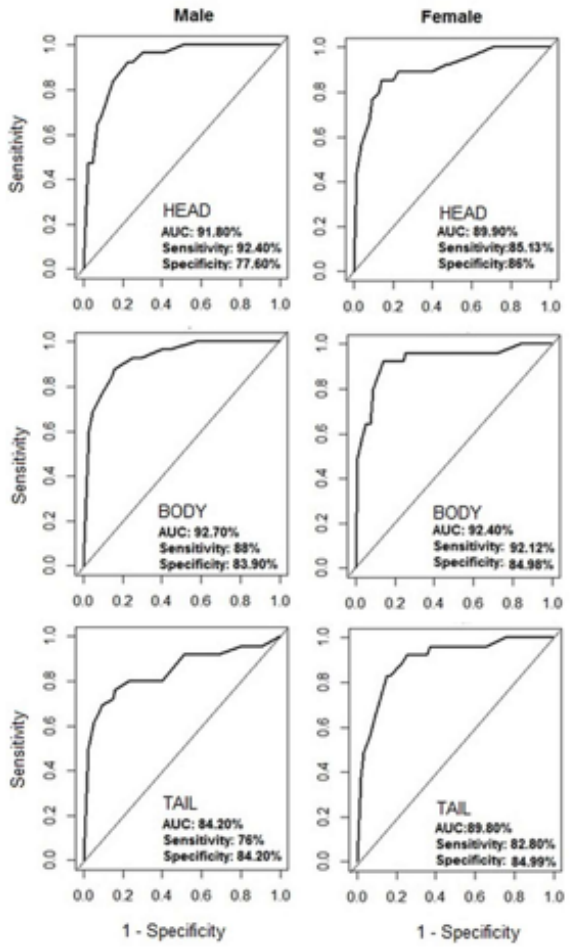

Fig. 4: ROC curves for three pancreatic parts using training data according to gender

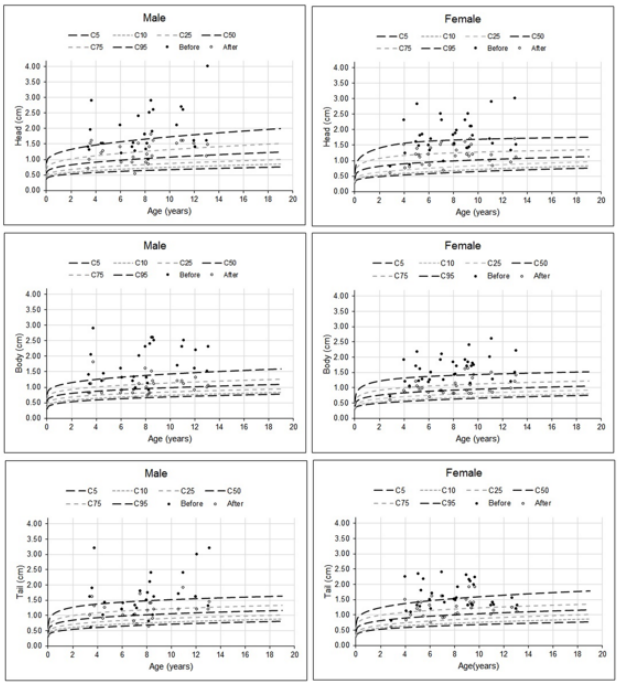

Fig. 5: Scatter plot showing pancreatic dimensions for males and females with reference to age in disease condition and after clinical recovery on the respective percentile plots.

showed statistically insignificant difference indicating the reduction in size of pancreas from the stage of presentation of AP.

In this study, hypoechogenicity in 61(98%) and hyperechogenicity in 1(2%) were observed at presentation, while iso-echogenicity was observed in all the cases after clinical recovery. Fleischer et al. reported hypoechogenicity in 79% cases during AP stage.[24] Further, they stated that decreased echogenicity of pancreas was a reliable indicator of the presence of pancreatitis in children. Clinical recovery was noticed within 6 days in mild, 8 days in moderately severe and 11 days in severe AP groups. Werlin et al.reported clinical recovery within 4-5 days in mild AP cases.[5]

There are some limitations of the present study. The number of diagnosed cases of AP was low due to low prevalence and being a single centric study. Prospectively, we plan to involve multiple such hospital centers and strengthen the thresholds to comment on the pancreatic enlargement in disease condition. MLR provides the overall enlargement of the pancreas in a disease condition. However, one of the limitations of this criterion is its practical utility in clinical and radiological settings. Accordingly, we have developed a web-based application to determine the enlargement by using the MLR method. Users can access the site www.acrs-edc.com and log in by using pancreas.ps as both username and password. The patient‘s details and dimensions can be entered to obtain the possible enlargement of the pancreas. The enlargement criterion in conjunction with the clinical and biochemical test can be used for strengthening the diagnosis of AP.

5. Conclusion

The study demonstrates the enlargement of pancreas in patients diagnosed with AP based on clinical and biochemical criteria. The raw measurements on each part showed reasonably good enlargement in cases along with hypoechogenicity; however, the part specific diagnostic strength differed between males and females. Hence, a multivariate approach, integrating the information from all the three parts was used, which proved to be a reliable indicator of enlargement in the disease condition.

6. Author’s Contribution

RDS was involved in conceptualizing, data generation of manuscript writing. DSA was involved in the statistical

programming and analysis of data, RDV was involved in statistical and machine learning approach design, SD was involved in generating radiographic data and DVP was involved in overall supervision and interpretation of the findings of the study.

7. Abbreviations

AP-Acute Pancreatitis, USG-Ultrasonography, ROC-receiver operating characteristic, ARP-acute recurrent pancreatitis, MLR-Multiple logistic regression, PE-Pancreatic echogenicity.

8. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

9. Source of Funding

None.

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Author biography

Dhanraj S Raut, Former Professor

Shubhangi A Desai, Biostantistician

Dhananjay V Raje, Head, Data Analysis Group

Dinesh Singh, Consultant

Vithalrao P Dandge, Retired HOD

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