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Tools and factors predictive of the severity of COVID-19

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Abstract: The outbreak of the novel coronavirus infection caused worldwide confusion. The problem with this infection is that it causes severe illness in some patients, resulting in a high rate of death if appropriate treatment is not given. If patients with severe illness that requires treatment are appropriately identified, treatment can be focused on these patients. However, in the early days of the COVID-19 outbreak, the inability to predict and diagnose the disease led to hospitals being overwhelmed. Therefore, various methods for the diagnosis of severe disease were developed early on, and various methods are still being investigated to predict high-risk patients. The currently available prediction methods are divided into those that predict the onset of severe disease and those used to determine the severity of the disease. Specifically, the main methods include genetic factors, serum humoral factors, laboratory tests, and diagnostic imaging. Since each of these factors has different features, using them in combination is likely to be advantageous.

***Keywords*:** SARS-CoV-2, severe illness, serum marker, genetic variation, artificial intelligence

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) infection, reached epidemic proportions worldwide. SARS-CoV2 is highly infectious and can rapidly spread if infection control measures are not taken, leading to an exponential increase in the number of COVID-19 cases.

COVID-19 causes mild to moderate symptoms in the early stages of infection, and many COVID-19 patients recover without sequelae. Some patients, however, transition from mild or moderate to severe symptoms (*1*). Although it would be desirable to detect patients with severe disease in the early stages of infection, identification of such patients has been difficult. Additionally, since delayed treatment leads to a lower survival rate for those who become severely ill, it is ideal to intervene early in the treatment of only those patients who are likely to develop severe illness.

At the beginning of the COVID-19 pandemic, hospitals received so many patients that they were quickly overwhelmed, delaying treatment for many and thus causing people to suffer. Therefore, several clinical studies evaluated predictive markers for detecting critically ill patients because of the high demand for such markers. This review summarizes these predictive markers of COVID-19 severity.

Predictive markers using biochemical tests

Laboratory biomarkers are inexpensive, rapid, and readily available. As such, they have become the preferred means of monitoring and predicting disease outcomes and prognosis.

Since laboratory biomarkers have always supported clinical decision-making in various infectious diseases, a better understanding of the profile of specific biomarker changes and differences in COVID-19 prognosis might help in the development of risk stratification methods in the treatment of patients with this disease.

At the beginning of the pandemic, a number of research teams reported markers that are predictive of severe disease, primarily based on laboratory tests. A large number of papers evaluating patients with different characteristics, such as country of residence, race, and testing parameters, were reported. Recently, several meta-analyses have been reported that have analyzed these numerous results and evaluated which factors were truly associated with the development of severe symptoms.

Malik *et al.* conducted a meta-analysis of 32 studies including 10,491 patients with COVID-19, based on laboratory tests reported to be predictive of the development of severe disease (Table 1) (*2*). Their meta-analysis indicated the following factors as being significantly predictive of severe symptoms: lymphopenia, thrombocytopenia, and elevated levels of D-dimer, C-reactive protein (CRP), procalcitonin (PCT), creatine kinase (CK), aspartate transaminase (AST), alanine transaminase (ALT), creatinine, and

lactate dehydrogenase (LDH). Multiple laboratory tests associated with severe illness have been narrowed down to identify the factors that really are important.

Predictive markers related to underlying disease

In addition to laboratory tests, the presence of underlying diseases has been reported to be associated with the onset of severe illness. In a report by Mudatsir *et al.*, it was confirmed that patients with underlying diseases are more likely to develop more severe symptoms (*3*). They included 19 papers documenting 1,934 mild and 1,644 severe COVID-19 cases, and identified the potential risk factors for severe illness. They assessed the influence of underlying diseases in addition to laboratory tests. Regarding laboratory tests, as reported in other meta-analyses, low levels of lymphocytes and hemoglobin, and elevated blood levels of leukocytes, AST, ALT, creatinine, blood urea nitrogen, high-sensitivity troponin, CK, high-sensitivity CRP, interleukin 6, D-dimer, ferritin, LDH, and PCT, as well as a high erythrocyte sedimentation rate (ESR) were all associated with severe COVID-19.

In particular, several comorbidities, including chronic respiratory disease, cardiovascular disease, diabetes mellitus, and hypertension, were more frequently observed in patients with severe COVID-19 (Table 2). A larger number of comorbidities were also observed in patients with severe COVID-19 than in those with mild disease. Further, dyspnea, anorexia, fatigue, increased respiratory rate, and increased systolic blood pressure were observed more often in patients with severe COVID-19 compared to those with mild COVID-19. These symptoms could thus be useful baseline parameters in the development of prognostic tools for COVID-19.

Table 1. Laboratory tests which are independently associated with higher risk of COVID-19 poor outcomes

Features	Pooled-OR (95% CI)	*p* value
Lymphopenia	3.33 (2.51–4.41)	< 0.00001
Thrombocytopenia	2.36 (1.64–3.40)	< 0.00001
Elevated D-dimer	3.39 (2.66–4.33)	< 0.00001
Elevated CRP	4.37 (3.37–5.68)	< 0.00001
Elevated PCT	6.33 (4.24–9.45)	< 0.00001
Elevated CK	2.42 (1.35–4.32)	0.003
Elevated AST	2.75 (2.30–3.29)	< 0.00001
Elevated ALT	1.71 (1.32–2.20)	< 0.00001
Elevated creatinine	2.84 (1.80–4.46)	< 0.00001
LDH	5.48 (3.89–7.71)	< 0.00001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin. This table was modified from Malik P, *et al.* BMJ 2020.

Table 2. Underlying diseases which are independently associated with higher risk of COVID-19 poor outcomes

Features	Pooled-OR (95% CI)	*p* value
Chronic respiratory disease	2.31 (1.37–3.89)	0.002
Cardiovascular diseases	1.71 (1.05–2.78)	0.03
Diabetes mellitus	2.10 (1.32–3.34)	0.002
Hypertension	2.32 (1.43–3.78)	0.0007
Dyspnea	3.28 (2.09–5.15)	< 0.00001
Anorexia	1.83 (1.00–3.34)	0.05
Fatique	2.00 (1.25–3.21)	0.004
Dizziness	2.24 (1.08–4.65)	0.03
Respiratory rate	0.57 (0.14–1.01)	0.01
Systolic blood pressure	0.33 (0.14–0.52)	0.0005

This table was modified from Mudatsir M, *et al*. F1000Reasearch 2021.

Predictive markers using humoral factors

Interleukin-6 (IL-6)

In previous analyses of humoral factors associated with the severity of illness, IL-6 has often been the focus of attention since the early days of COVID-19 (*4-6*). Indeed, use of inhibitors of the IL-6 pathway have been indicated as a potentially useful treatment strategy (*7*). Data showing that IL-6 is associated with severe disease showed a significant difference in its median value between hospitalized and non-hospitalized groups (*8*). Significant differences were also found between the short and long hospitalization groups. This indicates that IL-6 has utility as a biomarker of the degree of severity of illness. However, since these studies analyzed patients after hospitalization for severe disease, it is not clear whether IL-6 is a useful predictor of the severity of illness. On the other hand, as shown in Figure 1, IL-6 levels in COVID-19 have been reported as being not as high as in previous IL-6-related diseases, indicating data that IL-6 is unlikely to be a main constituent of the

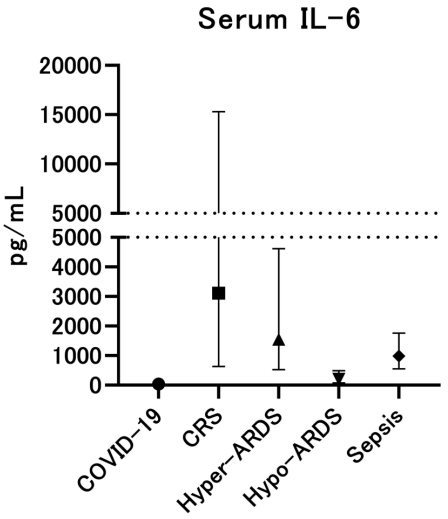

Figure 1. Serum IL-6 levels in cytokine related inflammatory diseases. Serum IL-6 concentrations of COVID-19, CRS, hyper-ARDS, hypo-ARDS, and sepsis are shown in this graph. This data is original and is not published. Hyper-ARDS, hyperinflammatory acute respiratory distress syndrome; Hypo-ARDS, hypoinflammatory acute respiratory distress syndrome; CRS, cytokine release syndrome.

disease (*4*).

In Japan, IL-6 testing is approved by health insurance for the assessment of severe systemic disease. It is regulated for the purpose of diagnosing the severity of severe illness in patients with severe disease, but not for the prediction of the onset of severe illness. By this test, physicians may be able to determine if high IL-6 is the cause of the severe disease.

Interferon-lambda 3 (IFN-λ3)

From the beginning of the COVID-19 outbreak, our research team has been searching for diagnostic markers that can predict which patients will transition to severe or critical illness (*9*). By measuring approximately 70 humoral factors in the blood, our research team was able to identify several factors that are characteristically altered in patients with severe or critical disease before the disease worsened. These factors include IFN-λ3, C-X-C motif chemokine (CXCL) 9, CXCL10, IL-6, and C-C motif ligand (CCL) 17 (*10*). At the time of that study, results regarding CXCL9, CXCL10, and IL-6 had also been previously reported from overseas, and our results corroborated those, while IFN-λ3 and CCL17 were newly reported biomarkers of disease severity. These markers were found to be more accurate as predictive markers than previous laboratory tests and humoral factors (*10*). In fact, these two biomarkers are now included in the Japanese insurance system as tests that can be used to predict severe or critical COVID-19. Use of the IFN-λ test in real-world clinical practice reproduced the IFN-λ kinetics shown in our first paper (*11*).

IFN-λ3 is a member of the gene family called type III interferons, and is one of the most widely conserved genes in living organisms (*12,13*). In humans, the presence of IFN-λ1 to 4 has been shown, with their number varying among organisms. In viral and other infectious diseases, IFN-λs are involved in the initial response to infection and are characterized by the expression of a large number of receptors for IFN-λs, especially in epithelial tissues. This suggests that IFN-λs play a different role than IFN-α/β, which are known to act in the whole body.

Although a relationship between COVID-19 and the IFN-λ family has been suggested, details of this relationship are not yet clear. The extremely high sequence homology of the human IFN-λ family makes it difficult to quantify them separately, and it is common practice to analyze the IFN-λ family together (*12,13*). By quantifying the IFN-λ family members separately, our research team showed for the first time in humans that IFN-λ3 is important in COVID-19 (*10*).

Analysis of changes in IFN-λ3 during the course of COVID-19 revealed that patients transitioning from mild to severe disease show a characteristic peak value a few days before the transition (*9*). The change is characterized by a transient high value followed by a rapid decrease, with no cases being observed in which the value remained persistently high (Figure 2, A-C). Furthermore, in the course of the decrease in IFN-λ3 values, the patients' condition became severe, requiring oxygen and ventilators. With regard to the peak value, the higher this value, the more severe the symptoms tended to be, although we are currently in the process of accumulating more data on this point.

CCL17

CCL17 (also known as Thymus and activation-regulated chemokine, TARC) is a chemokine known to be associated with the activation of antibody-producing cells (*14*). The blood level of CCL17 in healthy humans is about 1,000 pg/mL at birth, decreasing to about 400 pg/mL during subsequent growth. CCL17 is particularly associated with allergies, and high levels of CCL17 in atopic dermatitis and asthma are associated with severe symptoms. In atopic dermatitis, in which the testing for CCL17 is covered by insurance, the higher the serum CCL17 level, the more severe the condition (*14*).

On the other hand, low levels of CCL17 are found to be associated with severe symptoms in COVID-19 (*9*); humans who recovered from mild disease with COVID-19 had levels similar to those in healthy individuals, while those who went on to develop severe disease already had levels below 87.5 pg/mL in the early, mild stage of infection (Figure 2, D and E). This suggests that CCL17 might be a predictive marker of severe disease that can be used in the early stages of COVID-19 infection.

At the time of the report, this result was a new phenomenon, as there were few reports showing an association between low CCL17 levels and disease. Thus, at this point, our research team believes that this phenomenon is specific to COVID-19 severity, although the detailed mechanism is not clear.

Based on previous reports and our review, it has not been reported that CCL17 values tend to decrease with increasing age. While it is clear that elderly people are more susceptible to severe disease, it is also clear that this is limited to a subset of the elderly. Based on these facts, our research team speculates that this phenomenon of CCL17 decline is due to SARS-CoV-2 infection. Basic analysis is currently underway to elucidate the mechanism of this phenomenon.

Predictive markers using genetic factors

The viral life cycle requires human host genes. Polymorphisms in human genes involved in viral entry and replication might contribute to disease prognosis and outcome. In other words, human genetic polymorphisms might affect the course of COVID-19. The most studied genes are those that interact directly with spike proteins

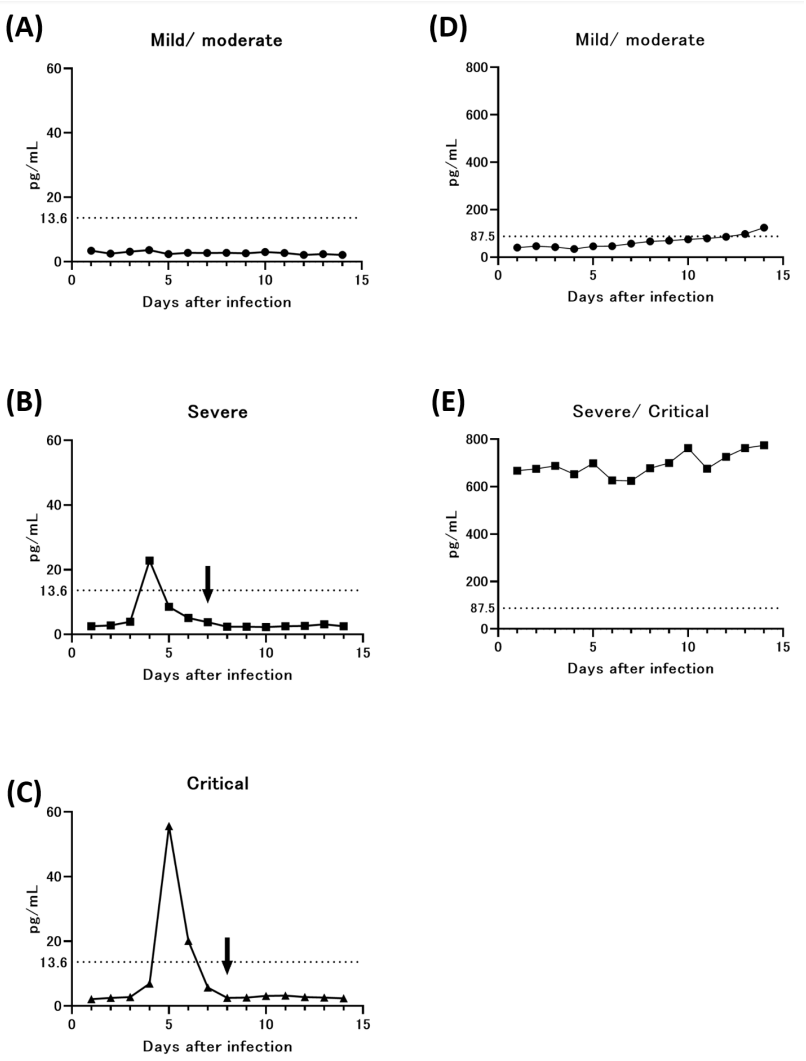

Figure 2. Dynamics of serum IFN-l3 and CCL17 levels in COVID-19. Representative profiles of serum IFN-λ3 and CCL17 are shown in COVID-19 patients. The dynamics of serum IFN-λ3 are in **(A)** mild/ moderate, **(B)** severe, and **(C)** critical patients. The dynamics of serum CCL17 are in **(D)** mild/ moderate, **(E)** severe/ critical patients. The threshold line for predicting severe and critical illness was set at more than 13.6 pg/mL for IFN-λ3 and less than 87.5 pg/mL for CCL17. Arrow shows the point of the onset of severe or critical symptoms. This data is original and is not published.

(*15*). Single nucleotide polymorphisms (SNPs) in ACE2 and TMPRSS2 might contribute to selective binding of SARS-CoV-2. Since there are many published reports on the involvement of these genes in viral entry (*16*), a meta-analysis has been conducted on this, although its data is still awaited (*17*).

ACE1 rs4646994 is an insertion or deletion polymorphism. Meta-analysis showed that this genetic polymorphism is significantly associated with an increased risk of developing severe COVID-19 (*17*), as observed in the allelic model (D *vs*. I, $p < 0.0001$), dominant model (DD *vs.* II + ID, $p < 0.0001$), homozygous model (DD vs. II, p = 0.0004), and additive model (DD *vs*. ID, $p = 0.0006$), while there was no association in the recessive model (DD + ID *vs.* II, $p = 0.55$) (Table 3). These results suggested that the deletion mutation was associated with severe disease.

A meta-analysis evaluating ACE2 rs2285666 polymorphism and the risk of severe disease showed a significant association between them. A significant association between ACE2 rs2285666 polymorphism and an increased risk of developing severe COVID-19 was found in two genetic models (recessive GG *vs.* GA + AA, $p = 0.005$; additive GG *vs.* GA, $p = 0.02$), indicating an increased risk of developing COVID-19 with an extremely significant difference between those with and without these polymorphisms. In contrast to the above findings, the remaining three genetic models showed no statistically significant differences in the onset of severe illness (allele G *vs*. A, $p = 0.15$; dominant GG + GA *vs.* AA, $p = 0.64$; homozygous GG *vs*. AA, $p = 0.11$) (Table 3) (*17*).

The meta-analysis also established a significant relationship between TMPRSS2 rs12329760 polymorphism and the high risk of developing severe COVID-19 only in the allelic model (C *vs.* T, $p = 0.04$), although no association was found in the remaining models (Table 3). However, since fewer than 10 studies

Table 3. Genetic factors which are independently associated with higher risk of COVID-19 poor outcomes

Features	Pooled-OR (95% CI)	*p* value
ACE1 rs4646994		
D allele *vs*. I allele	1.62 (1.28–2.05)	0.0001
DD *vs*. DI+II	2.06 (1.45–2.93)	0.0001
DD+DI *vs*. II	1.20 (0.66–2.20)	0.55
DD *vs*. II	2.29 (1.44–3.62)	0.0004
DD *vs*. DI	1.99 (1.35–2.95)	0.0006
ACE2 rs2285666		
G allele *vs*. A allele	1.64 (0.83–3.25)	0.15
GG+GA *vs*. AA	1.33 (0.40–4.39)	0.64
GG *vs*. GA+AA	2.14 (1.26–3.66)	0.005
GG *vs*. GA	2.14 (1.14–4.01)	0.02
GG *vs*. AA	1.98 (0.85–4.61)	0.11
TMPRSS2 rs12329760		
C allele *vs*. T allele	1.32 (1.01–1.73)	0.04
CC+CT *vs*. TT	1.56 (0.45–5.37)	0.48
CC *vs*. CT+TT	1.38 (0.99–1.92)	0.05
CC *vs*. CT	1.29 (0.91–1.81)	0.15
CC *vs*. TT	1.74 (0.47–6.44)	0.41

D allele, deletion allele; I allele, insertion allele; DD, DD genotype; II, II genotype. This table was modified from Saengsiwaritt W, *et al*. Rev Med Virol. 2020.

were included in the meta-analysis of this genetic polymorphism, tests of funnel plot asymmetry, meta-regression analysis, and sensitivity analysis were not performed.

In addition, a large number of other genetic polymorphisms have been reported to be associated with the severity of COVID-19 (*16,18-20*). However, no genetic polymorphisms strongly associated with severe disease that could be used for diagnosis have been reported, suggesting that genetic factors have a limited impact on the severity of the disease.

Predictive AI model using biochemical and humoral factors

When the COVID-19 pandemic initially began, there were no effective drugs or treatments available because there was not enough information on or experience with this disease. Therefore, there was an urgent and important need to find new technologies for its early diagnosis, detection, and treatment. Artificial intelligence (AI) driven by multi-model data was used as a solution in this situation. During the COVID-19 pandemic, AI provided cutting-edge applications in terms of determining its pathogenesis, best practices, and treatment. The application of AI to diagnosis also helped predict disease progression, enabling the early detection and treatment of high-risk patients.

Li *et al.* investigated AI quantification of initial chest CT in COVID-19 patients for predicting disease progression and clinical outcomes (*21*). In their study, the CT severity score (CT-SS) was calculated according to the extent of lesions, and ground-glass opacity and consolidation volume were quantified by AI. In terms of imaging parameters, consolidation volume was the most effective in discriminating non-severe from severe patients (AUC = 0.796, $p < 0.001$), as well as identifying the presence of critical events (AUC = 0.754, $p < 0.001$). The results showed that consolidation volume and age were the two major predictors of disease progression.

Similarly, Yang *et al.* applied chest CT-SS as an imaging tool for evaluating the progression of COVID-19 (*22*). In their model, the optimal CT-SS threshold for identifying severe COVID-19 was 19.5, with a sensitivity of 83.3% and specificity of 94%. This suggests that CT-SS can rapidly and objectively assess the severity of pulmonary lesions in patients with COVID-19.

Yan *et al.* developed a predictive model based on the XGBoost model (*23*). They identified three important clinical characteristics from more than 300 factors as being useful for predicting COVID-19 outcomes: LDH, lymphocyte count, and high-sensitivity CRP. The model was able to predict survival of COVID-19 patients with greater than 90% accuracy.

Description of predictive markers of severe symptoms in representative guidelines

Blood tests are helpful in understanding the condition of patients, and should be performed in patients with risk factors for severe disease or those with moderate or severe disease. Many studies have been conducted in many countries, especially on biomarkers (markers of severity of illness) that contribute to the determination of severity of illness and patient prognosis. The use of these biomarkers is expected to improve the quality of medical care and the effective use of medical resources.

Guidelines provided by the Japanese Ministry of Health, Labour and Welfare (MHLW) provide an introduction to predictive markers for severe disease. This guideline presents a recent meta-analysis, which describes the following markers as being associated with severe or critical symptoms: lymphocytopenia, thrombocytopenia, and elevated levels of D-dimer, CRP, PCT, CK, AST, ALT, creatinine, and LDH.

In addition, a report was introduced that showed a higher percentage of genetic mutations associated with decreased interferon alpha production in severe cases. Furthermore, IFN- λ3 is known to be elevated in the blood of patients infected with SARS-CoV-2 from about 1 to 3 days before symptoms indicating the need for oxygen administration. This measurement in patients hospitalized due to SARS-CoV-2 positivity could predict the severity of the disease.

TARC (CCL17) levels are also known to be low in the blood of patients infected with SARS-CoV-2 from the early onset of COVID-19 until the onset of severe disease in patients who develop severe disease that requires oxygen administration.

On the other hand, although there is no explicit mention of predictive markers of severe disease in

the NIH guidelines, some markers were introduced as described below. Patients with certain underlying comorbidities are at an increased risk of developing severe COVID-19 progression. These comorbidities include being over 65 years of age, having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, chronic kidney disease, pregnancy, being a smoker, being a transplant patient, and receiving immunosuppressive therapy. Hence, medical professionals should closely monitor these patients until they have clinically recovered. Laboratory tests include complete blood counts (fractions) and metabolic profiles (*e.g.*, liver and renal function tests) are available, although inflammatory markers such as CRP, D-dimer, and ferritin are not regularly measured as a part of standard care, their results might be prognostically useful (*24-26*).

It is essential to note that our research team could not find adequate information for predictive markers of severe symptoms in the UK or WHO guidelines(*27*). As many papers have been reported on predictive markers of severe symptoms, adequate evidence needs to be accumulated to prepare for the next pandemic.

Conclusion

This unprecedented infectious disease that struck humanity has led to numerous studies worldwide. For new infectious diseases, in order to control them at as early a stage as possible, diagnostic and therapeutic methods should be developed as early as possible. Numerous studies have been conducted since the beginning of the COVID-19 outbreak to predict the severity of COVID-19. A number of tools for predicting severe illness have been reported, including genetic factors, humoral factors, and diagnostic imaging techniques.

Historically, respiratory infections have recurred many times, and there is no doubt that another outbreak will occur in the near future. It is hoped that these biomarkers and diagnostic techniques developed all over the world for the COVID-19 pandemic will be useful in the future as well.

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