

Gastrointestinal symptoms characteristics of coronavirus disease 2019 patients: a cohort study

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SUBJECT AREAS

Gastroenterology & Hepatology Infectious Diseases

KEYWORDS

SARS-CoV-2, COVID-19, gastrointestinal symptoms, cohort study

Abstract

Background: To describe the frequency and distribution characteristics of gastrointestinal symptoms of coronavirus disease 2019 (COVID-19) patients.

Methods: As a cohort study, all confirmed COVID-19 patients with gastrointestinal symptoms at Xiangyang No.1 people's hospital were included until February 21st, 2020. Course of disease no less than 21 days. Gastrointestinal symptoms relevant data were extracted and analyzed. The frequency histograms of the symptoms were plotted. Main symptom characteristics were summarized.

Results: Of 50 included patients with gastrointestinal symptoms, 21 were male, 29 were female. The mean age was 53 (SD 16) years. Course of disease ranged from 21 to 34 days with a median of 26 days. Among all patients, 16 were critically ill and five died, 12 discharged. Thirty-one clinical symptoms occurred 3168 times in total, 6 gastrointestinal symptoms occurred 439 (13.86%) times and 25 non-gastrointestinal symptoms occurred 2729 (86.14%) times. All symptoms and non-gastrointestinal symptoms distributed in 1 to 34 days, reached peak on 6th day of follow up, first seven days were the fastigium and decreasing in the rest days. Gastrointestinal symptoms mainly distributed in 1 to 34 days, reached a peak of 36 times per day on 6th of follow-up with a fastigium during 6 to 12 day, showed a trend of rise first and then fall. Nausea, vomit and abdominal discomfort occurred 133, 70 and 62 times, respectively.

Conclusions: A symptom frequency to time distribution model could describe the disease process quantitatively, indicating the change law of gastrointestinal symptoms and the organ damages in gastrointestinal system, could help us to better understand and treat the new disease. Females showed higher incidence of gastrointestinal symptoms, whether there is a sex difference in susceptibility needs to be further confirmed.

Trial registration: retrospectively registered

Authors Guoxin Huang and Shengduo Pei contributed equally to this work.

Background

In early December 2019, a novel virus-infected pneumonia outbreak in Wuhan, China. It has spread to all over China and the world within a short period of time and has become a big public health threat.

(1) Through whole genome sequencing, Zhu et al identified it as a new β - coronavirus with an enveloped positive-sense single-stranded RNA, highly homologous with the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). (2, 3) On 11th Feb 2020, the International Committee on Taxonomy of viruses officially named the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On the same day, World Health Organization announced the name of the disease cause by the virus which is COVID-19, in short of "coronavirus disease 2019".(4) Early patients were associated with a seafood market,(5) bats are considered as intermediate host.(6) SARS-CoV-2 spreads mainly through respiratory tract and close contact, the vertical transmission during pregnancy is not confirmed yet.(7-9) Some researchers reported that they have successfully isolated virus from infected patients' feces. COVID-19 manifests mainly fever, cough, sputum production,(10, 11) fatigue and shortness of breath with a fatality rate of 3%. (12, 13)

Until 21st Feb 2020, 76 288 confirmed cases and 5 365 suspected cases have been reported.(14) Recent clinical studies have revealed some informations about COVID-19. Chang et al reported major clinical manifestations including cough, myalgia and headache.(15) Huang et al showed fever and cough as major symptoms and patients with diarrhea occupied 3% of all.(16) In the study of Chen et al, some patients had diarrhea, nausea and vomit as clinical manifestation.(17) Moreover, Wang et al have reported COVID-19 patients symptoms including gastrointestinal symptoms like diarrhea (10.1%), nausea (10.1%), vomit (3.6%), abdominal pain (2.2%).(18) Zhong et al have isolated virus from patients' feces, indicating that virus may exists in gastrointestinal tract. Xiao et al provided evidence of gastrointestinal infections.(19) Taken all together, SARS-CoV-2 is highly susceptible of infecting gastrointestinal system and induce associated symptoms.

Methods

Study design and participants

For this prospective and single-center study, we enrolled COVID-19 patients who were admitted to Xang Yang No.1 People's Hospital before February 9, 2020. COVID-19 were diagnosed according to Diagnosis Guidebook for Novel Coronavirus Pneumonia the 6th Edition published by National Health

Commission of the People's Republic of China.(20) To investigate gastrointestinal symptoms in COVID-19 patients, we included patients that had been with COVID-19 for more than 21 days and developed gastrointestinal symptoms. Patients' data were collected until February 21, 2020. The study was approved by the ethics review board at Xiang Yang No.1 People's Hospital (No. 2020GCP012).

Data collection

We extracted the patient's data from the hospital information system in two groups (two physicians per one group) and cross-checked after completion. The data included demographic characteristics, clinical symptoms, chief complaint, management and outcome. We recorded symptom occurrence for each patient as 'showing' if the patient manifested the symptom in that day, regardless of the frequency and severity. To describe the variation of symptom occurrence, we summed the number of patients with 'showing' by symptoms per day and plotted the frequency over time when individual patient had initial symptoms as the first day.

Outcomes

We included epidemiological features, overall symptoms, gastrointestinal symptoms, non-gastrointestinal symptoms etc, management and outcome as the outcomes in this study.

Statistical analysis

Categorical data were described using frequency and percentage. We tested normality of continuous data and used mean±standard deviation to describe variables with normal distribution, otherwise median were used. All the analyses were performed in Stata 14.

Results Participants

The cohort collected data of 314 patients admitted in Xiangyang No.1 people's hospital until February 9th, 2020 and followed up until February 25th, 2020. 107 patients diagnosed with COVID-19 of which 94 patients developed gastrointestinal symptoms. However, we found that loss of appetite occurrence was significantly different from the distribution of other gastrointestinal symptoms(Figure 1A), and loss of appetite is a symptom that can be induced by many factors, not only specific to gastrointestinal diseases. Hence, we categorized loss of appetite into non-gastrointestinal symptoms.

After the exclusion of 32 patient that only developed loss of appetite and 12 patients with disease course less than 21 days, we finally included 50 patients as participants in this study.

Epidemiological features

There were 21 males and 29 females (male: female = 0.72), ranging from 15 to 90 years old (mean age: 53 ± 16 years old). Hypertension, diabetes, coronary artery disease, tuberculosis and pharyngitis were the main comorbidities. Disease course ranged from 21 to 34 days, with a median of 26 days.

There were 16 severe cases (32%), with an average age of 67 ± 12 years old, of which five cases (10%) died (mean age: 74 ± 12 years old). There were 12 cases cured and discharged.

Clinical symptoms

Totally, we observed 31 distinct clinical symptoms, mainly including fever, cough, expectoration, loss of appetite, diarrhea, nausea, vomiting and abdominal pain etc; all the symptoms occurred 3168 times during the follow-up, of which 439 times (13.86%) were for six gastrointestinal symptoms and 2729 (86.14%) for 25 non-gastrointestinal symptoms (Table 1).

Figure 1B-1E showed the variation of symptom occurrences over time. Clinical symptoms occurred lasted for 34 days in the patients, with a peak of 226 occurrences/day in the 2th and 6th day, and the first seven days were the peak period. Gastrointestinal symptoms occurred in the first 34 days, with a peak of 36 occurrences/day in the 6th day; the peak period was 6th -12th day, during which the occurrences first increased and then decreased. Non-gastrointestinal symptoms distributed in the first 34 days, with a peak of 208 occurrences/day in the 2rd day; the first six days were the peak period, during which the occurrences declined gradually.

Gastrointestinal symptoms

We observed six gastrointestinal symptoms, which were diarrhea, nausea, vomiting, abdominal pain, acid reflux and heartburn. Patients with gastrointestinal symptoms were treated with Montmorillonite powder, Domperidone ect.

Diarrhea occurred 150 times (34.17%) in 32 patients during the first 16 days, with a peak of 13 occurrences/day in the 6th, 10th and 11th days; two high points can be observed in the frequency plot, respectively in 5th -7th and 9th-12th day (Figure 2A). 12 patients had abnormal stool with 45

occurrences; 8 patients had watery stool, three had mushy stool and one had yellow loose stool (Figure 2B).

Nausea happened 133(30.30%) times in 29 patients during the first 28 days and peaked in the 6th and 10th day with 11 occurrence/day; 6th-10th day were the peak period, during which the occurrences first increased and then decreased (Figure 3A); nausea and vomiting occurred 195 times (44.42%) during the first 28 days, with a peak of 15 times/day in the 6th day; 6th-10th day were the peak period, where the occurrences first increased and then decreased (Figure 3B).

Abdominal discomfort occurred 70 times (15.95%) in the first 34 days; six patients manifested acid reflux (18 times) and three had heartburn (6 times).

Discussion

COVID-19 is a newly emerging viral infectious disease and has been inadequately studied. Its development, progression and clinical characteristics require in-depth research.(21-24) It has been well acknowledged that symptoms are manifestations of diseases' development and changes, and the changes of symptoms can reflect the natural progression of the disease to a certain degree in the absence of interventions. Therefore, analyzing symptoms provides us an effective and vital method to explore a new disease.

Symptom information belongs to descriptive data and convey unclear messages, especially on quantitative scales, such as severity, in most cases, thereby with little comparability across patients. To make up this limitation, we characterized the symptoms as "yes" and "no" regardless of the frequency and severity in that day. Using this way, information from a single case with multiple records constructed a picture of the time-varying distribution of symptoms and multiple cases with multiple records described the frequency distribution on the time axis. It is of great significance and practice to construct such a distribution of several common clinical symptoms to study a disease objectively and quantitatively.

Of 107 COVID-19 patients, around 46.73% had gastrointestinal symptoms (only second to respiratory symptoms). In addition, we found that most symptoms basically disappeared after 21- 28 days, and only a few patients had symptoms, such as cough and sputum, and breathing difficulty (in severe

patients with impaired respiratory function). In the present study, we included patients with disease courses longer than 21 days (ranging from 21 to 34 days with a median of 26 days). Although our findings could not represent symptom change during the entire disease course, it reflected the changes in the acute phase of COVID-19 at least. Our study understood the nature of the disease by studying related symptoms, thereby facilitating the diagnose and treatment for the disease. Among 50 patients, there were 21 males and 29 females. The ratio of male to female was 0.72 indicating a sex-specific susceptibility to symptoms or damage of the gastrointestinal system. However, observed sex difference needs further verification given a limited number of patients we included.

The average age of included patients was 53 years old. There were 16 critically ill cases with a mean age of 67 years old and 5 death with a mean age of 74 years old. The ratio of critical illness and death was 32% and 10%, respectively, which was higher than previous cross-sectional studies. We also found that COVID-19 mainly occurred among middle-aged and elderly patients. The risk of severe illness and death elevated with the increasing age, which might be explained by the decline in regeneration and repair ability, and immunity among the elderly. Notably, the ratio of severe illness and death was also higher in patients with significant gastrointestinal symptoms, suggesting that the invasive ability of 2019-nCoV is stronger than expected and the virus may cause multi-system dysfunction and more serious consequences.

The frequency of nausea, vomiting, and acid reflux accounted for 49.89% of gastrointestinal symptoms, mainly indicating the pathological changes in esophagus and stomach, and partly in liver, gallbladder and pancreas. Diarrhea accounted for 34.17% and were mainly related to colon and ileal jejunal dysfunction. The frequency and severity of above symptoms indicated the level of damage to the relevant organs. However, the organ localization was unclear for certain symptoms, such as decreased appetite and abdominal discomfort. In addition, the effects of the virus on the gastrointestinal system were more likely to be an extensive damage to the entire gastrointestinal system with a clear feature of more and worse upper gastrointestinal tract symptoms. Recent studies have shown that 2019-nCoV invades cells by binding to cell surface ACE-2 receptors that widely exist

in a variety of human cells.(25–28) Therefore, 2019-nCoV virus can not only cause damage to lung tissues, but also other tissues and organs, thereby causing systemic cell damage. The patients with systemic infection had clinical manifestations in multiple organs, as well as more a higher rate of severe illness and death.

By analyzing the time distribution of symptom frequency, we found significant differences across the distribution patterns of “all symptoms”, “non-gastrointestinal symptoms” and “gastrointestinal symptoms”. Especially, we detected a difference of damages in nature caused by SARS-CoV-2 when focusing the differences of “non-gastrointestinal symptoms” and “gastrointestinal symptoms” distributions. Taking distribution patterns and the ratio of severe illness and death together, COVID-19 with significant gastrointestinal symptoms was a unique type of COVID-19. The presence of gastrointestinal symptoms indicated that the virus not only invaded the respiratory system, but also caused damage to the gastrointestinal and even multiple systems. Multiple system damage might be the reason for the high ratio of severe illness and mortality in patients with gastrointestinal symptoms. Further research is needed on the exact location, mechanism, and extent of gastrointestinal damage.

We additionally performed separate analyses for 4 symptoms that occurred more than 5% of the total frequency of gastrointestinal symptoms. Diarrhea, nausea, and vomiting were typical symptoms occurring in 1–16 days with a peaking in 6–12 days. These symptoms can exactly reflect the pathological changes of gastrointestinal system caused by COVID-19. Watery stool is the distinguished gastrointestinal symptom and caused by intestinal mucosal hyperemia, especially colonic mucosal hyperemia, and increased secretion. The watery stool symptom appears and peaks at an earlier stage, normally in 1–12 days.

There are several limitations in the present study. Although our study collected and analyzed the data after 21 days since the onset of COVID-19, it might not completely reflect the whole disease course given a possible even longer disease course of COVID-19. We noticed that the observation of patients in the later stage was insufficient and might not exactly reflect the recovery process of COVID-19, which warrants more study. During data extraction, we found that doctors paid more attention to

severe patients and their main symptoms, whereas the documentation was less accurate and clear regarding the disease's development process of chief complaint before the hospitalization, accompanying symptoms and the mild discomfort of the patients during the rehabilitation period, which might bias our findings. We treated symptom information as dichotomous data ("yes and no"), which was less likely to reflect the severity of symptoms, the frequency within a single day, and the frequency change of symptoms. Thus, our findings should be cautiously interpreted when taking the change of severity of symptoms and corresponding cumulative effects into consideration. In addition, symptom records were scarce for critically ill patients with unconsciousness and therefore, could not reflect the exact change of the disease at this stage for this type of patients.

Conclusions

The frequency to time distribution model of specific symptom enabled us to describe the course of COVID-19 objectively and quantitatively, revealed the change law of the disease and to improve the diagnosis and treatment. Significant differences were observed between gastrointestinal symptoms and non-gastrointestinal symptoms, which indicates the organ damage of gastrointestinal system. COVID-19 patients with multi-system dysfunction were more likely to show gastrointestinal symptoms, made them become the subgroup with higher risks. Among all included patients, females occupied a bigger proportion and showed higher incidence of studied symptoms. However, further studies of the susceptibility between genders of SARS- CoV-2 infection-caused gastrointestinal dysfunction are needed.

List Of Abbreviations

COVID-19:Corona Virus Disease 2019;SARS-CoV-2:Severe Acute Respiratory Syndrome Coronavirus 2;RNA:Ribonucleic Acid;ACE-2:adaptive communication environment-2

Declarations

Ethics approval and consent to participate

The study was approved by the ethics review board at Xiang Yang No.1 People's Hospital (No. 2020GCP012). Conventional informed consent was not necessary in this study, due to the retrospective nature of the study, informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request;E-mail: xyxzyxzx@163.com.

Competing interests

The authors declare that they have no competing interests

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Concept and design: G. Huang, S. Pei, Y. Wang, and B. Pei; Recruited patients: X. Liu, J. Chen, L. Wang, J. Ai, Y. Wang; Data extraction: G. Huang, S. Pei, Y. G. Qu, M. Zhang, H. Zhu, L. Chen; Performed data analysis: G. Huang, S. Pei, B. Pei; Drafted and revised the manuscript: G. Huang, S. Pei, B. Pei, B. Tang, and S. Yuan. All authors provided critical review of the manuscript and approved the final draft for publication. G. Huang, S. Pei Contributed equally.

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Tables

Table 1. Clinical symptoms of the participants.

Symptoms	No. of patients	Frequency	Perc
Gastrointestinal symptoms		439	
Diarrhea	32	150	
Nausea	29	133	
Vomiting	18	62	
Abdominal pain	16	70	
Acid reflux	6	18	
Heartburn	3	6	
Non-gastrointestinal symptoms		2729	
Total		3168	

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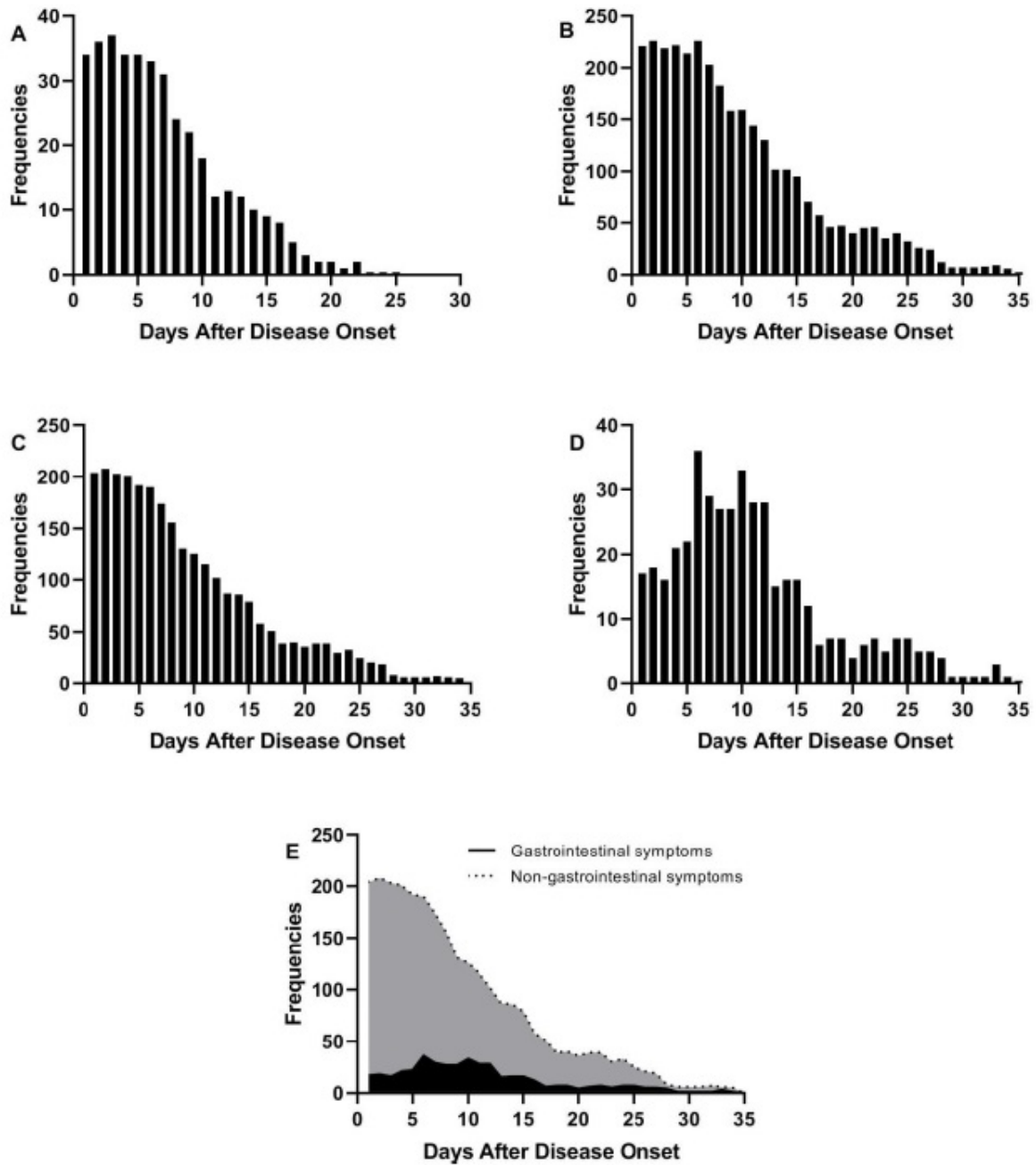
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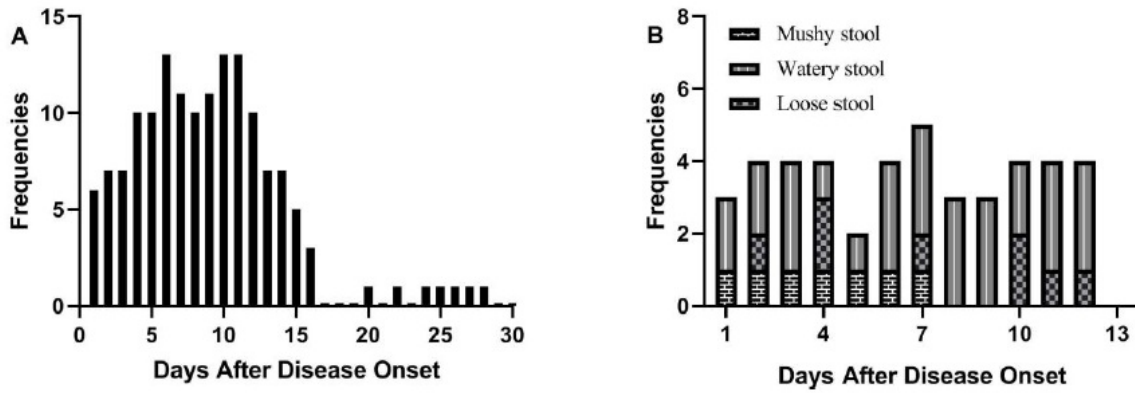
Figures



A Loss of appetite ;B All symptoms ;C Non-gastrointestinal symptoms;D Gastrointestinal symptoms;E Comparison between gastrointestinal and non-gastrointestinal symptoms.

Figure 1

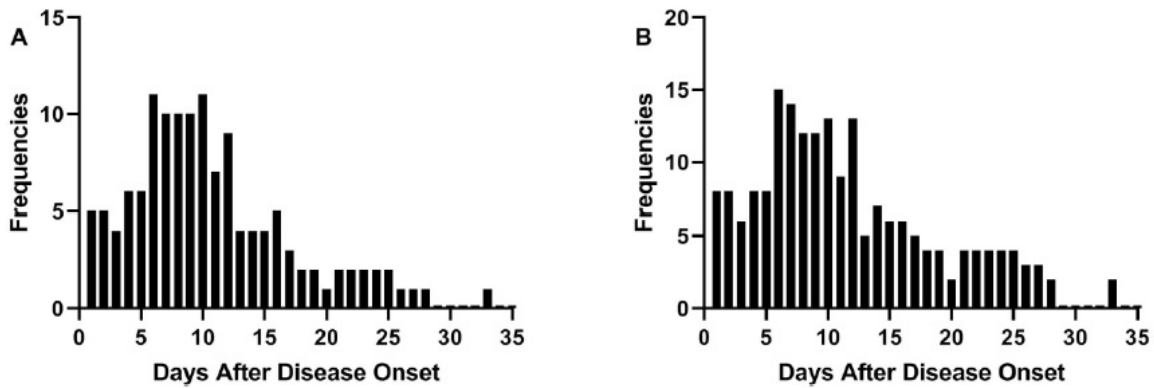
The variation of symptom occurrence over times.



A Diarrhea;B Abnormal stool

Figure 2

The variation of diarrhea and abnormal stool occurrence over time.



A Nausea;B Nausea and Vomiting

Figure 3

The variation of nausea and vomiting occurrence over time.

Supplementary Files

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