Original Research

Serum homocysteine is a valuable marker for predicting aggravation of infection in intestinal obstruction patients

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Impact statement

Intestinal obstruction constitutes a major cause of death and financial expense in hospitals around the world and a major cause of admissions to emergency surgical units. However, the gold standard of laboratory examination to the treatment of intestinal obstruction is remaining uncertain. Thus, in this manuscript, we aimed to investigate the expression of serum homocysteine (HCY), procalcitonin (PCT), and C-reactive protein (CRP) in abdominal infectious disease and analyze their relationship with the degree of abdominal infection. The difference was statistically significant in the HCY level between non-operation group and operation group in patients with intestinal obstruction($P < 0.001$). Serum HCY maybe a valuable marker for predicting aggravation of infection in patients with intestinal obstruction. These results might help us to ease patient pain, reduce the hospital costs and patients' repeated computed tomography examination and material consumption, and shorten average length of stay, and eventually benefit the patients.

Abstract

The aim of this study was to investigate the expression of serum homocysteine (HCY), procalcitonin (PCT), and C-reactive protein (CRP) in abdominal infectious disease and analyze their relationship with the degree of abdominal infection. We conducted a retrospective study involving 157 patients with abdominal infections at Xuzhou Central Hospital between January 2016 and October 2019. The patients were composed of intestinal obstruction (73 cases), appendicitis (45 cases), perforation of the digestive tract (25 cases), and cholecystitis (14 cases). The HCY, PCT, and CRP levels of patients with abdominal infections were detected using enzyme-linked immunosorbent assay (ELISA), and correlation analysis between the HCY, PCT, and CRP levels and abdominal infection was performed using Pearson's correlation analysis. Compared with before treatment, the HCY, PCT, and CRP levels in the four groups decreased significantly after treatment. The levels in the patients in the intestinal obstruction group decreased more markedly than in those in the other groups. There were positive correlations among the HCY level, PCT, and CRP before treatment only in patients with intestinal obstruction ($P < 0.001$). The difference was statistically significant in the HCY level between the non-operation and the operation groups in patients with intestinal obstruction ($P < 0.001$). Serum HCY may be a valuable marker for predicting aggravation of infection in patients with intestinal obstruction.

Keywords: HCY, intestinal obstruction, PCT, CRP

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Introduction

Acute abdomen is a general term for the sudden onset of severe abdominal pain likely to require emergency surgery and is caused by a wide variety of conditions.[1] Common acute abdominal diseases in general surgery include intestinal obstruction (IO), appendicitis, perforation of the digestive tract, and cholecystitis. Among them, IO is defined as a blockage or partial blockage of the passage of the intestinal contents. It is one of the most common acute abdominal disorders requiring emergency surgical admission and has high mortality of 3–30% across the globe.[2,3] In a global-based report of the World Health Organization, approximately 3.2 million cases of bowel obstruction occurred in 2015, which resulted in 264,000 deaths.[4] Both sexes are equally affected, and the condition can occur at any age.[5] It constitutes a significant cause of death and financial expense in hospitals worldwide and a major cause of admissions to emergency surgical units.

However, there is not enough high-quality evidence for the management of IO. The management of acute IO depends on the presumption and experience of the general surgeon. Consequently, the decision to perform surgery or treat IO patients is often difficult and requires assimilating patient information, laboratory findings, and radiological studies. Currently, the gold standard of laboratory examination for the treatment of IO remains uncertain. As a result, effective serum markers are urgently needed. Plasma markers have been continuously advocated as pointers to estimate the degree of abdominal infection. However, there are no established serum parameters with appropriate sensitivity or specificity for the diagnosis of IO.

Table 1. Clinical characteristics of patients included in this study.

	Intestinal obstruction ($n=73$)	Appendicitis ($n=45$)	Perforation of digestive tract ($n=25$)	Cholecystitis ($n=14$)	*P* value
Gender					0.232
Male	36 (49.32%)	26 (57.78%)	8 (32%)	7 (50%)	
Female	37 (50.68%)	19 (42.22%)	17 (68%)	7 (50%)	
Age (mean ± SD)	59 ± 16.06	53.55 ± 12.81	56.48 ± 17.78	52.93 ± 13.85	0.217

SD: standard deviation.

Homocysteine (HCY) is a sulfur-containing amino acid that is not a constituent of proteins. It is part of the intermediary metabolism and is synthesized in the HCY–methionine cycle by a multistep process. HCY is metabolized in the kidneys and liver, whereas trans-sulfuration occurs in the pancreas and small intestine. The normal levels of HCY range between 5 and 15 μmol/L. In the last few years, a growing body of evidence has pointed to a critical role of elevated plasma levels of HCY in the pathophysiology of several inflammatory and vascular disorders, such as cardiovascular disease (CVD), renal dysfunction, bone fractures, and cognitive decline.[5–8] In particular, in atherosclerosis, HCY is now recognized as a key inflammatory molecule that induces endothelial cell damage, impairs flow-mediated arterial dilatation, and triggers vascular inflammation. In conclusion, HCY is defined as a biomarker of inflammatory and vascular disorders.

IO is often accompanied by intestinal vascular disorder and infection. Studies have confirmed that HCY is an important indicator of vascular disorder and that procalcitonin (PCT) and C-reactive protein (CRP) are directly involved in inflammation. However, there are few studies on the expression of HCY, PCT, and CRP in IO and their relationship with the extent of IO. This study aimed to explore the expression of HCY, PCT, and CRP in acute abdominal diseases and to analyze their relationship with the degree of IO.

Materials and methods

General information

A retrospective analysis of 157 patients with abdominal infections were selected as study subjects in Xuzhou Central Hospital between January 2016 and October 2019. Mental diseases such as brain dysfunction and depression were excluded. In addition, diseases combined with coronary heart disease, cerebral thrombosis, and liver and kidney insufficiency were also excluded. The clinical information of all the candidates was complete, and patients or their family members signed the informed consent form. General information is provided in Table 1. The study was approved by the Ethics Committee of Xuzhou Central Hospital (Xuzhou, China).

Treatment methods

For patients with appendicitis, perforation of the digestive tract and cholecystitis, the treatment refers to conventional surgery. However, the treatment for patients with IO contains non-operative and operative treatment. The operation group was treated with operation. The non-operative group was treated with rehydration, anti-inflammatory, and other non-surgical treatments.

Detection of HCY, PCT, and CRP

A total of 3 mL fasting peripheral venous blood was taken from the patients and centrifuged at 2600 × g for 8 min at 4°C. Serum was used to detect HCY, CRP, and PCT levels using enzyme-linked immunosorbent assay (ELISA). The specific method of operation was strictly in accordance with the protocol. The average value of each index was taken as the final result after three consecutive tests.

Statistical analysis

SPSS 23.0 statistical software was used for analysis (SPSS Inc., Chicago, IL, USA). The differences between groups were examined using chi-square tests, while the measurement data were expressed as the mean ± standard deviation and compared using *t*-tests. The correlation analysis between the HCY, CRP, and PCT levels in serum was performed using Pearson's correlation analysis. $P<0.05$ indicated a statistically significant difference.

Results

Characteristics of the patients

A total of 157 patients were identified for this audit. Table 1 summarizes the clinical characteristics of the eligible patients. The disease cases of the patients were composed of IO (73 cases), appendicitis (45 cases), perforation of the digestive tract (25 cases), and cholecystitis (14 cases). There was no significant difference in age or gender between the groups ($P>0.05$) (Table 1).

HCY, PCT, and CRP levels before treatment

The average of HCY, PCT, and CRP in all patient enrolled in this study were 27.24 ± 8.77 μmol/L, 13.96 ± 17.67 ng/mL, 127.69 ± 76.98 mg/L. As shown in the above data, the levels of HCY, PCT, and CRP were higher than the upper limit of normal (HCY < 15 μmol/L, PCT < 0.046 ng/mL, CRP < 3 mg/L). Furthermore, there was no significant difference in age and gender of HCY, PCT, and CRP ($P<0.001$) (Figure 1).

Changes in HCY, PCT, and CRP levels before and after treatment

The levels of HCY, PCT, and CRP before treatment were significantly higher than those after treatment in the above four diseases ($P<0.001$) (Figure 2). There was no significant difference in age and gender of the changes in HCY, PCT, and CRP levels before and after treatment.

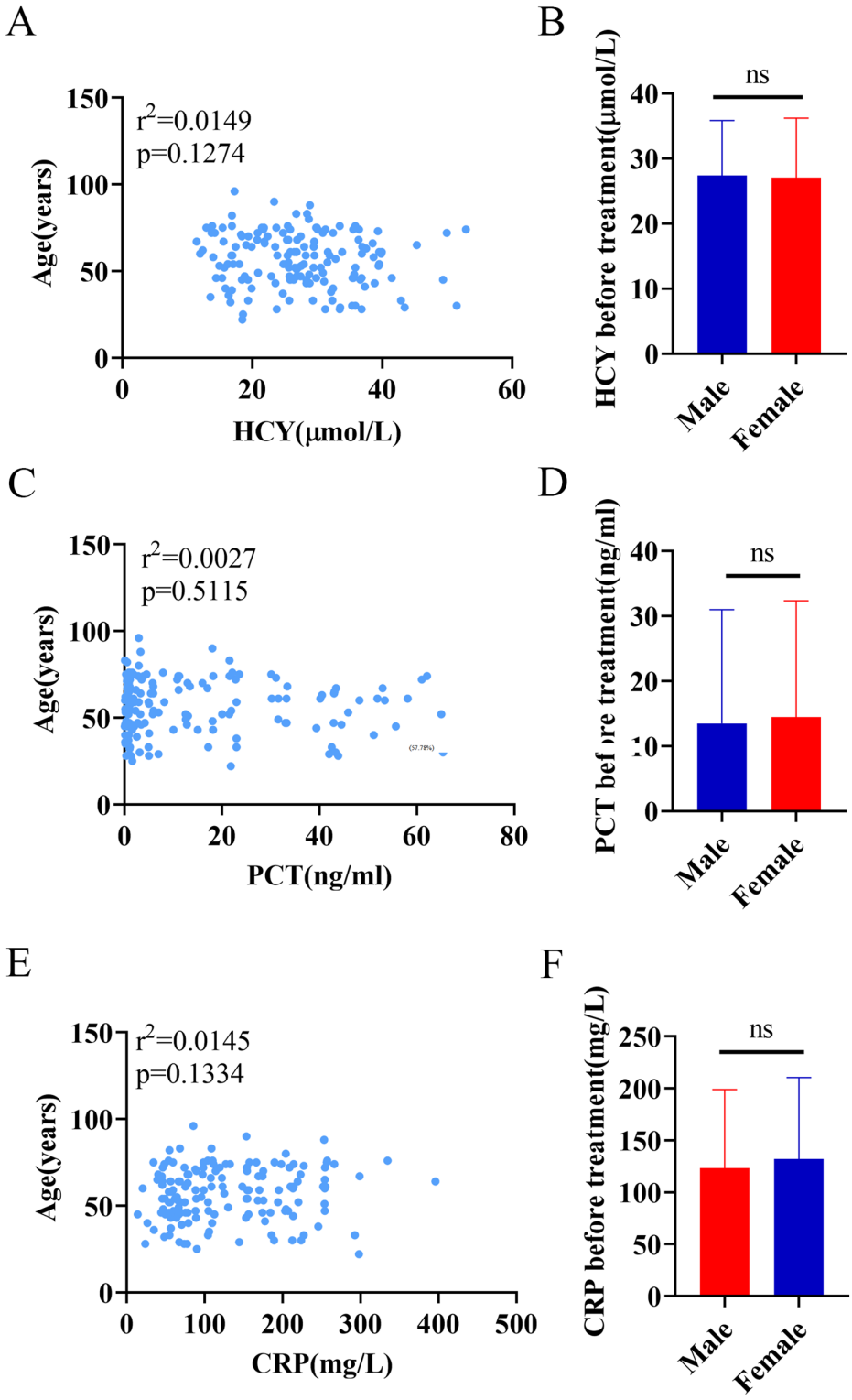

Figure 1. Correlation between HCY and age before treatment (A). Comparison of HCY with gender before treatment (B). Correlation between PCT and age before treatment (C). Comparison of PCT with gender before treatment (D). Correlation between CRP and age before treatment (E). Comparison of CRP with gender before treatment (F).

Correlations among HCY, PCT, and CRP in IO, appendicitis, perforation of the digestive tract, and cholecystitis

It was found that the HCY level was positively correlated with PCT before treatment only in patients with IO ($P < 0.001$) (Figures 3 to 6). In addition, there was also a positive correlation between HCY and CRP before treatment in patients with IO or perforation of the digestive tract (Figures 3 and 5). There was also a positive correlation between CRP and PCT before ($P < 0.001$) and after ($P < 0.05$) treatment in patients with IO or cholecystitis (Figures 3 and 6). Only in IO group were there any correlations between HCY, PCT, and CRP in pairs.

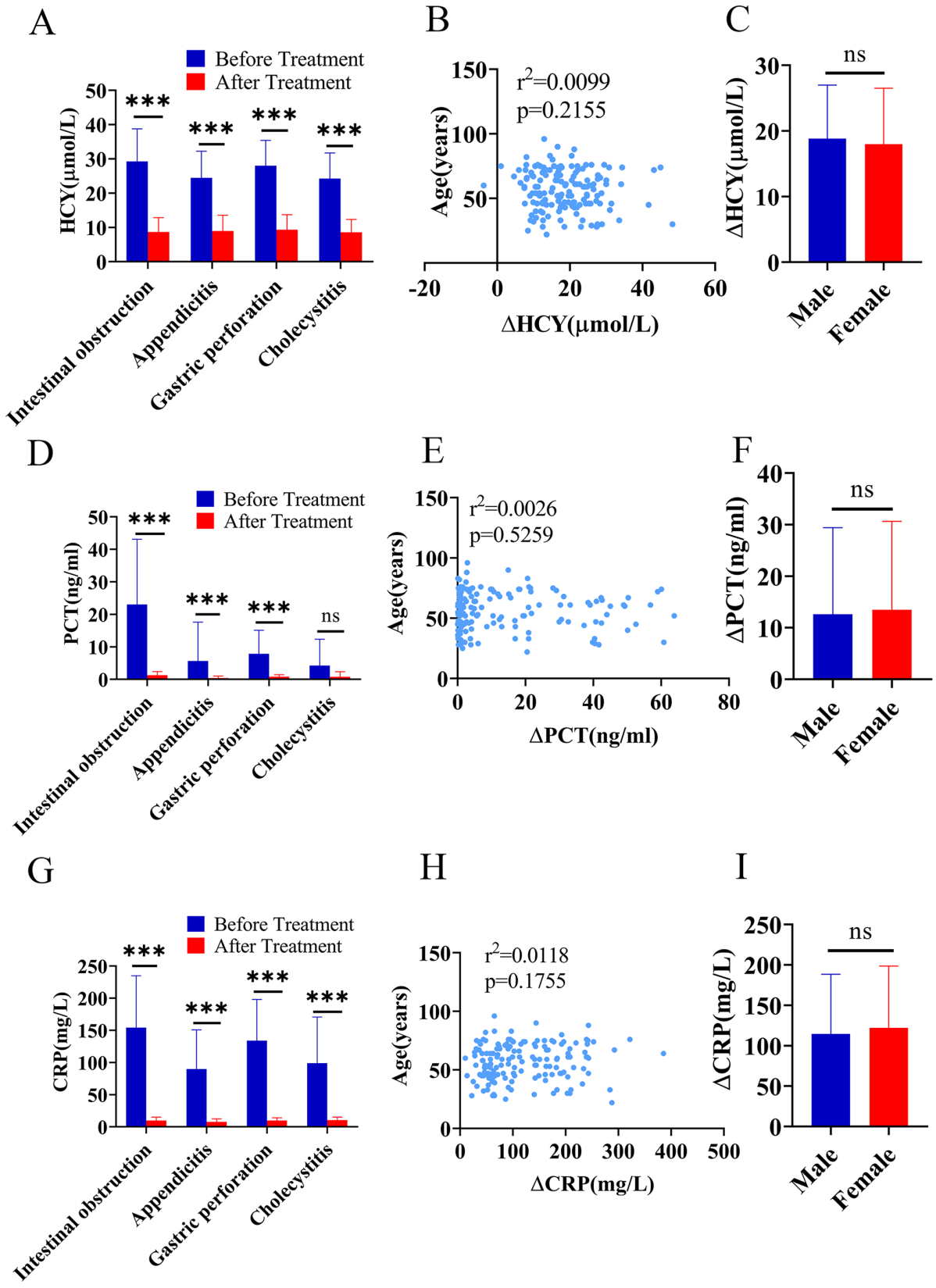

Figure 2. Comparison of HCY changes in patients with acute abdomen before and after treatment (A). Correlation between HCY changes and age (B), Δ HCY indicated the HCY changes before and after treatment. Comparison of HCY changes with gender (C). Comparison of PCT changes in patients with acute abdomen before and after treatment (D). Correlation between PCT changes and age (E), Δ PCT indicated the PCT changes before and after treatment. Comparison of PCT changes with gender (F). Comparison of CRP changes in patients with acute abdomen before and after treatment (G). Correlation between CRP changes and age (H), Δ CRP indicated the CRP changes before and after treatment. Comparison of CRP changes with gender (I).
***$P < 0.001$.

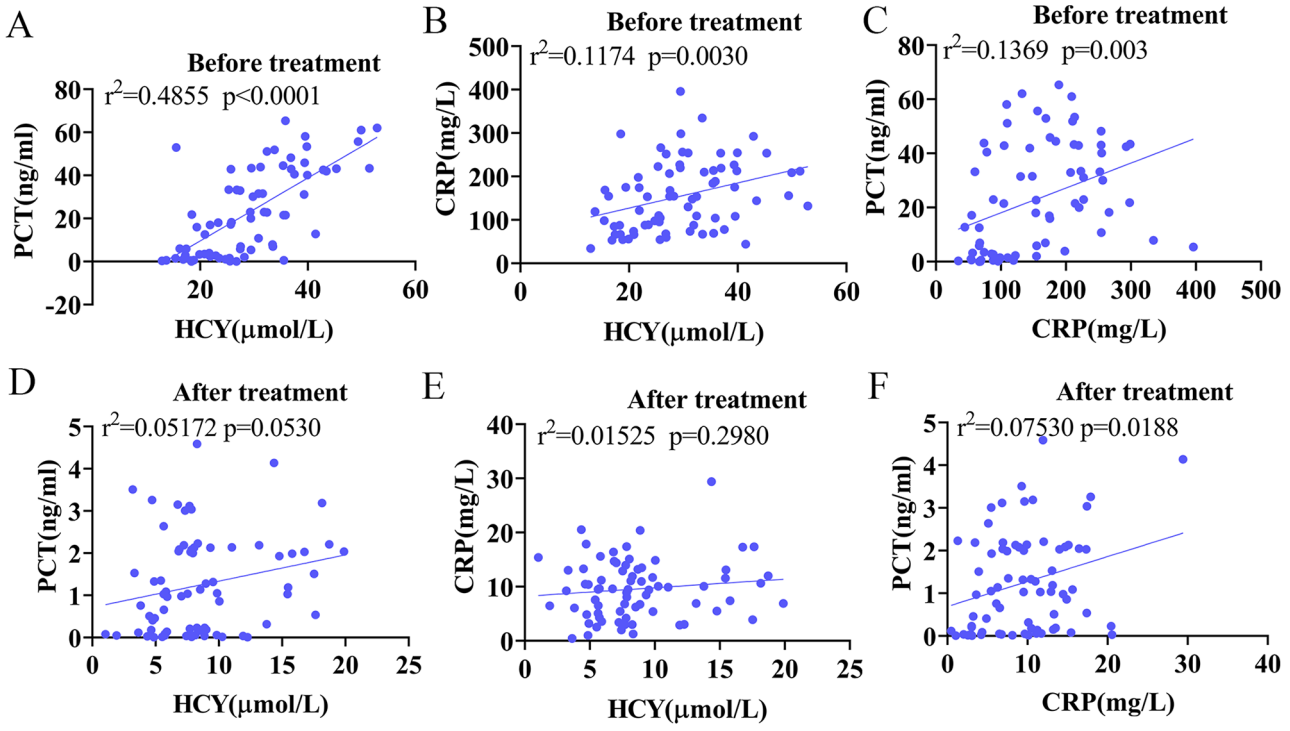

Figure 3. Correlation between HCY and PCT before treatment in intestinal obstruction (A). Correlation between HCY and CRP before treatment in intestinal obstruction (B). Correlation between CRP and PCT before treatment in intestinal obstruction (C). Correlation between HCY and PCT after treatment in intestinal obstruction (D). Correlation between HCY and CRP after treatment in intestinal obstruction (E). Correlation between CRP and PCT after treatment in intestinal obstruction (F).

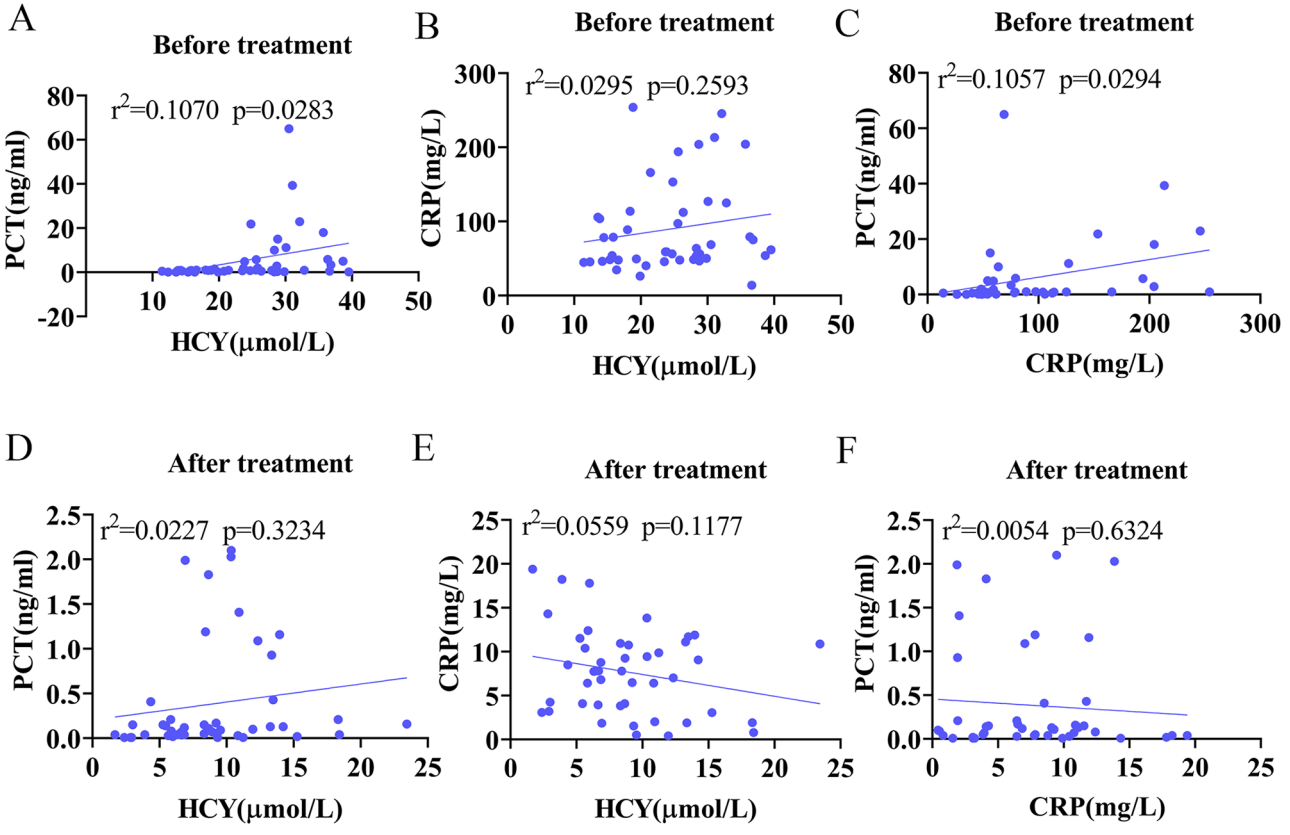

Figure 4. Correlation between HCY and PCT before treatment in appendicitis (A). Correlation between HCY and CRP before treatment in appendicitis (B). Correlation between CRP and PCT before treatment in appendicitis (C). Correlation between HCY and PCT after treatment in patients with appendicitis (D). Correlation between HCY and CRP after treatment in appendicitis (E). Correlation between CRP and PCT after treatment in appendicitis (F).

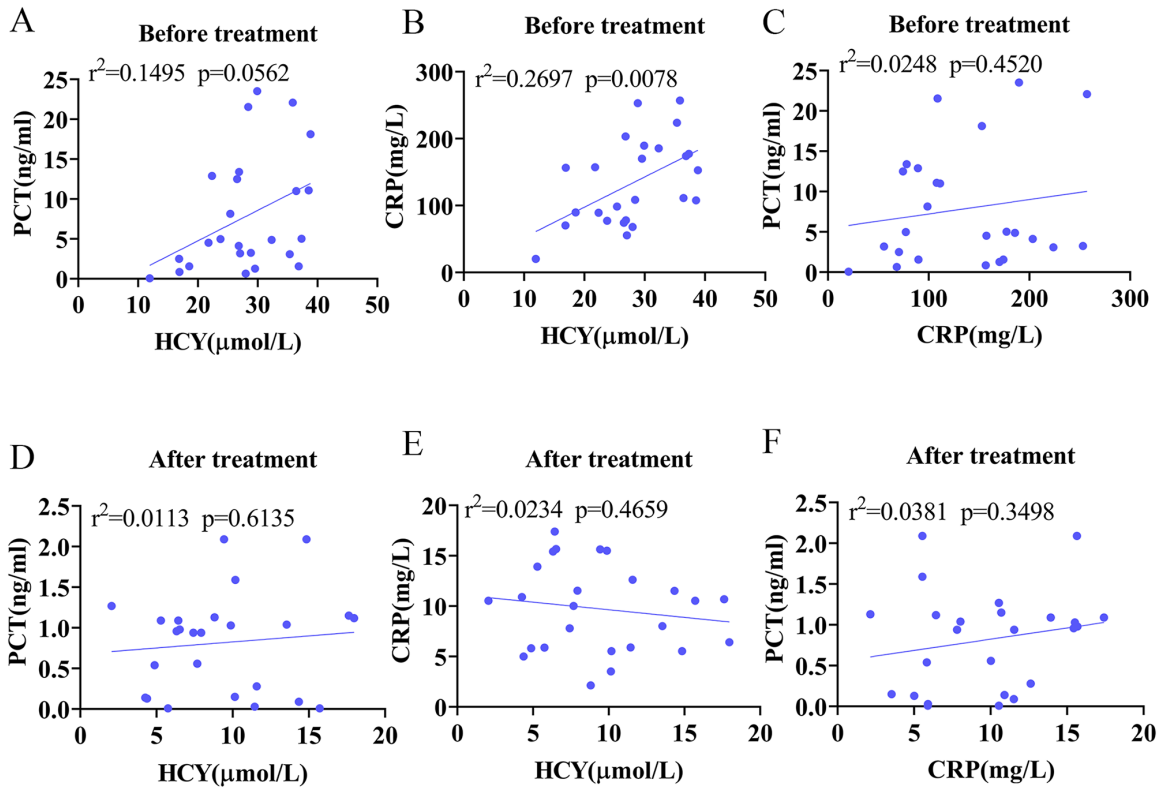

Figure 5. Correlation between HCY and PCT before treatment in perforation of the digestive tract (A). Correlation between HCY and CRP before treatment in perforation of the digestive tract (B). Correlation between CRP and PCT before treatment in perforation of the digestive tract (C). Correlation between HCY and PCT after treatment in perforation of the digestive tract (D). Correlation between HCY and CRP after treatment in perforation of the digestive tract (E). Correlation between CRP and PCT after treatment in perforation of the digestive tract (F).

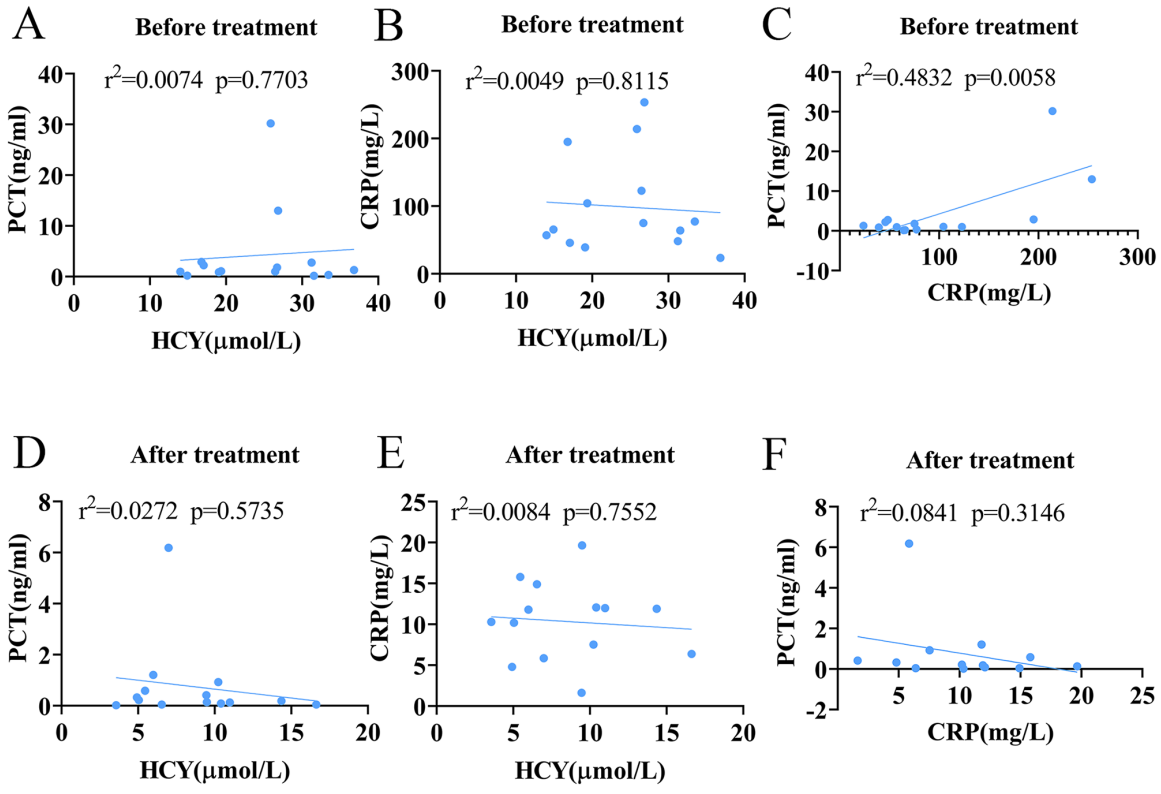

Figure 6. Correlation between HCY and PCT before treatment in cholecystitis (A). Correlation between HCY and CRP before treatment in cholecystitis (B). Correlation between CRP and PCT before treatment in cholecystitis (C). Correlation between HCY and PCT after treatment in cholecystitis (D). Correlation between HCY and CRP after treatment in cholecystitis (E). Correlation between CRP and PCT after treatment in cholecystitis (F).

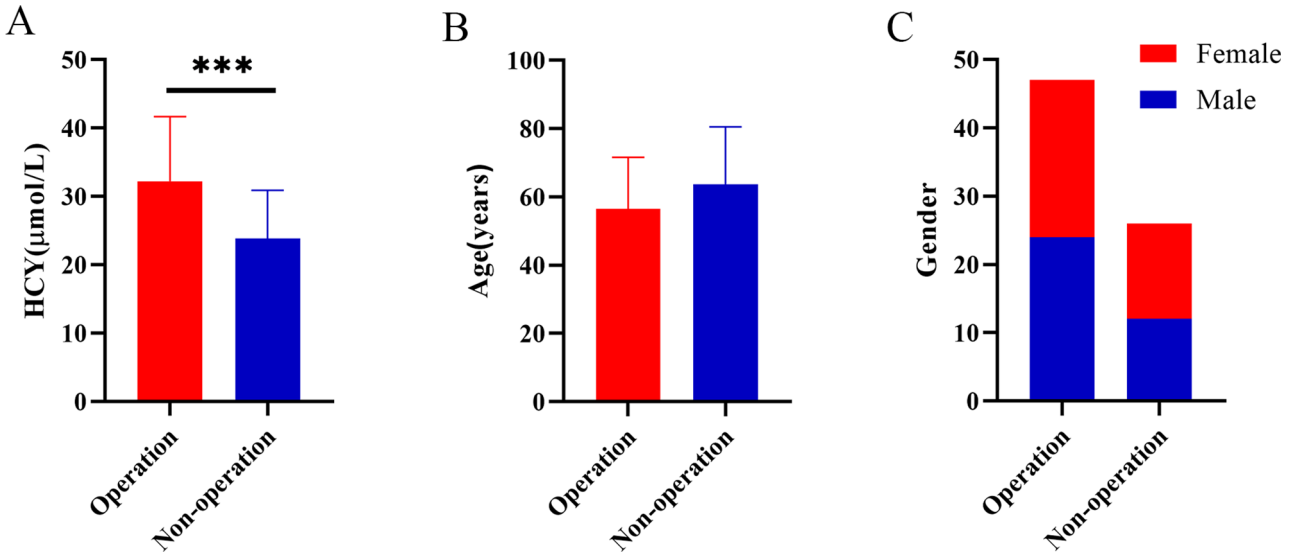

Figure 7. Comparison of HCY in patients in the operation and non-operation groups (A). Comparison of age and gender in the operation and non-operation groups (B and C).
***$P < 0.001$.

HCY levels between the non-operation group and the operation group

The difference was statistically significant in the HCY level between the non-operation group and the operation group in patients with IO ($P < 0.001$) (Figure 7). There was no significant difference in age or gender between the two groups ($P > 0.05$).

Discussion

IO is one of the most common acute abdomens. Accurate diagnosis and prompt initiation of treatment are critical for patients with IO. However, there is a lack of knowledge about specific criteria for the time of surgery. This study investigated the HCY level in patients with IO. As a result, we concluded that the serum level of HCY was increased in patients with IO and that surgery should be started when the serum HCY is elevated.

The intestinal barrier prevents the loss of water and electrolytes and the entry of antigens and microorganisms into the body.[9] In some conditions, such as IO, inflammatory bowel disease (IBD), and total parenteral nutrition (TPN), the intestinal barrier is disrupted, which can lead to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). The intestinal epithelial barrier is composed of a single layer of cells allowing the absorption of microbial and dietary metabolites and limiting the access of harmful antigens and commensal bacteria to the underlying tissues.[10,11] The intestinal epithelial cells at the top of the villi die, and the actively cycling LGR5 + stem cells at the intestinal crypts proliferate to compensate for the lost cells.[12,13] This process generally takes 4–7 days and maintains epithelial integrity and intestinal homeostasis. In some pathological conditions, intestinal homeostasis is disturbed, such as IO. As IO progresses, it results in increased luminal pressure, proximal intestinal lumen distension, and blood gyrus poor flow, causing intestinal epithelial cell ischemia and hypoxia and increasing HCY. After that, intracellular structure destruction and intestinal mucosal membrane permeability increase. Finally, bacteria and toxins can enter the body through the barrier.

HCY is a sulfur-containing amino acid that can participate in the metabolism of methionine.[14] Methionine is the sole source of HCY, which can reform methionine (remethylation pathway) or be metabolized to Cys (trans-sulfuration pathway), or can cyclize to form homocysteine thiolactone (HTL). Elevated levels of plasma HCY, called hyperhomocysteinemia (HHCY), have been implicated in cytotoxic, proinflammatory, and proatherogenic effects linked to CVD, diabetes, inflammatory bowel disease and non-alcoholic seatohepatitis (NASH).[15–18]

The underlying mechanism for the relationship between HCY and inflammation in IO may be due to the destruction of the intestinal barrier induced by obstruction, which leads to bacterial entry into the blood. Based on the current literature, HCY might play an important role in the pathogenesis of IO. To test the above idea, we examined the relationship between plasma HCY and common clinical inflammatory factors, such as CRP and PCT. CRP and PCT are non-specific inflammation markers, and CRP and PCT levels are dramatically increased when an individual is exposed to infection or tissue damage. Clinical practice has shown that CRP and PCT are directly involved in inflammation. Our results analysis shows that HCY is related to abdominal infection, including IO, gastrointestinal perforation, appendicitis, and cholecystitis. In addition, CRP and PCT levels also changed in the four above diseases before and after treatment. However, there were positive correlations between the HCY level and CRP and PCT before treatment only in patients with IO. This might be caused by the IO-induced intestinal epithelial cell ischemia and hypoxia. The difference with regard to degree of infection in the four diseases might be caused by the different pathogenesis or cohort size of four diseases.

To further explore whether the HCY level could be an indicator of the time to surgery, we compared the different HCY expression levels in the operation and non-operation

groups. The HCY expression level in the operation group was significantly higher than that in the non-operation groups in patients with IO ($P < 0.001$) (Figure 4). The above result suggested that HCY might be correlated with the degree of infection. Based on these observations, we suggest for the first time that elevated HCY can predict the aggravation of IO infection conducive to surgical treatment decision-making.

Compared with CRP and PCT, HCY might predict intestinal ischemia earlier, resulting in intestinal mucosal barrier destruction, further leading to flora displacement and bacteremia. Patients eventually need surgery to resolve the obstruction and control the infection. By the observation of HCY, we can find intestinal ischemia earlier for clinical intervention in time, rather than waiting until patients with peritonitis or bacteria through the serosa to the abdominal cavity for intervention. Thus, we can ease patient pain, reduce hospital costs and patients' repeated computed tomography examinations and material consumption, shorten the average length of stay, and eventually benefit patients.

There were also several limitations in this study. First, the cohort size of this study was small. Second, this study lacked follow-up results of serological indicator in patient after treatment. Further studies are needed to objectively identify the extent of IO by visualizing serum HCY expression.

In conclusion, the serum levels of HCY were increased in patients with IO, and HCY was positively correlated with PCT and CRP, which could be used as biochemical indicators for inflammation. More importantly, serum HCY might be a valuable marker for predicting aggravation of infection in patients with IO.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation of the studies, analysis of the data, and review of the manuscript. YLZ and RML conducted the experiments; XG, WTZ, BQL, CM, TS, and HX supplied critical reagents; YLZ and BQ wrote the manuscript. All authors read and approved the final manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of Xuzhou Central Hospital (Xuzhou, China). Signed informed consents were obtained from the patients or guardians.

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