

Proposed Modifications in the 6-Minute Walk Test for Potential Application in Patients With Mild COVID-19: A Step to Optimize Triage Guidelines

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GLOSSARY

6MWT = 6-minute walk test; **AIIMS** = All India Institute of Medical Sciences; **COVID-19** = coronavirus disease 2019; **CPET** = cardiopulmonary exercise testing; **CT** = computed tomography; **ECIL** = Electronics Corporation of India Limited; **HCW** = health care worker; **ICU** = intensive care unit; **IPC** = Infection Prevention and Control; **METS** = metabolic equivalents; **PPE** = personal protective equipment; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **Spo₂** = blood oxygen saturation; **WHO** = World Health Organization

THE COVID-19 INFECTION

Health care systems worldwide are currently focused on the management of coronavirus disease 2019 (COVID-19), an ongoing infectious syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.¹ There is a rapid change in basic, clinical, and public health sciences in confronting the problem. A recent viewpoint has expressed the need to accelerate the development of new protocols and prognostic tools for better clinical care.¹ Typical manifestation of the infection is pneumonia with resultant hypoxemia that may require advanced clinical care depending on the severity. Given the millions of patients infected globally with COVID-19, new, reliable, cost-effective screening measures need to be identified to risk stratify those likely to recover uneventfully from those most likely to require advanced medical care.

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CLINICAL CLASSIFICATION OF THE CASES AND CLINICAL COURSE

The confirmed cases are typically classified as mild, severe, and/or critical from a management standpoint. The majority of COVID-19 patients (81%) have uncomplicated or mild illness: nonpneumonia or mild pneumonia. About 14% develop severe illness with blood oxygen saturation (Spo₂) falling below 93% and requiring oxygen therapy. Approximately 5% develop critical illness with respiratory failure, septic shock, and multiple organ dysfunction requiring intensive care unit (ICU) treatment.² Patients with mild disease can quickly deteriorate to severe or critical cases. The median time from symptom onset to the development of pneumonia is approximately 5 days and that from symptom onset to severe hypoxemia and ICU admission is typically between 7 and 12 days.³ Therefore, there is a window of opportunity, albeit for a short period of a few days, before the onset of severe symptoms to allow for risk stratification.

Severity of the illness and mortality are related to advanced age, underlying respiratory disease, cardiovascular disease, hypertension, diabetes, cancer, and patients with decreased immunocompetence.³ Obesity is now recognized as an additional risk factor for the severity.⁴

Chest computed tomography (CT) imaging abnormalities occur even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities.⁵ Emerging data indicate that the mean viral load in severe cases is around 60 times higher than that of mild cases, suggesting that

higher viral loads might be associated with severe clinical outcomes.⁶

TRIAGE GUIDELINES TO OPTIMIZE HEALTH CARE RESOURCES

Prediction of the trajectory of illness from symptom onset is difficult, and prognostic tools and biomarkers are urgently needed.³ As the world transitions from the acute mitigation to a more chronic mitigation with the resumption of elective surgery, it is of increasing importance to be able to ration scarce hospital and/or critical care resources.

The World Health Organization (WHO) described the clinical syndromes according to severity of the COVID-19 infection and provided triage guidelines to optimize health care resources that are applicable in different countries worldwide.⁷

Briefly, they are advocating triaging the patients with laboratory-confirmed cases as mild, severe, or critical with Infection Prevention and Control (IPC) measures instituted early. All patients are required to wear a mask and these measures also include airborne precautions for the clinicians when performing aerosol-generating procedures at higher levels of care. The triage guidelines differentiate between “pneumonia” and “severe pneumonia.” The former is a case of an adult in whom no supplemental oxygen is required and the latter is a case in whom there is respiratory distress and oxygen saturation is $\leq 93\%$. Patients with mild disease do not require hospital interventions, but isolation is necessary to contain virus transmission as per national strategy and resources. The mild cases are observed for progression to the severe stage whereby they are transferred to higher level of care as required.

Those guidelines that were adopted as applicable to India are available in reference.⁸

In India with an estimated population of 1.37 billion, there are essentially 3 types of COVID dedicated facilities: COVID care centers, dedicated COVID Health Centers, and dedicated COVID hospitals. The COVID care centers are makeshift facilities that can include hostels, hotels, schools, lodges, etc, and care for mild cases. Mild cases are defined as those presenting with fever and/or upper respiratory tract illness and influenza like illness. These COVID care centers are staffed by AYUSH (alternative medicine) doctors and supervised by allopathic doctors. There are also nursing, paramedical, and support staff. They have a dedicated Basic Life Support ambulance equipped with sufficient oxygen support on a 24×7 basis, for ensuring safe transport of a case to dedicated higher facilities if the symptoms worsen. The dedicated COVID health centers are hospitals that deal with moderate cases. The criteria for defining a moderate case are pneumonia with respiratory rate

15–30/min and SpO₂ 90%–94% but without respiratory distress. The dedicated COVID hospitals are equipped with advanced facilities for respiratory care and ICU care for severe cases and beyond. Such cases include severe pneumonia (with respiratory rate ≥ 30 /min and/or SpO₂ <90% in room air) or acute respiratory distress syndrome or septic shock.

The WHO has provided guidelines on the rational use of personal protective equipment (PPE) for COVID-19. The Government of India has adopted those guidelines as applicable for different levels of care based on risk profile.⁹

PROPOSED MODIFICATIONS IN THE 6-MINUTE WALK TEST FOR POTENTIAL APPLICATION IN PATIENTS WITH MILD COVID-19

The 6-minute walk test (6MWT) is a validated clinical test to assess the cardiopulmonary reserve and fundamentally designed for use in adults with chronic respiratory disease^{10,11} and therefore may be an appropriate test to triage COVID-19 patients. The test involves having the patient walk as far as possible on a straight track ideally 100 feet in length, for example, corridor or hallway. The total distance walked is the primary objective of the test and is compared with reference standards for interpretation. The relationship between the distance walked and peak oxygen uptake on a progressive incremental cardiopulmonary exercise testing (CPET) was moderate to strong.¹¹ In addition, Sinclair et al¹² found that the test also predicts the anaerobic threshold obtained from the CPET in patients awaiting major noncardiac surgery. The authors obtained oxygen consumption at the anaerobic threshold from CPET and recorded the distance walked during a 6MWT. The regression-based lower and upper 6MWT distance cut-points were 1400 and 1847 feet, respectively. The anaerobic threshold is a marker for combined efficiency of the lungs, heart, and circulation and marks the onset of anaerobic metabolism as a result of inadequate oxygen delivery. We propose to utilize the 6MWT with the modifications of using continuous finger pulse oximetry for SpO₂ monitoring and wearing a surgical mask (Table) in laboratory-confirmed adult patients with uncomplicated or mild illness. Availability of 100 feet track is not mandatory as the total distance walked is important. Alternatively, step counters (1 step equals to about 2.5 feet), pedometers, and software applications for use with smartphone are available to measure the distance walked.

RATIONALE IN THE PROPOSED MODIFICATIONS IN THE 6MWT

We propose to perform the modified 6MWT test on the fourth or fifth day of clinical illness based on the viral load patterns in mild cases compared to severe cases.⁶

Table. Proposed Modifications in the 6-Min Walk Test for Potential Application in Patients With Mild COVID-19

Item	Existing ¹⁰	Suggested Modification
Timing	Not applicable	Fourth or fifth day of clinical illness
Additional contraindication specific to the present context	Not applicable	Patients aged ≥ 70 y or pregnant women
Wearing a surgical mask	Not applicable	Mandatory
Definition of abnormality	Distance walked compared with reference standards ^a	Single cutoff point for distance walked <0.26 mile (<1400 feet) ^{12b} or Sp _o ₂ falling below 90%
Contraindication	Room air Sp _o ₂ at rest $\leq 85\%$	Room air Sp _o ₂ at rest $\leq 93\%$
The presence of a physician	Not mandatory	Mandatory ^c
Evaluation of dyspnea and fatigue ^d	Optional	Mandatory
Stoppage of test	Saturation falling below 80%	Saturation falling below 90%
Resumption of test	When saturation improves	Abandon the test and recommend higher level of care

Abbreviations: COVID-19, coronavirus disease 2019; Sp_o₂, blood oxygen saturation.

^aOnline reference: <https://www.mdcalc.com/6-minute-walk-distance>.

^bThose manifesting the test abnormality should be transferred to higher level of care than the existing one. Those who walk more than 1400 feet but less than 1847 feet (0.35 mile) may be transferred to higher level of care based on clinical judgment, that is, other comorbid conditions. Similarly, in patients with saturation fall between 93 and 90, the decision could be influenced by other comorbid conditions.

^cRequirement for a physician is for the entire center. The test could be administered by nursing or paramedical staff with overall supervision and oversight of a physician.

^dThose manifesting dyspnea and fatigue without abnormality in the test may be transferred to higher level of care based on clinical judgment.

The consistent recommendation that symptomatic patients in health care settings should wear a mask cannot be ignored for this test. The suggested definition for abnormality, that is, the single-point cutoff for distance walked, that is, <0.26 mile (<1400 feet or <427 m) is related to anerobic threshold.¹² Elevated lactic dehydrogenase is common (about 40%) in hospitalized COVID-19 patients¹ and is considered a prognostic factor. The prior probability of severe and critical illness states is about 0.2 as opposed to 0.8 for mild illness and there could be potential problem of having false positives. Hence, a threshold value of 1400 feet is suggested. In terms of metabolic equivalents (METs), walking 1400 feet in 6 minutes will be equivalent to 3 METs (Supplemental Digital Content, Document, <http://links.lww.com/AA/D115>, formula to estimate METs from the 6MWT data). Another definition of abnormality,¹¹ a fall in saturation by more than 4%, was not considered in the present context because of possible effect of mask-induced rebreathing and thus could increase false positives. The exclusion of patients aged ≥ 70 years is based on the fact that the case-fatality ratio is about 8% in that group^{1,2} and may qualify for higher level of care without further testing. In addition, such exclusion is expected to improve the safety of the test. Similarly, pregnant women even with mild disease should be prioritized to enable access to specialized care. Because of the associated cardiovascular and respiratory physiological changes, any type of provocative test even at submaximal level may not be safe in pregnant women.

The finger pulse oximeters may not be very accurate when compared to saturation values obtained from blood gas analysis of arterial blood when the entire range from 70% to 100% is considered.¹³

However, in the range of saturation values applicable in the present context, that is, 90–100, the “limits of agreement,” is clinically acceptable.¹⁴ Hence, the use of finger pulse oximeters in the potential application of the 6MWT test should not pose a problem.

A screening tool, particularly one which can be utilized in low- and middle-income countries, must be cost effective. In the context of the scenario in India, the mild cases managed at COVID care centers are suitable for this test based on the inclusion criteria. The test could be administered by a nurse or paramedical staff with overall supervision and oversight of a physician. The inclusion and exclusion criteria are best evaluated by a physician including the decision to transfer to higher levels of care as demanded by the test results and other comorbid conditions. This is more pertinent initially, since there is no prior experience with the test for COVID-19. In the context of COVID care centers in India that take care of mild cases, they are staffed by physicians and paramedical staff. Hence, there should be no extra financial burden imposed by their requirement. All personnel medically supervising these infected patients during the test must wear complete airborne PPE that should include a face shield, triple-layered medical mask or N-95 mask, disposable gown with head cover, gloves. Finally, the test is not intended to be self-administered by the patient and to be done only at the health care center under supervision.

POTENTIAL USES OF THE ALGORITHM

Early identification of cases that are likely to progress to severe disease gives an opportunity for high level of care that has better facilities for respiratory care including the ICU coupled with advanced laboratory

services. Some of the findings known to be specific to COVID-19 infection and could aid in prognosis include lymphopenia, elevated prothrombin time, lactic dehydrogenase, D-dimer, C-reactive protein, and serum ferritin. Early therapeutic interventions such as antiviral drugs like remdesivir and convalescent plasma therapy potentially decrease the viral load or illness burden. Obviously, such interventions are subject to local regulatory permissions. The decreased viral load and resultant viral shedding could also limit the chances of human-to-human transmission¹⁵ and hence potentially could reduce chances of transmission to health care workers (HCWs) which are a serious problem with COVID-19.^{2,16} Also, the HCWs taking care of mild cases may not be as equipped with PPE as much as they do at higher centers of care.¹⁷ Hence, early identification and transfer to locations of higher level of care of those who are expected to have severe disease due to high viral load and shedding could also decrease the chances of HCW risk at locations dealing with mild cases. This approach to limiting the potential risk of HCW transmission may appear very optimistic, but represents pragmatic additional solution to a serious problem.

SUMMARY AND FUTURE DIRECTIONS

In summary, the proposed use of a modified 6MWT is based on the dynamics of the illness, to limit false positives, improve the margin of safety, economic viability, and practical applicability. The rationale is to identify those among mild cases that are likely to progress to severe illness and transfer them to a higher level of care. If the logistics relevant to a local area preclude testing all the mild cases, then one could consider targeting high-risk groups such as higher age and those with comorbid conditions. The proposed strategy could help strengthen the existing triage guidelines for optimizing the rationing of health care resources. Needless to say, strict adherence to other guidelines related to contraindications¹⁰ (eg, acute coronary syndromes, uncontrolled asthma, etc) and safety and isolation measures are expected to be followed. Patients with severe known underlying chronic respiratory disease also not suitable for the test for fear of unreliable test results. Moreover, such patients are suitable for care at a higher level without testing. The proposals are not intended to be rigid or dogmatic as they are based on the best guesses, given the current understanding of the dynamics of the disease. Instead, they may be regarded as preliminary suggestions for practical use of a simple, yet valuable test that could potentially be used in the risk stratification of mild cases of COVID-19. The views expressed may be limited by lack of data, but field experience from prudent application of the modified test in the real-world situations may help to further refine the

proposed algorithm that typically relies on the application of Bayesian principles in clinical care. The initial field experience could be in the form of a pilot study to evaluate the feasibility of a wider application.

Mobile phone pulse oximeter technology is already in the evolutionary phase.¹⁸

For example, a prototype of such monitoring “Monal 2020 remote health monitoring system” has been developed by Electronics Corporation of India Limited (ECIL), Hyderabad, India, and All India Institute of Medical Sciences (AIIMS), Rishikesh, India.¹⁹

It consists of an indigenously developed intelligent wearable instrument for measuring vital parameters of corona patient like, body temperature, SpO₂, heart rate, respiratory rate along with patient location and a novel application software that remotely displays these parameters on a mobile phone, laptop, or desktop computer for monitoring by doctors from any location.

If the 6MWT with required modifications as applicable for risk stratification of mild cases of COVID-19 proves useful, then such smartphone applications could be developed to integrate the scheme of the modified test with required alerts. Hopefully, such development may prove useful for public health authorities to gather useful clinical and epidemiological data from remote monitoring. ■■

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DISCLOSURES

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