

Gender Disparities in self-reported COVID-19 symptoms in young adults

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Abstract

Background

Young adults may constitute a significant proportion of COVID-19 cases but generally experience a milder disease course. The goal of our study was to characterize symptoms of disease in a cohort of generally healthy young adults and to examine possible gender-associated disparities in their clinical manifestations.

Methods

The study was designed as a retrospective survey study. The study questionnaire was sent to all post-COVID-19 IDF service members between 30 June 2020 and 30 September 2020. Univariate and multivariable analysis adjusting for differences in baseline characteristics were employed in the statistical analysis.

Results

A total of 3247 questionnaires were sent. After removing duplicate submissions, a total of 792 questionnaires were included in the analysis. The average male age was 24.2 years old, and average female age was 21 years old. More than 99% of participants spent their recovery period from COVID-19 at home or in a dedicated IDF led COVID-19 Centre. Only 3 participants were hospitalized. Approximately 97% of participants reported at least one COVID-19 symptom, only 45.8% reported fever above 38.0°C. Female participants reported significantly more symptoms of weakness, joint or muscle pain, rhinorrhea, dyspnea, sore throat, abdominal pain, nausea and vomiting and dysgeusia. Most of these differences were maintained in the multivariable analysis. Female participants also reported increased use of medications, particularly antipyretics.

Conclusions

Our findings show a high percentage of symptomatic infection with COVID-19 and suggest young generally healthy female patients experience symptoms of increased severity and duration compared to males.

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ¹. It was first identified in Wuhan, China on December 2019 and has since spread globally to pandemic proportions ². At the time of diagnosis, up to 40% of

infected individuals are asymptomatic or pre-symptomatic but potentially contagious to others³. Particularly, younger individuals have been found to have an increased rate of asymptomatic infection. Interestingly, several published reports show asymptomatic and pre-symptomatic patients were found in groups of military service members^{4,5}. While increasing age and comorbidities are important risk factors for higher morbidity and mortality in COVID-19 patients leading to a devastating number of deaths due to the pandemic, young adults generally experience a milder disease course⁶.

Publicly available online data published by the Israeli Health Ministry shows that 40.2% of diagnosed COVID-19 patients are individuals between the ages of 10–29. Thus, young adults may constitute a significant proportion of COVID-19 cases but only 2% of severely ill patients and 0.3% of fatalities.

Lower self-perceived risk from COVID-19 infection, and potentially a higher rate of asymptomatic or pre-symptomatic infections may drive young adult COVID-19 patients to play an important role in transmission of the virus to vulnerable populations.

Few reports have been published regarding gender-based differentiating factors in COVID-19^{7,8}. Some studies reported on increased morbidity and mortality in males compared to females^{9–12}, at least some of these differences may be gender as well as age dependent¹³.

Israeli Defense Force (IDF) service members are in the 18 to 68 age range. Approximately 70% of this group are during their period of conscription to compulsory service, between the ages 18–22. All IDF service-members confirmed as COVID-19 patients are diagnosed and cared for by the IDF medical corps. Reports in the IDF show infected service-members generally experience a typically mild disease course.

Description of various symptoms of COVID-19 and their duration, as subjectively perceived, are relatively scarce in younger age groups. While subjective, self-reported symptoms are fundamental to the diagnosis and management of COVID-19 patients who experience a milder disease course, as fever is not present in all patients, and most of them may not have specific or pathognomonic findings in physical examination. A recently published study in a similar cohort of IDF service-members showed self-reported fever and dysgeusia and/or anosmia are correlated with increased likelihood ratio of COVID-19 infection¹⁴.

The aim of the present study is to characterize symptoms of disease in a cohort of generally healthy young adults and examine gender-associated disparities in the clinical manifestations of COVID-19 in patients with a mild clinical course.

Methods

Study population and sample selection

In this retrospective cross-sectional survey study, we included all post-COVID-19 IDF service members between 30 June 2020 and 30 September 2020. Data was received from a dedicated IDF COVID-19 center. In all cases, diagnosis of COVID-19 was performed with SARS-CoV-2 PCR testing from

nasopharyngeal swabs. Criteria for SARS-CoV-2 PCR testing was either (a) close contact with known COVID-19 patient + one respiratory symptom, (b) at least two respiratory symptoms (c) dysgeusia and/or anosmia. Some testing was performed at the primary care physician's discretion or when a cluster of cases was found in the unit - even if close contact has not been established. Recovery from COVID-19 was defined as either two consecutively negative SARS-CoV-2 PCR testing or after at least ten days had elapsed since the first positive or borderline positive SARS-CoV-2 PCR test with at least 3 consecutive days with no defining symptoms such as fever, dyspnea or cough.

Research Tool and Survey Administration

An online questionnaire form was sent *via* text message to the study population. The study questionnaire was written in Hebrew, the participants native language, and contained a description of the study design, aims, and required the recipients informed consent to proceed. The questionnaire was anonymous and no personally identifiable information was collected from study participants, other than last 4 digits of personal ID number to allow for detection of duplicate submissions. All parts of the questionnaire were required for questionnaire submission, thus eliminating missing data.

The questionnaire allowed for data collection of age, military service status (recruits and enlisted personnel in compulsory service status, versus military career officers as well as non-commissioned and warrant officers), smoking habits, presence of chronic illnesses. Participants were required to report whether they suffered from each one of the presented symptoms and rate the duration and its perceived severity on a scale of 1 (mildest) to 5 (most severe). Finally, the participants were asked to report what medications they received for their symptoms.

The symptoms included in the questionnaire were: general weakness and/or fatigue, muscle and/or joint pain, cough, nasal congestion, shortness of breath, sore throat, diarrhea, stomach pain, nausea and/or vomiting, impaired sense of smell and impaired sense of taste. An English version of the questionnaire is available in the article's supplementary material.

Statistical analysis

Categorical variables were presented with frequencies and percent and continuous/ordinal variables were presented with mean (SD) [median, range]. The association between gender and categorical variables was determined using Chi-square test (or Fisher's exact test). For continuous/ordinal variable the T-test or Wilcoxon rank-sum test was used.

Prevalence ratios were presented along 95% confidence intervals (95%CI). Multivariable log-binomial regressions were performed (for the probability of having a symptoms as well as for the probability of having specific symptom), with age (continuous), rank (Officer/not officer), type of service (compulsory or military career) and chronic disease (yes/no) as potential confounding factors. Adjusted prevalence ratio were presented as well with 95%CI. The analyses were performed using SAS 9.4 software. $P < 0.05$ was considered significant.

We conducted a multivariable log-binomial regression analysis adjusting for age, military service type (compulsory vs. military career), officer rank vs. other ranks (including warrant and non-commissioned officers), and presence of any chronic illness as possible confounding factors

Ethical considerations

The institutional review board of the IDF approved the study (protocol number 2094 – 2020). All participants were asked to anonymously participate in the study by answering an online questionnaire with their informed consent.

Results

Overall, the study questionnaire was sent to 3247 patients who recovered from COVID-19 infection. The study population included 1845 (60.1%) males and 1234 (39.9%) females. A total of 970 questionnaires were submitted, of which 178 were duplicates and were excluded from analysis (Fig. 1). Data from questionnaires submitted by 792 patients (24.3% response rate), of which 354 were female and 438 were male, was analyzed. The average male age was 24.2 years old (median 21, 18-56). The average female age was 21 years old (median 20, range 18-44). A total of 747 patients younger than the age of 40 years, and only 44 patients aged 40 years and above were included in the study. More than 99% of participants in the study spent the course of disease until recovery in their homes or in a dedicated IDF recovery facility for ambulatory patients led by the IDF COVID-19 Center. Only 3 participants (0.38%) were hospitalized, all of whom were males aged 40 years old and above. Only one participant did not specify his age. No case fatalities were reported during the study period. The study population consisted of significantly more females during their compulsory service period, and significantly less females were ranked officers.

Baseline characteristics of the study population are shown in Table 1.

Reported symptoms

About 97% of the participants reported to have at least one of the COVID-19 known symptoms. Only 45.8% of participants reported fever above 38.0°C. No significant differences in development of fever during disease were found between males and females. The most prevalent symptom was general weakness/fatigue (86.36%), the second most common was sense of smell impairment (67.8%) and more than half of the participants reported on impairment of the sense of taste. The average number of symptoms reported was 6.1 (median 6, range 0-11), there was a statistically significant difference between males and females, 5.7 [median 6, range 0-11] versus 6.6 [median 7, range 0-11] respectively ($P>0.001$). Females reported significantly more symptoms of weakness, joint/muscle pain, rhinorrhea, dyspnea, sore throat, abdominal pain, nausea and vomiting, and dysgeusia compared of any severity compared to males. The significance increased when we compared severe symptoms subjectively graded by the participant as 4-5 (on a scale of 1-5, see *methods*). Females also reported significantly increased duration of weakness/fatigue, joint/muscle pain and sore throat associated with COVID-19, and

significantly increased duration of grade 4-5 weakness/fatigue and joint/muscle pain (Figures 2A and 2B). Interestingly, there were no significant differences in the presence or fever, highest measured temperature, and cough between genders (Tables 3A and 3B).

The multivariate analysis (as shown in Table 1) showed significant differences between males and females when comparing symptoms of any severity, as well as symptoms of significant severity (graded 4-5 on a scale of 1-5) (Tables 3A, 3B). Specifically, differences in any severity of sore throat, and high severity (grade 4-5) stomachache were not statistically significant in the multivariate analysis.

Medical therapy

Overall, 37.4% received medical treatment. One participant didn't answer the question regarding medical therapy and was excluded from this analysis. Seven participants specified that they used vitamin C, vitamin D or other vitamin supplements or responded they used medications but did not further specify. Overall, 289 participants (36.5%) reported on medical treatment. Older participants (>31y) used significantly more medications than the younger age groups ($P=0.005$). We observed a higher prevalence of medication use in females compared to males ($P=0.0146$). Specifically, analgetic and/or antipyretic medications were used significantly more by females ($P>0.001$). These results are shown in Table 3.

Discussion

While the primary efforts of healthcare systems worldwide when facing the COVID-19 pandemic continue to be treatment of the seriously ill and prevention of mortality, and COVID-19 vaccine programs are initiated in numerous countries, primary care providers are faced with a challenge of caring for significant number of COVID-19 patients experiencing mild illness.

The presence of fever, anosmia and dysgeusia raise high suspicion for COVID-19. However, there is significant overlap between symptoms of COVID-19 and other respiratory viruses. In the present study, we examined the prevalence of symptoms and use of medications among IDF service members infected with COVID-19, who are generally healthy young adults deemed fit for military service. we observed a substantially lower prevalence of fever (45.8%, compared to 78%) during COVID-19 infection, and a comparatively increased prevalence of fatigue, muscle or joint pain, gastrointestinal symptoms and changes in taste sensation, compared to a meta-analysis by Grant and colleagues¹⁵.

The results of the present study suggest significant gender-associated differences in COVID-19 symptoms, as well as their self-reported duration and perceived severity in healthy young patients experiencing a generally mild disease course. To our knowledge, these differences have not been demonstrated to date in published reports on COVID-19, which have primarily focused on population wide analysis of morbidity and mortality. The study population demonstrated significantly different male and female baseline characteristics, including age, military service status, body mass index and hypertension. However, gender-dependent reports on symptom severity were significant even when adjusted for these variables in a multivariate analysis.

Indeed, patient gender may affect susceptibility to numerous infectious diseases¹⁶⁻¹⁸, including COVID-19¹⁹. For example, women mount higher antibody responses and adverse effects after influenza vaccines.

Most young adults with no additional risk factors require no specific medical therapy during disease course and can be managed primarily with over-the-counter analgesics and antipyretics.

The principal strength of this study is a relatively large cohort of generally healthy young adults. The gender-associated differences are statistically significant in univariate and multivariate analyses. Study participants included all branches of the IDF. The proportion of participants from each gender as well as the proportion of military career versus compulsory service status corresponds to the proportions in the general population of IDF service members.

Our results may be affected by several limitations. The questionnaire response rate was only 24.4% of recovered COVID-19 possibly allowing for non-response bias. Participants recall bias is an important potential limitation as the results are based on patients' retrospective self-reports. Patients who chose to participate may have suffered more significant symptoms affecting our results and may perhaps be more willing to share. We used an original, non-standardized questionnaire to assess COVID-19 symptoms and their severity.

The study population represents a generally healthy cohort of young adults, all of them are IDF military personal. In Israel, military service is compulsory for all Jewish men and women, as well as some minority groups. People deemed medically unfit for service as well as specific ethnic groups in Israeli society, such as ultra-orthodox Jews and Israeli Arabs, are exempt from military service and so are not represented in the present study's population. Therefore, the external validity of this study to other populations could be limited.

Additionally, for a portion of the study period, the criteria of SARS-CoV-2 PCR testing in the IDF were stricter than Israeli Ministry of Health criteria, requiring the presence of multiple possible COVID-19 symptoms, or close contact with a known COVID-19 patient and symptoms. Criteria were broadened in the IDF on September 2020 to any suspected case at the primary care physician discretion. Indeed, the prevalence of symptoms in the current study are significantly higher than other scientific reports (97% suffered symptoms).

Multiple variables may confound the differences between self-reported symptoms of males and females. For example, young females in one published study were more knowledgeable of COVID-19 symptoms than men of the same age group²⁰. Socioeconomic considerations, gender roles, as well as potential differences in military role could affect patients reports.

Conclusions

Our findings show a high percentage of symptomatic infection with COVID-19 in young adults and suggest that young generally healthy female patients experience symptoms of increased severity and duration compared to males. The increased use of medications by females might be explained by the fact that they experienced a more symptomatic disease.

Our results raise the need for additional investigations of the manifestations of COVID-19 in young patients managed in an ambulatory setting. The biological mechanism explaining the gender disparity found in the present study is unknown. Evidence regarding gender-associated disparities in COVID-19 symptoms may assist clinicians in the diagnosis and management of COVID-19 patients as well as shed light on potential biological mechanisms by which SARS-CoV-2 and other viral pathogens manifest in male and female patients.

Declarations

Ethics approval and consent to participate

The institutional review board of the IDF approved the study (protocol number 2094-2020). All participants were asked to anonymously participate in the study by answering an online questionnaire with their informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

All authors were responsible for conceptualization of the study. BK was responsible for the data collection. NS performed the statistical analysis. DG, BK and YA oversaw the statistical analysis. The original draft was written by DG, BK, YA, and reviewed and edited by all authors. The study was supervised by SS.

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Not applicable

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Tables

Table 1. Baseline characteristics of study population, by gender

	Total (n=792)	Female (n=354, 44.7%)	Male (n=438, 55.3%)	p value
Age (years), (SD), [Median, range]	22.7 (6.6) [20, 18-56]	21 (4.3) [20, 18-44]	24.2 (7.6) [21, 18-56]	<.0001
<u>Age groups</u>				<.0001
18-22 n, (%)	607 (76.74%)	309 (87.29%)	298 (68.19%)	
23-30 n, (%)	97 (12.26%)	26 (7.34%)	71 (16.25%)	
31 and above n, (%)	87 (11%)	19 (5.37%)	68 (15.56%)	
Smokers n, (%)	168 (21.21%)	65 (18.36%)	103 (23.52%)	0.0777
BMI \geq 30 (kg/m ²) n, (5%)	30 (3.79%)	11 (3.11%)	19 (4.34%)	0.3671
Officer rank n, (%)	134 (16.92%)	41 (11.58%)	93 (21.23%)	0.0003
Compulsory service n, (%)	582 (73.48%)	290 (81.92%)	292 (66.67%)	<.0001
-	-			
-				0.0830
<u>Residence during COVID-19</u>				
Home residence n, (%)	423 (53.41%)	179 (50.56%)	244 (55.71%)	
IDF COVID-19 Centre n, (%)	366 (46.21%)	175 (49.44%)	191 (43.61%)	
Hospital n, (%)	3 (0.38%)	0	3 (0.68%)	
Any chronic disease n, (%)	118 (14.9%)	46 (12.99%)	72 (16.44%)	0.1760
Asthma n, (%)	46 (5.81%)	16 (4.52%)	30 (6.85%)	0.1635
Hypertension n, (%)	10 (1.26%)	0 (0%)	10 (2.28%)	0.0029
Other n, (%)	47 (5.93%)	21 (5.93%)	26 (5.94%)	0.9982

Abbreviations: SD, standard deviation; BMI, body mass index; IDF, Israeli Defense Force; COVID-19, coronavirus disease 2019.

Table 2. Reported COVID19 Symptoms

	Total	Female	Male	p value	PR ^a	95% CI	
						Lower	Upper
fever \geq 38°C	331 (45.8%)	148 (45.54%)	183 (45.98%)	0.9057	0.99	0.84	1.16
At least one of the following symptoms - any severity	766 (96.72%)	346 (97.74%)	420 (95.89%)	0.1464	1.02	0.99	1.05
Weakness / general fatigue	684 (86.36%)	323 (91.24%)	361 (82.42%)	0.0003	1.11	1.05	1.17
Joint / muscle pain	486 (61.36%)	238 (67.23%)	248 (56.62%)	0.0023	1.19	1.06	1.32
Cough	505 (63.76%)	227 (64.12%)	278 (63.47%)	0.8490	1.01	0.91	1.12
Runny nose (rhinorrhea)	454 (57.32%)	239 (67.51%)	215 (49.09%)	<.0001	1.38	1.22	1.55
Difficulty breathing	369 (46.65%)	183 (51.69%)	186 (42.56%)	0.0105	1.21	1.05	1.41
Sore throat	428 (54.11%)	210 (59.32%)	218 (49.89%)	0.0081	1.19	1.05	1.35
Diarrhea	333 (42.1%)	155 (43.79%)	178 (40.73%)	0.3872	1.08	0.91	1.27
Stomachache	331 (41.79%)	165 (46.61%)	166 (37.9%)	0.0135	1.23	1.04	1.45
Nausea / vomiting	268 (33.84%)	147 (41.53%)	121 (27.63%)	<.0001	1.50	1.24	1.83
Impairment of the sense of taste	424 (53.54%)	207 (58.47%)	217 (49.54%)	0.0122	1.18	1.04	1.34
Impairment of the sense of smell	537 (67.8%)	247 (69.77%)	290 (66.21%)	0.2858	1.05	0.96	1.16
At least one of the following symptoms – grade 4-5	657 (82.95%)	309 (87.29%)	348 (79.45%)	0.0035	1.26	1.09	1.45
Weakness / general fatigue	415 (52.4%)	217 (61.3%)	198 (45.21%)	<.0001	1.33	1.18	1.51
Joint / muscle pain	264 (33.33%)	143 (40.4%)	121 (27.63%)	0.0002	1.31	1.13	1.52
Cough	162 (20.45%)	75 (21.19%)	87 (19.86%)	0.6462	1.04	0.88	1.22
Runny nose (rhinorrhea)	134	67	67	0.1755	1.13	0.94	1.35

	(16.92%)	(18.93%)	(15.3%)				
Difficulty breathing	144 (18.18%)	81 (22.88%)	63 (14.38%)	0.0021	1.32	1.09	1.61
Sore throat	126 (15.91%)	74 (20.9%)	52 (11.87%)	0.0006	1.40	1.13	1.75
Diarrhea	115 (14.52%)	56 (15.82%)	59 (13.47%)	0.3509	1.09	0.90	1.32
Stomachache	116 (14.65%)	62 (17.51%)	54 (12.33%)	0.0402	1.22	0.99	1.50
Nausea / vomiting	70 (8.84%)	44 (12.43%)	26 (5.94%)	0.0014	1.54	1.13	2.10
Impairment of the sense of taste	287 (36.24%)	149 (42.09%)	138 (31.51%)	0.0021	1.24	1.07	1.42
Impairment of the sense of smell	419 (52.9%)	190 (53.67%)	229 (52.28%)	0.697	1.03	0.90	1.16

^a The prevalence ratio (PR) represents female-to-male prevalence ratio for the outcome.

Abbreviations : PR, prevalence ratio ;

Table 3. Multivariable analysis, comparing males and females

	Multivariable				Multivariable			
	Symptoms of any severity				Symptoms of high severity			
	p value	Adj. P	95%CI		P-value	Adj.PR	95%CI	
Low			Up	Low			Up	
At least one of the following	-	-	-	-	0.0121	1.08	1.02	1.14
Weakness / general fatigue	0.0002	1.11	1.05	1.17	<.0001	1.43	1.25	1.64
Joint / muscle pain	0.0001	1.25	1.12	1.41	<.0001	1.56	1.27	1.92
Runny nose (rhinorrhea)	<.0001	1.32	1.17	1.49	-	-	-	-
Difficulty breathing	0.0124	1.21	1.04	1.41	0.004	1.57	1.15	2.13
Sore throat	0.0556	1.14	1	1.3	0.0015	1.73	1.23	2.43
Stomachache	0.0371	1.2	1.01	1.42	0.0684	1.38	0.98	1.96
Nausea / vomiting	0.0001	1.49	1.22	1.83	0.0008	2.3	1.41	3.75
Impairment of the sense of taste	0.0089	1.2	1.05	1.37	0.0016	1.36	1.12	1.65

PR = prevalence ratio; Adj.PR = adjusted prevalence ratio;

Table 4. Medications used during COVID-19 by gender

	Total	Female	Male	P-value
	N=792	N=354	N=438	
Any treatment	296 (37.42%)	149 (42.09%)	147 (33.64%)	0.0146
Antipyretics painkillers	246 (31.1%)	131 (37.01%)	115 (26.32%)	0.0012
Cough medication	71 (8.98%)	34 (9.6%)	37 (8.47%)	0.5778
Decongestants	46 (5.82%)	26 (7.34%)	20 (4.58%)	0.0981
Antibiotics	20 (2.53%)	7 (1.98%)	13 (2.97%)	0.3743
Fluids / Inhalation / Inhaler	29 (3.67%)	9 (2.54%)	20 (4.58%)	0.1301

Figures

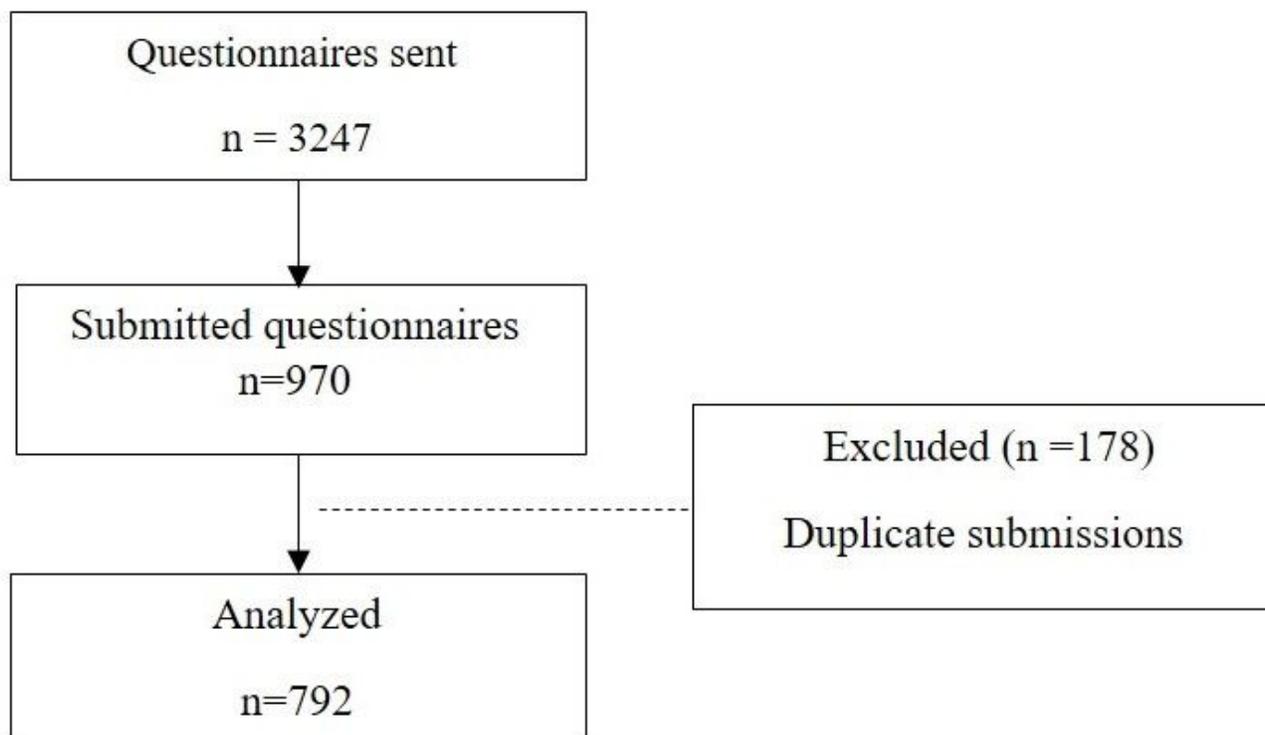


Figure 1

Study population flow chart. A total of 970 questionnaires were submitted by patients recovered from COVID-19 between 30 June 2020 and 30 September 2020. 178 questionnaires were duplicates and were removed from statistical analysis.

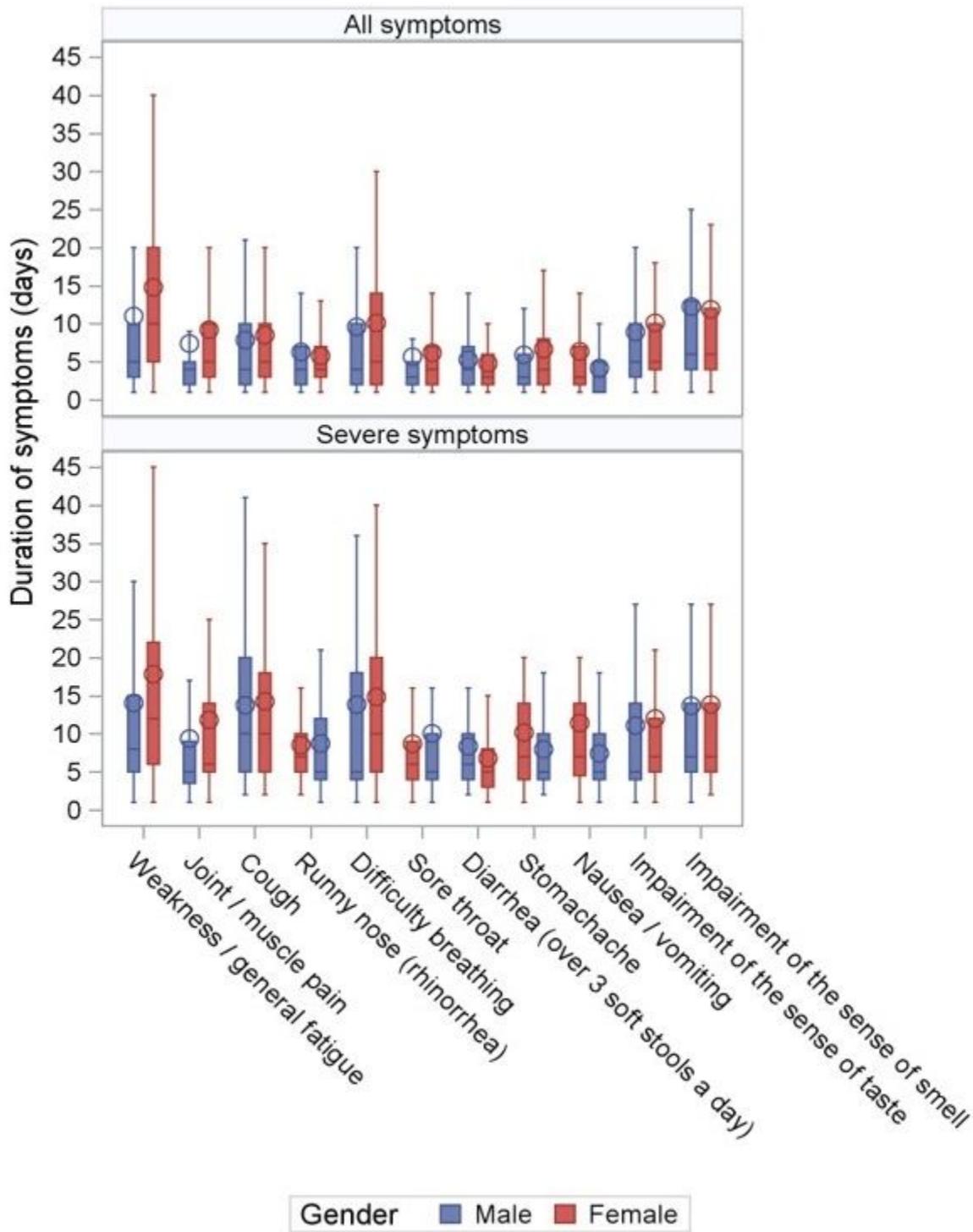


Figure 2

Box plot showing duration of symptoms of any severity (upper panel) or symptoms of high severity (grade 4,5) (lower panel). Boxes represent interquartile range within which a transverse line represents the median and a circle represents the mean. The bars ("whiskers") represent maximum and minimum observations. Data for females is represented in red and for males in blue.