The Role of Fecal Calprotectin as a Hypoxic Intestinal Damage Biomarker in COVID-19 Patients

by Deasy Natalia Idriana

Submission date: 30-Mar-2022 10:12PM (UTC+0800)
Submission ID: 1796959604
File name: Journal_FC_Deasy_10.03.22_REVISI_5TURNITINN.docx (485.02K)
Word count: 3365
Character count: 20249

The Role of Fecal Calprotectin as a Hypoxic Intestinal Damage Biomarker in COVID-19 Patients

Running title: Fecal calprotectin level and intestinal damage

ABSTRACT

Introduction: Gastrointestinal manifestation in Coronavirus Disease 2019 (COVID-19) appears to be substantial. Fecal calprotectin has been a promising biomarker of notice in COVID-19 associated gastrointestinal inflammation, however, its role in the severity of COVID-19 remains limited. We conducted a study analyzing the relationship between the severity of COVID-19 and hypoxic intestinal damage.

Methods: We assessed the severity of COVID-19 based on the PaO2/FiO2 (P/F) ratio, inflammatory markers were measured from blood samples, and fecal calprotectin was obtained from stool samples.

Results: Median levels of fecal calprotectin in COVID-19 patients were found to be markedly elevated along with the severity of hypoxemia, as seen in non-acute respiratory distress syndrome (ARDS) group 21.4 μg/g (5.2-120.9), mild ARDS 54.30 μg/g (5.2-1393.7), moderate ARDS 169.6 μg/g (43.4-640.5), and severe ARDS 451.6 μg/g (364.5-538.6). We also found significant differences in fecal calprotectin level based on the severity of ARDS (P <0.001) and the difference was still significant although divided into ARDS and non-ARDS groups (P <0.001). We furthermore found a strong negative correlation between the P/F ratio and fecal calprotectin level (r = -0.697, P <0.001).

Conclusion: Our findings support the potential role of fecal calprotectin as a biomarker of intestinal inflammation in COVID-19 as a consequence of hypoxic intestinal damage suggested by reduced P/F ratio.

Keywords: fecal calprotectin, P/F ratio, COVID-19

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). It was declared a pandemic in March 2020 and until the current time remains a global health issue (1–3). COVID-19 presents with various clinical conditions from respiratory disease to extrapulmonary manifestations including in the gastrointestinal system (4,5). It also appears with a wide spectrum ranging from asymptomatic course to severe pneumonia leading to an acute respiratory distress syndrome (ARDS) marked by decreased PaO2/FiO2 (P/F) ratio (6–8). Gastrointestinal symptoms such as anorexia, nausea, vomiting, and abdominal pain are commonly found in around 20-50% of COVID-19 cases; nonetheless, the intestinal injury might occur even without the presence of gastrointestinal symptoms (9–13).

The etiology of gastrointestinal injury in COVID-19 can be both primary and secondary. Primary injury occurs due to direct infection of SARS-CoV-2 in the gastrointestinal system, while secondary injury arises from several conditions (14–18). The injury might be related to hypoxemia marked by decreased P/F ratio that leads to hypoxic intestinal damage. The injury might also occur as a result of dysregulated immune response known as cytokine release syndrome that causes systemic inflammation (19–22). SARS-CoV-2 infection can also lead to hypercoagulability and microcirculatory dysfunction that in turn will instigate ischemia in the tissue, including in the gastrointestinal system (23,24). On the other hand, the inflammation process in the gastrointestinal may also worsen the ongoing systemic inflammation by a mechanism known as intestinal crosstalk (25). This inflammation might also be observed by the endoscopic procedure whose performance is limited during the COVID-19 pandemic due to safety issues (26).

Due to its stability in stool for 5-7 days, fecal calprotectin is a sensitive and noninvasive biomarker of intestinal inflammation (27,28). Interestingly, the concentration of fecal calprotectin as a primarily neutrophilic-specific protein is proportional to the

concentration of neutrophils in the intestinal mucosa whose functions are severely affected by ischemia (26,29,30). Therefore, fecal calprotectin is also potential a biomarker presenting hypoxic intestinal damage in COVID-19 patients.

Studies evaluating intestinal inflammation in COVID-19 cases through fecal calprotectin levels are still limited. Only six studies and one meta-analysis evaluated the subject (23,31–36). Among those studies, only three studies investigated the relationship between the severity of COVID-19 with intestinal inflammation. The three studies used various definitions of disease severity with contradictive analysis results (31,34,35). One study in Italy demonstrated a significant correlation between elevated fecal calprotectin and COVID-19 disease severity characterized by the presentation of pneumonia (34). Another study in Iran also suggested that elevated fecal calprotectin level may be the feature of severe disease with a significant positive association between disease severity and fecal calprotectin level (35). In contrast, the first fecal calprotectin in the COVID-19 study launched in the United States indicated no correlation between the concentration of fecal calprotectin and COVID-19 disease severity (31).

Therefore, we analyzed the association between COVID-19 disease severity based on its degree of hypoxemia measured by P/F ratio and intestinal inflammation caused by hypoxic intestinal damage determined by fecal calprotectin level. In addition, we also observed the characteristics of gastrointestinal manifestations, general symptoms, and inflammatory markers of COVID-19 patients in the Indonesian population.

METHODS

Study Design and Participant

This research was an observational analytic study with a cross-sectional approach. We analyzed the P/F ratio from blood gas analysis and fecal calprotectin from stool samples of 44 patients confirmed COVID-19 based on positive nasopharyngeal SARS-CoV-2 PCR swab with suggestive COVID-19 radiologic appearances (2,37). We included all hospitalized patients from non-ICU COVID-19 isolation units in Dr. Soetomo Teaching Hospital, Surabaya, Indonesia during October to December 2020 fulfilling the inclusion criteria. The exclusion criteria in this research involved those patients with gastrointestinal malignancies, inflammatory bowel disease, cirrhosis, and end-stage renal disease. Written informed consents were obtained from all patients and the study protocol was approved by the ethics committees of Dr. Soetomo Teaching Hospital Surabaya, Indonesia (0065/KEPK/IX/2020). We declare that all procedures contributing to this research comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 (as revised in 2008 and 2013).

COVID-19 disease severity

We obtained the P/F ratio from blood gas analysis collected within the same 24 hours with stool samples for fecal calprotectin. Blood gas from the arterial samples was sent to the laboratory within 15 minutes or stored in 0-4^{O}C. Samples were then analyzed using GEM Premier®. We used the P/F ratio to express COVID-19 disease severity to standardize the degree of hypoxemia in subjects with and without supplementary oxygen; thus, representing the severity of COVID-19 (38,39). We only included subjects with radiologic appearances suggestive COVID-19 to minimize the possibility of decreased P/F ratio due to other etiologies than COVID-19 ARDS. P/F ratio (mmHg) was then divided into categories based on The Berlin Criteria of ARDS (40).

Fecal Calprotectin

Stool samples were collected into clean containers with a minimum amount of 5 g, registered, and stored at 2-8^{O}C for 48 hours or -20OC for more than 48 hours, then used for fecal calprotectin measurement. Samples were analyzed using the PhiCal© Calprotectin enzyme-linked immunosorbent assay (ELISA) kit (Immundiagnostik AG, Stubenwald-Allee 8a, D-64625 Bensheim). Calprotectin samples remain stable in stool for 5-7 days with a reference normal value of <50 µg/g (27,28).

Additional Laboratory Measurements

All other laboratory parameters were obtained within the same 24 hours with the stool samples and determined in the hospital laboratory as a part of routine laboratory analysis. Samples from complete blood count such as leukocyte (/μL), thrombocyte (/μL), and neutrophil to lymphocyte ratio (NLR) were analyzed using Sysmex 1000®. Ferritin (ng/mL) was analyzed by two-site sandwich immunoassay with direct chemiluminometric technology using ADVIA Centaur Ferritin®. D-Dimer (ng/mL) was obtained from serum samples and analyzed using turbidimetric immunoassay using Sysmex CS-2500®. C-Reactive Protein (CRP) was analyzed by a particle enhanced turbidimetric immunoassay using Dimension® Clinical Chemistry System and defined in mg/L.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS® Statistics Version 25 (IBM Corp., USA). Demographic data and clinical characteristics were presented descriptively by frequency and percent for categorical data types (nominal and ordinal). Continuous data (interval and ratio) were shown as mean ± standard deviation (SD) and median (minimum-maximum). Normality test was carried out using the Shapiro-Wilk test. The independent

variable was the P/F Ratio presented as ordinal and ratio data. The dependent variable was fecal calprotectin level presented as nominal and ratio data. Independent t-tests were used to perform comparisons for normally distributed data, while Mann-Whitney and Kruskal-Wallis were used for the analysis of non-normal data. Analysis of association between variables in this study was carried out by correlational numerical analytic test performed by Spearman correlation. *P*-value <0.05 was considered statistically significant with a confidence interval (CI) of 95%.

RESULTS

Patient Demographic and Clinical Characteristics

In this present study of 44 hospitalized COVID-19 patients with suggestive radiologic appearance, 26 patients had negative fecal calprotectin (<50 μg/g) and 18 patients were with positive fecal calprotectin (≥50 µg/g). As shown in Table 1, there was no significant difference in gender between the group of fecal calprotectin positive and negative (P = 0.241). The mean age in the positive fecal calprotectin group was slightly higher than those in the fecal calprotectin negative group (49.9±14.8 vs 47.8±13.9 years); Nevertheless, there was no significant difference in age between the two groups (P = 0.573). Most of the patients (59.1%) had comorbidities and diabetes mellitus became the major comorbidity in all groups (total population, positive and negative fecal calprotectin group). There were no statistical differences in the frequency of underlying diseases among COVID-19 patients with fecal calprotectin positive and negative.

Coughing became the major complaint in all groups, followed by fever, dyspnea, and anosmia. No statistical differences were found in respiratory manifestations between positive and negative fecal calprotectin groups. According to laboratory findings shown in Table 1, no notable differences were found between positive and negative fecal calprotectin groups in hematological parameters (leukocyte and thrombocyte) as well as measured systemic inflammatory markers (NLR, ferritin, CRP, and D-Dimer).

Table 1. Baseline characteristics of hospitalized patients with COVID-19 stratified by fecal calprotectin level.

Characteristics	Total (n=44)	*Fecal Calprotectin* <50 µg/g (n=26)	*Fecal Calprotectin* ≥50 µg/g (n=18)	*P*-value
Gender				0.241
Male	23 (52.3%)	16 (61.5%)	7 (38.9%)	
Female	21 (47.7%)	10 (38.5%)	11 (61.1%)	
Age (years)	48.7±14.2	47.8±13.9	49.9±14.8	0.573
18 - 59	32 (72.7%)	19 (73.1%)	13 (72.2%)	
≥60	12 (27.3%)	7 (26.9%)	5 (27.8%)	
Any comorbidity*	26 (59.1%)	16 (61.5%)	10 (55.6%)	0.932
Hypertension	18 (40.9%)	12 (46.2%)	6 (33.3%)	0.590
Diabetes Mellitus	22 (50%)	13 (50%)	9 (50%)	1.000
Respiratory symptoms*				
Fever	31 (70.5%)	18 (69.2%)	13 (72.2%)	1.000
Cough	33 (75%)	19 (73.1%)	14 (77.8%)	1.000
Dyspnea	30 (68.2%)	18 (69.2%)	12 (66.7%)	1.000
Anosmia	4 (9.1%)	3 (11.5%)	1 (5.6%)	0.634
Gastrointestinal symptoms*				
Nausea	17 (38.6%)	1 (3.8%)	16 (88.9%)	**<0.001**
Vomiting	13 (29.5%)	0 (0%)	13 (72.2%)	**<0.001**
Diarrhea	14 (31.8%)	1 (3.8%)	13 (72.2%)	**<0.001**
Abdominal pain	5 (11.4%)	1 (3.8%)	4 (22.2%)	0.142
Decreased appetite	28 (63.6%)	13 (50%)	15 (83.3%)	0.052
Laboratory findings				
Leukocyte (/μL)	10 113.4±4471.21	9465.8±2802.4	11 048.9±6119.6	0.775
Thrombocyte (/μL)	335 227.3±135 671.3	345 884.6±135 865.9	319 833.3±137 793.6	0.537
NLR	7.5±8.2	6.3±3.3	4.58 (2.06-44.59)	0.567
Ferritin (ng/ml)	761.3±664.3	774.5±669.6	739.8±676.8	0.736
D-Dimer (ng/ml)	4469.4±8327.3	4536.7±8048.8	4372.2±8950.5	0.384
CRP (mg/L)	1.9±2.4	1.6±1.7	2.6±3.2	0.952

*Each patient might have more than one comorbidity or symptom. NLR, neutrophil to leukocyte ratio; CRP, C-reactive protein. Data are presented as numbers (percentages) or mean ± SD. Bold font indicates statistical significances at the P-value <0.05.

The frequency of gastrointestinal manifestations in Figure 1 shows that decreased appetite was the most reported gastrointestinal symptom in 44 COVID-19 patients (63.6%) as well as the patients within the negative fecal calprotectin group (50%). Nausea (88.9%) meanwhile became the major reported gastrointestinal manifestation in the positive fecal calprotectin group. As shown in Table 1, the frequency of all features of gastrointestinal symptoms was significantly higher in the positive fecal calprotectin group compared to the negative group. Statistical differences among the two distinct groups were also pointed for nausea (P <0.001), vomiting (P <0.001), and diarrhea (P <0.001).

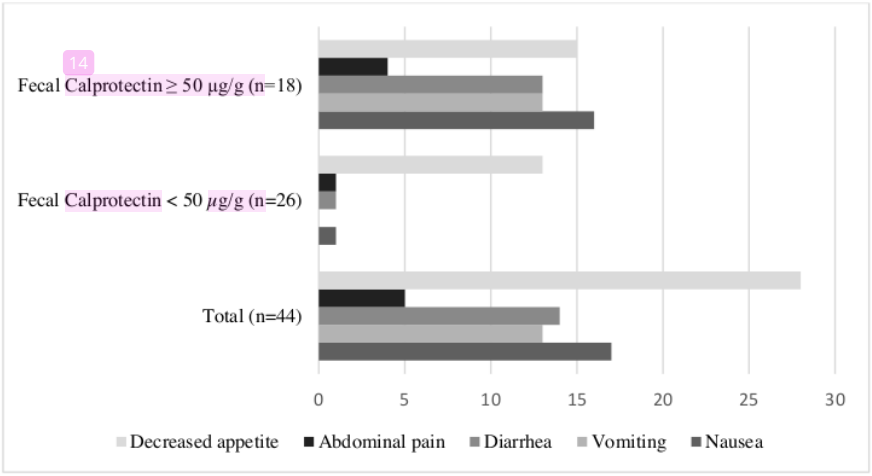


Figure 1. The proportion of gastrointestinal symptoms based on fecal calprotectin level.

Elevated fecal calprotectin level is associated with severity of hypoxemia

Half of the COVID-19 patients in this present study came from the non-ARDS group (n = 22/44; 50%) despite the inclusion criteria that involved only subjects with radiologic appearances suggestive for COVID-19. Interestingly, in the positive fecal calprotectin group most of the subjects were found to be in mild (n = 6/18; 33.3%) and moderate ARDS (n = 9/18; 50%). The mean P/F ratio was also significantly lower in the positive fecal calprotectin group (190.83±82.41 mmHg vs 396.19±100.45 mmHg). Statistical difference in the severity of hypoxemia by independent t-test was furthermore found between positive and negative fecal calprotectin groups (P <0.001) as illustrated in Figure 2.

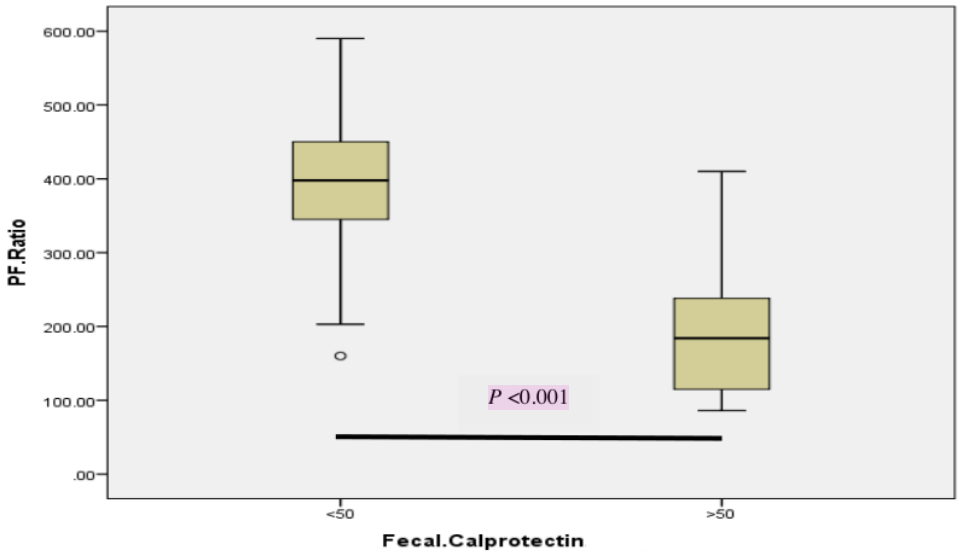


Figure 2. Comparison of P/F ratio (mmHg) value between positive (≥50 μg/g) and negative (<50 μg/g) fecal calprotectin groups by independent t-test

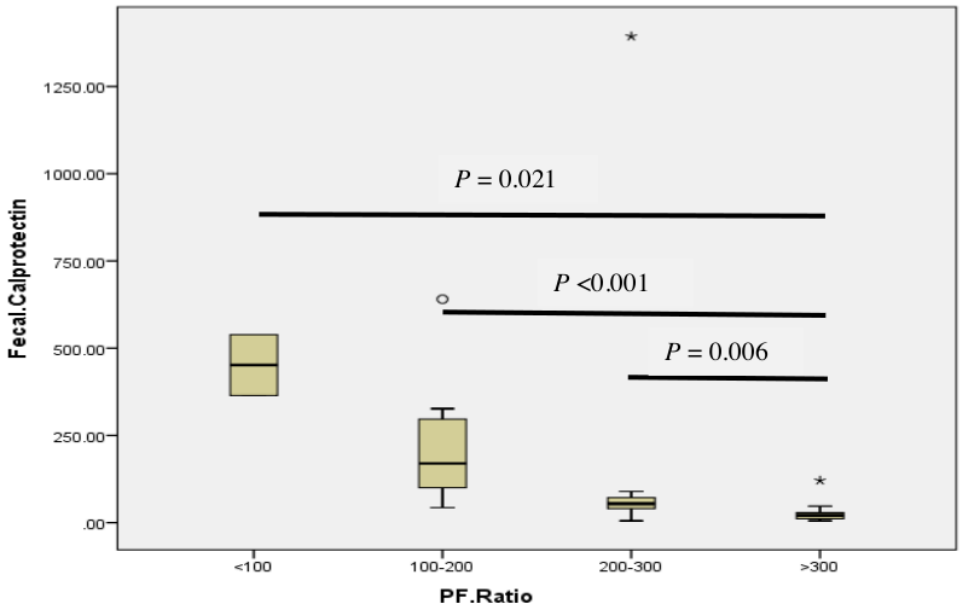
The analysis of fecal calprotectin level in COVID-19 patients stratified by degree of hypoxemia showed that median fecal calprotectin levels were elevated along with the severity of ARDS as seen in non-ARDS group 21.35 μg/g (5.20-120.90), mild ARDS 54.30 μg/g (5.20-1393.70), moderate ARDS 169.55 μg/g (43.40-640.50), and severe ARDS 451.55 μg/g (364.50-538.60). Kruskal-Wallis' analysis also showed a significant statistical difference of fecal calprotectin level stratified by severity of hypoxemia (P <0.001). We furthermore analyzed the difference among each group of hypoxemia severity and significant differences were discovered in all groups compared to the non-ARDS group as shown in Table 2.

Table 2. Fecal calprotectin levels stratified by severity of hypoxemia (P/F ratio)

P/F Ratio (mmHg)	Fecal Calprotectin (μg/g)	
	Median	*P*-value*
≤100 (Severe ARDS)	451.55 (364.50-538.60)	0.086
100< P/F ≤200 (Moderate ARDS)	169.55 (43.40-640.50)	
≤100 (Severe ARDS)	451.55 (364.50-538.60)	0.086
200< P/F ≤300 (Mild ARDS)	54.30 (5.20-1393.70)	
≤100 (ARDS Severe)	451.55 (364.50-538.60)	**0.021**
>300 (Non-ARDS)	21.35 (5.20-120.90)	
100< P/F ≤200 (Moderate ARDS)	169.55 (43.40-640.50)	**0.019**
200< P/F ≤300 (Mild ARDS)	54.30 (5.20-1393.70)	
100< P/F ≤200 (Moderate ARDS)	169.55 (43.40-640.50)	**<0.001**
>300 (Non-ARDS)	21.35 (5.20-120.90)	
200< P/F ≤300 (Mild ARDS)	54.30 (43.40-1393.70)	**0.006**
>300 (Non-ARDS)	21.35 (5.20-120.90)	

*Mann-Whitney test. Data are presented as median (minimum-maximum). Bold font indicates statistical significances at the *P*-value <0.05. P/F, PaO2/FiO2; ARDS, acute respiratory distress syndrome.

This analysis suggested that elevated fecal calprotectin among these patients may be the consequence of hypoxemia and thus the severity of COVID-19 as illustrated in Figure 3. To confirm this possibility, we then compared the fecal calprotectin level between ARDS (P/F ratio ≤300 mmHg) and non-ARDS (P/F ratio >300 mmHg) groups and a significant difference was found (P <0.001). A striking difference in median fecal calprotectin level was also found between ARDS and non-ARDS group (95 (5.20-1393.70) μg/g vs 21.35 (5.20-120.90) μg/g).



204 **Figure 3.** Concentration of fecal calprotectin (μg/g) stratified by severity of hypoxemia (P/F
205 ratio in mmHg)
206
207 Considering the hypothesis in this present study that disease severity based on the
208 degree of hypoxemia may be related to intestinal inflammation measured by fecal
209 calprotectin, we then established a correlation analysis. Spearman correlation as seen in
210 Figure 4 revealed a strong negative correlation between the P/F ratio and fecal calprotectin
211 level (r = -0.697, P <0.001). This result exposed the relationship between P/F ratio and fecal
212 calprotectin leading to a statistical conclusion that deteriorated intestinal inflammation
213 presented by elevated fecal calprotectin level was consistent with worsened hypoxemia
214 measured by reduced P/F ratio.
215

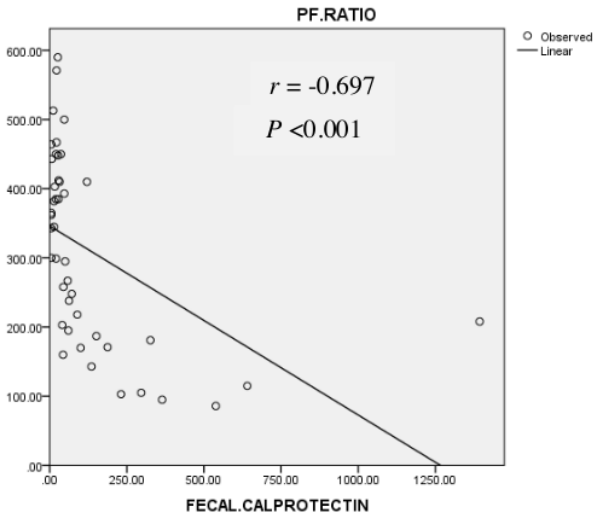


Figure 4. The relationship of P/F ratio (mmHg) and fecal calprotectin level (μg/g) analyzed by Spearman correlation

DISCUSSION

To our knowledge, this is the first study regarding the relationship between the P/F ratio and fecal calprotectin in COVID-19. Fecal calprotectin level was significantly increased in COVID-19 patients along with worsened hypoxemia. Statistical difference was also robustly found within the group of hypoxemia severity stratified by The Berlin Criteria of ARDS. A strong correlation between the P/F ratio and fecal calprotectin discovered in this study also highlighted the relationship of disease severity with intestinal inflammation due to hypoxic intestinal damage occurring in COVID-19 patients. Fecal calprotectin is a neutrophil-specific protein, whose roles are vastly impacted by intestinal ischemia (23,30). These results were consistent with the previous study in Italy that encountered a significant relationship between COVID-19 pneumonia and fecal calprotectin level in COVID-19 in which pneumonia represented the disease severity (34).

Interestingly, despite the significant association between the P/F ratio and fecal calprotectin level, our results exposed statistical differences between each degree of ARDS compared to the non-ARDS group and between ARDS and non-ARDS group. These results point us to the fact that fecal calprotectin's role in representing intestinal inflammation can be viewed primarily in comparison of conditions with and without hypoxemia but less prominent in between the degree of hypoxemia itself. This particular finding brings us to the theory of hypoxia and mucosal inflammation where the hypoxia-inducible factor (HIF) plays an important role. HIF is not only the regulation key in inflammatory hypoxia appearing in the intestine but it can also promote inflammatory resolution (41). Stimulation of HIF-1α in the intestine generates a barrier-protective pathway by enhancing mucus, defensin, and tight junctional proteins as well as refilling the ATP pool in the time of injury. The performance of pro-inflammatory cytokines and chemokines along with iron-absorptive genes will also be intensified by HIF-2α activation (42).

The main presented gastrointestinal symptom in this study was decreased appetite, except for the positive fecal calprotectin group in which nausea became the leading symptom. This finding is parallel to a systematic review and meta-analysis on the prevalence of gastrointestinal symptoms from 78 studies with 12,797 COVID-19 patients in which loss of appetite held the highest prevalence (approximately one-fifth of patients) (43). In contrast to two previous studies, nausea, vomiting, and diarrhea in our study exposed striking statistical differences in the positive fecal calprotectin group compared to the negative group (31,35). In this regard, a previous study in Austria stated that SARS-CoV-2 infection instigated inflammatory response in the intestine, as indicated by diarrhea and elevated fecal calprotectin (33). Nonetheless, since we did not evaluate SARS-CoV-2 PCR from fecal samples, it is premature to determine whether diarrhea and other gastrointestinal symptoms in this current study were developed from direct viral etiology or due to other inflammation processes in the intestinal mucosa.

Another notable finding is that no significant statistical differences between positive and negative fecal calprotectin groups for all inflammatory parameters were found in this current study. In this regard, a previous study found a significant correlation only between fecal calprotectin and serum IL-6 concentration (P <0.001), but not CRP or ferritin (33). The result from this previous study in Austria may support the hypothesis that SARS-CoV-2 could instigate gastrointestinal inflammation without direct invasion to the intestinal cells. Circulating inflammatory cytokines are capable of inducing cellular infiltration of the intestinal wall which in turn will lead to calprotectin release (35,44). Nonetheless, our results showed that in our population of study the role of this particular mechanism was less significant. In contrast to another previous study from Italy, we additionally found no significant difference in D-Dimer between fecal calprotectin groups (23). This result may

suggest that the role of hypercoagulability in triggering intestinal inflammation occurring in our subjects was subtle.

This study has several limitations. First, the sample size was relatively small as this was a single-center study; hence, the results should be validated with additional studies with larger sample sizes and multicenter studies if possible. Second, this is a cross-sectional and not a prospective study. It is difficult to determine the direction of the relationship between the P/F ratio and fecal calprotectin with this kind of approach as both variables are able to interfere with each other. A prospective study may also allow us to evaluate the trend of fecal calprotectin level throughout the hospitalization period and determine the outcome. Finally, we did not evaluate SARS-CoV-2 PCR from fecal samples, thus we could not eliminate whether there was the direct viral invasion to the intestinal mucosa instigating intestinal inflammation. Nevertheless, this study is valuable as a preliminary study to reinforce more studies in this field.

CONCLUSION

In summary, our findings support the current understanding of the relationship between the severity of COVID-19 and intestinal manifestation. Fecal calprotectin shows a potential role as a biomarker of intestinal inflammation in COVID-19 as a consequence of hypoxic intestinal damage suggested by reduced P/F ratio. Nonetheless, more studies are acquired to investigate the etiology of gastrointestinal manifestations and elevated fecal calprotectin levels in COVID-19 patients along with its potential in predicting gastrointestinal complications and clinical outcomes.

Acknowledgments

The authors would like to thank Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Conflicts of Interest

The authors declare no conflict of interest.

The Role of Fecal Calprotectin as a Hypoxic Intestinal Damage Biomarker in COVID-19 Patients

ORIGINALITY REPORT

15%	12%	10%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.nature.com Internet Source	2%
2	backend.orbit.dtu.dk Internet Source	2%
3	www.karger.com Internet Source	1%
4	Mohammed Hussien Ahmed, Hebat Allah Abdel Maksoud Ahmed, Nahla Abd el-Aziz Nosair, Asmaa Mbarak Hassan et al. "Fecal Calprotectin as a Predictor of COVID-19 Severity", Journal of Coloproctology, 2021 Publication	1%
5	Mauro Giuffrè, Stefano Di Bella, Gianluca Sambataro, Verena Zerbato et al. "COVID-19-Induced Thrombosis in Patients without Gastrointestinal Symptoms and Elevated Fecal Calprotectin: Hypothesis Regarding Mechanism of Intestinal Damage Associated with COVID-19", Tropical Medicine and Infectious Disease, 2020	1%

	Publication	
6	www.ncbi.nlm.nih.gov Internet Source	1 %
7	"ESICM LIVES 2019", Intensive Care Medicine Experimental, 2019 Publication	1 %
8	www.vidyawarta.com Internet Source	1 %
9	www.science.gov Internet Source	1 %
10	repository.unair.ac.id Internet Source	1 %
11	synapse.koreamed.org Internet Source	<1 %
12	Graham J Britton, Alice Chen-Liaw, Francesca Cossarini, Alexandra E Livanos et al. "SARS-CoV-2-specific IgA and limited inflammatory cytokines are present in the stool of select patients with acute COVID-19", Cold Spring Harbor Laboratory, 2020 Publication	<1 %
13	medcraveonline.com Internet Source	<1 %
14	Nathalie Blad, Richard Palmqvist, Pontus Karling. "Pre-diagnostic faecal calprotectin	<1 %

levels in patients with colorectal cancer: a retrospective study", BMC Cancer, 2022
Publication

15	apm.amegroups.com Internet Source	<1%
16	bmcpulmmed.biomedcentral.com Internet Source	<1%
17	Phillip Minar, Kimberly Jackson, Yi-Ting Tsai, Heidi Sucharew, Michael J Rosen, Lee A Denson. "Validation of Neutrophil CD64 Blood Biomarkers to Detect Mucosal Inflammation in Pediatric Crohn's Disease", Inflammatory Bowel Diseases, 2018 Publication	<1%
18	Verena Zerbato, Stefano Di Bella, Mauro Giuffrè, Anna Wladyslawa Jaracz et al. "High fecal calprotectin levels are associated with SARS-CoV-2 intestinal shedding in COVID-19 patients: A proof-of-concept study", World Journal of Gastroenterology, 2021 Publication	<1%
19	bmcanesthesiol.biomedcentral.com Internet Source	<1%
20	Miguel Villalona-Calero, Larry Schaaf, Gary Phillips, Gregory Otterson et al. "Thalidomide and celecoxib as potential modulators of irinotecan's activity in cancer patients",	<1%

	Cancer Chemotherapy and Pharmacology, 2006 Publication	
21	dergipark.org.tr Internet Source	<1 %
22	journals.plos.org Internet Source	<1 %
23	www.eurorad.org Internet Source	<1 %
24	www.medrxiv.org Internet Source	<1 %
25	Martine Rance. "Kinetic therapy positively influences oxygenation in patients with ALI/ARDS", Nursing in Critical Care, 1/2005 Publication	<1 %
26	brief.land Internet Source	<1 %
27	pure.rug.nl Internet Source	<1 %

Exclude quotes	Off	Exclude matches	< 10 words
Exclude bibliography	On		

The Role of Fecal Calprotectin as a Hypoxic Intestinal Damage Biomarker in COVID-19 Patients

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16

PAGE 17