# History of Coronary Heart Disease Increases the Mortality Rate of Coronavirus Disease 2019 (COVID-19) Patients: A Nested Case-Control Study Based on Publicly Reported Confirmed Cases in Mainland China

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## Abstract

**Background:**

China has experienced an outbreak of a novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since December 2019, and it was announced a worldwide pandemic in March 2020. There is limited evidence on the mortality risk effect of pre-existing comorbidity for clinical disease (coronavirus disease 2019 [COVID-19]), which has important implications for early treatment.

**Objective:**

To evaluate the risk of the common preexisting comorbidities, including hypertension, coronary heart diseases (CHD), respiratory diseases and diabetes on COVID-19 mortality, and provide clinical suggestions accordingly.

**Method:**

This study used a nested case-control design to assess the impact of pre-existing comorbidities on the hazard of COVID-19 in mainland China. A total of 321 publicly reported confirmed cases (146 cases and 175 controls) with trackable time-to-death information and history of comorbidities were collected between December 18$^{th}$, 2019 and March 8$^{th}$, 2020. Each case was matched with three controls on gender and age $\pm$ 3 years old. Inverse probability weighted Cox proportional hazard model was used to assess the death risk of comorbidities of interest.

**Results:**

History of comorbidity significantly increases the death risk of COVID-19: one additional pre-existing comorbidity will lead to an estimated 29% higher risk of death (p=0.01). Patients with CHD had a 92% higher risk of mortality, compared to patients without CHD (p=0.009), along with an estimated 13 days (95% CI: 11- 23 days) of median survival time.

**Conclusion:**

This study provides substantial evidence, related pathophysiological mechanisms and clinical suggestion for higher mortality risk in COVID-19 patients with pre-existing CHD. Extra care and early medical intervention maybe needed for patients with pre-existing CHD.

## Introduction

Since the first report of Coronavirus Disease 2019 (COVID-19) in December 2019 in Wuhan, Hubei Province, China, the novel virus infection has rapidly spread to other cities in China, and has now been detected in 186 countries and locations internationally[1]. On March 11th, 2020, the World Health Organization declared COVID-19 a pandemic, and has called for aggressive actions from all countries to fight the disease. Current research has indicated that COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a betacoronavirus similar to the severe acute respiratory syndrome-coronavirus (SARS-CoV) in the genetic sequence [2]. Epidemiological evidence suggests that initially reported cases in China had a history of exposure to the Huanan seafood market [3][4]. With the escalated spread of the infection, there has been clear evidence of human to human transmission [5][6]. The most common symptoms include fever, dry cough and fatigue [5][6][7][8], with presence of asymptomatic, yet contagious cases [9].

According to the COVID-19 situation reports of WHO, as of March 23rd, 2020, the infection has caused 81,498 confirmed cases in mainland China, including 3,267 deaths. Internationally, a total of 288,275 confirmed cases have been reported from 186 countries outside of, including 9,517 deaths. Considering the global public health threat posed by COVID-19, unraveling the prognostic factors for patients, especially the risk factors of mortality associated with COVID-19, has important implications for clinical practice and is urgently warranted.

Studies have indicated that severe cases tend to be older in age [6][8] and are more likely to have had pre-existing medical conditions, including but not limited to hypertension [3][6][8], diabetes [6][8], cardiovascular diseases [3][6][8], cerebrovascular diseases [6], chronic obstructive pulmonary disease (COPD) [3][8], cancer [10], and digestive diseases [11], in comparison to non-severe cases [3][6][8][9][10][11][12].

Recently, scholarly attention has been directed at identifying the risk factors for death from COVID-19. Some evidence suggests that the presence of pre-existing medical conditions are likely death risk factors for COVID-19. A study based on 72314 cases in China indicated that the case-fatality rate (CFR) tend to be higher among those with older, pre-existing cardiovascular disease, diabetes and hypertension compared to all the patients [9]. Similarly, Zhou et al [13] investigated the mortality risk factors among 191 COVID-19 patients in Wuhan City, Hubei

Province in China, and found that older age, higher Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1ug/ml at hospital admission were associated with increasing odds of in-hospital death. However, those suggestive findings on pre-existing comorbidities were from univariate comparison, which did not account for any important confounders of comorbidities such as age and gender [14][15][16][17].

In addition, upon the time of submission on March 23rd, the comorbidity-related study on COVID-19 has only been focusing on using risk factors to predict the binary outcome, simply whether or not the death will occur [13]. No study has been published to reveal the hazard of the identified risk factors over time, or the probability of survival at a given time. Moreover, most existing studies did not consider the location of diagnosis and pandemic stage when evaluating risk factors for mortality. Current research has found that the clinical symptom severity [5] and the fatality-case rate [9][18] to be higher in Hubei Province (the center of outbreak) than cities outside of Hubei Province in China. Further, it has been found that average daily attack rate in China was different before and after January 11th 2020, since non-pharmaceutical interventions were taken by the government before this date [19]. As a result, only examine cases in Hubei Province and assuming constant effect over time might be invalid under the rapidly changing pandemic situation.

Therefore, given the limited understanding about the risk factors for mortality associated with COVID-19, more empirical research and stronger statistical evidence is needed to evaluate the COVID-19 mortality risk attributed to pre-existing comorbidities, considering various confounders, temporal difference and including samples from locations outside of Hubei Province. The present study aimed to fill these gaps by evaluating the risk of the common pre-existing comorbidities, including hypertension, cardiovascular diseases, diabetes and respiratory diseases for COVID-19 mortality over time, and providing clinical suggestions accordingly. To attain this goal, we collected 321 publicly reported cases, including 146 deaths and 175 survivors. To minimize the potential selection bias, the data collection and inclusion criteria strictly follows the procedure of nested case-control design (NCC) [20], a popular epidemiological study design for identifying the risk factors for clinical events [21]. NCC has been widely used in studying the fatal disease risk effect in large pharmacoepidemiologic studies [22][23][24][25][26][27] and risk prediction in pandemic influenza A (H1N1) 2009 (pH1N1) [28]. Due to cost-effective in data collection, NCC is especially suitable in cases like studying

the death risk of COVID-19, where the number of event-free people exceeds those who experienced events [29].

## Method

### Study design and rationale

This study used a nested case-control (NCC) design to assess the impact of pre-existing comorbidities on the hazard of COVID-19 in mainland China. NCC, also called incidence density sampling or risk set sampling, is popular in rare-event epidemiological studies to reduce the cost of analyzing the large number of event-free observations [17]. In the NCC study design, all the events in the study cohort were included as "cases," while for each case, a certain number of "controls" were randomly sampled from people "at risk" when the case event was observed.

In this study, we routinely searched for daily news and public health reports on confirmed COVID-19 cases in mainland China, and collected corresponding demographic and clinical data on national/provincial/municipal health commission websites, the official COVID-19 data reporting websites in mainland China. The study cohort was defined as all the publicly reported laboratory-confirmed COVID-19 patients who had trackable survival dates and complete information on comorbidity history during the study period.

The data collection procedure began December 18$^{th}$, when the first laboratory-confirmed case was announced, and ended March 8$^{th}$, 2020. Follow-up time was defined as the duration from the date of disease onset till the end of observation on March 8$^{th}$ or when the participant died, whichever came first. For each eligible patient, we followed local reports to update their survial status until the end of follow-up time.

### Data collection

As illustrated in Figure 1, the inclusion criteria includes: (i) any publicly reported COVID-19 patients who had complete information on basic demographics (age, sex and region), follow-up date (disease onset date--the first time a patient became symptomatic, diagnosis date, death/discharge date) and history of comorbidities (hypertension, cardiovascular disease, diabetes and respiratory diseases); (ii) only those who was mentioned "no pre-existing medical condition/comorbidity" were included as comorbidity-free patients; and (iii) asymptomatic patients, whose onset time was unclear, were not included in this study.

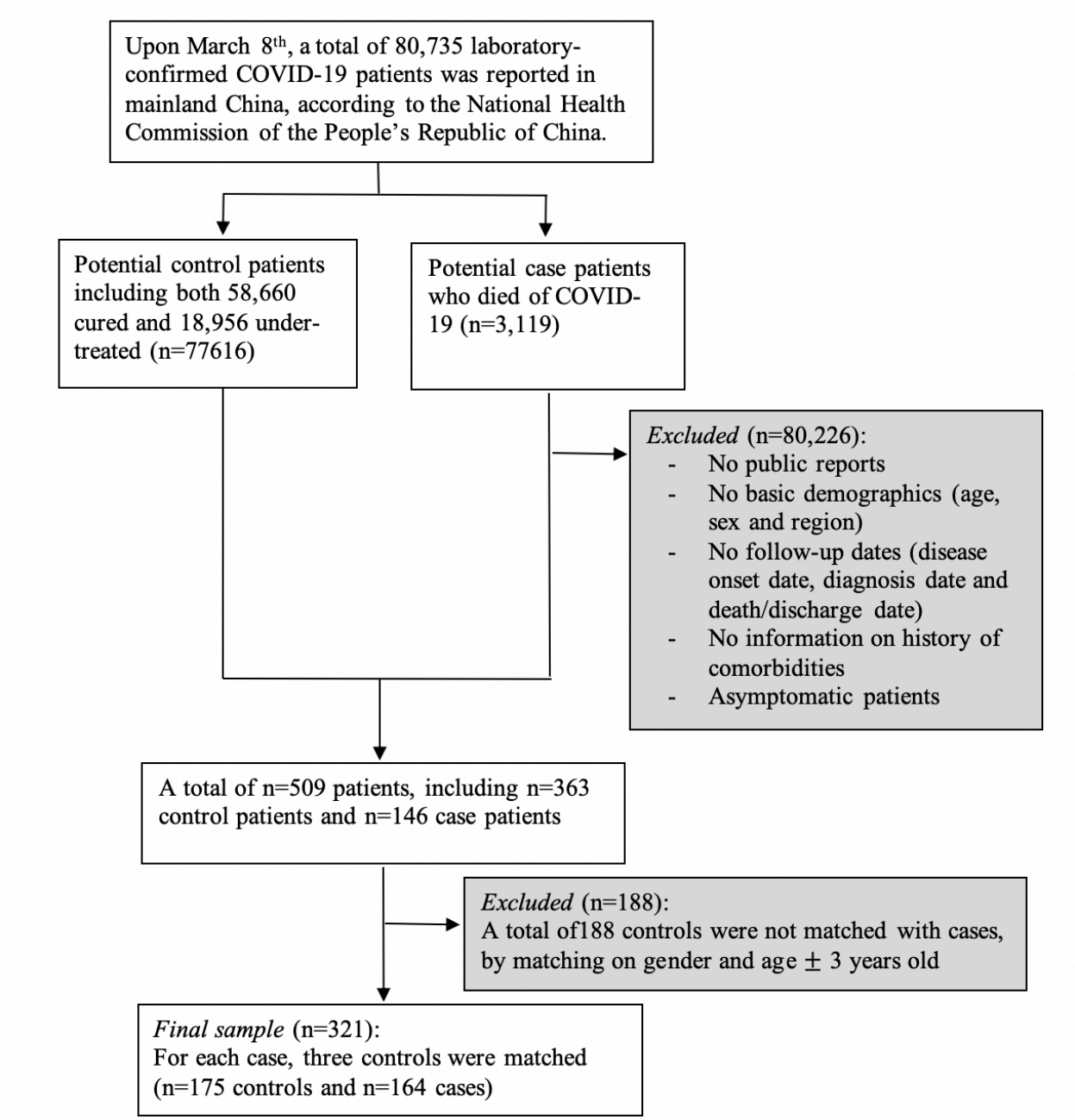


**Figure 1**: Patient flow diagram detailing included subjects and exclusion criteria

To increase efficiency and adjust for confounders, the corresponding controls of each case were also matched on gender and age ± 3 years old. The matching process was implemented via KMprob function in multipleNCC R package [30].

To minimize the impact of dropping patients with missing follow-up time, we used dynamic tracking to largely fill in the missing dates. For example, the No. 261 patient was collected in the following 3 steps:

**Step 1.** Search on Baidu (Chinese version of Google) using keywords "confirmed COVID-19 cases report" and "pre-existing comorbidities." We found on the website of Municipal Health Commission of Binzhou (Shandong Province) reported one confirmed case on February 17th:

"*the 15th confirmed case: 30-year-old male without pre-existing morbidities, who lives in the neighborhood of Xincun Village. This patient was diagnosed positive on February 16th and is being treated with precaution in Bincheng hospital."*

We recorded age, gender, region and comorbidity-free for this patient.

**Step 2.** We then determined the onset date of this patient from another announcement on the same website. In this announcement titled "*Possible exposure locations and times of the 15th confirmed case,*" it says, "*the patient was symptomatic on February 14th."*

**Step 3.** Finally, we confirmed the event status of this patient as discharged on March 3rd, by following the updates on this website.

**Statistical analysis**

Analyses were performed in R 3.6.2 (R Foundation for Statistical Computing). Baseline clinical characteristics and symptoms were shown as mean (SD), median (range), or number (%), with comparison of characteristics in subjects stratified by survival status via t test for continuous variables and chi-squared or Fisher's exact test for binary ones.

In order to utilize the time-to-event information under a retrospective nested case-control design, inverse probability weighting Cox proportional hazard regression model was employed [31]. The matching between cases and controls and relevant weights were simultaneously obtained via KMprob function in multipleNCC R package [30], by specifying the Kaplan-Meier type weights with additional matching on gender and age $\pm$ 3 years old. Only survivors were assigned weights, since all cases (deaths) were included as designed with a weight of one. Those survivors with sampling probabilities of zero was considered as "fail to match" and excluded from the study.

We combined all the lung-related disease (chronic obstructive pulmonary disease, chronic pneumonia, lung cancer etc.) as an integrated category, called lung disease. The total number of pre-existing comorbidities was defined as the total number of pre-existing among hypertension, coronary heart disease (CHD), chronic bronchitis, lung disease and diabetes, ranging from zero to four.

Kaplan-Meier curve were plotted to check the proportional hazard assumption and Pearson correlation test was used to rule out the multicollinearity concern before fitting any model. Univariate weighted Cox models were performed for each of the comorbidity of interest. Multivariate weighted Cox model was used to determine if pre-existing comorbidity yielded prognostic hazard information. Other than the common risk factors (age, gender and history of surgery), the multivariate model also adjusted for location of diagnosis (in vs. outside of Hubei Province) and early period of pandemic (after vs. before January 11$^{th}$, 2020 when no-intervention was taken by the government) [20]. Although matching was based on age and gender, we adjusted for the matching covariates, since the matching was broken with inverse probability weighting [31]. A separate multivariate model was built by using the total number of pre-existing comorbidities as an ordinal predictor, adjusting for the same covariates. Hazard ratios (HRs) from weighed Cox model were reported along with 95% confidence intervals (CIs) and p-values. Sensitivity analysis was performed using multivariate logistic regression to provide estimated odds ratio (ORs), which includes the same covariates as the multivariate weighted Cox model. Unweighted Cox model-based survival estimates were plotted to show unadjusted survival probability. Log-rank test was used to compare the median survival difference.

### Ethics Approval

The study was approved by Shanghai Jiao Tong University Public Health and Nursing Medical Research Ethics Committee (SJUPN-202001).

## Results

### Sample Description

Upon March 8$^{th}$, 2020, the National Health Commission of China reported 80,735 laboratory-confirmed COVID-19 patients, including 58,600 cured and 3,119 deaths across all Chinese provinces. In our sample, we had a total of 321 samples, 146 deaths and 175 survivors.

To visually illustrate how well our sample represents the national patient distribution in China, we plotted the sample distribution in Appendix Figure A1.

Table 1 summarizes the patient demographics and pre-existing medical conditions. Results are presented for all patient in the study (n=321), as well as for survivors (n=175) and deaths (n=146), respectively. The mean age of the total samples was 62.1 years old (SD=16.2, range [24, 91]), with an average of 56.5 years old in the survivor group and 68.9 years old in the death group. Median ages were similar to mean ages in both groups. We had a higher proportion of male sex (60.1%) in the sample, a half of whom survived, while around 60% of the female survived. Overall, 26.2% of patients were diagnosed in Hubei Province, among whom 71.4% died. In contrast, we have 151 survivors and 86 deaths from locations outside Hubei Province. In the sample, 60% of the total patients had COVID-19 onset after January 11$^{th}$, 2020, while 40% were infected before that.

Among all five pre-existing comorbidities of interest, hypertension was the most common (36.4%), followed by diabetes (25.9%), CHD (14%), lung disease (8.1%) and chronic bronchitis (4.0%), with the same order in both survivor and death groups. The total number in each cumulative comorbidity's category decreased as the number increased: a total of 43.9% patients had no pre-existing comorbidities, while around 30% had one, 20.9% had two, and less than 5% had three or four. Similar patterns can be observed in stratified groups.

**Table 1.** Patient Characteristics, stratified by survival status*

| | Overall (N=321), n (%) | Case (deaths) (N=146), n (%) | Control (survivors) (N=175), n (%) | P Value† |
|---|---|---|---|---|
| **Matching variables** | | | | |
| Age | | | | |
| Mean (SD) | 62.1(16.2) | 68.9 (13.8) | 56.5 (15.9) | <0.001 |
| Median (Min, Max) | 65.0 [24.0, 91.0] | 69.5 [25.0, 89.0] | 56.0 [24.0, 91.0] | - |
| Male | 193 (60.1) | 94 (64.4) | 99 (56.6) | NA |
| **Other covariates** | | | | |
| In Hubei Province | 84 (26.2) | 60 (41.1%) | 24 (13.7) | <0.001 |
| Before 01/11/2020 | 131 (40.8) | 66 (45.2%) | 65 (37.1) | 0.18 |
| History of surgery | 11 (3.4) | 9 (6.2) | 2 (1.1) | 0.03 |
| **Pre-existing comorbidities** | | | | |
| Hypertension | 117 (36.4) | 66 (45.2) | 51 (29.1) | 0.004 |
| CHD | 45 (14.0) | 33 (22.6) | 12 (6.9) | <0.001 |
| Chronic bronchitis | 13 (4.0) | 8 (5.5) | 5 (2.9) | 0.37 |
| Lung disease | 26 (8.1) | 18 (12.3) | 8 (4.6) | 0.02 |
| Diabetes | 83 (25.9) | 41 (28.1) | 42 (24.0) | 0.48 |
| Total number of pre-existing comorbidities | | | | |
| 0 | 141 (43.9) | 46 (31.5) | 95 (54.3) | <0.001 |
| 1 | 96 (29.9) | 47 (32.2) | 49 (28.0) | 0.49 |
| 2 | 67 (20.9) | 42 (28.8) | 25 (14.3) | 0.002 |
| 3 | 14 (4.4) | 9 (6.2) | 5 (2.9) | 0.24 |
| 4 | 3 (0.9) | 2 (1.4) | 1 (0.6) | 0.87 |

*Mean (standard deviation) is reported for the continuous variables and the counts (%) for categorical variables. p values were calculated by t test, $\chi 2$ test, or Fisher's exact test, as appropriate.

† NA: exact matching on categorical variablesex

CHD: coronary heart disease

## Survival time

The overall median follow-up was 43 days, during which 146 deaths were observed. Figure 1 shows the estimated survival probability over 80 days for patients with and without CHD. For patients with pre-existing CHD, the estimated median survival time was 13 days (95% CI [11-23] days), while it was over 80 days for those without CHD ($p<0.001$).

In addition, COVID-19 patients with pre-existing hypertension or lung disease also had a significantly shorter median survival time, compared to those without. The estimated median survival time was 25 days ($p<0.001$) and 13 ($p<0.001$) days, respectively.

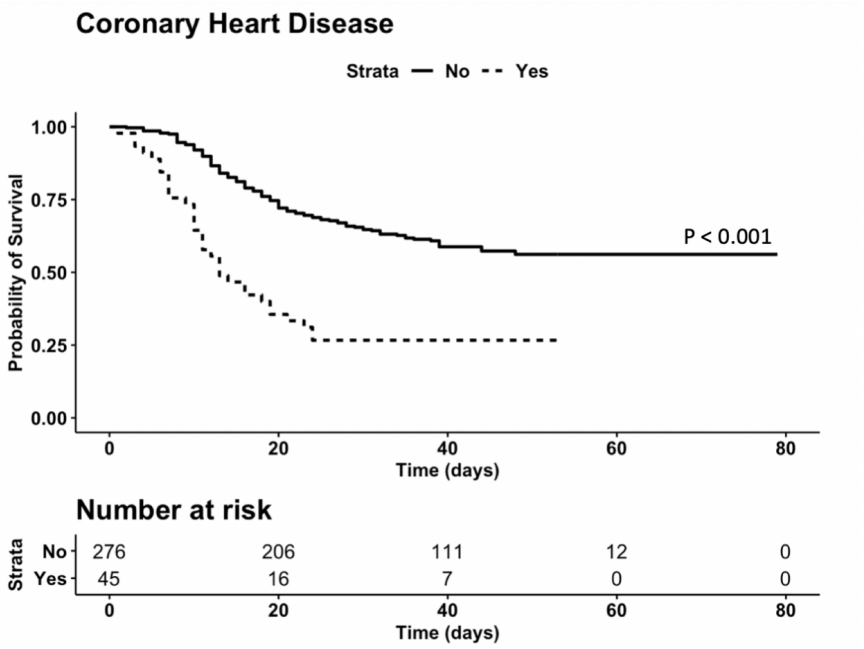


**Figure 2**: Kaplan-Meier survival curve estimated from unweighted & unadjusted Cox proportional hazard regression for patient with (dashed line) and without (solid line) CHD. The estimated median survival time was 13 days for patients with pre-existing CHD, while over 80 days for those without ($p<0.001$).

## Model Results

The result of Pearson correlation test and proportional hazard test (both not shown here) showed that the comorbidities of interest were not correlated, and the assumption of proportional hazard was not violated.

Table 2 presents the results of univariate and multivariate weighted Cox models. Older age, male sex and patients diagnosed in Hubei Province were associated with significantly higher death risk with similar magnitude across models. In the adjusted Cox model, every 5-year increase in age was associated with an estimated 33% higher risk of death ($p<0.001$); male sex had an estimated 72% higher death risk than females; and patients diagnosed in Hubei Province were estimated to be 2.64 times more likely to die, compared to those in other locations. Diseases onset during early no-intervention period was associated with a higher risk of death, although no significant hazard ratio was found. History of surgery was significant in unadjusted model (HR=5.6, 95% CI 2.2-14.5, $p<0.001$).

**Table 2.** Univariate and multivariate model result from weighted Cox proportional hazard regression

| Characteristic | Univariate | | Multivariate | | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Age | 1.07 (1.05-1.08) | **<0.001** | 1.06 (1.05-1.08) | **<0.001** | 1.06 (1.04-1.07) | **<0.001** |
| Male | 1.55 (1.01-2.38) | **0.05** | 1.78 (1.20-2.66) | **0.005** | 1.72 (1.14-2.61) | **0.01** |
| Hubei province | 3.18 (2.03-4.97) | **<0.001** | 2.64 (1.80-3.88) | **<0.001** | 2.64 (1.80-3.88) | **<0.001** |
| Before 01/11/2020 | 1.29 (0.85-1.96) | 0.23 | 1.20 (0.82-1.76) | 0.35 | 1.24 (0.84-1.83) | 0.27 |
| History of surgery | 5.60 (2.17-14.48) | **<0.001** | 0.76 (0.27-2.09) | 0.59 | 0.67 (0.21-2.08) | 0.48 |
| Hypertension | 2.52 (1.66-3.83) | **<0.001** | - | - | 1.43 (0.94-2.18) | 0.09* |
| CHD | 4.85 (2.87-8.17) | **<0.001** | - | - | 1.92 (1.17-3.14) | **0.009** |
| Chronic bronchitis | 1.41 (0.45-4.45) | 0.55 | - | - | 1.44 (0.74-2.81) | 0.29 |
| Lung disease | 3.99 (2.18-7.29) | **<0.001** | - | - | 1.49 (0.83-2.67) | 0.19 |
| Diabetes | 1.45 (0.91-2.31) | 0.12 | - | - | 0.87 (0.56-1.36) | 0.55 |
| Total number of comorbidities | 1.87 (1.53-2.29) | **<0.001** | 1.29 (1.06-1.57) | **0.01** | - | - |

HR=hazard ratio; CHD=coronary heart disease.

Bold: statistically significant $p<0.005$

* Marginally significant $p<0.1$

In a separate adjusted model, history of comorbidities was significantly associated with a higher death risk (p=0.01). Moreover, every unit increase in comorbidity was associate with 29% risk increase in mortality.

All comorbidities of interest were associated with higher risk of COVID-19 mortality in the univariate model, of which CHD had the largest hazard ratio (HR) of 4.85 (p<0.001), followed by lung disease (HR=3.99, p<0.001), hypertension (HR=2.52, p<0.001), diabetes (HR=1.45, p=0.12) and chronic bronchitis (HR=1.41, p=0.55). After adjusting for age, sex, in vs outside Hubei Province, early period and history of surgery, CHD was the only comorbidity that yielded a significant death risk. The result shows that COVID-19 patients with pre-existing CHD had an estimated 92% higher death risk than those without CHD, adjusting for other confounders. In addition, hypertension had a marginally significant HR of 1.43 (p=0.09).

**Discussion**

In this paper, we used survival analysis to estimate the fatal risk of pre-existing comorbidities in COVID-19 in mainland China, adjusting for the confounding effect of age, gender, history of surgery, locations in and outside of Hubei Province, and early period of pandemic when no-intervention was taken. We first showed that a history of comorbidities significantly increased the death risk of COVID-19: one additional pre-existing comorbidity led to an estimated 29% increase of death risk (p=0.01). However, after adjusting for confounders, CHD was the only significant risk factor for COVID-19 mortality after adjusting for confounders. Patients with CHD had 92% significantly higher risk of mortality in COVID-19, compared to patients without CHD (p=0.009). The estimated median survival times for those with CHD was 13 days (95% CI: 11-23 days), at lease 67 days shorter than those without CHD (p<0.001). Moreover, we estimated that COVID-19 patients with hypertension had 43% higher death risk, compared to those without hypertension (p=0.09). Although the p-value was marginally significant, it is worth noting since hypertension is a major risk factor of CHD [32].

To our best knowledge, the present study is the first to provide substantial statistical evidence to show the risk effect of CHD in COVID-19 in mainland China, which reinforces the previous finding that the case-fatality rate tends to be higher among patients with cardiovascular disease [9] [12]. It is worth pointing out that the existing studies [9][13] that investigate prognostic factors for death used chi-square tests or univariate logistic regression that does not

control for potential confounders. In contrast, by conducting weighted Cox proportional hazard regression model, our study used time-to-event outcomes, which offers more information and more statistical power to detect risk factors [33][34]. This can also explain the different statistical significance between the weighted Cox model (p=0.01) in the main analysis and the sensitivity analysis result using unweighted logistic regression (p=0.12) when evaluating the risk of total number of pre-existing comorbidities (Appendix Table A1).

Substantial studies have indicated that cardiovascular events following pneumonia may increase the risk of mortality [35][[36][[37][[38][[38][[40][[41][[41], which explained our finding from the point view of pathophysiological mechanisms. One potential mechanism underlying the association between pneumonia and cardiovascular events is inflammation [38]. Specifically, the inflammatory reaction following pneumonia can result in plague instability and damage in the blood vessels, where evidences of elevated local inflammation in the atherosclerotic coronary arteries following acute systemic infections have been shown in many studies [38][40]. Thus, infections may result in heightened loading imposed on cardiomyocytes, and lead to sympathetic hyperactivity, ischemia, which may increase the risk of arrhythmia and heart failure in COVID-19 patients with pre-existing CHD [37].

Given the limited understanding of the prognostic factors for COVID-19, more research is needed to investigate the mechanism by which pre-existing CHD may increase mortality risk among patients with COVID-19. From the clinical point of view, early evaluation of patient medical history is necessary to possibly decrease the mortality risk. we suggest monitoring the dynamic heart rate for patient with pre-existing CHD. For those severe-symptomatic patients who had pre-existing heart ischemia and abnormal heart function, early medical intervention maybe needed [45].

Our study contains 73.8% samples from regions outside Hubei Province. Our results indicate that the death risk of COVID-19 in the regions that had exceeded its maximum health care capacity (Hubei Province) was 2.64 times of those regions with sufficient medical resources (regions outside Hubei Province) ($p<0.001$). Similarly, the estimated median survival time was significantly lower in Hubei Province, compared to those outside of Hubei Province (19.5 days vs. over 80 days, $p<0.001$). This suggests that it is critical to save more patients by either quickly increasing the medical care capacity to accommodate the explosive infection number or quickly controlling the patient number beneath the capacity limit. This conclusion is consistent with the

CDC report [43] and another recent study which provided evidence of effective non-pharmaceutical interventions in controlling the pandemic in Wuhan by reducing the infective rate in a short amount of time [19].

Furthermore, our results indicated that hazard of COVID-19 death was significantly higher in male patients and patients at older age. Adjusting for others, every 5-year increase in age was associated with 33% increased risk of death, similarly to what was found in previous studies [8][9][13]. Unlike previous studies which did not find gender to be a significant factor predicting the risk of severe cases or mortality [3][6][7][13], we found that male patients had 72% higher risk of death compared to females ($p=0.01$). More research is needed to investigate the mechanism underlying gender differences in risk of mortality associated with COVID-19. Alongside the evidence of prognostic risk in CHD, we suggest that extra care is needed for those with CHD, especially for elderly male patients.

We applied NCC design in our data collection and sampling inclusion procedure, which is an optimal choice given the restricted availability of public data. Due to the fact that provincial/municipal government were responsible to report all deaths with detailed information, we were able to include almost all the reported deaths that were eligible to our study. Therefore, NCC is favored in our situation where the risk factor data and event of interest can be identified opportunistically from publicly reported confirmed cases [29].

The limitation of this analysis lies in the nature of publicly reported data. To evaluate the time-to-death risk of common comorbidities, we only included patients with clear history of comorbidity and trackable survival status at the end of follow-up. We applied dynamic tracking method to fill in the unclear/missing date, but those with missing information on comorbidity condition had to be excluded. Only those common pre-existing comorbidities were evaluated in this study, since publicly reported data may contain incomplete medical information, especially when patients had several medical conditions. A study of incubation period that also used publicly reported confirmed cases pointed out that this type of data usually over-represents severe cases [45]. In general, the over-representing of severe cases has little impact on our survival analysis result to predict death risk under NCC design, since the impact of symptom severity was not of interest in this study and cases were matched with corresponding controls.

This study provides substantial evidence, related pathophysiological mechanisms and clinical suggestion for high mortality risk in COVID-19 patients with pre-existing CHD. Extra care and early medical intervention maybe needed for patients with pre-existing CHD.

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