



Various Modalities Accurate in Diagnosing a Disrupted or Disconnected Pancreatic Duct in Acute Pancreatitis: A Systematic Review

Hester C. Timmerhuis^{1,2} · Sven M. van Dijk^{1,3} · Robert C. Verdonk⁴ · Thomas L. Bollen⁵ · Marco J. Bruno⁶ · Paul Fockens⁷ · Jeanin E. van Hooft⁷ · Rogier P. Voermans⁷ · Marc G. Besselink³ · Hjalmar C. van Santvoort^{2,8} · for the Dutch Pancreatitis Study Group

Received: 13 January 2020 / Accepted: 14 June 2020 / Published online: 27 June 2020
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Abstract

Background Severe pancreatitis may result in a disrupted pancreatic duct, which is associated with a complicated clinical course. Diagnosis of a disrupted pancreatic duct is not standardized in clinical practice or international guidelines. We performed a systematic review of the literature on imaging modalities for diagnosing a disrupted pancreatic duct in patients with acute pancreatitis.

Methods A systematic search was performed in PubMed, Embase and Cochrane library databases to identify all studies evaluating diagnostic modalities for the diagnosis of a disrupted pancreatic duct in acute pancreatitis. All data regarding diagnostic accuracy were extracted.

Results We included 8 studies, evaluating five different diagnostic modalities in 142 patients with severe acute pancreatitis. Study quality was assessed, with proportionally divided high and low risk of bias and low applicability concerns in 75% of the studies. A sensitivity of 100% was reported for endoscopic ultrasound and endoscopic retrograde cholangiopancreatography. The sensitivity of magnetic resonance cholangiopancreatography with or without secretin was 83%. A sensitivity of 92% was demonstrated for a combined cohort of secretin-magnetic resonance cholangiopancreatography and magnetic resonance cholangiopancreatography. A sensitivity of 100% and specificity of 50% was found for amylase measurements in drain fluid compared with ERCP.

Conclusions This review suggests that various diagnostic modalities are accurate in diagnosing a disrupted pancreatic duct in patients with acute pancreatitis. Amylase measurement in drain fluid should be standardized. Given the invasive nature of other modalities, secretin-magnetic resonance cholangiopancreatography or magnetic resonance cholangiopancreatography would be recommended as first diagnostic modality. Further prospective studies, however, are needed.

Keywords Acute necrotizing pancreatitis · Pancreatic fistula · Disrupted pancreatic duct · Disconnected pancreatic duct

Presented at the 13th E-AHPBA congress, Amsterdam on June 5th, 2019. Poster presentation at the 51st EPC congress, Bergen on June 28th, 2019. Poster presentation at the 27th UEG Week, Barcelona on October 23, 2019.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10620-020-06413-0>) contains supplementary material, which is available to authorized users.

✉ Hjalmar C. van Santvoort
h.vansantvoort@umcutrecht.nl

Extended author information available on the last page of the article

Introduction

Acute pancreatitis is one of the most common gastrointestinal diseases for acute hospital admission [1–3]. The disease course is generally mild. Around 20% of patients, however, develop necrosis of the pancreatic or peripancreatic tissue [4–7]. This necrosis of the pancreatic parenchyma results in loss of viable pancreatic tissue and potentially loss of integrity of the pancreatic duct [8]. This may cause either a disruption or disconnection of the pancreatic duct, causing leakage of pancreatic fluids in the surrounding tissue or to other organs. A complicated course often follows, which may be characterized by recurrent

or persistent peripancreatic fluid collections, pancreatic ascites, or pancreatic fistula including external fistulas following percutaneous catheter drainage [9–15]. This causes a major burden on the patient's quality of life and is associated with high healthcare resource utilization [8, 16–18].

The diagnosis of a disrupted or disconnected pancreatic duct syndrome is not standardized [19, 20]. Diagnostic modalities currently used are computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP) with or without secretin, or pancreatography during surgery [8, 13, 17, 21–29]. Nowadays, ERCP is still considered as the reference of standard, but this is an invasive procedure with a risk of complications such as secondary infection of pancreatic necrosis, flare of pancreatitis, bleeding and perforation [30, 31].

Because treatment success is related to the degree and location of the disruption [28, 32, 33], a timely and accurate diagnosis of a pancreatic duct disconnection and disruption is expected to facilitate treatment decisions. Evidence-based guidelines are variable regarding the preferred method and timing of diagnosing a disrupted or disconnected pancreatic duct syndrome in acute necrotizing pancreatitis and clear guidelines are missing [19, 20, 34, 35].

We performed a systematic review to determine the accuracy of the various diagnostic modalities to assess a pancreatic duct disruption and disconnection in patients with severe acute pancreatitis.

Methods

Search and Study Selection

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [36]. A systematic search was performed in PubMed, Embase and Cochrane Library from database inception until April 28, 2020. The Embase search was limited to Embase sources and restricted to publication types (inclusion of articles and systematic reviews). Grey literature (i.e., conference abstracts, editorials and dissertations) was excluded. Search terms included severe pancreatitis (study population), disconnected duct, pancreatic fistula (outcome) and all synonyms. A manual cross-reference check was performed on all studies reviewed during full-text article assessment. Detailed search details are presented in Appendix Table 1–3. The review protocol was not registered online (e.g., PROSPERO) but is available upon request.

Eligibility Criteria

Eligibility assessment was independently performed by two reviewers (HCT, SMvD) in a standardized manner. Discrepancies were resolved by consensus, after discussion in a meeting of the Dutch Pancreatitis Study Group. After removal of duplicates, the remaining articles were screened on relevance by title/abstract. Reviews, letters, case reports and book chapters were excluded. Selection was restricted to Dutch, German or English human studies with full-text availability. No other restrictions were imposed. Subsequently, full text was assessed for eligibility. Studies were considered eligible if they were cross-sectional studies, cohort studies (with a minimum number of 5 patients) or randomized trials including patients over 18 years of age with acute pancreatitis who underwent any diagnostic modality for a suspected disrupted or disconnected pancreatic duct.

Distinction between a disrupted (partial) and disconnected (complete) pancreatic duct disruption was considered but was not deemed possible owing to heterogeneous index test and the limited number of studies covering this subject.

Data Extraction and Critical Appraisal

Relevant study characteristics were extracted using a data extraction template based on the Standards of Reporting of Diagnostic Accuracy (STARD) studies checklist [37]. The following information was extracted: (1) country of origin, year of publication, design, setting, inclusion criteria; (2) the performed index test and reference standards; (3) total number of patients included and number of relevant patients; (4) accuracy measurements calculated by constructing 2×2 tables derived from each index test and its corresponding reference standard.

Data were extracted regarding the imaging characteristics: type of imaging modality, (quality) scoring criteria, data regarding diagnostic accuracy, technical features for each modality and reported observer experience.

The methodological quality of included study was assessed by two reviewers independently (HCT, SMvD) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [38]. Differences in assessment were resolved by consensus between the two reviewers, or after discussion in a meeting of the Dutch Pancreatitis Study Group.

Statistical Analysis

For each included study, a 2×2 contingency table was constructed for each imaging modality. If data were available, sensitivity, specificity, and overall accuracy were calculated

from the reconstructed tables. Pooled estimates were considered but were assumed trivial owing to heterogeneous index tests and the limited number of studies covering this subject.

Results

Search

The initial search yielded 4059 articles; 1565 articles returned from MEDLINE, 1718 from Embase, and 776 results from Cochrane library. After removal of duplicates, 2945 articles remained. Based on title and abstract screening, 76 articles remained for full-text review. Full-text assessment excluded 68 articles. No additional articles were identified after cross-reference check. Four articles evaluated diagnostic modalities; however, they did not provide sufficient data to reconstruct 2 × 2 tables and calculate the diagnostic accuracy values or even the sensitivity or specificity and were therefore excluded [11, 39–41]. Finally, 8 articles met the predetermined eligibility criteria [13, 21–25, 27, 28] (Fig. 1, Flowchart). The excluded-by-reason articles are reported in Appendix Table 2.

Study Characteristics

Study characteristics, including the reference standard for the diagnosis of a disrupted or disconnected pancreatic duct syndrome, are presented in Table 1. Data extracted regarding the imaging characteristics are presented in Appendix Table 3.

The 8 included studies were observational cohort studies published between 2003 and 2016. Two studies collected data in a prospective manner [22, 24]; Gillams et al. did not report the study design [27]. A total of 237 patients with moderate to severe acute pancreatitis, according the revised 2012 Atlanta classification, were included in the studies [4]. In 199 of the 271 patients, (peri)pancreatic necrosis was reported [13, 21, 24, 25, 28]. The number of relevant patients included in the study ranged from 6 to 31, with a total of 142 relevant patients. Four studies primarily investigated the diagnostic accuracy of an imaging modality [23, 24, 27], three studies primarily investigated the best therapy for a disrupted or disconnected pancreatic duct syndrome [13, 21, 22, 25], and in the last study both were performed [28].

The studies concerning amylase measurements in drain fluid compared their index test with ERCP as reference

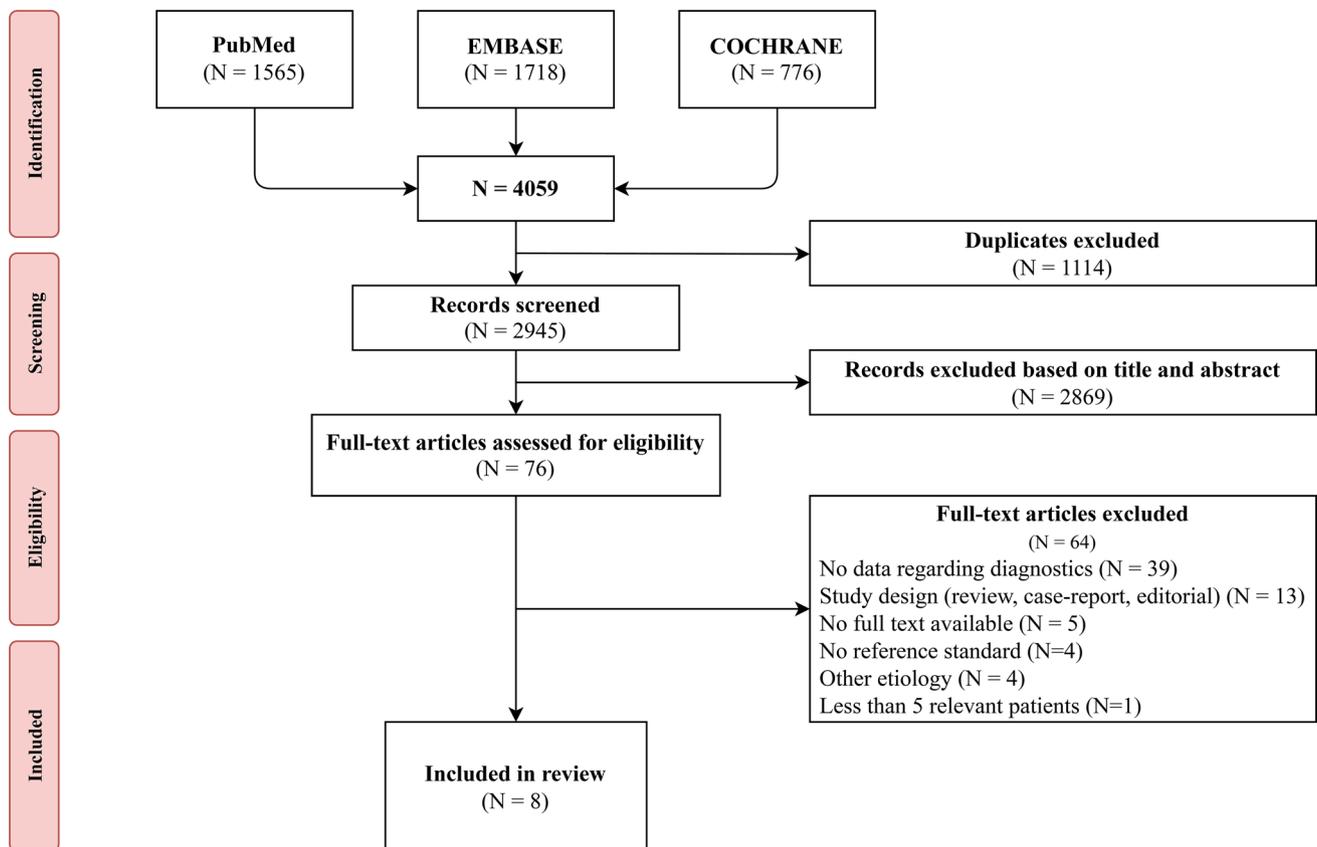


Fig. 1 Flowchart

Table 1 Study characteristics of included studies

Study	Year	Country	Study design	Inclusion period	Follow-up (median)	Nr of patients	Relevant patients	Study population	Index test	Reference standard	OE
Bakker et al.	2011	NL	Retrospective analysis of prospective cohort	2004–2007	NR	34	19	Infected necrotizing pancreatitis with pancreatic fistula	Amylase measurements	ERCP	No
Bang et al.	2016	USA	Prospective observational cohort study	2014–2015	> 90 days	42	21	Walled-off necrosis > 6 cm who underwent EUS guided drainage	EUS	Surgical/ERCP	No
Drake et al.	2012	USA	Retrospective cohort study	2000–2008	NR	31	31	Acute pancreatitis who underwent ERCP+MRI/MRCP	(Secretin)-MRCP	ERCP	No
Gillams et al.	2005	UK	Cohort study ^a	NR	6 months	17	6	Duct disruption e.c.i.: relevant acute pancreatitis	Secretin-MRCP	Surgical	No
Jang et al.	2016	South-Korea	Retrospective observational cohort study	2005–2013	512 days	84	18	Moderate to severe acute pancreatitis who underwent ERCP and/or MRCP	MRCP	ERCP	No
Smoczynski et al.	2015	Poland	Retrospective observational cohort study	2001–2013	> 1 year	22	10	Walled-off necrosis who underwent endoscopic transpapillary drainage	CECT	ERCP	No
Tam et al.	2003	USA	Retrospective observational cohort study	1995–2000	18 months	26	26	Acute pancreatitis with surgically confirmed duct disruption	ERCP/CECT	Surgical	No
Yokoi et al.	2016	Japan	Prospective observational cohort study	2005–2014	NR	15	13	Severe acute pancreatitis who underwent percutaneous drainage of fluid collection	Amylase measurements	ERCP	No

OE observer experience reported, NR not reported, MRCP magnetic resonance cholangiopancreatography, EUS endoscopic ultrasound, MRI magnetic resonance imaging, ERCP endoscopic retrograde cholangiopancreatography, CECT contrast-enhanced computed tomography

^aUnclear if prospective or retrospective design

standard [21, 25]. Tann et al. compared ERCP with surgical confirmation [13] and in the study by Bang et al. EUS was compared with either ERCP or surgical confirmation [24]. Contrast-enhanced CT was evaluated in two studies, as compared with ERCP by Smoczynski et al. [21] or surgical confirmation by Tann et al. [13]. Three studies compared either MRCP, secretin-MRCP, or both, with ERCP or surgical confirmation as reference standard. Gillams et al. investigated diagnostic accuracy of secretin-MRCP with surgical confirmation as reference standard [27], comparison of standard MRCP, with ERCP as reference standard, was done in the study by Jang et al. [28], and in the study of Drake et al., no distinction could be made between the patients who underwent standard MRCP or secretin-MRCP, as compared with ERCP [23].

Quality Assessment

The QUADAS-2 assessment for each domain is depicted in Fig. 2. [Figure 2, Summary of study quality (QUADAS-2)].

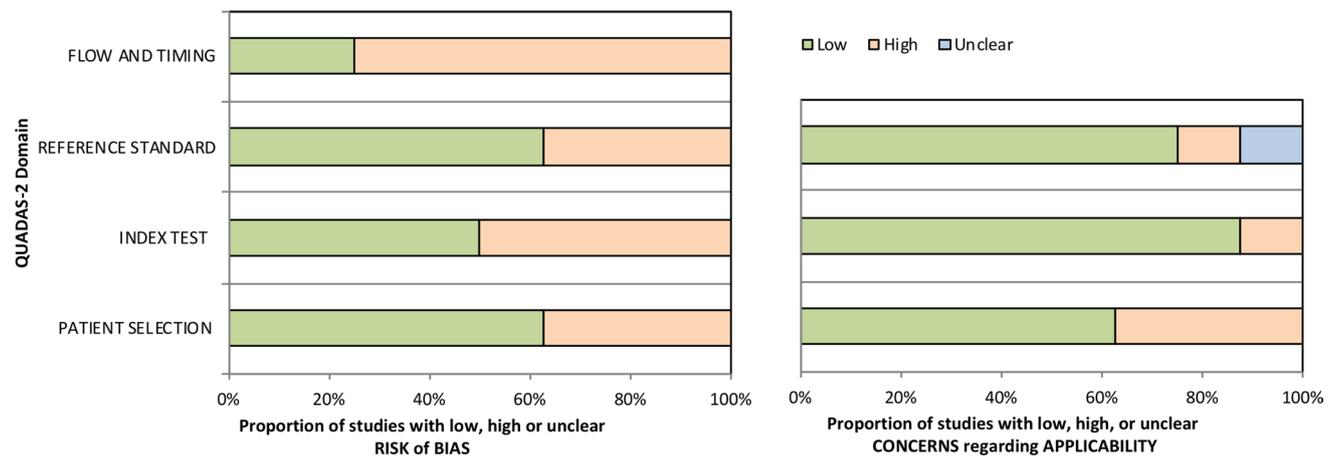


Fig. 2 Summary of study quality (QUADAS-2)

Table 2 Results of included studies

Study	Index test	Reference standard	Relevant patients	TP	FN	FP	TN	Sensitivity (%)	Specificity	Overall accuracy
Bakker et al.	Amylase measurements	ERCP	19	18	0	1	0	100		
Bang et al.	EUS	Surgical	21	1	0	–	–	100	–	–
	EUS	ERCP		20	0	–	–	100	–	–
Drake et al.	(secretin)-MRCP	ERCP	31	23	2	0	8	92	100%	94%
Gillams et al.	Secretin-MRCP	Surgical	6	5	1	–	–	83.3	–	–
Jang et al.	MRCP	ERCP	18	15	3	0	3	83.3	100%	85.7%
Smoczynski et al.	CT	ERCP	10	8	2	–	–	80	–	–
Tann et al.	ERCP	Surgical	26	26	0	–	–	100	–	–
	CT	Surgical		26	26			0		
Yokoi et al.	Amylase measurements	ERCP	13	6	0	7	7	100	50%	65%

with an amylase content of more than three times the normal serum amylase level. A comparison was made between amylase measurement and ERCP, with a similar sensitivity found of 100%. A specificity of 50%, resulting in an overall diagnostic accuracy of 65% for amylase measurements in drain fluid, was found by Yokoi et al. [22, 25].

ERCP

Tann et al. evaluated the diagnostic accuracy of ERCP. A disrupted or disconnected pancreatic duct was confirmed during surgical correction of a disrupted pancreatic duct with a sensitivity of 100%. No data could be extracted to calculate specificity. This study also evaluated prior CT-scans of patients diagnosed with disrupted or disconnected pancreatic duct syndrome by ERCP and none of the prior CT interpretation correctly identified a disrupted or disconnected pancreatic duct [13].

Endoscopic Ultrasound

A sensitivity of 100% for detecting a disrupted pancreatic duct with EUS was found in patients with a walled-off necrosis of > 6 cm, in whom the pancreatic duct was visible during EUS, as confirmed with histopathological confirmation after distal pancreatectomy or ERCP in the study by Bang et al. [24]. No specificity was reported or could be calculated.

Contrast-Enhanced CT

A sensitivity of 80% was found by Smoczynski et al. comparing contrast-enhanced CT with ERCP in patients with walled-off necrosis who underwent endoscopic transpapillary drainage [21]. Tann et al. compared contrast-enhanced CT with surgical confirmation during surgical correction for a disrupted pancreatic duct in patients with moderate to severe pancreatitis. A sensitivity of 0% was found [13]. For both studies, no specificity was reported or could be calculated from the extracted data.

MRCP

Jang et al. investigated the diagnostic yield of MRCP (without secretin) for detecting a pancreatic duct disruption, with ERCP as reference standard [28] in patients with moderate to severe pancreatitis. A sensitivity of 100% was reported. No specificity was reported and could not be calculated from the extracted data.

Secretin-MRCP

Secretin-MRCP, as compared with surgical confirmation of a disrupted pancreatic duct, was evaluated by Gillams et al. in

patients with moderate to severe pancreatitis with a reported sensitivity of 83.3%. Again, specificity was not reported or could not be calculated from the source data [27].

MRCP and Secretin-MRCP

In the study by Jang et al., both secretin-MRCP and MRCP were compared with ERCP in patients with moderate to severe pancreatitis, showing a sensitivity of 92%, a specificity of 100%, and an overall accuracy of 94%. The diagnostic difference between secretin-MRCP and MRCP was not reported upon [23].

Discussion

This is the first systematic review evaluating the various diagnostic modalities for diagnosing a disrupted pancreatic duct in moderate to severe acute pancreatitis. A sensitivity of 100% was demonstrated for amylase measurements in drain fluid and ERCP [13, 17, 22, 25]. The sensitivity for MRCP and for secretin-MRCP was 83%, both with a specificity of 100% [27, 28]. For a combined cohort of MRCP and secretin-MRCP a sensitivity of 92% was found [23]. Abdominal contrast-enhanced CT had the lowest sensitivity, ranging from 0 to 80% [13, 21].

In clinical practice, a suspicion on a disrupted or disconnected pancreatic duct is raised if amylase content in drain fluid contains more than three times the normal serum amylase level [13, 17, 22, 25, 42, 43]. Amylase measurement in drain fluid, however, does not distinguish between a partial and complete disruption. To confirm this suspicion and the degree of disruption, the current reference standard to diagnose a disrupted or disconnected pancreatic duct is ERCP. This imaging modality is, however, invasive and increases the risk of infected necrosis and other complications in this patient population [30, 31]. These risks do not occur with EUS or less invasive imaging modalities such as (secretin)-MRCP.

Studies on the accuracy of MRCP or EUS for detecting a disrupted duct in acute pancreatitis are scarce. Only Bang et al. evaluated EUS, which demonstrated a sensitivity of 100%. Notably, this study only included patients with a walled-off necrosis of more than 6 cm and a disrupted duct was present in 95% of cases. Moreover, 9 patients were excluded because EUS characterization of the pancreatic upstream gland was suboptimal. If this had been included, the sensitivity would have been considerably lower. Success of visualization was dependent on the size of the walled-off necrosis, which raises the suggestion that EUS is only of added value in a selective patient group [24]. Furthermore, complete disconnection may be seen on EUS, but visualization of a partial disruption is not possible on EUS. In this

review, we included two studies that used secretin during MRCP [23, 27]. One study evaluating secretin-MRCP was excluded due to the limited number of relevant patients ($n=3$); this study reported a sensitivity of 100% for secretin-MRCP compared with ERCP [26]. Secretin-MRCP or MRCP can be performed in nearly all patients [26]. Secretin is added for stimulation of pancreatic secretions to facilitate the identification of the pancreatic duct. No complications were reported after administration of secretin [26, 27]. In one study, only 6 of 31 patients received secretin and in 2 patients, who did not receive secretin, a disruption of the pancreatic duct was missed on MRCP. This raises the question of this may have been avoided with the use of secretin [23]. Even though the reported visualization of the pancreatic duct is generally very good, one study reported a poorer visualization by MRCP, as compared with ERCP, in patients with a partial disrupted pancreatic duct, as compared with patients with a completely disrupted pancreatic duct [28]. No secretin was used in this study, which may explain the poor visualization of the pancreatic duct. Another advantage of secretin-MRCP, besides accurate visualization of the pancreatic duct for detection of a disruption or disconnection, is an accurate visualization of the biliary duct. This may aid in establishing the cause of pancreatitis or evaluation of complications such as biliary obstruction due to peripancreatic collections or inflammation [26, 44].

Besides lack of clear evidence and guidelines for the diagnosis, there is also no consensus on the optimal treatment strategy of disrupted or disconnected duct. Several studies have reported high success rates of various treatment strategies including percutaneous drainage, endoscopic drainage and surgical resection [8, 11, 13, 14, 16, 18, 21–24, 26, 28, 29, 32, 33, 39–41, 45–60]. Yet, many of these studies were retrospective studies comprising selected patient cohorts. There are no large prospective studies of consecutive patients with necrotizing pancreatitis, specifically evaluating the prevalence or treatment outcome of a disrupted or disconnected pancreatic duct. The success rate of conservative treatment also is unknown [61]. Future studies should investigate the optimal timing, method and sequence of invasive interventions in this group of patients. To design these studies, a better understanding of the natural course of a disrupted or disconnected pancreatic duct in several subgroups of patients is needed. For instance, as success rates of different treatment strategies are probably related to the degree and location of the disruption, a distinction must be made between a partial and complete disruption. A partial disruption can often be bridged with a pancreatic duct stent, while it is very difficult to bridge a complete disruption [28, 32, 33]. Therefore, a timely and accurate diagnosis of a pancreatic duct disruption and disconnection will provide better possibilities to predict which treatment could be successful in a specific patient. There are currently no broadly accepted

definitions on a partial disrupted, a complete disrupted, a disconnected or disconnected gland syndrome [13]. Subsequently, the diagnostic criteria for a partial disrupted or complete disrupted or disconnected pancreatic duct syndrome varied in the studies included in this review. The distinction between a disrupted (partial) and disconnected (complete) pancreatic duct disruption in this systematic review was considered but was not possible owing to heterogeneous index tests and the limited number of studies covering this subject. Therefore, for this systematic review we have consciously chosen to focus on disruption and disconnection together to outline the different diagnostic modalities used to diagnose either disrupted or disconnected pancreatic duct. An important concern, diagnostic accuracy of a modality for a partial disruption may differ from the diagnostic accuracy for a complete disconnection. This difference could not be made on the extracted data and literature in this systematic review.

This study had some limitations. First, only a few studies could be included and hence number of eligible patients was relatively low. This should be taken into account when considering the calculated sensitivity. Second, most studies were performed in selected patient cohorts and were not designed to answer this question and suffered from high risk of bias. Subsequently, no clear pre-specified index test and clearly defined reference standard were used. Third, partial verification bias was present in some of the included studies [22, 23, 28] and the flow and timing of these tests may impose bias. Also, no standardized definitions for a disrupted pancreatic duct were used. As last, in four studies no specificity could be calculated [13, 21, 24, 27]. We have not registered our study in the PROSPERO database; however, our study protocol was prospectively designed.

This study is the only study comparing different diagnostic modalities in diagnosing a disrupted or disconnected pancreatic duct. Strengths of this review included the use of exhaustive search technique (in the major databases with small restrictions to publication type and grey literature) by two reviewers independently and validated systematic review methods, which strengthens our conclusions.

In conclusion, this systematic review suggests that EUS, ERCP, MRCP and secretin-MRCP appear all accurate in diagnosing a disruption or disconnection of the pancreatic duct in patients with acute pancreatitis. Amylase measurements in drain fluid should be standardized after percutaneous catheter drainage or surgical drain placement. Given the poor overall visualization of the pancreatic duct in a substantial number of patients with necrotizing pancreatitis on EUS and CT and the invasive nature of ERCP, MRCP or secretin-MRCP is recommended as first diagnostic modality. These results, however, should be taken with caution due to poor methodological quality of included studies and small sample sizes. Further prospective studies are needed to define the optimal timing and the accurate diagnostic value

of (secretin-)MRCP in different subgroups of patients with necrotizing pancreatitis.

Funding The execution of this review was funded by St. Antonius Hospital Research Fund.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Affiliations

Hester C. Timmerhuis^{1,2}  · Sven M. van Dijk^{1,3} · Robert C. Verdonk⁴ · Thomas L. Bollen⁵ · Marco J. Bruno⁶ · Paul Fockens⁷ · Jeanin E. van Hooft⁷ · Rogier P. Voermans⁷ · Marc G. Besselink³ · Hjalmar C. van Santvoort^{2,8} · for the Dutch Pancreatitis Study Group

Hester C. Timmerhuis
h.timmerhuis@antoniuziekenhuis.nl

Sven M. van Dijk
s.vandijk@antoniuziekenhuis.nl

Robert C. Verdonk
r.verdonk@antoniuziekenhuis.nl

Thomas L. Bollen
t.bollen@antoniuziekenhuis.nl

Marco J. Bruno
m.bruno@erasmusmc.nl

Paul Fockens
p.fockens@amsterdamumc.nl

Jeanin E. van Hooft
j.e.vanhooft@amsterdamumc.nl

Rogier P. Voermans
r.p.voermans@amsterdamumc.nl

Marc G. Besselink
m.g.besselink@amsterdamumc.nl

¹ Department of Research and Development, St. Antonius Hospital, PO 2500, 3430 EM Nieuwegein, The Netherlands

² Department of Surgery, St. Antonius Hospital, PO 2500, 3430 EM Nieuwegein, The Netherlands

³ Department of Surgery, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, PO 22660, 1100 DD Amsterdam, The Netherlands

⁴ Department of Gastroenterology and Hepatology, St. Antonius Hospital, PO 2500, 3430 EM Nieuwegein, The Netherlands

⁵ Department of Radiology, St. Antonius Hospital, PO 2500, 3430 EM Nieuwegein, The Netherlands

⁶ Department of Gastroenterology, Erasmus MC University Medical Center, PO 2040, 3000 CA Rotterdam, The Netherlands

⁷ Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, PO 22660, 1100 DD Amsterdam, The Netherlands

⁸ Department of Surgery, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands