

State of the Globe: The Trials and Tribulations of the COVID-19 Pandemic: Separated but Together, Telemedicine Revolution, Frontline Struggle against “Silent Hypoxia,” the Relentless Search for Novel Therapeutics and Vaccines, and the Daunting Prospect of “COVIFLU”

During the past 4 months, we have witnessed unfolding of the COVID-19 pandemic that by now has affected every corner of the planet, infecting more than 3.3 million people, killing more than 234,000,^[1,2] and directly or indirectly affecting billions of individuals.^[3] The quick rise in both cases and deaths was due to the high infectivity of the virus, quickly overwhelming health-care systems and prompting physical distancing measures of historically unprecedented scale.^[4] The speed and robustness of public health responses within individual countries appear to be associated with early successful containment, fewer cases, and lower mortality.^[5,6] Driven by fears just as powerful as hopes, the humanity is now firmly united in defeating the common enemy, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2).

As country after country fell victim to the relentless disease, disbelief gave way to horror as the “far-away problem” became one that hits all too close to home.^[7] One new fact after another emerged about our new mortal enemy – from its ruthless affinity for those with comorbid conditions to the high proportion of asymptomatic or presymptomatic transmission.^[4] With few exceptions, there is a striking yet expected relationship between the average recorded daily deaths per million population and both the average age and the percentage of geriatric population among countries around the world [Figure 1a and b]^[8-10]. There may also be a similar correlation between the number of symptomatic cases and the average population age,^[11] suggesting strongly that SARS-CoV-2 does not appear to discriminate by national wealth, per-capita income, or number of hospital beds per person.^[11-14] It is hoped that the costly lessons of what is believed to be only the first global wave of COVID-19 will help inform any subsequent waves of COVID-19 disease, as well as future pandemic response across both high-income countries (HICs) and low-and-middle-income countries (LMICs).^[14,15]

The collective learning among geographically separated members of the international medical community is another example of the new global age of instant scientific communication and synergy creation. In this context, several group experiences helped change and refine how

we treat patients. For example, the initial management approach in Europe and America was to intubate early, when the COVID-19 respiratory failure was still mild.^[16-18] However, this approach did not seem to reduce mortality in the affluent Lombardy region of Italy, where some of the highest mortality rates in the world were recorded.^[16] This aggressive intubation approach was contrasted to a study from China where patients with COVID-19 pneumonia were treated with high-flow nasal cannula (HFNC) as the first-line therapy, followed by a stepwise escalation to noninvasive ventilation (NIV) and then tracheal intubation for refractory cases.^[19] In the latter experience, only 4 out of 318 patients were eventually intubated.^[19] Similar experiences and success stories have been reported with early proning of nonintubated patients.^[4,20]

Recent reports also suggest that many patients with COVID-19 present with so-called “silent hypoxia” that is characterized by the apparent absence of dyspnea or overt air hunger.^[21,22] Of interest, patients with such “silent hypoxia” appear to be more likely to progress on to develop severe respiratory failure of COVID-19 within 2–4 days without early aggressive intervention (e.g., HFNC and nonintubated proning). Mechanistically, the damaged lungs have impaired O₂ handling, but the CO₂ exchange is still intact. Because CO₂ is the main driver for dyspnea, patients may feel falsely reassured and thus do not seek emergent medical attention. Instead, hypoxia is compensated by involuntary tachypnea for 2–4 days while the lung injury progresses, up until a cytokine storm occurs, with ensuing dyspnea, elevated CO₂, and the rapid development of severe respiratory failure.^[21,22] From public health perspective, this phenomenon requires early and aggressive implementation of home- or community-based pulse oximetry programs, combined with around-the-clock telemedicine services, to effectively intercept patients who may be entering the rapid deterioration phase of COVID-19.^[21,23-25]

To help address the impact of “silent hypoxia” in both LMIC and HIC settings, we recommend the following combined public/community health plus hospital based-management approach to decrease the need for invasive ventilation and overall mortality in the event of widespread community transmission:

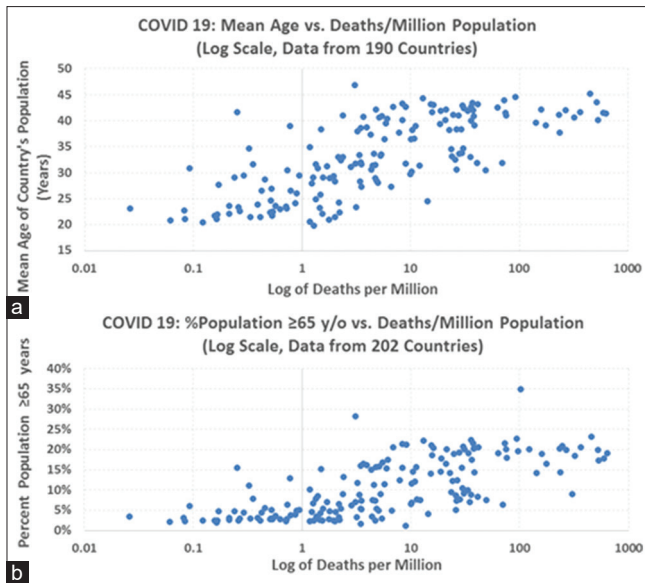


Figure 1: Deaths per million population versus (a, top) mean age of country's population and percentage of country's population ≥ 65 years (b, bottom)

1. Approximately 90% of COVID-19 patients do not require hospitalization, and it may be sufficient to isolate mildly symptomatic or asymptomatic cases in their homes for 14–28 days^[26]
2. When continuous pulse oximetry is not available, monitor those showing mild symptoms at least every 8–12 h for “silent hypoxia” – also see ACAIM-WACEM Joint Working Group clinical management algorithm^[22]
3. Public education and increased access to pulse oximetry near-patient homes will be critical to successful remediation of the “silent hypoxia” phenomenon
4. Once detected, treatment of silent hypoxia ($\text{SpO}_2 < 90\%$ – 93% or respiratory rate $> 25/\text{min}$) should be started according to the following stepwise escalation protocol:^[22,27]
 - a. Oxygen through nasal prongs or face mask 5–6 L/min
 - b. If SpO_2 remains $< 88\%$ on nasal prongs, use nonrebreathing masks 10–15 L/min
 - c. If SpO_2 remains $< 88\%$ on non-rebreathing masks, use either NIV or HFNC (depending on availability)
 - d. If SpO_2 remains $< 88\%$ on NIV or HFNC, consider invasive ventilation.
5. Keep patient in prone position alternating with sitting position for > 16 h/day or as long as reasonably feasible^[4,28]
6. Consider restricted use of intravenous fluids and the use of corticosteroids for severe respiratory failure as per recommendations,^[17] with appropriate medication including low molecular weight heparin and end-organ support as per prevailing recommendations.

As various hospital and intensive care therapies and management approaches take shape, so does an entire new universe of telemedicine as it comes of age. Following its inception, telehealth was viewed by some as a “modality

looking for indications.”^[29,30] This is no longer the case, as the Centers for Medicare and Medicaid Services recently adopted equivalency for tele- and in-person care, voiding the need for the existence of a prior patient–physician relationship to pay claims for telemedicine visits.^[31] This is just one way in which the COVID-19 pandemic permanently changed the health-care landscape, with true effects and the magnitude of such tectonic shift to be felt for years to come.^[25] In addition to enabling ongoing care of patients with chronic medical conditions, the new paradigm also enables innovative approaches to cross-border specialty expertise sharing as well as continued productive employment of health-care providers who may be under quarantine orders.^[4,25] The current pandemic is likely the beginning of a long-term trend toward sustainable, home-based care models.^[30,32]

As frontline medical personnel make important clinical discoveries and advances, so do basic and translational scientists. Despite multiple clinical studies, from retrospective reviews to prospective randomized trials, showing limited or no efficacy of one therapeutic agent after another, much hope remains as the resilient cycle of scientific discovery ploughs ahead.^[4,33–35] And although there is no “magic bullet” in sight, several important discoveries were made in the areas of antivirals (preliminary results suggesting that remdesivir may shorten the duration of illness) and vaccines.^[36–39] The first, and somewhat surprising finding, is the association between universal Bacillus Calmette–Guerin (BCG) national vaccination policies and reduced morbidity and mortality among COVID-19 patients.^[37] Clinical trials of BCG vaccination among health-care workers are ongoing.^[40–42] The second, and somewhat expected finding, is the apparent efficacy of convalescent plasma in the management of severe COVID-19 infections.^[43–45] A longer-term, sustainable derivative that builds on the theme of convalescent plasma is the identification and synthesis of highly effective anti-SARS-CoV-2 antibodies.^[35,46–48] Finally, important new developments are emerging in the race to produce an effective human vaccine,^[38,49,50] although the final product will likely not be available in the immediate future.

In addition to the development of new therapeutics and vaccines, there is a tremendous need for better understanding of the COVID-19 clinical disease. For example, we do not fully understand why the disease seems to take a largely binary course – for some, it appears to be a “flu-like illness,” while for others, it takes a much more acute course. The differentiation between the two “disease paths” seems to be occurring right around the 2nd week of the illness.^[51] Still, etiologic factors responsible for this phenomenon remain unknown. In another highly controversial observation, tobacco smokers appeared to be somewhat protected from the more severe manifestations of COVID-19, but it is not clear what factors (or unrecognized biases) may be responsible for these preliminary findings and confirmatory research will be required to substantiate any associated claims.^[52,53] The

ongoing recognition of new signs and symptoms, long after the first reported case of COVID-19, exemplifies the diverse number of presentations associated with the viral illness. For example, only recently was the phenomenon of “COVID toes” described,^[54] and there is a growing recognition of the association between COVID-19 and thromboembolic phenomena.^[55,56] There is also the spirit of innovation in the face of adversity. For example, when faced with acute shortage of N95 respirator masks and face shields, citizenry around the globe began designing, testing, and making their own substitute do-it-yourself products, with various degrees of success and air filtration effectiveness.^[57-59]

As the global fight against the pandemic continues, we must remember and persist in the hope that this traumatic event will eventually come to an end. With this optimistic outlook, we must start thinking about the humanity’s emergence from the state of “deep freeze,” physical distancing, and the respectful fear of the unknown. Key to this post-COVID-19 “rebirth” of sorts will be a well-organized, well-thought-out system of checks and balances that will allow the maintenance of appropriate safety measures while also permitting the return of economic activity in the broadest possible sense. A formidable new challenge will be the copresence of COVID-19 and influenza during the next annual “flu season,” effectively resulting in what the authors are coining as “Covi-Flu season.” The costs of dual testing, personal protective equipment, as well as the need for high degree of clinical vigilance are likely to create significant inefficiencies across our clinics and emergency departments. To overcome this and many other challenges, some degree of “collective sacrifice” will likely be necessary, whether it means large-scale testing and issuing vaccination/immunity certificates, or perhaps a protracted period of continued social distancing with associated ramification of being “together but separated.” Ultimately, these difficult questions will need to be answered by citizens of each region of the globe while maintaining the utmost respect for the prevailing cultural norms, individual freedoms, and the collective societal well-being. We live in special times, and we shall emerge from the great challenge of the COVID-19 pandemic together, as a one human family, stronger, wiser, and better.

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