Difference Between COVID-19 Alpha Variant B.1.1.7 and the Original Virus in Gastrointestinal Symptoms and Mortality: Does a Negative Correlation Exist?

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ABSTRACT

Background: Up to half the patients diagnosed with acute coronavirus disease 2019 (COVID-19) presented with gastrointestinal symptoms. Gastric mucosal cells, enterocytes, and colonocytes express the viral entry receptor angiotensin-converting enzyme 2 (ACE2) and coreceptor transmembrane protease serine 2 (TMPRSS2) and are prone to infection. Direct infection of gastrointestinal epithelial cells has been demonstrated. COVID-19 disease was first diagnosed in Israel at the end of February 2020 with 842,536 confirmed cases and 6428 deaths by the end of June 2021. In our multicenter, retrospective cohort study, we looked for gastrointestinal signs and symptoms in two periods and correlated them with mortality. Period 1 included the first and second waves and the original virus. Period 2 represented the third wave and the alpha variant.

Objectives: To reveal gastrointestinal signs and symptoms in two periods and correlate them with mortality.

Methods: From 22,302 patients hospitalized in general medical centers, we randomly selected 3582 from Period 1 and 1106 from Period 2. The study was performed before vaccinations were available.

Results: Gastrointestinal signs and symptoms, diarrhea, vomiting, abdominal pain, and taste/smell loss were significantly more prevalent during Period 1. Thirty-day mortality and in-hospital mortality were significantly higher in Period 2 than in Period 1, 25.20% vs. 13.68%, and 21.17% vs. 12.87%, respectively ($P < 0.001$).

Conclusions: Thirty-day mortality and in-hospital mortality rates were 1.84 and 1.64 times higher from 6 November 2020 to 15 January 2021, the alpha variant, and in negative correlation with gastrointestinal symptoms.

IMAJ 2023; 25: 453–455

KEY WORDS: case fatality rate, coronavirus disease 2019 (COVID-19), epidemic, gastrointestinal symptoms, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Up to half of patients diagnosed with acute coronavirus disease 2019 (COVID-19) disease had gastrointestinal symptoms [1]. Gastric mucosal cells, enterocytes, and colonocytes express the viral entry receptor angiotensin-converting enzyme 2 (ACE2) and coreceptor transmembrane protease serine 2 (TMPRSS2) and are prone to infection [2]. Recently, direct infection of gastrointestinal epithelial cells has been demonstrated. In addition, intestinal organoids are used as a tool to study specific replication behavior of different viral variants [3]. Reduced viral replication efficacy, less cell damage, reduced lactose dehydrogenase and high mobility group box 1 protein (HMGBB1) release of Omicron BA.1 and BA.2 compared with the B.1.617.2/Delta variant was recently found [4,5]. To the best of our knowledge, the spectrum of gastrointestinal symptoms has never been correlated with disease severity, complications, or case fatality rates, nor difference in their clinical presentation between variants of the virus was demonstrated.

COVID-19 was first diagnosed in Israel at the end of February 2020. By the end of June 2021, 842,536 confirmed cases and 6428 deaths had accumulated. In our multicenter, retrospective cohort study, which was published elsewhere, we described the clinical characteristics and outcome of the disease [6]. We looked at the same cohort for gastrointestinal signs and symptoms of the patients in two periods. Period 1 represented the first and second waves and the original virus, Period 2 represented the third wave and the alpha variant. We compared case fatality rates in the two periods.

PATIENTS AND METHODS

Between 28 February 2020 and 5 November 2020, 19,308 COVID-19 patients were hospitalized in 24 general hospitals in Israel. We randomly selected 3582 patients in the first and second waves (Period 1). Between 6 November 2020 and 15 January 2021, 2994 COVID-19 patients were hospitalized in six general hospitals. From this group, we randomly selected 1106 patients for the study in the third wave (Period 2). The study was conducted before vaccinations were available. The original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) characterized Period 1, and the British variant characterized Period 2. Only confirmed cases of COVID-19, defined by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected from a nasopharyngeal swab,

were included. Gastrointestinal symptoms, diarrhea, abdominal pains, vomiting, and smell and taste loss were computed for each patient and correlated with 30-day-mortality and in-hospital mortality rates for both periods.

STATISTICAL METHODS
Results are presented as percentage of the population and relative ratios. Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). Data from Period 1 (first and second waves combined) was compared with data of Period 2 (third wave). We performed multivariate analysis to correlate gastrointestinal symptoms with case fatality rates.

RESULTS
Gastrointestinal signs and symptoms, diarrhea, vomiting, abdominal pain, and loss of taste and smell were less prevalent in Period 2 than in Period 1 [Table 1, Figure 1]. The relative ratios between Period 2 and Period 1 for diarrhea, vomiting, abdominal pain and smell and taste loss were 0.53, 0.77, 0.60, and 0.63, respectively. Thirty-day mortality and in-hospital mortality rates were significantly higher in Period 2 than in Period 1, 25.20% vs. 13.68%, and 21.17% vs. 12.87%, respectively ($P < 0.001$), relative ratios 1.84 and 1.64, respectively.

The negative correlation between gastrointestinal symptoms and in-hospital mortality rate was also found within each period. We separated the hospitals of both periods into two groups: those with a relatively high CFR and those with a lower CFR. In Period 1, 5.42% and 6.59% of patients who died (in-hospital

Figure 1. Comparison of gastrointestinal symptom and mortality rates between COVID-19 pandemic waves 1 and 2 (Period 1) and wave 3 (Period 2)
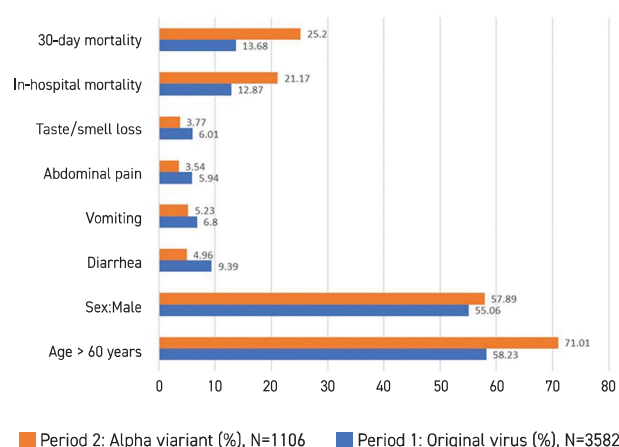
COVID-19 = coronavirus disease 2019

Table 1. Relative ratios of gastrointestinal symptoms correlated with case fatality rates: Period 1 and Period 2

Parameter	Period 1: Original virus (%), N=3582	Period 2: Alpha variant (%), N=1106	Relative ratio
Age: > 60 years	58.23	71.01	1.22
Sex: male	55.06	57.89	1.05
Diarrhea	9.39	4.96	0.53
Vomiting	6.80	5.23	0.77
Abdominal pain	5.94	3.54	0.60
Taste/smell loss	6.01	3.77	0.63
In-hospital mortality	12.87	21.17	1.64
30-day mortality	13.68	25.20	1.84

Table 2. Correlation between case fatality rates and taste/smell loss within the waves

	Original virus (waves 1+2), taste and smell loss (%), N=3582	Rate of in-hospital mortality (%)	Alpha variant (wave 3), taste and smell loss (%), N=1106	Rate of in-hospital mortality (%)
Case fatality rates: high (> 14%)	5.42	14.98	3.06	21.88
Case fatality rates: low (< 14%)	6.59	10.83	3.27	20.67
Relative ratio	0.82	1.38	0.72	1.06

Table 3. Correlation between case fatality rates and gastrointestinal symptoms in different cohorts

Parameter	Series				
	Niv [6] Period 1	Niv [6] Period 2	Liang [7]	Casas Rojo [8]	Rubio-Rivas [9]
Number	3462	1106	1590	15111	12066
Diarrhea (%)	9.39	4.96	4.2	23.7	24.4
Vomiting (%)	6.80	5.23	5.8	–	7.4
Abdominal pain (%)	6.94	3.54	3.2	–	6.1
Taste and smell loss (%)	6.01	3.77	–	7.1	9.9
Case fatality rates (%)	12.87	21.17	3.2	21	20.9

death) in hospitals with higher than 14% in-hospital-mortality rate or lower than 14%, had loss of taste and smell, respectively, relative ratio (RR) 0.82 for loss of taste and smell and 1.67 for in-hospital-mortality rate. The match figures for Period 2 were 3.06% and 4.27%, respectively, RR 0.72 for loss of taste and smell and 1.43 for in-hospital-mortality rate [Table 2].

In a multivariate analysis including age, sex, and gastrointestinal symptoms, only abdominal pain was found to be protective against in-hospital mortality in Period 1 ($P = 0.0006$), and vomiting had a trend in Period 2 ($P = 0.079$).

DISCUSSION

CFR was higher in Period 2 than in Period 1 of the pandemic, and in a negative correlation with gastrointestinal symptoms. In addition, for each period we found the same negative correlation between gastrointestinal symptoms and CFR, even though in a multivariate analysis, only abdominal pain reached significance in Period 1, and vomiting had a trend in Period 2. In three cohort studies published in 2020, a negative correlation between gastrointestinal symptoms and mortality was not demonstrated [Table 3] [7-9]. However, the investigators of these cohorts did not look for such a possible correlation. Their data are sparse and unrelated to our investigational question.

Our study has limitations, including being retrospective and having a small part of our database already published. Yet, we studied a cohort of 4688 patients, who were well representative of the hospitalized population in the three first waves of the COVID-19 pandemic. In addition, there is a presentation of two different variants: the original virus and the Alpha variant. We found that gastrointestinal symptoms were protective factors in the whole cohort as well as within each period.

A possible explanation for our observation could be the accumulation of the virus particles in the gastrointestinal tract, which prevented a significant attack of the lower respiratory tract and the lung and development of acute respiratory distress syndrome. Specific and higher affinity of the original virus and the Alpha variant to ACE2 and TMPRSS2 receptors on the mucosal cells of the gut may have prevented virus adhesion to the respiratory tract. Our hypothesis correlates with the concept of gut-lung axis [10-12]. The gut and lungs are anatomically distinct, but potential anatomic communications and complex pathways involving their respective microbiota have reinforced the existence of a gut–lung axis. Recent studies have highlighted the contribution of viruses in both digestive and respiratory tracts and crosstalk in maintaining host homeostasis and disease activity. Immune responses in the lungs may be influenced by the gut and may interfere with the course of respiratory diseases. The virus may induce gut microbial dysbiosis that causes diarrhea and can play a crucial role in modulating the immune responses of COVID-19 infected individual, preventing damage to vital organs, including the lungs [11]. Thus, re-formulating the gut microbiota may emerge as a new therapeutic target. Sencio and colleagues [13] claimed that gut microbiota had a critical role in pulmonary immu-

nity and host defense against viral respiratory infections.

Our observations were not supported by the literature and should be studied with other cohorts and databases of patients with COVID-19. If confirmed, the mechanisms by which gastrointestinal involvement with COVID-19 virus protects the patients and prevents mortality should be thoroughly investigated.

CONCLUSIONS

Up to half of the patients diagnosed with acute COVID-19 disease presented with gastrointestinal symptoms according to medical literature. Case fatality rate was lower in the first and second waves than in the third wave of the pandemic and negatively correlated with the rate of gastrointestinal symptoms, which were good prognostic factors. For each period we found the same negative correlation between gastrointestinal symptoms and case fatality rate.

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