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Describe the disease course in a cohort of outpatients with COVID-19 and evaluate factors predicting duration of symptoms.

Retrospective cohort study.

Telemedicine clinic at a large medical system in Atlanta, Georgia.

337 patients with acute COVID-19. Exclusion criteria included intake visit more than 10 days after symptom onset and hospitalisation prior to intake visit.

Main outcome measures

Symptom duration in days.

Common symptoms at intake visit are upper respiratory (73% cough, 55% loss of smell or taste, 57% sinus congestion, 32% sore throat) and systemic (66% headache, 64% body aches, 53% chills, 30% dizziness, 36% fever). Day of symptom onset was earliest for systemic and upper respiratory symptoms (median onset day 1 for both), followed by lower respiratory symptoms (day 3, 95% CI 2 to 4), with later onset of gastrointestinal symptoms (day 4, 95% CI 3 to 5), when present. Cough had the longest duration when present with median 17 days (95% CI 15 to 21), with 42% not resolved at final visit. Loss of smell or taste had the second longest duration with 14 days (95% CI 12 to 17), with 38% not resolved at final visit. Initial symptom severity is a significant predictor of symptom duration ($p<0.01$ for multiple symptoms).

COVID-19 illness in outpatients follows a pattern of progression from systemic symptoms to lower respiratory symptoms and persistent symptoms are common across categories. Initial symptom severity is a significant predictor of disease duration for most considered symptoms.

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Strengths and limitations of this study

By systematically calling patients throughout acute illness, we are able to provide a visual representation of symptoms of acute illness in outpatients.

Missing data are minimal during acute illness as patients are followed until symptom improvement.

We used standardised templates for all patients and are able to analyse predictors of symptom duration for specific variables including age, comorbidities and symptom severity.

We are a single-centre study with limited patient numbers.

We do not follow patients until disease resolution and cannot define an end date for all symptoms.

COVID-19 has brought large numbers of patients to medical attention within a span of months for care of a previously undescribed illness. Early reports on the presentation and natural history of COVID-19 appropriately focused attention on the severe cases and critically ill.

In March 2020, we established a virtual clinic for the care of patients in home isolation with COVID-19: the 'Virtual Outpatient Management Clinic' (VOMC), using available knowledge for assessment and

treatment guidelines. All patients underwent VOMC intake visits with a physician or advanced practice provider (APP), including assessment of specific COVID-19 symptoms using a standardised clinical note. Patients were followed for symptom management with regular telephone calls by registered nurses (RNs) and APPs until improvement or hospitalisation. Subsets from this cohort have been reported elsewhere in a small case series

As it became clear in clinical practice that symptom duration varies substantially between patients, we undertook this study to determine the predictors of the symptom course of our VOMC cohort. We hypothesised that a combination of demographics, comorbidities and initial symptom severity would predict symptom duration.

The study was a retrospective cohort study, conducted at Emory Healthcare, the largest academic health system in Georgia (serving the greater Atlanta metropolitan area), which includes more than 250 provider locations and 120 primary care locations. The VOMC comprised an intake team of 14 physicians and 3 APPs from two primary care clinics; and follow-up call teams included 19 redeployed RNs and 20 APPs. All intake providers were trained in the use of the risk assessment tool in a 1-hour webinar and conducted a median of 25 intake visits during the study period (range: 5–99), with the majority of intake visits conducted by physicians (83.6%).

We included outpatient adults who completed their VOMC intake visit between 24 March 2020 and 26 May 2020 with initial symptom dates between 17 March and 20 May. We excluded patients hospitalised prior to the intake visit and patients with an intake visit occurring more than 10 days after symptom onset in order to improve the accuracy of early symptom reporting.

During the study period, outpatient COVID-19 testing was conducted by medical providers using nasopharyngeal sampling for real-time reverse transcription-PCR (RT-PCR) detection of SARS-CoV-2. Testing of outpatients occurred primarily at a screening clinic (converted outpatient clinical space) and did not include a clinical assessment except for triage of visibly unstable patients. As test volume increased in April 2020, a drive-through site was added (accounting for 27% of VOMC referrals during the study period). Patients requiring in-person evaluation could be triaged at any time in their illness to the emergency department (ED) or a lower acuity ‘in-person’ Acute Respiratory Clinic (ARC), described elsewhere.

Adult patients with positive RT-PCR results from the outpatient sites or EDs were called by a result notification team to provide isolation advice and refer to the VOMC. All patients with positive RT-PCR were offered VOMC referral during the study period. The criteria for testing and details of care are outlined in

Virtual Outpatient Management Clinic (VOMC) care during study period

Outpatient COVID-19 testing criteria (March–April 2020):

Symptom(s): either (a) fever, cough or shortness of breath, or (b) two symptoms from the following: sore throat, congestion, myalgias, fatigue, diarrhoea, loss of smell.

Prioritise: (a) frontline healthcare workers, (b) students on campus and health professions, (c) Centers for Disease Control and Prevention employees, (d) patients with risk factors (age, comorbidity, immunosuppression, work in a communal setting).

Setting: outpatient clinic repurposed as testing site (12 March 2020) and additional drive-through site added to expand capacity (9 April 2020).

Emergency department COVID-19 testing criteria (March 2020):

Symptom(s): cough, fever, sore throat or shortness of breath.

Prioritise: (a) severe illness (difficulty breathing or other indication for admission), (b) high-risk comorbidities including chronic lung disease, heart disease, chronic kidney disease, diabetes, immunocompromising conditions, or (c) communal housing or living with high-risk individual.

Acute Respiratory Clinic in-person care site (April–May 2020):

Referrals for evaluation (and testing if needed) from sources: COVID-19 hotline (triage of incoming patient calls), physician offices and VOMC for in-person evaluation of VOMC patients.

Testing criteria: none specified, at provider discretion only.

Setting: primary care clinic repurposed as acute care site for respiratory complaints (known or possible COVID-19), with services including phlebotomy, plain radiography, ECG, pulse oximetry. Staffed daily by one to two physicians and advanced practice providers from the general internal medicine and one infectious disease specialist.

VOMC enrolment criteria:

Diagnosis of COVID-19 by nasopharyngeal PCR.

Requesting* outpatient monitoring and/or management of COVID-19 symptoms.

Able to complete telemedicine intake (synchronous audio/video connection by smartphone or computer preferred), with telephone-only visit as backup option.

Documentation template includes symptom history, symptom severity (patient-reported and provider-assessed), medical history, physical examination and risk assessment.

Symptoms assessed: 'systemic' (fever, chills, body aches, dizziness, headache, joint pain), 'upper respiratory' (loss of smell or taste, sinus congestion, sore throat, cough), 'lower respiratory' (chest tightness, shortness of breath with exertion, shortness of breath at rest, wheezing), 'gastrointestinal' (abdominal pain, nausea, diarrhoea), as well as confusion and rash. Note: symptoms assessed as a single list and not grouped into categories during assessment.

Provider gives advice for (1) symptom management, (2) home isolation guidance and (3) outpatient monitoring.

Provider-assessed symptom severity definition (at VOMC intake visit):

Respiratory: cough, sputum production.

Systemic: fever, chills, malaise, myalgia, anorexia, diarrhoea, vomiting, headache.

Respiratory: severe cough, dyspnoea on exertion, wheezing or sensation of mid-chest tightness.

Systemic: N/A (not provided in VOMC clinical guideline).

Resting dyspnoea, laboured breathing, resting pulse oximetry $\leq 92\%$, pleuritic pain, haemoptysis.

Systemic: acute confusion, severe weakness, syncope, acute decline in functional status.

Follow-up phone calls (March–June 2020):

Patients receive VOMC follow-up telephone calls based on hospitalisation risk tool

Low risk: every other day for a minimum of 7 days from symptom onset.

Intermediate risk: daily for a minimum of 14 days from symptom onset.

High risk: twice daily for a minimum of 21 days from symptom onset.

All patients called until the intervals above and for a minimum 3 days after improvement in fevers (without antipyretics) and improvement in respiratory symptoms (whichever criterion was longer).

Patients with improving or worsening symptoms could change risk level after enrolment at provider discretion.

*All patients with positive results were notified by telephone and offered VOMC referral.

Study data were obtained from two specific provider note types deployed in March 2020 within the Emory Healthcare electronic health record (Cerner Corp, Kansas City, Missouri, USA): (1) VOMC provider intake visit and (2) VOMC follow-up telephone call. The intake visit assessment note template included (1) documentation of specific COVID-19 symptoms including onset and offset dates, (2) patient-reported and provider-assessed symptom severity, and (3) documentation of specific medical conditions associated with risk of severe COVID-19 (based on medical literature search in March 2020). The VOMC follow-up telephone call template included an identical symptom list with 'yes/no' selection for documentation of the presence or absence of symptoms at follow-up.

If symptom onset date was not identified in VOMC notes, we conducted manual chart review of telephone records prior to VOMC enrolment. Additional demographic information including age, gender and race (if recorded) was included from the electronic health record.

To ensure that symptoms were counted only once a day per patient among patients receiving two calls per day, if a symptom was listed as present more than once for a particular day, it was counted only once. Among patients receiving calls every other day, if a symptom was present on both the preceding and subsequent days, it was listed as present on the single non-call day in between for symptom duration.

To create a visual representation of overall disease as a heat map, we define day 1 as the first day a patient had any symptom and each individual symptom is counted only on days present.

The main outcome was duration in days for each specific symptom, using the first and last documented dates a symptom was present. Because patients could be discharged from VOMC with ongoing symptoms, if a symptom was present on the last nurse phone call it was considered censored for survival analysis. If a symptom was not present on the last nurse phone call, then the symptom was considered resolved.

The secondary outcome was the day of symptom onset. Symptoms were grouped into systems: upper respiratory (cough, congestion, sore throat, loss of smell or taste), systemic (fever, body aches, chills, dizziness, headache, joint pain), lower respiratory (shortness of breath (SOB) with exertion, SOB at rest, chest tightness, wheezing) and gastrointestinal (nausea, abdominal pain, diarrhoea). Confusion and rash were not included into symptom groups. For initial symptom severity, we used the provider-assessed severity at the intake visit (criteria listed in

Testing criteria are noted in

Demographics, comorbidities and initial symptom severity were tested as predictors of symptom duration.

Survival analysis was used to analyse symptom start date by system and duration of individual symptoms. Kaplan-Meier curves were constructed for symptom onset (grouped by systems) to calculate median day of onset with pairwise log-rank test used to compare the system groupings. Kaplan-Meier curves were also used to determine the median duration for each symptom. Cox proportional hazard models were constructed but the proportional hazards requirement was not met for several covariate symptom combinations so Cox models were not used. Time-varying covariates can be included as strata but different baseline hazards are modelled for each strata so the effect of the strata covariate is not estimated.

online supplemental table 1

10.1136/bmjopen-2020-044154.supp1

Subsequent analysis showed accelerated failure time (AFT) models had a better fit. AFT models are an alternate method of survival analysis which is parametric and does not require proportional hazards. To decrease the chance of false positive findings, we screened each comorbidity to see if it was a significant predictor of symptom duration with symptom duration analysed as strata (

online supplemental table 2

online supplemental table 3

online supplemental table 4

online supplemental figure 1

online supplemental figure 2

online supplemental table 5

[10.1136/bmjopen-2020-044154.supp2](https://doi.org/10.1136/bmjopen-2020-044154.supp2)

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Patient and public involvement

Patients and the public were not involved in the design and conduct of the study, outcomes, recruitment or planned dissemination.

There were 551 intake visits completed in the VOMC between 24 March 2020 and 26 May 2020. We included 337 patients in the study after excluding: 198 patients with VOMC intake visit more than 10 days after symptom onset, 6 patients without documented positive RT-PCR test for SARS-CoV-2, 3 patients hospitalised prior to VOMC enrolment, 3 patients with blank or uninterpretable symptom entries and 4 patients with neither provider nor self-reported initial symptom severity. Of the included patients, 33 (10%) were subsequently hospitalised and 7 of the hospitalised patients resumed VOMC care after hospital discharge.

The testing location for included patients was primarily outpatient (n=304, 90%), followed by ED (n=33, 10%). During the study period (testing dates 15 March 2020–22 May 2020), the following number of

patients tested positive for SARS-CoV-2 by RT-PCR at Emory Healthcare: 730 in the outpatient setting, 170 in the ED, 740 in the inpatient setting, 1 in ambulatory surgery and 1 patient in hospice.

Characteristics of the study population

Demographics, comorbidities and symptoms at VOMC intake visit

Initial symptom severity

Symptom onset to first VOMC visit (days, 95% CI)*

Symptom onset to last phone call (days, 95% CI)†

Alcohol abuse/addiction

Coronary artery disease

Symptom present prior to or at intake visit

Dizziness when standing

Loss of smell or taste

*Number of days from initial symptom(s) of COVID-19 to completion of telemedicine intake visit for the VOMC, inclusive of time required for testing, result notification and scheduling with VOMC.

†Number of days from initial symptom(s) of COVID-19 to the final telephone call with VOMC. The calls would end with patient-reported symptom improvement (not necessary resolution) or hospital admission.

ANOVA, analysis of variance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SOB, shortness of breath; VOMC, Virtual Outpatient Management Clinic.

Symptoms at VOMC intake visit

The most frequently reported symptoms occurring prior to and at the time of the VOMC intake visit included: 73% cough, 66% headache, 64% body aches, 57% sinus congestion, 55% loss of smell or taste and 53% chills (

Time course of individual symptoms

Heat map of incidence of individual symptoms by illness day. (A) All patients, n=304 (% of patients having symptom each day of COVID-19 disease); (B) mild provider-assessed symptom severity, n=209 and (C) moderate provider-assessed symptom severity, n=91.

Time course of symptoms by initial symptom severity

The heat map findings for mild initial symptom severity group (n=209 for heat map) demonstrate similar rates of initial upper respiratory symptoms compared with the entire heat map cohort, with peak daily prevalence of cough in 52% and sinus congestion in 45% during the first week (

The heat map for moderate initial symptom severity (

There were too few non-hospitalised patients with severe initial symptom severity (n=4) to represent with a heat map. This group had high prevalence (100% within the first week) of chills, body aches, loss of smell or taste, sore throat, cough, chest tightness and SOB with exertion. At 30 days, three patients (75%) still had cough and SOB with exertion.

Timing of symptom onset by system

The median day of symptom onset determined by Kaplan-Meier curves is shown in

Median day of symptoms onset by system determined from Kaplan-Meier curves

Systemic=fever, body aches, chills, dizziness, headache, joint pain; upper=cough, congestion, sore throat, loss of smell or taste; lower=shortness of breath with exertion, shortness of breath at rest, chest tightness, wheezing; gastrointestinal=nausea, abdominal pain, diarrhoea.

Duration of each symptom

Median duration of symptoms from Kaplan-Meier curves for all patients*

Number of patients with symptom

Median duration in days (95% CI)

Loss of smell or taste

*Censoring symptoms if present at the final VOMC phone call.

SOB, shortness of breath; VOMC, Virtual Outpatient Management Clinic.

Patients reporting improving symptoms could be discharged from VOMC with symptoms present. The percentage of patients reporting resolution of each symptom is presented in

Symptoms unresolved at last phone call

Total patients with symptom at any time

Number of symptomatic at last phone call

Per cent unresolved at last phone call

Loss of smell or taste

SOB, short

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<https://www.ncbi.nlm.nih.gov/pmc/articles/7938467/>]

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