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Isolated peripancreatic necrosis (PPN) is associated with better clinical outcomes compared with combined pancreatic and peripancreatic involvement (CPN)- a systematic review and meta-analysis

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ABSTRACT

Background and aims: Peripancreatic necrosis (PPN) is considered as a distinct entity with a better outcome when compared with combined pancreatic and peripancreatic necrosis (CPN), but there is no systematic review to summarize the evidence. Our study aimed to perform a meta-analysis of existing observational studies comparing the outcomes of PPN with CPN.

Methods: Studies in adult patients comparing the outcomes of PPN and CPN from PubMed, Medline, and Scopus databases from inception to November 2018 were systematically searched. The primary outcome was mortality, and secondary outcomes included multi-organ failure, persistent organ failure, infected necrosis, need for interventions including open necrosectomy. Pooled adjusted odds ratios, and 95% confidence intervals (CI) were obtained by the random-effects model. Forrest plots were constructed to show the summary pooled estimate. Heterogeneity was assessed by using I2 measure of inconsistency.

Results: A total of 6 studies involving 1851 patients (1295 (70%) with CPN and 556 (30%) with PPN) were included. Patients with CPN had a significantly higher mortality (OR 2.49, 95% CI: 1.61–3.87), risk for multi-organ failure (OR 3.24, 95% CI: 2.38–4.43), persistent organ failure (OR 2.79, 95% CI: 1.53–5.08), and infected necrosis (OR 6.21, 95% CI: 3.85–10.03). They underwent more interventions (OR 5.86, 95% CI: 3.69–9.32), including open necrosectomy (OR 5.04, 95% CI: 3.33–7.63). Heterogeneity was low ($I2 = 18.1$, $p = 0.296$), and there was no publication bias.

Conclusion: Isolated peripancreatic necrosis portends an overall better prognosis when compared to necrosis involves pancreatic parenchyma. Clinicians should recognize this distinction for management decisions.

Background and aim

Acute pancreatitis (AP) is a dynamic inflammatory process of varying severity involving the pancreas, peripancreatic tissues, and less commonly remote organ systems [1–3]. Besides redefining AP into three levels of clinical severity, the Revised Atlanta classification categorized AP can be into two morphologic types based on presence or absence of necrosis; interstitial edematous pancreatitis and necrotizing pancreatitis [4]. Pancreatic necrosis is defined as non-enhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT) is seen in 5–10% of patients with AP [1,3–7]. Peripancreatic necrosis (PPN) is defined as the presence of heterogeneous, peripancreatic, ill-defined areas, commonly located in the retroperitoneum and lesser sac, while the pancreas enhances normally on CECT (Fig. 1) [7]. CPN is most common (Fig. 2), followed by PPN and isolated parenchymal necrosis. Since its initial description by Howard and Wagner in 1989 [8], multiple small series have emerged on PPN which is currently regarded as a distinct clinical entity [9–15]. Majority of these studies are small in number, given the relative infrequency of this entity. There are contradicting results regarding organ failure in patients with PPN alone, with some studies reporting a lower frequency of organ failure [10,12], while others show no difference

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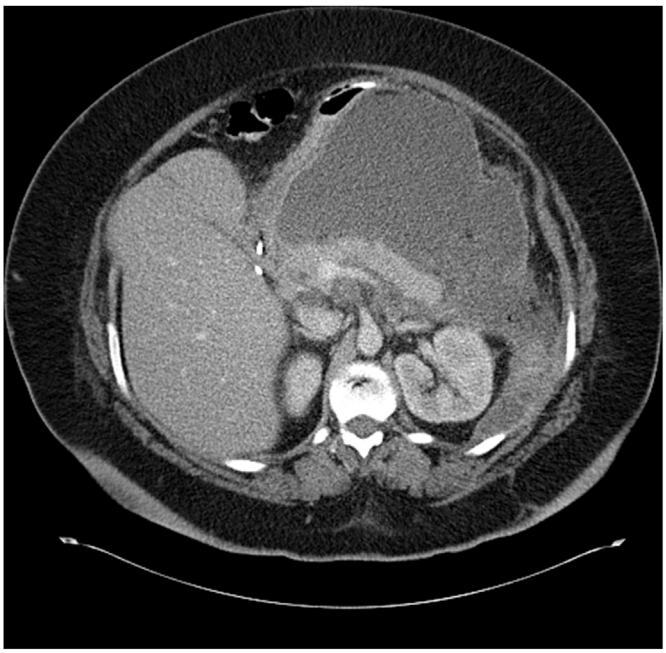


Fig. 1. Isolated peripancreatic necrosis (Image).

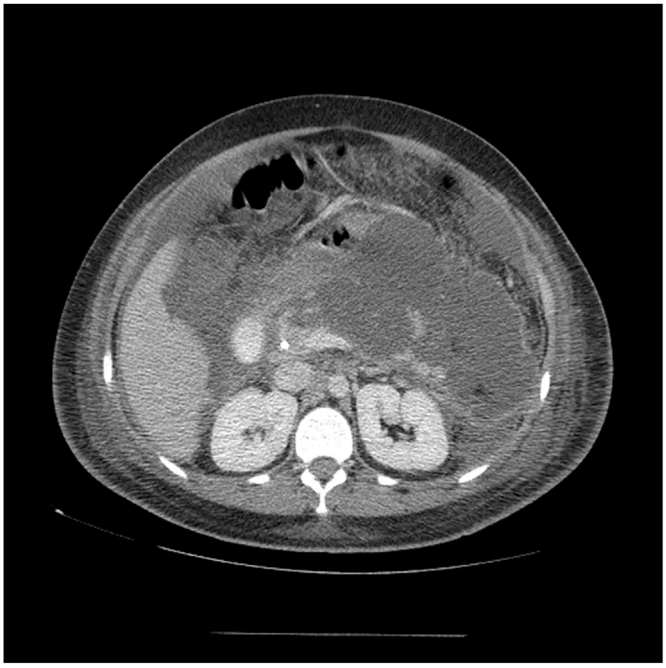


Fig. 2. Combined pancreatic and peripancreatic necrosis (Image).

[11,13]. A formal quantitative review that comprehensively examines the clinical course and outcomes of isolated PPN when compared with CPN was felt warranted. The aim of this study was to perform a structured meta-analysis of all existing observational studies comparing the clinical outcomes and management of isolated PPN with CPN (see Fig. 3). (see Table 1)

Methods

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies Epidemiology (MOOSE) guidelines [16,17].

Study identification

A comprehensive search of the English language literature was carried out to identify articles that examined the clinical outcomes of isolated PPN in comparison to CPN. A systematic search of PubMed, Medline, and Scopus databases for all studies published from inception to December 2018 was performed using the following search terms: 'peripancreatic necrosis,' 'extrapancreatic necrosis,' 'pancreatic necrosis,' and 'combined pancreatic necrosis. Abstracts were reviewed to determine their relevance, and full-text articles were obtained for all potential studies that met the eligibility criteria. References of all selected studies were examined to identify further relevant articles for inclusion. Two reviewers (A.D. and M.Y.K.) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any discrepancies were resolved by discussion with senior author (G.T).

Eligibility criteria

Studies including (case-control, cohort, and cross-sectional studies) were included if they were conducted in an adult population ($\geq$ 18 years), involving necrotizing pancreatitis, and had at least two groups for comparison (PPN group and CPN). The following exclusion criteria were used: Studies that did not evaluate peripancreatic necrosis, studies that did not compare CPN with PPN, those with insufficient data or lacked endpoint of interest, studies used a different methodology (post-surgical diagnosis), studies that overlapped the selected studies (studies from the same study group, institution and period of inclusion), case reports, reviews, editorials, and correspondence letters that did not report their own data.

Quality assessment

The methodological quality of all studies was assessed using the Newcastle-Ottawa scale (supplementary table). Studies were evaluated using the following categories: cohort selection (maximum 4 points), comparability of cohorts (maximum 2 points), and assessment of outcome (maximum 3 points). Studies could score a maximum of 9 points, with a higher score indicating a higher quality study.

Outcomes of interest

The primary outcome of interest was the same admission mortality in patients with combined pancreatic and peripancreatic necrosis (CPN) and isolated peripancreatic necrosis (PPN). Secondary outcomes measured included prevalence for multi-organ failure on admission, persistent organ failure (defined as organ failure >48 h), need for intensive care unit (ICU) transfer, need for intervention, need for open necrosectomy.

Data synthesis and statistical analysis

Dichotomous outcomes were evaluated in terms of odds ratio (ORs) with their 95% confidence intervals (CI) and summarized across studies through a random-effects model as described by DerSimonian and Laird for analysis. Forest plots were constructed to show the point estimates in each study about the summary pooled estimate. Two-sided P values of less than 0.05 were

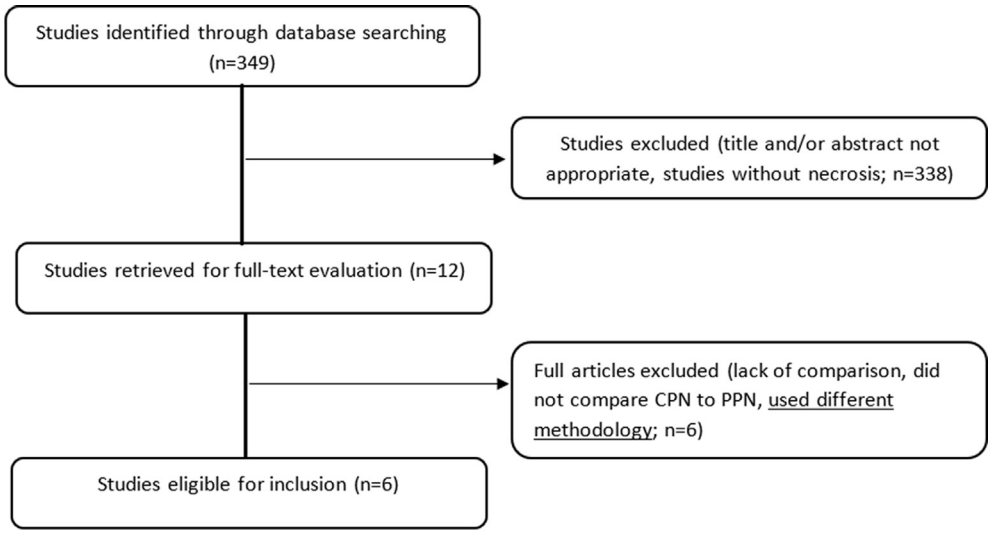


Fig. 3. Flow diagram representing the systematic literature search:
CPN combined pancreatic necrosis; PPN peripancreatic necrosis.

Table 1
Baseline characteristics and salient features of individual studies.

Studies (References)	Dhaka et al. [14]		Sternby et al. [15]		Koutroumpakis et al. [13]		Wang et al. [12]		Rana et al. [11]		Bakker et al. [10]	
Design	Prospective single center study		Prospective multicenter study		Prospective single center study		Retrospective single center study		Prospective single center study		Prospective multicenter study	
Country	India		Spain		USA		China		India		Netherlands	
Year	2018		2018		2016		2015		2014		2013	
Population	PPN	CPN	PPN	CPN	PPN	CPN	PPN	CPN	PPN	CPN	PPN	CPN
Sample Size (n)	40	285	75	133	29	124	49	285	48	144	315	324
Males	24	204	DNR	DNR	16	82	29	191	DNR	DNR	184	214
Age (years)	42.7 ± 13.4	38.5 ± 13.3	DNR	DNR	50 (16)	56 (19)	42.3 ± 10.7	45.8 ± 12.6	DNR	DNR	58 (44 −72)	58 (45 −69)
BMI (mean ± SEM)	23.1 ± 2.7	24 ± 3.8	DNR	DNR	29 (26 −34)	29 (24 −33)	28.2 ± 3	28.2 ± 3.4	DNR	DNR	NA	NA
APACHE II Score	DNR	DNR	DNR	DNR	DNR	DNR	8 (4–8.5)	8 (5–10.5)	DNR	DNR	7 (5–10)	8 (5–11)
Timing of CECT	5–7 days		DNR		3 days + follow-up		7–10 days		3–10 days		Final or before intervention	
Gallstones pancreatitis (%)	10 (25)	97 (34)	DNR	DNR	10 (34.5)	45 (36.3)	21 42.9)	146 51.2)	DNR	DNR	149 (47.3)	155 (47.8)
Alcohol induced pancreatitis (%)	19 (47.5)	142 (49.8)	DNR	DNR	1 (3.5)	29 (23.4)	5 (10.2)	38 (13.3)	DNR	DNR	76 (24.1)	74 (22.8)
Other/unknown etiology of pancreatitis (%)	11 (27.5)	46 (16.1)	DNR	DNR	18 (62.1)	50 (40.3)	23 (46.9)	101 (35.4)	DNR	DNR	90 (28.6)	95 (29.3)
Positive SIRS, admission (%)	DNR	DNR	DNR	DNR	16/28 (57)	61/112 (54)	DNR	DNR	DNR	DNR	DNR	DNR
Positive SIRS, 24 h (%)	DNR	DNR	DNR	DNR	14/26 (54)	66/106 (62)	DNR	DNR	DNR	DNR	DNR	DNR
Persistent SIRS, first week of onset (%)	DNR	DNR	DNR	DNR	DNR	DNR	12 (24.5)	145 (50.9)	DNR	DNR	DNR	DNR
Organ failure (%)	2 (5)	78 (37.4)	DNR	DNR	11 (37.9)	66 (53.2)	12 (24.5)	105 (36.8)	35 (72.9)	101 (70.1)	77 (24.4)	163 (50.3)
Multiorgan failure (%)	DNR	DNR	DNR	DNR	5 (17.2)	39 (31.5)	3 (6.1)	81 (28.4)	6 (12.5)	33 (22.9)	56 (17.8)	138 (42.6)
Persistent organ failure (%)	2 (5)	124 (43.5)	DNR	DNR	10 (34.5)	63 (50.8)	6 (12.2)	95 (33.3)	25 (52.1)	81 (56.3)	66 (21)	147 (45.4)
Sepsis	DNR	DNR	DNR	DNR	DNR	DNR	3 (6.1)	40 (14)	DNR	DNR	DNR	DNR
Infected necrosis (%)	2 (5)	91 (31.9)	DNR	DNR	1 (3.5)	29 (23.4)	10 (20.4)	204 (71.6)	DNR	DNR	51 (16.2)	151 (46.6)
ICU admission	2 (5)	136 (47.7)	12 (16)	63 (47.4)	11 (37.9)	71 (57.3)	23 (46.9)	221 (77.5)	DNR	DNR	DNR	DNR
Days in ICU (median)	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR
Conservative treatment (%)	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	DNR	258 (81.9)	139 (42.9)
Any Intervention (%)	DNR	DNR	8 (10.7)	62 (46.6)	2 (6.9)	66 (53.2)	DNR	DNR	7 (14.6)	47 (32.6)	57 (18.1)	185 (57.1)
Open necrosectomy (%)	0 (0.0)	40 (14)	DNR	DNR	DNR	DNR	8 (16.3)	174 (4.9)	2 (4.2)	12 (8.3)	DNR	DNR
Percutaneous drainage (%)	3 (7.5)	142 (49.8)	DNR	DNR	DNR	DNR	29 (59.2)	73 (25.6)	DNR	DNR	37 (11.7)	94 (29)
Mortality (%)	2 (5)	57 (20)	7 (9.3)	26 (19.6)	3 (10.3)	10 (8.1)	1 (2)	52 (18.2)	4 (8.3)	29 (20.1)	29 (9.2)	64 (19.8)

PPN peripancreatic necrosis; CPN combined pancreatic necrosis; BMI Body Mass Index; SEM standard error of the mean; CECT contrast-enhanced computed tomography; SIRS systemic inflammatory response syndrome; ICU, Intensive Care Unit; DNR data not reported.

considered as statistically significant. Width of the point estimates in the Forrest plots corresponded to the assigned weight of the study. Heterogeneity across studies was assessed through the Q test based on $\chi 2$ statistics, and inconsistency was quantified through the I^2 statistics. I^2 above 50% explains substantial heterogeneity as described in the Cochrane Handbook for Systematic Reviews for Interventions, version 5.1.0, Part 2: General Methods for Cochrane Reviews. Sensitivity analysis for significant heterogeneity was performed. The robustness of the meta-analysis to the publication bias was assessed by various bias indicators, including the Egger's test, the Begg's test and by visual inspection of funnel plots for asymmetry [18].

Results

Eligible studies

An initial literature search generated 349 articles. Titles of papers were reviewed in accordance with the predefined exclusion criteria, yielding 12 potentially relevant articles that were considered in depth. Among these, 6 studies (n = 1851) that met the inclusion criteria were included in the present analysis. There was a total of 556 subjects in PPN group compared with 1295 subjects in the CPN group. All the 6 studies were published as full-text articles in peer-reviewed journals [10–15]. Figure [3] shows the search results, baseline characteristics and salient features of each study are presented in table [1].

Primary outcome

Same admission mortality: Analysis included 1295 subjects in the CPN group and 556 subjects in the PPN group. There was statistically significant increase in mortality in the CPN group compared with PPN group [238 vs. 46 with odds ratio (OR) = 2.49, 95% confidence interval (CI) = 1.61–3.87, P < 0.00001, I2 = 17%] (Fig. 4A).

Secondary outcomes

1. Multi-organ failure (MOF): Four studies reported MOF with 877 subjects in the CPN group and 441 subjects in the PPN group. The prevalence of MOF was significantly higher in the CPN group compared to PPN group [291 vs. 70 with odds ratio (OR) = 3.24, 95% confidence interval (CI) = 2.38–4.43, P < 0.00001, I^2 = 0%] (Fig. 4B).
2. Persistent organ failure (POF): Five studies reported POF with 1162 patients in CPN group versus 481 patients in PPN group. CPN group had a larger number of cases with POF compared to PPN group [510 vs. 109 with odds ratio (OR) = 2.79, 95% confidence interval (CI) = 1.53–5.08, P = 0.0008, I^2 = 70%]. A running sensitivity analysis without Rana et al. [11] was associated with I^2 reduction to 49% with no change in statistical significance (Fig. 4C).
3. Infected Necrosis: There were a total of 1018 subjects in the CPN group and 433 subjects in PPN group. Analysis showed a statistically significant increase in infected necrosis in the CPN group compared to PPN group [475 vs. 64 with odds ratio (OR) = 6.21, 95% confidence interval (CI) = 3.85–10.03, P < 0.00001, I^2 = 27%] (Fig. 4D).
4. ICU admission: A total of 4 studies reported this outcome with 548 subjects in both groups. The CPN group required more ICU admissions compared to the PPN group [491 vs 57 with odds ratio (OR) = 3.29, 95% confidence interval (CI) = 2.30–4.69, P < 0.00001, I^2 = 0%] (Fig. 4E).
5. Need for intervention: Four studies reported the number of interventions performed. The CPN group required more interventions compared to the PPN group [360 vs 74 with odds ratio (OR) = 5.86, 95% confidence interval (CI) = 3.69–9.32, P < 0.00001, I2 = 35%] (Fig. 4F).
6. Open necrosectomy: Analysis comprised of four studies and showed a statistically significant number of subjects in the CPN group requiring open necrosectomy compared to the PPN group [355 vs. 50 with odds ratio (OR) = 5.04, 95% confidence interval (CI) = 3.33–7.63, P < 0.00001, I^2 = 10%] (Fig. 4G).

Quality assessment and publication bias

Included studies were of good quality in the representativeness of the cohorts, outcome assessment, and comparability of the two groups. The primary meta-analysis included all 6 of the studies and was evaluated using a random-effects model. No publication bias was found on the Egger's test with a P value of 0.622 and Begg's test with a P-value of 0.176. A symmetric inverted funnel plot also suggests publication bias unlikely (Fig. 5).

Discussion

Isolated PPN was associated with reduced risk of infected necrosis development, multi-organ failure, persistent organ failure, need for ICU stay, need for intervention including open necrosectomy and ultimately mortality when compared to CPN. To the best of our knowledge, this is the first meta-analysis which systematically explores the clinical outcome of isolated PPN when compared with CPN.

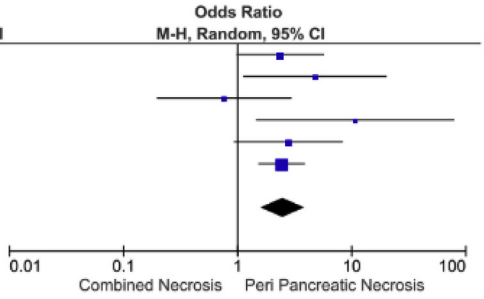
The prevalence of PPN ranged between 6 and 22% across the studies, except the study by Bakker et al., which reported 315 (49%) of 639 patients with NP had PPN [10–14]. This disparity can be attributed to the selection and referral bias, inconsistent reporting by radiologists, and the variable timing in performing a CT scan [14]. A recent multicenter study involving 285 patients across six European centers confirmed high inter-observer variability for PPN among radiologists (kappa range 0.326–0.408, signifying fair inter-observer agreement) for items pertaining to necrosis of peri-pancreatic tissues [19]. The authors reasoned that PPN is challenging to diagnose initially as detection is primarily based on subjective secondary findings, such as 'heterogeneity' or the detection of various densities (liquid and non-liquid) within collections, rather than using the more objective and reproducible criteria of perfusion characteristics used for detecting pancreatic parenchymal necrosis. However, it becomes easier as the disease process evolves over time which was confirmed by their results of improved kappa values for PPN diagnosis two weeks after onset of symptoms [19]. Future studies should focus on stricter radiological definitions to achieve stronger interobserver agreement among radiologists with varying expertise and experience.

Organ failure has been recognized as one of the key determinants for severity and mortality associated with acute pancreatitis [20,21]. It is typically biphasic with an early (primary) organ failure typically driven by intense systemic perturbation from a sterile inflammation in contrast to late (secondary) organ failure due to sepsis from infected necrosis [21,22]. Patients with CPN were at increased risk for both multi-organ failure [OR 3.24 (95% CI 2.38–4.43)] and persistent organ failure [OR 2.79 (95% CI 1.53–5.08)]. Consequently, more patients in the CPN group needed ICU transfer [OR 3.29 (95% CI 2.30–4.69)]. It has been speculated that trypsin activation within pancreatic acinar cells leads to autodigestion and local inflammation [23]. This precipitate a cascade of intracellular activities, following which the pancreatic

A

Study or Subgroup	Combined Necrosis Events	Total	Peri Pancreatic Necrosis Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2018 Sternby et al	26	133	7	75	19.3%	2.36 [0.97, 5.74]
2018 Dhaka et al	57	285	2	40	8.3%	4.75 [1.11, 20.27]
2016 Koutroumpakis et al	10	124	3	29	9.4%	0.76 [0.20, 2.96]
2015 Wang et al	52	285	1	49	4.6%	10.71 [1.45, 79.39]
2014 Rana et al	29	144	4	48	13.5%	2.77 [0.92, 8.35]
2013 Bakker et al	64	324	29	315	44.9%	2.43 [1.52, 3.88]
Total (95% CI)		**1295**		**556**	**100.0%**	**2.49 [1.61, 3.87]**
Total events	238		46			

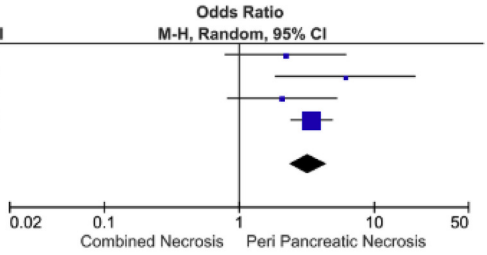
Heterogeneity: Tau² = 0.05; Chi² = 6.02, df = 5 (P = 0.30); I² = 17%
Test for overall effect: Z = 4.09 (P < 0.0001)



B

Study or Subgroup	Combine Necrosis Events	Total	Peri Pancreatic Necrosis Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2016 Koutroumpakis et al	39	124	5	29	9.0%	2.20 [0.78, 6.20]
2015 Wang et al	81	285	3	49	6.8%	6.09 [1.84, 20.13]
2014 Rana et al	33	144	6	48	11.0%	2.08 [0.81, 5.33]
2013 Bakker et al	138	324	56	315	73.3%	3.43 [2.39, 4.93]
Total (95% CI)		**877**		**441**	**100.0%**	**3.24 [2.38, 4.43]**
Total events	291		70			

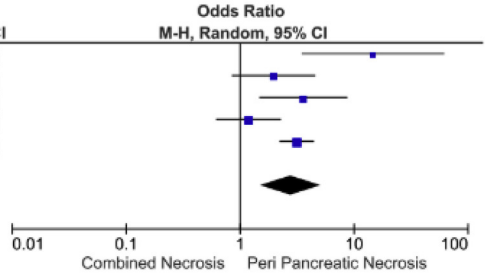
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 7.42 (P < 0.00001)



C

Study or Subgroup	Combined Necrosis Events	Total	Peri Pancreatic Necrosis Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2018 Dhaka et al	124	285	2	40	11.1%	14.63 [3.46, 61.83]
2016 Koutroumpakis et al	63	124	10	29	19.3%	1.96 [0.84, 4.56]
2015 Wang et al	95	285	6	49	18.5%	3.58 [1.47, 8.72]
2014 Rana et al	81	144	25	48	22.8%	1.18 [0.61, 2.28]
2013 Bakker et al	147	324	66	315	28.3%	3.13 [2.21, 4.44]
Total (95% CI)		**1162**		**481**	**100.0%**	**2.79 [1.53, 5.08]**
Total events	510		109			

Heterogeneity: Tau² = 0.30; Chi² = 13.31, df = 4 (P = 0.010); I² = 70%
Test for overall effect: Z = 3.36 (P = 0.0008)



D

Study or Subgroup	Combined Necrosis Events	Total	Peri Pancreatic Necrosis Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2018 Dhaka et al	91	285	2	40	9.8%	8.91 [2.10, 37.75]
2016 Koutroumpakis et al	29	124	1	29	5.2%	8.55 [1.11, 65.57]
2015 Wang et al	204	285	10	49	28.2%	9.82 [4.68, 20.60]
2013 Bakker et al	151	324	51	315	56.9%	4.52 [3.12, 6.55]
Total (95% CI)		**1018**		**433**	**100.0%**	**6.21 [3.85, 10.03]**
Total events	475		64			

Heterogeneity: Tau² = 0.07; Chi² = 4.08, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 7.47 (P < 0.00001)

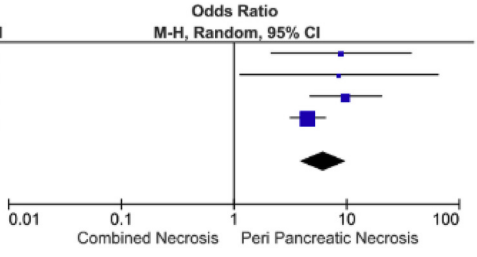


Fig. 4. Forrest plot depicting odds of outcomes in isolated peripancreatic necrosis and combined pancreatic and peripancreatic necrosis.

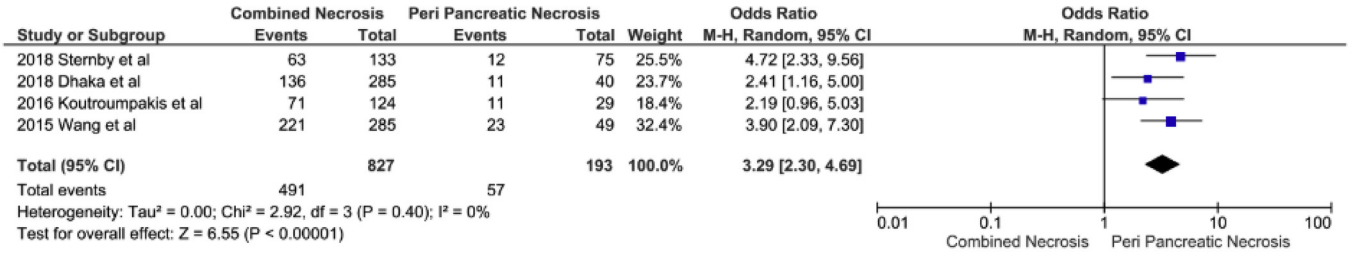
acinar cells become necrotic [10]. Extensive local inflammation causes severe systemic inflammatory response which may lead to organ failure. In PPN, since the pancreatic parenchyma is preserved, necrosis of the acinar cells does not seem to occur which results in a less severe local inflammatory response and less SIRS and less organ failure. The amount of released inflammatory mediators or cytokines in PPN has been hypothesized to be lower, which conceivably results in a less pronounced SIRS response as reported in two of the included studies [12,13].

In our study, patients with CPN were at increased risk for development of infection within the necrotic collection compared to those with isolated PPN [OR 6.21 (95% CI 3.85–10.03)]. Ductal disruption may occur with parenchymal necrosis which could potentiate bacterial invasion of pancreatic tissue [10].

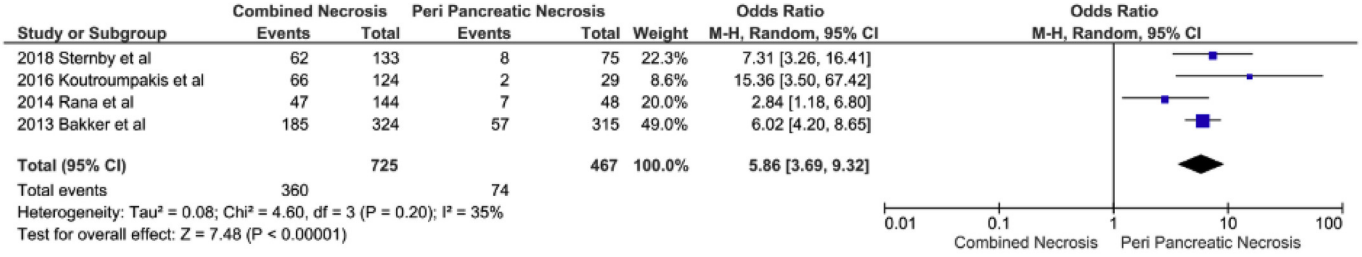
Not surprisingly, patients with CPN underwent more interventions than PPN [OR 5.86 (95% CI 3.69–9.32)] and needed more open necrosectomy [OR 5.04 (95% CI 3.33–7.63). It is unclear from these studies if these open necrosectomies were performed primarily or were performed as a result of the failed step-up approach. Regardless of the indication for the open necrosectomy, it should be acknowledged that this contributed to a significant portion of morbidity and perhaps mortality.

Two of the six studies performed a post-hoc analysis within the PPN group by comparing the management and outcome parameters between patients with limited and extensive PPN [11,13]. One study defined extensive PPN as necrosis extending into paracolic gutters or the pelvis [11]. In this study, patients with extensive PPN had a significantly increased frequency of pleural effusion, ascites and multi-organ failure, but similar frequency of mortality and need for intervention [11]. Other study quantified extensive PPN as collections >5 cm in transverse diameter or affecting >3 locations (the following 7 locations were considered peripancreatic space, root of the mesentery, transverse mesocolon, gastrosplenic ligament, hepatoduodenal and/or gastrohepatic ligament, right anterior and/or posterior pararenal space, left anterior and/or posterior pararenal space [13]. In this study, none of the patients with limited PPN required drainage/debridement and the rate of persistent organ failure and length of stay were similar to interstitial

E



F



G

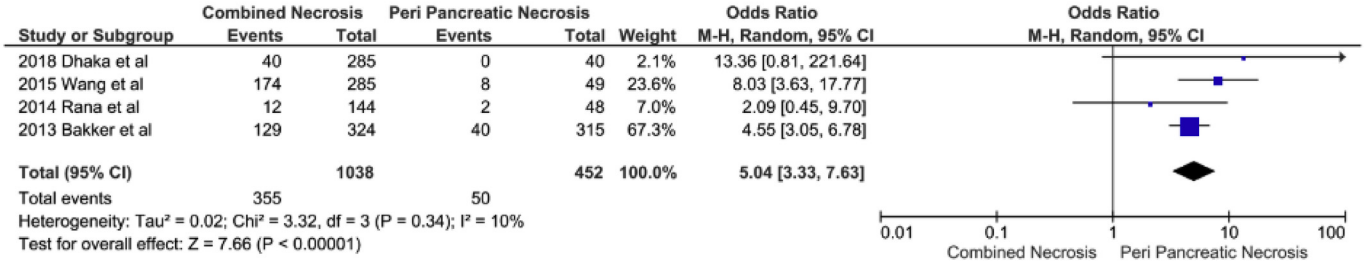


Fig. 4. (*continued*).

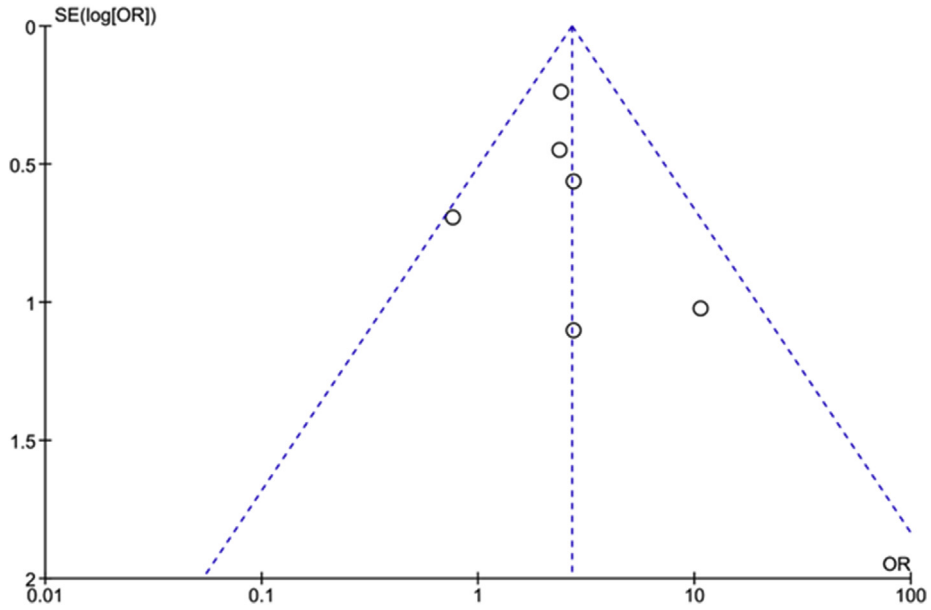


Fig. 5. Funnel plot indicating no significant publication bias.

pancreatitis. On the other hand, extensive PPN was associated with persistent organ failure, prolonged hospitalization, but rarely required pancreatic intervention. The conflicting results are likely because of the heterogeneity in the definitions of extensive PPN adopted with one study classifying the extent of involvement and the other study based on the size and number of locations [24]. Future studies should explore PPN volume and location while evaluating clinical outcome and management [25].

Exocrine and endocrine pancreatic insufficiency has been frequently reported as long term sequelae of AP particularly NP [3]. Recent metanalyses of observational studies show a pooled prevalence of exocrine pancreatic insufficiency of 27.1% (95% CI 20.3%–35.1%) and diabetes of 23% (95% CI 16%–31%) following AP [26,27]. Another study reported the long-term pancreatic metabolic sequelae of NP [9]. The authors reported that none of the patients developed endocrine or exocrine pancreatic insufficiency due to the lack of involvement of the pancreatic parenchyma, which connotes a more favorable long-term prognosis in isolated PPN [9].

Publication bias and selection bias can influence the summary estimates. In this meta-analysis, bias calculation by using the Egger bias indicator and the Begg-Mazumdar indicator showed no statistically significant bias, and this was confirmed by the symmetrical funnel plot.

Our meta-analysis has several limitations which need to be acknowledged. This analysis was based solely on observational studies which might be subject to confounding. All studies were performed in tertiary referral centers with their inherent selection and referral bias. Studies included also belonged to different periods during which the strategies for intervention has evolved from open necrosectomy to minimally invasive or endoscopic step-up approach guided on the local expertise and location of the collection. While it is possible that the outcomes were impacted by more patients undergoing open necrosectomy than current standards, this could have affected both the CPN and PPN arms. All studies in this meta-analysis used CECT to diagnose NP. There was considerable heterogeneity in the radiological diagnosis for PPN, and there was definite time variability in performing CECT imaging across the different studies. Thus, readers should exercise caution in interpreting the results of this study.

Nevertheless, the present study for the first time provides summative data of clinical outcomes from the literature, explicitly comparing isolated PPN and CPN. The results of this meta-analysis provide evidence-based risk stratification within NP, which has immediate applicability in triaging these patients on admission. Since isolated PPN is a separate entity, future research studies on new interventions in NP should report results in PPN separately.

Our meta-analysis provides further compelling evidence that isolated PPN may represent a distinct subgroup that portends a better prognosis than necrosis involving pancreatic parenchyma. It is imperative that clinicians and radiologists become more familiar with this entity and a diligent search for heterogeneity within pancreatic collections is crucial for an early distinction of PPN from interstitial pancreatitis. Stricter definitions of PPN and a consensus for the optimal time interval, seeking other imaging including MRI, which is superior in detecting necrotic material within collections is needed to improve interobserver agreement. Further studies are warranted to elucidate the mechanism responsible for the occurrence of PPN. More research evaluating how the extent and location of peripancreatic involvement impact the clinical outcome is necessary.

Disclosure

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Declaration of competing interest

Authors have no conflict of interest related to this work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pan.2019.10.004.

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