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Review Article

Effectiveness of contrast-enhanced ultrasound for the diagnosis of acute pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Objective: To systematically determine the diagnostic value of contrast-enhanced ultrasound (CEUS) in the assessment of acute pancreatitis.
Methods: Relevant studies were identified by searching the database up to December 2016. Patient clinical characteristics and diagnostic sensitivity and specificity were extracted. The summary receiver operating characteristic (ROC) curve was used to examine the accuracy of CEUS. A meta-analysis was performed to evaluate the clinical utility in the diagnosis and evaluation of acute pancreatitis.
Results: From 27 citations, seven were included in the meta-analysis, with a total of 421 cases. We detected the heterogeneity of the studies and evidence of publication bias. The methodological quality was moderate. The pooled weighted sensitivity with a corresponding 95% confidence interval (CI) was 0.92 (95% CI: 0.88, 0.95), the specificity was 0.84 (95% CI: 0.78, 0.90), the positive likelihood ratio was 5.38 (95% CI: 3.21, 9.00), the negative likelihood ratio was 0.13 (95% CI: 0.05, 0.36), and the diagnostic odds ratio was 49.37 (95% CI: 14.69, 165.94). The area under the ROC curve was 0.9273 (95% CI: 0.8916, 0.9790).
Conclusions: CEUS is a reliable, non-invasive imaging modality with no radiation exposure and a high sensitivity and specificity for the assessment of severity of acute pancreatitis. Nonetheless, it should be applied cautiously, and large-scale, well-designed trials are necessary to assess its clinical value.

1. Introduction

The incidence of acute pancreatitis (AP) has steadily increased over the past few decades [1]. For example, a study in the United States showed that hospital admissions for acute pancreatitis doubled within a 20-year period [2]. The mortality rate of AP, especially the severe form (SAP) can be as high as 15–48.4% [3]. The detection of AP is very important, because it can provide prognostic information and it may have therapeutic implications [4,5]. Early evaluation and treatment of severe cases of infected necrosis can reduce morbidity and mortality. Although computed tomography (CT) has been considered to be the primary and gold-standard modality for the assessment of AP, according to the revision of the Atlanta classification and definitions by international consensus [6], the examination requires the intravenous injection of iodinated contrast medium for the detection of hypoperfused areas in the pancreatic parenchyma. Iodinated contrast medium is linked with nephrotoxicity, which limits its use in patients with acute renal failure. Furthermore, CT contrast medium has the potential to aggravate AP in animal models by impairing the pancreatic microcirculation [7,8]. Therefore, an imaging procedure with fewer side effects deserves consideration as a safer alternative. Contrast-enhanced ultrasound (CEUS) is a new technique that has been reported to be useful for AP [9]. Nowadays, studies are increasingly focusing on the use of CEUS in the evaluation of AP and our meta-analysis provides summaries of the results of relevant studies, estimates of the diagnostic value of CEUS and evaluates the variability of the study findings around the estimates.

2. Materials and methods

2.1. Literature search

PubMed, Embase, Elsevier, and CNKI (China National Knowledge Infrastructure) database and Cochrane Trial Register searches were performed to identify all the eligible papers. The search terms used were as follows: contrast-enhanced or echo-enhanced, ultrasonography or ultrasound, acute pancreatitis. The publication languages

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Table 1
Characteristics of the seven clinical studies.

Authors Year	Patients	Gender		Age (year)	Imaging modality	Sensitivity	Specificity	Study design
		Male	Female					
Rickes et al. (2006) [9]	31	24	7	38 (19–67)	A	0.93	0.82	Prospective
Lu et al. (2011) [16]	33	21	12	46.1 ± 11.7 (29–84)	A	0.90	0.96	Prospective
Golea et al. (2010) [17]	25	18	7	46.16 (20–68)	A	0.55	0.71	Prospective
Ripollés et al. (2010) [18]	50	28	22	58.4 (23–86)	A	1.00	0.93	Prospective
Yang et al. (2012) [19]	54	34	20	49.8 ± 15.7 (29–84)	B	0.90	0.92	Retrospective
Zhong et al. (2013) [20]	32	17	15	41.1 ± 10.4 (18–78)	B	0.75	0.88	Retrospective
Cai et al. (2016) [21]	196	129	67	48.1 ± 13.9 (18–79)	A	0.97	0.75	Prospective

NA, not applicable; A, Low MI with SonoVu; B, High MI with Doppler mode.

were restricted to English and Chinese. Moreover, potentially relevant studies were evaluated by reviewing the titles and abstracts, and studies matching the criteria were carefully retrieved. If more than one study was published using the same data, only the study with the larger population was included. The literature search was updated to December 2016. This systematic review was planned, conducted, and reported in adherence with standards of quality for reporting meta-analyses.

2.2. Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met all the following criteria: (1) full text original article; (2) human study; (3) evaluation of CEUS for the AP; (4) inclusion of at least 20 patients; (5) published in English or Chinese; (6) all cases were compared with CT as the reference standard.

Exclusion criteria were (1) no evaluation of the value of CEUS for the diagnosis of acute pancreatitis; (2) samples less than 20 patients; (3) review article (including meta-analyses), corresponding letter or editorial not reporting original data; (4) published in abstract form only; (5) published more than once; (6) sufficient data including gender, age, evaluation of the degree of AP and imaging modality for AP were not provided.

2.3. Quality assessment of studies

The methodological quality of the studies included was assessed independently by two observers using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument, a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies [10]. The full QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of the risk of bias according to the signaling questions, and the first three domains were judged in terms of concerns regarding applicability. Each question was scored "yes" if reported, "no" if not reported, or "unclear" if there was inadequate information in the article to make a judgment. To resolve disagreement between the two reviewers, a third reviewer assessed all the items involved. The majority opinion was used for the analysis.

2.4. Data extraction

Three researchers extracted data from each study by using a structured sheet and entered the data into a database. The following data were extracted from each study: the first author's last name, publication year, source journal, research design, study duration, retention and drop-out rate, surgical methods, patient's sex and age, and sample size. For each study, values for true-positive (TP), false-positive (FP), true-negative (TN), false-negative (FN), sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) results for the detection of patients were extracted too, and 2×2 contingency tables were constructed.

2.5. Risk of bias assessment

Assessment of methodological quality was performed using the risk of bias assessment tool by the Cochrane Collaboration indicating the following bias domains: selection bias (random sequence generation, allocation concealment), performance/detection bias (blinding of participants and personnel/blinding of outcome assessment), attrition bias (incomplete data outcome), reporting bias (selective reporting), and other bias.

In addition, a bivariate box plot with egger testing was used to assess the distributional properties of sensitivity versus specificity and for identifying possible outliers. After omitting these outliers and according to the results of the subgroups analysis, sensitivity analysis was performed and the change in heterogeneity was observed.

2.6. Statistical analysis

The Q statistic of the Chi-squared value test and the inconsistency index (I-squared, I^2) were used to estimate the heterogeneity of the individual studies using STATA software 11.0 (Stata Corporation, College Station, TX, USA). I^2 values were interpreted according to the proposal of Higgins and Thompson [11], with heterogeneity determined as low ($I2 \leq 25\%$), medium ($25\% < I2 \leq 50\%$) or high ($50\% < I2 \leq 75\%$). In this study, meta-regression was used to explore such heterogeneity by relating the accuracy measurement to study level covariates. If notable heterogeneities were detected, the test performance was summarized by using a random-effects coefficient binary regression model; otherwise, a fixed-effect coefficient binary regression model was used [12].

In test accuracy studies, one of the primary causes of heterogeneity is the threshold effect, which arises when different cut-offs or thresholds are used in different studies to define a positive (or negative) test result. The Spearman correlation coefficient between the logit of sensitivity and the logit of 1-specificity was computed to assess the threshold effect using Review Manager 5.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A strong positive correlation would suggest a threshold effect of $P < 0.05$ [13]. We constructed hierarchical summary receiver operating characteristic (ROC) curves to assess accuracy [14]. The areas under the ROC curves (AUCs) were used to analyze the diagnostic precision of CEUS for the evaluation of acute pancreatitis.

Apart from variations due to the threshold effect, there are several other factors that can result in variations in accuracy estimates amongst different test accuracy studies in a review. The presence of publication bias was visually assessed by producing a Deeks' funnel plot and an asymmetry test with the STATA software. Publication

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