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Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis (Review)

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TABLE OF CONTENTS

[Diagnostic Test Accuracy Review]

Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

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ABSTRACT

Background

The treatment of people with acute abdominal pain differs if they have acute pancreatitis. It is important to know the diagnostic accuracy of serum amylase, serum lipase, urinary trypsinogen-2, and urinary amylase for the diagnosis of acute pancreatitis, so that an informed decision can be made as to whether the person with abdominal pain has acute pancreatitis. There is currently no Cochrane review of the diagnostic test accuracy of serum amylase, serum lipase, urinary trypsinogen-2, and urinary amylase for the diagnosis of acute pancreatitis.

Objectives

To compare the diagnostic accuracy of serum amylase, serum lipase, urinary trypsinogen-2, and urinary amylase, either alone or in combination, in the diagnosis of acute pancreatitis in people with acute onset of a persistent, severe epigastric pain or diffuse abdominal pain.

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 serum amylase, serum lipase, urinary trypsinogen-2, and urinary amylase for the diagnosis of acute pancreatitis. We excluded case-control studies because these studies are prone to bias. We accepted any of the following reference standards: biopsy, consensus conference definition, radiological features of acute pancreatitis, diagnosis of acute pancreatitis during laparotomy or autopsy, and organ failure. At least two review authors independently searched and screened the references located by the search to identify relevant studies.

Data collection and analysis

Two review authors independently extracted data from the included studies. The thresholds used for the diagnosis of acute pancreatitis varied in the trials, resulting in sparse data for each index test. Because of sparse data, we used -2 log likelihood values to determine which model to use for meta-analysis. We calculated and reported the sensitivity, specificity, post-test probability of a positive and negative index test along with 95% confidence interval (CI) for each cutoff, but have reported only the results of the recommended cutoff of three times normal for serum amylase and serum lipase, and the manufacturer-recommended cutoff of 50 mg/mL for urinary trypsinogen-2 in the abstract.

Main results

Ten studies including 5056 participants met the inclusion criteria for this review and assessed the diagnostic accuracy of the index tests in people presenting to the emergency department with acute abdominal pain. The risk of bias was unclear or high for all of the included studies. The study that contributed approximately two-thirds of the participants included in this review was excluded from the results of the analysis presented below due to major concerns about the participants included in the study. We have presented only the results where at least two studies were included in the analysis.

Serum amylase, serum lipase, and urinary trypsinogen-2 at the standard threshold levels of more than three times normal for serum amylase and serum lipase, and a threshold of 50 ng/mL for urinary trypsinogen-2 appear to have similar sensitivities (0.72 (95% CI 0.59 to 0.82); 0.79 (95% CI 0.54 to 0.92); and 0.72 (95% CI 0.56 to 0.84), respectively) and specificities (0.93 (95% CI 0.66 to 0.99); 0.89 (95% CI 0.46 to 0.99); and 0.90 (95% CI 0.85 to 0.93), respectively). At the median prevalence of 22.6% of acute pancreatitis in the studies, out of 100 people with positive test, serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL), 74 (95% CI 33 to 94); 68 (95% CI 21 to 94); and 67 (95% CI 57 to 76) people have acute pancreatitis, respectively; out of 100 people with negative test, serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL), 8 (95% CI 5 to 12); 7 (95% CI 3 to 15); and 8 (95% CI 5 to 13) people have acute pancreatitis, respectively. We were not able to compare these tests formally because of sparse data.

Authors' conclusions

As about a quarter of people with acute pancreatitis fail to be diagnosed as having acute pancreatitis with the evaluated tests, one should have a low threshold to admit the patient and treat them for acute pancreatitis if the symptoms are suggestive of acute pancreatitis, even if these tests are normal. About 1 in 10 patients without acute pancreatitis may be wrongly diagnosed as having acute pancreatitis with these tests, therefore it is important to consider other conditions that require urgent surgical intervention, such as perforated viscus, even if these tests are abnormal.

The diagnostic performance of these tests decreases even further with the progression of time, and one should have an even lower threshold to perform additional investigations if the symptoms are suggestive of acute pancreatitis.

PLAIN LANGUAGE SUMMARY

Blood and urine tests for the diagnosis of acute pancreatitis (sudden inflammation of pancreas)

Background

The pancreas is an organ in the abdomen (tummy) that secretes several digestive enzymes (substances that break down the food 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 such as insulin (which helps regulate blood sugar). Acute pancreatitis is sudden inflammation of the pancreas, which can lead to damage of the heart, lungs, and kidneys and cause them to fail. Acute pancreatitis usually manifests as upper abdominal pain radiating to the back. However, there are several potential causes of upper abdominal pain. It is important to determine if someone with abdominal pain has acute pancreatitis or another illness in order to start appropriate treatment. Blood tests such as serum amylase and serum lipase, as well as urine tests such as urinary trypsinogen-2 and urinary amylase, can be used to determine if someone with abdominal pain has acute pancreatitis. It is usually the case that a patient is considered to have acute pancreatitis only when amylase or lipase levels are three times the upper limit of normal. With regard to urinary trypsinogen-2, a level of more than 50 ng/mL of trypsinogen-2 in the urine is considered an indication of acute pancreatitis. With regard to urinary amylase, there is no clear-cut level beyond which someone with abdominal pain is considered to have acute pancreatitis. At present it is unclear whether these tests are equally effective or if one of the tests is better than the other in the diagnosis of acute pancreatitis in people with sudden-onset abdominal

pain. We determined to resolve this question by performing a literature search for studies reporting the accuracy of the above mentioned blood and urine tests. We included studies reported until 20 March 2017.

Study characteristics

We identified 10 studies reporting information on 5056 people with abdominal pain that started suddenly. The studies included pancreatitis due to all causes.

Quality of evidence

All of the studies were of unclear or low methodological quality, which may result in arriving at false conclusions. We excluded the study that contributed approximately two-thirds of the participants included in this review from the results of the analysis presented below due to concerns about whether the participants included in the study are typical of those seen in the emergency department.

Key results

The accuracy of serum amylase, serum lipase, and urinary trypsinogen-2 in making the diagnosis of acute pancreatitis was similar. About a quarter of people with acute pancreatitis fail to be diagnosed as having acute pancreatitis with these tests. The patient should be admitted and treated as having acute pancreatitis, even if these tests are normal, if there is a suspicion of acute pancreatitis. As about 1 in 10 patients without acute pancreatitis may be wrongly diagnosed as having acute pancreatitis with these tests, it is important to consider other conditions that require urgent surgery, even if these tests are abnormal. The diagnostic performance of these tests decreases even further with the progression of time, and additional investigations should be performed if there is a suspicion of acute pancreatitis.

BACKGROUND

The pancreas is an abdominal organ that secretes several digestive enzymes into the pancreatic ductal system, which empties into the small bowel. It also houses the islets of Langerhans, which secrete several hormones including insulin (NCBI 2014). 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 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 cases of acute pancreatitis 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).

- Acute onset of a persistent, severe epigastric pain often radiating to the back.
- Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal.
- 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, including spreading of the infection 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 col-

lection, and walled-off necrosis (Banks 2013). The 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). The mortality rate depends upon the severity of 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 complications, 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).

See Appendix 1 for a glossary of terms.

Target condition being diagnosed

Acute pancreatitis in people with acute epigastric pain or diffuse abdominal pain.

Index test(s)

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

Serum amylase

Amylase is an enzyme secreted by the pancreas. Various other tissues including salivary glands, small intestine, ovaries, adipose tissue, and skeletal muscles secrete amylase. There are two major isoforms of amylase: pancreatic amylase and salivary amylase. The normal range of amylase varies between laboratories, but is usually between 100 international units (IU)/L to 300 IU/L (Vissers 1999). Acute pancreatitis is one cause of increased amylase (hyperamylasaemia). The reason for this elevation is unclear, although capillary leakage due to obstruction of venous and lymphatic drainage of pancreatic and peripancreatic tissues, and transperitoneal absorption of amylase may be responsible (Vissers 1999). In acute pancreatitis, serum amylase levels usually rise within 6 to 24 hours, peak at 48 hours, and decrease to normal or near normal levels over the next 5 to 7 days (Vissers 1999). A common threshold used is three times the normal limit (Banks 2013).

Serum lipase

Lipase is another enzyme secreted by the pancreas. Acute pancreatitis is the main reason for an increase in lipase, although a number of other conditions such as chronic pancreatitis, acute cholecystitis, and bowel obstruction can increase lipase activity (Vissers 1999). In acute pancreatitis, serum lipase levels usually rise within 4 to 8 hours, peak at 24 hours, and decrease to normal or near normal levels over the next 8 to 14 days. Serum lipase remains elevated for a longer period of time compared to the period of elevation of serum amylase after acute pancreatitis (Vissers 1999). A common threshold used is three times the normal limit (Banks 2013).

Urinary trypsinogen level

Autodigestion because of trypsinogen activation is one of the mechanisms believed to result in acute pancreatitis. Since trypsinogen levels are elevated in acute pancreatitis, measurement of urinary trypsinogen-2 (an isoenzyme of trypsinogen) has been proposed as a test for diagnosing pancreatitis (Hedstrom 1994; Hedstrom 1996; Hedstrom 1996c). In acute pancreatitis, urinary trypsinogen levels usually rise to high levels within a few hours and decrease in three days (Matull 2006). A common threshold used is 50 ng/mL (Chang 2012).

Urinary amylase

Urinary amylase above 2000 IU/L is considered abnormal. Measurement of urinary amylase has been proposed as a test for the diagnosis of pancreatitis (Hedstrom 1996c; Kemppainen 1997c).

Clinical pathway

For people with acute onset of a persistent, severe epigastric pain or with diffuse abdominal pain starting 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 (index tests being evaluated in this review) 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 CT scan

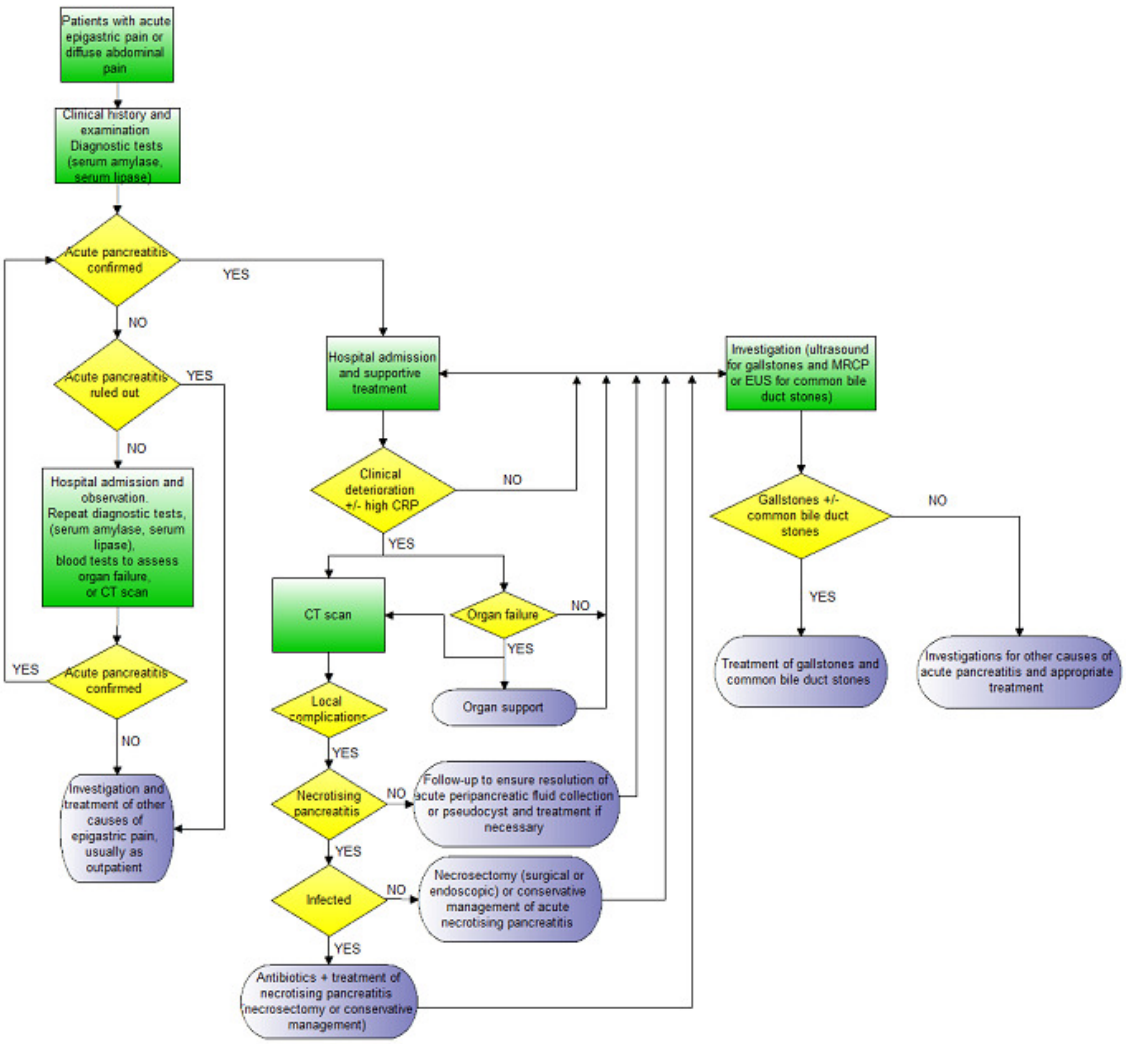
or MRI is not routinely performed if a diagnosis of acute pancreatitis is suspected. If acute pancreatitis can be ruled out, other causes of acute epigastric pain should be considered. Peptic ulcer, functional dyspepsia, and gallstones can present with acute epigastric pain (Gurusamy 2014; Moayyedi 2006). All of these alternative causes of epigastric pain are generally investigated and treated after discharge of the patient 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 patient is admitted to hospital and the severity of pancreatitis is 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 acute pancreatitis (Gurusamy 2013). Endoscopic sphincterotomy or common bile duct exploration may have 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. Patients are generally monitored clinically. If the patient improves clinically with supportive treatment, the patient with gallstone pancreatitis is discharged after cholecystectomy or after scheduling a cholecystectomy or on a planned list, within two weeks. For those patients with severe acute pancreatitis, cholecystectomy is undertaken when clinically appropriate after resolution of pancreatitis. If the patient deteriorates clinically, the patient undergoes a CT scan and may require high-dependency or intensive care in the presence of organ failure or infected pancreatic necrosis.

In the presence of organ failure, patients undergo a CT scan or MRI to identify any local complications. C-reactive protein, procalcitonin, and lactate dehydrogenase might distinguish between oedematous and necrotising pancreatitis (Alfonso 2003; Khanna 2013; Rau 1998), and could potentially be used as a triage test to identify patients who need further radiological tests in those without organ failure (Alfonso 2003). Some centres use C-reactive protein routinely to determine whether patients require radiological investigations to diagnose necrotising pancreatitis. Frequently, the rising trend in C-reactive protein, procalcitonin, or lactate dehydrogenase, rather than a single test, may be used to determine whether patients require radiological investigations to diagnose necrotising pancreatitis. It must 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 because of the results of the serum C-reactive protein. The various treatment strategies for 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 participants 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). If patients have infected pancreatic necrosis, appropriate antibiotics are administered in addition to the treatment outlined above for non-infected pancreatic necrosis. If patients have acute peripancreatic collections or pseudocysts on the radiological tests, clinical and radiological follow-up are required 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 patient 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 the patient does not have moderately severe or severe pancreatitis 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, patients 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 minimum prior test that is performed before these tests are conducted is clinical history and clinical examination, which includes obtaining the body temperature, heart rate, blood pressure, respiratory rate, and pulse oximetry (when available).

Role of index test(s)

The index tests are used for the diagnosis of acute pancreatitis in people with acute onset of a persistent, severe epigastric pain or 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). The current tests used are serum amylase and serum lipase. Urinary trypsinogen and urinary amylase are being evaluated as replacement tests for serum amylase and serum lipase.

Alternative test(s)

Other tests used in the diagnosis of acute pancreatitis include serum trypsinogen-2 (Hedstrom 1994), and radiological tests such as contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography (Banks 2013). Other biomarkers such as serum trypsin-2-alpha1-antitrypsin complex, carboxypeptidase B activation peptide (CAPAP), and urinary trypsinogen activation peptide (TAP) have been evaluated as diagnostic tests for acute pancreatitis (Hedstrom 1996d; Saez 2005), but these are not in routine use for the diagnosis of this condition.

Rationale

In addition to acute pancreatitis, there are several other causes of epigastric pain including peptic ulcer, functional dyspepsia, and gallstones (Gurusamy 2014; Moayyedi 2006). Of these various causes, people with acute pancreatitis and perforated peptic ulcer need emergency admission and treatment, while others may be discharged if pain control can be achieved. It is thus important to make a diagnosis of acute pancreatitis. Radiological findings of acute pancreatitis evolve over a few days, and the radiological examination may not demonstrate characteristic features in the early stages, or may even be normal (Banks 2013; Vissers 1999), thus radiological tests are not routinely performed for diagnosing this condition. In addition, acute pancreatitis can mimic perforated peptic ulcer (Kuzmich 2012), which is usually treated by surgery. Correct diagnosis of acute pancreatitis can avoid unnecessary surgery. Hence, an accurate diagnostic test for the diagnosis of acute pancreatitis is essential in people with suspected acute pancreatitis. Serum amylase and lipase are the tests most commonly used in the diagnosis of acute pancreatitis. It is important to understand the diagnostic accuracy of these tests. Urinary trypsinogen and amylase have been investigated as alternate tests, and it is important to understand whether they can replace serum amylase and lipase in the diagnosis of acute pancreatitis. If one or more of the tests being assessed has a high degree of accuracy, patients with acute pancreatitis can be identified and managed appropriately. At the same time, unnecessary hospital admission for observation can be avoided in patients without acute pancreatitis, resulting in considerable resource savings. There has been no systematic review and meta-analysis of the diagnostic accuracy of serum lipase and amylase activity or urinary amylase in the diagnosis of acute pancreatitis. The current consensus criteria about diagnosis of acute pancreatitis included serum lipase or amylase activity at least three times greater than the upper limit of normal as one of the criteria for diagnosis of acute pancreatitis (two of the three criteria must be met, the other two being acute abdominal pain and imaging characteristic of acute pancreatitis) (Banks 2013). However, these criteria are based on consensus rather than on systematic reviews. In addition, the threshold for amylase or lipase may need to be revised from three times normal to a different threshold if these tests are accurate at different thresholds. If this systematic review found that urinary amylase or trypsinogen-2 were better than serum amylase or lipase, the criteria for the diagnosis of acute pancreatitis would need to be altered. There have been two systematic reviews on the diagnostic test accuracy of urinary trypsinogen-2 in the diagnosis of acute pancreatitis (Chang 2012; Jin 2013). In both reviews, language restrictions (English and Chinese) were present. The searches were performed in 2011 and 2012, respectively. Only one of the reviews used appropriate statistical analysis (Chang 2012). There has been no Cochrane review on the role of urinary trypsinogen-2 in the diagnosis of acute pancreatitis. The change in diagnostic accuracy of these tests with different time intervals from presentation has not been previously assessed in a systematic review. A Cochrane systematic review of the diagnostic test accuracy of serum and urine tests in the diagnosis of acute pancreatitis was, therefore, necessary.

OBJECTIVES

To compare the diagnostic accuracy of serum amylase, serum lipase, urinary trypsinogen-2, and urinary amylase, either alone or in combination, in the diagnosis of acute pancreatitis in people with acute onset of a persistent, severe epigastric pain or diffuse abdominal pain.

Secondary objectives

We planned to explore the following sources of heterogeneity.

- Studies at low risk of bias in all of the domains 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 of organ failure. The accuracy of the test may depend upon the presence of organ failure.
- 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 patient population (see below). We included relevant studies irrespective of language or publication status (i.e. published as full text or abstract), 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 was made on an individual patient or a group of patients and which do not provide sufficient diagnostic test accuracy data, i.e. true positive, false positive, false negative, and true negative). We also excluded case-control studies because they are prone to bias (Whiting 2011).

Participants

Adults with acute epigastric or diffuse abdominal pain (with or without previous history of acute pancreatitis and with or without systemic signs and symptoms of acute pancreatitis), presenting to the hospital within three days of the onset of symptoms, irrespective of the interval between onset of symptoms and the time at which the test was performed.

Index tests

Serum amylase, serum lipase, urinary trypsinogen, and urinary amylase either alone or in combination. A variety of kits are available for measuring these tests. We included kits from all manufacturers, and included studies irrespective of the threshold used. Although we did not plan to include repeat tests, the diagnostic test accuracy of these index tests on later days might give some indication of the performance of these tests in patients with a prolonged period of symptoms before going to the hospital. We have therefore analysed and reported this information separately from the tests conducted on admission.

Target conditions

Acute pancreatitis (regardless of severity: mild, moderately severe, or severe)

Reference standards

While inflammation of the pancreas confirmed by biopsy can be considered to be the gold standard for the diagnosis of acute pancreatitis, for ethical reasons it is unlikely to be performed in any participant. As a result, different study authors may use different reference standards such as radiological features of acute pancreatitis or the presence of organ failure. However, such reference standards may miss some cases of mild acute pancreatitis, which will result in an underestimation of diagnostic test accuracy of the index tests. We also accepted the consensus conference definition of acute pancreatitis, that is when at least two of the following three features are present (Banks 2013).

- Acute onset of a persistent, severe epigastric pain often radiating to the back.
- Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal.
- Characteristic findings of acute pancreatitis on CECT, and less commonly on MRI or transabdominal ultrasonography.

We also accepted any of the following reference standards, used alone or in combination: biopsy, radiological features of acute pancreatitis (CT or MRI), diagnosis of acute pancreatitis during laparotomy or autopsy, organ failure, or the consensus conference definition (including or excluding the index test being evaluated). In terms of ranking the reference standards, we considered biopsy to be the best reference standard (although for ethical reasons it is unlikely to have been performed in any participant) followed by the consensus definition of acute pancreatitis; radiological, laparotomy, or autopsy features of acute pancreatitis; or the presence

of organ failure, in that order. However, we anticipated that the authors would exclude the test being assessed to be incorporated into the reference standard. For example, if serum amylase was being evaluated, the final diagnosis of acute pancreatitis would not depend upon the levels of serum amylase; this was not the case, as described below. If the test being assessed was incorporated into the reference standard, the diagnostic accuracy of the test would be overestimated.

Search methods for identification of studies

We included all studies irrespective of the language of publication and publication status. We obtained translations for 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 the same strategy for this review and another review on the diagnosis of pancreatic necrosis in people with established acute pancreatitis (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 (KSG and OK) independently searched the references to identify relevant studies. We obtained the full texts of references considered to be relevant by at least one of the review authors. Two review authors (KSG and GR or AH) independently screened the full-text papers against the inclusion criteria. Any disagreements in study selection were resolved by discussion. We planned to contact the study authors if there were any doubts about study eligibility.

Data extraction and management

Two review authors (KSG and GR or AH) independently extracted the following data from each included study using a data extraction form designed and piloted by KSG. Any differences were resolved by discussion.

1. First author.
2. Year of publication.
3. Study design (prospective or retrospective cohort studies; cross-sectional studies or randomised controlled trials).
4. Inclusion and exclusion criteria for individual studies.
5. Total number of participants.
6. Number of females.
7. Average age of the participants.
8. Average time between onset of symptoms and index test.
9. Aetiology of acute pancreatitis.
10. Proportion of participants with organ failure.
11. Description of the index test.
12. Threshold used for index test.
13. Reference standard.
14. Number of true positives, false positives, false negatives, and true negatives.

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 at each threshold. 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.

We defined a combination of tests as positive in two ways: 'at least one test positive' or 'all tests positive'. We planned to extract the number of true positives, false positives, false negatives, and true negatives for both the scenarios. If the study reported the test at multiple time points, we planned to use the results of the first test in the diagnosis of acute pancreatitis to calculate the true positives, false positives, false negatives, and true negatives, since the aim of this review was to assess the diagnostic accuracy in

people with acute epigastric pain and abdominal pain who have not undergone any prior tests other than routine clinical examination. However, the diagnostic test accuracy of these index tests on later days of hospital might give some indication on the performance of these tests in patients with a prolonged period of symptoms before going to hospital. We have therefore analysed and reported this information separately from the tests conducted on admission.

We planned to exclude patients with uninterpretable index test results (whatever the reason given for lack of interpretation), since in clinical practice, uninterpretable index test results will result in additional tests for the diagnosis of acute pancreatitis. However, we planned to record the number of uninterpretable index test results, as this would provide information on the applicability of the test in clinical practice 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. We sought further information from study authors where necessary.

Assessment of methodological quality

Two review authors (KSG and GR or AH) independently assessed study quality using the QUADAS-2 assessment tool (Whiting 2006; Whiting 2011). We resolved any differences by discussion and using the criteria to classify the different studies published in the protocol and available in Table 2. We considered studies classified as 'low risk of bias' and 'low concern' in all of the domains as studies with high methodological quality. 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 have reported the reference standards in each study included in the analysis and have analysed the studies at different threshold levels separately. 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. To estimate the summary sensitivity and specificity of each test at each threshold level, we attempted 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. However, because of sparse data, we used simpler models described by Takwoingi 2015 (random-effects model ignoring the inverse correlation between sensitivities and specificities in the different studies due to intrinsic threshold effect, and the fixed-effect model for either sensitivity or specificity, or both). We based the choice between the different models on the -2 log likelihood ratio and the distribution of sensitivities and specificities as noted in the forest plots or ROC space (Takwoingi 2015).

We performed the meta-analysis using the NLMIXED command in SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). We calculated the summary likelihood ratios and their confidence intervals from the functions of the parameter estimates from the bivariate model or other models that were fitted to estimate the summary sensitivities and specificities. We calculated the post-test probability using the median pre-test probability. Post-test probability associated with a positive test is the probability of having the target condition (acute 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) 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 patient has no target condition when the test is negative.

Investigations of heterogeneity

Of the eight sources of heterogeneity mentioned in the Secondary objectives section, we planned to use risk of bias, publication status, prospective or retrospective studies, and different test manufacturers as categorical covariates, and proportion of participants with a previous history of acute pancreatitis, proportion of participants with different aetiologies, proportion of participants with organ failure, and the average time to performance of the test as continuous covariates in the regression model. We planned to include one covariate at a time in the regression model. We planned to use the likelihood ratio test to determine whether the covariate was statistically significant. However, because of the paucity of data, we did not perform any of the above analyses.

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. However, we performed three post hoc sensitivity analyses.

- There was incorporation bias (index test was a part of the reference standard) in many of the studies that reported on the diagnostic accuracy of serum amylase and lipase. We performed a sensitivity analysis by excluding these studies.
- There was high risk of bias and applicability concerns in one retrospective study that contributed to most of the effect estimate (Chang 2011). We performed a sensitivity analysis by excluding this study.

- For urinary trypsinogen-2, the authors of one study appeared to have used the threshold suggested by the manufacturer (Aysan 2008); however, this was not stated clearly. We performed a sensitivity analysis by excluding this study.

Assessment of reporting bias

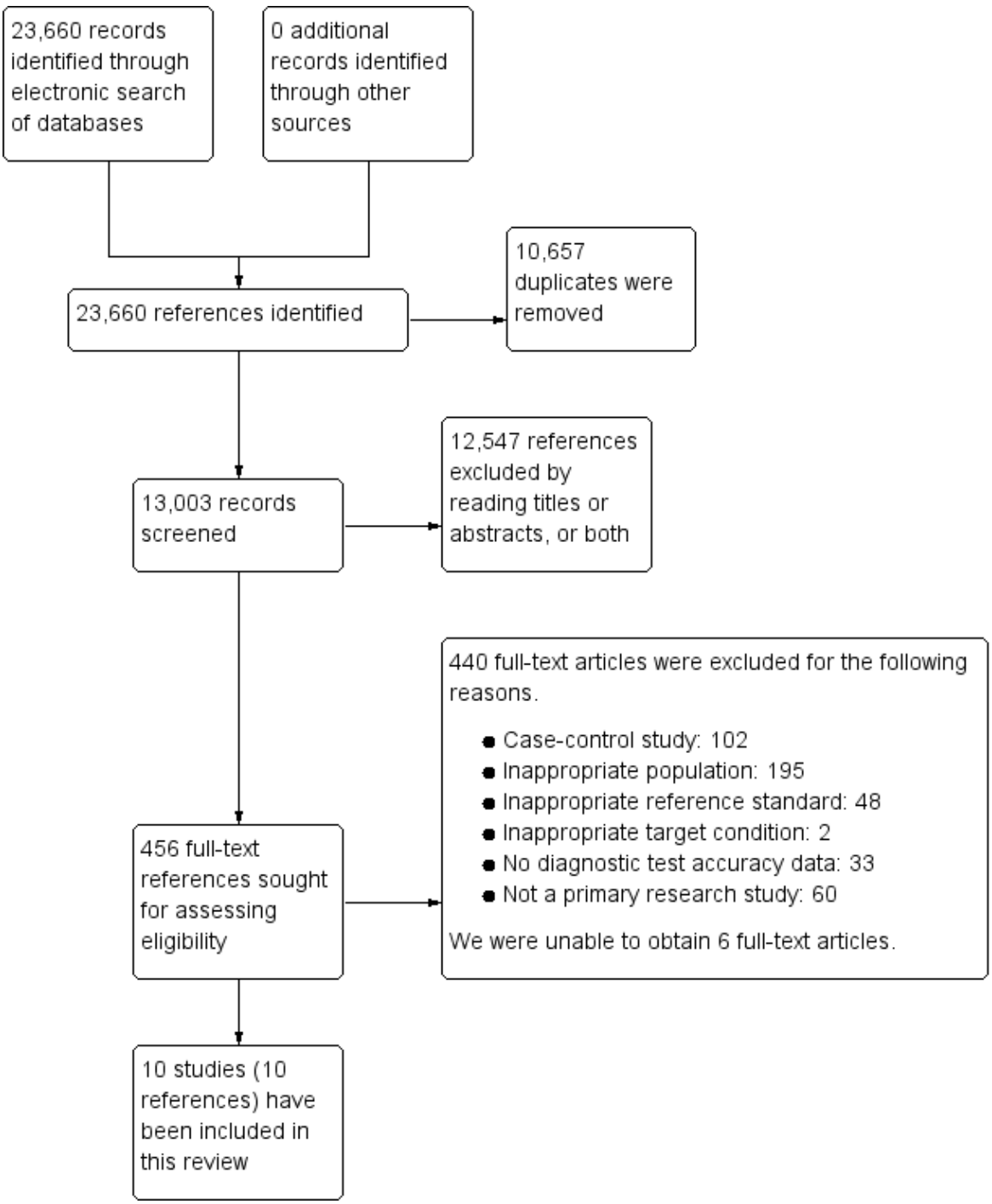
We planned to investigate whether the summary sensitivity and specificity differed between studies published as full texts and those that were available only as abstracts (at least two years prior to the search date) using the methods described in the Investigations of heterogeneity section. We did not perform this since all of the included studies were full texts.

RESULTS

Results of the search

We identified a total of 23,660 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 12,547 clearly irrelevant references through reading the titles or abstracts, or both. We sought full-text articles for 456 references, but were unable to obtain the full texts for six references (Anand 1956; Cherry 1953; Coppola 1954; Do Prado 1952; Lippi 2013; Stimac 1995). We retrieved full-text articles of 450 references for further assessment against our review protocol inclusion criteria. Of these 450 references, we excluded 440 references for the reasons provided in the Characteristics of excluded studies section. The reasons for exclusion were: case-control study: 102; inappropriate population: 195; inappropriate reference standard: 48; inappropriate target condition: 2; no diagnostic test accuracy data: 33; not a primary research study: 60; could not be obtained: 6. Ten studies (10 references) fulfilled the inclusion criteria and provided the diagnostic accuracy data for the review (Abraham 2011; Aysan 2008; Burkitt 1987; Chang 2011; Keim 1998; Mayumi 2012; Patt 1966; Saez 2005; Viel 1990; Wu 2009). We have shown the reference flow in Figure 2.

Figure 2. Study flow diagram.



Included studies

Ten studies including 5056 participants met the inclusion criteria for this review and assessed the diagnostic accuracy of the index tests in people presenting to the hospital emergency department with acute abdominal pain. The average age of participants in the studies ranged from 37 years to 59 years in the five studies that reported this information (Aysan 2008; Keim 1998; Mayumi 2012; Saez 2005; Wu 2009). About 45% of participants (442/970 participants) were females in the five studies that reported this information (Aysan 2008; Keim 1998; Mayumi 2012; Saez 2005; Wu 2009). Six studies were prospective studies (Abraham 2011; Aysan 2008; Burkitt 1987; Keim 1998; Mayumi 2012; Saez 2005); one study was a retrospective study (Chang 2011); and it was unclear whether three studies were prospective or retrospective (Patt 1966; Viel 1990; Wu 2009). All of the included studies were full-text publications. The studies did not report whether people with previous history of acute pancreatitis were included. Two studies clearly stated that they included patients with gallstone pancreatitis and alcoholic pancreatitis (Mayumi 2012; Saez 2005). None of the studies reported any restriction of inclusion criteria based on aetiology or provided diagnostic accuracy information separately for people with gallstone and alcoholic pancreatitis. None of the studies included only people with organ failure or excluded all people with organ failure. One study excluded people with renal failure, but there was no restriction on the basis of other organ failures (Chang 2011). None of the studies reported data separately for people with and without organ failure. Only one study reported that they included only people with less than 24 hours since onset of symptoms (Saez 2005). None of the other trials restricted participants based on the duration of symptoms. However, since all of the studies included participants with acute abdominal pain, it is likely that the onset of pain was less than two to three days prior to hospital admission.

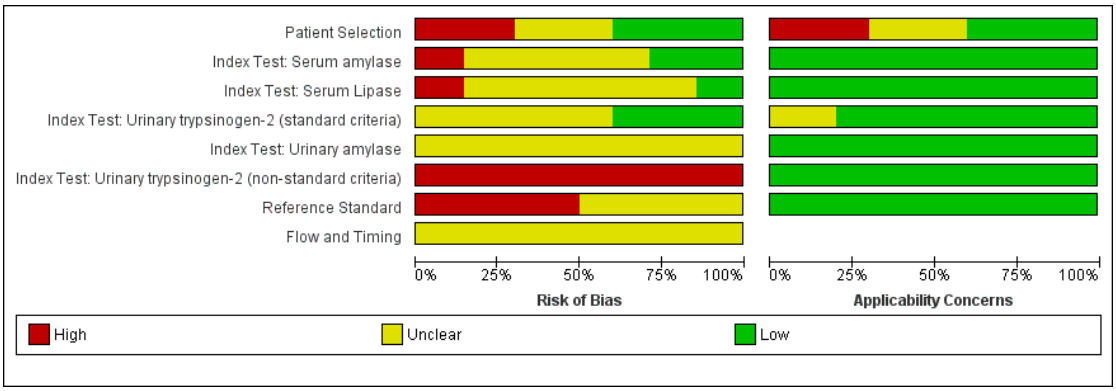
The studies measured the diagnostic accuracy on admission and used different thresholds for diagnosis of acute pancreatitis. Eight studies contributed to two or more analyses (Abraham 2011; Burkitt 1987; Chang 2011; Keim 1998; Mayumi 2012; Patt 1966; Saez 2005; Wu 2009). However, none of the studies reported the diagnostic accuracy of a combination of tests.

Methodological quality of included studies

The methodological quality of the included studies is shown in Characteristics of included studies, and summaries of the methodological quality are shown in Figure 3 and Figure 4.

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

Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.



Participant selection

A total of four studies were at low risk of bias in the participant selection domain (Abraham 2011; Mayumi 2012; Saez 2005; Viel 1990). A total of three studies were at high risk of bias in the participant selection domain (Burkitt 1987; Chang 2011; Patt 1966). In one study, some participants who had normal urinary amylase were excluded from analysis (Burkitt 1987); in another study, participants with parotid disease and end-stage renal failure were excluded (Chang 2011); and in a third study, only participants who underwent laparotomy or autopsy were included, that is only people with severe symptoms were included (Patt 1966). A total of three studies were at unclear risk of bias in the participant selection domain (Aysan 2008; Keim 1998; Wu 2009).

There was low concern in the participant selection domain in four studies (Abraham 2011; Mayumi 2012; Saez 2005; Viel 1990). There was high concern in the participant selection domain in three studies (Burkitt 1987; Chang 2011; Patt 1966). The reasons for high concern were the same as those for high risk of bias (Burkitt 1987). There was unclear concern in the participant selection domain in three studies (Aysan 2008; Keim 1998; Wu 2009).

Index test

One study was at low risk of bias for all index tests other than one threshold (urinary trypsinogen positive or most positive) (Mayumi 2012); for that threshold the study was at high risk of bias since the threshold was not prespecified (Mayumi 2012). One study was at high risk of bias for all index tests since the threshold was not prespecified (Keim 1998). The remaining trials were at unclear risk of bias since it was not clear whether the threshold was prespecified and whether blinded interpretation of the index tests was performed (Abraham 2011; Aysan 2008; Burkitt 1987; Chang 2011; Patt 1966; Saez 2005; Viel 1990; Wu 2009). All of the index tests reported in eight studies were at low concern about applicability (Abraham 2011; Burkitt 1987; Chang 2011; Keim 1998; Patt 1966; Saez 2005; Viel 1990; Wu 2009). One study was at unclear concern about applicability since the threshold used was not clearly reported by the authors (the authors appear to have used the manufacturer's suggested threshold, but this was not entirely clear) (Aysan 2008). One study was at high concern about applicability for all index tests except for one threshold level (positive or most positive), since this is not a standard threshold recommended by the manufacturer (Mayumi 2012).

Reference standard

Five studies were at high risk of bias in the reference standard domain because they did not use a biopsy or consensus definition (Aysan 2008; Chang 2011; Keim 1998; Viel 1990; Wu 2009). One of these studies also included the index test as part of the reference standard despite not using consensus definition (Wu 2009). Five studies were at unclear risk of bias about the reference standard since they did not report whether the people interpreting the reference standards were blinded to the index test results (Abraham 2011; Burkitt 1987; Mayumi 2012; Patt 1966; Saez 2005). However, it should be noted that three studies were at high risk of bias for the index tests serum amylase and serum lipase, which were part of the reference standards, but were at low risk

of bias for urinary trypsinogen-2 (Abraham 2011; Mayumi 2012; Saez 2005). As we included only studies in which the reference standard was adequately described, the applicability concern was low in all studies.

Flow and timing

All of the studies were at unclear risk of bias in the flow and timing domain since the studies either did not report whether any participants with uninterpretable results were excluded or did not state the time interval between the index test and reference standard.

Findings

The included studies reported the diagnostic test accuracy of the different tests in the diagnosis of acute pancreatitis at different test thresholds and on different days. Due to sparse data, we performed the meta-analysis using different models described by Takwoingi 2015. The data and the SAS code used are shown in Appendix 9. The model fit (-2 log likelihood ratios) for various analyses is reported in Appendix 10. The median pre-test probability of acute pancreatitis (proportion of people with acute pancreatitis out of the total number of included participants) was 22.6% with a minimum of 0.6% and a maximum of 69.4%. The lower and upper quartiles were 16.3% and 47.3%, respectively. The sensitivity and specificity along with the 95% confidence interval (CI) for each of the main analyses are shown in a forest plot (Figure 5) and ROC space (Figure 6). The sensitivities, specificities, post-test probabilities of a positive test, and post-test probabilities of a negative test at the median pre-test probability for the main analyses are presented in the Summary of findings and for all of the tests are presented in Table 3, Table 4, and Table 5.

Figure 5. Forest plot of serum amylase, serum lipase, and urinary trypsinogen at different thresholds. There was reasonable overlap of 95% confidence intervals except specificity for serum amylase > 3 times normal, sensitivity and specificity of serum lipase > 3 times normal, and specificity of urinary trypsinogen-2.

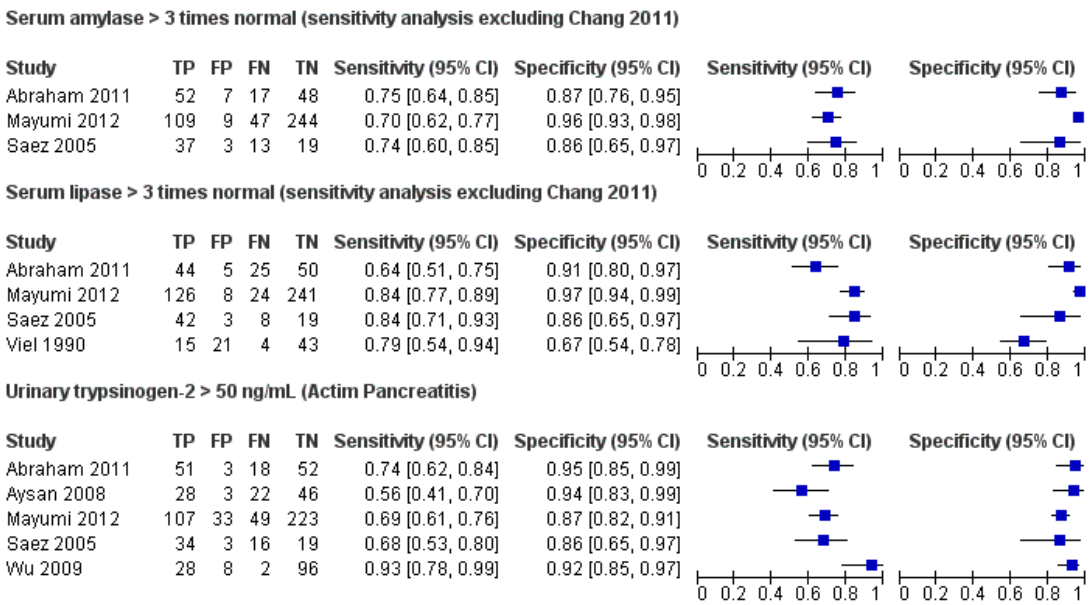
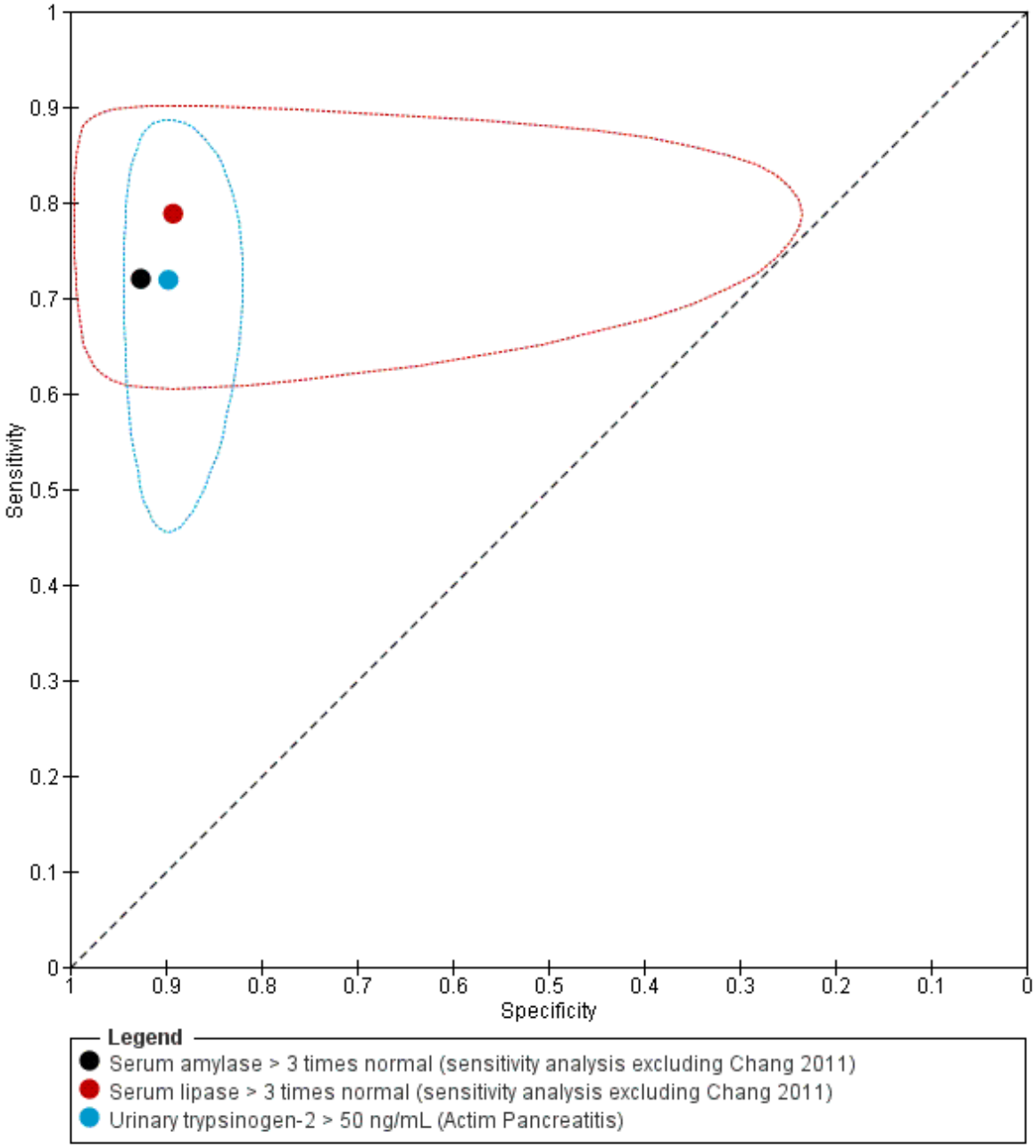


Figure 6. Summary estimates and 95% confidence region (ellipses) of the three main meta-analyses showing similar diagnostic test accuracies. No confidence regions could be computed for serum amylase due to small numbers of studies.



Serum amylase

More than three times normal on admission

A total of four studies (4056 participants) were included in this analysis (Abraham 2011; Chang 2011; Mayumi 2012; Saez 2005). It should be noted that except for Chang 2011, all of the studies suffered from incorporation bias (i.e. index test was part of reference standard). Based on the -2 log likelihood ratio, fixed-effect model for both sensitivity and specificity was used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.71 (95% CI 0.65 to 0.77) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.99 (95% CI 0.99 to 0.99).

Excluding three studies with incorporation bias, Abraham 2011, Mayumi 2012, and Saez 2005 (studies that used consensus definition as the reference standard) resulted in the inclusion of only Chang 2011, which used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.64 (95% CI 0.41 to 0.82) and the estimate of specificity for diagnosis of acute pancreatitis was 0.99 (95% CI 0.99 to 1.00).

Excluding Chang 2011, for which there was major concern about applicability, resulted in the inclusion of a total of three studies (605 participants) (Abraham 2011; Mayumi 2012; Saez 2005). Based on the -2 log likelihood ratio, the fixed-effect model for sensitivity and random-effects model for specificity were used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.72 (95% CI 0.59 to 0.82) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.93 (95% CI 0.66 to 0.99).

More than twice normal

On admission

A total of two studies (3704 participants) were included in this analysis (Chang 2011; Keim 1998). There was no incorporation bias in either study, as both studies used radiology as a reference standard. Based on the -2 log likelihood ratio, fixed-effect model for both sensitivity and specificity was used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.76 (95% CI 0.57 to 0.88) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.99 (95% CI 0.98 to 0.99). Excluding Chang 2011, for which there was major concern about applicability, resulted in the inclusion of one study (253 participants) in this analysis (Keim 1998). The estimate of sensitivity for diagnosis of acute pancreatitis was 0.72 (95% CI 0.53 to 0.86) and the estimate of specificity for diagnosis of acute pancreatitis was 0.98 (95% CI 0.95 to 0.99).

Two to three days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study as this study used radiology as a reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.25 (95% CI 0.12 to 0.44) and the estimate of specificity for diagnosis of acute pancreatitis was 0.97 (95% CI 0.93 to 0.99).

Four to five days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study as this study used radiology as a reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.06 (95% CI 0.01 to 0.22) and the estimate of specificity for diagnosis of acute pancreatitis was 0.93 (95% CI 0.89 to 0.96).

More than normal

On admission

A total of three studies (587 participants) were included in this analysis (Keim 1998; Patt 1966; Wu 2009). There was no incorporation bias in two studies: Keim 1998 used radiology and Patt 1966 used laparotomy or autopsy as the reference standard. Based on the -2 log likelihood ratio, fixed-effect model for both sensitivity and specificity was used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.88 (95% CI 0.77 to 0.94) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.88 (95% CI 0.84 to 0.91). Excluding Wu 2009, a study that had incorporation bias (although the authors did not use the consensus definition, they used a combination of pain, radiology, and raised amylase), resulted in a summary sensitivity and specificity for diagnosis of acute pancreatitis of 0.89 (95% CI 0.72 to 0.96) and 0.88 (95% CI 0.83 to 0.92), respectively. This was based on fixed-effect model for both sensitivity and specificity, the only model that converged.

Two to three days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study, as this study used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.66 (95% CI 0.47 to 0.81) and the estimate of specificity for diagnosis of acute pancreatitis was 0.83 (95% CI 0.77 to 0.87).

Four to five days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study, as this study used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.34 (95% CI 0.19 to 0.53) and the estimate of specificity for diagnosis of acute pancreatitis was 0.86 (95% CI 0.81 to 0.90).

Serum lipase

More than three times normal on admission

A total of five studies (4129 participants) were included in this analysis (Abraham 2011; Chang 2011; Mayumi 2012; Saez 2005; Viel 1990). Of these, there was no incorporation bias in two studies: Chang 2011 used radiology as the reference standard, while Viel 1990 used 3-fold increase of serum amylase and evidence of pancreatitis in radiology, endoscopic retrograde cholangiopancreatography (ERCP), or surgery as the reference standard. Based on the -2 log likelihood ratio, fixed-effect model for sensitivity and random-effects model for specificity were used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.80 (95% CI 0.73 to 0.86) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.93 (95% CI 0.00 to 1.00).

Excluding three studies with incorporation bias (these studies used consensus definition as the reference standard) (Abraham 2011; Mayumi 2012; Saez 2005), the summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.88 (95% CI 0.02 to 1.00) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.94 (95% CI 0.00 to 1.00). Only two models, fixed-effect model for sensitivity and random-effects model for specificity and fixed-effect models for both sensitivity and specificity, converged. Based on the -2 log likelihood ratio, fixed-effect model for sensitivity and random-effects model for specificity were used for meta-analysis.

Excluding Chang 2011, for which there was major concern about applicability, resulted in the inclusion of four studies (678 participants) in this analysis (Abraham 2011; Mayumi 2012; Saez 2005; Viel 1990). Based on the -2 log likelihood ratio, random-effects model for both sensitivity and specificity was used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.79 (95% CI 0.54 to 0.92) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.89 (95% CI 0.46 to 0.99).

More than twice normal

On admission

A total of two studies (3704 participants) were included in this analysis (Chang 2011; Keim 1998). There was no incorporation bias in either study, as both studies used radiology as the reference standard. Based on the -2 log likelihood ratio, fixed-effect model for both sensitivity and specificity was used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.96 (95% CI 0.78 to 0.99) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.98 (95% CI 0.98 to 0.99). Excluding Chang 2011, for which there was major concern about applicability, resulted in the inclusion of one study (253 participants) in this analysis (Keim 1998). The estimate of sensitivity for diagnosis of acute pancreatitis was 0.94 (95% CI 0.78 to 0.99) and the estimate of specificity for diagnosis of acute pancreatitis was 0.95 (95% CI 0.91 to 0.97).

Two to three days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study, as this study used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.69 (95% CI 0.50 to 0.83) and the estimate of specificity for diagnosis of acute pancreatitis was 0.91 (95% CI 0.86 to 0.94).

Four to five days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study, as this study used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.41 (95% CI 0.24 to 0.59) and the estimate of specificity for diagnosis of acute pancreatitis was 0.84 (95% CI 0.79 to 0.89).

More than normal

On admission

A total of two studies (453 participants) were included in this analysis (Keim 1998; Patt 1966). There was no incorporation bias in either study, as Keim 1998 used radiology as the reference standard, while Patt 1966 used laparotomy or autopsy as the reference standard. Based on the -2 log likelihood ratio, random-effects model for sensitivity and fixed-effect model for specificity were used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.96 (95% CI 0.00 to 1.00) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.83 (95% CI 0.47 to 0.96).

Two to three days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study, as this study used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.97 (95% CI 0.82 to 1.00) and the estimate of specificity for diagnosis of acute pancreatitis was 0.79 (95% CI 0.73 to 0.84).

Four to five days after admission

One study (253 participants) was included in this analysis (Keim 1998). There was no incorporation bias in this study, as this study used radiology as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.59 (95% CI 0.41 to 0.76) and the estimate of specificity for diagnosis of acute pancreatitis was 0.70 (95% CI 0.64 to 0.76).

Urinary trypsinogen-2

Actim Pancreatitis (Medix Biochemica) test (threshold: > 50 ng/mL)

A total of five studies (841 participants) were included in this analysis (Abraham 2011; Aysan 2008; Mayumi 2012; Saez 2005; Wu 2009). Of these, three studies used the consensus definition as the reference standard (Abraham 2011; Mayumi 2012; Saez 2005); Aysan 2008 used radiology as the reference standard; and Wu 2009 used pain, radiology, and amylase as the reference standard.
Based on the -2 log likelihood ratio, random-effects model for sensitivity and fixed-effect model for specificity were used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.72 (95% CI 0.56 to 0.84) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.90 (95% CI 0.85 to 0.93). While four studies clearly stated the threshold (Abraham 2011; Mayumi 2012; Saez 2005; Wu 2009), in one study the threshold was unclear. Based on the authors' description, it appears the manufacturer's threshold was used (Aysan 2008). Consequently, we included this study in the primary analysis, but performed a sensitivity analysis excluding this study. Based on the -2 log likelihood ratio, random-effects model for sensitivity and fixed-effect model for specificity were used for meta-analysis. The summary estimate of sensitivity for diagnosis of acute pancreatitis was 0.74 (95% CI 0.56 to 0.87) and the summary estimate of specificity for diagnosis of acute pancreatitis was 0.89 (95% CI 0.84 to 0.93), that is there was only a minor change in summary sensitivity and specificity by excluding this study.

Quantitative urinary trypsinogen (threshold: > 50 ng/mL)

One study (412 participants) was included in this analysis (Mayumi 2012). The reference standard used in this study was the consensus definition. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.71 (95% CI 0.63 to 0.78) and the estimate of specificity for diagnosis of acute pancreatitis was 0.89 (95% CI 0.84 to 0.92).

Urinary trypsinogen: only positive or most positive (threshold not reported)

One study (412 participants) was included in this analysis (Mayumi 2012). The reference standard used in this study was the consensus definition. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.60 (95% CI 0.51 to 0.67) and the estimate of specificity for diagnosis of acute pancreatitis was 0.92 (95% CI 0.88 to 0.95).

Urinary amylase

Above normal (quantitative test)

One study (134 participants) was included in this analysis (Wu 2009). This study used pain, radiology, and amylase as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.83 (95% CI 0.65 to 0.94) and the estimate of specificity for diagnosis of acute pancreatitis was 0.86 (95% CI 0.77 to 0.91).

One plus (qualitative test: 1+ (threshold level for 1+ not stated))

One study (218 participants) was included in this analysis (Burkitt 1987). This study used pain and amylase greater than 1000 (normal = 300 IU) as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.66 (95% CI 0.49 to 0.79) and the estimate of specificity for diagnosis of acute pancreatitis was 0.94 (95% CI 0.90 to 0.97).

Two plus (qualitative test: 2+ (threshold level for 2+ not stated))

One study (218 participants) was included in this analysis (Burkitt 1987). This study used pain and amylase greater than 1000 (normal = 300 IU) as the reference standard. The estimate of sensitivity for diagnosis of acute pancreatitis was 0.44 (95% CI 0.29 to 0.60) and the estimate of specificity for diagnosis of acute pancreatitis was 0.99 (95% CI 0.96 to 1.00).

Comparison of different tests

Although we attempted to perform hierarchical summary receiver operating characteristics curve (HSROC) analysis using test as a covariate in order to compare the accuracy of the tests, the models

did not converge. We were therefore unable to formally compare the diagnostic performance of the different tests.

Investigation of heterogeneity

Because of sparse data, we did not investigate heterogeneity.

Summary of findings

Population	People with abdominal pain seen in emergency care
Setting	Secondary care in various countries
Target condition	Acute pancreatitis
Reference standard	1. Consensus criteria. 2. Radiological features of acute pancreatitis. 3. Laparotomy or autopsy features of acute pancreatitis.
Pre-test probability (prevalence of acute pancreatitis)	22.6%

Index test	Sensitivity	Specificity	Post-test probability of a positive test [1]	Post-test probability of a negative test [1]	Number of false positives per 100 people having a positive test	Number of false negatives per 100 people having a negative test	Number of studies	Number of participants	Risk of bias	Applicability concerns	Inconsistency
Serum amylase (threshold: > 3 times normal) (on admission) [2]	0.72 (95% CI 0.59 to 0.82)	0.93 (95% CI 0.66 to 0.99)	74.0% (95% CI 33.4% to 94.1%)	8.1% (95% CI 5.4% to 12.1%)	26 (95% CI 6 to 67)	8 (95% CI 5 to 12)	3	605	Unclear	Low	Moderate
Serum lipase (threshold: > 3 times normal) (on ad-	0.79 (95% CI 0.54 to 0.92)	0.89 (95% CI 0.46 to 0.99)	68.1% (95% CI 21.4% to 94.3%)	6.6% (95% CI 2.7% to 15.1%)	32 (95% CI 6 to 79)	7 (95% CI 3 to 15)	4	678	Unclear	Low	Moderate

mission)[2]										
Urinary trypsinogen-2 (threshold: Actim Pancreatitis - all studies; > 50 ng/mL) (on admission)	0.72 (95% CI 0.56 to 0.84)	0.90 (95% CI 0.85 to 0.93)	67.2% (95% CI 57.3% to 75.7%)	8.4% (95% CI 5.2% to 13.3%)	33 (95% CI 24 to 43)	8 (95% CI 5 to 13)	5	5	841	High	Unclear	Moderate
Urinary trypsinogen-2 (quantitative) (threshold: > 50 ng/mL) (on admission)	0.71 (95% CI 0.63 to 0.78)	0.89 (95% CI 0.84 to 0.92)	65.6% (95% CI 57.0% to 73.3%)	8.7% (95% CI 6.9% to 10.9%)	34 (95% CI 27 to 43)	9 (95% CI 7 to 11)	7	1	412	High	Low	Not applicable
Urinary trypsinogen-2 (threshold: only + or most positive - the threshold for this was not available) (on admission)	0.60 (95% CI 0.51 to 0.67)	0.92 (95% CI 0.88 to 0.95)	69.1% (95% CI 59.0% to 77.6%)	11.4% (95% CI 9.6% to 13.5%)	31 (95% CI 22 to 41)	11 (95% CI 10 to 13)	1		412	High	Low	Not applicable
Urinary amylase (quantitative) (threshold: above normal) (on admission)	0.83 (95% CI 0.65 to 0.94)	0.86 (95% CI 0.77 to 0.91)	62.8% (95% CI 50.8% to 73.5%)	5.4% (95% CI 2.5% to 11.3%)	37 (95% CI 27 to 49)	5 (95% CI 2 to 11)	2	1	134	Unclear	Unclear	Not applicable

Urinary amylase (qualitative) (threshold: 1 plus) (on admission)	0.66 (95% CI 0.49 to 0.79)	0.94 (95% CI 0.90 to 0.97)	77.3% (95% CI 64.2% to 86.6%)	9.6% (95% CI 6.5% to 14.0%)	23 (95% CI 13 to 36)	10 (95% CI 6 to 14)	1	218	High	High	Not applicable
Urinary amylase (qualitative) (threshold: 2 plus) (on admission)	0.44 (95% CI 0.29 to 0.60)	0.99 (95% CI 0.96 to 1.00)	95.8% (95% CI 75.8% to 99.4%)	14.2% (95% CI 11.2% to 17.8%)	4 (95% CI 1 to 24)	14 (95% CI 11 to 18)	1	218	High	High	Not applicable

CI: confidence interval

[1]The post-test probabilities were calculated at the median pre-test probability. At the lower quartile of pre-test probability of 16.3%, the post-test probabilities of positive test for serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL) were 65.5% (95% CI 25.1% to 91.5%); 58.7% (95% CI 15.4% to 91.7%); and 57.7% (95% CI 47.2% to 67.5%), respectively. At the same pre-test probability of 16.3%, the post-test probabilities of negative test for serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL) were 5.6% (95% CI 3.7% to 8.4%); 4.5% (95% CI 1.8% to 10.6%); and 5.8% (95% CI 3.5% to 9.3%), respectively. At the upper quartile of pre-test probability of 47.3%, the post-test probabilities of positive test for serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL) were 89.7% (95% CI 60.7% to 98.0%); 86.7% (95% CI 45.6% to 98.1%); and 86.3% (95% CI 80.5% to 90.6%), respectively. At the same pre-test probability of 47.3%, the post-test probabilities of negative test for serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL) were 21.4% (95% CI 14.9% to 29.7%); 17.8% (95% CI 7.9% to 35.4%); and 22.0% (95% CI 14.4% to 32.0%), respectively.

[2]The results do not include one study for which there was high concern about applicability.

DISCUSSION

Summary of main results

Ten studies including 5056 participants met the inclusion criteria for this review and assessed the diagnostic accuracy of the index tests in people presenting to the emergency department with acute abdominal pain (Abraham 2011; Aysan 2008; Burkitt 1987; Chang 2011; Keim 1998; Mayumi 2012; Patt 1966; Saez 2005; Viel 1990; Wu 2009). These 10 studies reported the diagnostic test accuracy of the index tests at different thresholds. For the currently recommended threshold of above three times normal values, the summary sensitivities and specificities of admission serum amylase and admission serum lipase were as follows.

- Serum amylase: sensitivity 0.71 (95% CI 0.65 to 0.77) and specificity 0.99 (95% CI 0.99 to 0.99).
- Serum lipase: sensitivity 0.80 (95% CI 0.73 to 0.86) and specificity 0.93 (95% CI 0.00 to 1.00).

However, one retrospective study excluded people with parotid tumours and renal impairment; the inclusion of such patients will decrease the diagnostic accuracy (Chang 2011). After excluding this trial, which had high applicability concern in the participant selection domain, the summary sensitivities and specificities of admission serum amylase and admission serum lipase were as follows.

- Serum amylase: sensitivity 0.72 (95% CI 0.59 to 0.82) and specificity 0.93 (95% CI 0.66 to 0.99).
- Serum lipase: sensitivity 0.79 (95% CI 0.54 to 0.92) and specificity 0.89 (95% CI 0.46 to 0.99).

In comparison, the admission urinary trypsinogen-2 was associated with a sensitivity of 0.72 (95% CI 0.56 to 0.84) and a specificity of 0.90 (95% CI 0.85 to 0.93). Thus, the tests appear to have similar diagnostic test accuracy. While we could not perform a formal comparison of the diagnostic test accuracy because of sparse data, it is unlikely to demonstrate statistical significance given the significant overlap of confidence intervals of sensitivities (and specificities) in these three tests.

At the median prevalence of 22.6% of acute pancreatitis in the studies, out of 100 people with positive test, serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL), 74 (95% CI 33 to 94); 68 (95% CI 21 to 94); and 67 (95% CI 57 to 76) people have acute pancreatitis, respectively; out of 100 people with negative test, serum amylase (more than three times normal), serum lipase (more than three times normal), and urinary trypsinogen (more than 50 ng/mL), 8 (95% CI 5 to 12); 7 (95% CI 3 to 15); and 8 (95% CI 5 to 13) people have acute pancreatitis, respectively. This means that although negative index test result decreases the probability of a person having acute pancreatitis, a significant proportion of people with acute pancreatitis have negative results and require further investigations to rule out acute pancreatitis, depending upon the nature and intensity of their pain.

The diagnostic accuracy reported at other thresholds and times was based on even less data and is subject to significant systematic and random errors. The results presented should therefore be considered as exploratory information rather than information based on which conclusions can be made. They indicate that a threshold of twice the normal limit of both serum amylase and lipase should be explored as an alternative to thrice the normal limit for the diagnosis of acute pancreatitis. The diagnostic accuracy also appears to be less for both serum amylase and lipase as the time interval between admission and the performance of the test increases, with the diagnostic accuracy of serum amylase decreasing more than serum lipase. Even the diagnostic accuracy of serum lipase in the later days is not sufficiently accurate to have any clinical role. Unless future studies show a major improvement in diagnostic accuracy, it appears that these tests do not have major clinical roles, that is a patient who has clinical symptoms of acute pancreatitis with a long time interval between the onset of symptoms and performance of the test should undergo radiological tests directly to confirm or rule out acute pancreatitis. One could also explore urinary amylase as a potential triage test prior to radiological tests for later days, as amylase gets excreted mainly by urine.

Strengths and weaknesses of the review

One of the main strengths of this review was that we searched the literature thoroughly, without any publication or language restrictions. We did not use any diagnostic test accuracy filters in our literature search because such filters could have led us to exclude 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 the 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 (KSG and OK, GR, or AH) independently searched the references produced by the search to identify relevant studies; screened the full-text papers against the inclusion criteria; and extracted data. Data extractions by two 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. We had to interpret the results of serum amylase and lipase without

a study that included approximately two-thirds of the included participants because of major concerns about applicability. Another major methodological deficiency was that three of the four studies, Abraham 2011, Mayumi 2012, Saez 2005, and four of the five studies, Abraham 2011, Mayumi 2012, Saez 2005, Wu 2009, that contributed to the assessment of diagnostic accuracy of serum amylase and lipase used serum amylase and lipase as part of the reference standard, which might have overestimated their diagnostic test accuracy. Exclusion of these studies in a post hoc sensitivity analysis left only a few studies at high risk of bias and with applicability concerns to be included in the main analysis, and increased the unreliability of the evidence. None of the studies reported whether the index tests and reference standards were interpreted independently of one another. If they were not interpreted independently of each other, the accuracy of the tests would have been overestimated. Only four studies reported that they included all participants attending the emergency department with acute abdominal pain (Abraham 2011; Mayumi 2012; Saez 2005; Viel 1990). In three studies there was inappropriate exclusion of participants (Burkitt 1987; Chang 2011; Patt 1966). Of particular concern was the exclusion of people with parotid disease and end-stage renal failure in one study (Chang 2011), which can overestimate the diagnostic accuracy. Because of the large number of participants included in this study, this study could have significantly influenced the overall results and resulted in poor estimation of diagnostic test accuracy. Future meta-analyses on this topic should exclude Chang 2011 and other significantly biased studies that use a very large number of participants because of the influence of such studies on the result of the meta-analysis. It was unclear whether inappropriate exclusions were avoided in the remaining three studies (Aysan 2008; Keim 1998; Wu 2009). It was unclear whether some of the participants had indeterminate values in any of these six studies in which there were inappropriate exclusions or those that did not report participant flow. Exclusion of people with borderline values close to the threshold used or those with other causes of elevation of these tests will overestimate the diagnostic test accuracy of these tests.

Secondly, there was significant heterogeneity in some of the comparisons. In the analysis of lipase more than three times normal on admission with inclusion of Chang 2011, the confidence intervals covered the entire range of possible specificities. While we could have used the fixed-effect model to overcome these wide confidence intervals, this would have meant that we would have ignored heterogeneity that was evident in lack of overlap of confidence intervals. This model would also have had a poorer fit than the one we reported, leading us to make wrong conclusions as a result of ignoring heterogeneity. The various reasons for heterogeneity included different reference standards.

Thirdly, the sample sizes of the studies were small after the large study was excluded due to major concerns about applicability in the participant selection domain (Chang 2011), resulting in wide confidence intervals. We found a large number of studies using case-control study designs that compared the diagnostic performance of the tests between people with acute pancreatitis and healthy controls. While the inclusion of such studies would have improved precision, it would have resulted in significant overestimation of the results. This would have been meaningless in the context of how these tests are used in clinical practice, that is diagnose acute pancreatitis in people with acute abdominal pain. We therefore accepted inclusion of fewer studies to provide a reasonably reliable diagnostic test accuracy estimate. However, this trade-off resulted in sparse data and prevented us from formally comparing the different index tests and investigating heterogeneity. In particular, we were not able to assess whether the diagnostic performance changes with a time interval between onset of clinical symptoms and the performance of the test. As the half lifes of the different tests are different, this is of great clinical significance.

Comparison with other reviews

In the systematic review by Chang 2012, the summary estimate of urinary trypsinogen-2 was 0.82 (95% CI 0.79 to 0.85) and the specificity was 0.94 (95% CI 0.92 to 0.95). These results show greater diagnostic accuracy and a more precise estimate of the diagnostic accuracy compared to what we have found in this review. The likely reason for this is the inclusion of studies with an inadequate reference standard, which would have resulted in improved precision and may improve the diagnostic accuracy. The results of the other systematic review by Jin 2013 were similar to those of Chang 2012. Jin 2013 reported the diagnostic test accuracy of serum amylase, serum lipase, and urinary trypsinogen-2, and stated that the three tests had similar diagnostic test accuracies. We agree with the inference that the diagnostic accuracies of serum amylase, serum lipase, and urinary trypsinogen-2 are similar.

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. Most studies used the test in the same way that it is used in clinical practice, that is in people with acute abdominal pain. Consequently, the results are applicable in people with acute abdominal pain. None of the studies reporting the diagnostic accuracy of tests post-endoscopic retrograde cholangiopancreatography met the criteria for the reference standards used in this review, therefore the findings of this review may not be applicable in patients undergoing endoscopic retrograde cholangiopancreatography.

Use of the test in the clinical setting

The main role of the index test is diagnosis in clinical practice. Use of a test with good diagnostic accuracy makes it possible to decide on admission and appropriate management of patients with acute abdominal pain. The post-test probabilities of positive and negative test depend upon the pre-test probabilities of the test. The median pre-test probability observed in the trials included in this review was 22.6%. Depending upon the type of people arriving at the emergency department, this can vary; this pre-test probability seems to be higher than that routinely seen in clinical practice. This might be because the clinicians may have included only patients whom they suspect to have acute pancreatitis rather than any patients with abdominal pain. At the median pre-test probability of 22.6%, the post-test probabilities suggest that a significant proportion of people with negative tests, that is an average of 7% to 9%, have pancreatitis. Even at the lower quartile of pre-test probability of 16.3%, an average of 5% to 6% of people with negative tests have acute pancreatitis. People with severe abdominal pain suggestive of acute pancreatitis may therefore require admission for observation, pain control, and supportive treatment even if one or more of the index tests is negative, as the implications of missing acute pancreatitis in severe abdominal pain are high.

AUTHORS' CONCLUSIONS

Implications for practice

About a quarter of people with acute pancreatitis fail to be diagnosed as having acute pancreatitis with the tests evaluated in this review. Consequently, one should have a low threshold to admit the patient and treat as acute pancreatitis if the symptoms are suggestive of acute pancreatitis, even if these tests are normal. As about 1 in 10 patients without acute pancreatitis may be wrongly diagnosed as having acute pancreatitis with these tests, it is important to consider other conditions that require urgent surgical intervention such as perforated viscus even if these tests are abnormal.

The diagnostic performance of these tests decreases even further with the progression of time, and one should have an even lower threshold to perform additional investigations if the symptoms are suggestive of acute pancreatitis.

Implications for research

Further well-designed diagnostic test accuracy studies with prespecified index test threshold of serum amylase, serum lipase, and urinary trypsinogen-2 are required. Such studies should avoid including the index test in the reference standard. Further well-designed diagnostic test accuracy studies with prespecified index test threshold of urinary amylase and urinary trypsinogen-2 are required to investigate the potential of these tests to diagnose acute pancreatitis when there is a delay between onset of symptoms and performance of the test.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abraham 2011

Study characteristics		Study character
Patient sampling	Type of study: prospective study. Consecutive or random sample: consecutive patients.	
Patient characteristics and setting	Sample size: 124. Females: not stated. Median or median age: not stated. Presentation: Patients with acute abdominal pain. Setting: secondary care, India.	
Index tests	Index test: serum amylase. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal. Index test: serum lipase. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal. Index test: urinary trypsinogen-2. Further details: Technical specifications: Actim Pancreatitis (Medix Biochemica). Performed by: not stated. Criteria for positive diagnosis: > 50 ng/mL.	
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: consensus definition. Further details: Technical specifications: not applicable. Performed by: not stated. Criteria for positive diagnosis: consensus definition. For the index tests serum amylase and serum lipase, the answer for the signalling question 'Is the reference standard independent of the index test?' is 'No' and the risk of bias is 'High risk'	
Flow and timing	Number of indeterminates for whom the results of reference standard were available: not stated. Number of patients who were excluded from the analysis: not stated	
Comparative		
Notes	The index tests serum amylase and lipase were not independent of the reference standard, but urinary trypsinogen-2 was independent of the reference standard	

Abraham 2011 (*Continued*)

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?	Yes			
Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Serum amylase				**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?	Yes			
		Unclear	**Low**	
DOMAIN 2: Index Test Serum Lipase				**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?	Yes			
		Unclear	**Low**	
DOMAIN 2: Index Test Urinary trypsinogen-2 (standard criteria)				**DOMAIN 2: In dard criteria)**
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear			

Abraham 2011 (*Continued*)

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?	Yes			
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear			
Is the reference standard independent of the index test?	Yes			
		Unclear	**Low**	

DOMAIN 4: Flow and Timing				**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	Unclear			
Did all patients receive the same reference standard?	Yes			
Were all patients included in the analysis?	Yes			
Did all patients receive a reference standard?	Yes			
		Unclear		

Aysan 2008

Study characteristics		**Study character**
Patient sampling	Type of study: prospective study. Consecutive or random sample: unclear.	
Patient characteristics and setting	Sample size: 99. Females: 46 (46.5%). Median or median age: 37 years.	

Aysan 2008 (*Continued*)

	Presentation: Patients with abdominal pain. Exclusion criteria: Patients with trauma or who required emergency surgical intervention. Setting: secondary care, Turkey.
Index tests	Index test: urinary trypsinogen-2. Further details: Technical specifications: Medix Biochemica. Performed by: not stated. Criteria for positive diagnosis: not clearly stated (probably used the manufacturer's level of > 50 ng/mL)
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: CT scan. Further details: Technical specifications: not stated. Performed by: radiologists. Criteria for positive diagnosis: at least 1 of the following: • increase in diameter of pancreas; • irregular pancreas contours; • peripancreatic fluid; • peripancreatic gas accumulation.
Flow and timing	Number of indeterminates for whom the results of reference standard were available: not stated. Number of patients 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 Urinary trypsinogen-2 (standard criteria)				**DOMAIN 2: In dard criteria)**
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear			
If a threshold was used, was it pre-specified?	Yes			
		Unclear	**Unclear**	
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			
Is the reference standard independent of the index test?	Yes			
		High	**Low**	
DOMAIN 4: Flow and Timing				**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	Unclear			
Did all patients receive the same reference standard?	Yes			
Were all patients included in the analysis?	Unclear			
Did all patients receive a reference standard?	Yes			
		Unclear		

Burkitt 1987

Study characteristics				**Study character**
Patient sampling	Type of study: prospective study. Consecutive or random sample: neither.			
Patient characteristics and setting	Sample size: 306. Females: not stated. Median or median age: not stated. Presentation: People with abdominal pain. Note: 88 patients who had normal urinary amylase were excluded from analysis. Setting: seconday care, UK.			
Index tests	Index test: urinary amylase. Further details: Technical specifications: Rapignost-Amylase test. Performed by: not stated. Criteria for positive diagnosis: 1 plus. Second criteria for positive diagnosis: 2 plus.			
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: Phadebas Amylase > 1000 (normal limit 300) + abdominal pain. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: amylase > 1000 (normal limit 300) + abdominal pain			
Flow and timing	Number of indeterminates for whom the results of reference standard were available: not stated. Number of patients who were excluded from the analysis: 88 (28.8%)			
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?	No			
Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Unclear			

		High	**High**
DOMAIN 2: Index Test Urinary amylase			**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?	Unclear		
		Unclear	**Low**
DOMAIN 3: Reference Standard			**DOMAIN 3: Re**
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Is the reference standard independent of the index test?	Yes		
		Unclear	**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?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	

Chang 2011

Study characteristics				**Study character**
Patient sampling	Type of study: retrospective study. Consecutive or random sample: neither.			
Patient characteristics and setting	Sample size: 3451. Females: not stated. Median or median age: not stated. Presentation: Patients with acute abdominal pain and undergoing blood tests. Exclusion criteria Patients with parotid disease, intracranial haemorrhage, end-stage renal failure. Setting: secondary care, Hong Kong, China.			
Index tests	Index test: serum amylase. Further details: Technical specifications: Beckman Coulter chemistry analyser. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal. Second criteria for positive diagnosis: > twice normal. Index test: serum lipase. Further details: Technical specifications: Beckman Coulter chemistry analyser. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal. Second criteria for positive diagnosis: > twice normal.			
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: radiology (ultrasound or CT). 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: not stated. Number of patients 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?	No			

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**High**
DOMAIN 2: Index Test Serum amylase			**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?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test Serum Lipase			**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?	Unclear		
		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		
Is the reference standard independent of the index test?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			**DOMAIN 4: Fl**

Chang 2011 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	

Keim 1998

Study characteristics		**Study character**
Patient sampling	Type of study: prospective study. Consecutive or random sample: unclear.	
Patient characteristics and setting	Sample size: 253. Females: 108 (42.7%). Median or median age: 56 years. Presentation: Patients with acute abdominal pain and undergoing blood tests. Setting: secondary care, Germany.	
Index tests	Index test: serum amylase. Further details: Technical specifications: Boehringer Mannheim. Performed by: not stated. Criteria for positive diagnosis: > twice normal. Second criteria for positive diagnosis: > normal. Index test: serum lipase. Further details: Technical specifications: Boehringer Mannheim. Performed by: not stated. Criteria for positive diagnosis: > twice normal. Second criteria for positive diagnosis: > normal. Serum amylase and lipase were measured at the 2 specified thresholds for each test at 3 different time points (on admission, 2 to 3 days later, and 4 to 5 days later)	
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: radiology (ultrasound or CT). Further details: Technical specifications: not stated.	

Keim 1998 (*Continued*)

	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: not stated. Number of patients 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 Serum amylase				**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 2: Index Test Serum Lipase				**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			

Keim 1998 (*Continued*)

		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		
Is the reference standard independent of the index test?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	

Mayumi 2012

Study characteristics		**Study character**
Patient sampling	Type of study: prospective study. Consecutive or random sample: consecutive patients.	
Patient characteristics and setting	Sample size: 412. Females: 186 (45.1%). Median or median age: 55 years. Presentation: Adult patients with acute abdominal pain. Setting: secondary care, Japan.	

Index tests	Index test: serum amylase. Further details: Technical specifications: BioMajesty JCA-BM or LABOSPECT. Performed by: study collaborators. Criteria for positive diagnosis: > 3 times normal. Index test: serum lipase. Further details: Technical specifications: BioMajesty JCA-BM or LABOSPECT. Performed by: study collaborators. Criteria for positive diagnosis: > 3 times normal. Index test: urinary trypsinogen-2. Further details: Technical specifications: Actim Pancreatitis (Medix Biochemica). Performed by: study collaborators. Criteria for positive diagnosis: > 50 ng/mL. Second criteria for positive diagnosis: only + or most positive Index test: urinary trypsinogen-2. Further details: Technical specifications: quantitative immunoenzymometric assay trypsinogen-2 test (Medix Biochemica). Performed by: study collaborators. Criteria for positive diagnosis: > 50 ng/mL.
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: consensus definition. 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: not stated. Number of patients who were excluded from the analysis: not stated
Comparative	
Notes	The index tests serum amylase and lipase were not independent of the reference standard, but urinary trypsinogen-2 was independent of the reference standard

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?	Yes			

Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Serum amylase				**DOMAIN 2: In**
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?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Serum Lipase				**DOMAIN 2: In**
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?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Urinary trypsinogen-2 (standard criteria)				**DOMAIN 2: In dard criteria)**
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?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Urinary trypsinogen-2 (non-standard criteria)				**DOMAIN 2: In standard criteri**

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?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Is the reference standard independent of the index test?	Yes		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	

Patt 1966

Study characteristics				**Study character**
Patient sampling	Type of study: unclear whether prospective or retrospective study. Consecutive or random sample: neither.			
Patient characteristics and setting	Sample size: 200. Females: not stated. Median or median age: not stated. Presentation: • Patients with acute abdominal pain. • Underwent laparotomy or autopsy. Note: This indicates that only people with severe symptoms have been included. Setting: secondary care, USA.			
Index tests	Index test: serum amylase. Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: > normal. Index test: serum lipase. Further details: Technical specifications: calorimetric method. Performed by: not stated. Criteria for positive diagnosis: > normal.			
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: laparotomy or autopsy. 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: not stated. Number of patients 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?	No			

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**High**
DOMAIN 2: Index Test Serum amylase			**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?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Serum Lipase			**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?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			**DOMAIN 3: Re**
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Is the reference standard independent of the index test?	Yes		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			**DOMAIN 4: Fl**

Patt 1966 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	

Saez 2005

Study characteristics		**Study character**
Patient sampling	Type of study: prospective study. Consecutive or random sample: consecutive patients.	
Patient characteristics and setting	Sample size: 72. Females: not stated. Median or median age: not stated. Presentation: Patients with acute abdominal pain. Setting: secondary care, Spain.	
Index tests	Index test: serum amylase. Further details: Technical specifications: Amyl, Boehringer Mannheim Systems. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal. Index test: serum lipase. Further details: Technical specifications: Lip, Boehringer Mannheim Systems. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal. Index test: urinary trypsinogen-2. Further details: Technical specifications: Actim Pancreatitis test strip. Performed by: not stated. Criteria for positive diagnosis: > 50 ng/mL.	
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: 3-fold increase of serum amylase and evidence of pancreatitis in radiology or surgery.	

	Further details: Technical specifications: not stated. Performed by: not stated. Criteria for positive diagnosis: not stated. For the index test serum amylase, the answer for the signalling question 'Is the reference standard independent of the index test?' is 'No' and the risk of bias is 'High risk'
Flow and timing	Number of indeterminates for whom the results of reference standard were available: not stated. Number of patients who were excluded from the analysis: not stated
Comparative	
Notes	The index test serum amylase was not independent of the reference standard, but serum lipase and urinary trypsinogen-2 were independent of the reference standard

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?	Yes			
Was a case-control design avoided?	Yes			
Did the study avoid inappropriate exclusions?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Serum amylase				**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?	Yes			
		Low	**Low**	
DOMAIN 2: Index Test Serum Lipase				**DOMAIN 2: In**
Were the index test results interpreted without knowledge of the results of the reference stan-	Unclear			

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

		Unclear	

Viel 1990

Study characteristics				**Study character**
Patient sampling	Type of study: unclear whether prospective or retrospective study. Consecutive or random sample: consecutive patients.			
Patient characteristics and setting	Sample size: 83. Females: not stated. Median or median age: not stated. Presentation: Patients with acute abdominal pain. Setting: secondary care, France.			
Index tests	Index test: serum lipase. Further details: Technical specifications: Boehringer Mannheim. Performed by: not stated. Criteria for positive diagnosis: > 3 times normal.			
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: 3-fold increase of serum amylase and evidence of pancreatitis in radiology, endoscopic retrograde cholangiopancreatography, or surgery. 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: not stated. Number of patients 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?	Yes			
Was a case-control design avoided?	Yes			

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Serum Lipase			**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?	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		
Is the reference standard independent of the index test?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Did all patients receive a reference standard?	Yes		
		Unclear	

Wu 2009

Study characteristics				**Study character**
Patient sampling	Type of study: unclear whether prospective or retrospective study. Consecutive or random sample: unclear.			
Patient characteristics and setting	Sample size: 134. Females: 66 (49.3%). Median or median age: 48 years. Presentation: Patients with acute abdominal pain. Setting: secondary care, China.			
Index tests	Index test: serum amylase. Further details: Technical specifications: Beckman automatic biochemical analyzer. Performed by: not stated. Criteria for positive diagnosis: > normal.			
Target condition and reference standard(s)	Target condition: acute pancreatitis. Reference standard: 1. Characteristic pain. 2. Radiology. 3. Raised amylase. 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: not stated. Number of patients who were excluded from the analysis: not stated			
Comparative				
Notes	The index test serum amylase was not independent of the reference standard, but serum lipase and urinary amylase were independent of the reference standard			

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 Serum amylase				**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?	Yes			
		Unclear	**Low**	
DOMAIN 2: Index Test Urinary trypsinogen-2 (standard criteria)				**DOMAIN 2: In dard criteria)**
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear			
If a threshold was used, was it pre-specified?	Yes			
		Unclear	**Low**	
DOMAIN 2: Index Test Urinary amylase				**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?	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		
Is the reference standard independent of the index test?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			**DOMAIN 4: Fl**
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard?	Yes		
		Unclear	

CT: computed tomography

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

Study	Reason for exclusion
Abascal 1982	No diagnostic test accuracy data
Abate 1979	Inappropriate population
Acero 1982	Case-control study
Adam 1986	No diagnostic test accuracy data
Adams 1968	No diagnostic test accuracy data
Adler 1985	Inappropriate reference standard

(*Continued*)

Ahmed 2009	Inappropriate population
Aho 1988	No diagnostic test accuracy data
Aho 1989	No diagnostic test accuracy data
Alvarez 1998	Not a primary research study
Anand 1956	Inappropriate population
Andersen 2010	Case-control study
Andre 1967	Inappropriate population
Andren-Sandberg 1997	Not a primary research study
Andriushchenko 1998	Inappropriate population
Anonymous 1966	Not a primary research study
Anonymous 2012	Not a primary research study
Aparisi 1987	Not a primary research study
Apple 1991	Inappropriate reference standard
Arzoglou 1983	Inappropriate population
Arzoglou 1986	Case-control study
Bacchini 1980	Inappropriate population
Bachmann 1979	Case-control study
Baillie 1997	Not a primary research study
Baillie 1998	Not a primary research study
Bang 2016	Inappropriate population
Banks 1996	Inappropriate population
Barbado 1977	Case-control study
Barbieri 2016	Not a primary research study

(*Continued*)

Bargum 1983	No diagnostic test accuracy data
Barnett 1986	Inappropriate population
Batra 2015	Inappropriate population
Batsakis 1965	Not a primary research study
Benini 1987	Inappropriate reference standard
Benini 1987a	Inappropriate population
Benini 1992	Inappropriate reference standard
Berger 1976	Case-control study
Bernard 1959	No diagnostic test accuracy data
Bernard 1964	Not a primary research study
Bernard 1964a	Not a primary research study
Bernard 1964b	Not a primary research study
Berry 1982	Inappropriate population
Blamey 1983	Inappropriate population
Bluskina 1966	Case-control study
Bode 1987	Not a primary research study
Borda 1978	Case-control study
Borgstrom 1984	Inappropriate population
Borgstrom 2002	Not a primary research study
Bowen 1983	Inappropriate population
Brailski 1975	Not a primary research study
Branford 1948	No diagnostic test accuracy data
Brault 1985	Inappropriate population

(*Continued*)

Brisinda 1999	Inappropriate population
Brkic 1966	Not a primary research study
Brodie 1977	Inappropriate population
Brohee 1980	Inappropriate population
Brohee 1981	Not a primary research study
Brohee 1987	Not a primary research study
Brunner 1980	Not a primary research study
Buchler 1986	Inappropriate population
Budd 1959	Inappropriate population
Bunodiere 1975	Inappropriate population
Butler 2000	Not a primary research study
Caillens 1980	Inappropriate target condition
Calkins 1968	Inappropriate population
Cameron 1973	Inappropriate population
Campbell 1979	Inappropriate population
Caputo 1983	Inappropriate population
Cases 1988	Inappropriate population
Cevik 2010	Case-control study
Chase 1996	Inappropriate reference standard
Chen 1994	Case-control study
Chen 2004	Not a primary research study
Chen 2005	Inappropriate reference standard
Cheng 2004	Inappropriate population

(*Continued*)

Cheung 2015	No diagnostic test accuracy data
Choi 2009	Case-control study
Choudhary 2012	Not a primary research study
Christoforidis 2002	Inappropriate population
Chylinski 1972	Inappropriate population
Chylinski 1978	Inappropriate population
Cintra 1952	Inappropriate population
Cintra 1953	Inappropriate population
Clave 1995	Inappropriate reference standard
Close 1987	Not a primary research study
Coffey 2014	Inappropriate population
Coffey 2014a	Inappropriate population
Collins 1982	Case-control study
Concepcion Martin 2013	Inappropriate population
Concepcion-Martin 2016	No diagnostic test accuracy data
Corfield 1984	Inappropriate population
Cornett 2010	No diagnostic test accuracy data
Corsetti 1993	Inappropriate reference standard
Cote 1979	Inappropriate population
Courtois 1986	Inappropriate population
Dalgat 1986	Inappropriate population
Dankner 1951	Inappropriate population
Dati 1988	Not a primary research study

(*Continued*)

de Boer 1986	Not a primary research study
De Leo 1954	Not a primary research study
Dehesa 1979	Case-control study
Delcourt 1977	Not a primary research study
Deril 1989	Case-control study
Deril 1992	Not a primary research study
Devanath 2009	Inappropriate population
Diaz 2009	Inappropriate population
Distefano 1952	No diagnostic test accuracy data
Domenech 1999	No diagnostic test accuracy data
Donaldson 1977	No diagnostic test accuracy data
Dreiling 1974	Inappropriate population
Dreiung 1954	Inappropriate population
Dronov 2009	Inappropriate population
Drozdov 2003	Not a primary research study
Durr 1977	Inappropriate population
Durr 1983	No diagnostic test accuracy data
Eckfeldt 1985	No diagnostic test accuracy data
Elman 1942	Not a primary research study
Engel 1977	No diagnostic test accuracy data
Ermini 1964	Not a primary research study
Esber 1995	Inappropriate population
Esperov 1972	Inappropriate population

(*Continued*)

Fabris 1976	No diagnostic test accuracy data
Farkas 1967	No diagnostic test accuracy data
Farrar 1978	Inappropriate population
Finke 1978	Inappropriate population
Fiocca 1983	Inappropriate population
Fiorucci 1986	Inappropriate population
Fishman 1955	Inappropriate population
Flamion 1987	Inappropriate population
Forell 1959	Inappropriate population
Forest 1990	Inappropriate reference standard
Fridhandler 1972	Inappropriate population
Frost 1978	Inappropriate population
Fruchart 1974	Inappropriate population
Fruchart 1980	Inappropriate population
Fujiki 1980	Inappropriate population
Fujita 1989	Inappropriate population
Fukumoto 1981	Inappropriate population
Gambill 1975	Not a primary research study
Garden 1985	No diagnostic test accuracy data
Gilbert 1955	No diagnostic test accuracy data
Gluskina 1965	Inappropriate population
Gomez 2012	Inappropriate population
Gonzalez 1978	Case-control study

(*Continued*)

Grinblatt 1997	Not a primary research study
Grosberg 1979	Case-control study
Gullo 2005	Not a primary research study
Gumaste 1991	Inappropriate population
Gumaste 1992	Case-control study
Gumaste 1993	Case-control study
Gumaste 1993a	Not a primary research study
Gungor 2011	Inappropriate population
Gunn 1986	Inappropriate population
Guth 1960	Inappropriate population
Gwozdz 1990	Inappropriate reference standard
Haas 1985	Inappropriate population
Haffter 1981	Case-control study
Haffter 1983	Case-control study
Hale 2015	Inappropriate population
Hathaway 1983	Case-control study
Hayakawa 1985	Case-control study
Hayakawa 1989	Case-control study
Hedstroem 1998	Inappropriate reference standard
Hedstrom 1994	Case-control study
Hedstrom 1996	Case-control study
Hedstrom 1996a	Case-control study
Hedstrom 1996b	Case-control study

(*Continued*)

Hedstrom 1996c	Case-control study
Hedstrom 2001	Case-control study
Heer 1983	Case-control study
Hegewald 1998	Inappropriate population
Hegewald 1999	Inappropriate population
Hegewald 2001	Inappropriate population
Hemingway 1988	Case-control study
Hendry 1987	Inappropriate population
Henry 1957	Inappropriate population
Hoferichter 1964	Inappropriate population
Hoffman 1991	Inappropriate reference standard
Hofmeyr 2014	Inappropriate population
Holdsworth 1984	Case-control study
Holmes 2011	Inappropriate population
Horanyi 1984	Inappropriate population
Hostein 1976	Inappropriate population
Hostein 1977	Inappropriate population
Hostein 1978	Inappropriate population
Houry 1985	Inappropriate reference standard
Houry 1989	Inappropriate reference standard
Huang 2010	Inappropriate population
Huguet 1993	Inappropriate reference standard
Husain 2004	Inappropriate population

(*Continued*)

Hwang 2004	Case-control study
Ignjatovic 1997	Inappropriate reference standard
Ignjatovic 2000	Inappropriate reference standard
Im 2010	Inappropriate population
Imrie 1979	Inappropriate population
Ito 2007	Inappropriate population
Jacobson 1982	Not a primary research study
Jam 1978	Inappropriate population
Jang 2007	Inappropriate population
Jensen 1970	Inappropriate population
Jin 2012	Not a primary research study
Jin 2013	Not a primary research study
Jin 2013a	Not a primary research study
Johnson 2004	Inappropriate population
Jordanov 2009	Case-control study
Joshi 2008	Inappropriate reference standard
Junge 1982	Case-control study
Kaiser 1987	Inappropriate reference standard
Kamer 2007	Case-control study
Kameya 1985	Case-control study
Kameya 1986	Case-control study
Kapetanos 2007	Inappropriate population
Karlsson 1979	Inappropriate population

(*Continued*)

Kaw 2001	Inappropriate population
Kazmierczak 1991	Inappropriate reference standard
Kehl 1985	Inappropriate population
Keim 2003	Case-control study
Kemppainen 1997	Inappropriate reference standard
Kemppainen 1997a	Inappropriate population
Kemppainen 1997b	Inappropriate population
Kemppainen 1997c	Inappropriate reference standard
Kemppainen 1997d	Not a primary research study
Kerlin 1986	Inappropriate population
Khrapach 1992	Inappropriate population
Khvatova 1973	Inappropriate population
Kim 2015	Inappropriate population
King 1995	Inappropriate population
Kirchner 1976	Inappropriate population
Kitterer 2015	Inappropriate population
Kobayashi 2011	Inappropriate population
Koehler 1982	Inappropriate population
Kolars 1982	Inappropriate population
Kolars 1984	Inappropriate population
Kopacova 2010	Inappropriate population
Kubo 1975	Not a primary research study
Kulikovsky 2014	Inappropriate population

(*Continued*)

Kurti 2011	Inappropriate reference standard
Kusama 1956	Inappropriate population
Kutter 1983	Inappropriate population
Kylanpaa-Back 1999	Inappropriate reference standard
Kylanpaa-Back 2000	Inappropriate reference standard
Kylanpaa-Back 2000a	Inappropriate reference standard
Kylanpaa-Back 2002	Inappropriate reference standard
Lacher 1986	Inappropriate population
Lankisch 1977	Case-control study
Lankisch 1977a	Case-control study
Lankisch 1994	Inappropriate population
Lankisch 1994a	Inappropriate population
Lankisch 2006	Inappropriate population
Lankisch 2012	No diagnostic test accuracy data
Laurent-Puig 1992	Inappropriate population
Lauschke 1963	Inappropriate population
Leclerc 1983	Inappropriate population
Lee 1995	Case-control study
Lee 1996	Not a primary research study
Lempinen 2001	Inappropriate population
Lempinen 2003	Inappropriate population
Lessinger 1994	Case-control study
Levitt 1975	Not a primary research study

(*Continued*)

Lifton 1974	Inappropriate population
Lifton 1974a	Inappropriate population
Ligny 1987	Case-control study
Lin 1989	Case-control study
Lindahl 1979	No diagnostic test accuracy data
Liyanage 2012	Inappropriate population
Logrono 2000	Inappropriate reference standard
Long 1976	Case-control study
Loo 1992	Not a primary research study
Lott 1985	Not a primary research study
Lott 1985a	Not a primary research study
Lott 1986	Inappropriate population
Lott 1991	Not a primary research study
Lott 1991a	Case-control study
Luengo 1996	Inappropriate population
Lunghi 1984	Inappropriate population
MacArthur 2013	Inappropriate population
Macgregor 1976	Case-control study
Maekelae 1997	Inappropriate population
Majkicsingh 1986	Inappropriate population
Malfertheiner 1989	Inappropriate population
Mangano 1990	Inappropriate target condition
Marten 1976	Case-control study

(*Continued*)

Masoero 1978	Inappropriate population
Masoero 1980	Case-control study
Massey 1985	Inappropriate reference standard
Mayer 1985	Inappropriate reference standard
McCulloch 1984	Case-control study
McIntosh 1976	Not a primary research study
McMahon 1981	Inappropriate population
McMahon 1982	Inappropriate population
Merina 1957	Inappropriate population
Millat 1999	Not a primary research study
Miller 1973	Inappropriate population
Millson 1998	Inappropriate reference standard
Mimoz 1993	Inappropriate population
Mingxin 2001	Inappropriate reference standard
Mirmiranyazdy 1995	Inappropriate population
Mohamed 1989	Case-control study
Moller-Petersen 1983	Inappropriate reference standard
Moller-Petersen 1985	Inappropriate reference standard
Moller-Petersen 1986	Inappropriate reference standard
Morel 1981	Case-control study
Murray 1976	Inappropriate reference standard
Murray 1977	Inappropriate reference standard
Murray 1980	Inappropriate reference standard

(*Continued*)

Navarro 1984	Not a primary research study
Navarro 1987	Case-control study
Nechai 1973	Inappropriate population
Nechiporuk 1982	Inappropriate population
Neoptolemos 1990	No diagnostic test accuracy data
Neoptolemos 1993	Not a primary research study
Neoptolemos 2000	Inappropriate population
Neovius 1984	Inappropriate reference standard
Neves 1985	Inappropriate population
Newland 2002	Inappropriate population
Oellerich 1983	Case-control study
Orda 1982	Inappropriate reference standard
Orda 1984	Case-control study
Orebaugh 1994	Inappropriate population
Osipov 1970	Inappropriate population
Ostrovskii 2012	Inappropriate population
Otsuki 1995	Case-control study
Pace 1985	Inappropriate population
Pacheco 2003	Case-control study
Pakkala 2012	Inappropriate population
Panteghini 1989	Inappropriate population
Panteghini 1990	Inappropriate population
Panteghini 1992	Inappropriate population

(*Continued*)

Papaioannou 1996	Case-control study
Papp 1969	Case-control study
Parodi 1983	Case-control study
Pereiaslov 1999	Inappropriate population
Peromingo 2009	Inappropriate population
Pezzilli 1992	Case-control study
Pezzilli 1992a	Case-control study
Pezzilli 1994	Case-control study
Pezzilli 1997	Inappropriate population
Pezzilli 1998	Case-control study
Pezzilli 1999	Case-control study
Pezzilli 1999a	Case-control study
Pezzilli 2000	Case-control study
Pezzilli 2001	Inappropriate population
Pezzilli 2004	Case-control study
Phillip 2013	Inappropriate population
Pirolla 2015	Inappropriate population
Ponseti-Bosch 1977	Case-control study
Ponteziere 2001	Inappropriate reference standard
Popivanov 1963	No diagnostic test accuracy data
Protsenko 1966	No diagnostic test accuracy data
Raju 2003	Case-control study
Raty 2007	Inappropriate population

(*Continued*)

Reilly 2011	Inappropriate population
Rick 1968	Inappropriate population
Roberts 1985	Case-control study
Roberts 1987	Case-control study
Rodriguez-Cuartero 2000	No diagnostic test accuracy data
Rokicki 1976	Not a primary research study
Rosenblum 1991	Not a primary research study
Rosenburg 1957	No diagnostic test accuracy data
Rudis 2014	Inappropriate population
Ruzena 1989	No diagnostic test accuracy data
Sacchetti 1988	Inappropriate population
Sacchetti 1989	Inappropriate population
Sadowski 1992	Inappropriate population
Sainio 1995	Case-control study
Sankaralingam 2007	Inappropriate population
Satz 1989	Case-control study
Satz 1990	Case-control study
Satz 1990a	Case-control study
Saxon 1957	Case-control study
Schmidt 2004	Inappropriate population
Scholz 1979	No diagnostic test accuracy data
Schultis 1969	No diagnostic test accuracy data
Schultis 1969a	Inappropriate reference standard

(*Continued*)

Schultis 1973	Case-control study
Schwokowski 1979	Not a primary research study
Scottolini 1977	Not a primary research study
Serra 2011	Inappropriate population
Siede 1969	Not a primary research study
Singh 2002	Inappropriate population
Singh 2004	Inappropriate population
Smith 2005	Inappropriate population
Solomon 1978	Not a primary research study
Steinberg 1983	Inappropriate reference standard
Steinberg 1985	Case-control study
Sternby 1996	Inappropriate population
Strebel 1970	Inappropriate population
Su 2010	Inappropriate reference standard
Suehiro 1984	Case-control study
Sutton 2009	Inappropriate population
Szalaj 1973	Case-control study
Testoni 1999	Inappropriate population
Testoni 1999a	Inappropriate population
Testoni 2001	Inappropriate population
Thomson 1987	Inappropriate reference standard
Ticktin 1965	Inappropriate population
Tietz 1986	Inappropriate population

(*Continued*)

Tomaszewski 1984	Inappropriate population
Torrens 1998	No diagnostic test accuracy data
Tournut 1978	Inappropriate population
Treacy 2001	Inappropriate population
Tsai 1988	Inappropriate population
Tseng 2011	Inappropriate population
Tvorogova 1991	Not a primary research study
Uhl 1992	Case-control study
Uminska 1985	Case-control study
Van Hee 1979	Case-control study
Van Ingen 1992	Case-control study
Varas 1994	Inappropriate population
Vega 1981	Inappropriate reference standard
Ventrucci 1983	Case-control study
Ventrucci 1985	Inappropriate reference standard
Ventrucci 1986	Case-control study
Ventrucci 1989	Case-control study
Ventrucci 1992	Case-control study
Ventrucci 1994	Case-control study
Wajda 1978	Inappropriate population
Walker 2013	Inappropriate population
Waller 1971	Inappropriate population
Wang 2009	Inappropriate population

(*Continued*)

Warshaw 1975	Case-control study
Weaver 1985	Inappropriate population
Werner 1989	Case-control study
Wilson 2005	Case-control study
Winslet 1990	Inappropriate population
Wyatt 1974	No diagnostic test accuracy data
Wyllie 1979	Inappropriate population
Xu 2008	Case-control study
Xu 2010	Inappropriate reference standard
Yang 1987	Case-control study
Yang 2005	Case-control study
Zakrzewska 1982	Case-control study
Zakrzewska 1985	Case-control study
Zaninotto 1990	Case-control study
Zastrow 1973	Inappropriate population
Zeng 2010	Not a primary research study
Zeze 1975	Case-control study
Zhang 2010	Case-control study
Zharkovskaia 1978	Inappropriate population
Zheltvai 1969	Not a primary research study

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

Anand 1956a

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

Cherry 1953

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

Coppola 1954

Study characteristics		Study character
Patient sampling	Awaiting full text	

Coppola 1954 (*Continued*)

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

Do Prado 1952

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

Lippi 2013

Study characteristics		**Study character**
Patient sampling	Awaiting full text	
Patient characteristics and setting		
Index tests		
Target condition and reference standard(s)		

Lippi 2013 (*Continued*)

Flow and timing	
Comparative	
Notes	

Stimac 1995

Study characteristics		**Study character**
Patient sampling	Awaiting 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 Serum amylase > 3 times normal	4	4056
2 Serum amylase > 3 times normal (sensitivity analysis excluding studies with incorporation bias)	1	3451
3 Serum amylase > 3 times normal (sensitivity analysis excluding Chang 2011)	3	605
4 Serum amylase > twice normal	2	3704
5 Serum amylase > twice normal (sensitivity analysis excluding Chang 2011)	1	253
6 Serum amylase > twice normal (2 to 3 days)	1	253
7 Serum amylase > twice normal (4 to 5 days)	1	253
8 Serum amylase > normal	3	587
9 Serum amylase > normal (sensitivity analysis excluding studies with incorporation bias)	2	453
10 Serum amylase > normal (2 to 3 days)	1	253
11 Serum amylase > normal (4 to 5 days)	1	253
12 Serum lipase > 3 times normal	5	4129
13 Serum lipase > 3 times normal (sensitivity analysis excluding studies with incorporation bias)	2	3534
14 Serum lipase > 3 times normal (sensitivity analysis excluding Chang 2011)	4	678
15 Serum lipase > twice normal	2	3704
16 Serum lipase > twice normal (sensitivity analysis excluding Chang 2011)	1	253
17 Serum lipase > twice normal (2 to 3 days)	1	253
18 Serum lipase > twice normal (4 to 5 days)	1	253
19 Serum lipase > normal	2	453
20 Serum lipase > normal (2 to 3 days)	1	253

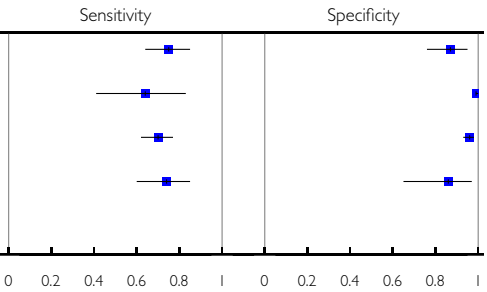
21 Serum lipase > normal (4 to 5 days)	1	253
22 Urinary trypsinogen-2 > 50 ng/mL (Actim Pancreatitis)	5	841
23 Urinary trypsinogen-2 > 50 ng/mL (Actim Pancreatitis - sensitivity analysis)	4	742
24 Urinary trypsinogen-2 > 50 ng/mL (quantitative method)	1	412
25 Urinary trypsinogen-2 only positive or most positive (threshold for this not available)	1	412
26 Urinary amylase > normal (quantitative)	1	134
27 Urinary amylase 1+ (qualitative)	1	218
28 Urinary amylase 2+ (qualitative)	1	218

Test 1. Serum amylase > 3 times normal.

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 1 Serum amylase > 3 times normal

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2011	52	7	17	48	0.75 [0.64, 0.85]	0.87 [0.76, 0.95]
Chang 2011	14	19	8	3410	0.64 [0.41, 0.83]	0.99 [0.99, 1.00]
Mayumi 2012	109	9	47	244	0.70 [0.62, 0.77]	0.96 [0.93, 0.98]
Saez 2005	37	3	13	19	0.74 [0.60, 0.85]	0.86 [0.65, 0.97]

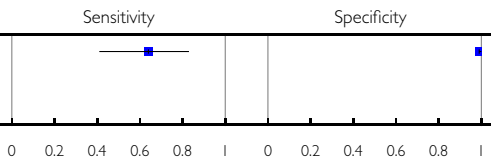


Test 2. Serum amylase > 3 times normal (sensitivity analysis excluding studies with incorporation bias).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 2 Serum amylase > 3 times normal (sensitivity analysis excluding studies with incorporation bias)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chang 2011	14	19	8	3410	0.64 [0.41, 0.83]	0.99 [0.99, 1.00]

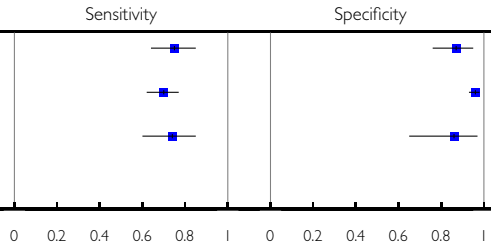


Test 3. Serum amylase > 3 times normal (sensitivity analysis excluding Chang 2011).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 3 Serum amylase > 3 times normal (sensitivity analysis excluding Chang 2011)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2011	52	7	17	48	0.75 [0.64, 0.85]	0.87 [0.76, 0.95]
Mayumi 2012	109	9	47	244	0.70 [0.62, 0.77]	0.96 [0.93, 0.98]
Saez 2005	37	3	13	19	0.74 [0.60, 0.85]	0.86 [0.65, 0.97]

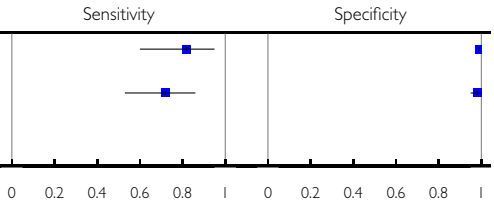


Test 4. Serum amylase > twice normal.

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 4 Serum amylase > twice normal

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chang 2011	18	36	4	3393	0.82 [0.60, 0.95]	0.99 [0.99, 0.99]
Keim 1998	23	4	9	217	0.72 [0.53, 0.86]	0.98 [0.95, 1.00]

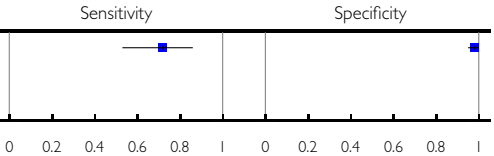


Test 5. Serum amylase > twice normal (sensitivity analysis excluding Chang 2011).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 5 Serum amylase > twice normal (sensitivity analysis excluding Chang 2011)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	23	4	9	217	0.72 [0.53, 0.86]	0.98 [0.95, 1.00]

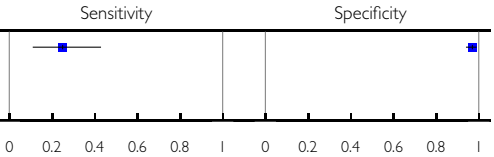


Test 6. Serum amylase > twice normal (2 to 3 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 6 Serum amylase > twice normal (2 to 3 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	8	7	24	214	0.25 [0.11, 0.43]	0.97 [0.94, 0.99]

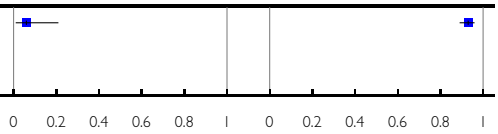


Test 7. Serum amylase > twice normal (4 to 5 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 7 Serum amylase > twice normal (4 to 5 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	2	15	30	206	0.06 [0.01, 0.21]	0.93 [0.89, 0.96]

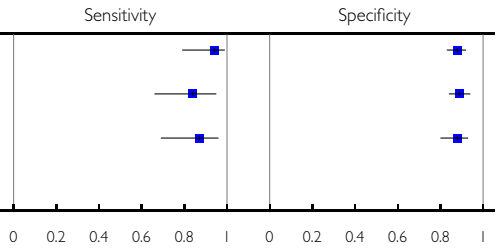


Test 8. Serum amylase > normal.

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 8 Serum amylase > normal

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	30	27	2	194	0.94 [0.79, 0.99]	0.88 [0.83, 0.92]
Patt 1966	26	18	5	151	0.84 [0.66, 0.95]	0.89 [0.84, 0.94]
Wu 2009	26	13	4	91	0.87 [0.69, 0.96]	0.88 [0.80, 0.93]

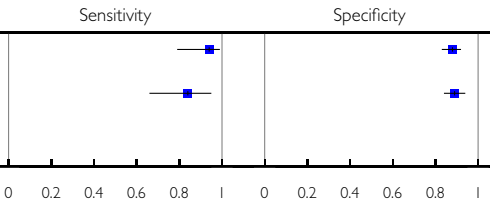


Test 9. Serum amylase > normal (sensitivity analysis excluding studies with incorporation bias).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 9 Serum amylase > normal (sensitivity analysis excluding studies with incorporation bias)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	30	27	2	194	0.94 [0.79, 0.99]	0.88 [0.83, 0.92]
Patt 1966	26	18	5	151	0.84 [0.66, 0.95]	0.89 [0.84, 0.94]

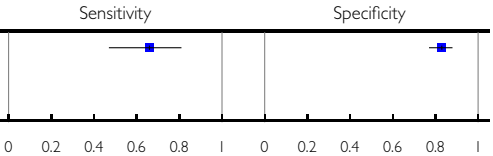


Test 10. Serum amylase > normal (2 to 3 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 10 Serum amylase > normal (2 to 3 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	21	38	11	183	0.66 [0.47, 0.81]	0.83 [0.77, 0.88]

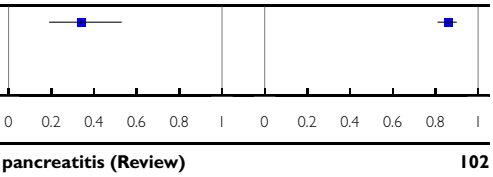


Test 11. Serum amylase > normal (4 to 5 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 11 Serum amylase > normal (4 to 5 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	11	31	21	190	0.34 [0.19, 0.53]	0.86 [0.81, 0.90]

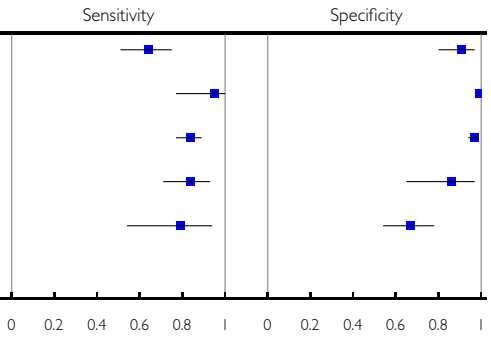


Test 12. Serum lipase > 3 times normal.

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 12 Serum lipase > 3 times normal

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2011	44	5	25	50	0.64 [0.51, 0.75]	0.91 [0.80, 0.97]
Chang 2011	21	29	1	3400	0.95 [0.77, 1.00]	0.99 [0.99, 0.99]
Mayumi 2012	126	8	24	241	0.84 [0.77, 0.89]	0.97 [0.94, 0.99]
Saez 2005	42	3	8	19	0.84 [0.71, 0.93]	0.86 [0.65, 0.97]
Viel 1990	15	21	4	43	0.79 [0.54, 0.94]	0.67 [0.54, 0.78]

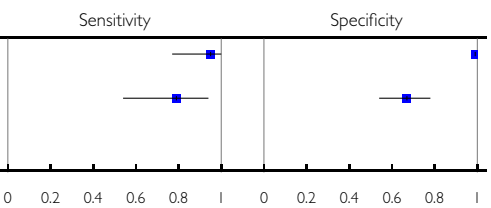


Test 13. Serum lipase > 3 times normal (sensitivity analysis excluding studies with incorporation bias).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 13 Serum lipase > 3 times normal (sensitivity analysis excluding studies with incorporation bias)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chang 2011	21	29	1	3400	0.95 [0.77, 1.00]	0.99 [0.99, 0.99]
Viel 1990	15	21	4	43	0.79 [0.54, 0.94]	0.67 [0.54, 0.78]

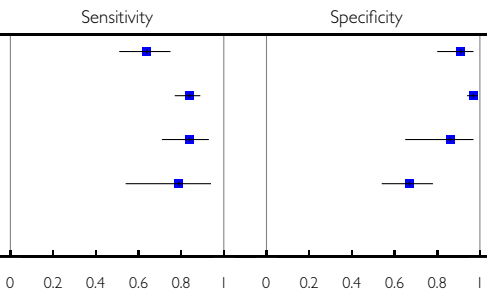


Test 14. Serum lipase > 3 times normal (sensitivity analysis excluding Chang 2011).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 14 Serum lipase > 3 times normal (sensitivity analysis excluding Chang 2011)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2011	44	5	25	50	0.64 [0.51, 0.75]	0.91 [0.80, 0.97]
Mayumi 2012	126	8	24	241	0.84 [0.77, 0.89]	0.97 [0.94, 0.99]
Saez 2005	42	3	8	19	0.84 [0.71, 0.93]	0.86 [0.65, 0.97]
Viel 1990	15	21	4	43	0.79 [0.54, 0.94]	0.67 [0.54, 0.78]

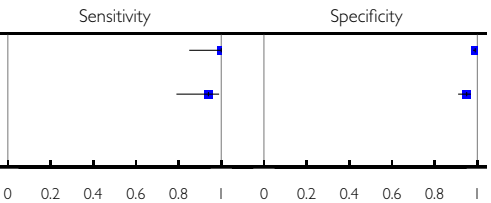


Test 15. Serum lipase > twice normal.

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 15 Serum lipase > twice normal

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chang 2011	22	51	0	3378	1.00 [0.85, 1.00]	0.99 [0.98, 0.99]
Keim 1998	30	11	2	210	0.94 [0.79, 0.99]	0.95 [0.91, 0.97]



Test 16. Serum lipase > twice normal (sensitivity analysis excluding Chang 2011).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 16 Serum lipase > twice normal (sensitivity analysis excluding Chang 2011)

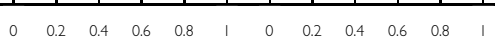
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Keim 1998	30	11	2	210	0.94 [0.79, 0.99]	0.95 [0.91, 0.97]		

Test 17. Serum lipase > twice normal (2 to 3 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 17 Serum lipase > twice normal (2 to 3 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Keim 1998	22	20	10	201	0.69 [0.50, 0.84]	0.91 [0.86, 0.94]		

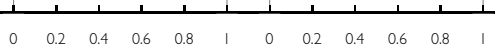


Test 18. Serum lipase > twice normal (4 to 5 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 18 Serum lipase > twice normal (4 to 5 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Keim 1998	13	35	19	186	0.41 [0.24, 0.59]	0.84 [0.79, 0.89]		

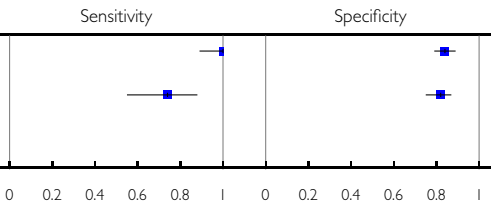


Test 19. Serum lipase > normal.

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 19 Serum lipase > normal

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	32	35	0	186	1.00 [0.89, 1.00]	0.84 [0.79, 0.89]
Patt 1966	23	31	8	138	0.74 [0.55, 0.88]	0.82 [0.75, 0.87]

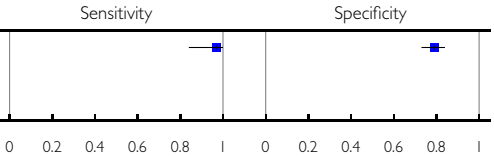


Test 20. Serum lipase > normal (2 to 3 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 20 Serum lipase > normal (2 to 3 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	31	46	1	175	0.97 [0.84, 1.00]	0.79 [0.73, 0.84]

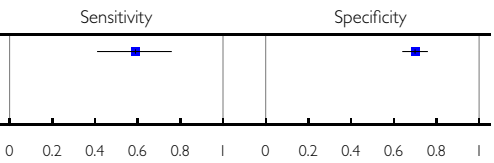


Test 21. Serum lipase > normal (4 to 5 days).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 21 Serum lipase > normal (4 to 5 days)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keim 1998	19	66	13	155	0.59 [0.41, 0.76]	0.70 [0.64, 0.76]

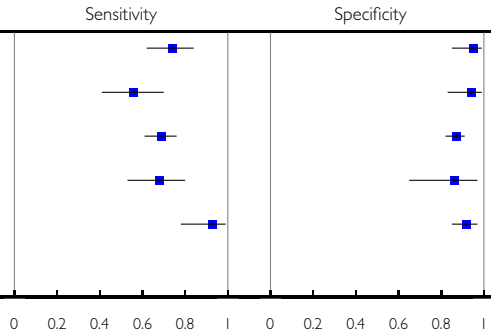


Test 22. Urinary trypsinogen-2 > 50 ng/mL (Actim Pancreatitis).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 22 Urinary trypsinogen-2 > 50 ng/mL (Actim Pancreatitis)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2011	51	3	18	52	0.74 [0.62, 0.84]	0.95 [0.85, 0.99]
Aysan 2008	28	3	22	46	0.56 [0.41, 0.70]	0.94 [0.83, 0.99]
Mayumi 2012	107	33	49	223	0.69 [0.61, 0.76]	0.87 [0.82, 0.91]
Saez 2005	34	3	16	19	0.68 [0.53, 0.80]	0.86 [0.65, 0.97]
Wu 2009	28	8	2	96	0.93 [0.78, 0.99]	0.92 [0.85, 0.97]

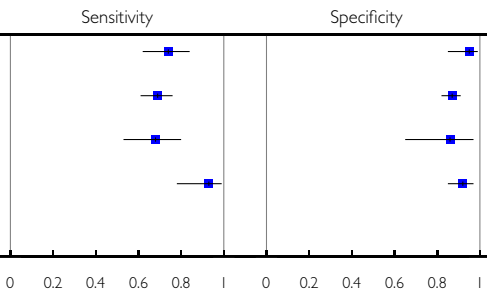


Test 23. Urinary trypsinogen-2 > 50 ng/mL (Actim Pancreatitis - sensitivity analysis).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 23 Urinary trypsinogen-2 > 50 ng/mL (Actim Pancreatitis - sensitivity analysis)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2011	51	3	18	52	0.74 [0.62, 0.84]	0.95 [0.85, 0.99]
Mayumi 2012	107	33	49	223	0.69 [0.61, 0.76]	0.87 [0.82, 0.91]
Saez 2005	34	3	16	19	0.68 [0.53, 0.80]	0.86 [0.65, 0.97]
Wu 2009	28	8	2	96	0.93 [0.78, 0.99]	0.92 [0.85, 0.97]

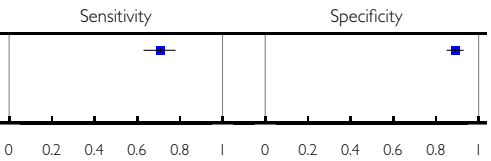


Test 24. Urinary trypsinogen-2 > 50 ng/mL (quantitative method).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 24 Urinary trypsinogen-2 > 50 ng/mL (quantitative method)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Mayumi 2012	111	28	45	228	0.71 [0.63, 0.78]	0.89 [0.85, 0.93]

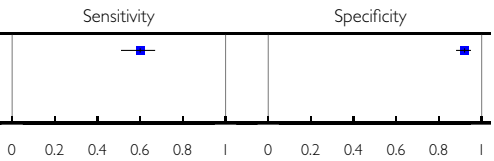


Test 25. Urinary trypsinogen-2 only positive or most positive (threshold for this not available).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 25 Urinary trypsinogen-2 only positive or most positive (threshold for this not available)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Mayumi 2012	93	20	63	236	0.60 [0.51, 0.67]	0.92 [0.88, 0.95]

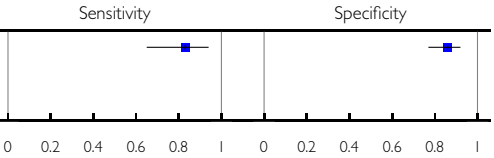


Test 26. Urinary amylase > normal (quantitative).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 26 Urinary amylase > normal (quantitative)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wu 2009	25	15	5	89	0.83 [0.65, 0.94]	0.86 [0.77, 0.92]

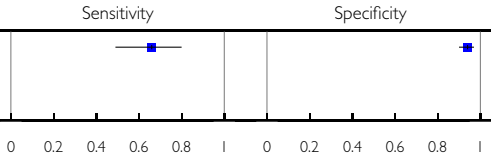


Test 27. Urinary amylase 1+ (qualitative).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 27 Urinary amylase 1+ (qualitative)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Burkitt 1987	27	10	14	167	0.66 [0.49, 0.80]	0.94 [0.90, 0.97]

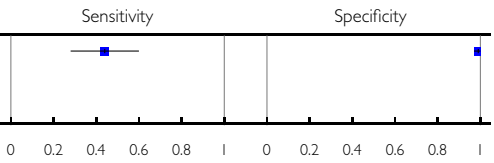


Test 28. Urinary amylase 2+ (qualitative).

Review: Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis

Test: 28 Urinary amylase 2+ (qualitative)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Burkitt 1987	18	1	23	176	0.44 [0.28, 0.60]	0.99 [0.97, 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 pancreatitis)

Domain 1: Participant selection	Patient sampling	Adult patients with acute epigastric or diffuse abdominal pain
	Was a consecutive or random sample of patients enrolled?	Yes: If a consecutive sample or a random sample of patients with acute epigastric or diffuse abdominal pain was included in the study. No: If a consecutive sample or a random sample of patients with acute epigastric or

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

		diffuse abdominal pain was not included in the study. Unclear: If this information was not available.
	Did the study avoid inappropriate exclusions?	Yes: If all patients with acute epigastric or diffuse abdominal pain suspected to be acute pancreatitis were included. No: If the study excluded patients based on high or low probability of acute pancreatitis (e.g. those with organ failure). 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	Yes: If all patients with acute epigastric or diffuse abdominal pain suspected to be acute pancreatitis were included. No: If a proportion of patients with acute epigastric or diffuse abdominal pain were excluded on the basis of the results of another diagnostic test (e.g. an arterial blood gas analysis performed after the index test) . Unclear: If it is not clear whether the patients have been included on the basis of the results of another diagnostic test (e.g. an arterial blood gas analysis performed after the index test)
	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 amylase, serum lipase, urinary trypsinogen-2, urinary amylase

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

	Were the index test results interpreted without knowledge of the results of the reference standard?	The index test would always be conducted, though not interpreted before the reference standard Yes: If the index test was conducted and interpreted without knowledge of the results of the reference standard. No: If the index test was interpreted with knowledge of the results of the reference standard. Unclear: If it was not clear whether the index test was interpreted without knowledge of 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 are clearly stated High concern: If the criteria for positive index test are not stated
Domain 3: Target condition and reference standard	Target condition and reference standard(s)	Target condition: acute pancreatitis (mild, moderately severe, or severe) While inflammation of the pancreas confirmed by biopsy can be considered to be the gold standard for the diagnosis of acute pancreatitis, for ethical reasons it is unlikely to performed in any participant. As a result, different study authors may use different reference standards such as radiological features of acute pancreatitis or the presence of organ failure. However, such reference standards can miss cases of mild acute pancreatitis, resulting in an underestimation of diagnostic test accuracy of the index tests. We also accepted the consensus conference

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

		definition of acute pancreatitis, i.e. when at least two of the following three features are present (Banks 2013). 1. Acute onset of 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 CECT and less commonly MRI or transabdominal ultrasonography. We accepted any of the following used alone or in combination as reference standards: biopsy, radiological features of acute pancreatitis, laparotomy, autopsy, organ failure, or the consensus conference definition (including or excluding the index test being evaluated). In terms of ranking the reference standards, we considered biopsy as the best reference standard (although for ethical reasons it is unlikely to have been performed in any participant) followed by the consensus definition of acute pancreatitis, radiological, surgical, or autopsy features of acute pancreatitis, or the presence of organ failure, in that order
	Is the reference standard likely to correctly classify the target condition?	Yes: If histological confirmation of acute pancreatitis is obtained or the consensus definition of acute pancreatitis is used. No: If the reference standard is radiological confirmation or organ failure. Unclear: If the reference standard was not adequately described
	Is the reference standard independent of the index test?	Yes: If the index test was not part of the reference standard. No: If the index test was part of the reference standard. Unclear: If it was not clear whether the index test was part of the reference standard. As anticipated, we classified all studies included in the review as 'yes' or 'no' for this item
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes: If the reference standard was interpreted without knowledge of the results of the index test. No: If the reference standard was inter-

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

		preted 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 all of the above three questions High risk of bias: If 'no' classification for any of the above three questions Unclear risk of bias: If 'unclear' classification for any of the above three questions but without a 'no' classification for any of the above three questions
	Are there concerns that the target condition as defined by the reference standard does not match the question?	As anticipated, we classified all of the included studies as 'low concern' based on the inclusion criteria for this review
Domain 4: Flow and timing	Flow and timing	Patients may have complete resolution of acute pancreatitis if they had acute pancreatitis, or may have an episode of acute pancreatitis if they did not have acute pancreatitis if the interval between the index test and reference standard is long
	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 one week. No: If the time interval between index test and reference standard was more than one week. 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 (we anticipate that all studies will be classified as 'yes').

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

		No: If different participants received different reference standards 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 due to uninterpretable results. 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

Table 3. Serum amylase at different thresholds and different times

Index test	Sensitivity	Specificity	Post-test probability of a positive test [1]	Post-test probability of a negative test[1]	Number of false positives per 100 people having a positive test	Number of false negatives per 100 people having a negative test	Number of studies (Number of participants)	Risk of bias / Applicability concerns / Inconsistency
Serum amylase (threshold: > 3 times normal) (on admission)	0.71 (95% CI 0.65 to 0.77)	0.99 (95% CI 0.99 to 0.99)	95.4% (95% CI 93.4% to 96.8%)	7.8% (95% CI 6.4% to 9.5%)	5 (95% CI 3 to 7)	8 (95% CI 6 to 9)	4 (4056)	High / High / No
Serum amylase (threshold: > 3 times normal) (on admission (exclud-	0.72 (95% CI 0.59 to 0.82)	0.93 (95% CI 0.66 to 0.99)	74.0% (95% CI 33.4% to 94.1%)	8.1% (95% CI 5.4% to 12.1%)	26 (95% CI 6 to 67)	8 (95% CI 5 to 12)	3 (605)	Unclear / Low / Moderate

Table 3. Serum amylase at different thresholds and different times (*Continued*)

ing Chang 2011))								
Serum amylase (threshold: > 3 times normal) (on admission (excluding studies with incorporation bias))	0.64 (95% CI 0.41 to 0.82)	0.99 (95% CI 0.99 to 1.00)	97.1% (95% CI 95.1% to 98.3%)	9.7% (95% CI 5.8% to 15.7%)	3 (95% CI 2 to 5)	10 (95% CI 6 to 16)	1 (3451)	High / High / Not applicable
Serum amylase (threshold: > twice normal) (on admission)	0.76 (95% CI 0.57 to 0.88)	0.99 (95% CI 0.98 to 0.99)	95.3% (95% CI 92.6% to 97.1%)	6.6% (95% CI 3.5% to 12.2%)	5 (95% CI 3 to 7)	7 (95% CI 4 to 12)	2 (3704)	High / High / No
Serum amylase (threshold: > twice normal) (on admission (excluding Chang 2011))	0.72 (95% CI 0.53 to 0.86)	0.98 (95% CI 0.95 to 0.99)	92.1% (95% CI 81.1% to 96.9%)	7.7% (95% CI 4.6% to 12.7%)	8 (95% CI 3 to 19)	8 (95% CI 5 to 13)	1 (253)	High / Unclear / Not applicable
Serum amylase (threshold: > twice normal) (2 to 3 days after admission)	0.25 (95% CI 0.12 to 0.44)	0.97 (95% CI 0.93 to 0.99)	69.8% (95% CI 47.3% to 85.6%)	18.5% (95% CI 15.6% to 21.7%)	30 (95% CI 14 to 53)	18 (95% CI 16 to 22)	1 (253)	High / Unclear / Not applicable
Serum amylase (threshold: > twice normal) (4 to 5 days after admission)	0.06 (95% CI 0.01 to 0.22)	0.93 (95% CI 0.89 to 0.96)	21.2% (95% CI 6.1% to 52.9%)	22.7% (95% CI 21.1% to 24.5%)	79 (95% CI 47 to 94)	23 (95% CI 21 to 24)	1 (253)	High / Unclear / Not applicable
Serum amylase (threshold: > nor-	0.88 (95% CI 0.77 to 0.94)	0.88 (95% CI 0.84 to 0.91)	68.7% (95% CI 61.6% to 75.	3 (587)	High / Unclear / No			

Table 3. Serum amylase at different thresholds and different times (*Continued*)

mal) (on admission)				1%)				
Serum amylase (threshold: > normal) (on admission (excluding studies with incorporation bias))	0.89 (95% CI 0.72 to 0.96)	0.88 (95% CI 0.83 to 0.92)	69.3% (95% CI 60.0% to 77.2%)	3.5% (95% CI 1.3% to 9.0%)	31 (95% CI 23 to 40)	4 (95% CI 1 to 9)	2 (453)	High / Unclear / No
Serum amylase (threshold: > normal) (2 to 3 days after admission)	0.66 (95% CI 0.47 to 0.81)	0.83 (95% CI 0.77 to 0.87)	52.8% (95% CI 43.2% to 62.1%)	10.8% (95% CI 7.0% to 16.4%)	47 (95% CI 38 to 57)	11 (95% CI 7 to 16)	1 (253)	High / Unclear / Not applicable
Serum amylase (threshold: > normal) (4 to 5 days after admission)	0.34 (95% CI 0.19 to 0.53)	0.86 (95% CI 0.81 to 0.90)	41.8% (95% CI 28.7% to 56.1%)	18.3% (95% CI 14.7% to 22.4%)	58 (95% CI 44 to 71)	18 (95% CI 15 to 22)	1 (253)	High / Unclear / Not applicable

CI: confidence interval

[1]The post-test probabilities were calculated at the median pre-test probability of 22.6%.

Table 4. Serum lipase at different thresholds and different times

Index test	Sensitivity	Specificity	Post-test probability of a positive test [1]	Post-test probability of a negative test [1]	Number of false positives per 100 people having a positive test	Number of false negatives per 100 people having a negative test	Number of studies (Number of participants)	Risk of bias / Applicability concerns / Inconsistency
Serum lipase (threshold: > 3 times normal) (on admission)	0.80 (95% CI 0.73 to 0.86)	0.93 (95% CI 0.00 to 1.00)	78.3% (95% CI 0.0% to 100.0%)	5.9% (95% CI 2.3% to 14.4%)	22 (95% CI 0 to 100)	6 (95% CI 2 to 14)	5 (4129)	High / High / Moderate

Table 4. Serum lipase at different thresholds and different times (*Continued*)

Serum lipase (threshold: > 3 times normal) (on admission (excluding Chang 2011))	0.79 (95% CI 0.54 to 0.92)	0.89 (95% CI 0.46 to 0.99)	68.1% (95% CI 21.4% to 94.3%)	6.6% (95% CI 2.7% to 15.1%)	32 (95% CI 6 to 79)	7 (95% CI 3 to 15)	4 (678)	Unclear / Low / Moderate
Serum lipase (threshold: > 3 times normal) (on admission (excluding studies with incorporation bias))	0.88 (95% CI 0.02 to 1.00)	0.94 (95% CI 0.00 to 1.00)	81.2% (95% CI 0.0% to 100.0%)	3.7% (95% CI 0.0% to 99.2%)	19 (95% CI 0 to 100)	4 (95% CI 0 to 99)	2 (3534)	High / High / High
Serum lipase (threshold: > twice normal) (on admission)	0.96 (95% CI 0.78 to 0.99)	0.98 (95% CI 0.98 to 0.99)	94.3% (95% CI 92.1% to 96.0%)	1.1% (95% CI 0.2% to 7.0%)	6 (95% CI 4 to 8)	1 (95% CI 0 to 7)	2 (3704)	High / High / No
Serum lipase (threshold: > twice normal) (on admission (excluding Chang 2011))	0.94 (95% CI 0.78 to 0.99)	0.95 (95% CI 0.91 to 0.97)	84.6% (95% CI 75.5% to 90.8%)	1.9% (95% CI 0.5% to 6.9%)	15 (95% CI 9 to 25)	2 (95% CI 1 to 7)	1 (253)	High / Unclear / Not applicable
Serum lipase (threshold: > twice normal) (2 to 3 days after admission)	0.69 (95% CI 0.50 to 0.83)	0.91 (95% CI 0.86 to 0.94)	69.0% (95% CI 57.9% to 78.2%)	9.1% (95% CI 5.7% to 14.4%)	31 (95% CI 22 to 42)	9 (95% CI 6 to 14)	1 (253)	High / Unclear / Not applicable
Serum lipase (threshold: > twice normal) (4 to 5 days after admission)	0.41 (95% CI 0.24 to 0.59)	0.84 (95% CI 0.79 to 0.89)	42.9% (95% CI 30.9% to 55.7%)	17.1% (95% CI 13.4% to 21.7%)	57 (95% CI 44 to 69)	17 (95% CI 13 to 22)	1 (253)	High / Unclear / Not applicable

Table 4. Serum lipase at different thresholds and different times (*Continued*)

Serum lipase (threshold: > normal) (on admission)	0.96 (95% CI 0.00 to 1.00)	0.83 (95% CI 0.47 to 0.96)	62.5% (95% CI 21.7% to 90.9%)	1.3% (95% CI 0.0% to 100.0%)	38 (95% CI 9 to 78)	1 (95% CI 0 to 100)	2 (453)	High / Unclear / Hight
Serum lipase (threshold: > normal) (2 to 3 days after admission)	0.97 (95% CI 0.82 to 1.00)	0.79 (95% CI 0.73 to 0.84)	57.7% (95% CI 51.1% to 64.0%)	1.1% (95% CI 0.2% to 7.4%)	42 (95% CI 36 to 49)	1 (95% CI 0 to 7)	1 (253)	High / Unclear / Not applicable
Serum lipase (threshold: > normal) (4 to 5 days after admission)	0.59 (95% CI 0.41 to 0.76)	0.70 (95% CI 0.64 to 0.76)	36.8% (95% CI 29.1% to 45.2%)	14.5% (95% CI 10.0% to 20.6%)	63 (95% CI 55 to 71)	14 (95% CI 10 to 21)	1 (253)	High / Unclear / Not applicable

CI: confidence interval

[1]The post-test probabilities were calculated at the median pre-test probability of 22.6%.

Table 5. Urinary tests

Index test	Sensitivity	Specificity	Post-test probability of a positive test [1]	Post-test probability of a negative test[1]	Number of false positives per 100 people having a positive test	Number of false negatives per 100 people having a negative test	Number of studies (Number of participants)	Risk of bias / Applicability concerns / Inconsistency
Urinary trypsinogen-2 (threshold: Actim Pancreatitis - all studies; > 50 ng/mL) (on admission)	0.72 (95% CI 0.56 to 0.84)	0.90 (95% CI 0.85 to 0.93)	67.2% (95% CI 57.3% to 75.7%)	8.4% (95% CI 5.2% to 13.3%)	33 (95% CI 24 to 43)	8 (95% CI 5 to 13)	5 (841)	High / Unclear / Moderate
Urinary trypsinogen-2 (threshold: Actim Pancre-	0.74 (95% CI 0.56 to 0.87)	0.89 (95% CI 0.84 to 0.93)	66.9% (95% CI 55.4% to 76.7%)	7.7% (95% CI 4.3% to 13.5%)	33 (95% CI 23 to 45)	8 (95% CI 4 to 14)	4 (742)	High / Unclear / Moderate

Table 5. Urinary tests (*Continued*)

atitis - sensitivity analysis; > 50 ng/mL) (on admission)								
Urinary trypsinogen-2 (quantitative) (threshold: > 50 ng/mL) (on admission)	0.71 (95% CI 0.63 to 0.78)	0.89 (95% CI 0.84 to 0.92)	65.6% (95% CI 57.0% to 73.3%)	8.7% (95% CI 6.9% to 10.9%)	34 (95% CI 27 to 43)	9 (95% CI 7 to 11)	1 (412)	High / Low / Not applicable
Urinary trypsinogen-2 (threshold: only + or most positive - the threshold for this was not available) (on admission)	0.60 (95% CI 0.51 to 0.67)	0.92 (95% CI 0.88 to 0.95)	69.1% (95% CI 59.0% to 77.6%)	11.4% (95% CI 9.6% to 13.5%)	31 (95% CI 22 to 41)	11 (95% CI 10 to 13)	1 (412)	High / Low / Not applicable
Urinary amylase (quantitative) (threshold: above normal) (on admission)	0.83 (95% CI 0.65 to 0.94)	0.86 (95% CI 0.77 to 0.91)	62.8% (95% CI 50.8% to 73.5%)	5.4% (95% CI 2.5% to 11.3%)	37 (95% CI 27 to 49)	5 (95% CI 2 to 11)	1 (134)	Unclear / Unclear / Not applicable
Urinary amylase (qualitative) (threshold: 1 plus) (on admission)	0.66 (95% CI 0.49 to 0.79)	0.94 (95% CI 0.90 to 0.97)	77.3% (95% CI 64.2% to 86.6%)	9.6% (95% CI 6.5% to 14.0%)	23 (95% CI 13 to 36)	10 (95% CI 6 to 14)	1 (218)	High / High / Not applicable
Urinary amylase (qualitative) (threshold: 2	0.44 (95% CI 0.29 to 0.60)	0.99 (95% CI 0.96 to 1.00)	95.8% (95% CI 75.8% to 99.4%)	14.2% (95% CI 11.2% to 17.8%)	4 (95% CI 1 to 24)	14 (95% CI 11 to 18)	1 (218)	High / High / Not applicable

Table 5. Urinary tests (*Continued*)

plus) (on admission)								

CI: confidence interval
[1]The post-test probabilities were calculated at the median pre-test probability of 22.6%.

APPENDICES

Appendix 1. Glossary of terms

Acute: sudden onset.
Adipose: fat.
Aetiology: cause.
Autodigestion: breaking down of the same organ that secretes the substance.
Cholecystectomy: removal of the gallbladder.
Cholecystitis: inflammation of the gallbladder.
Debridement: surgical removal of damaged, dead, or infected tissue; in this context, identical with necrosectomy.
Dyspepsia: discomfort in the upper abdomen or chest that may be described as gas, a feeling of fullness, or burning.
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.
Gastrointestinal: relating to the stomach and the intestines.
Heterogeneity: differences between studies.
Histological: by examination of the tissue under a microscope.
Hyperamylasaemia: excess amylase in circulation.
Interstitial: small, narrow spaces between tissues or parts of an organ.
Intraperitoneal: inside the abdominal cavity.
Isoforms: two or more functionally similar proteins that have a similar but not identical composition.
Laparotomy: surgical incision into the abdominal cavity, for diagnosis or treatment of intra-abdominal diseases.
Lymphatics: vessels carrying lymph in the body.
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.
Methodological: related to methods by which the study was conducted (in this context).
Mortality rate: death rate.
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.
Parenchyma: functional parts of an organ.
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.
Peritonitis: inflammation of the peritoneum (the inner lining of the abdominal wall).
Prognosis: health outcome.
Pulse oximetry: non-invasive method of measuring the oxygen level (oxygen saturation) of the blood, usually using infrared.
Radiating to the back: pain in front going to the back (in this context).
Retroperitoneal: behind the abdominal cavity.
SAS code: set of instructions for using an 'SAS' program to perform statistical analysis.
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.
Triage: determining whether the patient requires further tests (in this context).
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

Appendix 9. SAS code used for fitting different models

```
data DiagnosticTestMetaAnalysis;

input Study_id TP FP FN TN;

/* Modify the data for the different tests*/
datalines;

1 52 7 17 48

2 14 19 8 3410

3 109 9 47 244

4 37 3 13 19

run;

/* Modify the dataset for the bivariate analysis */

data dt;

set DiagnosticTestMetaAnalysis;

sens=1; spec=0; true=tp; n=tp+fn; output;

sens=0; spec=1; true=tn; n=tn+fp; output;

run;

/* Ensure that both records for a study are clustered together */

proc sort data=dt;

by study_id ;

run;

/* MODEL 1 */

/* Save NLMIXED output in the following datasets*/

ods output ParameterEstimates=pet1 FitStatistics=fitt1 additionalestimates=addest1

CovMatParmEst=covparmestt1 ConvergenceStatus=convgstatt1;

/* Run the bivariate random effects logistic regression model for sensitivity and specificity */
```

```
/* The cov option requests that a covariance matrix is printed for all model parameter estimates.*/

proc nlmixed data=dt cov tech=quanew lis=5;

parms msens=2 mspec=1 s2usens=0 s2uspec=0 covsesp=0;

logitp=(msens+usens)*sens+(mspec+uspec)*spec;

p = exp(logitp)/(1+exp(logitp));

model true ~ binomial(n,p);

random usens uspec ~ normal([0,0],[s2usens,covsesp,s2uspec]) subject=study_id out=randeffs;

estimate 'logLR+' log((exp(msens)/(1+exp(msens)))/(1-(exp(mspec)/(1+exp(mspec)))));

estimate 'logLR-' log((1-(exp(msens)/(1+exp(msens))))/(exp(mspec)/(1+exp(mspec))));

run;

/* Obtain summary sens and spec from the model 1*/

/* change the number if this is for a different model*/

data summary1;

set pet1;

if parameter = 'msens' then name = 'Sensitivity';

else if parameter = 'mspec' then name = 'Specificity';

if parameter = 'msens' or parameter ='mspec' then summary=100 * exp(estimate)/(1 + exp(estimate));

if parameter = 'msens' or parameter ='mspec' then summlower=100 * exp(lower)/(1 + exp(lower));

if parameter = 'msens' or parameter ='mspec' then summupper=100 *exp(upper)/(1 + exp(upper));

output;

run;

/* Obtain summary LR from the model 1 */

data summaryLR1;

set addest1;

summary=exp(estimate);

summlower=exp(lower);
```

```
summupper=exp(upper);

output;

run;

PROC EXPORT DATA= WORK.SUMMARY1
/* Modify the path for this outfile and the other outfiles */
OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Summary1.csv"

DBMS=CSV REPLACE;

RUN;

/* Export parameter estimates table */

PROC EXPORT DATA= WORK.pet1

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Parameter estimates1.csv"

DBMS=CSV REPLACE;

RUN;

/* Export the summary LR as an Excel .csv file */

PROC EXPORT DATA= WORK.SUMMARYLR1

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\SummaryLR1.csv"

DBMS=CSV REPLACE;

RUN;

/* Export Fit statistics table */

PROC EXPORT DATA= WORK.fitt1

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Fit statistics1.csv"

DBMS=CSV REPLACE;

RUN;

/* Export covariance parameter estimates table */

PROC EXPORT DATA= WORK.covparmestt1

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Covariance parameter estimates1.csv"

DBMS=CSV REPLACE;
```

```
RUN;

/* MODEL 2 */

ods output ParameterEstimates=pet2 FitStatistics=fitt2 additionalestimates=addest2 CovMatParmEst=covparmestt2 ConvergenceStatus=convgstatt2;

/* Run univariate random effects logistic regression models for sensitivity and specificity, i.e., ignore the correlation */

proc nlmixed data=dt cov tech=quanew lis=5;

parms msens=2 mspec=1 s2usens=0 s2uspec=0 ;

logitp=(msens+usens)*sens+(mspec+uspec)*spec;

p = exp(logitp)/(1+exp(logitp));

model true ~ binomial(n,p);

random usens uspec ~ normal([0,0],[s2usens,0,s2uspec]) subject=study_id out=randeffs;

estimate 'logLR+' log((exp(msens)/(1+exp(msens)))/(1-(exp(mspec)/(1+exp(mspec)))));

estimate 'logLR-' log((1-(exp(msens)/(1+exp(msens))))/(exp(mspec)/(1+exp(mspec))));

run;

/* Obtain summary sens and spec from the model 2*/

/* change the number if this is for a different model*/

data summary2;

set pet2;

if parameter = 'msens' then name = 'Sensitivity';

else if parameter = 'mspec' then name = 'Specificity';

if parameter = 'msens' or parameter ='mspec' then summary=100 * exp(estimate)/(1 + exp(estimate));

if parameter = 'msens' or parameter ='mspec' then summlower=100 * exp(lower)/(1 + exp(lower));

if parameter = 'msens' or parameter ='mspec' then summupper=100 *exp(upper)/(1 + exp(upper));

output;

run;

/* Obtain summary LR from the model 2 */

data summaryLR2;
```

```
set addest2;

summary=exp(estimate);

summlower=exp(lower);

summupper=exp(upper);

output;

run;

PROC EXPORT DATA= WORK.SUMMARY2

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Summary2.csv"

DBMS=CSV REPLACE;

RUN;

/* Export parameter estimates table */

PROC EXPORT DATA= WORK.pet2

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Parameter estimates2.csv"

DBMS=CSV REPLACE;

RUN;

/* Export the summary LR as an Excel .csv file */

PROC EXPORT DATA= WORK.SUMMARYLR2

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\SummaryLR2.csv"

DBMS=CSV REPLACE;

RUN;

/* Export Fit statistics table */

PROC EXPORT DATA= WORK.fitt2

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Fit statistics2.csv"

DBMS=CSV REPLACE;

RUN;

/* Export covariance parameter estimates table */
```

```
PROC EXPORT DATA= WORK.covparmestt2

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Covariance parameter estimates2.csv"

DBMS=CSV REPLACE;

RUN;

/* MODEL 3 */

ods output ParameterEstimates=pet3 FitStatistics=fitt3 additionalestimates=addest3

CovMatParmEst=covparmestt3 ConvergenceStatus=convgstatt3 additionalestimates=addest3;

/* Run random effects logistic regression model for sensitivity and fixed model for specificity */

proc nlmixed data=dt cov tech=quanew lis=5 qpoints=10;

parms msens=2 mspec=1 s2usens=0 ;

logitp=(msens+usens)*sens+(mspec)*spec;

p = exp(logitp)/(1+exp(logitp));

model true ~ binomial(n,p);

random usens ~ normal([0],[s2usens]) subject=study˙id out=randeffs;

estimate 'logLR+' log((exp(msens)/(1+exp(msens)))/(1-(exp(mspec)/(1+exp(mspec)))));

estimate 'logLR-' log((1-(exp(msens)/(1+exp(msens))))/(exp(mspec)/(1+exp(mspec))));

run;

/* Obtain summary sens and spec from the model 3*/

/* change the number if this is for a different model*/

data summary3;

set pet3;

if parameter = 'msens' then name = 'Sensitivity';

else if parameter = 'mspec' then name = 'Specificity';

if parameter = 'msens' or parameter ='mspec' then summary=100 * exp(estimate)/(1 + exp(estimate));

if parameter = 'msens' or parameter ='mspec' then summlower=100 * exp(lower)/(1 + exp(lower));

if parameter = 'msens' or parameter ='mspec' then summupper=100 *exp(upper)/(1 + exp(upper));
```

```
output;

run;

/* Obtain summary LR from the model 3 */

data summaryLR3;

set addest3;

summary=exp(estimate);

summlower=exp(lower);

summupper=exp(upper);

output;

run;

PROC EXPORT DATA= WORK.SUMMARY3

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Summary3.csv"

DBMS=CSV REPLACE;

RUN;

/* Export parameter estimates table */

PROC EXPORT DATA= WORK.pet3

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Parameter estimates3.csv"

DBMS=CSV REPLACE;

RUN;

/* Export the summary LR as an Excel .csv file */

PROC EXPORT DATA= WORK.SUMMARYLR3

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\SummaryLR3.csv"

DBMS=CSV REPLACE;

RUN;

/* Export Fit statistics table */

PROC EXPORT DATA= WORK.fitt3
```

```
OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Fit statistics3.csv"

DBMS=CSV REPLACE;

RUN;

/* Export covariance parameter estimates table */

PROC EXPORT DATA= WORK.covparmestt3

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Covariance parameter estimates3.csv"

DBMS=CSV REPLACE;

RUN;

/* MODEL 4 */

ods output ParameterEstimates=pet4 FitStatistics=fitt4 additionalestimates=addest4

CovMatParmEst=covparmestt4 ConvergenceStatus=convgstatt4;

/* Run fixed effect logistic regression model for sensitivity and random effects model for specificity */

proc nlmixed data=dt cov tech=quanew lis=5 qpoints=10;

parms msens=2 mspec=1 s2uspec=0 ;

logitp=(msens)*sens+(mspec+uspec)*spec;

p = exp(logitp)/(1+exp(logitp));

model true ~ binomial(n,p);

random uspec ~ normal([0],[s2uspec]) subject=study˙id out=randeffs;

estimate 'logLR+' log((exp(msens)/(1+exp(msens)))/(1-(exp(mspec)/(1+exp(mspec)))));

estimate 'logLR-' log((1-(exp(msens)/(1+exp(msens))))/(exp(mspec)/(1+exp(mspec))));

run;

/* Obtain summary sens and spec from the model 4*/

/* change the number if this is for a different model*/

data summary4;

set pet4;

if parameter = 'msens' then name = 'Sensitivity';
```

```
else if parameter = 'mspec' then name = 'Specificity';

if parameter = 'msens' or parameter ='mspec' then summary=100 * exp(estimate)/(1 + exp(estimate));

if parameter = 'msens' or parameter ='mspec' then summlower=100 * exp(lower)/(1 + exp(lower));

if parameter = 'msens' or parameter ='mspec' then summupper=100 *exp(upper)/(1 + exp(upper));

output;

run;

/* Obtain summary LR from the model 4 */

data summaryLR4;

set addest4;

summary=exp(estimate);

summlower=exp(lower);

summupper=exp(upper);

output;

run;

PROC EXPORT DATA= WORK.SUMMARY4

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Summary4.csv"

DBMS=CSV REPLACE;

RUN;

/* Export parameter estimates table */

PROC EXPORT DATA= WORK.pet4

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Parameter estimates4.csv"

DBMS=CSV REPLACE;

RUN;

/* Export the summary LR as an Excel .csv file */

PROC EXPORT DATA= WORK.SUMMARYLR4

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\SummaryLR4.csv"
```

```
DBMS=CSV REPLACE;

RUN;

/* Export Fit statistics table */

PROC EXPORT DATA= WORK.fitt4

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Fit statistics4.csv"

DBMS=CSV REPLACE;

RUN;

/* Export covariance parameter estimates table */

PROC EXPORT DATA= WORK.covparmestt4

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Covariance parameter estimates4.csv"

DBMS=CSV REPLACE;

RUN;

/* MODEL 5 */

ods output ParameterEstimates=pet5 FitStatistics=fitt5 additionalestimates=addest5

CovMatParmEst=covparmestt5 ConvergenceStatus=convgstatt5;

/* Run fixed effect logistic regression model for sensitivity and specificity */

proc nlmixed data=dt cov tech=quanew lis=5 qpoints=10;

parms msens=2 mspec=1;

logitp=(msens)*sens+(mspec)*spec;

p = exp(logitp)/(1+exp(logitp));

model true ~ binomial(n,p);

estimate 'logLR+' log((exp(msens)/(1+exp(msens)))/(1-(exp(mspec)/(1+exp(mspec)))));

estimate 'logLR-' log((1-(exp(msens)/(1+exp(msens))))/(exp(mspec)/(1+exp(mspec))));

run;

/* Obtain summary sens and spec from the model 5*/

/* change the number if this is for a different model*/
```

```
data summary5;

set pet5;

if parameter = 'msens' then name = 'Sensitivity';

else if parameter = 'mspec' then name = 'Specificity';

if parameter = 'msens' or parameter ='mspec' then summary=100 * exp(estimate)/(1 + exp(estimate));

if parameter = 'msens' or parameter ='mspec' then summlower=100 * exp(lower)/(1 + exp(lower));

if parameter = 'msens' or parameter ='mspec' then summupper=100 *exp(upper)/(1 + exp(upper));

output;

run;

/* Obtain summary LR from the model 5 */

data summaryLR5;

set addest5;

summary=exp(estimate);

summlower=exp(lower);

summupper=exp(upper);

output;

run;

PROC EXPORT DATA= WORK.SUMMARY5

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Summary5.csv"

DBMS=CSV REPLACE;

RUN;

/* Export parameter estimates table */

PROC EXPORT DATA= WORK.pet5

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Parameter estimates5.csv"

DBMS=CSV REPLACE;

RUN;
```

/* Export the summary LR as an Excel .csv file */

PROC EXPORT DATA= WORK.SUMMARYLR5

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\SummaryLR5.csv"

DBMS=CSV REPLACE;

RUN;

/* Export Fit statistics table */

PROC EXPORT DATA= WORK.fitt5

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Fit statistics5.csv"

DBMS=CSV REPLACE;

RUN;

/* Export covariance parameter estimates table */

PROC EXPORT DATA= WORK.covparmestt5

OUTFILE = "C:\Users\kurinchi2k\Downloads\Acute pancreatitis DTAR\SA˙3\SASFile\IndeterminatesExcluded\Covariance parameter estimates5.csv"

DBMS=CSV REPLACE;

RUN;

Appendix 10. Model fit for index tests for which meta-analysis was possible

Model fit	Bivariate random-effects model taking correlation into account	Bivariate random-effects model ignoring correlation	Random-effects univariate logistic regression model for sensitivity and fixed-effect model for specificity	Fixed-effect model for sensitivity and random-effects univariate logistic regression model for specificity	Fixed-effect model for both sensitivity and specificity
Serum amylase (threshold: > 3 times normal) (on admission)	No convergence	No convergence	No convergence	No convergence	***86.4***

(*Continued*)

Serum amylase (threshold: > 3 times normal) (on admission; excluding studies with incorporation bias)	No convergence	No convergence	No convergence	***30.9***	33.4
Serum amylase (threshold: > 3 times normal) (on admission; excluding Chang 2011)	89.9	91.9	178	***30.9***	33.4
Serum amylase (threshold: > twice normal) (on admission)	No convergence	No convergence	No convergence	30.8	***17.1***
Serum amylase (threshold: > normal) (on admission)	No convergence	No convergence	No convergence	30.8	***24.9***
Serum amylase (threshold: > normal) (on admission)	No convergence	No convergence	No convergence	No convergence	***17.3***
Serum lipase (threshold: > 3 times normal) (on admission)	89.9	91.9	178	***89.3***	183.5
Serum lipase (threshold: > 3 times normal) (on admission; excluding studies with incorporation bias)	No convergence	No convergence	125.7	***33.2***	125.7
Serum lipase (threshold: > 3 times normal) (on admission; excluding Chang 2011)	89.9	***49.6***	178	53.8	84.4
Serum lipase (threshold: > twice normal) (on admis-	89.9	91.9	178	30.6	***25***

(*Continued*)

sion)					
Serum lipase (threshold: > normal) (on admission)	89.9	91.9	***20.6***	30.6	26.9
Urinary trypsinogen-2 (threshold: Actim Pancreatitis - all studies; > 50 ng/mL) (on admission)	89.9	91.9	***57.4***	59.2	59.4
Urinary trypsinogen-2 (threshold: Actim Pancreatitis - sensitivity analysis; > 50 ng/mL excluding Aysan 2008) (on admission)	89.9	91.9	***45.5***	45.9	46

For each test with at least 2 studies, simpler models were fitted because of sparse data (Takwoingi 2015). The -2 log likelihood for the different models for each meta-analysis is shown. The lowest -2 log likelihood ratio for each test is shown in bold italic font. The corresponding model was used for meta-analysis

For each test w
studies, simpler m
ted because of
Takwoingi 2015
likelihood for
models for each
shown. The lowe
hood ratio for ea
in bold italic fo
sponding model
meta-analysis

Appendix 11. Statistical methods that were planned but not performed because of paucity of data

The statistical analysis and data synthesis below were planned but could not be performed because of the paucity of data.

We planned to stratify the analysis by the different reference standards (i.e. we planned to use different reference standards as different index tests). However, because of paucity of data, we did not stratify the studies based on reference standards.

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. We used the HSROC model to compare whether one test is superior to another since the HSROC model allows combining tests regardless of the thresholds and might overcome the problem of a limited number of studies included under each threshold. In case the study reported results at multiple thresholds, we used the threshold used by the authors for primary analysis for inclusion in the HSROC model. We planned to use likelihood ratio tests to compare the model with and without covariate (test type). We planned

to use a P value of less than 0.05 for the likelihood ratio test to indicate 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 perform more than one index test in all of the participants, individual index tests and combination of index tests in all of the participants, or randomised controlled trials in which participants have been 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 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. We planned to calculate the post-test probabilities using these pre-test probabilities and the summary positive and negative likelihood ratios. 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 present the pre-test probability versus post-test probability graph. We have not presented the likelihood ratios, as we had to provide the most important information in the table for a number of comparisons.

CONTRIBUTIONS OF AUTHORS

Gianluca Rompianesi, Angus Hann, and Oluyemi Komolafe were involved in study selection and data extraction. Angus Hann entered data into the Characteristics of studies tables. Stephen Pereira and Brian Davidson commented critically on the review. Kurinchi Selvan Gurusamy selected studies, extracted data, analysed the data, and wrote the review.

DECLARATIONS OF INTEREST

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GR: none known.

AH: none known.

OK: none known.

SPP: none known.

BRD: none known.

KSG: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Although we did not plan to include repeat tests in this review, the diagnostic test accuracy of these index tests on later days of hospital might indicate the performance of these tests in patients with a prolonged period of symptoms. We have therefore analysed and reported this information separately from the tests conducted on admission.

2. We have accepted visual inspection of pancreas during laparotomy or autopsy as a reference standard. This is at least as good as radiological examination for the diagnosis of acute pancreatitis.

3. The other methods that we planned but could not perform because of paucity of data are listed in Appendix 11.