Received: 18 June 2023 | Revised: 15 October 2023 | Accepted: 21 November 2023

DOI: 10.1111/1751-2980.13243

META ANALYSIS

Journal of Digestive Diseases WILEY

Prognostic significance of organ failure and infected pancreatic necrosis in acute pancreatitis: An updated systematic review and meta-analysis

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Funding information
Beijing Natural Science Foundation, Grant/Award Number: 7232123; National High Level Hospital Clinical Research Funding, Grant/Award Number: 2022-PUMCH-B-023; National Key Clinical Specialty Construction Project, Grant/Award Number: ZK108000; National Natural Science Foundation of China, Grant/Award Number: 32170788

Objectives: In patients with acute pancreatitis (AP), minimally invasive treatment and the step-up approach have been widely used to deal with infected pancreatic necrosis (IPN) in the last decade. It is unclear whether IPN has become a less important determinant of mortality relative to organ failure (OF). We aimed to statistically aggregate recent evidence from published studies to determine the relative importance of IPN and OF as determinants of mortality in patients with AP (PROSPERO: CRD42020176989).

Methods: Relevant studies were sourced from MEDLINE and EMBASE databases. Relative risk (RR) or weighted mean difference (WMD) was analyzed as outcomes. A two-sided *P* value of less than 0.05 was regarded as statistical significance.

Results: Forty-three studies comprising 11 601 patients with AP were included. The mortality was 28% for OF patients and 24% for those with IPN. Patients with OF without IPN had a significantly higher risk of mortality compared to those with IPN but without OF (RR 3.72, $P < 0.0001$). However, patients with both OF and IPN faced the highest risk of mortality. Additionally, IPN increased length of stay in hospital for OF patients (WMD 28.75, $P = 0.032$).

Conclusion: Though IPN remains a significant concern, which leads to increased morbidity and longer hospital stay, it is a less critical mortality determinant compared to OF in AP.

KEYWORDS
acute pancreatitis, infected pancreatic necrosis, mortality, organ failure

Wen Mo Hu, Tian Rui Hua, and Yue Lun Zhang contributed equally to this work.

The abstract of this article has been presented on the International Digestive Disease Forum (IDDF) 2021 as an e-Poster (no. IDDF2021-ABS-0134) and has been published on *Gut*. 2021;70 (Suppl 2):A131.

1 | INTRODUCTION

Acute pancreatitis (AP) is one of the most common gastrointestinal (GI) diseases worldwide, with a global incidence of 34 cases per 100 000 person-years (range 29–58 cases per 100 000 person-years) and an increasing trend.[1] Due to its considerable morbidity and mortality, the risk of recurrence and possibility of progression to chronic pancreatitis, AP is associated with a significant economic burden on both the patient's family and the healthcare system.[2] Patients with AP have highly variable outcomes, reflecting a wide range of disease severity.[3] For instance, patients with necrotizing pancreatitis have a much higher risk of developing organ failure (OF) during admission and a more significantly impaired quality of life after discharge compared to those with mild acute pancreatitis (MAP)[3] who usually recover without long-term sequelae. Systemic and local complications, including persistent organ failure (POF), sterile and infected pancreatic or peripancreatic necrosis, intestinal perforation, and abdominal hemorrhage, are closely associated with the severity of AP.[4–6]

In 2010, Petrov et al demonstrated that OF and infected pancreatic necrosis (IPN) were independent and virtually equivalent determinants of disease severity in patients with AP based on studies published over the preceding 17 years.[7] OF and IPN were associated with mortality rates of 30% and 32%, respectively; when OF and IPN both presented, the mortality raised to 43%. This provides the basis for the establishment of the Determinants Based Classification (DBC) of AP Severity[8] and the definition of the "critical" category of AP severity.[8] The alternative and more widely used grading system for AP severity is the Revised Atlanta Classification (RAC).[9] The primary difference between these two classifications is the significance attributed to IPN. In the DBC, IPN is regarded as severe acute pancreatitis (SAP), while in the RAC it is included in moderately severe acute pancreatitis (MSAP) and is not considered a feature of SAP.

There have been significant progresses in the management of IPN,[10–15] while notable progress in the management of OF is lacking. Minimally invasive therapies, such as percutaneous catheter drainage, minimally invasive retroperitoneal necrosectomy, endoscopic drainage or necrosectomy, and videoscopic assisted retroperitoneal debridement (VARD), have been introduced and widely used in clinical practice. The step-up approach has become the standard of care since the publication of the PANTER study in 2010.[14] In the light of these advances, it remains unknown whether IPN has become a less important determinant of mortality relative to OF.

Therefore, we performed this systematic review and meta-analysis aiming to systematically summarize evidence in this field during the last decade to determine the relative importance of IPN and OF as determinants of mortality in patients with AP.

2 | MATERIALS AND METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] The review was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) (registration no. CRD42020176989).

2.1 | Search strategy

We used a detailed search strategy, including both Indexing (MeSH and Emtree) and free-text terms. The search strategy included varying nomenclatures and combinations of the following terms: "acute pancreatitis", "infection", "organ failure", and "determinant-based classification". The detailed search strategies are summarized in Table S1. A comprehensive literature search for potentially eligible studies limited to human adults was performed in electronic databases including MEDLINE and EMBASE, covering all articles published between January 1, 2010 and December 31, 2019. No geographic or language restriction was applied. In addition, the reference lists of identified articles were also reviewed for additional pertinent studies. Abstracts of research articles presented at related major gastroenterological conferences, including Digestive Disease Week, United European Gastroenterology Week, and Asian Pacific Digestive Week, were also included.

2.2 | Eligibility criteria

The studies considered for this systematic review and meta-analysis were cohort studies (either prospective or retrospective), randomized controlled trials (RCTs), case–control studies, and case series containing no fewer than five patients, which reported adult (≥18 years) patients with AP of all etiologies that was diagnosed and graded based on the 2012 RAC[9] or 1992 Atlanta criteria.[17]

All studies reported IPN, which was defined by a positive Gram-stain or culture results of (peri)pancreatic necrosis from fine-needle aspiration, the first drainage procedure or necrosectomy, or by the presence of extraluminal gas in the non-enhanced (peri)pancreatic region on contrast-enhanced computed tomography (CECT).[9] OF included respiratory failure, circulatory failure, and renal failure, as defined by the modified Marshall scoring system[18] or the Sequential Organ Failure Assessment (SOFA) score.[19] Studies that reported transient organ failure (TOF), defined as OF presenting for ≤48 h, and POF, defined as OF that persisted for >48 h, were included.[9]

The primary end-point of the studies was in-hospital mortality. And the secondary end-points included length of stay (LOS) in hospital, intensive care unit (ICU) admission, and LOS in ICU.

We excluded studies reported only OF but no IPN. Reviews, meta-analyses, studies on animals, case reports or case series that included less than five patients were also excluded. We contacted the authors to confirm that the publication with the most complete and relevant dataset was selected when there were multiple publications of the same study population or to obtain the relevant information when the data on IPN or OF were insufficient for analysis.

2.3 | Data extraction

Two reviewers (W.M.H. and T.R.H.) independently extracted qualitative and quantitative information from all the eligible studies using a standardized data collection form. The following information was extracted: the first author's name, year of publication, country of the population studied, study design, etiology and classification of AP, diagnostic criteria of IPN and OF, and in-hospital outcomes. Based on the World Bank country classifications by income level (2019–2020), we defined countries that were considered high-income economies as "developed". Any disagreement was resolved by discussion and adjudicated by a third reviewer (D.W.).

2.4 | Risk of bias assessment

Risk of bias of each included study was assessed by using the QUality In Prognosis Studies (QUIPS) tool.[20] Rating of the overall quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[21]

2.5 | Statistical analysis

Patients with AP were categorized into four groups: (a) patients with OF and IPN (OF+IPN+); (b) patients with OF but not IPN (OF+IPN−); (c) patients without OF but with IPN (OF−IPN+); and (d) patients with neither OF nor IPN (OF−IPN−). Moreover, the outcomes were analyzed for the following five comparisons: (a) OF+IPN+ vs OF−IPN+; (b) OF+IPN+ versus OF+IPN−; (c) OF−IPN+ vs OF−IPN−; (d) OF+IPN− versus OF−IPN−; and (e) OF−IPN+ vs OF+IPN−.

The results for dichotomous outcomes, including in-hospital mortality and ICU admission, were expressed as relative risk (RR) with 95% confidence interval (CI), while those with continuous outcomes (LOS in hospital and in ICU) were expressed as mean difference (MD) with 95% CI. Statistical heterogeneity was assessed using the I^2 measure.[22] We employed the Mantel–Haenszel random-effects model to carry out the meta-analysis. Small-study effects and publication bias were assessed using the funnel plot asymmetry and the Egger's test was applied when more than 10 studies were included in the analysis. When there was significant publication bias, the trim-and-fill test was performed to evaluate the robustness of the results.

Subgroup analysis was conducted to examine the effect of the pre-defined study-level variables, including study design (prospective vs retrospective), year of publication (2010–2014 vs 2015–2019), countries of the population studied (developed countries vs developing countries), and language of the publications (English-language vs non-English-language). Also, the effect of the prognostic factors was evaluated, including duration of OF (TOF vs POF), diagnosis of IPN (culture vs CECT), and management of IPN (step-up approach vs non-step-up approach).

All the statistical analyses were conducted using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 16.0 (Stata Corp., College Station, TX, USA). A two-sided *P* value of less than 0.05 was regarded as statistical significance.

3 | RESULTS

3.1 | Characteristics of the included studies

A total of 4354 potentially relevant publications were identified during the initial search. Titles and abstracts were manually evaluated for relevance, and 3555 were excluded because of their study types (reviews, meta-analyses, studies on animals, case reports or case series including less than five patients, etc) (n = 484), irrelevance to the current analysis (n = 2846), animal (n = 34) or pediatric studies (n = 125), or duplications (n = 66). Of the 799 articles recruited for detailed evaluation, 385 articles were further excluded because they were conference abstracts without full text (n = 196), not original research (n = 7), insufficient data on the mortality or IPN (n = 180), and studies including the same population published before 2010 (n = 2). Full texts of the remaining 414 studies were retrieved to determine whether there were sufficient data for extraction. Of these, 371 studies were further excluded due to incomplete data (n = 365) and the same or overlapping study populations (n = 6). Finally, 43 original studies met the eligibility criteria and were included.[14,23–64] A flow diagram of the search process is shown in Figure 1.

Of the 43 studies published from 2010 to 2019 (Table 1), there were 34 retrospective cohort studies, eight prospective cohort studies, and one RCT. Nineteen studies were conducted in Europe, 18 in Asia, five in North America, and one in Australia. All studies were in English except for two in Chinese.[36,43] Fourteen studies included consecutive patients diagnosed with all grades of AP,[32,38,45,46,49,50,56–62,64] eight studies included patients with SAP,[23,28,33,36,37,39,42,47] one study included MSAP only,[55] four studies included patients with confirmed pancreatic necrosis,[34,48,51,54] three studies included ICU patients with AP,[42,44,63] and 14 studies only included patients with diagnosed or suspected IPN. As for the etiology of AP, one study included only biliary pancreatitis,[28] two studies had over 80% patients diagnosed with alcohol-induced pancreatitis,[23,27] three studies did not report the etiology,[24,36,62] and the others included patients with AP of naturally distributed etiology.

3.2 | OF and IPN

The OF definition provided by the authors and the approaches taken to the diagnosis of IPN in each study are summarized in Table S2. Five of the studies adopted non-step-up approaches in AP management, including endoscopic, laparoscopic, and open pancreatic necrosectomy, without prior percutaneous drainage (PCD) or endoscopic drainage.[24,30,33,37,46] In addition, five studies set comparison groups between the step-up approaches and non-step-up approaches.[14,29,34,35,42]

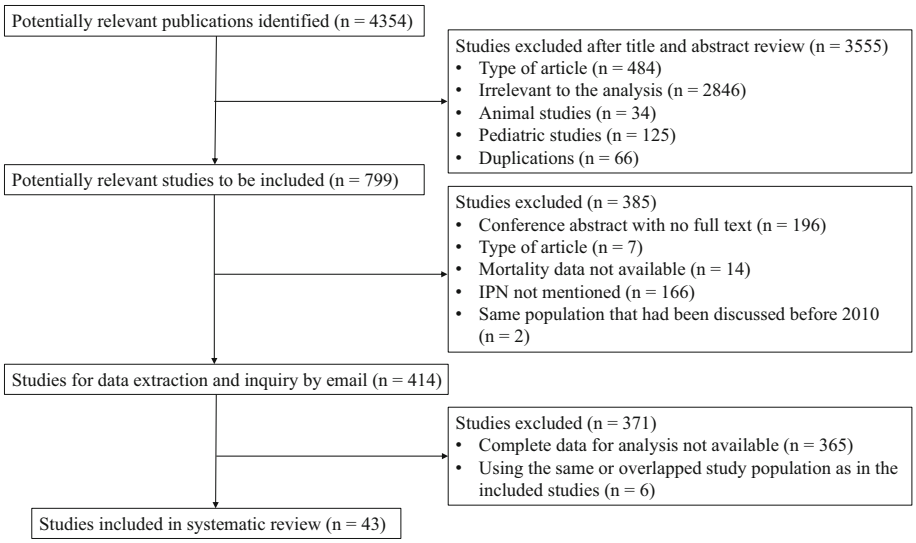

FIGURE 1 Flowchart of the process of study selection. IPN, infected pancreatic necrosis.

3.3 | Characteristics of the patients

The 43 studies included in the systematic review contained a total of 11 601 patients with AP (Table 1). All 43 studies reported in-hospital mortality and events including OF and IPN. The prevalences of OF and IPN were 25% (2900/11 601) and 18% (2113/11 601), respectively. Overall mortality was 8% (889/11 601). Of these, 28% (814/2900) died with OF and 24% (504/2113) with IPN. The mortality of the OF+IPN+, OF+IPN−, OF−IPN+ and OF−IPN− groups was 34.1%, 22.7%, 5.2%, and 0.9%, respectively (Figure S1).

3.4 | Risk of bias

As shown in the Table S3, the overall rating of the risk of bias in all the 43 studies was low.

3.5 | Influence of IPN on mortality in patients with OF

The mortality in patients with OF+IPN+ vs OF+IPN− was reported in 24 studies.[23,28,32,33,37,38,42,44–51,56–64] The mortality was 38.6% (405/1048) in OF+IPN+ patients, but only 22.7% (349/1538) in OF+IPN− patients. The forest plot with the pooled estimate for the risk of mortality in OF+IPN+ patients compared with those OF+IPN− is shown in Figure 2. The OF+IPN+ patients had a significantly increased risk of mortality (number of studies = 24; RR 1.50, 95% CI 1.16–1.95, $P = 0.002$) (Table 2). Substantial heterogeneity was observed among these studies ($I^2 = 68.0\%$, $P < 0.0001$). Figure S2 shows the funnel plot and significant publication bias (Egger's test $P = 0.009$). Further analysis with the trim-and-fill test indicated that this publication bias had great impact on the estimates (number of studies = 33; RR 1.05, 95% CI 0.791–1.398, $P = 0.731$).

A sensitivity test constrained to studies reporting natural distribution of AP etiology also revealed a significant difference of the risk of mortality (number of studies = 22; RR 1.50, 95% CI 1.15–1.97, $P = 0.003$). In the sensitivity analysis, the range of RR was between 1.38 (95% CI 1.08–1.77) and 1.59 (95% CI 1.22–2.07).

In the pre-specified subgroup analysis, an increased risk of mortality was not significant in the developed countries subgroup (RR 1.28, 95% CI 0.94–1.75) when compared with the developing countries subgroup (RR 1.80, 95% CI 1.14–2.84), although the difference was not significant ($P_{interaction} = 0.22$) (Figure S3). Details of the remaining pre-specified subgroup analyses are shown in the Supplementary Material and Figure S4. All the results of the subgroup analyses are summarized in Table S4.

3.6 | Influence of OF on mortality in patients with IPN

Thirty-four studies provided data to compare mortality in patients with OF+IPN+ vs those with OF−IPN+.[14,25–27,29–32,34–36,38–43,45,46,48–54,56–61,63,64] The mortality was 36.7% (402/1096) in OF+IPN+ patients, but only 4.8% (33/691) in those with OF−IPN+. OF+IPN+ was associated with a significantly increased risk of mortality (number of studies = 34; RR 4.58, 95% CI 3.15–6.68, $P < 0.0001$) (Table 2, Figure 3). A low level of heterogeneity was observed ($I^2 = 21.7\%$). Figure S5 shows the funnel plot, and there was publication bias on the Egger's test ($P = 0.02$). Further analysis with the trim-and-fill test indicated that this publication bias did not influence the estimates (number of studies = 43; RR 3.58, 95% CI 2.54–5.05, $P < 0.0001$).

In the sensitivity study, the pooled estimate ranged from 4.20 (95% CI 2.89–6.11) to 5.08 (95% CI 3.69–6.99) after the omission of single studies. A sensitivity test constrained to studies reporting natural distribution of AP etiology also revealed a significantly increased risk of mortality for OF+IPN+ group (number of studies = 32; RR 4.55, 95% CI 3.07–6.75, $P < 0.0001$). The pre-specified sensitivity test

TABLE 1 Characteristics of the included studies.

First author (year of publication)	Country	Study design	Total patients (n)	Patients with OF		Patients with IPN		Overall mortality	
				n	%	n	%	n	%
Oiva[23] (2010)	Finland	Prospective	13	13	100	5	38	2	15
van Santvoort[14] (2010)	The Netherlands	RCT	88	71	81	88	100	15	17
Hamouda[24] (2011)	United Kingdom	Prospective	6	3	50	6	100	0	0
Sleeman[25] (2011)	United States	Retrospective	62	15	24	62	100	5	8
Zerem[26] (2011)	Bosnia and Herzegovina	Retrospective	86	59	69	86	100	8	9
Nadkarni[27] (2013)	India	Retrospective	9	1	11	9	100	1	11
Neri[28] (2013)	Italy	Retrospective	60	43	72	6	10	4	7
Pascual[29] (2013)	Spain	Retrospective	39	27	69	39	100	12	31
Tu[30] (2013)	China	Retrospective	18	12	67	18	100	1	5
Wroński[31] (2013)	Poland	Retrospective	18	2	11	18	100	3	17
Nawaz[61] (2013)	United States	Prospective	256	65	25	18	7	10	4
Acevedo-Piedra[32] (2014)	Spain	Retrospective	543	20	4	15	3	16	3
Kiss[33] (2014)	Romania	Retrospective	145	145	100	120	83	36	25
Kumar[34] (2014)	United States	Retrospective	24	1	4	24	100	1	4
Tan[35] (2014)	France	Retrospective	32	14	44	32	100	3	9
Shen[53] (2015)	China	Retrospective	12	7	58	12	100	1	8
Chen[58] (2015)	China	Retrospective	395	68	17	72	18	35	9
Guo[60] (2015)	China	Retrospective	973	72	7	38	4	27	3
Xu[62] (2015)	China	Retrospective	573	218	38	9	1.6	4	0.7
Feng[36] (2016)	China	Retrospective	12	7	58	12	100	3	25
Ji[37] (2016)	China	Retrospective	115	115	100	39	34	13	11
Kadiyala[38] (2016)	United States	Retrospective	338	83	25	7	2	14	4
Yokoi[39] (2016)	Japan	Retrospective	15	5	33	13	87	3	20
Bansal[57] (2016)	United Kingdom	Retrospective	228	30	13	14	6	15	7
Fernandes[59] (2016)	Portugal	Retrospective	525	56	11	28	5	31	6
Zubia-Olaskoaga[63] (2016)	Spain	Prospective	374	211	56	95	25	108	29
Cao[40] (2017)	China	Prospective	74	30	41	74	100	5	7
Šileikis[42] (2017)	Lithuania	Retrospective	128	120	94	107	83	69	54
He[41] (2017)	China	Prospective	24	15	63	24	100	1	4
Choi[56] (2017)	South Korea	Retrospective	748	77	10	63	8	21	3
Padhan[45] (2018)	India	Retrospective	614	274	45	283	46	111	18
Reuken[46] (2018)	Germany	Retrospective	93	33	35	57	61	11	12
Gao[43] (2018)	China	Retrospective	89	42	47	89	100	6	7
Garret[44] (2018)	France	Retrospective	132	106	80	62	47	10	8
Shilton[51] (2018)	Australia	Retrospective	38	17	45	13	34	4	10
Saumoy[54] (2018)	United States	Prospective	9	1	11	9	100	1	11
Thorsen[52] (2018)	Denmark	Retrospective	5	3	60	5	100	2	40
Wang[64] (2018)	China	Retrospective	480	36	7	32	7	12	3
Huang[47] (2019)	China	Retrospective	309	309	100	30	10	33	11
Sternby[49] (2019)	Spain	Nationwide prospective cohort	1655	113	7	59	4	70	4
Schepers[48] (2019)	The Netherlands	Retrospective	639	240	37	202	32	93	14
Wu[50] (2019)	China	Retrospective	1102	121	11	70	6	63	6
Shu[55] (2019)	China	Retrospective	503	0	0	49	10	6	1
Overall			11 601	2900	25	2113	18	889	8

Abbreviations: OF, organ failure; IPN, infected pancreatic necrosis; RCT, randomized controlled trial.

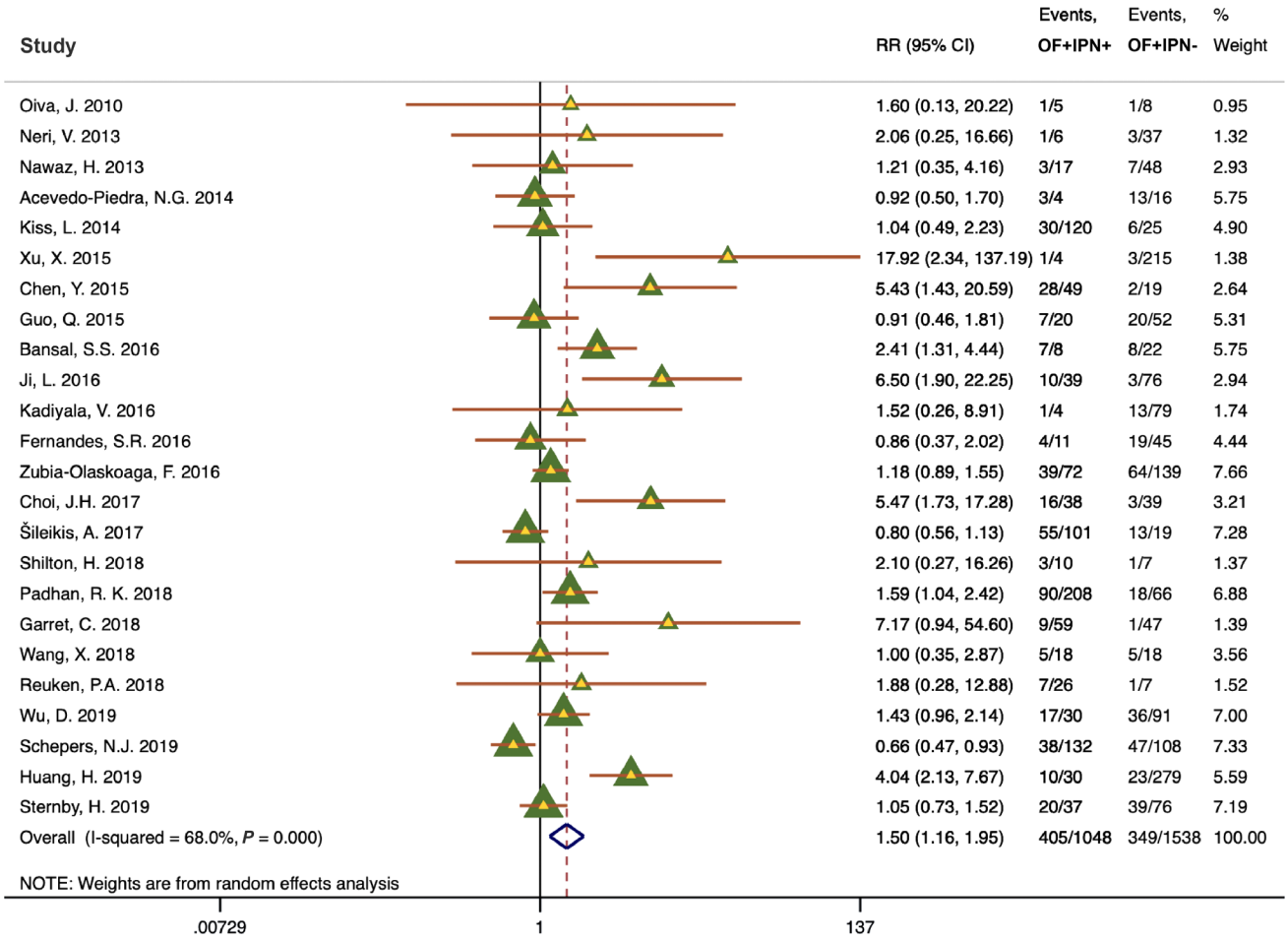

FIGURE 2 Forest plot of mortality of patients with organ failure (OF) and infected pancreatic necrosis (IPN) (OF+IPN+) compared with those with OF but without IPN (OF+IPN−). Relative risk (RR) (triangles) is presented alongside 95% confidence interval (CI) (error bars).

constrained to studies reporting confirmed necrosis only did not reveal a change in the pooled estimate of the risk of mortality. Details of the pre-specified subgroup analyses are available in the Supplementary Material and Figure S6.

3.7 | Influence of IPN on mortality in patients without OF

Twelve studies provided data for determining the relationship between the presence or absence of IPN and mortality in patients with AP but without OF.[42,45,46,48–50,55,56,58,59,63,64] The mortality was 7.1% (28/395) in OF−IPN+ patients, as opposed to 0.6% (36/5512) in OF−IPN−. Figure 4 shows the forest plot with the pooled estimate for the risk of mortality in OF−IPN+ patients compared with those with OF−IPN−, and a statistically significant difference was reported (number of studies = 12; RR 7.09, 95% CI 2.18–23.06, $P = 0.001$) (Table 2). A substantial heterogeneity was observed ($I^2 = 69.0\%$).

The pooled estimate was robust: omission of a primary study by Chen et al[58] resulted in the range of RR between 5.60 (95% CI 1.69–18.55) and 9.48 (95% CI 3.08–29.14) after omission of the study by Šileikis et al.[42]

The pre-specified subgroup analyses did not show a statistically significant difference between the risk estimates.

3.8 | Influence of OF on mortality in patients without IPN

Twenty studies compared the mortality in OF+IPN− and OF−IPN− patients.[28,32,38,42,44–46,48–51,56–64] The mortality was 27.5% (316/1150) in OF+IPN− patients, as opposed to 0.5% (37/7499) in those with OF−IPN−. Figure S7 shows the forest plot with the pooled estimate for risk of death in OF+IPN− patients compared with those OF−IPN−, and a statistically significant difference was reported (number of studies = 20; RR 30.10, 95% CI 15.32–59.13, $P < 0.0001$) (Table 2). A substantial heterogeneity was observed ($I^2 = 68.9\%$). The pooled estimate was robust: omission of a primary study resulted in the range of RR between 26.63 (95% CI 13.62–52.05) after omission of the study by Acevedo-Piedra et al[32] and 37.53 (95% CI 20.70–68.04) after omission of the study by Šileikis et al.[42] Etiology of AP had no significant effect on the pooled estimation of risk of mortality.

In a pre-specified subgroup analysis, the estimated risk of mortality was significantly different in studies restricting the definition of

TABLE 2 Influence of organ failure (OF) and infected pancreatic necrosis (IPN) on outcomes of patients with acute pancreatitis (AP).

Comparisons	In-hospital mortality						LOS in hospital				ICU admission				LOS in ICU			
	Studies (n)	Patients (n)	Risk ratio (95% CI)	*P* value	I^2 (%)	Quality[a]	n	WMD (95% CI)	*P* value	I^2 (%)	n	RR (95% CI)	*P* value	I^2 (%)	n	WMD (95% CI)	*P* value	I^2 (%)
OF+IPN+ vs OF−IPN+	34	1787	4.58 (3.15–6.68)	<0.0001	21.7	⊕⊕◯◯ Low	5	10.97 (−27.10 to 49.04)	0.572	86	8	2.78 (1.65–4.69)	<0.0001	67.9	4	15.10 (−8.37 to 28.57)	0.207	78.4
OF+IPN+ vs OF+IPN−	24	2586	1.50 (1.16–1.95)	0.002	68.0	⊕◯◯◯ Very low	5	28.75 (2.53–54.97)	0.032	94.9	7	1.34 (0.99–1.80)	0.056	86.7	5	1.69 (−12.40 to 15.78)	0.815	90.4
OF−IPN+ vs OF−IPN−	12	5907	7.09 (2.18–23.06)	0.001	69.0	⊕⊕⊕⊕ High	3	11.43 (7.81–15.05)	0.017	0	7	10.23 (2.13–49.01)	0.026	91.8	4	36.11 (6.47–65.75)	0.017	91.4
OF+IPN− vs OF−IPN−	20	8649	30.10 (15.32–59.13)	<0.0001	68.9	⊕⊕⊕⊕ High	4	8.34 (−3.25 to 19.93)	0.159	92.0	8	21.06 (8.48–52.29)	<0.0001	91.3	3	15.64 (−33.41 to 64.70)	0.532	98.1
OF+IPN− vs OF−IPN+	18	1289	3.72 (2.02–6.84)	<0.0001	42.3	⊕⊕⊕◯ Moderate	NA				7	2.30 (1.22–4.34)	0.026	66.9	NA			

Abbreviations: CI, confidence interval; LOS, length of stay; NA, not applicable; RR, relative risk; WMD, weighted mean difference.

[a]Grade assessment of quality of evidence. ⊕⊕⊕⊕, high quality; ⊕⊕⊕◯, moderate quality; ⊕⊕◯◯, low quality; ⊕◯◯◯, very low quality.

OF to POF (RR 51.66, 95% CI 27.28–97.82) than those identified both POF and TOF (RR 8.85, 95% CI 1.88–41.64, $P_{interaction} = 0.04$) (Figure S8). The remaining pre-specified subgroup analyses did not show a statistically significant difference between the risk estimates.

3.9 | Influence of OF vs IPN on mortality in patients with AP

Eighteen studies provided data to compare the mortality of OF+IPN− patients versus those with OF−IPN+.[32,38,42,44–46,48–51,56–61,63,64] The mortality was 34.5% (310/898) in OF+IPN− patients, but only 5.6% (22/391) in those with OF−IPN+. OF+IPN− patients had a significantly increased risk of mortality as compared with those with OF−IPN+ (number of studies = 18; RR 3.72, 95% CI 2.02–6.84, $P < 0.0001$) (Table 2, Figure S9). Moderate heterogeneity was observed ($I^2 = 42.3\%$, $P = 0.03$), although no statistical evidence of publication bias was found based on the Egger's test ($P = 0.885$).

The pooled estimate ranged from 3.32 (95% CI 1.76–6.25) to 4.43 (95% CI 2.55–7.71) in the sensitivity analysis. The pre-specified subgroup analyses did not show a statistically significant difference between the risk estimates.

3.10 | Secondary outcomes

LOS in hospital, LOS in ICU, and ICU admission were analyzed in the abovementioned comparisons if appropriate data were available. Five studies[28,32,42,44,49] provided data to compare LOS in hospital with the presence or absence of IPN in patients with OF. Patients with OF+IPN+ had a significantly longer LOS in hospital than OF+IPN− patients (weighted MD [WMD] 28.75, 95% CI 2.53–54.97, $P = 0.032$; $I^2 = 94.9\%$) (Table 2, Figure S10). However, ICU admission (RR 1.34, 95% CI 0.99–1.80, $P = 0.056$; $I^2 = 86.7\%$) and LOS in ICU (WMD 1.69, 95% CI −12.40 to 15.78, $P = 0.815$; $I^2 = 90.4\%$) did not differ significantly (Table 2). Eight studies provided data to compare secondary outcomes with the presence or absence of OF in patients with IPN.[24,32,42,46,49,56,60,61,64] OF+IPN+ patients had significantly increased ICU admission compared to OF−IPN+ patients (RR 2.78, 95% CI 1.65–4.69, $P < 0.0001$; $I^2 = 67.9\%$) (Table 2, Figure S11). The LOS in hospital and in ICU showed no significant difference. In the comparison between OF+IPN− patients and OF−IPN+ patients, the former group had a significantly higher rate of ICU admission (RR 2.30, 95% CI 1.22–4.34, $P = 0.026$; $I^2 = 66.9\%$) (Table 2, Figure S12).[32,46,49,56,60,61,64] Three studies provided data on OF−IPN+ patients and OF−IPN− patients,[32,42,55] indicating statistically longer LOS in hospital in the former group (WMD 11.43, 95% CI 7.81–15.05, $P = 0.017$; $I^2 = 0\%$) (Table 2, Figure S13). In addition, OF−IPN+ patients had a significantly higher rate of ICU admission (RR 10.23, 95% CI 2.13–49.01, $P = 0.026$; $I^2 = 91.8\%$) (Table 2, Figure S14)[32,46,49,56,60,61,64] and longer LOS in ICU than OF−IPN− patients (WMD 36.11, 95% CI 6.47–65.75, $P = 0.017$; $I^2 = 91.4\%$) (Table 2, Figure S15).[32,42,49,55]

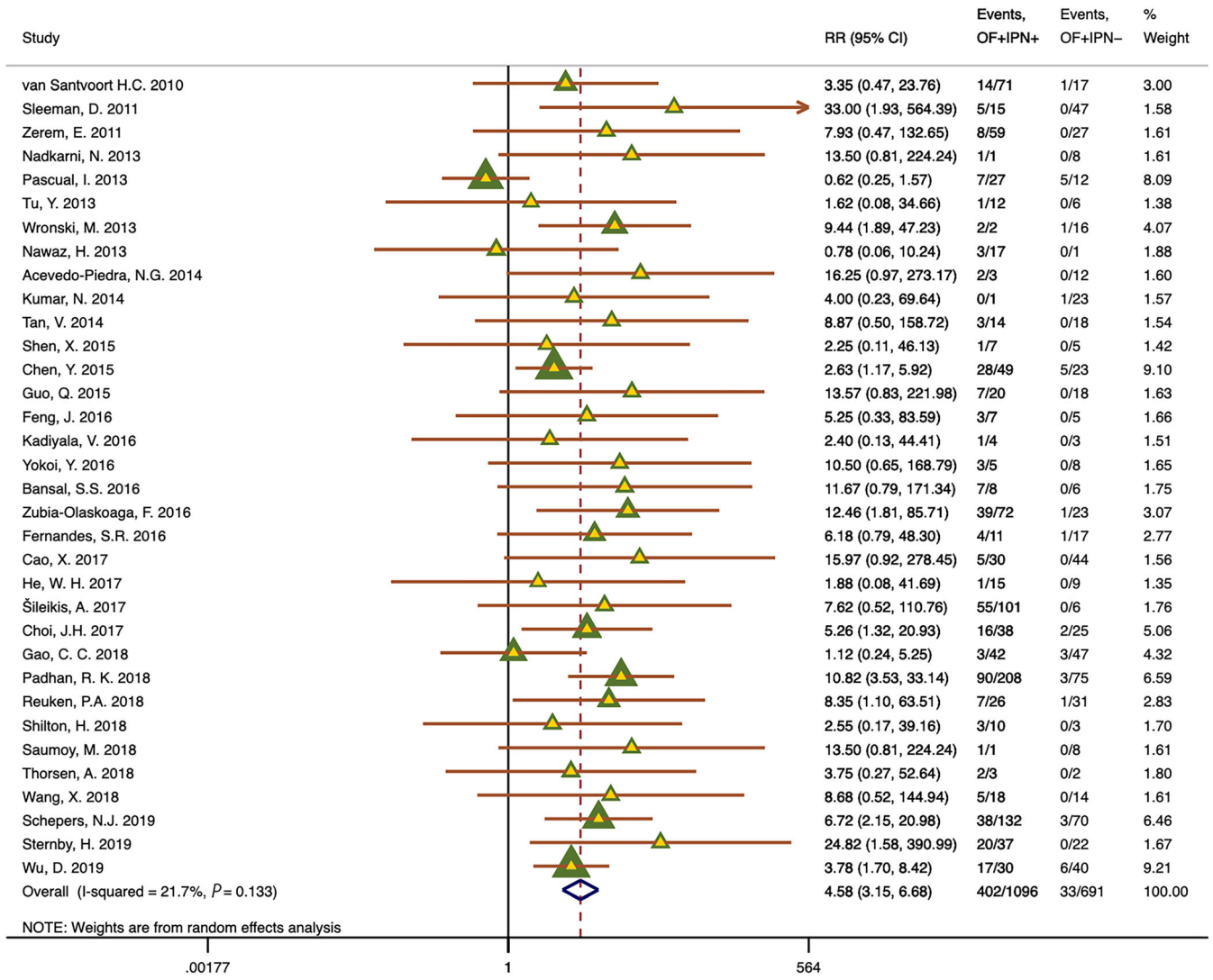

FIGURE 3 Forest plot for mortality associated with organ failure (OF) and infected pancreatic necrosis (IPN) (OF+IPN+) compared with no OF but with IPN (OF−IPN+). Weighted mean difference (WMD) is presented alongside 95% confidence interval (CI) (error bars). RR, relative risk.

4 | DISCUSSION

Published data from the last decade indicates that IPN is a less important determinant of mortality than OF, unlike a previous study,[7] which in part reflects the advancement in minimally invasive treatment of IPN.[15] In this systematic review and meta-analysis, we divided the patients into four groups and the mortality of each group was 34.1% (OF+IPN+), 22.7% (OF+IPN−), 5.2% (OF−IPN+), and 0.9% (OF−IPN−), respectively, indicating that the patients with IPN only had a much less risk of mortality than those with OF.

It has been reported that OF and IPN are equivalent and independent determinants of severity in patients with AP.[7] The authors revealed that the presence of both OF and IPN doubled the risk of mortality compared with either OF or IPN alone. This is the basis for defining the "critical" severity category.[7] Moreover, the authors failed to demonstrate a significant difference between the mortality rate of OF and IPN in patients with AP. However, data from the most recent decade indicate that IPN is no longer equivalent to OF as a determinant of mortality, although there remains a positive interaction (synergism) between them. In the current study, we included studies in which TOF was not excluded from the total OF event, which effectively strengthens our findings. This is due to the reason that the inclusion of TOF is expected to reduce the morbidity, mortality, and LOS associated with OF. And yet, we still revealed that patients with OF+IPN− had a significantly higher risk of mortality than those with OF−IPN+, even when both POF and TOF were included. This leads to the finding that IPN is an even less important risk factor than OF for mortality in AP. While IPN was still associated with a prolonged hospital stay, possibly reflecting the inefficiency of the available treatment options.

Significant advances have been made in the timing and techniques for managing IPN. The step-up approach, as validated in the PANTER trial in 2010, entailed waiting for encapsulation for an arbitrary and undertaking drainage (percutaneous or endoscopic) and for the established route to then be used for debridement if required.[14]

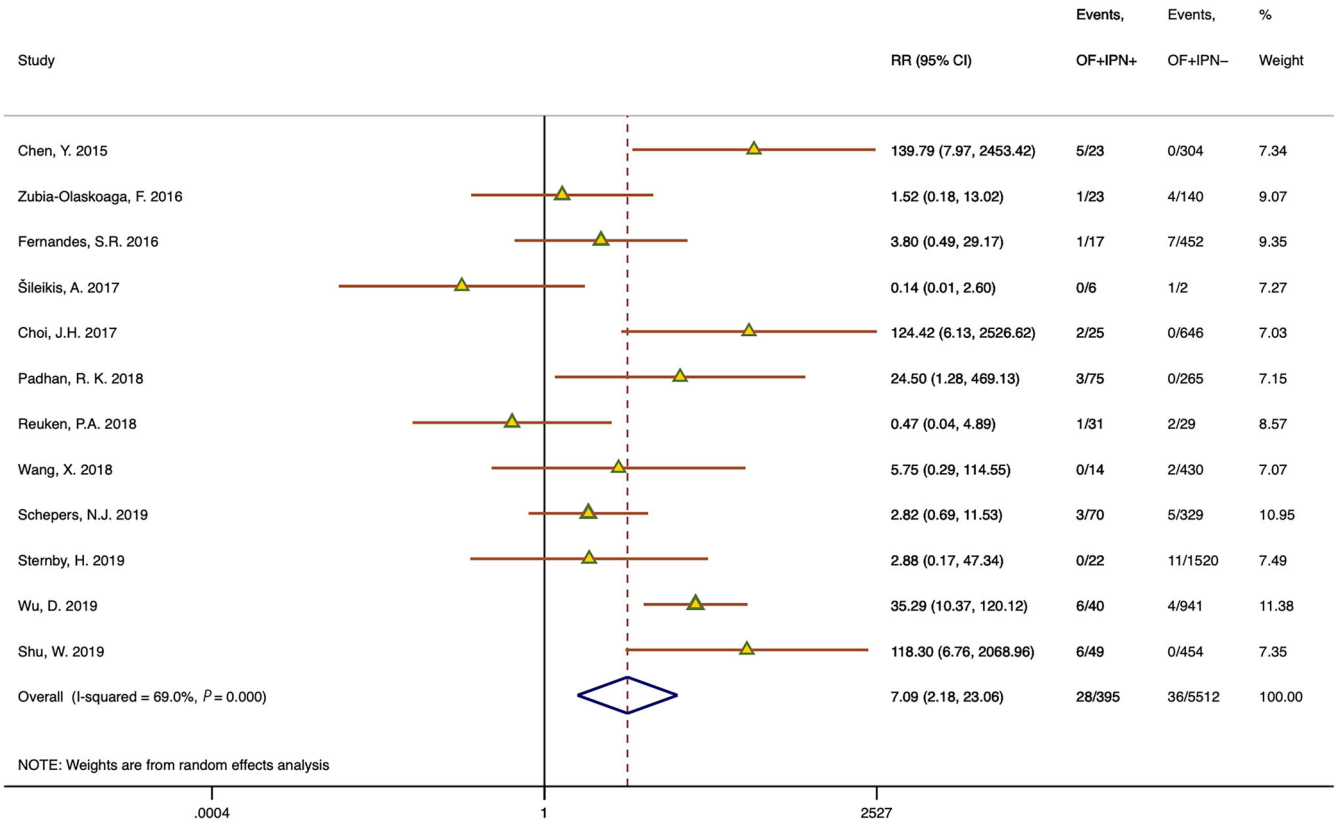

FIGURE 4 Forest plot for mortality associated with no organ failure (OF) but with infected pancreatic necrosis (OF−IPN+) compared with neither OF nor IPN (OF−IPN−). Weighted mean difference (WMD) is presented alongside 95% confidence interval (CI) (error bars). RR, relative risk.

Open surgical necrosectomy was indicated if less invasive approaches to necrosectomy failed. We found in the current study that the step-up approach affected the influence of OF on mortality in those with IPN by lowering the risk of mortality in patients with IPN and without OF. And this approach was supported by the findings that open necrosectomy was associated with a higher risk of new-onset OF.[14] Some studies have also reported that the step-up approach decreases the incidence of new-onset OF and postoperative adverse events compared with open necrosectomy.[14,29,35,42] Although such patients require longer hospital stay and often more interventions, the evidence is compelling that the step-up approach has reduced the impact of IPN on mortality. Data also indicate that different step-up approaches are not equivalent in this respect. Endoscopic step-up approach is associated with a reduced LOS and risk of pancreatic fistula compared with surgical step-up approaches.[12] There is worldwide regional variation in the influence of IPN on mortality in patients with OF, suggesting that there is scope to reduce mortality, with potential improvements in the management of IPN with the wider adoption of the step-up approach. Besides, although the advances in the management of IPN may have great impact on decreasing the mortality due to IPN, other factors such as a more active use of enteral nutrition and the rational use of antibiotics may also contribute to it. And the specific reason of a decreased risk of IPN needs to be further studied.

When faced with the decision whether to transfer a patient to a tertiary center, it is sufficient to determine whether or not the patient has SAP or predicted SAP. While for research and audits, it is important to stratify patients further, especially when evaluating the impact of treatment. The present study defines three phenotypically different cohorts within the group of SAP or predicted SAP, ie, OF+IPN+, OF−IPN+, and OF+IPN−. The former has been defined as "critical" AP. Although IPN is a lesser determinant of mortality, these patients still have the worst prognosis.[8,37,44,47,56–59,62,63] When OF is present without IPN, there is a high mortality but low morbidity.[50,63] When IPN is present without OF, on the contrary, there is a low mortality but high morbidity.[50,63]

This is the first meta-analysis to reevaluate major determinants of mortality in patients with AP since the introduction of the step-up approach to the management of IPN, and there were several limitations to this study. First, our analysis was based on observational studies, and adequate control of confounding factors was absent in most of the included studies. Only one study reported an adjusted hazard ratio in multivariate analysis of risk for mortality with an adjustment for age, sex, and computed tomography severity index (CTSI).[48] Similar mortality rates were observed in patients with OF+IPN+ compared with those with OF+IPN−, based on both adjusted and unadjusted results in this study.[48] Second, we observed certain publication biases among the included studies, which were detected by using the Egger's test, and had an impact on the pooled estimates. Despite that, and after the trim-and-fill test, IPN remained a weaker determinant of severity compared with OF. Third, there

were different definitions for OF (including POF and POF + TOF), and there were different protocols for managing IPN (including step-up and non-step-up approaches) across the original studies, which contributed to significant heterogeneity and limit the reliability of the estimates. To address this problem, the pre-specified subgroup analyses addressing definitions of OF and IPN interventions have indicated that these characteristics do influence the pooled estimates. The results are consistent with the suggested explanation that the step-up approach decreased the influence of IPN on mortality. Lastly, we were not able to investigate the effect of the timing and etiology of OF and its relationship with mortality in the present systematic review and meta-analysis, as the data were not available in most of the included studies. The pattern of OF used to be described as bimodal, with an early and late peak, and it was said that OF was driven by different processes, ie, sterile inflammatory drivers for early peak and infection-related drivers for late peak. It is not that clearcut now. IPN is not necessarily a late event,[65] and there is evidence that IPN can develop within 2–3 weeks after the onset of AP,[66] and it appears that the late mortality peak is no longer a feature.[67] The timing of OF might still be important, though we were not able to evaluate its impact as the included studies provided limited information of the timing of OF development. Future studies should disclose more information about the timing and cause of OF and mortality to help solve this problem. There are conflicting results regarding whether early or late OF has a high mortality rate[56,68–70] or whether there is any difference.[48,71] As reported by Schepers et al[48] and Shi et al,[67] recent improvements in the treatment of IPN appear to have erased the second mortality peak, leaving a single peak in the incidence of OF and mortality during the first week of AP. Shi et al also reported a relationship between the duration of OF (>2 weeks) and mortality.

In conclusion, in this systematic review and meta-analysis we demonstrated that OF and IPN were determinants of mortality in patients with AP, but they were not equivalent.[50,63] It is clear that OF is the more important determinant of mortality, despite improvements in the treatment of IPN it is still responsible for increased morbidity and a prolonged hospital stay. The risk of mortality was highest (36.7%) when both OF and IPN were present (termed "critical" AP), while OF alone led to higher (22.7%) mortality than IPN alone (5.2%). This study supports the definition of SAP based on POF alone, as per the RAC.[9] It also supports the use of the "critical" AP category (ie, OF+IPN+) as per the DBC[8] and supports subdividing the "severe" AP category into two groups (ie, OF+IPN− and OF−IPN+) as per the modified DBC.[50,63] Distinguishing these will help define more homogenous categories for clinical trials, assist clinical decision-making, and audit clinical outcome.

ACKNOWLEDGMENTS

The authors thank Dr. Reuken (Jena University Hospital, University of Jena, Jena, Germany), Dr. Audrius Šileikis (Vilnius University, Vilnius, Lithuania), Dr. Vincenzo Neri (University of Foggia, Foggia, Italy), and Dr. Enrique De-Madaria (Alicante University General Hospital, Alicante, Spain) for providing additional data on their studies.

FUNDING INFORMATION

This research received financial support from the National Natural Science Foundation of China (32170788), the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-023), the National Key Clinical Specialty Construction Project (ZK108000), and the Beijing Natural Science Foundation (7232123).

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no known competing financial, professional, or personal conflicts that could have appeared to influence the work reported in this article.

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SUPPORTING INFORMATION

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How to cite this article: Hu WM, Hua TR, Zhang YL, et al. Prognostic significance of organ failure and infected pancreatic necrosis in acute pancreatitis: An updated systematic review and meta-analysis. *J Dig Dis*. 2023;24(12):648-659. doi:10.1111/1751-2980.13243