Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

the bedside of patients who appeared to have months to live, and were then unable to return quickly enough after a sudden deterioration. Moreover, patients in their final days and hours are often minimally responsive and unable to interact with family members; the opportunity to spend so-called quality time has passed. Otani and colleagues[5] found that being present at the time of death was not associated with any difference in the incidence of complicated grief among family members, but having the opportunity for meaningful conversation (eg, being able to say goodbye) was associated with reduced symptoms of depression and complicated grief.

Limiting the number of visitors allowed at one time might seem a reasonable compromise, but it can also lead to problems. Considering that cohabiting family members often visit at the same time, separating them at the bedside does not reduce the chances of transmission to each other or to the patient. Instead, they often choose to take turns, cycling between being at the bedside and being outside the hospital multiple times in a single day. Because the greatest risk of transmission occurs during the removal of personal protective equipment and transit within the hospital (eg, encountering other staff, travel in elevators), this cycling is likely to increase the risk of transmission substantially more than simply allowing all visitors to remain at the bedside for the duration of their visit (space permitting).

We have also found that inconsistent visitor policies among different sites can be problematic. Patient transfers are very common as patients near the end of life and are transferred from acute care to palliative settings. But if the receiving facility has stricter limits on visiting than the sending facility, patients often refuse the transfer, which increases the burden on the acute care facilities by adding to the population of those classed in the so-called alternate level of care.

The broad visitor restrictions put in place by many health-care facilities at the start of the pandemic were reasonable responses to a new and previously unknown pathogen. With the benefit of experience, and provided that sufficient personal protective equipment is available, we propose that health-care organisations adopt a new end-of-life visitor policy (panel) that would reduce restrictions overall without necessarily putting patients, staff, and family members at a substantially increased risk of COVID-19 transmission. Elements of this policy might be reasonable outside the end-of-life context, and Munshi and colleagues[6] recently proposed more general relaxation of visitor policies. This proposal is not intended as a criticism of those who recommended more rigid restrictions at the start of the pandemic. But the threats of COVID-19 must be placed in context of other threats to health, including those that are harder to appreciate in the short term.

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α1-Antitrypsin deficiency and the risk of COVID-19: an urgent call to action

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The COVID-19 pandemic is a global emergency. Identifying populations who are at risk of severe complications is crucial in developing special measures to prevent or reduce severe illness and mortality in vulnerable patients.[1] Emerging evidence indicates that alpha$_1$-proteinase inhibitor might inhibit infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). α1-Antitrypsin also has anticoagulation

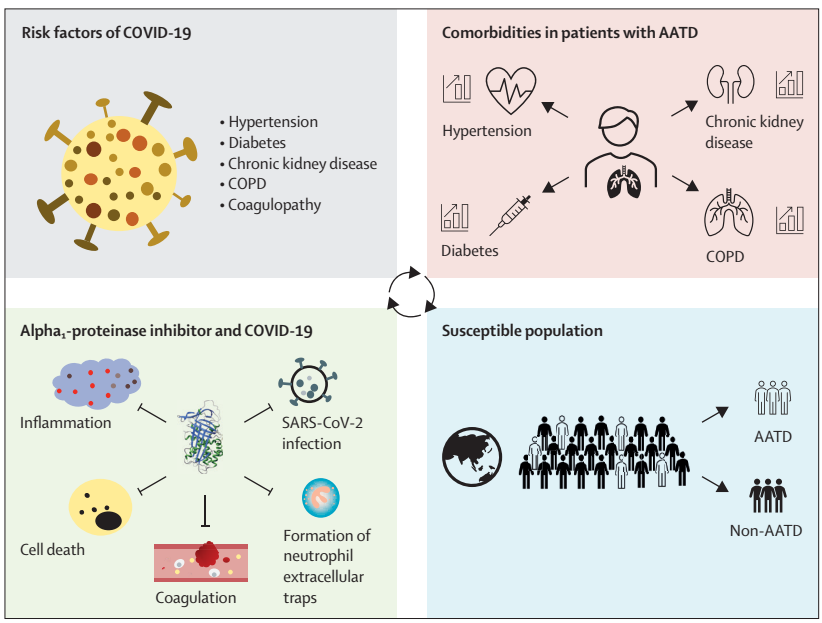

Figure: **Patients with AATD as a population that is susceptible to COVID-19**
AATD=α1-antitrypsin deficiency. COPD=chronic obstructive pulmonary disease. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

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effects and can protect against inflammation, cell death, and the formation of neutrophil extracellular traps, so this multifunctional protein has been considered as a candidate for COVID-19 treatment.[2] Several clinical trials of alpha$_1$-proteinase inhibitor have been initiated. An urgent need exists to address the possibility that patients with α1-antitrypsin deficiency (AATD) might be at increased risk of SARS-CoV-2 infection and development of severe COVID-19.

Human α1-antitrypsin is the most abundant serine proteinase inhibitor in human plasma and is encoded by the *SERPINA1* gene, which is located on human chromosome 14q32.1. In individuals with one of several inherited mutations in *SERPINA1*, low circulating α1-antitrypsin concentrations increase the risk of destructive diseases, particularly emphysema and bronchiectasis. Infusion of alpha$_1$-proteinase inhibitor has been shown to have therapeutic benefits in patients with AATD.[3]

TMPRSS2 is a cell membrane-bound protease that facilitates entry of viruses (including SARS-CoV-2) into host cells by proteolytically cleaving and activating viral envelope glycoproteins. Preliminary evidence indicates that alpha$_1$-proteinase inhibitor might impede SARS-CoV-2 infection by inhibiting TMPRSS2 activity.[4] Alpha$_1$-proteinase inhibitor is being tested as a treatment for patients with COVID-19 in four clinical trials, in Saudi Arabia (NCT04385836), Spain (NCT04495101), the USA (NCT04547140), and Ireland (EudraCT 2020-001391-15). In patients with COVID-19 who were admitted to the intensive care unit (ICU), higher ratios of interleukin (IL)-6 to α1-antitrypsin predicted a prolonged ICU stay and higher mortality, whereas lower ratios of IL-6 to α1-antitrypsin were associated with clinical resolution.[5]

According to the Johns Hopkins University and Medicine Coronavirus Resource Center, Spain, Italy, France, and the UK have reported Europe's highest numbers of confirmed COVID-19 cases and deaths. The numbers of individuals with *PI*ZZ*, *PI*SZ*, and *PI*MZ* genotypes of AATD in these countries are also the highest in Europe.[6] Vianello and Braccioni used data from the Italian registry for AATD to show that the geographical distribution of people with AATD is similar to that of the confirmed distribution of people with COVID-19.[7] A significant positive correlation was reported between the combined frequencies of the *PI*SZ* genotype in 67 countries and their reported COVID-19 mortality.[8] These observations are intriguing, but interpretations are challenged by many confounding factors (eg, socioeconomic status and ethnicity) and further investigations are required.

The comorbidities of AATD[9] mirror key risk factors predisposing patients to severe COVID-19.[10] Patients with AATD have a higher prevalence of hypertension, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and diabetes than do members of the general population.[9] These diseases are not only independently associated with increased prevalence of COVID-19 but also associated with poor prognosis in patients with the disease.

We propose that patients with AATD are a susceptible population for COVID-19. First, for patients with AATD who do not have enough functional α1-antitrypsin, TMPRSS2 would be activated more easily, allowing SARS-CoV-2 entry into cells. Second, α1-antitrypsin has inhibitory effects on thrombin and plasmin, so AATD could be associated with an increased risk of coagulation disorder.[11] Third, insufficient anti-inflammation, anti-cell death, anti-protease, and anticoagulation effects of α1-antitrypsin could increase the likelihood of severe acute lung injury. Patients with AATD who are infected with SARS-CoV-2 might, therefore, have worse outcomes than do members of the general population (figure). Since patients with AATD might have an

increased risk of adverse outcomes from COVID-19, we propose the following call to action for the management of patients with AATD, with or without COVID-19.

Clinicians should screen patients who are recovering from COVID-19 for AATD to examine the effects of various AATD genotypes on the incidence and severity of COVID-19. Measurements of α1-antitrypsin concentrations in plasma, frequently used for clinical screening purposes, can detect severe deficiencies but might miss carriers whose plasma α1-antitrypsin concentrations are near the normal range (ie, 1·0–2·7 g/L). Studies of patients who have recovered from COVID-19 should include assessment of *SERPINA1* status via genotyping. A prevalence of deficiency genotypes that is higher than expected in patients who have recovered from COVID-19, particularly if associated with increased disease severity, would establish the clinical importance of AATD.

Public health agencies should recommend that patients with a high risk of AATD be screened for the *SERPINA1* genotypes at the same time as screening and testing for COVID-19 to establish the association between different *SERPINA1* genotypes and incidence of SARS-CoV-2 infection. Screening would include foremost the family members of individuals with known AATD and people with disorders that are commonly associated with AATD, particularly the many unscreened patients with COPD. Multiple registries, both locally and internationally, collect data for COVID-19 or AATD; collaborations among these agencies should be advocated.

Patients with AATD and their immediate family members should be aware of the higher risk of infection by SARS-CoV-2 and the possibility of worse clinical outcomes, if they are infected, than in the general population. Clinicians should pay special attention to patients with AATD and their immediate family members, if diagnosed with COVID-19. Plasma α1-antitrypsin concentrations should be measured for these patients. For individuals receiving augmentation therapy at standard doses (ie, 60 mg/kg per week), clinicians should plan to continue infusions should patients become acutely ill. Such patients might require admission to hospital to continue receiving infusions from health-care providers with appropriate personal protective equipment. Higher than standard maintenance doses should be considered.

Although clinical trials have been done to examine the potential benefits of alpha$_1$-proteinase inhibitor in patients with COVID-19, basic and translational research is needed to study the mechanisms of alpha$_1$-proteinase inhibitor's therapeutic benefits and its safety, timing, dosing, limitations, and use in combination with other concurrent therapeutics.

As AATD represents a large population in countries that have a high incidence of COVID-19 and high mortality associated with the disease, these actions for patients with AATD could help to reduce COVID-19-related morbidity and mortality. As the COVID-19 pandemic continues, strategies are needed to address the risks for patients with AATD as a matter of urgency.

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