Research Article
Volume 8:2, 2023

Journal of Inflammatory Bowel Diseases & Disorders

ISSN: 2476-1958 Open Access

Can High Calprotectin Level Predict Mortality in Patients with COVID-19?

Maryam Sadat Mousavi*

Department of Gastroenterology, Vali-e-Asr University of Rafsanjan, Rafsanjan, Iran

Abstracts

Background: Some biomarkers such as C-Reactive Protein (CRP) and Fecal Calprotectin (FC) have been reported to be related to the prognosis of the Coronavirus disease 2019 (COVID-19).

Methods: This case control study included 76 IBD patients in clinical remission and COVID-19 patients from December 2021 to March 2022. A checklist including demographic and clinical parameters was filled out for each participant. Two stool samples in 2 stages (during one month) and one blood sample were collected to test for FC and CRP, respectively. Data were analyzed using Wilcoxon, Mann Whitney, Spearman, T-test, ANOVA and K2 tests and $P<0.05$ was considered significant.

Results: 33 COVID-19 patients and 43 remission IBD cases with a mean age of 51.53 ± 15.155 years take part in the study. In COVID-19 group, mean FC ± SE in the first samples were 184.46 ± 59.01 (µg/g) and 144.58 ± 38.68 (µg/g) in the second samples one month later. In IBD patients in clinical remission mean FC in the first and in the second samples were 170.25 ± 42.23 (µg/g) and 204, 35 ± 68.33 (µg/g). The reduction in FC was significant among patients with COVID-19 (severe and moderate) after one month. 8 and 11 cases with COVID-19 and IBD had FC1 above or equal 200 (µg/g), respectively. Among 8 COVID-19 patients with high level FC1, 5 cases died. Mean CRP was 44.30 ± 3.47 in COVID-19 and 4.93 ± 1.00 in IBD patients ($P<0.05$). In cases, a correlation was seen between FC1 and CRP ($rs=0.353$, $P=0.04$).

Conclusion: Our findings showed gastrointestinal inflammation in COVID-19 patients even a month after recovery. More mortality was observed in patients with FC above 200. Higher level FC is presented in older COVID-19 patients that show the patients need special attention. Further studies are needed to understand the role of calprotectin in predicting COVID-19 mortality.

Keywords: Fecal calprotectin • Mortality • COVID-19 • World Health Organization (WHO) • Bilateral patchy

Introduction

Coronavirus Disease 2019 (COVID-19), which was seen first time in China, has quickly spread worldwide and was labelled as a pandemic by World Health Organization (WHO) in March 2020 [1]. It infected millions and ruined the world's economies [2]. Although COVID-19 is an airborne infection and patients present pulmonary symptoms such as fever, aches, cough, headache, fatigue and shortness of breath, the presence of a large number of receptors of Angiotensin-Converting Enzyme type 2 (ACE2) in Gastrointestinal (GI) tract, also causes gastrointestinal symptoms [3,4]. Diarrhea, anorexia, nausea, vomiting and abdominal pain are reported in some COVID-19 patients [4-6]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been detected in infected feces [7].

There are known biomarkers, such as C-Reactive Protein (CRP), that help specialists to predict complications in patients with COVID-19 [8]. Recently some documents showed that calprotectin, a calcium and zinc-binding protein, is mainly derived from neutrophils and macrophages and has an essential role in predicting COVID-19 outcomes [9,10]. Usually, the expression level of calprotectin increases following trauma, inflammation and infection [11]. It is detected in different body fluids relative to the degree of inflammation, but its concentration in feces is higher than in plasma [12].

Fecal Calprotectin (FC) is a valid biomarker in the diagnosis of Inflammatory Bowel Disease (IBD) [13]. IBD is a group of gastrointestinal diseases with relapse and period [14]. Intestinal inflammation increases inflammatory markers caused by any etiology

***Address for Correspondence:** Maryam sadat Mousavi, Department of Gastroenterology, Vali-e-Asr University of Rafsanjan, Rafsanjan, Iran, Tel:9133257859; E-mail: Maryam.m16974@gmail.com*

Received: 12 January, 2023, Manuscript No. JIBDD-23-86963; **Editor assigned:** 16 January, 2023, PreQC No. JIBDD-23-86963 (PQ); **Reviewed:** 31 January, 2023, QC No. JIBDD-23-86963; **Revised:** 18 April, 2023, Manuscript No. JIBDD-23-86963 (R); **Published:** 26 April, 2023, DOI: 10.37421/2476-1958.2023.08.175

factor. So, a high level of FC may be detected in COVID-19 and IBD patients. Comparison of FC level, as a new marker and CRP, as a known marker, in these two groups of patients may help to rapidly and correctly diagnose and manage the diseases. Also, few studies reported that Calprotectin might have a role in predicting mortality in patients with COVID-19. Accordingly, in this study, FC and CRP levels were compared between patients with COVID-19 and IBD in Isfahan, Iran, in 2022.

Materials and Methods

Seventy-six patients with COVID-19 and IBD were enrolled in a case control study between 20 December 2021 and 20 March 2022. The study's aim was explained to participants, and formed consent obtained from each subject. The research ethics committee of Isfahan university of medical sciences, Isfahan, Iran approved the research protocol.

COVID-19 patients

Thirty-three patients with COVID-19 that had been hospitalized in peak of the Omicron variant in AL-Zahra hospital, the biggest hospital in the central area of Iran, were selected by non-random sampling after confirmation of their COVID-19 by real time PCR on a nasopharyngeal swab and/or chest CT scan. Cases less than 18 years, acute and subacute gastrointestinal infections such as shigellosis, salmonellosis and campylobacter infection, and patients with advanced malignancy, heart diseases, and pregnancy; were excluded from the study.

The demographic data and clinical symptoms were extracted from patients' electronic records, and a checklist was completed. The fecal samples were collected in two stages, first when the subjects were hospitalized and one month later as second sample. In stage 2 sampling, patients were invited to a gastroenterology clinic for follow-up by telephone. Samples were transferred to the hospital laboratory and analyzed for calprotectin. A CRP blood test was performed for all the patients during hospitalization.

IBD patients

Forty-three IBD patients in clinical remission referred to a gastroenterology clinic who were selected by non-random sampling method. The inclusion criteria were the age of more than 18 years. Patients checked for COVID-19 and positive cases were excluded from the study. Patients with deep vein thrombosis, and pneumonia thrombosis embolism were also excluded.

With a face to face interview, the researcher completed a checklist that included demographic and clinical information and symptoms. Also, in this group the fecal samples were collected in two stages, during a routine checkup and one month later. With the first fecal sample, a blood sample was collected for CRP.

Statistical analysis

Data were analyzed using SPSS version 22 software (SPSS Inc., Chicago, IL, USA). The normal distribution of the variables was checked by plots (Shapiro-Wilk). FC did not have a normal distribution, and we could not make it normal. The Wilcoxon test was used to compare FC1 and FC2 in patients with COVID-19. Mann-Whitney compared FC levels among patients with COVID-19 and IBD. CRP had normal distribution, and a student t-test (or ANOVA) was performed. The *Chi-square* test was used for evaluating potential risk factors. The p-value <0.05 was considered significant.

Results

In this study, 76 subjects, including 33 (43.4%) confirmed COVID-19 patients and 43 (56.6%) remission IBD cases with a mean age of 51.53 ± 15.155 (range 19 to 84) years participated.

COVID-19 patients

20 (60.6%) men with a mean age of 57.80 ± 14.94 and 13 (39.4%) women with a mean age of 51.92 ± 22.86 years were hospitalized with COVID-19. Four (12.1%), 20 (60.6%), and 9 (27.3%) cases were mild, moderate and severe COVID-19, respectively. The most common symptoms were myalgia 32 (97%), which were followed by cough 31 (93.9%), fever 24 (72.2%), shortness of breath and nasal congestion 17 (51.5%), fatigue 16 (48.5), sore throat and conjunctival congestion 13(39.4%), headache 12 (36.4%), sputum 11 (33.3%) and chills 7 (21.2%). Some patients had gastrointestinal symptoms: diarrhea 26 (78.8%) and vomiting 17 (51.5%). Bilateral patchy, local patchy, ground glass and interstitial abnormalities were found in 11 (33.3%), 9 (27.3%), 7 (21.2%) and 6 (18.2%) patients, respectively. Nineteen (57.6%) subjects had never smoked; there were 8 (24.2%) former and 6 (18.2%) current smokers.

Mean FC ± SE in the first (FC1) and second (FC2) times were 184.46 ± 59.01 and 144.58 ± 38.68, (µg/g), respectively. Seven (21.2%) COVID-19 patients died, and five (15.2%) cases refused to take part in the research, so only 21 (63.6%) cases had two samples for FC. As Table 1 presents, the percentage reduction of FC (FC1-FC2/FC1) decreased by 21.62% in one month. Also, the percentages reduction of FC in moderate and severe COVID-19 was 10.4% and 26.67%. The percentage reduction of FC according to moderate and severe chest CT severity was 33.61% and 67.15%, respectively.

Variables		Fecal calprotectin (N=21)			CRP (N=33)	
		FC1	FC2	P-value*		P-value*
Mean ± SE		184.46 ± 59.01	144.58 ± 38.68	0.001	44.30 ± 3.47	-
Sex	Male	231.15 ± 89.43	153.87 ± 56.57	0.004	44.10 ± 4.05	0.944
	Female	112.63 ± 58.17	129.48 ± 47.46	0.05	44.62 ± 6.45	
Age	<50 years	47.48 ± 20.73	89.47 ± 34.63	0.021	39.92 ± 5.32	0.317

	≤ 50 years	273.5 ± 91.88	205.20 ± 68.81	0.009	47.15 ± 4.56	
Smoking	Yes	370.13 ± 263.84	60.61 ± 24.03	0.144	50.33 ± 10.58	
	No	143.20 ± 43.63	164.34 ± 46.43	0.001	42.96 ± 3.6	0.421
Chest CT severity	Mild	123.5 ± 57.03	274.62 ± 202.15	0.109	33 ± 2.74	0.312
	Moderate	206.06 ± 85.57	136.81 ± 38.05	0.005	47.14 ± 4.54	
	Severe	162.58 ± 90.01	53.4 ± 20.48	0.109	45. 4 ± 10.07	
Vomiting	Yes	74.63 ± 28.04	102.28 ± 41.02	0.028	39.88 ± 4.94	0.194
	No	301.16 ± 112.56	200.98 ± 70.32	0.008	49.00 ± 4.74	
Diarrhea	Yes	225.13 ± 73.07	171.84 ± 45.37	0.001	50.15 ± 3.54	<0.001
	No	33.41 ± 10.02	28.75 ± 13.38	0.715	22.57 ± 2.94	
Clinical symptoms	Mild	46.66 ± 12.83	17.49 ± 13.47	0.655	30 ± 9.21	0.129
	Moderate	135.88 ± 50.49	121.75 ± 49.83	0.002	43 ± 4.40	
	Sever	353.67 ± 179.74	259.35 ± 59.38	0.043	53.56 ± 6.14	
Outcome	Dead	628.82 ± 203.02	-	-	67.14 ± 5.71	0.001
	Live	47.65 ± 15.04	144.58 ± 38.68	0.001	39.48 ± 3.87	

*P value<0.05 was significantly statistics.

Table 1. Studied variables in COVID-19 patients.

Eight patients with COVID-19 had FC1 above or equal to 200 (μg/g). Five (62.5%) and three (37.5%) cases were moderate and severe COVID-19. Two (25%), four (50%), and two (25%) patients were mild, moderate and severe for chest CT severity. In the eight patients, the mean FC1, FC2 and CRP were 619.04 ± 170.66 (μg/g), 672.25 (μg/g) (only 1 case) and 61.88 ± 6.76, respectively. FC1 ≥ 200 (μg/g) was significantly detected more in older patients. In cases with FC ≥ 200 (μg/g), the only symptoms of COVID-19 that showed a statistically significant difference were shortness of breath and sputum (P<0.05). There was a difference in CRP between patients with FC1 lower and higher than 200 (μg/g) (P=.003).

Among eight subjects, five cases died; 2 females and three males with a mean age=of 76.8 ±8.59 years. The mean FC1 was 818.8 ± 234.25 (μg/g), and CRP was 75.2 ± 3.02 for them. Antifungal and remdesivir were used for 2 and 3 dead patients, respectively (Table 2). The chest X-ray/CT scan findings in those who died were ground-glass for 4 cases and bilateral patchy for one patient. Two and three patients were moderate and severe COVID-19, respectively.

Variable		COVID-19 N=33			IBD N=43		
		FC1<200 N=25	FC1 ≥ 200 N=8	p-value	FC1<200 N=32	FC1 ≥ 200 N=11	p-value
Sex	Male	14 (70)	6 (30)	0.431	11 (57.9)	8 (42.1)	0.027
	Female	11 (84.6)	2 (15.4%)		21 (87.5)	3 (12.5)	
Age mean ± SE		51 ± 3.55	69.50 ± 4.5	0.011	49.41 ± 2.17	45.82 ± 2.62	0.377
Smoking	Yes	4 (16)	2 (25)	0.616	0	1 (9.1)	0.256
Symptoms COVID-19*	Sputum pro	6 (24)	5 (62.5)	0.044	-	-	-
	Shortness of breath	10 (40)	7 (87.5)	0.039	-	-	-
GI symptoms	Vomiting	15 (60)	2 (25)	0.118	-	-	-
	Diarrhea	18 (72)	8 (100)	0.092	-	-	-
CRP		38.68 ± 3.39	61.88 ± 6.76	0.003	3.68 ± 0.49	8.56 ± 3.55	0.202
Death		2 (9.1)	5 (83.3)	0.001	-	-	-

*- Other COVID symptom including myalgia, cough, fever, nasal congestion, fatigue, sore throat, conjunctival congestion, headache and chills did not show a significantly difference between groups.

Table 2. Association between demographic and clinical characteristics with high fecal calprotectin level in participants.

A correlation was seen between FC1 and CRP (rs=0.353, P=0.04).

Remission IBD

This group included 19 (44.2%) men with a mean age of 51.58 ± 12.56 and 24 (55.8.%) women with a mean age of 46.04 ± 10.17 years. 97.7% of IBD patients had never smoked, and 1 (2.3%) was a current smoker.

Mean ± SE was 170.25 ± 42.23 (µg/g), 204, 35 ± 68.33 (µg/g) and 4.93 ± 1.00 for FC1, FC2 and CRP, respectively. Differences between FC1 and FC2 were not significant (p=0.269). FC1 in males was significantly higher than in females (282.14 ± 81.84 *vs.* 81.67± 30.21. P=0.017); FC2 and CRP were not significantly important differences between women and men.

No significant differences were seen between age groups for FC1, FC2 and CRP. There is not a correlation was seen between FC1 and CRP (rs=0.029, P=0.854).

25.6% subjects had FC1 above or equal 200 (µg/g). In the cases, the mean FC1, FC2 and CRP were 554.93 ± 93.31 (µg/g), 541.43 ± 211.78 (µg/g) and 8.56 ± 3.55, respectively. There was a significant difference between men and women for FC1 ≥ 200 (µg/g) (Table 2).

Comparison between COVID-19 and IBD patients.

Table 3 shows no difference was seen in FC1 and FC2 between COVID-19 and IBD patients.

Variable	Total (N=76)	COVID-19 (N=33)	IBD (N=43)	p-value
FC1 (Mean ± SE)	176. 42 ± 34.80	184.46 ± 59.01	170.25 ± 42.23	0.506
FC2* (Mean ± SE)	184.74 ± 47.54	144.58 ± 38.68	204. 35 ± 68.33	0.13
CRP (Mean ± SE)	22.03 ± 2.76	44.30 ± 3.47	4.93 ± 1.00	<0.001
Age year (Mean ± SE)	51.53 ± 1.74	55.48 ± 3.20	48.49 ±1.75	0.06
Sex (Male)	39 (51.3)	20 (60.6)	19 (44.2)	0.156
Dead	7 (9.9)	7 (25)	0	0.001

Table 3. Comparison biomarkers and demographic information between COVID-19 and IBD patients.

CRP in patients with COVID was higher than in IBD subjects. Seven deaths occurred in COVID patients. CRP were 39.48 ± 3.87 and 67.14 ± 1.04 for survivors and died patients, respectively (p=0.001) FC and CRP have a parallel predictive capacity for deaths during COVID-19. Although, due to the study's design, comparing markers FC and CRP are impossible.

Discussion

Our data showed that in COVID-19 patients, FC reduced more than 20% in one month. According to the used kit's manufacturer, FC in the normal population should be below 50 (µg/g). Despite the reduction, FC in patients with COVID-19 is still three times higher than in the normal population, and it did not have a significant difference with remission IBD patients. It is worth mentioning that in the COVID-19 Omicron variant, most of the patients experienced GI symptoms. Some studies have shown an association between FC and COVID-19. In a pilot study in Austria, FC was reported in COVID-19 patients. A higher level of FC was seen in patients with COVID-19 having diarrhea [13]. FC level was elevated in COVID-19 patients, along with exacerbating hypoxemia in Japan [14,15]. In Ojetti et al. study, a correlation was observed between COVID-19 and FC level [16]. Of course, a research in a hospital in the USA did not support our results. Despite gastrointestinal symptoms seen in patients with COVID-19, FC did not elevate in patients [17].

CRP was significantly higher in COVID-19 patients than in patients with IBD, although no significant difference was seen in FC level between the two groups. The issue was logical; in remission IBD patients, inflammation stops, and CRP is an acute phase protein that rises in infection or inflammation [18]. Several studies assessed FC and CRP as accurate biomarkers in COVID-19 patients. Mago, et al. reported that FC is a superior marker to CRP. A study showed that however, it seems FC could be a candidate biomarker for the presentation of inflammation in COVID-19 patients.

Five of seven dead patients with COVID-19 had FC1 ≥ 200. In Romualdo's study, 66 patients with COVID-19 participated; 8 dead and 58 survived. The serum calprotectin level was compared between dead and alive patients. The calprotectin was 7.1 (mg/L) for non-survivors and 3.1 (mg/L) for survivors that this difference with p=0.005 was significant. The calprotectin was higher in dead patients in both studies. We more studies need to be conducted to evaluate the role of the biomarker in patients.

Our study has some limitations; firstly, the sample size was small, and we had to be cautious in interpreting our findings. Secondly, we had no information about the duration of hospitalization and onset of symptoms with sample collection, which can affect inflammation.

Finally, if the presence of the virus in the feces samples had been checked, we could assess the relationship between FC and viruses.

Conclusion

Our findings showed gastrointestinal involvement in COVID-19 patients even a month after recovery. More mortality was observed in patients with FC above 200. Higher level FC is presented in older subjects that show the patients need special attention. It seems the digestive system has an essential role in COVID-19 infections, and monitoring of FC as an intestinal inflammation biomarker could guide the physician to help patients with COVID-19. Further studies are needed to understand the role of different biomarkers in patients.

References

1. Galanopoulos, Michail, Filippos Gkeros, Aris Doukatas, and Grigorios Karianakis, et al. "COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract." *World J Gastroenterol* 26 (2020): 4579.
2. Wang, Fantao, Shiliang Zheng, Chengbin Zheng, and Xiaodong Sun, et al. "Attaching clinical significance to COVID-19-associated diarrhea." *Life Sci* 260 (2020): 118312.
3. Xiao, Fei, Meiwen Tang, Xiaobin Zheng, and Ye Liu, et al. "Evidence for gastrointestinal infection of SARS-CoV-2." *Gastroenterology* 158 (2020): 1831-1833.
4. Ungaro, Ryan C, Timothy Sullivan, Jean-Frederic Colombel, and Gopi Patel, et al. "What should gastroenterologists and patients know about COVID-19?." *Clin Gastroenterol Hepatol* 18 (2020): 1409-1411.
5. Perisetti, Abhilash, Hemant Goyal, Mahesh Gajendran, and Umesha Boregowda, et al. "Prevalence, mechanisms, and implications of gastrointestinal symptoms in COVID-19." *Front Med* 7 (2020): 588711.
6. Fei, Fei, John A Smith, and Liyun Cao. "Clinical laboratory characteristics in patients with suspected COVID-19: One single-institution experience." *J Med Virol* 93 (2021): 1665-1671.
7. Mahler, Michael, Pier-Luigi Meroni, Maria Infantino, and Katherine A Buhler, et al. "Circulating calprotectin as a biomarker of COVID-19 severity." *Expert Rev Clin Immunol* 17 (2021): 431-443.
8. Udeh, Raphael, Shailesh Advani, Luis Garcia de Guadiana Romualdo, and Xenia Dolja-Gore, et al. "Calprotectin, an emerging biomarker of interest in COVID-19: A systematic review and meta-analysis." *J Clin Med* 10 (2021): 775.
9. Wang, Siwen, Rui Song, Ziyi Wang, and Zhaocheng Jing, et al. "S100A8/A9 in Inflammation." *Front Immunol* 9 (2018): 1298.
10. Pathirana, WPN Ganga W, SA Paul Chubb, Melissa J Gillett, and Samuel D Vasikaran, et al. "Faecal calprotectin." *Clin Biochem Rev* 39 (2018): 77.
11. Magro, Fernando, Joanne Lopes, Paula Borralho, and Susana Lopes, et al. "Comparison of different histological indexes in the assessment of UC activity and their accuracy regarding endoscopic outcomes and faecal calprotectin levels." *Gut* 68 (2019): 594-603.
12. Khaki-Khatibi, Fatemeh, Durdi Qujeq, Mehrdad Kashifard, Soheila Moein, Mahmood Maniati, and Mostafa Vaghari-Tabari. "Calprotectin in inflammatory bowel disease." *Clinica Chimica Acta* 510 (2020): 556-565.
13. Adriana, Deasy Natalia, Titong Sugihartono, Iswan Abbas Nusi, and Poernomo Boedi Setiawan, et al. "Role of fecal calprotectin as a hypoxic intestinal damage biomarker in COVID-19 patients." *Gut Pathog* 14 (2022): 34.
14. Ojetti, Veronica, Angela Saviano, Marcello Covino, and Nicola Acampora, et al. "COVID-19 and intestinal inflammation: Role of fecal calprotectin." *Dig Liver Dis* 52 (2020): 1231-1233.
15. Britton, Graham J, Alice Chen-Liaw, Francesca Cossarini, and Alexandra E Livanos, et al. "Limited intestinal inflammation despite diarrhea, fecal viral RNA and SARS-CoV-2-specific IgA in patients with acute COVID-19." *medRxiv* 11 (2021): 13308.
16. Sproston, Nicola R, and Jason J Ashworth. "Role of C-reactive protein at sites of inflammation and infection." *Front Immunol* 9 (2018): 754.
17. Mago, Sheena, Haleh Vaziri, and Micheal Tadros. "The usefulness of fecal calprotectin in the era of the COVID-19 pandemic." *Gastroenterology* 160 (2021): 2623-2625.
18. de Guadiana Romualdo, Luis Garcia, Maria Dolores Rodriguez Mulero, and Marta Hernandez Olivo, et al. "Circulating levels of GDF-15 and calprotectin for prediction of in-hospital mortality in COVID-19 patients: A case series." *J Infect* 82 (2021): 40-42.

How to cite this article: Mousavi, Maryam Sadat. "Can High Calprotectin Level Predict Mortality In Patients With COVID-19?." *J Inflam Bowel Dis Disorder* 8 (2023): 175.