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Gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among 1,942 non-hospitalized patients with COVID-19

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Short title: Non-respiratory symptoms among patients with COVID-19

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What’s new?

This study used data from a cross-sectional survey to assess the self-reported prevalence of gastrointestinal symptoms and olfactory or taste disorders in 1,942 non-hospitalized patients with coronavirus disease 2019 (COVID-19) in Poland. The sample size is relatively high, compared to other currently published studies. Our findings indicate that more than half of patients with mild COVID-19 reported gastrointestinal symptoms (53.6%) or neurological manifestations (54.2%) of COVID-19 (olfactory or taste disorders). The present findings also indicate that self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during the COVID-19 course was significantly higher among women than men. This finding suggests that gastrointestinal symptoms and olfactory or taste disorders should be considered as potential clinical manifestations of COVID-19 among patients with mild to moderate symptoms.
Abstract

Introduction: The Coronavirus Disease 2019 (COVID-19) is a communicable disease caused by novel coronavirus.

Objectives: This study aimed to assess self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders in non-hospitalized patients with COVID-19 in Poland.

Patients and methods: This cross-sectional survey was conducted between April 17 and 18, 2020, among 4,516 non-hospitalized patients with COVID-19 in Poland. The questionnaire included eight questions related to the health status, symptoms of COVID-19, comorbidities, and smoking status.

Results: Completed questionnaires were obtained from 1,942 patients with COVID-19, a response rate of 43%. The median age of the respondents was 50 years; 60.2% were women. Among non-hospitalized patients with COVID-19, 21.3% had hypertension, 4.5% had diabetes, and 3.1% of COVID-19 cases had chronic respiratory disease. Regular tobacco use was declared by 11.2% of patients with COVID-19. At least one gastrointestinal symptom was reported by 53.6% of patients. Almost half of patients (47%) with COVID-19 reported lack of appetite and 24.2% reported diarrhea. Among 1,942 interviewed patients, 54.2% reported at least one olfactory or taste disorder and 42.5% reported both alterations. Self-reported olfactory and taste disorders were 49.2% and 47.5%, respectively. Self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during COVID-19 course was significantly higher (p<0.001) among women than men.

Conclusions: In conclusion, this study demonstrated that olfactory and taste disorders are frequent symptoms in mild-to-moderate COVID-19 patients. Moreover, our study indicates gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among non-hospitalized patients with COVID-19.

Key words: COVID-19, gastrointestinal symptoms; SARS-CoV-2, smell, taste;
INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) [1,2]. To confirm diagnosis of COVID-19, it is required to detect SARS-CoV-2 ribonucleic acid (RNA) by reverse transcription-polymerase chain reaction (RT-PCR) [3]. Most COVID-19 cases (approximately 80%) manifest only mild to moderate symptoms while in 14% of cases, symptoms are severe (dyspnea, hypoxia, or >50% lung involvement on imaging) and only 5% of COVID-19 cases are critical (respiratory failure, shock, or multi-organ system dysfunction) [2,4,5]. Older age and comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer are risk factors for a severe course of illness, complications, and death from COVID-19 [6,7].

The most common COVID-19 symptoms are fever (83–99%), cough (59–82%), and fatigue (44–70%). Less common reported symptoms include shortness of breath (31–40%), expectoration of sputum (28–33%), muscle and joint pain (11–35%), headaches (10-15%), rhinitis and sore throat (14-15%), hemoptysis (<10%), nausea or vomiting (5.8%), and diarrhea (3.8-4.2%) [2,5,8-10]. Moreover, it is suggested that the clinical presentation of COVID-19 may include gastrointestinal symptoms and olfactory or gustatory dysfunctions [11-15]. However, data on the frequency of gastrointestinal and neurological manifestation of non-hospitalized patients with mild or asymptomatic COVID-19 courses have not been sufficiently documented.

This study aimed to assess self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders in non-hospitalized patients with COVID-19 in Poland.

PATIENTS AND METHODS

Study Design and Population
This cross-sectional survey was carried out between April 17 and 18, 2020, among 4,516 non-hospitalized patients with COVID-19 in Poland. In Poland, all mild and moderate cases of COVID-19 may be referred to as institution-based isolation or home-based isolation, depending on the physician's decision. All COVID-19 cases in home-based isolation were eligible to be included in the research. As of April 17, 2020, a total of 8,379 laboratory-confirmed COVID-19 cases were reported in Poland (including severe and fatal cases).

Laboratory diagnosis of COVID-19 was based on the detection SARS-CoV-2 RNA in thorat or nasal swabs samples by reverse transcription-polymerase chain reaction. Laboratory testing for COVID-19 followed the European Centre for Disease Prevention and Control guidelines [3].

Detailed contact information for adults of Polish nationality was available for 4,516 cases. All the patients with COVID-19 in home-based isolation were called by phone as part of sanitary and epidemiological supervision. Participation in the study was voluntary. Participants had the right to refuse to participate without giving a reason. The data was encoded anonymously, making it impossible to identify individuals. All procedures followed the ethical standards of the national research committee and the 1964 Helsinki Declaration (and its later amendments).

Study questionnaire

The questionnaire included eight questions related to the health status, symptoms of COVID-19, comorbidities, and smoking status. Questions also addressed attitudes toward the potential SARS-CoV-2 vaccine.

Self-reported presence of symptoms of COVID-19 was based on a positive response to the following: “During your illness, did you suffer from the following symptoms: (1) lack of appetite, (2) diarrhea, (3) olfactory disorder, (4) taste disorder?”. The presence of comorbidities was based on a positive response to the following: “Do you suffer from any of
the following: (1) hypertension, (2) cardiovascular disease, (3) diabetes, (4) chronic respiratory disease, (5) chronic kidney disease?"

Smoking status was based on a positive response to the following: “Do you currently smoke?”

Attitude toward potential SARS-CoV-2 vaccine was based on the question “If a coronavirus vaccine arrives, will you get vaccinated against SARS-CoV-2 coronavirus?” (Yes/No).

The desire to obtain a high response rate was one of the main goals of the study. Because of this, the number of questions was limited to those having practical implications for mitigating the early spread of the SARS-CoV-2 epidemic in Poland.

**Statistical analysis**

Data analysis was performed using the procedures available in the Statistica 13 package. The distribution of categorical variables was shown by frequencies and proportions along with 95% confidence intervals (95% CI). Statistical testing to compare categorical variables was completed using the independent samples chi-square test. Statistical significance was based on the p-value < 0.05.

**RESULTS**

Completed questionnaires were obtained from 1,942 patients with COVID-19, a response rate of 43% (41.8% among males and 43.8% among females). The median age of the respondents was 50 years. The group included more women (60.2%) than men (39.8%). Among non-hospitalized patients with COVID-19, 21.3% had hypertension, 4.5% had diabetes, and 3.1% of COVID-19 cases suffered from chronic respiratory disease (Table 1). Regular tobacco use was declared by 11.2% of patients with COVID-19.

If a coronavirus vaccine arrives, 72.7% of non-hospitalized patients with COVID-19 declared willingness to get vaccinated against SARS-CoV-2 coronavirus (70.5% among women and 76.6% among men; p=0.03).
At least one gastrointestinal symptom was reported by 53.6% of patients (Figure 1). Both gastrointestinal symptoms (lack of appetite and diarrhea) were reported by 17.6% of patients with COVID-19. Almost half of patients (47%) with mild symptoms of COVID-19 reported lack of appetite and 24.2% reported diarrhea during COVID-19 course. Among 1,942 interviewed patients, 54.2% reported at least one olfactory or taste disorder and 42.5% reported both alterations. Self-reported olfactory and taste disorders were 49.2% and 47.5% respectively. None of the gastrointestinal symptoms and olfactory or taste disorders was reported by 31.6% of patients.

There were gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among non-hospitalized patients with COVID-19 (Table 2). Self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during COVID-19 course was significantly higher (p < 0.001) among women than men. Details are presented in Table 2.

**DISCUSSION**

This study used data from a cross-sectional survey to assess the self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders in 1,942 non-hospitalized patients with COVID-19 in Poland. Our findings indicate that more than half of patients with mild COVID-19 course reported gastrointestinal symptoms (53.6%) or neurological manifestations (olfactory or taste disorders) (54.2%) of COVID-19. The present findings also point to gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among non-hospitalized patients with COVID-19. Self-reported frequency of gastrointestinal symptoms and olfactory or taste disorders during the COVID-19 course was significantly higher among women than men. This finding suggests that gastrointestinal symptoms and
olfactory or taste disorders should be considered as potential clinical manifestations of COVID-19 among patients with mild to moderate symptoms.

We observed a higher proportion of COVID-19 among women than men. The frequency of smoking (11.2%) among non-hospitalized patients with COVID-19 was lower compared to the general population (21%) [16]. However, this study includes only non-hospitalized patients with mild COVID-19 course. A study by Mehra et al. showed that smoking almost doubled (OR: 1.79) the risk of in-hospital death among patients hospitalized with Covid-19 [17].

The majority of currently available data on gastrointestinal symptoms in COVID-19 has been performed among hospitalized patients. Among 138 hospitalized patients with COVID-19 in Wuhan, China, 39.9% reported anorexia/lack of appetite and 10.1% had diarrhea [9]. Another study carried out among 651 patients in China, showed that 11.4% of hospitalized patients presented with at least one gastrointestinal symptom [12]. A multicenter cohort study across nine hospitals in the United States (US) showed that 61.3% patients reported at least one gastrointestinal symptom, wherein 34.8% of patients reported anorexia and 33.7% reported diarrhea [11]. To the authors’ best knowledge, our study is one of the few studies conducted in non-hospitalized COVID-19 patients. Our findings indicate that more than half of non-hospitalized patients with COVID-19 (53.6%) reported at least one gastrointestinal symptom, wherein 47% reported lack of appetite and 24.2% diarrhea. The frequency of gastrointestinal symptoms in our study is higher than in studies from China but comparable to those observed in the US.

Moreover, it is suggested that a significant part of COVID-19 patients may report olfactory or gustatory dysfunctions [13-15]. In a multicenter PCR-based case-control study in Spain, out of 79 patients enrolled, 35.4% reported smell disorder and 31.6% reported taste disorder [18]. The study carried out in Wuhan, China, among 214 patients with COVID-19, showed that
5.6% reported taste impairment and 5.1% smell impairment [15]. A higher frequency of olfactory and gustatory dysfunctions was observed in a multicenter European study by Lechien et al. [13]. Among 417 mild-to-moderate COVID-19 patients, olfactory dysfunction was reported by 85.6% of patients and 88% reported gustatory dysfunctions [13]. In our study, 49.2% of patients reported olfactory disorder and 47.5% reported taste disorder. Our findings are in line with the study by Lechien et al. [13] and indicate that olfactory and taste disorders are frequent symptoms in European COVID-19 patients.

Our findings indicate, that the frequency of gastrointestinal symptoms and olfactory or taste disorders during COVID-19 is higher among women than men. This phenomenon may be explained by the sex differences in human olfaction [19]. Study by Oliveira-Pinto et al. showed that females have more neurons and gial cells in the olfactory bulbs than males [19]. Moreover, the impact of hormonal modulation on the gustatory system should be considered [20]. Further studies may be required to address non-respiratory symptoms among patients with COVID-19 and gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders in COVID-19.

This study has several limitations. The presence of symptoms of COVID-19 was self-reported and was not confirmed by physician diagnosis. Secondly, the list of COVID-19 symptoms was limited to four key questions. However, most of the currently available studies on COVID-19 are based on electronic health records of COVID-19 patients. Third, this study was carried out among non-hospitalized patients so the results cannot be generalized to the whole population of COVID-19 patients. We can not exclude selection bias. Nevertheless, our study is one of the first cross-sectional surveys focusing on non-respiratory symptoms of COVID-19. Moreover, the sample size is relatively high compared to other currently published studies.
In conclusion, this study demonstrated that olfactory and taste disorders are frequent symptoms in mild-to-moderate COVID-19 patients. Moreover, our study indicates gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among non-hospitalized patients with COVID-19. This study suggests that non-respiratory symptoms should be considered as potential clinical manifestations of COVID-19 during diagnosis.

CONTRIBUTION STATEMENT:

RS, JP, MJ, MG and ŁS conceived of the survey study, its design, questionnaire development, crude data collection and interpretation. RS, JP and ŁS are the authors of the conception of current research questions addressed into the article. RS, MJ, WSZ and WW were responsible for methodology of advanced data management and statistical analysis. RS, JP, MJ, WSZ, WW, MG and ŁS worked on manuscript. MG and ŁS were responsible for linguistic correction and adjustment of the manuscript. All authors read and approved the final manuscript.
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Figure 1. Self-reported symptoms of COVID-19 among 1,942 non-hospitalized patients.
Table 1. Baseline characteristics of 1,942 non-hospitalized patients with COVID-19.

| Parameter                        | Overall (n=1,942) |
|----------------------------------|-------------------|
|                                  | n (%)             |
| Age, median, years               | 50                |
| **Sex**                          |                   |
| Female                           | 1169 (60.2)       |
| Male                             | 773 (39.8)        |
| **Comorbidities**                |                   |
| Hypertension                     | 413 (21.3)        |
| Cardiovascular disease           | 116 (6.0)         |
| Diabetes                         | 88 (4.5)          |
| Chronic respiratory disease      | 60 (3.1)          |
| Chronic kidney disease           | 29 (1.5)          |
| **Current smokers (n=1087)**     |                   |
| Yes                              | 122 (11.2)        |
| No                               | 965 (88.8)        |
Table 2. Gender differences in the prevalence of gastrointestinal symptoms and olfactory or taste disorders among 1,942 non-hospitalized patients with COVID-19.

| Symptom                | Overall n=1,942 | Female n=1,169 | Male n=773 | p       |
|------------------------|-----------------|----------------|------------|---------|
|                        | n     | % (95%CI) | n     | % (95%CI) | n     | % (95%CI) |       |
| Lack of appetite       | 912   | 47.0 (44.8, 49.2) | 637   | 54.5 (51.6, 57.3) | 275   | 35.6 (32.3, 39.0) | <0.001 |
| Diarrhea               | 470   | 24.2 (22.4, 26.2) | 311   | 26.6 (24.2, 29.2) | 159   | 20.6 (17.9, 23.6) | 0.002  |
| Olfactory disorder     | 956   | 49.2 (47.0, 51.5) | 636   | 54.4 (51.5, 57.2) | 320   | 41.4 (38.0, 44.9) | <0.001 |
| Taste disorder         | 923   | 47.5 (45.3, 49.8) | 617   | 52.8 (49.9, 55.6) | 306   | 39.6 (36.2, 43.1) | <0.001 |