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META-ANALYSIS

Prediction of the severity of acute pancreatitis on admission by urinary trypsinogen activation peptide: A meta-analysis

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Abstract

AIM: To undertake a meta-analysis on the value of urinary trypsinogen activation peptide (uTAP) in predicting severity of acute pancreatitis on admission.

METHODS: Major databases including Medline, Embase, Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials in the Cochrane Library were searched to identify all relevant studies from January 1990 to January 2013. Pooled sensitivity, specificity and the diagnostic odds ratios (DORs) with 95%CI were calculated for each study and were compared to other systems/biomarkers if mentioned within the same study. Summary receiver-operating curves were conducted and the area under the curve (AUC) was evaluated.

RESULTS: In total, six studies of uTAP with a cut-off value of 35 nmol/L were included in this meta-analysis. Overall, the pooled sensitivity and specificity of uTAP for predicting severity of acute pancreatitis, at time of admission, was 71% and 75%, respectively (AUC = 0.83, DOR = 8.67, 95%CI: 3.70-20.33). When uTAP was compared with plasma C-reactive protein, the pooled sensitivity, specificity, AUC and DOR were 0.64 *vs* 0.67, 0.77 *vs* 0.75, 0.82 *vs* 0.79 and 6.27 *vs* 6.32, respectively. Similarly, the pooled sensitivity, specificity, AUC and DOR of uTAP *vs* Acute Physiology and Chronic Health Evaluation Ⅱ within the first 48 h of admission were found to be 0.64 *vs* 0.69, 0.77 *vs* 0.61, 0.82 *vs* 0.73 and 6.27 *vs* 4.61, respectively.

CONCLUSION: uTAP has the potential to act as a stratification marker on admission for differentiating disease severity of acute pancreatitis.

Key words: Acute pancreatitis; Urinary trypsinogen activation peptide; C-reactive protein; Acute Physiology and Chronic Health Evaluation Ⅱ score; Meta-analysis

Core tip: Currently, the assessment of acute pancreatitis severity on admission remains a challenge to clinicians. A single, rapid biochemical marker is the preferred choice than clinical and computed tomography scoring systems. In this study, the value of urinary

trypsinogen activation peptide (uTAP), on admission, in predicting severity of acute pancreatitis was assessed. It was found that the ability of uTAP to predict severity of acute pancreatitis on admission was comparable to C-reactive protein (at 48 h) and was potentially better than the Acute Physiology and Chronic Health Evaluation Ⅱ score (at 48 h), the most frequently used biochemical marker and clinical scoring system in acute pancreatitis, respectively.

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INTRODUCTION

Acute pancreatitis causes up to 210000 admissions in the United States annually and remains a diagnostic, prognostic and therapeutic dilemma for surgeons and physicians[1]. Although mild acute pancreatitis is associated with virtually no mortality, severe acute pancreatitis continues to be at the other end of the spectrum with mortality reaching up to 30%, mainly due to pancreatic necrosis and organ failure[2].

As severe acute pancreatitis may progress very quickly and is normally associated with a complicated clinical course and higher mortality, it is vital to identify these patients as early as possible to initiate appropriate supportive management, especially within the first 24 h after symptoms onset[3]. Therefore, in the last few decades many biomarkers[4], radiological[5] and clinical scoring systems[6,7] have been developed and validated to fulfil this role. These, however, have not been entirely successful. The Glasgow[8], Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ)[9], and Ranson[10] scoring systems and plasma C-reactive protein (CRP)[11] are still the most widely used parameters and form part of many guidelines, however, their use does come with its own limitations.

There is enough evidence to establish trypsinogen activation as one of the earliest steps in the pathophysiology of the disease[12,13], and consequently, trypsinogen activation peptide (TAP) has been shown to be an excellent marker for severity stratification in different experimental acute pancreatitis models[14]. In human acute pancreatitis, TAP is rapidly excreted in urine and in urinary[15] and peritoneal fluid[16]. TAP concentrations correlate well with disease severity. Therefore, it is reasonable to hypothesize that pancreas-specific activation peptides would be elevated (in the urine) from the onset of disease and could potentially serve as early biomarkers. Urinary TAP (uTAP) is the most studied peptide for predicting severity of acute pancreatitis[17], but its diagnostic value in severe acute pancreatitis has not been systematically assessed. In this study, a meta-analysis was carried out to evaluate existing evidence of uTAP in predicting the severity of acute pancreatitis.

MATERIALS AND METHODS

Study selection

A comprehensive literature search of Medline, Embase, Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials in The Cochrane Library was carried out to identify studies evaluating the prognostic efficacy of uTAP from January 1990 (the first human study)[15] to February 2013. The following medical subject headings (MeSH) and keywords were used: "trypsinogen activation peptide" or "activation peptide" and "acute pancreatitis" or "severe acute pancreatitis" or "post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis". Equivalent free-text search terms were used in the search strategy. All abstract supplements from published literature or from relevant international meetings were searched manually. Relevant papers were also identified from the reference lists of previous papers. Only studies which were published in English as full-text articles were included. Final inclusion of articles was determined by consensus; when this failed, a third author adjudicated. Severe acute pancreatitis was defined as the development of organ failure and/or local complications[15,18].

Inclusion and exclusion criteria

Two authors independently identified and screened the search findings for potentially eligible studies.

Inclusion criteria: (1) English language studies published as full text articles in peer-reviewed journals; (2) Human studies; (3) Studies with available data; and (4) When similar studies were reported by the same institution, the best quality study was included.

Exclusion criteria: (1) Abstracts, letters, editorials, expert opinions, reviews and case reports; (2) Where only concentration or *P* value was reported; (3) Studies assessing the efficacy of serum/plasma TAP in predicting the severity of acute pancreatitis; and (4) Studies assessing the efficacy of uTAP in diagnosing acute pancreatitis.

Data extraction and quality assessment

Data were extracted by two independent observers using standardized forms. The recorded data included study design, demographics (age, gender, etiology and country of origin), severity of disease, duration from symptoms onset to admission, time point for the collection of samples and cut-off values. Diagnostic parameters including true positivity (TP), false positivity (FP), false negativity (FN) and true negativity (TN) were extracted directly or by calculating the sensitivity and specificity of uTAP for predicting the severity of acute pancreatitis. TP, FP, FN and

Table 1 Characteristics of included prospective studies for urinary trypsinogen activation peptide as a predictor of severity of acute pancreatitis

Ref.	Year	Country	Sampling time after admission	Cut-off value (nmol/L)	Total (*n*)	Male/ female (*n*)	Mild/ severe (*n*)	Mean age: male/ female (yr)	Etiology
Neoptolemos *et al*[32]	2000	Multicenter	On admission	35	172	87/85	137/35	52 (29-84)	Biliary 74, alcoholic 62, other 36
Liu *et al*[34]	2002	China	On admission	35	41	NA	29/12	NA	NA
Khan *et al*[33]	2002	United States	On admission	35	58	33/25	39/19	69 ± 19	Biliary 26, alcoholic 18, HTC 3, postoperative (including ERCP) 9, idiopathic 2
Lempinen *et al*[35]	2003	Finland	On admission	35	127	NA	98/29	NA	Biliary 24, alcoholic 74, other 29
Johnson *et al*[37]	2004	Multicenter	On admission	35	190	104/86	164/26	54 (42-70)	Biliary 70, alcohol 65, other 55
Huang *et al*[38]	2010	China	On admission	35	187	112/75	149/38	60.4 ± 6.7; 59.5 ± 8.1	Biliary 139, alcoholic 19, other 29

ERCP: Endoscopic retrograde cholangiopancreatography; HTC: Hypercholesterolemic; NA: Not available.

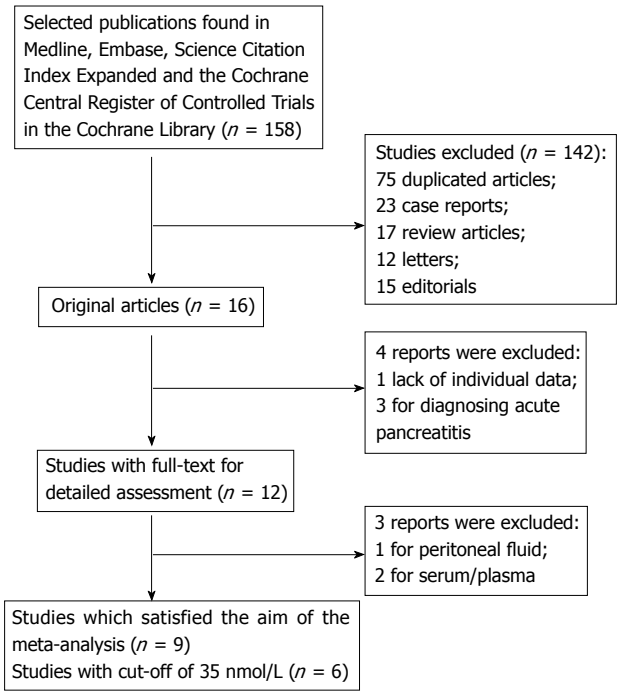

Figure 1 Flow diagram illustrating the process of identification of relevant studies.

TN were also extracted for serum CRP and APACHE Ⅱ score at the highest diagnostic values during the first 2 d after admission if these were reported in the included studies. The quality of the included studies was assessed independently by two reviewers using the Standards for Reporting of Diagnostic Accuracy (STARD) initiative guidelines[19]. Studies with a STARD score of ≥ 16 were considered as high quality studies.

Statistical analysis

The meta-analysis was performed with Meta-DiSc 1.4 software (Hospital Ramón y Cajal, Madrid, Spain). Pooled sensitivity, specificity, and diagnostic odds ratio (DOR) with diagnostic value Q were calculated. The mentioned parameters were pooled respectively with a corresponding 95%CI. Receiver operating characteristics were also generated and expressed by area under curve (AUC). The AUC represents the accuracy of diagnosis and DOR indicates its diagnostic capability for differentiating disease groups from negative groups[20]. Heterogeneity was evaluated using Cochran's Q test and a P value of 0.1 was considered significantly different. I^2 statistics were used to measure the percentage of total variation across the studies due to heterogeneity (I^2 of 50% or more indicating the presence of heterogeneity)[21]. The publication bias of included studies was assessed using a funnel plot of the effect of effective sample size weighted regression tests of asymmetry[22]. The meta-analysis was performed using a fixed-effect model if there was no heterogeneity among the studies, otherwise the random effects model was used[23]. The sensitivity analyses were undertaken by excluding each study from the analysis to ascertain its effect on the overall results. Subgroup analyses were dependent on the following items: high quality studies, sample size ≥ 50 in each study, single center studies and severity defined by the 1992 Atlanta Classification[18].

RESULTS

Description of included trials in the meta-analysis

Details of the literature research are shown in Figure 1 and 16 clinical studies were identified. Seven studies were excluded: one due to lack of data for analysis[24], one studied peritoneal fluid TAP[25], two studied serum/plasma TAP[26,27], three for diagnosing acute pancreatitis, but not for assessing the severity[28] or post-ERCP pancreatitis[29,30]. Of the 9 studies[15,31-38] that were potentially useful for analysis, only six had the cut-off of 35 nmol/L; it being variable in the remaining three and therefore, these six studies were included in the final analysis.

Study and patient characteristics

Table 1 describes the included studies and patient characteristics. All of the six included studies were prospectively designed and were of high quality (STARD score ≥ 16). There were 2 multicenter[32,37] and 4 single center[33-35,38] trials. Five studies[32-35,38] defined the severity of acute pancreatitis by the 1992 Atlanta Classification, in which severe cases included the moderate and the severe groups according to the revised Atlanta Classification[39]. One

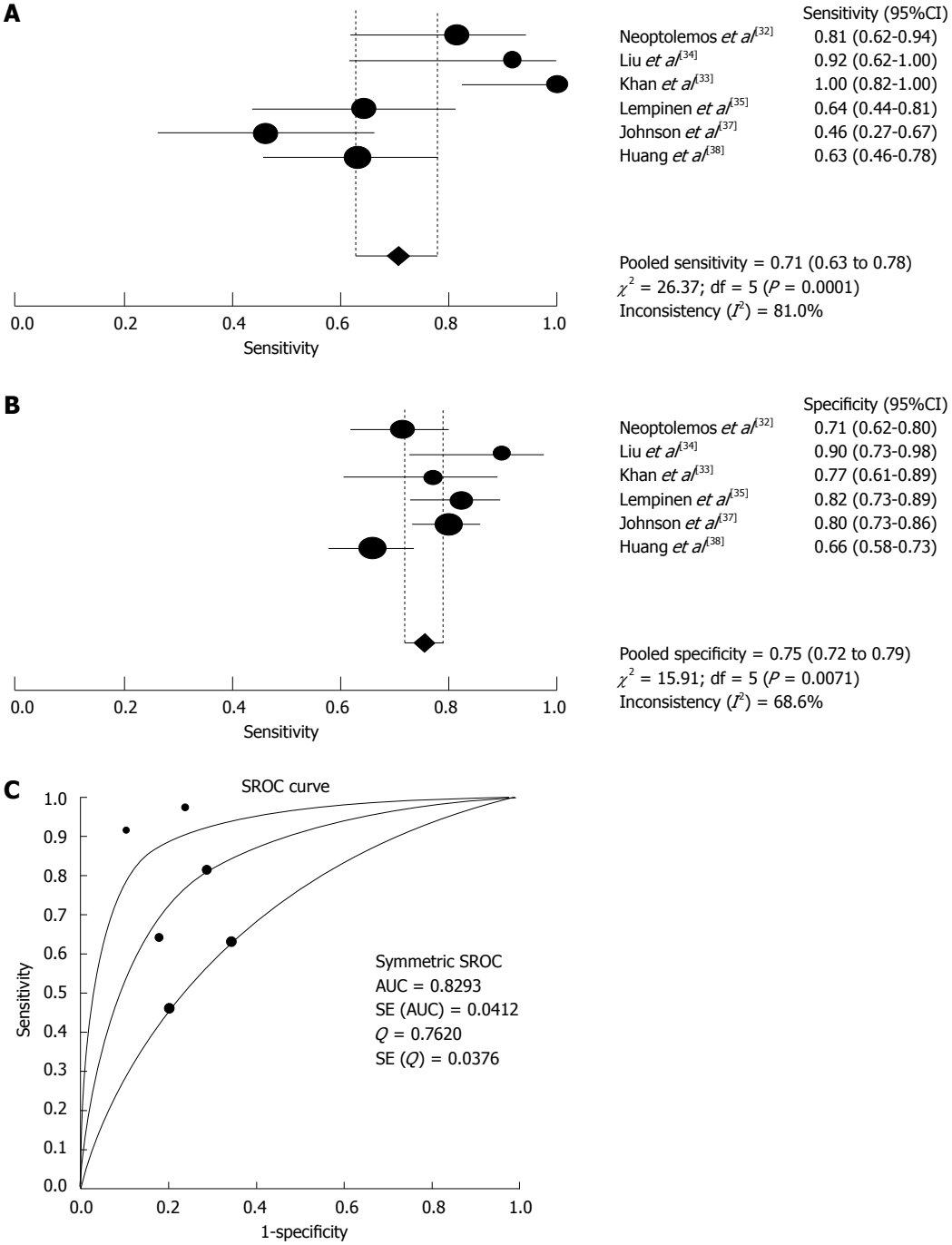

Figure 2 Forest plots of sensitivity (A), specificity (B), and summary receiver operating characteristic curve (C) for on admission urinary trypsinogen activation peptide in predicting severe acute pancreatitis. SROC: Summary receiver operating characteristic; AUC: Area under the curve.

Table 2 Diagnostic parameters of included studies

Ref.	Patients (*n*)	Patients analyzed (mild/severe)	TP	FP	FN	TN
Neoptolemos *et al*[32]	172	132 (105/27)	22	30	5	75
Liu *et al*[34]	41	41 (29/12)	11	3	1	26
Khan *et al*[33]	58	58 (39/19)	19	9	0	30
Lempinen *et al*[35]	127	118 (90/28)	18	16	10	74
Johnson *et al*[37]	190	190 (164/26)	12	33	14	131
Huang *et al*[38]	187	187 (149/38)	24	51	14	98

TP: True positive; FP: False positive; FN: False negative; TN: True negative.

study defined severe acute pancreatitis as the presence of local complications or the presence of persistent organ failure that was more than 48 h[37]. The predominant etiology in recruited patients was biliary in origin followed by alcoholic, ERCP and idiopathic.

Meta-analysis results

Results of the data extraction are shown in Table 2 and results of the meta-analysis are shown in Figures 2 and 3, and summarized in Table 3.

Table 3 Meta-analysis outcomes of included studies

	Trials (*n*)	Patients (*n*)	AUC	DOR (95%CI)	*Q*	*P* value	I^2
All studies	6	726	0.83	8.67 (3.70-20.33)	15.88	0.0072	68.50%
Study subgroups							
Sample size ⩾ 50	5	685	0.80	6.48 (3.05-13.74)	10.28	0.0360	61.10%
Single center	4	413	0.86	14.25 (3.39-59.80)	12.92	0.0048	76.80%
1992 Atlanta Classification	5	536	0.84	11.97 (4.17-34.36)	13.65	0.0085	70.70%

AUC: Area under the curve; DOR: Diagnostic odds ratios.

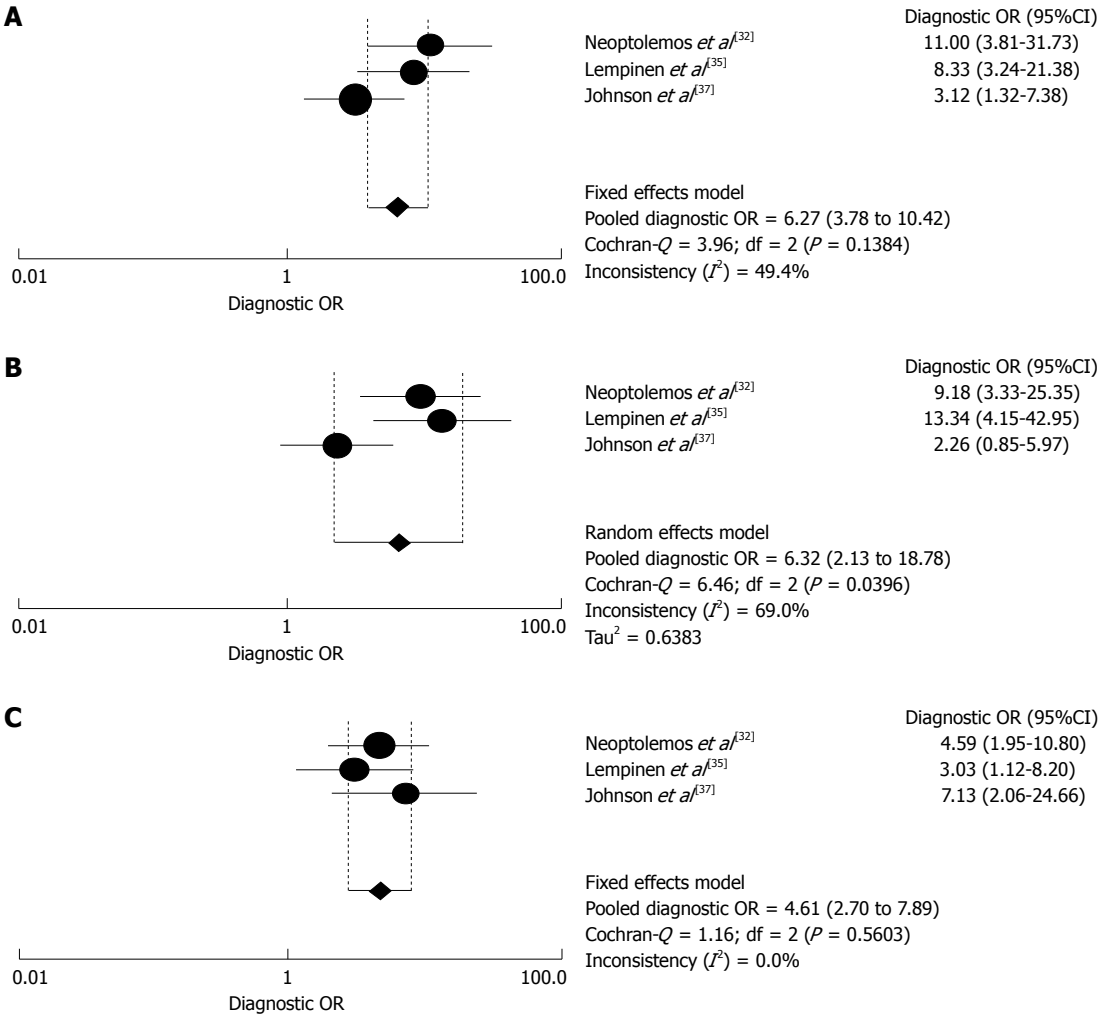

Figure 3 Forest plots of diagnostic OR for urinary trypsinogen activation peptide *vs* serum C-reactive protein and urinary trypsinogen activation peptide *vs* Acute Physiology and Chronic Health Evaluation Ⅱ score in predicting severe acute pancreatitis. The pooled diagnostic odds ratios of on-admission urinary trypsinogen activation peptide (A), plasma C-reactive protein at 48 h (B) and Acute Physiology and Chronic Health Evaluation Ⅱ score at 48 h (C).

On admission uTAP for predicting the severity of acute pancreatitis: Data from the six included studies (775 patients with 726 analyzed) revealed that the pooled sensitivity, specificity, AUC and DOR were 71% (95%CI: 63-78), 75% (95%CI: 72-79), 0.83 and 8.67 (95%CI: 3.70-20.33), respectively. Data are shown in Figure 2 and Table 3. These data suggest that uTAP has the potential to predict the severity of acute pancreatitis.

uTAP *vs* plasma CRP for severity stratification: There were 3 studies[32,35,37] that compared the prognostic value of on admission uTAP (440 patients analyzed) with plasma CRP (458 patients analyzed) within the first 48 h after admission in the severity stratification for acute pancreatitis. The pooled sensitivity, specificity, AUC value and DOR were 0.64 *vs* 0.67, 0.77 *vs* 0.75, 0.82 *vs* 0.79 and 6.27 *vs* 6.32, respectively (Figure 3A and B) for uTAP and CRP (best diagnostic values at 48 h). As suggested by the data, prognostic efficacy of the two markers was found to be similar.

uTAP *vs* APACHE-Ⅱ score for severity stratification: There were 4 studies[32,34,35,37] that compared the prognos-

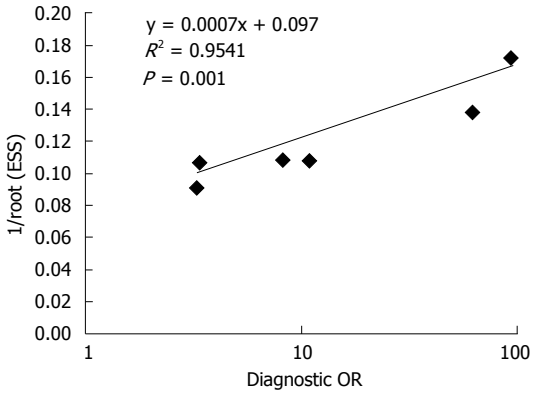

Figure 4 Funnel plot of the effect of effective sample size weighted regression tests of asymmetry for included studies. ESS: Effective sample size.

tic value of on admission uTAP with APACHE Ⅱ score within first 48 h after admission. Of these, 3 studies[32,35,37] used an APACHE Ⅱ score ⩾ 8 (422 patients analyzed) for defining severity and compared with uTAP (440 patients analyzed). The pooled sensitivity, specificity, AUC value and DOR were 0.64 *vs* 0.69, 0.77 *vs* 0.61, 0.82 *vs* 0.73 and 6.27 *vs* 4.61 for uTAP (values on admission) and APACHE Ⅱ score (best diagnostic values at 48 h), respectively (Figure 3A and C). These data suggest that uTAP may have a better prognostic value than the APACHE Ⅱ score in predicting the severity of acute pancreatitis.

Sensitivity and subgroup analysis: Outcomes for sensitivity and subgroup analysis are shown in Table 3. All six studies included were of high quality and sensitivity analysis demonstrated that significant heterogeneity still existed in these high quality studies (Q = 15.88, P = 0.0072, I^2 = 68.5%). Subgroup analysis showed that significant heterogeneity also existed in studies with sample size ⩾ 50 (Q = 10.28, P = 0.0360, I^2 = 61.1%), single center (Q = 12.92, P = 0.0048, I^2 = 76.8%), and severity defined by the 1992 Atlanta Classification (Q = 13.65, P = 0.0085, I^2 = 70.7%).

Publication bias: A funnel plot was created to demonstrate bias in the studies. The shape of the funnel plot showed asymmetry and this was confirmed by P = 0.001, showing that more significant results were present in smaller studies (Figure 4).

DISCUSSION

Upon admission, severity prediction of acute pancreatitis is crucial. This is still controversial, not universal and is mired by institutional differences. The current commonly used severity prediction systems include clinical assessment, biochemical markers, and both clinical and radiological scoring systems[40,41]. Clinical assessment provides a relatively high specificity (83%-98%) for ruling out mild acute pancreatitis, but has poor sensitivity (34%-64%) for the same[40]. When compared with clinical scoring systems, contrast-enhanced computed tomography (CECT) was not found to be superior in predicting outcomes of acute pancreatitis on admission[5].

Ideally, the best biomarker for predicting disease severity should be accurate, rapid, inexpensive and non-invasive. The pancreas-specific biomarkers are generally thought to be related to disease severity[14]. In 1988, a TAP assay with a detection limit of 10 picomolar concentration was developed by Hurley *et al*[42], enabling the detection of TAP in the body fluid to become more feasible. In a multicenter study conducted by Neoptolemos *et al*[32] that recruited 172 acute pancreatitis patients, uTAP concentration was found to be significantly different between mild and severe acute pancreatitis from 0-96 h after symptoms onset. Most importantly, uTAP values at both 24 and 48 h after admission provided the highest prognostic values for severe acute pancreatitis when compared to plasma CRP and clinical scoring systems (APACHE-Ⅱ, Glasgow and Ranson).

For the six studies included in this meta-analysis, the pooled results indicated that uTAP has potential for predicting the severity of acute pancreatitis upon hospital admission (AUC = 0.83, DOR = 8.67, 95%CI: 3.7-20.33). This is at least comparable with the current in-use biomarkers[6]. While most of the currently used biomarkers are non-specific in nature (specific for inflammation and other aspects), TAP is specific to the pancreas and is liberated within the first few hours after the onset of symptoms[15,32]. The prognostic value of uTAP (on admission) was similar to the APACHE-Ⅱ score obtained 24 h after admission in this meta-analysis. It is noteworthy that despite the APACHE-Ⅱ score being one of the most frequently used clinical scores to assess the severity of acute pancreatitis, it is cumbersome to use and has dubious use in certain settings; *i.e.,* in critical care environments where physiology has been corrected. Therefore, there is a need for simple and quick severity prediction techniques.

The prognostic value of an on-admission uTAP was also compared with plasma CRP (obtained 0-48 h after admission), currently the most widely used severity biomarker in acute pancreatitis and other acute inflammatory diseases[43]. uTAP had a relatively higher diagnostic value than plasma CRP, which suggested that uTAP might be a highly valuable biomarker for the quick assessment of acute pancreatitis severity on admission. It is unsurprising, therefore, that the revised Atlanta Classification[39] introduced the potential use of uTAP for severity stratification, although, as yet, it has not been widely adopted in the clinical arena.

To investigate the presence of heterogeneity, sensitivity and subgroup analyses were performed, based on sample size, study center and definition of severity. There was significant heterogeneity among studies with sample size ⩾ 50, single center and severity defined by the 1992 Atlanta Classification. It has been shown in many previous studies that multicenter studies tend to have better and more reliable results than single center studies. Similar to increasing sample size. Most of our studies used the Atlanta criteria for severity stratification, albeit one which represented a small proportion of the same cohort. From a clinical perspective, heterogeneity may also be caused by the defi-

nition of severity. All the severe acute pancreatitis cases included in this meta-analysis had two distinct entities: the moderate and the severe categories according to the revised Atlanta Classification. The proportion of moderate and severe cases may have had a significant impact on the results of uTAP. On the other hand, the proportion of patients who had pancreatic necrosis may also have an impact on the uTAP levels. Moreover, whether etiology plays a role in this regard remains unknown. Unsurprisingly, there was publication bias towards more significant effects reported in smaller sample sizes. This may have implications on the interpretation of the pooled sensitivity and specificity. These problems can only be overcome in the future by larger studies being performed.

The 1992 Atlanta Classification defines severe acute pancreatitis if organ failure/or local complications such as pancreatic necrosis, abscess, or pseudocyst are present[17]. Pancreatic necrosis, however, is only characterized by an area more than 30% necrosis non-enhanced on CECT, which might lead to false negative results of uTAP when pancreatic necrosis is less than 30%. The revised Atlanta Classification categorizes severity of acute pancreatitis into mild, moderate and severe classes[39]; the determinant-based classification stratifies severity of acute pancreatitis into mild, moderate, severe and critical categories[44]. These classifications consider pancreatic necrosis and persistent organ failure as the key determinants of outcome of acute pancreatitis. Compared to the 1992 Atlanta Classification, the new definition of pancreatic necrosis is described as the detection of any area of non-enhancement or every heterogeneous peri-pancreatic collection on CECT. These updated definitions and classifications might prove to be very useful in re-assessing the importance of an on-admission uTAP for the quick assessment of severity in acute pancreatitis. One might postulate that uTAP may have high prognostic accuracy in identifying patients with a disease course that is at least moderate to severe or for ruling out mild patients.

This review suffers from a relatively small sample size, publication bias in smaller studies and heterogeneity in some of the inclusion criteria. To the best of our knowledge, this is the most comprehensive meta-analysis on the subject to date. We have tried to summarize the existing data, identify problems in undertaking that, point out potential areas of improvement and suggest guidelines for future studies.

In summary, uTAP is a rapid assay for the assessment of acute pancreatitis severity on admission and provides good prognostic accuracy for severe acute pancreatitis based on the 1992 Atlanta Classification. New studies should assess its value in a larger patient cohort with uniform inclusion criteria and in line with the newly proposed classification systems.

COMMENTS

Background

Assessment of the severity of acute pancreatitis is crucial upon admission. Currently, clinical assessment, biochemical markers, and both clinical and computed tomography scoring systems are used individually or in combination to fulfil the need. However, a single, inexpensive and rapid biochemical marker is preferred due to practical and economic reasons. In this regard, urinary trypsinogen activation peptide (uTAP) has been developed and validated in many clinical studies, showing good diagnostic value in predicting severe acute pancreatitis. However, these results have not been systematically assessed.

Research frontiers

To conduct a meta-analysis on the value of uTAP in predicting the severity of acute pancreatitis on admission.

Innovations and breakthroughs

The Revised Atlanta Classification has introduced the potential use of uTAP in the prediction of severity stratification. However, current clinical studies regarding this topic have not been systemically analyzed to provide evidence on uTAP to ensure its wide adoption in the clinical arena. This is the first meta-analysis summarizing data obtained from six studies in which the uTAP cut-off concentration (35 nmol/L) was the same for severity stratification. The meta-analysis showed that the diagnostic value of uTAP (on admission) for the severity of acute pancreatitis was comparable to CRP (at 48 h after admission) and was potentially better than the APACHE-Ⅱ score (at 48 h after admission), the most frequently used biochemical marker and clinical scoring system in acute pancreatitis, respectively.

Applications

The results of the meta-analysis encourage the use of uTAP in routine clinical practice, although this needs to be established in further well designed studies with possible comparisons to the new severity classification systems.

Peer review

This is a well written study that provides useful data on the usefulness of uTAP in the diagnostic/staging algorithm for acute pancreatitis. It is a powerful study that essentially means that uTAP is unlikely to find a widespread place in acute pancreatitis prognostic scoring as there are other more widely used tests available that are equivalent.

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