

REVIEW ARTICLE

# Diagnosis and management of postpancreatectomy hemorrhage: a systematic review and meta-analysis

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## Abstract

**Background:** Postpancreatectomy hemorrhage is a potentially lethal complication after pancreatic resection. The objective of this systematic review is to provide insight in the current status of incidence, detection, management and clinical outcomes of late postpancreatectomy hemorrhage.

**Methods:** A systematic search was conducted on the literature from February 2007 to July 2018 in PubMed, Embase and the Cochrane library. Included were clinical studies with clinical outcomes on late postpancreatectomy hemorrhage defined according to the International Study Group of Pancreatic Surgery definition (i.e. occurring >24 h after pancreatic resection).

**Results:** A total of 14 studies on 467 patients with late postpancreatectomy hemorrhage were included. The incidence of late postpancreatectomy hemorrhage ranged from 3% to 16% (weighted mean: 5%). Seventy-four patients received conservative treatment; 252 patients underwent primary endovascular intervention; 82 patients underwent primary relaparotomy; 56 patients underwent primary endoscopic intervention; and three patients died before any intervention could be performed. CT-scan and diagnostic angiography were able to identify the source of hemorrhage in 67% (66/98) and 69% (114/166) of patients, respectively. The most frequent origin of the hemorrhage was the gastroduodenal artery stump (79/275; 29%), followed by the common hepatic artery (51/275; 19%) and splenic artery (32/275; 12%). Overall mortality was 21% (98/464 patients; range 0%–38%). Mortality was lower after primary interventional angiography as compared to primary relaparotomy (16% vs 37% respectively).

**Conclusions:** This systematic review provides a comprehensive overview of the current literature for severe late postpancreatectomy hemorrhages. CT-scan and diagnostic angiography are equally sensitive in detecting the bleeding source. Interventional angiography appears to be associated to lower mortality as compared to relaparotomy and endoscopy as first intervention for postpancreatectomy hemorrhage.

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## Introduction

Pancreatic surgery is complex and remains, despite a drastic decline in mortality rates to under 3% in high volume centers,<sup>1–3</sup> associated with an undesirably high postoperative morbidity (20–60%).<sup>4,5</sup> Postpancreatectomy hemorrhage is one of the most feared complications after pancreatectomy, for it is

associated with a high mortality. In accordance to the International Study Group on Pancreatic Surgery (ISGPS) definition, postpancreatectomy hemorrhage is graded based on onset, location and severity. Where early postpancreatectomy hemorrhage (i.e. occurring <24 h after index pancreatic resection) is often due to inadequate hemostasis or an underlying

coagulopathy, late postpancreatectomy hemorrhage is often the result of a multifactorial pathophysiological mechanism, including an association with other pancreatectomy specific complications, such as postoperative pancreatic fistula. Leakage of activated amylase rich fluid in the close approximation of peripancreatic vessels may lead to erosion of the vessels and hemorrhages.<sup>6</sup>

Severe postpancreatectomy hemorrhage requires a fast and effective management. The management of early postpancreatectomy hemorrhage is mostly through relaparotomy, whereas the management of late postpancreatectomy hemorrhage is more complex.<sup>7,8</sup> The general assumption is that a minimally invasive endovascular approach currently offers the best treatment available through embolization or covered stenting.<sup>9–13</sup> However, the incidence of postpancreatectomy hemorrhage is low and literature on postpancreatectomy hemorrhage mostly consists of retrospective cohorts and small case series. Therefore, a complete overview of the literature might provide more insight in the best treatment strategy of this potentially lethal complication.

The objective of this systematic review is to provide an overview of the incidence, detection, management and clinical outcomes of treatment strategies for late postpancreatectomy hemorrhage.

## Methods

### Literature search strategy

This study was performed in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.<sup>14</sup> A systematic literature search was conducted from February 2007 to July 2018. The search was restricted to the publication date of the consensus definition of postpancreatectomy hemorrhage established by the ISGPS in February 2007.<sup>6</sup> The search was applied to the following electronic databases: Pubmed/MEDLINE, Embase and Cochrane Library using the subsequent terms, including their synonyms, abbreviations and related spellings: ‘pancreatic surgery’, ‘pancreatic resection’, ‘pancreatoduodenectomy’, ‘postpancreatectomy hemorrhage’, ‘relaparotomy’, ‘angiography’, ‘endovascular’, ‘stent’, ‘coiling’, and ‘endoscopy’. Title and abstract of all studies identified were screened for the eligibility criteria. Possible, eligible studies were screened full text by two authors (AFvO and FJS) before inclusion in this analysis. Additional studies were identified by scanning reference lists of primary studies.

### Eligibility criteria

Included were studies evaluating clinical outcomes of late postpancreatectomy hemorrhage requiring (minimally) invasive interventions, as well as conservative treatment. Excluded were studies not reporting mortality or number of re-interventions

after initial intervention for postpancreatectomy hemorrhage, studies not using the ISGPS definition on postpancreatectomy hemorrhage, studies reporting solely on pancreatic transplantation or post-trauma pancreatectomy, non-English studies, reports on less than five patients and studies not reporting separate outcomes for early and late postpancreatectomy hemorrhage. Late postpancreatectomy hemorrhage was defined according to the ISGPS definition as a postoperative hemorrhage occurring at least 24 h after pancreatic resection.<sup>6</sup>

### Assessment of risk of bias

The Newcastle–Ottawa Scale (NOS) for nonrandomized studies was used to assess methodological quality of included studies.<sup>15</sup>

### Data extraction

A data extraction sheet was developed and pilot-tested on five included studies and then refined accordingly. The following data were extracted from included studies: (i) study characteristics (i.e., publication year, study period, country of origin, study design, number of included patients, incidence of postpancreatectomy hemorrhage, length of follow-up), (ii) patient characteristics (i.e., age, gender, underlying pathology, details on index pancreatectomy, and incidence of postoperative pancreatic fistula), (iii) details on (minimally) invasive interventions for late postpancreatectomy hemorrhage, and (iv) outcome measures (including mortality, rebleeding and re-intervention rates). If available, data on diagnostic accuracy of abdominal imaging, including data on source of hemorrhage and incidence of other (invasive intervention) related complications were extracted. Authors were contacted if any of these data were not presented in the paper.

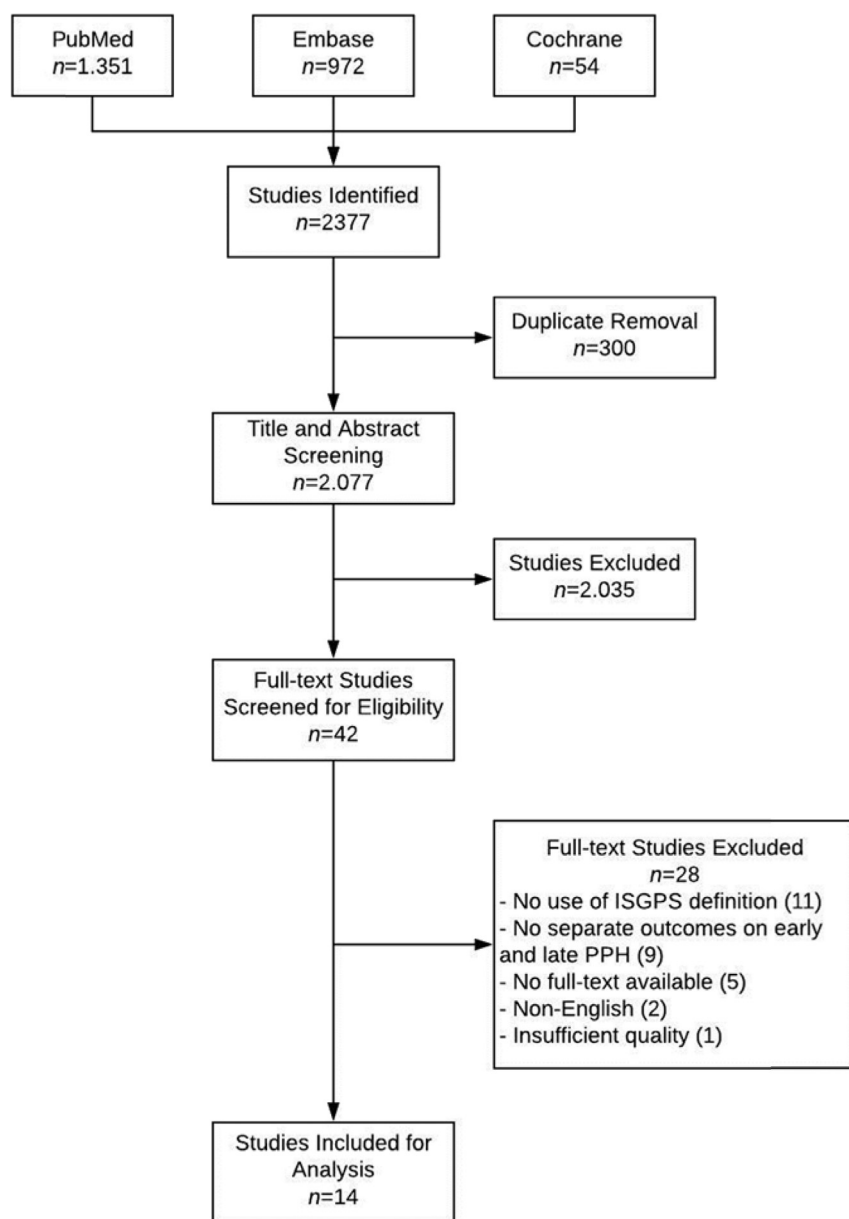
### Statistical analysis

Mean [standard deviation (SD)] or median (range) values for all continuous outcomes were extracted or obtained from authors if not available in the publications. Using the mean (SD) values, the weighted mean (SD) values were calculated, or calculated from median (range) values, using the method reported by Hozo *et al.*<sup>16</sup> Weighted incidences were calculated for dichotomous outcomes. For statistical analysis, patients were divided into groups based upon the initial invasive intervention for postpancreatectomy hemorrhage (i.e. endovascular interventions, endoscopy, and relaparotomy). Primary outcome measure was 30-day mortality after first (minimally) invasive intervention. Secondary outcome measures included success rate of first invasive intervention, defined as discharge alive without need for additional invasive intervention. Abstentions of angiographic interventions due to an inability to find the source of the hemorrhage, were regarded as diagnostic failure instead of interventional failure, in which case the subsequent intervention was considered to be the initial intervention.

## Results

The search identified 2,077 unique studies for title and abstract screening. Forty-two studies were eligible for full-text reviewing, after which a total of 14 studies were included (see Fig. 1 for a summary of the selection process). The characteristics of the studies are shown in Table 1. Seven studies described outcomes after endovascular interventions, relaparotomy and endoscopic interventions,<sup>7,9,10,17–20</sup> three studies described outcomes after endovascular interventions and relaparotomy,<sup>11,21,22</sup> and four studies only described outcomes after endovascular interventions.<sup>12,13,20,23</sup>

A total of 464 patients with late postpancreatectomy hemorrhage were included in this study (range 9–69 patients per study). Seventy-five percent of patients was male, mean age was 63 years (range 32–85 years). Eleven studies reported both the total number of pancreatectomies and the incidence of late postpancreatectomy hemorrhage. The incidence of late postpancreatectomy hemorrhage ranged from 3% to 16% (weighted mean: 5%). Pancreatic fistula rate was reported in 9 studies. In 161/284 (57%) patients with late hemorrhage suffered from clinically relevant pancreatic fistula. Patient characteristics are described in Table 2.



**Figure 1** Flow-chart depicting selection process of studies for review

**Table 1** Study characteristics

Study	Year	Study Period	Country	Study Design	Pancreatectomies (n)	Incidence PPH (%)	Patients Included (n)	Therapy (n)				
								Cons.	Endo.	Endovascular		Relap.
										CSP	Embo.	
Asari <i>et al.</i> <sup>10</sup>	2016	2003–2013	Japan	RR	553	35 (6%)	29	5 (17%)	3 (10%)	–	17 (59%)	3 (10%)
Beyer <i>et al.</i> <sup>11</sup>	2009	2005–2008	France	RR	87	9 (10%)	9	–	–	1 (11%)	7 (78%)	1 (11%)
Ching <i>et al.</i> <sup>20</sup>	2016	2007–2014	USA	RR	NR	NR	28	–	–	18 (67%)	9 (33%)	–
Correa-Gallego <i>et al.</i> <sup>7</sup>	2012	2006–2011	USA	RR	1.122	33 (3%)	26	11 (42%)	3 (11%)	–	8 (31%)	3 (11%)
Darnis <i>et al.</i> <sup>19</sup>	2013	2005–2010	Germany	RR	285	46 (16%)	46	15 (33%)	3 (7%)	–	14 (30%)	14 (30%)
Feng <i>et al.</i> <sup>18</sup>	2014	2000–2010	China	RR	840	73 (9%)	54	18 (33%)	12 (22%)	1 (2%)	11 (21%)	11 (21%)
Hassold <i>et al.</i> <sup>23</sup>	2016	2008–2015	Germany	RR	366	NR	27	–	–	16 (59%)	11 (41%)	–
Huo <i>et al.</i> <sup>21</sup>	2015	2008–2013	China	RR	357	29 (8%)	21	–	–	8 (38%)	10 (48%)	3 (14%)
Jilesen <i>et al.</i> <sup>22</sup>	2014	1992–2012	NL	RR	1.035	NR	47	19 (40%)	–	14 (30%)	–	13 (28%)
Khalsa <i>et al.</i> <sup>9</sup>	2015	2003–2013	USA	RR	337	10 (3%)	10	1 (10%)	3 (30%)	5 (50%)	–	4 (40%)
Pottier <i>et al.</i> <sup>12</sup>	2016	2005–2013	France	RR	NR	NR	69	–	–	6 (10%)	52 (90%)	–
Sanjay <i>et al.</i> <sup>13</sup>	2012	2002–2011	UK	RR	120	9 (8%)	9	1 (11%)	–	3 (33%)	5 (56%)	–
Wang <i>et al.</i> <sup>17</sup>	2017	2009–2014	China	RR	1.056	78 (7%)	58	–	24 (41%)	27 (47%)	–	10 (17%)
Wei <i>et al.</i> <sup>24</sup>	2009	1980–2007	Taiwan	RR	628	58 (9%)	31	2 (7%)	–	9 (29%)	–	20 (65%)
Total								72 (16%)	56 (12%)	252 (54%)	–	82 (18%)

RR, retrospective review; NR, not reported; Cons., conservative; Endo., endoscopy; CSP, covered stent placement; Embo., embolization; Relap., relaparotomy; –, not performed; POPF, postoperative pancreatic fistula.

### Methodological assessment

The results of the methodological quality assessment are presented in Table 3. All studies were retrospective cohort studies, seven of these studies extracted data from a prospectively maintained database.<sup>7,12,13,17,19,22</sup> Ten studies failed to report the source of their data, which may have led to inclusion bias. In 11 studies, the late postpancreatectomy hemorrhage patients were selected in a consecutive matter within a fixed inclusion period. Three studies only included late postpancreatectomy hemorrhage patients who received angiographic interventions, resulting in an intermediate risk of selection bias.<sup>12,13,23</sup> One study included all patients with postpancreatectomy hemorrhage. The researchers were, however, only able to trace back the time of onset of 55% of the postpancreatectomy hemorrhage patients.<sup>24</sup> Seven studies used multivariable regression analysis to correct for confounders in the comparison of different interventions. Ideally, all studies would have reported on predefined criteria for late postpancreatectomy hemorrhage intervention, as well as re-interventions. However, the report rates were low, and if they were reported the criteria varied substantially per study. The follow-up time was reported in 9 studies with a median duration of 90 days (range 30 days to 21.6 months). In general, the methodological quality was assessed to be low to moderate, resulting in an uncertain risk of bias.

### Diagnostic measures

Nine studies described the accuracy of diagnostic tests to identify the source of late postpancreatectomy hemorrhage. Accuracy of

abdominal computed tomography with angiography (CTA) was described in two studies evaluating 55 patients with (suspected) postpancreatectomy hemorrhage and was able to identify the source of the hemorrhage in 31 patients (mean sensitivity 56%). Conventional computed tomography (CT) was used in 5 studies evaluating 126 patients with postpancreatectomy hemorrhage and was able to identify the source of the hemorrhage in 66 patients (mean sensitivity 67%). Diagnostic angiography without prior CT was described in 5 studies and diagnostic angiography with prior CT was reported in 1 study evaluating in total 166 patients and was able to identify the source of the hemorrhage in 114 patients (mean sensitivity 69%). In addition, one study correlated the initially identified vessels on CT-scan with secondary diagnostic angiography in 69 patients.<sup>12</sup> In 48 patients (70%), the identified vessel matched between the CT-scan and diagnostic angiography.

The source of the hemorrhage was reported in 11 studies and identified in 275/335 patients. The hemorrhage source was not found in 11 patients in the endoscopy group (31%), 26 patients in the endovascular radiology (13%) group and 2 patients in the relaparotomy group (3%). Most hemorrhages originated from the gastroduodenal artery stump (79/275; 29%), followed by the common hepatic artery (51/275; 19%) and the splenic artery (32/275; 12%; Table 2).

### Clinical outcomes

Clinical outcomes are presented in Table 4. Overall mortality, reported in all 14 studies, was 98 patients out of 464 patients with

**Table 2** Patient characteristics

<b>Patient Characteristics</b>	
<b>Reported in (n)</b>	<b>10 studies, 299 patients</b>
Male	223
Female	76
Age (mean (SD) of median (IQR)??)	63 (32–85)
<b>Underlying Pathology</b>	
<b>Reported in (n)</b>	<b>14 studies, 465 patients</b>
PDAC	102 (22%)
Ampullary carcinoma	38 (8%)
Cholangiocarcinoma	34 (7%)
NET	25 (5%)
IPMN	24 (5%)
Papillary Carcinoma	11 (2%)
Pancreatitis (chronic or acute)	11 (2%)
Benign lesions	20 (4%)
Other	80 (17%)
Not reported	120 (26%)
<b>Index pancreatectomy</b>	
<b>Reported in (n)</b>	<b>12 studies, 465 patients</b>
Pancreaticoduodenectomy	262 (57%)
PPPD	94 (20%)
Distal Pancreatectomy	23 (5%)
Central Pancreatectomy	11 (2%)
Total Pancreatectomy	9 (2%)
Enucleation	8 (2%)
Other	14 (3%)
Not Reported	44 (10%)
<b>Location of the bleed</b>	
<b>Reported in (n)</b>	<b>8 studies, 236 patients</b>
Intraluminal	95 (40%)
Extraluminal	128 (54%)
Both	4 (2%)
Other	2 (1%)
Unknown	7 (3%)
<b>Origins of the Bleeding</b>	
<b>Reported in (n)</b>	<b>11 studies; 300 patients</b>
Gastroduodenal Artery Stump (GDA)	79 (26%)
Common Hepatic Artery (CHA)	51 (17%)
Splenic Artery (SA)	32 (11%)
Superior Mesenteric Artery (SMA)	21 (7%)
Proper Hepatic Artery (PHA)	20 (7%)
Other	64 (21%)
Unknown	33 (11%)
<b>Postoperative Pancreatic Fistula</b>	
<b>Reported in (n)</b>	<b>9 studies; 284 patients</b>
Co-occurrence with PPH	161 (57%)

Values reported as sum (percentage) or as median (range).

postpancreatectomy hemorrhage (weighted mean: 21%; range 0%–38%). Nine studies specified the mortality rate per primary interventional group. Endovascular interventions, relaparotomy, endoscopic interventions, resulted in 31/202 (15%), 14/38 (37%) and 5/21 (24%) reported deaths, respectively. Mortality was lower in the interventional angiography group as compared to the relaparotomy group (16% vs 37% respectively). The number needed to treat through angiography in order to prevent one death is 5 patients.

Sixty-five patients underwent primary endoscopic intervention, 82 patients underwent primary relaparotomy and 252 patients underwent primary endovascular intervention. Success rates, defined as percentage of late postpancreatectomy hemorrhage patients discharged alive without need for re-intervention, were described in 14 studies and did not differ between the endoscopic group, with 23 out of 48 patients, and interventional angiography groups, with 47 out of 84 patients (48% vs 56% respectively). The comparison of interventional angiography and relaparotomy was also similar. Interventional angiography was successful in 81 out of 133 patients and relaparotomy in 46 out of 82 patients (61% vs 56% respectively) (see Table 5).

### Covered stent versus embolization

In the studies that evaluated specific subgroups of endovascular treatment, 52 patients received a covered stent and 133 patients underwent embolization. Covered stent placements were successful in 36/52 patients (69%). A re-bleed occurred in 10 unsuccessful stent placements, of which 7 occurred at a new site, 1 at the old site and 2 were not reported. Six patients died due to multi-organ failure ( $n = 3$ ), renal failure ( $n = 2$ ) and acute myocardial infarction ( $n = 1$ ). Embolization was successful in 62/94 patients (68%), and success rate was unreported in 39 patients. A re-bleed occurred in 27 patients and 4 patients died to multi-organ failure ( $n = 3$ ) and hepatic failure ( $n = 1$ ). The mortality after covered stent placement and embolization was at 21% (6/29) and 22% (15/69) respectively.

### Discussion

This systematic review provides a comprehensive overview of the current literature on severe hemorrhage after pancreatectomy. According to the current literature, late postpancreatectomy hemorrhage remains a relatively uncommon complication with a mean incidence of 5%. However, overall mortality continues to be high at 21%. This review showed that sensitivity of angiography (69%) to identify the source of the hemorrhage was comparable to the CT-scan (67%). Endoscopy failed to identify the location of bleeding in 31% of patients with an overt luminal bleeding. The mortality rate was lower after a primary endovascular approach as compared to primary relaparotomy and primary endoscopy (i.e. 15%, 37%, 24%, respectively). Endovascular approach was the primary treatment for most late

**Table 3** Methodological Quality Assessment.

Study	Oxford Level of Evidence	Study Design	Representative of exposed cohort	Outcome of Interest	Comparability	Outcome Assessment	Follow-up Duration	Follow-up Complete
Asari <i>et al.</i> (10)	2b	RR	●	●	○	●	●	○
Beyer <i>et al.</i> (11)	2b	RR	●	●	○	●	○	○
Ching <i>et al.</i> (20)	2b	RR	●	●	●	●	●	○
Correa-Gallego <i>et al</i> (7)	2b	RR	●	●	●	●	●	○
Darnis <i>et al.</i> (19)	2b	RR	●	●	○	●	○	●
Feng <i>et al.</i> (18)	2b	RR	●	●	●	●	○	○
Hassold <i>et al.</i> (23)	2b	RR	●	●	○	●	●	○
Huo <i>et al</i> (21)	2b	RR	●	●	○	●	●	○
Jillesen <i>et al</i> (22)	2b	RR	●	●	●	●	○	○
Khalsa <i>et al.</i> (9)	2b	RR	●	●	○	●	●	○
Pottier <i>et al.</i> (12)	2b	RR	●	●	●	●	●	○
Sanjay <i>et al.</i> (13)	2b	RR	●	●	○	●	●	○
Wang <i>et al.</i> (17)	2b	RR	●	●	●	●	●	○
Wei <i>et al.</i> (24)	2b	RR	○	●	●	●	○	○

RR, retrospective review; ●, Has met the criteria: low risk of bias; ●, has partly met the criteria, moderate risk of bias; ○ failed to meet criteria, high risk of bias; NA, not applicable.

postpancreatectomy hemorrhage cases. However, 17% of patients is still primarily treated through relaparotomy. However, these results should be interpreted with care, for included studies were subjective to considerable confounding by indication.

Late postpancreatectomy hemorrhage is the result of a multifactorial pathogenesis in which postoperative pancreatic fistula play an important role. Intraoperatively, the peripancreatic vessels are often manipulated and injured due to lymphadenectomy and the ligation of the arteries.<sup>25</sup> This can lead to the corrosion of the vessel wall and subsequent vascular lesions, rendering the peripancreatic vessels vulnerable to further damage. Postoperative pancreatic fistula is associated with late postpancreatectomy hemorrhage for leakage of enzyme rich fluid into the abdomen might cause vessel erosion, which can result in the formation of a pseudoaneurysm. Pseudoaneurysms are known to rupture and as a consequence can cause late hemorrhage.<sup>26</sup>

A possible explanation for the difference in mortality rates between the interventional strategies, might lay in their respective indications. In most cases, relaparotomy is used as a last resort for hemodynamic instable patients.<sup>7,10,17,19</sup> Major surgical

trauma can lead to a lethal systemic inflammatory response, especially considering that these patients are often severely ill and potentially affected by postoperative pancreatic fistula.<sup>6,8,27</sup> Moreover, identification of the source of the hemorrhage during relaparotomy can be challenging, especially in a patient with severe postoperative pancreatic fistula. In this systematic review, especially the studies that focussed solely on an endovascular approach for late postpancreatectomy hemorrhage, started implementing embolization and covered stenting in hemodynamic instable cases.<sup>7,23</sup> As for endovascular treatment the indications for different techniques (with respect to the origin of the hemorrhage and preference of interventional radiologist) often go unreported in most studies.<sup>11,22,23</sup> Interventional endoscopy, on the other hand, prevails as the first-line intervention for intraluminal hemorrhage. Even in intraluminal hemorrhage, endoscopy fails to adequately identify the source of the hemorrhage and therefore almost always results in a delay of the adequate treatment, resulting in possible fatal outcomes.

This systematic review has attempted to elucidate the best diagnostic measure for late postpancreatectomy hemorrhage. Controversy remains between the use of a CT-scan and the use of



**Table 4** Mortality

Study	Total patients (n)	Overall Mortality per Study	Mortality Initial Treatment						
			Before Therapy	Cons.	Endo.	Endovascular			Relap.
						CSP	Embo.	NOS	
Asari <i>et al.</i> <sup>10</sup>	23	6 (21%)	1/29	1/5	0/3		3/17		1/3
Beyer <i>et al.</i> <sup>11</sup>	9	0 (0%)				0/1	0/7		0/1
Ching <i>et al.</i> <sup>20</sup>	27	2 (7%)				NR	NR	2/28	
Correa-Gallego <i>et al.</i> <sup>7</sup>	25	1 (4%)	1/26	0/11	0/3		0/8		0/3
Darnis <i>et al.</i> <sup>19</sup>	46	10 (22%)		0/15	NR		NR		NR
Feng <i>et al.</i> <sup>18</sup>	54	16 (30%)		0/18	4/12	0/1	6/11		6/11
Hassold <i>et al.</i> <sup>23</sup>	27	9 (34%)				3/16	3/11		
Huo <i>et al.</i> <sup>21</sup>	21	5 (24%)				0/8	3/10		2/3
Jilesen <i>et al.</i> <sup>22</sup>	38	6 (13%)	1/47					1/14	4/13
Khalsa <i>et al.</i> <sup>9</sup>	13	2 (20%)			1/3			0/5	1/4
Pottier <i>et al.</i> <sup>12</sup>	58	6 (9%)				NR	NR	6/57	
Sanjay <i>et al.</i> <sup>13</sup>	9	3 (33%)		0/1		3/3	0/5		
Wang <i>et al.</i> <sup>17</sup>	61	22 (38%)			NR			NR	NR
Wei <i>et al.</i> <sup>24</sup>	31	10 (32%)				NR	NR		NR
Total		98 (21%)	3/3 (100%)	1/50 (2%)	5/21 (24%)	7/29 (24%)	15/69 (22%)	9/104 (9%)	14/38 (37%)
						31/202 (15%)			

NOS, not otherwise specified; CS, covered stents; Embo., embolization. Values presented as whole and as percentage per total interventions performed.

diagnostic angiography. Angiography appears to be the most specific and sensitive diagnostic measure to detect late post-pancreatectomy hemorrhage.<sup>27</sup> On the other hand, the CT-scan

is an effective, less invasive alternative to detect late post-pancreatectomy hemorrhage, as well as related pancreatectomy specific complications.<sup>8</sup> However, the advantage of the use of

**Table 5** Success rate primary intervention

Study	Total <i>n</i> patients	Success Rate Initial Treatment					Relaparotomy
		Conservative	Endoscopy	Angiography			
				Covered Stent	Embolization	NOS	
Asari <i>et al.</i> <sup>10</sup>	23		3/3 (100%)		13/17 (77%)		2/3 (67%)
Beyer <i>et al.</i> <sup>11</sup>	9			1/1 (100%)	4/7 (57%)		0/1 (0%)
Ching <i>et al.</i> <sup>20</sup>	27			12/18 (67%)	8/9 (89%)		
Correa-Gallego <i>et al.</i> <sup>7</sup>	25	11/11 (100%)	3/3 (100%)		8/8 (100%)		3/3 (100%)
Darnis <i>et al.</i> <sup>19</sup>	46	15/15 (100%)	2/3 (67%)		7/14 (50%)		8/14 (57%)
Feng <i>et al.</i> <sup>18</sup>	54	18/18 (100%)	4/12 (33%)			3/13 (23%)	5/11 (46%)
Hassold <i>et al.</i> <sup>23</sup>	27			11/16 (69%)	8/11 (73%)		
Huo <i>et al.</i> <sup>21</sup>	21			8/8 (100%)	5/10 (50%)		1/3 (33%)
Jilesen <i>et al.</i> <sup>22</sup>	38	19/19 (100%)				9/14 (64%)	9/13 (69%)
Khalsa <i>et al.</i> <sup>9</sup>	13	1/1 (100%)	0/3 (0%)			4/5 (80%)	1/4 (25%)
Pottier <i>et al.</i> <sup>12</sup>	58			4/6 (67%)	34/52 (65%)		
Sanjay <i>et al.</i> <sup>13</sup>	9	1/1 (100%)		0/3 (0%)	4/5 (80%)		
Wang <i>et al.</i> <sup>17</sup>	61		11/24 (46%)			12/27 (44%)	1/10 (10%)
Wei <i>et al.</i> <sup>24</sup>	31					7/11 (64%)	16/20 (80%)
Total		65/65 (100%)	23/48 (48%)	36/52 (69%)	91/133 (68%)	35/70 (50%)	46/82(56%)
				162/255 (64%)			

NOS, not otherwise specified; Values represented as a whole and as percentage of total treatment group.

diagnostic angiography is that it can immediately resolve a postpancreatectomy hemorrhage once it is detected. Nevertheless, one study reports that diagnostic angiography fails to identify the hemorrhage in 25% of the cases.<sup>12</sup> This is likely due to the intermittent nature of postpancreatectomy hemorrhage. In these instances, a CT scan can provide extra information such as location of hematoma and a (partially) thrombosed false aneurysm. Future prospective trials should evaluate the true sensitivity and specificity of CT-scans and diagnostic angiography for late postpancreatectomy hemorrhage. Endoscopy fails to identify the hemorrhage source in a substantial number of patients and may therefore be of limited use as a first line diagnostic measure for overt luminal bleeding. Diagnostic angiography or CT-scan have a higher sensitivity and are more informative for physicians.

This systematic review has several limitations. First, few studies directly compare the clinical outcomes of different interventions and usually have relatively small sample sizes. As the decision on what invasive intervention should be performed is most likely dictated by the clinical presentation of postpancreatectomy hemorrhage: i.e. confounding by indication. Especially, since only a few studies report the indications of the intervention, limiting our abilities to correct for this form of bias. Second, all studies are designed as a retrospective review and this introduces several forms of bias. However, it should be noted that due to the lack of RCTs it remains difficult to properly compare the invasive interventions and draw strong conclusions from the results.

The current literature shows postpancreatectomy hemorrhage is relatively rare, with an incidence of 5%, yet associated with a mortality of 21%, making it the most lethal pancreatectomy specific complication. Diagnostic accuracy of CT and angiography are similar, both show a sensitivity of almost 70%. Hemorrhage occurs in about 30% of patients from the gastroduodenal stump. Endovascular approach appears to be superior to relaparotomy and endoscopy as primary treatment for late postpancreatectomy hemorrhage, for this is associated with a lower mortality.

#### Conflicts of interest

None declared.

#### References

- Lewis R, Drebin JA, Callery MP, Fraker D, Kent TS, Gates J *et al.* (2012) A contemporary analysis of survival for resected pancreatic ductal adenocarcinoma. *HPB* 15:49–60.
- He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA *et al.* (2014) 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. *HPB* 16:83–90.
- Van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, Bosscha K, Van Dam RM *et al.* (2017) Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. *HPB* 19:919–926.
- Braga M, Capretti G, Pecorelli N, Balzano G, Doglioni C, Ariotti R *et al.* (2011) A prognostic score to predict major complications after pancreaticoduodenectomy. *Ann Surg* 254:702–708.
- Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Carlo V Di. (2008) Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. *Br J Surg* 95:357–362.
- Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ *et al.* (2007 Jul) Postpancreatectomy hemorrhage (PPH): an international study group of pancreatic surgery (ISGPS) definition. *Surgery* 142: 20–25.
- Correa-Gallego C, Brennan MF, D'Angelica MI, DeMatteo RP, Fong Y, Kingham TP *et al.* (2012 Nov) Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. *J Am Coll Surg* 215:616–621.
- Blanc T, Cortes A, Goere D, Sibert A, Pessaux P, Belghiti J *et al.* (2007) Hemorrhage after pancreaticoduodenectomy: when is surgery still indicated? *Am J Surg* 194:3–9.
- Khalsa BS, Imagawa DK, Chen JI, Dermirjian AN, Yim DB, Findeiss LK. (2015) Evolution in the treatment of delayed postpancreatectomy hemorrhage. *Pancreas* 44:953–958.
- Asari S, Matsumoto I, Toyama H, Yamaguchi M, Okada T, Shinzeki M *et al.* (2016) Recommendation of treatment strategy for postpancreatectomy hemorrhage: lessons from a single-center experience in 35 patients. *Pancreatol* 16:454–463.
- Beyer L, Bonmardion R, Marciano S, Hartung O, Ramis O, Chabert L *et al.* (2009 May) Results of non-operative therapy for delayed hemorrhage after pancreaticoduodenectomy. *J Gastrointest Surg* 13:922–928.
- Pottier E, Ronot M, Gaujoux S, Cesaretti M, Barbier L, Sauvanet A *et al.* (2016 Oct) Endovascular management of delayed post-pancreatectomy haemorrhage. *Eur Radiol* 26:3456–3465.
- Sanjay P, Kellner M, Tait IS. (2012 Dec) The role of interventional radiology in the management of surgical complications after pancreatoduodenectomy. *HPB* 14:812–817.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA *et al.* (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 6:1–28.
- Newcastle-Ottawa quality assessment scale case control studies, case control (pp. 2–4). (2013), pp. 2–4. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). [Accessed 12 July 2017].
- Hozo SP, Djulbegovic B, Hozo I. (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 5:1–10.
- Wang W-G, Fu L, Babu SR, Wang L, Liang C-P, Tian B-L. (2018) Incidence of and risk factors and reinterventions for post-pancreatoduodenectomy hemorrhage: retrospective analysis. *Dig Surg* 35:19–27.
- Feng J, Chen Y, Dong J, Chen M, Cai S, Huang Z. (2014) Postpancreaticoduodenectomy hemorrhage risk factors, managements and outcomes. *Hepatobiliary Pancreat Dis Int* 13:513–522.
- Darnis B, Lebeau R, Chopin-Laly X, Adham M. (2013 Mar) Postpancreatectomy hemorrhage (PPH): predictors and management from a prospective database. *Langenbeck's Arch Surg* 398:441–448.
- Ching KC, Santos E, McCluskey KM, Orons PD, Bandi R, Friend CJ *et al.* (2016 Jan) Covered stents and coil embolization for treatment of postpancreatectomy arterial hemorrhage. *J Vasc Interv Radiol* 27:73–79.
- Huo Y, Chi J, Zhang J, Liu W, Liu D, Li J *et al.* (2015) Endovascular intervention for delayed post-pancreaticoduodenectomy hemorrhage:



- clinical features and outcomes of transcatheter arterial embolization and covered stent placement. *Int J Clin Exp Med* 8:7457–7466.
- 22.** Jilesen APJ, Tol JAMG, Busch ORC, Gouma DJ. (2014) Emergency management in patients with late hemorrhage after pancreaticoduodenectomy for a periampullary tumor. *World J Surg* 38:2438–2447.
- 23.** Hassold N, Wolfschmidt F, Dierks A, Klein I, Bley T, Kickuth R. (2016 Nov) Effectiveness and outcome of endovascular therapy for late-onset postpancreatectomy hemorrhage using covered stents and embolization. *J Vasc Surg* 64:1373–1383.
- 24.** Wei H, Wang S, Shyr Y, Tseng H. (2009) Risk factors for post-pancreaticoduodenectomy bleeding and finding an innovative approach to treatment. *Dig Surg*, 297–305.
- 25.** Porte RJ, Coerkamp EG, Koumans RKJ. (1996) False aneurysm of a hepatic artery branch and a recurrent subphrenic abscess. *Surg Endosc* 10:161–163.
- 26.** Yekebas EF, Wolfram L, Cataldegirmen G, Habermann CR, Bogoevski D, Koenig AM *et al.* (2007) Postpancreatectomy hemorrhage: diagnosis and treatment. *Ann Surg* 246:269–280.
- 27.** de Castro SMM, Kuhlmann KFD, Busch ORC, van Delden OM, Lameris JS, van Gulik TM *et al.* (2005) Delayed massive hemorrhage after pancreatic and biliary surgery. *Ann Surg* 241:85–91.