https://doi.org/10.55453/rjmm.2023.126.2.4
The article was received on November 8, 2022, and accepted for publishing on February 2, 2023.

REVIEW

Prognostic Value of Serum Biomarkers in Secondary Peritonitis - A Literature Review

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Abstract: *Background: Infection and sepsis represent major complications after abdominal surgery for secondary peritonitis. Finding new tools that can help identify patients at risk for developing postoperative complications is of the utmost importance for clinicians. We tried to evaluate the use of different biomarkers in evaluating the postoperative prognosis of patients with secondary peritonitis. Methods: We searched the available literature on the usefulness of serum biomarkers in evaluating prognosis in patients with secondary peritonitis. Results: Elevated postoperative lactate levels and high procalcitonin (PCT) levels were associated with negative outcomes. C-reactive protein values increase rapidly in response to the surgical insult but have no value in assessing the overall prognosis. Conclusion: Procalcitonin (PCT) is superior to other biomarkers in predicting severe septic complications and overall mortality in patients with secondary peritonitis.*

Keywords: *biomarkers, peritonitis, C-reactive protein, lactate, procalcitonin, presepsin*

INTRODUCTION

Secondary peritonitis is a condition caused by the spread of bacteria and contents of intraabdominal organs into the peritoneal cavity [1] and is the second leading cause of sepsis in intensive care units worldwide [2]. Overall mortality is 6%, but mortality rises to 35% in patients who develop severe sepsis [2]. Secondary peritonitis requires immediate surgical intervention but after the initial procedure, persisting or new-onset abdominal sepsis continues to be a major problem in the postoperative course [3].

Using clinical symptoms such as fever, tachycardia, tachypnea, non-specific laboratory findings, and scoring systems are valuable tools to assess overall severity and prognosis but will not allow a differentiation between an infectious and non-infectious etiology of a systemic inflammatory response. The clinical assessment of sepsis biomarkers has gained considerable interest in identifying patients at risk for severe complications following surgical intervention for secondary peritonitis [1].

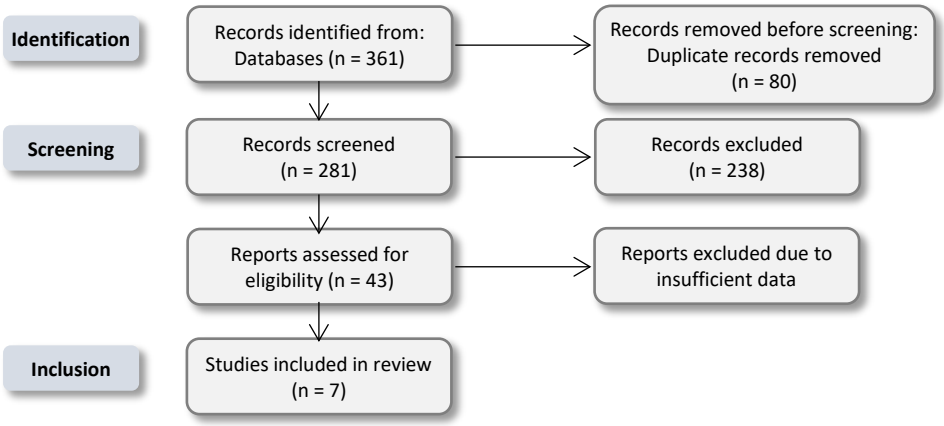
This review aimed to identify the most important biomarkers evaluated in patients with secondary peritonitis and their association with prognosis.

MATERIALS AND METHODS

We searched in three databases using the keywords „peritonitis“ and „prognosis“ in the title or abstract AND specific biomarkers by full name and abbreviated form in full text: lactate, C-reactive protein (CRP), procalcitonin (PCT), presepsin.

Due to the scarcity of the results, a broader search was conducted using the keywords „peritonitis“ AND „biomarker“ to ensure that all relevant literature is covered. The search was last updated on 24/06/2022. A total of 361 publications were primarily retrieved in PubMed, Embase, and Web of Science. No articles were added after manually searching major scientific journals and other references. After excluding 80 duplicates, 281 titles were screened for eligibility and 43 articles were assessed for full-text evaluation. Only English-written human studies were accepted and most articles were excluded due to irrelevancy. We focused only on circulating biomarkers for prognosis in secondary peritonitis. No cut-off point was set for the date of publishing due to the paucity of articles. At the end of the process, seven articles were included in the review. The search strategy is detailed in Figure 1.

Figure 1: Search strategy – identification of studies via databases and registers



OVERVIEW OF THE SELECTED ARTICLES

Seven articles were included in the current review. Four studies were prospective and three were retrospective, and one study included a control group. Biomarkers of interest were lactate, procalcitonin, and C-reactive protein. No study evaluating presepsin was identified. All studies focused on mortality and severity of septic shock induced by secondary peritonitis.

Further details on the selected studies are summarized in Table 1.

SERUM BIOMARKERS CORRELATED WITH PROGNOSIS IN SECONDARY PERITONITIS

Lactate

Lactate is the metabolic end product of anaerobic glycolysis. Approximately 1500 mmol of lactate is produced daily in all tissues, but mostly in skeletal muscle, brain, intestine, and red blood cells [6,9]. The concentration of arterial lactate is a reflection of the delicate balance between net production and clearance. Disturbances in lactate production, clearance, or both lead to hyperlactatemia and it is seen in a variety of conditions such as sepsis, shock, cardiac arrest, tissue hypoxia, burns, or after some pharmacological agents [6].

The prognostic value of lactate in patients with secondary peritonitis was evaluated in four studies. Negi et al. conducted a prospective study to evaluate the utility of arterial lactate measured on admission (AL1) and 24h after surgery (AL24) as well as lactate clearance as prognostic indicators for mortality in patients with secondary peritonitis. The study concluded that mean values of initial lactate, postoperative lactate, and percentage lactate clearance correlated significantly with higher morbidity and mortality [6]. Of these three lactate indices, postoperative lactate (AL24) was the most accurate in predicting morbidity and mortality [6]. Elevated lactate levels persisting postoperatively probably indicate irreversible pathophysiological changes and global tissue hypoperfusion, indicative of poor lactate clearance and higher morbidity and mortality. Andreevich et al., after conducting a retrospective study, concluded that increased lactate levels both before and 72h post-operatively were associated with a negative prognostic[8]. In the study conducted by Suarez-de-la-Rica et al., 24h postoperative lactate concentrations predicted mortality in the Surgical Critical Care Units, but overall mortality was predicted better by concurrent high procalcitonin and lactate peak concentrations [7].

Jung et al. conducted a retrospective study that aimed to compare the performance of the qSOFA score alone with a combined score derived from qSOFA and serum lactate levels for predicting in-hospital mortality for patients with secondary peritonitis. The study results showed that the qSOFA score alone has poor sensitivity and a modest predictive performance in patients with secondary peritonitis [5]. The addition of one point for hyperlactatemia (plasma lactate level > 2.0 mmol/L) resulted in improved sensitivity (5). The use of the qSOFA + lactate score can be useful to assist clinicians in immediately assessing the risk of mortality in patients with secondary peritonitis [5].

Most studies agreed that elevated post-operative lactate levels correlate better with negative outcomes than preoperative lactate levels.

Procalcitonin

Procalcitonin (PCT) is the 116-amino acid pro-peptide of the biologically active hormone calcitonin [10]. The clinical value of PCT assessment in infection and sepsis has been investigated in almost every medical discipline so far. Most studies have shown that, in general, only in the presence of systemic host response to bacterial or fungal stimuli, does PCT concentration rise above the reference range of 0.5 ng/mL. However, new data demonstrated an early production of PCT related to tissue damage after trauma and the magnitude of

the hypovolemic challenge, yet unrelated to infection (4, 10). We analyzed four studies on the usefulness of PCT measurements in predicting negative outcomes in patients with secondary peritonitis. In 246 patients with intraoperatively proven secondary peritonitis of various origins, Reith et al. showed that PCT is a sensitive parameter for the prediction of severe septic complications. Moreover, the study demonstrated that PCT reflects the effectiveness of the surgical procedure in eliminating the septic intra-abdominal focus in the postoperative course (4, 10). PCT was of excellent prognostic value and achieved a sensitivity of 84% and a specificity of 91% in discriminating survivors from non-survivors within the first four postoperative days [4]. Similar observations have been reported in a study conducted by Rau et al. on 82 patients with intraoperatively proven secondary peritonitis. Pro-calcitonin values were elevated in patients who developed septic multiple organ dysfunction syndromes (MODS) with peak levels on the third and fourth days after the onset of symptoms. Comparing the preoperative and postoperative courses, PCT concentrations were significantly elevated in patients with septic MODS during the immediate postoperative course. A persistent procalcitonin elevation beyond the first week after the onset of symptoms was evident in non-survivors, whereas normal concentrations were measured in survivors [3].

Table 1: Studies focused on mortality and severity of septic shock induced by secondary peritonitis

Author	Study design	Biomarker	No. of patients	Correlation with prognosis
Akcay et al (2014)	prospective	procalcitonin (PCT), C-reactive protein (CRP)	84	Serum PCT levels follow a falling trend after surgery as long as the postoperative course remains uneventful. PCT was a better marker than CRP in following postoperative complications and overall prognosis.
Reith et al (2000)	prospective	procalcitonin (PCT), C-reactive protein (CRP)	246	A reduction in the PCT concentration correlated with improvement in the infection and sepsis and was found in all surviving patients. Compared with the values for CRP, PCT showed significant differences between survivors and patients who died, while CRP did not [4].
Rau et al (2007)	prospective	procalcitonin (PCT), C-reactive protein (CRP)	82	The cumulative analysis of all PCT and CRP values measured in the first, second, and third to fourth weeks identified persisting PCT levels greater than 1 ng/mL as an excellent means to assess the overall outcome. Irrespective of the interval, PCT was significantly better than CRP in assessing overall prognosis [3].
Jung et al (2018)	retrospective	lactate	457	The qSOFA score alone has poor sensitivity and a modest predictive performance in patients with secondary peritonitis. The addition of one point for hyperlactatemia (plasma lactate level > 2.0 mmol/L) resulted in improved sensitivity. The use of the qSOFA + lactate score will assist clinicians in immediately assessing the risk of mortality in patients with secondary peritonitis [5].
Negi et al (2020)	prospective	lactate	224	Mean values of initial lactate, postoperative lactate, and percentage lactate clearance were found to correlate significantly with higher morbidity and mortality in patients with secondary peritonitis. Of these three lactate indices, postoperative lactate was the most accurate in predicting morbidity and mortality [6].
Suarez-de-la-Rica et al (2014)	retrospective	lactate, C-reactive protein (CRP), procalcitonin (PCT)	221	Both PCT and lactate provided early prognostic information, more accurate than clinical scores, for overall mortality [7].
Andreevich et al (2021)	retrospective	lactate, C-reactive protein (CRP)	136	Increased lactate and CRP values both before and 72 h after surgery were associated with negative prognostic. PCT value before surgery was insignificant and only an increase in PCT 72h after surgery was associated with a negative outcome [8].

In a prospective study conducted on 84 patients, Akcay et al. were able to demonstrate that serum PCT levels follow a falling trend after surgery as long as the postoperative course remains uneventful. In addition, they showed that after the surgical intervention PCT was a better marker than CRP in following postoperative complications and overall prognosis in patients with secondary peritonitis [1].

Suarez-de-la-Rica et al. compared the prognostic value of lactate, procalcitonin, and c-reactive protein. Peak lactate (>1,8 mmol/L) and PCT (>100 ng/mL) concentrations were associated with mortality, but peak PCT level was the best biomarker for overall mortality. In this study, concomitant high peak lactate and peak PCT concentrations considered as a single dummy variable were highly predictive of overall mortality [7].

C-Reactive Protein

C-reactive protein (CRP), named for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumoniae, was the first acute-phase protein to be described [11]. CRP is an evolutionarily conserved protein. From arthropods to humans, CRP has been found in every organism where its presence has been sought [12].

C-reactive protein is a useful marker of systemic inflammation without discriminating infection from other inflammatory processes [7]. When it comes to the value of CRP in evaluating prognosis in patients with secondary peritonitis, after searching the available literature, we found five studies that included this biomarker. All studies agreed that measured CRP values, which increase rapidly in response to the surgical insult, had no value in assessing overall prognosis. C-reactive protein did not reveal any differences between patients with or without septic MODS or in non-survivors and survivors in the perioperative course [3].

CONCLUSIONS

Although a multitude of biomarkers is elevated in patients with secondary peritonitis in the perioperative course, only a few are reliable parameters for assessing the course and prognosis in this category of patients. Many studies have clearly shown that procalcitonin (PCT) is superior to other biomarkers in predicting severe septic complications and overall mortality. In combination with careful clinical patient assessment, PCT offers distinct advantages for the evaluation of response to treatment and prediction of outcome in patients with secondary peritonitis. In regards to the fact that procalcitonin is a well-known „sepsis“ parameter, this may not embrace the real properties of PCT, which remain to be defined.

Further studies must be conducted to obtain more knowledge about the importance of serum biomarkers in patients with secondary peritonitis and their correlation with prognosis.

Conflicts of interest and sources of funding
The authors declare no conflict of interest.

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