Diarrhoea after treatment: an adverse drug reaction in patients with COVID-19

Xiang-Yu Li
Department of Gastroenterology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Ying Wang
Department of Pharmacy, Huai'an Second People's Hospital, Affiliated Huai'an Hospital Xuzhou Medical University

Xu-Sheng An
Intensive Care Unit, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Shu-Feng Yang
Department of Infectious Diseases and Intensive Care Unit, Huai'an Fourth People's Hospital

Peng Shen
Department of Gastroenterology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Xiao-Zhong Yang (xz_yang1023@aliyun.com)
Department of Gastroenterology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Hong-Gang Wang (jgzwhg@njmu.edu.cn)
Department of Gastroenterology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Research Article

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Abstract

The coronavirus disease (COVID-19) is currently prevalent worldwide. We analysed the occurrence of diarrhoea of these patients after treatment. All patients were treated with nebulised α-interferon and oral administration of Lopinavir/Ritonavir tablets. Of the 62 patients, 38 (61.3%) developed diarrhoea after treatment. Of these 38 cases, 63.2% (24/38 cases) had their first diarrhoea within 24 hours after medication. Only 13.2% (5/38 cases) had more than 5 bowel movements per day with a maximum of 10 per day. Patients with diarrhoea had lower white blood cell counts. Leukopenia was a risk factor for the development of diarrhoea. We conclude that COVID-19 patients had a relatively high rate of diarrhoea after treatment. Lopinavir/Ritonavir was speculated to contribute to diarrhea, which is a common adverse drug reaction to Lopinavir/Ritonavir. Patients with reduced white blood cell counts at admission may be more likely to develop diarrhoea after admission.

Background

In December 2019, an outbreak of pneumonia caused by a novel coronavirus infection occurred in Wuhan, China[1]. The World Health Organization named the disease “coronavirus disease 2019” (COVID–19) [2] and the International Committee of Viral Classification named the virus “severe acute respiratory syndrome coronavirus–2” (SARS- CoV–2) [3]. Currently, COVID–19 is becoming increasingly prevalent around the world[4,5]. In addition to China, COVID–19 has also appeared in more than 100 countries, including South Korea, Italy, Iran, France, Germany, the United States and other countries. COVID–19 has become a global public health safety concern due to the difficulty in identifying SARS- CoV–2 carriers[6].

At present, there are no effective drug treatments for COVID–19. Nebulised α-interferon and oral Lopinavir/Ritonavir tablets are recommended by the National Health Commission of China[7–9]. The incidence of adverse reactions in the treatment of respiratory virus infection by aerosol inhalation of α-interferon is only 0.3% [10]. Lopinavir/Ritonavir is commonly used to treat human immunodeficiency virus–1 (HIV–1) infections. The most frequent adverse reactions of this drug are diarrhoea, nausea, vomiting, hypertriglyceridemia, and hypercholesterolemia[11,12] with diarrhoea being the most common, showing an incidence of > 10% and may occur at the start of drug treatment[13–16]. However, the current data of adverse reactions are only limited to HIV-infected patients and no studies have been performed on COVID–19 patients.

Gastrointestinal discomfort is the most common adverse reaction during hospitalisation of COVID–19 patients, among which diarrhoea is the most observed[17]. In this study, the incidence of diarrhoea in COVID–19 patients during hospitalisation was analysed to investigate the correlation between diarrhoea and clinical characteristics, therapeutic drugs, laboratory tests, and hospital stay.

Methods

Subjects

In this study, we enrolled 62 patients diagnosed with COVID-19. They were admitted to Huai'an Fourth People's Hospital on 25 January to 22 February 2020. Inclusion criteria were patients 1) with positive throat swab SARS-CoV-2 nucleic acid test, 2) without diarrhoea before admission, 3) whose dietary habits have not changed after admission, 4) without history of chronic abdominal diarrhoea, and 5) without other history of chronic bowel diseases such as inflammatory bowel disease, colon cancer, and irritable bowel syndrome. Diarrhoea is defined as the passage of three or more loose or liquid stools per day. All the subjects participating signed an informed consent form, and the study was approved by the ethical review committee of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. All methods were carried out in accordance with relevant guidelines and regulations of the hospital.

Therapeutic intervention

The therapeutic drugs involved in this research all refer to the diagnosis and treatment plan of the National Health Commission of China[7-9]. All 62 COVID-19 patients received α- interferon and Lopinavir/Ritonavir treatments. The medication method was aerosol inhalation of a mixture of 5,000,000 U α-interferon and 2 ml sterilised injection water each time, twice a day, at an interval of 8 hours and oral administration of Lopinavir/Ritonavir Tablets, 400mg/100mg each time, twice a day, at an interval of 12 hours. Other drugs were used in combination with these two drugs when required. In addition, symptomatic support therapy was needed to maintain the balance of water and electrolyte homeostasis.

Data collection

The medical history and hospitalisation history of all patients were recorded, including the characteristics and frequency of stool in the six days after admission as well as the date of admission and discharge. Peripheral blood data were retrieved from the laboratory management system. The laboratory data included routine blood parameters such as white blood cell count, neutrophil count, lymphocyte count, macrophage count, eosinophil count, haemoglobin, platelet count. In addition, we also included liver tests (total bilirubin, albumin, alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transferase and lactate dehydrogenase, creatine kinase, prealbumin), renal tests (blood urea nitrogen, creatinine, uric acid), blood coagulation function tests (prothrombin, partial thromboplastin time, fibrinogen, D-dimer), high sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and procalcitonin.

Statistical analysis

SPSS 23.0 software was used for data processing and analysis. The counting data was represented by the number of cases (percentage). The continuous data was non-normally distributed and represented by the median (interquartile range). Chi-square test was used for inter-group comparison. Rank sum test was

used for non-parametric data and binary logistic regression analysis was used for categorical data. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of patients

Of the 62 COVID-19 patients, 33 (53.2%) were males and 29 (46.8%) were females with a median age of 43 years. The median body mass index (BMI) was 24.16 kg/m^2. The median course of disease from onset to admission was six days. Forty six cases (74.2%) had been exposed to COVID-19 patients within 14 days. Five had diabetes, 11 had hypertension, and 13 had a history of surgery. All 62 patients were treated with aerosolised α-interferon and oral Lopinavir/Ritonavir. In combination with these two drugs, 18 patients received Abidol, 21 received antibiotics, 10 received corticosteroids, and 20 received intravenous immunoglobin treatment. The remaining 18 patients did not receive any of the above four drugs. Majority of the patients (74.2%) were discharged with a median hospital stay of 12 days. These clinical features are shown in Table 1 and Table 2.

Occurrence of diarrhoea

The majority of the patients (n = 38, 61.3%) developed diarrhoea after treatment (Table 1). Among these patients with diarrhoea, 63.2% (24/38 cases) developed diarrhoea within 24 hours after medication (Figure 1) and 36.8% (14/38 cases) within 2-6 days after treatment. Only 13.2% (5/38 cases) of these had more than five stools per day with a maximum of ten stools per day (Figure 2).

Influence of clinical characteristics on diarrhoea

We analysed the effect of clinical characteristics on the occurrence of diarrhoea (Table 1). The results showed that the occurrence of diarrhoea was not significantly correlated with age, gender, BMI, course of disease, contact history of confirmed patients, history of diabetes, hypertension, or surgery, and length of hospital stay. The combination of Abidol, antibiotics, corticosteroids, and intravenous immunoglobin also had no significant effect on the occurrence of diarrhoea.

Diarrhoea and laboratory tests

We further analysed the blood parameters of these patients (Table 2). Compared with the group without diarrhoea, patients with diarrhoea had a lower white blood cell count ($P = 0.036$) and no significant difference in other blood parameters. The incidence of diarrhoea was 75.0% (21/28) in patients whose white blood cell count was below the normal limit (4×10^9/L), which was higher than the group with higher white blood cell count (50.0%, 17/34). Further logistic regression analysis showed that patients

with leukopenia were three times more likely to have diarrhoea after treatment for COVID-19. After adjusting for age, gender, BMI, and course of disease, the relative risk was 3.844. These differences were all statistically significant ($P < 0.05$) (Table 3).

Discussion

The pathogenic factor of COVID-19, SARS-CoV-2, is mainly transmitted through the respiratory tract and contaminated aerosol contact[18]. While wearing masks is considered important in prevention and control measures, it is insufficiently effective by itself. Faecal- oral transmission is also currently considered as a potential route of transmission of SARS- CoV-2[12,19]. Although the most common clinical symptoms of COVID-19 are fever and cough[5,20,21], diarrhoea has been reported as the first symptom[19]. In most recent studies, diarrhoea occurred in 2% to 14% of COVID-19 patients[5,22-29]. Of the patients we treated, four had diarrhoea prior to admission and were not included in this study. Research into the mechanism of COVID-19 may offer some explanations why patients have diarrhoea. The receptor of SARS-CoV-2 is ACE2 with which the virus binds to before entering the cell to initiate disease[30,31]. Although ACE2 protein is expressed in the lungs, it is also highly expressed in the small intestine and colon[32]. An autopsy of a deceased COVID-19 patient showed segmental stenosis of the small intestine[33]. The attack of SARS-CoV-2 on intestinal epithelial cells may be an explicable cause of the occurrence of diarrhoea.

In previous medical recommendations in China, aerosolised α-interferon administration and oral Lopinavir/Ritonavir were recommended for the treatment of COVID-19[7-9]. Lopinavir/Ritonavir is commonly used to treat HIV infection, and its incidence of diarrhea is about 15% [16, 34], which is an acceptable range. However, the efficacy and safety of the drug in patients with COVID-19 have not been demonstrated in clinical studies with large sample sizes. Some studies have indicated that diarrhoea is a common side effect of COVID- 19 patients during hospitalisation[17], but it is not clear which drug causes this adverse reaction. Our study analysed the incidence of diarrhoea in COVID-19 patients during hospitalisation and examined the association between diarrhoea and clinical characteristics, therapeutic drugs, laboratory tests, and hospital stay. We found that the incidence of diarrhoea in COVID-19 after treatment was as high as 61.3% and 63.2% of diarrhoea patients developed diarrhoea within 24 hours after medication. The combination of Abidol, antibiotics, corticosteroids, and intravenous immunoglobulins did not significantly affect the incidence of diarrhoea. Considering that all patients in this study were treated with interferon and Lopinavir/Ritonavir, diarrhoea was most likely due to these two drugs. As the adverse reactions of α-interferon inhalation are rare, Lopinavir/Ritonavir was most likely the cause of diarrhoea.

Another result of our study was that 75.0% of COVID-19 patients with white blood cell counts below the normal limit at admission (4×10^9/L) had diarrhoea after treatment. We conclude that COVID-19 with leukopenia was associated with an increased risk of diarrhoea after treatment. We hypothesised that if COVID-19 patients were to be treated with Lopinavir/Ritonavir on admission, probiotics on admission to prevent diarrhoea might be a good option. Intestinal tract is an important immune organ of human body

and maintaining the balance of intestinal flora is conducive to the recovery of viral pneumonia patients[21]. Prior to the occurrence of diarrhoea in patients with COVID-19, even for those who are not ill, intervention or prophylaxis regulating intestinal flora can be given. However, how this should be achieved has not yet been elucidated. Lopinavir/Ritonavir alone can inhibit the SARS coronavirus[35,36] although the combination with other drugs was not found to be superior in improving the clinical symptoms of COVID-19 and accelerating virus clearance[17]. Considering the uncertain efficacy of Lopinavir/Ritonavir and the high incidence of diarrhoea after treatment, advanced development of new drugs is necessary. The antiviral drug Remdesivir, which is mainly used to treat Ebola haemorrhagic fever and MERS[37,38], has been in clinical trials in COVID-19 patients in China[39]. Cepharanthine, a traditional Chinese medicine, is thought to be effective against SARS-CoV-2 now[40]. We expect drugs with good efficacy and few side effects to be used in the clinic as soon as possible.

There are several shortcomings in our research. 1) This study was a retrospective study. The cases collected were from a single centre and the sample size was limited. 2) Since the main therapeutic drugs used in our centre are α-interferon and Lopinavir/Ritonavir, it was impossible to include patients without Lopinavir/Ritonavir as the control group. Therefore, this study could only speculate that diarrhoea was more likely to be caused by Lopinavir/Ritonavir. 3) Due to limited conditions, this study was unable to conduct in-depth research on the mechanism of diarrhoea such as intestinal flora.

Conclusion

COVID-19 patients had a relatively high incidence of diarrhoea after treatment and this adverse reaction was most likely attributed to Lopinavir/Ritonavir. Patients with reduced white blood cell counts at admission may be more likely to develop diarrhoea after treatment. This study provides an important reference for the clinical treatment of COVID-19 patients.

Declarations

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None.

Author contributions

Xiang-Yu Li, Xu-Sheng An and Ying Wang collected the clinical data. Peng Shen and Shu- Feng Yang performed the statistical analysis. Hong-Gang Wang and Xiao-Zhong Yang designed the study and drafted the manuscript. All authors reviewed the manuscript and have approved the submitted version.

Competing interests

The authors declare no competing interests.

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Ethics approval and consent to participate

The study was approved by the ethical review committee of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. Written informed consent was waived given the urgent need to collect clinical data.

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Tables

Table 1 Clinical features of COVID-19 patients and diarrhoea after treatment

Variables	Total (n=62)	Without diarrhea (n=24)	With Diarrhea (n=38)	Chi-square value	P values
Sex, n (%)				0.410	0.522
Male	33 (53.2)	14 (58.3)	19 (50)		
Female	29 (46.8)	10 (41.7)	19 (50)		
Exposure to source of transmission, n (%)	46 (74.2)	17 (70.8)	29 (76.3)	0.231	0.631
Coexisting disorders, n (%)					
Diabetes	5 (8.1)	2 (8.3)	3 (7.9)	0.004	0.951
Hypertension	11 (17.7)	3 (12.5)	8 (21.1)	0.737	0.391
Surgery history, n (%)	13 (21.0)	3 (12.5)	10 (26.3)	1.980	0.159
Combined drugs, n (%)					
Arbidol	18 (29.0)	10 (41.7)	8 (21.1)	3.034	0.082
Antibiotics	21 (33.9)	8 (33.3)	13 (34.2)	0.005	0.943
Corticosteroids	10 (16.1)	2 (8.3)	8 (21.1)	1.596	0.206
Intravenous immunoglobin	20 (32.2)	5 (20.8)	15 (39.5)	2.339	0.126
Without the above four drugs	18 (29.0)	7 (29.2)	11 (28.9)	0.0003	0.985

Table 2 Laboratory tests in patients with and without diarrhoea

Variables	Total (n=62)	Without diarrhea (n=24)	With diarrhea (n=38)	P values
Age (year)	43 (32-53)	47 (33-51)	40 (31-53)	0.613
BMI (kg/m^2)	24.16 (22.47-26.73)	23.43 (21.48-26.81)	25.12 (22.86-26.73)	0.231
Course of disease (days)	6 (4-9)	7 (5-10)	5 (3-7)	0.068
Length of hospital stay (days)	12 (10-15)	11 (10-13)	13 (10-16)	0.114
White blood cell counts (× 10^9/L)	4.24 (3.75-5.71)	4.89 (3.87-6.33)	3.88 (3.44-4.99)	0.036
Neutrophil counts (× 10^9/L)	2.72 (2.06-3.51)	3.02 (2.05-4.00)	2.56 (2.06-3.13)	0.133
Lymphocyte counts (× 10^9/L)	1.31 (0.91-1.70)	1.48 (1.01-1.73)	1.19 (0.85-1.62)	0.155
Monocyte counts (× 10^9/L)	0.36 (0.29-0.47)	0.41 (0.32-0.52)	0.33 (0.28-0.45)	0.054
Eosinophil counts (× 10^9/L)	0.02 (0.01-0.04)	0.03 (0.01-0.07)	0.02 (0.01-0.03)	0.220
Hemoglobin (g/L)	147 (132-157)	143 (132-155)	149 (135-160)	0.402
Platelet counts (× 10^9/L)	156 (127-199)	155 (125-202)	158 (128-199)	0.914
hsCRP (mg/L)	8.83 (2.47-24.01)	8.79 (1.66-23.15)	10.42 (2.91-26.82)	0.954
ESR (mm/h)	26 (14-44)	25 (10-54)	27 (14-34)	0.880
Total bilirubin (umol/L)	13.21 (8.75-18.13)	13.95 (10.03-18.43)	12.4 (8.15-17.9)	0.308
Albumin (g/L)	41.3 (37.8-42.5)	39.2 (36.8-41.9)	41.1 (39.3-42.9)	0.199
Alanine transaminase (U/L)	29 (20-40)	25 (14-40)	29 (22-40)	0.347
Aspartate aminotransferase (U/L)	23 (19-33)	24 (17-33)	22 (20-34)	0.732
Alkaline phosphatase (U/L)	60 (49-72)	59 (49-68)	60 (48-72)	0.802
Gamma-glutamyl transferase (U/L)	34 (17-54)	34 (21-57)	33 (17-47)	0.894
Lactate dehydrogenase (U/L)	202 (160-251)	202 (158-243)	202 (160-257)	0.732
Creatine kinase (U/L)	60 (43-90)	58 (41-146)	61.5 (46-88)	0.783
Blood urea nitrogen (mmol/L)	4.15 (3.44-5.16)	4.42 (3.45-5.84)	3.88 (3.42-5.02)	0.180
Creatinine (umol/L)	70 (55-82)	64 (53-80)	73 (56-83)	0.280
Uric acid (umol/L)	253 (201-313)	211 (191-322)	259 (225-312)	0.125
Total cholesterol (mmol/L)	3.87 (3.34-4.41)	3.82 (3.50-4.45)	3.94 (3.18-4.38)	0.851
Triglyceride (mmol/L)	1.08 (0.92-1.64)	1.30 (1.04-1.49)	0.98 (0.79-1.61)	0.188
Fasting blood glucose (mmol/L)	5.75 (5.14-6.33)	5.48 (4.71-6.02)	5.79 (5.28-6.79)	0.094
Prealbumin (mg/L)	163 (132-201)	162 (130-192)	163 (135-201.5)	0.683
High density liptein cholesterol (mmol/L)	0.99 (0.87-1.16)	1.03 (0.89-1.22)	0.98 (0.86-1.15)	0.283
Low density lipoprotein (mmol/L)	2.29 (1.83-2.75)	2.14 (1.84-2.52)	2.39 (1.8-2.73)	0.411
Procalcitonin (ng/ml)	0.19 (0.10-0.27)	0.24 (0.15-0.31)	0.17 (0.19-0.25)	0.151
Prothrombin time (s)	13.2 (12.8-13.7)	13.4 (12.8-13.8)	13.1 (12.8-13.6)	0.282
Partial thromboplastin time (s)	35.5 (32.5-37.55)	35.3 (32.5-38.0)	35.5 (32.3-37.5)	0.974
Fibrinogen (g/L)	4.12 (3.01-4.81)	4.16 (3.06-5.40)	4.12 (3.47-4.78)	0.712
D-dimer (ug/ml)	0.27 (0.12-0.47)	0.31 (0.21-0.52)	0.23 (0.07-0.41)	0.064

Table 3 Logistic regression analysis of the odds ratios (ORs) for diarrhea relative to white blood cell count

WBC < 4 × 10^9/L	ORs	95% CI	P value
Model 1	3.000	1.011-8.905	0.048
Model 2	3.251	1.030-10.262	0.044
Model 3	3.844	1.084-13.636	0.037

Model 1: not adjusting;
Model 2: adjusting for age and gender;
Model 3: adjusting for age, gender, BMI and course of disease

Figures

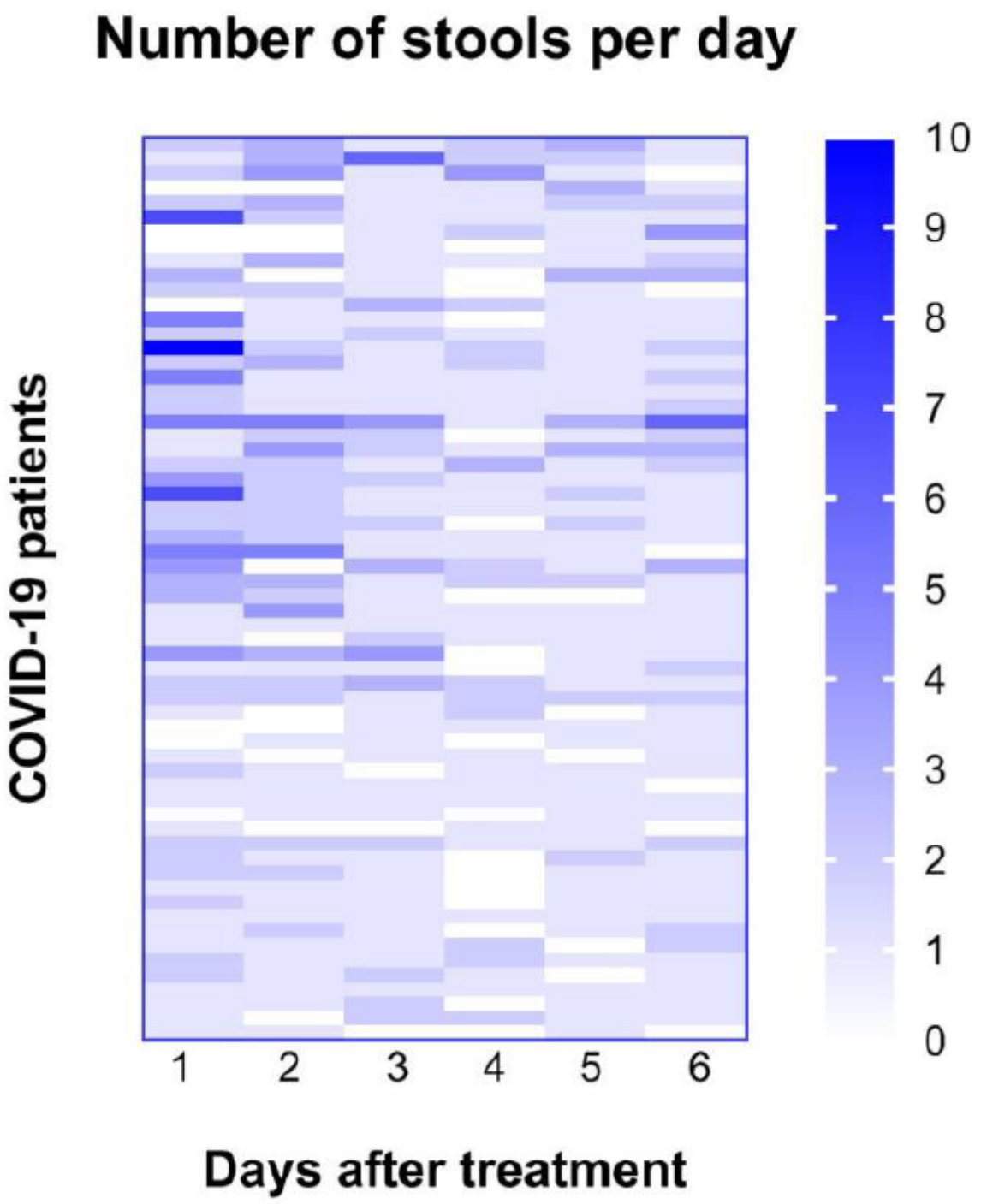

Figure 1

Number of stools per day of COVID-19 after treatment. Day 1 refers within 24 hours after treatment, day 2 refers within 48 hours and analogy to day 3, day 4, day 5, and day 6.

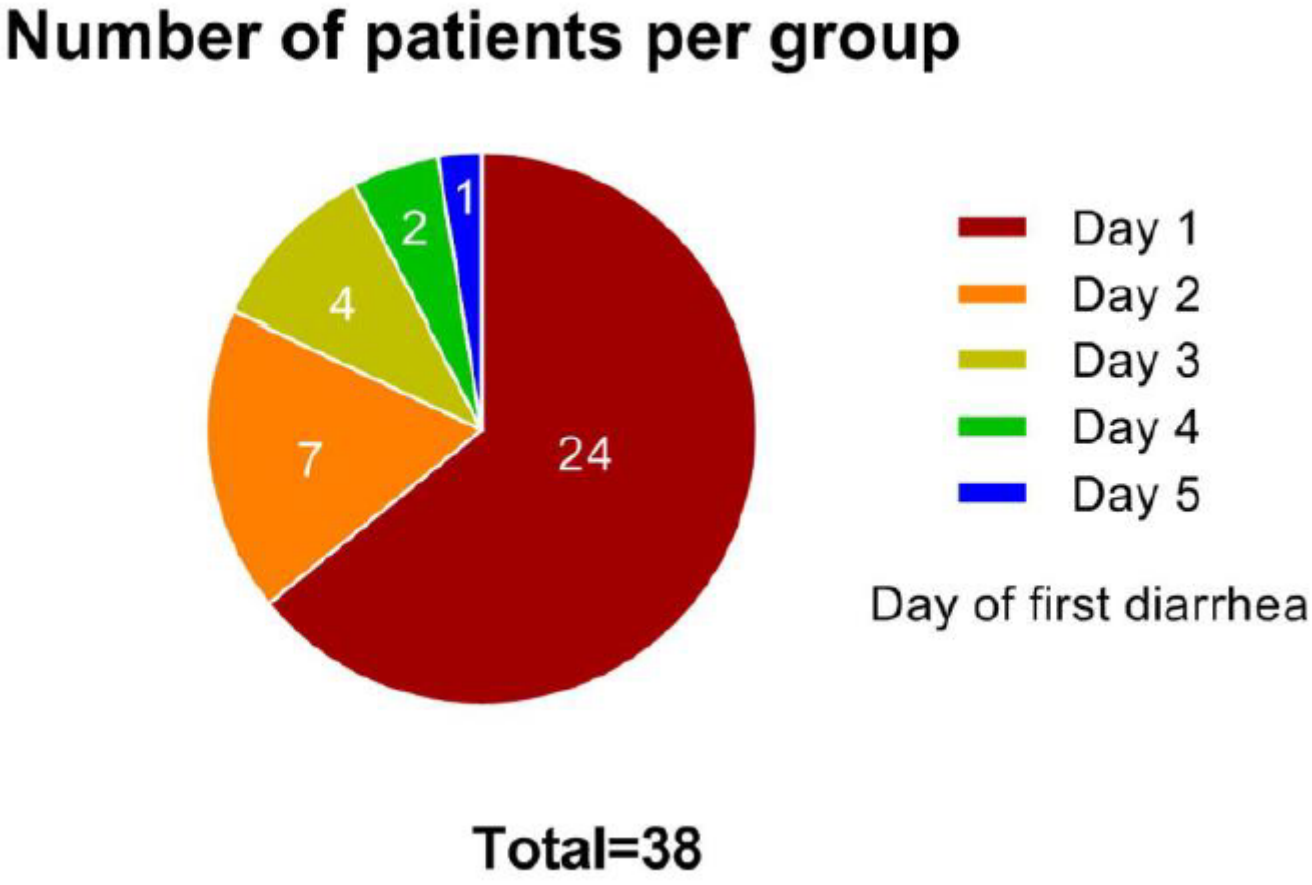

Figure 2

The day of first diarrhea occurred in COVID-19 after treatment.