Risk assessment of progression to severe conditions for patients with COVID-19 pneumonia: a single-center retrospective study

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Abstract

Background

Management of high mortality risk due to significant progression requires prior assessment of time-to-progression. However, few related methods are available for COVID-19 pneumonia.

Methods

We retrospectively enrolled 338 adult patients admitted to one hospital between Jan 11, 2020 to Feb 29, 2020. The final follow-up date was March 8, 2020. We compared characteristics between patients with severe and non-severe outcome, and used multivariate survival analyses to assess the risk of progression to severe conditions.

Results

A total of 76 (31.9%) patients progressed to severe conditions and 3 (0.9%) died. The mean time from hospital admission to severity onset is 3.7 days. Age, body mass index (BMI), fever symptom on admission, co-existing hypertension or diabetes are associated with severe progression. Compared to non-severe group, the severe group already demonstrated, at an early stage, abnormalities in biomarkers indicating organ function, inflammatory responses, blood oxygen and coagulation function. The cohort is characterized with increasing cumulative incidences of severe progression up to 10 days after admission. Competing risks survival model incorporating CT imaging and baseline information showed an improved performance for predicting severity onset (mean time-dependent AUC = 0.880).

Conclusions

Multiple predisposition factors can be utilized to assess the risk of progression to severe conditions at an early stage. Multivariate survival models can reasonably analyze the progression risk based on early-stage CT images that would otherwise be misjudged by artificial analysis.

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Introduction

Since its first report in Wuhan, China, in December 2019, the SARS-CoV-2's outbreak has quickly became a global public health issue, with a total of 168,019 infected, 6,610 deaths and 148 countries affected as of Mar 16, 2020 (World Health Organization, WHO[1]). One of main challenges facing its medical care is the lack of effective tools for selecting patients posing a high risk of mortality at an early stage. Previous studies have explored risk factors associated with severity levels of the pneumonia. For example, Zhou et.al[2] identified that the older age and a high level of D-dimer are associated with in-hospital death, while Shi et.al[3] found that the manifestation of chest CT imaging abnormalities correlates with disease states. However, the joint analysis of time and progression event, as well as the integration of multiple types of input data into risk prediction, have not been thoroughly investigated.

In this study, we reported a retrospectively collected cohort characterized with a large proportion of imported cases. We used this cohort data to develop a competing risks survival model that can predict the real-time risk of progression to severe conditions upon hospital admission for COVID-19 patients.

Methods

Detail methods used for this study can be found in the Supplementary Methods.

Results

Disease process and clinical outcomes

All 338 adult patients enrolled in this study were treated at Shenzhen Third People's hospital, the only designated hospital for COVID-19 patients in Shenzhen city, China. A typical disease process for the patient can be illustrated in Figure S1 (Supplementary Appendix). After hospital admission, one can either progress to severe conditions, or recover from the pneumonia without any severe progression. Among 76 (31.9%) patients who experienced severity, 18 (5.3%) further progressed to critical conditions. As of Mar 8, 2020, 3 (0.9%) patients died, and 45 (13.3%) remained hospitalized. All others were discharged from hospital with recovered health status. The mean duration from symptom onset to hospital admission was 5.1 days, and from admission to severity onset was 3.7 days (Table S1 in the Supplementary Appendix).

Characteristics of the study cohort

To evaluate the progression-related features, we classified the patients as severe or non-severe group based on their severity experience. The time intervals between symptom onset and admission were not significantly different among the two groups (p value=0.264). The summary statistics are shown in Table S2 (Supplementary Appendix). The patient age is bi-modally distributed, with one mode located around 35 years and another at 60 years (Figure 1A). The mean age of the severe group is significantly higher than that of the non-severe group (58.7 versus 46.1). Moreover, the severe group appears to be more overweighed as compared to the non-severe group (Figure 1B). The majority of patients (79%) has a travel history to Wuhan region, the epicenter of initial outbreak, within 14 days before symptom onset. Gender does not have a strong association.

Blood type is not associated with severity outcome, either.

Disease history is not significantly enriched in the severe group, but co-existing hypertension or diabetes do have such significance. The common symptoms at admission are fever (60.7%), cough (52.4%), fatigue (15.1%), sore throat (10.9%), muscle ache (10.1%) and diarrhea (9.8%). The severe group has a significantly higher rate of presenting fever or fatigue when compared to the non-severe group.

Laboratory testing results

The testing was performed on blood samples collected immediately after hospital admission. Their association with severity classification were summarized in Table S3 (Supplementary Appendix). The severe group has a significantly lower number of platelet and lymphocytes but increased levels of coagulation function indicators such as fibrinogen, d-dimer and activated partial thromboplastin time. As for blood biochemistry, the biomarkers with a significantly increased level in severe group as compared to that of non-severe group include lactate dehydrogenase, myoglobin, aspartate transaminase, mitochondrial-aspartate transaminase, creatine kinase myocardial band, troponin I, N-terminal brain natriuretic peptide, γ-glutamyl transpeptidase and alpha-hydroxybutyrate dehydrogenase, while those with decreased levels include albumin and prealbumin. For the infection-related biomarkers, we observed a significant increase in C-reactive protein, interleukin-6, procalcitonin and erythrocyte sedimentation rate in severe group, all of which have a mean level beyond the upper bound of normal reference. We also observed an abnormal level of blood oxygen like PaO2/FiO2 ratio and kidney function indicators including

glomerular filtration rate, cystatin C and β2-Microglobulin. The lactic acid tested at an early stage is not associated with severity outcome.

To investigate the pattern of dynamic variation of CD4+ T cells, we plotted the cell counts against the time since symptom onset, stratified by the severity classification (Figure 1C). The severe group has decreased number of the cells in first 10 days after symptom onset. This number increased in next 10 days and plateaued after then. We also observed that the levels of C-reactive protein tend to converge at a late stage during hospitalization for the two groups (Figure 1C).

Pattern of disease progression

To assess the risk pattern of disease progression during hospitalization, we performed competing risks analysis on the time-to-event data. The cumulative probability (aka. cumulative incidence function) of severity onset continues to increase immediately after hospital admission, but arrives its change point at day 10 (Figure 2). In contrast, the cumulative incidence of the competing risks event, that is, being discharged because of recovery, is much smaller during the high risk period of severity onset. However, such incidence dramatically increases from around day 12 to 29.

Risk prediction of progression

To personalize the time-dependent risk assessment of severe progression, we incorporated CT image data with baseline information for the risk modeling (Figure 3). A total of 348 quantitative features were extracted from 3D re-constructed chest CT scan images generated upon admission. Clustering analysis showed that there exists a subset of features that can distinguish severe from

non-severe group (Figure 3A). We then computed same features from earliest CT scans after admission for each patient, and trained a risk prediction score using high-dimensional survival modeling. The model integrating CT and baseline variables significantly outperformed the univariate model and multivariate model using only baseline information (Figure 3B, 3C). The best model achieved a mean time-dependent AUC of 0.880 (sd=0.011) and a mean prediction error of 0.079 (sd=0.024). We also developed a model integrating laboratory biomarkers tested at a time within one day of admission. This model has a mean AUC of 0.884 (sd=0.049) and a mean prediction error of 0.103 (sd=0.031) (Figure S2 in Supplementary Appendix).

We presented four cases of study to exemplify the usage of the CT image-based risk assessment tool (Figure 4). Case I and II are similar in age and BMI. Case I had unilateral ground-glass opacities on CT images, while case II had more obviously bilateral opacities (Figure 4A, 4B). However, in reality, case I, rather than case II, had progressed to severe conditions. Consistently, our model predicts the cumulative probabilities of developing severity for case I within next 1, 3, and 5 days as 0.032, 0.073, 0.121, as compared to 0.001, 0.003, 0.005 for case II, respectively (Figure 4C). The presence of fever symptom on admission for case I adds the discriminative power for the model. In another scenario, case III and IV have similar age, BMI and fever symptom, but case III had multifocal ground-glass opacities and consolidations (Figure 4A, 4B). Case III progressed quickly within 2 days after CT scan, while case IV had no severe progression. Accordingly, our model predicts the cumulative probabilities of developing severity for case III within next 1, 3, and 5 days as 0.215, 0.427, 0.613, as compared to 0.026, 0.058, 0.098 for case IV, respectively (Figure 4C). The disparity in CT imaging manifestation contributes significantly to

the reasonable risk assessment for this example.

Discussion

We delineated the characteristics of a retrospective cohort of 338 adult patients collected at a single center from Shenzhen city of China, and developed a non-invasive method to evaluate the risk of progression to severe conditions. The independent predisposition factors of progression include old age, high BMI, fever, and co-existing hypertension or diabetes diseases. However, using age as a single prognostic factor could lead to erroneous results since young patients were not necessarily progression-free. Different from previous studies[4-6], the severe group in this cohort has a significantly higher proportion of patients with fever symptom at admission (82.9% vs. 54.2%). Moreover, we identified, for the first time, that overweight is associated with disease severity. These findings benefit the risk assessment analysis as we showed that a model combining these indicators can substantially improve the prediction performance as compared to a model that only contains univariate predictor (mean time-dependent AUC= 0.824 versus 0.751).

SARS-CoV-2 entry host cell through angiotensin-converting enzyme 2 (ACE2)[7], whose expression can be enhanced by the usage of hypertension medicine such as ACE inhibitors or angiotensin II type-I receptor blockers (ARBs)[8]. Whether such medication is a causal factor for a higher risk of COVID-19 progression is thus under investigation[9]. In our study, we observed that the co-occurred hypertension disorder is significantly related to severe progression, but we did not found association between the medication and severity outcome among hypertension patients.

COVID-19 pneumonia is a multistate disease with clinically relevant intermediate endpoint like severity onset. Most survival data analyses set the onset as the primary end point, and censor recovery or hospital discharge. However, when competing risks of severity onset are present, this analytical method induces bias. In this study, the risk of severe progression assessed without considering the competition would be overestimated because the patients who would never progress (those who discharged from hospital without progression) were treated as if they could progress. The extent of such bias and its adjustment by competing risks modeling have been evaluated in clinical virology and oncology research[10-13]. We incorporated high-dimensional variable selection techniques into the competing risks modeling so that quantitative image features can be extensively evaluated according to their contribution to risk prediction. Our evaluation results showed that incorporating CT image can significantly improve the prediction performance as compared to those only based on demographical and clinical information (mean time-dependent AUC = 0.880 versus 0.824). In particular, such improvement was achieved with only one additional image feature, suggesting the importance of using multi-modality data in risk analysis.

The laboratory testing results in this study showed that, at the time of admission, the severe group patients already presented a sign of function impairment in organs such as liver (eg: lactate dehydrogenase and prealbumin), heart (eg: multiple types of myocardial enzymes including troponin I, N-terminal brain natriuretic peptide, creatine kinase myocardial band, mitochondrial-Aspartate transaminase and Aspartate transaminase) and kidney (eg: glomerular filtration rate, cystatin C and β2-Microglobulin). The signal of abnormality in blood oxygen also emerges, as PaO2/FiO2, a ratio used to determine severity onset in this study, showed a significant,

although not ideal, difference between the two groups upon admission. Consistent with previous studies[2,5,6,14,15], the severe group of this cohort demonstrated, at an early stage, a substantial increase in inflammatory factors such as C-reactive protein and interleukin-6, and dysfunction of coagulation. Incorporating laboratory biomarkers tested at an early stage can also significantly improve risk prediction performance as compared to the best model without considering them (mean AUC = 0.884 versus 0.813).

We are still left with a few possible extensions. First, the laboratory testing data had not been integrated into the CT image-based model because blood sample was not collected along with imaging in the center. A more complicated statistical model is required to account for the error caused by time difference inherent in input data. Second, the occurrence of severity may depend on other factors such as treatment, viral load or genetic factors. Our model can include such additional covariates. However, the availability of well-processed data on these factors is scarce, and we have shown that the current model can have reasonable prediction performance even without considering them. Third, because of limited sample size of patients progressed to severity, we only evaluated model prediction performance by cross-validation. Further validation needs to be conducted on external datasets. Fourth, we restricted our analysis of the severe group up to the severity onset. Factors related to the recovery from severe conditions have not been evaluated. Finally, this study does not include young patients (age<18).

To our knowledge, this is the first attempt to estimate the real-time occurrence risk of severity from a cohort featured with a significant amount of imported cases. We believe that the results

from this study will be helpful to medical practitioners as they consider how to better manage the care of COVID-19 pneumonia patients upon admission.

Reference

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Figure 1: Analysis of representative features significantly associated with the severe group. A, the age distribution of the study cohort, which is overlaid with kernel density estimates (solid curve); B, boxplot summary of the age and BMI as stratified by the severe and non-severe group; C, levels of individual laboratory biomarker plotted along with the time after symptom onset. Data at the same day from multiple patients were collapsed together and only the median value (solid dots) was shown.

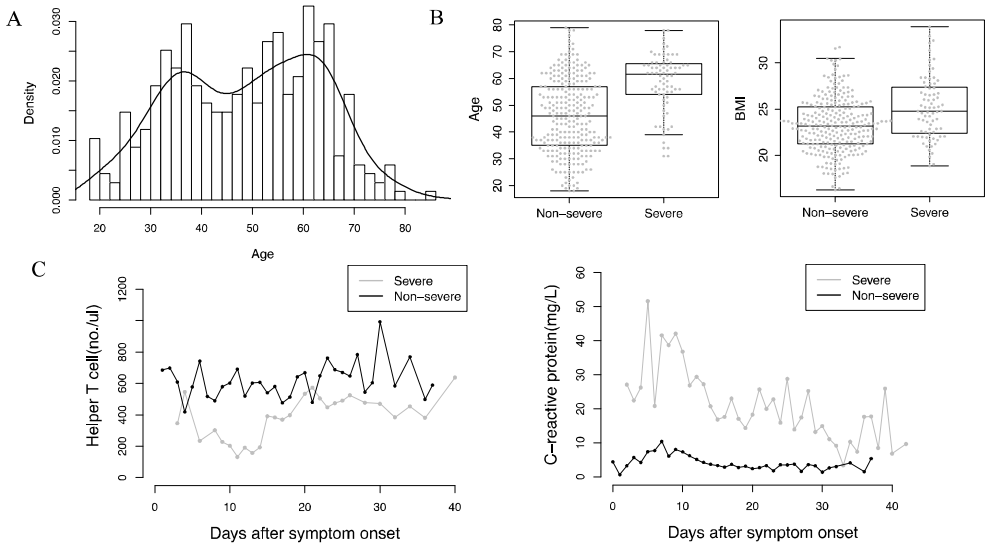

Figure 2: Cumulative probability of developing severe conditions or being discharged from hospital after hospital admission for the study cohort.

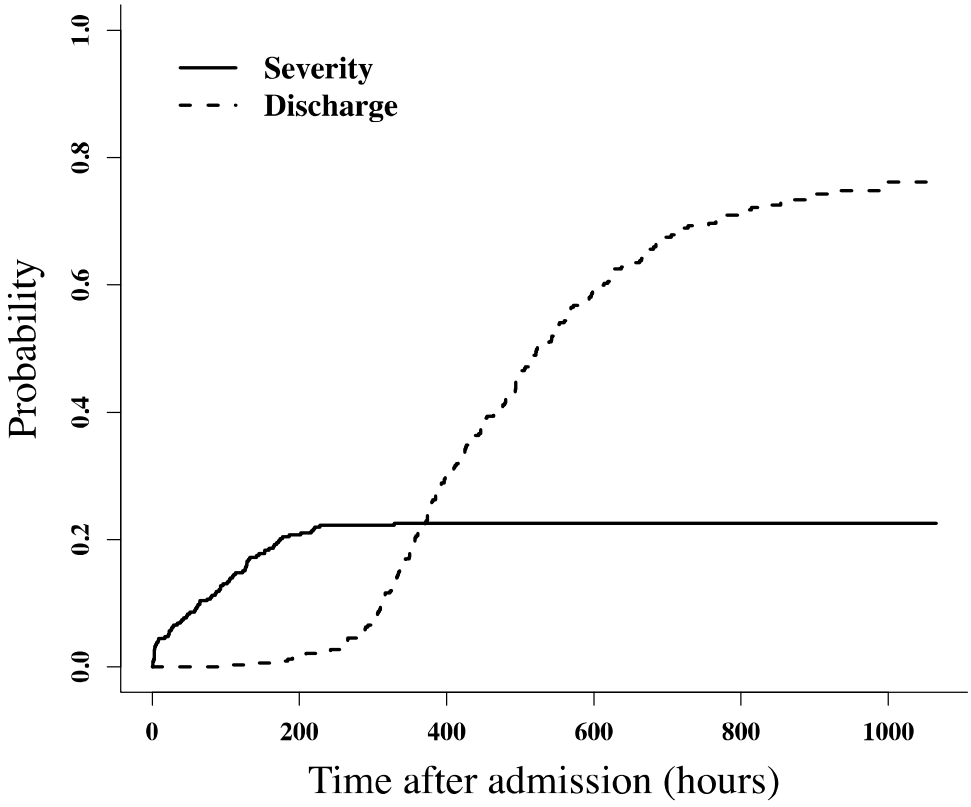

Figure 3: Workflow of the CT-based risk prediction model development. A, heatmap analysis of quantitative features extracted from CT images, stratified by progression outcome; B, model prediction performance evaluation by time-dependent ROC method; C, model prediction performance evaluation by time-dependent prediction error method.

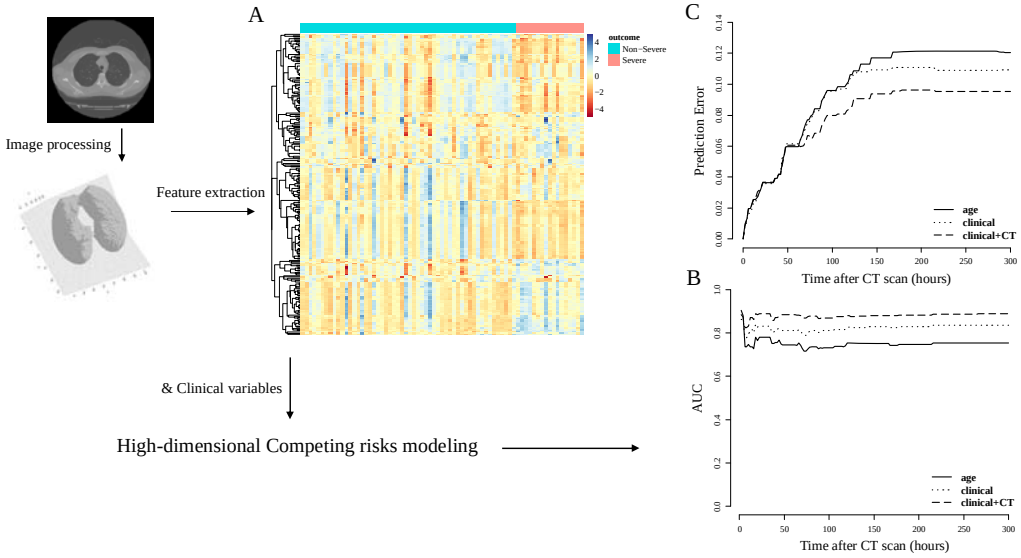

Figure 4: Illustration of applying the risk prediction model in clinical setting. A, Baseline information about the four example cases. The time interval indicates the time between CT scan and severity onset if with severe progression, or time between admission and hospital discharge if with no such progression; B, CT scan of the four cases; C, Risk prediction results of the four cases. Red arrow indicates the lesion of patient IV. The prediction score is shown in the figure legend.

A

Case ID	Age	BMI	Fever at admission	Severe progression	Time interval (hours)
I	36	21	Yes	Yes	167
II	37	19	No	No	574
III	64	26	Yes	Yes	48
IV	68	32	Yes	No	905