Review Article

Procalcitonin and Liver Disease: A Literature Review

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Abstract

Procalcitonin (PCT) is a widely used biomarker for the diagnosis of bacterial infections. It is produced by various organs and the liver is considered to be the most important site of production. Severe liver dysfunction has been shown to influence PCT levels. Patients with no sources of infection who have liver disease are observed to have increased serum levels of PCT, thereby reducing the diagnostic utility and value within this particular patient subset. Here, we have summarized the relationship between PCT and liver disease, including liver cirrhosis, liver failure, and liver transplantation.
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Introduction

Procalcitonin (PCT) is a widely used biomarker for the diagnosis of bacterial infections.[1] It is produced by thyroid C cells, with very low concentration (< 0.05 ng/mL) in the blood of healthy individuals under normal physical conditions.[2] During an inflammatory response, however, and especially those induced by bacterial infections, various tissues and cells can produce and release PCT into the bloodstream.

Serum PCT level increases during bacterial infections but usually remains low during viral infections and nonspecific inflammatory diseases. As such, serum PCT is recognized to be an important biomarker for bacterial infections. For example, PCT has diagnostic value for bacterial infections in advanced liver disease and spontaneous bacterial peritonitis (SBP). Recent studies have shown that the concentration of PCT can reflect hepatocellular injury and that the severity of liver disease might also influence the diagnostic value of PCT for infections.[3]

The findings from recent studies have been summarized below.

Severe liver diseases and PCT

PCT production

Initially, high levels of PCT were observed in thyroid surgery patients, which drove a common consensus that the synthesis of PCT took place in thyroid tissues.[4] Later, it was discovered in a baboon model of septic shock that PCT production was almost undetectable when the liver was resected, indicating that the liver was the main source of PCT during infection.[5] Various tissues, including the liver, lungs, kidneys, adrenal glands, prostate gland, small intestines and testes as well as peripheral blood mononuclear cells and granulocytes, have been shown to produce PCT. However, the liver is still the most significant site of PCT production.

During the early stages of proinflammatory conditions, PCT is secreted by cytokine-activated macrophages while interacting with endothelial cells.[6] Driven by a sustained concentration of proinflammatory mediators in the blood, further PCT production and release are initiated in the parenchyma of a variety of organs, resulting in a 10,000- to 100,000-fold increase of PCT plasma concentration.[7]

PCT levels in advanced liver diseases

Theoretically, liver diseases should affect the synthesis of PCT and therafter decline its production in blood concentration. However, clinical observations have revealed that serum PCT levels of patients with steatohepatitis and simple steatosis were similar to control groups.[8] However, in patients with advanced liver diseases, baseline PCT levels were observed to rise even when bacterial infections were absent, suggesting a more complex relationship between liver and PCT. Serum PCT levels were also reportedly higher in uncomplicated cirrhosis patients without established bacterial infection, regardless of the causes and the severity of cirrhosis.[9]

Rule et al.[10] found that PCT values from patients with chronic liver disease (0.104 ng/mL) significantly differed from those in patients with acute liver failure (ALF) (2.0 ng/mL). And, the PCT concentrations in most ALF patients were near or above a cut-off that generally indicates severe sepsis. Sugihara et al.[11] also discovered that serum PCT levels were significantly higher in patients with ALF compared to patients with non-ALF (0.25 (0.13–2.66) ng/mL vs. 0.165 (0.03–1.08) ng/mL, $p < 0.01$). They suggested that with a PCT cut-off

value of 0.5 ng/mL, ALF could be demonstrated to be present with low sensitivity (37.5%), high specificity (96.5%) and high positive (85.7%) and negative (72.9%) predictive value.

PCT levels in liver transplant patients also exhibit dynamic changes. Generally, it shows an initial rise before falling gradually and usually takes 7 days post-surgery to reach a low level of PCT.[12,13] In fact, it is not uncommon to observe an increase in PCT levels in patients with noninfectious diseases. Such observations are usually made in cases of more critical diseases, such as acute ischemic stroke[14] and congestive heart failure.[15] From the aforementioned studies, it is shown that in patients without infectious liver disease, a raised PCT is only seen in advanced liver diseases, such as in liver failure and decompensated liver cirrhosis.

Causes for PCT level increase

There are several potential causes for increases in PCT levels observed in patients with advanced liver disease (Fig. 1).

Endotoxin: Endotoxin, a lipopolysaccharide present in the outer cell membrane of Gram-negative bacteria, can be recognized by the host Toll-like receptor 4, a transmembrane receptor expressed in different immune cells, such as neutrophils, monocytes, macrophages, and dendritic cells.[16] On activation, these cells produce inflammatory mediators (e.g., the tumor necrosis factor (TNF) and interleukin (IL)-1beta, IL-6, IL-8, IL-10), which leads to the induction of a variety of inflammatory processes.[17,18] During the early stages of proinflammatory conditions, PCT is secreted by
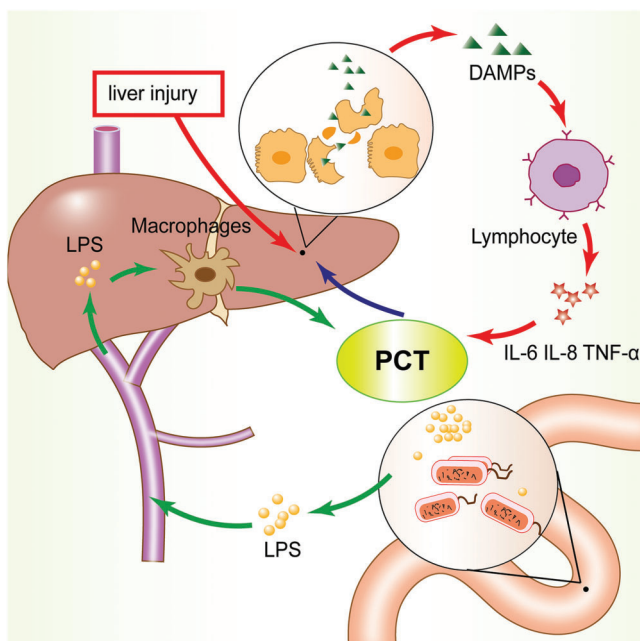
Fig. 1. Possible pathophysiological mechanisms of the relationship between PCT and liver damage. Endotoxin: The endotoxins are directly released into the circulation through the small intestines and the colon, raising blood concentration levels and resulting in the synthesis of a large amount of PCT. DAMPs: Liver injury results in the death of a vast amount of liver cells, releasing DAMPs. DAMPs, through sensors and effector cells, release IL-6, IL-8 and TNF-α, that can induce the expression of PCT. The vicious cycle of PCT and liver cell damage: A rise in PCT accelerates cell damage and results in a vicious cycle. Abbreviations: DAMPs, damage-associated molecular patterns; IL, interleukin; PCT, procalcitonin; TNF, tumor necrosis factor.

cytokine-activated macrophages while interacting with endothelial cells.[6]

In patients with liver transplantation, during the anhepatic phase, endotoxins are directly released into the circulation through the small intestines and the colon, raising blood concentration levels. At the same time, the liver's capability to eliminate endotoxins is reduced after the transplant, resulting in the synthesis of a large amount of PCT.[13,19,20] Due to damage of the intestinal barrier, patients with cirrhosis and liver failure also suffer from endotoxemia, which may then result in increased synthesis of PCT.

Damage-associated molecular patterns (DAMPs): DAMPs are a range of intracellular molecules with immuno-modulatory activity. Liver injury results in the death of a vast amount of liver cells, releasing DAMPs in the process. In return, DAMPs, through sensors and effector cells, release mediators and biomarkers with impact on liver function. The process is not specific to the liver.[21] Other organs like brain, lung and kidney, and systems like cardiovascular, gut and micro-circulation, release DAMPs and are also affected by such. The DAMPs induce autoimmunity or immune tolerance through the pattern recognition receptor [21,22] and share the same sensors and effector cells as pathogen-associated molecular patterns. The activation of the downstream pathway of DAMPs/pathogen-associated molecular patterns may cause systemic inflammation.[21]

High levels of IL-6, IL-8, and TNF-α indicate the presence of systemic inflammation.[23] Furthermore, a significant rise in IL-1β and TNF-α can induce the expression of PCT.[24,25] Liver cell damage and inflammatory response may be the reason behind the positive correlation between PCT levels and severity of liver diseases. This can partially explain the mechanism behind the increased PCT levels in patients with liver failure.

The vicious cycle of PCT and liver cell damage: A rise in PCT also accelerates cell damage and results in a vicious cycle. Research by Sauer and Doss[26] found that even a very low level of serum PCT (starting at 0.25 ng/mL) can initiate a dose-dependent cell lysis, as evidenced by high and increasing levels of lactate dehydrogenase in cell culture supernatant (2.04 ± 0.07-fold *vs*. control, $p < 0.001$). The study also showed that PCT, in a dose-dependent manner, is capable of affecting all qualities of cellular functions, such as proliferation, induction of cell death, metabolism, integrity, microalbumin synthesis, and detoxification capacity to only half of that of control cells (0.46 ± 0.14-fold vs. control for 0.01 ng/mL, $p < 0.001$). This suggests that PCT may be responsible for inducing hepatocyte dysfunction and impairment of cellular integrity. In this way, as part of a vicious cycle of sterile inflammation and liver cell necrosis, PCT may self-propagate its own release into the systemic circulation, resulting in raised PCT levels in patients with advanced liver diseases.

Application of PCT in liver diseases

PCT in predicting prognosis for advanced liver diseases

Liver failure: Liver failure indicates severe liver damage and can be caused by a variety of factors. It results in a severe disorder or decompensation in functions, such as synthesis, detoxification, excretion, and bioconversion, leading to a clinical syndrome which can include coagulopathy, jaundice, hepatic encephalopathy and ascites.[27] The severity of liver failure is correlated with high mortality and thus it is

important to identify biomarkers that will help predict prognosis in these patients.

Sugihara *et al.*[11] found that the cumulative survival rate of patients with liver failure was significantly lower when serum PCT concentrations were ≥0.5 ng/mL. However, PCT was not an independent prognostic factor. Creatinine ≥175 μmol/L, C-reactive protein (CRP) ≥25 mg/L, multisite infection, acute-on-chronic liver failure, and advanced hepatocellular carcinoma were also identified as independent predictors of 90-day mortality in cirrhotic patients with systemic inflammatory response syndrome (commonly known as SIRS). Similarly, another study also demonstrated that a procalcitonin level of ≥1.0 ng/mL can predict the 90-day mortality rate for liver cirrhosis, but only in univariate analysis.[28]

If combined with other markers (i.e. peripheral blood neutrophil, lymphocyte ratio, model for end-stage liver disease (MELD) score, and age), the prognostic value of PCT for liver failure can be improved. Zhou *et al.*[29] found that both age and PCT are positively correlated with MELD scores (i.e. the older the patient, the more concentrated the PCT level and hence a higher MELD score and a higher risk of death). The specificity of the MELD score combined with PCT was 100%, and the positive prediction value was 1.00. PCT also significantly predicted the 90-day survival rate for alcoholic hepatitis. Specifically, the 90-day mortality rate of patients with PCT levels <0.6 ng/mL was 14.9% versus 60% in patients with PCT levels ≥0.6 ng/mL ($p < 0.001$).[30]

However, there are still few studies exploring the relationship between PCT and the prognosis for liver failure. Since a significant increase of PCT levels in patients with liver failure may be related to the DAMPs and inflammatory mediators released after liver damage, PCT may prove a useful biomarker for liver damage. More studies are needed to investigate the value of PCT as a prognostic indicator in patients with liver failure.

Liver transplantation: As for liver transplantation, the survival rate of patients with early post-transplant sepsis is generally low. One study indicated that higher rates of sepsis are correlated with patients who have a pretransplant serum PCT level of >0.5 ng/mL. Therefore, researchers have suggested re-evaluating patient fitness and postponing liver transplant in patients with a pretransplant serum PCT level of >0.5 ng/mL.[31]

PCT as a diagnostic biomarker

Patients with the severe liver disease are prone to having bacterial infections, but often lack significant symptoms in the early stage of infection. Common inflammatory indicators such as white blood cells and neutrophils are easily affected by hypersplenism[32] and so their diagnostic value is limited. There is an urgent need to identify more sensitive biomarkers for diagnosis in this population. PCT is used for the diagnosis of various bacterial infections, such as pneumonia, sepsis, septic shock, and blood infections. However, no agreeable consensus has been made on its clinical value for liver diseases with bacterial infections.

Some scholars have acknowledged the diagnostic value of PCT for bacterial infections in advanced liver disease. Bota *et al.*[33] believe that PCT levels do not differ noticeably between patients with and without cirrhosis and are not related to the severity of cirrhosis. According to research carried out in 2015 among SIRS patients, PCT levels were observed to be higher in those with infection (0.89 ng/mL)

than those without infection (0.35 ng/mL); the cut-off value to rule out infections was 0.25 ng/mL.[30] Another study also confirmed the diagnostic value of PCT for infection in alcoholic hepatitis. In that research, the authors found that a cut-off value of 0.57 ng/mL performed well (with a sensitivity of 79% and specificity at 82%) in the diagnosis of sepsis.[34] A meta-analysis also drew the same conclusions, claiming that PCT is better than CRP in differentiating the causes of infections and systemic inflammatory response.[35]

The diagnostic value of PCT for SBP has been well studied. Cekin *et al.*[36] demonstrated that serum PCT levels were positively correlated with the severity of SBP, and PCT performed better than traditional inflammatory biomarkers, such as CRP, in the prediction of SBP.[36] A cohort from China consisting of 88 advanced cirrhotic patients compared PCT and CRP as diagnostic markers for SBP. The serum CRP levels could not efficiently differentiate patients with SBP from the noninfected controls. However, with a cut-off value of >0.78 ng/mL, PCT was shown to be a good predictor of SBP, with a sensitivity and specificity of 77.5% and 60.4% respectively.

From these findings, serum PCT levels appear to accurately diagnose SBP in advanced cirrhotic patients.[37] A later meta-analysis that included 7 studies and 742 suspected cases of SBP found the following: the 339 confirmed cases of SBP showed that, for the diagnosis of SBP, PCT had a sensitivity of 0.82 and a specificity of 0.86, with an area under the curve of 0.92.[38] Thus, with high positive predictive value and high clinical suspicion, serum PCT can be a relatively sensitive and specific biomarker to help diagnose SBP.

When combined with other biomarkers for infection, PCT can help make a more accurate diagnosis. Cai *et al.*[39] have found serum PCT levels to be a satisfactory early diagnostic biomarker for infection in patients with decompensated liver cirrhosis with ascites. For the combined PCT and white blood cell/platelet measurements, the sensitivity was 76.8% and 83.6% for the diagnosis of infections or SBP in decompensated liver cirrhotic patients with ascites, respectively. A combination of PCT and ascitic albumin also helps improve the diagnostic accuracy for SBP.[40]

In liver transplant patients, although PCT exhibits dynamic changes, Kaido *et al.*[41] discovered that a PCT level >2 ng/mL and <0.5 ng/mL can be used to diagnose or rule-out bacteremia. Hence, identifying a suitable threshold and monitoring serum PCT dynamically can contribute to a faster diagnosis of severe infections after liver transplant. Gur *et al.*[42] drew a similar conclusion. Another article pointed out that the only independent risk factor for post-transplant sepsis is pretransplant PCT levels of >0.5 ng/mL.[31] Hence, some have suggested the use of serial PCT measurements, which may be more reliable than a single measurement in guiding early treatments for infection after organ transplantations.[43]

Limitations of PCT as a biomarker

Some scholars consider the diagnostic value of PCT for infections in cirrhotic patients no better than that of other inflammatory indicators, such as CRP and IL-6. Lin *et al.*[44] claimed that, among cirrhotic patients, the diagnostic value of PCT is lower than IL-6 (for an IL-6 cut-off value of ≥135 pg/mL). For the diagnosis of bacterial infections during the early stages of fever, it was shown that IL-6 has a sensitivity of 94.5% and a specificity of 93.7%, which are significantly higher than that of PCT. Hamed *et al.*[45] discovered that when the cut-off value for CRP is set at 10.5 ng/mL, the

sensitivity and specificity for the diagnosis of infection in patients with liver disease are 91% and 97% respectively, higher than that of PCT (cut-off value: 495 pg/mL, sensitivity: 90%, specificity: 92%). Wang *et al.*[46] also drew a similar conclusion, showing that a cut-off value of 0.59 μg/mL for PCT concentrations in patients during the early stages of liver cirrhosis yielded a sensitivity of only at 61.7% and a high cost to benefit ratio for the diagnosis of infection.

In comparison, IL-6 has a higher sensitivity and a lower cost-to-benefit ratio and its incremental cost-effectiveness ratio is also significantly lower than that of PCT. As a result, IL-6 is considered to be more economical and a better indicator of bacterial infections during the early stages of fever in cirrhotic patients. PCT is also an unsatisfactory biomarker for sepsis during the early phase following liver transplantation, whilst IL-6 performs much better for detecting postoperative bacterial sepsis.[47]

From the above studies, it can be observed that the PCT thresholds for diagnosis of infections in most studies concerning patients with liver diseases are at least 0.5 ng/mL. This value is 10-times the normal threshold. This raises a new question on whether the threshold needs to be raised when diagnosing infections in a population of patients with liver diseases.

Qu *et al.*[3] have discovered a positive correlation between serum PCT and serum total bilirubin (TBIL) level and suggested the diagnostic threshold should be adjusted according to the stages of liver function. Serum TBIL affects the threshold of PCT, as a result, the diagnostic cut-offs of PCT require adjustment according to the state of liver function: when TBIL is <5 mg/mL, the optimum threshold for predicting bacterial infections is 0.38 ng/mL; when TBIL is equal to or greater than 5 mg/mL but under 10 mg/mL, the optimum threshold for PCT is 0.54 ng/mL; and, when TBIL is between 10 and 20 mg/mL or above 20 mg/mL, the thresholds for PCT are 0.61 ng/mL and 0.94 ng/mL, respectively. However, further clinical studies are required to confirm this conclusion.

There are also a number of scholars who deny the diagnostic value of PCT for infections in ALF patients. For instance, Rule *et al.*[10] believe that, in ALF patients, severe necrosis accompanying infections is the cause of the increase of PCT level and that PCT is very poor at picking up nonbacterial infections in ALF patients. Mallet *et al.*[48] suggest that the diagnostic value of PCT for infections in patients with liver failure is related to the cause of disease.

At present, there is still much need for more research with regards to the application of PCT as a diagnostic marker for infection in patients with liver disease. Serial PCT measurements during the first week following liver transplantation are not effective in identifying bacterial infections in patients. Instead, PCT is proposed to be a more useful indicator to use after the first week of liver transplantation.[12]

Conclusions

In summary, although PCT is an efficient biomarker for the diagnosis of infections among the general population, this is not the case for patients with severe liver disease, including liver cirrhosis, liver failure, and liver transplantation. In this group of patients, its diagnostic thresholds and effectiveness need to be reconsidered. PCT alone may not be effective enough to predict the presence of bacterial infections, but combining it with other biomarkers may increase diagnostic value.

A meta-analysis has demonstrated that using PCT to guide the initiation and duration of antibiotic treatments leads to lower mortality risks, reduced antibiotic use and lower risks of antibiotic-related side effects.[49] However, whether PCT carries the same instructive value for the use of antibiotics when treating infection in patients with liver disease requires further exploration. As a result, when making the diagnosis of infections using PCT, it is essential to take into consideration other clinical features and indicators before reaching any clinical decisions. The prognostic value of PCT for liver diseases also requires further exploration.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Writing of the paper (RD, BW), data collection (RD, YZ, SL) and conception of the study and review of the final paper (MW, JH, YW, YW, NZ, YZ).

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