

## Correlation between C-Reactive Protein Level and Blood Urea Nitrogen-Creatinine Ratio in COVID-19 Patients

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### ABSTRACT

Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). C-Reactive Protein (CRP) is an inflammation marker that increases significantly in COVID-19 patients. SARS-CoV-2 can affect kidney function and increase the Blood Urea Nitrogen (BUN)-creatinine ratio. The previous study showed that CRP and BUN-creatinine ratios could be used as predictors of the severity and survival of COVID-19 patients. This study aimed to determine the correlation between CRP levels and the BUN-creatinine ratio in COVID-19 patients. A retrospective cross-sectional study was conducted on 34 COVID-19 patients who were diagnosed by PCR test at Dr. Kariadi Hospital, Semarang from March to September 2020. The Spearman correlation test was used for statistical analysis. The median CRP value was 4.59 (0.36-27.48) mg/L and BUN-creatinine ratio was 15.06 (5.79-37.04), while the correlation between CRP and BUN-creatinine ratio showed  $p=0.003$  and  $r=0.502$ . There was a moderate positive correlation between CRP level and BUN-creatinine ratio. C-reactive protein plays a role in the infiltration process of inflammatory cells and increases adhesion molecules, which can directly or indirectly damage kidney function. SARS-CoV-2 can enter the kidney directly through the ACE-2 receptor and activate the renin-angiotensin-aldosterone system, which will increase water and sodium absorption in the renal tubules, passive reabsorption of BUN, and creatinine filtration in the glomerulus resulting in increased BUN-creatinine ratio.

**Keywords:** COVID-19, CRP, BUN-creatinine ratio

### INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). COVID-19 was declared by the World Health Organization (WHO) as a pandemic on March 11, 2020.<sup>1-3</sup> The virus was first found in pneumonia patients in Wuhan, Hubei, China in December 2019 and was identified as a new strain of coronavirus. COVID-19 was first reported in Indonesia on March 2, 2020.<sup>1,2</sup> On July 27, 2020, more than 15 million people were confirmed positive for COVID-19 with a death toll of 640,016 worldwide.<sup>4</sup> Most cases occurred in males (51.4%), age of 30-79 years, and the least cases occurred at the age of <10 years (1%). Common signs and symptoms of COVID-19 include symptoms of acute respiratory distress such as fever, cough, and shortness of breath. In severe cases, it can cause pneumonia, kidney failure, and even death.<sup>1</sup>

Cytokines and inflammatory markers increase in large numbers in SARS-CoV-2 infection. If left untreated, inflammation will get out of control and there will be a cytokine storm that can lead to Acute

Respiratory Distress Syndrome (ARDS), sepsis, and other complications. C-Reactive Protein (CRP) is one of the inflammatory markers, which significantly increase in COVID-19 patients. Several studies have shown that CRP is a parameter that can be used as a predictor of the severity and survival of COVID-19 patients.<sup>5,6</sup>

The coronavirus enters the body's cells through the Angiotensin-Converting Enzyme-2 (ACE-2) receptor. These receptors are widely expressed in the lower respiratory tract such as type II alveolar cells (AT2) from the lungs, upper esophagus, enterocytes, cholangiocytes, myocardial cells, renal proximal tubular cells, and bladder epithelial cells.<sup>2,3,7</sup> Organs that can express ACE2 receptors not only cause breathing problems, but also disorders in other organs including the kidneys of COVID-19 patients.<sup>8</sup> The expression of ACE-2 in the kidneys was found to be 100 times higher than in the lungs based on RNA sequencing data in the existing tissues. Research by Naiker *et al.* found the presence of SARS-CoV-2 in the urine of COVID-19 patients. This supports that the kidney is one of the target organs of the coronavirus.<sup>9</sup>

SARS CoV-2 can affect kidney function and cause an increase in the ratio of Blood Urea Nitrogen (BUN) to creatinine through activation of the renin-angiotensin-aldosterone system. The blood urea nitrogen-creatinine ratio is a routine, simple, and rapid laboratory test. Several previous studies have shown this ratio is better at predicting the development of acute renal failure than a single measurement of BUN or serum creatinine levels. Research by Ok *et al.*, and Liu *et al.* showed that the BUN-creatinine ratio can be used as a predictor of severity and survival in COVID-19 patients.<sup>10,11</sup>

This study was conducted to prove the relationship between CRP levels and the BUN-creatinine ratio in COVID-19 patients. This research has never been performed and is expected to be a marker and predictor of worsening condition and death in COVID-19 patients.

## METHODS

An observational analytical study with a cross-sectional approach was carried out on patients diagnosed with COVID-19 by PCR test who were treated at Dr. Kariadi Hospital, Semarang from March to September 2020. Inclusion criteria were male patients, aged 35-60 years, liver function test results within the reference range (ALT < 60 U/dL, AST < 35 U/dL), and normal body temperature (36.4°C-37.2°C). Exclusion criteria were patients with malignancy, patients with chronic kidney disease, and a history of kidney transplantation. This research has received ethical permission from the Medical and Health Research Ethics Committee of Dr. Kariadi Hospital Semarang with the number 638/EC/KEPK-RSDK/2020.

The data on CRP protein levels and the BUN-creatinine ratio of patients were collected and processed using the SPSS Statistics IBM version 25 program. Descriptive analysis (distribution, frequency and mean) and hypothesis testing were used for statistical analysis. The data normality was

determined using the Shapiro-Wilk test. The data of BUN, CRP, and BUN-creatinine ratios were not normally distributed; therefore, data transformation was carried out. The correlation between CRP and the ratio of BUN to creatinine in COVID-19 patients was determined using the Spearman correlation test.

## RESULTS AND DISCUSSIONS

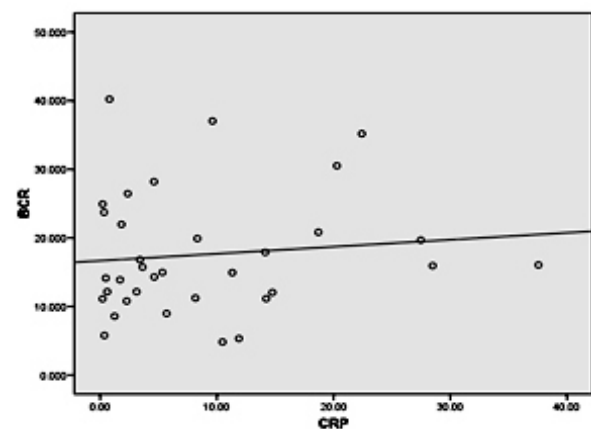
The characteristics of research subjects can be seen in Table 1.

**Table 2.** The correlation test results between CRP and BUN-creatinine ratio

Variable	BUN-Creatinine Ratio		Interpretation
	p	r	
CRP <sup>φ</sup>	0.003*	0.502	Significant, positive, moderate

<sup>φ</sup> Spearman's Rho, \*p < 0.05

The results showed that there was a moderate positive correlation between CRP and BUN-creatinine ratio.



**Figure 1.** Scatter diagram of the correlation between CRP and BUN-creatinine ratio

**Table 1.** Characteristics of research subjects (n=34)

Variable	Mean±SD	Median (min-max)
Age (years)	50.00±7.80	51 (36-60)
AST (U/dL)	28.18±5.56	28.5 (16-34)*
ALT (U/dL)	35.97±14.36	36.5 (13-59)*
Blood urea nitrogen (mg/dL)	20.30±10.49	16.67 (6.94-52.32)*
Creatinine (mg/dL)	1.22±0.56	1.09 (0.59-3.7)*
BUN-creatinine ratio	17.26±7.49	15.06 (5.79-37.04)*
CRP (mg/L)	7.07±7.01	4.59 (0.36-27.48)*

Abbreviations: SD (Standard Deviation); min (minimum); max (maximum), \*Abnormal distribution AST, Aspartate Transaminase; ALT, Alanine Transaminase; CRP, C-Reactive Protein

The results of this study on CRP levels showed increased CRP levels in COVID-19 patients. C-reactive protein is an acute-phase protein that is mainly produced in the liver and is increased in conditions of inflammation, infection, and tissue damage. The increase in CRP levels in COVID-19 patients is induced by the production of large amounts of proinflammatory cytokines and tissue damage. Several other studies also suggest that kidney damage is directly related to CRP levels in the blood. C-reactive protein levels were found to be higher in patients with severe degrees compared with mild to moderate degrees with an AUC value of 0.858 in the study of Liu.<sup>12,13</sup> In addition to its known role as a marker of inflammation, CRP is also known as a pathogenic mediator of angiotensin II, which can induce cardiovascular disease, diabetic kidney disease, and obstructive nephropathy by increasing the signaling Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) in tubular epithelial cells. Transforming growth factor- $\beta$  will inhibit the proliferation of tubular epithelial cells by inhibiting the transition of the G1 to S phase in the cell cycle and increasing the inflammatory state in the kidney.<sup>14</sup> C-reactive protein also plays a role in the infiltration of inflammatory cells, activates the coagulation cascade, and increases adhesion molecules that directly or can indirectly damage the function of the kidneys resulting in an increased BUN-creatinine ratio.<sup>15</sup>

Both BUN and creatinine are end products of nitrogen metabolism in the body. Blood urea nitrogen and serum creatinine can be easily filtered by nephrons because of their small size. Blood urea nitrogen, serum creatinine, and BUN-creatinine ratio are parameters that can indicate kidney function that can be routinely measured and easily obtained. This study showed increased BUN-creatinine ratio in COVID-19 patients. This was following a study by Liu *et al.*, which found a higher BUN-creatinine ratio in COVID-19 patients compared to the general population. In addition to CRP, kidney function in COVID-19 patients can also be affected by the coronavirus itself. SARS-CoV-2 can enter kidney cells directly via the ACE-2 receptor and activate the renin-angiotensin-aldosterone system. This system increases the absorption of water and sodium in the renal tubules and causes passive reabsorption of blood urea nitrogen. These systemic effects cause renal vasoconstriction, decreased glomerular filtration, and decreased excretion of BUN. Creatinine will be filtered through the glomerulus and not reabsorbed, resulting in an increased BUN-creatinine ratio.<sup>10,11,16</sup>

This study showed that there was a moderate

positive correlation between CRP levels and BUN-creatinine ratio with  $p < 0.003$  and  $r = 0.502$ . This suggests that inflammation with higher severity will affect kidney function in COVID-19 patients. The moderate correlation in this study might be caused by various factors. A history of chronic illness and secondary infection in some cases might affect the increasing serum CRP levels in addition to the SARS-CoV-2 infection itself. However, data collection in this study did not distinguish the severity of the patients that it might lead to selection bias.

No data presented on other factors that can affect BUN levels, such as high protein diet, parenteral nutrition, protein catabolism status, steroid administration, and gastrointestinal bleeding remains the limitation of this study.

## CONCLUSIONS AND SUGGESTIONS

This study showed a moderate positive correlation between CRP and BUN-creatinine ratio. Increased levels of these parameters in COVID-19 patients were expected to be used for early detection of kidney function disorders and as a consideration in patient management. Further research needs to be performed by considering confounding factors that can affect blood urea nitrogen levels, such as high protein diet, parenteral nutrition, protein catabolism status, steroid administration, and gastrointestinal bleeding.

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