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Diffusion weighted MRI and neutrophil lymphocyte ratio non-invasively predict infection in pancreatic necrosis: a pilot study

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Key words
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Abstract

Background: Infected pancreatic necrosis (IPN) is a major determinant of mortality in acute pancreatitis (AP). Non-invasive diagnosis of IPN could guide the intervention in AP. We aimed to investigate the role of non-invasive methods like diffusion weighted magnetic resonance imaging (DW-MRI) and clinico-laboratory parameters as predictors of IPN.
Methods: Prospective evaluation for predictors of IPN by diffusion restriction (DR) on DW-MRI and clinico-laboratory parameters was performed.
Results: Out of 39 patients included, 31 were analysed after exclusion. Twenty-six (83.8%) patients had moderately severe AP, and the rest had severe disease. They were categorized into Group A: patients with documented infection after intervention ($n = 17$) and Group B: successfully managed without intervention or negative culture after intervention ($n = 14$). On univariate analysis, Group A had significantly more incidence of fever ($P = 0.020$), persistent unwellness ($P = 0.003$), elevated neutrophil count ($P = 0.007$), lymphocyte count ($P = 0.007$), neutrophil lymphocyte ratio (NLR) ($P = 0.028$), DR on DW-MRI ($P = 0.001$) and low apparent diffusion coefficient (ADC) ($P = 0.086$). Multivariate analysis revealed DR on DW-MRI ($P = 0.004$) and NLR ($P = 0.035$) as significant predictors of IPN, among other factors. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DW-MRI were 94.1%, 78.6%, 91.66%, and 84.21%, respectively. The area under curve of NLR on the ROC plot was 0.85 and the best cutoff was >3.5, with sensitivity, specificity, PPV, and NPV of 70.6%, 78.6%, 80%, and 68.7% respectively.
Conclusion: DW-MRI and NLR are promising non-invasive tools for accurate prediction of IPN and hence can guide the need for intervention in acute pancreatitis.

Introduction

The infection of pancreatic necrosis is known to be a key event in the course of acute pancreatitis (AP), which determines the severity and hence the clinical outcome, and the mortality ranges from 4% to 29%.[1,2] Therefore, timely detection of the presence of infection and intervention in IPN is of utmost importance. On the other hand, intervention in non-infected pancreatic necrosis runs the risk of converting sterile walled off pancreatic necrosis (WON) into IPN. Till date, image guided fine-needle aspiration (FNA) and culture have been the only modality to positively detect infection in pancreatic necrosis, with reported sensitivity as high as 88%–96%.[3] A study by Van Baal *et al*. advised against routine use of FNA as it does not add significant value to clinical and imaging features of IPN.[4] Moreover, it is associated with procedure related risks like bleeding, perforation, and iatrogenic infection. An online survey among 118 pancreatologists revealed none of the respondents preferred FNA routinely; 85% selectively used it, whereas 15% would never utilize it for the diagnosis of IPN.[5]

The presence of gas bubbles in pancreatic necrosis on computed tomography has been associated with low sensitivity, and hence its absence does not rule out infection.[6] Similarly, the routinely used laboratory markers are often nonspecific, thus adding to the diagnostic dilemma of differentiating between infected and sterile pancreatic necrosis.[7] The individual components of the differential leukocyte count, like neutrophil to lymphocyte ratio (NLR), were

found to be superior to the total leukocyte count alone in predicting necrosis and organ dysfunction in AP.[8] Additionally, procalcitonin (PCT) level has been used as a relatively accurate and readily available parameter that is predictive of infection and thus helps distinguish infected from sterile necrosis.[9] However, PCT levels may get elevated in other infective foci and may be elevated in the initial weeks in the presence of multiorgan dysfunction regardless of the presence of infection.[10]

Diffusion weighted magnetic resonance imaging (DW-MRI) is functional imaging that utilizes the differences in motion of water molecules in both intracellular and extracellular spaces. It can be added to existing imaging protocols and yield both qualitative and quantitative information at the cellular level.[11] Its diagnostic potential has been established for soft tissue infections in the abdomen and pelvis like intra-abdominal abscesses, liver abscesses, and pyonephrosis.[12] Furthermore, the apparent diffusion coefficient (ADC) map obtained from the DW-MRI images gives quantitative analysis of diffusion restriction.[13] Though the diagnostic potential of DW-MRI has been explored in pancreatitis,[14,15] its role in detection of infection in pancreatic acute necrotic collection (ANC) and walled off necrosis (WON) has drawn the attention of researchers only recently. One study by Islim *et al*. compared CT and DW-MRI findings in infected pancreatic collection diagnosed by positive fluid culture on FNA and revealed better sensitivity and accuracy for DW-MRI.[16] We hypothesized that non-invasive modalities like DW-MRI and laboratory markers will help predict IPN.

Patients and methods

This prospective study was conducted as a pilot study at the Institute of Liver and Biliary Sciences, New Delhi, India, from September 2015 to December 2018, after obtaining approval from the Institutional Ethics Committee (IRB Number: 37/6).

The diagnosis of AP and definition of various terminologies related to it were based on the 'revised Atlanta criteria'.[17] The patients with moderately severe or severe AP beyond the third week of the onset of acute pancreatitis were included for this study. Persistent unwellness in these patients was defined as the presence of either persistent abdominal pain, nausea, vomiting, and nutritional failure. The patients with mild AP, severe AP deemed unfit for MRI study, claustrophobia, indwelling metallic implants, the presence of gas in the pancreatic necrosis on CT abdomen, or who had prior percutaneous intervention were excluded. The antibiotic prescription was usually delayed, except in patients with a strong suspicion of sepsis. In the later scenario, an MRI was performed before administering antibiotics.

The NLR was calculated by dividing the percentage of neutrophil and lymphocyte count. All included patients underwent MR imaging at 3T MRI unit (Wipro GE Signa HDxt 3T Volumer MR). Our protocol included coronal and axial T2-weighted (T2W) single shot fast spin echo (FSE) sequences, axial respiratory triggered fat suppressed T2W FSE sequence, and axial breath hold T1-weighted (T1W) dual echo spoiled gradient recalled echo sequence (Fig. 1a). The axial DW sequence was performed at b-values of 0, and 1000 sec/mm^2 and ADC for quantification of DR were generated (Fig. 1b,c). To minimize subjectivity, the radiologist interpreting the imaging data was blind to the final diagnosis. The diffusion-weighted images at b values of 0 and 1000 s/mm^2 were qualitatively assessed to evaluate whether the collection exhibited DR (Fig. 1b–d). If the signal on $b = 1000$ s/mm^2 images remained the same or showed minimal decrease as compared to the $b = 0$ s/mm^2 image, this was taken as DR. Contrary to this, if the lesion showed definite loss of signal on $b = 1000$ images, this was taken as no DR. The DW-MRI images were analysed in conjunction with ADC maps (to avoid T2 'shine through' effects), in which the lesions showing restricted diffusion were hypointense and those with unrestricted diffusion were hyperintense. The ADC values are expressed in ($\times 10^{-3}$) as mm^2/s up to two decimal places.

The treating physicians were blinded for the DWMRI findings. The decision for intervention was based on the combination of clinical and laboratory evidence of sepsis presumed to be of pancreatic origin or those with persistent organ failure (>48 h). Signs and symptoms of sepsis for intervention were defined as probable pancreatic source of infection along with the presence of any three of these for >24 h: temperature of >38°C or <36°C, persistent tachycardia >90/min, respiratory rate of >20/min, total leukocyte count >12 000 or <4000/mm^3. The organ failure (respiratory, cardiovascular, and renal) was defined according to a score of 2 or more for any of these three organ systems using the 'modified Marshall scoring system' For those who underwent any intervention, pancreatic tissue fluid was sent for bacterial culture at the time of the first intervention. The patients not requiring any intervention were further followed up for clinical assessment. For the purpose of analysis, the patients who went on to require any form of intervention within 1 week of performing the DW-MRI were classified as the 'intervention group', whereas, those who recovered without intervention or underwent intervention beyond 1 week were assigned to the 'no intervention group' (Fig. 2).

Statistical analysis

Analyses were done with the SPSS statistic Version 22 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using a 2-tailed, unpaired t test/Mann Whitney U test as applicable for independent samples. All the values are expressed as mean ± SD. The categorical data were compared using the chi-square test. Univariate and multivariate analysis was done with logistic regression analysis. P values <0.05 were considered to be significant.

Results

Sixty-five patients were admitted with pancreatitis at author's institution during the study period. Out of them, 39 patients were included for this pilot study. After exclusion, 36 patients underwent DW-MRI. The demographic and clinical parameters are provided in Table 1. Twenty-eight of these patients had CECT abdomen performed in the early phase of their illness.

The intervention for drainage of collection was done in 24 (66.6%) patients. The first intervention was percutaneous catheter insertion in 19 patients, surgery in four patients (laparotomy: one; laparoscopic cystogastrostomy: three, and endoscopic cystogastrostomy in one patient). The IPN was strongly suspected

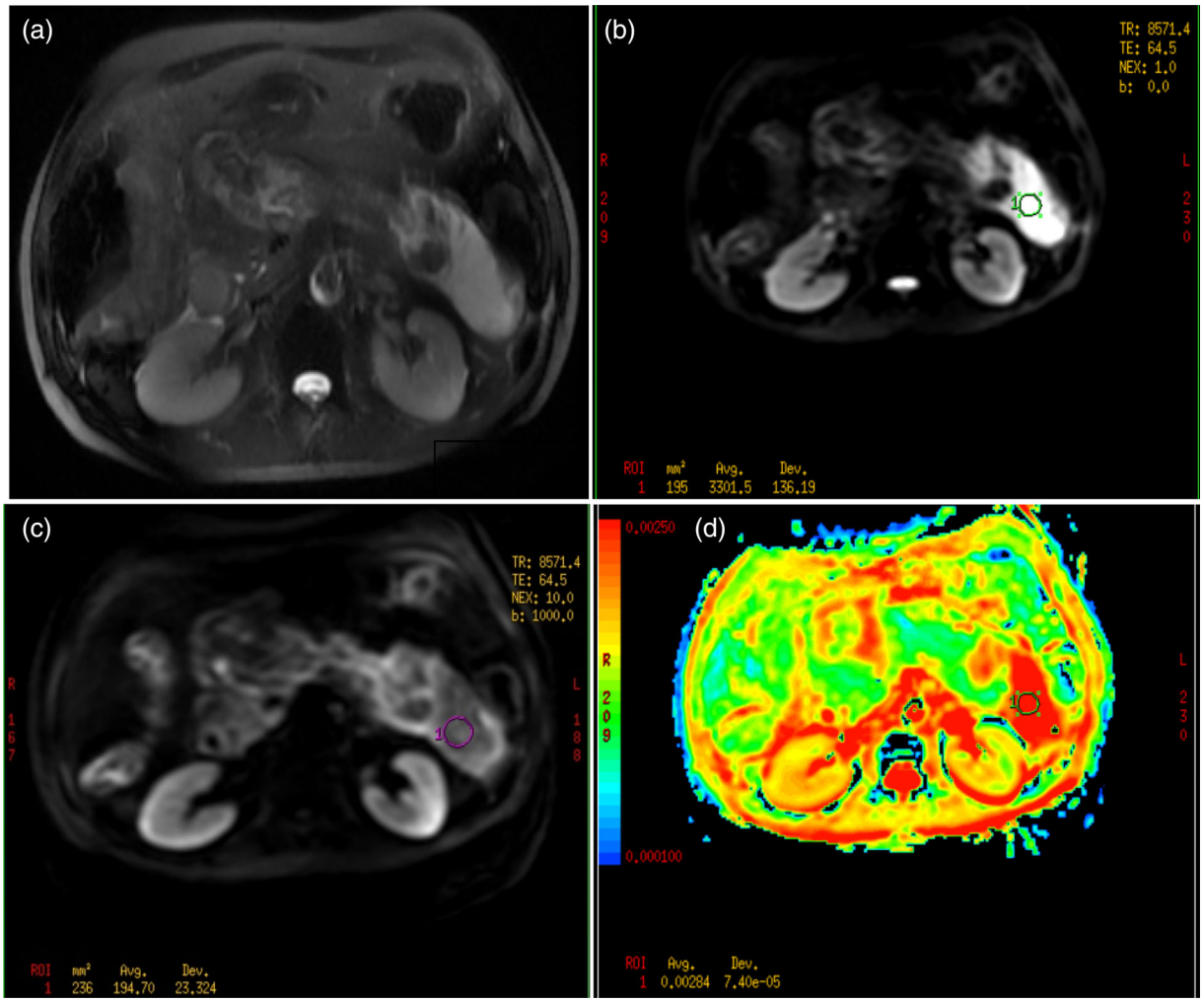

Fig. 1. (a–d) A 54-year man with pancreatitis of biliary aetiology presented at 12th week of onset of the disease. (a) Axial T2-weighted single-shot fast spin-echo with fat saturation image showing the pancreatic necrotic collection in body and tail; (b) diffusion weighted image (*b* value = 0 mm^2/s) with ADC mapping of region of interest (ROI). (c) Diffusion weighted image (*b* value = 1000 mm^2/s) with ADC mapping of ROI. (d) ADC depicting value of ROI.

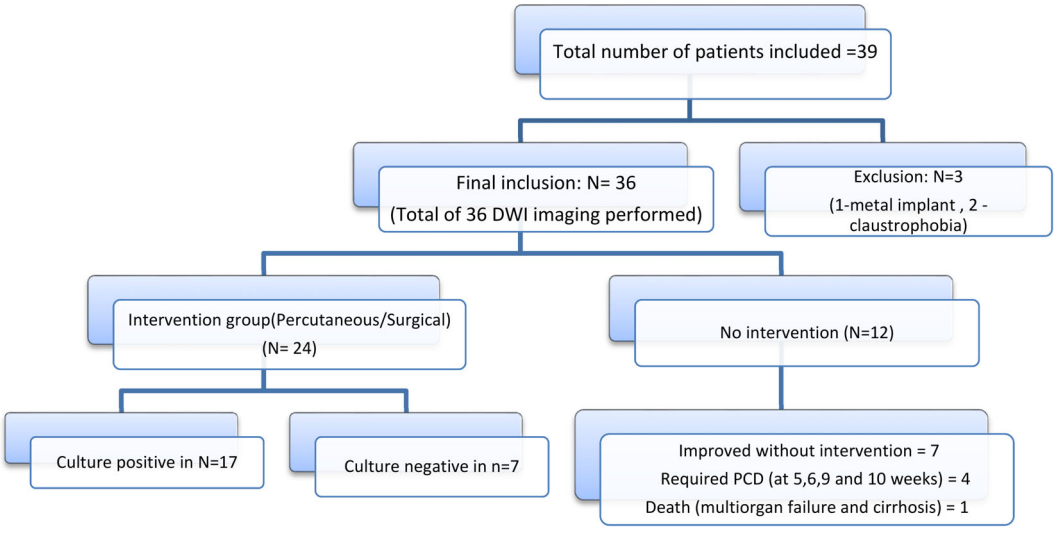

Fig. 2. Flow chart of the patients in the study group.

in these patients, except for the patients who underwent laparoscopic or endoscopic cystogastrostomy, had pressure symptoms and pain in abdomen as predominant complaints.

Twelve patients did not undergo any intervention within 1 week of DW-MRI, and their clinical course was followed. Among these, one had underlying chronic liver disease and died 3 weeks later due to multiorgan failure. Four patients required percutaneous intervention of WON for persistent sepsis later at 5, 6, 9, and 10 weeks of onset of pancreatitis (all beyond 1 week of DW-MRI). Though the drainage fluid revealed bacterial growth in all these patients, they were not considered harbouring infection at the time of DW-MRI. Seven patients recovered without intervention. Among these, three patients had diffusion restriction in a small portion of the larger collection. The reasons for not intervening in these three patients were multiple small collections with extensive omental and bowel stranding and no window for percutaneous intervention in one; clinical improvement and resolution of symptoms in the other two. They were followed up closely (8–22 weeks) and recovered without intervention. All patients of both groups were followed up for at least 3 months. A total of nine patients later required percutaneous nephroscopic necrosectomy on follow-up and one of them subsequently needed open necrosectomy. The technique of percutaneous nephroscopic necrosectomy (PCNN) has been described by the authors previously.[18]

To elucidate the utility of DW-MRI and laboratory parameters in predicting infection, after excluding five patients (four who underwent cystogastrostomy for pressure symptoms or pain and one who died due to decompensation of underlying chronic liver disease), a total of 31 patients were categorized into two groups as shown in Table 2. 'Group A', those who had ascertained infection on culture after intervention; and 'Group B', those who had negative bacterial cultures or those improved on conservative treatment.

Among the variables studied, the presence of fever and persistent unwellness, neutrophil and lymphocyte count, NLR, and presence of diffusion restriction had a significant association with 'group A'.

There were three patients who had diffusion restriction only in a part of a larger collection and were considered to have restriction. Of the 17 patients who had documented infection on culture samples, 16 had bacterial growth, and one revealed fungal growth of Candida species. The DW-MRI was found to be a very accurate predictor of infection when these 17 patients were analysed with a sensitivity of 94%, specificity of 100%, PPV of 100%, and NPV of 90%. On multivariate analysis with backward elimination, the presence of DR on DW-MRI and NLR was statistically significant and

Table 1 Clinical characteristics of the study group

Variable	Value
Age	Median 36.5 (14–80)
Sex (M:F)	32:4
Aetiology	
Biliary	15 (41.6%)
Ethanol	10 (27.7%)
Unknown	10 (27.7%)
Drug induced	1 (2.7%)
Severity (CTSI)	
10 ($n = 13$)	Mean score = 7.5
8 ($n = 11$)	Median score = 9 (4–10)
6 ($n = 3$)	
4 ($n = 1$)	
Severity (Revised Atlanta classification)	
Moderately severe	30 (83.3%)
Severe	6 (16.6%)

Abbreviation: CTSI, Computed Tomography Severity Index.

Table 2 Clinical, laboratory and imaging characteristics in non-infected and infected patients

Variable	Group A (infection; $N = 17$)	Group B (no infection; $N = 14$)	*P* value
Clinical			
Fever	15 (88.2%)	7 (50%)	0.020
Pain	16 (94.1%)	13 (92.9%)	0.700
Persistent unwellness	17 (100%)	8 (57.1%)	0.003
Necrosis			
0	2 (11.8%)	1 (7.1%)	0.460
<30%	5 (29.4%)	7 (50%)	
>30%	10 (58.8%)	6 (42.9%)	
Revised Atlanta			
Moderate	14 (82.4%)	12 (85.7%)	0.570
Severe	3 (17.6%)	2 (14.3%)	
CTSI (mean ± SD)	8.93 ± 1.48	8.67 ± 1.41	0.660
Total leukocyte count	15.6 ± 6.2	16.8 ± 2.16	0.084
Neutrophil (%)	77 ± 8.4	64.2 ± 10.5	0.007
Lymphocyte (%)	13.4 ± 6.32	25.4 ± 10.5	0.007
NLR (median and range)	5.5 (3.1–47)	2.5 (1.1–10.1)	0.028
CRP (median and range)	124 (26–324)	39.5 (7–252)	0.159
Procalcitonin			
<0.5	12 (70.6%)	13 (92.8%)	0.530
0.5–2	2 (11.8%)	0	
2–10	2 (11.8%)	1 (7.1%)	
>10	1 (7.1%)	0	
ADC value ($\times 10^{-3}$)	1.9 ± 0.56	2.3 ± 0.61	0.086
Restriction on DW-MRI	16 (94.1)	3 (21.4%)	0.001

Abbreviations: ADC, apparent diffusion coefficient; CRP, C-reactive protein; CTSI, Computed Tomography Severity Index; DW-MRI, diffusion weighted magnetic resonance imaging; NLR, neutrophil lymphocyte ratio; SD, standard deviation.

is shown in Table 3. The sensitivity and specificity of DW-MRI imaging are shown in Table 4.

The area under ROC (AUROC) plot of NLR with infection showed the AUC value of 0.857, indicating it as a good predictor. The best cutoff was obtained with an NLR of >3.5 and had a sensitivity of 76.5% and specificity of 78.6% for the presence of infection (Fig. 3).

Discussion

The multivariate logistic regression analysis revealed NLR and DR on DW MRI to be the only significant factors for predicting IPN. When we considered only the culture positive patients, DW-MRI was able to predict the infection in 16 of 17 patients with a sensitivity of 94%, specificity of 100%, PPV of 100%, and NPV of 90%. DW-MRI missed one patient with positive cultures, and this patient had fungal growth (*Candida albicans*) on culture. If we exclude this patient as the isolate was not of bacterial origin, the sensitivity of diffusion restriction also improves to 100%, again reiterating the accuracy of DW-MRI in predicting infection. NLR was also found to be a good predictor of infection with an AUROC of 0.857 and a best cutoff value obtained at the level of >3.5. Since both were found to be significant predictors, their utility when used in combination or in isolation was studied. The presence of both NLR >3.5 and diffusion restriction improved the specificity to 100% with a minor decrease in sensitivity. The presence of either of these also revealed excellent sensitivity (100%) (Table 4).

Table 3 Univariate analysis and Multivariate analysis of predictors of infection in pancreatic necrosis

Univariate analysis Variables	Odds ratio	CI	*P* value
Fever	7.500	1.228–45.807	0.020
Persistent unwellness	3.125	1.765–5.534	0.003
Neutrophil (%)	1.173	1.044–1.317	0.007
Lymphocyte (%)	0.841	0.741–0.953	0.007
NLR	1.397	1.036–1.882	0.028
CRP	1.008	0.997–1.018	0.159
DR on DW-MRI	58.667	5.377–640.146	0.001
ADC ($\times 10^{-3}$)	0.297	0.074–1.189	0.086
Multivariate analysis			
NLR	1.405	1.024–1.928	0.035
DR on DW-MRI	—	—	0.004
ADC ($\times 10^{-3}$)	0.104	0.008–1.352	0.084

Abbreviations: ADC, apparent diffusion coefficient; CI, confidence interval; CRP, C-reactive protein; DR, diffusion restriction; DW-MRI, diffusion weighted magnetic resonance imaging; NLR, neutrophil lymphocyte ratio.

Since the infection in pancreatic necrosis usually necessitates percutaneous, endoscopic, or surgical drainage; its early and non-invasive detection would be invaluable in deciding the need of such interventions. On the other hand, the persistent symptoms attributed to sepsis could be due to SIRS in the absence of infection. Any intervention in these patients would convert the sterile WON to infected one. We designed this pilot study to evaluate the combination of DW-MRI and laboratory markers as a non-invasive tool to predict IPN. To best of our knowledge, this is the first observational study, which specifically focuses on role of two objective parameters for determining existence of infection in pancreatic collection or necrosis.

The usefulness of both NLR and diffusion restriction in determining the presence of infection in WON and the necessity of intervention is currently unsupported by any evidence. As a result, we followed the current guidelines for any such procedure based on clinical characteristics.[19] In order to evaluate the actual sensitivity and specificity of the suggested investigations, the four patients who had indications for intervention other than suspicion of infection were eliminated. Thirty-one patients were split into two groups (Group A: infection and Group B: no infection; Fig. 2) based on

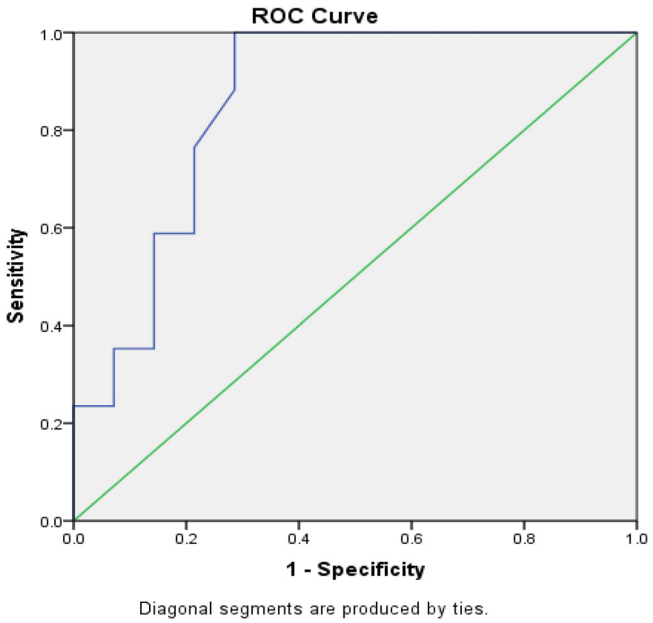

Fig. 3. The receiver operating characteristic (ROC) plot of neutrophil lymphocyte ratio (NLR) with infection.

Table 4 Sensitivity and Specificity analysis of significant predictors

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DR on DW-MRI	94.1	78.6	84.21	91.66
NLR	70.59	78.57	80	68.75
Both DR and NLR	64.7	100	100	70
Either DR and NLR	100	64.29	77.27	100

Abbreviations: DR, diffusion restriction; DW-MRI, diffusion weighted magnetic resonance imaging NLR, neutrophil lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value.

the tissue fluid culture report and exclusion from both arms. These groups were then compared for a number of study criteria.

Since most of the infection in pancreatic necrosis happens in the second week and beyond,[20] we have included patients 3 weeks after the onset of the disease. Previously, image guided FNA has been considered as the gold standard test for the diagnosis of IPN. However, in view of the risk of secondary infection, the recent guidelines suggest that its routine use is not recommended.[21] Therefore, we performed microbiological culture only in those who underwent intervention, and the rest were considered non-infected. Despite the strong clinical suspicion of infection, those with negative bacterial culture were considered 'non-infected'.

Although there are few studies on the utility of DR on DW-MRI for various abdominal infections like liver abscess and pyonephrosis[22,23] its role in detecting IPN has not been explored thoroughly. In first such study, the utility of diffusion restriction on DW-MRI to identify the infection in pancreatic necrosis was evaluated by Islim *et al*.[16] The authors performed FNA for the confirmation of IPN, and they found that the sensitivity for prediction of infection was bettered by DW-MRI (sensitivity 100%) in comparison to CT abdomen (sensitivity 60%). Another study on evaluation of DW-MRI and quantitative estimation of ADC values of pancreatic collection concluded that DW images improve MR diagnostic accuracy to detect infection in collection. They also found that IPN showed significantly lower ADC as compared with non-infected necrosis.[24] One recent study also found DW-MRI to have superior diagnostic value than conventional CT scans for detection of IPN.[6]

The NLR, another non-invasive tool at a high cutoff level, has been found to be a sensitive predictor (sensitivity 77%–82%) of SAP on ROC analysis by Han *et al*.[25] Another retrospective study found that the higher NLR predicts both severity and organ failure in AP (cutoff of 4.76 and 4.88, respectively).[26] In addition, one recently conducted meta-analysis of 10 research articles looking at the significance of NLR in prediction of SAP found moderately high diagnostic value of the marker.[27] None of these studies evaluated NLR as a predictor for IPN. Subsequently, a study by Shen *et al*. described that a reduced lymphocyte count within 48 h of the onset of pancreatitis predicts IPN.[28] A recent study observed that a falling trend of NLR following percutaneous drainage of pancreatic collection predicts clinical response.[29] According to the results of the current study, we believe elevated NLR predicts IPN and is a surrogate marker of increased severity of pancreatitis and organ failure as found in previous studies. Moreover, estimation of NLR can be easily done from the routine complete blood profile.

Although the usefulness of PCT and CRP for predicting infection has been considered by a few previous studies[9,30] their role has been refuted citing their nonspecific nature in predicting the source of infection by others.[30] Our study revealed no correlation between serum levels of these two markers and IPN. Similarly, no established correlation between the extent of necrosis and the risk of infection has been found in this study.

One of the study limitations was the small sample size. Other limitation of our study was the presence of DR in three patients in a part of a large collection who could be managed without the need for intervention. In addition, they responded to antibiotic treatment, suggesting that patients with diffusion restriction only in a part of a large collection may have milder forms of infection that can be managed with antibiotics. Although the ADC value did not reach statistical significance on multivariate analysis ($P = 0.084$), its mean value was lower in the infection group (Tables 2 and 3). Hence, there remains a need for further validation of DW-MRI in a larger cohort, and cutoffs should be determined with regard to quantitative ADC assessment of the necrotic area with DR. Despite these shortcomings, our study revealed remarkable specificity of combined DR on DW-MRI and NLR and very good sensitivity with use of either of the modality.

To summarize, diffusion restriction on DW-MRI and NLR with a cutoff of >3.5 were found to be accurate predictors of infection with sensitivity or NPV of 100% for either of these and specificity or PPV of 100% when both are used in combination. The quantitative assessment of DR by ADC mapping merits further evaluation in larger studies.

Conclusion

Both DW-MRI and NLR are highly sensitive and accurate non-invasive tools to predict IPN. When combined together, they are highly specific too and hence can be used to guide the decision for intervention in patients with AP.

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Author contributions

Rommel Sandhyav: Conceptualization; data curation; formal analysis; methodology; validation; writing – original draft; writing – review and editing. **Nihar Mohapatra:** Data curation; formal analysis; methodology; validation; writing – original draft; writing – review and editing. **Nikhil Agrawal:** Conceptualization; data curation; methodology; supervision; validation; writing – review and editing. **Yashwant Patidar:** Data curation; methodology; validation; writing – review and editing. **Asit Arora:** Conceptualization; methodology; validation; writing – review and editing. **Tushar Kanti Chattopadhyay:** Conceptualization; methodology; validation; writing – review and editing.

Conflicts of interest

None declared.

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