

Clinical Diagnosis of COVID-19: a Prompt, Feasible, Costless, and Highly Sensitive Diagnostic Tool for COVID-19 Based on a 1,757-Patient Cohort (The AndroCoV Clinical Scoring for COVID-19 Diagnosis).

Flavio A. Cadegiani (✉ flavio.cadegiani@unifesp.br)

Federal University of São Paulo <https://orcid.org/0000-0002-2699-4344>

Rute Alves Pereira

Centro Nacional de Pesquisa em Energia e Materiais, Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

Ricardo Ariel Zimmerman

Department of Internal Medicine, Santa Casa de Porto Alegre, RS, Brazil

Bruno Campello de Souza

Department of Management Sciences, Federal University of Pernambuco, Recife, PE, Brazil

John McCoy

Applied Biology Inc., Irvine, CA, USA. <https://orcid.org/0000-0003-1577-9910>

Carlos Gustavo Wambier

Department of Dermatology, Alpert Medical School of Brown University, Providence, RI, USA
<https://orcid.org/0000-0002-4636-4489>

Andy Goren

Applied Biology Inc., Irvine, CA, USA. <https://orcid.org/0000-0002-8190-2289>

Research Article

Keywords: COVID-19, SARS-CoV-2, pandemic, diagnosis, COVID-19 diagnosis, anosmia, ageusia, clinical diagnosis of COVID-19, rtPCR, rtPCR-SARS-CoV-2

Posted Date: January 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-135219/v2>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Clinical Diagnosis of COVID-19: a Prompt, Feasible, Costless, and Highly Sensitive Diagnostic Tool for COVID-19 Based on a 1,757-Patient Cohort (The AndroCoV Clinical Scoring for COVID-19 Diagnosis).

Flávio Adsuara Cadegiani*, MD, PhD^{1,2}, Rute Alves Pereira e Costa, PhD³, Ricardo Ariel Zimerman, MD⁴, Bruno Campello de Souza, DSc⁵, John McCoy, PhD⁶, Carlos Gustavo Wambier, MD, PhD⁷, Andy Goren, MD⁶.

¹Department of Clinical Endocrinology, Federal University of São Paulo Medical School, Sao Paulo, SP, Brazil

²Corpomatria Institute, Brasília, DF, Brazil

³Centro Nacional de Pesquisa em Energia e Materiais, Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

⁴Department of Internal Medicine, Santa Casa de Porto Alegre, RS, Brazil

⁵Department of Management Sciences, Federal University of Pernambuco, Recife, PE, Brazil

⁶Applied Biology, Inc. Irvine, CA, USA.

⁷Department of Dermatology, The Alpert Medical School of Brown University, RI, USA

***Corresponding author:**

Flavio A. Cadegiani,
Federal University of São Paulo
Rua Pedro de Toledo, 791, 13th floor
São Paulo, SP, Brazil, 04125-000
flavio.cadegiani@unifesp.br

Flavio Adsuara Cadegiani ORCID: 0000-0002-2699-4344

Rute Alves Pereira e Costa - ruteapc@yahoo.com

Ricardo Ariel Zimerman - dr.ricardoarielzimerman@gmail.com

Bruno Campello de Souza - bruno.campello@ufpe.br

John McCoy ORCID: 0000-0003-1577-9910 - johnm@appliedbiology.com

Carlos Gustavo Wambier ORCID: 0000-0002-4636-4489 - carlos.wambier@brown.edu

Andy Goren ORCID: 0000-0002-8190-2289 - andyg@appliedbiology.com

Funding sources: None

Conflicts of Interest: None declared.

IRB approval status: The study was approved by an ethics committee and registered with clinicaltrials.gov (NCT04446429), and also approved by Brazilian National Ethics Committee (Approval number 4.173.074; CAAE 34110420.2.0000.0008; Comitê de Ética em Pesquisa (CEP) of the Comitê Nacional de Ética em Pesquisa (CONEP) of the Ministry of Health (MS)) (CEP/CONEP/MS).

Manuscript word count: 3,480 words (Introduction: 950 words)

Abstract word count: 3,387 characters (with spaces)

References: 23

Tables: 0

Figures: 7

Keywords: COVID-19, SARS-CoV-2, pandemic, diagnosis, COVID-19 diagnosis, anosmia, ageusia, clinical diagnosis of COVID-19, rtPCR, rtPCR-SARS-CoV-2

List of abbreviations

PPV = positive predictive value

NPV = negative predictive value

rtPCR = real-time polymerase chain reaction

COVID-19 = infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Key Points

Question: Can a clinical diagnosis of COVID-19 be sensitive, accurate, and feasible?

Findings: The present analysis of a 1,757-subject cohort demonstrated that a clinical scoring for diagnosis of COVID-19 can provide a more sensitive and prompt diagnosis than the current gold-standard diagnostic method (rtPCR-SARS-CoV-2 test), with an accuracy above 80%.

Meaning: A clinical diagnosis of COVID-19 precludes missed diagnosis due to insufficient sensitivity due to incorrect timing of the performance of a rtPCR-SARS-CoV-2 test, reduces diagnostic costs, and avoid delays for specific therapeutic managements that can prevent the progression to more states. In addition, unlike rtPCR-SARS-CoV-2, clinical diagnosis of COVID-19 based on case-sensitive detection allows to detect COVID-19 still during viral replication stage, when potential antiviral agents can have the opportunity to demonstrate efficacy against COVID-19, showing a still underexplored possible window of opportunity in the treatment of COVID-19, in a similar manner to what is observed with the use of oseltamivir in the first three days of infection by *Influenza A*.

Abstract

Importance: A major barrier for successful therapeutic approaches to COVID-19 is the inability during the viral replication stage, when drugs with potential antiviral activity could demonstrate efficacy and preclude progression to more severe stages. Reasons that hamper an earlier diagnosis of COVID-19 include the unspecific and mild symptoms during the first stage, the delay in the diagnosis and specific management caused by the requirement of a rtPCR-SARS-CoV-2 for the diagnosis of COVID-19, and the insufficient sensitivity of the a rtPCR-SARS-CoV-2, oppositely to what is recommended for a screening test during an outbreak. More sensitive and earlier diagnostic tools for COVID-19 should be unraveled as a key strategy for an breakthrough change in the disease course and response to specific therapies, particularly those that target the blockage of viral shedding. We aimed to create an accurate, sensitive, easy-to-perform and intuitive clinical scoring for the diagnosis of COVID-19 without the need of a rtPCR-SARS-CoV-2 (termed as The AndroCoV Clinical Scoring for COVID-19 Diagnosis), resulted from a 1,757 population cohort, eo eventually encourage the management of patients with high pre-clinical likelihood of presenting COVID-19, independent of a rtPCR-SARS-COV-2 test, to avoid delays and loss of appropriate timing for potential therapies.

Materials and methods: This is a *post-hoc* analysis of clinical data prospectively collected of the Pre-AndroCoV and AndroCov Trials, that resulted in scorings for clinical diagnosis of COVID-19, based on the likelihood of presenting actual COVID-19 according to the number of symptoms, presence of anosmia, and known positive household contact. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and accuracy were calculated for subjects screened in two different periods and both periods together, for females, males and both, in a total of nine different scenarios, according to combinations between one, two, or three or more symptoms, or presence of anosmia in subjects without known positive household contacts, and no symptoms, one, two, or three or more symptoms, or presence of anosmia or ageusia in subjects with known positive household contacts. Scorings that yielded the highest pre-test probability, sensitivity and accuracy were selected.

Results: Of the 1,757 patients screened, 1,284 were diagnosed for COVID-19. The scoring that required: 1. Two or more symptoms, or anosmia or ageusia alone, for subjects without known contact; or 2. One or more symptoms, including anosmia or ageusia alone, when with known positive contacts presented the highest accuracy (80.4%) among all combinations attempted, and higher sensitivity (85.7%) than rtPCR-SARS-CoV-2 commercially available kit tests.

Conclusion: The AndroCoV Clinical Scoring for COVID-19 Diagnosis demonstrated to be a feasible, easy, costless, and sensitive diagnostic tool for clinical diagnosis of COVID-19. Because clinical diagnosis of COVID-19 avoids delays in specific treatments, particularly for high-risk populations, prevents false-negative diagnosis, and reduces diagnostic costs, this diagnostic tool should be considered as an option for COVID-19 diagnosis, at least while SARS-CoV-2 is the prevailing circulating virus and vaccination rate is below the required for herd immunity.

Introduction

While COVID-19 pandemic has affected millions of people worldwide, its early stage remains poorly elucidated [1]. Our inability to better characterize the exact pathophysiological mechanisms as well as clinical and biochemical presentation during the first days of the COVID-19 disease course may be explained by the challenging and peculiar characteristics of SARS-CoV-2 and its consequent disease (COVID-19).

First, exact transmission patterns and incubation period remains not entirely unveiled, and may vary according to viral mutations, which precludes from precise estimations of the disease timing within each infected subject. Second, symptoms in the first stage of COVID-19 are essentially unspecific, since clinical manifestations can resemble those usually present in upper respiratory tract infection (URTI), dengue fever, and/or gastrointestinal (GI) infections [2-5], reducing the chances of a subject to be clinically suspected for COVID-19 before more severe stages, unless there was contact with a household known to be positive for COVID-19. Third, researches on COVID-19 have mainly focused on approaches to reduce mortality in already severely affected COVID-19 subjects [1]. Fourth, in contrast to the first stage, the pathophysiology of the second stage of COVID-19 has been thoroughly described as being fundamentally mediated by overreactive, dysfunctional inflammatory responses, including the phenomena of cytokine storm [1]. Conversely, virological activity in the second stage becomes trivial, and does not play an important role for the typical clinical state observed during this

phase. Despite the elucidation of the prevailing pathophysiological mechanisms during the second stage, pharmacological approaches targeting antiviral effects have been persistently tested for this stage, when efficacy for improvement of COVID-19 outcomes would be unexpected, while studies with potential antiviral agents during viral replication stage, i.e., during actual early and mild COVID-19, in an outpatient setting (before hospitalization), lack [6-8]. The apparent inability to change COVID-19 course before hospitalization due to supposed lack of effective pharmacological approaches to early COVID-19 likely demotivated basic and clinical researches at this stage of the disease.

In addition to the challenges in the management of COVID-19 during its earliest stages due to the inherent characteristics of SARS-CoV-2, while many subjects are under-suspected due to lack of typical clinical characteristics of early COVID-19, whenever COVID-19 is suspected, the prerequisite of a positive real time Polymerase Chain Reaction (rtPCR) for SARS-CoV-2 (rtPCR-SARS-CoV-2) for the diagnosis of COVID-19 delays its diagnosis and specific treatments.

Although rtPCR-SARS-CoV-2 remains as the gold standard diagnostic test for COVID-19, its sensitivity demonstrates wide variations between different commercially available kit tests [9-11], and is overall insufficient for screening purposes. The overwhelming number of false negative rtPCR-SARS-CoV-2 tests [12-18] precludes the diagnosis of COVID-19, since rtPCR-SARS-CoV-2 is the only widely acceptable diagnostic tool for COVID-19, allowing progression to severe states in several undetected subjects.

The inability to detect COVID-19 in earlier stages is a major concern particularly for subjects at higher risk for severe COVID-19, including those above 60 y/o, with obesity, hypertension and type 2 diabetes mellitus (T2DM), with pulmonary preexisting conditions, males with androgenetic alopecia (AGA) [19-21] and females with hyperandrogenism [22].

Finally, it seems unfeasible to detect COVID-19 in the earliest days of the disease, since subjects are either under-suspected or their diagnosis are delayed due to the necessary positive rtPCR-SARS-CoV-2 for a definitive diagnosis. The lack of diagnostic options for early COVID-19, i.e. during the viral replication period, hampers the possibilities to test the efficacy of potential antiviral approaches to COVID-19, which would eventually be the only actual option to change disease course.

The increased time-to-diagnosis and large number of false negative rtPCR-SARS-CoV-2 tests that precluded the correct timing for testing specific antiviral approaches for COVID-19 contributed to the lack of randomized clinical trials (RCTs) conducted during actual early COVID-19. Some RCTs that claimed to have been conducted in mild, early COVID-19 subjects actually presented criteria or signs of COVID-19 in later stages in the majority of the subjects enrolled in these RCTs [6-8], allowing misleading conclusions regarding efficacy of certain approaches to early COVID-19.

It seems urgent that more sensitive and earlier methods of COVID-19 detection are developed, and could be the key for a breakthrough change in the COVID-19 disease course and response to specific therapeutic strategies, since the majority of new molecules and drug repurposing focused on their potential antiviral activity, which would find the most effective results earliest in the disease.

Indeed, in the AndroCoV Trial, we considered as suspected for COVID-19 subjects presenting any symptom, regardless of contact with a positive household. The change towards more sensitive COVID-19 detection may justify the very few complications in our RCTs, rather than the therapeutic options. This points to the fact that timing of

COVID-19 diagnosis and management may play a more important role than the which therapeutic options to be employed, as demonstrated in one of our studies [5]. Considering that: 1. Clinical or radiological criteria for other viral infections is sufficient for the diagnosis of these infections; 2. The need of a positive rtPCR-SARS-CoV-2 for the diagnosis of COVID-19 is a barrier in terms of cost and diagnostic delays; 3. Infections caused by other agents are unlikely to occur during the pandemic, when SARS-CoV-2 is the prevailing virus circulating and other infections are effectively prevented by the spread use of masks; 4. Since SARS-CoV-2 is the prevailing virus during the pandemics, a range of different and unspecific symptoms are more likely to be caused by SARS-CoV-2, rather than any other microorganism; and 5. For screening purposes, diagnostic tools more sensitive than rtPCT-SARS-CoV-2 are highly recommended, our objective was to propose a clinical scoring for the diagnosis of COVID-19 with high sensitivity, accuracy, and higher pretest probability than the rtPCT-SARS-CoV-2, validated in a large population sample, in order to encourage the management of patients with high pre-clinical likelihood of presenting COVID-19, at least during the pandemics, without the need of a confirmatory rtPCR-SARS-COV-2 result.

Materials and methods

Design

This is a *post-hoc* analysis of clinical data collected prospectively from subjects screened for COVID-19 for the Pre-AndroCoV Trial, AndroCov Trial, and without participating in any of the RCTs, but followed the same clinical protocol [2-5]. Data analyzed included the number of symptoms presented prior to the diagnosis of COVID-19, presence or absence of anosmia or ageusia, and whether there were positive household contacts before the diagnosis.

The following symptoms were actively searched and considered for the diagnosis of COVID-19: 1. Manifestations specific to COVID-19: hyposmia, anosmia, dysgeusia or ageusia; 2. Symptoms typically present in dengue fever (dengue fever-like syndrome): myalgia, arthralgia, upper back pain, conjunctival hyperemia, pre-orbital pain; 3. Symptoms of upper respiratory tract infection (URTI) (URTI-like syndrome): nasal congestion, rhinorrhea, dry cough, self-reported perception of “sinusitis”, or self-reported perception of “sore throat”; 4. Symptoms of acute gastroenteritis (GE) (GE-like syndrome): nausea, vomiting, or abdominal pain 5. Unspecific symptoms: lower back pain, leg pain, feverish, fatigue, weakness, dizziness and headache. For subjects that experimented symptoms frequently or presented prior to any suspect of COVID-19, changes in the patterns of these manifestations were required to be counted as a symptom.

A subset of 200 subjects were presumedly diagnosed for COVID-19 based on the resulting clinical scoring that demonstrated the highest accuracy and pre-test probability higher than rtPCR-SARS-CoV-2 sensitivity, and were followed prospectively, and treated accordingly. All 200 patients underwent a first rtPCR-SARS-CoV-2, and those with negative results underwent a second rtPCR-SARS-CoV-2, between 24 and 72 hours later the first one.

Scenarios for clinical diagnosis of COVID-19 were tested for precision-related statistical parameters. *Scenarios* tested for preciseness for COVID-19 diagnosis included combination between the following parameters: when one, two, or three or more symptoms were present, or when anosmia or ageusia were presented, in the

presence or absence of known positive households. *Scenarios* were tested for three periods, including two distinct periods, and a third period that encompassed the two periods evaluated distinctly from each other. The first period comprised the observational study of the AndroCoV Trial (pre-AndroCoV Trial), between May 2020 and July 2020, and the second period comprised the AndroCoV RCTs and the follow-up of untreated patients, between July 2020 and December 2020. Each *scenario* was tested for the three periods, for males, females, and overall subjects. Accuracy and sensitivity were compared for different *scenarios*, and those that disclosed the highest values were employed as the base for the development of the clinical scorings in a manner to allow the clinical diagnosis of COVID-19 when a minimum number of points was reached in a manner that reflected the *scenarios* with highest accuracy and sufficient sensitivity.

Statistical analysis

Sensitivity, specificity, pretest probability, positive and negative predictive value, accuracy, and positive likelihood ratio were calculated. For the calculations, screening of subjects without symptoms and without known positive household contacts were not considered, since there is no justification to screen for COVID-19 in this population. This article was previously posted to the ResearchGate preprint server on December 24th 2020.

Results

Subjects

In total, 1,757 subjects were screened for COVID-19, including 1,557 analyzed retrospectively and 200 that were presumedly diagnosed for COVID-19 and followed-up prospectively. Of the 1,757 subjects, 1041 were males (59.2%) and 716 were females (40.8%). In the first period, 755 patients were screened (42.7%), including 413 males (54.7% of 755 patients) and 342 females (45.3% of 755 patients). In second period, 1002 patients were screened (57.3%), including 628 males (62.7% of 1002 patients) and 374 females (37.3% of 1002 patients). No non-binary or non-cissexual subjects were screened.

Of the 1,757 subjects screening, 1,284 (73.1%) were diagnosed for COVID-19, including 585 subjects enrolled in the observational study (pre-AndroCoV trial), 94 in the spironolactone arm of the AndroCoV Trial (SPIRO AndroCoV-Trial), 138 in the dutasteride arm of the AndroCoV Trial (DUTA AndroCoV-Trial), 169 patients in the proxalutamide arm of the AndroCoV Trial (PROXA AndroCoV-Trial), and 198 subjects followed as untreated controls.

Analysis of the scenarios

The positivity rates of the rtPCR-SARS-CoV-2 tests according to the number of symptoms, presence of anosmia or ageusia, and contact with a positive household are displayed in Figure 1 (the full descriptions of scenarios with males, females, or both, in the first period, second period, or both periods together, are shown in Supplement 1). We found positivity rates above 60% when at least two symptoms not including anosmia or ageusia were present irrespective of household contact, above 80% when at least one symptom was present in subjects with known positive household contact, or three or more symptoms were present without known positive contact, and above 95% when anosmia or ageusia was present, irrespective of previous known contact with

positive households, or when three or more symptoms were present with known positive household. All patients with anosmia or ageusia and known positive household were positive for COVID-19.

Figure 2 presents the sensitivity, specificity, accuracy, PPV and NPV values to detect COVID-19 using clinical scorings in different combinations, according to the number of symptoms, presence of anosmia or ageusia, and known positive households. (Full characterization of each scenario is disclosed in Supplement 2, and the full tables with the number of subjects encompassed in each combination, as well as the number of true positives, true negatives, false positives and false negatives, and sensitivity, specificity, PPV, NPV, accuracy, and positive likelihood ratio values for each of the nine possible *scenarios* are shown in Supplement 3).

Combinations that demonstrated sensitivity and accuracy above 80% and 70% respectively, *i.e.*, a pretest probability higher than the rtPCR-SARS-CoV-2 sensitivity, were those that required: 1. One or more symptoms with or without known positive household; 2. Two or more symptoms or anosmia or ageusia without known positive household or contact with a known positive household with or without symptoms; 3. Two or more symptoms or anosmia or ageusia without known positive household or one or more symptom with known positive household; 4. Three or more symptoms or anosmia or ageusia without known positive household or contact with a known positive household with or without symptoms; 5. Three or more symptoms without known positive household or contact with a known positive household with or without symptoms; or 6. Whenever anosmia or ageusia was present, irrespective of known positive household or whenever there was contact with a positive household. Among these combinations, the combination of two or more symptoms without known contact or one or more symptoms with known positive contact presented the highest accuracy (80.4%).

Figure 3 displays the recommendations for diagnostic management in cases suspected for COVID-19 according to number of symptoms, presence of anosmia or ageusia, and contact with positive household, based on sensitivity, pre-test probability and risk for COVID-19 complications, when delays in specific approaches should be avoided. During the COVID-19 pandemic, when two or more symptoms among the listed ones or whenever anosmia or ageusia is present, irrespective of known positive contact, or when one symptom is present after contact with a positive household, COVID-19 can be diagnosed clinically, and managed accordingly. Recommendations are valid while SARS-CoV-2 remains as the prevailing circulating virus, use of masks remains forced and spread, and vaccination rate is below the expected for herd immunity.

Prospective follow-up

From the diagnostic management proposed in Figure 3, 200 subjects, including 169 from the PROXA Andro-CoV Trial and 29 not enrolled in any RCT, were screened using the AndroCoV-derived Diagnostic Management flowchart, and then followed prospectively.

Of these, 169 (84.5%) were virologically diagnosed in the first rtPCR-SARS-CoV-2, 29 (11.5%) were diagnosed in the second rtPCR-SARS-CoV-2, and two (1%) remained negative. Using two consecutive rtPCRs, the accuracy of the proposed clinical scoring combinations was 99% (Figure 4).

Clinical Scoring for COVID-19 Diagnosis

From the results presented in Figures 1 to 5, a scoring for the clinical diagnosis of COVID-19 was developed and validated, based on likelihood of a subject to present

COVID-19 according to the number of symptoms, presence of anosmia, and contact with known positive household (Figure 5). The term ‘The AndroCoV Clinical Scoring for COVID-19 Diagnosis’ was coined for this scoring. In addition, a simplified scoring with slightly lower accuracy was also developed (‘The Simplified AndroCoV Clinical Scoring for COVID-19 Diagnosis’) (Figure 6).

Characteristics more specifically and critically related to COVID-19 counted as more points. The pointing system that best matched the most accurate combination for clinical diagnosis is displayed in Figure 5 (above 80%). However, an alternative, more simple, easy-to-use, diagnostic flowchart, with acceptable sensitivity (above 70%) and accuracy (above 75%) was also presented and shown in Figure 6.

For the clinical diagnosis of COVID-19, six or more points are necessary, above which rtPCR-SARS-CoV-2 becomes unnecessary, since the pre-test probability is higher than the rtPCR-SARS-CoV-2 sensitivity.

When subjects score between four and five points, the diagnosis of COVID-19 is likely, and a rtPCR-SARS-CoV-2 is required. If the test is negative, a second rtPCR-SARS-CoV-2 should be performed between one and three days after the first test, since the sensitivity of rtPCR-SARS-CoV-2 tends to be lower in the beginning of the disease. Exceptionally, for high-risk patients, specific approaches or treatments for COVID-19 should be started independently of the rtPCR-SARS-CoV-2 result, and should only be interrupted in case two consecutive tests are negative. Scores of three points or below represent a scenario of possible but not likely COVID-19, and rtPCR-SARS-CoV-2 is only recommended for high risk subjects.

As per the scoring and the pre-test probability and accuracy, presence of two or more symptoms, or anosmia or ageusia, or any symptom when with positive household contact are the three key diagnostic possibilities for clinical diagnosis of COVID-19. The present scoring is valid while use of masks is obligatory, population vaccinated in the region of the subjects screened is below 70%, and transmission rate is > 1.0 or < 1.0 for less than four weeks.

High risk patients

The determination of which subjects were at high risk for COVID-19 was based on the medical literature, and include subjects above 60 y/o, males with androgenetic alopecia (AGA), females with hyperandrogenic states, and those presenting metabolic-related conditions, including obesity, diabetes mellitus, and hypertension (16).

Follow-up

Subjects that do not fulfill criteria for COVID-19 should be reassessed for clinical symptoms and diagnosis of household contacts on a daily basis for three days following the first day of clinical screening, particularly those with four or five points, since new symptoms may appear in subjects with actual COVID-19, raising the scoring in the following days and allowing the clinical diagnosis of COVID-19. Whenever a rtPCR-SARS-CoV-2 is indicated, subjects should be clinically reassessed irrespective of the results, since false negative rtPCR-SARS-CoV-2 is correlated with early COVID-19 and milder symptoms.

Discussion

Clinical diagnosis of COVID-19 based on a sensitive case-detection finds multiple advantages over the *desideratum* of a rtPCR-SARS-CoV-2 test, including avoidance of the non-negligible cost of a rtPCR-SARS-CoV-2 test, avoidance of further delays in potential therapeutical approaches for COVID-19, when timing may be critical for successfulness, and has few severe harms compared to multiple potential benefits of earlier diagnosis, when ‘overdiagnosis’ is preferred over ‘underdiagnosis’ in the times of COVID-19 pandemics.

With the present thorough analysis of 1,757 subjects suspected for COVID-19, we found sufficient substantiation to recommend against a mandatory rtPCR-SARS-CoV-2 for the diagnosis of COVID-19 when COVID-19 is likely. This should reduce screening expenses and therefore the inequity caused by the lack of wide access to rtPCR-SARS-CoV-2 kit tests. For patients clinically diagnosed for COVID-19 through our clinical scoring system, the performance of a rtPCR-SARS-CoV-2 test should be avoided because clinical diagnosis has demonstrated higher accuracy than commercially available rtPCR-SARS-CoV-2 kit tests. Indeed, when diagnosis of COVID-19 is clinically confirmed using the scoring, a rtPCR-SARS-CoV-2 test may lead to a misdiagnosis, rather than clarification, if performed, in case of a non-insignificant risk of a false negative result. In rtPCR-SARS-CoV-2 result is negative, which may occur in between 10% and 40% of the causes, because of its overwhelming risk of a false negative result, clinical diagnosis, rather than the test result, must be considered. To overcome false negative rtPCR-SARS-CoV-2 that may lead to loss of timely detection of subjects developing severe COVID-19, we proposed a for moderately suspected patients, a second consecutive rtPCR-SARS-CoV-2 to be repeated between 24 and 72 hours after the first test, since more than 80% of those with a first negative rtPCR-SARS-CoV-2 showed a positive result when performed again.

A clinical and early diagnosis of COVID-19 is remarkably critical for subjects at higher risk to develop severe COVID-19. In particular, elders may present lower sensitivity for a rtPCR-SARS-CoV-2 test while their clinical presentation may not always be as typical as the already unspecific symptoms usually presented in COVID-19. This population could be especially benefited from the clinical diagnosis of COVID-19 to prevent further progression to more severe states.

Additional interesting findings were unveiled by the present analysis. Approximately one in every seven subjects with COVID-19 (14.4%) had anosmia or ageusia with known household contact, which means that for every seven patients with COVID-19, six will not present anosmia and known contact with positive household. This finding finds importance to drive improvements in the policies for detection of COVID-19.

The unique characteristics of the virus including transmission patters, overall behavior, clinical course and heterogeneous presentation not only contributed to the occurrence of the COVID-19 pandemic but also to the lack of successfulness of multiple approaches. Accordingly, the peculiarities of the SARS-CoV-2 do not allow the determination of an undisputed method of clinical criteria for COVID-19 diagnosis. However, a clinical diagnostic tool based on suspecting of subjects with any sign of potential COVID-19, including symptoms, whether being specific to COVID-19 or not, contact with confirmed household, or both, may be able to detect virtually 100% of the cases. The only non-encompassed group that could miss sensitivity for COVID-19 diagnosis were asymptomatic patients without known confirmed contacts. However, this population is least likely affected and should not be tested randomly.

Shortness of breath and oxygen saturation have a particular correlation in COVID-19. The presence of shortness of breath with oxygen saturation above 92% is more likely due to anxiety induced by COVID-19 than the disease *per se*. Oppositely, ‘happy

hypoxia' is a common phenomenon observed in COVID-19 in which shortness of breath only occurs when oxygen saturation is overtly low (commonly below 80%). However, since the present clinical diagnostic tool aims to counteract the prevailing inertia and underdiagnosis that has likely led to an excessive number of deaths due to COVID-19, we recommend for the investigation of shortness of breath, regardless of oxygen saturation levels.

Similarly, although the number of symptoms alone can lead to a large number of false positive COVID-19 diagnosis, a counterbalance for the highly specific but insufficiently sensitive rtPCR-SARS-CoV-2 test in the current context of the pandemics is critically needed, when high sensitivity must be pursued.

Clinical scoring for the diagnosis of COVID-19: understanding each aspect of the scoring

The prevalence of anosmia or ageusia was lower in the present analysis than in our own data of the RCTs because part of the subjects positive for COVID-19 developed these symptoms after the diagnosis, once these symptoms tend to appear later in the early stage of the disease. However, the presence of anosmia or ageusia before the diagnosis is highly specific to COVID-19, showing alone a specificity of 98.8% for the COVID-19 diagnosis, irrespective of contact with positive households, and showed to be the most accurate sign for COVID-19 diagnosis, rather than rtPCR-SARS-CoV-2. For this reason, one between anosmia or ageusia alone scores six points in the clinical scoring proposed in the present analysis, sufficient for the clinical diagnosis of COVID-19.

Hyposmia and dysgeusia are highly specific as well, but may suffer interferences of other URTIs, and provide therefore five points. Only the rare cases of subjects with anosmia or hyposmia prior to COVID-19 should be excluded for this evaluation.

Contact with a household confirmed for COVID-19 raises the risk of COVID-19 to 50% to 60% if the positive contact was a female and the suspected subject is a male, and 20% to 30% if the positive contact was a male and the suspected case is a female, as demonstrated in our analysis of the same set of subjects (2;13-15). Although the risk of transmission is approximately two times higher when transmission occurs from female to male than the opposite direction, contact with positive households should not count as different points according to the sex of the contact. Females tend to less severely affected by COVID-19 and present fewer symptoms than males. Hence, the relative importance of a positive contact is higher for suspected females than males, which compensates the lower risk of being infected from a positive male contact.

Contact with positive working partner also raises the risk of COVID-19, although less substantially than when living with a positive contact. In addition, data on labor transmission is less explored and undisputed. For this reason, a positive working partner counts as one point only.

Except for anosmia and ageusia, since symptoms of COVID-19 are unspecific in the beginning of the disease, each symptom, not restricted to those classically related to COVID-19, counts as three points each. For matching similar sensitivity, two symptoms are sufficient for the clinical diagnosis, since the likelihood of being infected by other viruses or bacteria is low while SARS-CoV-2 is the prevailing circulating virus and use of masks is spread, since transmission of other viruses and bacteria seems to be more effectively prevented by use of masks than SARS-CoV-2 [18].

Although two unspecific symptoms allow the clinical diagnosis of COVID-19, manifestations resulted from the anxiety generated by the risk of presenting COVID-19 and the inability to differentiate between symptoms commonly experimented by

subjects and new-onset symptoms may lead to overdiagnosis of COVID-19, and should be considered for the scoring when anxiety states related to COVID-19 are detected. As shown in the scoring system, four points is sufficient to start specific approaches and treatments for high risk patients. This is particularly important for elders that present an exponential risk with aging and at the same time clinical manifestations tend to be less typical and less pronounced until progression to more severe states occurs. Reduction in the SARS-CoV-2 circulation and high vaccination rate may decrease the accuracy of the proposed clinical diagnosis. When criteria of spread use of masks and vaccination rate are no longer met, a possible increase from six to eight points for the clinical diagnosis of COVID-19, for example, should be considered, and the present scoring system should be evaluated continuously.

Implications of the clinical diagnosis of COVID-19

The earlier diagnosis of COVID-19 enabled by the present clinical scoring should have multiple consequences for the disease course and management. First, policies for contention of transmission should become more effective. Second, earlier interventions in high risk populations, that corresponds in the majority of the cases to those subjects less likely suspected for COVID-19 because of the lack of overt and usual symptoms, may allow effective and dramatic changes in the disease course and outcomes. Third, clinical diagnosis of COVID-19 allows the diagnosis still during the viral replication period, allowing the demonstration of efficacy of potential antiviral agents, unveiling the still underreported window of opportunity for antiviral approaches, similarly to what has been observed for oseltamivir for *Influenza A*, which shows efficacy only if used in the first three days of the disease [23].

Recommendations based on the findings

Whenever clinical diagnosis of COVID-19 has higher pre-test probability than rtPCR-SARS-CoV-2 test, we recommend for the presumed clinical diagnosis of COVID-19 as being sufficient. We recommend against the use of rtPCR-SARS-CoV-2 if our proposed clinical scoring indicate the diagnosis of COVID-19.

Six points in the AndroCoV Clinical Scoring for COVID-19 Diagnosis has sufficient substantiation to allow the diagnosis of COVID-19 without a rtPCR-SARS-CoV-2 test. Alternatively, three points in the simplified AndroCoV Clinical Scoring for COVID-19 Diagnosis also allows its diagnosis.

The present recommendation is a translation of the fact that subjects with no household positive contact but presenting at least two symptoms among those listed in the flowcharts (Figures 6 and 7), anosmia alone, or ageusia alone should be considered as clinically diagnosed for COVID-19. In case of positive household contact, one symptom is sufficient to fulfill criteria for clinical diagnosis of COVID-19.

Four to five points in the clinical scoring and two points in the simplified model of clinical scoring shows the diagnosis of COVID-19 to be likely, and a confirmatory rtPCR-SARS-CoV-2 is required. Nonetheless, high risk patients should not depend on the test result to start specific therapeutic approaches. Whenever rtPCR-SARS-CoV-2 is negative, subjects should be clinically reassessed daily, and a second rtPCR-SARS-CoV-2 should be performed between one and three days after the first test. For high risk patients, specific management should only be interrupted in case of two consecutive negative rtPCR-SARS-CoV-2 tests.

While SARS-CoV-2 remains as the prevailing circulating virus, the use of masks that effectively blocks bacterial and other viruses infections, and rtPCR-SARS-CoV-2 test still misses between 10% and 40% of the diagnosis of COVID-19, allowing further progress to severe states in undiagnosed subjects, the use of an easy and intuitive scoring flowchart for clinical diagnosis of COVID-19 should be considered as a first line diagnostic tool for COVID-19.

Anosmia or ageusia are symptoms highly specific to COVID-19, and, should be considered, in the current context, as pathognomonic of COVID-19 when acquired during the pandemics.

Since sensitivity to detect COVID-19 using rtPCT-SARS-CoV-2 varies according to the time of disease and viral load, clinical diagnosis should be preferred over virological methods.

The employment of rtPCT-SARS-CoV-2 as the sole diagnostic method for patients with pretest probability of COVID-19 above 80% should be considered as a misuse of the test, at least while tests do not become more sensitive than the current commercially available test kits.

The determination of the exact pretest probability, above which a rtPCT-SARS-CoV-2 test becomes unnecessary, is challenging due to the lacking data regarding viral transmission patterns and actual number of infected subjects. Hence, thresholds should not only depend on the test sensitivity and pretest and posttest probability, but also on the consequences of missing a timely diagnosis of COVID-19 with consequent delays in approaches and lower efficacy of any therapeutic strategy. Contrariwise, earlier diagnosis, even if leads to an excessive number of ‘overdiagnoses’, may find more benefits than harms in the present context.

The AndroCoV Clinical Scoring for the diagnosis of COVID-19 may be adapted for regional specificities in terms of clinical presentation, transmission rates, and potential viral mutations that occur in different regions.

The present clinical scoring for the diagnosis of COVID-19 should be valid while transmission rate is above 1.0, below 1.0 for less than 4 weeks, while masks are widely used, and when less than 70% of population is vaccinated for SARS-CoV-2.

COVID-19 was diagnosed only after the end of the viral replication stage due to two consecutive delays, of the lack of clinical suspect in the beginning of the disease, followed by awaiting time until the result of rtPCR-SARS-CoV-2 test, which precluded potential antiviral agents to demonstrate efficacy. In contrast to COVID-19 diagnosed through rtPCT-SARS-CoV-2 or chest CT scan, clinical diagnosis of COVID-19 based on a more sensitive case-detection allows earlier and timely diagnosis still during the viral replication stage. Consequently, we strongly encourage for the reassessment of the efficacy of drugs with potential antiviral activity when COVID-19 is diagnosed clinically, since the diagnosis during viral replication may represent the still underreported window of opportunity for antiviral approaches, in a similar manner of oseltamivir for *Influenza A*.

Limitations

While we based the positivity rates of COVID-19 according to clinical presentation and contact with positive household on matches with two consecutive results of commercially available rtPCR-SARS-CoV-2 kit tests, the determination of pre-test probability is imprecise due to the challenging and still largely unclear understanding of the COVID-19 transmission patterns. The present scoring system was based on SARS-

CoV-2 transmission dynamics and clinical characteristics of a specific region (Brasilia, Brazil) and may not precisely reflect patterns observed in other regions.

Conclusions

A clinical diagnosis of COVID-19 based on the presence of two or more symptoms, or anosmia alone, or ageusia alone, or one symptom when in contact with a positive household, which was translated to the AndroCoV Clinical Scoring for the Diagnosis of COVID-19, was demonstrated to be a feasible, fast, costless and sensitive diagnostic tool for the diagnosis of COVID-19.

Clinical diagnosis of COVID-19 avoids delays in specific approaches and precludes missed diagnosis due to relative low sensitivity of rtPCR-SARS-CoV-2 tests, and should be considered to become an option for COVID-19 diagnosis for public health policies.

Statements

Acknowledgments

We acknowledge the Corpometria Institute and Applied Biology Inc teams, who actively helped to screen and enroll patients, and provided full support to patients during their period of COVID-19. We also acknowledge Laboratório Exame, DASA Diagnósticos da América (Brasília, DF and São Paulo, SP, Brazil), for their efforts to provide physical space to see enrolled subjects, Corpometria Institute and Applied Biology Inc, and for providing physical space for the research with no cost, and EMS Pharmacological Industry (Campinas, SP, Brazil), for donating drugs for supportive care for the AndroCoV RCTs.

Funding statement

The funding of present study was fully supported by Corpometria Institute (Brasilia, DF, Brazil) and Applied Biology Inc (Irvine, CA, USA).

Conflict of interest statement

Authors declare no conflict of interest with any of the pharmacological interventions proposed by the present study.

Data availability

Full raw data of the observational AndroCoV trials are available at a public repository, in the following electronic address: <https://osf.io/cm4f8/>, that has been made public available. Data from the AndroCoV RCTs and for the present study are available under request to flavio.cadegiani@unifesp.br.

Ethics approval statement

The present study was approved by the Institutional Review Board (IRB) of the Ethics Committee of the National Board of Ethics Committee of the Ministry of Health, Brazil (CEP/CONEP: Parecer 4.173.074 / CAAE: 34110420.2.0000.0008), and is registered at ClinicalTrials.gov (Identifier: NCT04446429. Available at clinicaltrials.gov

<https://clinicaltrials.gov/ct2/show/NCT04446429?term=NCT04446429&draw=2&rank=1>).

Patient consent statement

Patients included for the present analysis provided a written consent exactly as approved by the Institutional Review Board (IRB) of the Ethics Committee of the National Board of Ethics Committee of the Ministry of Health, Brazil (CEP/CONEP: Parecer 4.173.074 / CAAE: 34110420.2.0000.0008), alongside with the currently ongoing randomized clinical trial (RCT) registered at ClinicalTrials.gov (Identifier: NCT04446429. Available at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT04446429?term=NCT04446429&draw=2&rank=1) (<https://clinicaltrials.gov/ct2/show/NCT04446429?term=NCT04446429&draw=2&rank=1>)).

Authorship

Authors FAC, AG, CGW and JM contributed equally for the present study. FAC, AG, CGW and JM designed the study. FAC enrolled, provided medical assistance to all patients and compiled all data, while FAC, AG, CGW and JM contributed for the analysis of the data and development of the manuscript in its current format.

References

1. Tay MZ, Poh CM, Rénia L *et al.* The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 20, 363–374 (2020). <https://doi.org/10.1038/s41577-020-0311-8>.
2. Cadegiani FA, Goren A, Wambier CG, McCoy J. Azithromycin with nitazoxanide, hydroxychloroquine or ivermectin, with or without dutasteride, for early stage COVID-19: an open-label prospective observational study in males with mild-to-moderate COVID-19 (The Pre-AndroCoV Male Trial)., 08 October 2020, PREPRINT (Version 1) available at Research Square [[+https://doi.org/10.21203/rs.3.rs-88952/v1](https://doi.org/10.21203/rs.3.rs-88952/v1)]
3. Cadegiani FA, Goren A, Wambier CG, McCoy J. Early COVID-19 Therapy with Azithromycin Plus Nitazoxanide, Ivermectin or Hydroxychloroquine in Outpatient Settings Significantly Reduced Symptoms Compared to Known Outcomes in Untreated Patients. medRxiv 2020.10.31.20223883; doi:<https://doi.org/10.1101/2020.10.31.20223883>
4. Cadegiani FA, Goren A, Wambier CG, McCoy J. An open-label prospective observational study of antiandrogen and non-antiandrogen early pharmacological approaches in females with mild-to-moderate COVID-19. The Pre-AndroCoV Female Trial. medRxiv 2020.10.05.20206870; doi:<https://doi.org/10.1101/2020.10.05.20206870>
5. Cadegiani FA, Goren A, McCoy J *et al.* Hydroxychloroquine, nitazoxanide and ivermectin have similar effects in early COVID-19: a head-to-head comparison of the Pre-AndroCoV Trial., 29 October 2020, PREPRINT (Version 1) available at Research Square [[+https://doi.org/10.21203/rs.3.rs-98106/v1](https://doi.org/10.21203/rs.3.rs-98106/v1)]. <https://www.researchsquare.com/article/rs-98106/v1>

6. Cadegiani FA. Repurposing existing drugs for COVID-19: an endocrinology perspective. *BMC Endocr Disord*. 2020 Sep 29;20(1):149. doi: 10.1186/s12902-020-00626-0. PMID: 32993622; PMCID: PMC7523486.
7. Cadegiani FA, Wambier CG, Goren A. Spironolactone: An Anti-androgenic and Anti-hypertensive Drug That May Provide Protection Against the Novel Coronavirus (SARS-CoV-2) Induced Acute Respiratory Distress Syndrome (ARDS) in COVID-19. *Front Med (Lausanne)*. 2020 Jul 28;7:453. doi: 10.3389/fmed.2020.00453.
8. Cadegiani FA, Goren A, Wambier CG. Spironolactone may provide protection from SARS-CoV-2: Targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RAAS). *Med Hypotheses*. 2020 Jul 16;143:110112. doi: 10.1016/j.mehy.2020.110112.
9. Böger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19 [published online ahead of print, 2020 Jul 10]. *Am J Infect Control*. 2020;S0196-6553(20)30693-3. doi:10.1016/j.ajic.2020.07.011
10. Zhang ZL, Hou YL, Li DT, Li FZ. Diagnostic efficacy of anti-SARS-CoV-2 IgG/IgM test for COVID-19: A meta-analysis. *J Med Virol*. 2020 Jun 22;10.1002/jmv.26211. doi: 10.1002/jmv.26211.
11. Skittrall JP, Wilson M, Smielewska AA, et al. Specificity and positive predictive value of SARS-CoV-2 nucleic acid amplification testing in a low-prevalence setting [published online ahead of print, 2020 Oct 14]. *Clin Microbiol Infect*. 2020;S1198-743X(20)30614-5. doi:10.1016/j.cmi.2020.10.003
12. Di Paolo M, Iacovelli A, Olmati F, et al. False-negative RT-PCR in SARS-CoV-2 disease: experience from an Italian COVID-19 unit. *ERJ Open Res*. 2020;6(2):00324-2020. Published 2020 Jul 13. doi:10.1183/23120541.00324-2020
13. Brogna B, Bignardi E, Brogna C, et al. Typical CT findings of COVID-19 pneumonia in patients presenting with repetitive negative RT-PCR [published online ahead of print, 2020 Sep 19]. *Radiography (Lond)*. 2020;S1078-8174(20)30199-1. doi:10.1016/j.radi.2020.09.012
14. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA*. 2020 May 12;323(18):1843-1844. doi: 10.1001/jama.2020.3786. PMID: 32159775; PMCID: PMC7066521.
15. Pakdemirli E, Mandalia U, Monib S. Positive Chest CT Features in Patients With COVID-19 Pneumonia and Negative Real-Time Polymerase Chain Reaction Test. *Cureus*. 2020 Aug 22;12(8):e9942. doi: 10.7759/cureus.9942. PMID: 32850265; PMCID: PMC7444987.
16. Woloshin S, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2 Infection - Challenges and Implications. *N Engl J Med*. 2020 Aug 6;383(6):e38. doi: 10.1056/NEJMp2015897. Epub 2020 Jun 5. PMID: 32502334.
17. Long DR, Gombor S, Hogan CA, Greninger AL, O'Reilly Shah V, Bryson-Cahn C, Stevens B, Rustagi A, Jerome KR, Kong CS, Zehnder J, Shah NH, Weiss NS, Pinsky BA, Sunshine J. Occurrence and Timing of Subsequent SARS-CoV-2 RT-PCR Positivity Among Initially Negative Patients. medRxiv [Preprint]. 2020 May 8:2020.05.03.20089151. doi: 10.1101/2020.05.03.20089151. Update in: *Clin Infect Dis*. 2020 Jun 07;: PMID: 32511542; PMCID: PMC7274223.
18. Zhang Y, Wang C, Han M, Ye J, Gao Y, Liu Z, He T, Li T, Xu M, Zhou L, Zou G, Lu M, Zhang Z. Discrimination of False Negative Results in RT-PCR Detection of SARS-CoV-2 RNAs in Clinical Specimens by Using an Internal Reference. *Virol Sin*. 2020

Aug 4:1–10. doi: 10.1007/s12250-020-00273-8. Epub ahead of print. Erratum in: *Virology*. 2020 Sep 21; PMID: 32749593; PMCID: PMC7399361.

19. McCoy J, Wambier CG, Herrera S, Vaño-Galván S, Gioia F, Comeche B, Ron R, Serrano-Villar S, Iwasow RM, Tayeb MA, Cadebiani FA, Mesinkovska NA, Shapiro J, Sinclair R, Goren A. Androgen Receptor Genetic Variant Predicts COVID-19 Disease Severity: A Prospective Longitudinal Study of Hospitalized COVID-19 Male Patients. *J Eur Acad Dermatol Venereol*. 2020 Sep 25.
20. Wambier CG, Mehta N, Goren A, Cadebiani FA. COVID-19, androgens, and androgenic alopecia. *Dermatological Reviews*. 2020; 1- 8. <https://doi.org/10.1002/der2.50>
21. Wambier CG, Vaño-Galván S, McCoy J, Pai S, Dhurat R, Goren A, Androgenetic alopecia in COVID-19: compared to age-matched epidemiologic studies and hospital outcomes with or without the Gabrin sign. *J Am Acad Dermatol*. 2020, doi: <https://doi.org/10.1016/j.jaad.2020.07.099>.
22. Cadebiani FA, Lim RK, Goren A, McCoy J, Situm M, Kovacevic M, Vaño Galván S, Sinclair R, Tosti A, Wambier CG. Clinical symptoms of hyperandrogenic women diagnosed with COVID-19. *J Eur Acad Dermatol Venereol*. 2020 Oct 21. doi: 10.1111/jdv.17004. Epub ahead of print. PMID: 33089570.
23. Ishiguro N, Oyamada R, Nasuhara Y, Yamada T, Miyamoto T, Imai S, Akizawa K, Fukumoto T, Iwasaki S, Iijima H, Ono K. Three-day regimen of oseltamivir for postexposure prophylaxis of influenza in wards. *J Hosp Infect*. 2016 Oct;94(2):150-3. doi: 10.1016/j.jhin.2016.05.012. Epub 2016 May 25. PMID: 27346624.

Figure legend.

Figure 1. Positivity rates for rtPCR-SARS-CoV-2 according to clinical characteristics and contact with positive household.

Figure 2. AndroCoV Clinical Diagnostic Scoring combinations.

Figure 3. Diagnostic management for COVID-19 according to clinical characteristics and known household contact.

Figure 4. Simplified application of the presumed diagnosis of COVID-19.

Figure 5. AndroCoV Clinical COVID-19 diagnosis.

Figure 6. Simplified AndroCoV Clinical COVID-19 diagnosis to be employed for screening in general population.

Supplement material - legend.

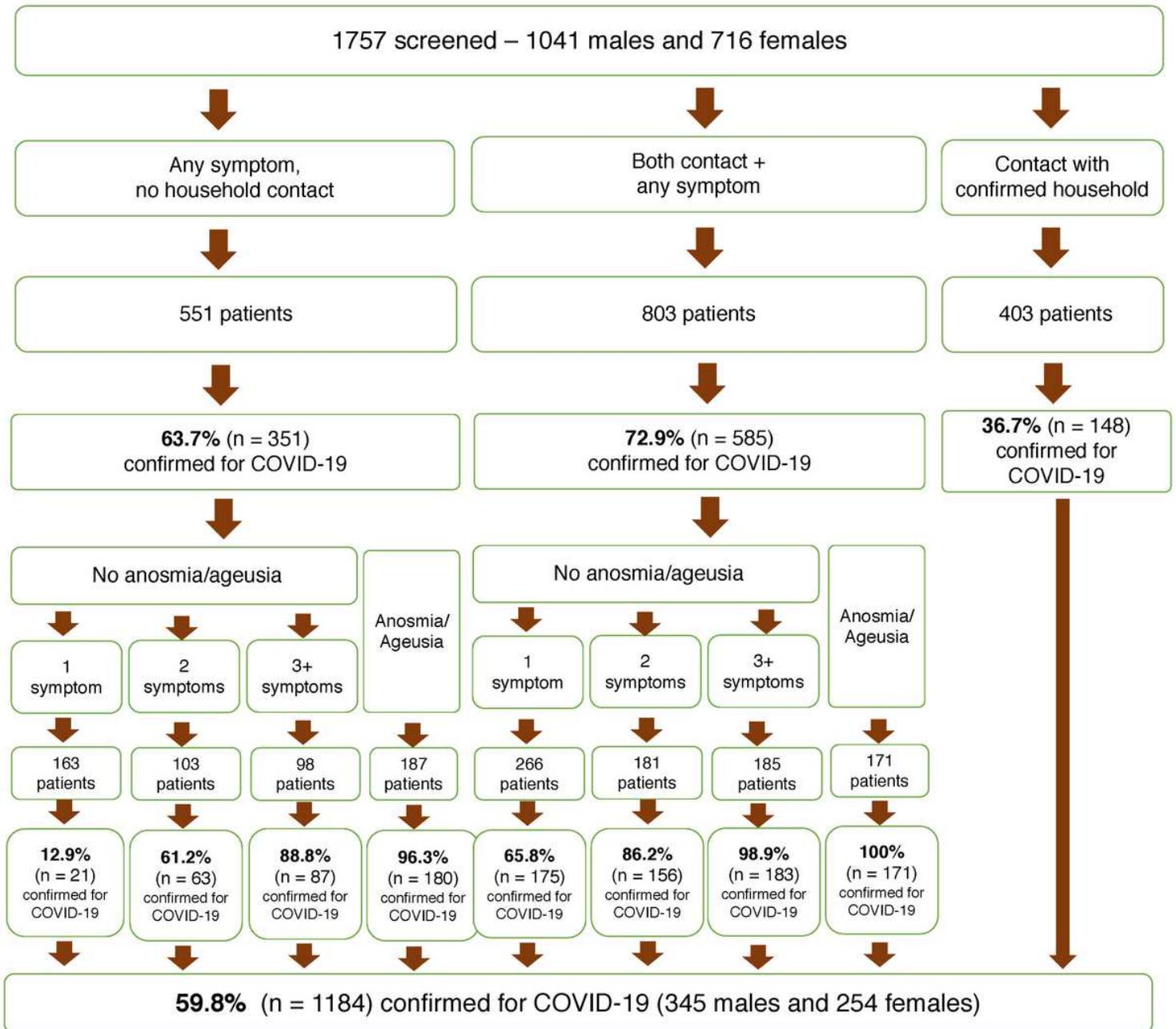
Supplement 1. Positivity rates for rtPCR-SARS-CoV-2 according to clinical characteristics, sex, and period.

Supplement 2. Descriptive AndroCoV Clinical Diagnostic Scoring combinations.

Supplement 3. Illustrative AndroCoV Clinical Diagnostic Scoring combinations.

Figures

Figure 1. Positivity rates for rtPCR-SARS-CoV-2 according to clinical characteristics and contact with positive household.



RCT = Randomized clinical trials (AndroCoV Trials)
 Observational = Pre-AndroCoV trials

Figure 1

Positivity rates for rtPCR-SARS-CoV-2 according to clinical characteristics and contact with positive household.

Figure 2. AndroCoV Clinical Diagnostic Scoring combinations.

		Positive household contact				
		No anosmia/ageusia				Anosmia/ Ageusia
		Asymptomatic	1 symptom	2 symptoms	3+ symptoms	
No household contact	Asymptomatic	NOT SCREENED				
	No anosmia/ageusia	1757 screened 59.4% PPV n/a NPV 100% sensitivity 0% specificity 67.4% accuracy	1354 screened 76.5% PPV 63.3% NPV 87.5% sensitivity 44.5% specificity 73.5% accuracy			
	1 symptom	1594 screened 73.0% PPV 87.1% NPV 98.2% sensitivity 25.0% specificity 74.3% accuracy	1191 screened 85.2% PPV 70.1% NPV 85.7% sensitivity 69.3% specificity 80.4% accuracy	925 screened 90.8% PPV 58.7% NPV 70.9% sensitivity 85.2% specificity 75.6% accuracy		
	2 symptoms	1491 screened 73.8% PPV 68.4% NPV 92.9% sensitivity 31.8% specificity 73.0% accuracy	1088 screened 78.3% PPV 65.3% NPV 72.0% sensitivity 76.3% specificity 73.4% accuracy	822 screened 82.4% PPV 56.5% NPV 57.2% sensitivity 92.4% specificity 68.6% accuracy	641 screened 81.3% PPV 49.6% NPV 44.0% sensitivity 96.5% specificity 61.1% accuracy	
	3+ symptoms	1393 screened 72.7% PPV 53.0% NPV 85.6% sensitivity 33.7% specificity 68.6% accuracy	990 screened 87.4% PPV 58.4% NPV 73.1% sensitivity 78.2% specificity 74.7% accuracy	724 screened 95.3% PPV 52.2% NPV 58.3% sensitivity 94.1% specificity 69.9% accuracy	543 screened 98.3% PPV 46.6% NPV 45.1% sensitivity 98.4% specificity 62.5% accuracy	358 screened 98.0% PPV 40.4% NPV 29.6% sensitivity 98.8% specificity 52.2% accuracy
Anosmia/ Ageusia						
Excluded for screening when without known household contact	1206 screened 69.1% PPV 36.3% NPV 70.4% sensitivity 34.9% specificity 58.8% accuracy	803 screened 85.3% PPV 47.7% NPV 57.8% sensitivity 79.4% specificity 64.9% accuracy	537 screened 95.0% PPV 44.7% NPV 43.1% sensitivity 79.4% specificity 60.1% accuracy	356 screened 99.4% PPV 40.7% NPV 29.9% sensitivity 99.6% specificity 52.6% accuracy	171 screened 100.0% PPV 36.1% NPV 14.4% sensitivity 100% specificity 42.3% accuracy	

PPV = Positive predictive value
NPV = Negative predictive value

Figure 2

AndroCoV Clinical Diagnostic Scoring combinations.

Figure 3. Diagnostic management for COVID-19 according to clinical characteristics and known household contact.

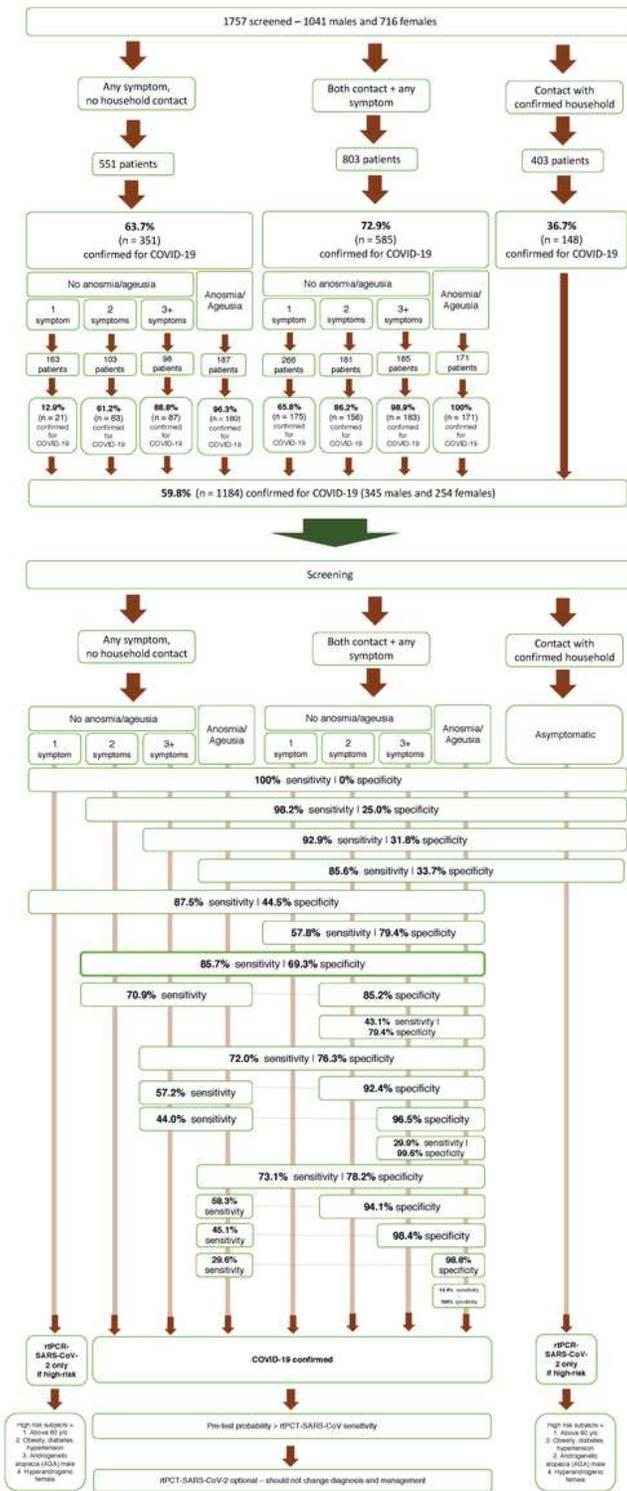


Figure 3

Diagnostic management for COVID-19 according to clinical characteristics and known household contact.

Figure 4. Simplified application of the presumed diagnosis of COVID-19.

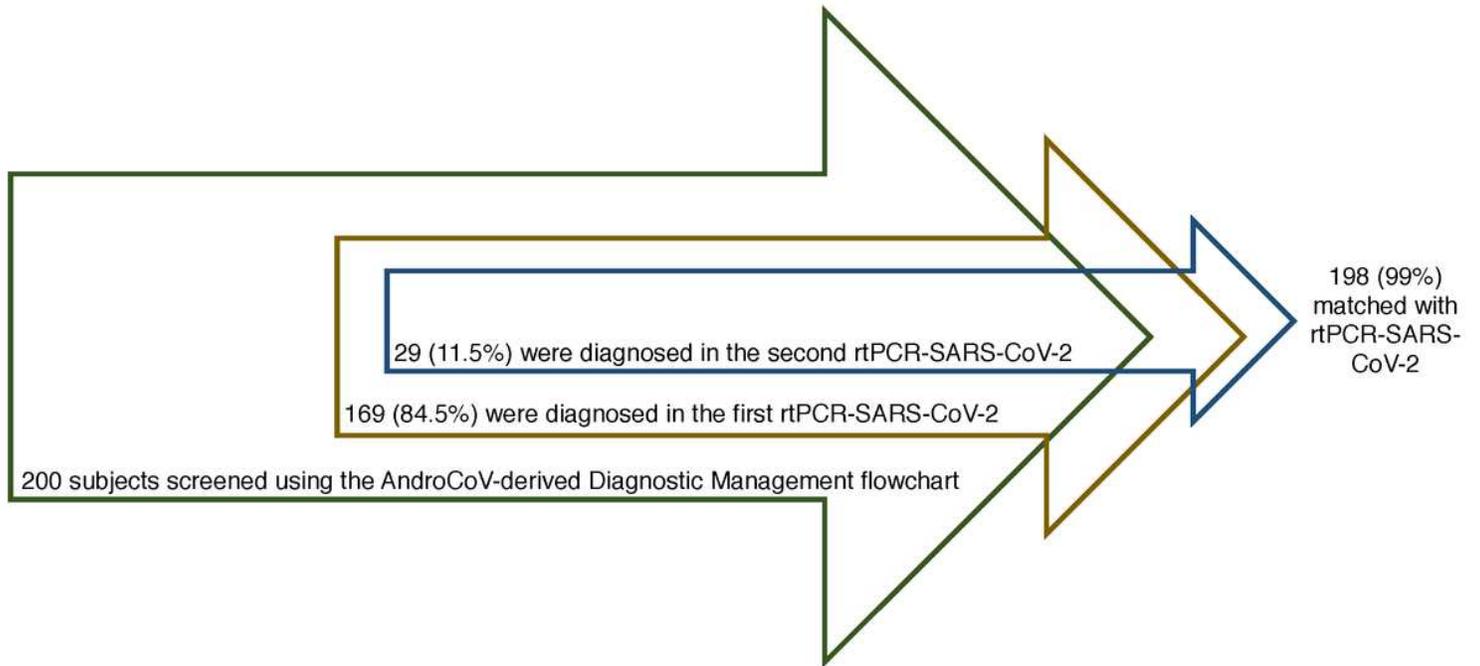


Figure 4

Simplified application of the presumed diagnosis of COVID-19.

Figure 5. AndroCoV Clinical Scoring for COVID-19 Diagnosis

AndroCoV Clinical Scoring for COVID-19 Diagnosis

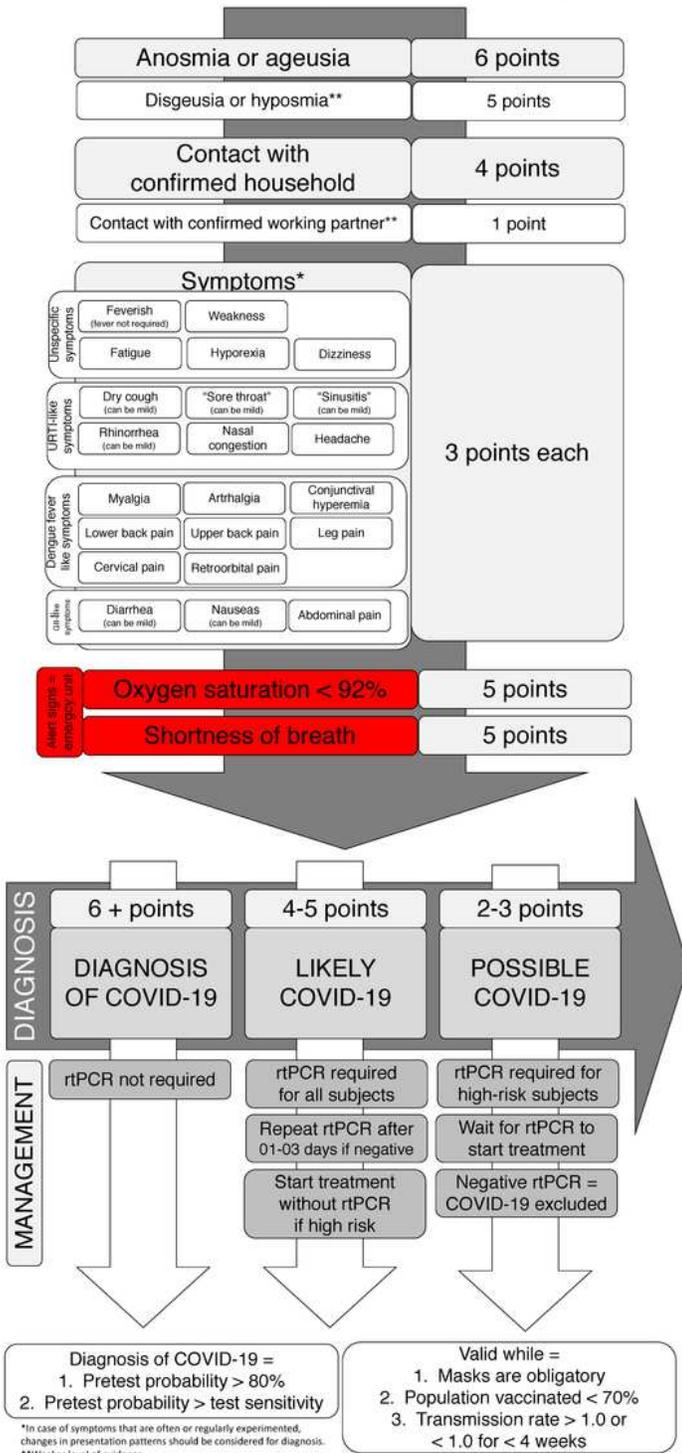


Figure 5

AndroCoV Clinical COVID-19 diagnosis.

Figure 6 Simplified AndroCoV Clinical COVID-19 diagnosis to be employed for screening in general population.

AndroCoV Clinical Scoring for COVID-19 Diagnosis

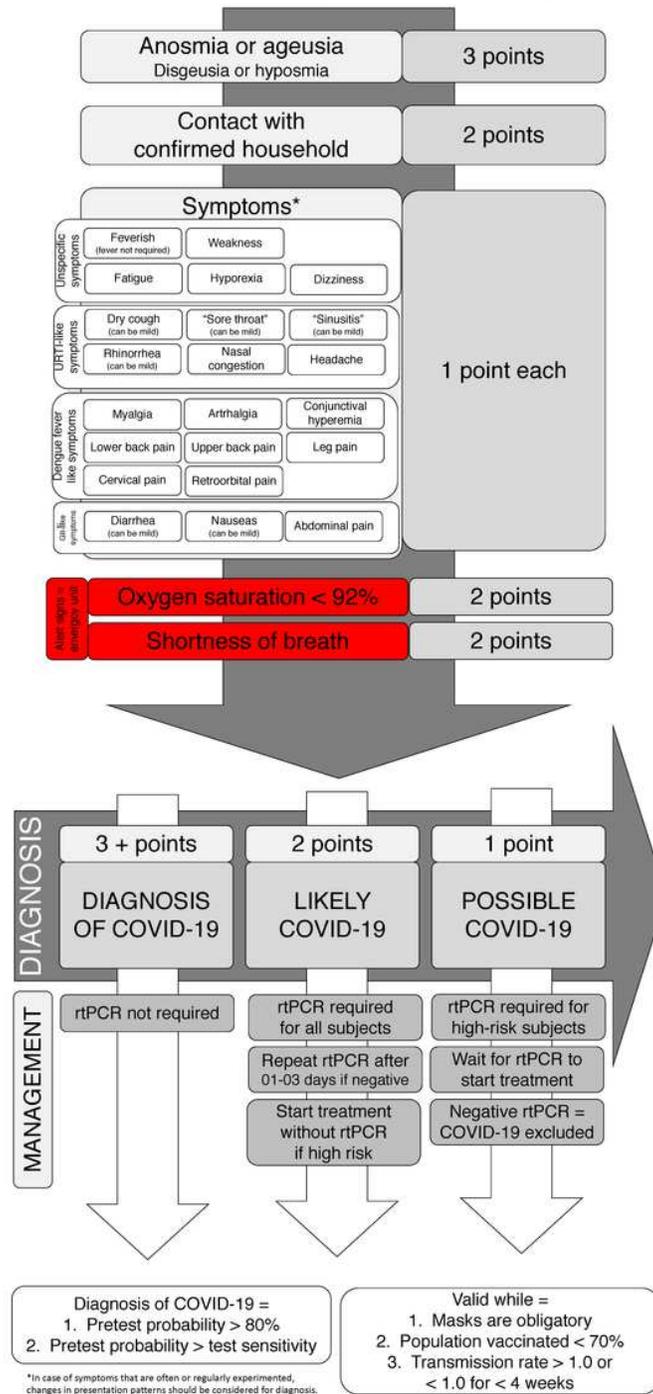


Figure 6

Simplified AndroCoV Clinical COVID-19 diagnosis to be employed for screening in general population.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplement1.PositivyratesforrtPCRSARSCoV2accordingtoclinicalcharacteristicssexandperiod..png](#)
- [Supplement2.DescriptiveAndroCoVClinicalDiagnosticScoringcombinations..png](#)
- [Supplement3.IllustrativeAndroCoVClinicalDiagnosticScoringcombinations..png](#)