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Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection (Review)

Davidson TBU, Yaghoobi M, Davidson BR, Gurusamy KS

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[Diagnostic Test Accuracy Review]

Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection

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ABSTRACT

Background

The treatment of people with clinically significant postoperative pancreatic leaks is different from those without clinically significant pancreatic leaks. It is important to know the diagnostic accuracy of drain fluid amylase as a triage test for the detection of clinically significant pancreatic leaks, so that an informed decision can be made as to whether the patient with a suspected pancreatic leak needs further investigations and treatment. There is currently no systematic review of the diagnostic test accuracy of drain fluid amylase for the diagnosis of clinically relevant pancreatic leak.

Objectives

To determine the diagnostic accuracy of amylase in drain fluid at 48 hours or more for the diagnosis of pancreatic leak in people who had undergone pancreatic resection.

Search methods

We searched MEDLINE, Embase, the Science Citation Index Expanded, and the National Institute for Health Research Health Technology Assessment (NIHR HTA) websites up to 20 February 2017. We searched the references of the included studies to identify additional studies. We did not restrict studies based on language or publication status, or whether data were collected prospectively or retrospectively. We also performed a 'related search' and 'citing reference' search in MEDLINE and Embase.

Selection criteria

We included all studies that evaluated the diagnostic test accuracy of amylase in the drain fluid at 48 hours or more for the diagnosis of pancreatic leak in people who had undergone pancreatic resection excluding total pancreatectomy. We planned to exclude case-control studies because these studies are prone to bias, but did not find any. At least two authors independently searched and screened the references produced by the search to identify relevant studies.

Data collection and analysis

Two review authors independently extracted data from the included studies. The included studies reported drain fluid amylase on different postoperative days and measured at different cut-off levels, so it was not possible to perform a meta-analysis using the bivariate model as planned. We have reported the sensitivity, specificity, post-test probability of a positive and negative drain fluid amylase along with 95% confidence interval (CI) on each of the different postoperative days and measured at different cut-off levels.

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Main results

A total of five studies including 868 participants met the inclusion criteria for this review. The five studies included in this review reported the value of drain fluid amylase at different thresholds and different postoperative days. The sensitivities and specificities were variable; the sensitivities ranged between 0.72 and 1.00 while the specificities ranged between 0.73 and 0.99 for different thresholds on different postoperative days. At the median prevalence (pre-test probability) of 15.9%, the post-test probabilities for pancreatic leak ranged between 35.9% and 95.4% for a positive drain fluid amylase test and ranged between 0% and 5.5% for a negative drain fluid amylase test.

None of the studies used the reference standard of confirmation by surgery or by a combination of surgery and clinical follow-up, but used the International Study Group on Pancreatic Fistula (ISGPF) grade B and C as the reference standard. The overall methodological quality was unclear or high in all the studies.

Authors' conclusions

Because of the paucity of data and methodological deficiencies in the studies, we are uncertain whether drain fluid amylase should be used as a method for testing for pancreatic leak in an unselected population after pancreatic resection; and we judge that the optimal cut-off of drain fluid amylase for making the diagnosis of pancreatic leak is also not clear. Further well-designed diagnostic test accuracy studies with pre-specified index test threshold of drain fluid amylase (at three times more on postoperative day 5 or another suitable pre-specified threshold), appropriate follow-up (for at least six to eight weeks to ensure that there are no pancreatic leaks), and clearly defined reference standards (of surgical, clinical, and radiological confirmation of pancreatic leak) are important to reliably determine the diagnostic accuracy of drain fluid amylase in the diagnosis of pancreatic leak.

PLAIN LANGUAGE SUMMARY

Amylase in drain fluid for the diagnosis of pancreatic leak after partial removal of the pancreas

Background

The pancreas is an organ in the abdomen that secretes pancreatic juice that aids digestion; and it contains cells that produce important hormones such as insulin. Partial removal of the pancreas (pancreatic resection) is performed to remove cancerous and non-cancerous growths in the pancreas. During this process, new connections (anastomoses) are made between the pancreas and intestines and bile duct (a tube that transports bile from the liver to the intestines). These connections may break down and result in leakage of pancreatic content into the abdomen; this can lead to severe infections within the abdomen and in the blood stream, which can even lead to the death of the patient.

At the end of the operation, a drainage tube is inserted into the abdomen for two purposes: firstly, the detection of any fluid collections within the abdomen (intra-abdominal collections), usually resulting from the pancreatic leaks; and secondly, as the treatment of intra-abdominal collections, so that fluid collection decreases or, at least, does not worsen within the abdomen. The fluids from the drain can be tested for amylase (one of the contents of the pancreatic juice which digests carbohydrates) to find out whether the fluid in the drain is because of a pancreatic leak. If there is a high suspicion of a pancreatic leak, further scans are performed to confirm it or to rule it out. If the leak is major and the patient is unwell, urgent reoperation may be required. Moderate leaks can lead to intra-abdominal infections: patients may need antibiotics, drugs that decrease pancreatic secretion, insertion of a new drainage tube or repositioning of the existing drainage tube to drain the infected collection, and supportive care to recover. Currently, it is unclear whether measuring the amylase content in the fluid from the drain inserted after pancreatic resection is useful in identifying pancreatic leaks.

Study characteristics

We performed a thorough literature search for studies reporting the accuracy of drain fluid amylase in identifying pancreatic leaks. We included studies reported up to 20 February 2017. We identified five studies reporting information on 868 people who underwent pancreatic resections for cancer and non-cancerous growths. Most studies included only people in whom the head of the pancreas (right side of the pancreas) was removed.

Key results

Variations in when the studies measured the amylase content in the drain and what level was considered abnormal meant that we were not able to combine the data to provide the overall results. We are uncertain whether drain fluid amylase is useful in identifying pancreatic leaks because of the following reasons.

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1. The way that study authors confirmed that a participant had or did not have pancreatic leak was itself subject to error (i.e. there was no true 'gold standard').

2. The studies included few participants. As a result, there was significant uncertainty in the results.

3. The studies were of poor methodological quality. This introduced additional uncertainty in the results.

Quality of evidence

All of the studies were of unclear or low methodological quality, which may result in arriving at false conclusions.

BACKGROUND

Please see glossary of terms in Appendix 1.

The pancreas is an abdominal organ that secretes several digestive enzymes into the pancreatic ductal system that empties into the small bowel. It also houses the Islets of Langerhans, which secrete several hormones including insulin (NCBI 2014). Pancreatic resection is performed to treat pancreatic diseases, including pancreatic cancer, pre-cancerous pancreatic lesions, and chronic pancreatitis. Pancreatic resection is in the form of pancreaticoduodenectomy for lesions and disease of the head of the pancreas, and distal pancreatectomy for lesions in the body and tail of the pancreas (Park 2013). After pancreaticoduodenectomy, pancreato-enteric anastomosis is performed to allow the drainage of pancreatic fluid into the small bowel. After distal pancreatectomy, the cut surface of the pancreatic remnant (pancreatic stump) is closed using staples or sutures (Diener 2011). Generally, an abdominal drain is placed after pancreatic resection, although this practice has been questioned (van der Wilt 2013).

Pancreatic resection is a surgical procedure with high morbidity. It carries a postoperative mortality of around 4.5% (Gurusamy 2013). Approximately 30% of patients develop one or more postoperative complications (Gurusamy 2013). Approximately 18% of patients develop postoperative pancreatic leak or postoperative pancreatic fistula (POPF) making it one of the common complications of pancreatic resection (Gurusamy 2013). POPF is an abnormal communication containing enzyme-rich pancreatic fluid between the pancreatic ductal epithelium and another epithelial surface. It represents a failure of healing or sealing of the pancreato-enteric anastomosis or it may represent a parenchymal leak not directly related to an anastomosis, such as a leak from the raw pancreatic surface after distal pancreatectomy (Bassi 2005). Pancreatic leak includes leak of pancreatic fluid or intestinal contents into the general abdominal cavity. The leak may be self-contained and minimal or may lead to peritonitis or life-threatening general sepsis.

Clinically, POPF can be defined as an output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than three times the upper normal serum value according to the definition by the International Study Group on Pancreatic Fistula (ISGPF) (Bassi 2005). Various other definitions exist (Bassi 2005). ISGPF has graded postoperative fistulas as Grade A, Grade B, and Grade C based on their respective clinical impact, as shown below and Table 1 (Bassi 2005).

- Grade A: This grade of fistula has no clinical impact and requires little change in management or deviation from the normal clinical pathway.
- Grade B: This grade of fistula requires a change in management or adjustment in the clinical pathway. Many people with this grade of fistula can be discharged with drains in situ and observed in the outpatient setting. However, there is no requirement for an invasive procedure.
- Grade C: This grade of fistula requires a major change in clinical management or deviation from the normal clinical pathway. People with this grade of fistula typically require an extended hospital stay with a major delay in hospital discharge; and they often undergo reoperation.

Various interventions to decrease postoperative leaks include pancreaticogastrostomy rather than pancreaticojejunostomy after pancreatic resections (McKay 2006), somatostatin analogues to decrease pancreatic fluid secretion (Gurusamy 2013), and fibrin sealants (in the form of glue (Suzuki 1995) or patches (Montorsi 2012)) to seal the pancreatic stump. Despite one or more of these measures, approximately 14% of patients develop a pancreatic fistula (Gurusamy 2013).

Target condition being diagnosed

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Clinically significant postoperative pancreatic leak (clinically significant pancreatic fistula or other leaks requiring intervention).

Index test(s)

Amylase in drain fluid

Amylase is an enzyme secreted by the pancreas. Various other tissues including salivary glands, small intestines, ovaries, adipose tissue and skeletal muscles secrete amylase. There are two major isoforms of amylase - pancreatic amylase and salivary amylase (Vissers 1999). High amylase in the drain fluid indicates pancreatic leak since the pancreas is the source of pancreatic amylase and without a leak, the pancreatic fluid drains into the small intestine. Amylase can be measured by immunochemical assays, usually with monoclonal antibodies (Maeda 2008; Mifflin 1985). The test is conducted by the laboratory technicians and interpreted by the clinicians managing the patient. Drain fluid amylase content greater than three times the upper normal serum value is considered to be abnormal (Bassi 2005). Normal serum amylase can vary between laboratories but is usually between 100 IU/L and 300 IU/L (Vissers 1999).

Clinical pathway

When there is a high suspicion of pancreatic fistula, usually based on high amylase content of drain fluid, further radiological investigations such as a computed tomography (CT) scan are performed to identify and subsequently deal with identified pancreatic leaks. Grade A POPF is not associated with any peripancreatic fluid collections and the patient is clinically well. The major difference in management of people with Grade A POPF and those without pancreatic fistula is the delayed removal of drains. Grade B POPF may be associated with peripancreatic collections on CT scan. The patient may require repositioning of the drain if there is a peripancreatic collection, and usually requires enteral or parenteral nutritional support. Depending upon the clinical signs and symptoms such as abdominal pain, fever, and elevated white cell count, antibiotics and somatostatin analogues may be required. Grade C POPF is usually associated with peripancreatic fluid collections on CT scan and these often require reoperation. Patients with grade B and C POPF usually require enteral or parenteral nutritional support, intravenous antibiotics, and somatostatin analogues, and are usually managed in an intensive therapy unit setting. If there is clinical deterioration and development of sepsis and organ dysfunction, reoperation with a view to repair the site of leakage, conversion to an alternative means of pancreatoenteric anastomosis (e.g. conversion of pancreaticojejunostomy to pancreaticogastrostomy), or a complete pancreatectomy may be necessary. Thus, the presence and grade of pancreatic leak alters the treatment pathway. This is shown in Figure 1. If there is a high suspicion of pancreatic leak because of the presence of peritonitis or sepsis, patients may undergo further radiological investigations directly, without waiting for the drain fluid amylase measurement.

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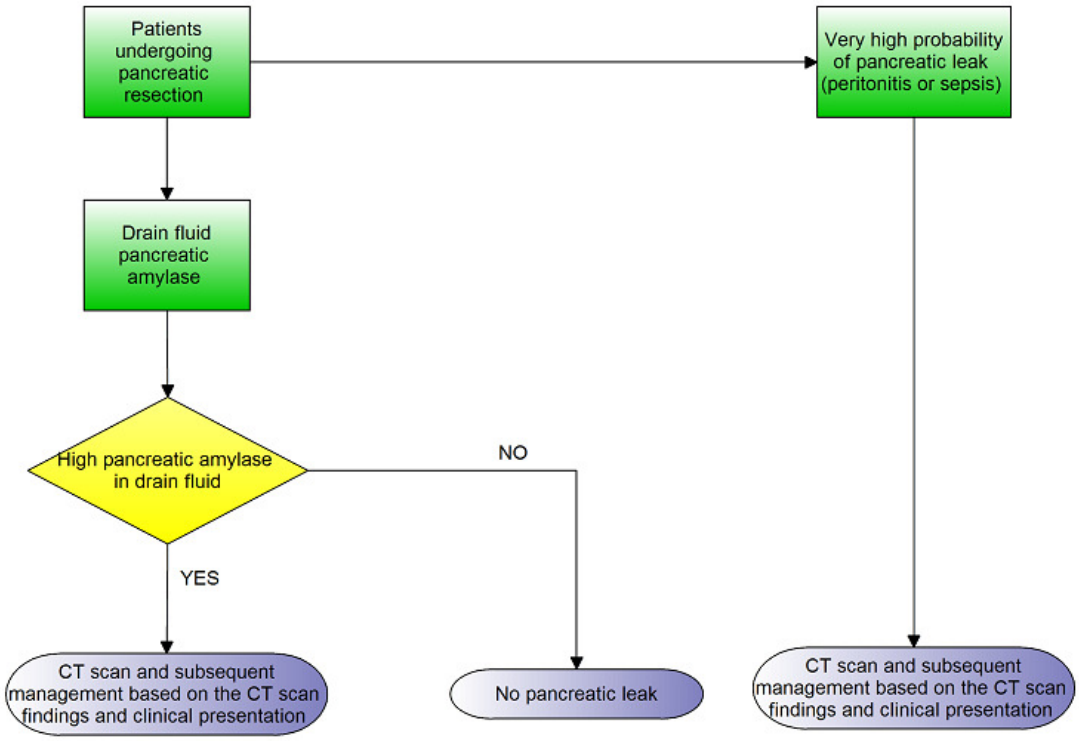
Figure 1. Clinical pathway



Prior test(s)

Amylase in the drain fluid (the index test) is usually the first investigation performed in people with suspected pancreatic leak.

Role of index test(s)

The index test is used to test for pancreatic leak in an unselected population after pancreatic resection. It is usually followed by CT scan or magnetic resonance cholangiopancreatography (MRCP) to confirm the presence or absence of peripancreatic collection and pancreatic leak. Thus, drain fluid amylase can be considered as a triage test prior to CT scan or MRCP in the diagnosis of pancreatic leak.

Rationale

The treatment of patients with clinically significant pancreatic leaks is different from those without clinically significant pancreatic leaks as mentioned in the clinical pathway. It is important to know the true diagnostic accuracy of drain fluid amylase as a method for testing for clinically significant pancreatic leak in an unselected population after pancreatic resection, so that an informed decision can be made as to whether the person with a suspected pancreatic leak needs further investigations. There is currently no systematic review of the diagnostic test accuracy of amylase in the drain fluid for the diagnosis of pancreatic leak. Hence, a Cochrane Review of this subject is necessary.

OBJECTIVES

To determine the diagnostic accuracy of amylase in drain fluid at 48 hours or more for the diagnosis of pancreatic leak in people who had undergone pancreatic resection.

Secondary objectives

If we identified heterogeneity, we planned to explore heterogeneity by using the following sources of heterogeneity as covariate(s) in the regression model.

1. Studies at low risk of bias in all the domains versus those at unclear or high risk of bias (as assessed by the QUADAS-2 tool, recommended by the Cochrane Diagnostic Test Accuracy Group) (Whiting 2006; Whiting 2011).

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2. Full-text publications versus abstracts (this can give an idea about publication bias since there may be an association between the results of the study and the study reaching full publication status) (Eloubeidi 2001).
3. Prospective studies versus retrospective studies.
4. Pancreatoduodenectomies versus distal pancreatic resection.
5. Participants with cancers versus those with benign diseases.
6. Different reference standards (confirmation by surgical resection in all participants versus a combination of surgical resection and clinical follow-up).

METHODS

Criteria for considering studies for this review

Types of studies

We included all studies that evaluated the diagnostic test accuracy of amylase in drain fluid for the diagnosis of clinically significant pancreatic leak in people who had undergone pancreatic resection excluding total pancreatectomy. We included studies that provided information on the index test and reference standards irrespective of language or publication status, or whether the data was collected prospectively or retrospectively. However, we excluded case reports that describe how the diagnosis of pancreatic leak was made on an individual participant or a group of participants and which did not provide sufficient diagnostic test accuracy data, i.e. true positive, false positive, false negative, and true negative. We also excluded case-control studies because these studies are prone to bias (Whiting 2011).

Participants

People who have undergone pancreatic resection with drain fluid at least 48 hours after pancreatic resection irrespective of the volume of the drain fluid.

Index tests

Drain fluid amylase.

Target conditions

Clinically significant pancreatic leak (pancreatic leaks that require radiological or surgical intervention)

Reference standards

We planned to accept one of the following reference standards as per our review protocol. However, according to these reference standards we could not have included any studies as none of the studies reported used one of the two reference standards below.

1. Pancreatic leak confirmed at surgery. This is confirmation of pancreatic leak at surgery usually on the basis of the presence of partial or complete separation of the anastomosis allowing leakage of contents, abdominal collections, or fistula (a tract between the anastomosis and exterior), and is a subjective decision made by the surgeon. Nevertheless, this is the best reference standard available.
2. Pancreatic leak confirmed at surgery for participants with elevated amylase and clinical follow-up for a minimum period of six weeks (to ensure that they do not have complications due to pancreatic leak such as abdominal collections requiring drainage, intra-abdominal sepsis, generalised sepsis resulting from intra-abdominal sepsis, or mortality due to intra-abdominal sepsis) in people with negative amylase. The clinical follow-up should have included clinical examination of the patient, and may or may not have included radiological follow-up done as follow-up of suspected pancreatic leak or routine radiological follow-up to detect the recurrence of cancer. In retrospective studies, we accepted hospital records of physical examination of the patient after a minimum follow-up period of six weeks as an acceptable reference standard. The presence of one or more complications due to pancreatic leak such as abdominal collections requiring drainage, intra-abdominal sepsis, generalised sepsis resulting from intra-abdominal sepsis, or mortality due to intra-abdominal sepsis was considered as a positive reference standard. Because of the lack of any studies using one of the two reference standards mentioned above, we accepted ISGPF grades B and C POPF as reference standards. People with grade C POPF require surgery while those with grade B POPF usually do not undergo surgery but may require additional radiological drainage (Bassi 2005). These people with grade B POPF do not have systemic sepsis but have localised intra-abdominal infection. Although the intra-abdominal infections are usually because of pancreatic leaks in people undergoing pancreatic resection (these leaks are usually at least partially 'contained' (i.e. the effects limited) by the body's defence mechanism), one cannot be sure that the intra-abdominal infection was because of pancreatic leak. So, the reference standards used in this review might misclassify the target condition of pancreatic leak.

Search methods for identification of studies

We included all studies irrespective of the language of publication and publication status. We obtained translations for articles found in non-English language.

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Electronic searches

We searched the following databases up to 20 February 2017.

1. MEDLINE OvidSP (January 1946 to 20 February 2017) (Appendix 2).
2. Embase OvidSP (January 1947 to 20 February 2017) (Appendix 3).
3. Science Citation Index Expanded via Web of Knowledge (January 1980 to 20 February 2017) (Appendix 4).
4. National Institute for Health Research (NIHR HTA) via Centre for Reviews and Dissemination (up to 20 February 2017) (Appendix 5).

Searching other resources

We searched the references of the included studies to identify additional studies. We also searched for articles related to the included studies by performing the 'related search' function in MEDLINE (OvidSP) and Embase (OvidSP) and a 'citing reference' search (by searching the articles which cite the included articles; Sampson 2008) in these two databases.

Data collection and analysis

Selection of studies

Two review authors (TD and KG) independently searched the references produced by the search to identify relevant studies. We obtained the full texts of the references that were considered relevant by at least one of the review authors. Two authors (TD and KG) independently screened the full-text papers against the inclusion criteria. We resolved any differences in study selection by discussion. We selected studies that met the inclusion criteria for data extraction irrespective of the publication status.

Data extraction and management

Two review authors (TD and KG) independently extracted the following data from each included study using a pre-piloted data extraction form; the two authors settled any differences by discussion.

1. First author and contact details.
2. Year of publication.
3. Publication status (abstract or full-text).
4. Study design (prospective or retrospective cohort studies; cross-sectional studies or randomised controlled trials).
5. Inclusion and exclusion criteria for individual studies.
6. Total number of participants.
7. Number of females.
8. Average age of the participants.
9. Proportion of pancreatoduodenectomies.
10. Proportion of participants with cancers.
11. Description of the index test.
12. Threshold used for index test.
13. Reference standard.
14. Number of true positives, false positives, false negatives, and true negatives (diagnostic test accuracy data).

If the same study reported the index test at different thresholds, we planned to calculate true positives, false positives, false negatives, and true negatives for the index test at different thresholds, and extract this information for each threshold. We excluded participants with uninterpretable index test results (no matter the reason given for lack of interpretation, for example low volume of drain fluid) since in clinical practice, uninterpretable index test results will result in additional tests such as CT scan for diagnosis of pancreatic leak. However, we recorded the number of uninterpretable index test results as this provides information on the applicability of the test in clinical practice, and may affect the cost-effectiveness of a test (the cost-effectiveness is outside the scope of this review; cost-effectiveness studies may use data from this review). Further information was sought from study authors if necessary.

Assessment of methodological quality

Two authors (TD and KG) independently assessed study quality using the QUADAS-2 assessment tool (Whiting 2006; Whiting 2011). We resolved any differences in the methodological quality assessment by discussion between us until we reached a consensus. The criteria used for this is shown in Table 2; we decided these a priori and published them in the protocol (except for the reference standard, which was revised to include the new reference standard that we accepted). We considered studies which were classified as 'low risk of bias' and 'low concern' in all the domains as studies of high methodological quality.

Statistical analysis and data synthesis

We plotted study estimates of sensitivity and specificity on forest plots and in receiver operating characteristics (ROC) space to explore variation in the performance of drain fluid amylase due to differences in threshold. When a study evaluated an increasing trend in drain fluid amylase values (by repeated testing) in the same cohort study group, we considered this as the 'threshold' for the purpose of this review.

To estimate the summary sensitivity and specificity of drain fluid amylase at each threshold, we had planned to perform meta-analyses using the bivariate model (Chu 2006; Reitsma 2005). However, because there were few studies and the studies were performed on different postoperative days using different thresholds, meta-analysis was not possible. To summarise the findings from individual studies, we estimated median, and lower and upper quartiles of pre-test probabilities across the included studies. Post-test probabilities were then calculated for each study using these pre-test probabilities and the positive and negative likelihood ratios

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from the study. The post-test probability associated with a positive test is the probability of having pancreatic leak following a positive amylase test result. The post-test probability associated with a negative test is the probability of having pancreatic leak following a negative test result.

Investigations of heterogeneity

We had planned to use bivariate meta-regression (adding a covariate to a bivariate model) to investigate the following potential sources of heterogeneity: risk of bias, publication status, type of recruitment (prospective versus retrospective), type of pancreatic resection (pancreatoduodenectomies versus distal pancreatic resection), different aetiologies, and different reference standards. We were unable to formally explore heterogeneity as we did not perform a meta-analysis.

Sensitivity analyses

We did not plan to conduct any sensitivity analyses except when the data available from the studies were ambiguous (for example, the numbers in the text are different from the numbers in the figures); we did not find any such ambiguity in our review.

Assessment of reporting bias

We did not explore any of the planned investigation to see whether the summary sensitivity and specificity were different between studies that are published as full texts and those that are available only as abstracts (at least two years prior to the search date). This is because only one of the included studies was published as an abstract and the thresholds of index tests were different between the included studies (Araki 2012).

RESULTS

Results of the search

We identified a total number of 2701 references through the electronic searches of MEDLINE (n = 594), Embase (n = 1695), Science Citation Index Expanded (n = 389), and National Institute for Health Research (NIHR HTA) (n = 23). We excluded 897 duplicates and 1724 clearly irrelevant references through reading the titles or abstracts, or both. We retrieved full-text articles of 80 references for further assessment against our review protocol inclusion criteria. Of the 80 references (68 studies), we excluded 73 references (63 studies) for the reasons listed in Characteristics of excluded studies. Five studies (seven references) fulfilled the inclusion criteria and provided the diagnostic accuracy data for the review (Araki 2012; El Nakeeb 2013; Facy 2012; Kong 2008; Kosaka 2014). We have shown the reference flow in Figure 2.

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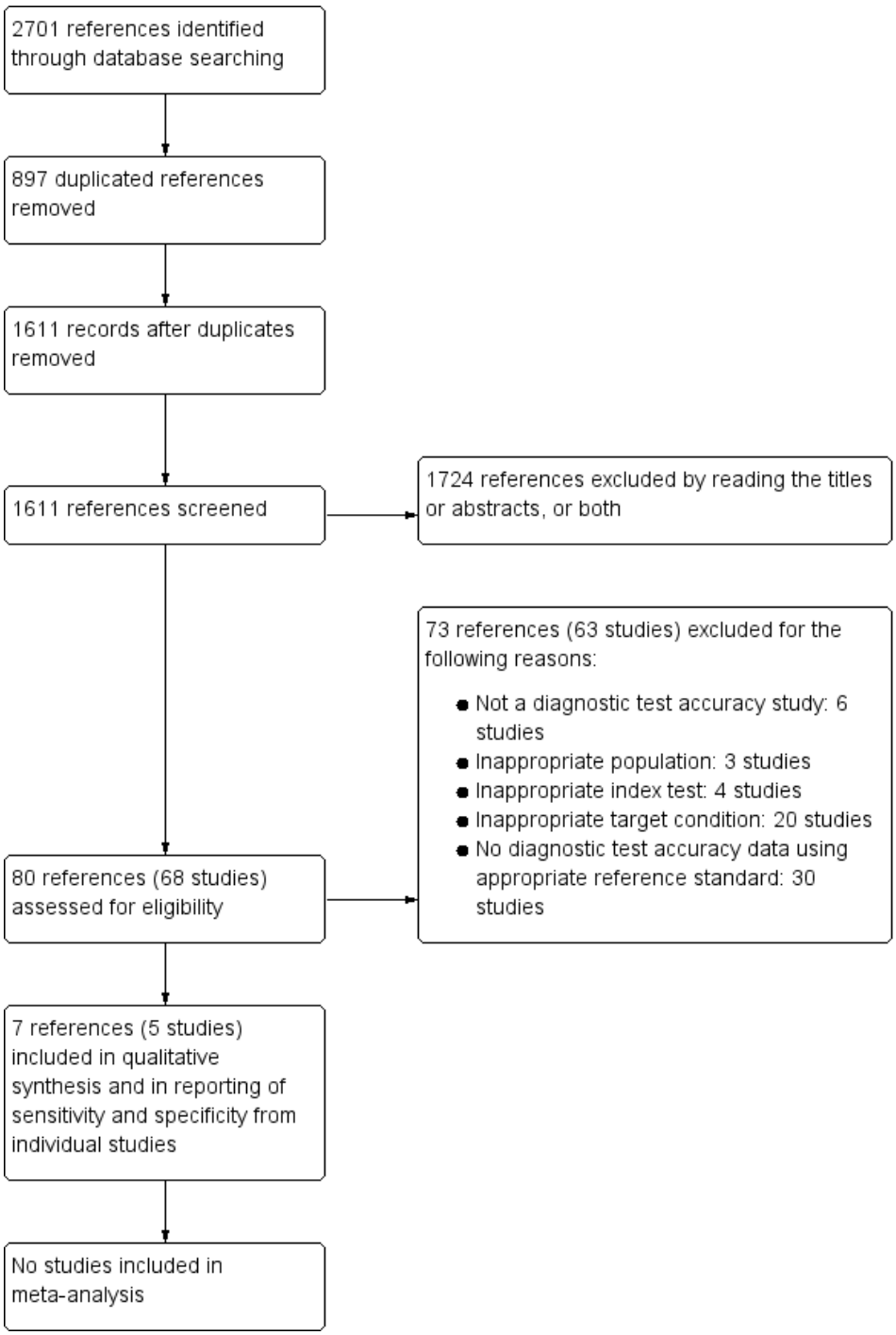
Figure 2. Study flow diagram.



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Included studies

All the included studies assessed pancreatic leak following pancreatic resection excluding total pancreatectomy. A total of 868 participants were analysed in the five included studies. All the studies except Facy 2012 included only participants who underwent pancreaticoduodenectomy. The average age of participants in the studies that reported this information ranged between 53 years and 67 years; and about a third of participants (32%) were females in these four studies (El Nakeeb 2013; Facy 2012; Kong 2008; Kosaka 2014). Except for Araki 2012, which was an abstract, the remaining four studies were full-text publications. Only two studies were prospective (Facy 2012; Kong 2008); the remaining three studies were retrospective studies (Araki 2012; El Nakeeb 2013; Kosaka 2014).

Excluded studies

A total of 64 studies were excluded at the full-text stage for the following reasons.

- Not a diagnostic test accuracy study: six studies (Fong 2016; Palani Velu 2015; Ramesh 2006; Sutcliffe 2015; Teixeira 2016; Yang 2015).
- Inappropriate population: three studies (Kanda 2014; Kobayashi 2015; Mcmillan 2015).
- Inappropriate index test: four studies (Kawai 2011; Kosaka 2013; Kosaka 2014a; Prakash 2011).
- Inappropriate target condition: 20 studies (Cherian 2010; Cirocchi 2015; Israel 2014; Kumar 2013; Lee 2014; Malleo 2014; Menon 2012; Molinari 2007; Nissen 2012; Partelli 2014; Raja 2015; Sanchez Acedo 2013; Saxena 2014; Shi 2009; Shinchi 2006; Shyr 2003; Srivastava 2016; Sutcliffe 2012; Sutcliffe 2014; Zelga 2015).
- No diagnostic test accuracy data using appropriate reference standard: 30 studies (Ansorge 2014; Burdy 1999; Ceroni 2014; Chen 2015; Chhabra 2011; Dugalic 2014; Furukawa 2015; Gebauer 2012; Graham 2013; Hashimoto 2003; Hashimoto 2014; Hiyoshi 2013; Ho 2014; Kim 2014; Kurahara 2011; Mimura 2012; Moskovic 2010; Musiewicz 2010; Noji 2012; Okano 2011; Robinson 2010; Shimizu 2015; Sugimoto 2013; Tang 2015; Tsujie 2012; Uemura 2011; Uemura 2014; Veillette 2010; Ven Fong 2015; Yamaguchi 2003).

Methodological quality of included studies

The methodological quality of the included studies is shown in Characteristics of included studies table and a summary of the methodological quality is shown in Figure 3.

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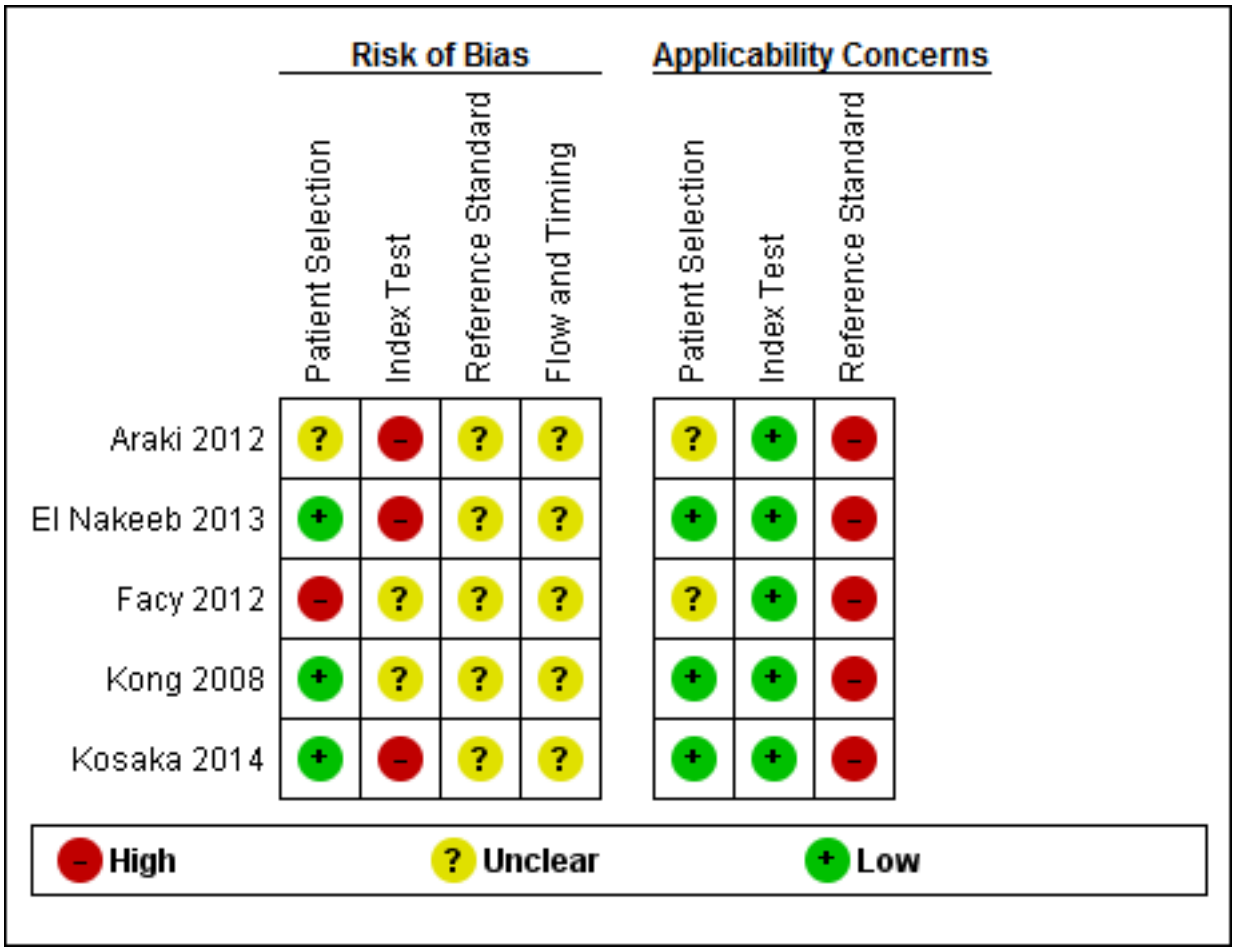
Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study



Participant selection

Three studies had low risk of bias and low applicability concerns regarding the selection of participants, as these studies included consecutive patients (El Nakeeb 2013; Kong 2008; Kosaka 2014). One study had high risk of bias regarding the selection of participants and unclear applicability concerns because the participants without lipase tests were excluded (Facy 2012). The remaining one study was at unclear risk of bias with unclear concerns about applicability because this study did not mention whether a consecutive or random sample of patients was included, and whether there were any exclusions that we considered inappropriate (Araki 2012).

Index test

Regarding the index test, Facy 2012 and Kong 2008 were at unclear risk of bias; and Araki 2012, El Nakeeb 2013 and Kosaka 2014 were at high risk of bias. Three studies, in which it was clear that the thresholds were based on the ROC curve, were classified as high risk of bias (Araki 2012; El Nakeeb 2013; Kosaka 2014). It was not clear whether the index test results were interpreted without knowledge of the reference standard results in any of the studies. So, all studies have been classified as unclear or high risk of bias. All included studies had low concerns about applicability in the 'index test' domain because the criteria for positive index tests were clearly stated in the included studies.

Reference standard

None of the studies were at low risk of bias in this domain. All included studies were at unclear risk of bias because the reference

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standards used were the ISGPF definition. It was also not clear whether the reference standards were interpreted without knowledge of the index test results. All studies were at high concern about applicability. This is because the reference standards used in all the studies were the ISGPF definitions (grade B or C). There is a possibility of misclassification of target condition by this reference standard as detailed in the discussion.

Flow and timing

All the studies were at unclear risk of bias since the studies did not report the period that they followed up participants to determine whether they had grade B or C POPF. In addition, it was not clear whether some participants were excluded prior to analysis in two studies (Araki 2012; Facy 2012).

Findings

The included studies reported the value of drain fluid amylase measured on different days and at different thresholds, so a meta-analysis was not performed. Three studies reported the participant flow clearly; in these studies, none of the participants has uninterpretable results (El Nakeeb 2013; Kong 2008; Kosaka 2014). The remaining two studies did not report any participants with uninterpretable results; however, one cannot rule out uninterpretable results in these studies since the participant flow was not reported (Araki 2012; Facy 2012).

The median pre-test probability of clinically significant pancreatic leak (proportion with pancreatic leak out of total number of included participants) was 15.9%, with minimum of 6% and maximum of 32%. The lower and upper quartiles were 7.6% and 21.5% respectively. The sensitivity and specificity along with the 95% CI for each different threshold on different postoperative days are shown in forest plot (Figure 4), ROC space (Figure 5), and in the Summary of findings.

Figure 4. Forest plot of tests: The numbers following POD (postoperative day) indicate the number of the postoperative day. The numbers or text following DFA (drain fluid amylase) indicate the threshold. The drain fluid amylase measured on 5th postoperative day using a threshold of more than three times serum amylase provides the best sensitivity with high specificity. However, this is based on a single study with small sample size. Another study which used the same threshold between 3 days and 5 days has much less diagnostic test accuracy introducing significant uncertainty in the findings.

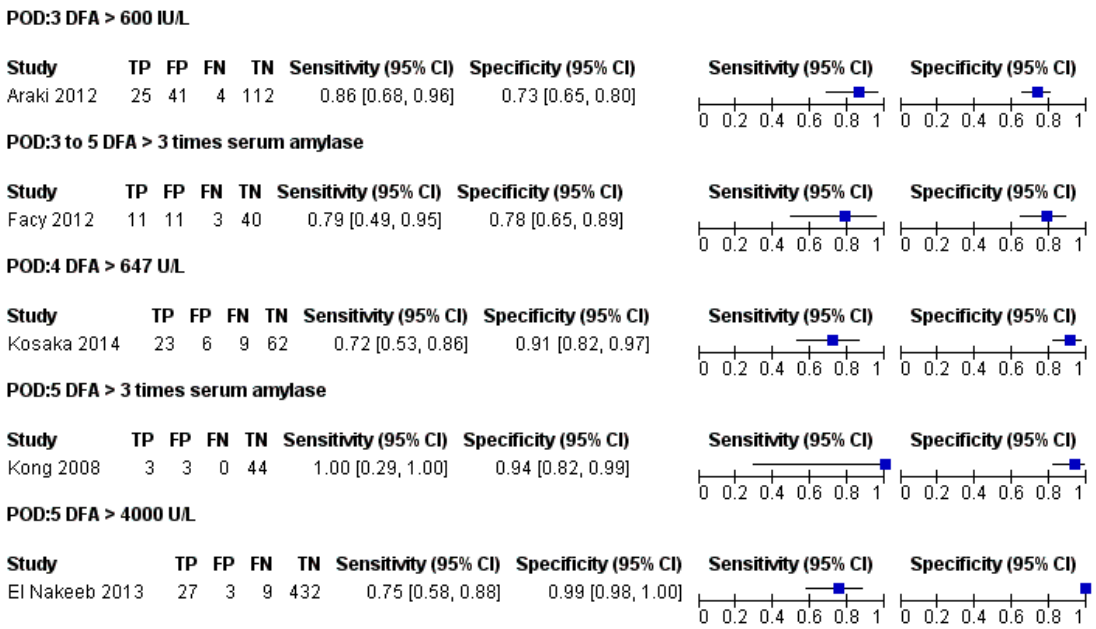

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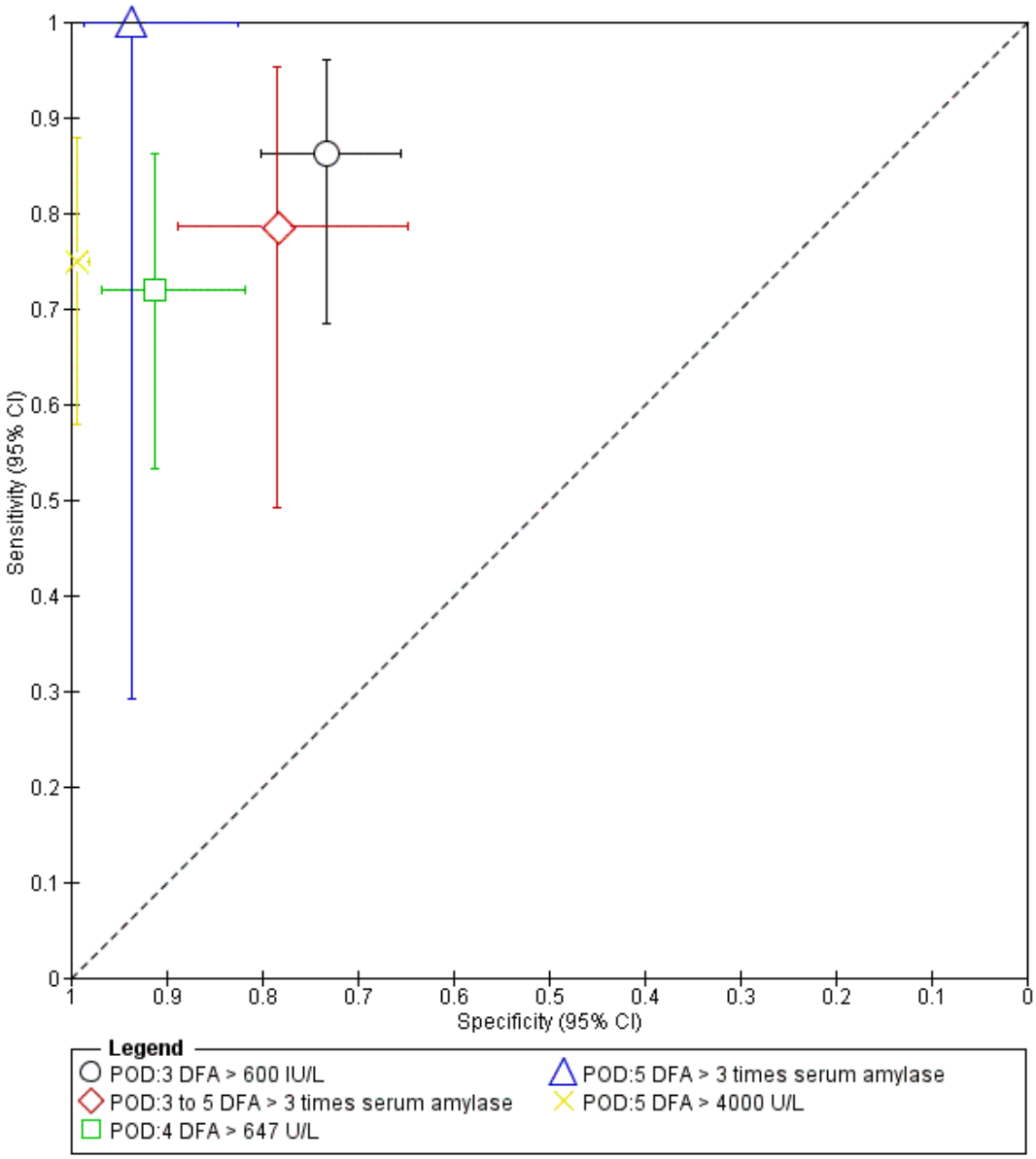
Figure 5. Plot of sensitivity and specificity in the ROC (receiver operating characteristics) space: The numbers following POD (postoperative day) indicate the number of the postoperative day. The numbers or text following DFA (drain fluid amylase) indicate the threshold. The drain fluid amylase measured on 5th postoperative day using a threshold of more than three times serum amylase provides the best sensitivity with high specificity. However, this is based on a single study with small sample size. Another study which used the same threshold between 3 days and 5 days has much less diagnostic test accuracy introducing significant uncertainty in the findings.



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Drain fluid amylase at a cut-off of greater than 600 IU/L on postoperative day 3

There were 182 participants in the only study with drain fluid amylase measured on postoperative day 3 using a cut-off level of more than 600 IU/L (Araki 2012). At this threshold level, the sensitivity of diagnosing clinically relevant pancreatic leak was 0.86 (95% CI 0.68 to 0.96) and the specificity was 0.73 (95% CI 0.65 to 0.80).

Drain fluid amylase at a cut-off of greater than three times serum amylase on postoperative days 3 to 5

There were 65 participants in the only study with drain fluid amylase measured on postoperative days 3 to 5 using a cut-off value of more than three times serum amylase level (Facy 2012). At this cut-off value, the sensitivity of diagnosing clinically significant pancreatic leak was 0.79 (95% CI 0.49 to 0.95) and its specificity was 0.78 (95% CI 0.65 to 0.89).

Drain fluid amylase at a cut-off of greater than 647 IU/L on postoperative day 4

There were 100 participants in the only study with a drain fluid amylase measured on postoperative day 4 using a cut-off value of more than 647 IU/L (Kosaka 2014). At this cut-off value, the sensitivity of diagnosing clinically relevant pancreatic leak was 0.72 (95% CI 0.53 to 0.86) and its specificity was 0.91 (95% CI 0.82 to 0.97).

Drain fluid amylase at a cut-off of greater than three times serum amylase on postoperative day 5

There were 50 participants in the only study with a drain fluid amylase measured on postoperative day 5 using a cut-off value of more than three times serum amylase level (Kong 2008). At this cut-off value, the sensitivity of diagnosing clinically relevant pancreatic leak was 1.00 (95% CI 0.29 to 1.00) and the specificity of this index test was 0.94 (95% CI 0.82 to 0.99).

Drain fluid amylase at a cut-off of greater than 4000 IU/L on postoperative day 5

There were 471 participants in the only study with drain fluid amylase measured on postoperative day 5 using a cut-off value of more than 4000 IU/L (El Nakeeb 2013). At this cut-off level, the sensitivity of clinically significant pancreatic leak diagnostic accuracy was 0.75 (95% CI 0.58 to 0.88) and the specificity was 0.99 (95% CI 0.98 to 1.00).

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Summary of findings

Population	People undergoing pancreatic resection
Setting	Secondary care in various countries
Target condition	Clinically significant pancreatic leak
Reference standard	International Study Group on Pancreatic Fistula (ISGPF) grade B or C
Median prevalence of pancreatic leak	15.9%

Index test[1]	Sensitivity	Specificity	Post-test probability of a positive test[2]	Post-test probability of a negative test[2]	Number of studies	Number of participants	Risk of bias	Applicability concerns	Plain language interpretation
POD:3 DFA > 600 IU/L	0.86 (95% CI 0.68 to 0.96)	0.73 (95% CI 0.65 to 0.80)	37.9% (95% CI 31.1% to 45.1%)	3.4% (95% CI 1.4% to 8.2%)	1	182	Unclear	High	At the median pre-test probability of 16%, out of 100 people with positive test, 38 people (95% CI 31 to 45) have clinically significant pancreatic leak. At the same pre-test probability, out of 100 people with negative test, 3 people (95% CI 1 to 8) have clinically significant pancreatic leak

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POD:3 to 5 DFA > 3 times serum amylase	0.79 (95% CI 0.49 to 0.95)	0.78 (95% CI 0.65 to 0.89)	40.8% (95% CI 27.7% to 55.5%)	4.9% (1.8% to 12.5%)	1	65	High	High	At the median pre-test probability of 16%, out of 100 people with positive test, 41 people (95% CI 28 to 56) have clinically significant pancreatic leak. At the same pre-test probability, out of 100 people with negative test, 5 people (95% CI 2 to 13) have clinically significant pancreatic leak
POD:4 DFA > 647 U/L	0.72 (95% CI 0.53 to 0.86)	0.91 (95% CI 0.82 to 0.97)	60.7% (95% CI 41.1% to 77.4%)	5.5% (95% CI 3.2% to 9.3%)	1	100	High	High	At the median pre-test probability of 16%, out of 100 people with positive test, 61 people (95% CI 41 to 77) have clinically significant pancreatic leak. At the same pre-test probability, out of 100 people with negative test, 6 people (95% CI 3 to 9) have clinically significant pancreatic leak

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POD:5 DFA > 3 times serum amylase	1.00 (95% CI 0.29 to 1.00)	0.94 (95% CI 0.82 to 0.99)	74.8% (95% CI 49.8% to 89.9%)	0% (95% CI not estimable)	1	50	Unclear	High	At the median pre-test probability of 16%, out of 100 people with positive test, 75 people (95% CI 50 to 90) have clinically significant pancreatic leak. It was not possible to estimate the number of people with clinically significant pancreatic leak when the test was negative
POD:5 DFA > 4000 U/L	0.75 (95% CI 0.58 to 0.88)	0.99 (95% CI 0.98 to 1.00)	95.4% (95% CI 86.8% to 98.5%)	4.6% (95% CI 2.6% to 7.8%)	1	471	High	High	At the median pre-test probability of 16%, out of 100 people with positive test, 95 people (95% CI 87 to 99) have clinically significant pancreatic leak. At the same pre-test probability, out of 100 people with negative test, 5 people (95% CI 3 to 8) have clinically significant pancreatic leak

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Interpretation	The drain fluid amylase measured on 5th postoperative day using a threshold of more than three times serum amylase provides the best sensitivity with high specificity. A negative test more or less rules out pancreatic leak. However, this is based on a single study with small sample size. Another study which used the same threshold between 3 days and 5 days has much less diagnostic test accuracy introducing significant uncertainty in the findings

[1]The numbers following POD (postoperative day) indicate the number of the postoperative day. The numbers or text following DFA (drain fluid amylase) indicate the threshold.

[2]All post-test probabilities were calculated at the median prevalence (pre-test probability) of pancreatic leak in the studies. At the lower quartile of the prevalence of 7.6%, the post-test probabilities of pancreatic leak of positive POD:3 DFA > 600 IU/L, POD:3 to 5 DFA > 3 times serum amylase, POD:4 DFA > 647 U/L, POD:5 DFA > 3 times serum amylase, and POD:5 DFA > 4000 U/L were 21.0% (95% CI 16.5% to 26.4%), 23.2% (95% CI 14.3% to 35.2%), 40.3% (95% CI 23.4% to 59.9%), 56.5% (95% CI 30.3% to 79.5%), and 90.0% (95% CI 74.2% to 96.6%) respectively. At the same pre-test probability, the post-test probabilities of pancreatic leak of negative POD:3 DFA > 600 IU/L, POD:3 to 5 DFA > 3 times serum amylase, POD:4 DFA > 647 U/L, POD:5 DFA > 3 times serum amylase, and POD:5 DFA > 4000 U/L were 1.5% (95% CI 0.6% to 3.7%), 2.2% (95% CI 0.8% to 5.9%), 2.5% (95% CI 1.4% to 4.3%), 0% (95% CI not estimable), and 2.0% (95% CI 1.2% to 3.5%) respectively. At the upper quartile of the prevalence of 21.5%, the post-test probabilities of pancreatic leak of positive POD:3 DFA > 600 IU/L, POD:3 to 5 DFA > 3 times serum amylase, POD:4 DFA > 647 U/L, POD:5 DFA > 3 times serum amylase, and POD:5 DFA > 4000 U/L were 46.9% (95% CI 39.6% to 54.4%), 50.0% (95% CI 35.7% to 64.3%), 69.1% (95% CI 50.3% to 83.2%), 81.1% (95% CI 59.0% to 92.8%), and 96.8% (95% CI 90.5% to 98.9%) respectively. At the same pre-test probability, the post-test probabilities of pancreatic leak of negative POD:3 DFA > 600 IU/L, POD:3 to 5 DFA > 3 times serum amylase, POD:4 DFA > 647 U/L, POD:5 DFA > 3 times serum amylase, and POD:5 DFA > 4000 U/L were 4.9% (95% CI 2.0% to 11.4%), 7.0% (95% CI 2.7% to 17.1%), 7.8% (95% CI 4.6% to 12.9%), 0% (95% CI not estimable), and 6.5% (95% CI 3.8% to 10.8%) respectively.

CI = confidence intervals

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DISCUSSION

Summary of main results

A total of five studies including 868 participants met the inclusion criteria for this review (Araki 2012; El Nakeeb 2013; Facy 2012; Kong 2008; Kosaka 2014). The median prevalence of clinically significant POPF (grades B and C) was 15.9%.

The five studies included in this review reported the value of drain fluid amylase at different thresholds and different postoperative days. We were unable to perform any meta-analysis or exploration of heterogeneity because of paucity of data. The sensitivities and specificities were variable: the sensitivities ranged between 0.72 and 1.00 while the specificities ranged between 0.73 and 0.99 for different thresholds on different postoperative days. At the median prevalence (pre-test probability) of 15.9%, the mean post-test probabilities for pancreatic leak ranged between 35.9% and 95.4% for a positive drain fluid amylase test and ranged between 0% and 5.5% for a negative drain fluid amylase test.

Strengths and weaknesses of the review

Strengths

One of the main strengths of this review was that we searched the literature thoroughly, without any publication or language restrictions. We did not use any diagnostic test accuracy filters in our literature search because filters of this kind could lead to exclusion of some relevant studies (Doust 2005). Inclusion of abstracts and non-English articles may decrease the impact of publication bias to a certain extent although the determinants and extent of publication bias and selective reporting are not well known for diagnostic accuracy studies. We also planned to exclude case-control studies because these studies are prone to bias (Whiting 2011). Two review authors (TD and KG) independently searched the references produced by the search to identify relevant studies, screened the full-text papers against the inclusion criteria and extracted data. Data extractions by two authors potentially reduce the errors related to a single author data extraction (Buscemi 2006). Another strength of this review is that we used the recommended methodological quality methods to assess the risk of bias and applicability concerns in the included studies and took these into consideration while interpreting the evidence.

Weaknesses

There were several shortcomings in our review. First and foremost is the change of reference standard. In the protocol, we stated that we would use either surgical confirmation of presence or absence of pancreatic leak in all participants or at least surgical confirmation of presence or absence of pancreatic leak in participants with positive drain fluid amylase and clinical follow-up in those with negative drain fluid amylase. We did not identify any studies that used either of these reference standards. So, we have accepted ISGPF grades B and C POPF as reference standards. While grade C POPF equates to surgical confirmation of presence of pancreatic leak, grade B POPF includes only POPF that do not require reoperation. However, grade B POPF includes POPF with intra-abdominal infection and drainage usually persists for more than three weeks. Although persistent drainage of POPF can be managed by discharging the patient home with a drain with intermittent follow-up visits to the hospital, it is likely to have a significant impact on return to work. So, there is no controversy on whether grade B POPF is clinically significant; the controversy is whether these are caused by pancreatic leaks. Pancreatic leak is the major cause of intra-abdominal infection in people who undergo pancreatic resections. However, one cannot be absolutely sure that there was a clinically significant pancreatic leak in people with grade B POPF. While major aspects of treatment in people with grade B POPF is the same as that of confirmed pancreatic leaks not requiring reoperation but causing intra-abdominal collections (minimally invasive drainage, antibiotics, and supportive treatment), knowing whether the fistula is due to pancreatic leak may help in deciding whether patients require interventions such as somatostatin analogues to decrease the pancreatic secretion. So, it is useful to distinguish the cause of grade B POPF. By using grade B or C POPF, there is a possibility of misclassification of the target condition (pancreatic leak) by the reference standards used (grade B or C POPF), i.e. some people without pancreatic leak may have been classified as having pancreatic leak by the reference standards used. The use of grade C POPF alone as reference standards would have resulted in an error in the opposite direction, i.e. some people with clinically significant pancreatic leak may have been misclassified as not having pancreatic leak. However, we were not able to test the diagnostic accuracy of the index test using grade C POPF as the reference standards since none of the studies reported diagnostic test accuracy data using grade C POPF alone as reference standards. While we agree that surgical confirmation cannot be performed in everyone with suspected pancreatic leak, one can expect that surgical confirmation can be performed in people with high suspicion of pancreatic leak based on the index test (drain pancreatic amylase) and clinical follow-up for at least six weeks in those with low suspicion of pancreatic leak based on the index test (drain pancreatic amylase). Because of lack of these appropriate reference standards (and use of grade B or C as reference standards), there is a possibility of underestimation or overestimation of diagnostic accuracy of the index test.

Second, there were other methodological deficiencies besides the bias and concern related to reference standards. For example, three studies did not pre-specify the drain fluid amylase threshold (Araki 2012; El Nakeeb 2013; Kosaka 2014); this would have resulted in

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overestimation of the diagnostic test accuracy. In addition, none of the studies reported whether the index tests and references standards were interpreted independent of each other. If they were not interpreted independent of each other, the accuracy of the tests would have been overestimated. None of the studies reported whether the participants were followed up for sufficient period of time to rule out grade B or C POPF. This could cause underestimation or overestimation of the diagnostic accuracy.

Third, the sample sizes in most of the studies were small, resulting in wide confidence intervals. It was not possible to perform a meta-analysis since the studies reported drain fluid amylase on different postoperative days using different thresholds. Additionally, the measurement of drain fluid amylase on different postoperative days using different thresholds for diagnosis of pancreatic leak made it impossible for us to explore whether the results could be replicated in another group of people.

Comparison with other reviews

We identified two systematic reviews which evaluated the ability of drain fluid amylase on postoperative day 1 to predict the development of pancreatic fistula (Giglio 2016; Lu 2016); and one systematic review which included drain fluid amylase measured at any time in the diagnosis of any POPF (Yang 2015). All these studies concluded that drain fluid amylase on the first postoperative day is a good predictor of development of pancreatic fistula. However, the objectives of this review were different; we wanted to evaluate the role of drain fluid amylase in the diagnosis of clinically significant pancreatic leak. We were unable to find any systematic reviews addressing this question.

Applicability of findings to the review question

Generalisability of the results

Most of the participants included in this review were people who underwent pancreaticoduodenectomy surgery for benign and malignant conditions involving the pancreas. So, the findings of this review are applicable only for those undergoing pancreaticoduodenectomy.

Use of the test in clinical setting

The main role of the index test is as a triage test to identify people who require further scanning such as CT or MRI. Such a test needs to be a highly sensitive test, so that it is possible to rule out pancreatic leak, which will result in avoidance of further testing and allow the drain to be removed. The median prevalence of grade B or C POPF in the studies included in the review was 15.9%. The mean post-test probabilities of pancreatic leak when the drain fluid amylase was negative ranged between 0% and 5.5%. However, the confidence intervals in these studies were higher and these ranged between 0% and 12.5%. Adding to this uncertainty were random errors resulting from small sample sizes: these generated a lot of systematic errors, resulting in further uncertainty. Because of these uncertainties, the role of drain fluid amylase in the diagnosis of pancreatic leak in people who undergo pancreatic resection is not clear.

AUTHORS' CONCLUSIONS

Implications for practice

Because of the paucity of data and methodological deficiencies in the studies, it is not possible to arrive at any definitive conclusions i.e. there is no clear evidence whether clinicians should continue to use drain fluid amylase as a method for testing for clinically significant pancreatic leak in an unselected population after pancreatic resection; the optimal cut-off of drain fluid amylase for making the diagnosis of pancreatic leak is also not clear.

Implications for research

Further well-designed diagnostic test accuracy studies with a pre-specified index test threshold of drain fluid amylase (at three times more on postoperative day 5 or another suitable pre-specified threshold), appropriate follow-up (for at least six to eight weeks to ensure that there are no pancreatic leaks), and clearly defined reference standard (of surgical, clinical, and radiological confirmation of pancreatic leak) are important to determine the diagnostic accuracy of drain fluid amylase reliably.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Araki 2012

Study characteristics			
Patient sampling	Type of study: retrospective study. Consecutive or random sample: unclear.		
Patient characteristics and setting	Sample size: 182. Females: not stated. Age: not stated. Presentation: people who underwent pancreaticoduodenectomy in a single center in Japan between April 2003 and May 2012 were included. Setting: secondary care, Japan.		
Index tests	Index test: postoperative day 3 drain fluid amylase. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: > 600 IU/L.		
Target condition and reference standard(s)	Target condition: clinically significant pancreatic leak. Reference standard: ISGPF grade B or C. Further details: Technical specifications: not applicable. Performed by: clinicians. Criteria for positive diagnosis: ISGPF definitions.		
Flow and timing	Number of indeterminates for whom the results of reference standard was available: 0 (0%). Number of patients who were excluded from the analysis: not stated		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

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Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

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El Nakeeb 2013

Study characteristics			
Patient sampling	Type of study: retrospective study. Consecutive or random sample: consecutive sample.		
Patient characteristics and setting	Sample size: 471. Females: 193 (41.0%). Age: 53 years. Presentation: people who underwent pancreaticoduodenectomy from January 2001 to June 2012 were included. Setting: secondary care, Egypt.		
Index tests	Index test: postoperative day 5 drain fluid amylase. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: > 4000 U/L.		
Target condition and reference standard(s)	Target condition: clinically significant pancreatic leak. Reference standard: ISGPF grade B or C. Further details: Technical specifications: not applicable. Performed by: clinicians. Criteria for positive diagnosis: ISGPF definitions.		
Flow and timing	Number of indeterminates for whom the results of reference standard was available: 0 (0%). Number of patients who were excluded from the analysis: 0 (0%)		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

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DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

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Facy 2012

Study characteristics	
Patient sampling	Type of study: prospective study. Consecutive or random sample: neither.
Patient characteristics and setting	Sample size: 65. Females: 31 (47.69%). Age: 62 years. Presentation: people who underwent pancreatic resection between 2008 and 2010 and had the concentration of amylase and lipase measured in abdominal drains were included. People who underwent total pancreatectomy were not included. People in whom the lipase concentration was not measured were excluded from analysis. Setting: tertiary care, France.
Index tests	Index test: post operative day 3 to 5 drain fluid amylase. Further details: Technical specifications: Dimension Vista Colorimetric Analyser. Performed by: Dr David Masson. Criteria for positive diagnosis: 3 times normal limit.
Target condition and reference standard(s)	Target condition: clinically significant pancreatic leak. Reference standard: ISGPF grade B or C. Further details: Technical specifications: not applicable. Performed by: clinicians. Criteria for positive diagnosis: ISGPF definitions.
Flow and timing	Number of indeterminates for whom the results of reference standard was available: 0 (0%). Number of participants who were excluded from the analysis: not stated
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

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Facy 2012 (*Continued*)

		High	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

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Kong 2008

Study characteristics			
Patient sampling	Type of study: prospective study.. Consecutive or random sample: consecutive patients.		
Patient characteristics and setting	Sample size: 50. Females: 15 (30%). Age: 67 years. Presentation: people who underwent modified extended pancreaticoduodenectomy for a periampullary tumour between April 2004 and August 2006 at two hospitals in Australia were included. Setting: secondary and tertiary care, Australia.		
Index tests	Index test: postoperative day 5 drain fluid amylase. Further details: Technical specifications: Roche Modular System and Roche Reagent Assays. Performed by: not stated. Criteria for positive diagnosis: > 125 u/ml (3 times serum amylase and 50 mls/24 h on D5)		
Target condition and reference standard(s)	Target condition: clinically significant pancreatic leak. Reference standard: ISGPF grade B or C. Further details: Technical specifications: not applicable. Performed by: clinicians. Criteria for positive diagnosis: ISGPF definitions.		
Flow and timing	Number of indeterminates for whom the results of reference standard was available: 0 (0%). Number of patients who were excluded from the analysis: 0 (0%)		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

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DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

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Kosaka 2014

Study characteristics			
Patient sampling	Type of study: retrospective study. Consecutive or random sample: consecutive patients.		
Patient characteristics and setting	Sample size: 100. Females: 36 (36%). Age: 67 years. Presentation: people who underwent pancreaticoduodenectomy between January 2009 and October 2012 were included. Setting: secondary care, Japan.		
Index tests	Index test: postoperative day 4 drain fluid amylase Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: 647 U/L.		
Target condition and reference standard(s)	Target condition: clinically significant pancreatic leak. Reference standard: ISGPF grade B or C. Further details: Technical specifications: not applicable. Performed by: clinicians. Criteria for positive diagnosis: ISGPF definitions		
Flow and timing	Number of indeterminates for whom the results of reference standard was available: 0 (0%). Number of patients who were excluded from the analysis: 0 (0%)		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

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DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

ISGPF = International Study Group on Pancreatic Fistula

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ansorge 2014	No diagnostic test accuracy data using appropriate reference standard
Burdy 1999	No diagnostic test accuracy data using appropriate reference standard
Ceroni 2014	No diagnostic test accuracy data using appropriate reference standard
Chen 2015	No diagnostic test accuracy data using appropriate reference standard
Cherian 2010	Inappropriate target condition (target condition not defined adequately)
Chhabra 2011	No diagnostic test accuracy data using appropriate reference standard
Cirocchi 2015	Inappropriate target condition
Dugalic 2014	No diagnostic test accuracy data using appropriate reference standard
Fong 2016	Not a diagnostic test accuracy study.
Furukawa 2015	No diagnostic test accuracy data using appropriate reference standard
Gebauer 2012	No diagnostic test accuracy data using appropriate reference standard
Graham 2013	No diagnostic test accuracy data using appropriate reference standard
Hashimoto 2003	No diagnostic test accuracy data using appropriate reference standard
Hashimoto 2014	No diagnostic test accuracy data using appropriate reference standard
Hiyoshi 2013	No diagnostic test accuracy data using appropriate reference standard
Ho 2014	No diagnostic test accuracy data using appropriate reference standard
Israel 2014	Inappropriate target condition
Kanda 2014	Inappropriate population (patients without pancreatic fistula were excluded from the study)
Kawai 2011	Inappropriate index test (drain fluid amylase was measured on post-operative day 1 only)
Kim 2014	No diagnostic test accuracy data using appropriate reference standard
Kobayashi 2015	Inappropriate population (not in patients undergoing pancreatic resection)
Kosaka 2013	Inappropriate index test (not on drain fluid amylase)

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(*Continued*)

Kosaka 2014a	Inappropriate index test
Kumar 2013	Inappropriate target condition
Kurahara 2011	No diagnostic test accuracy data using appropriate reference standard
Lee 2014	Inappropriate target condition
Malleo 2014	Inappropriate target condition
Mcmillan 2015	Inappropriate population (people with amylase > 5000 IU were initially excluded; in addition, people with low unvalidated fistula risk score were excluded from the analysis)
Menon 2012	Inappropriate target condition
Mimura 2012	No diagnostic test accuracy data using appropriate reference standard
Molinari 2007	Inappropriate target condition
Moskovic 2010	No diagnostic test accuracy data using appropriate reference standard
Musiewicz 2010	No diagnostic test accuracy data using appropriate reference standard
Nissen 2012	Inappropriate target condition
Noji 2012	No diagnostic test accuracy data using appropriate reference standard
Okano 2011	No diagnostic test accuracy data using appropriate reference standard
Palani Velu 2015	Not a diagnostic test accuracy study
Partelli 2014	Inappropriate target condition
Prakash 2011	Inappropriate index test
Raja 2015	Inappropriate target condition
Ramesh 2006	Not a diagnostic test accuracy study
Robinson 2010	No diagnostic test accuracy data using appropriate reference standard
Sanchez Acedo 2013	Inappropriate target condition
Saxena 2014	Inappropriate target condition
Shi 2009	Inappropriate target condition

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(*Continued*)

Shimizu 2015	No diagnostic test accuracy data using appropriate reference standard
Shinchi 2006	Inappropriate target condition
Shyr 2003	Inappropriate target condition
Srivastava 2016	Inappropriate target condition.
Sugimoto 2013	No diagnostic test accuracy data using appropriate reference standard
Sutcliffe 2012	Inappropriate target condition
Sutcliffe 2014	Inappropriate target condition
Sutcliffe 2015	Not a diagnostic test accuracy study
Tang 2015	No diagnostic test accuracy data using appropriate reference standard
Teixeira 2016	Not a diagnostic test accuracy study
Tsujie 2012	No diagnostic test accuracy data using appropriate reference standard
Uemura 2011	No diagnostic test accuracy data using appropriate reference standard
Uemura 2014	No diagnostic test accuracy data using appropriate reference standard
Veillette 2010	No diagnostic test accuracy data using appropriate reference standard
Ven Fong 2015	No diagnostic test accuracy data using appropriate reference standard
Yamaguchi 2003	No diagnostic test accuracy data using appropriate reference standard
Yang 2015	Not a diagnostic test accuracy study (systematic review)
Zelga 2015	Inappropriate target condition

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DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

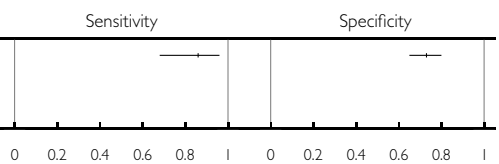
Test	No. of studies	No. of participants
1 POD:3 DFA > 600 IU/L	1	182
2 POD:3 to 5 DFA > 3 times serum amylase	1	65
3 POD:4 DFA > 647 U/L	1	100
4 POD:5 DFA > 3 times serum amylase	1	50
5 POD:5 DFA > 4000 U/L	1	471

Test 1. POD:3 DFA > 600 IU/L.

Review: Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection

Test: 1 POD:3 DFA > 600 IU/L

Study	TP	FP	FN	TN	Sensitivity	Specificity
Araki 2012	25	41	4	112	0.86 [0.68, 0.96]	0.73 [0.65, 0.80]



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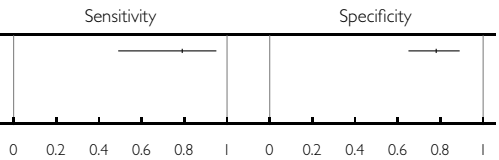
Test 2. POD:3 to 5 DFA > 3 times serum amylase.

Review: Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection

Test: 2 POD:3 to 5 DFA > 3 times serum amylase

Study	TP	FP	FN	TN	Sensitivity	Specificity
Facy 2012	11	11	3	40	0.79 [0.49, 0.95]	0.78 [0.65, 0.89]

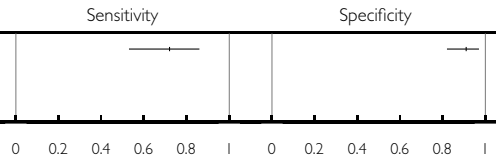


Test 3. POD:4 DFA > 647 U/L.

Review: Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection

Test: 3 POD:4 DFA > 647 U/L

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kosaka 2014	23	6	9	62	0.72 [0.53, 0.86]	0.91 [0.82, 0.97]

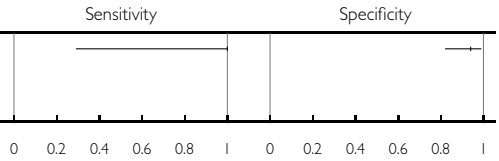


Test 4. POD:5 DFA > 3 times serum amylase.

Review: Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection

Test: 4 POD:5 DFA > 3 times serum amylase

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kong 2008	3	3	0	44	1.00 [0.29, 1.00]	0.94 [0.82, 0.99]



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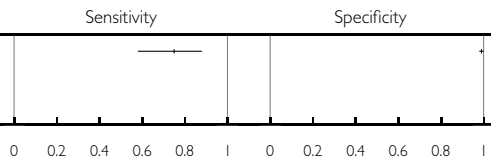
Test 5. POD:5 DFA > 4000 U/L.

Review: Amylase in drain fluid for the diagnosis of pancreatic leak in post-pancreatic resection

Test: 5 POD:5 DFA > 4000 U/L

Study	TP	FP	FN	TN	Sensitivity	Specificity
El Nakeeb 2013	27	3	9	432	0.75 [0.58, 0.88]	0.99 [0.98, 1.00]



ADDITIONAL TABLES

Table 1. International study group postoperative pancreatic fistula

Grade	A	B	C
Clinical conditions	Well	Often well	Usually ill
Ultrasound/CT (computed tomogram) (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to postoperative pancreatic fistula	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Modified from Bassi 2005.

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Table 2. QUADAS-2 classification

Domain 1: Patient selection	Patient sampling	Patients who have undergone pancreatic resection with drain fluid at least 48 hours after pancreatic resection irrespective of the volume of the drain fluid
	Was a consecutive or random sample of patients enrolled?	Yes: if a consecutive sample or a random sample of patients with pancreatic resection with drain fluid at least 48 hours after pancreatic resection was included in the study. No: if a consecutive sample or a random sample of patients with pancreatic resection with drain fluid at least 48 hours after pancreatic resection was not included in the study. Unclear: if this information was not available.
	Was a case-control design avoided?	Yes: if a cohort of patients with pancreatic resection with drain fluid at least 48 hours after pancreatic resection was studied. No: if patients with pancreatic leak were compared with patients without pancreatic leak (controls). We planned to exclude such studies. Unclear: as anticipated, we were able to determine whether the design was case-control. There were no case-control studies. Hence, as anticipated, all studies included in the review were classified as 'yes' for this item
	Did the study avoid inappropriate exclusions?	Yes: if all patients with pancreatic resection with drain fluid at least 48 hours after pancreatic resection were included. No: if the study excluded patients based on high or low probability of pancreatic leak (for example, those with high volume in the drain). Unclear: if this information was not available.
	Could the selection of patients have introduced bias?	Low risk of bias: if 'yes' classification for all of the above 3 questions High risk of bias: if 'no' classification for any of the above 3 questions Unclear risk of bias: if 'unclear' classification for any of the above 3 questions but without a 'no' classification for any of the above 3 questions

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Table 2. QUADAS-2 classification (*Continued*)

	Patient characteristics and setting	Yes: if all patients with pancreatic resection with drain fluid at least 48 hours after pancreatic resection were included. No: if some patients with pancreatic resection with drain fluid at least 48 hours after pancreatic resection were excluded on the basis of the results of drain fluid volume. Unclear: if it was not clear whether the patients had been included on the basis of the results of drain fluid volume
	Are there concerns that the included patients and setting do not match the review question?	Low concern: if the patient characteristics and setting were classified as 'yes' Unclear concern: if the patient characteristics and setting were classified as 'unclear' High concern: if the patient characteristics and setting were classified as 'no'
Domain 2: Index test	Index test(s)	Amylase in drain fluid.
	Were the index test results interpreted without knowledge of the results of the reference standard?	The index test would always be conducted though not interpreted before the reference standard Yes: if the index test was conducted and interpreted without the knowledge of the results of the reference standard. No: if the index test was interpreted with the knowledge of the results of the reference standard. Unclear: if it was not clear whether the index test was interpreted without the knowledge of the results of the reference standard
	If a threshold was used, was it pre-specified?	Yes: if a pre-specified threshold was used. No: if a pre-specified threshold was not used. Unclear: if it was not clear whether the threshold used was pre-specified
	Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias: if 'yes' classification for both of the above questions High risk of bias: if 'no' classification for any of the above 2 questions Unclear risk of bias: if 'unclear' classification for any of the above 2 questions but without a 'no' classification for any of the above 2 questions

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Table 2. QUADAS-2 classification (*Continued*)

	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern: if the criteria for positive index test was clearly stated High concern: if the criteria for positive index test was not stated
Domain 3: Target condition and reference standard	Target condition and reference standard(s)	Target condition: clinically significant pancreatic leak (requiring clinical intervention) Planned reference standards (see below). 1. Pancreatic leak confirmed at surgery. 2. Pancreatic leak confirmed at surgery for patients with elevated amylase and clinical follow-up for a minimum period of 6 weeks (to ensure that they do not have complications due to pancreatic leak such as abdominal collections requiring drainage, intra-abdominal sepsis, or generalised sepsis) in people with negative amylase.
	Is the reference standard(s) likely to correctly classify the target condition?	Yes: if pancreatic leak was confirmed at re-operation. No: if the reference standard was a combination of pancreatic leak and clinical follow-up for a minimum period of 6 weeks (to ensure that they do not have complications due to pancreatic leak such as abdominal collections requiring drainage, intra-abdominal sepsis, or generalised sepsis) in people with negative amylase Unclear: although we planned to exclude studies if the reference standard was not described adequately or was not one of the above planned reference standards, this would have meant that there would have been no studies included in the review. So, we accepted the ISGPF grades B and C as an appropriate references standard and classified the answer to this signalling question as unclear
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes: if the reference standard was interpreted without the knowledge of the results of the index test. No: if the reference standard was interpreted with the knowledge of the results of the index test. Unclear: it is not clear if the reference standard was interpreted without the knowledge of the results of the index test

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Table 2. QUADAS-2 classification (*Continued*)

	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias: if 'yes' classification for both of the above 2 questions High risk of bias: if 'no' classification for any of the above 2 questions Unclear risk of bias: if 'unclear' classification for any of the above 2 questions but without a 'no' classification for any of the above 2 questions
	Are there concerns that the target condition as defined by the reference standard does not match the question?	Although we anticipated that all of the included studies would be classified as 'low concern' because of the reference standards we planned to use, we have classified all the studies as 'high concern' because of the reference standards that we accepted
Domain 4: Flow and timing	Flow and timing	Patients may have progression or resolution of pancreatic leak if there is a long delay between index test and reference standard. An arbitrary 2 weeks was chosen as an acceptable delay between index test and reference standard
	Was there an appropriate interval between index test and reference standard?	Yes: if the time interval between index test and reference standard was less than 2 weeks. No: if the time interval between index test and reference standard was more than 2 weeks. Unclear: if the time interval between index test and reference standard was unclear
	Did all patients receive a reference standard?	Yes: if all patients received a reference standard. No: if some of the patients did not receive a reference standard. Such studies were excluded. Unclear: if it was not clear whether all patients received a reference standard. Such studies were excluded. As anticipated, all studies included in the review were classified as 'yes' for this item
	Did all patients receive the same reference standard?	Yes: if all the patients received the same reference standard. No: if different patients received different reference standards Unclear: if this information was not clear. Because of the inclusion criteria, all the

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Table 2. QUADAS-2 classification (*Continued*)

		studies in this review were classified as 'yes' for this signalling question
	Were all patients included in the analysis?	Yes: if all the patients are included in the analysis irrespective of whether the results were interpretable. No: if some patients are excluded from the analysis because of uninterpretable results. Unclear: if this information is not clear.
	Could the patient flow have introduced bias?	Low risk of bias: if 'yes' classification for all the above 4 questions High risk of bias: if 'no' classification for any of the above 4 questions Unclear risk of bias: if 'unclear' classification for any of the above 4 questions but without a 'no' classification for any of the above 4 questions

ISGPF = International Study Group on Pancreatic Fistula

APPENDICES

Appendix 1. Glossary

Analogues: a substance that is similar to another substance.
Anastomoses: to be linked by anastomosis.
Anastomosis: connection of two structures (in this context, connection between pancreas and small bowel).
Antibodies: a blood protein produced in response to and counteracting a specific antigen.
Covariate: variable that is possibly predictive of the outcome under study.
Enteral: intestinal.
Epithelial surface: a surface lined by epithelium.
Epithelium: membranous tissue composed of one or more layers of cells. It forms the covering of most internal and external surfaces of the body and its organs.
Fistula: an abnormal duct or passage connecting a cavity or hollow organ to the body surface or to another hollow organ.
Heterogeneity: differences in results between studies.
Immunochemical: using antibodies (blood proteins produced in response to and counteracting a specific antigen such as bacteria, virus, or part of tissue) to find the presence of a substance or to measure the amount of a substance.
In situ: in its original position in the body.
Intra-abdominal: situated within the abdomen.
Isoforms: two or more functionally similar proteins that have a similar but not identical composition.
Magnetic resonance cholangio pancreatography: medical imaging technique that uses magnetic resonance imaging (use of magnetic field to differentiate between different structures) to visualize the biliary and pancreatic ducts in a non-invasive manner.
Monoclonal: forming a clone from a single individual or cell.
Morbidity: illness (in this context, it means complications).

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Mortality: death.
Pancreatectomy: removal of part of pancreas.
Pancreatic ductal system: tubular system that transports the pancreatic juice secreted by the pancreatic cells to the small intestine.
Pancreatic leak: leakage of pancreatic section or intestinal contents into the abdomen, resulting in localised or blood stream infection.
Pancreaticoduodenectomy: removal of part of pancreas and duodenum (first part of the small intestine).
Pancreaticogastrostomy: connecting the pancreatic duct to the stomach.
Pancreaticojejunostomy: connecting the pancreatic duct to the jejunum (second part of the small intestine).
Pancreato-enteric: connecting the pancreatic duct to the intestine.
Parenchymal: functional parts of an organ.
Parenteral: administered into the body in a manner other than through the gut (in this context by a drip).
Paucity: presence of something in a small amount.
Percutaneous: through the skin.
Peripancreatic: adjacent to the pancreas.
Peritonitis: inflammation of the lining of the abdomen, usually due to chemical irritation or infection.
Resection: the surgical removal of a body part.
Sepsis: life-threatening illness due to blood infection with bacteria, fungus, or virus.
Thresholds: limits.

Appendix 2. MEDLINE search strategy

1. (ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*).ti,ab.
2. exp "Ampulla of Vater"/ or exp Pancreas/ or exp Bile Ducts/ or exp Duodenum/
3. 1 or 2
4. (surger* or surgical* or operat* or resection*).ti,ab.
5. 3 and 4
6. (pancreatect* or pancreaticojejunost* or pancreaticogastros* or pancreaticoduodenect* or duodenopancreatectom*).ti,ab.
7. exp Pancreatectomy/
8. exp Pancreaticojejunostomy/
9. exp Pancreaticoduodenectomy/
10. 5 or 6 or 7 or 8 or 9
11. (amylase or amylases).ti,ab.
12. exp Amylases/
13. 11 or 12
14. (drain* or leak or fistula).ti,ab.
15. exp Drainage/
16. exp Anastomotic Leak/
17. exp Pancreatic Fistula/
18. 14 or 15 or 16 or 17
19. 10 and 13 and 18

Appendix 3. Embase search strategy

1. (ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*).ti,ab.
2. exp duodenum cancer/ or Vater papilla tumor/ or exp pancreas cancer/ or exp bile duct tumor/
3. 1 or 2
4. (surger* or surgical* or operat* or resection*).ti,ab.
5. exp Surgery/
6. 4 or 5
7. 3 and 6
8. (pancreatect* or pancreaticojejunost* or pancreaticogastros* or pancreaticoduodenect* or duodenopancreatectom*).ti,ab.

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9. exp pancreas surgery/
10. 7 or 8 or 9
11. amylase.ti,ab.
12. exp amylase/
13. 11 or 12
14. (drain* or leak or fistula).ti,ab.
15. exp drain/
16. exp anastomosis leakage/
17. exp pancreas fistula/
18. 14 or 15 or 16 or 17
19. 10 and 13 and 18

Appendix 4. Science Citation Index search strategy

#1 TS=(ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*)
#2 TS=(operat* OR surger* OR surgical* OR resection*)
#3 #1 AND #2
#4 TS=(pancreatect* OR pancreaticojejunost* OR pancreaticogastros* OR pancreaticoduodenect* OR duodenopancreatectom*)
#5 #3 OR #4
#6 TS=(amylase)
#7 TS=(drain* or leak or fistula)
#8 #5 AND #6 AND #7

Appendix 5. National Institute for Health Research - Health Technology Assessment search strategy

pancrea* AND amylase

CONTRIBUTIONS OF AUTHORS

TD independently screened the literature, extracted and analysed data. TD also wrote the first draft of the review based on a previously published protocol as per part of a MSc project in Evidence-based Healthcare.

KS Gurusamy wrote the protocol, independently screened the literature, extracted data, and guided and supervised TD. He also revised the review draft significantly after submission of the MSc project.

M Yaghoobi and BR Davidson critically commented on the review.

DECLARATIONS OF INTEREST

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TBUD: none known.

MY: none known.

BD: none known.

KSG: none known.

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SOURCES OF SUPPORT

Internal sources

- University College London, UK.

Support salary, consumables (including printing, photocopying), and equipment (including laptop, scanner, printer, and any other equipment) necessary to complete the review in addition to payment for editorial support.

External sources

- National Institute for Health Research, UK.

Support salary, consumables (including printing, photocopying), and equipment (including laptop, scanner, printer, and any other equipment) necessary to complete the review in addition to payment for editorial support.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Because of the lack of any studies using the reference standards described in the protocol, we accepted ISGPF grades B and C POPF as reference standards. People with grade C POPF require surgery while those with grade B POPF usually do not undergo surgery and may require minimally invasive drainage (Bassi 2005). These people with grade B POPF do not have sepsis but have localised intra-abdominal infection. Although the intra-abdominal infections are usually because of pancreatic leaks in people undergoing pancreatic resection (these leaks are usually at least partially 'contained' (i.e. the effects limited) by the body's defence mechanism), one cannot be sure that the intra-abdominal infection was because of pancreatic leak. So, the reference standards used in this review might misclassify the target condition of pancreatic leak.

2. We searched MEDLINE through OvidSP platform rather than the PubMed platform. This was to avoid limitations of the search strategy in truncating the words searched to 600 variations when truncation terms were used.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pancreatectomy; *Pancreaticoduodenectomy; Amylases [*analysis]; Anastomotic Leak [*diagnosis]; Biomarkers [analysis]; Clinical Enzyme Tests [*standards]; Drainage; Pancreas [surgery]; Prospective Studies; Retrospective Studies; Sensitivity and Specificity

MeSH check words

Aged; Female; Humans; Male; Middle Aged

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