Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Self-reported symptoms from exposure to Covid-19 provide support to clinical diagnosis, triage and prognosis: An exploratory analysis

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ABSTRACT

Background: Symptomatic COVID-19 is prevalent in the community. We identify factors indicating COVID-19 positivity in non-hospitalized patients and prognosticators of moderate-to-severe disease.
Methods: Appeals conducted in April–June 2020 in social media, collaborating medical societies and patient advocacy groups recruited 20,476 participants ≥18 years who believed they had COVID-19 exposure. Volunteers consented on-line and reported height, weight, concomitant illnesses, medication and supplement use, residential, occupational or community COVID-19 exposure, symptoms and symptom severity on a 4-point scale. Of the 12,117 curated analytic population 2279 reported a COVID-19 viral test result: 865 positive (COVID+) and 1414 negative (COVID-).
Results: The triad of anosmia, ageusia and fever best distinguished COVID+ from COVID-participants (OR 6.07, 95% CI: 4.39 to 8.47). COVID + subjects with BMI≥30, concomitant respiratory disorders or an organ transplant had increased risk of moderate-to- severe dyspnoea. Race and anti-autoimmunity medication did not affect moderate-to-severe dyspnea risk.
Conclusions: The triad of anosmia, ageusia and fever differentiates COVID-19. Elevated risks of severe symptoms outside the hospital were most evident among the obese and those with pulmonary comorbidity. Race and use of medication for autoimmune disease did not predict severe disease. These findings should facilitate rapid COVID-19 diagnosis and triage in settings without testing.

1. Introduction

Limited information is available concerning the symptomatology of human coronavirus disease 2019 (COVID-19) outside of the hospital [1, 2]. Here we follow a research model developed in collaboration with the European Medicines Agency that validated person-generated health--data as a reliable method for pharmacovigilance [3], and use established best practices for patient registries that have been particularly useful in pandemic threats [4–6]. We build on these models using community-driven research to characterize symptoms indicative of a positive COVID-19 viral test result and identify risk factors for development of serious symptoms of COVID-19 infection outside the hospital setting.

2. Methods

Respondent-driven sampling in the US from April 2nd to July 14th, 2020 inclusive, yielded 20,476 adults who completed registration, demographics and symptoms forms at www.helpstopCOVID19.com. Participants were recruited using social media, with additional awareness raising activities undertaken by medical societies and patient advocacy groups. Every state in the US is represented, with most participants coming from populous states with high infection rates: California (9%), New York (9%), Florida (7%) and Texas (6%). Participants provided information about testing and test results; noting that only viral testing was available during this sampling timeframe and most participants reported not having been tested (70%). Reported were: COVID-19-like symptoms using a checklist [7] and ranked the reported symptoms on a 4-point severity scale from very mild to severe; comorbidities;

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presence of fever, use of prescription and non-prescription medication, vitamins and supplements; occupation as well as age, gender, race and ethnicity. Survey respondents were invited to participate in longitudinal follow-up twice a week for four weeks and every two weeks for the following two months. Participants were not required to answer every question. No remuneration was provided.

A curated analytic data set (n = 12,117) was created for adults who completed baseline screening of symptoms and demographics, and which excluded likely fabricated entries based on a combination of clinical flags (e.g., body mass index (BMI) <15 or >60, height < 4 ft) and likely duplicates, determined by nearly identical respondent entries within 10 minutes of each other. No missing data were imputed. Participants who tested positive (COVID+) were compared to those who tested negative (COVID-). Odds ratios (OR) and 95% confidence interval (CI) were used to estimate the likelihood that a symptom or characteristic (or constellation thereof) would be present given a positive test result. A multivariable logistic regression was used to estimate the OR (95%CI) of developing moderate or severe dyspnea among COVID + participants. Two models were applied – a reduced model that included demographic characteristics and a full model that added comorbidities and medication use.

3. Results

A total of 12,117 participants were included in the curated dataset (71% female; median age 43 years and 24% non-Caucasian), out of which n = 2279 (19%) reported a COVID-19 test result. Baseline data are shown for 2279 participants, including COVID+ (n = 863) and COVID- (n = 1414). Participants reporting a COVID-19 test result had a mean age of 41 years, with 13% over 60 years of age, and nearly twice as many females as males; 20% of participants reported education level of "high school or less" (Table 1).

Fever, cough, fatigue and aches and pains were the most commonly reported symptoms, with more symptoms reported on average by COVID + than COVID-participants (5.5 vs 3.4) (Table 2). Five symptoms had strong associations with COVID+: anosmia (OR 4.81 95%CI 3.84, 6.02), ageusia (OR 4.41 95%CI 3.55, 5.47), bluish color of lips and face (OR 3.29 95%CI 2.05, 5.27), fever (OR 3.24 95%CI 2.69, 3.89), and vomiting (OR 2.38 95%CI 1.76, 3.22) (Table 2). The triad of anosmia, ageusia and fever was strongly associated with a positive COVID-19 test (OR 6.07 95%CI 4.39, 8.47); participants were six times more likely to test positive in the presence of this triad. COVID + participants who reported anosmia or ageusia also had a mean of nine symptoms, in contrast to a mean of just two for those without either symptom.

Moderate or severe dyspnea was more frequently reported by COVID+ (24%) than COVID- (15%) participants. Among COVID + participants the risk of moderate or severe dyspnea did not differ by age, gender, race, or ethnicity. Particularly, risk was elevated among the obese (BMI>30) (OR 2.30 95%CI 1.40, 3.78) and those taking medications for respiratory disorders (OR 3.68 95%CI 2.04, 6.62). There was no strong evidence of elevated risk for dyspnea among participants with cardiovascular disease or those taking medications for diabetes, hypertension and autoimmune conditions (Table 3).

4. Discussion

This research program is unusual in its evaluation of symptomatology for COVID-19 in the community setting [8] and may be particularly helpful in a number of travel medicine related settings, e.g. on board cruise ships and in other maritime settings, including naval vessels; during military deployments and in remote or resource poor settings [9–13]. Anosmia and ageusia were the most likely symptoms indicative of a positive test results, and participants reporting either of these had more symptoms and of greater severity [8]. This is in line with previous findings and experimental evidence supporting involvement of the olfactory apparatus [14,15]. The triad of anosmia, ageusia and fever provided a particularly powerful symptom constellation differentiating COVID+ from COVID-in the community. This triad may offer an expeditious way to identify probable COVID-19 infections in the community, especially in the absence of reliable, widespread testing [9,16,17] The triad could be taken as pathognomonic during the pandemic and trigger *anti*-COVID interventions in the absence of reliable near-patient diagnostics. This may be particularly helpful in many travel medicine or community based settings including resource-poor, logistically challenged or remote settings, as well as in closed community settings e.g. the military, prisons, care homes, seagoing vessels. Further support for a clinical diagnosis of COVID-19 might also be a history of vomiting. Although non-specific, vomiting is in general not a feature of respiratory tract infections in the community [18,19].

Severe dyspnea is indicative of severe disease that may require hospitalization and may presage possible pulmonary fibrosis or other sequelae [20–23]. While our findings are congruent with obesity being a known risk factor for severe disease, the association of significant

Table 1
Characteristics of participants included in the curated dataset and by reported COVID-19 test result.

Total	All	COVID+	COVID-
	n = 12,117	n = 865	n = 1414
Demographics			
Age in years, mean (SD)	43 (14)	40 (13)	41 (13)
Age group	N (%)	N (%)	N (%)
19–29	2382 (19.6)	207 (23.9)	285 (20.2)
30–39	2634 (21.7)	206 (23.8)	324 (22.9)
40–49	2613 (21.6)	200 (23.1)	341 (24.1)
50–59	2219 (18.3)	126 (14.6)	248 (17.5)
60+	1572 (13.0)	70 (8.1)	124 (8.8)
Did not respond	697 (5.8)	56 (6.5)	92 (6.5)
Gender			
Female	8638 (71.3)	591 (68.3)	1001 (70.8)
Male	3326 (27.4)	268 (31.0)	396 (28.0)
Self-reported as other	153 (1.3)	6 (0.7)	17 (1.2)
Race			
Black or African American	924 (7.6)	121 (14.0)	120 (8.5)
White	9208 (76.0)	554 (64.0)	1042 (73.7)
Other/Multiracial	1957 (16.2)	188 (21.7)	251 (17.8)
Did not respond	28 (0.2)	2 (0.2)	1 (0.1)
Ethnicity, Hispanic	1439 (11.9)	193 (22.3)	183 (12.9)
Education			
High school or less	2333 (19.3)	170 (19.7)	230 (16.3)
Some college/2-year degree	4284 (35.4)	296 (34.2)	445 (31.5)
4-year college degree	2802 (23.1)	209 (24.2)	338 (23.9)
>4-year college degree	2658 (21.9)	188 (21.7)	396 (28.0)
Did not respond	40 (0.3)	2 (0.2)	5 (0.4)
BMI category[a]			
Normal (<25)	3859 (31.8)	245 (28.3)	463 (32.7)
Overweight (25–30)	3037 (25.1)	194 (22.4)	354 (25.0)
Obese (≥30)	4004 (33.0)	320 (37.0)	455 (32.2)
Comorbidities[a]			
Pregnant	85 (0.7)	11 (1.3)	10 (0.7)
Nicotine addiction (Smoker)	2090 (17.2)	98 (11.3)	255 (18.0)
Lung disease	1485 (12.3)	114 (13.2)	224 (15.8)
Organ transplant	99 (0.8)	22 (2.5)	17 (1.2)
Cancer	126 (1.0)	25 (2.9)	16 (1.1)
Cardiovascular disease	735 (6.1)	54 (6.2)	107 (7.6)
Taking prescription medications for the following conditions[b]			
Hypertension	2153 (17.8)	151 (17.5)	252 (17.8)
Diabetes	973 (8.0)	84 (9.7)	128 (9.1)
Autoimmune disease	897 (7.4)	42 (4.9)	135 (9.5)
Lung disease	1128 (9.3)	72 (8.3)	184 (13.0)
Household exposure to COVID-19 or influenza-like illness			
Yes	2600 (21.5)	371 (42.9)	331 (23.4)

Abbreviations: COVID+, participants who reported having had a positive COVID-19 test result; COVID-, participants who reported having had a negative COVID-19 test result; SD, standard deviation.

[a] Approximately 10–12% of participants did not respond to one or more of these questions.

[b] N = 852 (7%) of all participants, n = 80 (9.2%) of COVID+ and n = 97 (6.9%) of COVID-participants did not provide an answer in this section.

Table 2
COVID-19 like symptoms and likelihood of having a positive COVID-19 test result.

	Any symptom			Moderate or severe symptom[a]		
	COVID+	COVID-		COVID+	COVID-	
N of participants	865	1414		865	1414	
Symptom	n (%)	n (%)	OR (95%CI)	n (%)	n (%)	OR (95%CI)
Aches and pains	382 (44.2)	433 (30.6)	1.79 (1.50, 2.13)	256 (29.6)	282 (19.9)	1.69 (1.39, 2.06)
Bluish color to lips and face	52 (6.0)	27 (1.9)	3.29 (2.05, 5.27)	24 (2.8)	13 (0.9)	3.08 (1.56, 6.07)
Cough	488 (56.4)	557 (39.4)	1.99 (1.68, 2.36)	213 (24.6)	213 (15.1)	1.90 (1.53, 2.35)
Decreased appetite	256 (29.6)	224 (15.8)	2.23 (1.82, 2.74)	180 (20.8)	143 (10.0)	2.34 (1.84, 2.97)
Anosmia (decreased sense of smell)	296 (34.2)	138 (9.8)	4.81 (3.84, 6.02)	235 (27.2)	94 (6.6)	5.25 (4.06, 6.80)
Ageusia (decreased sense of taste)	310 (35.8)	159 (11.2)	4.41 (3.55, 5.47)	232 (26.8)	105 (7.4)	4.57 (3.56, 5.87)
Diarrhea	256 (29.6)	278 (19.7)	1.72 (1.41, 2.09)	159 (18.4)	154 (10.9)	1.84 (1.45, 2.34)
Fatigue	473 (54.7)	604 (42.7)	1.62 (1.36, 1.92)	311 (36.0)	389 (27.5)	1.50 (1.24, 1.80)
Fever	410 (47.4)	308 (21.8)	3.24 (2.69, 3.89)	156 (18.0)	97 (6.9)	3.19 (2.43, 4.18)
Nasal congestion	276 (31.9)	314 (22.2)	1.64 (1.36, 1.99)	150 (17.3)	156 (11.0)	1.68 (1.32, 2.14)
Nausea	199 (23.0)	217 (15.3)	1.65 (1.33, 2.04)	104 (12.0)	111 (7.9)	1.60 (1.21, 1.13)
New onset of confusion	70 (8.1)	75 (5.3)	1.57 (1.12, 2.20)	38 (4.4)	31 (2.2)	2.05 (1.26, 3.32)
Persistent pain or pressure in the chest	204 (23.6)	266 (18.8)	1.33 (1.08, 1.64)	140 (16.2)	167 (11.8)	1.44 (1.13, 1.84)
Runny nose	239 (27.6)	266 (18.8)	1.65 (1.35, 2.01)	91 (10.5)	102 (7.2)	1.51 (1.12, 2.03)
Shortness of breath/difficulty breathing	352 (40.6)	380 (26.9)	1.87 (1.56, 2.23)	205 (23.7)	210 (14.9)	1.79 (1.45, 2.22)
Sore throat	268 (31.0)	322 (22.8)	1.52 (1.26, 1.84)	128 (14.8)	153 (10.8)	1.44 (1.12, 1.85)
Trouble waking up after sleeping	105 (12.1)	149 (10.5)	1.17 (0.90, 1.53)	66 (7.6)	106 (7.5)	1.02 (0.74, 1.40)
Vomiting	108 (12.5)	80 (5.7)	2.38 (1.76, 3.22)	58 (6.7)	41 (2.9)	2.41 (1.60, 3.63)
Combination of symptoms						
Decreased sense of smell, taste and vomiting	50 (5.8)	22 (1.6)	3.88 (2.29, 6.78)			
Decreased sense of smell, taste, and fever	160 (18.5)	51 (3.6)	6.07 (4.39, 8.47)			
Decreased sense of smell, taste, vomiting and fever	45 (5.2)	17 (1.2)	4.51 (2.51, 8.46)			
Number of Symptoms						
Average N symptoms	5.5	3.4		3.2	1.8	
No symptoms reported	134 (15.5)	464 (32.8)		313 (36.2)	750 (53.0)	

Abbreviations: COVID+, participants who reported having had a positive COVID-19 test result; COVID-, participants who reported having had a negative COVID-19 test result; OR, odds ratio; CI, confidence interval.

[a] Participants ranked their symptoms as very mild, mild, moderate or severe. Among participants reporting symptoms, severity was missing for <3% for most except for cough, fatigue and fever (5–8% missing). Participants who did not complete symptom severity information were excluded from the calculation of ORs.

dyspnea with obesity in a community setting raises concerns about referral thresholds. It may well be prudent to have a very low threshold for referral and admission of symptomatic obese patients. The same consideration could also apply to patients with underlying respiratory disorders. However, there was no evidence for a marked increase in risk among people who reported underlying cancer or cardiovascular disease, or those taking medications for autoimmune disease, diabetes, or hypertension. The absence of increased risk of severe disease in users of medication for auto-immune disorders is similar to previous findings indicating that use of disease modifying agents does not increase the risk of complications from seasonal influenza [24]. The findings of increased risk of severe disease in the presence of obesity were in line with existing evidence on COVID-19 [25] and are somewhat in contrast with previous findings in seasonal influenza, which pointed to decreasing risk of influenza complications with increasing BMI [26], supporting the distinct pathology and immunopathology of COVID-19.

Our findings would be strengthened by complementary analyses of other clinical and treatment information for obese participants and those on medication for auto-immune disorders, including if and how they are being treated for these underlying conditions; a possible explanation may be that individuals with more severe conditions were underrepresented in our study, but this remains speculative. Further validation may be derived from additional data collection and analysis from subsequent waves of infection, a process that has already been initiated.

It is important to keep in mind that these data are voluntarily reported, are not a representative sample of the US population, and thus will not support inferences about distribution of symptoms in the US. Recognizing that self-reported information has limitations, comparisons between respondents may nevertheless indicate true causal relationships and can serve to stimulate further research as the medical and scientific community seek to learn more about this infection. This

Table 3
Risk of moderate or severe shortness of breath among those reporting a positive COVID-19 test result.

	Reduced model (n = 788) OR (95% CI)	Full model (n = 671) OR (95% CI)
Age group		
19–29	ref	ref
30–39	0.92 (0.57, 1.49)	0.87 (0.50, 1.49)
40–49	0.99 (0.61, 1.61)	0.93 (0.54, 1.60)
50–59	0.74 (0.42, 1.32)	0.71 (0.38, 1.34)
60+	0.64 (0.31, 1.30)	0.47 (0.21, 1.08)
Gender		
Male	ref	ref
Female	1.35 (0.91, 2.02)	1.33 (0.85, 2.07)
Race		
White	ref	ref
Black	1.02 (0.60, 1.73)	1.30 (0.73, 2.32)
Other/Multiracial	1.56 (0.96, 2.53)	1.28 (0.73, 2.25)
BMI category		
Underweight or Normal weight (BMI < 25.0)	ref	ref
Overweight (25.0≤BMI < 30.0)	1.95 (1.18, 3.21)	1.89 (1.11, 3.22)
Obese (BMI≥30.0)	2.31 (1.46, 3.65)	2.30 (1.40, 3.78)
Ethnicity Hispanic		
No	ref	ref
Yes	0.61 (0.37, 0.99)	0.67 (0.38, 1.16)
Education		
4-year college degree	ref	ref
High school or less than high school	1.20 (0.73, 1.98)	1.59 (0.91, 2.80)
Some college or 2-year college degree	0.84 (0.54, 1.31)	0.83 (0.51, 1.35)
More than 4-year college degree	0.74 (0.45, 1.23)	0.70 (0.39, 1.25)
Comorbidities and medication use[a]		
Nicotine addiction (smoker)		1.36 (0.78, 2.40)
Organ Transplant		3.07 (0.72, 13.09)
Cancer		0.27 (0.06, 1.22)
Cardiovascular disease		1.23 (0.54, 2.79)
Medication for hypertension		0.73 (0.44, 1.22)
Medication for diabetes		1.21 (0.66, 2.21)
Medication for autoimmune disease		0.86 (0.35, 2.10)
Medication for lung disease		3.68 (2.04, 6.62)

Notes: shortness of breath and severity assessed at baseline. Participants who reported shortness of breath, but did not report severity of the symptom were excluded from this analysis (n = 11).

[a] Referent category includes participants who reported not having the condition of interest or not taking the medication of interest.

methodology appears to be useful in capturing relevant real world data, particularly symptom severity, without requiring physical presentation for clinical assessment, and offers valuable perspective on the true burden of illness as well as signaling those at particularly high risk of severe symptoms and, in parallel, those unlikely to be at such increased risk. The findings may help guide diagnosis and triage in settings where there is not ready access to rapid and reliable diagnostic testing.

Trial registration

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CRediT authorship contribution statement

Nancy A. Dreyer: Conceptualization, Methodology, interpretation, Writing - original draft, Supervision. **Matthew Reynolds:** Conceptualization, Methodology, Supervision. **Christina DeFilippo Mack:** Conceptualization, Formal analysis, interpretation. **Emma Brinkley:** Conceptualization, Data curation, Software. **Natalia Petruski-Ivleva:** Formal analysis, Data curation, Writing - original draft. **Kalyani Hawaldar:** Data curation, Validation, Formal analysis. **Stephen Toovey:** Conceptualization, Supervision, Writing - review & editing. **Jonathan Morris:** Conceptualization, Supervision.

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