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***Retrospective Study***

**Procalcitionin as diagnosis marker to distinguish upper and lower** **gastrointestinal perforation**

Gao Y *et al.* Procalcitionin on gastrointestinal perforation

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**Abstract**

***AIM***

To assess accuracy and efficacy of procalcitionin (PCT) as diagnosis marker in verifying upper and lower gastrointestinal perforation(GIP).

***METHODS***

This retrospective study included 46 patients from SICU ward of the Second Affiliated Hospital of Harbin Medical University who were confirmed to be with GIP between June 2013 and December 2016. Demographic and clinical patient data were recorded on admission to ICU. Patients were divided into upper (*n* = 19) and lower (*n* = 27) GIP groups according to perforation site above or below Treitz ligament. PCT and WBC count was obtained before laparotomy and then compared between groups. Meanwhile diagnosis effect of PCT was analyzed.

***RESULTS***

Patients withlower GIP exhibited significantly higher APACHE II score, SOFA score and serum PCT level than patients with upper GIP (*P* = 0.017, 0.004, 0.001,respectively). There was a significant positive correlation between serum PCT level and APACHE II score, SOFA score (correlation coefficients were *r* = 0.715 and *r* = 0.611, respectively), while there was a significant negative correlation between serum PCT level and Prognosis (correlation coefficients was *r* = -0.414). WBC count was not significantly different between groups, and WBC count showed no significant correlation with serum PCT level, APACHE II score, SOFA score and prognosis. The area under the curve of PCT predictive value to distinguish upper or lower GIP was 0.778. Patients with serum PCT level above 17.94 ng/dL had a high likelihood of lower GIP, of which sensitivity and specificity were 100% and 42.1%, respectively.

***CONCLUSION***

Serum PCT level was a reliable and accurate diagnosis marker in identifying upper or lower GIP before laparotomy.

**Key words:** Procalcitionin; White blood cell count; Gastrointestinal perforation; Sepsis; APACHE II score; SOFA score

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**Core tip:** Procalcitionin (PCT) is a rapid, reliable and accurate predictive marker and contributes to assisting the clinicians in identifying upper or lower gastrointestinal perforation(GIP) before laparotomy, and it can be used as a useful supplementary tool for early clinical judgment of perforation site. The results showed that patients withlower GIP exhibited significantly higher APACHE II score, SOFA score and serum PCT level than patients with upper GIP, which might be related to the differences of bacterial load and the severity of sepsis between upper and lower GIP.

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**INTRODUCTION**

Gastrointestinal perforation is one of the most common acute abdominal diseases in department of general surgery with high mortality rates, which could easily lead to shock and need rescue therapy of ICU. GIP is a life-threatening acute abdominal disease, especially for elder people, which usually needs active rescue of ICU and emergency laparotomy[[1](#_ENREF_1)]. In general, GIP is related to the factors such as older age, diabetes, antecedent diverticulitis, glucocorticoid therapy, usage of non-steroidal anti-inflammatory drugs (NSAIDs) and so on[[2-4](#_ENREF_2)]. It is still a challenge to accurately predict upper or lower GIP before laparotomy, despite increased available clinical and biological variables. To our knowledge, this study is the first one to evaluate the role of PCT in predicting upper or lower GIP before laparotomy as a useful supplementary tool. Before laparotomy, early diagnosis of perforation site had beneficial effects on operative procedure, selecting antibiotics and even judging the severity of infection and prognosis.

Serum Procalcitionin (PCT) concentration was discovered to be significantly higher in patients with bacterial and fungal infections, and sepsis first in 1993[[5](#_ENREF_5)], which had been proved to be a rapid, reliable and accurate diagnosis marker, and was used to identify infectious and non-infectious diseases now[[6-8](#_ENREF_6)]. Sepsis could promote secretion of PCT through stimulating various types of cells in a variety of tissues[[9](#_ENREF_9)], which was typically produced by C cells of thyroid. More importantly, PCT concentration was related to bacterial load[[10](#_ENREF_10)] as well as the severity of sepsis[[11](#_ENREF_11)], and even prognosis[[12](#_ENREF_12),[13](#_ENREF_13)]. Owing to different perforation site and contents, the severity of sepsis and bacterial load were obviously different, especially when comparing upper and lower GIP. We hypothesized that, due to less bacteria, the severity of sepsis caused by upper GIP was lower than that caused by lower GIP, which could be reflected by serum PCT level. Thus, serum PCT level might be a useful supplementary tool for clinical judgment of perforation site.

But so far the diagnostic validity and accuracy of PCT in predicting upper or lower GIPs was lacking. To the best of our knowledge, few researches had formally assessed its role in this area. In this retrospective study, serum PCT level was evaluated as a diagnosis marker in distinguishing upper or lower GIPs before laparotomy.

**MATERIALS AND METHODS**

***Study design***

This current study is a retrospective study performed in SICU ward of the Second Affiliated Hospital of Harbin Medical University (Harbin, China). Patients were enrolled from June 2013 to December 2016. Study protocol was approved by the ethics committee of our school.

***Study population***

Patients who met the following criteria were included: (1) ICU admission; (2) patients were definitely diagnosed as GIP by laparotomy; (3) serum PCT level and WBC count were detected before laparotomy; and (4) with ages of >18. Patients who met following criteria were excluded: (1) uncertain of perforation site; (2) women in gestation or breast-feeding; (3) being in blood purification treatment; and (4) who received antibiotic therapy before ICU admission. In addition, patients with incomplete medical records were also excluded. All enrolled patients were treated by same experienced physicians.

***Diagnosis of GIP***

GIP was defined as the destruction of integrity of digestive tract, i.e., a complete non-traumatic penetration of wall of esophagus, stomach, small or large bowel[[2](#_ENREF_2)]. Patients were divided into upper and lower GIP groups according to perforation site above or below Treitz ligament. Owing to the complexity of GIP diagnosis, a careful and thorough clinical examination was necessary.

***Serum PCT level and WBC count measurement***

Serum PCT level and WBC count were measured following ICU admission immediately before laparotomy. Mini VIDAS (Hain lifescience GmbH; Nehren, Germany) was applied to measure serum PCT level.

***Data collection***

**Baseline data:** gender, age, height, weight, Body Mass Index (BMI), prognosis, acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score and perforation site were obtained from patient medical records.

Demographic and clinical data of selected patients were recorded on admission to SICU with blood samples taken for Serum PCT level and WBC count test immediately. APACHE II score and SOFA score were calculated using data collected from the first 24 hours after admission.

***Statistical analyses***

Data are described as the mean ± SD and SPSS 13.0 (SPSS Inc., Chicago, IL, United States) was used for the analysis. To compare baseline data between groups, independent sample t test and χ2 test were employed. Independent sample *t* test was used to compare APACHE II score, SOFA score and WBC count between groups. Owing to non-normality, serum PCT level between groups was analyzed with Manny-Whitney rank sum test. Correlation between parameters was analyzed by Pearson or Spearman correlation. Area under ROC curvewas calculated to evaluate the predictive value of PCT and to determine optimal cut-off value for distinguishing between upper and lower GIP before laparotomy. *P* < 0.05 was considered to be statistically significant.

**RESULTS**

***Patient baseline data***

A total of 46 patients were enrolled in this retrospective study who underwent serum PCT level and WBC count measure following ICU admission immediately before laparotomy. Of all patients, GIP was proved by laparotomy. Nineteen patients were divided into upper GIP group, while the rest patients in lower GIP group. As shown in Table 1, no significant differences were observed in baseline data with the exception of age (*P* = 0.028).

***Diagnosis value of serum PCT level and WBC count***

Patients withlower GIP exhibited significantly higher APACHE II score, SOFA score and serum PCT level than patients with upper GIP (*P* = 0.017, 0.004, 0.001, respectively). However, WBC count showed no significant difference between groups, and WBC count showed no significant correlation with serum PCT level, APACHE II score, SOFA score and prognosis (Table 2). The area under the curve of PCT predictive value to distinguish upper or lower GIP was 0.778 (Figure 1). Patients with serum PCT level above 17.94 ng/dL had a high likelihood of lower GIP, with a sensitivity and specificity of 100% and 42.1%, respectively (Table 3).

**DISCUSSION**

PCT is pre-peptide protein of calcitonin, which had been proved to be a sensitive and specific predictive marker for bacterial infection[[14](#_ENREF_14), [15](#_ENREF_15)], and thus was used to guide antibacterial therapy and reduce its length[[16-19](#_ENREF_16)] without affected by hepatic or renal dysfunction[[20-22](#_ENREF_20)]. PCT had many advantages of an ideal marker for routine clinical application, including simplicity, accuracy, specificity, stability and availability[[23](#_ENREF_23)]. However, little was known on predictive value of PCT in judging perforation site before laparotomy. We speculated that, when upper or lower GIP happened, they were different in bacterial load and the severity of sepsis owing to leakage of different digestive tract content, which could be reflected by serum PCT level. Antibiotic therapy might have an impact on bacterial load, and even serum PCT level, therefore, patients who had used antibiotics before ICU admission were excluded[[24](#_ENREF_24)].

APACHE II score and SOFA score were usually applied to evaluate the severity of disease[[25](#_ENREF_25)], especially suitable for critically ill adult patients in ICU, which were closely related to mortality[[25-29](#_ENREF_25)]. Therefore, in our study, they were chosen to assess the degree of illness. In particular, SOFA score was an important part of sepsis diagnosis in The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[[30](#_ENREF_30)].

The results of the present study showed that patients withlower GIP exhibited significantly higher APACHE II score, SOFA score and serum PCT level than patients with upper GIP, which might be related to the differences of bacterial load and the severity of sepsis between upper and lower GIP. In contrast, our findings did not show a significant different between groups regarding WBC count. In other words, WBC count did not have a predictive value of sepsis which was in accordance with previous researches[[31](#_ENREF_31)]. Further correlation analysis showed that there was a significant positive correlation between serum PCT level and APACHE II score, SOFA score, and a significant negative correlation between serum PCT level and prognosis. By analyzing ROC curve, an optimal cut-off value was selected as a predictive value to distinguish between upper and lower GIP before laparotomy.

There were several limitations in this present study. First, patients were selected from one single center, which makes the evidence level for this study relatively low. Secondly, the sample size was relatively small. Thus, experiments with larger sample size are needed to verify this in the future. At last, this study only concerned serum PCT level measured immediately after ICU admission and before laparotomy, but lacked of dynamic observation of serum PCT level changes after laparotomy, and this should also be performed in the future study.

In conclusion, PCT is a rapidly reliable and accurate predictive marker and contributed to assist the clinicians toward identifying upper or lower GIP before laparotomy, which can be used as a useful supplementary tool for early clinical judgment of perforation site.

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**COMMENTS**

***Background***

Gastrointestinal perforation (GIP) is one of the most common acute abdominal diseases in department of general surgery with high mortality rates, which could easily lead to shock and need rescue therapy of ICU. It is still a challenge to accurately predict upper or lower GIP before laparotomy, despite increased available clinical and biological variables. Serum Procalcitionin (PCT) concentration was related to bacterial load as well as the severity of sepsis, and even prognosis. Thus, the authors hypothesized that, due to less bacteria, the severity of sepsis caused by upper GIP was lower than that caused by lower GIP, which could be reflected by serum PCT level.

***Research frontiers***

At present, the researches on PCT have mainly focused on the following aspects, such as predictive marker for bacterial infection, distinguishing between bacterial and non-bacterial infections, guiding antibacterial therapy and reducing its length and so on. But so far the diagnostic validity and accuracy of PCT in predicting upper or lower GIPs was lacking. To the best of our knowledge, few researches had formally assessed its role in this area.

***Innovations and breakthroughs***

This study is the first one to evaluate the role of PCT in predicting upper or lower GIP before laparotomy as a useful supplementary tool. This study had confirmed that PCT was a rapidly reliable and accurate predictive marker and can be used for early clinical judgment of perforation site.

***Applications***

When upper or lower GIP happened, they were different in bacterial load and the severity of sepsis owing to leakage of different digestive tract content, which could be reflected by serum PCT level. Therefore, PCT was contributed to assist the clinicians toward identifying upper or lower GIP before laparotomy, which had beneficial effects on operative procedure, selecting antibiotics and even judging the severity of infection and prognosis.

***Terminology***

PCT is pre-peptide protein of calcitonin, which was discovered to be significantly higher in patients with bacterial and fungal infections, and sepsis first in 1993. GIP was defined as the destruction of integrity of digestive tract, i.e., a complete non-traumatic penetration of wall of esophagus, stomach, small or large bowel. Patients were divided into upper and lower GIP groups according to perforation site above or below Treitz ligament.

***Peer-review***

This is an interesting study about the procalcitionin as diagnosis marker to distinguish upper and lower gastrointestinal perforation. In this retrospective study, the authors included 46 patients from SICU ward of the Second Affiliated Hospital of Harbin Medical University who were confirmed to be with GIP between June 2013 and December 2016. There was a significant positive correlation between serum PCT level and APACHE II score, SOFA score, while there was a significant negative correlation between serum PCT level and Prognosis. Patients with serum PCT level above 17.94 ng/dL had a high likelihood of lower GIP, which sensitivity and specificity were 100% and 42.1%, respectively.

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**Table 1 Patient baseline data**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Upper**  ***n* = 19** | **Lower**  ***n* = 27** | ***t* value** | ***P* value** |
| Age | 58.84 | 67.59 | -2.2801 | 0.028 |
| Gender |  | | | |
| Male | 7 | 14 | 1.013 | 0.314 |
| Female | 12 | 13 |
| Height | 168.47 | 165.37 | 1.3164 | 0.1949 |
| Weight | 63.42 | 58.37 | 1.5885 | 0.1193 |
| BMI | 22.27 | 21.21 | 1.1764 | 0.2458 |
| APACHEII | 12.47 | 18.15 | -2.4765 | 0.017 |
| SOFA | 5.84 | 9.33 | -3.0411 | 0.004 |
| PCT | 33.26 | 40.73 | -3.079 | 0.001 |
| WBC | 13.67 | 11.27 | 1.1049 | 0.275 |

APACHE II: Acute physiology and chronic health evaluation II; SOFA: Sequential organ failure assessment score.

**Table 2 Correlation analysis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **APACHEII** | **SOFA** | **PCT** | **WBC** | **Prognosis** |
| PCT | 0.715 | 0.611 | 1 | -0.143 | -0.414 |
| < 0.001 | < 0.001 | < 0.001 | 0.342 | 0.004 |
| WBC | -0.242 | -0.033 | -0.143 | 1 | 0.112 |
| 0.105 | 0.829 | 0.342 |  | 0.457 |

PCT: Procalcitionin.

**Table 3 Area under ROC curve**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Area** | **Std. Error** | **Asymptotic Sig.** | **Asymptotic 95%CI** | |
| **Lower bound** | **Upper bound** |
| 0.778 | 0.077 | 0.001 | 0.628 | 0.928 |

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**Figure 1 ROC curve showed that area under the curve of Procalcitionin predictive value to distinguish upper or lower gastrointestinal perforation was 0.778.**