

Banjarmasin Ulin Hospital is the main referral hospital in South Kalimantan. This research, especially in South Kalimantan, has never been done before, so this research is expected to be representative of the South Kalimantan region. The importance of understanding the biomarkers of gastrointestinal manifestations can help early diagnosis which will reduce morbidity and mortality.

Methods

This study is an observational study using a cross-sectional design to determine the correlation between CRP, TLC, and NLR levels and gastrointestinal manifestations in COVID-19 patients.

This research was conducted at the ULIN Banjarmasin Regional General Hospital in 2020–2022. The population in this study were patients with confirmed COVID-19 using the RT-PCR swab method who had CRP, NLR, and TLC data. The inclusion criteria for this patient were medical record data for patients aged 18–70 years, medical record data for patients with confirmed COVID-19 using the PCR swab method for the period April 2020–April 2021, and medical record data of patients with gastrointestinal symptoms as the main complaint in the form of decreased appetite, diarrhea, nausea, vomiting, and abdominal pain. Exclusion criteria in this study were medical record data of immunocompromised patients (pulmonary TB, HIV, and malignancy), medical record data of patients with chronic inflammatory disorders (chronic liver disease, chronic kidney disease, and gastrointestinal malignancy), and incomplete patient medical record data.

The independent variables in this study were TLC, NLR, and CRP levels (related/unrelated), the dependent variable was patients who were confirmed positive for COVID-19 with gastrointestinal manifestations.

The data collected are tabulated. Data on patient characteristics were analyzed using descriptive analysis to determine whether the characteristics of the two groups in the study were the same or different. Bivariate analysis using the Chi-square test (if there are cells <5) was carried out to determine the correlation between CRP, TLC, NLR, and gastrointestinal manifestations on a nominal scale in COVID-19 patients.

Results

The number of samples in this study was 88 subjects. The data that have been collected is checked first to ensure that all subject data has been filled in. The

descriptive analysis presented in this study is based on age, gender, and gastrointestinal manifestations.

Based on gender, Table 1 shows that the majority of participants in this study were male, namely 64 (72.7%) participants, while 24 (27.3%) participants were female. The results of the bivariate analysis showed that gender did not affect appearance of gastrointestinal symptoms in COVID-19.

Based on age, Table 1 shows that the mean and median age in the symptomatic gastrointestinal (GI) groups were 52.68 + 10.58 and 53 (24–69) years, while in the asymptomatic group (without gastrointestinal symptoms), the mean and median age participants were 50.68 + 10.78 and 51 (20–69) years. Participants aged >60 years were 1.56 times more likely to experience gastrointestinal symptoms in COVID-19 than participants aged 18–60 years ($p = 0.589$).

Participants who had a history of diabetes mellitus with gastrointestinal symptoms and without gastrointestinal symptoms were 7 people (15.9%) and 8 people (18.2%). Participants who had a history of hypertension with gastrointestinal symptoms and without gastrointestinal symptoms were 10 people (22.7%) and 14 people (31.8%). In subjects with gastrointestinal symptoms, none of the subjects had a history of coronary heart disease (CHD). In the group without gastrointestinal symptoms, there were 3 subjects (6.8%) who had a history of CHD. Participants in both groups had no history of stroke. Participants with gastrointestinal symptoms and without gastrointestinal symptoms who had smoking habits were 8 people (18.2%) and 6 people (13.6%). History of diabetes mellitus, hypertension, CHD, and smoking did not have a significant effect on the appearance of gastrointestinal symptoms in COVID-19 infection (Table 1).

In this study, Figure 1 shows that gastrointestinal symptoms were often found in COVID-19 patients, mainly in the form of nausea and vomiting in 30 participants (68.2%), diarrhea in 11 participants (25%), followed by a decrease in appetite and abdominal pain in 7 participants (15.9%) each.

Based on Table 2, decreased TLC was found in 31 participants (70.5%) in the group with gastrointestinal symptoms and 24 subjects (54.5%) in

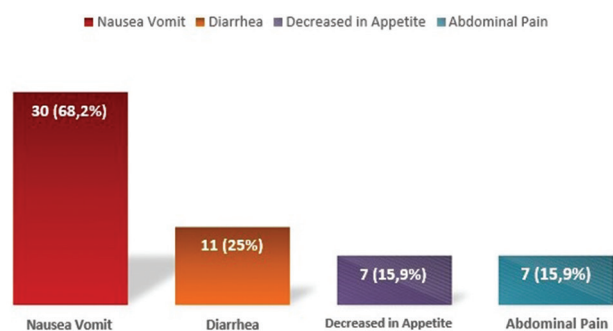


Figure 1: Gastrointestinal manifestation

Table 1: Characteristics of research subject data

Characteristics (n=88)	Gastrointestinal manifestations		OR (95% CI)	p-value
	With, n (%)	Without, n (%)		
Gender				
Man	32 (72.7)	32 (72.7)	1.000 (0.391–2.556)	1.000
Woman	12 (27.3)	12 (27.3)		
Age (years)				
18–60	10 (22.7)	7 (15.9)	1.555 (0.532–4.543)	0.589
>60	34 (77.3)	37 (84.1)		
Diabetes mellitus				
Yes	7 (15.9)	8 (18.2)	0.851 (0.280–2.592)	1.000
No	37 (84.1)	36 (81.8)		
Hypertension				
Yes	10 (22.7)	14 (31.8)	0.630 (0.244–1.627)	0.473
No	34 (77.3)	30 (68.2)		
CHD				
Yes	0	3 (6.8)	-	0.240
No	44 (100)	41 (93.2)		
Stroke				
Yes	0	0	-	-
No	44 (100)	44 (100)		
Smoking				
Yes	8 (18.2)	6 (13.6)	1.407 (0.445–4.456)	0.771
No	36 (81.8)	38 (86.4)		

The value is considered significant if the $p < 0.05$. Categorical data are presented with a frequency distribution value (%). Chi-square/Fisher's exact test (nominal categorical data). OR: Odds ratio, CI: Confidence interval, CHD: Coronary heart disease.

the group without gastrointestinal symptoms. Based on the chi-square test obtained a $p = 0.186$. This value is >0.05 , which means that the hypothesis is not accepted or has the conclusion that TLC levels have no effect on manifestations in COVID-19 patients.

Table 2: Effect of total lymphocyte count on gastrointestinal symptoms

Variable	n (88)	Gastrointestinal symptoms		OR (95% CI)	p-value
		With, n (%)	Without, n (%)		
TLC				1.987 (0.826–4.783)	0.186
Decrease	55	31 (70.5)	24 (54.5)		
No decrease	33	13 (29.5)	20 (45.5)		

*Significant at $p < 0.05$. Categorical data are presented with a frequency distribution value (%). Chi-square/Fisher's exact test (nominal categorical data). OR: Odds ratio, CI: Confidence interval, TLC: Total lymphocyte count.

Based on Table 3, increased CRP was found in 30 participants (68.2%) in the group with gastrointestinal symptoms and 12 participants (27.3%) in the group without gastrointestinal symptoms. An increase in CRP allows participants to experience gastrointestinal symptoms when infected with COVID-19 by 5.71 times compared to participants who do not experience an increase in CRP, which is significant ($p < 0.0001$). This value is <0.05 , which means that the hypothesis is accepted or has the conclusion that CRP has a correlation with gastrointestinal manifestations in COVID-19 patients.

Table 3: Effect of C-reactive protein levels on gastrointestinal symptoms

Variable	n (88)	Gastrointestinal manifestations		OR (95% CI)	p-value
		With, n (%)	Without, n (%)		
CRP				5.714 (2.282–14.309)	$<0.0001^*$
Increase	42	30 (68.2)	12 (27.3)		
No increase	46	14 (31.8)	32 (72.2)		

*Significant at $p < 0.05$. Categorical data are presented with a frequency distribution value (%). Chi-square/Fisher's exact test (nominal categorical data). OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein.

Based on Table 4, there were 30 participants (68.2%) in the group with gastrointestinal symptoms and 19 participants (43.2%) in the group without gastrointestinal symptoms who experienced an increase in NLR. An increase in NLR allows participants to experience gastrointestinal symptoms when infected

Table 4: Effect of neutrophil-to-lymphocyte ratio on gastrointestinal symptoms

Variable	n (88)	Gastrointestinal manifestations		OR (95% CI)	p-value
		With, n (%)	Without, n (%)		
NLR				2.820	0.032*
Increase	49	30 (68.2)	19 (43.2)	(1.180–6.735)	
No increase	39	14 (31.8)	25 (56.8)		

*Significant at $P < 0.05$. Categorical data are presented with a frequency distribution value (%). Chi-square/Fisher's exact test (nominal categorical data). OR: Odds ratio, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio.

with COVID-19 by 2.82 times compared to participants who do not experience an increase in NLR, which is significant ($p = 0.032$). This value is <0.05 , which means that the hypothesis is accepted or has the conclusion that NLR has a correlation with gastrointestinal manifestations in COVID-19 patients.

Because the independent and dependent variables are categorical, in the multivariate analysis a logistic regression test was performed on variables that had a $p < 0.25$ after bivariate analysis was performed, namely CRP and NLR variables (Table 5). The variable that influences the emergence of gastrointestinal symptoms in COVID-19 is the increase in CRP. The greatest strength of the correlation is found in the increase in the CRP odds ratio (OR=5.71).

Table 5: Logistic regression multivariate analysis results

Variable	p-value	OR	CI 95%
CRP			
Increase	0.001*	5.71	2.28–14.31
No increase			
NLR			
Increase	0.178	2.82	1.180–6.735
No increase			

*Signifikan pada $p < 0.05$, Keterangan, Uji Regresi Logistik. OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio.

Discussion

In this study, information was obtained that the majority of subjects were male, totaling 32 people in each group. The results of the bivariate analysis showed that gender did not affect the appearance of gastrointestinal symptoms in COVID-19. The gender factor is associated with increased morbidity, risk severity, and reduced survival rate of COVID-19 patients but has no significant correlation with clinical presentation at initial admission [8].

The mean age in the group with gastrointestinal symptoms in this study was $52.68 + 10.58$ years, while in the group without gastrointestinal symptoms, the mean age of the participants was $50.68 + 10.78$ and $51 (20–69)$ years. In a study conducted by Kaiyasa *et al.* assessing the clinical characteristics of 521 patients with COVID-19 also showed there was no significant difference in age with GI symptoms [8].

This study shows that gastrointestinal symptoms are often found in COVID-19 patients, mainly in the form of nausea and vomiting ($n = 30$; 68.2%) followed by diarrhea ($n = 11$; 25%). Many

reasons can cause nausea and vomiting to be the most common symptoms in patients with COVID-19. Several factors, including viral infection, systemic inflammatory response, drug side effects, and psychological stress, can stimulate the chemoreceptor trigger zone which can trigger nausea and vomiting [9].

Subjects who had a history of hypertension in the group with gastrointestinal symptoms and without gastrointestinal symptoms were 10 people (22.7%) and 14 people (31.8%). In those with gastrointestinal symptoms, there were no subjects with a history of CHD, whereas in the group without gastrointestinal symptoms, there were 3 subjects (6.8%) who had a history of CHD. History of diabetes mellitus, hypertension, CHD, and smoking did not have a significant effect on the appearance of gastrointestinal symptoms when infected with COVID-19 [10]. In a study conducted by Koc in 412 patients, it was found that variant B.1.617.2 more often infects patients with a history of CHD and hypertension, which can increase mortality [11].

In this study, elevated CRP was found in 30 (68.2%) participants with gastrointestinal symptoms and 12 (27.3%) participants in the group without gastrointestinal symptoms. An increase in CRP allows participants to experience gastrointestinal symptoms when infected with COVID-19 by 5.71 times compared to participants who do not experience an increase in CRP, which is significant ($p < 0.0001$). The results of the multivariate analysis stated that the variable that had an effect on the emergence of gastrointestinal symptoms in COVID-19 was an increase in CRP.

In the study by Kaiyasa *et al.*, in 521 COVID-19 patients at the Rashid Dubai hospital, an increase in CRP levels was found, where patients with GI had a significantly increased CRP compared to non-GI [8]. CRP level has a predictive value that can reflect the activity of the inflammatory process [12]. CRP as an acute phase reactant protein can be elevated in high levels during inflammation, endothelial dysfunction, or physical trauma [13]. CRP not only acts as a biomarker of infection and inflammation but is also an important mediator of the inflammatory process. Significantly elevated CRP serum levels in COVID-19 patients may indicate an excessive level of inflammation, which can lead to severe/critical conditions or even death [13], [14].

In this study, there were 30 participants (68.2%) in the group with gastrointestinal symptoms and 19 participants (43.2%) in the group without gastrointestinal symptoms who experienced an increase in NLR. Participants with an increased NLR were 2.82 times more likely to experience gastrointestinal symptoms when infected with COVID-19 than participants who did not experience an increased NLR ($p = 0.032$). The results of this study are in line with the study conducted by Hashem *et al.*, where the NLR was found to be significantly lower in the GI patient group [15].

NLR is assessed as a marker of inflammation

in COVID-19 cases. Systemic inflammation suppresses T-cell-mediated immunity resulting in decreased levels of T lymphocytes. Neutrophils are the first leukocytes to reach the site of viral infection, enter infected cells, and mediate tissue damage and apoptosis of virus-infected cells. Neutrophils stimulate B lymphocytes to initiate humoral immunity. The serum levels of IL-6, IL-8, TNF- α , interferon-gamma, and granulocyte colony-stimulating factor increase after viral infection. These factors activate neutrophils which lead to proliferation and migration of neutrophils to virus-infected sites [16]. Improved NLR results can be used as a strong predictive and prognostic indicator for severe COVID-19.

In this study, decreased TLC was found in 31 subjects (70.5%) with gastrointestinal symptoms and 24 (54.5%) participants in the group without gastrointestinal symptoms. A decrease in TLC allows subjects to experience gastrointestinal symptoms when infected with COVID-19 by 1.99 times compared to participants who do not experience a decrease in TLC, but this is not statistically significant ($p = 0.186$).

There are significant differences in this study which can be caused by:

(1) GI symptoms in COVID-19 patients in this study may not be related to inflammatory reactions and organ dysfunction [17]; (2) There is a correlation between decreased lymphocyte levels in younger COVID-19 patients as compared to older patients [18]. There is a theory that aging of the immune system can contribute to a "non-reactive" state of the immune system, thereby causing a relative decrease in the number of stable lymphocytes, while in younger populations, the decline in highly active lymphocytes can be influenced by several factors, thus contributing to a relatively higher average difference between younger populations [5]; (3) A meta-analysis study by Huang and Pranata showed that lymphopenia is associated with severe COVID-19. In this study, it was not examined regarding the degree of disease severity in COVID-19 patients. This can lead to a bias that causes the decrease in TLC to be insignificant [5].

The limitations of this study are: (1) We did not assess the condition of the degree of COVID-19 at the time of admission, which could affect the variables studied; (2) This study has several confounding variables which are not controlled perfectly; (3) Additional tests in the form of SARS-CoV-2 RNA in the stool of COVID-19 patients were not carried out.

Conclusion

Based on the analysis and discussion of the conclusions given by the researchers in this study, an increase in CRP levels >48 mg/L and levels of NLR

>6, respectively, allowed the subject to experience gastrointestinal symptoms by 5.71 times and 2.82 times when infected with COVID-19, while a decrease in total lymphocyte count <1740 was not proven to have a significant correlation with gastrointestinal manifestations.

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