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Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis (Review)

Komolafe O, Pereira SP, Davidson BR, Gurusamy KS

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[Diagnostic Test Accuracy Review]

Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis

Oluyemi Komolafe[1], Stephen P Pereira[2], Brian R Davidson[3], Kurinchi Selvan Gurusamy[3]

[1]University College London, London, UK. [2]UCL Institute for Liver and Digestive Health, Royal Free Hospital Campus, London, UK. [3]Department of Surgery, Royal Free Campus, UCL Medical School, London, UK

Contact address: Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Pond Street, London, NW3 2QG, UK. k.gurusamy@ucl.ac.uk.

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ABSTRACT

Background

The treatment of people with pancreatic necrosis differs from that of people with oedematous pancreatitis. It is important to know the diagnostic accuracy of serum C-reactive protein (CRP), serum procalcitonin, and serum lactate dehydrogenase (LDH) as a triage test for the detection of pancreatic necrosis in people with acute pancreatitis, so that an informed decision can be made as to whether the person with pancreatic necrosis needs further investigations such as computed tomography (CT) scan or magnetic resonance imaging (MRI) scan and treatment for pancreatic necrosis started. There is currently no standard clinical practice, although CRP, particularly an increasing trend of CRP, is often used as a triage test to determine whether the person requires further imaging. There is also currently no systematic review of the diagnostic test accuracy of CRP, procalcitonin, and LDH for the diagnosis of pancreatic necrosis in people with acute pancreatitis.

Objectives

To compare the diagnostic accuracy of CRP, procalcitonin, or LDH (index test), either alone or in combination, in the diagnosis of necrotising pancreatitis in people with acute pancreatitis and without organ failure.

Search methods

We searched MEDLINE, Embase, Science Citation Index Expanded, National Institute for Health Research (NIHR HTA and DARE), and other databases until March 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 CRP, procalcitonin, and LDH for the diagnosis of pancreatic necrosis in people with acute pancreatitis using the following reference standards, either alone or in combination: radiological features of pancreatic necrosis (contrast-enhanced CT or MRI), surgeon's judgement of pancreatic necrosis during surgery, or histological confirmation of pancreatic necrosis. Had we found case-control studies, we planned to exclude them because they are prone to bias; however, we did not locate any. Two review authors independently identified the relevant studies from the retrieved references.

Data collection and analysis

Two review authors independently extracted data, including methodological quality assessment, from the included studies. As the included studies reported CRP, procalcitonin, and LDH on different days of admission and measured at different cut-off levels, 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 index test along with 95% confidence interval (CI) on each of the different days of admission and measured at different cut-off levels.

Main results

A total of three studies including 242 participants met the inclusion criteria for this review. One study reported the diagnostic performance of CRP for two threshold levels (> 200 mg/L and > 279 mg/L) without stating the day on which the CRP was measured. One study reported the diagnostic performance of procalcitonin on day 1 (1 day after admission) using a threshold level of 0.5 ng/mL. One study reported the diagnostic performance of CRP on day 3 (3 days after admission) using a threshold level of 140 mg/L and LDH on day 5 (5 days after admission) using a threshold level of 290 U/L. The sensitivities and specificities varied: the point estimate of the sensitivities ranged from 0.72 to 0.88, while the point estimate of the specificities ranged from 0.75 to 1.00 for the different index tests on different days of hospital admission. However, the confidence intervals were wide: confidence intervals of sensitivities ranged from 0.51 to 0.97, while those of specificities ranged from 0.18 to 1.00 for the different tests on different days of hospital admission. Overall, none of the tests assessed in this review were sufficiently accurate to suggest that they could be useful in clinical practice.

Authors' conclusions

The paucity of data and methodological deficiencies in the studies meant that it was not possible to arrive at any conclusions regarding the diagnostic test accuracy of the index test because of the uncertainty of the results. Further well-designed diagnostic test accuracy studies with prespecified index test thresholds of CRP, procalcitonin, LDH; appropriate follow-up (for at least two weeks to ensure that the person does not have pancreatic necrosis, as early scans may not indicate pancreatic necrosis); and clearly defined reference standards (of surgical or radiological confirmation of pancreatic necrosis) are important to reliably determine the diagnostic accuracy of CRP, procalcitonin, and LDH.

PLAIN LANGUAGE SUMMARY

Blood tests for the diagnosis of pancreatic necrosis (pancreatic destruction due to inflammation of pancreas)

Background

The pancreas is an organ in the abdomen (tummy) that secretes several digestive enzymes (substances that break down the food that we eat) into the pancreatic ductal system, which empties into the small bowel. The pancreas also contains the islets of Langerhans, which secrete several hormones including insulin (which helps regulate blood sugar). Acute pancreatitis is a sudden inflammation of the pancreas that can lead to destruction of the pancreas (pancreatic necrosis). The treatment of people with pancreatic necrosis differs from that of people without pancreatic necrosis. Blood tests such as C-reactive protein (CRP), procalcitonin, and lactate dehydrogenase (LDH) may be used to find out whether a person with acute pancreatitis has pancreatic necrosis. This is usually followed by CT scan to confirm that the person has pancreatic necrosis. If the person is found to have pancreatic necrosis, the intensity of care is increased and additional treatments are performed as required. At present it is unclear whether measuring the levels of CRP, procalcitonin, or LDH is useful in identifying pancreatic necrosis.

Study characteristics

We performed a thorough literature search for studies reporting the accuracy of CRP, procalcitonin, or LDH in identifying pancreatic necrosis. We included studies reported until 20 March 2017. We identified three studies reporting information on 242 people with pancreatitis. The studies included pancreatitis due to all causes.

Key results

Variations in when the studies carried out the blood tests and what level was considered abnormal meant that we were unable to combine the data to provide the overall results. It was not possible to arrive at any firm conclusions about how accurate the tests are for the following reasons.

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

• The studies were of poor methodological quality, which introduced additional uncertainty in the results.

• For the results to be trusted, they must be reproduced in another group of participants. Since this was not done, there was 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

(See Appendix 1 for a glossary of terms.)

The pancreas is an abdominal organ that secretes several digestive enzymes into the pancreatic ductal system, which empties into the small bowel. It also contains the islets of Langerhans, which secrete several hormones, including insulin (NCBI 2014a). Acute pancreatitis is a sudden inflammatory process in the pancreas, with variable involvement of adjacent organs or other organ systems (Bradley 1993). The annual incidence of acute pancreatitis ranges from 5 to 30 per 100,000 population (Roberts 2013; Yadav 2006). In the last one to two decades there has been an increase in the incidence of acute pancreatitis in the UK and the USA (Roberts 2013; Yang 2008). Acute pancreatitis is the most common gastrointestinal (digestive tract) cause of hospital admission in the USA (Peery 2012). Gallstones and alcohol are the two main causes of acute pancreatitis. Approximately 50% to 70% of acute pancreatitis cases are caused by gallstones (Roberts 2013; Yadav 2006). Increasing age, male gender, and lower socioeconomic class are associated with a higher incidence of acute pancreatitis (Roberts 2013).

According to a consensus conference on the classification of acute pancreatitis, the diagnosis of acute pancreatitis is generally made when at least two of the following three features are present (Banks 2013).

1. Acute onset of a persistent, severe epigastric pain often radiating to the back.

2. Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal.

3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and, less commonly, magnetic resonance imaging (MRI) or transabdominal ultrasonography.

Acute pancreatitis can be classified into interstitial oedematous pancreatitis (diffuse or occasionally localised enlargement of the pancreas due to inflammatory oedema as seen on CECT) or necrotising pancreatitis (necrosis involving either the pancreas or peripancreatic tissues or both) (Banks 2013). Approximately 90% to 95% of people with acute pancreatitis have interstitial oedematous pancreatitis, while the remainder have necrotising pancreatitis (Banks 2013). Necrotising pancreatitis may be sterile or infected (Banks 2013). Various theories exist as to how pancreatic and peripancreatic tissues become infected. These include spread from blood circulation, lymphatics, bile, from the small bowel (duodenum) through the pancreatic duct, and migration through the large bowel wall (translocation) (Schmid 1999).

Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis (Banks 2013). Systemic complications of acute pancreatitis include worsening of pre-existing illnesses, such as heart or chronic lung disease (Banks 2013). The mortality rate following an attack of acute pancreatitis is between 6% and 20% (Roberts 2013; Yadav 2006), and depends upon the severity of the acute pancreatitis and the presence of infection. Acute pancreatitis can be classified as mild, moderate, or severe depending upon the presence of local or systemic complications, transient organ failure involving one of more of lungs, kidneys, and cardiovascular system (heart and blood vessels) lasting up to 48 hours, or persistent failure of the same organs mentioned above, lasting beyond 48 hours. In mild pancreatitis, there are no local or systemic complications, or organ failure. In moderately severe acute pancreatitis, there may be local or systemic complications, or transient organ failure. In severe acute pancreatitis, there is persistent organ failure (Banks 2013). (See summary in Table 1.) Acute severe pancreatitis carries the worst prognosis in terms of mortality, while mild pancreatitis has the best prognosis (Banks 2013). Infected necrotising pancreatitis carries a significantly worse prognosis than sterile necrotising pancreatitis, with an average in-hospital mortality of more than 30% for people with infected necrotising pancreatitis, which increases to more than 40% in the subgroup of people with organ failure in addition to infection (Petrov 2010).

Target condition being diagnosed

Acute necrotising pancreatitis in people with an established diagnosis of acute pancreatitis.

Index test(s)

All of the index tests evaluated in this review are performed by the laboratory technician and interpreted by the clinician.

Diagnosis of necrotising pancreatitis in people with an established diagnosis of acute pancreatitis

Serum C-reactive protein (CRP)

C-reactive protein is a plasma protein that increases during inflammation and after tissue damage (NCBI 2014b). Inflammation and tissue damage occur in people with pancreatic necrosis. However, activation of inflammatory pathways is considered to be one of the reasons for the clinical manifestation of acute pancreatitis (Banks 2013), and hence serum CRP can be elevated even in oedematous pancreatitis. One of the thresholds proposed for distinguishing oedematous pancreatitis and necrotising pancreatitis is 140 mg/L (Rau 1998). An increasing trend in the values of the test may also be used for the triage of people who require radiological examination.

Serum procalcitonin

Procalcitonin is the precursor of the hormone calcitonin found in the thyroid C cells and the pulmonary endocrine cells. However, all tissues have the potential to produce procalcitonin. In people with sepsis and severe inflammation, procalcitonin is elevated (Becker 2010). Since pancreatic necrosis is associated with severe inflammation, serum procalcitonin may distinguish between oedematous pancreatitis and necrotising pancreatitis. Procalcitonin levels are undetectable in healthy adults. Hence, any detectable levels of serum procalcitonin can be considered to be abnormal. An increasing trend in the values of the test may also be used for the triage of people who require radiological examination.

Serum lactate dehydrogenase (LDH)

Lactate dehydrogenase is an indicator of cell death. Since pancreatic necrosis is associated with cell death, LDH may distinguish between oedematous pancreatitis and pancreatic necrosis. Normal LDH levels range from 140 units/L to 280 units/L. One of the thresholds proposed for distinguishing oedematous pancreatitis and necrotising pancreatitis is 290 units/L (Rau 1998). An increasing trend in the values of the test may also be used for the triage of people who require radiological examination.

Clinical pathway

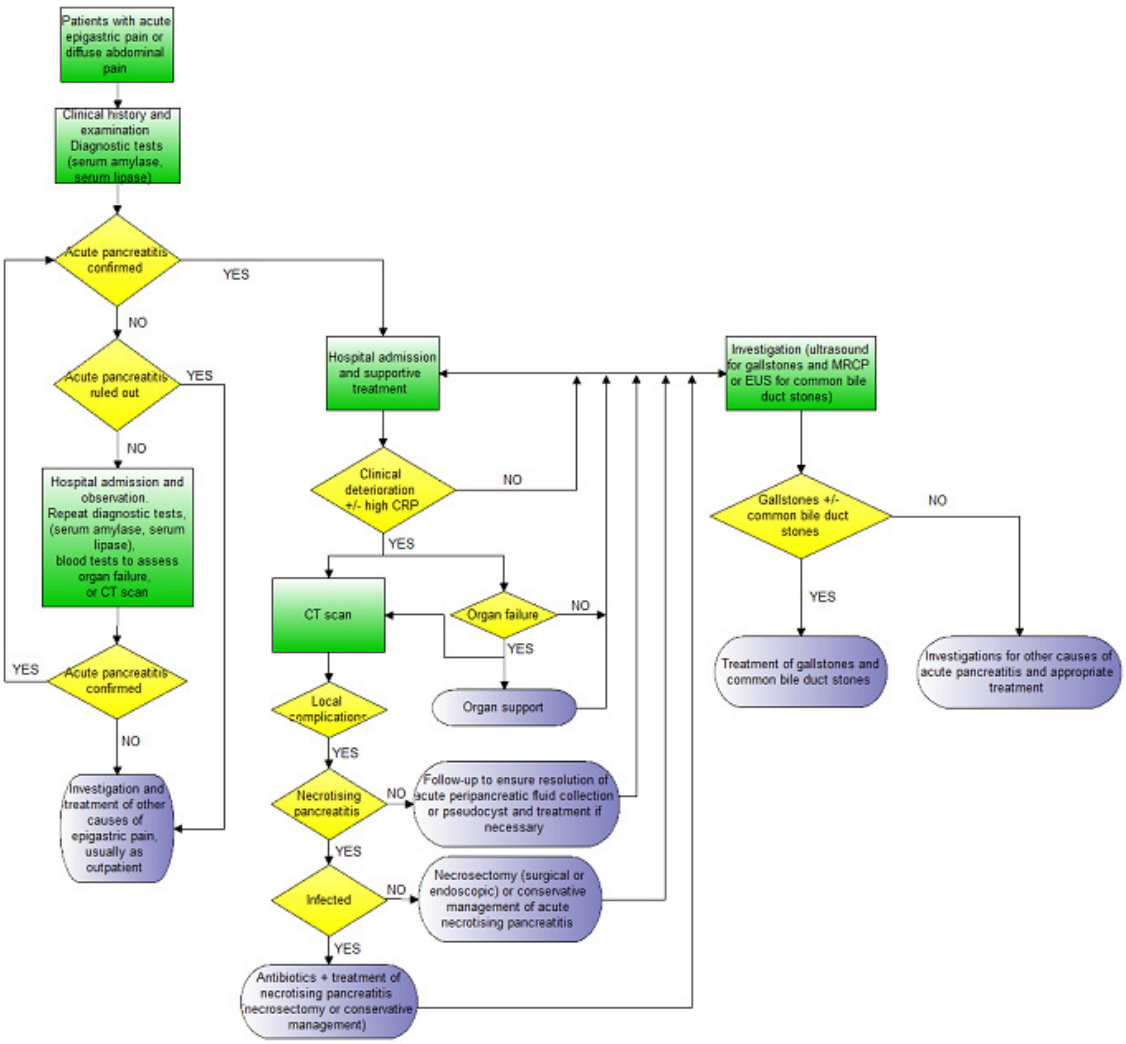
For people with acute onset of a persistent, severe, epigastric pain or people with diffuse abdominal pain that started in the epigastric region (or if the person is unsure about the region in which diffuse abdominal pain began), clinical examination including recording of blood pressure, pulse rate, and oxygen saturations (when available) are performed. Routine blood tests such as full blood count, urea, creatinine, and electrolytes are also performed. Blood tests such as amylase and lipase are performed to confirm (or rule out) the diagnosis of acute pancreatitis. Radiological findings of acute pancreatitis evolve over a few days, and the radiological features may not be apparent in the early stages, or may even be normal (Banks 2013; Vissers 1999); thus, one cannot rely on radiological tests to diagnose acute pancreatitis, at least in the early stages. Radiological examination with computed tomography (CT scan) or MRI scan is not routinely performed if a diagnosis of acute pancreatitis is suspected. If acute pancreatitis can be ruled out, other causes of acute epigastric pain should be considered. Peptic ulcer, functional dyspepsia, and gallstones can present with acute epigastric pain (Gurusamy 2014; Moayyedi 2006). All of these alternative causes of epigastric pain are generally investigated and treated after discharge of the person unless there is a strong suspicion of perforated peptic ulcer, usually because of features of peritonitis or because pain control could not be achieved. In such instances, either a plain X-ray of the abdomen or emergency CT scan, or both may be performed to identify the presence of free-intraperitoneal gas (Ghekiere 2007; Grassi 2004). The usual treatment for perforated peptic ulcer is emergency surgical closure, which can be performed by open or laparoscopic surgery (Sanabria 2013).
If a diagnosis of acute pancreatitis can be established, usually based on the consensus criteria, the person is admitted to hospital and the severity of pancreatitis assessed. The treatment of acute pancreatitis is generally supportive treatment, that is maintenance of fluid and electrolyte imbalance. Despite various pharmacological interventions being evaluated in acute pancreatitis, none is currently recommended as treatment. Abdominal ultrasound and magnetic resonance cholangiopancreatography or endoscopic ultrasound may be performed to investigate the aetiology of acute pancreatitis. In the presence of gallstones, cholecystectomy is performed. The timing of cholecystectomy in acute pancreatitis is controversial, and different factors must be considered depending upon the severity of the acute pancreatitis (Gurusamy 2013). Endoscopic sphincterotomy or common bile duct exploration may need to be performed in the presence of common bile duct stones (Ayub 2004; Larson 2006). In the absence of gallstones, investigation of other causes of acute pancreatitis is required. People are generally monitored clinically. If the person improves clinically with supportive treatment, the person with gallstone pancreatitis is discharged after cholecystectomy or after scheduling a cholecystectomy or on a planned list, within the two weeks. For those people with severe acute pancreatitis, cholecystectomy is undertaken when clinically appropriate after resolution of pancreatitis

(NCEPOD 2016). If the person deteriorates clinically, the person undergoes a CT scan and may require high-dependency or intensive care unit care in the presence of organ failure or in the presence of infected pancreatic necrosis.

In the presence of organ failure, the person undergoes a CT scan or MRI to identify any local complications. C-reactive protein, procalcitonin, and LDH might distinguish between oedematous and necrotising pancreatitis (Alfonso 2003; Khanna 2013; Rau 1998), and could potentially be used as a triage test to identify who among those without organ failure needs further radiological tests (Alfonso 2003). Some centres use CRP routinely to determine whether people require radiological investigations to diagnose necrotising pancreatitis. Frequently, a rising trend in CRP, procalcitonin, or LDH rather than a single test may be used to determine whether people require radiological investigations to diagnose necrotising pancreatitis. It should be noted that CT scan or MRI is not routinely performed during the initial stages of acute pancreatitis but usually in the presence of organ failure or due to the results of the serum CRP. The various treatment strategies in acute necrotising pancreatitis include non-surgical (conservative) treatment, percutaneous drainage, endoscopic transluminal drainage, early surgical debridement (necrosectomy, which can be performed by open surgery or by minimally invasive retroperitoneal debridement), delayed necrosectomy (delaying the surgery by about four weeks), or a step-up approach that consists of endoscopic or percutaneous drainage followed by laparoscopic necrosectomy if required, and non-surgical (conservative) treatment (Bakker 2012; Mouli 2013; Tenner 2013; van Brunschot 2014; van Santvoort 2010; van Santvoort 2011). A recent Cochrane systematic review found that a step-up approach may be preferable to direct surgery in people with acute necrotising pancreatitis (Gurusamy 2016). All of these treatments are supported by appropriate fluid therapy and nutritional support. This is in comparison with severe acute oedematous pancreatitis, where the main treatment is supportive treatment for systemic complications including organ failure and treatment of local complications such as pseudocyst if symptomatic (Cannon 2009; Cheruvu 2003; Johnson 2009; Varadarajulu 2008; Varadarajulu 2013). In the case of infected pancreatic necrosis, appropriate antibiotics are administered in addition to the treatment outlined above for non-infected pancreatic necrosis. In the case of acute peripancreatic collections or pseudocysts on the radiological tests, the person requires clinical and radiological follow-up to ensure resolution of these collections.

If the diagnosis of acute pancreatitis cannot be ruled out on the basis of the clinical presentation and serum amylase or lipase, the person is admitted to hospital and the evolution of signs and symptoms is noted. Serum amylase and lipase may be repeated, or radiological examinations may be performed to establish or rule out acute pancreatitis with a reasonable amount of certainty. Tests for organ failure (e.g. urea and creatinine for identifying renal failure, blood pressure, pulse rate, respiratory rate, urine output, and arterial blood gases) may also be performed to ensure that moderately severe or severe pancreatitis is not present irrespective of the results of serum amylase and lipase. The possible clinical pathway in the diagnosis and management of acute pancreatitis is shown in Figure 1.

Figure 1. Clinical pathway.Footnotes:Acute pancreatitis is usually confirmed by consensus criteria (Banks 2013).Irrespective of the CT scan findings and presence or absence of necrosis, people with organ failure will require organ support and will receive a CT scan.CT scan may also be performed in people without organ failure if there is clinical deterioration (not amounting to organ failure) or in some centres based on an elevated CRP.Necrotising pancreatitis is usually confirmed by the findings on the CT scan and by histopathological examination of the biopsy obtained during necrosectomy if early necrosectomy is performed.Infected necrotising pancreatitis is usually confirmed by the findings on the CT scan and by microbiological examination of fluid aspirated under radiological guidance or from the tissue biopsy obtained during necrosectomy if early necrosectomy is performed.Organ failure is diagnosed on the basis of clinical examination and blood tests (urea, creatinine, blood pressure, pulse rate, respiratory rate, arterial blood gas analysis).Abbreviations:CRP: C-reactive proteinCT: computed tomographyEUS: endoscopic ultrasoundMRCP: magnetic resonance cholangiopancreatography



Prior test(s)

The tests that are performed before the index tests, such as serum lipase or amylase, are used to establish the diagnosis of acute pancreatitis. If necessary, these are supported with radiological tests such as CECT, MRI, or transabdominal ultrasonography, and clinical examination and blood tests to rule out organ failure (e.g. urea and creatinine for identifying renal failure, blood pressure, pulse rate, respiratory rate, urine output, and arterial blood gases). Of these tests, serum tests for the diagnosis of acute pancreatitis, clinical examination, and blood tests to rule out organ failure are routinely performed, while CT scan is performed if there is uncertainty in the diagnosis of acute pancreatitis. The minimum prior tests are thus serum lipase, serum amylase, clinical examination, and blood tests to rule out organ failure.

Role of index test(s)

Currently, if necrotising pancreatitis is suspected in people without organ failure, radiological investigations are performed directly, although some units may use CRP (in particular an increasing trend in CRP values) to identify those who require radiological investigations. In people where the diagnosis of acute pancreatitis was based on CT scan, it is quite possible that the radiological features of necrosis are not manifest initially, as there may be a delay in their appearance (Banks 2013). In such cases, CRP may be used to identify people who require additional radiological investigations. We evaluated the index tests (CRP, procalcitonin, and LDH) as triage tests for detecting pancreatic necrosis in people with acute pancreatitis in whom the diagnosis of pancreatic necrosis has not been made. Further radiological tests such as CECT will be necessary for confirming pancreatic necrosis, and the location and extent of pancreatic necrosis, before treatment can be planned. We did not evaluate the role of these tests in monitoring necrotising pancreatitis once the diagnosis of necrotising pancreatitis is made.

Alternative test(s)

Other tests used in the diagnosis of pancreatic necrosis include CECT, MRI, or transabdominal ultrasonography (Banks 2013). Various other blood tests such as blood haematocrit, blood urea, serum creatinine, and procarboxypeptidase B have been evaluated as diagnostic tests for pancreatic necrosis, but these are not in routine use for the diagnosis of pancreatic necrosis (Muddana 2009; Rau 1998).

Rationale

The treatment of people with acute pancreatitis differs between people with and those without pancreatic necrosis, as mentioned in the clinical pathway (Figure 1). People with organ failure routinely undergo radiological investigations, while those without organ failure do not routinely undergo CT scans. Some units already use CRP as a triage test to identify people without organ failure who require radiological investigations and admission to high dependency unit or intensive therapy unit, while others do not. The role of CRP, procalcitonin, and LDH as triage tests is thus unclear. There is no current systematic review of the diagnostic test accuracy of CRP, procalcitonin, or LDH in the diagnosis of pancreatic necrosis. A Cochrane systematic review of the diagnostic test accuracy of CRP, procalcitonin, or LDH in the diagnosis of pancreatic necrosis was needed to understand the value of these tests as triage tests to identify people who require radiological investigation.

OBJECTIVES

To compare the diagnostic accuracy of CRP, procalcitonin, or LDH, either alone or in combination, in the diagnosis of necrotising pancreatitis in people with acute pancreatitis and without organ failure.

Secondary objectives

We planned to explore the following sources of heterogeneity.

- Studies at low risk of bias versus those at unclear or high risk of bias (as assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, recommended by the Cochrane Diagnostic Test Accuracy Group) (Whiting 2006; Whiting 2011).
- Prospective studies versus retrospective studies (to determine whether there is a difference in diagnostic accuracy between prospective and retrospective studies).
- Full-text publications versus abstracts (this can be indicative of publication bias, since there may be an association between the results of the study and the study reaching full publication status) (Eloubeidi 2001).
- Previous history of acute pancreatitis.
- Different aetiology for acute pancreatitis (gallstone versus alcohol versus other aetiology). The accuracy of the test may depend upon the aetiology of the acute pancreatitis.
- Presence or absence of infection. The accuracy of the test may depend upon the presence or absence of infection.
- Pancreatic versus peripancreatic necrosis.
- Average time to performance of the test. The accuracy of the test may depend upon the interval between the onset of clinical symptoms and the performance of the test.
- Different test manufacturers.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that evaluated the accuracy of the index tests mentioned above in the appropriate population (see below). We included relevant studies irrespective of language or publication status; whether the data were collected prospectively or retrospectively; and whether there was a comparison between the tests. However, we excluded case reports (which describe how the diagnosis of acute pancreatitis or acute necrotising pancreatitis was made on an individual participant or a group of participants and which do not provide sufficient diagnostic test accuracy data, i.e. true positive, false positive, false negative, and true negative). We also planned to exclude case-control studies because they are prone to bias (Whiting 2011); however, we did not identify any case-control studies.

Participants

Adult participants with acute pancreatitis within 14 days of the onset of symptoms (irrespective of the interval between the onset of symptoms and the time at which the test was performed). The diagnosis of acute pancreatitis should have been made on the basis of the consensus conference definition (Banks 2013). Participants who had already developed organ failure at the time of performing these tests were excluded, since all such participants undergo radiological investigations. Although we had planned to exclude participants in whom pancreatic necrosis was present on the CT scan used to diagnose acute pancreatitis, this information was not available from the studies.

Index tests

Serum CRP, procalcitonin, and LDH either alone or in combination immediately prior to radiological investigation. A variety of kits are available for measuring these tests. We included kits from all manufacturers, and included studies irrespective of the threshold used. We included studies that reported a single test and sequential tests of serum CRP, procalcitonin, and LDH. If the study reported sequential testing, we planned to consider a progressive increase as a positive index test irrespective of the degree of increase, and stationary or decrease in the levels as a negative test; however, none of the studies reported this information despite measuring the levels on different days.

Target conditions

Pancreatic necrosis (i.e. infected or sterile pancreatic or peripancreatic necrosis)

Reference standards

While considered to be the gold standard for confirming necrosis, biopsy may not have been performed in all participants due to ethical concerns over performing an invasive treatment (during which biopsy is taken) in those without a diagnosis of pancreatic necrosis. As a result, study authors may use radiological features of pancreatic necrosis (an area of reduced enhancement or non-enhancing area of pancreatic parenchyma on CECT or contrast-enhanced MRI). However, this reference standard may miss some cases of pancreatic necrosis, resulting in underestimation of diagnostic test accuracy of the index tests. In addition, using radiological features of pancreatitis might introduce an intrinsic threshold effect because of interobserver variation between radiologists. As per protocol, we accepted any of the following reference standards, used alone or in combination: radiological features of pancreatic necrosis (CECT or contrast-enhanced MRI) or histological confirmation of pancreatic necrosis. We also included a combination of radiological features of pancreatic necrosis (CECT or contrast-enhanced MRI) and surgeon's judgement of pancreatic necrosis during surgery, as we considered this equivalent to radiologist judgement of the presence of pancreatic necrosis on CECT or contrast-enhanced MRI. In terms of ranking the reference standards, we considered biopsy in all participants as the best reference standard (although it is unlikely to be performed in participants with a negative test for pancreatic necrosis) followed by biopsy in participants with positive test and radiological or surgical features of pancreatic necrosis in participants with negative test, and radiological tests or surgery alone as the reference standard, in that order.

Search methods for identification of studies

We included all studies irrespective of the language of publication and publication status. We translated non-English language articles.

Electronic searches

We searched the following databases.

1. MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)) via OvidSP (January 1946 to 20 March 2017) (Appendix 2).
2. Embase via OvidSP (January 1947 to 20 March 2017) (Appendix 3).
3. Science Citation Index Expanded via Web of Knowledge (January 1980 to 20 March 2017) (Appendix 4).

4. Conference Proceedings Citation Index-Science (CPCI-S) via Web of Knowledge (January 1990 to 20 March 2017) (Appendix 4)

5. National Insitute for Health Research (NIHR HTA and DARE) via Centre for Reviews and Dissemination (20 March 2017) (Appendix 5).

6. Zetoc via British Library (20 March 2017) (Appendix 6).

7. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) (20 March 2017) (Appendix 7).

8. ClinicalTrials.gov (clinicaltrials.gov/) (20 March 2017) (Appendix 8).

We used this same strategy in another review on diagnosis of acute pancreatitis in people with acute epigastric or diffuse abdominal pain (Gurusamy 2015).

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 that cite the included articles) in these databases (Sampson 2008).

Data collection and analysis

Selection of studies

Two review authors (OK and KSG) independently identified relevant studies from the retrieved references. We obtained the full texts of references considered to be relevant by at least one of the review authors. Two review authors independently screened the full-text papers against the inclusion criteria and resolved any differences through discussion. We planned to contact the study authors if there were any doubts about study eligibility.

Data extraction and management

Two review authors (OK and KSG) independently extracted the following data from each included study using a data extraction form designed and piloted by KSG, resolving any differences by discussion.

- First author.
- Year of publication.
- Study design (prospective or retrospective cohort studies; cross-sectional studies or randomised comparisons of index tests).
- Inclusion and exclusion criteria for individual studies.
- Total number of participants.
- Number of females.
- Average age of the participants.
- Average time between onset of symptoms and index test.
- Aetiology of acute pancreatitis.
- Proportion of participants with infected pancreatic necrosis.
- Description of the index test.
- Threshold used for the index test.
- Reference standard.
- Information to complete the QUADAS-2 assessment (please see below).
- Number of true positives, false positives, false negatives, and true negatives.

If the same study reported multiple index tests, we extracted the number of true positives, false positives, false negatives, and true negatives for each index test. If the same study reported the number of true positives, false positives, false negatives, and true negatives for each index test at different thresholds, we extracted this information for each threshold. If the study reported the results for a combination of tests, we planned to extract the number of true positives, false positives, false negatives, and true negatives for each different combination of tests; however, we did not find any such studies.

A common way that the diagnostic accuracy of a combination of tests is assessed is at least one test positive versus all tests positive. We planned to extract the number of true positives, false positives, false negatives, and true negatives for both the scenarios (at least one test positive and all tests positive). If the study reported the test at multiple time points, we planned to obtain the trend in sequential testing of CRP, procalcitonin, or LDH if the author used a progressively increasing trend in index test values for distinguishing acute necrotising pancreatitis and oedematous pancreatitis. For this purpose, we planned to consider an increasing trend as a positive index test irrespective of the degree of increase, and consider stationary levels or a decrease in the levels as a negative test in order to calculate the number of true positives, false positives, false negatives, and true negatives. If the authors provided the final values of these index tests prior to radiological examination, we planned to obtain these values for calculating the true positives, false positives, false negatives, and true negatives. We did this because we wanted to evaluate the role of these index tests used as a test with a prespecified threshold, and the role of an increasing trend in the values of these index tests for distinguishing acute necrotising pancreatitis and oedematous pancreatitis. The rationale for using the final values to calculate the diagnostic test accuracy is as follows. Participants may receive treatment for organ failure if they developed organ failure between the index test and reference standard. We anticipated that a radiological investigation would have been performed within 24 hours of diagnosis of organ failure. Pancreatic necrosis does not resolve in 24 hours, and there will be no alteration of the final diagnosis by the treatment in participants with pancreatic necrosis. People with oedematous pancreatitis and organ failure may develop pancreatic necrosis in the absence of appropriate treatment. Consequently, there is a possible interaction between inadequate treatment and the final diagnosis.

The final values, which have the shortest time interval between the index test and reference standard, are the least likely to be affected by inappropriate treatment and are likely to provide the best estimates of diagnostic test accuracy. Although studies measured the index tests at several time points, the diagnostic test accuracy results were provided only at a specific time point, therefore we did not use trend in values as a threshold in this review.

We excluded participants with uninterpretable index test results (irrespective of the reason given for lack of interpretation) from the diagnostic test accuracy data since in clinical practice, uninterpretable index test results would result in additional tests for the diagnosis of acute pancreatitis. However, we recorded the number of uninterpretable index test results in a separate data column, as this would provide information on the applicability of the test in clinical practice (i.e. the number of individuals in whom the test provides interpretable results) and may affect the cost-effectiveness of a test. Although cost-effectiveness is outside the scope of this review, cost-effectiveness studies may use data from this review. If there was an overlap of participants between multiple reports, as suggested by common authors and centres, we planned to contact the study authors to seek clarification about the overlap. If we were unable to contact the authors, we planned to extract the maximum possible information from all of the reports. However, we did not find any such reports. We attempted to contact the study authors for further information where necessary.

Assessment of methodological quality

Two review authors (OK and KSG) independently assessed study quality using the QUADAS-2 assessment tool (Whiting 2006; Whiting 2011). Any differences were resolved by discussion using the QUADAS-2 table from the protocol shown in Table 2. We considered studies classified as 'low risk of bias' and 'low concern' in all of the domains (except for the reference standard domain, where we accepted a 'No' for the signalling question 'Is the reference standard likely to correctly classify the target condition?') as studies with high methodological quality, that is we accepted a study to be of high methodological quality despite not using histological confirmation of pancreatic necrosis (as it is unethical to perform a biopsy in a person with a low likelihood of not having pancreatic necrosis), provided that it was classified as at low risk of bias for all other domains and low concern in all domains. We have presented the results in a 'Risk of bias' summary and graphs in addition to a narrative summary.

Statistical analysis and data synthesis

We stratified the analysis by the test thresholds (i.e. tests at different thresholds were considered as different index tests) and planned to stratify the analysis by different reference standards (if the same test was assessed in different studies using different reference standards, it was considered as different index tests). If the study used increasing trend in the values of CRP, procalcitonin, or LDH as the diagnostic criteria for distinguishing necrotising pancreatitis from oedematous pancreatitis, we planned to consider this as the 'threshold' for the purpose of this review. We plotted study estimates of sensitivity and specificity on forest plots and in receiver operating characteristic (ROC) space to explore between-study variation in the performance of each test stratified by the threshold and reference standard. To estimate the summary sensitivity and specificity of each test at each threshold level and each reference standard, we planned to perform the meta-analysis by fitting the bivariate model (Chu 2006; Reitsma 2005). This model accounts for between-study variability in estimates of sensitivity and specificity through the inclusion of random effects for the logit sensitivity and logit specificity parameters of the bivariate model. If sparse data resulted in unreliable estimation of the covariance matrix of the random effects as indicated by very large variance of logit sensitivity and specificity, we planned to perform the analysis using simpler models suggested by Takwoingi 2015 and colleagues using the distribution of sensitivities and specificities as noted in the forest plots or ROC space and -2 log likelihood to choose the model.

We planned to compare the diagnostic accuracy of the different tests by including a single covariate term for test type in the bivariate model to estimate differences in the sensitivity and specificity of the tests. We planned to consider a combination of tests for each of the scenarios (any test positive or all tests positive) as different index tests. We planned to allow the variances of the random effects and their covariance to also depend on test type, thus allowing the variances to differ between tests. We planned to use the hierarchical summary receiver operating characteristics curve (HSROC) to test hypotheses about whether one test is superior to another and to investigate heterogeneity (Rutter 2001). For this purpose, we planned to combine tests irrespective of the thresholds and reference standards, as we expected few studies at each threshold level and reference standard. In case the study reported results at multiple thresholds, we planned to employ the threshold used for primary analysis by the authors for inclusion in the HSROC model. We planned to use likelihood ratio tests to compare the model with and without covariate (test type). A P value of less than 0.05 for the likelihood ratio test would have indicated differences in diagnostic accuracy between the tests. We also planned to compare the estimates of sensitivity and specificity between models to check the robustness of our assumptions about the variances of the random effects. If at least four studies that evaluated different tests in the same study population were available (e.g. in studies that performed more than one index test in all participants, individual index tests and combination of index tests in all participants, or randomised controlled trials in which participants were randomised to the different index tests), we planned to perform a direct head-to-head comparison by limiting the test comparison to such studies. We also planned to present the relative sensitivities and relative specificities of the index tests from

the direct comparisons in a table.

We planned to perform the meta-analysis using the NLMIXED command in SAS version 9.3 (SAS Institute Inc, Cary, North Carolina, USA). We planned to create a graph of pre-test probabilities (using the observed median and range of prevalence from the included studies) against post-test probabilities for each test stratified by different thresholds and reference standards. The post-test probabilities would have been calculated using these pre-test probabilities and the summary positive and negative likelihood ratios. The summary likelihood ratios and their confidence intervals would have been calculated from the functions of the parameter estimates from the bivariate model that we planned to fit to estimate the summary sensitivities and specificities. Post-test probability associated with positive test is the probability of having the target condition (acute pancreatitis or acute necrotising pancreatitis) on the basis of a positive test result, and is the same as the term 'positive predictive value' used in a single diagnostic accuracy study. Post-test probability associated with a negative test is the probability of having the target condition (acute pancreatitis or acute necrotising pancreatitis) on the basis of a negative test result and is 1 - 'negative predictive value'. Negative predictive value is the term used in a single diagnostic accuracy study to indicate the chance that the participant has no target condition when the test is negative. We planned to report the summary sensitivity, specificity, positive and negative likelihood ratios, and post-test probabilities for the median, lower quartile, and upper quartile of the pre-test probabilities.

However, because of paucity of data, we did not perform any meta-analysis. We calculated the sensitivity and specificity of each test and have reported these with their 95% confidence intervals (95% CI), along with the post-test probability of positive and negative test at the pre-test probability in the studies.

Investigations of heterogeneity

Of the nine sources of heterogeneity mentioned in the Secondary objectives, we planned to use risk of bias, prospective or retrospective studies, publication status, presence or absence of infection, and different test manufacturers as categorical covariates, and the proportion of participants with a previous history of acute pancreatitis, the proportion of participants with different aetiologies, the proportion of participants with pancreatic necrosis and peripancreatic necrosis, and the average time to performance of the test as continuous covariates in the regression model. As before, we planned to include one covariate at a time in the regression model and use the likelihood ratio test to determine whether the covariate is statistically significant. We did not investigate heterogeneity because of the paucity of data.

Sensitivity analyses

We did not plan any sensitivity analyses except when the data available from the studies were ambiguous (e.g. the numbers in the text differed from the numbers in the figures), in which case we planned to assess the impact of different data used by a sensitivity analysis. We did not find any ambiguous data in the studies.

Assessment of reporting bias

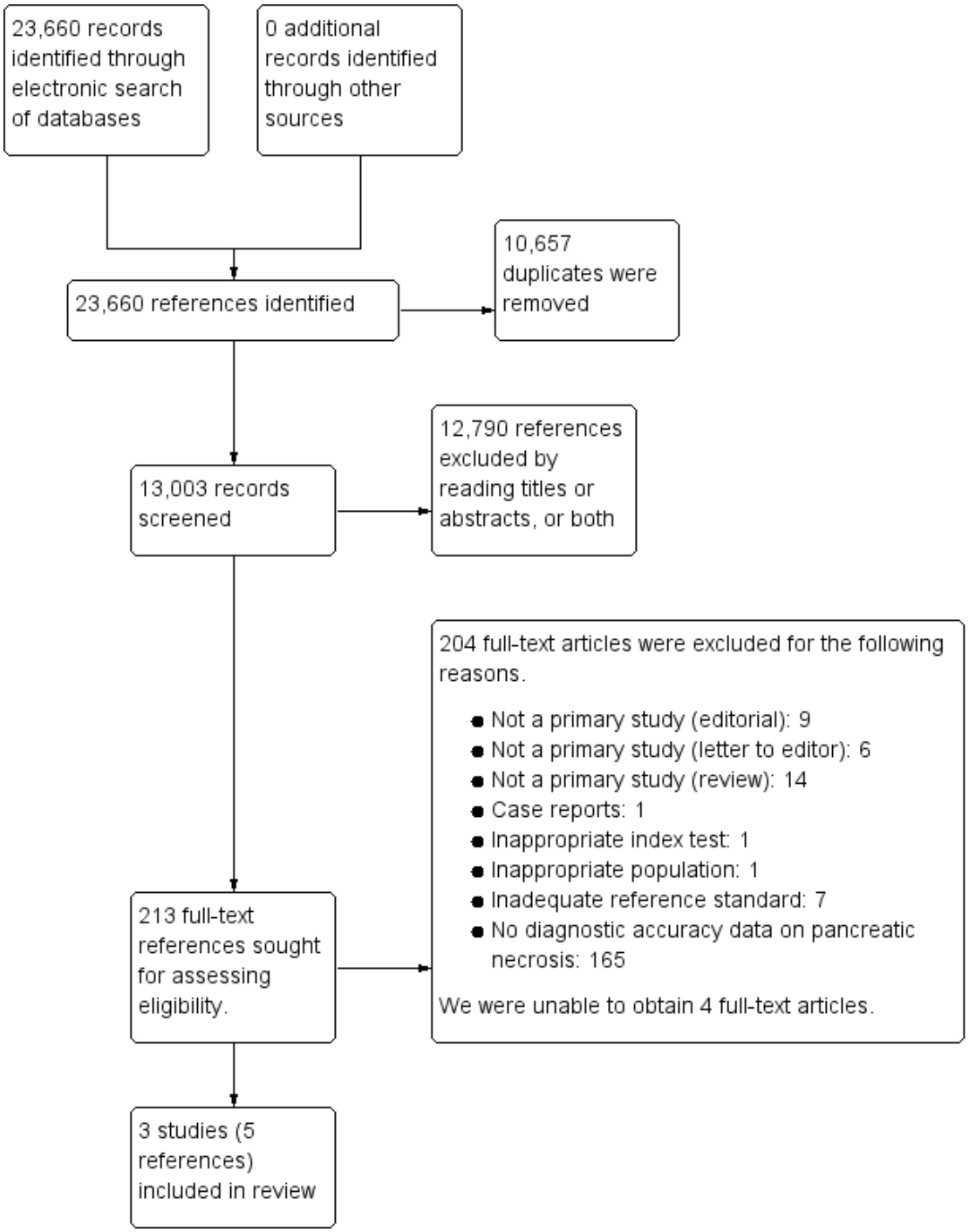
We planned to investigate whether the summary sensitivity and specificity were different between studies published as full text and those that were available only as abstracts (at least two years prior to the search date) using the methods described in the Investigations of heterogeneity section. We did not investigate reporting bias because of the paucity of data.

RESULTS

Results of the search

We identified a total of 23,360 references through the electronic searches of MEDLINE (n = 7326), Embase (n = 11,502), Science Citation Index Expanded (n = 4293), National Institute for Health Research (NIHR HTA and DARE) (n = 142), Zetoc (n = 360), WHO ICTRP (n = 1), and ClinicalTrials.gov (n = 36). We excluded 10,657 duplicates and 12,790 clearly irrelevant references through reading the titles or abstracts, or both. We sought full-text articles for 213 references, but were unable to obtain the full text for four references (Djurasinovic 2013; Grenier 1968; Issekutz 2003; Pindak 2003). We retrieved the full-text articles of 209 references for further assessment against our review protocol inclusion criteria. We excluded 204 of these 209 references for the reasons provided in the Characteristics of excluded studies section. Three studies (five references) fulfilled the inclusion criteria and provided the diagnostic accuracy data for the review (Alfonso 2003; Bertsch 1997; Rau 1998). We have shown the reference flow in Figure 2.

Figure 2. Study flow diagram.



Included studies

Three studies including 242 participants met the inclusion criteria for this review and assessed the diagnostic accuracy of the index tests in participants with established acute pancreatitis. The average age of participants in the studies was 49 years (Rau 1998), 53 years (Bertsch 1997), and 67 years (Alfonso 2003). About two-fifths of participants (41%) were females in these three studies (Alfonso 2003; Bertsch 1997; Rau 1998). One study was a prospective study (Rau 1998), and one was a retrospective study (Alfonso 2003). It was unclear whether the third study was prospective or retrospective (Bertsch 1997). All of the studies were full-text publications. The studies did not report whether they included participants with a previous history of acute pancreatitis. Two studies reported that they included acute pancreatitis of varied aetiology (Alfonso 2003; Bertsch 1997); information on aetiology was not available in the third study (Rau 1998). None of the studies reported data separately for different aetiologies. None of the studies reported the presence or absence of infection in participants. One study clearly indicated that the presence of pancreatic and peripancreatic necrosis was considered as the target condition (Rau 1998); the remaining studies did not provide this information. None of the studies reported data separately for pancreatic and peripancreatic necrosis.

One study reported the diagnostic performance of CRP for two threshold levels (> 200 mg/L and > 279 mg/L) without stating the day on which the CRP was measured (Alfonso 2003). One study reported the diagnostic performance of procalcitonin on day 1 using a threshold level of 0.5 ng/mL (Bertsch 1997). One study reported the diagnostic performance of CRP on day 3 using a threshold level of 140 mg/L and LDH on day 5 using a threshold level of 290 U/L (Rau 1998).

Excluded studies

We excluded a total of 204 studies at the full-text stage for the following reasons.

- Not a primary study (editorial): 9 (Chen 2004; Fan 1994; Folch-Puy 2007; Gosling 1992; Lipsett 2001; Lott 1991; Manabe 2004; Petrov 2011; Samso 2002).
- Not a primary study (letter to editor): 6 (Beger 1989; Bihari 2004; Choudhary 2012; Economou 1997; Neoptolemos 2001; Wilson 1989b).
- Not a primary study (review): 14 (Bassi 1994; Brailski 1975; Buchler 1991; Frossard 2001; Geng 2014; Johnson 2003; Korczowski 2006; Lempinen 2005; Liu 2008; Malfertheiner 1993; Millat 1999; Mulholland 1996; Purkayastha 2006; Rau 2004).
- Case reports: 1 (Wong 1993).
- Inappropriate index test: 1 (Pezzilli 1998b).
- Inappropriate population: 1 (Machiedo 1974).
- Inadequate reference standard: 7 (Barauskas 2004; Cardoso 2013; Gluskina 1967; Khanna 2013; Pallisera 2014; Puolakkainen 1987; Schaffler 2010).
- No diagnostic accuracy data on pancreatic necrosis: 165 (Abishek 2014; Aggelopoulos 1996; Ammori 2003; Appasani 2011a; Appasani 2011b; Appasani 2012; Bajec 2010; Bapat 1986; Berry 1982; Bezmarevic 2012a; Bezmarevic 2012b; Bezmarevic 2012c; Blum 2001; Boskovic 2014; Brand 2014; Brisinda 1999; Buchler 1986a; Buchler 1986b; Buchler 1986c; Buchler 1987; Bulbuller 2006; Cai 2014; Cardoso 2011; Cardoso 2015; Chen 1992; Chen 2012; Choi 2012; Choi 2013; Chooklin 2010; Cooper 1981; Cravo 1988; d'Eril 2000; Dambrauskas 2010; Dammann 1979; Daniel 2010; de Beaux 1996; De la Pena 1991; Del Prete 2001; Digalakis 2009; Duarte-Rojo 2009; Ferguson 1990; Fisic 2013; Frasquet 2003; Gao 2014; Garcia-Cantu 2004; Garcia Lozano 1992; Gelfand 2005; Gross 1990; Guenther 2010; Gurda-Duda 2008; Gurleyik 2004; Gurleyik 2005; Gvozdenovic 2001; Hamalainen 2002; Han 2011; Hjalmarsson 2009; Huang 2013; Huang 2015; Imamura 2002a; Imamura 2002b; Inagaki 1997; Isenmann 1993; Isogai 1998; Jia 2015; Jiang 2004; Jimenez 2015; Jimin 2015; Kaiyasah 2013; Kaya 2007; Kazda 2002; Khvatova 1973; Khvatova 1977; Kibar 2016; Kim 2013a; Kim 2013b; Kitsanou 2004; Kusnierz-Cabala 2004; Kylanpaa-Back 2001a; Kylanpaa-Back 2001b; Kylanpaa-Back 2001c; Leese 1987; Leese 1988; Lempinen 1999; Lewandowski 2007; Li 2013; Liang 2014; Lindner 1995; Lobo 1999; Ma 2013; Makay 2003; Makela 2007; Mandi 2000a; Mandi 2000b; Manes 1994; Mantke 2002; Marek 1996; Mayer 1984; Mayer 2002; Melzi D'Eril 2000; Modrau 2005; Modzelewski 2005; Muller 1997; Muller 2000; Nunes 2009; Oezcueruemez-Porsch 1998; Olah 2005; Omoto 2015; Ostrovskii 2012; Paajanen 1995; Palani 1977; Park 2012; Park 2013; Pezzilli 1994; Pezzilli 1995a; Pezzilli 1995b; Pezzilli 1997; Pezzilli 1998a; Pezzilli 2000; Pongprasobchai 2010; Qiu 2014; Raraty 2002; Rau 1997; Rau 2000; Rau 2007; Ricardo 2011; Riche 2003; Ruzafa 1991; Sanchez-Lozada 2005; Santotoribio 2015; Sato 2004; Savel'ev 2002; Schaffler 2011; Sharma 2011; Stimac 2010; Stimac 2012; Stimac 2013; Stoelben 1996; Sugumar 2011; Tao 2013; Teerenhovi 1988; Tesinsky 2008; Trunin 1985; Uhl 1991; Uomo 1995; Vaz 2013; Vesentini 1993; Viedma 1992; Viedma 1994; Vlachos 2014; Wei 2013; Wetherill 2012; Wetherill 2013a; Wetherill 2013b; Wilson 1987; Wilson 1988; Wilson 1989a; Woo 2011; Xu 2015; Yadav 2015a; Yadav 2015b; Yasuda 2011; Yin 2014; Yu 2011; Zhu 2013; Zrnic 2007).

Methodological quality of included studies

We have summarised the methodological quality of included studies in Figure 3 and Figure 4.

Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

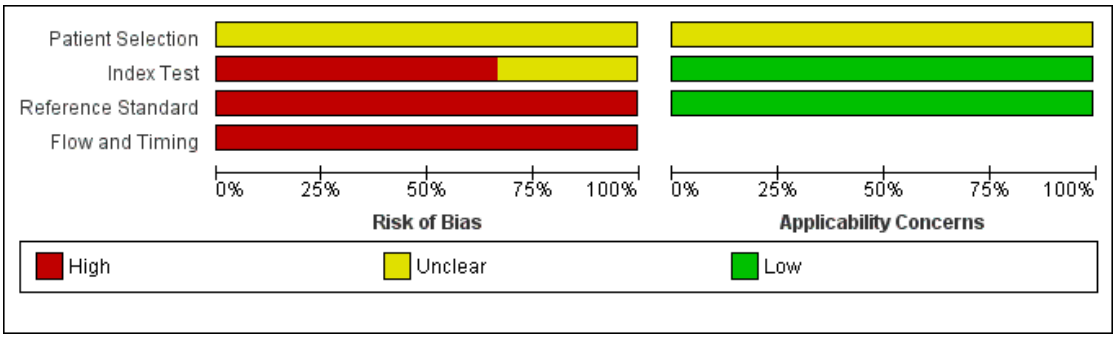
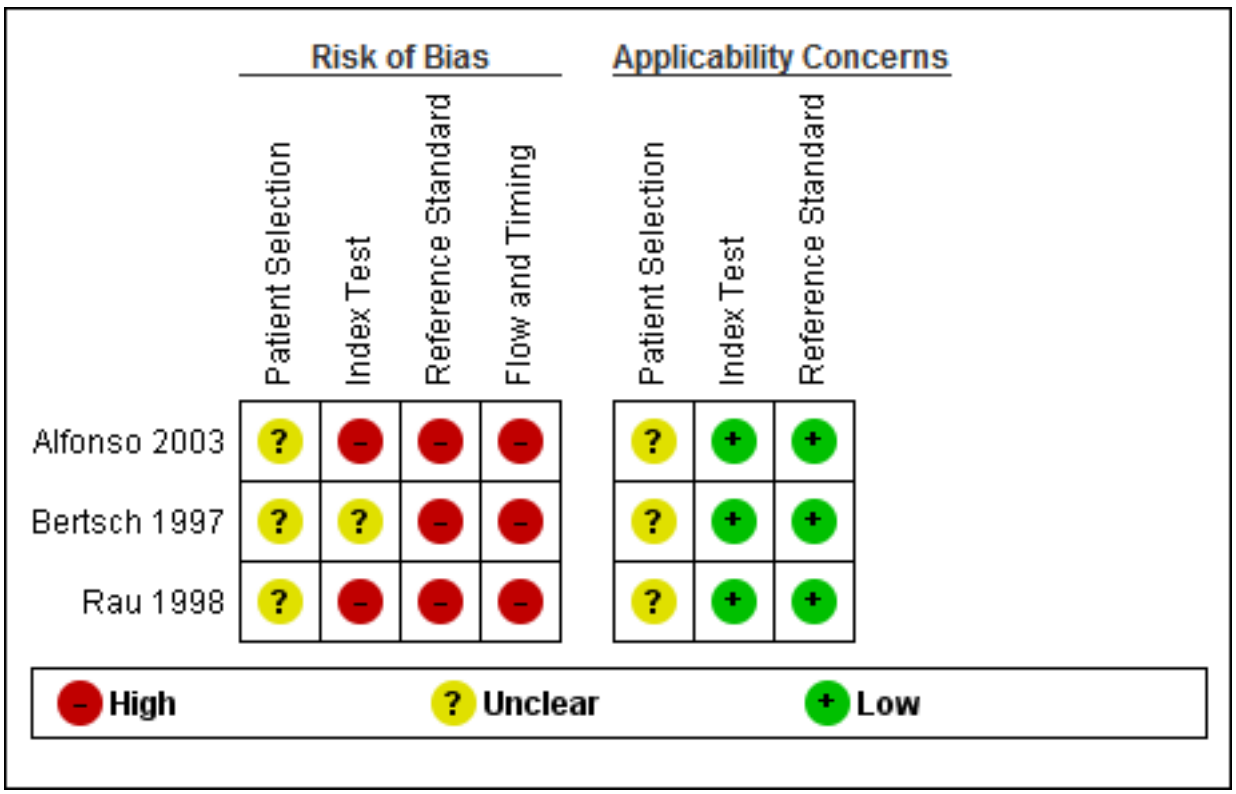


Figure 4. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



Participant selection

All studies were at unclear risk of bias in the participant selection domain and were also of unclear concern about applicability in this domain, because none of the included studies mentioned if participants were excluded inappropriately or whether a consecutive or random selection of participants was included.

Index test

Two studies were at high risk of bias in the index test domain, because the thresholds used were not prespecified; it was also unclear whether the index tests were interpreted without knowledge of the reference standard (Alfonso 2003; Rau 1998). One study had an unclear risk of bias, because it was unclear whether the index tests were interpreted without knowledge of the reference standard (Bertsch 1997). However, all studies were of low concern with regards to applicability since all studies reported the threshold at which the diagnosis was made.

Reference standard

All studies were at high risk of bias in the reference standard domain; in two studies the reference standard was CECT alone (Alfonso 2003; Bertsch 1997), and in the third study the reference standard was a combination of CT scan and laparotomy findings (Rau 1998). We considered all of the studies to be low concern with regards to applicability since they all used pancreatic or peripancreatic necrosis, or both as the target condition.

Flow and timing

All studies were at high risk of bias in this domain because the interval between the measurement of the index test and the reference standard in all studies was longer than 24 hours.

Findings

Since the studies reported the tests at different thresholds, we did not perform meta-analysis. The sensitivities and specificities and their 95% confidence intervals (CI) are visually represented in the forest plots and ROC space in Figure 5 and Figure 6. The sensitivities and specificities are summarised in Summary of findings. The median pre-test probability in the studies was 53.3%. The days indicate the number of days after admission that the measurements were made.

Figure 5. Forest plot of tests: 1 C-reactive protein (day 3) > 140 mg/L; 2 C-reactive protein (day not stated) > 200 mg/L; 3 C-reactive protein (day not stated) > 279 mg/L; 4 Procalcitonin (day 1) > 0.5 ng/mL; 5 Lactate dehydrogenase (day 5) > 290 U/L.

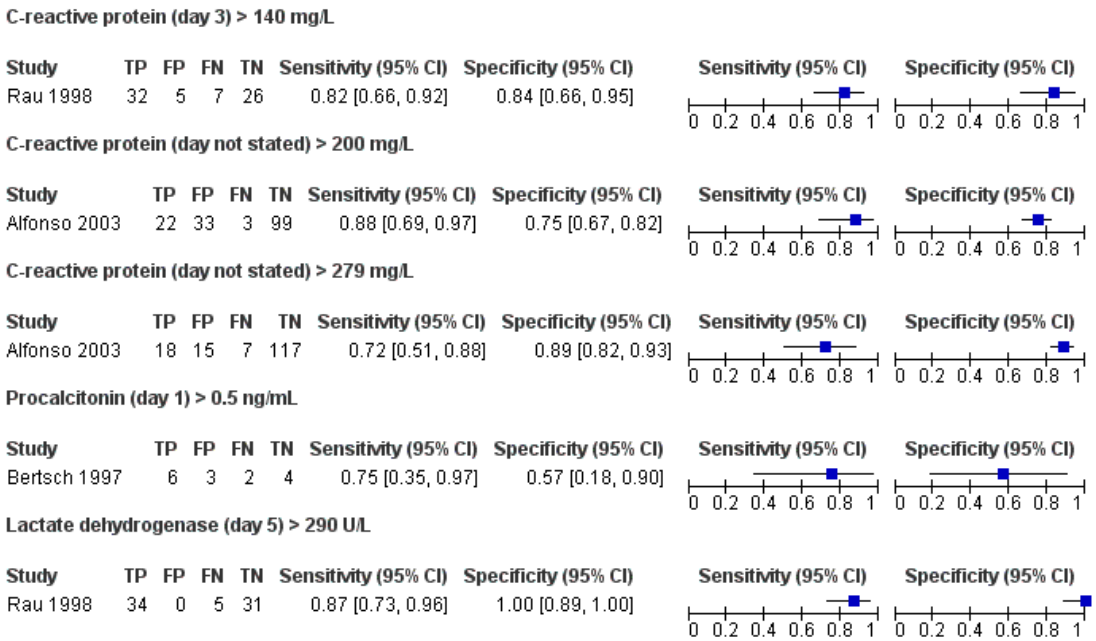
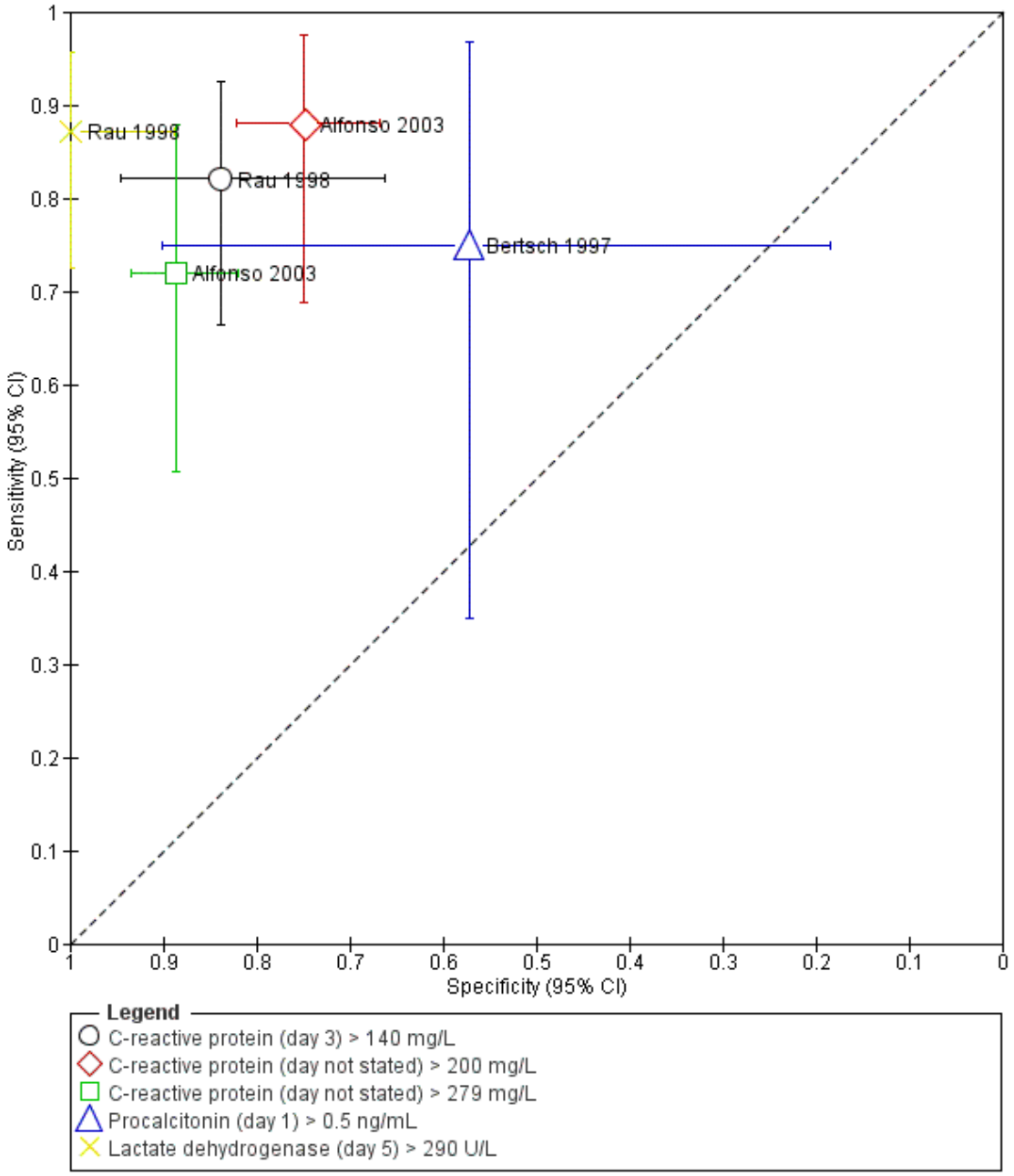


Figure 6. Summary ROC plot of tests: 1 C-reactive protein (day 3) > 140 mg/L; 2 C-reactive protein (day not stated) > 200 mg/L; 3 C-reactive protein (day not stated) > 279 mg/L; 4 Procalcitonin (day 1) > 0.5 ng/mL; 5 Lactate dehydrogenase (day 5) > 290 U/L.



C-reactive protein

Day 3: > 140 mg/L

One study including 70 participants reported the diagnostic accuracy of day 3 CRP at threshold > 140 mg/L (Rau 1998). The sensitivity and specificity of CRP at this threshold was 0.82 (95% CI 0.66 to 0.92) and 0.84 (95% CI 0.66 to 0.95), respectively. The positive and negative likelihood ratios were 5.08 (95% CI 2.25 to 11.50) and 0.21 (95% CI 0.11 to 0.43), respectively. At the pre-test probability of 53.3%, the post-test probabilities of pancreatic necrosis of positive and negative tests were 85.3% (95% CI 72.0% to 92.9%) and 19.7% (95% CI 10.9% to 32.7%), respectively.

Day not stated: > 200 mg/L

One study including 157 participants reported the diagnostic accuracy of CRP (day not stated) at threshold > 200 mg/L (Alfonso 2003). The sensitivity and specificity of CRP at this threshold was 0.88 (95% CI 0.69 to 0.97) and 0.75 (95% CI 0.67 to 0.82), respectively. The positive and negative likelihood ratios were 3.52 (95% CI 2.53 to 4.89) and 0.16 (95% CI 0.06 to 0.46), respectively. At the pre-test probability of 53.3%, the post-test probabilities of pancreatic necrosis of positive and negative tests were 80.1% (95% CI 74.3% to 84.8%) and 15.5% (95% CI 5.9% to 34.7%), respectively.

Day not stated: > 290 mg/L

One study including 157 participants reported the diagnostic accuracy of CRP (day not stated) at threshold > 290 mg/L (Alfonso 2003). The sensitivity and specificity of CRP at this threshold was 0.72 (95% CI 0.51 to 0.88) and 0.89 (95% CI 0.82 to 0.93), respectively. The positive and negative likelihood ratios were 6.34 (95% CI 3.71 to 10.82) and 0.32 (95% CI 0.17 to 0.59), respectively. At the pre-test probability of 53.3%, the post-test probabilities of pancreatic necrosis of positive and negative tests were 87.9% (95% CI 80.9% to 92.5%) and 26.5% (95% CI 16.1% to 40.4%), respectively.

Procalcitonin (day 1 > 0.5 ng/mL)

One study including 15 participants reported the diagnostic accuracy of day 1 procalcitonin at threshold > 0.5 ng/mL (Bertsch 1997). The sensitivity and specificity of procalcitonin at this threshold was 0.75 (95% CI 0.35 to 0.97) and 0.57 (95% CI 0.18 to 0.90), respectively. The positive and negative likelihood ratios were 55.79 (95% CI 3.64 to 856.23) and 0.13 (95% CI 0.06 to 0.29), respectively. At the pre-test probability of 53.3%, the post-test probabilities of pancreatic necrosis of positive and negative tests were 66.7% (95% CI 43.8% to 83.7%) and 33.3% (95% CI 11.4% to 66.1%), respectively.

Lactate dehydrogenase (day 5 > 290 U/L)

One study including 70 participants reported the diagnostic accuracy of day 5 LDH at threshold > 0.5 ng/mL (Rau 1998). The sensitivity and specificity of LDH at this threshold was 0.87 (95% CI 0.73 to 0.96) and 1.00 (95% CI 0.89 to 1.00), respectively. The positive and negative likelihood ratios were 1.75 (95% CI 0.68 to 4.50) and 0.44 (95% CI 0.11 to 1.71), respectively. At the pre-test probability of 53.3%, the post-test probabilities of pancreatic necrosis of positive and negative tests were 98.5% (95% CI 80.6% to 99.9%) and 12.8% (95% CI 6.1% to 24.9%), respectively.

Investigation of heterogeneity and reporting bias

We did not investigate heterogeneity because of the paucity of data. We did not assess reporting bias since all of the studies were full-text publications.

Summary of findings

Population	People with acute pancreatitis
Setting	Secondary care in various countries
Target condition	Acute pancreatic (or peripancreatic) necrosis
Reference standard	Radiology (contrast enhanced computed tomography scan) or surgery
Median prevalence of pancreatic leak	53.3%

Index test[1]	Sensitivity	Specificity	Study specific pre-test probability	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
C-reactive protein (day 3) > 140 mg/L	0.82 (95% CI 0.66 to 0.92)	0.84 (95% CI 0.66 to 0.95)	55.7%	85.3% (95% CI 72.0% to 92.9%)	19.7% (95% CI 10.9% to 32.7%)	1	70	High	Unclear	At the pre-test probability of 56%, out of 100 people with positive test, 85 people (95% CI 72 to 93) have pancreatic necrosis. At the same pre-test probability, out of 100 people with negative

									test, 20 people (95% CI 11 to 33) have pancreatic necrosis
C-reactive protein (day not stated) > 200 mg/L	0.88 (95% CI 0.69 to 0.97)	0.75 (95% CI 0.67 to 0.82)	15.9%	80.1% (95% CI 74.3% to 84.8%)	15.5% (95% CI 5.9% to 34.7%)	1	157	High	Unclear	At the pre-test probability of 16%, out of 100 people with positive test, 80 people (95% CI 74 to 85) have pancreatic necrosis. At the same pre-test probability, out of 100 people with negative test, 16 people (95% CI 6 to 35) have pancreatic necrosis
C-reactive protein (day not stated) > 279 mg/L	0.72 (95% CI 0.51 to 0.88)	0.89 (95% CI 0.82 to 0.93)	15.9%	87.9% (95% CI 80.9% to 92.5%)	26.5% (95% CI 16.1% to 40.4%)	1	157	High	Unclear	At the pre-test probability of 16%, out of 100 people with positive test, 88 people (95% CI 81 to 93) have pancreatic necrosis. At the

									same pre-test probability, out of 100 people with negative test, 27 people (95% CI 16 to 40) have pancreatic necrosis
Procalcitonin (day 1) > 0.5 ng/mL	0.75 (95% CI 0.35 to 0.97)	0.57 (95% CI 0.18 to 0.90)	53.3%	66.7% (95% CI 43.8% to 83.7%)	33.3% (95% CI 11.4% to 66.1%)	1	15	High	Unclear	At the pre-test probability of 56%, out of 100 people with positive test, 67 people (95% CI 44 to 84) have pancreatic necrosis. At the same pre-test probability, out of 100 people with negative test, 33 people (95% CI 11 to 66) have pancreatic necrosis
Lactate dehydrogenase (day 5) > 290 U/L	0.87 (95% CI 0.73 to 0.96)	1.00 (95% CI 0.89 to 1.00)	55.7%	98.5% (95% CI 80.6% to 99.9%)	12.8% (95% CI 6.1% to 24.9%)	1	70	High	Unclear	At the median pre-test probability of 56%, out of 100 people with positive test, 99 people

	(95% CI 81 to 100) have pancreatic necrosis. At the same pre-test probability, out of 100 people with negative test, 13 people (95% CI 6 to 25) have pancreatic necrosis
Intepretation: Lactate dehydrogenase (day 5) > 290 U/L appears to perform best, missing the diagnosis in 13 (95% CI 4 to 27) out of 100 people with acute pancreatic necrosis and overdiagnosing in 0 (95% CI 0 to 11) out of 100 people without acute pancreatic necrosis. However, the study is at high risk of bias, and neither the day on which the measurement was made nor the threshold for positive diagnosis was determined in advance, which is likely to increase the test performance incorrectly. Consequently, the results are highly unreliable	

[1]The number following 'day' indicates the number of days after admission that the index test was performed. The information that follows this indicates the threshold.

2 The post-test probabilities were calculated at the median pre-test probability.

CI: confidence interval

DISCUSSION

Summary of main results

Three studies including 242 participants met the inclusion criteria for this review and assessed the diagnostic accuracy of the index tests in participants with established acute pancreatitis (Alfonso 2003; Bertsch 1997; Rau 1998). These three studies reported the diagnostic test accuracy of the index tests at different thresholds and different time points. C-reactive protein was assessed at three different time points (day 3 and not known for two thresholds), and the point estimate of the sensitivities ranged from 0.72 to 0.88, while the point estimate of the specificities ranged from 0.75 to 0.89. The confidence intervals of the sensitivities ranged from 0.51 to 0.97, and those of the specificities ranged from 0.66 to 0.93. Procalcitonin was assessed on day 1 using a threshold of 0.5 ng/mL, and LDH was assessed on day 5 using a threshold of 290 U/L. The sensitivity and specificity of procalcitonin were 0.75 (95% CI 0.35 to 0.97) and 0.57 (95% CI 0.18 to 0.90), respectively, while the sensitivity and specificity of LDH were 0.87 (95% CI 0.73 to 0.96) and 1.00 (95% CI 0.89 to 1.00), respectively.

Avoiding CECT may be beneficial to the patient, as it avoids unnecessary radiation exposure, particularly if the patient has undergone CECT for the diagnosis of acute pancreatitis. It also benefits the healthcare funder, as it can decrease costs thereby allowing limited resources to be used more appropriately. In addition, patients with acute gallstone pancreatitis may be able to undergo early laparoscopic cholecystectomy, if the patient is stable and acute necrotising pancreatitis can be ruled out early. A triage test to avoid CECT is thus useful. However, such a triage test should have high sensitivity with at least a reasonable specificity. If it has a low specificity, it is not a useful triage test even if it has a very high sensitivity, since one might skip the test altogether and perform CECT directly. The sensitivity of the tests varied and was moderate, with mean sensitivities between 0.75 and 0.89 for all of the tests. This means that these tests can miss about 11% to 25% of people with pancreatic necrosis. To miss 11% to 25% of people with pancreatic necrosis is unacceptable clinically, as patients can be discharged or denied further investigations or intensive treatment. Overall, none of the tests assessed in this review was sufficiently accurate to suggest that they may be useful in clinical practice. In clinical practice, a rising trend is usually considered important rather than a single value, although very high values of CRP or LDH along with organ failure will raise the suspicion of necrotising pancreatitis. However, we were unable to determine the accuracy of a rising trend in CRP or LDH, as none of the studies reported this information.

Strengths and weaknesses of the review

Strengths

One of the main strengths of this review was that the literature was searched thoroughly, without any publication or language restrictions. We did not use any diagnostic test accuracy filters in our literature search because such filters could have led to the 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 (OK and KSG) independently searched the references located by the search to identify relevant studies, screened the full-text papers against the inclusion criteria, and extracted data. Data extractions by two review authors potentially reduced the chance of errors related to data extraction by a single review author (Buscemi 2006). Another strength of this review was 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. Firstly, the studies included in the review had several methodological deficiencies. The major methodological deficiency was that the two studies that contributed the most participants to this review did not use a prespecified threshold (Alfonso 2003; Rau 1998). In one of these studies it was unclear how the day on which the measurement was performed was determined (Alfonso 2003), while in the other study, the day of measurement was determined by selecting the day (along with the threshold) on which the test had maximum accuracy (Rau 1998). This is likely to overestimate the diagnostic accuracy. In addition, none of the studies reported whether the index tests and reference standards were interpreted independently of each other. If they were not interpreted independently of each other, the accuracy of the tests would have been overestimated. None of the studies reported whether all the participants were included in the study. Exclusion of participants with borderline values close to the threshold used or participants with other causes of elevation of these tests will overestimate the diagnostic test accuracy of these tests.

Secondly, the sample sizes in the studies were small, resulting in wide confidence intervals. It was not possible to perform a meta-analysis to improve the precision since the studies reported the tests on different days of admission using different thresholds. Additionally, the measurement of CRP on different days using different thresholds for diagnosis of pancreatic necrosis made it impossible for us to explore whether the results could be replicated in another group of participants.

Comparison with other reviews

We did not identify any other systematic reviews on the topic.

Applicability of findings to the review question

Generalisability of the results

The studies did not restrict the participants to specific aetiologies of acute pancreatitis, therefore the findings of this review are applicable to all aetiologies of acute pancreatitis. Although the studies did not specify the restriction of participants to acute severe pancreatitis, it is likely that two studies used these tests in participants with acute severe pancreatitis, since more than 50% of participants in these studies had pancreatic necrosis (Bertsch 1997; Rau 1998). These two studies reported procalcitonin and LDH along with CRP > 140 mg/L (Bertsch 1997; Rau 1998). Consequently, the results of these two studies are applicable to people with severe pancreatitis, while the results from the third study, which reported CRP > 200 mg/L and CRP > 290 mg/L (Alfonso 2003), are applicable to all people with acute pancreatitis.

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. Such a test needs to be highly sensitive with at least reasonable specificity, so that it is possible to rule out pancreatic necrosis, which will avoid further testing. The confidence intervals of post-test probability of a negative test ranged from 1% to 66.1% when the pre-test probability was 15.9%, and from 5.9% to 66.1% when the pre-test probability was 53.3%. Adding to the uncertainty due to random errors resulting from small sample sizes, there were many systematic errors, resulting in further uncertainty. Given these uncertainties, the role of these tests in people with acute pancreatitis is not clear.

AUTHORS' CONCLUSIONS

Implications for practice

Because of the paucity of data and methodological deficiencies in the studies, it was not possible to arrive at any conclusions regarding the diagnostic test accuracy of C-reactive protein, procalcitonin, and lactate dehydrogenase.

Implications for research

Further well-designed diagnostic test accuracy studies with a prespecified index test threshold of C-reactive protein, procalcitonin, and lactate dehydrogenase, as well as appropriate follow-up (for at least two weeks to ensure that the person does not have pancreatic necrosis; early scans may not indicate pancreatic necrosis) and a clearly defined reference standard (of surgical or radiological confirmation of pancreatic necrosis) are important to determine the diagnostic accuracy of C-reactive protein, procalcitonin, and lactate dehydrogenase reliably.

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REFERENCES

References to studies included in this review

Alfonso 2003 *{published and unpublished data}*
Alfonso V, Gomez F, Lopez A, Moreno-Osset E, del Valle R, Anton MD, et al. C-reactive protein level in the detection of necrosis in acute pancreatitis. *Gastroenterologia y Hepatologia* 2003;**26**(5):288–93.

Bertsch 1997 *{published data only}*
Bertsch T, Richter A, Hofheinz H, Bohm C, Hartel M, Aufenanger J. Procalcitonin - a new marker for the acute-phase reaction in acute pancreatitis. *Langenbecks Archiv fur Chirurgie* 1997;**382**(6):367–72.

Rau 1998 *{published data only}*
* Rau B, Cebulla M, Uhl W, Schoenberg MH, Beger HG. The clinical value of human pancreas-specific protein procarboxypeptidase B as an indicator of necrosis in acute pancreatitis : Comparison to CRP and LDH. *Pancreas* 1998;**17**(2):134–9.
Rau B, Steinbach G, Baumgart K, Gansauge F, Grunert A, Beger HG. Serum amyloid A versus C-reactive protein in acute pancreatitis: Clinical value of an alternative acute-phase reactant. *Critical Care Medicine* 2000;**28**(3):736–42.
Rau B, Steinbach G, Gansauge F, Mayer JM, Grunert A, Beger HG. The potential role of procalcitonin and interleukin 8 in the prediction of infected necrosis in acute pancreatitis. *Gut* 1997;**41**(6):832–40.

References to studies excluded from this review

Abishek 2014 *{published data only}*
Abishek V, Babu V, Muthukumaran, Ramkumar, Balamurali, Murali A, et al. Role of C-reactive protein in

predicting severity of acute pancreatitis. *Indian Journal of Gastroenterology* 2014;**33**(Suppl 1):A92.

Aggelopoulos 1996 *{published data only}*
Aggelopoulos C, Aloizos S, Touliatou A, Papanastasopoulos C, Tsaglis B, Papanastasopoulous B. APACHE III and CRP as early predictive indexes in acute pancreatitis. *HPB Surgery* 1996;**9**(Supp 2):121. P200]

Ammori 2003 *{published data only}*
Ammori BJ, Becker KL, Kite P, Snider RH, Nylen ES, White JC, et al. Calcitonin precursors in the prediction of severity of acute pancreatitis on the day of admission. *British Journal of Surgery* 2003;**90**(2):197–204.

Appasani 2011a *{published data only}*
Appasani S, Thandassery RB, Dixit P, Yadav TD, Attri SV, Rana SV, et al. Serum ADA levels in predicting the severity in acute pancreatitis. *Indian Journal of Gastroenterology* 2011;**1**:A87.

Appasani 2011b *{published data only}*
Appasani S, Thandassery RB, Varma N, Yadav TD, Attri SV, Rana SV, et al. D-dimer as a single marker for early prediction of severity, necrosis, organ failure and mortality in acute pancreatitis. *Indian Journal of Gastroenterology* 2011;**1**:A12.

Appasani 2012 *{published data only}*
Appasani S, Rana S, Babu Thandassery R, Basha J, Yadav TD, Attri SV, et al. Serum ADA levels in predicting the severity in acute pancreatitis. *Journal of Gastroenterology and Hepatology* 2012;**27**:374–5.

Bajec 2010 *{published data only}*
Bajec D, Gunjic D, Radenkovic D, Gregoric P, Karadzic B, Pejovic I. Evaluation of Glasgow and APACHE II scores and CRP in prediction of severity of acute pancreatitis. *Pancreatology* 2010;**10**(2-3):349.

Bapat 1986 *{published data only}*
Bapat RD, Nazareth HM, Kulkarni AG, Shah AB. Prognostic markers in acute pancreatitis - a prospective study. *Indian Journal of Gastroenterology* 1986;**5**(2):113–5.

Barauskas 2004 *{published data only}*
Barauskas G, Svagzdys S, Maleckas A. C-reactive protein in early prediction of pancreatic necrosis. *Medicina* 2004;**40** (2):135–40.

Bassi 1994 *{published data only}*
Bassi C. Infected pancreatic necrosis. *International Journal of Pancreatology* 1994;**16**(1):1–10.

Beger 1989 *{published data only}*
Beger HG, Buchler M. C-reactive protein and acute pancreatitis. *British Journal of Surgery* 1989;**76**(8):877.

Berry 1982 *{published data only}*
Berry AR, Taylor TV, Davies GC. Diagnostic tests and prognostic indicators in acute pancreatitis. *Journal of the Royal College of Surgeons of Edinburgh* 1982;**27**(6):345–52.

Bezmarevic 2012a *{published data only}*
Bezmarevic M, Kostic Z, Jovanovic M, Mickovic S, Mirkovic D, Soldatovic I, et al. Procalcitonin and BISAP score versus C-reactive protein and APACHE II score in early assessment of severity and outcome of acute pancreatitis. *Vojnosanitetski Pregled* 2012;**69**(5):425–31.

Bezmarevic 2012b *{published data only}*
Bezmarevic M, Mirkovic D, Mickovic S, Perisic N. BISAP score and procalcitonin versus APACHE II score and C-reactive protein in early assessment of the severity and outcome of acute pancreatitis. *Pancreatology* 2012;**12**(6): 534.

Bezmarevic 2012c *{published data only}*
Bezmarevic M, Mirkovic D, Soldatovic I, Stamenkovic D, Mitrovic N, Perisic N, et al. Correlation between procalcitonin and intra-abdominal pressure and their role in prediction of the severity of acute pancreatitis. *Pancreatology* 2012;**12**(4):337–43.

Bihari 2004 *{published data only}*
Bihari D. Monitoring procalcitonin is of value in acute pancreatitis. *BMJ* 2004;**329**(7459):232.

Blum 2001 *{published data only}*
Blum T, Maisonneuve P, Lowenfels AB, Lankisch PG. Fatal outcome in acute pancreatitis: Its occurrence and early prediction. *Pancreatology* 2001;**1**(3):237–41.

Boskovic 2014 *{published data only}*
Boskovic A, Pasic S, Soldatovic I, Milinic N, Stankovic I. The role of D-dimer in prediction of the course and outcome in paediatric acute pancreatitis. *Pancreatology* 2014;**14**(5):330–4.

Brailski 1975 *{published data only}*
Brailski KH. Acute pancreatitis (etiology, pathogenesis and pathobiochemistry). *Vutreshni Bolesti* 1975;**14**(4):1–11.

Brand 2014 *{published data only}*
Brand M, Gotz A, Zeman F, Behrens G, Leitzmann M, Brunnler T, et al. Acute necrotizing pancreatitis: Laboratory, clinical, and imaging findings as predictors of patient outcome. *American Journal of Roentgenology* 2014; **202**(6):1215–31.

Brisinda 1999 *{published data only}*
Brisinda G, Maria G, Ferrante A, Civello IM. Evaluation of prognostic factors in patients with acute pancreatitis. *Hepato-Gastroenterology* 1999;**46**(27):1990–7.

Buchler 1986a *{published data only}*
Buchler M, Malfertheiner P, Schoetensack C, Uhl W, Beger HG. Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis - results of a prospective clinical-study. *International Journal of Pancreatology* 1986;**1**(3-4):227–35.

Buchler 1986b *{published data only}*
Buchler M, Malfertheiner P, Schoetensack C, Uhl W, Scherbaum W, Beger HG. Value of biochemical and imaging procedures for the diagnosis and prognosis of acute pancreatitis - results of a prospective clinical study. *Zeitschrift Fur Gastroenterologie* 1986;**24**(2):100–9.

Buchler 1986c *{published data only}*
Buchler M, Malfertheiner P, Uhl W, Beger HG. A new staging system in patients with acute-pancreatitis using

serum alpha-2-macroglobulin and C-reactive protein. *Gastroenterology* 1986;**90**(5):1361.

Buchler 1987 ***{published data only}***
Buchler M, Malfertheiner P, Uhl W, Beger HG. C-reactive protein as a marker of inflammation and necrosis in gastroenterology. *Medizinische Klinik* 1987;**82**(5):180–5.

Buchler 1991 ***{published data only}***
Buchler M. Objectification of the severity of acute-pancreatitis. *Hepato-Gastroenterology* 1991;**38**(2):101–8.

Bulbuller 2006 ***{published data only}***
Bulbuller N, Dogru O, Ayten R, Akbulut H, Ilhan YS, Cetinkaya Z. Procalcitonin is a predictive marker for severe acute pancreatitis. *Ulusal Travma ve Acil Cerrahi Dergisi [Turkish Journal of Trauma & Emergency Surgery: TJTES]* 2006;**12**(2):115–20.

Cai 2014 ***{published data only}***
Cai YY, Ee J, Liew YX, Lee WN, Chlebicki MP, Goh YC, et al. A procalcitonin-based guideline promotes shorter duration of antibiotic use safely in acute pancreatitis. *Journal of Infection* 2014;**69**(4):412–5.

Cardoso 2011 ***{published data only}***
Cardoso F, Ricardo L, Oliveira A, Rodrigues C, Horta D, Figueiredo A, et al. Value of C-reactive protein in predicting organ failure, complications and mortality in acute pancreatitis. *Pancreas* 2011;**40**(8):1315.

Cardoso 2013 ***{published data only}***
Cardoso FS, Ricardo LB, Oliveira AM, Canena JM, Horta DV, Papoila AL, et al. C-reactive protein prognostic accuracy in acute pancreatitis: Timing of measurement and cutoff points. *European Journal of Gastroenterology & Hepatology* 2013;**25**(7):784–9.

Cardoso 2015 ***{published data only}***
Cardoso FS, Ricardo L, Gondar P, Deus JR, Horta D. C-reactive protein may influence decisively the prescription of prophylactic antibiotics in acute pancreatitis: a population-based cohort study. *Pancreas* 2015;**44**(3):404–8.

Chen 1992 ***{published data only}***
Chen CC, Wang SS, Chao Y, Lu CW, Lee SD, Tsal YT, et al. C-reactive protein and lactate-dehydrogenase isoenzymes in the assessment of the prognosis of acute-pancreatitis. *Journal of Gastroenterology and Hepatology* 1992;**7**(4):363–6.

Chen 2004 ***{published data only}***
Chen CC. Serum markers in the early assessment of severity of acute pancreatitis: Which is the most useful?. *Journal of the Chinese Medical Association: JCMA* 2004;**67**(9):439–41.

Chen 2012 ***{published data only}***
Chen D, Lu S, Xu F. Study for the value of serum lactate dehydrogenase in predicting multiple organ dysfunction syndrome caused by acute pancreatitis. *Chinese Journal of Critical Care Medicine* 2012;**32**(4):349–51.

Choi 2012 ***{published data only}***
Choi JS, Cho JH, Jeon TJ, Kim HM, Kim YJ, Han KJ, et al. Prognostic value of procalcitonin, CRP, BISAP, RANSON'S, APACHE II and CTSI scores according to the various etiologies of acute pancreatitis. *Pancreas* 2012;**41**(8):1353.

Choi 2013 ***{published data only}***
Choi JS, Cho JH, Jeon TJ, Kim HM, Kim YJ, Han KJ, et al. Prognostic value of procalcitonin, CRP, BISAP RANSON'S, APACHE II and CTSI scores according to the various etiologies of acute pancreatitis. *Pancreatology* 2013; **13**(2):e20.

Chooklin 2010 ***{published data only}***
Chooklin S, Lyba M, Bihalskyy I. Pancreatic necrosis markers in severe acute pancreatitis. *European Journal of Clinical Investigation* 2010;**40**:14.

Choudhary 2012 ***{published data only}***
Choudhary RK, Choudhary M. A useful diagnostic and prognostic tool for acute appendicitis and acute pancreatitis. *BMJ* 2012;**344**:e1404; author reply e9.

Cooper 1981 ***{published data only}***
Cooper MJ, Whicher JT, Walters G, Williamson RCN. Predictive value of C-reactive protein and complement in acute-pancreatitis. *Gastroenterologie Clinique Et Biologique* 1981;**5**(10):920–1.

Cravo 1988 ***{published data only}***
Cravo M, Santos P, Marques A, Deus J, Santos ML, Geada H, et al. Antiproteases and C-reactive protein in the early assessment of severity of acute-pancreatitis. *Digestion* 1988; **40**(2):74.

d'Eril 2000 ***{published data only}***
d'Eril GM, Merlini G, Finazzi S, Bosoni T, Barakat B, Pezzilli R. Procalcitonin is not a reliable marker for the assessment of severity in acute pancreatitis without infectious complications. *Clinical Chemistry* 2000;**46**(3): 428–30.

Dambrauskas 2010 ***{published data only}***
Dambrauskas Z, Gulbinas A, Pundzius J, Barauskas G. Value of the different prognostic systems and biological markers for predicting severity and progression of acute pancreatitis. *Scandinavian Journal of Gastroenterology* 2010; **45**(7-8):959–70.

Dammann 1979 ***{published data only}***
Dammann HG, von Wichert P, Schreiber HW. Prognostic indices in acute pancreatitis. *Zentralblatt Fur Chirurgie* 1979;**104**(6):397–404.

Daniel 2010 ***{published data only}***
Daniel P, Lesniowski B, Mokrowiecka A, Jasinska A, Pietruczuk M, Malecka-Panas E. Circulating levels of Visfatin, Resistin and pro-inflammatory cytokine Interleukin-8 in acute pancreatitis. *Pancreatology* 2010;**10** (4):477–82.

de Beaux 1996 ***{published data only}***
de Beaux AC, Goldie AS, Ross JA, Carter DC, Fearon KC. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. *British Journal of Surgery* 1996;**83**(3):349–53.

De la Pena 1991 ***{published data only}***
De la Pena J, De las Heras G, Galo Peralta F, Casafont F, Pons Romero F. Prospective study of the prognostic value

of C reactive protein, alpha 1-antitrypsin and alpha 1-acid glycoprotein in acute pancreatitis. *Revista Espanola de Enfermedades Digestivas* 1991;**79**(5):337–40.

Del Prete 2001 ***{published data only}***
Del Prete M, Castiglia D, Meli M, Perri S, Nicita A, Dalla Torre A, et al. Prognostic value of C reactive protein in acute pancreatitis. *Chirurgia Italiana* 2001;**53**(1):33–8.

Digalakis 2009 ***{published data only}***
Digalakis MK, Katsoulis IE, Biliri K, Themeli-Digalaki K. Serum profiles of C-reactive protein, interleukin-8, and tumor necrosis factor-alpha in patients with acute pancreatitis. *HPB Surgery* 2009;**2009**:878490.

Duarte-Rojo 2009 ***{published data only}***
Duarte-Rojo A, Suazo-Barahona J, Ramirez-Iglesias MT, Uscanga LF, Robles-Diaz G. Time frames for analysis of inflammatory mediators in acute pancreatitis: Improving admission triage. *Digestive Diseases and Sciences* 2009;**54**(10):2282–7.

Economou 1997 ***{published data only}***
Economou MS. The potential role of procalcitonin and interleukin-8 in the prediction of infected necrosis in acute pancreatitis. *Hellenic Journal of Gastroenterology* 1997;**10**(3):248–9.

Fan 1994 ***{published data only}***
Fan ST. Early recognition of severe acute-pancreatitis. *Journal of Gastroenterology and Hepatology* 1994;**9**(3):289–90.

Ferguson 1990 ***{published data only}***
Ferguson CM, Bradley EL. Can markers for pancreatic necrosis be used as indicators for surgery?. *American Journal of Surgery* 1990;**160**(5):459–61.

Fisic 2013 ***{published data only}***
Fisic E, Poropat G, Bilic-Zulle L, Licul V, Milic S, Stimac D. The role of IL-6, 8, and 10, sTNFr, CRP, and pancreatic elastase in the prediction of systemic complications in patients with acute pancreatitis. *Gastroenterology Research and Practice* 2013;**2013**:282645.

Folch-Puy 2007 ***{published data only}***
Folch-Puy E. Markers of severity in acute pancreatitis. *Medicina Clinica* 2007;**128**(11):417–8.

Frasquet 2003 ***{published data only}***
Frasquet J, Saez J, Trigo C, Martinez J, Such J, Perez-Mateo M. Early measurement of procalcitonin does not predict severity in patients with acute pancreatitis. *British Journal of Surgery* 2003;**90**(9):1129–30.

Frossard 2001 ***{published data only}***
Frossard JL, Hadengue A, Pastor CM. New serum markers for the detection of severe acute pancreatitis in humans. *American Journal of Respiratory and Critical Care Medicine* 2001;**164**(1):162–70.

Gao 2014 ***{published data only}***
Gao K, Zhang LJ, Wang GY, Li J, Zhang H. Role of serum IL-6, IL-8 and procalcitonin in diagnosis of secondary infection in severe acute pancreatitis. *World Chinese Journal of Digestology* 2014;**22**(16):2343–6.

Garcia-Cantu 2004 ***{published data only}***
Garcia-Cantu DA, Gonzalez-Gonzalez JA, Dominguez NR, Perez DOR, Maldonado-Garza HJJ. A simple score plus serum C-reactive protein at admission increase the positive predictive value for organ failure in severe acute pancreatitis. A prospective trial. *Gastroenterology* 2004;**126**(4):A227.

Garcia Lozano 1992 ***{published data only}***
Garcia Lozano A, Garcia-Villanova J, Martin L, Martinez D, Mansilla D, Rodenas V, et al. The prediction of the severity of acute pancreatitis by C-reactive protein. *Revista Espanola de Enfermedades Digestivas* 1992;**82**(4):231–3.

Gelfand 2005 ***{published data only}***
Gelfand B, Filimonov M, Burnevich S, Brazhnik T, Sergeyeva N. The procalcitonin test in the evaluation of clinical severity in patients with acute pancreatitis. *Critical Care* 2005;**9**(Supp 1):P171.

Geng 2014 ***{published data only}***
Geng P, Ding Y. Advances in studies on procalcitonin and acute pancreatitis. *Chinese Journal of Gastroenterology* 2014;**19**(7):439–41.

Gluskina 1967 ***{published data only}***
Gluskina VM. On the differential diagnosis of edema and hemorrhagic necrosis of the pancreas. *Vestnik Khirurgii Imeni I. I. Grekova* 1967;**99**(9):69–72.

Gosling 1992 ***{published data only}***
Gosling P, Shearman CP. Can we predict disease severity in acute-pancreatitis. *Annals of Clinical Biochemistry* 1992;**29**:9–10.

Gross 1990 ***{published data only}***
Gross V, Scholmerich J, Leser HG, Salm R, Lausen M, Ruckauer K, et al. Granulocyte elastase in assessment of severity of acute-pancreatitis - comparison with acute-phase proteins C-reactive protein, alpha-1-antitrypsin, and protease inhibitor alpha-2-macroglobulin. *Digestive Diseases and Sciences* 1990;**35**(1):97–105.

Guenther 2010 ***{published data only}***
Guenther A, Aghdassi AA, Nitsche CJ, Schulte J, Struck J, Lerch MM, et al. Comparison of peroxiredoxin-4 with CRP as a severity marker for acute pancreatitis. *Pancreatology* 2010;**10**(2-3):345.

Gurda-Duda 2008 ***{published data only}***
Gurda-Duda A, Kusnierz-Cabala B, Nowak W, Naskalski JW, Kulig J. Assessment of the prognostic value of certain acute-phase proteins and procalcitonin in the prognosis of acute pancreatitis. *Pancreas* 2008;**37**(4):449–53.

Gurleyik 2004 ***{published data only}***
Gurleyik G, Cirpici OZ, Aktekin A, Saglam A. The value of Ranson and APACHE II scoring systems, and serum levels of interleukin-6 and C-reactive protein in the early diagnosis of the severity of acute pancreatitis. *Ulusal Travma Ve Acil Cerrahi Dergisi* 2004;**10**(2):83–8.

Gurleyik 2005 ***{published data only}***
Gurleyik G, Emir S, Kilicoglu G, Arman A, Saglam A. Computed tomography severity index, APACHE II score,

and serum CRP concentration for predicting the severity of acute pancreatitis. *Journal of the Pancreas* 2005;**6**(6):562–7.

Gvozdenovic 2001 ***{published data only}***
Gvozdenovic M, Lausevic Z, Ignjatovic S, Bukumirovic V. Significance of C-reactive protein in the treatment of acute necrotizing pancreatitis. *Acta Chirurgica Iugoslavica* 2001; **48**(3):29–34.

Hamalainen 2002 ***{published data only}***
Hamalainen MT, Gronroos P, Gronroos JM. Do normal leucocyte count and C-reactive protein on admission to hospital exclude a life-threatening attack of acute pancreatitis?. *Scandinavian Journal of Surgery* 2002;**91**(Part 4):353–6.

Han 2011 ***{published data only}***
Han L, Lu S. Early predictive value of lactate dehydrogenase, serum creatinine and C-reactive protein in severe acute pancreatitis. *Chinese Journal of Critical Care Medicine* 2011; **31**(Part 12):1058–61.

Hjalmarsson 2009 ***{published data only}***
Hjalmarsson C, Stenflo J, Borgstrom A. Activated protein C-protein C inhibitor complex, activation peptide of carboxypeptidase B and C-reactive protein as predictors of severe acute pancreatitis. *Pancreatology* 2009;**9**(5):700–7.

Huang 2013 ***{published data only}***
Huang HL, Nie X, Cai B, Tang JT, He Y, Miao Q, et al. Procalcitonin levels predict acute kidney injury and prognosis in acute pancreatitis: a prospective study. *PLoS ONE* 2013;**8**(12):e82250.

Huang 2015 ***{published data only}***
Huang J, Wu ZW, Lu SQ, Shen JQ, Kong XM, Shen YP. Soluble B7-H2 as a novel marker in early evaluation of the severity of acute pancreatitis. *Labmedicine* 2015;**46**(2): 109–17.

Imamura 2002a ***{published data only}***
Imamura T, Tanaka S, Yoshida H. Significance of measurement of high-sensitivity C-reactive protein in acute pancreatitis. *Journal of Gastroenterology* 2002;**37**(Part 11): 935–8.

Imamura 2002b ***{published data only}***
Imamura T, Tanaka S, Yoshida H, Kitamura K, Takahashi A, Ikegami A, et al. Clinical significance of measurement of high-sensitivity C-reactive protein in acute pancreatitis. *Gastroenterology* 2002;**122**(4):A368.

Inagaki 1997 ***{published data only}***
Inagaki T, Hoshino M, Hayakawa T, Ohara H, Yamada T, Yamada H, et al. Interleukin-6 is a useful marker for early prediction of the severity of acute pancreatitis. *Pancreas* 1997;**14**(1):1–8.

Isenmann 1993 ***{published data only}***
Isenmann R, Buchler M, Uhl W, Malfertheiner P, Martini M, Beger HG. Pancreatic necrosis: An early finding in severe acute pancreatitis. *Pancreas* 1993;**8**(3):358–61.

Isogai 1998 ***{published data only}***
Isogai M, Yamaguchi A, Hori A, Kaneoka Y. LDH to AST ratio in biliary pancreatitis - a possible indicator of pancreatic necrosis: preliminary results. *American Journal of Gastroenterology* 1998;**93**(3):363–7.

Jia 2015 ***{published data only}***
Jia R, Tang M, Qiu L, Sun R, Cheng L, Ma X, et al. Increased interleukin-23/17 axis and C-reactive protein are associated with severity of acute pancreatitis in patients. *Pancreas* 2015;**44**(2):321–5.

Jiang 2004 ***{published data only}***
Jiang CF, Shiau YC, Ng KW, Tan SW. Serum interleukin-6, tumor necrosis factor alpha and C-reactive protein in early prediction of severity of acute pancreatitis. *Journal of the Chinese Medical Association* 2004;**67**(9):442–6.

Jimenez 2015 ***{published data only}***
Jimenez E, Moreno S, De Guadiana LG, Pedregosa J, Jimenez R, Rebollo S, et al. Procalcitonin for predicting severity of acute pancreatitis. *Clinical Chemistry and Laboratory Medicine* 2015;**53**:S941.

Jimin 2015 ***{published data only}***
Jimin Z, Jian Z, Juncha G. Early evaluations of BISAP plus C-reactive protein in predicting the severity of acute pancreatitis. *Zhonghua Yi Xue za Zhi* 2015;**95**(12):925–8.

Johnson 2003 ***{published data only}***
Johnson CD. Early severity indexes in acute pancreatitis. *Acta Gastro-Enterologica Belgica* 2003;**66**(2):174–6.

Kaiyasah 2013 ***{published data only}***
Kaiyasah H, Alozaibi L, Anwar S, Al-Jufairi F, Naim R. Can serum procalcitonin be a reliable single bio-marker in predicting the severity of acute pancreatitis?. *Journal of Gastroenterology and Hepatology* 2013;**28**:681.

Kaya 2007 ***{published data only}***
Kaya E, Dervisoglu A, Polat C. Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. *World Journal of Gastroenterology* 2007;**13**(22): 3090–4.

Kazda 2002 ***{published data only}***
Kazda A, Brodska H, Valenta J, Uhrova I, Hendl J, Belohlavek J, et al. Procalcitonin in acute pancreatitis and in septic states. *Klinicka Biochemie a Metabolismus* 2002;**10** (1):32–7.

Khanna 2013 ***{published data only}***
Khanna AK, Meher S, Prakash S, Tiwary SK, Singh U, Srivastava A, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE II, CTSI scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. HPB Surgery 2013 Sep 24 [Epub ahead of print]:32–7. [DOI: 10.1155/2013/367581]

Khvatova 1973 ***{published data only}***
Khvatova EA. Role of certain enzymatic systems in different forms of acute pancreatitis. *Klinicheskaia Khirurgiia* 1973; **2**:48–53.

Khvatova 1977 ***{published data only}***
Khvatova EA. Value of thermal fractionation of lactate dehydrogenase and the protein composition of the blood in

the differential diagnosis of the phases of acute pancreatitis. *Vestnik Khirurgii Imeni I. I. Grekova* 1977;**118**(1):34–7.

Kibar 2016 ***{published data only}***
Kibar YI, Albayrak F, Arabul M, Dursun H, Albayrak Y, Ozturk Y. Resistin: New serum marker for predicting severity of acute pancreatitis. *Journal of International Medical Research* 2016;**44**(2):328–37.

Kim 2013a ***{published data only}***
Kim BG, Noh MH, Ryu CH, Nam HS, Woo SM, Ryu SH, et al. A comparison of the BISAP score and serum procalcitonin for predicting the severity of acute pancreatitis. *Korean Journal of Internal Medicine* 2013;**28**(3):322–9.

Kim 2013b ***{published data only}***
Kim KH, Kim BG, Ryu CH, Nam HS, Woo SM, Ryu SH, et al. Comparative analysis of BISAP system and serum procalcitonin for predicting severity of acute pancreatitis. *Pancreatology* 2013;**13**(Supp):S25–7.

Kitsanou 2004 ***{published data only}***
Kitsanou M, Katsanos KH, Christodoulou D, Kalabokis G, Katsaraki A, Kontodimou N, et al. The role of PMN elastase and CRP on the diagnosis and assessment of severity of acute pancreatitis. *Gastroenterology* 2004;**126**(4):A228.

Korczowski 2006 ***{published data only}***
Korczowski B. Diagnostic usefulness of procalcitonin in acute pancreatitis. *Gastroenterologia Polska* 2006;**13**(1): 63–5.

Kusnierz-Cabala 2004 ***{published data only}***
Kusnierz-Cabala B, Naskalski JW, Kedra B, Panek J. Comparison of sensitivity and specificity of serum poly-C avid ribonuclease activity and C-reactive protein concentration in detection of mild and severe acute pancreatitis. *Clinical Chemistry and Laboratory Medicine* 2004;**42**(5):549–55.

Kylanpaa-Back 2001a ***{published data only}***
Kylanpaa-Back ML, Takala A, Kemppainen E, Puolakkainen P, Haapiainen R, Repo H. Procalcitonin strip test in the early detection of severe acute pancreatitis. *British Journal of Surgery* 2001;**88**(2):222–7.

Kylanpaa-Back 2001b ***{published data only}***
Kylanpaa-Back ML, Takala A, Kemppainen EA, Puolakkainen PA, Haapiainen RK, Repo H. The strip test of procalcitonin in early detection of severe acute pancreatitis. *Gastroenterology* 2001;**120**(5):A469.

Kylanpaa-Back 2001c ***{published data only}***
Kylanpaa-Back ML, Takala A, Kemppainen EA, Puolakkainen PA, Leppaniemi AK, Karonen SL, et al. Procalcitonin, soluble interleukin-2 receptor, and soluble E-selectin in predicting the severity of acute pancreatitis. *Critical Care Medicine* 2001;**29**(1):63–9.

Leese 1987 ***{published data only}***
Leese T, Fuller M, Holliday M. C-reactive protein and alpha-2 macroglobulin in the assessment and monitoring of acute-pancreatitis. *Digestion* 1987;**38**(1):35–6.

Leese 1988 ***{published data only}***
Leese T, Shaw D, Holliday M. Prognostic markers in acute pancreatitis: Can pancreatic necrosis be predicted?. *Annals of the Royal College of Surgeons of England* 1988;**70**(4): 227–32.

Lempinen 1999 ***{published data only}***
Lempinen M, Kylanpaa-Back ML, Stenman UH, Puolakkainen P, Haapiainen R, Finne P, et al. Predicting the severity of acute pancreatitis by rapid measurement of trypsinogen-2 in urine. *Clinical Chemistry* 1999;**47**(12): 2103–7.

Lempinen 2005 ***{published data only}***
Lempinen M, Puolakkainen P, Kemppainen E. Clinical value of severity markers in acute pancreatitis. *Scandinavian Journal of Surgery: SJS* 2005;**94**(2):118–23.

Lewandowski 2007 ***{published data only}***
Lewandowski A, Kopec W, Diakowska D, Garbien M. Proinflammatory cytokines IL-6, IL-8 and C-reactive protein in acute pancreatitis - the role of IL-8 in prognosing complications. *Gastroenterologia Polska* 2007;**14**(3):165–72.

Li 2013 ***{published data only}***
Li Y, Li Y, Lu S. The value of lactate dehydrogenase combined with BISAP scoring in predicting the prognosis of acute pancreatitis. *Chinese Journal of Critical Care Medicine* 2013;**33**(Part 6):523–6.

Liang 2014 ***{published data only}***
Liang K. Early predictive value of serum calcium, C-reactive protein and serum amylase like protein A on severe acute pancreatitis. *Chinese Journal of Critical Care Medicine* 2014; **34**(Part 8):720–3.

Lindner 1995 ***{published data only}***
Lindner J, Skokanova V. Acute phase proteins in acute pancreatitis. *Rozhledy V Chirurgii* 1995;**74**(1):21–4.

Lipsett 2001 ***{published data only}***
Lipsett PA. Serum cytokines, proteins, and receptors in acute pancreatitis: Mediators, markers, or more of the same? . *Critical Care Medicine* 2001;**29**(8):1642–4.

Liu 2008 ***{published data only}***
Liu C, Haldene C. C-reactive protein or lactate dehydrogenase to assess the severity of pancreatic necrosis. *Emergency Medicine Journal* 2008;**25**(10):687–8.

Lobo 1999 ***{published data only}***
Lobo SM, Meirelles RF, Lupino P, Pires MD, Kuga ML, Beolchi G. Increased procalcitonin serum levels as predictive parameter of multiple organ failure and outcome in acute pancreatitis patients. *Critical Care* 1999;**3**(Supp 1):P93.

Lott 1991 ***{published data only}***
Lott JA. The value of clinical laboratory studies in acute-pancreatitis. *Archives of Pathology & Laboratory Medicine* 1991;**115**(4):325–6.

Ma 2013 ***{published data only}***
Ma J, Fan H, Kou JT, Li LX, He Q. Clinical significance for monitoring of serum ghrelin in acute pancreatitis severity assessment. *National Medical Journal of China* 2013;**93**(48): 3864–6.

Machiedo 1974 *{published data only}*
Machiedo GW, Brown CS, Rush BF Jr. Comparison of biochemical changes in blood and abdominal fluid during acute hemorrhagic pancreatitis. *Review of Surgery* 1974;**31**(1):60–2.

Makay 2003 *{published data only}*
Makay R, Issekutz A, Banga P, Belagyi T, Olah A. Role of procalcitonin rapid test in the differential diagnosis of uninfected and infected forms of acute pancreatitis. *Magyar Sebeszet* 2003;**56**(1):31–3.

Makela 2007 *{published data only}*
Makela JT, Eila H, Kiviniemi H, Laurila J, Laitinen S. Computed tomography severity index and C-reactive protein values predicting mortality in emergency and intensive care units for patients with severe acute pancreatitis. *American Journal of Surgery* 2007;**194**(1):30–4.

Malfertheiner 1993 *{published data only}*
Malfertheiner P, Dominguez-Munoz JE. Prognostic factors in acute-pancreatitis. *International Journal of Pancreatology* 1993;**14**(1):1–8.

Manabe 2004 *{published data only}*
Manabe T, Okada Y. Serum markers for predicting the severity of acute pancreatitis. *Journal of Gastroenterology* 2004;**39**(5):504–6.

Mandi 2000a *{published data only}*
Mandi Y, Farkas G, Takacs T, Boda K, Lonovics J. Diagnostic relevance of procalcitonin, IL-6, and sICAM-1 in the prediction of infected necrosis in acute pancreatitis. *International Journal of Pancreatology* 2000;**28**(1):41–9.

Mandi 2000b *{published data only}*
Mandi Y, Farkas G, Skolak E, Takacs T. Relevance of procalcitonin in infected pancreatic necrosis. 5th World Congress on Trauma, Shock, Inflammation and Sepsis: Pathophysiology, Immune Consequences and Therapy; 2000 Feb 29-Mar 4; Munich, Germany. Augusta (GA): BioMedical, 2000:419–24.

Manes 1994 *{published data only}*
Manes G, Rabitti PG, Laccetti M, Perrotti F, Cavallera A, Uomo G. Early prognostic assessment of acute pancreatitis with sterile necrosis. A perspective clinical study. *Recenti Progressi in Medicina* 1994;**85**(10):490–3.

Mantke 2002 *{published data only}*
Mantke R, Pross M, Kunz D, Ebert M, Kahl S, Peters B, et al. Soluble thrombomodulin plasma levels are an early indication of a lethal course in human acute pancreatitis. *Surgery* 2002;**131**(4):424–32.

Marek 1996 *{published data only}*
Marek TA, Nowak A, Dziurkowska-Marek A, Nowakowska-Dulawa E, Cholewka A, Kaczor R, et al. C-reactive protein (CRP) in the early assessment of severity in acute biliary pancreatitis (ABP). *Gastroenterology* 1996;**110**(4):A415.

Mayer 1984 *{published data only}*
Mayer AD, McMahon MJ, Bowen M, Cooper EH. C-reactive protein - an aid to assessment and monitoring of acute-pancreatitis. *Journal of Clinical Pathology* 1984;**37**(2):207–11.

Mayer 2002 *{published data only}*
Mayer JM, Raraty M, Slavin J, Kemppainen E, Fitzpatrick J, Hietaranta A, et al. Serum amyloid A is a better early predictor of severity than C-reactive protein in acute pancreatitis. *British Journal of Surgery* 2002;**89**(2):163–71.

Melzi D'Eril 2000 *{published data only}*
Melzi D'Eril GV, Merlini G, Finazzi S, Bosoni T, Barakat B, Pezzilli R. Procalcitonin is not a reliable marker for the assessment of severity in acute pancreatitis without infectious complications. *Clinical Chemistry* 2000;**46**(3):428–30.

Millat 1999 *{published data only}*
Millat B. Acute pancreatitis. Etiology, diagnosis, prognosis. *Revue du Praticien* 1999;**49**(3):311–9.

Modrau 2005 *{published data only}*
Modrau IS, Floyd AK, Thorlacius-Ussing O. The clinical value of procalcitonin in early assessment of acute pancreatitis. *American Journal of Gastroenterology* 2005;**100**(7):1593–7.

Modzelewski 2005 *{published data only}*
Modzelewski B, Holynski J. The role of selected enzymes and acute phase proteins in necrotizing pancreatitis. *Polski Merkuriusz Lekarski* 2005;**18**(106):412–4.

Mulholland 1996 *{published data only}*
Mulholland MW, Eckhauser FE. Prognostic criteria in necrotizing pancreatitis. *Problems in General Surgery* 1996;**13**(4):29–36.

Muller 1997 *{published data only}*
Muller C, Uhl W, Printzen G, Friess K, Vogel R, Reber P, et al. Value of procalcitonin (PCT) and granulocyte colony-stimulating factor (G-CSF) in predicting infected pancreatic necrosis. *Gut* 1997;**41**:A134.

Muller 2000 *{published data only}*
Muller CA, Uhl W, Printzen G, Gloor B, Bischofberger H, Tcholakov O, et al. Role of procalcitonin and granulocyte colony stimulating factor in the early prediction of infected necrosis in severe acute pancreatitis. *Gut* 2000;**46**(2):233–8.

Neoptolemos 2001 *{published data only}*
Neoptolemos JP. Procalcitonin strip test in the early detection of severe acute pancreatitis. *British Journal of Surgery* 2001;**88**(10):1418.

Nunes 2009 *{published data only}*
Nunes QM, Gardner-Thorpe J, Dajani K, Raraty M, Ghaneh P, Sutton R, et al. CRP as an indicator for using CT-guided fine needle aspiration in the diagnosis of infected pancreatic necrosis. *Pancreatology* 2009;**9**(4):454.

Oezcueruemez-Porsch 1998 *{published data only}*
Oezcueruemez-Porsch M, Kunz D, Hardt PD, Fadgyas T, Kress O, Schulz HU, et al. Diagnostic relevance of interleukin pattern, acute-phase proteins, and procalcitonin in early phase of post-ERCP pancreatitis. *Digestive Diseases and Sciences* 1998;**43**(8):1763–9.

Olah 2005 *{published data only}*
Olah A, Belagyi T, Issekutz A, Makay R, Zaborszky A. Value of procalcitonin quick test in the differentiation between sterile and infected forms of acute pancreatitis. *Hepato-Gastroenterology* 2005;**52**(61):243–5.

Omoto 2015 *{published data only}*
Omoto S, Kitano M, Sakamoto H, Imai H, Yamao K, Kamata K, et al. Usefulness of serum procalcitonin for diagnosis of acute pancreatitis. *Journal of Gastroenterology and Hepatology* 2015;**30**:141.

Ostrovskii 2012 *{published data only}*
Ostrovskii VK, Rodionov PN, Makarov SV. Some of criteria in the evaluation of severity and prognosis with different forms of acute pancreatitis. *Anesteziologiia i Reanimatologiia* 2012, (3):56–9.

Paajanen 1995 *{published data only}*
Paajanen H, Laato M, Jaakkola M, Pulkki K, Niinikoski J, Nordback I. Serum tumour necrosis factor compared with C-reactive protein in the early assessment of severity of acute pancreatitis. *British Journal of Surgery* 1995;**82**(2):271–3.

Palani 1977 *{published data only}*
Palani CK, Sehgal LR, Kraft AR, Duarte B, Dulski R, Levine H, et al. Predictive value of biochemical indexes in acute alcoholic pancreatitis. *Surgical Forum* 1977;**28**:441–3.

Pallisera 2014 *{published data only}*
Pallisera A, Jorba R, Ramia JM, Rodriguez JA, Subirana H, de Zarate LO, et al. Biological markers of severity in acute pancreatitis. *Central European Journal of Medicine* 2014;**9** (4):550–5.

Park 2012 *{published data only}*
Park JY, Jeon TJ, Hwang JT, Sinn DH, Oh TH, Shin WC, et al. Bedside index for severity in acute pancreatitis: an early marker of severity. *Journal of Gastroenterology and Hepatology* 2012;**27**:355.

Park 2013 *{published data only}*
Park JY, Jeon TJ, Ha TH, Hwang JT, Sinn DH, Oh TH, et al. Bedside index for severity in acute pancreatitis: Comparison with other scoring systems in predicting severity and organ failure. *Hepatobiliary & Pancreatic Diseases International* 2013;**12**(6):645–50.

Petrov 2011 *{published data only}*
Petrov MS. Predicting the severity of acute pancreatitis: Choose the right horse before hitching the cart. *Digestive Diseases and Sciences* 2011;**56**(12):3402–4.

Pezzilli 1994 *{published data only}*
Pezzilli R, Billi P, Plate L, Barakat B, Bongiovanni F, Miglioli M. Human pancreatic secretory trypsin inhibitor in the assessment of the severity of acute pancreatitis. A comparison with C-reactive protein. *Journal of Clinical Gastroenterology* 1994;**19**(2):112–7.

Pezzilli 1995a *{published data only}*
Pezzilli R, Billi P, Miniero R, Fiocchi M, Cappelletti O, Sprovieri G, et al. Serum-beta-2 microglobulin in the early assessment of the severity of acute pancreatitis - a comparative study with Interleukin-6, Interleukin-8 and C-reactive protein. *Gastroenterology* 1995;**108**(4 Suppl):A384.

Pezzilli 1995b *{published data only}*
Pezzilli R, Billi P, Miniero R, Fiocchi M, Cappelletti O, Morselli-Labate AM, et al. Serum interleukin-6, interleukin-8, and beta 2-microglobulin in early assessment of severity of acute pancreatitis. Comparison with serum C-reactive protein. *Digestive Diseases and Sciences* 1995;**40** (11):2341–8.

Pezzilli 1997 *{published data only}*
Pezzilli R, Billi P, Cappelletti O, Barakat B. Serum C-positive protein in acute biliary pancreatitis. Is it a reliable marker for the early assessment of severity of the disease?. *Italian Journal of Gastroenterology and Hepatology* 1997;**29** (6):554–7.

Pezzilli 1998a *{published data only}*
Pezzilli R, Labate AMM, Barakat B, Fiocchi M, Cappelletti O, Miglio F. Is the association of serum lipase with beta 2-microglobulin or with C-reactive protein useful in simultaneously establishing the diagnosis and prognosis of patients with acute pancreatitis?. *Gastroenterology* 1998;**114** (4):A490–1.

Pezzilli 1998b *{published data only}*
Pezzilli R, Morselli-Labate AM, Barakat B, Fiocchi M, Cappelletti O. Is the association of serum lipase with alpha-2-microglobulin or C-reactive protein useful for establishing the diagnosis and prognosis of patients with acute pancreatitis?. *Clinical Chemistry and Laboratory Medicine* 1998;**36**(12):963–8.

Pezzilli 2000 *{published data only}*
Pezzilli R, D'Eril GVM, Morselli-Labate AM, Merlini G, Barakat B, Bosoni T. Serum amyloid A, procalcitonin, and C-reactive protein in early assessment of severity of acute pancreatitis. *Digestive Diseases and Sciences* 2000;**45**(6): 1072–8.

Pongprasobchai 2010 *{published data only}*
Pongprasobchai S, Jianjaroonwong V, Charatcharoenwitthaya P, Komoltri C, Tanwandee T, Leelakusolvong S, et al. Erythrocyte sedimentation rate and C-reactive protein for the prediction of severity of acute pancreatitis. *Pancreas* 2010;**39**(8):1226–30.

Puolakkainen 1987 *{published data only}*
Puolakkainen P, Valtonen V, Paananen A, Schroder T. C-reactive protein (CRP) and serum phospholipase-A2 in the assessment of the severity of acute pancreatitis. *Gut* 1987; **28**(6):764–71.

Purkayastha 2006 *{published data only}*
Purkayastha S, Chow A, Athanasiou T, Cambaroudis A, Panesar S, Kinross J, et al. Does serum procalcitonin have a role in evaluating the severity of acute pancreatitis? A question revisited. *World Journal of Surgery* 2006;**30**(9): 1713–21.

Qiu 2014 *{published data only}*
Qiu L, Yu Q, Yu J, Wang H, Zhou Y, Li Q, et al. The prognostic value of CD14+HLA-DRlow/- for evaluating the

severity of acute pancreatitis. *Chinese Journal of Microbiology and Immunology* 2014;**34**(8):620–3.

Raraty 2002 ***{published data only}***
Raraty MGT, Mayer JM, Slavin M, Kemppainen E, Fitzpatrick J, Hietaranta A, et al. Serum amyloid A is a better early predictor of severity than C-reactive protein in acute pancreatitis. *British Journal of Surgery* 2002;**89**(3): 380.

Rau 1997 ***{published data only}***
Rau B, Steinbach G, Gansauge F, Mayer J, Gruenert A, Beger HG. The role of procalcitonin and interleukin-8 in the prediction of infected necrosis in acute pancreatitis. *Gastroenterology* 1997;**112**(4):A476.

Rau 2000 ***{published data only}***
Rau B, Steinbach G, Baumgart K, Gansauge F, Grunert A, Beger HG. The clinical value of procalcitonin in the prediction of infected necrosis in acute pancreatitis. *Intensive Care Medicine* 2000;**26**:S159–64.

Rau 2004 ***{published data only}***
Rau B, Kruger CM, Schilling MK. Procalcitonin: Improved biochemical severity stratification and postoperative monitoring in severe abdominal inflammation and sepsis. *Langenbecks Archives of Surgery* 2004;**389**(2):134–44.

Rau 2007 ***{published data only}***
Rau BM, Kemppainen EA, Gumbs AA, Buchler MW, Wegscheider K, Bassi C, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): a prospective international multicenter study. *Annals of Surgery* 2007;**245**(5):745–54.

Ricardo 2011 ***{published data only}***
Ricardo L, Cardoso F, Oliveira A, Rodrigues C, Horta D, Figueiredo A, et al. Comparison of BISAP, Ranson's, and CTSI scores, and C-reactive protein in predicting organ failure, complications and mortality in acute pancreatitis. *Pancreas* 2011;**40**(8):1351.

Riche 2003 ***{published data only}***
Riche FC, Cholley BP, Laisne MJ, Vicaut E, Panis YH, Lajeunie EJ, et al. Inflammatory cytokines, C reactive protein, and procalcitonin as early predictors of necrosis infection in acute necrotizing pancreatitis. *Surgery* 2003; **133**(3):257–62.

Ruzafa 1991 ***{published data only}***
Ruzafa A, Granada ML, Gener J, Manterola JM, Oller B, Mesalles E, et al. C reactive protein concentrations, measured by a latex slide test, as a prognostic factor in acute pancreatitis. *Revista de la Sociedad Espanola de Quimica Clinica* 1991;**10**(5):372–6.

Samso 2002 ***{published data only}***
Samso CT. Early assessment of severity in acute pancreatitis. *Revista Espanola De Enfermedades Digestivas* 2002;**94**(9): 519–22.

Sanchez-Lozada 2005 ***{published data only}***
Sanchez-Lozada R, Camacho-Hernandez MI, Vega-Chavaje RG, Garza-Flores JH, Campos-Castillo C, Gutierrez-Vega R. Acute pancreatitis: Five year experience at the hospital general de Mexico. *Gaceta Medica de Mexico* 2005;**141**(2): 123–7.

Santotoribio 2015 ***{published data only}***
Santotoribio JD, Canavate-Solano C, Garcia-De La Torre A, Arce-Matute F, Perez-Ramos S. C-reactive protein for diagnosis of severe acute pancreatitis. *Clinical Chemistry and Laboratory Medicine* 2015;**53**:S1250.

Sato 2004 ***{published data only}***
Sato N, Endo S, Kasai T, Inoue Y, Fujino Y, Onodera M, et al. Relationship of the serum procalcitonin level with the severity of acute pancreatitis. *Research Communications in Molecular Pathology & Pharmacology* 2004;**115-116**:243–9.

Savel'ev 2002 ***{published data only}***
Savel'ev VS, Gel'fand BR, Filimonov MI, Burnevich SZ, Sergeeva NA, Brazhnik TB, et al. Clinical significance of the procalcitonin test in differential diagnosis of systemic inflammatory reaction in pancreatonecrosis. *Anesteziologiia i Reanimatologiia* 2002, (1):25–9.

Schaffler 2010 ***{published data only}***
Schaffler A, Hamer O, Dickopf J, Goetz A, Landfried K, Voelk M, et al. Admission resistin levels predict peripancreatic necrosis and clinical severity in acute pancreatitis. *American Journal of Gastroenterology* 2010;**105** (11):2474–84.

Schaffler 2011 ***{published data only}***
Schaffler A, Hamer OW, Dickopf J, Goetz A, Landfried K, Voelk M, et al. Admission visfatin levels predict pancreatic and peripancreatic necrosis in acute pancreatitis and correlate with clinical severity. *American Journal of Gastroenterology* 2011;**106**(5):957–67.

Sharma 2011 ***{published data only}***
Sharma M, Goswami B. C reactive protein, PCV and CT scan in assessing severity of acute pancreatitis. *Journal of Gastroenterology and Hepatology* 2011;**26**(Supp 5):232.

Stimac 2010 ***{published data only}***
Stimac D, Fisic E, Zulle LB, Zrnic IK, Milic S. Clinical value of C-reactive protein and elastase in assessment of acute pancreatitis. *Pancreatology* 2010;**10**(2-3):347.

Stimac 2012 ***{published data only}***
Stimac D, Fisic E, Poropat G, Bilic Zulle L, Licul V, Milic S. The role of IL-6, IL-8, IL-10, sTNFr CRP and pancreatic elastase in the prediction of systemic complications in patients with acute pancreatitis. *Pancreas* 2012;**41**(8):1405.

Stimac 2013 ***{published data only}***
Stimac D, Fisic E, Poropat G, Bilic Zulle L, Licul V, Milic S. The role of IL-6, IL-8, IL-10, sTNFr, CRP and pancreatic elastase in the prediction of systemic complications in patients with acute pancreatitis. *Pancreatology* 2013;**13**(2): e75–6.

Stoelben 1996 ***{published data only}***
Stoelben E, Nagel M, Ockert D, Quintel M, Scheibenbogen C, Klein B, et al. Clinical relevance of cytokines IL-6, IL-8, and C-reactive protein in the blood of patients with acute pancreatitis. *Chirurg* 1996;**67**(12):1231–6.

Sugumar 2011 *{published data only}*
Sugumar A, Alkubeyyer M, Erickson B, Vege SS. Can machine learning predict the severity of acute pancreatitis. *Gastroenterology* 2011;**1**:S853.

Tao 2013 *{published data only}*
Tao J, Li L, Wu B. The value of combining earlier period C reactive protein and hematocrit level in acute pancreatitis. *Journal of Gastroenterology and Hepatology* 2013;**28**:455.

Teerenhovi 1988 *{published data only}*
Teerenhovi O, Nordback I. C-reactive protein (CRP) and pancreatic necrosis in acute necrotizing pancreatitis. *Annales Chirurgiae Et Gynaecologiae* 1988;**77**(2):61–3.

Tesinsky 2008 *{published data only}*
Tesinsky P, Holubec L. P016 predictive value of procalcitonin and cytokines in ERCP induced acute pancreatitis. *Clinical Nutrition Supplements* 2008;**3**(Supp 1):35.

Trunin 1985 *{published data only}*
Trunin MA, Khvatova EA. Lactate dehydrogenase enzymes and isoenzymes in the diagnosis of forms of acute and postoperative pancreatitis. *Khirurgiia* 1985, (1):50–5.

Uhl 1991 *{published data only}*
Uhl W, Buchler M, Malfertheiner P, Martini M, Beger HG. PMN-elastase in comparison with CRP, antiproteases, and LDH as indicators of necrosis in human acute pancreatitis. *Pancreas* 1991;**6**(3):253–9.

Uomo 1995 *{published data only}*
Uomo G, Rabitti PG, Laccetti M, Manes G, Carraturo I, Esposito P, et al. Predictive evaluation of acute necrotizing pancreatitis: Results of a prospective study. *Presse Medicale* 1995;**24**(5):263–6.

Vaz 2013 *{published data only}*
Vaz PS, Caldeira A, Sousa R, Gouveia A, Banhudo A, Loureiro A. The value of procalcitonin, antithrombin III and BISAP score at predicting the severity of acute pancreatitis. *Pancreatology: Abstracts presented at the 45th Annual Meeting of the European Pancreatic Club, 2013 June 26-29, Zurich, Switzerland* 2013;**13**(Supp):S34–5.

Vesentini 1993 *{published data only}*
Vesentini S, Bassi C, Talamini G, Cavallini G. Prospective comparison of C-reactive protein level, Ranson score and contrast-enhanced computed tomography in the prediction of septic complications of acute pancreatitis. *British Journal of Surgery* 1993;**80**(6):755.

Viedma 1992 *{published data only}*
Viedma JA, Perez-Mateo M, Dominguez JE, Carballo F. Role of interleukin-6 in acute pancreatitis. Comparison with C-reactive protein and phospholipase A. *Gut* 1992;**33**(9):1264–7.

Viedma 1994 *{published data only}*
Viedma JA, Perez-Mateo M, Agullo J, Dominguez JE, Carballo F. Inflammatory response in the early prediction of severity in human acute pancreatitis. *Gut* 1994;**35**(6):822–7.

Vlachos 2014 *{published data only}*
Vlachos S, Tsaroucha AK, Konstantoudakis G, Papachristou F, Trypsianis G, Schizas D, et al. Serum profiles of M30, M65 and Interleukin-17 compared with C-reactive protein in patients with mild and severe acute pancreatitis. *Journal of Hepato-Biliary-Pancreatic Sciences* 2014;**21**(12):911–8.

Wei 2013 *{published data only}*
Wei H, Wang YX. Significance of C-reactive protein to prediction and severity evaluation of acute pancreatitis. *Journal of Gastroenterology and Hepatology* 2013;**28**(Suppl 3):885–6.

Wetherill 2012 *{published data only}*
Wetherill C, Melling J, Jones M. C-reactive protein accurately predicts severity of acute pancreatitis in children. *Pancreas* 2012;**41**(8):1412–3.

Wetherill 2013a *{published data only}*
Wetherill C, Melling J, Jones M. 48 hour C-reactive protein accurately predicts severity of acute pancreatitis in children. *Pancreatology* 2013;**13**(1):e6.

Wetherill 2013b *{published data only}*
Wetherill C, Melling J, Jones M. C-reactive protein accurately predicts severity of acute pancreatitis in children. *Pancreatology* 2013;**13**(2):e84.

Wilson 1987 *{published data only}*
Wilson C, Fraser WD, Gardner MD, Imrie CW. Source of lactate-dehydrogenase elevation in acute-pancreatitis. *Digestion* 1987;**38**(1):64.

Wilson 1988 *{published data only}*
Wilson C, Shenkin A, Imrie CW. Value of C-reactive protein and antiproteases in the objective monitoring of acute pancreatitis. *Gut* 1988;**29**(2):A269.

Wilson 1989a *{published data only}*
Wilson C, Heads A, Shenkin A, Imrie CW. C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis. *British Journal of Surgery* 1989;**76**(2):177–81.

Wilson 1989b *{published data only}*
Wilson C, Shenkin A, Imrie C. C-reactive protein and acute pancreatitis - reply. *British Journal of Surgery* 1989;**76**(8):877.

Wong 1993 *{published data only}*
Wong ECC, Butch AW, Rosenblum JL, Ladenson JH, Scott MG. (Washington University Case Conference) The clinical chemistry laboratory and acute pancreatitis. *Clinical Chemistry* 1993;**39**(2):234–43.

Woo 2011 *{published data only}*
Woo SM, Noh MH, Kim BG, Hsing CT, Han JS, Ryu SH, et al. Comparison of serum procalcitonin with Ranson, APACHE II, Glasgow and Balthazar CT severity index scores in predicting severity of acute pancreatitis. *Korean Journal of Gastroenterology* 2011;**58**(1):31–7.

Xu 2015 *{published data only}*
Xu YH, Yan L, Bian C, Tian ZB, Jing X. Value of procalcitonin in assessing severity of acute pancreatitis. *World Chinese Journal of Digestology* 2015;**23**(30):4898–904.

Yadav 2015a *{published data only}*
Yadav A, Rafferty S, Rasool J, Keohane J, Sengupta S. C reactive protein - a rapid and cost effective marker of severity of acute pancreatitis. *Gastroenterology* 2015;**148**(4):S684.

Yadav 2015b *{published data only}*
Yadav A, Rafferty S, Rasool J, Keohane J, Sengupta S. C-reactive protein: A rapid and cost effective marker of acute pancreatitis severity. *Irish Journal of Medical Science* 2015; **184**:S217.

Yasuda 2011 *{published data only}*
Yasuda H, Suzaki S. Is procalcitonin useful to the diagnosis of infected pancreatic necrosis and pancreatic abscess?. *Critical Care Medicine* 2011;**39**:104.

Yin 2014 *{published data only}*
Yin G, Hu G, Cang X, Yu G, Hu Y, Xing M, et al. C-reactive protein: Rethinking its role in evaluating the severity of hyperlipidemic acute pancreatitis. *Pancreas* 2014; **43**(8):1323–8.

Yu 2011 *{published data only}*
Yu YH, Han DS, Kim EK, Park HS, Kim TY, Eun CS, et al. Prevalence, mortality rate and predictive factors for severe acute pancreatitis according to the revised Atlanta classification. *Journal of Gastroenterology and Hepatology* 2011;**26**:235.

Zhu 2013 *{published data only}*
Zhu GF. Early predictive values of the combined detection of serum calcium and CRP in the severity of acute pancreatitis. *Journal of Gastroenterology and Hepatology* 2013;**28**:891–2.

Zrnic 2007 *{published data only}*
Zrnic IK, Milic S, Fisic E, Radic M, Stimac D. C-reactive protein and lactate dehydrogenase as single prognostic factors of severity in acute pancreatitis. *Lijecnicki Vjesnik* 2007;**129**(1):1–3.

References to studies awaiting assessment

Djurasinovic 2013 *{published data only}*
Djurasinovic T, Subota V, Vujanic S, Andjelic T, Pejovic J, Bezmarevic M. Prognostic values of procalcitonin and CRP in acute pancreatitis. *Biochimica Clinica* 2013;**37**:S663.

Grenier 1968 *{published data only}*
Grenier JF, Gillet M, Sava G, Crevoisier R, Weiss AG. Acute pancreatitis. Anatomo-clinical and biological confrontations; diagnostic, prognostic and therapeutic deductions. Apropos of a statistic of 37 cases. *Presse Medicale* 1968;**76**(29):1481–4.

Issekutz 2003 *{published data only}*
Issekutz A, Belagy T, Olah A. Clinical value of procalcitonin test in severe acute pancreatitis. *Hpb* 2003;**5, SUPP 1**:140.

Pindak 2003 *{published data only}*
Pindak D, Parrak V, Pechan J, Vavrecka A, Kuzela L, Fuchs D, et al. The clinical value of the procalcitonin in prediction of severity and outcome in acute pancreatitis. *Hepato-Gastroenterology* 2003;**50**(Suppl 2):ccviii–ccix.

Additional references

Ayub 2004
Ayub K, Slavin J, Imada R. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD003630.pub2]

Bakker 2012
Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012;**307**(10):1053–61.

Banks 2013
Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;**62**(1):102–11.

Becker 2010
Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. *British Journal of Pharmacology* 2010; **159**(2):253–64.

Bradley 1993
Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis; 1992 September 11-13; Atlanta, GA. *Archives of Surgery* 1993;**128**(5):586–90.

Buscemi 2006
Buscemi N, Hartling L, Vandermeer B, Tjosvold L, Klassen TP. Single data extraction generated more errors than double data extraction in systematic reviews. *Journal of Clinical Epidemiology* 2006;**59**(7):697–703.

Cannon 2009
Cannon JW, Callery MP, Vollmer CM Jr. Diagnosis and management of pancreatic pseudocysts: What is the evidence?. *Journal of the American College of Surgeons* 2009; **209**(3):385–93.

Cheruvu 2003
Cheruvu CV, Clarke MG, Prentice M, Eyre-Brook IA. Conservative treatment as an option in the management of pancreatic pseudocyst. *Annals of the Royal College of Surgeons of England* 2003;**85**(5):313–6.

Chu 2006
Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *Journal of Clinical Epidemiology* 2006;**59** (12):1331–2.

Doust 2005
Doust JA, Pietrzak E, Sanders S, Glasziou PP. Identifying studies for systematic reviews of diagnostic tests was difficult due to the poor sensitivity and precision of methodologic filters and the lack of information in the abstract. *Journal of Clinical Epidemiology* 2005;**58**(5):444–9.

Eloubeidi 2001
Eloubeidi MA, Wade SB, Provenzale D. Factors associated with acceptance and full publication of GI

endoscopic research originally published in abstract form. *Gastrointestinal Endoscopy* 2001;**53**(3):275–82.

Ghekiere 2007
Ghekiere O, Lesnik A, Hoa D, Laffargue G, Uriot C, Taourel P. Value of computed tomography in the diagnosis of the cause of nontraumatic gastrointestinal tract perforation. *Journal of Computer Assisted Tomography* 2007; **31**(2):169–76.

Grassi 2004
Grassi R, Romano S, Pinto A, Romano L. Gastro-duodenal perforations: conventional plain film, US and CT findings in 166 consecutive patients. *European Journal of Radiology* 2004;**50**(1):30–6.

Gurusamy 2013
Gurusamy KS, Nagendran M, Davidson BR. Early versus delayed laparoscopic cholecystectomy for acute gallstone pancreatitis. *Cochrane Database of Systematic Reviews* 2013, Issue 9. [DOI: 10.1002/14651858.CD010326.pub2]

Gurusamy 2014
Gurusamy KS, Davidson BR. Gallstones. *BMJ* 2014;**348**: g2669.

Gurusamy 2016
Gurusamy KS, Belgaumkar AP, Haswell A, Pereira SP, Davidson BR. Interventions for necrotising pancreatitis. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD011383.pub2]

Johnson 2009
Johnson MD, Walsh RM, Henderson JM, Brown N, Ponsky J, Dumot J, et al. Surgical versus nonsurgical management of pancreatic pseudocysts. *Journal of Clinical Gastroenterology* 2009;**43**(6):586–90.

Larson 2006
Larson SD, Nealon WH, Evers BM. Management of gallstone pancreatitis. *Advances in Surgery* 2006;**40**:265–84.

Moayyedi 2006
Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia?. *JAMA* 2006;**295**(13):1566–76.

Mouli 2013
Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology* 2013;**144**(2):333–40.e2.

Muddana 2009
Muddana V, Whitcomb DC, Khalid A, Slivka A, Papachristou GI. Elevated serum creatinine as a marker of pancreatic necrosis in acute pancreatitis. *American Journal of Gastroenterology* 2009;**104**(1):164–70.

NCBI 2014a
NCBI. MeSH. NLM Controlled Vocabulary. Pancreas. www.ncbi.nlm.nih.gov/mesh/68010179 2014 (accessed 4 July 2014).

NCBI 2014b
NCBI. MeSH. NLM Controlled Vocabulary. C-reactive protein. www.ncbi.nlm.nih.gov/mesh/68010179 2014 (accessed 2 August 2014).

NCEPOD 2016
NCEPOD. National Confidential Enquiry Into Patient Outcome and Death. Acute pancreatitis: Treat the cause (2016). www.ncepod.org.uk/2016ap.html 2016 (accessed 19 September 2016).

Peery 2012
Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012;**143** (5):1179–87.

Petrov 2010
Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010;**139**(3):813–20.

Reitsma 2005
Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of Clinical Epidemiology. 2005/ 09/20 2005; Vol. 58, issue 10:982–90.

Roberts 2013
Roberts SE, Akbari A, Thorne K, Atkinson M, Evans PA. The incidence of acute pancreatitis: impact of social deprivation, alcohol consumption, seasonal and demographic factors. *Alimentary Pharmacology and Therapeutics* 2013;**38**(5):539–48.

Rutter 2001
Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Statistics in Medicine* 2001;**20**(19):2865–84.

Sampson 2008
Sampson M, Shojania KG, McGowan J, Daniel R, Rader T, Iansavichene AE, et al. Surveillance search techniques identified the need to update systematic reviews. *Journal of Clinical Epidemiology* 2008;**61**(8):755–62.

Sanabria 2013
Sanabria A, Villegas MI, Morales Uribe CH. Laparoscopic repair for perforated peptic ulcer disease. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/ 14651858.CD004778.pub3]

Schmid 1999
Schmid SW, Uhl W, Friess H, Malfertheiner P, Buchler MW. The role of infection in acute pancreatitis. *Gut* 1999; **45**(2):311–6.

Takwoingi 2015
Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Statistical Methods in Medical Research 2015 Jun 26 [Epub ahead of print]. [DOI: 10.1177/0962280215592269]

Tenner 2013
Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *American Journal of Gastroenterology* 2013;**108**(9):1400–15.

van Brunschot 2014
van Brunschot S, Fockens P, Bakker OJ, Besselink MG, Voermans RP, Poley JW, et al. Endoscopic transluminal necrosectomy in necrotising pancreatitis: a systematic review. *Surgical Endoscopy* 2014;**28**(5):1425–38.

van Santvoort 2010
van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *New England Journal of Medicine* 2010;**362**(16):1491–502.

van Santvoort 2011
van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011;**141**(4):1254–63.

Varadarajulu 2008
Varadarajulu S, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointestinal Endoscopy* 2008;**68**(6):1102–11.

Varadarajulu 2013
Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013;**145**(3):583–90.

Vissers 1999
Vissers RJ, Abu-Laban RB, McHugh DF. Amylase and lipase in the emergency department evaluation of acute pancreatitis. *Journal of Emergency Medicine* 1999;**17**(6):1027–37.

Whiting 2006
Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Medical Research Methodology. 2006/03/08 2006; Vol. 6: 9.

Whiting 2011
Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011;**155**(8):529–36.

Yadav 2006
Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006;**33**(4):323–30.

Yang 2008
Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Archives of Internal Medicine* 2008;**168**(6):649–56.

References to other published versions of this review

Gurusamy 2015
Gurusamy KS, Davidson BR. Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis and serum C-reactive protein, procalcitonin and lactate dehydrogenase for the diagnosis of pancreatic necrosis. *Cochrane Database of Systematic Reviews* 2015, Issue 12. [DOI: 10.1002/14651858.CD012010]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alfonso 2003

Study characteristics				**Study character**
Patient sampling	Type of study: retrospective study. Consecutive or random sample: unclear.			
Patient characteristics and setting	Sample size: 157. Females: 63 (40.1%). Age: 67 years. Presentation: Participants with acute pancreatitis. Setting: secondary setting in Spain.			
Index tests	Index test: C-reactive protein (day not stated). Further details: Technical specifications: Nephelometry (Dade Behring Marburg GmbH, Marburg, Germany). Performed by: not stated. Criteria for positive diagnosis: > 200 mg/L and > 279 mg/L.			
Target condition and reference standard(s)	Target condition: pancreatic necrosis. Reference standard: CT scan.			
Flow and timing	Number of indeterminates for whom the results of reference standard were available: 0 (0%). Number of participants who were excluded from the analysis: not stated			
Comparative				
Notes	This study reported the diagnostic test accuracy at 2 threshold levels			
Methodological quality				**Methodological**
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**	
DOMAIN 1: Patient Selection				**DOMAIN 1: Pa**
Was a consecutive or random sample of patients enrolled?	Unclear			
Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Unclear			
		Unclear	**Unclear**	

Alfonso 2003 (*Continued*)

DOMAIN 2: Index Test All tests				**DOMAIN 2: In**
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				**DOMAIN 3: Re**
Is the reference standards likely to correctly classify the target condition?	No			
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear			
		High	**Low**	
DOMAIN 4: Flow and Timing				**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	No			
Did all patients receive the same reference standard?	Yes			
Were all patients included in the analysis?	Unclear			
		High		

Bertsch 1997

Study characteristics		**Study character**
Patient sampling	Type of study: unclear whether prospective or retrospective study. Consecutive or random sample: unclear.	

Bertsch 1997 (*Continued*)

Patient characteristics and setting	Sample size: 15. Females: 5 (33.3%). Age: 53 years. Presentation: Participants with acute pancreatitis. Setting: secondary care setting, Germany.
Index tests	Index test: procalcitonin (day 1). Further details: Technical specifications: a luminometric immunoassay (Fa.Brahms, Berlin). Performed by: not stated. Criteria for positive diagnosis: > 0.5 ng/mL.
Target condition and reference standard(s)	Target condition: pancreatic necrosis. Reference standard: CT scan. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: not stated.
Flow and timing	Number of indeterminates for whom the results of reference standard were available: 0 (0%). Number of participants who were excluded from the analysis: not stated
Comparative	
Notes	

Methodological quality				**Methodological**
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**	
DOMAIN 1: Patient Selection				**DOMAIN 1: Pa**
Was a consecutive or random sample of patients enrolled?	Unclear			
Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Unclear			
		Unclear	**Unclear**	
DOMAIN 2: Index Test All tests				**DOMAIN 2: In**
Were the index test results interpreted without knowledge of the results of the reference stan-	Unclear			

Bertsch 1997 (*Continued*)

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

Rau 1998

Study characteristics	**Study character**
Patient sampling	Type of study: prospective study. Consecutive or random sample: unclear.
Patient characteristics and setting	Sample size: 70. Females: 31 (44.3%). Age: 49 years. Presentation: Participants with acute pancreatitis (within fewer than 4 days of onset of symptoms). Setting: secondary care setting, Germany.

Rau 1998 (*Continued*)

Index tests	Index test: C-reactive protein (day 3). Further details: Technical specifications: laser nephelometry. Performed by: not stated. Criteria for positive diagnosis: > 140 mg/L. Index test: lactate dehydrogenase (day 5). Further details: Technical specifications: enzyme kinetic method. Performed by: not stated. Criteria for positive diagnosis: > 290 U/L.
Target condition and reference standard(s)	Target condition: pancreatic necrosis. Reference standard: CT scan or intra-operative findings, or both. Further details: Technical specifications: CT scan: CT 9800 (General Electric) and CT Twin Flash (Elscint); Surgery: not applicable. Performed by: not stated. Criteria for positive diagnosis: not stated.
Flow and timing	Number of indeterminates for whom the results of reference standard were available: 0 (0%). Number of participants who were excluded from the analysis: not stated
Comparative	
Notes	This study reported 2 index tests. Authors provided additional information that the index tests were interpreted without knowledge of reference standards. The authors also stated that the interval between the index tests and CT scan was 2 to 6 days, and the interval between index tests and laparotomy was 18 days

Methodological quality				**Methodological**
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**	
DOMAIN 1: Patient Selection				**DOMAIN 1: Pa**
Was a consecutive or random sample of patients enrolled?	Unclear			
Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Unclear			
		Unclear	**Unclear**	
DOMAIN 2: Index Test All tests				**DOMAIN 2: In**

Rau 1998 (*Continued*)

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

CT: computed tomography

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

Study	Reason for exclusion
Abishek 2014	No diagnostic accuracy data on pancreatic necrosis
Aggelopoulos 1996	No diagnostic accuracy data on pancreatic necrosis
Ammori 2003	No diagnostic accuracy data on pancreatic necrosis
Appasani 2011a	No diagnostic accuracy data on pancreatic necrosis
Appasani 2011b	No diagnostic accuracy data on pancreatic necrosis
Appasani 2012	No diagnostic accuracy data on pancreatic necrosis
Bajec 2010	No diagnostic accuracy data on pancreatic necrosis
Bapat 1986	No diagnostic accuracy data on pancreatic necrosis
Barauskas 2004	Inadequate reference standard
Bassi 1994	Not a primary study (review)
Beger 1989	Not a primary study (letter to editor)
Berry 1982	No diagnostic accuracy data on pancreatic necrosis
Bezmarevic 2012a	No diagnostic accuracy data on pancreatic necrosis
Bezmarevic 2012b	No diagnostic accuracy data on pancreatic necrosis
Bezmarevic 2012c	No diagnostic accuracy data on pancreatic necrosis
Bihari 2004	Not a primary study (letter to editor)
Blum 2001	No diagnostic accuracy data on pancreatic necrosis
Boskovic 2014	No diagnostic accuracy data on pancreatic necrosis
Brailski 1975	Not a primary study (review)
Brand 2014	No diagnostic accuracy data on pancreatic necrosis
Brisinda 1999	No diagnostic accuracy data on pancreatic necrosis
Buchler 1986a	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Buchler 1986b	No diagnostic accuracy data on pancreatic necrosis
Buchler 1986c	No diagnostic accuracy data on pancreatic necrosis
Buchler 1987	No diagnostic accuracy data on pancreatic necrosis
Buchler 1991	Not a primary study (review)
Bulbuller 2006	No diagnostic accuracy data on pancreatic necrosis
Cai 2014	No diagnostic accuracy data on pancreatic necrosis
Cardoso 2011	No diagnostic accuracy data on pancreatic necrosis
Cardoso 2013	Inadequate reference standard
Cardoso 2015	No diagnostic accuracy data on pancreatic necrosis
Chen 1992	No diagnostic accuracy data on pancreatic necrosis
Chen 2004	Not a primary study (editorial)
Chen 2012	No diagnostic accuracy data on pancreatic necrosis
Choi 2012	No diagnostic accuracy data on pancreatic necrosis
Choi 2013	No diagnostic accuracy data on pancreatic necrosis
Chooklin 2010	No diagnostic accuracy data on pancreatic necrosis
Choudhary 2012	Not a primary study (letter to editor)
Cooper 1981	No diagnostic accuracy data on pancreatic necrosis
Cravo 1988	No diagnostic accuracy data on pancreatic necrosis
d'Eril 2000	No diagnostic accuracy data on pancreatic necrosis
Dambrauskas 2010	No diagnostic accuracy data on pancreatic necrosis
Dammann 1979	No diagnostic accuracy data on pancreatic necrosis
Daniel 2010	No diagnostic accuracy data on pancreatic necrosis
de Beaux 1996	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

De la Pena 1991	No diagnostic accuracy data on pancreatic necrosis
Del Prete 2001	No diagnostic accuracy data on pancreatic necrosis
Digalakis 2009	No diagnostic accuracy data on pancreatic necrosis
Duarte-Rojo 2009	No diagnostic accuracy data on pancreatic necrosis
Economou 1997	Not a primary study (letter to editor)
Fan 1994	Not a primary study (editorial)
Ferguson 1990	No diagnostic accuracy data on pancreatic necrosis
Fisic 2013	No diagnostic accuracy data on pancreatic necrosis
Folch-Puy 2007	Not a primary study (editorial)
Frasquet 2003	No diagnostic accuracy data on pancreatic necrosis
Frossard 2001	Not a primary study (review)
Gao 2014	No diagnostic accuracy data on pancreatic necrosis
Garcia Lozano 1992	No diagnostic accuracy data on pancreatic necrosis
Garcia-Cantu 2004	No diagnostic accuracy data on pancreatic necrosis
Gelfand 2005	No diagnostic accuracy data on pancreatic necrosis
Geng 2014	Not a primary study (review)
Gluskina 1967	Inadequate reference standard
Gosling 1992	Not a primary study (editorial)
Gross 1990	No diagnostic accuracy data on pancreatic necrosis
Guenther 2010	No diagnostic accuracy data on pancreatic necrosis
Gurda-Duda 2008	No diagnostic accuracy data on pancreatic necrosis
Gurleyik 2004	No diagnostic accuracy data on pancreatic necrosis
Gurleyik 2005	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Gvozdenovic 2001	No diagnostic accuracy data on pancreatic necrosis
Hamalainen 2002	No diagnostic accuracy data on pancreatic necrosis
Han 2011	No diagnostic accuracy data on pancreatic necrosis
Hjalmarsson 2009	No diagnostic accuracy data on pancreatic necrosis
Huang 2013	No diagnostic accuracy data on pancreatic necrosis
Huang 2015	No diagnostic accuracy data on pancreatic necrosis
Imamura 2002a	No diagnostic accuracy data on pancreatic necrosis
Imamura 2002b	No diagnostic accuracy data on pancreatic necrosis
Inagaki 1997	No diagnostic accuracy data on pancreatic necrosis
Isenmann 1993	No diagnostic accuracy data on pancreatic necrosis
Isogai 1998	No diagnostic accuracy data on pancreatic necrosis
Jia 2015	No diagnostic accuracy data on pancreatic necrosis
Jiang 2004	No diagnostic accuracy data on pancreatic necrosis
Jimenez 2015	No diagnostic accuracy data on pancreatic necrosis
Jimin 2015	No diagnostic accuracy data on pancreatic necrosis
Johnson 2003	Not a primary study (review)
Kaiyasah 2013	No diagnostic accuracy data on pancreatic necrosis
Kaya 2007	No diagnostic accuracy data on pancreatic necrosis
Kazda 2002	No diagnostic accuracy data on pancreatic necrosis
Khanna 2013	Inadequate reference standard
Khvatova 1973	No diagnostic accuracy data on pancreatic necrosis
Khvatova 1977	No diagnostic accuracy data on pancreatic necrosis
Kibar 2016	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Kim 2013a	No diagnostic accuracy data on pancreatic necrosis
Kim 2013b	No diagnostic accuracy data on pancreatic necrosis
Kitsanou 2004	No diagnostic accuracy data on pancreatic necrosis
Korczowski 2006	Not a primary study (review)
Kusnierz-Cabala 2004	No diagnostic accuracy data on pancreatic necrosis
Kylanpaa-Back 2001a	No diagnostic accuracy data on pancreatic necrosis
Kylanpaa-Back 2001b	No diagnostic accuracy data on pancreatic necrosis
Kylanpaa-Back 2001c	No diagnostic accuracy data on pancreatic necrosis
Leese 1987	No diagnostic accuracy data on pancreatic necrosis
Leese 1988	No diagnostic accuracy data on pancreatic necrosis
Lempinen 1999	No diagnostic accuracy data on pancreatic necrosis
Lempinen 2005	Not a primary study (review)
Lewandowski 2007	No diagnostic accuracy data on pancreatic necrosis
Li 2013	No diagnostic accuracy data on pancreatic necrosis
Liang 2014	No diagnostic accuracy data on pancreatic necrosis
Lindner 1995	No diagnostic accuracy data on pancreatic necrosis
Lipsett 2001	Not a primary study (editorial)
Liu 2008	Not a primary study (review)
Lobo 1999	No diagnostic accuracy data on pancreatic necrosis
Lott 1991	Not a primary study (editorial)
Ma 2013	No diagnostic accuracy data on pancreatic necrosis
Machiedo 1974	Inappropriate population
Makay 2003	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Makela 2007	No diagnostic accuracy data on pancreatic necrosis
Malfertheiner 1993	Not a primary study (review)
Manabe 2004	Not a primary study (editorial)
Mandi 2000a	No diagnostic accuracy data on pancreatic necrosis
Mandi 2000b	No diagnostic accuracy data on pancreatic necrosis
Manes 1994	No diagnostic accuracy data on pancreatic necrosis
Mantke 2002	No diagnostic accuracy data on pancreatic necrosis
Marek 1996	No diagnostic accuracy data on pancreatic necrosis
Mayer 1984	No diagnostic accuracy data on pancreatic necrosis
Mayer 2002	No diagnostic accuracy data on pancreatic necrosis
Melzi D'Eril 2000	No diagnostic accuracy data on pancreatic necrosis
Millat 1999	Not a primary study (review)
Modrau 2005	No diagnostic accuracy data on pancreatic necrosis
Modzelewski 2005	No diagnostic accuracy data on pancreatic necrosis
Mulholland 1996	Not a primary study (review)
Muller 1997	No diagnostic accuracy data on pancreatic necrosis
Muller 2000	No diagnostic accuracy data on pancreatic necrosis
Neoptolemos 2001	Not a primary study (letter to editor)
Nunes 2009	No diagnostic accuracy data on pancreatic necrosis
Oezcueruemez-Porsch 1998	No diagnostic accuracy data on pancreatic necrosis
Olah 2005	No diagnostic accuracy data on pancreatic necrosis
Omoto 2015	No diagnostic accuracy data on pancreatic necrosis
Ostrovskii 2012	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Paajanen 1995	No diagnostic accuracy data on pancreatic necrosis
Palani 1977	No diagnostic accuracy data on pancreatic necrosis
Pallisera 2014	Inadequate reference standard
Park 2012	No diagnostic accuracy data on pancreatic necrosis
Park 2013	No diagnostic accuracy data on pancreatic necrosis
Petrov 2011	Not a primary study (editorial)
Pezzilli 1994	No diagnostic accuracy data on pancreatic necrosis
Pezzilli 1995a	No diagnostic accuracy data on pancreatic necrosis
Pezzilli 1995b	No diagnostic accuracy data on pancreatic necrosis
Pezzilli 1997	No diagnostic accuracy data on pancreatic necrosis
Pezzilli 1998a	No diagnostic accuracy data on pancreatic necrosis
Pezzilli 1998b	Inappropriate index test
Pezzilli 2000	No diagnostic accuracy data on pancreatic necrosis
Pongprasobchai 2010	No diagnostic accuracy data on pancreatic necrosis
Puolakkainen 1987	Inappropriate reference standards
Purkayastha 2006	Not a primary study (review)
Qiu 2014	No diagnostic accuracy data on pancreatic necrosis
Raraty 2002	No diagnostic accuracy data on pancreatic necrosis
Rau 1997	No diagnostic accuracy data on pancreatic necrosis
Rau 2000	No diagnostic accuracy data on pancreatic necrosis
Rau 2004	Not a primary study (review)
Rau 2007	No diagnostic accuracy data on pancreatic necrosis
Ricardo 2011	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Riche 2003	No diagnostic accuracy data on pancreatic necrosis
Ruzafa 1991	No diagnostic accuracy data on pancreatic necrosis
Samso 2002	Not a primary study (editorial)
Sanchez-Lozada 2005	No diagnostic accuracy data on pancreatic necrosis
Santotoribio 2015	No diagnostic accuracy data on pancreatic necrosis
Sato 2004	No diagnostic accuracy data on pancreatic necrosis
Savel'ev 2002	No diagnostic accuracy data on pancreatic necrosis
Schaffler 2010	inadequate reference standard
Schaffler 2011	No diagnostic accuracy data on pancreatic necrosis
Sharma 2011	No diagnostic accuracy data on pancreatic necrosis
Stimac 2010	No diagnostic accuracy data on pancreatic necrosis
Stimac 2012	No diagnostic accuracy data on pancreatic necrosis
Stimac 2013	No diagnostic accuracy data on pancreatic necrosis
Stoelben 1996	No diagnostic accuracy data on pancreatic necrosis
Sugumar 2011	No diagnostic accuracy data on pancreatic necrosis
Tao 2013	No diagnostic accuracy data on pancreatic necrosis
Teerenhovi 1988	No diagnostic accuracy data on pancreatic necrosis
Tesinsky 2008	No diagnostic accuracy data on pancreatic necrosis
Trunin 1985	No diagnostic accuracy data on pancreatic necrosis
Uhl 1991	No diagnostic accuracy data on pancreatic necrosis
Uomo 1995	No diagnostic accuracy data on pancreatic necrosis
Vaz 2013	No diagnostic accuracy data on pancreatic necrosis
Vesentini 1993	No diagnostic accuracy data on pancreatic necrosis

(*Continued*)

Viedma 1992	No diagnostic accuracy data on pancreatic necrosis
Viedma 1994	No diagnostic accuracy data on pancreatic necrosis
Vlachos 2014	No diagnostic accuracy data on pancreatic necrosis
Wei 2013	No diagnostic accuracy data on pancreatic necrosis
Wetherill 2012	No diagnostic accuracy data on pancreatic necrosis
Wetherill 2013a	No diagnostic accuracy data on pancreatic necrosis
Wetherill 2013b	No diagnostic accuracy data on pancreatic necrosis
Wilson 1987	No diagnostic accuracy data on pancreatic necrosis
Wilson 1988	No diagnostic accuracy data on pancreatic necrosis
Wilson 1989a	No diagnostic accuracy data on pancreatic necrosis
Wilson 1989b	Not a primary study (letter to editor)
Wong 1993	Case reports
Woo 2011	No diagnostic accuracy data on pancreatic necrosis
Xu 2015	No diagnostic accuracy data on pancreatic necrosis
Yadav 2015a	No diagnostic accuracy data on pancreatic necrosis
Yadav 2015b	No diagnostic accuracy data on pancreatic necrosis
Yasuda 2011	No diagnostic accuracy data on pancreatic necrosis
Yin 2014	No diagnostic accuracy data on pancreatic necrosis
Yu 2011	No diagnostic accuracy data on pancreatic necrosis
Zhu 2013	No diagnostic accuracy data on pancreatic necrosis
Zrnic 2007	No diagnostic accuracy data on pancreatic necrosis

Characteristics of studies awaiting classification *[ordered by study ID]*

Djurasinovic 2013

Study characteristics		Study character
Patient sampling	Unable to obtain full text	
Patient characteristics and setting		
Index tests		
Target condition and reference standard(s)		
Flow and timing		
Comparative		
Notes		

Grenier 1968

Study characteristics		Study character
Patient sampling	Unable to obtain full text	
Patient characteristics and setting		
Index tests		
Target condition and reference standard(s)		
Flow and timing		
Comparative		
Notes		

Issekutz 2003

Study characteristics		Study character
Patient sampling	Unable to obtain full text	

Issekutz 2003 (*Continued*)

Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	

Pindak 2003

Study characteristics		**Study character**
Patient sampling	Unable to obtain full text	
Patient characteristics and setting		
Index tests		
Target condition and reference standard(s)		
Flow and timing		
Comparative		
Notes		

DATA

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

Tests. Data tables by test

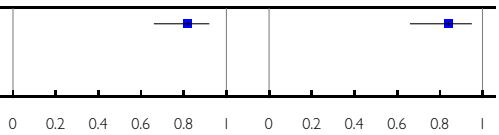
Test	No. of studies	No. of participants
1 C-reactive protein (day 3) > 140 mg/L	1	70
2 C-reactive protein (day not stated) > 200 mg/L	1	157
3 C-reactive protein (day not stated) > 279 mg/L	1	157
4 Procalcitonin (day 1) > 0.5 ng/mL	1	15
5 Lactate dehydrogenase (day 5) > 290 U/L	1	70

Test 1. C-reactive protein (day 3) > 140 mg/L.

Review: Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis

Test: 1 C-reactive protein (day 3) > 140 mg/L

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Rau 1998	32	5	7	26	0.82 [0.66, 0.92]	0.84 [0.66, 0.95]		



Test 2. C-reactive protein (day not stated) > 200 mg/L.

Review: Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis

Test: 2 C-reactive protein (day not stated) > 200 mg/L

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Alfonso 2003	22	33	3	99	0.88 [0.69, 0.97]	0.75 [0.67, 0.82]		

Test 3. C-reactive protein (day not stated) > 279 mg/L.

Review: Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis

Test: 3 C-reactive protein (day not stated) > 279 mg/L

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Alfonso 2003	18	15	7	117	0.72 [0.51, 0.88]	0.89 [0.82, 0.93]		

Test 4. Procalcitonin (day 1) > 0.5 ng/mL.

Review: Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis

Test: 4 Procalcitonin (day 1) > 0.5 ng/mL

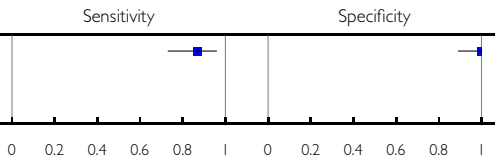
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Bertsch 1997	6	3	2	4	0.75 [0.35, 0.97]	0.57 [0.18, 0.90]		

Test 5. Lactate dehydrogenase (day 5) > 290 U/L.

Review: Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis

Test: 5 Lactate dehydrogenase (day 5) > 290 U/L

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rau 1998	34	0	5	31	0.87 [0.73, 0.96]	1.00 [0.89, 1.00]



ADDITIONAL TABLES

Table 1. Acute pancreatitis classification

Mild acute pancreatitis	Moderate acute pancreatitis	Severe acute pancreatitis
• No local or systemic complications. • No organ failure. • Interstitial oedematous pancreatitis.	• Local or systemic complications (peripancreatic fluid collection, pancreatic pseudocyst, necrosis) may be present. • Transient organ failure (up to 48 hrs) may be present. • May be interstitial oedematous pancreatitis or necrotising pancreatitis. • Necrotising pancreatitis may be infected or sterile.	• Local or systemic complications may be present. • Persistent organ failure (> 48 hrs) present. • May be interstitial oedematous pancreatitis or necrotising pancreatitis. • Necrotising pancreatitis may be infected or sterile.

Table 2. QUADAS-2 classification (acute necrotising pancreatitis)

Domain 1: Participant selection	Patient sampling	Adult participants with acute pancreatitis and without organ failure
	Was a consecutive or random sample of patients enrolled?	Yes: If a consecutive sample or a random sample of participants with acute pancreatitis and without organ failure was included in the study. No: If a consecutive sample or a random sample of participants with acute pancre-

Table 2. QUADAS-2 classification (acute necrotising pancreatitis) (*Continued*)

		atitis and without organ failure was not included in the study. Unclear: If this information was not available.
	Did the study avoid inappropriate exclusions?	Yes: If all participants with acute pancreatitis and without organ failure were included. No: If the study excluded participants based on high or low probability of pancreatic necrosis (e.g. those with normal white cell count were excluded). Unclear: If this information was not available.
	Could the selection of participants have introduced bias?	Low risk of bias: If 'yes' classification for both of the above two questions High risk of bias: If 'no' classification for either of the above two questions Unclear risk of bias: If 'unclear' classification for either of the above two questions, but without a 'no' classification for either of the above two questions
	Participant characteristics and setting	We recorded the following characteristics: sample size, females, age, presentation (inclusion and exclusion criteria), and setting (primary or secondary care and country)
	Are there concerns that the included participants and setting do not match the review question?	Low concern: If the participant characteristics and setting is classified as 'yes' Unclear concern: If the participant characteristics and setting is classified as 'unclear' High concern: If the participant characteristics and setting is classified as 'no'
Domain 2: Index test	Index test(s)	Serum C-reactive protein, procalcitonin, lactate dehydrogenase
	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 is conducted and interpreted without knowledge of the results of the reference standard. No: If the index test is interpreted with knowledge of the results of the reference standard. Unclear: If it is not clear whether the index test was interpreted without knowledge of

Table 2. QUADAS-2 classification (acute necrotising pancreatitis) (*Continued*)

		the results of the reference standard
	If a threshold was used, was it prespecified?	Yes: If a prespecified threshold was used. No: If a prespecified threshold was not used. Unclear: If it was not clear whether the threshold used was prespecified
	Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias: If 'yes' classification for both of the above two questions High risk of bias: If 'no' classification for either of the above two questions Unclear risk of bias: If 'unclear' classification for either of the above two questions, but without a 'no' classification for either of the above two questions
	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 were clearly stated High concern: If the criteria for positive index test were not stated
Domain 3: Target condition and reference standard	Target condition and reference standard(s)	Target condition: pancreatic or peripancreatic necrosis (infected or sterile) While considered to be the gold standard for confirming necrosis, biopsy may not have been performed in all participants due to ethical concerns over performing an invasive treatment (during which biopsy is taken) in those without a diagnosis of pancreatic necrosis. As a result, study authors may use radiological features of pancreatic necrosis (an area of impairment enhancement or non-enhancing area of pancreatic parenchyma on CECT) or surgical features of pancreatic necrosis during surgery (presence of necrotic tissue). However, this reference standard may miss some cases of pancreatic necrosis In terms of ranking the reference standards, we considered biopsy in all participants as the best reference standard (although it is unlikely to be performed in participants with negative test for pancreatic necrosis) followed by biopsy in participants with positive test and radiological or surgical features of pancreatic necrosis in participants with negative test, and radiological tests or surgical tests alone as the reference stan-

Table 2. QUADAS-2 classification (acute necrotising pancreatitis) (*Continued*)

		dard, in that order
	Is the reference standard likely to correctly classify the target condition?	Yes: If histological confirmation of pancreatic necrosis was obtained in all participants or at least all participants with positive test. No: If the reference standard was CECT (or contrast enhanced MRI) in all participants Unclear: If the reference standard was not described adequately
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes: If the reference standard was interpreted without knowledge of the results of the index test. No: If the reference standard was interpreted with knowledge of the results of the index test. Unclear: If it was not clear if the reference standard was interpreted without knowledge of the results of the index test
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias: If 'yes' classification for both of the above two questions High risk of bias: If 'no' classification for either of the above two questions Unclear risk of bias: If 'unclear' classification for either of the above two questions, but without a 'no' classification for either of the above two questions As anticipated, we assessed all studies as at high risk of bias as they all used CECT or surgery as the reference standard and were therefore classified as 'no' for the question "Is the reference standard likely to correctly classify the target condition?"
	Are there concerns that the target condition as defined by the reference standard does not match the question?	As anticipated, considering the inclusion criteria for this review, we classified all of the included studies as 'low concern', as they all reported on pancreatic necrosis
Domain 4: Flow and timing	Flow and timing	Participants may have progression or regression of pancreatic necrosis if there is a long delay between index test and reference standard. In addition, participants may receive treatment for organ failure if they develop organ failure between the index test and reference standard. We anticipated that a radiological investigation would have

Table 2. QUADAS-2 classification (acute necrotising pancreatitis) (*Continued*)

		been performed within 24 hours of diagnosis of organ failure. Pancreatic necrosis does not resolve in 24 hours, and there will be no alteration of the final diagnosis by the treatment in participants with pancreatic necrosis. People with oedematous pancreatitis and organ failure may develop pancreatic necrosis in the absence of appropriate treatment. Consequently there is a possible interaction between inadequate treatment and the final diagnosis. We have minimised this misclassification error due to the final diagnosis being altered by inappropriate treatment by choosing 24 hours 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 24 hours. No: If the time interval between index test and reference standard was more than 24 hours. Unclear: If the time interval between index test and reference standard was unclear
	Did all participants receive a reference standard?	Yes: If all participants received a reference standard. No: If some participants did not receive a reference standard. Such studies were excluded. Unclear: If it was not clear whether all participants received a reference standard. Such studies were excluded As anticipated, we classified all studies included in the review as 'yes' for this item
	Did all participants receive the same reference standard?	Yes: If all participants received the same reference standard. No: If the reference standard participants received varied. Unclear: If this information was not clear.
	Were all participants included in the analysis?	Yes: If all participants were included in the analysis irrespective of whether the results were interpretable. No: If some participants were excluded from the analysis because of uninterpretable results.

Table 2. QUADAS-2 classification (acute necrotising pancreatitis) (*Continued*)

		Unclear: If this information was not clear.
	Could the patient flow have introduced bias?	Low risk of bias: If 'yes' classification for all of the above four questions High risk of bias: If 'no' classification for any of the above four questions Unclear risk of bias: If 'unclear' classification for any of the above four questions, but without a 'no' classification for any of the above four questions

CECT: contrast enhanced computed tomography
MRI: magnetic resonance imaging

APPENDICES

Appendix 1. Glossary of terms

Adipose: fat.
Aetiology: cause.
Autodigestion: breaking down of the same organ that secretes the substance.
Debridement: surgical removal of damaged, dead, or infected tissue; in this context, identical with necrosectomy.
Endoscopic: using an endoscope, a flexible tube with a light and camera attached to it to view the inner aspects of the food pipe, stomach, and upper small intestine.
Epigastric: upper central abdomen.
Heterogeneity: differences between studies.
Histological: by examination of the tissue under a microscope.
Hyperamylasaemia: excess amylase in circulation.
Inflammation: localised physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to injury or infection.
Interstitial: small, narrow spaces between tissues or parts of an organ.
Intraperitoneal: inside the abdominal cavity.
Laparoscopic: key-hole surgery.
Magnetic resonance cholangiopancreatography: medical imaging technique that uses magnetic resonance imaging (use of magnetic field to differentiate between different structures) to visualise the biliary and pancreatic ducts in a non-invasive manner.
Necrosectomy: removal of dead tissue.
Necrosis: death and decomposition of living tissue usually caused by lack of blood supply, but can be the result of other pathological insult.
Necrotising: presence of necrosis.
Oedema: swelling.
Oedematous: tissue with an excess of interstitial fluid.
Pancreatic ductal system: tubular system that transports the pancreatic juice secreted by the pancreatic cells to the small intestine.
Pancreatic pseudocysts: fluid collections in the pancreas or the tissues surrounding the pancreas, enclosed by a well-defined wall and containing only fluid with little or no solid material.
Pancreatitis: inflammation of the pancreas.

Parenchyma: functional parts of an organ.
Paucity: insufficient.
Percutaneous: through the skin.
Percutaneous drainage: drainage carried out by insertion of drain from the external surface of the body, usually guided by an ultrasound or computed tomography (CT) scan.
Peripancreatic tissues: tissues surrounding the pancreas.
Radiating to the back: pain in front going to the back (in this context).
Retroperitoneal: behind the abdominal cavity.
Sphincterotomy: partial division of the sphincter of Oddi, a circular band of muscle at the junction of the biliary tree (tubes that conduct bile from the liver to the small intestine) and pancreatic duct (tubes that conduct pancreatic juice into the second part of the duodenum).
Transabdominal: through the abdominal cavity.
Transluminal: through the lumen (inner cavity of a tubular structure).
Transperitoneal: through the abdominal cavity.
Ultrasonography: using high-frequency sound to view internal structures of the body (in this context).

Appendix 2. MEDLINE search strategy

1. Pancreatitis, Acute Necrotizing/
2. Pancreatitis/et
3. Pancreas/ab, pa, pp
4. (acute adj3 pancrea*).mp.
5. (necro* adj3 pancrea*).mp.
6. (inflam* adj3 pancrea*).mp.
7. ((interstitial or edema* or oedema*) adj2 pancrea*).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Amylases/ or exp Lipase/ or exp Trypsinogen/
10. (amylase or lipase or trypsinogen or hyperamylasaemia or hyperamylasemia).mp.
11. exp C-Reactive Protein/
12. ("c-reactive protein" or "c reactive protein" or CRP).mp.
13. procalcitonin.mp.
14. exp L-Lactate Dehydrogenase/
15. ("lactate dehydrogenase" or LDH).mp.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 8 and 16

Appendix 3. Embase search strategy

1. acute hemorrhagic pancreatitis/
2. Pancreatitis/et
3. acute pancreatitis/
4. (acute adj3 pancrea*).mp.
5. (necro* adj3 pancrea*).mp.
6. (inflam* adj3 pancrea*).mp.
7. ((interstitial or edema* or oedema*) adj2 pancrea*).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp amylase/
10. exp triacylglycerol lipase/
11. exp trypsinogen/
12. (amylase or lipase or trypsinogen or hyperamylasaemia or hyperamylasemia).mp.
13. exp C reactive protein/
14. ("c-reactive protein" or "c reactive protein" or CRP).mp.

15. exp procalcitonin/
16. procalcitonin.mp.
17. exp lactate dehydrogenase/
18. ("lactate dehydrogenase" or LDH).mp.
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 8 and 19

Appendix 4. Science Citation Index and Conference Proceedings Citation Index-Science search strategy

1 TS=((acute or necro* or inflam* or interstitial or edema* or oedema*) near/3 pancrea*)
2 TS=(amylase or lipase or trypsinogen or hyperamylasaemia or hyperamylasemia or "c-reactive protein" or "c reactive protein" or CRP or procalcitonin or "lactate dehydrogenase" or LDH)
3 #2 AND #1

Appendix 5. National Institute for Health Research - HTA and DARE search strategy

acute pancreatitis

Appendix 6. Zetoc search strategy

Each of the following lines will be searched separately. since the Boolean operator 'or' is not available for searching Zetoc database.
1. acute pancreatitis amylase
2. acute pancreatitis lipase
3. acute pancreatitis trypsinogen
4. acute pancreatitis hyperamylasaemia
5. acute pancreatitis hyperamylasemia
6. acute pancreatitis "c-reactive protein"
7. acute pancreatitis "c reactive protein"
8. acute pancreatitis CRP
9. acute pancreatitis procalcitonin
10. acute pancreatitis "lactate dehydrogenase"
11. acute pancreatitis LDH

Appendix 7. WHO ICTRP search strategy

Title: (amylase or lipase or trypsinogen or hyperamylasaemia or hyperamylasemia or "c-reactive protein" or "c reactive protein" or CRP or procalcitonin or "lactate dehydrogenase" or LDH)
Condition: acute pancreatitis

Appendix 8. ClinicalTrials.gov search strategy

amylase OR lipase OR trypsinogen OR hyperamylasaemia OR hyperamylasemia OR "c-reactive protein" OR "c reactive protein" OR CRP OR procalcitonin OR "lactate dehydrogenase" OR LDH | acute pancreatitis

CONTRIBUTIONS OF AUTHORS

Oluyemi Komolafe wrote the first draft of the review.

Kurinchi Selvan Gurusamy wrote the protocol and revised the review.

Stephen P Pereira and Brian R Davidson critically commented on the review.

DECLARATIONS OF INTEREST

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OK: none known.

SPP: none known.

BRD: none known.

KSG: none known.

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External sources

- National Institute for Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As per protocol, we accepted any of the following reference standards, used alone or in combination: radiological features of pancreatic necrosis (contrast-enhanced computed tomography or magnetic resonance imaging) or histological confirmation of pancreatic necrosis. In addition, we also included a combination of radiological features of pancreatic necrosis (contrast-enhanced computed tomography or magnetic resonance imaging) and surgeon's judgement of pancreatic necrosis during surgery, as we considered this equivalent to radiologist judgement of the presence of pancreatic necrosis on radiology.