

Management of Oligosymptomatic Patients with Respiratory Infection in the Era of SARS-Cov2. Experience from Rural German General Practitioners and Proposition of a New Screening Model

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Abstract

Background: Covid-19 is causing a pandemic and forces physicians to restructure their daily work. We want to share our successful experience in the outpatient management of potentially infected patients with colleagues from other countries.

Methods: We analyzed all patients with respiratory symptoms reporting to our three rural general practitioner (GP) offices in North Rhine Westphalia, Germany, from 27.01-20.04.2020 (n=489 from a total of 6090 patients). A history of symptoms was taken at the doorstep following a specific questionnaire. Patients with respiratory symptoms were examined in a separated isolation area, while the others were allowed to enter the office.

Results: Eighty patients (16.36%, mean age: 47.03years+18.08) were sent to a nasopharyngeal smear following the screening algorithm of the Robert-Koch Institute, Berlin, Germany. 5 patients (6.25%) turned out to be positive, 4 of which had established risk factors for COVID-19. Overall, the most common symptoms were cough (83.75%), sore throat (71.25%), as well as myalgia and fatigue (66.25%). The most common diagnoses were rhinopharyngitis (37.22%) and acute bronchitis (30.27%). Clinically, it was impossible to differentiate ordinary respiratory infections from COVID-19 patients in our low-risk population, although a *sore throat* was more common in positively tested patients (80% vs. 12%). None of our employees called in sick during this period, which emphasizes the efficacy and safety of our screening methods. We suggest a novel risk score integrating patient history, symptoms, pulmonary ultrasound and environmental risks to stratify patients as candidates for SARS-Cov2-PCR.

Conclusion: A clinical distinction between ordinary respiratory infections and COVID-19 is not possible in a low-risk population. Our model to prevent unprotected physical contact, screen patients in front of the office with protective equipment, and to examine respiratory infections in separated areas works in the GP setting without overt health risks for employees. Thus, this approach should be used as a GP standard to uphold patient care without major health risks for the personnel. We introduce a new combinatorial scoring model to assess COVID-19 probability in the GP setting.

Background

Originating from Wuhan, China, coronavirus disease 2019 (COVID-19) has spread around the world as a pandemic and created enormous health, political, economical problems(1, 2)with 3366714 confirmed cases worldwide and 239345 deaths as per 02.05.2020(3).

Clinical predictors of mortality have been suggested from a cohort of patients from Wuhan(4–6) and recommendations for outpatient(7) and inpatient care(6) as well as intensive care treatment(8) have been proposed. Patients admitted to intensive care units are older, and tend to have higher leukocyte counts, D-Dimers, LDH, creatinine and troponin levels(5). Elevated troponin as a marker for myocardial injury heralds a poor prognosis(9).

The most common symptoms, depending on the time windows during the course of infection, are symptoms associated with respiratory diseases, such as fever, cough, sore throat, headache, chills, fatigue and myalgia, smell and taste dysfunction and gastrointestinal problems(10, 11), but recently more severe cases have been associated with neurological symptoms, such as acute cerebral vascular disease, skeletal muscle injury and impaired consciousness(12). Perniosis- like skin symptoms may also be present(13, 14). Risk factors for more severe cases of COVID-19 are hypertension, coronary artery disease, immunosuppression, chronic lung disease(15).

Less severe cases often present to the general practitioner (GP) in the outpatient setting, which requires precautions to avoid infection in medical personnel. In Germany, testing for SARS-Cov2 infection has been widely established(16, 17). Additionally, containment as a means to reduce exponential growth has been implemented at an early stage(18), which

may account for the relatively low German case-mortality rate (4.1%) compared to other European countries(19, 20). As per 02.05.2020 164077 patients had been infected und 6736 had died in Germany(3). Furthermore, standard and elective examinations have been postponed to limit physical physician-patient contact to the necessary minimum(21).

The German government as well as national and federal medical institutions have made considerable efforts to prevent less critical but potentially infective patients from showing up in the GP office by installing telephone and video conferences to provide medical council without physical contact. In practice, however, concerned patients fearing to be infected keep showing up and need to be screened in isolation rooms in case of symptoms suggestive of COVID-19. This requires office re-organisation and efforts to receive personal protective equipment (PPE) which, however, has been difficult to get for some time.

The German Robert Koch Institute (RKI) has issued recommendations for COVID-19 screening in the outpatient setting(22). However, differentiation between oligosymptomatic COVID-positives and ordinary infections seems almost impossible. Here, we present real-life data from our three large rural GP offices in North Rhine Westphalia, Germany, between January 27th and April 20th 2020 to demonstrate the difficulty to filter oligosymptomatic patients with low pre-test probability but to aim at the same time to decipher a new window of opportunity to better stratify highly suspected infected individuals. Our aim is to share our experience as GP's with colleagues from other countries, where infection rates are still rising and viral doubling time is very low.

Methods

We analyzed data from our three GP offices in rural North Rhine Westphalia, Germany, from 27.01.2020 until 20.04.2020 and selected all patients reporting symptoms of respiratory tract infection. According to the current RKI guidelines to screen patients for potential COVID-19 infection, we either chose to send patients to a nasopharyngeal smear or to treat them conservatively. Due to limited availability of smear testing in our rural area we are not able to perform the smears in our office, but had to transfer patients to the local hospital. Patients were put into isolation until the results of the tests are available. We have made satisfactory experience with the following procedures and algorithm: One GP with PPE consisting of a gown, goggles, caps, gloves and an FFP (filtering face piece)-3 mask screens every patient in front of our office asking the following questions:

1. Are you currently suffering from a cough or sore throat?
2. Have you measured a temperature > 38.5 degrees Celsius in the last 5 days?
3. Have you had direct contact to a person tested positive for COVID-19?
4. Are you employed in a medical profession?
5. Are you suffering from loss of smell or taste?
6. Are you suffering from myalgia, fatigue and headache?
7. Are you suffering from diarrhea or vomiting?
8. Are you suffering from immunosuppressive disease?

The question: „Have you been travelling to a risk area in the last 2 weeks (initially, we explicitly named the risk areas)?“ has been withdrawn, because contact restrictions have restrained travel.

If two of these questions were answered with *yes*, patients were directed to an isolation room, which was supplied with all basic medical devices to provide a fast clinical exam. Patient history was documented vigorously. In case of persisting suspicion following the diagnostic algorithm of the RKI for COVID-19(23), patients were directly referred to our smear centre. If an ordinary respiratory infection was given as a diagnosis, people were instructed on the general

hygiene recommendations and treated conservatively. Only patients with symptoms not suggestive of respiratory disease were allowed to enter the regular office.

Results

The mean age of all tested patients (n = 80) was 47.03 years +-18.08 (mean age of positively tested, 50.20years+-13.76; n = 5), while the mean age of all symptomatic patients (n = 489) was 52.69years+-14.75. Symptoms across all respiratory infections are provided in Table 1; Fig. 1 illustrates data collection. 13.75% of patients with respiratory tract infections were recent returners from currently risk areas of transmission defined by the RKI (mainly from Austria and the Netherlands). 8.75% had significant (at least 15 minutes) contact with a person tested positive for COVID-19.

Table 1
Symptoms of patients with respiratory tract infections

Symptoms in all patients (n = 489)	Symptoms- negatively tested (n = 75)	Symptoms- positively tested (n = 5)
Cough n = 407 (83.23%)	Cough n = 63 (84.00%)	Cough n = 4 (80.00%)
Sore throat n = 70 (14.35%)	Sore throat n = 9 (12.00%)	Sore throat n = 4 (80.00%)
Myalgia and fatigue n = 309 (63.19%)	Myalgia and fatigue n = 50 (66.67%)	Myalgia and fatigue n = 3 (60.00%)
Headache n = 158 (32.31%)	Headache n = 22 (29.33%)	Headache n = 2 (40.00%)
Rhinitis n = 245 (50.10%)	Rhinitis n = 20 (26.67%)	Rhinitis n = 3 (60.00%)
Fever > 38.5 degree Celsius n = 70 (14.31%)	Fever > 38.5 degree Celsius n = 9 (12.00%)	Fever > 38.5 degree Celsius n = 1 (20.00%)
Smell and taste dysfunction n = 51 (10.43%)	Smell and taste dysfunction n = 9 (12.00%)	Smell and taste dysfunction n = 0 (0.00%)
Chills n = 69 (14.11%)	Chills n = 8 (10.67%)	Chills n = 1 (20.00%)
Earache n = 41 (8.38%)	Earache n = 4 (5.33%)	Earache n = 0 (0.00%)

Table 1. Symptoms associated with respiratory tract infection between 27.01.2020 and 20.04.2020 in all patients (n = 489), patients negatively (n = 75) and positively tested (n = 5).

By far the most common diagnoses in the entire clientel were rhinopharyngitis and acute bronchitis; pneumonia was less often found (Table 2.). Due to the low number of positive tests we did not perform mean comparison tests, data were depicted as absolute values and percentages.

Table 2
Diagnoses of patients reporting with respiratory tract infections

Diagnosis in all patients (n = 489)	Diagnosis- negatively tested(n = 75)	Diagnosis- positively tested (n = 5)
Rhinopharyngitis: n = 182 (37.22%)	Rhinopharyngitis n = 23 (30.67%)	Rhinopharyngitis n = 2 (40%)
Acute bronchitis n = 148 (30.27%)	Acute bronchitis n = 25 (33.33%)	Acute bronchitis n = 3 (60%)
Acute sinusitis n = 52 (10.64%)	Acute sinusitis n = 19 (25.33%)	Acute sinusitis n = 0 (0%)
Tonsillitis n = 34 (6.95%)	Tonsillitis n = 3(4.00%)	Tonsillitis n = 0 (0%)
Otitis media n = 34 (6.95%)	Otitis media n = 2(2.67%)	Otitis media n = 0 (0%)
Pneumonia n = 31 (6.33%)	Pneumonia n = 3(4.00%)	Pneumonia n = 0 (0%)
Laryngitis n = 8 (1.64%)	Laryngitis n = 0 (0%)	Laryngitis n = 0 (0%)

Table 2. Distribution of diagnoses in all patients reporting with signs of respiratory infection (n = 489), patients negatively tested (n = 75) and positively tested (n = 5) between 27.01.2020 and 20.04.2020. A diagnosis of pneumonia was established in case of significant auscultation and one additional symptom, such as fever or productive sputum. Chest X-ray was not available.

From 80 patients who met the RKI criteria(23) and were sent to the smear centre, only 5 turned out to be positive. The most common symptoms in positive patients were cough (4/5), sore throat (4/5), myalgia and fatigue (3/5) and rhinitis (3/5). Headache (2/5), chills (1/5) and fever (1/5) were less common. None of these positively tested patients suffered from smell or taste dysfunction or earache. Table 3 illustrates the comorbidities of positively and negatively tested patients. In both groups no skin alterations were detected.

Table 3
Prevalence of comorbidities in patients tested for SARS Cov2

Tested positive	Tested negative
Diabetes: n = 2 (40.00%)	Diabetes: n = 2 (2.67%)
Arterial hypertension: n = 3 (60.00%)	Arterial hypertension: n = 23 (30.67%)
Hypothyroidism: n = 0 (0%)	Hypothyroidism: n = 11 (14.67%)
Immunosuppression: n = 1 (20.00%)	Immunosuppression: n = 6 (8.00%)
Atrial fibrillation: n = 1 (20.00%)	Atrial fibrillation: n = 5 (6.67%)
Coronary artery disease: n = 0 (0%)	Coronary artery disease: n = 3 (4.00%)
Lung disease: n = 2 (40.00%)	Lung disease: n = 10 (13.33%)
Depression: n = 1 (20.00%)	Depression: n = 11 (14.67%)
Chronic kidney disease: n = 0 (0%)	Chronic kidney disease: n = 2 (2.67%)
RAAS inhibitors: n = 2 (40.00%)	RAAS inhibitors: n = 15 (20.00%)
Oral anticoagulation: n = 1 (20.00%)	Oral anticoagulation: n = 5 (6.67%)
Platelet Inhibitors: n = 1 (20.00%)	Platelet Inhibitors: n = 1 (1.33%)

Table 3. Prevalence of comorbidities in patients tested positive (n = 5) and negative (n = 75) for COVID-19. Immunosuppression was defined as autoimmune disease or cancer in patient history. Lung disease was defined as chronic obstructive lung disease or asthma under medical treatment. Chronic kidney disease was defined as a glomerular filtration rate (GFR) < 60 ml/min for at least three months. Oral anticoagulants included vitamin K-antagonists (VKA) and new oral anticoagulants (NOAK.), platelet inhibitors included Aspirine, Clopidogrel, Ticagrelor or Prasugrel. RAAS inhibitors: renin-angiotensin-aldosterone system inhibitors.

Discussion

We analyzed data from our three GP offices in rural Germany between the onset of Covid-19 in our country on 27.01.2020 until 20.04.2020. The mean age of our patients was 47.03 years, which is quite young considering that mortality seems to increase in COVID-19 patients beyond 65 years; patients less than 65 with little predisposing factors may be at a low risk of severe disease(5). Although we also treat more elderly patients in our offices, this observation may mean that oligosymptomatic patients directly stay at home to reduce their physical contacts, or in case of progressing symptoms, directly report to the clinic.

Only five out of 80 tested patients were positive for COVID-19 (positives). Due to this low number and a potential reporting bias of symptoms, we refrained from using mean comparison tests and only depicted absolute values. However, we noticed that almost all patients in the positives suffered from a sore throat (4/5; 80%), while only 12% in the negatively tested group (negatives) showed this symptom (9/75). Furthermore, rhinitis was more prominent in the positives (60% vs. 26.67%). Although results have to be interpreted with caution, these two symptoms may be clinically particularly relevant to assess probability for COVID-19 positivity.

Known comorbidities, especially pre-existing lung and cardiovascular disease, in positives and negatives were quite low (see Table 3). The most common cardiovascular risk factor was arterial hypertension, which has already been published(5). SARS-Cov2 uses ACE-2 as a cellular entry point(24) and has raised concern about continuation of RAAS inhibitor intake in patients with chronic heart failure(25). However, recent data has shown that there is no evidence of increased disease severity or mortality in hospitalized patients on RAAS blockers(26). Additionally, pharmacological data suggests that ACE-2 expression is not increased in patients on RAAS blockers(27). Thus, current recommendations support continuation of RAAS blockers in patients with arterial hypertension and chronic heart failure(25). In our study two out of five positively tested patients were on RAAS blockers and did not display more severe symptoms than the others. Also in the negatives RAAS blockers were the most commonly prescribed antihypertensive drugs (15 out of 23 patients received RAAS blockers) showing no difference in clinical severity.

We constantly tried to apply the algorithm provided by the RKI(23) to decide which patient needed a smear. However, it seems quite problematic to handle patients with persistent symptoms (mainly unproductive cough), who have been isolated and treated conservatively and who report to the office several times. A rather liberal management of smear-taking could be applied in persistent symptoms refractory to conservative methods, such as inhalation, analgetics and antiphlogistics. Although we would wish for a nationwide testing to get maximal clarity on the real number of positive, oligo- or asymptomatic COVID-19 patients, this vision is still hampered by limited availability of tests, especially in rural areas. Additionally, since a median incubation period of 5 days was estimated(28), the general practitioner will have difficulties to retrieve a patient's contacts in the asymptomatic phase, which makes restriction of viral spread even more difficult.

Due to a reliable recall system from our offices, the clinic with the smear centre and the health department, we were able to confirm that none of the patients negatively tested for COVID-19 progressed to COVID-19 positivity later on. Those five patients tested positive were kept in quarantine for at least two weeks. If symptoms had resided by then,

patients were allowed to take part in public life again. In case of persisting symptoms quarantine was upheld and ambulatory medical services were sent to examine the patients whenever necessary. Moreover, due to regular communication with the local health department we can confirm that none of the patients who were sent home without a smear and treated conservatively, experienced symptom progression, which would have forced us to organize a smear. In summary, the communication between GP offices, hospitals with smear centres and the health department is satisfactory to ensure the best possible patient care, despite the limited smear capacity. In the future, wearables, such as smartwatches, may improve patient surveillance by constantly recording vitals and providing feedback about potential health deteriorations at home. For GPs this would be a great opportunity to improve patient care.

In Germany we have a health system based on solidarity, in which most people have health insurance and thus have easy access to health care. GP's, usually as the first medical contacts, have to filter many patients directly in the office. The Center for Disease Control (CDC) has issued similar recommendations for the public as the RKI in Germany, namely (1) to cover mouth and nose with a cloth, (2) call the GP's office first instead of showing up directly, (3) not to get in close physical contact to others and (4) engage in regular disinfection of hands and surfaces, (5) and self-monitor symptoms(29).

The death rate of SARS-Cov2 is currently 4.1%, almost 90% are over 70 years of age. The rate of infection in the high risk cohort of elderly (> 80) patients is still rising in Germany (approximately 300 per 100.000 inhabitants in the group 80–89 years and 475 in the group 90-99years, as per 23.04.2020)(30), but testing frequency is declining again (peak: 30.03–05.04.2020 > 400.000 tests in Germany, 13.04–19.04.2020: 320.000 tests)(30). This generates fear of a „second wave“ of infection. Similar to Germany, the CDC reported that 80% of deaths occurred in the age group > 65 years(29).

A fast incline of infection rates has occurred in Germany in February 2020, while in the US infections have risen in April (as per 21.04.2020: 802.583 total cases, 44.575 total deaths)(29) and GP's in the States will be facing the same enormous logistic problems as in Germany earlier in the year. The paramount aim of medical personnel in this crisis is to maintain optimal medical care and personal health in a high-risk environment. Thus, stringent algorithms for GP's and other medical specialties need to be introduced to achieve this goal. By segregating patients suggestive of respiratory infection and treating them under high standards of hygiene and protection, we believe that we have achieved this goal in a practicable and efficient manner. Until the date of submission, none of our employees called in sick, which may suggest that our stringent selection process prior to entering the office is a success. Our experience could now help colleagues in other countries with a later onset of COVID- 19 than Germany to organize their offices with the available resources. Transparency of strategies from different countries on how to deal with COVID-19 in inpatient and ambulatory settings is of paramount importance to optimize further patient care and improve educational measures(31).

Lung ultrasound seems to be a very promising tool to detect COVID-19, since it has been shown that B-lines are present in early stages of the disease. Later hyperechoic images, called „white lung“, and finally consolidation can be found in lung imaging(32). Although B-lines are not specific for COVID-19 they can easily be assessed by trained sonographers and can and should be established in emergency departments and outpatient (GP) care.

Our data shows that it is not possible to accurately differentiate between oligosymptomatic COVID-19 patients and ordinary respiratory infection by analyzing symptoms alone. A few days ago, Arons et al. published the spread of COVID- 19 in a US nursing home, in which more than half of positively tested patients were asymptomatic(33, 34). This clearly demonstrates that strategies focusing only on symptoms fail to prevent further transmission. Since the capacity of testing is limited, we suggest the introduction of a new scoring system to stratify patients for COVID-19 that should be tested. This scoring system should embrace the established clinical signs of (unspecific) respiratory symptoms. The two symptoms *sore throat* and *rhinitis* clearly prevailing in positively tested patients should be used as essential

symptomatic markers to stratify for obligatory testing. Known risk factors, such as arterial hypertension, chronic obstructive lung disease and immunosuppression should be additional selection criteria for essential testing. Contact to infected patients and working in high risk areas (such as the medical profession itself) and sonographic signs of lung damage (e.g. B-lines, consolidations) should also be essential components of the score.

We provide a combinatorial score to pre-clinically estimate the risk of SARS-Cov2 infection (Fig. 2). Given the recent observations that sonography is an easy and reliable method to assess suspicion of COVID19, we here add pulmonary sonography as an integral part in our proposed scorings system to stratify patients with unclear respiratory infections for obligatory Cov2 PCR testing.

We awarded 2 points each for sonographic signs of parenchymal or interstitial pulmonary infiltration, suggestive of pneumonia or edema/congestion. 65 years as a cut-off is arbitrary, but Wang et al. (2020) showed that severe COVID-19 infection is rare below 65, which may justify this value(5). We suggest that a total score > 5 points justifies to send patients to Cov2-PCR testing. This means that, theoretically, an asymptomatic patient could qualify for PCR, if there are enough risk factors (disease and environment); this was also demonstrated by Arons et al.(34) We suggest to verify our 20 point-model in a larger cohort of suspected COVID-19 patients. The development and improvement of such a new combinatorial score as proposed here will help GP's to better stratify patients for necessary testing than current suggestions.

Conclusion

In summary, we provide real-life data from rural GP offices in Germany that demonstrate the difficulty to distinguish oligosymptomatic COVID-19 patients from ordinary respiratory tract infection. We provide a well-working example on how to re-organize a GP's office to separate potentially infectious patients from the rest with minimal risk of further spreading the disease. We propose a concise screening score which integrates clinical symptoms, sonographic data and history of previous diseases. Such a score is needed to stratify patients that should be obligatorily tested.

Abbreviations

ACE-2

Angiotensin converting enzyme

CDC

Center for Disease Control

COVID-19

Corona Virus Disease 2019

FFP-3

Filtering face piece

GFR

Glomerular filtration rate

GP

General practitioner

PPE

Personal protective equipment

RAAS

Renin-angiotensine-aldosterone system

RKI

Robert Koch Institut
SARS-Cov2
Severe acute respiratory syndrome- Corona virus 2
VKA
Vitamine K antagonist

Declarations

Ethics approval and consent to participate: No ethics committee was involved in the study. This was no clinical trial according to WHO definitions, data analysis was done according to WHO guidelines (<https://www.who.int/about/ethics/code-of-conduct-for-responsible-research>). Data collection was done within the daily clinical routine and analysis was performed anonymously. All patients or their legal guardians have signed a form that their results may be used for medical purposes and analyses.

Consent for publication: not applicable.

Availability of data and materials: The datasets analyzed during the current study are not publicly available, but will be made available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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The results have not been presented elsewhere.

Authors' contribution: All authors read and approved the final manuscript. SW coined the idea to systematically analyze symptoms and risk factors of patients with potential COVID-19. He created the risk score, wrote the manuscript (together with SW) and performed the systematic analysis of data. TF collected the data from all offices and was responsible for the compilation of the database. EW had the idea to integrate ultrasound as a modality into our score, meticulously analyzed the literature and wrote the manuscript (together with SW).

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Authors' information: SW is a preventive cardiologist who focuses on primary and secondary disease prevention, he has profound experience in the intensive care management of cardiological and pneumological patients and is an active emergency doctor. He is currently employed in the GPs office. Due to his large experience in both inpatient and outpatient management, he analyzed the COVID-19 crisis in our area from a clinical and ambulatory perspective. EW is a professor of anatomy and cell biology, whose main focus of science is to explore neuroimmune and complement activation mechanisms of neurocardiovascular diseases and neurotropic virus infections. EW provided basic scientific background to compile this paper. TF is the head of all our GP offices and has a long-lasting experience in the administration and care of ambulatory patients. After onset of the crisis in Germany he rapidly designed a working schedule for our offices to combine patient care and safety for medical personnel. The fact that none of our personnel has developed symptoms so far is mainly due to his foresighted thinking.

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35. **Titles of Figures.**

Figures

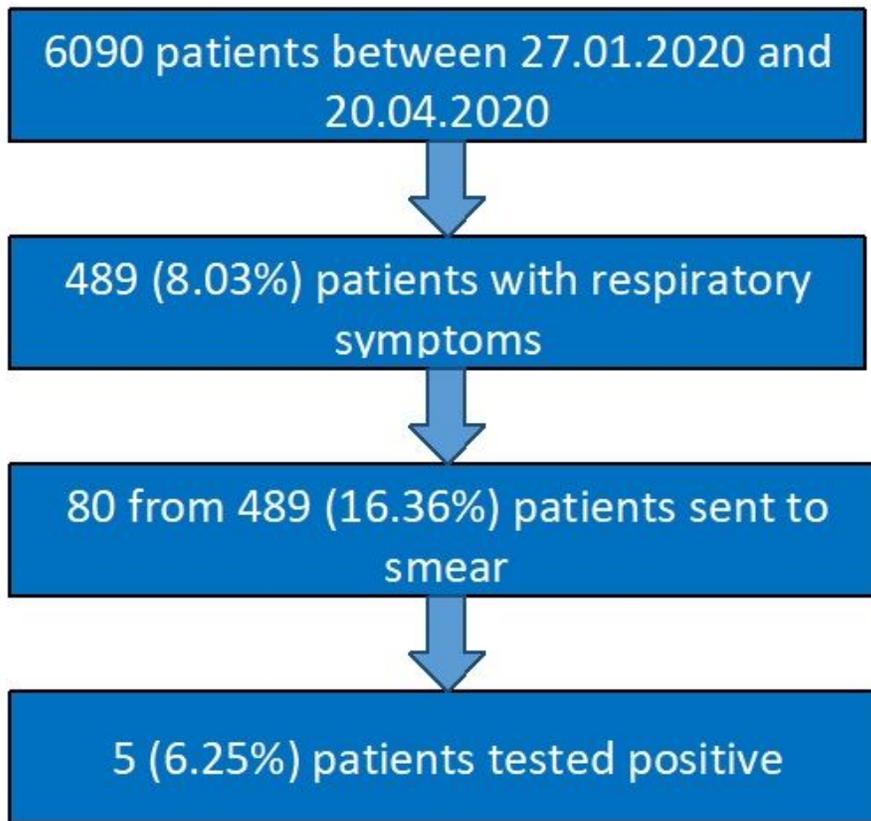


Figure 1

Algorithm of patient recruitment

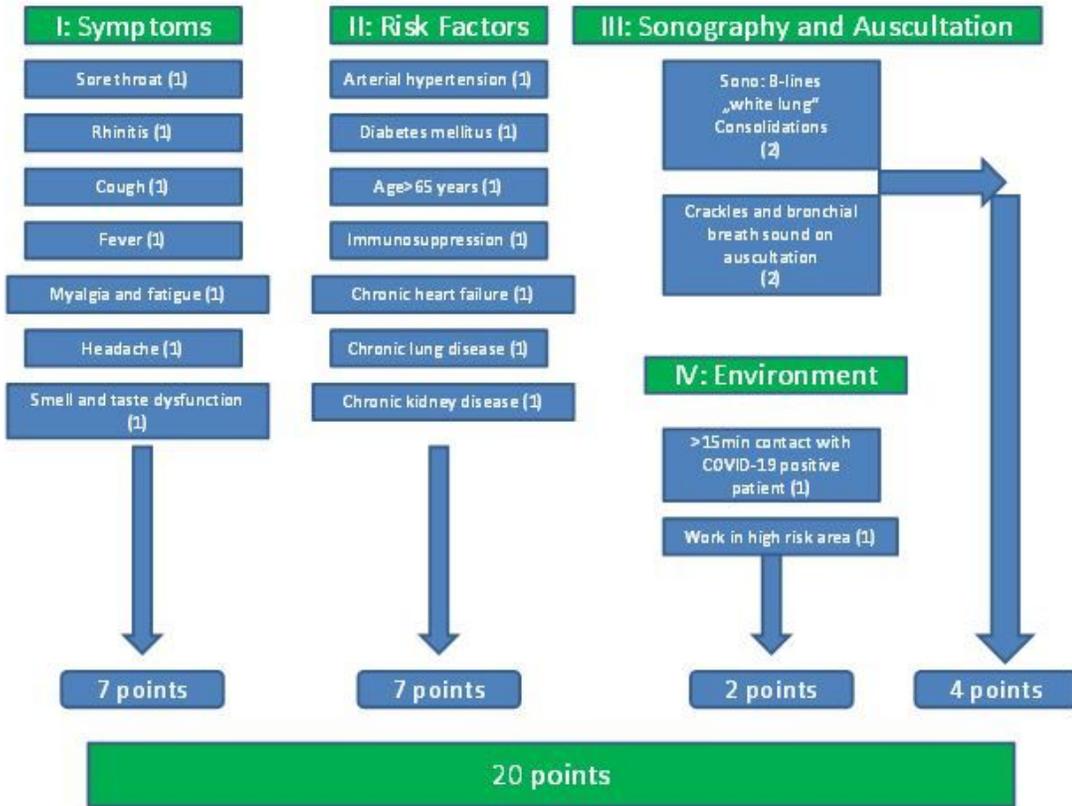


Figure 2

Combinatorial model for preclinical assessment of COVID-19.