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Review article

Infection increases mortality in necrotizing pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Objectives: To assess the influence of infection on mortality in necrotizing pancreatitis.
Methods: Eligible prospective and retrospective studies were identified through manual and electronic searches (August 2015). The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). Meta-analyses were performed with subgroup, sensitivity, and meta-regression analyses to evaluate sources of heterogeneity.
Results: We included 71 studies (n = 6970 patients). Thirty-seven (52%) studies used a prospective design and 25 scored ≥5 points on the NOS suggesting a low risk of bias. Forty studies were descriptive and 31 studies evaluated invasive interventions. In total, 801 of 2842 patients (28%) with infected necroses and 537 of 4128 patients (13%) with sterile necroses died with an odds ratio [OR] of 2.57 (95% confidence interval [CI], 2.00–3.31) based on all studies and 2.02 (95%CI, 1.61–2.53) in the studies with the lowest bias risk. The OR for prospective studies was 2.96 (95%CI, 2.51–3.50). In sensitivity analyses excluding studies evaluating invasive interventions, the OR was 3.30 (95%CI, 2.81–3.88). Patients with infected necrosis and organ failure had a mortality of 35.2% while concomitant sterile necrosis and organ failure was associated with a mortality of 19.8%. If the patients had infected necrosis without organ failure the mortality was 1.4%.
Conclusions: Patients with necrotizing pancreatitis are more than twice as likely to die if the necrosis becomes infected. Both organ failure and infected necrosis increase mortality in necrotizing pancreatitis.

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1. Introduction

Infection in pancreatic necrosis is a major concern in the late phase of acute pancreatitis [1,2]. It is unknown whether the infection per se increases the risk of death [3–6]. Diagnosing infected pancreatic necrosis can be challenging. Currently there is no international consensus. Different diagnostic strategies are used. The recommended methods include contrast enhanced computed tomography (CT) and culturing from fine needle aspiration. When infected necrosis is present, current guidelines recommend minimally invasive intervention when the necrosis is encapsulated to a walled-off necrosis after 3–4 weeks.

Two reviews have previously evaluated prognosis of patients with acute pancreatitis [7,8]. One review included a meta-analysis of *P* values evaluating the influence of infected necrosis on mortality in patients who underwent open surgery [7]. The review included 11 observational studies and found that infection had no effect on mortality. The second review included 14 observational studies of patients with acute pancreatitis and found that those with both organ failure and infected necrosis had increased mortality [8]. There are no systematic reviews evaluating if infection increases mortality in patients with necrotizing pancreatitis. Numerous studies may provide data to allow such an assessment. We therefore conducted this systematic review with meta-analysis of all available clinical studies.

2. Methods

2.1. Study identification

We conducted this review based on a registered protocol (PROSPERO 2015:CRD42015017601). We included clinical studies regardless of their design, publication status, year of publication, blinding, or language. Studies evaluating secondary infections developed after interventions, chronic pancreatitis, or pancreatic pseudocysts were excluded. In case a study was reported in more than one publication, we extracted data from the publication with the largest number of patients and the longest duration of follow-up.

Eligible studies were identified through electronic searches in Medline, Embase, The Cochrane Library, and Web of Science. The last update was August 2015. The search strategy included the following terms ((necroti* pancreatitis) OR ("walled-off pancreatic necrosis")) AND infection AND (study OR trial)). We also scanned reference lists from original articles and reviews.

The primary outcome measure was mortality. Secondary outcomes measures were organ failure, multiple organ failure, and admission to an intensive care unit.

The included patients had necrotizing pancreatitis as defined by non-enhancement of pancreatic parenchyma on contrast enhanced CT or intraoperative findings of necrotic tissue. Pancreatic collections were defined according to the revised Atlanta classification [9]. In studies published before the revised classifications, we included pancreatic abscess, necroma, and organized necrosis as synonymous with walled-off pancreatic necrosis. Infected necrosis should be proven by either Gram staining or culturing. If patients were categorized as having infected necrosis by the presence of gas on CT-scan or clinical suspicion, and no information on culturing was provided, the studies were excluded.

2.2. Data extraction

Two authors (M.W. and S.N.) independently extracted data. Disagreements were resolved through discussion before analyses. In case of disagreement, a third author (L.L.G.) acted as ombudsman. The following data were extracted: Patient characteristics (aetiology, alcohol consumption, smoking, age, gender, proportion with Gram-negative, Gram-positive, fungal, and polymicrobial infections); disease severity score (Ranson and APACHE (Acute Physiology and Chronic Health Evaluation) II); type of treatment (antibiotic prophylaxis, conservative/supportive management only, minimally invasive interventions, and open surgery); trial design (including study period and country of origin); outcomes (mortality, organ failure, and admission to the intensive care unit).

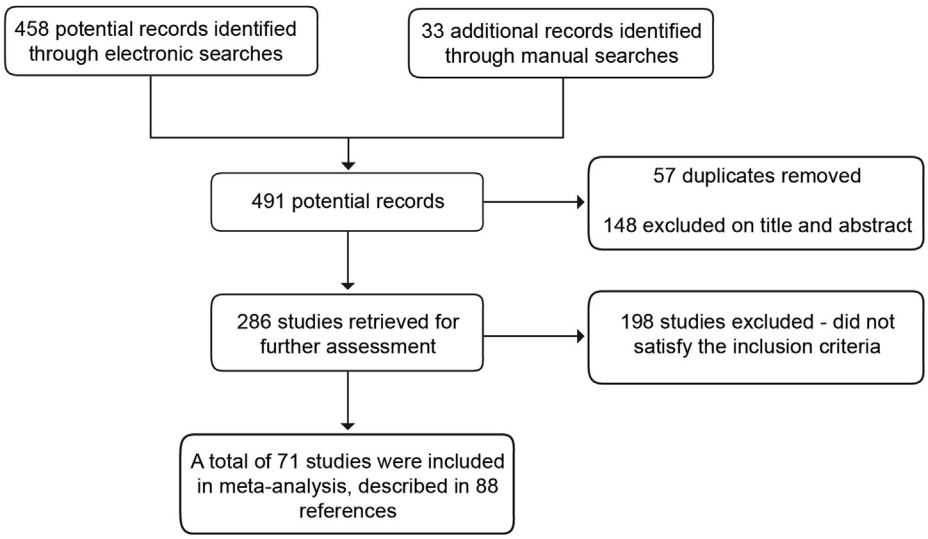

Fig. 1. Flow diagram of the study selection process.

Table 1
Characteristics of included studies with bias assessment (Newcastle-Ottawa Scale).

First author, publication year, settings	Study period	Study design	Mean age	Gender (% male)	Aetiology (% alcohol) (% gallstone)	Open surgery (%)	AB prophylaxis (%)	NOS-score S = selection C = comparability O = outcome	PN, (N)	IPN, N (%)	Overall mortality, N (%)
Beger 1986 Germany [11]	1978–1982	Pro	43.0	70.2	57.9 16.7	100	34.2	S: 3; C: 1; O: 1	114	45 (39.5)	23 (20.2)
Allardyce 1987 Canada [12]	1981–1984	Retro	N/A	N/A	N/A	39.5	N/A	S: 3; C: 0; O: 1	43	17 (39.5)	14 (32.6)
Stanten 1990 USA [13]	1982–1989	Retro	49.5	66.0	34.0 28.0	100	N/A	S: 3; C: 0; O: 1	50	45 (90.0)	7 (14.0)
Bradley 1991 USA [14]	1986–1989	Pro	N/A	N/A	N/A	73.7	N/A	S: 3; C: 0; O: 1	38	27 (71.1)	4 (30.0)
Függer 1991 Austria [15]	1983–1989	Retro	50.0	76.5	39.2 31.4	100	N/A	S: 3; C: 0; O: 1	102	33 (32.4)	36 (35.3)
Rattner 1992 USA [16]	1985–1989	Retro	57.5	72.6	19.2 34.2	100	N/A	S: 3; C: 0; O: 1	62	44 (71.0)	25 (24.2)
Fagniez 1994 France [17]	1986–1990	Pro	54.5	56.6	31.5 46.2	100	N/A	S: 3; C: 0; O: 1	79	38 (48.1)	26 (32.9)
Howard 1995 USA [18]	1977–1992	Retro	41.2	66.1	25.8 17.7	59.7	N/A	S: 3; C: 2; O: 1	62	45 (72.6)	13 (21.0)
Luiten 1995 Holland [19]	1990–1993	Pro	55.5	58.8	30.4 35.3	41.2	N/A	S: 3; C: 0; O: 2	102	29 (28.4)	29 (28.4)
Uomo 1996 Italy [20]	1984–1993	Retro	55.4	87.0	15.1 60.3	26.6	N/A	S: 3; C: 0; O: 2	194	30 (15.5)	29 (14.9)
Mier 1997 Mexico [21]	1990–1993	Pro	39.6	61.1	44.4 33.3	100	100	S: 3; C: 0; O: 1	36	22 (61.1)	17 (47.2)
Tenner 1997 USA [22]	1992–1996	Retro	48.0	43.1	27.5 47.1	N/A	66.7	S: 3; C: 2; O: 1	51	18 (35.3)	4 (7.8)
Branum 1998 USA [23]	1990–1996	Retro	52.0	54.0	14.0 42.0	100	N/A	S: 3; C: 0; O: 2	50	42 (84.0)	6 (12.0)
Gambiez 1998 France [24]	1990–1995	Retro	49.0	66.0	45.3 32.1	17.0	100	S: 3; C: 0; O: 1	53	22 (41.5)	7 (13.2)
Gentile 1998 USA [25]	1985–1994	Retro	54.0	70.0	30.0 27.5	100	100	S: 3; C: 0; O: 1	40	24 (60.0)	12 (30.0)
Oleynikov 1998 USA [26]	1990–1997	Retro	51.0	61.5	23.1 42.3	100	N/A	S: 3; C: 0; O: 1	26	15 (57.7)	5 (19.2)
Takeda 1998 Japan [27]	1991–1994	Pro	N/A	76.8	48.5 13.8	47.8	N/A	S: 3; C: 0; O: 1	375	156 (41.6)	78 (20.8)
Tsiotos 1999 USA [28]	1983–1995	Pro	61.0	68.1	8.3 37.5	100	N/A	S: 3; C: 0; O: 1	72	57 (79.2)	17 (25.0)
Isenmann 1999 Germany [3]	1982–1996	Retro	51.4	66.3	51.3 25.3	73.7	N/A	S: 3; C: 2; O: 2	300	99 (33.0)	51 (17.0)
Kasperk 1999 Germany [29]	1989–1995	Pro	N/A	59.2	32.9 55.3	100	N/A	S: 3; C: 0; O: 1	56	22 (39.3)	7 (12.5)
Kriwanek 1999 Austria [30]	1988–1997	Pro	50.3	N/A	46.0 30.0	100	N/A	S: 3; C: 1; O: 1	100	86 (86.0)	19 (19.0)
Talamini 1999 Italy [31]	1990–1995	Pro	53.3	63.8	14.7 68.1	N/A	100	S: 3; C: 0; O: 1	163	11 (6.7)	19 (11.7)
Piotrowski 2000 Poland [32]	1983–1999	Retro	47.2	36.0	N/A	100	100	S: 3; C: 0; O: 1	50	38 (76.0)	15 (30.0)
Poves 2000 Spain [33]	1992–1997	Retro	52.2	61.1	N/A	69.8	N/A	S: 3; C: 0; O: 1	63	29 (46.0)	23 (36.5)
Ala-Kokko 2001 Finland [34]	1996–1999	Retro	53.0	77.6	61.2 23.9	34.2	100	S: 3; C: 0; O: 1	67	24 (35.8)	14 (20.9)
Gloor 2001 Switzerland [4]	1994–2000	Pro	56.8	62.1	34.9 45.3	33.0	100	S: 3; C: 2; O: 3	106	34 (32.1)	10 (9.4)
Le Mée 2001 France [35]	1986–1998	Pro	58.3	N/A	37.2 44.2	65.1	100	S: 4; C: 0; O: 1	43	27 (62.8)	10 (23.3)
Beattie 2002 Scotland [36]	1991–1999	Retro	50.7	53.7	25.9 51.9	100	59.3	S: 3; C: 0; O: 1	54	34 (63.0)	23 (42.6)
Hartwig 2002 Germany [37]	1993–2001	Pro	N/A	N/A	N/A	32.2	100	S: 3; C: 0; O: 1	121	41 (33.9)	12 (9.9)
Hungness 2002 USA [38]	1993–2000	Retro	51.0	69.2	34.6 34.6	N/A	96.2	S: 2; C: 0; O: 1	26	18 (69.2)	6 (23.1)
Perez 2002 USA [39]	1995–1999	Retro	52.4	56.6	26.3 39.4	37.5	43.8	S: 3; C: 0; O: 1	99	37 (37.4)	14 (14.1)
Götzinger 2003 Austria [40]	1986–1998	Pro	51.5	70.4	27.6 28.0	100	100	S: 3; C: 0; O: 1	250	86 (34.4)	97 (38.8)
Manes 2003 Italy [41]	1996–2001	Pro	55.8	60.2	11.4 64.2	17.6	100	S: 3; C: 0; O: 1	176	22 (12.5)	22 (12.5)
Maravi-Poma 2003 Spain [42]	20 months	Pro	55.8	68.5	27.2 59.8	N/A	100	S: 3; C: 0; O: 1	92	27 (29.3)	17 (18.5)
Riché 2003 France [43]	1994–1999	Pro	56.1	70.8	52.1 33.3	8.3	N/A	S: 3; C: 2; O: 1	48	15 (31.3)	3 (6.3)
	1996–2003	Pro	59.4	N/A		N/A	87.3	S: 3; C: 1; O: 1	73	55 (76.4)	23 (31.9)

Table 1 (*continued*)

First author, publication year, settings	Study period	Study design	Mean age	Gender (% male)	Aetiology (% alcohol) (% gallstone)	Open surgery (%)	AB prophylaxis (%)	NOS-score S = selection C = comparability O = outcome	PN, (N)	IPN, N (%)	Overall mortality, N (%)
Connor 2004 England [44]					36.1 25.0						
De Waele 2004 Belgium [5]	1994–2003	Retro	56.0	62.5	37.5 33.9	100	N/A	S: 3; C: 1; O: 1	56	26 (46.4)	22 (39.3)
Wig 2004 India [45]	N/A	Retro	42.0	74.1	56.9 32.8	100	100	S: 3; C: 0; O: 1	58	44 (75.9)	17 (29.3)
King 2005 England [46]	1992–2001	Retro	43.3	60.0	53.3 33.3	97.0	100	S: 3; C: 0; O: 1	30	19 (63.3)	7 (23.3)
Olah 2005 Hungary [47]	2001	Pro	49.0	75.0	N/A	45.8	100	S: 3; C: 0; O: 1	24	12 (50.0)	4 (16.7)
Radenkovic 2005 Serbia [48]	1996–2000	Pro	54.1	62.9	28.6 42.9	100	100	S: 3; C: 0; O: 1	35	27 (77.1)	12 (34.3)
Chang 2006 Taiwan [49]	1996–	Pro	N/A	N/A	47.4 26.3	N/A	N/A	S: 3; C: 0; O: 2	19	15 (78.9)	3 (15.8)
Charnley 2006 England [50]	2002–2004	Retro	49.8	69.2	N/A	N/A	N/A	S: 3; C: 0; O: 3	13	11 (84.6)	2 (15.4)
Manes 2006 Italy [51]	2002–2005	Pro	54.4	64.4	22.0 55.9	25.4	100	S: 3; C: 0; O: 1	59	13 (22.0)	6 (10.2)
Olakowski 2006 Poland [52]	1998–2003	Retro	54.0	56.9	6.9 57.6	87.5	100	S: 3; C: 0; O: 1	144	61 (42.4)	26 (18.1)
Remes-Troche 2006 Mexico [53]	1997–2002	Retro	42.5	63.0	27.8 37.0	25.9	100	S: 3; C: 0; O: 1	54	14 (15.4)	6 (11.1)
Tireli 2006 Turkey [54]	1991–2003	Pro	51.3	57.9	21.1 44.7	60.5	100	S: 3; C: 0; O: 1	38	13 (34.2)	9 (23.7)
Besselink 2007 Holland [7]	1995–2004	Retro	54.5	64.2	13.2 41.5	100	84.9	S: 3; C: 0; O: 1	53	44 (83.0)	19 (35.8)
Dambrauska 2007 Lithuania [55]	N/A	Pro	51.1	46.2	65.4 23.1	28.8	100	S: 3; C: 2; O: 1	52	25 (48.1)	12 (23.1)
Dellinger 2007 Multinational [56]	2003–2004	Pro	52.0	70.0	44.0 34.0	19.0	77.0	S: 3; C: 0; O: 1	100	15 (15.0)	18 (18.0)
Howard 2007 USA [6]	1993–2005	Retro	53.0	57.8	14.7 46.1	100	N/A	S: 3; C: 1; O: 1	102	76 (74.5)	12 (11.8)
Luftarakhmanov 2007 Russia [57]	N/A	Pro	49.3	54.2	27.8 19.4	95.8	100	S: 3; C: 2; O: 1	72	26 (36.1)	17 (23.6)
Kingham 2008 USA [58]	1999–2003	Retro	52.6	58.6	13.8 51.7	100	72.4	S: 3; C: 0; O: 2	29	19 (23.6)	4 (13.8)
Lytras 2008 Greece [59]	2002–2006	Pro	65.4	54.7	12.7 65.1	100	30.9	S: 3; C: 0; O: 1	55	17 (30.9)	9 (16.4)
Rodriguez 2008 USA [60]	1990–2005	Retro	57.0	62.0	15.0 44.0	100	84.0	S: 3; C: 1; O: 1	158	113 (71.5)	19 (12.0)
García-Barrasa 2009 Spain [61]	1999–2003	Pro	63.0	70.7	17.1 65.9	46.3	73.2	S: 3; C: 0; O: 1	41	16 (39.0)	6 (14.6)
Radenkovic 2009 Serbia [62]	2005–2006	Pro	57.0	57.1	6.6 64.8	42.7	N/A	S: 3; C: 0; O: 1	33	10 (30.3)	8 (24.2)
Rocha 2009 USA [63]	2000–2004	Retro	52.9	62.5	29.7 35.9	37.5	N/A	S: 3; C: 0; O: 1	64	15 (23.4)	10 (15.6)
Tsui 2009 China [64]	2000–2008	Pro	50.9	43.2	18.8 48.8	18.2	100	S: 3; C: 2; O: 1	336	65 (19.3)	31 (9.2)
Garg 2010 India [65]	1997–2008	Pro	41.3	60.6	18.0 34.6	17.8	100	S: 3; C: 0; O: 1	253	107 (42.3)	61 (24.1)
Alvi 2011 Pakistan [66]	1998–2007	Retro	47.3	66.0	8.5 46.8	34.0	N/A	S: 3; C: 0; O: 1	47	18 (38.3)	9 (19.1)
Noor 2011 India [67]	1 year	Pro	41.8	78.4	41.2 33.3	43.1	100	S: 3; C: 0; O: 1	51	19 (37.3)	29 (56.9)
Van Santvoort 2011 Holland [68]	2004–2008	Pro	57.7	62.3	23.5 47.6	19.6	N/A	S: 3; C: 0; O: 1	639	202 (31.6)	93 (14.6)
Lu 2012 China [69]	2008–2009	Pro	52.4	66.7	13.3 43.3	23.3	100	S: 3; C: 2; O: 1	30	18 (60.0)	2 (6.7)
Cacopardo 2013 Italy [70]	2006–2011	Pro	63.0	52.2	30.4 45.6	35.6	100	S: 3; C: 0; O: 1	46	34 (73.9)	7 (15.2)
Koziel 2013 Poland [71]	2004–2010	Retro	56.9	68.0	30.9 46.6	43.2	100	S: 3; C: 0; O: 1	44	28 (63.6)	16 (36.4)
Brand 2014 Germany [72]	2005–2010	Retro	51.5	63.6	33.3 31.3	23.2	N/A	S: 3; C: 1; O: 2	99	25 (25.3)	12 (12.1)
Guo 2014 China [73]	2009–2012	Pro	46.8	60.0	10.1 51.0	N/A	100	S: 3; C: 2; O: 1	447	134 (30.0)	58 (13.0)
Schmidt 2014 Denmark [74]	2005–2011	Retro	52.3	62.8	30.8 42.3	0	69.2	S: 3; C: 1; O: 1	78	55 (70.5)	9 (11.5)
Talukdar 2014 India [75]	2013–2013	Pro	38.0	77.0	43.5 27.5	N/A	66.7	S: 3; C: 0; O: 1	73	18 (24.7)	11 (15.1)

(*continued on next page*)

Table 1 (*continued*)

First author, publication year, settings	Study period	Study design	Mean age	Gender (% male)	Aetiology (% alcohol) (% gallstone)	Open surgery (%)	AB prophylaxis (%)	NOS-score S = selection C = comparability O = outcome	PN, (N)	IPN, N (%)	Overall mortality, N (%)
Dhingra 2015 India [76]	2012–2013	Retro	38.8	72.1	21.8 38.8	9.7	N/A	S: 3; C: 0; O: 1	103	74 (71.8)	23 (22.3)
Overall									**6970**	**2842 (40.8)**	**1338 (19.2)**

PN: Pancreatic necrosis; IPN: Infected pancreatic necrosis; Retro: Retrospective; Pro: Prospective; NOS: Newcastle-Ottawa Scale; N/A: not available.

Conservative management was defined as supportive treatment only i.e. treatment with fluids, nutrition, and antibiotics. Minimally invasive treatment was defined as percutaneous drainage, video-assisted retroperitoneal debridement, and/or endoscopic transmural drainage and debridement.

2.3. Bias control

Bias control was assessed using the Newcastle-Ottawa Scale (NOS) [10]. For each study a quality score was calculated based on the selection of patients in the infected and sterile groups (maximum 4 points), the comparability of the infected and sterile groups (maximum 2 points), and the ascertainment of the outcome of interest (maximum 3 points). A lower score represented a greater risk of bias. We defined studies with at least five points as 'high quality' of bias control.

2.4. Statistical analysis

We combined the results of the included studies in random-effects and fixed-effects meta-analyses. We reported the results of the random-effects models, due to the expected clinical heterogeneity for all analyses and the fixed-effect models only if the conclusions of the two models differed. The results are reported as odds ratio (OR) with 95% confidence intervals (CI) and the I^2 statistic as a measure of heterogeneity. We defined I^2 values as unimportant (I^2 < 30%), moderate (I^2 30–50%), substantial (I^2 51–75%), or considerable (I^2 > 75%). We tested the risk of publication bias and other small study effects in regression analysis (Harbord's test). Subgroup and sensitivity analyses were performed to compare the studies with the lowest and highest risk of bias (based on the NOS score). In sensitivity analyses studies in which all patients underwent invasive interventions and studies using antibiotic prophylaxis were excluded. Studies published before the first Atlanta Classification were also excluded in sensitivity analyses. To distinguish between older studies using early necrosectomy and later studies using delayed interventions, we performed subgroup analysis of studies before 1997 and from 1997. We conducted random-effects meta-regression analysis to evaluate the influence of the following predictors: intervention (proportion of patients undergoing invasive interventions, including minimally invasive and open surgery), aetiology (proportion with pancreatitis due to alcohol or gallstones), antibiotic prophylaxis, mean age, gender (proportion of men), microbiology (proportion with fungus or polymicrobial infections), disease severity score (Ranson and APACHE II), and year of publication.

3. Results

3.1. Study and patient characteristics

The search strategy generated 458 potentially eligible records from the electronic databases and an additional 33 records from manual searches (Fig. 1). After reading titles and abstracts, 286 studies were retrieved for detailed evaluation. We excluded 198 studies because they did not evaluate acute pancreatitis or did not evaluate clinical outcomes. Finally, 71 studies described in 88 references were included in the quantitative and qualitative analyses [3–7,11–76]. The studies were published as full-paper articles from 1986 to 2015 and were conducted from 1977 to 2013. Sixty-seven studies were published in English. The remaining four studies were published in Spanish, French, Turkish, or Russian and were translated by medical personnel fluent in the relevant language.

The studies included 6970 patients; 2842 (41%) had infected necroses and 4128 (59%) had sterile necroses. The mean age ranged from 38 to 65 years and the proportion of men from 36 to 87% (Table 1). The studies included a proportion of patients with alcoholic pancreatitis (range: 7–65%) or gallstone pancreatitis (range: 14–68%). The infections were characterised as Gram-negative (range: 49–93%), Gram-positive (range: 27–86%), and fungal (range: 0–41%). The proportion of polymicrobial infections ranged from 0 to 80%. Mean Ranson score ranged from 2.1 to 5.9 and mean APACHE II score from 7 to 20.5.

Open surgery was assessed in 26 studies and three evaluated minimally invasive interventions. Two studies evaluated a combination of open surgery and minimally invasive interventions. Accordingly, all patients underwent invasive interventions in 31 studies. The remaining 40 studies were descriptive evaluating a mixture of conservative treatment and invasive interventions.

3.2. Bias assessment

Thirty-four of the 71 studies were retrospective and 37 were prospective (Table 1). The NOS assessment resulted in the following distribution of scores: 8 points (n = 1), 7 points (n = 1), 6 points (n = 10), 5 points (n = 13), 4 points (n = 45), and 3 point (n = 1). Twenty-five scored at least five points, and 46 studies scored less than five points.

3.3. Mortality

We were able to gather data on mortality from all studies. In total, 801 of 2842 (28%) patients with infected necroses and 537 of 4128 (13%) patients with sterile necroses died. Random-effects meta-analysis revealed that patients with infected necroses had a higher risk of death than patients with sterile necroses with an OR of 2.57 (95%CI, 2.00–3.31; I^2 = 62.2%; Fig. 2). The regression analysis (Harbord's test) showed no evidence of small study effects (P = 0.63).

3.4. Sensitivity, subgroup, and meta-regression analyses

In sensitivity analyses excluding studies in which all patients underwent invasive interventions the OR for mortality associated with infected necrosis was increased to 3.30 (95%CI, 2.81–3.88; Fig. 3). Sensitivity analyses excluding studies using antibiotic prophylaxis found an OR of 2.19 (95%CI, 1.83–2.62). The OR for studies published after the first Atlanta Classification was 2.49 (95%CI,

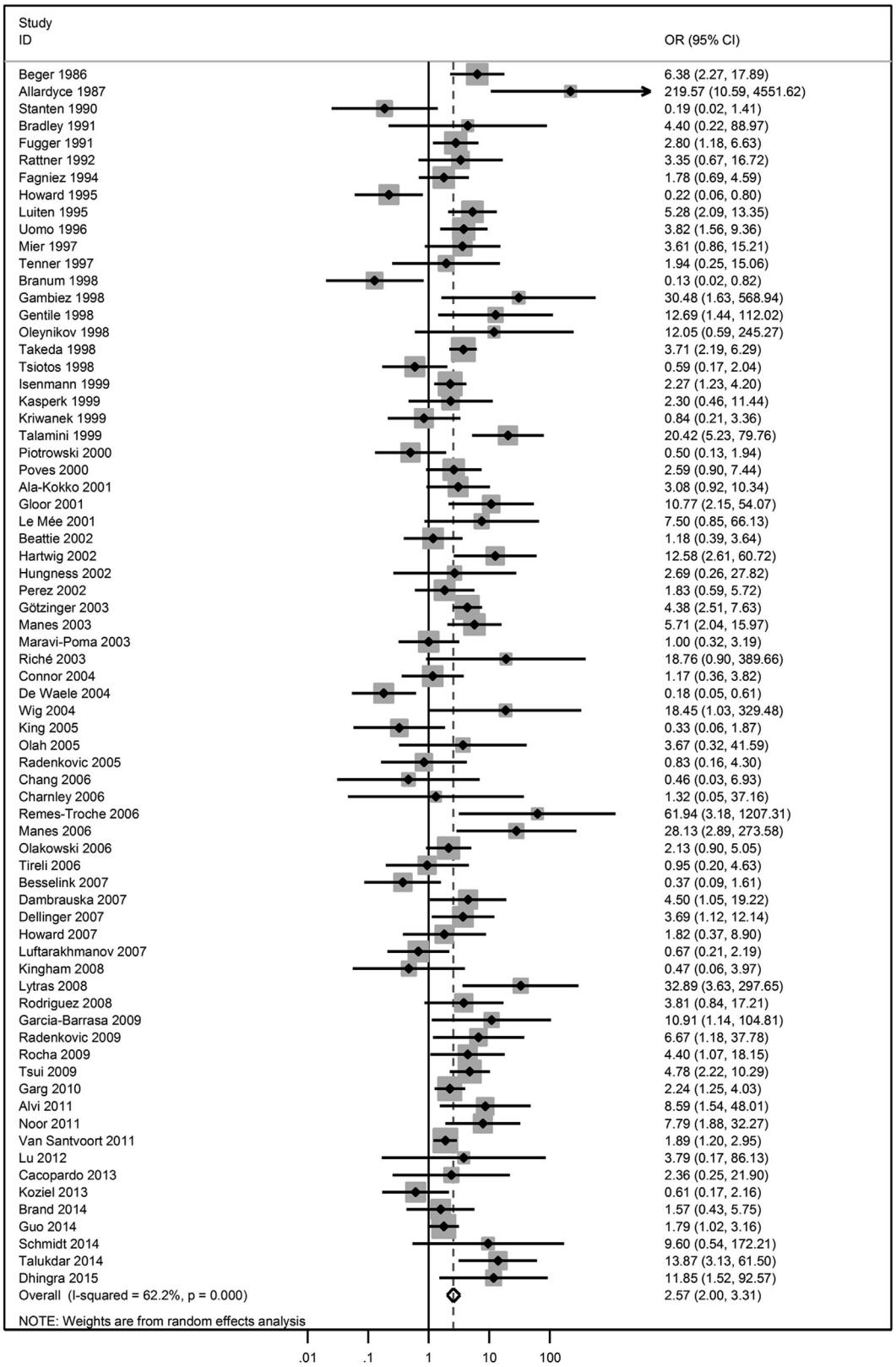

Fig. 2. Forest plot of 71 clinical studies evaluating mortality in patients with infected necroses in comparison with sterile necroses.

2.47–2.85). Subgroup analyses showed no statistical difference ($P = 0.08$) between studies with the lowest risk of bias (OR, 2.02; 95%CI, 1.61–2.53) and studies with the highest risk of bias (OR, 2.92; 95%CI, 2.49–3.44; Table 2). A statistical difference was found ($P = 0.001$) when studies were stratified by study design. The OR for prospective studies was 2.96 (95%CI, 2.5–3.50) and 2.07 (95%CI, 1.67–2.57) for retrospective studies. In the meta-regression analyses, the proportion of patients who underwent invasive

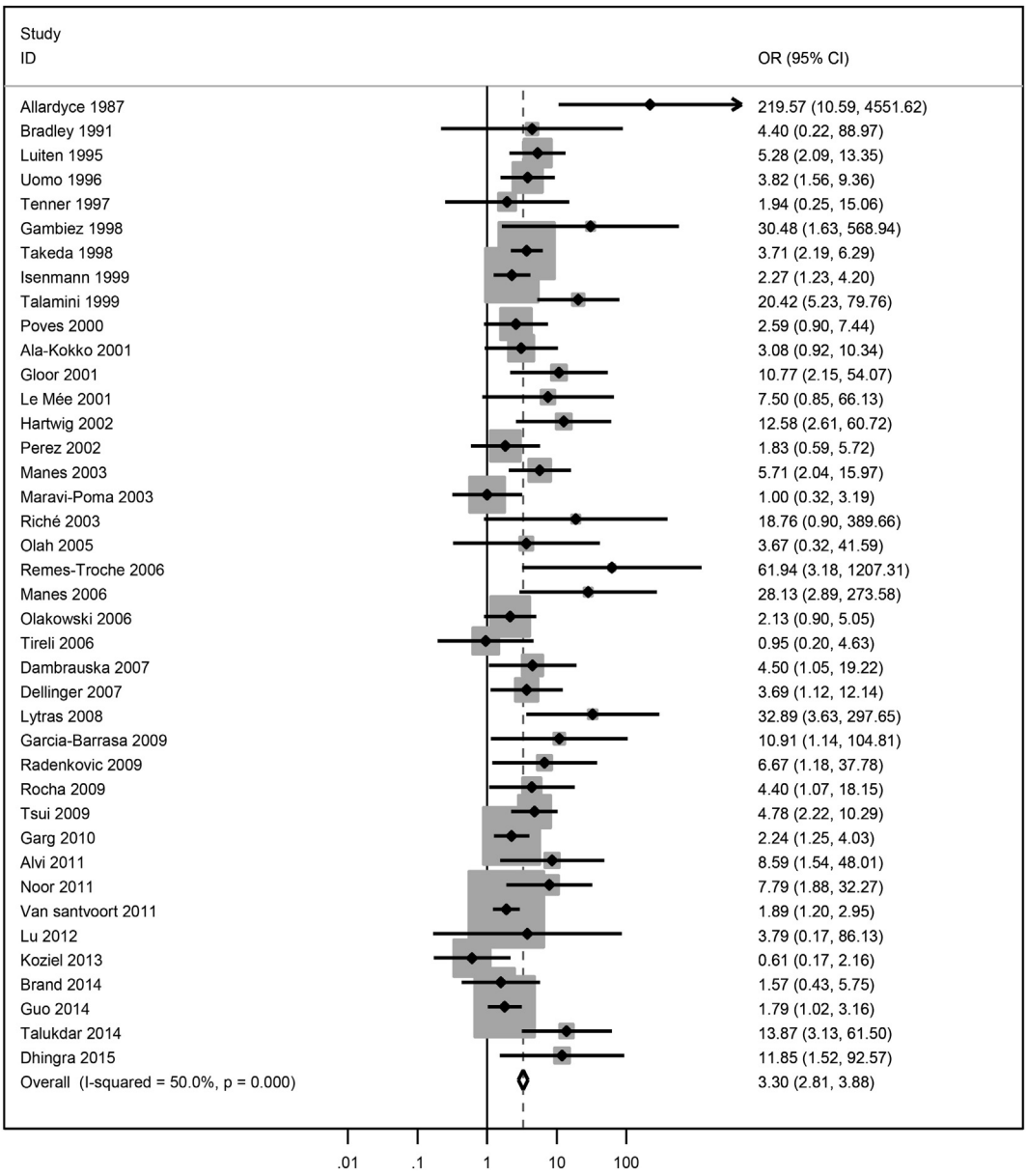

Fig. 3. Sensitivity meta-analysis excluding studies evaluating invasive interventions.

interventions was the only significant predictor of the outcome ($P < 0.001$; Table 3 and Fig. 4).

3.5. Secondary outcomes

Infected necrosis increased the risk of organ failure (OR, 2.89; 95%CI, 1.86–4.49; $I^2 = 57.7\%$; 15 studies) and multiple organ failure (OR, 3.01; 95%CI, 1.77–5.13; $I^2 = 55.7\%$; 11 studies). There was no evidence of publication bias or other small study effects (Harbord's test $P = 0.80$ and $P = 0.58$). Infections was also associated with increased risk of admission to the intensive care unit (OR, 4.33; 95% CI, 2.07–9.05; $I^2 = 52.2\%$; 5 studies).

Of the fifteen studies providing data on organ failure, ten had sufficient data to stratify patients according to infected necrosis, organ failure, and death. A total of 281 patients were classified as infected and 464 as sterile. In the infected group, 74 of 210 patients with organ failure died (35.2%). In the sterile group, 39 of 197 patients with organ failure died (19.8%). In each of the groups without organ failure only one patient died, giving a mortality of 1.4% for the infected and 0.4% for the sterile necrosis.

4. Discussion

Our review includes 71 studies with 6790 patients and found that infection in pancreatic necroses increased the risk of death. Overall, patients with infected necroses were more than twice as likely to die compared to patients with sterile necroses. The risk of organ failure was at least three times higher and the risk of admission to the intensive care unit four times higher for patients with infected necroses compared to patients with sterile necroses.

When excluding studies evaluating invasive interventions, the OR of death increased from 2.57 to 3.30. This could suggest that the intervention may influence the risk of death associated with infection. Although our data do not allow for a direct assessment, our results indicate that invasive interventions may reduce the impact of infection and thereby improve the prognosis of patients with infected necroses. Theoretically, the invasive interventions also worsen the prognosis of patients with sterile necroses through

Table 2
Results of subgroup analyses using a fixed-effects model.

Subgroup	Number of studies	Odds ratio	Confidence interval 95%	*P* value	Heterogeneity I^2 (%)	Subgroup heterogeneity (*P* value)
Study design						
Retrospective	34	2.07	1.67–2.57	<0.001	65.9	0.001
Prospective	37	2.96	2.51–3.50	<0.001	54.1	
Settings						
Europa	39	2.49	2.10–2.96	<0.001	62.5	0.017
USA and Canada	16	1.93	1.32–2.81	0.001	67.4	
Rest of the world	15	3.13	2.44–4.01	<0.001	54.7	
NOS score						
NOS < 5	46	2.92	2.49–3.44	<0.001	59.5	0.084
NOS ≥ 5	25	2.02	1.61–2.53	<0.001	66.0	
Early vs delayed intervention						
Before 1997	10	2.92	2.06–4.15	<0.001	74.7	0.604
From 1997	61	2.53	2.19–2.91	<0.001	59.8	

Table 3
Results of univariable random-effects meta-regression. The outcome measure is mortality. The analyses compare patients with infected and sterile pancreatic necroses.

Covariate	Coefficient	Standard error	*P* value
Age	−0.006	0.028	0.826
Gender	0.031	0.016	0.062
Alcohol	0.004	0.011	0.667
Gallstones	0.017	0.012	0.147
Intervention	−0.018	0.004	<0.001
Antibiotic prophylaxis	0.002	0.011	0.840
Ranson score	−0.389	0.301	0.216
APACHE II score	−0.034	0.059	0.566
Polymicrobial	0.002	0.014	0.917
Fungus	−0.018	0.023	0.421
Year or publication	0.004	0.023	0.864
NOS score	−0.146	0.167	0.387

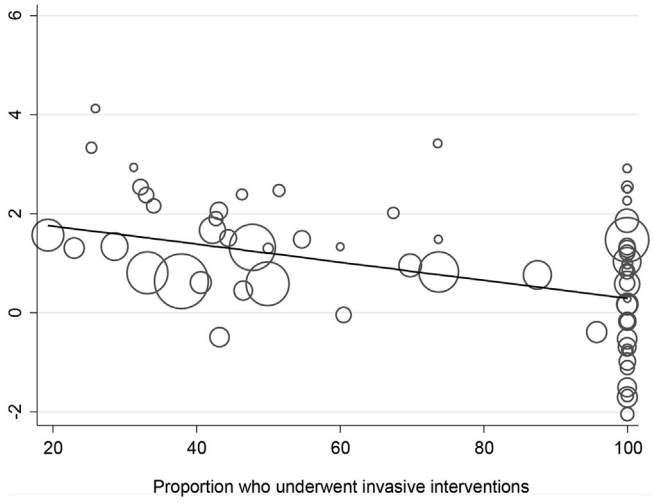

Fig. 4. Meta-regression analysis of the proportion of patients undergoing interventional treatment as a predictor of the outcome. The outcome measure is mortality. The comparison groups are patients with necrotizing pancreatitis and infected or sterile necroses. The line shows the regression line. Each circle represents a study. The circle sizes depend on the precision of each study.

superinfection. The mortality for sterile necroses decreased when the studies evaluating invasive interventions were excluded. In our meta-regression analysis, we found that the proportion of patients who underwent invasive interventions was a significant predictor of mortality associated with infection. The combined results suggest that additional studies are needed to evaluate interventions for patients with infected necroses, but also the optimal strategy for patients with sterile necroses.

We found an association between organ failure and infected necrosis. In agreement with previous evidence [8], we found that both organ failure and infected necroses increase mortality and concomitant infected necrosis and organ failure carries the greatest risk of death. In this setting, the timing of organ failure is important. Unfortunately, most studies do no report if organ failure developed early or late in the disease course, why we were unable to investigate this association more extensively. Another issue is the influence of the extent and location of the necrosis on the difference in mortality between sterile and infected necroses [77,78]. However, due to missing information, we were not able to perform analyses on the influence of the extent and location of necrosis on the outcome.

4.1. What this study adds to previous evidence

No previous systematic reviews or meta-analyses have included a sufficiently large number of trials to evaluate the influence of infected necrosis compared with sterile necrosis in necrotizing pancreatitis. The large number of studies in this analysis allowed us to evaluate the influence of patient characteristics and interventions. Our sensitivity and meta-regression analyses were predefined, but the conclusions remain hypothesis generating. A previous meta-analysis, found no effect of infection on mortality [7]. The meta-analysis included 11 studies on open surgery. We included studies evaluating open surgery, but also studies in which only a subgroup of patients underwent invasive interventions. Our review does suggest that invasive interventions reduce the risks associated with infected necroses. However, we did find an increased mortality risk associated with infection when including 26 studies evaluating open surgery. The difference between our review and the previous meta-analysis may reflect both the identification and selection of studies. It may also reflect differences in sample size. Other factors such as differences between hospital volume and experience in the included studies may also be important [79–81]. Included studies were conducted at hospitals with considerable experience in the diagnosis and management of patients with necrotizing pancreatitis. It is possible that the risks associated with infections are greater if patients are managed at centres with more limited experience. On the other hand, the fact that the more complicated patients will be referred to tertiary hospitals can lead to spectrum bias.

While minimally invasive interventions are recommended for patients with infected necroses [82,83], small case-series and case reports have reported successful conservative management of infected necroses [1,84,85]. Two prospective studies have found that conservative management improves the prognosis of patients with sterile necroses [14,77]. We were unable to evaluate the effect of conservative management directly, but our data suggest that conservative management should be used with caution in patients with infected necrosis. We have not identified any randomized controlled

trials that specifically compare conservative management versus open surgery/minimally invasive interventions for patients with sterile or infected necroses. Additional research is needed, but difficult to conduct in order to achieve sufficient statistical power.

Current guidelines do not recommend the use of prophylactic antibiotics in necrotizing pancreatitis [82,83]. After excluding studies using antibiotic prophylaxis, the OR decreased from 2.57 to 2.19. The difference is small, but does suggest that antibiotic prophylaxis may influence the risk of death associated with infection. Prolonged use of antibiotics promotes the development of opportunistic infections with resistant bacteria and fungal species. In agreement with our findings, two randomized placebo controlled trials found that antibiotic prophylaxis increased the mortality of patients with infected necroses [56,61]. Our analyses concur with these findings, though the reporting and lack of individual patient data in the included studies limit the strength of our conclusions.

4.2. Strengths and weaknesses of this review

We chose to include a clinically heterogeneous group of studies. This may be viewed as a weakness because our conclusions become less focused. On the other hand, the generalizability of our findings is increased by the inclusion of studies that covered different patient populations, settings, and treatment modalities. The fact that we included several different groups of studies also means that we were able to conduct sensitivity and meta-regression analyses to evaluate the influence of patient and intervention characteristics. Based on the large number of studies, patients, and events, we were able to identify important predictors of mortality.

4.3. Implications for clinical practice and future research

Despite the use of broad-spectrum antibiotics, infection in necrotizing pancreatitis still poses a challenge to the clinicians. A number of issues need to be addressed. The question of timing of infection needs further elucidation. Thus, it is unclear whether infection early in the course of necrotizing pancreatitis does as much harm as infection later in the disease course. Does microbial flora change during the disease course [74]? Does polymicrobial infection carry a greater risk of death than monomicrobial infection? Does the type of microbe matter? Does fungal infection worsen the disease course? These are relevant and important questions that need to be resolved. Today FNA is used to diagnose infected necrosis. However, FNA entails a risk of complications including secondary infections [86]. The development of markers to early determination of infection is essential and may reduce the number of necessary aspirations and improve the timing of intervention. The findings in our meta-analysis question the efficacy of systemic antibiotic treatment in this specific group of patients. An important question in this regard is whether systemic antibiotics are able to penetrate into the necroses sufficiently. As results from studies on the penetrability of systemic antibiotics have been conflicting, alternative treatment modalities such as local administration of antibiotics in the necrosis should be considered.

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