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A primary care approach to the COVID-19 pandemic: clinical features and natural history of 2,073 suspected cases in the Corona Sao Caetano programme, Sao Paulo, Brazil

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3 **A primary care approach to the COVID-19 pandemic: clinical features and natural**
4 **history of 2,073 suspected cases in the Corona São Caetano programme, São Paulo,**
5 **Brazil**
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55 **KEY WORDS:** SARS-CoV-2, COVID-19, pandemic, community, primary care, Brazil
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ABSTRACT

Background: Despite most cases not requiring hospital care, there are limited community-based clinical data on COVID-19.

Methods: The Corona São Caetano program is a primary care initiative offering COVID-19 care to all residents of São Caetano do Sul, Brazil. After triage of potentially severe cases, consecutive patients presenting between 13th April and 13th May 2020 were tested at home with SARS-CoV-2 reverse transcriptase (RT) PCR; positive patients were followed up for 14 days. RT-PCR-negative patients were offered SARS-CoV-2 serology. We describe the clinical features, virology and natural history of this prospective population-based cohort.

Findings: Of 2,073 suspected COVID-19 cases, 1,583 (76.4%) were tested by RT-PCR, of whom 444 (28.0%, 95%CI: 25.9% - 30.3%) were positive; 604/1,136 (53%) RT-PCR-negative patients underwent serology, of whom 52 (8.6%) tested SARS-CoV-2 seropositive. The most common symptoms of COVID-19 were cough, fatigue, myalgia and headache; whereas self-reported fever (OR 3.0, 95%CI 2.4-3.9), anosmia (OR 3.3, 95%CI 2.6-4.4), and ageusia (2.9, 95%CI 2.3-3.8) were most associated with a positive COVID-19 diagnosis. RT-PCR cycle thresholds were lower in men, older patients, those with fever and arthralgia, and around symptom onset. The rates of hospitalization and death among 444 RT-PCR-positive cases were 6.7% and 0.7%, respectively, with older age and obesity more frequent in the hospitalized group.

Conclusion: COVID-19 presents in a similar way to other mild respiratory disease in the community, but some symptoms can assist the differential diagnosis. Most patients recovered without requiring hospitalization with a low fatality rate compared to hospital-based studies.

Strengths and limitations of this study

1. The clinical features of COVID-19 have mostly been described in hospital-based studies which are necessarily biased towards severe disease
2. We report a prospective cohort of suspected and confirmed COVID-19 cases from a primary care initiative in the Brazilian municipality of São Caetano do Sul
3. By systematically testing consecutive suspected community cases with molecular and serological tests we were able to address the diagnostic value of clinical features of mild-moderate COVID-19 in primary care
4. Prospective follow-up of confirmed cases and linkage with hospital datasets allowed us to describe the natural history of a primary care COVID-19 population
5. A limitation of the work was that not all participants underwent serology testing due to loss to follow-up

INTRODUCTION

A comprehensive public health response is vital but difficult to achieve during an epidemic. The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in China in late 2019.¹ According to the World Health Organization (WHO)² and others³, the ideal early response should have been multipronged, with identification, isolation, treatment and contact tracing of symptomatic cases, relying on a strong testing programme. Primary health care (PHC) is well placed to implement such a response, by identifying cases early and managing them in a way that minimizes overcrowding of emergency rooms and intensive care units.⁴ Real-time data analysis coming from these primary care response systems can inform policy decisions.

In Brazil, the first case of COVID-19 was identified in the city of São Paulo on 26th February 2020.⁵ As of 15th June 2020 there were 1,400,000 cases nationally with São Paulo contributing a fifth of these.⁶ In March 2020, the Municipal Health Department of the municipality of São Caetano do Sul – part of the Greater Metropolitan Region of São Paulo – began to develop a clinical and testing platform to organize its COVID-19 response. The aim was to provide universal detection and management of symptomatic cases and their contacts. The platform was developed in partnership with two local universities – the Municipal University of São Caetano do Sul (USCS) and the University of Sao Paulo (USP) – and called “Corona São Caetano”.

Large scale community-based observational cohorts are difficult to establish under epidemic circumstances, particularly if the risk of exposure for research personnel is high. Hence, most COVID-19 epidemiological and clinical studies have been hospital-based,^{7–9} and therefore tend to include more severe cases whose findings may not be generalizable to the general population.¹⁰ The objectives of this study were to describe the epidemiological indicators of the early phase of the programme rollout; and to describe the clinical, virologic and natural history features (including hospitalization and deaths) of SARS-CoV-2 infection among patients identified in primary care.

METHODS

Setting

The municipality of São Caetano do Sul has a population of 161,000 inhabitants.¹¹ The active aging index (i.e., the ratio of population aged >60 yr / population aged ≤14 yr) is 135, compared to the Brazilian average of 52, reflecting an aging population;¹¹ its Human Development Index is one of the highest in the country; nearly all (97.4%) children aged 6-14 are in education and 31% of the population have completed higher education¹² (Brazilian national average is 11%).

Corona São Caetano platform

Residents of the municipality aged 12 years and older with suspected COVID-19 symptoms were encouraged to contact the dedicated Corona São Caetano platform via the website (access at <https://coronasaocaetano.org/>) or by phone. They were invited to complete an initial screening questionnaire that included socio-demographic data; information on symptoms type, onset and duration; and recent contacts.

Patients meeting the suspected COVID-19 case definition (i.e., having at least two of the following symptoms: fever, cough, sore throat, coryza, or change in/loss of smell (anosmia); or one of these symptoms plus at least two other symptoms consistent with COVID-19) were further evaluated, whilst people not meeting these criteria were reassured, advised to stay at home and contact the service again if they were to develop new symptoms or worsening of current ones. Patients were then called by a medical student to complete a risk assessment. All pregnant women, and patients meeting pre-defined triage criteria for severe disease (see Supplemental Material), were advised to attend a hospital service - either an emergency department or outpatient service, depending on availability. All other patients were offered a home visit for self-collection of a nasopharyngeal swab.

Sample collection

Nasopharyngeal swabs (NPS – both nostrils and throat) were collected at the patients' homes under the supervision of trained healthcare personnel. A link to a video

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3 (<https://youtu.be/rWZzV2ZP7KY>) was sent to the patients, before the home visit, to provide
4 guidance on self-collection procedures. Healthcare personnel were instructed to maintain a
5 distance of six feet from the patient and to wear personal protective equipment at all times.
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7 Samples were immediately put on a cool box between 2-8°C and stored at 4°C in a fridge
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9 until shipment to the lab within 24 hours.
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13 **Follow-up procedures**

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17 Patients testing SARS-CoV-2 RT-PCR positive were followed up to 14 days (a maximum of
18 7 phone calls) from completion of their initial questionnaire. They were contacted every 48
19 hours by a medical student who completed another risk assessment and recorded any ongoing
20 or new symptoms. Patients testing RT-PCR negative were followed up by the primary health
21 care program for their residential area. They were advised to contact the platform for a new
22 consultation if they developed new symptoms. Starting on May 19th, when serological
23 testing became available, RT-PCR-negative patients were re-contacted to offer antibody
24 (IgG/IgM combined) testing 14 days after their initial registration as long as they had become
25 asymptomatic.
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34 **Study dates**

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37 The Corona São Caetano programme was launched on 6th April 2020 and is still ongoing at
38 the time of writing. For this analysis, we opted to include all patients making their first
39 contact with the programme between 13th April and 13th May 2020. This comprises the first
40 31 days of the response, having excluded the first week, which corresponded to a pilot phase
41 designed to test instruments before roll-out. The period of follow-up (last date of data
42 extraction) was 4th June 2020, to account for the accrual period (three weeks) of possible
43 hospitalizations in the last included patients.
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51 **Laboratory methods**

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54 Due to shortages of some reagents, two RT-PCR platforms were used at different times
55 during the study: ALTONA RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Hamburg, Germany)
56 and the Mico BioMed RT-qPCR kit (Seongnam, South Korea). For serology we tested 10µL
57 of serum or plasma (equivalent in performance) using a qualitative rapid chromatographic
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3 immunoassay (Wondfo Biotech Co., Guangzhou, China), that jointly detects anti-SARS-
4 CoV-2 IgG/IgM. The assay has been found to have a sensitivity of 81.5% and specificity of
5 99.1% in a US study¹³. In our local validation, after two weeks of symptoms, the sensitivity
6 in 59 RT-PCR confirmed cases was 94.9%, and specificity in 106 biobank samples from
7 2019 was 100%.

13 **Statistical methods**

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17 We estimated the contribution of our platform to COVID-19 diagnosis in São Caetano do
18 Sul. We compared the number of cases diagnosed in our programme with official data
19 released by the Municipal Department of Health in its daily bulletins (accessed here
20 <https://coronavirus.saocaetanodosul.sp.gov.br>).

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26 Clinical and demographic data were extracted directly from the Corona São Caetano
27 information system, with the last export on 5th June, to allow for follow-up of patients at the
28 end of the study period. To analyse clinical presentation, we first calculated the proportion
29 and exact binomial 95% confidence intervals (CI) of cases reporting each symptom in the
30 three testing groups: SARS-CoV-2 RT-PCR positive; RT-PCR negative / seropositive; and
31 RT-PCR negative / seronegative. We next combined RT-PCR and serology positive cases to
32 make confirmed COVID-19 group, and those negative on both tests to make a SARS-CoV-2
33 negative control group. We express the association between each symptom and a positive
34 COVID-19 diagnosis as odds ratios (OR) and 95% CIs.

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43 Next, we assessed associations between RT-PCR cycle thresholds (Cts) and other clinical
44 features. ALTONA and MiCo BioMed RT-PCR kits each separately amplify two different
45 SARS-CoV-2 viral genes, as such each patient had two Ct values. There was a high
46 concordance between Cts for the two genes within each kit (Figure S1), and we opted therefore
47 to use the mean of the two Ct values for each patient in all analyses. We calculated univariable
48 associations between Cts and age, sex, delay from symptom onset to NPS collection, and
49 presenting symptoms using simple linear regression. We then built a multivariable linear
50 regression model to assess independent associations between presenting symptoms and RT-
51 PCR Cts. As age, sex, and time of swab collection may confound this relationship we included
52 these variables, as well as the RT-PCR platform (ALTONA vs MiCo BioMed), as covariates
53 in the model.

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5 For RT-PCR positive patients (followed up for 14 days), hospitalizations and deaths were
6 extracted from the study platform. To extend the follow-up period and to capture RT-PCR
7 negative patients and those initially triaged to hospital (no study follow-up), hospitalization
8 and vital status was confirmed by linkage with two administrative databases: the municipal
9 epidemiological surveillance dataset, as well as the state-wide influenza-like illness
10 notification system (SIVEP-Gripe). Linkage was last performed on 5th June 2020, 23 days
11 after the last patient was enrolled. Categorical patient characteristics were compared
12 according to hospitalization status using a Chi-squared or Fisher exact test. Continuous
13 variables were compared using the Wilcoxon rank sum test.
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22 The cohort sample included consecutive cases presenting to the Corona São Caetano program
23 and a formal sample size calculation was not performed. Missing data were excluded. All
24 analyses were conducted in R Software for Statistical Computing, version 3.6.3.¹⁴
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29 **Ethics**

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32 The study was approved by the local ethics committee (Comissão de Ética para Análise de
33 Projeto de Pesquisa - CAPPesq, protocol No. 13915, dated June 03, 2020). The committee
34 waived the need for informed consent and allowed the development of an analytical dataset
35 with no personal identification for the current analysis.
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41 **Patient and public involvement**

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44 Patients were not involved in the planning of this research.
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RESULTS

Epidemiological and programmatic indicators

Between 13th April and 13th May 2020, there were 2,073 presentations, from 2,011 individual patients, that met the criteria for a suspected COVID-19 case (See Figure 1 for study flow). At initial phone interview, 132 (6%) potential cases were advised to go directly to a health service based on the triage questions, and 12 (0.6%) because of pregnancy. Only four (3%) of referred patients were admitted to hospital and none died.

In total 1,583 individual patients were tested with RT-PCR for SARS-CoV-2; 444 (28.0%, 95%CI 25.9%-30.3%) were positive. The proportion of positive results was stable over the study (Figure S2). Among the RT-PCR negative group, 604 (53% of 1,136) underwent serology testing, of whom 52 (8.6%, 95%CI 6.6% - 11.1%) were seropositive. The median [IQR] time from symptom onset to serology collection was 31 [26 – 37] days. The age-sex structure of patients being tested differed from the underlying population of São Caetano do Sul (Figure S3) with an overrepresentation of working-age adults and women. At the beginning of programme roll out, 75% of notified COVID-19 cases in São Caetano do Sul were diagnosed in outpatient or hospital services. Over the study period, adherence to the programme increased, and by May 13th, 2020, 78% of cases in the municipality were diagnosed within our programme.

Of 444 RT-PCR positive patients eligible for longitudinal follow-up, 326 (73%) had their final follow-up visit at least 14 days after their initial presentation. Of the seven possible follow-up questionnaires, 384 (86%) COVID-19 patients completed three or more, and 162 (36%) completed all seven.

Participant characteristics

Patient characteristics are shown in Table 1. Although women were overrepresented in the cohort, there were proportionally more males in the RT-PCR positive and seropositive groups compared to the seronegative group. Of note, 55% of RT-PCR negative/seronegative patients had completed higher education compared to 35% RT-PCR-positive patients ($p < 0.001$, Chi-

squared test). The median number of days from symptom onset to swab collection was 5.0 (interquartile range [IQR], 4.0-7.0) among RT-PCR positive patients and 6.0 (IQR, 4.0-8.3) among RT-PCR negative/seropositive patients ($p = 0.06$, Wilcoxon rank sum) (Figure S4). Chronic respiratory disease was less frequent in RT-PCR positive than dual-negative patients.

Symptoms of COVID-19

The prevalence of individual symptoms at presentation is shown in Figure 2A stratified by final diagnostic category. The most frequent symptoms among RT-PCR and seropositive patients were headache (82% and 75%), myalgia (80% and 80%), cough (77% and 63%), and fatigue (77% and 79%). Anosmia was present in 56% and 63% of RT-PCR positive and seropositive patients, respectively, compared to 30% in those testing doubly negative. A similar pattern was observed for ageusia (53% and 53% versus 30%). Upper respiratory tract symptoms - including coryza, blocked nose, ageusia, and anosmia - were more frequent in younger people (Figure 2B). The evolution of symptoms over time among RT-PCR positive patients is shown in Figure S5.

The odds ratios for testing positive for SARS-CoV-2 (RT-PCR or serology) associated with each presenting symptom are shown in Figure 3. The symptoms with strongest associations were anosmia (OR 3.3, 95%CI 2.6-4.4), fever (3.0, 95%CI 2.4-3.9) and ageusia (2.9, 95%CI 2.3-3.8). The presence of sore throat (0.53, 95%CI 0.41-0.68) and diarrhoea (0.72, 95%CI 0.55-0.96) were associated with a negative SARS-CoV-2 test.

Associations between SARS-CoV-2 RT-PCR Cycle threshold (Ct) values, and demographic and clinical features

Figure 4 shows the associations between mean RT-PCR cycle threshold and demographic features and symptoms at presentation. Older age was associated with lower cycle thresholds, with a change in mean Ct of -0.05 (95%CI -0.09 to -0.01) for each additional year of age. The mean difference in Ct value was -1.36 (95% CI -2.49 to -0.23) in men compared to women. For each doubling in the number of days from symptom onset to swab collection the mean Ct value increased by 3.28 (95%CI 2.33 to 4.03). Presenting symptoms of fever and arthralgia were associated with lower Cts, whereas anosmia, ageusia, vomiting, diarrhoea, and nausea were associated with higher Cts (Figure 4 and Table S1). After adjustment for age, sex, delay

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3 from symptom onset, and RT-PCR platform used, fever (-0.06, 95%CI -2.11 to -0.001) and
4 arthralgia (-1.24, -2.18 to -0.10) remained associated with lower Cts, and anosmia (2.21, 1.0
5 to 3.29), ageusia (1.96, 0.88 to 3.0), and diarrhoea (1.36, 0.12 to 2.61) with higher Cts
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7 (Table S1).
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10 11 **Hospitalizations and deaths**

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15 Of the 444 RT-PCR positive patients, 30 (6.8%) had been hospitalized by 5th June 2020,
16 when the database linkage was last updated, and three (0.7%) had died; in-hospital mortality
17 was therefore 10% (3/30). In 28 cases the date of admission was available. The median time
18 from symptom onset to hospital admission was 7 (range 2 to 14) days. Among 1,136 RT-
19 PCR-negative patients, six (0.5%) had been admitted to hospital. One (<0.01% of 1,136) of
20 these six patients died. None of the 604 RT-PCR negative patients that underwent serology
21 were admitted to hospital or died. Table 2 compares patient characteristics by hospitalization
22 status. Notably, hospitalized patients were older, had more cardiovascular comorbidities and
23 were more frequently obese.
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DISCUSSION

We present a community-based cohort of suspected COVID-19 cases recruited through a primary care initiative in the Brazilian municipality of São Caetano do Sul. Offering RT-PCR testing to all patients presenting with symptoms compatible with COVID-19, the positivity rate was 28%, with 8.6% of those testing negative subsequently found to be seropositive - i.e. > 35% of the cohort had a diagnosis of COVID-19. Anosmia, ageusia, and self-reported fever provided the greatest diagnostic value in identifying COVID-19. The rate of hospitalization and deaths among RT-PCR positive patients was low, at 6.8% and 0.7%, respectively. Our results provide important information on the clinical presentation, diagnostic testing and natural history of COVID-19 identified in the community.

Extrapolating the seropositivity rate among RT-PCR negative patients to the 532 that were not tested with serology, we estimate that an additional 46 seropositive cases would have been identified. This corresponds to a false-negative rate of 18% among potential symptomatic COVID-19 cases. This is lower than a recent pooled analysis: nadir of 20% at three days post-symptom onset.¹⁵ Viral load peaks around the time of symptom onset and remains high over the first symptomatic week (also see Figure 4A).^{16,17} Consistent with this, we found a slightly longer delay to swab collection in RT-PCR false-negative patients than RT-PCR positive patients (Figure S4).

COVID-19 presents in a similar way to other respiratory viral illnesses. Indeed, in our cohort the most common symptoms of COVID-19 - such as cough, fatigue, headache, etc. - were reported with a similar frequency among patients testing negative. It is therefore important to have identified anosmia, ageusia, self-reported fever, myalgia, and anorexia as the symptoms with greatest value in the differential diagnosis of COVID-19 in primary care. Conversely, sore throat and diarrhoea - both considered symptoms of COVID-19 in other settings –¹⁸ were more frequently due to other aetiologies in this primary care context. These results are robust for a number of reasons. Firstly, our sample is representative of the population of interest - i.e. consecutive patients with suspected COVID-19 in the community - instead of extrapolating from hospital cases. Symptom data were collected prospectively, eliminating recall or interviewer bias. Finally, we have a control group of patients who were negative for both RT-PCR and serology, minimizing misclassification due to false negative RT-PCR.

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5 In our study, the proportion of patients with a positive SARS-CoV-2 RT-PCR requiring
6 hospitalization was low (7%). Early reports from China were of 13.8% of cases being
7 severe¹⁹, but this value was lower when under ascertainment of cases was accounted for.^{20,21}
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9 This is because our cohort reflects mild to moderate cases, as severely ill patients are likely to
10 have attended hospital directly. As such, only 3% of patients we triaged to attend health
11 services were ultimately hospitalized, possibly due to self-selection of patients presenting to
12 our service. Supporting this notion, our overall case fatality ratio among RT-PCR positive
13 patients was 0.7%.
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21 Our study has some limitations. Serology was not performed on all RT-PCR negative patients
22 due to on-going symptoms, loss to follow-up, or patient refusal. Of note, none of the RT-
23 PCR-negative patients that were admitted to hospital underwent serology testing. This
24 suggests that patients who were not tested with serology may have had a higher prevalence of
25 COVID-19 than those that were tested. In addition, imperfect serology test performance
26 (81% sensitivity)¹³ will introduced false-negative results. Taken together, these biases may
27 have underestimated the true seroprevalence among RT-PCR-negative cases, as well as the
28 false-negative rate of RT-PCR. The latter calculation may also have been influenced by the
29 inclusion of RT-PCR positive patients in the denominator, introducing an incorporation bias.²²
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38 A key strength to our study relates to the provision of primary healthcare in Brazil and its
39 symbiosis with medical training nationwide. Primary health care - within the family health
40 strategy (*Estratégia Saúde da Família*) - is centered around a healthcare unit with a multi-
41 professional team that is responsible for all residents in the immediate catchment area²³. São
42 Caetano do Sul has 100% coverage with the family health strategy, and medical students
43 from the municipal university (USCS) are integrated into the healthcare teams and
44 progressively trained from the first year of medical school. Our initiative took advantage of
45 this existing system, with the addition of an online platform allowing remote clinical
46 assessment and follow-up. The suspension of normal clinical training at the medical school
47 provided the workforce. The partnership with the University of São Paulo, which provided
48 the laboratory diagnostics, created the unique opportunity to establish our prospective
49 community cohort of suspected and confirmed COVID-19 cases. But we believe that this
50 infrastructure can be implemented in other regions with less resources. Other respiratory
51 disease such as influenza, measles, or tuberculosis may benefit from similar approach.
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CONTRIBUTION STATEMENT

FL, MC, SC, MC, RB, and ES conceived and designed the study. FL, RG, and JB provided clinical oversight and supervision of medical students. FL, MC, LB, HD, and SS collected and curated the data. MC, TM, LV, and LS performed the laboratory analysis. LB performed the formal statistical analysis with assistance from FL, SS, NA, PM, ES. LB, FL, PM and ES wrote the first draft, and all authors reviewed, contributed to and approved the final version.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interests.

FUNDING STATEMENT

The municipal health department of São Caetano do Sul (Secretaria Municipal de Saúde da Prefeitura de São Caetano do Sul) funded the establishment and implementation of the platform. We also acknowledge an award from FAPESP (2018/14389-0) and the UK Medical Research Council (MR/S0195/1) to the Brazil-UK Centre for Arbovirus Discovery, Diagnosis, Genomics and Epidemiology (CADDE).

DATA SHARING STATEMENT

Data will be made available by reasonable request to the corresponding author and following local ethnics approval.

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17 TABLE LEGENDS

18 **Table 1 Demographic and clinical characteristics of 1,048 suspected COVID-19 cases** 19 **undergoing diagnostic testing in the Corona São Caetano program.** * Security,

20 emergency services, supermarket, public transport, and pharmacy workers. IQR: interquartile
21 range; HCW: health care workers, COPD: chronic obstructive pulmonary disease. Missing
22 data – educational level 2; essential occupation 2; body mass index 4; cardiovascular disease
23 28; diabetes 31 mellitus; chronic resp. disease 65; chronic kidney disease 27; COPD 28. P-
24 values calculated by Chi-squared, Fisher exact, or Wilcoxon rank sum.
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33 **Table 2 Characteristics of RT-PCR positive patients stratified by hospitalization status.**

34 Missing data – body mass index 2; cardiovascular disease 12; diabetes mellitus 12; chronic
35 respiratory disease 29; COPD 11; chronic kidney disease 12; COPD - chronic obstructive
36 pulmonary disease; IQR - interquartile range.
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42 FIGURE LEGENDS

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44 **Figure 1** Patient flowchart for the Corona São Caetano platform between 13th April and 13th
45 May 2020. In the upper section (white background) the numbers correspond to individual
46 presentations to the system; among suspected cases 2,073 suspected cases, 60 had two
47 presentations and one had three. In the lower section (grey background) numbers correspond
48 to individual patients making up the final analytic groups.
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55 **Figure 2** Panel A presents prevalence (point) and exact binomial 95% confidence intervals
56 (vertical lines) of symptoms at presentation among patients with suspected COVID-19
57 according to RT-PCR result and serostatus (A). Panels B and C present the prevalence of
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3 presenting symptoms among patients with COVID-19 (RT-PCR and serology positive)
4 stratified by age (B) and sex (C).
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8 **Figure 3** Odds ratios (black dot) and 95% confidence intervals (lines) for testing positive for
9 COVID-19 (RT-PCR positive or serology positive) associated with the presence of each
10 presenting symptom. Horizontal axis is on log scale. Point estimates of odds ratios are shown
11 inline with their corresponding symptom.
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16 **Figure 4** Relationship between mean RT-PCR cycle threshold (Ct) and day of illness course
17 when the nasopharyngeal swab was collected (A), patient age (B), patient sex (C), and
18 different symptoms at presentation. Panels A and B show the best fit linear regression lines,
19 panels C and D are violin plots (rotated kernel density plots showing the full distribution of
20 data) of the Ct values with median (black dot) and interquartile range (black line).
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Table 1

	RT-PCR +ve (G1) N = 444 n (%) or median (IQR)	RT-PCR -ve Sero +ve (G2) N=52 n (%) or median (IQR)	RT-PCR -ve Sero -ve (G3) N = 552 n (%) or median (IQR)	p-value G1 versus G2	p-value G1 versus G3
Sex					
Male	200 (45.0)	23 (44.2)	185 (33.5)	1.0	<0.001
Female	244 (55.0)	29 (55.8)	367 (66.5)		
Age groups (years)					
10 to 19	29 (6.5)	1 (1.9)	25 (4.5)	0.07	0.40
20 to 39	197 (44.4)	17 (32.7)	236 (42.8)		
40 to 59	158 (35.6)	28 (53.8)	218 (39.5)		
60+	60 (13.5)	6 (11.5)	73 (13.2)		
Educational level					
Up to primary education	75 (16.9)	7 (13.5)	56 (10.2)	0.10	<0.001
High school	214 (48.3)	19 (36.5)	194 (35.2)		
University	154 (34.8)	26 (50.0)	301 (54.6)		
Essential Occupation					
Non-HCW essential job *	137 (30.9)	12 (23.1)	148 (26.9)	0.45	0.01
Carers	10 (2.3)	0 (0.0)	8 (1.5)		
HCW	32 (7.2)	5 (9.6)	73 (13.2)		
No	264 (59.6)	35 (67.3)	322 (58.4)		
Body mass index (kg/m²)					
<25	151 (34.2)	22 (42.3)	211 (38.4)	0.62	0.14
25-29	182 (41.2)	17 (32.7)	187 (34.0)		
30-35	79 (17.9)	9 (17.3)	112 (20.4)		
35+	30 (6.8)	4 (7.7)	40 (7.3)		
Comorbidities					
Cardiovascular disease	88 (20.4)	9 (17.6)	129 (24.0)	0.89	0.40
Diabetes mellitus	48 (11.1)	4 (7.8)	39 (7.3)	0.86	0.12
Any chronic resp. disease	37 (8.9)	9 (18.0)	79 (15.3)	0.13	0.01
COPD	24 (5.5)	5 (9.8)	54 (10.1)	0.47	0.03
Chronic kidney disease	1 (<1)	0 (0.0)	3 (1.0)	1.0	0.83
Time from symptom onset to swab collection (days), median (IQR)					
	5.0 (4.0-7.0)	6.0 (4.0-8.3)	6.0 (4.0-9.0)	0.06	<0.001

Table 2

	Hospitalized n=30 n (%) or median (IQR)	Not hospitalized n=414 n (%) or median (IQR)	p-value
Age (years)			
10 to 19	1 (3)	28 (97)	
20 to 39	6 (3)	191 (97)	
40 to 59	14 (9)	144 (91)	
60+	9 (15)	51 (85)	0.006
Sex			
Female	16 (7)	228 (93)	
Male	14 (7)	186 (93)	0.852
Comorbidities			
Cardiovascular disease	11 (13)	77 (87)	0.001
Diabetes mellitus	8 (17)	40 (83)	0.007
Any chronic resp. disease	2 (5)	35 (95)	1.0
COPD	1 (5)	23 (95)	1.0
Chronic kidney disease	1 (100)	0 (0)	0.06
Body mass index (Kg/m²)			
<25	4 (3)	147 (97)	
25-29	8 (4)	174 (96)	
30-35	12 (15)	67 (85)	
35+	6 (20)	24 (80)	<0.001
Time to presentation (days)	3 (3 to 4)	4 (3 to 5)	0.072

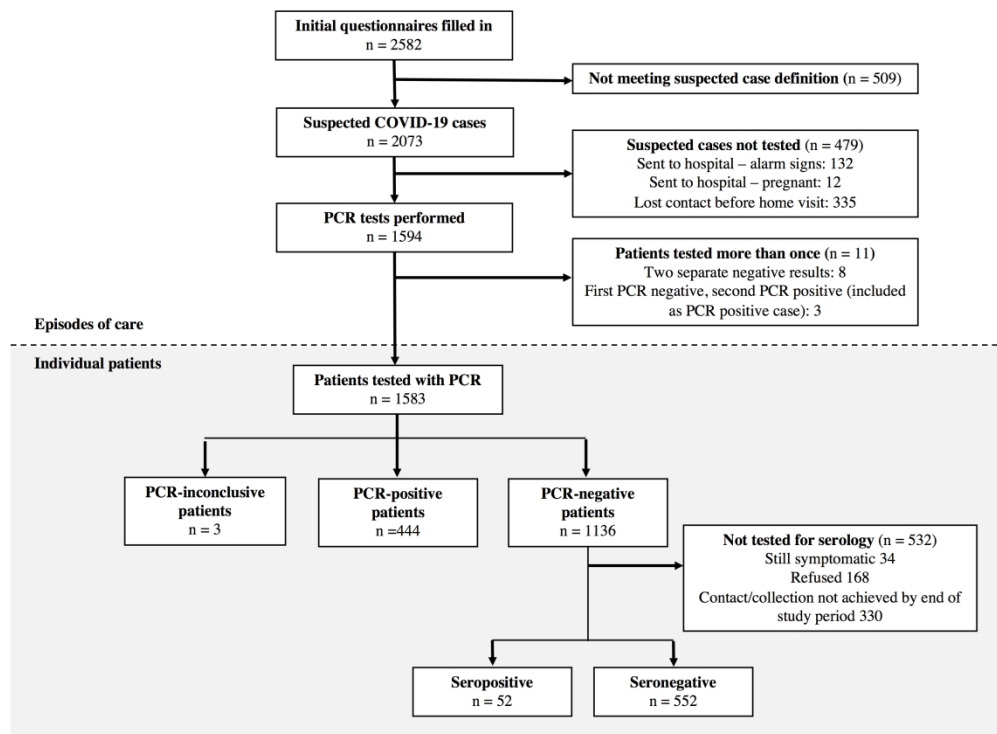


Figure 1

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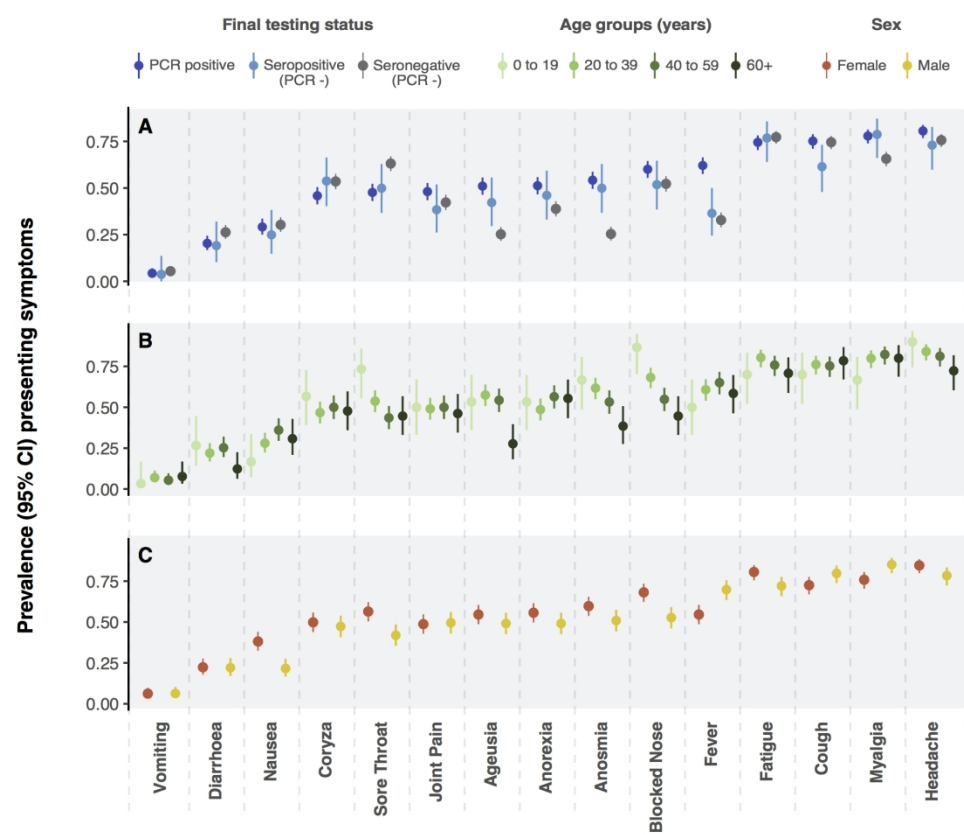


Figure 2

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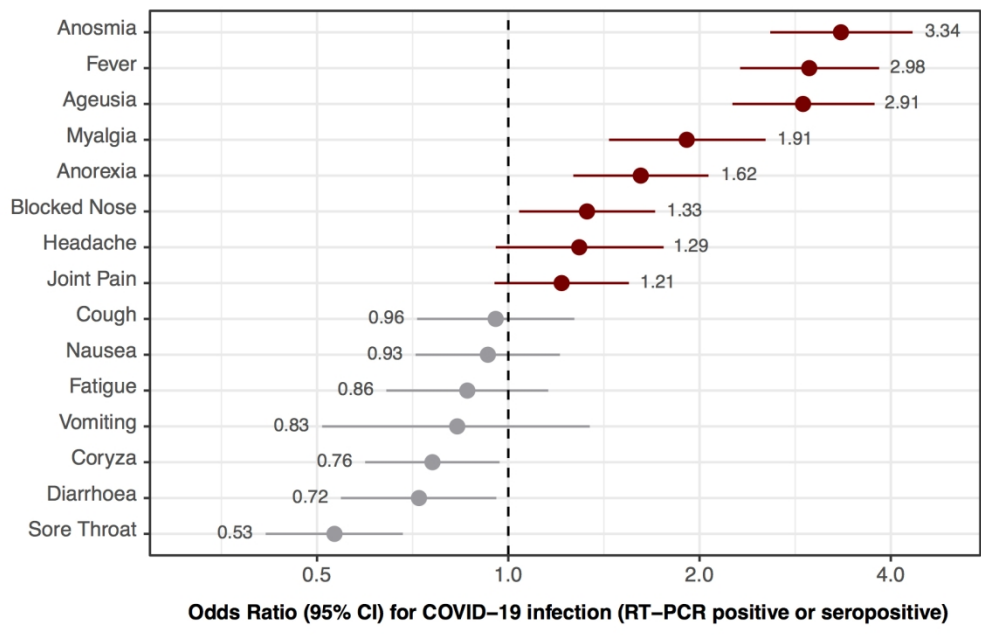


Figure 3

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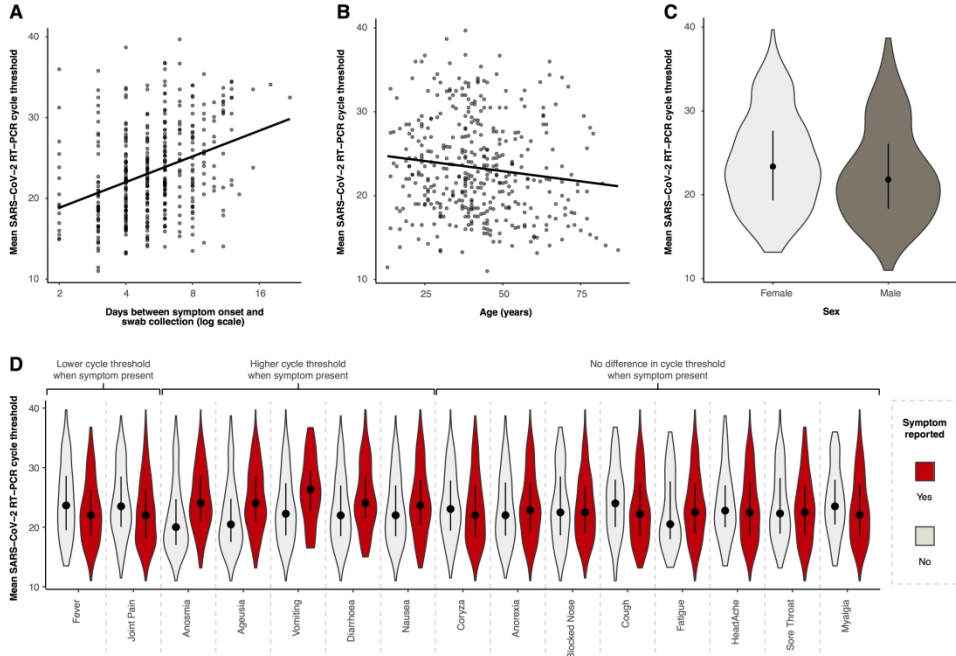


Figure 4

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Supplemental material

Initial risk assessment

Patients meeting the definition of a suspected case were called by a medical student (under supervision) to complete a risk assessment. All patients were asked a set of standardized questions:

- Do you feel short of breath?
- Are you breathing quickly or finding it difficult to breath?
- If yes, can you count your respiratory rate over one minute? (respiratory rate >20 breaths/minute was considered tachypnoea)
- Has your fever worsened over the last 3 days or have you had a new fever after 2 days being fever-free?
- Have you felt confused or lethargic?

If the patient answered “yes” to any of these questions they were advised to attend a specialist health service. Among the 132 patients that were triaged to hospital, 76 (58% of 132) had shortness of breath, 76 (58% of 132) reported rapid breathing, 33 (25% of 132) persistent fever and 22 (17% of 132) altered mental status.

Table S1 Univariable and adjusted associations between RT-PCR cycle thresholds and patient characteristics

	Unadjusted analysis		Adjusted analysis *	
	Beta (difference in means)	95% Confidence interval	Beta (difference in means)	95% Confidence interval
Age (years)	-0.05	-0.09 to -0.01	-0.06	-0.09 to -0.03
Male sex	-1.36	-2.49 to -0.23	-1.05	-2.09 to <0.001
Days from symptom onset to swab collection (days, log ₂)	3.28	2.33 to 4.03	3.27	0.42 to 7.70
PCR platform (ALTONA as reference)	-1.19	-2.37 to -0.02	-1.53	-2.6 to -0.45
Symptoms at presentation				
Fever	-1.78	-2.96 to -0.59	-1.11	-2.11 to -0.001
Myalgia	-1.31	-2.75 to 0.12	-0.78	-2.11 to 0.53
Arthralgia	-1.64	-2.77 to -0.52	-1.24	-2.18 to -0.10
Anosmia	3.15	2.04 to 4.25	2.21	1.0 to 3.29
Agusia	2.99	1.89 to 4.09	1.96	0.88 to 3.0
Diarrhea	2.19	0.84 to 3.53	1.36	0.12 to 2.61
Nausea	1.50	0.28 to 2.72	1.09	-0.04 to 2.24
Vomiting	2.99	0.52 to 5.46	2.02	-0.28 to 4.33
Anorexia	0.56	-0.57 to 1.70	0.47	-0.58 to 1.51
Headache	-0.58	-2.12 to 0.97	-0.81	-2.25 to 0.63
Fatigue	0.84	-0.50 to 2.18	0.34	-0.91 to 1.59
Coryza	-0.78	-1.92 to 0.34	-0.68	-1.72 to 0.34
Blocked nose	-0.36	-1.53 to 0.81	-1.48	-2.59 to -0.37
Cough	-1.33	-2.70 to 0.03	-1.60	-2.86 to -0.33
Sore throat	-0.49	-1.62 to 0.64	-0.45	-1.52 to 0.61

* All variables adjusted for age (continuous in years), sex (female as reference group), PCR platform (ALTONA platform as the reference group) and time between symptom onset and swab collection (log base 2). Analysis was performed within a linear regression framework. Positive beta coefficients indicate higher cycle thresholds (lower viral load) associated with that variable, whereas negative beta coefficients indicate lower cycle thresholds when the variable is present. Results in bold reached statistical significance.

Supplemental figure legends

Figure S1 Comparison of cycle thresholds across PCR platforms and genes amplified. Upper two panels show the concordance between cycle thresholds for the two separate genes amplified by the ALTONA (left) and Mico Biomed (right) kits. Lower left panel – distribution of cycle thresholds by gene amplified and RT-PCR platform used. Lower right-hand panel – distribution of the mean cycle threshold (mean of cycle thresholds for separate genes) between different RT-PCR platforms.

Figure S2 Time series of presentations to the Corona São Caetano platform. Dashed vertical lines denote the weekends with a reduced number of presentations. Thick black line corresponds to the right-hand y-axis: proportion of RT-PCRs performed with positive result.

Figure S3 Age-sex distribution the city of São Caetano do Sul compared with that of patients accessing the Corona São Caetano system and being tested with RT-PCR (left-hand panel) and those testing positive for SARS-CoV-2 (right-hand panel).

Figure S4 Distribution of delay between symptom onset and swab collection among 444 RT-PCR-positive patients and 52 RT-PCR-negative patients that subsequently tested seropositive (left-hand panel). Histogram of delay between symptom onset and swab collection among patients with COVID-19 (right-hand panel).

Figure S5 Left hand figures show symptoms at each follow-up questionnaire among patients testing RT-PCR positive and undergoing follow-up. Individual patients are stacked on the y-axis ordered according to the delay from symptom onset to presentation. Each point represents the response to a questionnaire and its position on the horizontal axis the time after symptom onset that the questionnaire was filled in. Grey points are questionnaires where the patient denied the presence of a given symptom. The coloured points correspond to questionnaires in which the patient reported a given symptom. The right-hand figures results from grouping the horizontal axis time into two-day windows and calculating the proportion of completed questionnaires in which each symptom was reported. The denominators for the horizontal axis groups (number of questionnaires completed within a given time window from symptom onset) are 104 at [0-2] days, 192 at (2-4], 185 at (4-6], 293 at (6-8], 338 at (8-10], 329 at (10-12], 335 at (12-14], 324 at (14-16], 280 at (16-18] and 201 at (18-20].

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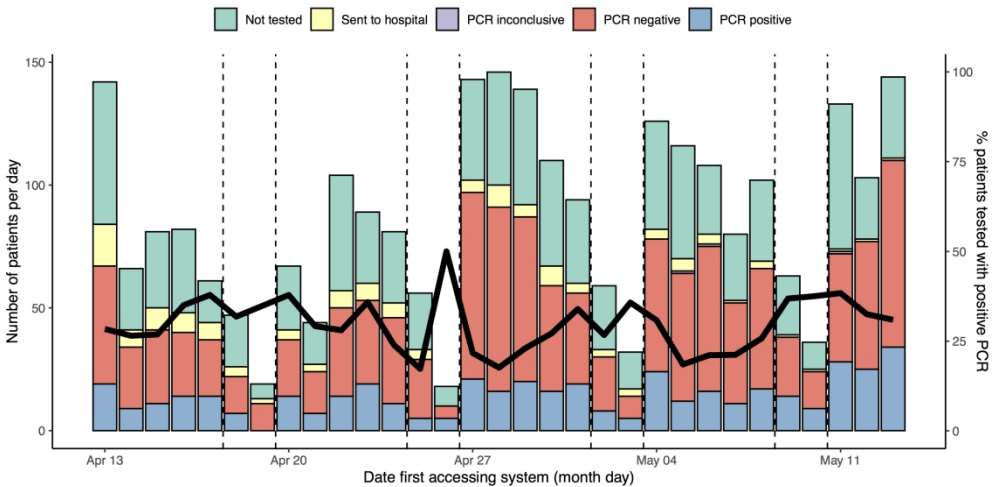


Figure S2

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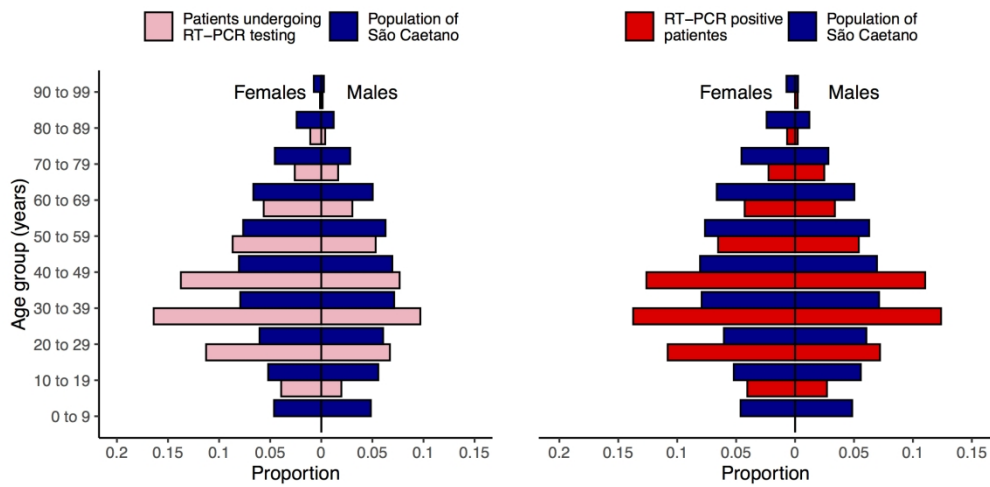


Figure S3

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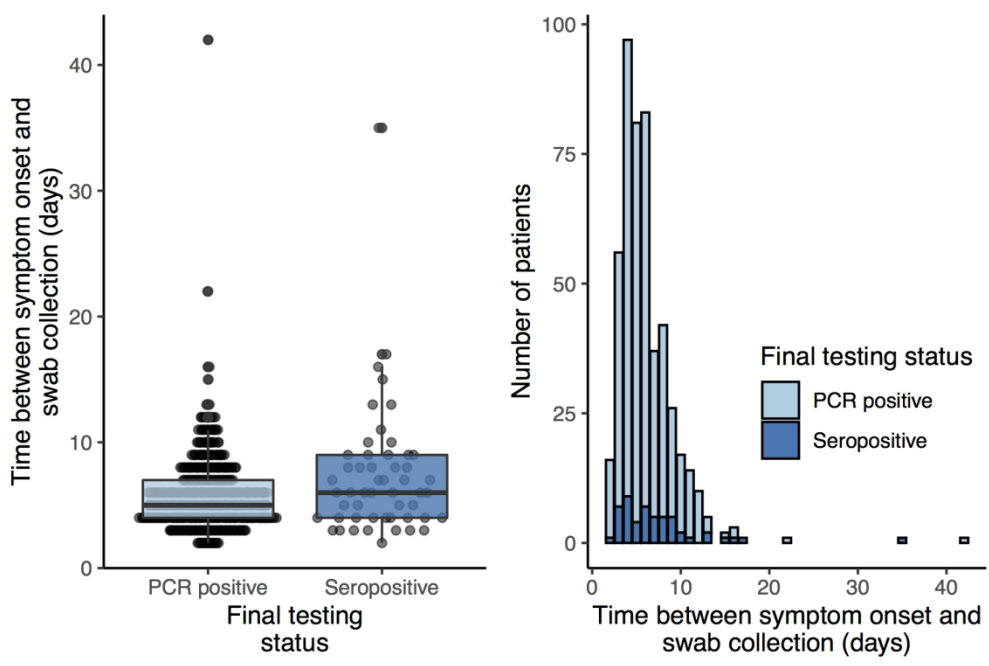


Figure S4

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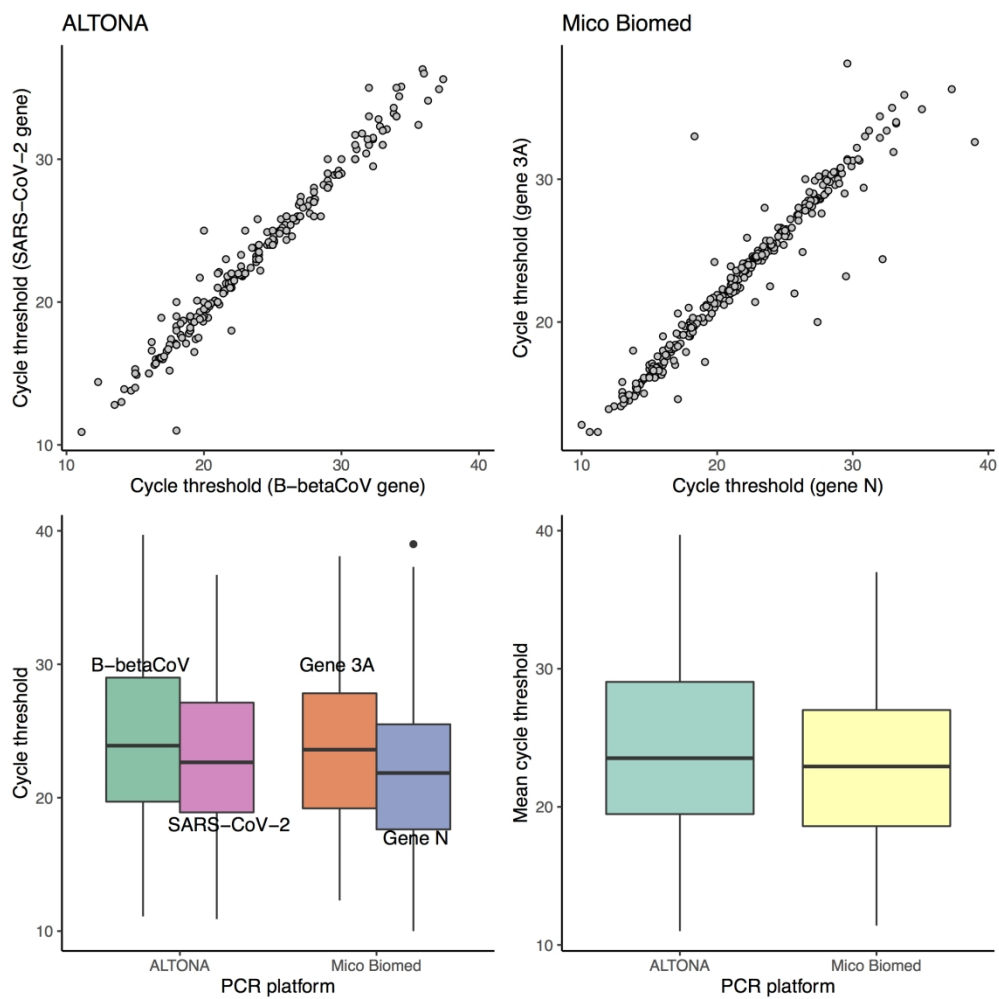


Figure S1

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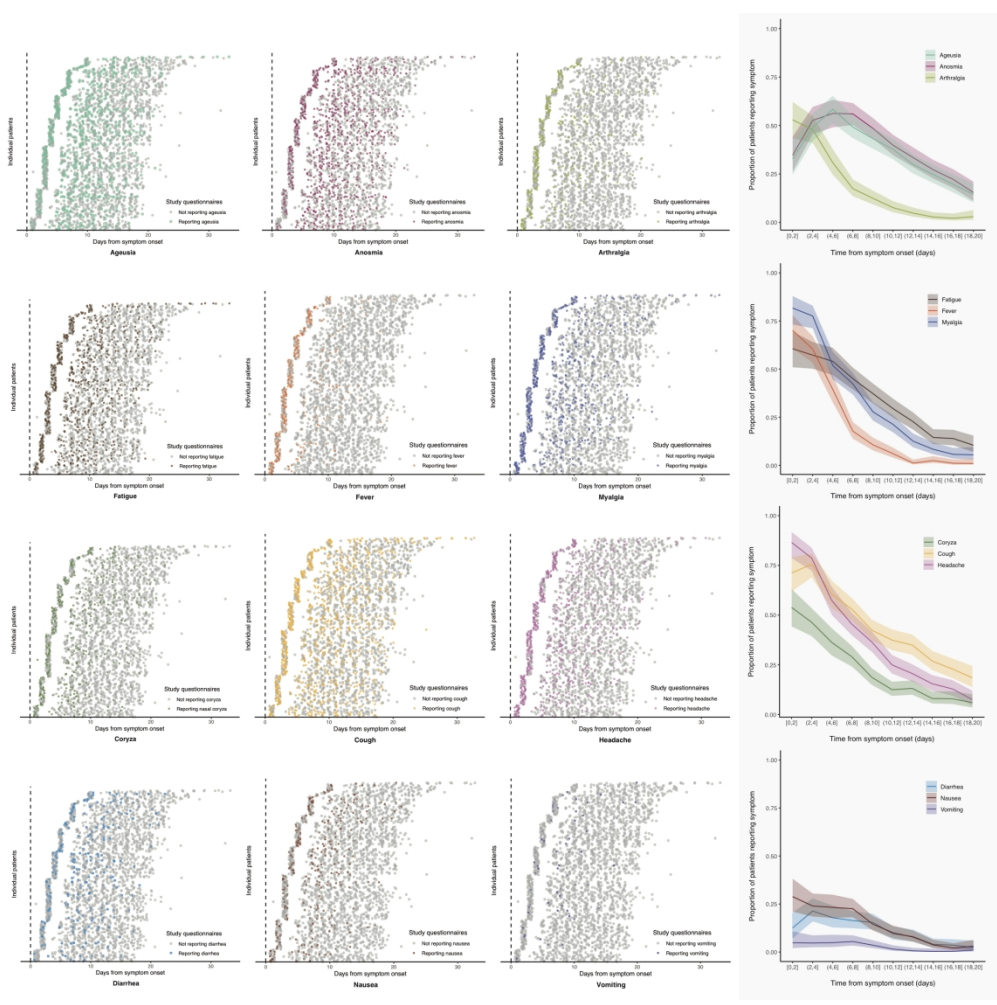


Figure S5

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5 to 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 to 6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	A – 5 B - NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 to 7
Bias	9	Describe any efforts to address potential sources of bias	7 to 8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	A – 7 to 8 B – NA C – 8 D – NA E – NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 and page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	A – table 1 and pages 9to10 B - Table 1 and 2 legends

		(c) Summarise follow-up time (eg, average and total amount)	C – page 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7 and results section
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Clinical features and natural history of the first 2,073 suspected COVID-19 cases in the Corona São Caetano primary care programme: a prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042745.R1
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Keywords:	PRIMARY CARE, Epidemiology < TROPICAL MEDICINE, INFECTIOUS DISEASES, PUBLIC HEALTH

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3 **Clinical features and natural history of the first 2,073 suspected COVID-19 cases in the**
4 **Corona São Caetano primary care programme: a prospective cohort study**
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53 KEY WORDS: SARS-CoV-2, COVID-19, pandemic, community, primary care, Brazil
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ABSTRACT

Background: Despite most cases not requiring hospital care, there are limited community-based clinical data on COVID-19.

Methods: The Corona São Caetano program is a primary care initiative providing care to all residents with COVID-19 in São Caetano do Sul, Brazil. It was designed to capture standardised clinical data on community COVID-19 cases. After triage of potentially severe cases, consecutive patients presenting to a multimedia screening platform between 13th April and 13th May 2020 were tested at home with SARS-CoV-2 reverse transcriptase (RT) PCR; positive patients were followed up for 14 days with phone calls every 2 days. RT-PCR-negative patients were offered additional SARS-CoV-2 serology testing to establish their infection status. We describe the clinical, virologic and natural history features of this prospective population-based cohort.

Findings: Of 2,073 suspected COVID-19 cases, 1,583 (76.4%) were tested by RT-PCR, of whom 444 (28.0%, 95%CI: 25.9-30.3) were positive; 604/1,136 (53%) RT-PCR-negative patients underwent serology, of whom 52 (8.6%) tested SARS-CoV-2 seropositive. The most common symptoms of confirmed COVID-19 were cough, fatigue, myalgia and headache; whereas self-reported fever (OR 3.0, 95%CI: 2.4-3.9), anosmia (OR 3.3, 95%CI: 2.6-4.4), and ageusia (2.9, 95%CI: 2.3-3.8) were most strongly associated with a positive COVID-19 diagnosis by RT-PCR or serology. RT-PCR cycle thresholds were lower in men, older patients, those with fever and arthralgia, and closer to symptom onset. The rates of hospitalization and death among 444 RT-PCR-positive cases were 6.7% and 0.7%, respectively, with older age and obesity more frequent in the hospitalized group.

Conclusion: COVID-19 presents in a similar way to other mild community-acquired respiratory diseases, but the presence of fever, anosmia, and ageusia can assist the specific diagnosis. Most patients recovered without requiring hospitalization with a low fatality rate compared to other hospital-based studies.

Strengths and limitations of this study

1. The clinical features of COVID-19 have mostly been described in hospital-based studies which are biased towards severe disease
2. We report a prospective cohort of suspected and confirmed COVID-19 cases from a primary care initiative in the Brazilian municipality of São Caetano do Sul
3. By systematically testing consecutive suspected community cases with molecular and serological tests we were able to address the diagnostic value of clinical features of mild-moderate COVID-19 in primary care
4. Prospective follow-up of confirmed cases and linkage with hospital datasets allowed us to describe the natural history of a primary care COVID-19 population
5. A limitation of the work was that not all PCR-negative participants underwent serology testing due to loss to follow-up

INTRODUCTION

A comprehensive public health response is vital but difficult to achieve during an epidemic. The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in China in late 2019.¹ According to the World Health Organization (WHO)^{2,3} and others^{4,5}, the ideal early response should have been multipronged, with identification, isolation, treatment and contact tracing of symptomatic cases, relying on a strong testing programme. Primary health care is well placed to implement such a response, by identifying cases early and managing them in a way that minimizes overcrowding of emergency rooms and intensive care units.^{6,7} Real-time data analysis coming from these primary care response systems can inform policy decisions.

Primary health care (PHC) in Brazil is provided by the publicly funded Unified Health System (SUS – Portuguese acronym) within the family health strategy (*Estratégia Saúde da Família*). Provision of care is centred around a healthcare unit with a multi-professional team that is responsible for all residents in the immediate catchment area⁸. Nearly two-thirds of the Brazilian population is covered by the family health strategy⁸.

In Brazil, the first case of COVID-19 was identified in the city of São Paulo on 26th February 2020.⁹ As of 15th June 2020 there were 1,400,000 cases nationally, with São Paulo contributing a fifth of these.¹⁰ In March 2020, the Municipal Health Department of the municipality of São Caetano do Sul – part of the Greater Metropolitan Region of São Paulo – began to develop a clinical and testing platform to organize its COVID-19 response. The aim was to provide universal detection and management of symptomatic cases and their contacts. The platform was developed in partnership with two local universities – the Municipal University of São Caetano do Sul (USCS) and the University of Sao Paulo (USP) – and called “Corona São Caetano”.

Large scale community-based observational cohorts are difficult to establish under epidemic circumstances, particularly if the risk of exposure for research personnel is high. Hence, most COVID-19 epidemiological and clinical studies have been hospital-based,¹¹⁻¹³ and therefore tend to include more severe cases whose findings may not be generalizable to the general population¹⁴, although some limited descriptions from ambulatory settings are available¹⁵⁻¹⁷.

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3 The objectives of this study were to describe the epidemiological indicators of the early phase
4 of the programme rollout; and to describe the clinical, virological and natural history features
5 (including hospitalization and deaths) of SARS-CoV-2 infection among patients identified in
6 primary care.
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10 11 **METHODS**

12 13 14 15 **Setting**

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18 The municipality of São Caetano do Sul has a population of 161,000 inhabitants.¹⁸ The city's
19 population is older than the Brazilian population¹⁸ and its Human Development Index is one
20 of the highest in the country. Nearly all (97.4%) children aged 6-14 are in education and 31%
21 of the population have completed higher education¹⁹ (Brazilian national average is 11%).
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26 27 **Corona São Caetano platform**

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30 The objective of the platform was to offer clinical care for patients with flu syndrome and
31 suspected COVID-19. Through the multimedia platform, patients could be triaged and guided
32 in relation to their clinical needs and tested, without having to leave their homes or go to
33 health facilities, unless seriously ill. This strategy aimed at reducing the workload in health
34 units and the risk of SARS-CoV-2 transmission in the population served by these health
35 units. Patients' GPs were informed of lab results and had access to clinical data stored in the
36 platform. GPs were expected to call patients being assisted by the platform and provide
37 medical assistance through home visits or at the primary care clinic if needed. In general, the
38 drugs prescribed through the platform were restricted to analgesics and antipyretics. The
39 platform was designed so that clinical information was collected in a standardized way for
40 research purposes.
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51 Residents of the municipality aged 12 years and older with suspected COVID-19 symptoms
52 were encouraged, through local media reports, to contact the dedicated Corona São Caetano
53 platform via the website (access at <https://coronasaocaetano.org/>) or by phone. They were
54 invited to complete an initial screening questionnaire that included socio-demographic data;
55 information on symptoms type, onset and duration; and recent contacts.
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3 Patients meeting the suspected COVID-19 case definition (i.e., having at least two of the
4 following symptoms: fever, cough, sore throat, coryza, or change in/loss of smell (anosmia);
5 or one of these symptoms plus at least two other symptoms consistent with COVID-19) were
6 further evaluated, whilst people not meeting these criteria were reassured, advised to stay at
7 home and contact the service again if they were to develop new symptoms or worsening of
8 current ones. The case definition was developed in consultation with infectious disease and
9 primary care specialists to encompass the known symptoms of COVID-19 and is similar to
10 the Brazilian national case definition²⁰. Patients were then called by a medical student to
11 complete a risk assessment. All pregnant women, and patients meeting pre-defined triage
12 criteria for severe disease (see Supplemental Material), were advised to attend a hospital
13 service - either an emergency department or outpatient service, depending on availability.
14 All other patients were offered a home visit for self-collection of a nasopharyngeal swab.

25 26 **Sample collection**

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29 Patients self-collected nasopharyngeal swabs (NPS – both nostrils and throat) at their own
30 homes under the supervision of trained healthcare personnel. We sent a link to an
31 instructional video (<https://youtu.be/rWZzV2ZP7KY>) before the home visit to provide
32 guidance on self-collection procedures. Nasopharyngeal swabs for the molecular detection of
33 SARS-CoV-2 has been recommended as an alternative method of collection for samples from
34 patients with suspected COVID-19²¹, as well as other respiratory diseases, and has the
35 advantage of reducing the chance of aerosol transmission to healthcare professionals.
36 Healthcare personnel were instructed to maintain a distance of six feet from the patient and to
37 wear personal protective equipment at all times. Samples were immediately put on a cool box
38 between 2-8°C and stored at 4°C in a fridge until shipment to the lab within 24 hours.

41 42 43 **Follow-up procedures**

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48 Patients testing SARS-CoV-2 RT-PCR positive were followed up to 14 days²² (a maximum
49 of 7 phone calls) from completion of their initial questionnaire. They were contacted every 48
50 hours by a medical student who completed another risk assessment and recorded any ongoing
51 or new symptoms. The purpose of the follow-up was to assess clinical evolution. Where
52 patients were judged to be deteriorating or developing severe disease they were signposted to
53 secondary care services. Patients testing RT-PCR negative were followed up by the primary
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3 health care program for their residential area. They were advised to contact the platform for a
4 new consultation if they developed new symptoms. Starting on May 19th, when serological
5 testing became available, RT-PCR-negative patients were re-contacted to offer antibody
6 (IgG/IgM combined) testing 14 days after their initial registration as long as they had become
7 asymptomatic.
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13 **Study dates**

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17 The Corona São Caetano programme was launched on 6th April 2020, with a one week pilot
18 phase designed to test instruments before roll-out. For this analysis, we included all patients
19 making their first contact with the programme in its first month, ie between 13th April and
20 13th May 2020. The period of follow-up (last date of data extraction) was 4th June 2020, to
21 account for the accrual period (three weeks) of possible hospitalizations in the last included
22 patients.
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29 **Laboratory methods**

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32 Due to shortages of some reagents, we used two RT-PCR platforms at different times during
33 the study: ALTONA RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Hamburg, Germany) and the
34 Mico BioMed RT-qPCR kit (Seongnam, South Korea). For serology we tested 10µL of
35 serum or plasma (equivalent in performance) using a qualitative rapid chromatographic
36 immunoassay (Wondfo Biotech Co., Guangzhou, China), that jointly detects anti-SARS-
37 CoV-2 IgG/IgM. The assay has been found to have a sensitivity of 81.5% and specificity of
38 99.1% in a US study²³. In our local validation, after two weeks of symptoms, the sensitivity
39 in 59 RT-PCR confirmed cases was 94.9%, and specificity in 106 biobank samples from
40 2019 was 100%.
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50 **Statistical methods**

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53 We estimated the contribution of our platform to total number of COVID-19 cases diagnosed
54 in São Caetano do Sul. To do this, we compared the number of cases diagnosed in our
55 programme with official data released by the Municipal Department of Health in its daily
56 bulletins (accessed here <https://coronavirus.saocaetanodosul.sp.gov.br>).
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3 Clinical and demographic data were extracted directly from the Corona São Caetano
4 information system. To analyse clinical presentation, we first calculated the proportion and
5 exact binomial 95% confidence intervals (CI) of cases reporting each symptom in the three
6 testing groups: SARS-CoV-2 RT-PCR positive; RT-PCR negative / seropositive; and RT-
7 PCR negative / seronegative. We next combined RT-PCR and serology positive cases to
8 make a confirmed COVID-19 group, and those negative on both tests to make a SARS-CoV-
9 2 negative control group. We express the association between each symptom and a positive
10 COVID-19 diagnosis as odds ratios (OR) and 95% CIs.
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19 Next, we assessed associations between RT-PCR cycle thresholds (Cts) and other clinical
20 features. ALTONA and MiCo BioMed RT-PCR kits each separately amplify two different
21 SARS-CoV-2 viral genes, as such each patient had two Ct values. There was a high
22 concordance between Cts for the two genes within each kit (Figure S1), and we opted therefore
23 to use the mean of the two Ct values for each patient in all analyses. We calculated univariable
24 associations between Cts and age, sex, delay from symptom onset to NPS collection, and
25 presenting symptoms using simple linear regression. We then built a multivariable linear
26 regression model to assess independent associations between presenting symptoms and RT-
27 PCR Cts. As age, sex, and time of swab collection may confound this relationship we included
28 these variables, as well as the RT-PCR platform (ALTONA vs MiCo BioMed), as covariates
29 in the model.
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39 For RT-PCR positive patients, hospitalizations and deaths were extracted from the study
40 platform. To extend the follow-up period and to capture RT-PCR negative patients and those
41 initially triaged to hospital (no study follow-up), hospitalization and vital status was
42 confirmed by linkage with two administrative databases: the municipal epidemiological
43 surveillance dataset, as well as the state-wide influenza-like illness notification system
44 (SIVEP-Gripe). Linkage was last performed on 5th June 2020, 23 days after the last patient
45 was enrolled, by the author SRPS who did not have access to the full analytic dataset. This
46 author searched the SIVEP-Gripe system and the municipal epidemiological surveillance
47 dataset using full name and date of birth. Categorical patient characteristics were compared
48 between patients requiring and those not requiring hospitalization using a Chi-squared or
49 Fisher exact test. Continuous variables were compared using the Wilcoxon rank sum test. A
50 multivariate analysis was not conducted due to the small number of individuals experiencing
51 this outcome.
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5 The cohort sample included consecutive cases presenting to the Corona São Caetano program
6 and a formal sample size calculation was not performed. Missing data were excluded. All
7 analyses were conducted in R Software for Statistical Computing, version 3.6.3.²⁴
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10 11 12 **Ethics**

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15 The study was approved by the local ethics committee (Comissão de Ética para Análise de
16 Projeto de Pesquisa - CAPPesq, protocol No. 13915, dated June 03, 2020). The committee
17 waived the need for informed consent and allowed the development of an analytical dataset
18 with no personal identification for the current analysis.
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23 24 **Patient and public involvement**

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27 Patients were not involved in the planning of this research.
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30 31 **RESULTS**

32 33 34 **Epidemiological and programmatic indicators**

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37 Over the study period, there were 2,073 presentations, from 2,011 individual patients, that
38 met the criteria for a suspected COVID-19 case (See Figure 1 for study flow). At initial
39 phone interview, 132 (6%) potential cases were advised to go directly to a health service
40 based on the triage questions, and 12 (0.6%) because of pregnancy. Only four (3%) of
41 referred patients were admitted to hospital and none died.
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48 In total 1,583 individual patients were tested with RT-PCR for SARS-CoV-2; 444 (28.0%,
49 95%CI: 25.9-30.3) were positive. The proportion of positive results was stable over the study
50 (Figure S2). Among the RT-PCR negative group, 604 (53% of 1,136) underwent serology
51 testing, of whom 52 (8.6%, 95%CI: 6.6-11.1) were seropositive. The median [IQR] time from
52 symptom onset to serology collection was 31 [26–37] days. The age-sex structure of patients
53 being tested differed from the underlying population of São Caetano do Sul (Figure S3) with
54 an overrepresentation of working-age adults and women. At the beginning of programme role
55 out, 25% of notified COVID-19 cases in São Caetano do Sul were diagnosed in our
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3 programme. Over the study period, adherence to the programme increased, and by May 13th,
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5 2020, this figure had risen to 78%.
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8 Of 444 RT-PCR positive patients eligible for longitudinal follow-up, 326 (73%) had their
9 final follow-up visit at least 14 days after their initial presentation. Of the seven possible
10 follow-up questionnaires, 384 (86%) COVID-19 patients completed three or more, and 162
11 (36%) completed all seven.
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15 16 17 **Participant characteristics**

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19 Patient characteristics are shown in Table 1. Although women were overrepresented in the
20 cohort, there were proportionally more males in the RT-PCR positive and seropositive groups
21 compared to the seronegative group. Of note, 55% of RT-PCR negative/seronegative patients
22 had completed higher education compared to 35% RT-PCR-positive patients ($p < 0.001$, Chi-
23 squared test). The median number of days from symptom onset to swab collection was 5.0
24 (IQR, 4.0-7.0) among RT-PCR positive patients and 6.0 (IQR, 4.0-8.3) among RT-PCR
25 negative/seropositive patients ($p = 0.06$, Wilcoxon rank sum) (Figure S4). Chronic
26 respiratory disease was less frequent in RT-PCR positive than dual-negative patients.
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36 **Symptoms of COVID-19**

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38 The prevalence of individual symptoms at presentation is shown in Figure 2A stratified by
39 final diagnostic category. The most frequent symptoms among RT-PCR and seropositive
40 patients were headache (82% and 75%), myalgia (80% and 80%), cough (77% and 63%), and
41 fatigue (77% and 79%). Anosmia was present in 56% and 63% of RT-PCR positive and
42 seropositive patients, respectively, compared to 30% in those testing doubly negative. A
43 similar pattern was observed for ageusia (53% and 53% versus 30%). Upper respiratory tract
44 symptoms - including coryza, blocked nose, ageusia, and anosmia - were more frequent in
45 younger people (Figure 2B). The evolution of symptoms over time among RT-PCR positive
46 patients is shown in Figure S5.
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56 The odds ratios for testing positive for SARS-CoV-2 (RT-PCR or serology) associated with
57 each presenting symptom are shown in Figure 3. The symptoms with strongest associations
58 were anosmia (OR 3.3, 95%CI: 2.6-4.4), fever (3.0, 95%CI: 2.4-3.9) and ageusia (2.9,
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95%CI: 2.3-3.8). The presence of sore throat (0.53, 95%CI: 0.41-0.68) and diarrhoea (0.72, 95%CI: 0.55-0.96) were associated with a negative SARS-CoV-2 test.

Associations between SARS-CoV-2 RT-PCR Cycle threshold (Ct) values, and demographic and clinical features

Figure 4 shows the associations between mean RT-PCR cycle threshold and demographic features and symptoms at presentation (the median [IQR] time from presentation to swab was 1 [1-2] day). Older age was associated with lower cycle thresholds, with a change in mean Ct of -0.05 (95%CI -0.09 to -0.01) for each additional year of age. The mean difference in Ct value was -1.36 (95% CI -2.49 to -0.23) in men compared to women. For each doubling in the number of days from symptom onset to swab collection the mean Ct value increased by 3.28 (95%CI 2.33 to 4.03). Presenting symptoms of fever and arthralgia were associated with lower Cts, whereas anosmia, ageusia, vomiting, diarrhoea, and nausea were associated with higher Cts (Figure 4 and Table S1). After adjustment for age, sex, delay from symptom onset, and RT-PCR platform used, fever (-0.06, 95%CI: -2.11 to -0.001) and arthralgia (-1.24, 95%CI: -2.18 to -0.10) remained associated with lower Cts, and anosmia (2.21, 95%CI: 1.0-3.29), ageusia (1.96, 95%CI: 0.88-3.0), and diarrhoea (1.36, 95%CI: 0.12-2.61) with higher Cts (Table S1).

Hospitalizations and deaths

Of the 444 RT-PCR positive patients, 30 (6.8%) had been hospitalized by 5th June 2020, when the database linkage was last updated, and three (0.7%) had died; in-hospital mortality was therefore 10% (3/30). In 28 cases the date of admission was available. The median time from symptom onset to hospital admission was 7 (range 2 to 14) days. Among 1,136 RT-PCR-negative patients, six (0.5%) had been admitted to hospital. One (<0.01% of 1,136) of these six patients died. None of the 604 RT-PCR negative patients that underwent serology were admitted to hospital or died. Table 2 compares patient characteristics by hospitalization status. Notably, hospitalized patients were older, had more cardiovascular comorbidities and were more frequently obese.

DISCUSSION

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5 We present a community-based cohort of suspected COVID-19 cases recruited through a
6 primary care initiative in the Brazilian municipality of São Caetano do Sul. Offering RT-PCR
7 testing to all patients presenting with symptoms compatible with COVID-19, the positivity
8 rate was 28%, with 8.6% of those testing negative subsequently found to be seropositive - i.e.
9 > 35% of the cohort had a diagnosis of COVID-19. Anosmia, ageusia, and self-reported fever
10 provided the greatest diagnostic value in identifying COVID-19. The rate of hospitalization
11 and deaths among RT-PCR positive patients was low, at 6.8% and 0.7%, respectively. Our
12 results provide important information on the clinical presentation, diagnostic testing and
13 natural history of COVID-19 identified in the community.
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22 The profile of suspected cases that tested positive for COVID-19 differed in some important
23 respects from those testing negative. The lower educational level among positive cases
24 suggests that, in São Caetano do Sul, the risk of exposure to COVID-19 follows a
25 socioeconomic gradient, consistent with other findings from Brazil^{25,26}. Although more
26 women presented to the platform, proportionally more men tested positive, consistent with
27 data from São Paulo showing a higher seroprevalence in men than women²⁷, but also
28 potentially reflecting different health seeking behaviours. Comorbidities were mostly similar,
29 although chronic respiratory disease was less frequent in those testing RT-PCR positive. This
30 may be due to a proportion of presentations in those with chronic respiratory disease being
31 explained by exacerbations of their underlying pathology from aetiologies other than SARS-
32 CoV-2, as well as higher anxiety about COVID-19 in those with pre-existing respiratory
33 disease.
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45 Extrapolating the seropositivity rate among RT-PCR negative patients to the 532 who were
46 not tested with serology, we estimate that an additional 46 seropositive cases would have
47 been identified. As such, 18% (98/542) of COVID-19 cases were missed by RT-PCR in the
48 setting of symptomatic presentations to primary care. This is similar to a pooled analysis
49 showing a false-negative rate for RT-PCR of 20% at three days post-symptom onset.²⁸ Viral
50 load peaks around the time of symptom onset and remains high over the first symptomatic
51 week (also see Figure 4A).^{29,30} Consistent with this, we found a slightly longer delay to swab
52 collection (due to delay in presentation to the platform) in RT-PCR false-negative patients
53 than RT-PCR positive patients (Figure S4).
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3 COVID-19 presents in a similar way to other respiratory viral illnesses. Indeed, in our cohort
4 the most common symptoms of COVID-19 - such as cough, fatigue, headache, etc. - were
5 reported with a similar frequency among patients testing negative. It is therefore important to
6 have identified anosmia, ageusia, self-reported fever, myalgia, and anorexia as the symptoms
7 with greatest value in the differential diagnosis of COVID-19 in primary care. This is
8 consistent with systematic review evidence highlighting anosmia and ageusia as key
9 diagnostic features of COVID-19³¹. It is of note that 30% of jointly RT-PCR and serology
10 negative patients reported these symptoms, indicating that although indicative of COVID-19,
11 the specificity of these symptoms is not high enough to rule in the diagnosis alone. Sore
12 throat and diarrhoea - both considered symptoms of COVID-19 in other settings –³² were
13 more frequently due to other possible aetiologies in this primary care context.

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24 These results are robust for a number of reasons. Firstly, our sample is representative of the
25 population of interest - i.e. consecutive patients with suspected COVID-19 in the community
26 - instead of extrapolating from hospital cases. Symptom data were collected prospectively,
27 eliminating recall or interviewer bias. Finally, we have a control group of patients who were
28 negative for both RT-PCR and serology, minimizing misclassification due to false negative
29 RT-PCR.

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36 In our study, the proportion of patients with a positive SARS-CoV-2 RT-PCR requiring
37 hospitalization was low (7%). Early reports from China were of 13.8% of cases being
38 severe³³, but this value was lower when under ascertainment of cases was accounted for.^{34,35}
39 This is because our cohort reflects mild to moderate cases, as severely ill patients are likely to
40 have attended hospital directly. As such, only 3% of patients we triaged to attend health
41 services were ultimately hospitalized, possibly due to self-selection of patients presenting to
42 our service. Supporting this, our overall case fatality ratio among RT-PCR positive patients
43 was 0.7%. The rate of hospitalization was lower (0.5%) in those testing PCR-negative. These
44 patients were admitted with a severe acute respiratory syndrome of an aetiology other than
45 SARS-CoV-2. The 14-fold higher admission rate among PCR-positive cases highlights the
46 importance of molecular testing for SARS-CoV-2 in patients presenting with features of
47 respiratory viral illness to primary care.

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58 As expected, the main determinant of Ct was the delay between symptom onset and swab
59 collection, mostly due to the delay in reporting to the platform. After adjusting for this, as
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3 well as age and sex, we found that a self-reported fever and arthralgia were associated with
4 lower Cts. The presence of these symptoms may identify patients with a higher viral load in
5 the community. However, these results should be seen as purely exploratory, and the wide
6 spread of Ct values around the regression line precludes a direct clinical application at
7 present.
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13 Our study has some limitations. Firstly, serology was not performed on all RT-PCR negative
14 patients due to on-going symptoms, loss to follow-up, or patient refusal. Of note, none of the
15 RT-PCR-negative patients that were admitted to hospital underwent serology testing. This
16 suggests that patients who were not tested with serology may have had a higher prevalence of
17 COVID-19 than those that were tested. In addition, imperfect serology test performance
18 (81% sensitivity)²³ will introduced false-negative results. Taken together, these biases may
19 have underestimated the true seroprevalence among RT-PCR-negative cases, as well as the
20 false-negative rate of RT-PCR. The latter calculation may also have been influenced by the
21 inclusion of RT-PCR positive patients in the denominator, introducing an incorporation bias.³⁶
22 Furthermore, the association between symptoms and COVID-19 diagnosis was based on the
23 comparison with doubly PCR and serology negative individuals. It is not clear how the
24 exclusion of individuals that did not undergo serology testing would have influenced these
25 associations. Finally, patients were not involved in the planning of the Corona platform or the
26 research proposal.
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39 A key strength to our study relates to the provision of primary healthcare in Brazil and its
40 symbiosis with medical training nationwide. Primary health care - within the family health
41 strategy (*Estratégia Saúde da Família*) - is centered around a healthcare unit with a multi-
42 professional team that is responsible for all residents in the immediate catchment area ⁸. São
43 Caetano do Sul has enough GP units within the family health strategy that all residents have
44 access to primary care. Medical students from the municipal university (USCS) are integrated
45 into the primary healthcare teams and progressively trained from the first year of medical
46 school. Our initiative took advantage of this existing system, with the addition of an online
47 platform allowing remote clinical assessment and follow-up. The suspension of normal
48 clinical training at the medical school provided the workforce. The partnership with the
49 University of São Paulo, which provided the laboratory diagnostics, created the unique
50 opportunity to establish our prospective community cohort of suspected and confirmed
51 COVID-19 cases. But we believe that this infrastructure could be implemented in other
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3 regions with less resources. Other respiratory disease such as influenza, measles, or
4 tuberculosis may benefit from similar approach. However, further evaluation of the impact of
5 the Corona Platform are required.
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10 **CONCLUSION**

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13 Systematic testing of all suspected COVID-19 cases was feasible within primary care
14 services in a Brazilian municipality. Anosmia, ageusia, and fever provide the greatest
15 diagnostic discrimination from other similar primary care presentations. Home-care is a valid
16 approach for most for most of these patients with a low rate of hospitalization and death.
17 Our programme model – integrating multimedia technology, telehealth with universal access
18 to primary care – may be successful in other contexts.
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25 **CONTRIBUTION STATEMENT**

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29 FEL, MCMC, SFC, MC, RB, and ECS conceived and designed the study. FEL, RMZG, and
30 JCSB provided clinical oversight and supervision of medical students. FEL, MCMC, LFB,
31 HD, OT, LC, and SRPS collected and curated the data. MCMC, TRTM, LSVB, and LCOS
32 performed the laboratory analysis. LFB performed the formal statistical analysis with
33 assistance from FEL, SRPS, NDEA, PM, ECS and OT. LFB, FEL, PM and ECS wrote the
34 first draft, and all authors reviewed, contributed to and approved the final version.
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41 **CONFLICTS OF INTEREST STATEMENT**

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44 The authors have no conflicts of interests. FL, RG, and JB were involved in providing
45 clinical care within the Corona São Caetano Platform.
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55 platform. We also acknowledge an award from FAPESP (2018/14389-0) and the UK Medical
56 Research Council (MR/S0195/1) to the Brazil-UK Centre for Arbovirus Discovery,
57 Diagnosis, Genomics and Epidemiology (CADDE).
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DATA SHARING STATEMENT

Data will be made available via the linked Figshare repository (URL) upon acceptance of the manuscript.

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TABLE LEGENDS

Table 1 Demographic and clinical characteristics of 1,048 suspected COVID-19 cases undergoing diagnostic testing in the Corona São Caetano program. * Security, emergency services, supermarket, public transport, and pharmacy workers. IQR: interquartile range; HCW: health care workers, COPD: chronic obstructive pulmonary disease. Missing data – educational level 2; essential occupation 2; body mass index 4; cardiovascular disease 28; diabetes 31 mellitus; chronic resp. disease 65; chronic kidney disease 27; COPD 28. P-values calculated by Chi-squared, Fisher exact, or Wilcoxon rank sum.

Table 2 Characteristics of RT-PCR positive patients stratified by hospitalization status. Missing data – body mass index 2; cardiovascular disease 12; diabetes mellitus 12; chronic respiratory disease 29; COPD 11; chronic kidney disease 12; COPD - chronic obstructive pulmonary disease; IQR - interquartile range.

FIGURE LEGENDS

Figure 1 Patient flowchart for the Corona São Caetano platform between 13th April and 13th May 2020. In the upper section (white background) the numbers correspond to individual presentations to the system; among suspected cases 2,073 suspected cases, 60 had two presentations and one had three. In the lower section (grey background) numbers correspond to individual patients making up the final analytic groups.

Figure 2 Panel A presents prevalence (point) and exact binomial 95% confidence intervals (vertical lines) of symptoms at presentation among patients with suspected COVID-19 according to RT-PCR result and serostatus (A). Panels B and C present the prevalence of presenting symptoms among patients with COVID-19 (RT-PCR and serology positive) stratified by age (B) and sex (C).

Figure 3 Odds ratios (black dot) and 95% confidence intervals (lines) for testing positive for COVID-19 (RT-PCR positive or serology positive) associated with the presence of each presenting symptom. Horizontal axis is on log scale. Point estimates of odds ratios are shown inline with their corresponding symptom.

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3 **Figure 4** Relationship between mean RT-PCR cycle threshold (Ct) and day of illness course
4 when the nasopharyngeal swab was collected (A), patient age (B), patient sex (C), and
5 different symptoms at presentation. Panels A and B show the best fit linear regression lines,
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7 panels C and D are violin plots (rotated kernel density plots showing the full distribution of
8 data) of the Ct values with median (black dot) and interquartile range (black line).
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Table 1

	RT-PCR +ve (G1) N = 444 n (%) or median (IQR)	RT-PCR -ve Sero +ve (G2) N=52 n (%) or median (IQR)	RT-PCR -ve Sero -ve (G3) N = 552 n (%) or median (IQR)	p-value G1 versus G2	p-value G1 versus G3
Sex					
Male	200 (45.0)	23 (44.2)	185 (33.5)	1.0	<0.001
Female	244 (55.0)	29 (55.8)	367 (66.5)		
Age groups (years)					
10 to 19	29 (6.5)	1 (1.9)	25 (4.5)	0.07	0.40
20 to 39	197 (44.4)	17 (32.7)	236 (42.8)		
40 to 59	158 (35.6)	28 (53.8)	218 (39.5)		
60+	60 (13.5)	6 (11.5)	73 (13.2)		
Educational level					
Up to primary education	75 (16.9)	7 (13.5)	56 (10.2)	0.10	<0.001
High school	214 (48.3)	19 (36.5)	194 (35.2)		
University	154 (34.8)	26 (50.0)	301 (54.6)		
Essential Occupation					
Non-HCW essential job *	137 (30.9)	12 (23.1)	148 (26.9)	0.45	0.01
Carers	10 (2.3)	0 (0.0)	8 (1.5)		
HCW	32 (7.2)	5 (9.6)	73 (13.2)		
No	264 (59.6)	35 (67.3)	322 (58.4)		
Body mass index (kg/m²)					
<25	151 (34.2)	22 (42.3)	211 (38.4)	0.62	0.14
25-29	182 (41.2)	17 (32.7)	187 (34.0)		
30-35	79 (17.9)	9 (17.3)	112 (20.4)		
35+	30 (6.8)	4 (7.7)	40 (7.3)		
Comorbidities					
Cardiovascular disease	88 (20.4)	9 (17.6)	129 (24.0)	0.89	0.40
Diabetes mellitus	48 (11.1)	4 (7.8)	39 (7.3)	0.86	0.12
Any chronic resp. disease	37 (8.9)	9 (18.0)	79 (15.3)	0.13	0.01
COPD	24 (5.5)	5 (9.8)	54 (10.1)	0.47	0.03
Chronic kidney disease	1 (<1)	0 (0.0)	3 (1.0)	1.0	0.83
Time from symptom onset to swab collection (days), median (IQR)	5.0 (4.0-7.0)	6.0 (4.0-8.3)	6.0 (4.0-9.0)	0.06	<0.001

Table 2

	Hospitalized n=30 n (%) or median (IQR)	Not hospitalized n=414 n (%) or median (IQR)	p-value
Age (years)			
10 to 19	1 (3)	28 (97)	
20 to 39	6 (3)	191 (97)	
40 to 59	14 (9)	144 (91)	
60+	9 (15)	51 (85)	0.006
Sex			
Female	16 (7)	228 (93)	
Male	14 (7)	186 (93)	0.852
Comorbidities			
Cardiovascular disease	11 (13)	77 (87)	0.001
Diabetes mellitus	8 (17)	40 (83)	0.007
Any chronic resp. disease	2 (5)	35 (95)	1.0
COPD	1 (5)	23 (95)	1.0
Chronic kidney disease	1 (100)	0 (0)	0.06
Body mass index (Kg/m²)			
<25	4 (3)	147 (97)	
25-29	8 (4)	174 (96)	
30-35	12 (15)	67 (85)	
35+	6 (20)	24 (80)	<0.001
Time to presentation (days)	3 (3 to 4)	4 (3 to 5)	0.072

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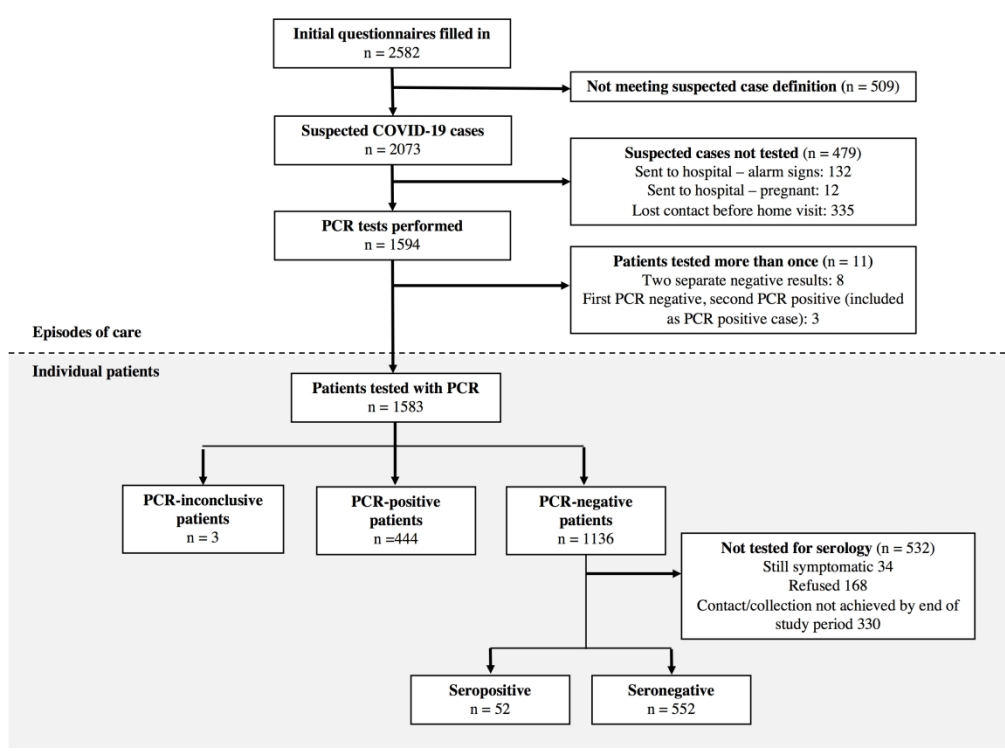


Figure 1

246x181mm (300 x 300 DPI)

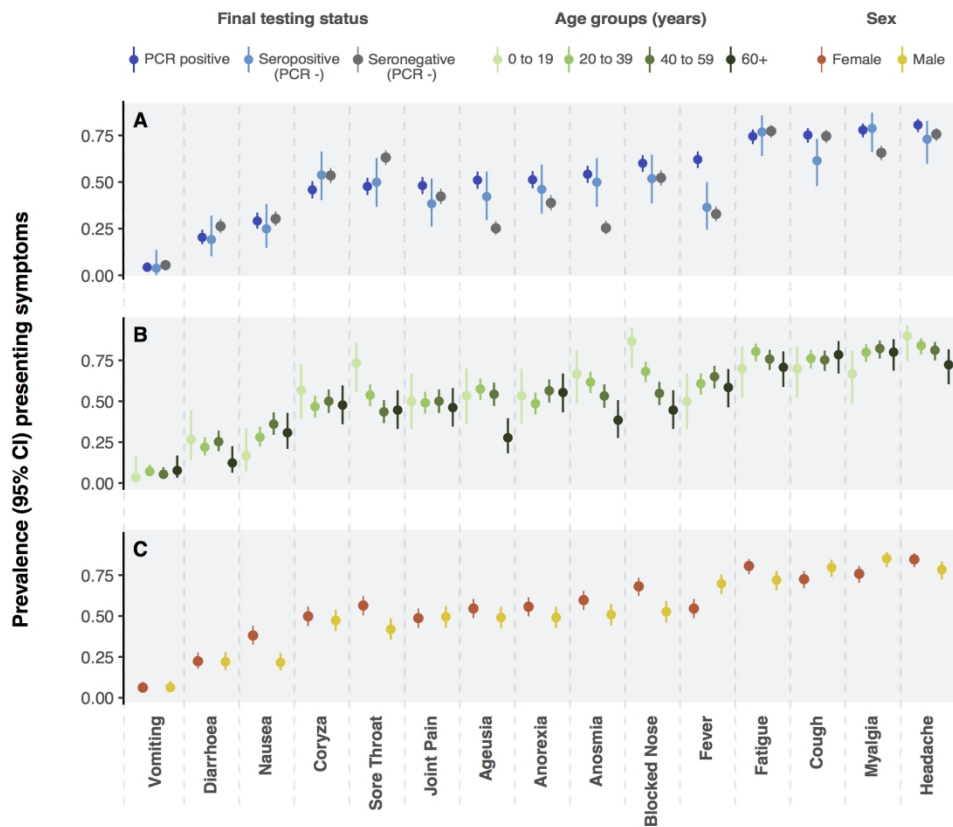


Figure 2

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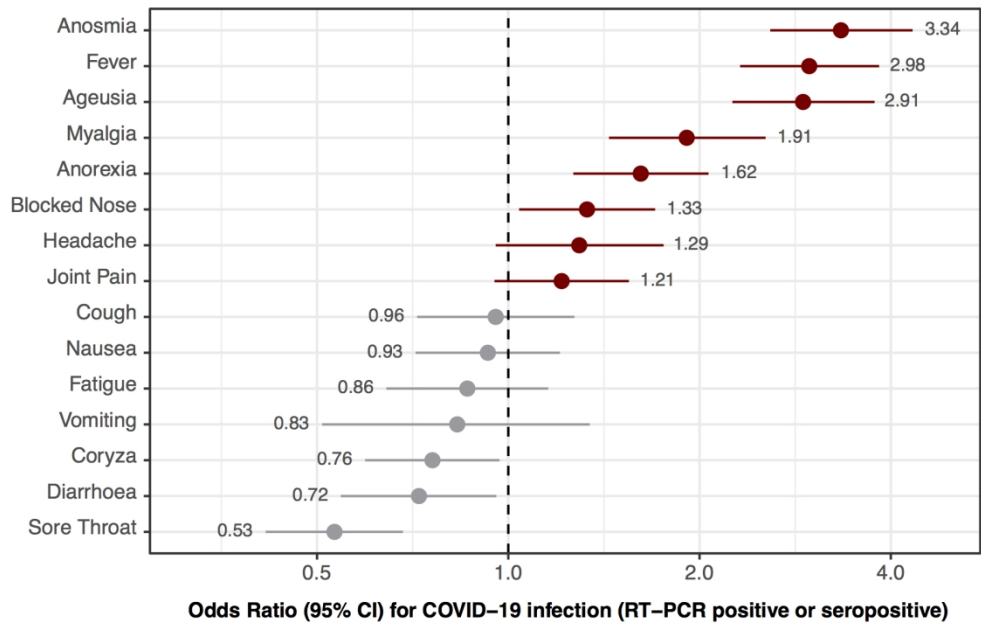


Figure 3

154x100mm (300 x 300 DPI)

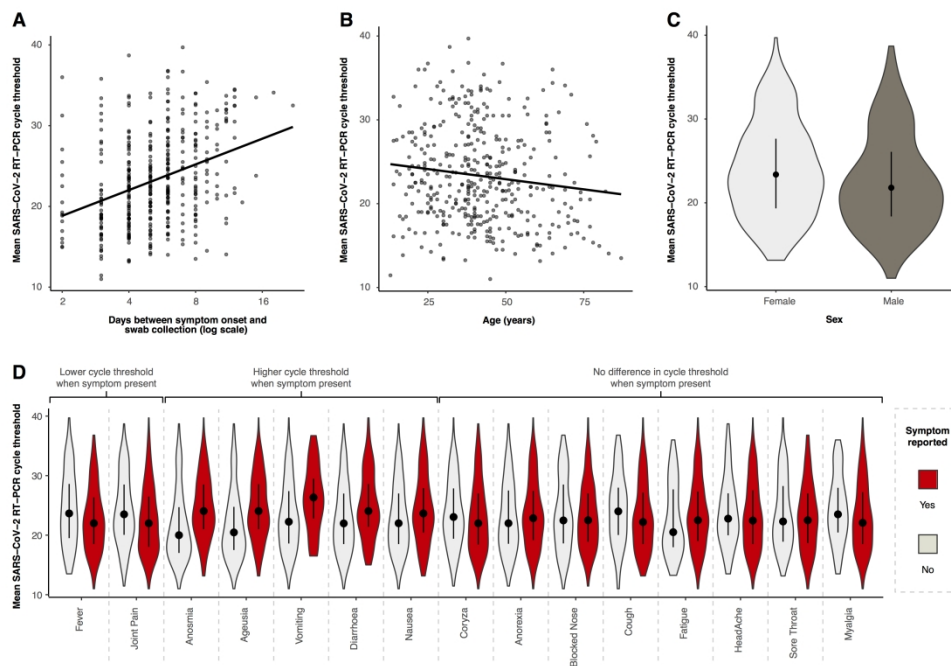


Figure 4

327x222mm (300 x 300 DPI)

Supplemental material

Initial risk assessment

Patients meeting the definition of a suspected case were called by a medical student (under supervision) to complete a risk assessment. All patients were asked a set of standardized questions:

- Do you feel short of breath?
- Are you breathing quickly or finding it difficult to breath?
- If yes, can you count your respiratory rate over one minute? (respiratory rate >20 breaths/minute was considered tachypnoea)
- Has your fever worsened over the last 3 days or have you had a new fever after 2 days being fever-free?
- Have you felt confused or lethargic?

If the patient answered “yes” to any of these questions they were advised to attend a specialist health service. Among the 132 patients that were triaged to hospital, 76 (58% of 132) had shortness of breath, 76 (58% of 132) reported rapid breathing, 33 (25% of 132) persistent fever and 22 (17% of 132) altered mental status.

Table S1 Univariable and adjusted associations between RT-PCR cycle thresholds and patient characteristics

	Unadjusted analysis		Adjusted analysis *	
	Beta (difference in means)	95% Confidence interval	Beta (difference in means)	95% Confidence interval
Age (years)	-0.05	-0.09 to -0.01	-0.06	-0.09 to -0.03
Male sex	-1.36	-2.49 to -0.23	-1.05	-2.09 to <0.001
Days from symptom onset to swab collection (days, log ₂)	3.28	2.33 to 4.03	3.27	0.42 to 7.70
PCR platform (ALTONA as reference)	-1.19	-2.37 to -0.02	-1.53	-2.6 to -0.45
Symptoms at presentation				
Fever	-1.78	-2.96 to -0.59	-1.11	-2.11 to -0.001
Myalgia	-1.31	-2.75 to 0.12	-0.78	-2.11 to 0.53
Arthralgia	-1.64	-2.77 to -0.52	-1.24	-2.18 to -0.10
Anosmia	3.15	2.04 to 4.25	2.21	1.0 to 3.29
Agusia	2.99	1.89 to 4.09	1.96	0.88 to 3.0
Diarrhea	2.19	0.84 to 3.53	1.36	0.12 to 2.61
Nausea	1.50	0.28 to 2.72	1.09	-0.04 to 2.24
Vomiting	2.99	0.52 to 5.46	2.02	-0.28 to 4.33
Anorexia	0.56	-0.57 to 1.70	0.47	-0.58 to 1.51
Headache	-0.58	-2.12 to 0.97	-0.81	-2.25 to 0.63
Fatigue	0.84	-0.50 to 2.18	0.34	-0.91 to 1.59
Coryza	-0.78	-1.92 to 0.34	-0.68	-1.72 to 0.34
Blocked nose	-0.36	-1.53 to 0.81	-1.48	-2.59 to -0.37
Cough	-1.33	-2.70 to 0.03	-1.60	-2.86 to -0.33
Sore throat	-0.49	-1.62 to 0.64	-0.45	-1.52 to 0.61

* All variables adjusted for age (continuous in years), sex (female as reference group), PCR platform (ALTONA platform as the reference group) and time between symptom onset and swab collection (log base 2). Analysis was performed within a linear regression framework. Positive beta coefficients indicate higher cycle thresholds (lower viral load) associated with that variable, whereas negative beta coefficients indicate lower cycle thresholds when the variable is present. Results in bold reached statistical significance.

Supplemental figures

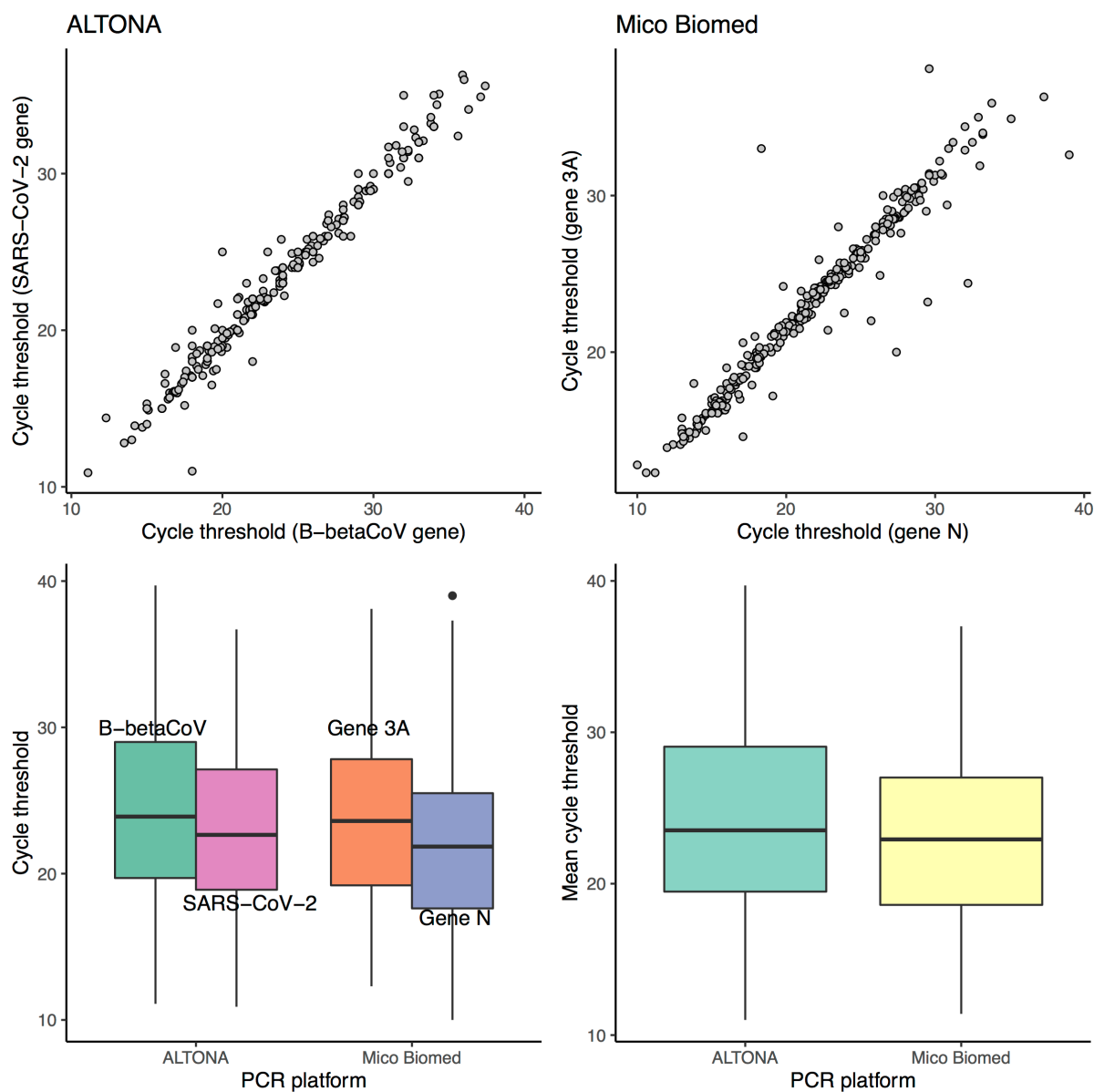


Figure S1 Comparison of cycle thresholds across PCR platforms and genes amplified. Upper two panels show the concordance between cycle thresholds for the two separate genes amplified by the ALTONA (left) and Mico Biomed (right) kits. Lower left panel – distribution of cycle thresholds by gene amplified and RT-PCR platform used. Lower right-hand panel – distribution of the mean cycle threshold (mean of cycle thresholds for separate genes) between different RT-PCR platforms.

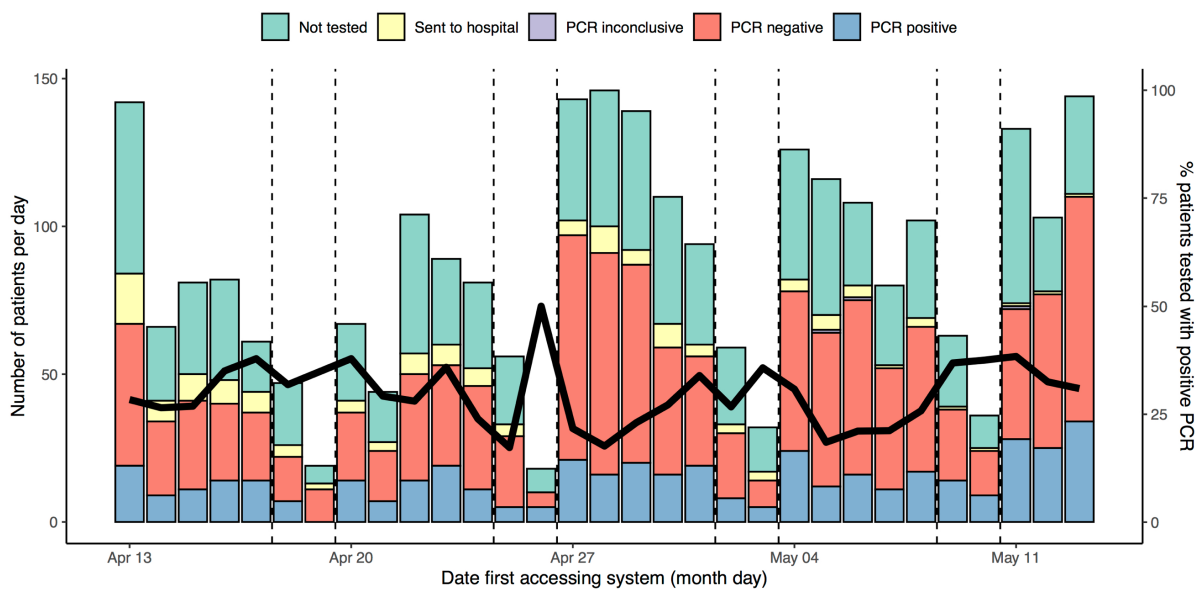


Figure S2 Time series of presentations to the Corona São Caetano platform. Dashed vertical lines denote the weekends with a reduced number of presentations. Thick black line corresponds to the right-hand y-axis: proportion of RT-PCRs performed with positive result.

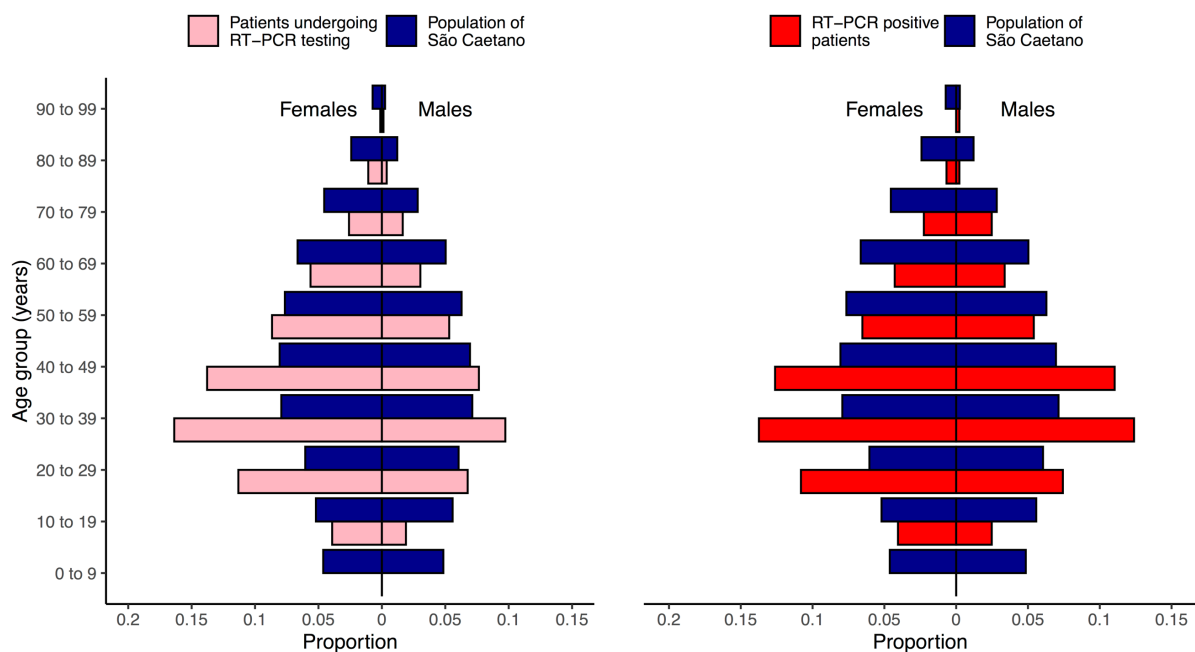


Figure S3 Age-sex distribution the city of São Caetano do Sul compared with that of patients accessing the Corona São Caetano system and being tested with RT-PCR (left-hand panel) and those testing positive for SARS-CoV-2 (right-hand panel).

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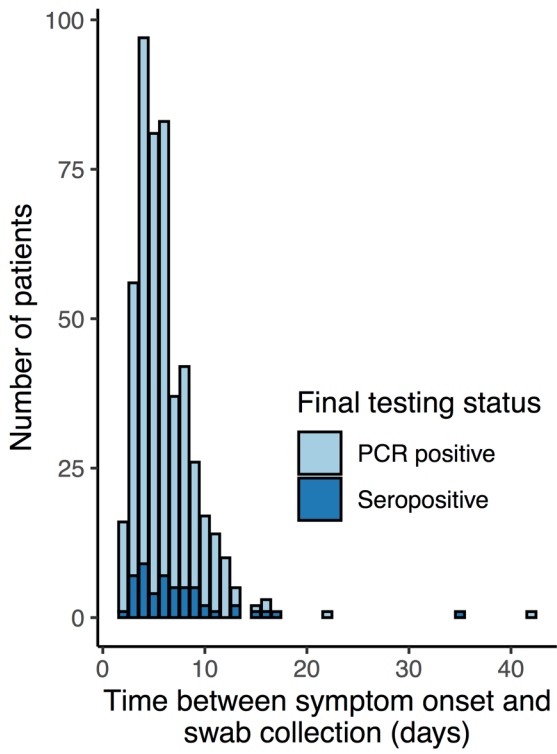


Figure S4 Histogram of delay between symptom onset and swab collection among patients with COVID-19.

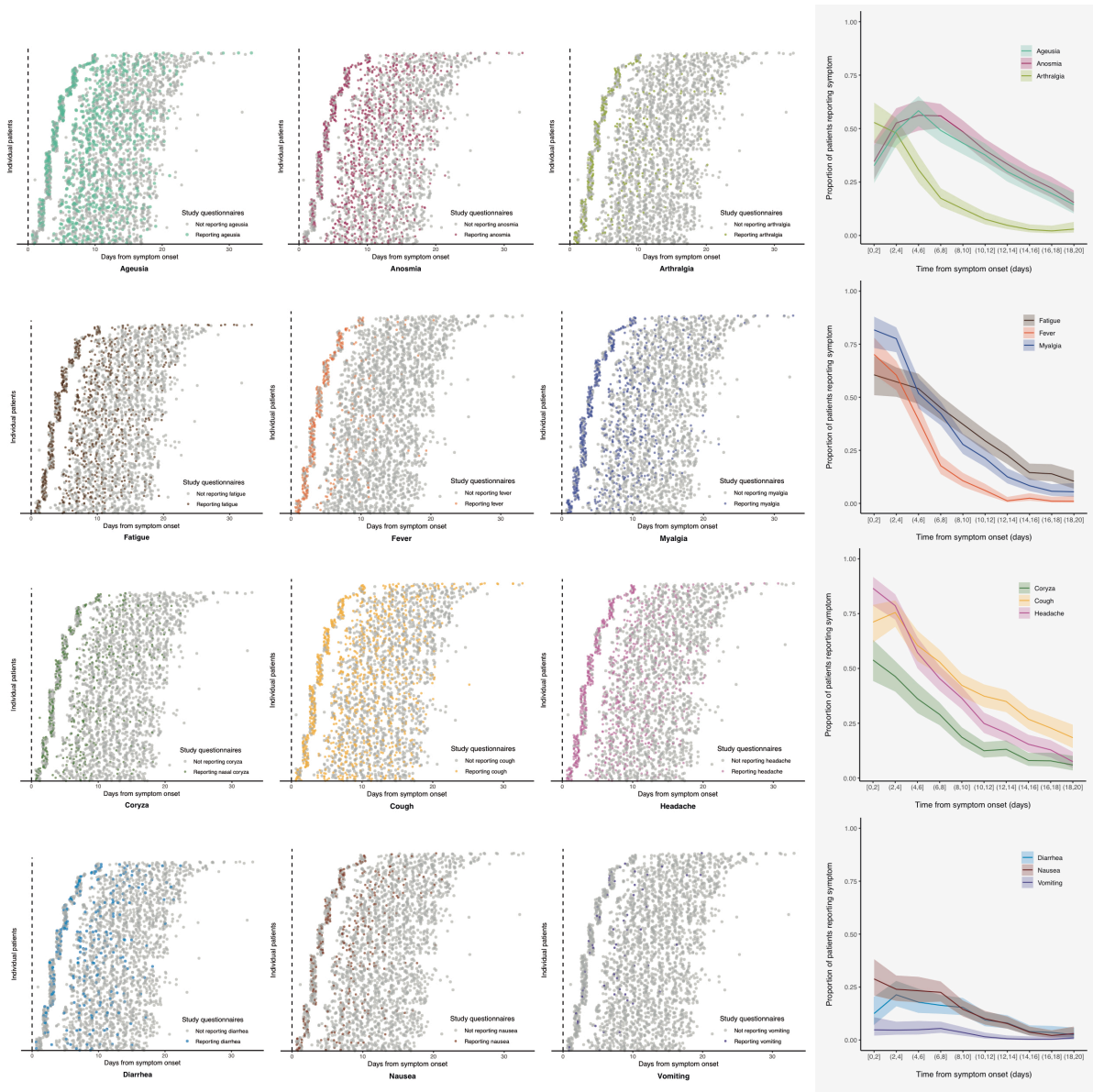


Figure S5 Left hand figures show symptoms at each follow-up questionnaire among patients testing RT-PCR positive and undergoing follow-up. Individual patients are stacked on the y-axis ordered according to the delay from symptom onset to presentation. Each point represents the response to a questionnaire and its position on the horizontal axis the time after symptom onset that the questionnaire was filled in. Grey points are questionnaires where the patient denied the presence of a given symptom. The coloured points correspond to questionnaires in which the patient reported a given symptom. The right-hand figures results from grouping the horizontal axis time into two-day windows and calculating the proportion of completed questionnaires in which each symptom was reported. The denominators for the horizontal axis groups (number of questionnaires completed within a given time window from symptom onset) are 104 at [0-2] days, 192 at (2-4], 185 at (4-6], 293 at (6-8], 338 at (8-10], 329 at (10-12], 335 at (12-14], 324 at (14-16], 280 at (16-18] and 201 at (18-20].

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5 to 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 to 6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	A – 5 B - NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 to 7
Bias	9	Describe any efforts to address potential sources of bias	7 to 8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	A – 7 to 8 B – NA C – 8 D – NA E – NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 and page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	A – table 1 and pages 9to10 B - Table 1 and 2 legends

		(c) Summarise follow-up time (eg, average and total amount)	C – page 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7 and results section
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Clinical features and natural history of the first 2,073 suspected COVID-19 cases in the Corona São Caetano primary care programme: a prospective cohort study

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health, Global health

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Keywords:	PRIMARY CARE, Epidemiology < TROPICAL MEDICINE, INFECTIOUS DISEASES, PUBLIC HEALTH

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3 **Clinical features and natural history of the first 2,073 suspected COVID-19 cases in the**
4 **Corona São Caetano primary care programme: a prospective cohort study**
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53 KEY WORDS: SARS-CoV-2, COVID-19, pandemic, community, primary care, Brazil
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ABSTRACT

Background: Despite most cases not requiring hospital care, there are limited community-based clinical data on COVID-19.

Methods: The Corona São Caetano program is a primary care initiative providing care to all residents with COVID-19 in São Caetano do Sul, Brazil. It was designed to capture standardised clinical data on community COVID-19 cases. After triage of potentially severe cases, consecutive patients presenting to a multimedia screening platform between 13th April and 13th May 2020 were tested at home with SARS-CoV-2 reverse transcriptase (RT) PCR; positive patients were followed up for 14 days with phone calls every 2 days. RT-PCR-negative patients were offered additional SARS-CoV-2 serology testing to establish their infection status. We describe the clinical, virologic and natural history features of this prospective population-based cohort.

Findings: Of 2,073 suspected COVID-19 cases, 1,583 (76.4%) were tested by RT-PCR, of whom 444 (28.0%, 95%CI: 25.9-30.3) were positive; 604/1,136 (53%) RT-PCR-negative patients underwent serology, of whom 52 (8.6%) tested SARS-CoV-2 seropositive. The most common symptoms of confirmed COVID-19 were cough, fatigue, myalgia and headache; whereas self-reported fever (OR 3.0, 95%CI: 2.4-3.9), anosmia (OR 3.3, 95%CI: 2.6-4.4), and ageusia (2.9, 95%CI: 2.3-3.8) were most strongly associated with a positive COVID-19 diagnosis by RT-PCR or serology. RT-PCR cycle thresholds were lower in men, older patients, those with fever and arthralgia, and closer to symptom onset. The rates of hospitalization and death among 444 RT-PCR-positive cases were 6.7% and 0.7%, respectively, with older age and obesity more frequent in the hospitalized group.

Conclusion: COVID-19 presents in a similar way to other mild community-acquired respiratory diseases, but the presence of fever, anosmia, and ageusia can assist the specific diagnosis. Most patients recovered without requiring hospitalization with a low fatality rate compared to other hospital-based studies.

Strengths and limitations of this study

1. The clinical features of COVID-19 have mostly been described in hospital-based studies which are biased towards severe disease
2. We report a prospective cohort of suspected and confirmed COVID-19 cases from a primary care initiative in the Brazilian municipality of São Caetano do Sul
3. By systematically testing consecutive suspected community cases with molecular and serological tests we were able to address the diagnostic value of clinical features of mild-moderate COVID-19 in primary care
4. Prospective follow-up of confirmed cases and linkage with hospital datasets allowed us to describe the natural history of a primary care COVID-19 population
5. A limitation of the work was that not all PCR-negative participants underwent serology testing due to loss to follow-up

INTRODUCTION

A comprehensive public health response is vital but difficult to achieve during an epidemic. The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in China in late 2019.¹ According to the World Health Organization (WHO)^{2,3} and others^{4,5}, the ideal early response should have been multipronged, with identification, isolation, treatment and contact tracing of symptomatic cases, relying on a strong testing programme. Primary health care is well placed to implement such a response, by identifying cases early and managing them in a way that minimizes overcrowding of emergency rooms and intensive care units.^{6,7} Real-time data analysis coming from these primary care response systems can inform policy decisions.

Primary health care (PHC) in Brazil is provided by the publicly funded Unified Health System (SUS – Portuguese acronym) within the family health strategy (*Estratégia Saúde da Família*). Provision of care is centred around a healthcare unit with a multi-professional team that is responsible for all residents in the immediate catchment area⁸. Nearly two-thirds of the Brazilian population is covered by the family health strategy⁸.

In Brazil, the first case of COVID-19 was identified in the city of São Paulo on 26th February 2020.⁹ As of 1st Dec 2020 there were over 6 million confirmed cases nationally, with São Paulo contributing a fifth of these.¹⁰ The reasons for the exceptionally large epidemic in Brazil have been discussed elsewhere^{11–13}. In March 2020, the Municipal Health Department of the municipality of São Caetano do Sul – part of the Greater Metropolitan Region of São Paulo – began to develop a clinical and testing platform to organize its COVID-19 response. The aim was to provide universal detection and management of symptomatic cases and their contacts. The platform was developed in partnership with two local universities – the Municipal University of São Caetano do Sul (USCS) and the University of São Paulo (USP) – and called “Corona São Caetano”.

Large scale community-based observational cohorts are difficult to establish under epidemic circumstances, particularly if the risk of exposure for research personnel is high. Hence, most COVID-19 epidemiological and clinical studies have been hospital-based,^{14–16} and therefore tend to include more severe cases whose findings may not be generalizable to the general

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4 population¹⁷, although some limited descriptions from ambulatory settings are available^{18–20}.

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6 The objectives of this study were to describe the epidemiological indicators of the early phase
7 of the programme rollout; and to describe the clinical, virological and natural history features
8 (including hospitalization and deaths) of SARS-CoV-2 infection among patients identified in
9 primary care.
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13 14 **METHODS**

15 16 17 **Setting**

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21 The municipality of São Caetano do Sul has a population of 161,000 inhabitants.²¹ The city's
22 population is older than the Brazilian population²¹ and its Human Development Index is one
23 of the highest in the country. Nearly all (97.4%) children aged 6-14 are in education and 31%
24 of the population have completed higher education²² (Brazilian national average is 11%).
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30 31 **Corona São Caetano platform**

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33 The objective of the platform was to offer clinical care for patients with flu syndrome and
34 suspected COVID-19. Through the multimedia platform (website of phone call), patients
35 could be triaged and guided in relation to their clinical needs and tested, without having to
36 leave their homes or go to health facilities, unless seriously ill. This strategy aimed at
37 reducing the workload in health units and the risk of SARS-CoV-2 transmission in the
38 population served by these health units. Patients' GPs were informed of lab results and had
39 access to clinical data stored in the platform. GPs were expected to call patients being
40 assisted by the platform and provide medical assistance through home visits or at the primary
41 care clinic if needed. In general, the drugs prescribed through the platform were restricted to
42 analgesics and antipyretics. The platform was designed so that clinical information was
43 collected in a standardized way for research purposes.
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54 Residents of the municipality aged 12 years and older with suspected COVID-19 symptoms
55 were encouraged, through local media reports, to contact the dedicated Corona São Caetano
56 platform via the website or by phone. They were invited to complete an initial screening
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3 questionnaire that included socio-demographic data; information on symptoms type, onset
4 and duration; and recent contacts.
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8 Patients meeting the suspected COVID-19 case definition (i.e., having at least two of the
9 following symptoms: fever, cough, sore throat, coryza, or change in/loss of smell (anosmia);
10 or one of these symptoms plus at least two other symptoms consistent with COVID-19) were
11 further evaluated, whilst people not meeting these criteria were reassured, advised to stay at
12 home and contact the service again if they were to develop new symptoms or worsening of
13 current ones. The case definition was developed in consultation with infectious disease and
14 primary care specialists to encompass the known symptoms of COVID-19 and is similar to
15 the Brazilian national case definition²³. Patients were then called by a medical student to
16 complete a risk assessment. All pregnant women, and patients meeting pre-defined triage
17 criteria for severe disease (see Supplemental Material), were advised to attend a hospital
18 service - either an emergency department or outpatient service, depending on availability.
19 All other patients were offered a home visit for self-collection of a nasopharyngeal swab.
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30 **Sample collection**

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33 Patients self-collected nasopharyngeal swabs (NPS – both nostrils and throat) at their own
34 homes under the supervision of trained healthcare personnel. We sent a link to an
35 instructional video (<https://youtu.be/rWZzV2ZP7KY>) before the home visit to provide
36 guidance on self-collection procedures. Nasopharyngeal swabs for the molecular detection of
37 SARS-CoV-2 has been recommended as an alternative method of collection for samples from
38 patients with suspected COVID-19²⁴, as well as other respiratory diseases, and has the
39 advantage of reducing the chance of aerosol transmission to healthcare professionals.
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Healthcare personnel were instructed to maintain a distance of six feet from the patient and to
wear personal protective equipment at all times. Samples were immediately put on a cool box
between 2-8°C and stored at 4°C in a fridge until shipment to the lab within 24 hours.

53 **Follow-up procedures**

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Patients testing SARS-CoV-2 RT-PCR positive were followed up to 14 days²⁵ (a maximum
of 7 phone calls) from completion of their initial questionnaire. They were contacted every 48
hours by a medical student who completed another risk assessment and recorded any ongoing

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3 or new symptoms. The purpose of the follow-up was to assess clinical evolution. Where
4 patients were judged to be deteriorating or developing severe disease they were signposted to
5 secondary care services. Patients testing RT-PCR negative were followed up by the primary
6 health care program for their residential area. They were advised to contact the platform for a
7 new consultation if they developed new symptoms. Starting on May 19th, when serological
8 testing became available, RT-PCR-negative patients were re-contacted to offer antibody
9 (IgG/IgM combined) testing 14 days after their initial registration as long as they had become
10 asymptomatic.
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18 **Study dates**

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22 The Corona São Caetano programme was launched on 6th April 2020, with a one week pilot
23 phase designed to test instruments before roll-out. For this analysis, we included all patients
24 making their first contact with the programme in its first month, ie between 13th April and
25 13th May 2020. The period of follow-up (last date of data extraction) was 4th June 2020, to
26 account for the accrual period (three weeks) of possible hospitalizations in the last included
27 patients.
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34 **Laboratory methods**

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37 Due to shortages of some reagents, we used two RT-PCR platforms at different times during
38 the study: ALTONA RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Hamburg, Germany) and the
39 Mico BioMed RT-qPCR kit (Seongnam, South Korea). For serology we tested 10µL of
40 serum or plasma (equivalent in performance) using a qualitative rapid chromatographic
41 immunoassay (Wondfo Biotech Co., Guangzhou, China), that jointly detects anti-SARS-
42 CoV-2 IgG/IgM. The assay has been found to have a sensitivity of 81.5% and specificity of
43 99.1% in a US study²⁶. In our local validation, after two weeks of symptoms, the sensitivity
44 in 59 RT-PCR confirmed cases was 94.9%, and specificity in 106 biobank samples from
45 2019 was 100%.
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54 **Statistical methods**

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57 We estimated the contribution of our platform to total number of COVID-19 cases diagnosed
58 in São Caetano do Sul. To do this, we compared the number of cases diagnosed in our
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3 programme with official data released by the Municipal Department of Health in its daily
4 bulletins (accessed here <https://coronavirus.saocaetanodosul.sp.gov.br>).

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8 Clinical and demographic data were extracted directly from the Corona São Caetano
9 information system. To analyse clinical presentation, we first calculated the proportion and
10 exact binomial 95% confidence intervals (CI) of cases reporting each symptom in the three
11 testing groups: SARS-CoV-2 RT-PCR positive; RT-PCR negative / seropositive; and RT-
12 PCR negative / seronegative. We next combined RT-PCR and serology positive cases to
13 make a confirmed COVID-19 group, and those negative on both tests to make a SARS-CoV-
14 2 negative control group. We express the association between each symptom and a positive
15 COVID-19 diagnosis as odds ratios (OR) and 95% CIs.

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24 Next, we assessed associations between RT-PCR cycle thresholds (Cts) and other clinical
25 features. ALTONA and MiCo BioMed RT-PCR kits each separately amplify two different
26 SARS-CoV-2 viral genes, as such each patient had two Ct values. There was a high
27 concordance between Cts for the two genes within each kit (Figure S1), and we opted therefore
28 to use the mean of the two Ct values for each patient in all analyses. We calculated univariable
29 associations between Cts and age, sex, delay from symptom onset to NPS collection, and
30 presenting symptoms using simple linear regression. We then built a multivariable linear
31 regression model to assess independent associations between presenting symptoms and RT-
32 PCR Cts. As age, sex, and time of swab collection may confound this relationship we included
33 these variables, as well as the RT-PCR platform (ALTONA vs MiCo BioMed), as covariates
34 in the model.

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44 For RT-PCR positive patients, hospitalizations and deaths were extracted from the study
45 platform. To extend the follow-up period and to capture RT-PCR negative patients and those
46 initially triaged to hospital (no study follow-up), hospitalization and vital status was
47 confirmed by linkage with two administrative databases: the municipal epidemiological
48 surveillance dataset, as well as the state-wide influenza-like illness notification system
49 (SIVEP-Gripe). Linkage was last performed on 5th June 2020, 23 days after the last patient
50 was enrolled, by the author SRPS who did not have access to the full analytic dataset. This
51 author searched the SIVEP-Gripe system and the municipal epidemiological surveillance
52 dataset using full name and date of birth. Categorical patient characteristics were compared
53 between patients requiring and those not requiring hospitalization using a Chi-squared or
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3 Fisher exact test. Continuous variables were compared using the Wilcoxon rank sum test. A
4 multivariate analysis was not conducted due to the small number of individuals experiencing
5 this outcome.
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10 The cohort sample included consecutive cases presenting to the Corona São Caetano program
11 and a formal sample size calculation was not performed. Missing data were excluded. All
12 analyses were conducted in R Software for Statistical Computing, version 3.6.3.²⁷
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16 17 **Ethics**

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20 The study was approved by the local ethics committee (Comissão de Ética para Análise de
21 Projeto de Pesquisa - CAPPesq, protocol No. 13915, dated June 03, 2020). The committee
22 waived the need for informed consent and allowed the development of an analytical dataset
23 with no personal identification for the current analysis.
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29 **Patient and public involvement**

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32 Patients were not involved in the planning of this research.
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36 **RESULTS**

37 38 39 **Epidemiological and programmatic indicators**

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42 Over the study period, there were 2,073 presentations (49% phone call, 51% website), from
43 2,011 individual patients, that met the criteria for a suspected COVID-19 case (See Figure 1
44 for study flow). At initial phone interview, 132 (6%) potential cases were advised to go
45 directly to a health service based on the triage questions, and 12 (0.6%) because of
46 pregnancy. Only four (3%) of referred patients were admitted to hospital and none died.
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53 In total 1,583 individual patients were tested with RT-PCR for SARS-CoV-2; 444 (28.0%,
54 95%CI: 25.9-30.3) were positive. The proportion of positive results was stable over the study
55 (Figure S2). Among the RT-PCR negative group, 604 (53% of 1,136) underwent serology
56 testing, of whom 52 (8.6%, 95%CI: 6.6-11.1) were seropositive. The median [IQR] time from
57 symptom onset to serology collection was 31 [26–37] days. The age-sex structure of patients
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3 being tested differed from the underlying population of São Caetano do Sul (Figure S3) with
4 an overrepresentation of working-age adults and women. At the beginning of programme role
5 out, 25% of notified COVID-19 cases in São Caetano do Sul were diagnosed in our
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7 programme. Over the study period, adherence to the programme increased, and by May 13th,
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9 2020, this figure had risen to 78%.
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13 Of 444 RT-PCR positive patients eligible for longitudinal follow-up, 326 (73%) had their
14 final follow-up visit at least 14 days after their initial presentation. Of the seven possible
15 follow-up questionnaires, 384 (86%) COVID-19 patients completed three or more, and 162
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17 (36%) completed all seven.
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20 21 22 **Participant characteristics**

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24 Patient characteristics are shown in Table 1. Although women were overrepresented in the
25 cohort, there were proportionally more males in the RT-PCR positive and seropositive groups
26 compared to the seronegative group. Of note, 55% of RT-PCR negative/seronegative patients
27 had completed higher education compared to 35% RT-PCR-positive patients ($p < 0.001$, Chi-
28 squared test). The median number of days from symptom onset to swab collection was 5.0
29 (IQR, 4.0-7.0) among RT-PCR positive patients and 6.0 (IQR, 4.0-8.3) among RT-PCR
30 negative/seropositive patients ($p = 0.06$, Wilcoxon rank sum) (Figure S4). Chronic
31 respiratory disease was less frequent in RT-PCR positive than dual-negative patients.
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41 **Symptoms of COVID-19**

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43 The prevalence of individual symptoms at presentation is shown in Figure 2A stratified by
44 final diagnostic category. The most frequent symptoms among RT-PCR and seropositive
45 patients were headache (82% and 75%), myalgia (80% and 80%), cough (77% and 63%), and
46 fatigue (77% and 79%). Anosmia was present in 56% and 63% of RT-PCR positive and
47 seropositive patients, respectively, compared to 30% in those testing doubly negative. A
48 similar pattern was observed for ageusia (53% and 53% versus 30%). Upper respiratory tract
49 symptoms - including coryza, blocked nose, ageusia, and anosmia - were more frequent in
50 younger people (Figure 2B). The evolution of symptoms over time among RT-PCR positive
51 patients is shown in Figure S5.
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The odds ratios for testing positive for SARS-CoV-2 (RT-PCR or serology) associated with each presenting symptom are shown in Figure 3. The symptoms with strongest associations were anosmia (OR 3.3, 95%CI: 2.6-4.4), fever (3.0, 95%CI: 2.4-3.9) and ageusia (2.9, 95%CI: 2.3-3.8). The presence of sore throat (0.53, 95%CI: 0.41-0.68) and diarrhoea (0.72, 95%CI: 0.55-0.96) were associated with a negative SARS-CoV-2 test.

Associations between SARS-CoV-2 RT-PCR Cycle threshold (Ct) values, and demographic and clinical features

Figure 4 shows the associations between mean RT-PCR cycle threshold and demographic features and symptoms at presentation (the median [IQR] time from presentation to swab was 1 [1-2] day). Older age was associated with lower cycle thresholds, with a change in mean Ct of -0.05 (95%CI -0.09 to -0.01) for each additional year of age. The mean difference in Ct value was -1.36 (95% CI -2.49 to -0.23) in men compared to women. For each doubling in the number of days from symptom onset to swab collection the mean Ct value increased by 3.28 (95%CI 2.33 to 4.03). Presenting symptoms of fever and arthralgia were associated with lower Cts, whereas anosmia, ageusia, vomiting, diarrhoea, and nausea were associated with higher Cts (Figure 4 and Table S1). After adjustment for age, sex, delay from symptom onset, and RT-PCR platform used, fever (-0.06, 95%CI: -2.11 to -0.001) and arthralgia (-1.24, 95%CI: -2.18 to -0.10) remained associated with lower Cts, and anosmia (2.21, 95%CI: 1.0-3.29), ageusia (1.96, 95%CI: 0.88-3.0), and diarrhoea (1.36, 95%CI: 0.12-2.61) with higher Cts (Table S1).

Hospitalizations and deaths

Of the 444 RT-PCR positive patients, 30 (6.8%) had been hospitalized by 5th June 2020, when the database linkage was last updated, and three (0.7%) had died; in-hospital mortality was therefore 10% (3/30). In 28 cases the date of admission was available. The median time from symptom onset to hospital admission was 7 (range 2 to 14) days. Among 1,136 RT-PCR-negative patients, six (0.5%) had been admitted to hospital. One (<0.01% of 1,136) of these six patients died. None of the 604 RT-PCR negative patients that underwent serology were admitted to hospital or died. Table 2 compares patient characteristics by hospitalization status. Notably, hospitalized patients were older, had more cardiovascular comorbidities and were more frequently obese.

DISCUSSION

We present a community-based cohort of suspected COVID-19 cases recruited through a primary care initiative in the Brazilian municipality of São Caetano do Sul. Offering RT-PCR testing to all patients presenting with symptoms compatible with COVID-19, the positivity rate was 28%, with 8.6% of those testing negative subsequently found to be seropositive - i.e. > 35% of the cohort had a diagnosis of COVID-19. Anosmia, ageusia, and self-reported fever provided the greatest diagnostic value in identifying COVID-19. The rate of hospitalization and deaths among RT-PCR positive patients was low, at 6.8% and 0.7%, respectively. Our results provide important information on the clinical presentation, diagnostic testing and natural history of COVID-19 identified in the community.

The profile of suspected cases that tested positive for COVID-19 differed in some important respects from those testing negative. The lower educational level among positive cases suggests that, in São Caetano do Sul, the risk of exposure to COVID-19 follows a socioeconomic gradient, consistent with other findings from Brazil^{13,28}. Although more women presented to the platform, proportionally more men tested positive, consistent with data from São Paulo showing a higher seroprevalence in men than women¹¹, but also potentially reflecting different health seeking behaviours. Comorbidities were mostly similar, although chronic respiratory disease was less frequent in those testing RT-PCR positive. This may be due to a proportion of presentations in those with chronic respiratory disease being explained by exacerbations of their underlying pathology from aetiologies other than SARS-CoV-2, as well as higher anxiety about COVID-19 in those with pre-existing respiratory disease.

Extrapolating the seropositivity rate among RT-PCR negative patients to the 532 who were not tested with serology, we estimate that an additional 46 seropositive cases would have been identified. As such, 18% (98/542) of COVID-19 cases were missed by RT-PCR in the setting of symptomatic presentations to primary care. This is similar to a pooled analysis showing a false-negative rate for RT-PCR of 20% at three days post-symptom onset.²⁹ Viral load peaks around the time of symptom onset and remains high over the first symptomatic week (also see Figure 4A).^{30,31} Consistent with this, we found a slightly longer delay to swab

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3 collection (due to delay in presentation to the platform) in RT-PCR false-negative patients
4 than RT-PCR positive patients (Figure S4).
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8 COVID-19 presents in a similar way to other respiratory viral illnesses. Indeed, in our cohort
9 the most common symptoms of COVID-19 - such as cough, fatigue, headache, etc. - were
10 reported with a similar frequency among patients testing negative. It is therefore important to
11 have identified anosmia, ageusia, self-reported fever, myalgia, and anorexia as the symptoms
12 with greatest value in the differential diagnosis of COVID-19 in primary care. This is
13 consistent with systematic review evidence highlighting anosmia and ageusia as key
14 diagnostic features of COVID-19³². It is of note that 30% of jointly RT-PCR and serology
15 negative patients reported these symptoms, indicating that although indicative of COVID-19,
16 the specificity of these symptoms is not high enough to rule in the diagnosis alone. Sore
17 throat and diarrhoea - both considered symptoms of COVID-19 in other settings –³³ were
18 more frequently due to other possible aetiologies in this primary care context.
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29 These results are robust for a number of reasons. Firstly, our sample is representative of the
30 population of interest - i.e. consecutive patients with suspected COVID-19 in the community
31 - instead of extrapolating from hospital cases. Symptom data were collected prospectively,
32 eliminating recall or interviewer bias. Finally, we have a control group of patients who were
33 negative for both RT-PCR and serology, minimizing misclassification due to false negative
34 RT-PCR.
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41 In our study, the proportion of patients with a positive SARS-CoV-2 RT-PCR requiring
42 hospitalization was low (7%). Early reports from China were of 13.8% of cases being
43 severe³⁴, but this value was lower when under ascertainment of cases was accounted for.^{35,36}
44 This is because our cohort reflects mild to moderate cases, as severely ill patients are likely to
45 have attended hospital directly. As such, only 3% of patients we triaged to attend health
46 services were ultimately hospitalized, possibly due to self-selection of patients presenting to
47 our service. Supporting this, our overall case fatality ratio among RT-PCR positive patients
48 was 0.7%. The rate of hospitalization was lower (0.5%) in those testing PCR-negative. These
49 patients were admitted with a severe acute respiratory syndrome of an aetiology other than
50 SARS-CoV-2. The 14-fold higher admission rate among PCR-positive cases highlights the
51 importance of molecular testing for SARS-CoV-2 in patients presenting with features of
52 respiratory viral illness to primary care.
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5 As expected, the main determinant of Ct was the delay between symptom onset and swab
6 collection, mostly due to the delay in reporting to the platform. After adjusting for this, as
7 well as age and sex, we found that a self-reported fever and arthralgia were associated with
8 lower Cts. The presence of these symptoms may identify patients with a higher viral load in
9 the community. However, these results should be seen as purely exploratory, and the wide
10 spread of Ct values around the regression line precludes a direct clinical application at
11 present.
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19 Our study has some limitations. Firstly, serology was not performed on all RT-PCR negative
20 patients due to on-going symptoms, loss to follow-up, or patient refusal. Of note, none of the
21 RT-PCR-negative patients that were admitted to hospital underwent serology testing. This
22 suggests that patients who were not tested with serology may have had a higher prevalence of
23 COVID-19 than those that were tested. In addition, imperfect serology test performance
24 (81% sensitivity)²⁶ will introduced false-negative results. Taken together, these biases may
25 have underestimated the true seroprevalence among RT-PCR-negative cases, as well as the
26 false-negative rate of RT-PCR. The latter calculation may also have been influenced by the
27 inclusion of RT-PCR positive patients in the denominator, introducing an incorporation bias.³⁷
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29 Furthermore, the association between symptoms and COVID-19 diagnosis was based on the
30 comparison with doubly PCR and serology negative individuals. It is not clear how the
31 exclusion of individuals that did not undergo serology testing would have influenced these
32 associations. Finally, patients were not involved in the planning of the Corona platform or the
33 research proposal.
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45 A key strength to our study relates to the provision of primary healthcare in Brazil and its
46 symbiosis with medical training nationwide. Primary health care - within the family health
47 strategy (*Estratégia Saúde da Família*) - is centered around a healthcare unit with a multi-
48 professional team that is responsible for all residents in the immediate catchment area⁸. São
49 Caetano do Sul has enough GP units within the family health strategy that all residents have
50 access to primary care. Medical students from the municipal university (USCS) are integrated
51 into the primary healthcare teams and progressively trained from the first year of medical
52 school. Our initiative took advantage of this existing system, with the addition of an online
53 platform allowing remote clinical assessment and follow-up. The suspension of normal
54 clinical training at the medical school provided the workforce. The partnership with the
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3 University of São Paulo, which provided the laboratory diagnostics, created the unique
4 opportunity to establish our prospective community cohort of suspected and confirmed
5 COVID-19 cases. But we believe that this infrastructure could be implemented in other
6 regions with less resources. Other respiratory disease such as influenza, measles, or
7 tuberculosis may benefit from similar approach. However, further evaluation of the impact of
8 the Corona Platform are required.
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15 **CONCLUSION**

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18 Systematic testing of all suspected COVID-19 cases was feasible within primary care
19 services in a Brazilian municipality. Anosmia, ageusia, and fever provide the greatest
20 diagnostic discrimination from other similar primary care presentations. Home-care is a valid
21 approach for most of these patients with a low rate of hospitalization and death.
22 Our programme model – integrating multimedia technology, telehealth with universal access
23 to primary care – may be successful in other contexts.
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30 **CONTRIBUTION STATEMENT**

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34 FEL, MCMC, SFC, MC, RB, and ECS conceived and designed the study. FEL, RMZG, and
35 JCSB provided clinical oversight and supervision of medical students. FEL, MCMC, LFB,
36 HD, OT, LC, and SRPS collected and curated the data. MCMC, TRTM, LSVB, and LCOS
37 performed the laboratory analysis. LFB performed the formal statistical analysis with
38 assistance from FEL, SRPS, NDEA, PM, ECS and OT. LFB, FEL, PM and ECS wrote the
39 first draft, and all authors reviewed, contributed to and approved the final version.
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46 **CONFLICTS OF INTEREST STATEMENT**

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49 The authors have no conflicts of interests. FL, RG, and JB were involved in providing
50 clinical care within the Corona São Caetano Platform.
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54 **FUNDING STATEMENT**

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58 The municipal health department of São Caetano do Sul (Secretaria Municipal de Saúde da
59 Prefeitura de São Caetano do Sul) funded the establishment and implementation of the
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3 platform. We also acknowledge an award from FAPESP (2018/14389-0) and the UK Medical
4 Research Council (MR/S0195/1) to the Brazil-UK Centre for Arbovirus Discovery,
5 Diagnosis, Genomics and Epidemiology (CADDE).
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9 **DATA SHARING STATEMENT**

11 Anonymized data are available at
12 https://figshare.com/articles/dataset/Clinical_features_and_natural_history_of_the_first_2_07_3_suspected_COVID-19_cases_in_the_Corona_S_o_Caetano_primary_care_programme_a_prospective_cohort_study/13322474
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TABLE LEGENDS

Table 1 Demographic and clinical characteristics of 1,048 suspected COVID-19 cases undergoing diagnostic testing in the Corona São Caetano program. * Security, emergency services, supermarket, public transport, and pharmacy workers. IQR: interquartile range; HCW: health care workers, COPD: chronic obstructive pulmonary disease. Missing data – educational level 2; essential occupation 2; body mass index 4; cardiovascular disease 28; diabetes 31 mellitus; chronic resp. disease 65; chronic kidney disease 27; COPD 28. P-values calculated by Chi-squared, Fisher exact, or Wilcoxon rank sum.

Table 2 Characteristics of RT-PCR positive patients stratified by hospitalization status. Missing data – body mass index 2; cardiovascular disease 12; diabetes mellitus 12; chronic respiratory disease 29; COPD 11; chronic kidney disease 12; COPD - chronic obstructive pulmonary disease; IQR - interquartile range.

FIGURE LEGENDS

Figure 1 Patient flowchart for the Corona São Caetano platform between 13th April and 13th May 2020. In the upper section (white background) the numbers correspond to individual presentations to the system; among suspected cases 2,073 suspected cases, 60 had two presentations and one had three. In the lower section (grey background) numbers correspond to individual patients making up the final analytic groups.

Figure 2 Panel A presents prevalence (point) and exact binomial 95% confidence intervals (vertical lines) of symptoms at presentation among patients with suspected COVID-19 according to RT-PCR result and serostatus (A). Panels B and C present the prevalence of presenting symptoms among patients with COVID-19 (RT-PCR and serology positive) stratified by age (B) and sex (C).

Figure 3 Odds ratios (black dot) and 95% confidence intervals (lines) for testing positive for COVID-19 (RT-PCR positive or serology positive) associated with the presence of each presenting symptom. Horizontal axis is on log scale. Point estimates of odds ratios are shown inline with their corresponding symptom.

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3 **Figure 4** Relationship between mean RT-PCR cycle threshold (Ct) and day of illness course
4 when the nasopharyngeal swab was collected (A), patient age (B), patient sex (C), and
5 different symptoms at presentation. Panels A and B show the best fit linear regression lines,
6 panels C and D are violin plots (rotated kernel density plots showing the full distribution of
7 data) of the Ct values with median (black dot) and interquartile range (black line).
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Table 1

	RT-PCR +ve (G1) N = 444 n (%) or median (IQR)	RT-PCR -ve Sero +ve (G2) N=52 n (%) or median (IQR)	RT-PCR -ve Sero -ve (G3) N = 552 n (%) or median (IQR)	p-value G1 versus G2	p-value G1 versus G3
Sex					
Male	200 (45.0)	23 (44.2)	185 (33.5)	1.0	<0.001
Female	244 (55.0)	29 (55.8)	367 (66.5)		
Age groups (years)				0.07	0.40
10 to 19	29 (6.5)	1 (1.9)	25 (4.5)		
20 to 39	197 (44.4)	17 (32.7)	236 (42.8)		
40 to 59	158 (35.6)	28 (53.8)	218 (39.5)		
60+	60 (13.5)	6 (11.5)	73 (13.2)		
Educational level				0.10	<0.001
Up to primary education	75 (16.9)	7 (13.5)	56 (10.2)		
High school	214 (48.3)	19 (36.5)	194 (35.2)		
University	154 (34.8)	26 (50.0)	301 (54.6)		
Essential Occupation				0.45	0.01
Non-HCW essential job *	137 (30.9)	12 (23.1)	148 (26.9)		
Carers	10 (2.3)	0 (0.0)	8 (1.5)		
HCW	32 (7.2)	5 (9.6)	73 (13.2)		
No	264 (59.6)	35 (67.3)	322 (58.4)		
Body mass index (kg/m²)				0.62	0.14
<25	151 (34.2)	22 (42.3)	211 (38.4)		
25-29	182 (41.2)	17 (32.7)	187 (34.0)		
30-35	79 (17.9)	9 (17.3)	112 (20.4)		
35+	30 (6.8)	4 (7.7)	40 (7.3)		
Comorbidities				0.89	0.40
Cardiovascular disease	88 (20.4)	9 (17.6)	129 (24.0)		
Diabetes mellitus	48 (11.1)	4 (7.8)	39 (7.3)		
Any chronic resp. disease	37 (8.9)	9 (18.0)	79 (15.3)		
COPD	24 (5.5)	5 (9.8)	54 (10.1)		
Chronic kidney disease	1 (<1)	0 (0.0)	3 (1.0)	1.0	0.83
Time from symptom onset to swab collection (days), median (IQR)	5.0 (4.0-7.0)	6.0 (4.0-8.3)	6.0 (4.0-9.0)	0.06	<0.001

Table 2

	Hospitalized n=30 n (%) or median (IQR)	Not hospitalized n=414 n (%) or median (IQR)	p-value
Age (years)			
10 to 19	1 (3)	28 (97)	
20 to 39	6 (3)	191 (97)	
40 to 59	14 (9)	144 (91)	
60+	9 (15)	51 (85)	0.006
Sex			
Female	16 (7)	228 (93)	
Male	14 (7)	186 (93)	0.852
Comorbidities			
Cardiovascular disease	11 (13)	77 (87)	0.001
Diabetes mellitus	8 (17)	40 (83)	0.007
Any chronic resp. disease	2 (5)	35 (95)	1.0
COPD	1 (5)	23 (95)	1.0
Chronic kidney disease	1 (100)	0 (0)	0.06
Body mass index (Kg/m²)			
<25	4 (3)	147 (97)	
25-29	8 (4)	174 (96)	
30-35	12 (15)	67 (85)	
35+	6 (20)	24 (80)	<0.001
Time to presentation (days)	3 (3 to 4)	4 (3 to 5)	0.072

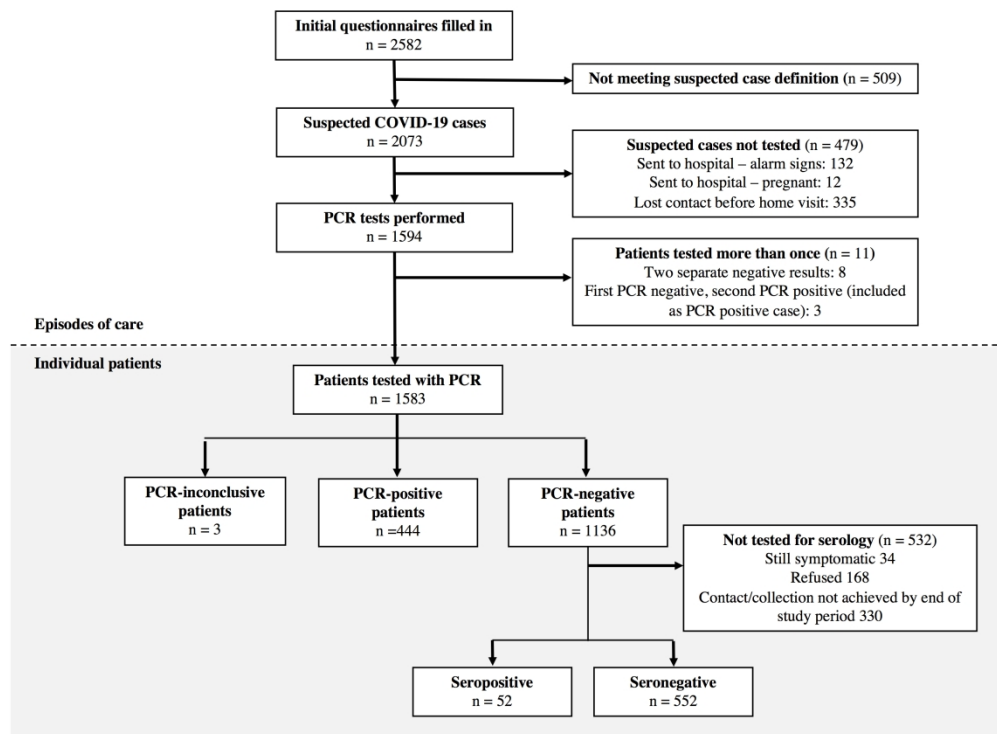


Figure 1

246x181mm (300 x 300 DPI)

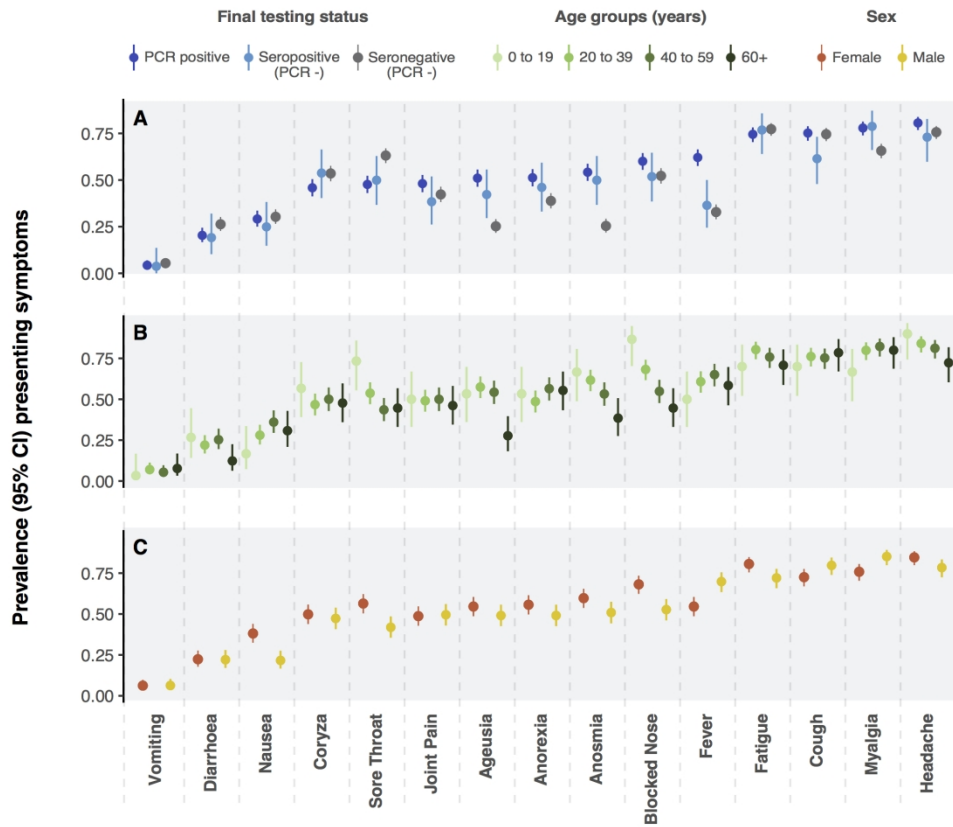


Figure 2

187x158mm (300 x 300 DPI)

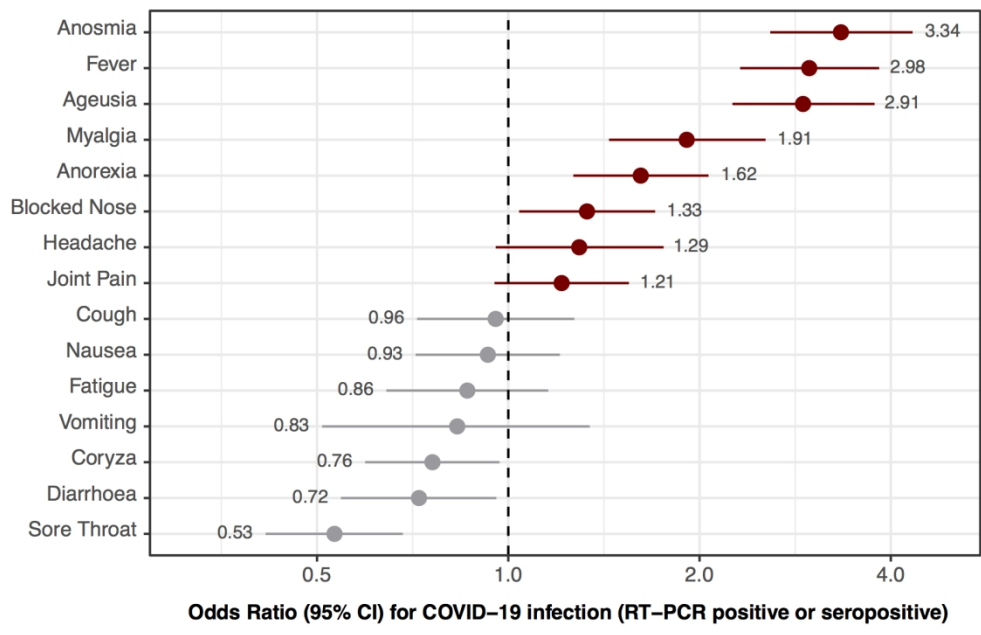


Figure 3

154x100mm (300 x 300 DPI)

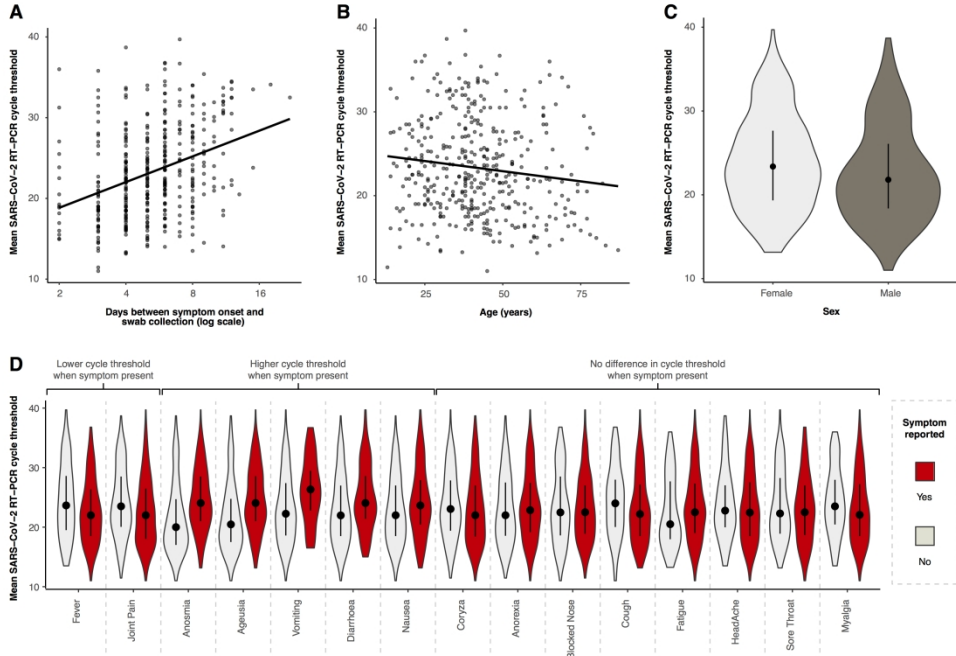


Figure 4

327x222mm (300 x 300 DPI)

Supplemental material

Contents:

1. Initial risk assessment
2. Screen shots of multimedia platform and the initial questionnaire
3. Supplemental Table S1
4. Supplemental figs S1-S5

Initial risk assessment

Patients meeting the definition of a suspected case were called by a medical student (under supervision) to complete a risk assessment. All patients were asked a set of standardized questions:

- Do you feel short of breath?
- Are you breathing quickly or finding it difficult to breath?
- If yes, can you count your respiratory rate over one minute? (respiratory rate >20 breaths/minute was considered tachypnoea)
- Has your fever worsened over the last 3 days or have you had a new fever after 2 days being fever-free?
- Have you felt confused or lethargic?

If the patient answered “yes” to any of these questions they were advised to attend a specialist health service. Among the 132 patients that were triaged to hospital, 76 (58% of 132) had shortness of breath, 76 (58% of 132) reported rapid breathing, 33 (25% of 132) persistent fever and 22 (17% of 132) altered mental status.

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4 **Screen shots showing examples of the initial questionnaire completed**
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8 1) Welcome page
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2) Zipcode confirmation

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The screenshot shows a mobile application interface for the Prefeitura Municipal de São Caetano do Sul. At the top, there is the city's coat of arms and the text 'PREFEITURA MUNICIPAL SÃO CAETANO DO SUL'. Below this is a blue banner with the text 'Corona São Caetano do Sul'. The main content area has the heading 'Informe seu CEP' followed by a text input field containing '09581-670'. A green button labeled 'Continuar' is positioned below the input field. At the bottom, there is a copyright notice: 'Copyright © 2020 MRS - Modular Resarch System. Todos os direitos reservados.'

Corona São Caetano do Sul

Informe seu CEP

09581-670

Continuar

Copyright © 2020 MRS - Modular Resarch System.
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3) Patient basic information

The screenshot shows a web form for 'Corona São Caetano do Sul'. At the top is the logo of the Prefeitura Municipal São Caetano do Sul. Below the logo is a blue header with the text 'Corona São Caetano do Sul'. Underneath the header, there is a red instruction: 'Preencha as informações abaixo'. The form contains four input fields: 'Nome' (with a search icon), 'Sobrenome', 'Celular com DDD', and 'Sexo:' (a dropdown menu with '- selecionar -' selected).

view only

4) Access code confirmation



5) Questionnaire

Perguntas obrigatórias, favor responder:

Dados demográficos

Se do sexo feminino, está grávida?

Não

Sim

Não se aplica

A partir do dia 1º de Março você atuou em alguma destas áreas:

Não

Profissional da saúde

Áreas essenciais (segurança, bombeiro, farmácia, supermercado, transporte público)

Cuidador (a)

Dados clínicos

Teve febre?

Não

Sim

Se sim, você mediu a febre?

Não

Sim

Se sim, qual foi a temperatura mais alta?

Você tem tosse?

Não

Sim

6) Orientation page

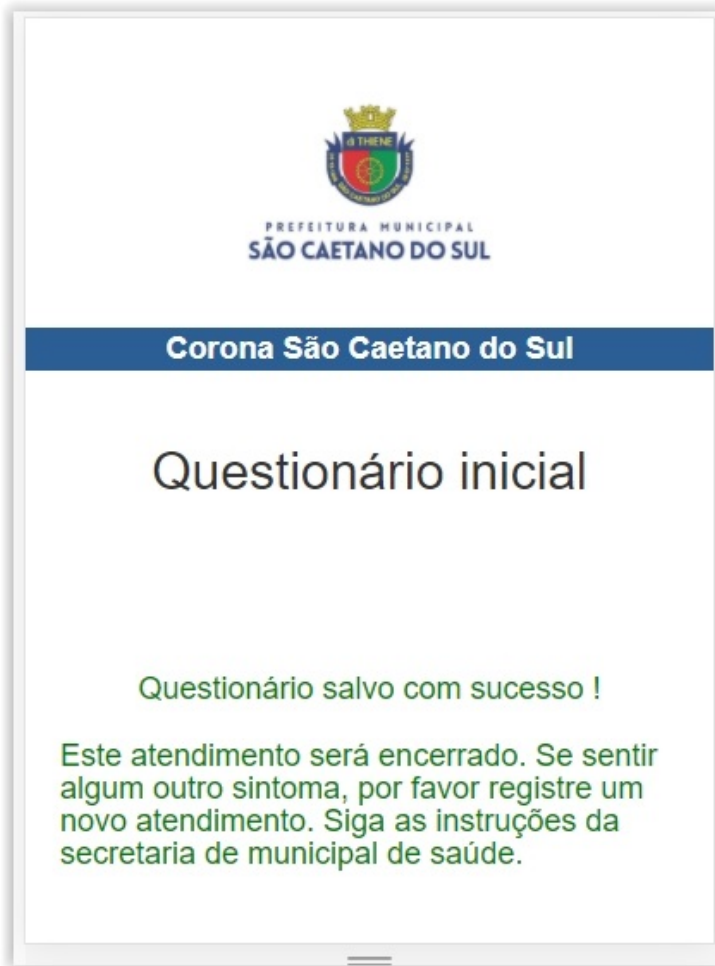


Table S1 Univariable and adjusted associations between RT-PCR cycle thresholds and patient characteristics

	Unadjusted analysis		Adjusted analysis *	
	Beta (difference in means)	95% Confidence interval	Beta (difference in means)	95% Confidence interval
Age (years)	-0.05	-0.09 to -0.01	-0.06	-0.09 to -0.03
Male sex	-1.36	-2.49 to -0.23	-1.05	-2.09 to <0.001
Days from symptom onset to swab collection (days, log ₂)	3.28	2.33 to 4.03	3.27	0.42 to 7.70
PCR platform (ALTONA as reference)	-1.19	-2.37 to -0.02	-1.53	-2.6 to -0.45
Symptoms at presentation				
Fever	-1.78	-2.96 to -0.59	-1.11	-2.11 to -0.001
Myalgia	-1.31	-2.75 to 0.12	-0.78	-2.11 to 0.53
Arthralgia	-1.64	-2.77 to -0.52	-1.24	-2.18 to -0.10
Anosmia	3.15	2.04 to 4.25	2.21	1.0 to 3.29
Agusia	2.99	1.89 to 4.09	1.96	0.88 to 3.0
Diarrhea	2.19	0.84 to 3.53	1.36	0.12 to 2.61
Nausea	1.50	0.28 to 2.72	1.09	-0.04 to 2.24
Vomiting	2.99	0.52 to 5.46	2.02	-0.28 to 4.33
Anorexia	0.56	-0.57 to 1.70	0.47	-0.58 to 1.51
Headache	-0.58	-2.12 to 0.97	-0.81	-2.25 to 0.63
Fatigue	0.84	-0.50 to 2.18	0.34	-0.91 to 1.59
Coryza	-0.78	-1.92 to 0.34	-0.68	-1.72 to 0.34
Blocked nose	-0.36	-1.53 to 0.81	-1.48	-2.59 to -0.37
Cough	-1.33	-2.70 to 0.03	-1.60	-2.86 to -0.33
Sore throat	-0.49	-1.62 to 0.64	-0.45	-1.52 to 0.61

* All variables adjusted for age (continuous in years), sex (female as reference group), PCR platform (ALTONA platform as the reference group) and time between symptom onset and swab collection (log base 2). Analysis was performed within a linear regression framework. Positive beta coefficients indicate higher cycle thresholds (lower viral load) associated with that variable, whereas negative beta coefficients indicate lower cycle thresholds when the variable is present. Results in bold reached statistical significance.

Supplemental figures

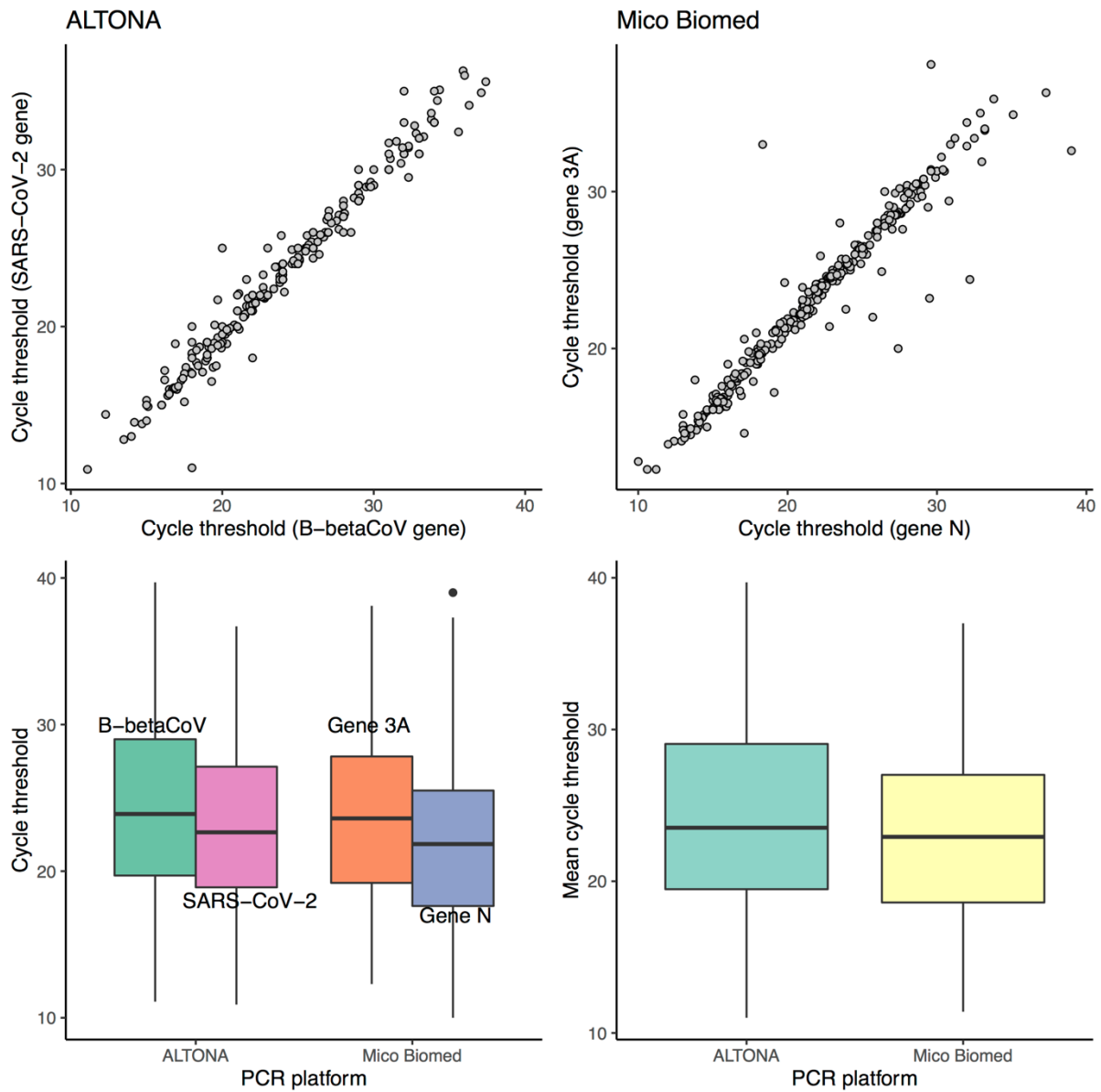


Figure S1 Comparison of cycle thresholds across PCR platforms and genes amplified. Upper two panels show the concordance between cycle thresholds for the two separate genes amplified by the ALTONA (left) and Mico Biomed (right) kits. Lower left panel – distribution of cycle thresholds by gene amplified and RT-PCR platform used. Lower right-hand panel – distribution of the mean cycle threshold (mean of cycle thresholds for separate genes) between different RT-PCR platforms.

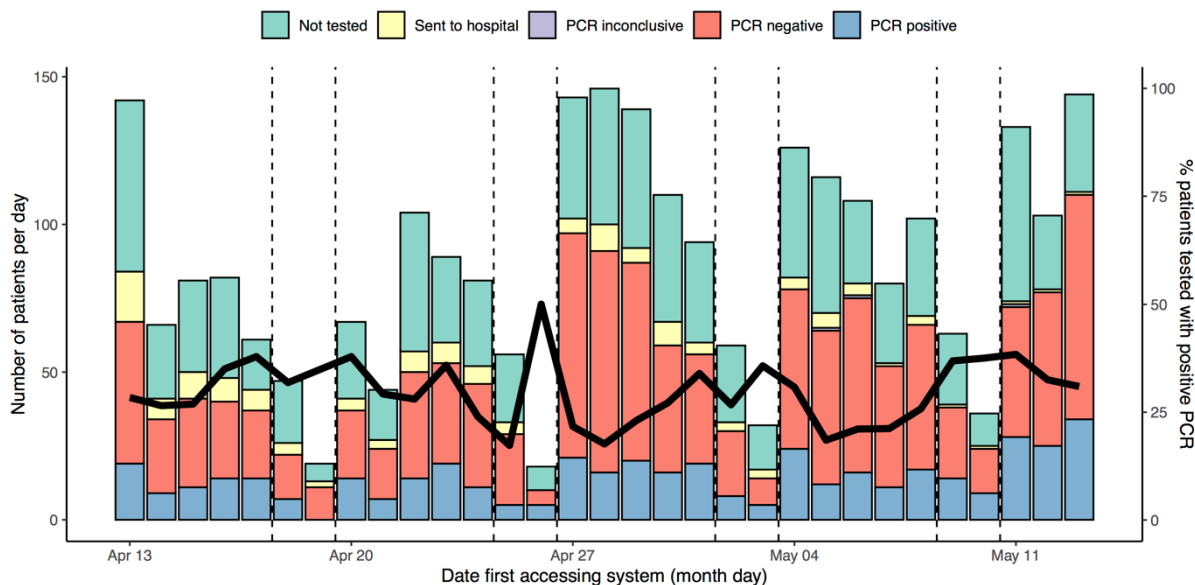


Figure S2 Time series of presentations to the Corona São Caetano platform. Dashed vertical lines denote the weekends with a reduced number of presentations. Thick black line corresponds to the right-hand y-axis: proportion of RT-PCRs performed with positive result.

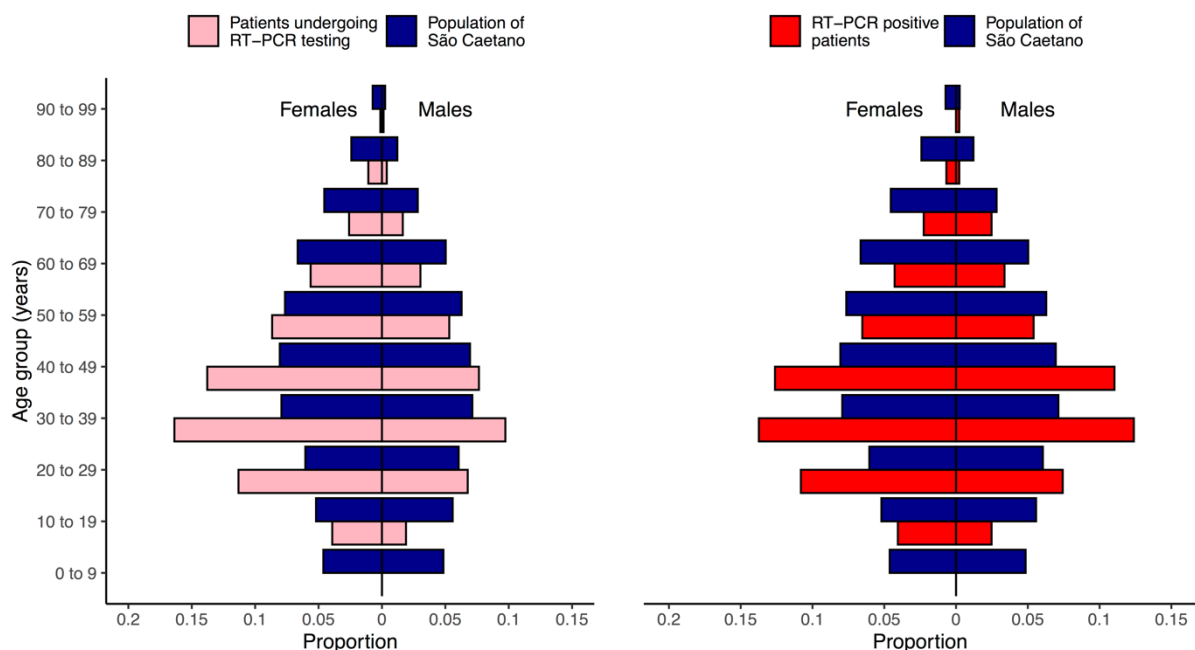


Figure S3 Age-sex distribution the city of São Caetano do Sul compared with that of patients accessing the Corona São Caetano system and being tested with RT-PCR (left-hand panel) and those testing positive for SARS-CoV-2 (right-hand panel).

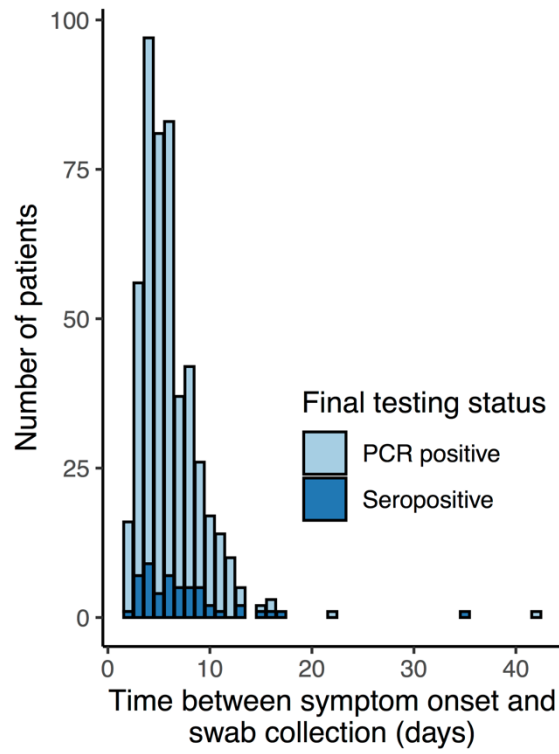


Figure S4 Histogram of delay between symptom onset and swab collection among patients with COVID-19.

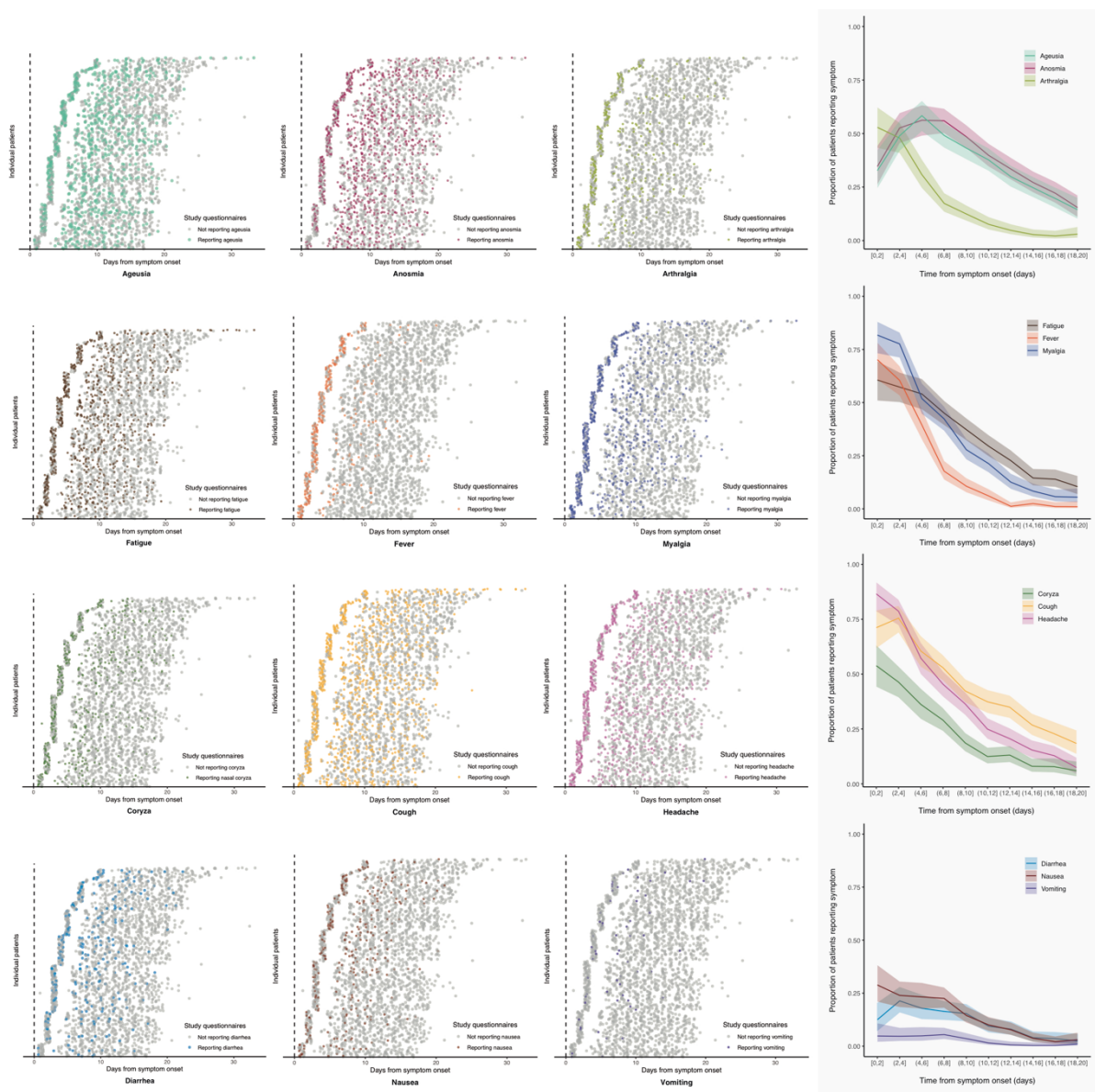


Figure S5 Left hand figures show symptoms at each follow-up questionnaire among patients testing RT-PCR positive and undergoing follow-up. Individual patients are stacked on the y-axis ordered according to the delay from symptom onset to presentation. Each point represents the response to a questionnaire and its position on the horizontal axis the time after symptom onset that the questionnaire was filled in. Grey points are questionnaires where the patient denied the presence of a given symptom. The coloured points correspond to questionnaires in which the patient reported a given symptom. The right-hand figures results from grouping the horizontal axis time into two-day windows and calculating the proportion of completed questionnaires in which each symptom was reported. The denominators for the horizontal axis groups (number of questionnaires completed within a given time window from symptom onset) are 104 at [0-2] days, 192 at (2-4], 185 at (4-6], 293 at (6-8], 338 at (8-10], 329 at (10-12], 335 at (12-14], 324 at (14-16], 280 at (16-18] and 201 at (18-20].

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5 to 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 to 6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	A – 5 B - NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 to 7
Bias	9	Describe any efforts to address potential sources of bias	7 to 8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	A – 7 to 8 B – NA C – 8 D – NA E – NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 and page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	A – table 1 and pages 9to10 B - Table 1 and 2 legends

		(c) Summarise follow-up time (eg, average and total amount)	C – page 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7 and results section
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Clinical features and natural history of the first 2,073 suspected COVID-19 cases in the Corona São Caetano primary care programme: a prospective cohort study

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health, Global health

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Keywords:	PRIMARY CARE, Epidemiology < TROPICAL MEDICINE, INFECTIOUS DISEASES, PUBLIC HEALTH

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3 **Clinical features and natural history of the first 2,073 suspected COVID-19 cases in the**
4 **Corona São Caetano primary care programme: a prospective cohort study**
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53 KEY WORDS: SARS-CoV-2, COVID-19, pandemic, community, primary care, Brazil
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ABSTRACT

Background: Despite most cases not requiring hospital care, there are limited community-based clinical data on COVID-19.

Methods: The Corona São Caetano program is a primary care initiative providing care to all residents with COVID-19 in São Caetano do Sul, Brazil. It was designed to capture standardised clinical data on community COVID-19 cases. After triage of potentially severe cases, consecutive patients presenting to a multimedia screening platform between 13th April and 13th May 2020 were tested at home with SARS-CoV-2 reverse transcriptase (RT) PCR; positive patients were followed up for 14 days with phone calls every 2 days. RT-PCR-negative patients were offered additional SARS-CoV-2 serology testing to establish their infection status. We describe the clinical, virologic and natural history features of this prospective population-based cohort.

Findings: Of 2,073 suspected COVID-19 cases, 1,583 (76.4%) were tested by RT-PCR, of whom 444 (28.0%, 95%CI: 25.9-30.3) were positive; 604/1,136 (53%) RT-PCR-negative patients underwent serology, of whom 52 (8.6%) tested SARS-CoV-2 seropositive. The most common symptoms of confirmed COVID-19 were cough, fatigue, myalgia and headache; whereas self-reported fever (OR 3.0, 95%CI: 2.4-3.9), anosmia (OR 3.3, 95%CI: 2.6-4.4), and ageusia (2.9, 95%CI: 2.3-3.8) were most strongly associated with a positive COVID-19 diagnosis by RT-PCR or serology. RT-PCR cycle thresholds were lower in men, older patients, those with fever and arthralgia, and closer to symptom onset. The rates of hospitalization and death among 444 RT-PCR-positive cases were 6.7% and 0.7%, respectively, with older age and obesity more frequent in the hospitalized group.

Conclusion: COVID-19 presents in a similar way to other mild community-acquired respiratory diseases, but the presence of fever, anosmia, and ageusia can assist the specific diagnosis. Most patients recovered without requiring hospitalization with a low fatality rate compared to other hospital-based studies.

Strengths and limitations of this study

1. The clinical features of COVID-19 have mostly been described in hospital-based studies which are biased towards severe disease
2. We report a prospective cohort of suspected and confirmed COVID-19 cases from a primary care initiative in the Brazilian municipality of São Caetano do Sul
3. By systematically testing consecutive suspected community cases with molecular and serological tests we were able to address the diagnostic value of clinical features of mild-moderate COVID-19 in primary care
4. Prospective follow-up of confirmed cases and linkage with hospital datasets allowed us to describe the natural history of a primary care COVID-19 population
5. A limitation of the work was that not all PCR-negative participants underwent serology testing due to loss to follow-up

INTRODUCTION

A comprehensive public health response is vital but difficult to achieve during an epidemic. The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in China in late 2019.¹ According to the World Health Organization (WHO)^{2,3} and others^{4,5}, the ideal early response should have been multipronged, with identification, isolation, treatment and contact tracing of symptomatic cases, relying on a strong testing programme. Primary health care is well placed to implement such a response, by identifying cases early and managing them in a way that minimizes overcrowding of emergency rooms and intensive care units.^{6,7} Real-time data analysis coming from these primary care response systems can inform policy decisions.

Primary health care (PHC) in Brazil is provided by the publicly funded Unified Health System (SUS – Portuguese acronym) within the family health strategy (*Estratégia Saúde da Família*). Provision of care is centred around a healthcare unit with a multi-professional team that is responsible for all residents in the immediate catchment area⁸. Nearly two-thirds of the Brazilian population is covered by the family health strategy⁸.

In Brazil, the first case of COVID-19 was identified in the city of São Paulo on 26th February 2020.⁹ As of 1st Dec 2020 there were over 6 million confirmed cases nationally, with São Paulo contributing a fifth of these.¹⁰ The reasons for the exceptionally large epidemic in Brazil have been discussed elsewhere^{11–13}. In March 2020, the Municipal Health Department of the municipality of São Caetano do Sul – part of the Greater Metropolitan Region of São Paulo – began to develop a clinical and testing platform to organize its COVID-19 response. The aim was to provide universal detection and management of symptomatic cases and their contacts. The platform was developed in partnership with two local universities – the Municipal University of São Caetano do Sul (USCS) and the University of São Paulo (USP) – and called “Corona São Caetano”.

Large scale community-based observational cohorts are difficult to establish under epidemic circumstances, particularly if the risk of exposure for research personnel is high. Hence, most COVID-19 epidemiological and clinical studies have been hospital-based,^{14–16} and therefore tend to include more severe cases whose findings may not be generalizable to the general

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4 population¹⁷, although some limited descriptions from ambulatory settings are available^{18–20}.

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6 The objectives of this study were to describe the epidemiological indicators of the early phase
7 of the programme rollout; and to describe the clinical, virological and natural history features
8 (including hospitalization and deaths) of SARS-CoV-2 infection among patients identified in
9 primary care.
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13 14 **METHODS**

15 16 17 **Setting**

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21 The municipality of São Caetano do Sul has a population of 161,000 inhabitants.²¹ The city's
22 population is older than the Brazilian population²¹ and its Human Development Index is one
23 of the highest in the country. Nearly all (97.4%) children aged 6-14 are in education and 31%
24 of the population have completed higher education²² (Brazilian national average is 11%).
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30 31 **Corona São Caetano platform**

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33 The objective of the platform was to offer clinical care for patients with flu syndrome and
34 suspected COVID-19. Through the multimedia platform (website or phone call), patients
35 could be triaged and guided in relation to their clinical needs and tested, without having to
36 leave their homes or go to health facilities, unless seriously ill. This strategy aimed at
37 reducing the workload in health units and the risk of SARS-CoV-2 transmission in the
38 population served by these health units. Patients' GPs were informed of lab results and had
39 access to clinical data stored in the platform. GPs were expected to call patients being
40 assisted by the platform and provide medical assistance through home visits or at the primary
41 care clinic if needed. In general, the drugs prescribed through the platform were restricted to
42 analgesics and antipyretics. The platform was designed so that clinical information was
43 collected in a standardized way for research purposes.
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54 Residents of the municipality aged 12 years and older with suspected COVID-19 symptoms
55 were encouraged, through local media reports, to contact the dedicated Corona São Caetano
56 platform via the website or by phone. They were invited to complete an initial screening
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3 questionnaire that included socio-demographic data; information on symptoms type, onset
4 and duration; and recent contacts.
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8 Patients meeting the suspected COVID-19 case definition (i.e., having at least two of the
9 following symptoms: fever, cough, sore throat, coryza, or change in/loss of smell (anosmia);
10 or one of these symptoms plus at least two other symptoms consistent with COVID-19) were
11 further evaluated, whilst people not meeting these criteria were reassured, advised to stay at
12 home and contact the service again if they were to develop new symptoms or worsening of
13 current ones. The case definition was developed in consultation with infectious disease and
14 primary care specialists to encompass the known symptoms of COVID-19 and is similar to
15 the Brazilian national case definition²³. Patients were then called by a medical student to
16 complete a risk assessment. All pregnant women, and patients meeting pre-defined triage
17 criteria for severe disease (see Supplemental Material), were advised to attend a hospital
18 service - either an emergency department or outpatient service, depending on availability.
19 All other patients were offered a home visit for self-collection of a nasopharyngeal swab.
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30 **Sample collection**

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33 Patients self-collected nasopharyngeal swabs (NPS – both nostrils and throat) at their own
34 homes under the supervision of trained healthcare personnel. We sent a link to an
35 instructional video (<https://youtu.be/rWZzV2ZP7KY>) before the home visit to provide
36 guidance on self-collection procedures. Nasopharyngeal swabs for the molecular detection of
37 SARS-CoV-2 has been recommended as an alternative method of collection for samples from
38 patients with suspected COVID-19²⁴, as well as other respiratory diseases, and has the
39 advantage of reducing the chance of aerosol transmission to healthcare professionals.
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Healthcare personnel were instructed to maintain a distance of six feet from the patient and to
wear personal protective equipment at all times. Samples were immediately put on a cool box
between 2-8°C and stored at 4°C in a fridge until shipment to the lab within 24 hours.

53 **Follow-up procedures**

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Patients testing SARS-CoV-2 RT-PCR positive were followed up to 14 days²⁵ (a maximum
of 7 phone calls) from completion of their initial questionnaire. They were contacted every 48
hours by a medical student who completed another risk assessment and recorded any ongoing

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3 or new symptoms. The purpose of the follow-up was to assess clinical evolution. Where
4 patients were judged to be deteriorating or developing severe disease they were signposted to
5 secondary care services. Patients testing RT-PCR negative were followed up by the primary
6 health care program for their residential area. They were advised to contact the platform for a
7 new consultation if they developed new symptoms. Starting on May 19th, when serological
8 testing became available, RT-PCR-negative patients were re-contacted to offer antibody
9 (IgG/IgM combined) testing 14 days after their initial registration as long as they had become
10 asymptomatic.
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18 **Study dates**

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22 The Corona São Caetano programme was launched on 6th April 2020, with a one week pilot
23 phase designed to test instruments before roll-out. For this analysis, we included all patients
24 making their first contact with the programme in its first month, ie between 13th April and
25 13th May 2020. The period of follow-up (last date of data extraction) was 4th June 2020, to
26 account for the accrual period (three weeks) of possible hospitalizations in the last included
27 patients.
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34 **Laboratory methods**

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37 Due to shortages of some reagents, we used two RT-PCR platforms at different times during
38 the study: ALTONA RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Hamburg, Germany) and the
39 Mico BioMed RT-qPCR kit (Seongnam, South Korea). For serology we tested 10µL of
40 serum or plasma (equivalent in performance) using a qualitative rapid chromatographic
41 immunoassay (Wondfo Biotech Co., Guangzhou, China), that jointly detects anti-SARS-
42 CoV-2 IgG/IgM. The assay has been found to have a sensitivity of 81.5% and specificity of
43 99.1% in a US study²⁶. In our local validation, after two weeks of symptoms, the sensitivity
44 in 59 RT-PCR confirmed cases was 94.9%, and specificity in 106 biobank samples from
45 2019 was 100%.
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54 **Statistical methods**

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57 We estimated the contribution of our platform to total number of COVID-19 cases diagnosed
58 in São Caetano do Sul. To do this, we compared the number of cases diagnosed in our
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3 programme with official data released by the Municipal Department of Health in its daily
4 bulletins (accessed here <https://coronavirus.saocaetanodosul.sp.gov.br>).

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8 Clinical and demographic data were extracted directly from the Corona São Caetano
9 information system. To analyse clinical presentation, we first calculated the proportion and
10 exact binomial 95% confidence intervals (CI) of cases reporting each symptom in the three
11 testing groups: SARS-CoV-2 RT-PCR positive; RT-PCR negative / seropositive; and RT-
12 PCR negative / seronegative. We next combined RT-PCR and serology positive cases to
13 make a confirmed COVID-19 group, and those negative on both tests to make a SARS-CoV-
14 2 negative control group. We express the association between each symptom and a positive
15 COVID-19 diagnosis as odds ratios (OR) and 95% CIs.
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24 Next, we assessed associations between RT-PCR cycle thresholds (Cts) and other clinical
25 features. ALTONA and MiCo BioMed RT-PCR kits each separately amplify two different
26 SARS-CoV-2 viral genes, as such each patient had two Ct values. There was a high
27 concordance between Cts for the two genes within each kit (Figure S1), and we opted therefore
28 to use the mean of the two Ct values for each patient in all analyses. We calculated univariable
29 associations between Cts and age, sex, delay from symptom onset to NPS collection, and
30 presenting symptoms using simple linear regression. We then built a multivariable linear
31 regression model to assess independent associations between presenting symptoms and RT-
32 PCR Cts. As age, sex, and time of swab collection may confound this relationship we included
33 these variables, as well as the RT-PCR platform (ALTONA vs MiCo BioMed), as covariates
34 in the model.
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44 For RT-PCR positive patients, hospitalizations and deaths were extracted from the study
45 platform. To extend the follow-up period and to capture RT-PCR negative patients and those
46 initially triaged to hospital (no study follow-up), hospitalization and vital status was
47 confirmed by linkage with two administrative databases: the municipal epidemiological
48 surveillance dataset, as well as the state-wide influenza-like illness notification system
49 (SIVEP-Gripe). Linkage was last performed on 5th June 2020, 23 days after the last patient
50 was enrolled, by the author SRPS who did not have access to the full analytic dataset. This
51 author searched the SIVEP-Gripe system and the municipal epidemiological surveillance
52 dataset using full name and date of birth. Categorical patient characteristics were compared
53 between patients requiring and those not requiring hospitalization using a Chi-squared or
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3 Fisher exact test. Continuous variables were compared using the Wilcoxon rank sum test. A
4 multivariate analysis was not conducted due to the small number of individuals experiencing
5 this outcome.
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10 The cohort sample included consecutive cases presenting to the Corona São Caetano program
11 and a formal sample size calculation was not performed. Missing data were excluded. All
12 analyses were conducted in R Software for Statistical Computing, version 3.6.3.²⁷
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16 17 **Ethics**

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20 The study was approved by the local ethics committee (Comissão de Ética para Análise de
21 Projeto de Pesquisa - CAPPesq, protocol No. 13915, dated June 03, 2020). The committee
22 waived the need for informed consent and allowed the development of an analytical dataset
23 with no personal identification for the current analysis.
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29 **Patient and public involvement**

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32 Patients were not involved in the planning of this research.
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36 **RESULTS**

37 38 39 **Epidemiological and programmatic indicators**

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42 Over the study period, there were 2,073 presentations (49% phone call, 51% website), from
43 2,011 individual patients, that met the criteria for a suspected COVID-19 case (See Figure 1
44 for study flow). At initial phone interview, 132 (6%) potential cases were advised to go
45 directly to a health service based on the triage questions, and 12 (0.6%) because of
46 pregnancy. Only four (3%) of referred patients were admitted to hospital and none died.
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53 In total 1,583 individual patients were tested with RT-PCR for SARS-CoV-2; 444 (28.0%,
54 95%CI: 25.9-30.3) were positive. The proportion of positive results was stable over the study
55 (Figure S2). Among the RT-PCR negative group, 604 (53% of 1,136) underwent serology
56 testing, of whom 52 (8.6%, 95%CI: 6.6-11.1) were seropositive. The median [IQR] time from
57 symptom onset to serology collection was 31 [26–37] days. The age-sex structure of patients
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3 being tested differed from the underlying population of São Caetano do Sul (Figure S3) with
4 an overrepresentation of working-age adults and women. At the beginning of programme role
5 out, 25% of notified COVID-19 cases in São Caetano do Sul were diagnosed in our
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7 programme. Over the study period, adherence to the programme increased, and by May 13th,
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9 2020, this figure had risen to 78%.
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13 Of 444 RT-PCR positive patients eligible for longitudinal follow-up, 326 (73%) had their
14 final follow-up visit at least 14 days after their initial presentation. Of the seven possible
15 follow-up questionnaires, 384 (86%) COVID-19 patients completed three or more, and 162
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17 (36%) completed all seven.
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20 21 22 **Participant characteristics** 23

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25 Patient characteristics are shown in Table 1. Although women were overrepresented in the
26 cohort, there were proportionally more males in the RT-PCR positive and seropositive groups
27 compared to the seronegative group. Of note, 55% of RT-PCR negative/seronegative patients
28 had completed higher education compared to 35% RT-PCR-positive patients ($p < 0.001$, Chi-
29 squared test). The median number of days from symptom onset to swab collection was 5.0
30 (IQR, 4.0-7.0) among RT-PCR positive patients and 6.0 (IQR, 4.0-8.3) among RT-PCR
31 negative/seropositive patients ($p = 0.06$, Wilcoxon rank sum) (Figure S4). Chronic
32 respiratory disease was less frequent in RT-PCR positive than dual-negative patients.
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41 **Symptoms of COVID-19** 42

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44 The prevalence of individual symptoms at presentation is shown in Figure 2A stratified by
45 final diagnostic category. The most frequent symptoms among RT-PCR and seropositive
46 patients were headache (82% and 75%), myalgia (80% and 80%), cough (77% and 63%), and
47 fatigue (77% and 79%). Anosmia was present in 56% and 63% of RT-PCR positive and
48 seropositive patients, respectively, compared to 30% in those testing doubly negative. A
49 similar pattern was observed for ageusia (53% and 53% versus 30%). Upper respiratory tract
50 symptoms - including coryza, blocked nose, ageusia, and anosmia - were more frequent in
51 younger people (Figure 2B). The evolution of symptoms over time among RT-PCR positive
52 patients is shown in Figure S5.
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3 The odds ratios for testing positive for SARS-CoV-2 (RT-PCR or serology) associated with
4 each presenting symptom are shown in Figure 3. The symptoms with strongest associations
5 were anosmia (OR 3.3, 95%CI: 2.6-4.4), fever (3.0, 95%CI: 2.4-3.9) and ageusia (2.9,
6 95%CI: 2.3-3.8). The presence of sore throat (0.53, 95%CI: 0.41-0.68) and diarrhoea (0.72,
7 95%CI: 0.55-0.96) were associated with a negative SARS-CoV-2 test.
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13 **Associations between SARS-CoV-2 RT-PCR Cycle threshold (Ct) values, and** 14 **demographic and clinical features** 15 16

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18 Figure 4 shows the associations between mean RT-PCR cycle threshold and demographic
19 features and symptoms at presentation (the median [IQR] time from presentation to swab was
20 1 [1-2] day). Older age was associated with lower cycle thresholds, with a change in mean Ct
21 of -0.05 (95%CI -0.09 to -0.01) for each additional year of age. The mean difference in Ct
22 value was -1.36 (95% CI -2.49 to -0.23) in men compared to women. For each doubling in
23 the number of days from symptom onset to swab collection the mean Ct value increased by
24 3.28 (95%CI 2.33 to 4.03). Presenting symptoms of fever and arthralgia were associated with
25 lower Cts, whereas anosmia, ageusia, vomiting, diarrhoea, and nausea were associated with
26 higher Cts (Figure 4 and Table S1). After adjustment for age, sex, delay from symptom
27 onset, and RT-PCR platform used, fever (-0.06, 95%CI: -2.11 to -0.001) and arthralgia (-
28 1.24, 95%CI: -2.18 to -0.10) remained associated with lower Cts, and anosmia (2.21, 95%CI:
29 1.0-3.29), ageusia (1.96, 95%CI: 0.88-3.0), and diarrhoea (1.36, 95%CI: 0.12-2.61) with
30 higher Cts (Table S1).
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43 **Hospitalizations and deaths** 44 45

46 Of the 444 RT-PCR positive patients, 30 (6.8%) had been hospitalized by 5th June 2020,
47 when the database linkage was last updated, and three (0.7%) had died; in-hospital mortality
48 was therefore 10% (3/30). In 28 cases the date of admission was available. The median time
49 from symptom onset to hospital admission was 7 (range 2 to 14) days. Among 1,136 RT-
50 PCR-negative patients, six (0.5%) had been admitted to hospital. One (<0.01% of 1,136) of
51 these six patients died. None of the 604 RT-PCR negative patients that underwent serology
52 were admitted to hospital or died. Table 2 compares patient characteristics by hospitalization
53 status. Notably, hospitalized patients were older, had more cardiovascular comorbidities and
54 were more frequently obese.
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DISCUSSION

We present a community-based cohort of suspected COVID-19 cases recruited through a primary care initiative in the Brazilian municipality of São Caetano do Sul. Offering RT-PCR testing to all patients presenting with symptoms compatible with COVID-19, the positivity rate was 28%, with 8.6% of those testing negative subsequently found to be seropositive - i.e. > 35% of the cohort had a diagnosis of COVID-19. Anosmia, ageusia, and self-reported fever provided the greatest diagnostic value in identifying COVID-19. The rate of hospitalization and deaths among RT-PCR positive patients was low, at 6.8% and 0.7%, respectively. Our results provide important information on the clinical presentation, diagnostic testing and natural history of COVID-19 identified in the community.

The profile of suspected cases that tested positive for COVID-19 differed in some important respects from those testing negative. The lower educational level among positive cases suggests that, in São Caetano do Sul, the risk of exposure to COVID-19 follows a socioeconomic gradient, consistent with other findings from Brazil^{13,28}. Although more women presented to the platform, proportionally more men tested positive, consistent with data from São Paulo showing a higher seroprevalence in men than women¹¹, but also potentially reflecting different health seeking behaviours. Comorbidities were mostly similar, although chronic respiratory disease was less frequent in those testing RT-PCR positive. This may be due to a proportion of presentations in those with chronic respiratory disease being explained by exacerbations of their underlying pathology from aetiologies other than SARS-CoV-2, as well as higher anxiety about COVID-19 in those with pre-existing respiratory disease.

Extrapolating the seropositivity rate among RT-PCR negative patients to the 532 who were not tested with serology, we estimate that an additional 46 seropositive cases would have been identified. As such, 18% (98/542) of COVID-19 cases were missed by RT-PCR in the setting of symptomatic presentations to primary care. This is similar to a pooled analysis showing a false-negative rate for RT-PCR of 20% at three days post-symptom onset.²⁹ Viral load peaks around the time of symptom onset and remains high over the first symptomatic week (also see Figure 4A).^{30,31} Consistent with this, we found a slightly longer delay to swab

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3 collection (due to delay in presentation to the platform) in RT-PCR false-negative patients
4 than RT-PCR positive patients (Figure S4).
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8 COVID-19 presents in a similar way to other respiratory viral illnesses. Indeed, in our cohort
9 the most common symptoms of COVID-19 - such as cough, fatigue, headache, etc. - were
10 reported with a similar frequency among patients testing negative. It is therefore important to
11 have identified anosmia, ageusia, self-reported fever, myalgia, and anorexia as the symptoms
12 with greatest value in the differential diagnosis of COVID-19 in primary care. This is
13 consistent with systematic review evidence highlighting anosmia and ageusia as key
14 diagnostic features of COVID-19³². It is of note that 30% of jointly RT-PCR and serology
15 negative patients reported these symptoms, indicating that although indicative of COVID-19,
16 the specificity of these symptoms is not high enough to rule in the diagnosis alone. Sore
17 throat and diarrhoea - both considered symptoms of COVID-19 in other settings –³³ were
18 more frequently due to other possible aetiologies in this primary care context.
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29 These results are robust for a number of reasons. Firstly, our sample is representative of the
30 population of interest - i.e. consecutive patients with suspected COVID-19 in the community
31 - instead of extrapolating from hospital cases. Symptom data were collected prospectively,
32 eliminating recall or interviewer bias. Finally, we have a control group of patients who were
33 negative for both RT-PCR and serology, minimizing misclassification due to false negative
34 RT-PCR.
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41 In our study, the proportion of patients with a positive SARS-CoV-2 RT-PCR requiring
42 hospitalization was low (7%). Early reports from China were of 13.8% of cases being
43 severe³⁴, but this value was lower when under ascertainment of cases was accounted for.^{35,36}
44 This is because our cohort reflects mild to moderate cases, as severely ill patients are likely to
45 have attended hospital directly. As such, only 3% of patients we triaged to attend health
46 services were ultimately hospitalized, possibly due to self-selection of patients presenting to
47 our service. Supporting this, our overall case fatality ratio among RT-PCR positive patients
48 was 0.7%. The rate of hospitalization was lower (0.5%) in those testing PCR-negative. These
49 patients were admitted with a severe acute respiratory syndrome of an aetiology other than
50 SARS-CoV-2. The 14-fold higher admission rate among PCR-positive cases highlights the
51 importance of molecular testing for SARS-CoV-2 in patients presenting with features of
52 respiratory viral illness to primary care.
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5 As expected, the main determinant of Ct was the delay between symptom onset and swab
6 collection, mostly due to the delay in reporting to the platform. After adjusting for this, as
7 well as age and sex, we found that a self-reported fever and arthralgia were associated with
8 lower Cts. The presence of these symptoms may identify patients with a higher viral load in
9 the community. However, these results should be seen as purely exploratory, and the wide
10 spread of Ct values around the regression line precludes a direct clinical application at
11 present.
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19 Our study has some limitations. Firstly, the small sample size precluded a multivariate analysis
20 of factors associated with hospitalization or death. Next, serology was not performed on all
21 RT-PCR negative patients due to on-going symptoms, loss to follow-up, or patient refusal. Of
22 note, none of the RT-PCR-negative patients that were admitted to hospital underwent
23 serology testing. This suggests that patients who were not tested with serology may have had
24 a higher prevalence of COVID-19 than those that were tested. In addition, imperfect serology
25 test performance (81% sensitivity)²⁶ will introduced false-negative results. Taken together,
26 these biases may have underestimated the true seroprevalence among RT-PCR-negative
27 cases, as well as the false-negative rate of RT-PCR. The latter calculation may also have been
28 influenced by the inclusion of RT-PCR positive patients in the denominator, introducing an
29 incorporation bias.³⁷ Furthermore, the association between symptoms and COVID-19
30 diagnosis was based on the comparison with doubly PCR and serology negative individuals.
31 It is not clear how the exclusion of individuals that did not undergo serology testing would
32 have influenced these associations. Finally, patients were not involved in the planning of the
33 Corona platform or the research proposal.
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46 A key strength to our study relates to the provision of primary healthcare in Brazil and its
47 symbiosis with medical training nationwide. Primary health care - within the family health
48 strategy (*Estratégia Saúde da Família*) - is centered around a healthcare unit with a multi-
49 professional team that is responsible for all residents in the immediate catchment area⁸. São
50 Caetano do Sul has enough GP units within the family health strategy that all residents have
51 access to primary care. Medical students from the municipal university (USCS) are integrated
52 into the primary healthcare teams and progressively trained from the first year of medical
53 school. Our initiative took advantage of this existing system, with the addition of an online
54 platform allowing remote clinical assessment and follow-up. The suspension of normal
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3 clinical training at the medical school provided the workforce. The partnership with the
4 University of São Paulo, which provided the laboratory diagnostics, created the unique
5 opportunity to establish our prospective community cohort of suspected and confirmed
6 COVID-19 cases. But we believe that this infrastructure could be implemented in other
7 regions with less resources. Other respiratory disease such as influenza, measles, or
8 tuberculosis may benefit from similar approach. However, further evaluation of the impact of
9 the Corona Platform are required.
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17 **CONCLUSION**

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20 Systematic testing of all suspected COVID-19 cases was feasible within primary care
21 services in a Brazilian municipality. Anosmia, ageusia, and fever provide the greatest
22 diagnostic discrimination from other similar primary care presentations. Home-care is a valid
23 approach for most of these patients with a low rate of hospitalization and death.
24 Our programme model – integrating multimedia technology, telehealth with universal access
25 to primary care – may be successful in other contexts.
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32 **CONTRIBUTION STATEMENT**

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35 FEL, MCMC, SFC, MC, RB, and ECS conceived and designed the study. FEL, RMZG, and
36 JCSB provided clinical oversight and supervision of medical students. FEL, MCMC, LFB,
37 HD, OT, LC, and SRPS collected and curated the data. MCMC, TRTM, LSVB, and LCOS
38 performed the laboratory analysis. LFB performed the formal statistical analysis with
39 assistance from FEL, SRPS, NDEA, PM, ECS and OT. LFB, FEL, PM and ECS wrote the
40 first draft, and all authors reviewed, contributed to and approved the final version.
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48 **CONFLICTS OF INTEREST STATEMENT**

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51 The authors have no conflicts of interests. FL, RG, and JB were involved in providing
52 clinical care within the Corona São Caetano Platform.
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56 **FUNDING STATEMENT**

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3 The municipal health department of São Caetano do Sul (Secretaria Municipal de Saúde da
4 Prefeitura de São Caetano do Sul) funded the establishment and implementation of the
5 platform. We also acknowledge an award from FAPESP (2018/14389-0) and the UK Medical
6 Research Council (MR/S0195/1) to the Brazil-UK Centre for Arbovirus Discovery,
7 Diagnosis, Genomics and Epidemiology (CADDE).
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13 DATA SHARING STATEMENT

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15 Anonymized data are available at

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17 https://figshare.com/articles/dataset/Clinical_features_and_natural_history_of_the_first_2_07_3_suspected_COVID-19_cases_in_the_Corona_S_o_Caetano_primary_care_programme_a_prospective_cohort_study/13322474
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TABLE LEGENDS

Table 1 Demographic and clinical characteristics of 1,048 suspected COVID-19 cases undergoing diagnostic testing in the Corona São Caetano program. * Security, emergency services, supermarket, public transport, and pharmacy workers. IQR: interquartile range; HCW: health care workers, COPD: chronic obstructive pulmonary disease. Missing data – educational level 2; essential occupation 2; body mass index 4; cardiovascular disease 28; diabetes 31 mellitus; chronic resp. disease 65; chronic kidney disease 27; COPD 28. P-values calculated by Chi-squared, Fisher exact, or Wilcoxon rank sum.

Table 2 Characteristics of RT-PCR positive patients stratified by hospitalization status. Missing data – body mass index 2; cardiovascular disease 12; diabetes mellitus 12; chronic respiratory disease 29; COPD 11; chronic kidney disease 12; COPD - chronic obstructive pulmonary disease; IQR - interquartile range.

FIGURE LEGENDS

Figure 1 Patient flowchart for the Corona São Caetano platform between 13th April and 13th May 2020. In the upper section (white background) the numbers correspond to individual presentations to the system; among suspected cases 2,073 suspected cases, 60 had two presentations and one had three. In the lower section (grey background) numbers correspond to individual patients making up the final analytic groups.

Figure 2 Panel A presents prevalence (point) and exact binomial 95% confidence intervals (vertical lines) of symptoms at presentation among patients with suspected COVID-19 according to RT-PCR result and serostatus (A). Panels B and C present the prevalence of presenting symptoms among patients with COVID-19 (RT-PCR and serology positive) stratified by age (B) and sex (C).

Figure 3 Odds ratios (black dot) and 95% confidence intervals (lines) for testing positive for COVID-19 (RT-PCR positive or serology positive) associated with the presence of each presenting symptom. Horizontal axis is on log scale. Point estimates of odds ratios are shown inline with their corresponding symptom.

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3 **Figure 4** Relationship between mean RT-PCR cycle threshold (Ct) and day of illness course
4 when the nasopharyngeal swab was collected (A), patient age (B), patient sex (C), and
5 different symptoms at presentation. Panels A and B show the best fit linear regression lines,
6 panels C and D are violin plots (rotated kernel density plots showing the full distribution of
7 data) of the Ct values with median (black dot) and interquartile range (black line).
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Table 1

	RT-PCR +ve (G1) N = 444 n (%) or median (IQR)	RT-PCR -ve Sero +ve (G2) N=52 n (%) or median (IQR)	RT-PCR -ve Sero -ve (G3) N = 552 n (%) or median (IQR)	p-value G1 versus G2	p-value G1 versus G3
Sex					
Male	200 (45.0)	23 (44.2)	185 (33.5)	1.0	<0.001
Female	244 (55.0)	29 (55.8)	367 (66.5)		
Age groups (years)				0.07	0.40
10 to 19	29 (6.5)	1 (1.9)	25 (4.5)		
20 to 39	197 (44.4)	17 (32.7)	236 (42.8)		
40 to 59	158 (35.6)	28 (53.8)	218 (39.5)		
60+	60 (13.5)	6 (11.5)	73 (13.2)		
Educational level				0.10	<0.001
Up to primary education	75 (16.9)	7 (13.5)	56 (10.2)		
High school	214 (48.3)	19 (36.5)	194 (35.2)		
University	154 (34.8)	26 (50.0)	301 (54.6)		
Essential Occupation				0.45	0.01
Non-HCW essential job *	137 (30.9)	12 (23.1)	148 (26.9)		
Carers	10 (2.3)	0 (0.0)	8 (1.5)		
HCW	32 (7.2)	5 (9.6)	73 (13.2)		
No	264 (59.6)	35 (67.3)	322 (58.4)		
Body mass index (kg/m²)				0.62	0.14
<25	151 (34.2)	22 (42.3)	211 (38.4)		
25-29	182 (41.2)	17 (32.7)	187 (34.0)		
30-35	79 (17.9)	9 (17.3)	112 (20.4)		
35+	30 (6.8)	4 (7.7)	40 (7.3)		
Comorbidities				0.89	0.40
Cardiovascular disease	88 (20.4)	9 (17.6)	129 (24.0)		
Diabetes mellitus	48 (11.1)	4 (7.8)	39 (7.3)		
Any chronic resp. disease	37 (8.9)	9 (18.0)	79 (15.3)		
COPD	24 (5.5)	5 (9.8)	54 (10.1)		
Chronic kidney disease	1 (<1)	0 (0.0)	3 (1.0)	1.0	0.83
Time from symptom onset to swab collection (days), median (IQR)	5.0 (4.0-7.0)	6.0 (4.0-8.3)	6.0 (4.0-9.0)	0.06	<0.001

Table 2

	Hospitalized n=30 n (%) or median (IQR)	Not hospitalized n=414 n (%) or median (IQR)	p-value
Age (years)			
10 to 19	1 (3)	28 (97)	
20 to 39	6 (3)	191 (97)	
40 to 59	14 (9)	144 (91)	
60+	9 (15)	51 (85)	0.006
Sex			
Female	16 (7)	228 (93)	
Male	14 (7)	186 (93)	0.852
Comorbidities			
Cardiovascular disease	11 (13)	77 (87)	0.001
Diabetes mellitus	8 (17)	40 (83)	0.007
Any chronic resp. disease	2 (5)	35 (95)	1.0
COPD	1 (5)	23 (95)	1.0
Chronic kidney disease	1 (100)	0 (0)	0.06
Body mass index (Kg/m²)			
<25	4 (3)	147 (97)	
25-29	8 (4)	174 (96)	
30-35	12 (15)	67 (85)	
35+	6 (20)	24 (80)	<0.001
Time to presentation (days)	3 (3 to 4)	4 (3 to 5)	0.072

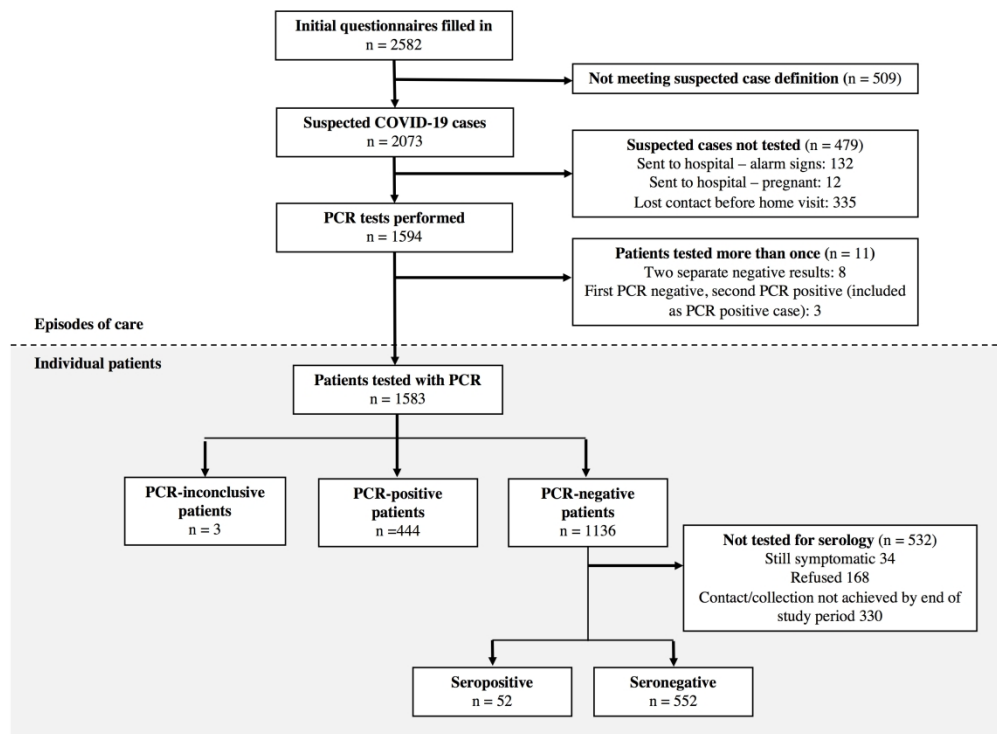


Figure 1

246x181mm (300 x 300 DPI)

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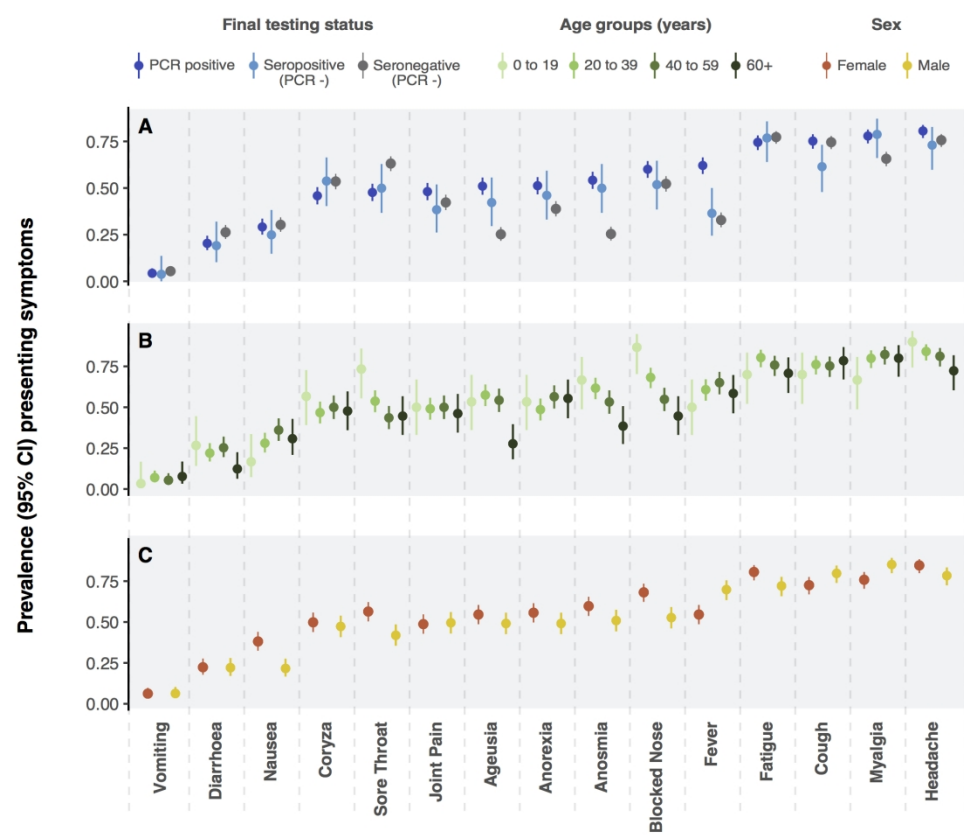


Figure 2

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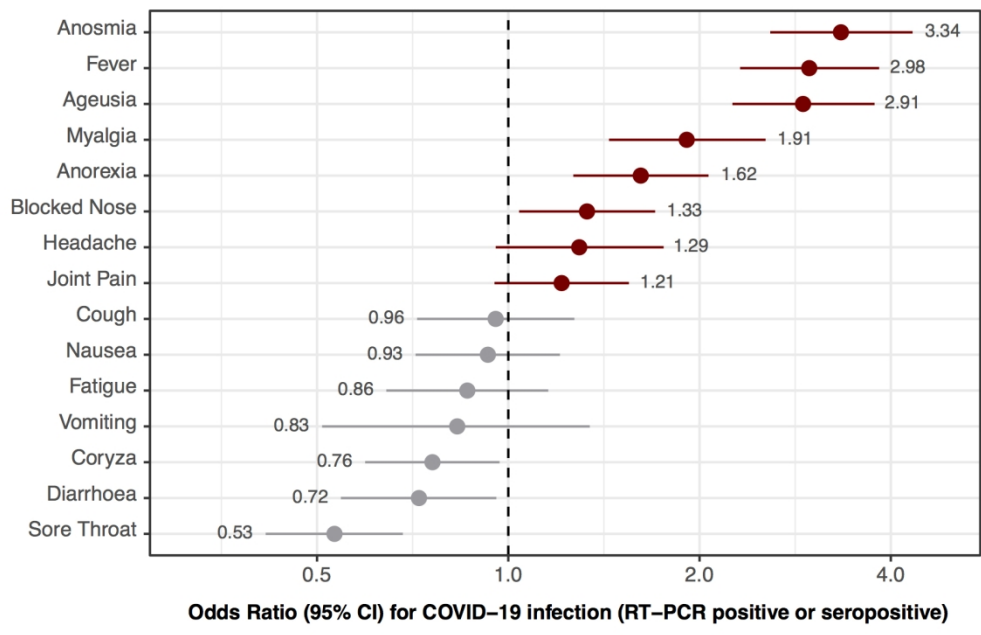


Figure 3

154x100mm (300 x 300 DPI)

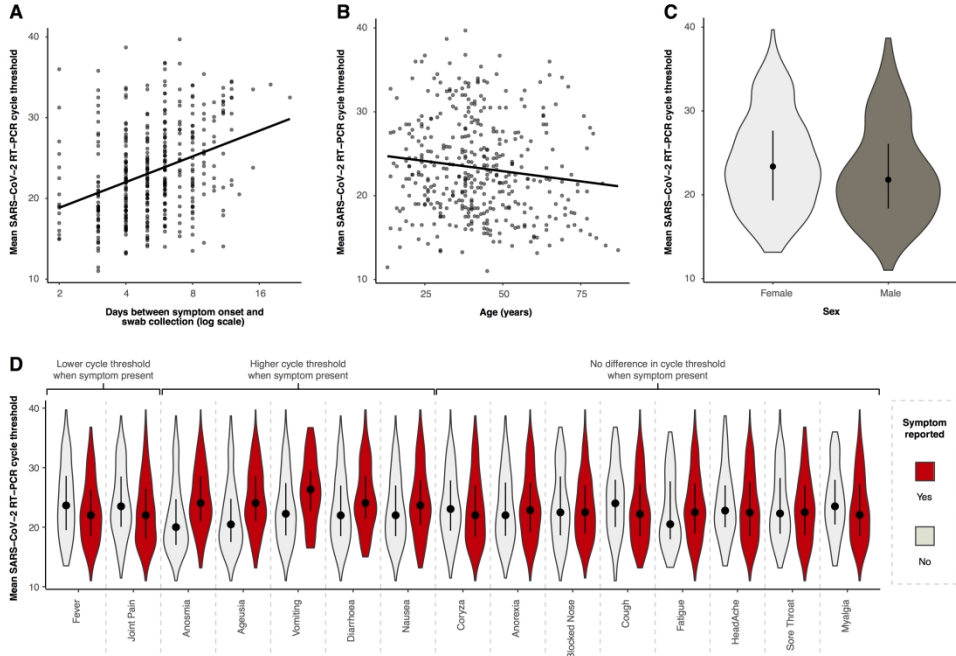


Figure 4

327x222mm (300 x 300 DPI)

Supplemental material

Contents:

1. Initial risk assessment
2. Screen shots of multimedia platform and the initial questionnaire
3. Supplemental Table S1
4. Supplemental figs S1-S5

Initial risk assessment

Patients meeting the definition of a suspected case were called by a medical student (under supervision) to complete a risk assessment. All patients were asked a set of standardized questions:

- Do you feel short of breath?
- Are you breathing quickly or finding it difficult to breath?
- If yes, can you count your respiratory rate over one minute? (respiratory rate >20 breaths/minute was considered tachypnoea)
- Has your fever worsened over the last 3 days or have you had a new fever after 2 days being fever-free?
- Have you felt confused or lethargic?

If the patient answered “yes” to any of these questions they were advised to attend a specialist health service. Among the 132 patients that were triaged to hospital, 76 (58% of 132) had shortness of breath, 76 (58% of 132) reported rapid breathing, 33 (25% of 132) persistent fever and 22 (17% of 132) altered mental status.

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4 **Screen shots showing examples of the initial questionnaire completed**
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8 1) Welcome page
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2) Zipcode confirmation

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PREFEITURA MUNICIPAL
SÃO CAETANO DO SUL

Corona São Caetano do Sul

Informe seu CEP

09581-670

Continuar

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3) Patient basic information

The screenshot shows a web form for 'Corona São Caetano do Sul'. At the top is the logo of the 'PREFEITURA MUNICIPAL SÃO CAETANO DO SUL'. Below the logo is a blue header with the text 'Corona São Caetano do Sul'. Underneath the header, the instruction 'Preencha as informações abaixo' is displayed in red. The form contains four input fields: 'Nome' (with a search icon), 'Sobrenome', 'Celular com DDD', and 'Sexo:' (a dropdown menu with '- selecionar -' selected). A large, light blue watermark 'view only' is overlaid diagonally across the bottom right of the form area.

4) Access code confirmation



5) Questionnaire

Perguntas obrigatórias, favor responder:

Dados demográficos

Se do sexo feminino, está grávida?

Não

Sim

Não se aplica

A partir do dia 1º de Março você atuou em alguma destas áreas:

Não

Profissional da saúde

Áreas essenciais (segurança, bombeiro, farmácia, supermercado, transporte público)

Cuidador (a)

Dados clínicos

Teve febre?

Não

Sim

Se sim, você mediu a febre?

Não

Sim

Se sim, qual foi a temperatura mais alta?

Você tem tosse?

Não

Sim

6) Orientation page

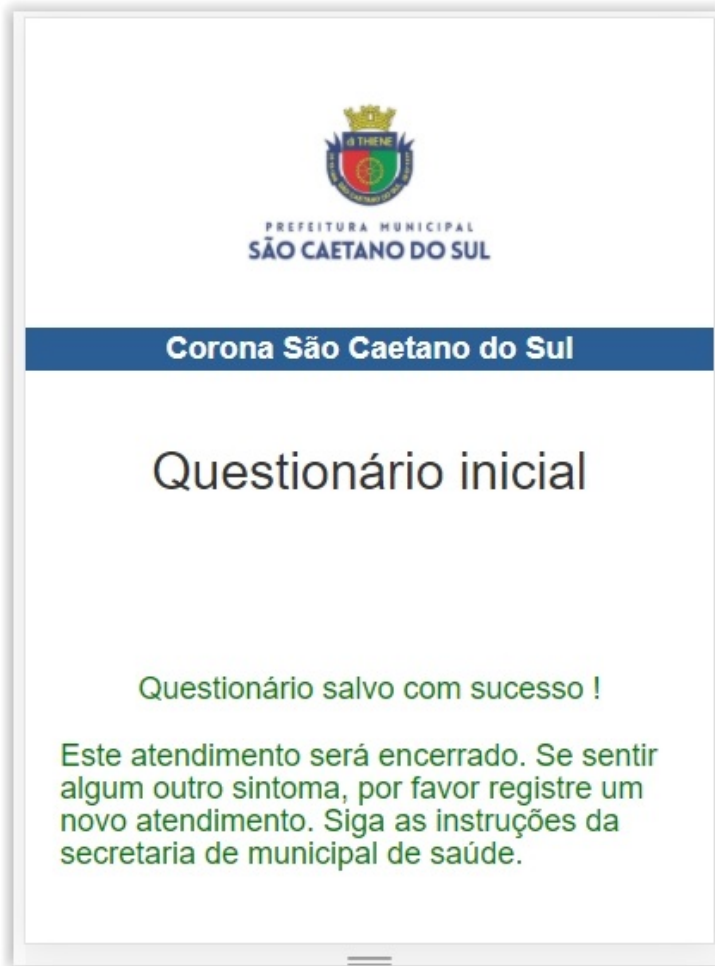


Table S1 Univariable and adjusted associations between RT-PCR cycle thresholds and patient characteristics

	Unadjusted analysis		Adjusted analysis *	
	Beta (difference in means)	95% Confidence interval	Beta (difference in means)	95% Confidence interval
Age (years)	-0.05	-0.09 to -0.01	-0.06	-0.09 to -0.03
Male sex	-1.36	-2.49 to -0.23	-1.05	-2.09 to <0.001
Days from symptom onset to swab collection (days, log ₂)	3.28	2.33 to 4.03	3.27	0.42 to 7.70
PCR platform (ALTONA as reference)	-1.19	-2.37 to -0.02	-1.53	-2.6 to -0.45
Symptoms at presentation				
Fever	-1.78	-2.96 to -0.59	-1.11	-2.11 to -0.001
Myalgia	-1.31	-2.75 to 0.12	-0.78	-2.11 to 0.53
Arthralgia	-1.64	-2.77 to -0.52	-1.24	-2.18 to -0.10
Anosmia	3.15	2.04 to 4.25	2.21	1.0 to 3.29
Agusia	2.99	1.89 to 4.09	1.96	0.88 to 3.0
Diarrhea	2.19	0.84 to 3.53	1.36	0.12 to 2.61
Nausea	1.50	0.28 to 2.72	1.09	-0.04 to 2.24
Vomiting	2.99	0.52 to 5.46	2.02	-0.28 to 4.33
Anorexia	0.56	-0.57 to 1.70	0.47	-0.58 to 1.51
Headache	-0.58	-2.12 to 0.97	-0.81	-2.25 to 0.63
Fatigue	0.84	-0.50 to 2.18	0.34	-0.91 to 1.59
Coryza	-0.78	-1.92 to 0.34	-0.68	-1.72 to 0.34
Blocked nose	-0.36	-1.53 to 0.81	-1.48	-2.59 to -0.37
Cough	-1.33	-2.70 to 0.03	-1.60	-2.86 to -0.33
Sore throat	-0.49	-1.62 to 0.64	-0.45	-1.52 to 0.61

* All variables adjusted for age (continuous in years), sex (female as reference group), PCR platform (ALTONA platform as the reference group) and time between symptom onset and swab collection (log base 2). Analysis was performed within a linear regression framework. Positive beta coefficients indicate higher cycle thresholds (lower viral load) associated with that variable, whereas negative beta coefficients indicate lower cycle thresholds when the variable is present. Results in bold reached statistical significance.

Supplemental figures

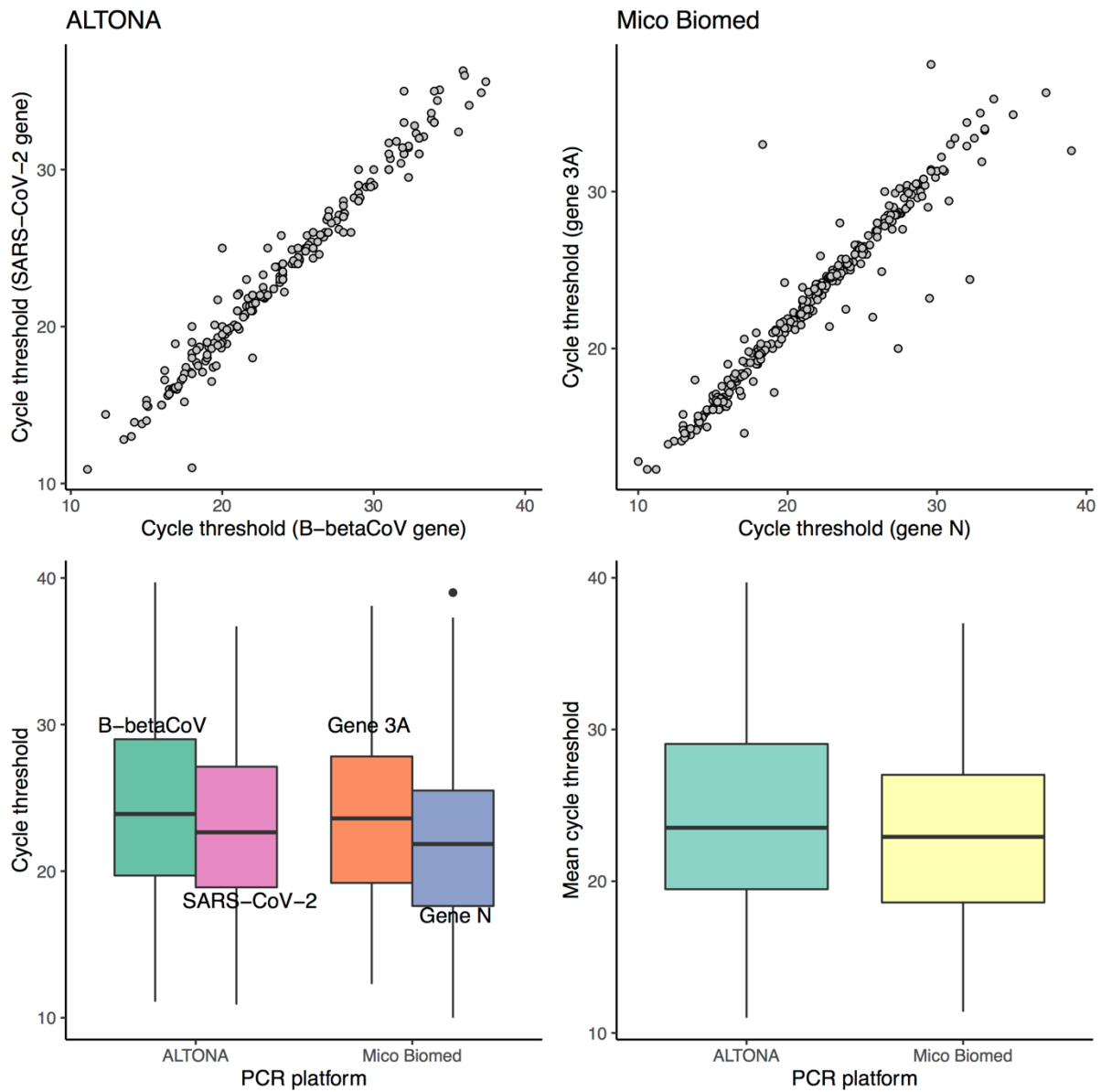


Figure S1 Comparison of cycle thresholds across PCR platforms and genes amplified. Upper two panels show the concordance between cycle thresholds for the two separate genes amplified by the ALTONA (left) and Mico Biomed (right) kits. Lower left panel – distribution of cycle thresholds by gene amplified and RT-PCR platform used. Lower right-hand panel – distribution of the mean cycle threshold (mean of cycle thresholds for separate genes) between different RT-PCR platforms.

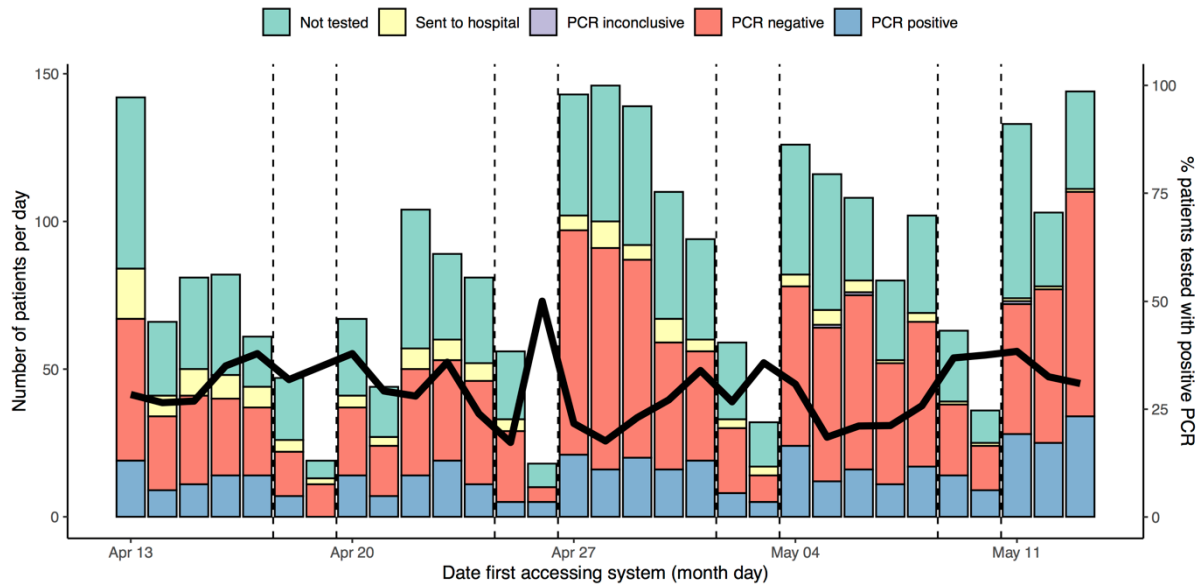


Figure S2 Time series of presentations to the Corona São Caetano platform. Dashed vertical lines denote the weekends with a reduced number of presentations. Thick black line corresponds to the right-hand y-axis: proportion of RT-PCRs performed with positive result.

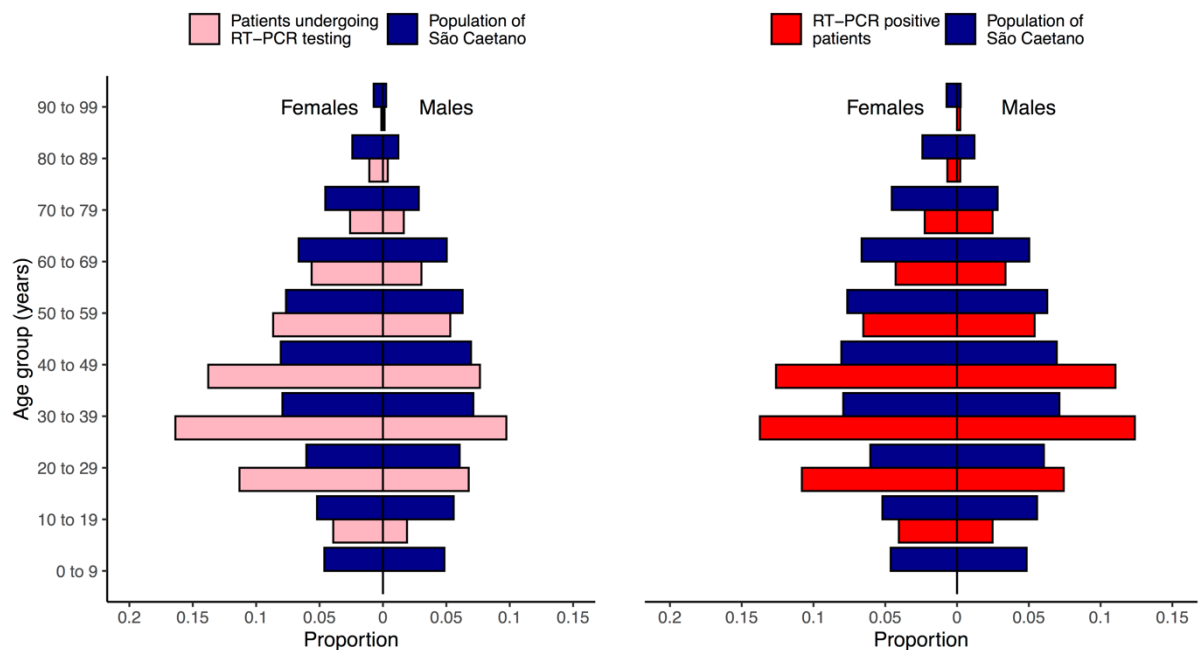


Figure S3 Age-sex distribution the city of São Caetano do Sul compared with that of patients accessing the Corona São Caetano system and being tested with RT-PCR (left-hand panel) and those testing positive for SARS-CoV-2 (right-hand panel).

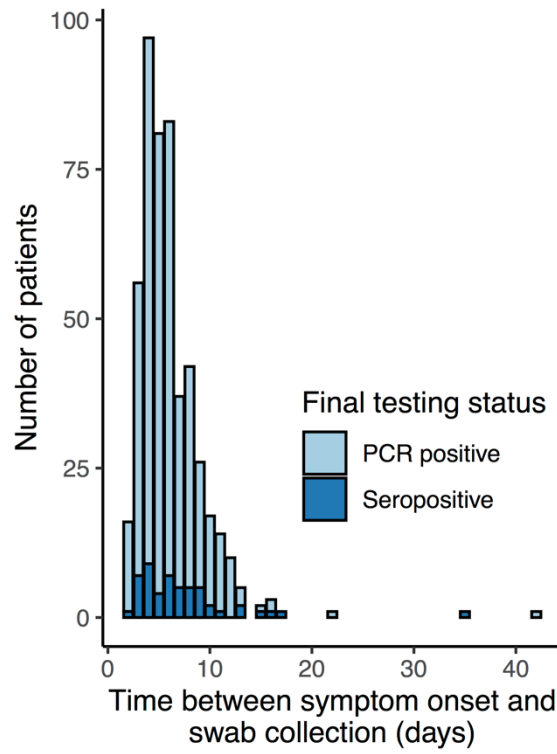


Figure S4 Histogram of delay between symptom onset and swab collection among patients with COVID-19.

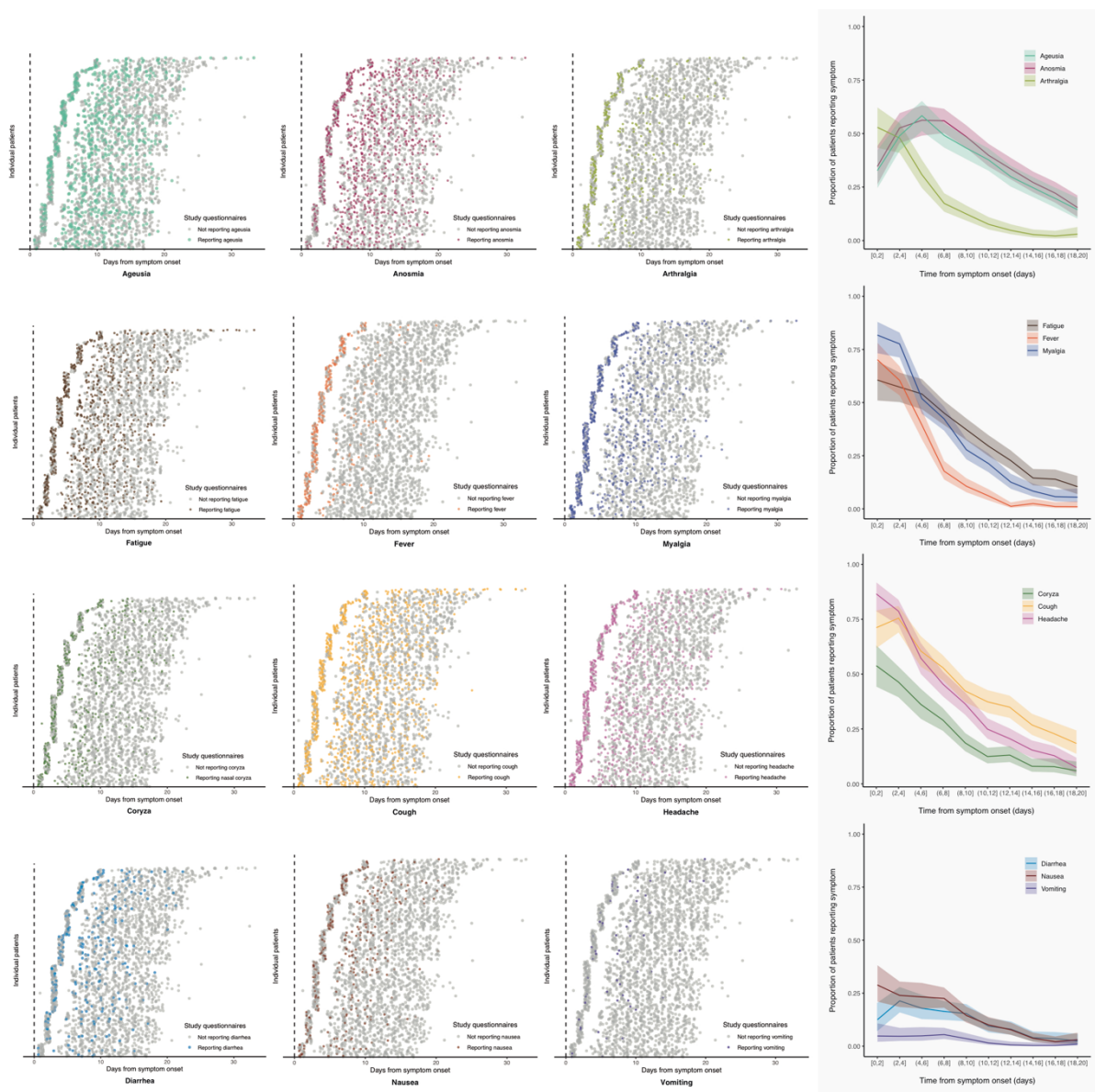


Figure S5 Left hand figures show symptoms at each follow-up questionnaire among patients testing RT-PCR positive and undergoing follow-up. Individual patients are stacked on the y-axis ordered according to the delay from symptom onset to presentation. Each point represents the response to a questionnaire and its position on the horizontal axis the time after symptom onset that the questionnaire was filled in. Grey points are questionnaires where the patient denied the presence of a given symptom. The coloured points correspond to questionnaires in which the patient reported a given symptom. The right-hand figures results from grouping the horizontal axis time into two-day windows and calculating the proportion of completed questionnaires in which each symptom was reported. The denominators for the horizontal axis groups (number of questionnaires completed within a given time window from symptom onset) are 104 at [0-2] days, 192 at (2-4], 185 at (4-6], 293 at (6-8], 338 at (8-10], 329 at (10-12], 335 at (12-14], 324 at (14-16], 280 at (16-18] and 201 at (18-20].

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5 to 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 to 6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	A – 5 B - NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 to 7
Bias	9	Describe any efforts to address potential sources of bias	7 to 8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	A – 7 to 8 B – NA C – 8 D – NA E – NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1 and page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	A – table 1 and pages 9to10 B - Table 1 and 2 legends

		(c) Summarise follow-up time (eg, average and total amount)	C – page 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7 and results section
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.