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Gastrointestinal Manifestations and Neutrophil-to-Lymphocyte Ratio as Marker of Occult Bleeding in COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) was initially recognized as a respiratory illness; however, it has been gradually recognized as a disease that affects multiple organ systems, including the gastrointestinal (GI) tract. GI involvement ranges from mild symptoms, such as nausea and diarrhea, to complications like gastrointestinal bleeding. The neutrophil-to-lymphocyte ratio (NLR) has been proposed as a simple biomarker of inflammation and disease severity in COVID-19.

Objective: To describe gastrointestinal manifestations of COVID-19 and examine the association between NLR levels and occult gastrointestinal bleeding.

Methods: This cross-sectional study was conducted in 2021 at the New-Emerging and Re-Emerging Infectious Diseases inpatient unit of Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia. COVID-19-positive patients aged ≥18 years with gastrointestinal symptoms were included, excluding those who were pregnant or had pre-existing GI disorders. Data were collected from medical records and patient interviews. Statistical analysis was performed using the Mann–Whitney U test, with $p < 0.05$ considered significant

Results: The most frequent symptoms were appetite loss and nausea (93%), bloating and vomiting (87%), and diarrhea (57%). Occult GI bleeding occurred in seven patients (23.3%) who had significantly higher NLR values than those without bleeding ($p = 0.041$).

Conclusion: The most frequent GI manifestations of COVID-19 are loss of appetite, nausea, bloating, vomiting, and diarrhea, while occult gastrointestinal bleeding occurs in about one-fourth of cases. Elevated NLR levels are associated with occult bleeding, suggesting its potential role as a simple and accessible biomarker of intestinal inflammation and disease severity.

Keywords: COVID-19, gastrointestinal manifestation, occult bleeding, the neutrophil-to-lymphocyte ratio.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2 in December 2019, infected millions of people worldwide and significantly disrupted global health and economic and social stability. As of July 2020, over 14 million people had contracted the infection, with nearly 620,000 deaths.[1] Indonesia ranked among the top 10 nations with the highest COVID-19 mortality rates in August 2021, reporting 3,930,000 confirmed cases and 122,633 deaths, according to World Health Organization (WHO) data.[2] Aceh, the western province of Indonesia, has also been affected with over 6000 people infected and a rising number of confirmed cases.[3]

The predominant manifestations of

COVID-19 are fever, dry coughing, and shortness of breath, which are common symptoms of acute respiratory syndrome. Gastrointestinal (GI) manifestations like nausea, vomiting, diarrhea, and abdominal discomfort were common during the SARS-CoV-2 infection. While respiratory symptoms are the hallmark of COVID-19, gastrointestinal manifestations are also commonly observed and may contribute significantly to the clinical presentation of the disease. Gastrointestinal manifestations were found in almost half of COVID-19 patients, in addition to fever and respiratory symptoms. Some COVID-19 individuals developed these manifestations without any respiratory symptom involvement. COVID-19 patients with gastrointestinal manifestations require a more extended hospital stay than those without gastrointestinal manifestations. Gastrointestinal bleeding (GIB) is a common and serious complication affecting 4-13.7% of critically ill patients. Studies have demonstrated that hospitalized patients with GIB experience high mortality rates. Several therapies used in COVID-19 patients (i.e., glucocorticoids, antiviral agents, mechanical ventilation extracorporeal membrane oxygenation (ECMO), and anticoagulants) might contribute to digestive tract injury.[4,5]

SARS-CoV-2 has been shown to penetrate intestinal epithelial cells through the co-expression of *angiotensin-converting enzyme* 2 (ACE2) and Transmembrane Protease Serine 2 (TMPRSS2), establishing the gastrointestinal tract as an additional site of viral replication. This epithelial invasion may disrupt mucosal integrity and contribute to gastrointestinal manifestations, including the potential for occult bleeding. Despite increasing evidence of fecal viral shedding, the clinical implications of intestinal involvement remain unclear, underscoring the need for further investigation into its role in COVID-19–related morbidity. The biomarker utility of a few startlingly simple results from blood counts performed as part of normal clinical practice has been pointed out in several recent studies. In particular neutrophil-to-lymphocyte ratio (NLR), consisting of the absolute count of circulating neutrophils divided by lymphocytes, has been assessed as a biomarker for disease course and outcome in various conditions including also occult bleeding. Several recent studies have highlighted the biomarker potential of simple blood count parameters routinely obtained in clinical practice. Among these, the neutrophil-to-lymphocyte ratio (NLR), calculated as the absolute neutrophil count divided by the lymphocyte count, has been evaluated as a prognostic indicator in various conditions, including occult bleeding.[6] Elevated NLR values reflect an enhanced inflammatory response and have been consistently associated with all-cause mortality, independent of other clinical markers.[6,7] In the context of COVID-19, NLR has been widely studied as a marker of systemic inflammation, where increased values reflect neutrophilia combined with lymphopenia, a pattern frequently observed in patients with severe inflammatory responses[5]. Persistent inflammation may compromise gastrointestinal mucosal integrity, predisposing patients to micro-injury and occult gastrointestinal bleeding.

Supporting this, endoscopic findings in COVID-19 patients have revealed mucosal lesions such as erosions, ulcers, and hemorrhagic gastritis, consistent with inflammation-mediated tissue injury.[8] Moreover, reviews on gastrointestinal bleeding in COVID-19 have emphasized that systemic inflammation, endothelial dysfunction, and coagulation disturbances collectively contribute to both overt and occult bleeding.[4] Thus, an elevated NLR not only indicates systemic inflammation but may also serve as an indirect biomarker of gastrointestinal involvement, including the risk of occult bleeding, in COVID-19 patients. This study aimed to identify the most common gastrointestinal symptoms in COVID-19 patients in Aceh Province, Indonesia, and to investigate whether the neutrophil-to-lymphocyte ratio (NLR) is associated with occult gastrointestinal bleeding.

Methods

A cross-sectional study was conducted at Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia, between January and December 2021. The study population consisted of adult patients diagnosed with COVID-19 who were admitted to the New, Emerging, and Re-emerging Infectious Diseases inpatient ward. Prior to participation, all patients provided informed consent for inclusion in the study and for the collection of information regarding their clinical complaints. Data were obtained from both primary and secondary sources. Primary data were collected through structured interviews conducted directly with patients. Secondary data were extracted from patients' medical records, including laboratory results of blood and fecal examinations.

These data were used to evaluate relevant biochemical parameters and to calculate the neutrophil-to-lymphocyte ratio (NLR). Routine hematological examinations were conducted in the hospital's central laboratory using an automated hematology analyzer. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (NLR =neutrophil count / lymphocyte count). Occult blood in stool samples was examined using an immunochemical fecal occult blood test (iFOBT) following the manufacturer's standard operating procedures. The severity of COVID-19 infection was classified as mild, moderate, or severe according to the World Health Organization (WHO) interim guidance issued in May 2020. This classification was based on clinical presentation, oxygen saturation (SpO_2), respiratory rate, and radiologic findings.

The sample size was determined using a non-probability total sampling technique based on predefined inclusion and exclusion criteria. All participants included in the study were adults (aged ≥18 years) who tested positive for COVID-19 by RT-PCR and presented with gastrointestinal symptoms. Patients with pre-existing gastrointestinal disorders, such as dyspepsia, irritable bowel syndrome, gastroesophageal reflux disease (GERD), gastric ulcer, or duodenal ulcer, were excluded. Pregnant and breastfeeding women were also excluded from the study. The final sample consisted of 30 subjects, representing all eligible patients admitted during the study period. Although the number of subjects was relatively small, it reflected the specific inclusion criteria and limited availability of hospitalized COVID-19 patients presenting with gastrointestinal symptoms, thus capturing the entire accessible population within the given timeframe

The data were descriptively analyzed and statistically presented. Statistical analyses were performed using SPSS software version 23. A descriptive analysis summarized the baseline characteristics of the subjects. The Mann-Whitney U test was performed to assess differences in neutrophil, lymphocyte, and NLR between occult bleeding patients. The level of significance was set to <0.05 to be considered statistically significant.

The ethical approval of this study was registered with the Medical and Health Research Ethics Committee (057/EA/FK-RSUDZA/2021) and further approved by the appropriate institute's ethics committee.

Results

A total of 30 patients were included in the study. The subject's characteristics are shown in Table 1. The majority of COVID-19 patients (80%) had mild symptoms, with moderate and severe being 3.3% and 16.7%, respectively. The most common gastrointestinal manifestations were nausea and loss of appetite (93%), followed by bloating (87%) and vomiting and diarrhea (57%). A smaller proportion of patients experienced difficulty in defecating (23.3%) and ageusia (6.6%).

Based on blood examinations of COVID-19 patients with gastrointestinal symptoms, no organ function abnormalities were found, although mild anemia was present in six patients (Table 2).

Occult hematuria in fecal samples was observed among seven patients. The study found that patients with occult bleeding had higher neutrophil absolute and lower lymphocyte absolute levels than those without. The neutrophil-lymphocyte ratio was higher in patients with occult bleeding (p=0.041), as shown in Table 3.

Table 1 Patient Characteristics with Gastrointestinal Symptoms from COVID-19 (n=30)

Characteristics	n (%)
Age (year) (mean ± SD)	47,9 ±14.3
Gender, n (%)	
Male	19 (63.3)
Female	11 (36.7)
Degree of COVID-19, n (%)	
Mild	24 (80)
Moderate	1 (3.3)
Severe	5 (16.7)
Gastrointestinal symptoms, n (%)	
Nausea	28 (93)
Vomit	17 (57)
Bloating	26 (87)
Constipation	7 (23.3)
Diarrhea	17 (57)
Ageusia	2 (6.6)
Loss of appetite	28 (93)

Table 2 Biochemical Parameters of COVID-19 Patients with Gastrointestinal Symptoms

Parameter	Value (mean ± SD)
Hemoglobin (gr/dL)	13.22±2.25
Hematocrit (%)	39.22±5.70
Platelets (10^3/µl)	281.53±143.90
White blood cells (10^3/µl)	8.84±4.65
Eosinophil	0.12±0.30
Basophil	0.06±0.11
Neutrophil	5.63±4.47
Lymphocyte	1.32±0.97
Monocyte	0.54±0.29
Serum urea (mg/dL)	39.53±34.89
Serum creatinine (mg/dL)	1.42±1.33
Blood glucose (mg/dL)	156.50±83.60
Aspartate aminotransferase (U/L)	33.73±14.36
Alanine aminotransferase (U/L)	35.60±24.20

Discussions

Gastrointestinal manifestations occurred in 61.3% of COVID-19 patients; loss of appetite (34.8%), diarrhea (33.7%), and vomiting (26.4%) were dominant symptoms reported, similar to this study's results. Another study reported abdominal pain was present in COVID-19 patients.[9–11] In severe conditions, patients may experience gastrointestinal bleeding (GIT).[12] Diarrhea seems to be the most severe gastrointestinal symptom experienced in COVID-19 patients, where 10.4% of patients reported the cases.[10,13,14]a newly identified coronavirus (severe acute respiratory syndrome coronavirus (SARS-CoV-2 Despite diarrhea being the predominant gastrointestinal manifestation, the exact underlying causes remain uncertain, as GIT symptoms are observed in nearly one-fifth of COVID-19 patients. Although heartburn was reported in some studies, SARS-CoV-2 infection has not been linked to esophageal symptoms.[9,11,13]

The mechanism causing COVID-19 diarrhea is not entirely known, but viral infections influence intestinal permeability and cause enterocyte malabsorption.[15,16] The most likely cause of diarrhea in COVID-19 patients is epithelial cell injury due to SARS-CoV-2 and the use of antibiotics, which disrupts the gut microbiota balance.[10,17] The intestinal ACE 2 receptor is a significant regulator of amino acid balance, regulating antimicrobial peptide expression, innate immunity, and promoting intestinal microbiota balance. A mouse model study found changes in ACE 2 were associated with colitis, and viral activity causing enzyme modification was observed, increasing the likelihood of intestinal inflammation and diarrhea.[15,18] A previous study confirmed that inflammation occurs in the intestines of COVID-19 patients. Fecal calprotectin, the newly discovered specific biomarker, increased higher in patients with diarrhea, indicating that intestinal inflammation can cause diarrhea by disturbing the intestinal microbiota balance. Some COVID-19 patients revealed occult blood and fungus in stool examinations.[10,19]

Several factors contribute to gastrointestinal manifestations in COVID-19 patients: a) ACE2 receptor binding sites in the digestive tract, b) inflammatory response due to the virus, and c) gut microbiota imbalance. The intestine is the largest immune organ in the human body and the mucosal immune system influences the respiratory tract through changes in the gut microbiota and function.[20,21] Additionally, disruptions in respiratory tract microbiota affect immune regulation in the gastrointestinal tract, a phenomenon known

Table 3 Occult Bleeding and Neutrophil-To-Lymphocyte Ratio

Characteristics	Occult Bleeding Median (min – max)		p-value
	Present occult bleeding (n=7)	Not present (n=23)	
Neutrophil absolute	6.61 (4.76-15.20)	4.60 (1.32-21.41)	0.194
Lymphocyte absolute	0.96 (0.64-1.80)	1.52 (0.40-3.93)	0.229
Neutrophil-lymphocyte ratio	6.04 (4.29-18.20)	3.05 (1.21-48)	0.041

as the gut-lung axis, which explains the clinical gastrointestinal manifestations in COVID-19 patients with pneumonia.[14]

Functional abnormalities of COVID-19 patients in the gastrointestinal tract arise from viral interactions with squamous and columnar epithelial cells disrupted by the ACE2 receptor. ACE2 receptor expression is lower in the esophagus and stomach compared to the intestine. Similarly, expression of the serine protease complex TMPRSS2 is lower in the esophagus and stomach than in the intestinal mucosa. ACE2 serves as the primary receptor for viral entry into gut epithelial cells, which are abundant in the intestine. The virus enters enterocytes, replicates, triggers an inflammatory response, and induces the production of various proinflammatory chemokines and cytokines, some of which increase permeability. Consequently, clinical manifestations of COVID-19 patients are more commonly observed in the upper gastrointestinal tract than in the lower gastrointestinal tract.[15,22] The neutrophil-to-lymphocyte ratio (NLR) has emerged as a reliable and readily available marker of systemic inflammation in COVID-19 patients. Elevated NLR reflects both neutrophil activation and lymphocyte depletion, indicating an exaggerated inflammatory response and immune dysregulation. Several studies have demonstrated that high NLR values correlate with disease severity, cytokine storm, and poor clinical outcomes in COVID-19 patients.[23] Gastrointestinal manifestations, including nausea, vomiting, diarrhea, and even occult gastrointestinal bleeding, have been linked to systemic inflammation and mucosal injury mediated by cytokine release and viral replication within enterocytes. Patients exhibiting gastrointestinal bleeding or occult blood in stool often present with significantly higher NLR values, suggesting more severe systemic inflammation and endothelial damage in the gastrointestinal tract.[24]. Increased NLR in these patients may indicate infiltration of activated neutrophils and reduced lymphocytic immune regulation, leading to disruption of intestinal mucosal integrity. This relationship supports the hypothesis that gastrointestinal involvement in COVID-19 is not only a localized viral effect but also a manifestation of systemic inflammatory burden, in which NLR serves as a simple but powerful biomarker of underlying immune dysfunction.[19]

Nausea and vomiting are acute and early symptoms of COVID-19. Several pathways may cause the mechanism of nausea and vomiting, such as the direct effect of SARS-CoV-2 in the blood acting directly on the brain stem and the release of hormones from enteroendocrine cells in the gastrointestinal tract mucosa.[17]although variable, is comparable with diarrhea. Poor definition of N, confusion with appetite loss, and reporting of N and/or V as a single entity may contribute to reporting variability and likely underestimation. We propose that emetic mechanisms are activated by mediators released from the intestinal epithelium by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 The most frequently reported symptom is loss of appetite, but the symptoms are nonspecific and thought to result from systemic inflammation and malaise associated with SARS-CoV-2 infection and certain medications. Neurosensory symptoms like dysgeusia and anosmia are common in mild COVID-19 cases.[9,13,25]including nausea, vomiting, diarrhea, lack of appetite, abdominal pain, and dysgeusia, in survivors of both mild and severe COVID-19 worldwide and to discuss the potential pathogenesis. Methods: Three databases (PubMed, Scopus, and Web of Science Dysgeusia, also known as parageusia, represents taste disturbances generally with varies prevalence from 3% to 20% in COVID-19 patients. Some studies report rates exceeding 30%. This condition is prevalent taste impairment and affects food intake and quality of life, involving the cranial nerves VII, IX, and X, responsible for taste sensation. Pathogenic factors for dysgeusia in SARS-CoV-2 infection include cranial nerve dysfunction, zinc deficiency, viral interaction with sialic acid receptors, and direct viral attack on the oral cavity.[26,27]

In this study, 23.3% of patients experienced occult gastrointestinal bleeding. These patients exhibited lower lymphocyte counts and significantly higher neutrophil-to-lymphocyte ratios (NLR), suggesting more severe inflammation. An elevated NLR reflects increased neutrophil activation and relative lymphopenia, both markers of systemic inflammatory burden. Previous studies have shown that a high NLR is associated with severe COVID-19, extensive lung involvement on CT scans, and worse clinical outcomes. Thus, NLR can serve as a useful surrogate biomarker for inflammatory status in COVID-19 patients presenting with gastrointestinal involvement[5,28]

This research is limited by the sample size, limiting robust scientific conclusions. It also

focuses narrowly on exploring additional factors influencing gastrointestinal symptoms in these patients without extensive study into comorbidities and their impact on COVID-19 outcomes. Despite limited evidence, further studies of possible pathways for occult bleeding during COVID-19 infection and NLR are recommended as biomarkers in this context.

In conclusion, COVID-19 patients commonly present with gastrointestinal symptoms such as appetite loss, nausea, bloating, vomiting, diarrhea, constipation, and dysgeusia. Diarrhea may be associated with occult gastrointestinal bleeding and elevated neutrophil-to-lymphocyte ratio (NLR), indicating increased systemic inflammation. NLR may serve as a simple and practical biomarker for identifying COVID-19 patients at risk of intestinal involvement or severe disease. These findings also support the gut–lung axis concept, emphasizing the need for an integrated approach in managing COVID-19 that considers both respiratory and gastrointestinal inflammations.

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