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Complete List of Authors:	Gu, Tian; University of Michigan, Biostatistics Chu, Qiao; Shanghai Jiao Tong University School of Medicine, School of Public Health Zhang-Sheng, Yu; Shanghai Jiao Tong University, Department of Bioinformatics and Biostatistics Fa, Botao; Shanghai Jiao Tong University, Department of Bioinformatics and Biostatistics Li, Anqi; East China Normal University, School of Social Development Xu, Lei; Shanghai Chest Hospital, Department of Cardiology; Shanghai Jiao Tong University Wu, Ruijun; East China Normal University, School of Social Development He, Yaping; Shanghai Jiao Tong University, School of Public Health; Shanghai Jiao Tong University, Center for Health Technology Assessment
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History of coronary heart disease increases the mortality rate of COVID-19 patients: a nested case-control study

Tian Gu[1], MS, Qiao Chu [2], Ph.D., Zhangsheng Yu[3], Ph.D., Botao Fa[3], MS, Anqi Li[4], MS, Lei Xu[5], MD, Ruijun Wu[4], Ph.D., Yaping He[2], Ph.D.

Affiliations:

1. Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI
2. School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
3. Department of Bioinformatics and Biostatistics, Shanghai Jiao Tong University, Shanghai, China
4. School of Social Development, East China Normal University, Shanghai, China
5. Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Corresponding authors:

Prof. Ruijun Wu: School of Social Development, East China Normal University, 500 Dongchuan Rd., Shanghai 200241, China (rjwu@re.ecnu.edu.cn).

Prof. Yaping He: College of Public Health, Shanghai Jiao Tong University School of Medicine, South Chongqing Rd., No. 227, Shanghai 200025, China (hypcyr@sina.com).

Abstract

Objective: Evaluate the risk of pre-existing comorbidities on COVID-19 mortality, and provide clinical suggestions accordingly.

Setting: Confirmed cases reports released from news or national/provincial health/municipal commission of China between December 18th, 2019 and March 8th, 2020.

Participants: Patients with confirmed SARS-CoV-2 infection in mainland China outside of Hubei Province.

Outcome measures: Patient demographics, survival time and status, and history of comorbidities.

Method: This study used a nested case-control design. A total of 94 publicly reported deaths were included as cases. Each case was matched with up to three controls, based on gender and age ± 1 year old (94 cases and 181 controls). Survival time was from symptom onset to death/end of study. The inverse probability weighted Cox proportional hazard model was used to evaluate the mortality risk of pre-existing comorbidities associated with survival time.

Results: History of comorbidities significantly increased the death risk of COVID-19: one additional pre-existing comorbidity led to an estimated 40% higher risk of death ($p<0.001$). The estimated mortality risk in patients with CHD was three times of those without CHD ($p<0.001$). The estimated 30-day survival probability for a profile patient with pre-existing CHD (65-year-old female with no other comorbidities) was 0.53 (95% CI [0.34-0.82]), while it was 0.85 (95% CI [0.79-0.91]) for those without CHD. Older age was also associated with increased death risk: every 5-year increase in age was associated with a 20% increased risk of mortality ($p<0.001$).

Conclusion: Extra care and early medical intervention are needed for patients with pre-existing comorbidities, especially CHD.

Strengths and limitations of this study

Strengths: (i) The study used data outside of the epicenter of the outbreak in mainland China, which avoided the competing death risk caused by insufficient health care resources and revealed the true underlying impact of pre-existing comorbidities on mortality; (ii) we accounted for the confounding effects of death risk during analysis to provide accurate esimation, which were in general not considered in the existing literature; and (iii) the survival-time-related statistical results can help guide the early clinical intervention to reduce the mortality.

limitations: Publicly reported data does not contain patient clinical test results, which restricted further investigation on the association between comorbidity-related clinical index and mortality.

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 beta-coronavirus 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 [5-8], with presence of asymptomatic, yet contagious cases [9].

According to the COVID-19 situation reports of WHO, as of March 29th, 2020, the infection has caused 81,445 confirmed cases in mainland China, including 3,300 deaths. Internationally, a total of 601,020 confirmed cases have been reported from 186 countries outside of China, including 28,747 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, 10-12], cerebrovascular diseases [6], chronic obstructive pulmonary disease (COPD) [3, 8], cancer [13], and digestive diseases [14], in comparison to non-severe cases [3, 6, 8-15].

Recently, scholarly attention focuses on identifying the risk factors for death from COVID-19. Some evidence suggests that pre-existing medical conditions are likely death risk factors for COVID-19. For example, a study based on 72,314 cases in China indicated that the case-fatality rate (CFR) tends to be higher among those with older age, and having pre-existing cardiovascular disease, diabetes, and hypertension compared to all the patients [9]. Similarly, by conducting logistic regression on odds of in-hospital death among 54 diseased patients and 137 recovered patients in Wuhan City, Hubei Province, Zhou et al. [16] found that older age, higher Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1ug/ml at hospital admission were associated with increased odds of in-hospital death. Chen et al. (2020) found that pre-existing hypertension and other cardiovascular complications were more common among diseased patients than recovered patients (unpublished data).

However, several gaps remain in the understanding of risk factors for mortality of COVID-19. First, most current research on pre-existing comorbidities of COVID-19 was based on univariate comparison, which did not account for important confounders such as age and gender [17-20]. Second, no studies have investigated the hazard of the identified risk factors over time, or the probability of survival at a given time. Under the rapidly changing pandemic situation, it is crucial to provide timely survival-time guidance for implementing the targeted treatment to the high-risk patients in clinical practice. Third, most existing studies on mortality risk factors were focused on patients diagnosed in Wuhan, Hubei Province, with little understanding about the mortality risk factors outside of Hubei Province. The risk factors are likely different inside and outside of Hubei Province, since current research has found that the clinical symptom severity [5] and the fatality-case rate [9, 21] to be higher in Hubei Province (the center of outbreak) than cities outside of Hubei Province in China. Fourth, no studies thus far have taken into account the pandemic stage when evaluating mortality risk factors. 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 [22]. The change of pandemic stage may also influence the risk factors for fatality associated with COVID-19.

To fill the above research gaps in the existing literature about the morality risk factors for COVID-19, the present study conducted a nested case-control (NCC) study, aiming to evaluate the risk of the common pre-existing comorbidities (hypertension, coronary heart disease, diabetes and etc.) for mortality associated with COVID-19 in mainland China outside of Hubei Province. NCC, also called risk set sampling, has been widely used in studying the fatal disease risk effect in large pharmacoepidemiologic studies [23-28] and risk prediction in pandemic influenza A (H1N1) 2009 (pH1N1) [29]. NCC is cost-effective in data collection, and is especially suitable for research on the death risk of diseases such as COVID-19, where the number of event-free people largely exceeds those who experienced events [30]. To attain this goal, we employed survival analysis on 275 publicly reported confirmed cases, adjusting for age, gender and the change in the pandemic stage in China (i.e., before and after January 11th, 2020).

Method

Study Design and Rationale

This study performed survival analysis under a nested case-control (NCC) design to assess the roles of common comorbidities (cardiocerebrovascular, endocrine and respiratory disease, etc.) in predicting mortality for COVID-19, among patients in mainland China outside of Hubei Province. The study period was from December 18th, 2019, when the first laboratory-confirmed case was announced in China, till March 8th, 2020.

The study cohort was defined as all the publicly reported confirmed COVID-19 patients outside of Hubei Province in mainland China between the study period. During this period, 112 deaths outside of Hubei Province were reported by the National Health Committee of China, and 18 were excluded from the present study due to missingness of important clinical information. A total of 408 publicly reported laboratory-confirmed COVID-19 cases (94 deaths and 314 survivors) were initially collected. The data collection procedure was blinded to patient comorbidity information. All deaths were included as cases, and each case was matched with up to three controls on gender and age ± 1 year old (94 cases and 181 controls). The sample distribution across all 32 province-level regions in mainland China is presented in Supplementary Table S1.

Data Collection Procedure

We routinely searched for daily news and public health reports on confirmed COVID-19 cases in all areas in mainland China outside of Hubei Province. Patients' clinical and comorbidity characteristics were recorded and doubly confirmed by national/provincial/municipal health commission websites, the official COVID-19 data reporting websites in China. Follow-up time was defined as the duration from the date of disease onset till the end of observation on March 8th or when the participant died, whichever came first. For each eligible patient, we followed local reports to update their survival status until the end of follow-up time.

As illustrated in Figure 1, the inclusion criterion was publicly reported COVID-19 patients who had complete information on basic demographics (age, gender and region), disease onset date--the first time a patient became symptomatic, and history of comorbidities (include but not limited to hypertension, cardiovascular disease, diabetes and respiratory diseases) were included in the analysis. Asymptomatic patients were not included in this study. In addition, we defined "comorbidity-free patients" as those who were specifically described as "no pre-existing medical condition/comorbidity" on the national/provincial/municipal health commission websites.

In the following three steps, we used the No. 261 patient in the sample as an example to introduce the dynamic tracking method we used to identify any missing dates:

Step 1. Conducting an internet search on confirmed cases on baidu.com, the largest search engine in China, using keywords "confirmed COVID-19 cases report" and "pre-existing comorbidities." A search result pertained to one confirmed case reported on the website of Municipal Health Commission of Binzhou (Shandong Province) on February 17th, described as "*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 based on 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 were shown as mean (SD), median (range), or number (%), with a comparison of characteristics in subjects stratified by case and control via t-test for continuous variables and chi-squared or Fisher's exact test for binary variables.

In order to utilize the time-to-event information under the NCC design, the inverse probability weighting Cox proportional hazard regression model was employed [32]. The matching between cases and controls, and relative weights were simultaneously obtained via KMprob function in multipleNCC R package [31], by specifying the Kaplan-Meier type weights with additional matching on gender and age ± 1 year 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 were considered as "fail to match" and excluded from the study.

The total number of comorbidities was defined as the summation of comorbidities, ranging from zero to four or above. Kaplan-Meier curve was plotted to check the proportional hazard assumption and the Pearson correlation test was used to rule out the multicollinearity concern before fitting any model. Univariate weighted Cox models were performed for each comorbidity. The multivariate weighted Cox model was used to determine if pre-existing comorbidity yielded prognostic hazard information. We included those comorbidities that were marginally significant ($p<0.1$) in the univariate analysis to the multivariate model. Other than the common risk factors (age and gender), the multivariate model also adjusted for early period of pandemic (after vs. before January 11th, 2020 when no-intervention was taken by the government) [22]. Although matching was based on age and gender, we adjusted for the matching covariates, since the matching was broken with inverse probability weighting [32]. 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 the weighted 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.

Weighted Cox model-based survival estimates were plotted for an example patient profile (65-year-old female with no other comorbidities) to compare the survival probability over time with and without CHD. The log-rank test was used to compare the median survival difference.

Results

Sample Description

Table 1 summarizes patient demographics and pre-existing medical conditions. Results are presented for all patients in the study (n=275), as well as for cases (n=94) and controls (n=181), respectively. Patients were 24-94 years old ($Mean_{age}$ = 66.4, SD_{age} =14.5). The average age tended to be older in the case group (70.7 years old) than in the control group (64.2 years old). Median ages were similar to mean ages in both groups. A majority (62.9%) of the patients were male. Overall, 25.5% of the total patients had clinical symptoms associated with COVID-19 before January 11th, 2020. A relatively small proportion of the total sample had COPD, renal failure, history of surgery and hepatic failure (4.4%, 4.4%, 3.6% or 1.1%). Among all pre-existing comorbidities with over 5% of the total sample, hypertension was the most common (39.6%), followed by diabetes (26.2%), CHD (14.5%), cardiac failure (8%), cerebral infarction (6.9%) and chronic bronchitis (6.9%). Patients in the case group had more CHD (p<0.001) and more cerebral infarction (p=0.05), compared to those in the control group. A majority of the total sample had at least one pre-existing comorbidity (67.6%), specifically around 25% had one, 22% had two, 11% had three, and 10% had four or more. Compared to the control group, more patients in the case group had pre-existing comorbidities (p=0.02), especially those who had four or more comorbidities (p<0.001).

Table 1. Patient Characteristics, stratified by survival status*

	Overall (N=275), n (%)	**Case (deaths) (N=94), n (%)**	**Control (survivors) (N=181), n (%)**	**P Value †**
Matching variables				
Age				
Mean (SD)	66.4 (14.5)	70.7 (13.3)	64.2 (14.7)	**<0.001**
Median (Min, Max)	68.0 [24.0, 94.0]	72.5 [25.0, 94.0]	67.0 [24.0, 90.0]	-
Male	173 (62.9)	56 (59.6)	117 (64.6)	0.49
Other covariates				
Before 01/11/2020	70 (25.5)	27 (28.7%)	43 (23.8)	0.52
History of surgery	10 (3.6)	4 (4.3)	6 (3.3)	0.74
Cardiocerebrovascular diseases				
Hypertension	109 (39.6)	42 (44.7)	67 (37.0)	0.27
CHD	40 (14.5)	25 (26.6)	15 (8.3)	**<0.001**
Cardiac failure	22 (8.0)	10 (10.6)	12 (6.6)	0.35
Cerebral infarction	19 (6.9)	11 (11.7)	8 (4.4)	**0.05**

Endocrine diseases				
Diabetes	72 (26.2)	26 (25.4)	46 (27.7)	0.80
Respiratory diseases				
Chronic bronchitis	19 (6.9)	7 (7.4)	12 (6.6)	1.00
COPD	12 (4.4)	7 (7.4)	5 (2.8)	0.14
Other diseases				
Renal failure	12 (4.4)	6 (6.4)	6 (3.3)	0.38
Hepatic failure	3 (1.1)	3 (3.2)	0 (0)	0.07
Total number of comorbidities				
0	89 (32.4)	21 (22.3)	68 (37.6)	**0.02**
1	68 (24.7)	18 (19.1)	50 (27.6)	0.16
2	61 (22.2)	22 (23.4)	39 (21.5)	0.84
3	30 (10.9)	14 (14.9)	16 (8.8)	0.19
4 and above	27 (9.8)	19 (20.2)	8 (4.4)	**<0.001**

CHD: coronary heart disease;

COPD: chronic obstructive pulmonary disease.

*Mean (standard deviation) is reported for the continuous variables and the counts (%) for categorical variables. p values were calculated by t test, χ2 test, or Fisher's exact test, as appropriate.

Bold: statistically significant using threshold p<0.05.

Model Results

Results of the Pearson correlation test showed no significant correlations among the presence of comorbidities of interest, and the assumption of the proportional hazard was not violated.

Table 2 presents the results of univariate and multivariate weighted Cox models. Older age was associated with significantly higher death risk with similar magnitude in univariate and multivariate models. In the adjusted model, every 5-year increase in age was associated with an estimated 20% higher risk of death (p<0.001). No significant hazard difference was found between male and female patients. Disease infection during the early no-intervention period was associated with a higher risk of death, although not statistically significant.

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	HR (95% CI)	P Value
Age	1.1 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**
Male	0.8 (0.5-1.2)	0.24	1.1 (0.7-1.7)	0.74	1.1 (0.7-1.7)	0.71	1.0 (0.6-1.6)	0.99
Before 01/11/2020	1.1 (0.7-1.8)	0.66	1.3 (0.8-2.1)	0.29	1.2 (0.7-1.9)	0.48	1.2 (0.7-2.0)	0.45
Total number of comorbidities	1.6 (1.4-1.9)	**<0.001**	1.4 (1.2-1.7)	**<0.001**	-	-	-	-
Cardiocerebrovascular								
CHD	4.2 (2.5-7.1)	**<0.001**	-	-	2.9 (1.7-4.9)	**<0.001**	3.0 (1.8-5.0)	**<0.001**
Hypertension	1.4 (0.9-2.2)	0.17	-	-	-	-	-	-
Cardiac failure	1.9 (0.9-3.9)	0.10	-	-	-	-	-	-
Cerebral infarction	2.9 (1.4-5.8)	**0.004**	-	-	-	-	1.9 (0.9-3.8)	0.07
Respiratory								
Chronic bronchitis	1.1 (0.4-2.5)	0.55	-	-	-	-	-	-
COPD	2.6 (1.2-5.6)	**0.01**	-	-	-	-	1.9 (0.9-3.9)	0.10
Endocrine								
Diabetes	1.1 (0.7-1.9)	0.61	-	-	-	-	-	-
Others								
Renal failure	2.3 (0.9-6.0)	0.09	-	-	-	-	2.0 (0.8-5.1)	0.13
History of surgery	1.7 (0.6-5.1)	0.34	-	-	-	-	-	-

HR=hazard ratio;
CHD=coronary heart disease;
COPD=chronic obstructive pulmonary disease;
Bold: statistically significant using threshold p<0.05.

The increasing number of cumulative comorbidities was associated with higher mortality risk in both unadjusted and adjusted models (p<0.001). Moreover, one additional pre-existing comorbidity was associated with a 40% increased risk in mortality of COVID-19. All pre-existing comorbidities were associated with a higher risk of COVID-19 mortality in the univariate model, of which CHD had the largest hazard ratio (HR) of 4.2 (p<0.001), followed by cerebral infarction (HR=2.9, p=0.004), COPD (HR=2.6, p=0.01), renal failure (HR=2.3, p=0.09), cardiac failure (HR=1.9, p=0.1), history of surgery (HR=1.7, p=0.34), hypertension (HR=1.4, p=0.17), diabetes (HR=1.1, p=0.61) and chronic bronchitis (HR=1.1, p=0.55). After adjusting for age, gender, and early period of pandemic in China, CHD was the only comorbidity that yielded a significant death risk: COVID-19 patients with pre-existing CHD had an estimated 2.9 times death risk of those without CHD. In addition, cerebral infarction, COPD, and renal failure all had an estimated HR of around 2.0, respectively. Similar results were observed by using unweighted logistic regression in a sensitivity analysis (Supplementary Table S2).

The overall median follow-up was 40 days, during which 94 deaths were observed. Figure 2 shows the estimated survival probability over 70 days for an example patient profile with and without CHD (65-year-old female with no other comorbidities). For such patient profile, having pre-existing CHD led to a significantly shorter survival probability over time, compared to those without CHD (p<0.001). For those with CHD, the estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]), with an estimated 34 days' median survival time. On the other hand, the estimated 30-day probability was 0.85 (95% CI [0.79-0.91]) for those without CHD, with the corresponding median survival time over 70 days.

Discussion

In this paper, we used survival analysis to estimate the fatal risk of pre-existing comorbidities in COVID-19, based on publicly reported confirmed cases and adjusted for the confounding effect of age, gender, and early period of the pandemic when no-intervention was taken. There were three major findings: First, a history of comorbidities significantly increased the death risk of COVID-19: one additional pre-existing comorbidity led to an estimated 40% increase of death risk (p<0.001). Second, after adjusting for confounders, CHD was the only significant risk factor for COVID-19 mortality. Patients with CHD had a 200% higher risk of mortality in COVID-19, compared to patients without CHD (p<0.001). For a patient profile (65-year-old female without other comorbidities), the estimated median survival times for those with CHD was 34 days, while it was over 70 days for those without CHD (p<0.001). Third, older age was associated with increased death risk. Specifically, every 5-year increase in age was associated with a 20% increased risk of mortality (p<0.001).

To our best knowledge, the present study is the first to provide substantial statistical evidence to show the effect of CHD in predicting mortality for COVID-19. This result is consistent with previous studies that found higher case-fatality rate among patients with cardiovascular disease [9, 15]. It is worth pointing out that the existing studies [9, 16] 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 models, our study used time-to-event outcomes, which offers more survival-time-related information to help guide the clinical intervention and more statistical power to detect risk factors [33-34].

Previous studies have indicated that cardiovascular events following pneumonia may increase the risk of mortality [35-41], which explained our findings 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 evidence 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].

From the clinical point of view, early evaluation of patient medical history is necessary to implement early medical interventions and decrease the mortality risk. We suggest monitoring the dynamic heart rate for patients with pre-existing CHD. For those severe-symptomatic patients who had pre-existing heart ischemia and abnormal heart function, early medical intervention may be needed [41]. Furthermore, our results indicated that the hazard of COVID-19 death was significantly higher in patients at older ages. Adjusting for others, every 5-year increase in age was associated with a 22% increased risk of death, similarly to what was found in previous studies [8, 9, 16]. Alongside the evidence of prognostic risk in CHD, we suggest that extra care is needed for those with CHD, especially for elderly patients.

The design of excluding patients from Hubei Province was based on the concerns of unknown confounders caused by insufficient medical resources in the epicenter. CDC's report has pointed out that the rapidly increasing number of infections could easily crash the health care system by exceeding its maximum capacity [42]. Therefore, analyzing patient data outside of Hubei Province can avoid the competing death risk caused by insufficient health care resources, and reveal the true underlying impact of pre-existing comorbidities on COVID-19 mortality [44].

One limitation of the present study lies in the nature of publicly reported data. Researchers have pointed out that severe cases may be over-represented in publicly reported data [45]. Nevertheless, we have managed to reduce the potential bias caused by severe case over-representation, through the appropriate matching between cases and controls in NCC design. The auto-matching procedure via statistical program also prevented the possibility of tendentiously selecting survivors with comorbidity-free history during data collection. Since NCC design is favored in our situation where the risk factor data and event of interest can be identified opportunistically from publicly reported confirmed cases [30], NCC was the optimal choice, given the restricted availability of public data.

Given the limited understanding of the prognostic factors for COVID-19, more research, potentially prospective studies, are needed to investigate the mechanism by which pre-existing CHD may influence the survival probability among patients with COVID-19. In addition, further investigation is suggested on the association between comorbidity-related clinical index and mortality based on patient clinical test results.

In conclusion, our findings provided preliminary yet strong evidence supporting the association between pre-existing CHD and mortality risk for patients with COVID-19. Based on our findings, close monitoring, extra care, and early medical intervention are needed for patients with pre-existing CHD, to reduce the mortality risk associated with COVID-19.

Footnotes

Author Contributions

TG conducted the analysis, interpreted the data, drafted the article and rechecked the transcribed manuscript. QC conducted literature review and drafted the article. ZY guided and supervised the statistical analysis. BF helped with data analysis.AL helped data collection, management, and quality check. LX provided clinical support and interpretation of the results. RW collected, pre-processed and managed data, and conducted preliminary data analysis. YH guided and supervised the research process, and provided funding support. All authors critically revised the manuscript for intellectual content, approved the final draft, and agree to accountability for all aspects of the work.

Conflict of Interest

The authors have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics Approval

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

Patient and Public Involvement

This study used publicly reported patient-level data. All data were available online to the public. No patient recruitment was involved in the study design, and no personal information can be identified from the data.

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Data sharing statement

Raw data is available at https://github.com/GuTian-TianGu/COVID-19_NCCstudy.git.

Word count

3220

Reference

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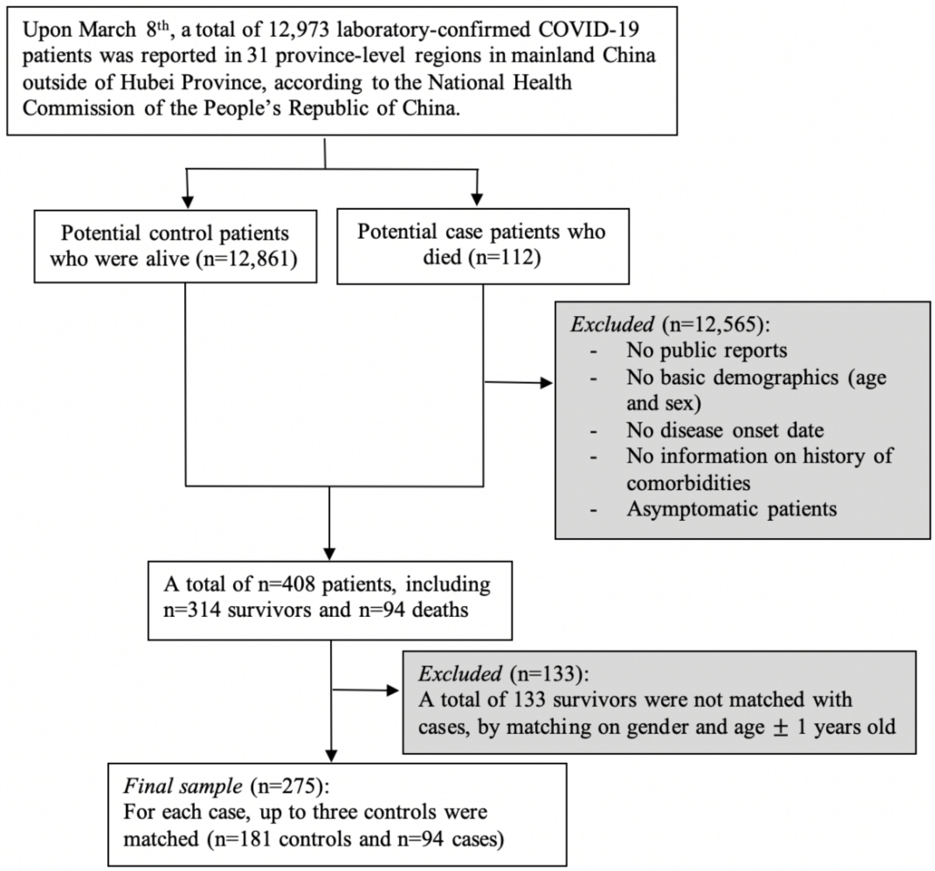

Figure 1: Patient flow diagram detailing included subjects and exclusion criteria

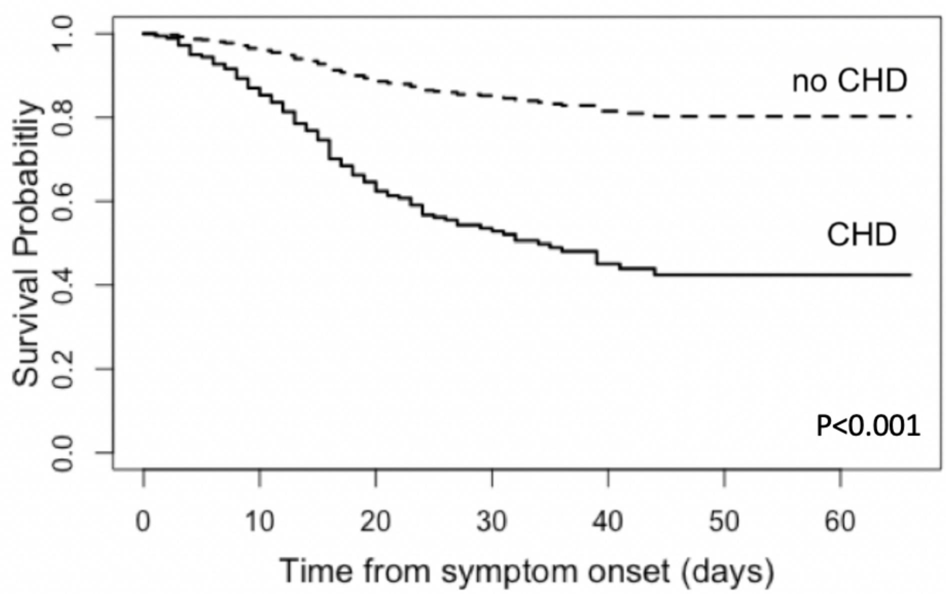

Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for an example patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) for patients with pre-existing CHD, while 0.85 (95% CI [0.79-0.91]) for those without (p<0.001). CHD=coronary heart disease.

Supplementary Table S1. Sample distribution across all 32 province-level in mainland China

Province	Survivors		Deaths	
	National total n	Sample n (%)	National total n	Sample n (%)
Guangdong	1343	9 (0.67)	8	8 (100.00)
Henan	1265	7 (0.55)	22	17 (77.30)
Zhejiang	1205	10 (0.83)	1	1 (100.00)
Hunan	1003	15 (1.50)	4	2 (50.00)
Anhui	981	9 (0.92)	6	6 (100.00)
Jiangxi	932	3 (0.32)	1	1 (100.00)
Shandong	692	66 (9.54)	6	6 (100.00)
Jiangsu	618	13 (2.10)	0	0 (100.00)
Chongqing	576	0 (0.00)	6	6 (100.00)
Sichuan	535	4 (0.75)	3	3 (100.00)
Heilongjiang	475	6 (1.26)	13	9 (69.20)
Beijing	425	3 (0.71)	8	3 (37.50)
Shanghai	339	3 (0.88)	3	3 (100.00)
Hebei	312	6 (1.92)	6	6 (100.00)
Fujian	294	2 (0.68)	1	1 (100.00)
Guangxi	250	2 (0.80)	2	2 (100.00)
Shaanxi	239	6 (2.51)	1	1 (100.00)
Yunnan	171	3 (1.75)	2	1 (50.00)
Hainan	163	5 (3.07)	6	6 (100.00)
Guizhou	144	2 (1.39)	2	2 (100.00)
Tianjin	132	4 (3.03)	3	3 (100.00)
Shanxi	131	2 (1.53)	0	0 (100.00)
Liaoning	125	0 (0.00)	1	0 (0.00)
Gansu	123	1 (0.81)	2	2 (100.00)
Jilin	92	1 (1.09)	1	1 (100.00)
Xinjiang	76	0 (0.00)	3	3 (100.00)
Neimenggu	73	2 (2.74)	1	1 (100.00)
Ningxia	75	0 (0.00)	0	0 (100.00)
Hubei*	NA	NA	NA	NA
Total	12698	275 (2.17)	112	94 (83.9)

*Hubei Province was excluded from this study

Supplementary Table S2: Results from unweighted logistic regression

			Multivariate			
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.0 (1.0-1.1)	**0.03**	1.0 (1.0-1.1)	**0.007**	1.0 (1.0-1.1)	**0.05**
Male	1.1 (0.6-1.7)	0.98	1.1 (0.6-1.8)	0.87	1.0 (0.5-1.7)	0.89
Before 01/11/2020	1.7 (0.9-3.1)	0.09	1.6 (0.9-2.9)	0.12	1.7 (0.9-3.1)	0.09
Total number of comorbidities	1.2 (1.2-1.8)	**<0.001**				
CHD			3.3 (1.6-6.9)	**0.002**	3.4 (1.7-7.4)	**0.001**
Cerebral infarction					2.5 (0.9-7.0)	0.08
COPD					2.5 (0.7-9.4)	0.14
Renal failure					1.9 (0.5-7.0)	0.30

OR=odds ratio; CHD=coronary heart disease; COPD=chronic obstructive pulmonary disease.

Bold: statistically significant using threshold $p<0.05$

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History of coronary heart disease increased the mortality rate of COVID-19 patients: a nested case-control study

Tian Gu, MS[1]; Qiao Chu, PhD[2]; Zhangsheng Yu, PhD[3]; Botao Fa, MS[3]; Anqi Li, MS[4]; Lei Xu, MD[5]; Ruijun Wu, PhD[4]; Yaping He, PhD[2]

Author affiliations:

1. Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA
2. School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
3. Department of Bioinformatics and Biostatistics, Shanghai Jiao Tong University, Shanghai, China
4. School of Social Development, East China Normal University, Shanghai, China
5. Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Corresponding authors:

Prof. Ruijun Wu: School of Social Development, East China Normal University, 500 Dongchuan Rd., Shanghai 200241, China (rjwu@re.ecnu.edu.cn).

Prof. Yaping He: College of Public Health, Shanghai Jiao Tong University School of Medicine, South Chongqing Rd., No. 227, Shanghai 200025, China (hypcyr@sina.com).

Abstract

Objective: Evaluate the risk of pre-existing comorbidities on COVID-19 mortality, and provide clinical suggestions accordingly.

Setting: A nested case-control design using confirmed cases reports released from news or national/provincial/municipal health commission of China between December 18th, 2019 and March 8th, 2020.

Participants: Patients with confirmed SARS-CoV-2 infection in mainland China outside of Hubei Province, excluding asymptomatic patients.

Outcome measures: Patient demographics, survival time and status, and history of comorbidities.

Method: A total of 94 publicly reported deaths in locations outside of Hubei Province, mainland China, between December 18th, 2019 and March 8th, 2020 were included as cases. Each case was matched with up to three controls, based on gender and age $\pm$ 1 year old (94 cases and 181 controls). The inverse probability-weighted Cox proportional hazard model was performed, controlling for age, gender, and early period of the outbreak.

Results: Of the 94 cases, the median age was 72.5 years old (IQR=16), and 59.6% were male, while in the control group the median age was 67 years old (IQR=22) and 64.6% were male. Adjusting for age, gender, and early period of outbreak, poor health conditions were associated with a higher risk of COVID-19 mortality (HR of comorbidity score, 1.31 [95% CI: 1.11-1.54]; p=0.001). The estimated mortality risk in patients with pre-existing CHD was three times of those without CHD (p<0.001). The estimated 30-day survival probability for a profile patient with pre-existing CHD (65-year-old female with no other comorbidities) was 0.53 (95% CI, 0.34-0.82), while it was 0.85 (95% CI, 0.79-0.91) for those without CHD. Older age was also associated with increased death risk: every 1-year increase in age was associated with a 4% increased risk of mortality (p<0.001).

Conclusion: Extra care and early medical interventions are needed for patients with pre-existing comorbidities, especially CHD.

Strengths and limitations of this study

(i) Using data outside of the epicenter of the outbreak in mainland China avoided the competing death risk caused by insufficient health care resources; (ii) the study controlled for the confounding effects of age, gender and early period of pandemic, which were in general not considered in the existing literatures; (iii) the survival-time-related statistical results can help guide the early clinical intervention to reduce the mortality; (iv) Lacking medical test results in the publicly reported data restricted further investigation on the association between comorbidity-related clinical index and mortality; (v) missing at random assumption could not be verified.

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 beta-coronavirus 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]-[8], with presence of asymptomatic, yet contagious cases [9].

According to the COVID-19 situation reports of WHO, as of June 13th, 2020, the infection has caused 83,132 confirmed cases in mainland China, including 4,634 deaths. Internationally, a total of 7.41 million confirmed cases have been reported from 186 countries outside of China, including 418,000 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], [10]-[12], cerebrovascular diseases [6], chronic obstructive pulmonary disease (COPD) [3], [8], cancer [13], and digestive diseases [14], in comparison to non-severe cases [3], [6], [8]-[15].

Recently, scholarly attention focuses on identifying the risk factors for death from COVID-19. Some evidence suggests that pre-existing medical conditions are likely death risk factors for COVID-19. For example, a study based on 72,314 cases in China indicated that the case-fatality rate (CFR) tends to be higher among those with older age, and having pre-existing cardiovascular disease, diabetes, and hypertension compared to all the patients [9]. Similarly, by conducting logistic regression on odds of in-hospital death among 54 diseased patients and 137 recovered patients in Wuhan City, Hubei Province, Zhou et al. [16] found that older age, higher Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1ug/ml at hospital admission were associated with increased odds of in-hospital death. Chen et al. (2020) found that pre-existing hypertension and other cardiovascular complications were more common among diseased patients than recovered patients (unpublished data).

However, several gaps remain in the understanding of risk factors for mortality of COVID-19. First, most current research on pre-existing comorbidities of COVID-19 was based on univariate comparison, which did not account for important confounders such as age and gender [17]-[20]. Second, no studies have investigated the hazard of the identified risk factors over time, or the probability of survival at a given time. Under the rapidly changing pandemic situation, it is crucial to provide timely survival-time guidance for implementing the targeted treatment to the high-risk patients in clinical practice. Third, most existing studies on mortality risk factors were focused on patients diagnosed in Wuhan, Hubei Province, with little understanding about the mortality risk factors outside of Hubei Province. The risk factors are likely different inside and outside of Hubei Province, since current research has found that the clinical symptom severity [5] and the fatality-case rate [9], [21] to be higher in Hubei Province (the center of outbreak) than cities outside of Hubei Province in China. Fourth, no studies thus far have taken into account the pandemic stage when evaluating mortality risk factors. It has been found that average daily attack rate in China was different before and after January 22^{nd} 2020, since non-pharmaceutical interventions were taken by the government before this date

[22]. The change of pandemic stage may also influence the risk factors for fatality associated with COVID-19.

To fill the above research gaps in the existing literature about the mortality risk factors for COVID-19, the present study conducted a nested case-control (NCC) study, aiming to evaluate the risk of the common pre-existing comorbidities (hypertension, coronary heart disease, diabetes and etc.) for mortality associated with COVID-19 in mainland China outside of Hubei Province. NCC, also called risk set sampling, has been widely used in studying the fatal disease risk effect in large pharmacoepidemiologic studies [23]-[28] and risk prediction in pandemic influenza A (H1N1) 2009 (pH1N1) [29]. NCC is cost-effective in data collection, and is especially suitable for research on the death risk of diseases such as COVID-19, where the number of event-free people largely exceeds those who experienced events [30]. To attain this goal, we employed survival analysis on 275 publicly reported confirmed cases, adjusting for age, gender and the change in the pandemic stage in China (i.e., before and after January 11th, 2020).

Method

Study Design and Rationale

This study performed survival analysis under a nested case-control (NCC) design to assess the roles of common comorbidities (cardiocerebrovascular, endocrine and respiratory disease, etc.) in predicting mortality for COVID-19, among patients in mainland China outside of Hubei Province. The study period was from December 18th, 2019, when the first laboratory-confirmed case was announced in China, till March 8th, 2020.

The study cohort was defined as all the publicly reported confirmed COVID-19 patients outside of Hubei Province in mainland China between the study period. During this period, 112 deaths outside of Hubei Province were reported by the National Health Committee of China, and 18 were excluded from the present study due to missingness of important clinical information. A total of 448 publicly reported laboratory-confirmed COVID-19 cases (94 deaths and 354 survivors) were initially collected. To avoid selection bias due to intentionally collecting patient with certain pre-existing comorbidities, two authors independently collected, compared and reviewed the full text of each case report. Following the typical NCC design setting where all events are included and a certain numbers of control are matched with replacement, all deaths were included as cases, and each case was matched with up to three controls on gender and age

± 1 year old (94 cases and 181 controls). The sample distribution across all 32 province-level regions in mainland China is presented in Supplementary Table S1.

Data Collection Procedure

We routinely searched for daily news and public health reports on confirmed COVID-19 cases in all areas in mainland China outside of Hubei Province. Patients' clinical and comorbidity characteristics were recorded and doubly confirmed by national/provincial/municipal health commission websites, the official COVID-19 data reporting websites in China. Follow-up time was defined as the duration from the date of disease onset till the end of observation on March 8th or when the participant died, whichever came first. For each eligible patient, we followed local reports to update their survival status until the end of follow-up time. Pre-existing comorbidities were recorded based on the description of case reports.

As illustrated in Figure 1, the inclusion criterion was publicly reported COVID-19 patients who had complete information on basic demographics (age, gender and region), disease onset date--the first time a patient became symptomatic, and history of comorbidities (include hypertension, CHD, cardiac failure, cerebral infarction, diabetes, chronic bronchitis, COPD, renal failure, hepatic and history of surgery) were included in the analysis. Asymptomatic patients were not included in this study. In addition, we defined "comorbidity-free patients" as those who were specifically described as "no pre-existing medical condition/comorbidity" on the national/provincial/municipal health commission websites.

In the following three steps, we used the No. 213 patient in the sample as an example to introduce the dynamic tracking method we used to identify any missing dates:

<u>**Step 1**</u>**.** Conducting an internet search on confirmed cases on baidu.com, the largest search engine in China, using keywords "confirmed COVID-19 cases report" and "pre-existing comorbidities." A search result pertained to one confirmed case reported on the website of Municipal Health Commission of Binzhou (Shandong Province) on February 17th, described as "*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.

<u>Step 2</u>. We then determined the onset date of this patient based on 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.*"

<u>Step 3</u>. 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) through RStudio version 1.2.5042. Data and code are available online at GitHub (https://github.com/GuTian-TianGu/COVID-19_NCCstudy). Baseline clinical characteristics were shown as mean (SD), median (range), or number (%), with a comparison of characteristics in subjects stratified by case and control via the non-parametric Mann–Whitney U test for continuous variables and chi-squared or Fisher's exact test for binary variables.

In order to utilize the time-to-event information under the NCC design, the inverse probability weighting Cox proportional hazard regression model was employed [32]. The matching between cases and controls, and relative weights were simultaneously obtained via KMprob function in multipleNCC R package [31], by specifying the Kaplan-Meier type weights with additional matching on gender and age $\pm$1 year old. Only survivors were assigned weights, since all cases (deaths) were included as designed with a weight of one. A total of 113 survivors (mean age 46.5) with sampling probabilities of zero were considered as "fail to match" and excluded from the study, mainly due to younger age than cases. A majority of the excluded patients were from Shandong Province (38.1%) due to relatively high representation of the sample (detailed information of excluded survivors is available online at Github). In a sensitivity analysis adjusting for Shandong Province (results not shown here), we observed the consistent results as the main analysis.

The comorbidity score was defined as the summation of nine comorbidities that have been specifically mentioned in relation to COVID-19 outcomes (CHD, hypertension, cardiac failure, cerebral infarction, chronic bronchitis, COPD, diabetes, renal failure and history of surgery), ranging from zero to nine. Kaplan-Meier curve was plotted to check the proportional hazard assumption and the Pearson correlation test was used to rule out the multicollinearity concern before fitting any model. Univariate weighted Cox models were performed for each comorbidity. The multivariate weighted Cox model was used to determine if pre-existing comorbidity yielded prognostic hazard information. We included those comorbidities that were marginally significant ($p<0.1$) in the univariate analysis to the multivariate model. Other than the common risk factors (age and gender), the multivariate model also adjusted for early period of pandemic (after vs. before January 22nd, 2020 when no-intervention was taken by the government) **Error! Reference source not found.**. Although matching was based on age and gender, we adjusted for the matching covariates, since the matching was broken with inverse probability weighting [32]. A separate multivariate model was built by using the comorbidity score as a continuous predictor, adjusting for the same covariates. Hazard ratios (HRs) from the weighted 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.

Weighted Cox model-based survival estimates were plotted for an example patient profile (65-year-old female with no other comorbidities) to compare the survival probability over time with and without CHD. The log-rank test was used to compare the median survival difference.

Results

Sample Description

Table 1 summarizes patient demographics and pre-existing medical conditions. Results are presented for all patients in the study (n=275), as well as for cases (n=94) and controls (n=181), respectively. Patients were 24-94 years old ($Mean_{age} = 66.4$, $SD_{age} = 14.5$). The average age tended to be older in the case group (70.7 years old) than in the control group (64.2 years old). Median ages were similar to mean ages in both groups. A majority (62.9%) of the patients were male. Overall, 25.5% of the total patients had clinical symptoms associated with COVID-19 before January 11th, 2020. A relatively small proportion of the total sample had COPD, renal failure, history of surgery and hepatic failure (4.4%, 4.4%, 3.6% or 1.1%). Among all pre-existing comorbidities with over 5% of the total sample, hypertension was the most common (39.6%), followed by diabetes (26.2%), CHD (14.5%), cardiac failure (8%), cerebral infarction (6.9%) and chronic bronchitis (6.9%). Patients in the case group had more CHD ($p<0.001$) and more cerebral infarction ($p=0.05$), compared to those in the control group. The mean comorbidity score was 1.22 (SD=1.21) in the overall sample, whereas 1.6 (SD=1.32) in the case and 1.02 (SD=1.10) in the control group (p<0.001).

Model Results

Results of the Pearson correlation test showed no significant correlations among the presence of comorbidities of interest, and the assumption of the proportional hazard was not violated.

Table 2 presents the results of univariate and multivariate weighted Cox models. Older age was associated with significantly higher death risk with similar magnitude in univariate and multivariate models. In the adjusted model, every 1-year increase in age was associated with an estimated 4% higher risk of death (p<0.001). No significant hazard difference was found between male and female patients. Disease infection during the early no-intervention period was associated with a higher risk of death, although not statistically significant.

In a separate model using comorbidity score as predictor, we observed that higher comorbidity score was associated with higher mortality risk in both unadjusted and adjusted models (p=0.009 and p=0.03, respectively). All pre-existing comorbidities had HR over one in the univariate model, of which CHD had the largest hazard ratio (HR) of 4.2 (p<0.001), followed by cerebral infarction (HR=2.9, p=0.004), COPD (HR=2.6, p=0.01), renal failure (HR=2.3, p=0.09), cardiac failure (HR=1.9, p=0.1), history of surgery (HR=1.7, p=0.34), hypertension (HR=1.4, p=0.17), diabetes (HR=1.1, p=0.61) and chronic bronchitis (HR=1.1, p=0.55), but not all statistically significant. After adjusting for age, gender, and early period of pandemic in China, CHD was the only comorbidity that yielded a significant death risk: COVID-19 patients with pre-existing CHD had an estimated 2.9 times death risk of those without CHD. In addition, cerebral infarction, COPD, and renal failure all had an estimated HR of around 2.0, respectively. Similar results were observed by using unweighted logistic regression in a sensitivity analysis (Supplementary Table S2).

The overall median follow-up was 40 days, during which 94 deaths were observed. Figure 2 shows the estimated survival probability over 70 days for an example patient profile with and without CHD (65-year-old female with no other comorbidities). For such patient profile, having pre-existing CHD led to a significantly shorter survival probability over time, compared to those without CHD (p<0.001). For those with CHD, the estimated 30-day survival probability was

0.53 (95% CI [0.34-0.82]), while on the other hand, this number was 0.85 (95% CI [0.79-0.91]) for those without CHD.

Discussion

In this paper, we used survival analysis to estimate the fatal risk of pre-existing comorbidities in COVID-19, based on publicly reported confirmed cases and adjusted for the confounding effect of age, gender, and early period of the pandemic when no-intervention was taken. There were three major findings: First, poor health condition was associated with higher death risk of COVID-19. Second, after adjusting for confounders, CHD was the only significant risk factor for COVID-19 mortality. Patients with pre-existing CHD was 3.11 times more likely of death, compared to those without (p<0.001). For a patient profile (65-year-old female without other comorbidities), the estimated 30-day survival probability for those with CHD was 0.53, while it was 0.85 for those without CHD (p<0.001). Third, older age was associated with increased death risk. Specifically, every 1-year increase in age was associated with a 4% increased risk of mortality (p<0.001).

To our best knowledge, the present study is the first to provide substantial statistical evidence to show the effect of CHD in predicting mortality for COVID-19. This result is consistent with previous studies that found higher case-fatality rate among patients with cardiovascular disease [9], [15]. It is worth pointing out that the existing studies [9], [16] 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 models, our study used time-to-event outcomes, which offers more survival-time-related information to help guide the clinical intervention and more statistical power to detect risk factors [33][34].

Previous studies have indicated that cardiovascular events following pneumonia may increase the risk of mortality [35]-[41], which explained our findings from the viewpoint 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 plaque instability and damage in the blood vessels, where evidence 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, potentially prospective studies, are needed to investigate the mechanism by which pre-existing CHD may influence the survival probability among patients with COVID-19. From the clinical point of view, early evaluation of patient medical history is necessary to implement early medical interventions and decrease the mortality risk. We suggest monitoring the dynamic heart rate for patients with pre-existing CHD. For those severe-symptomatic patients who had pre-existing heart ischemia and abnormal heart function, early medical intervention may be needed [41].

Furthermore, our results indicated that the hazard of COVID-19 death was significantly higher in patients at older ages. Adjusting for others, every 5-year increase in age was associated with a 22% increased risk of death, similarly to what was found in previous studies [8][9], [16]. Alongside the evidence of prognostic risk in CHD, we suggest that extra care is needed for those with CHD, especially for elderly patients.

Previous studies yielded mixed results regarding gender differences in mortality risk of COVID-19. Some studies found male sex was associated with higher death risk of COVID-19 [42], whereas other studies did not find gender to be a significant factor predicting the mortality risk of COVID-19 [43][44]. In the current study, gender was not a significant mortality risk factor for COVID-19. It calls more future research to further our understanding of gender difference in the outcome of COVID-19 and the underlying mechanism.

The design of excluding patients from Hubei Province was based on the concerns of unknown confounders caused by insufficient medical resources in the epicenter. CDC's report has pointed out that the rapidly increasing number of infections could easily crash the health care system by exceeding its maximum capacity [45]. Therefore, analyzing patient data outside of Hubei Province can avoid the competing death risk caused by insufficient health care resources, and reveal the true underlying impact of pre-existing comorbidities on COVID-19 mortality [46].

It is worth noting that the data were collected when COVID-19 was spreading rapidly in China, and the health authorities and researchers had limited understanding of the incubation period, modes of viral transmission and effective treatment. Whether our findings can be generalized to later epidemic phases warrant future research.

One limitation of the present study lies in the nature of publicly reported data. Researchers have pointed out that severe cases may be over-represented in publicly reported data [47]. Nevertheless, we have managed to reduce the potential bias caused by severe case over-representation, through the appropriate matching between cases and controls in NCC design. The auto-matching procedure via statistical program also prevented the possibility of tendentiously selecting survivors with comorbidity-free history during data collection. In addition, NCC design is favored in our situation where the risk factor data and event of interest can be identified opportunistically from publicly reported confirmed cases [30]. Therefore, NCC was the optimal choice, given the restricted availability of public data. Moreover, due to the lack of information of treatment in the health reports published by the local health commission websites, we did not include treatment information into analysis, which may produce confounding effects. It calls for future research to investigate the mortality risk effect of pre-existing comorbidities by adding treatment as a covariate in the model. Lastly, we were not able to verify the missing at random assumption of the 18 missing deaths (9 from Heilongjiang, 5 from Henan, 3 from Beijing, and 2 from Hunan) as well as the survivors.

In conclusion, our findings provided preliminary yet strong evidence supporting the association between pre-existing CHD and mortality risk for patients with COVID-19. Based on our findings, close monitoring, extra care, and early medical intervention are needed for patients with pre-existing CHD, to reduce the mortality risk associated with COVID-19.

Footnotes

Author Contributions

TG conducted the analysis, interpreted the data, drafted the article and rechecked the transcribed manuscript. QC conducted literature review and drafted the article. ZY guided and supervised the statistical analysis. BF helped with data analysis. AL helped data collection, management, and quality check. LX provided clinical support and interpretation of the results. RW collected, pre-processed and managed data, and conducted preliminary data analysis. YH guided and supervised the research process, and provided funding support. All authors critically revised the manuscript for intellectual content, approved the final draft, and agree to accountability for all aspects of the work.

Conflict of Interest

The authors have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics Approval

The data published in news reports and websites were open to the public and free of identifiers. The study was approved by Shanghai Jiao Tong University Public Health and Nursing Medical Research Ethics Committee (SJUPN-202001).

Patient and Public Involvement

This study used publicly reported patient-level data. All data were available online to the public. No patient recruitment was involved in the study design, and no personal information can be identified from the data.

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Data sharing statement

Raw data is available at GitHub https://github.com/GuTian-TianGu/COVID-19_NCCstudy.git.

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Word count

3506

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Correspondence

Address offprint requests to Dr. Wu at School of Social Development, East China Normal University, 500 Dongchuan Rd., Shanghai 200241, China (rjwu@re.ecnu.edu.cn), or Dr. He at College of Public Health, Shanghai Jiao Tong University School of Medicine, South Chongqing Rd., No. 227, Shanghai 200025, China (hypcyr@sina.com), respectively.

Tables and Figures

Table 1. Patient Characteristics, stratified by survival status*

	Overall (N=275), n (%)	Case (deaths) (N=94), n (%)	Control (survivors) (N=181), n (%)	P Value †
Matching variables				
Age				
Mean (SD)	66.4 (14.5)	70.7 (13.3)	64.2 (14.7)	**<0.001**
Median (IQR)	68.0 [22]	72.5 [16]	67.0 [22]	**-**
Male	173 (62.9)	56 (59.6)	117 (64.6)	0.49
Other covariates				
Before 01/22/2020	70 (25.5)	27 (28.7%)	43 (23.8)	0.52
History of surgery	10 (3.6)	4 (4.3)	6 (3.3)	0.74
Cardiocerebrovascular diseases				
Hypertension	109 (39.6)	42 (44.7)	67 (37.0)	0.27
CHD	40 (14.5)	25 (26.6)	15 (8.3)	**<0.001**
Cardiac failure	22 (8.0)	10 (10.6)	12 (6.6)	0.35
Cerebral infarction	19 (6.9)	11 (11.7)	8 (4.4)	**0.05**
Endocrine diseases				
Diabetes	72 (26.2)	26 (25.4)	46 (27.7)	0.80
Respiratory diseases				
Chronic bronchitis	19 (6.9)	7 (7.4)	12 (6.6)	1.00
COPD	12 (4.4)	7 (7.4)	5 (2.8)	0.14
Other diseases				
Renal failure	12 (4.4)	6 (6.4)	6 (3.3)	0.38
Hepatic failure	3 (1.1)	3 (3.2)	0 (0)	0.07
Comorbidity score				
Mean (SD)	**1.22 (1.21)**	**1.60 (1.32)**	**1.02 (1.10)**	**<0.001**

CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease.

*Mean (standard deviation) is reported for the continuous variables and the counts (%) for categorical variables. p values were calculated by the Mann–Whitney U test, $\chi 2$ test, or Fisher's exact test, as appropriate.

Bold: statistically significant using threshold p<0.05

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

Characteristic	Univariate HR (95% CI)	P Value	HR (95% CI)	P Value	Multivariate HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.05 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**	1.04 (1.02-1.06)	**<0.001**
Male	0.76 (0.5-1.2)	0.24	1.1 (0.7-1.7)	0.74	1.1 (0.7-1.7)	0.71	0.997 (0.62-1.60)	0.99
Before 01/22/2020	1.12 (0.7-1.8)	0.66	1.3 (0.8-2.1)	0.29	1.2 (0.7-1.9)	0.48	1.21 (0.74-1.98)	0.45
Comorbidity Score	1.50 (1.27-1.75)	**<0.001**	1.31 (1.11-1.54)	**0.001**	NA	NA	NA	NA
Cardiocerebrovascular								
CHD	4.19 (2.5-7.1)	**<0.001**	NA	NA	2.9 (1.7-4.9)	**<0.001**	3.01 (1.82-4.98)	**<0.001**
Hypertension	1.37 (0.9-2.2)	0.17	NA	NA	NA	NA	NA	NA
Cardiac failure	1.85 (0.9-3.9)	0.10	NA	NA	NA	NA	NA	NA
Cerebral infarction	2.86 (1.4-5.8)	**0.004**	NA	NA	NA	NA	1.90 (0.94-3.8)	0.07
Respiratory								
Chronic bronchitis	1.05 (0.4-2.5)	0.55	NA	NA	NA	NA	NA	NA
COPD	2.61 (1.2-5.6)	**0.01**	NA	NA	NA	NA	1.85 (0.89-3.85)	0.10
Endocrine								
Diabetes	1.14 (0.7-1.9)	0.61	NA	NA	NA	NA	NA	NA
Others								
Renal failure	2.30 (0.9-6.0)	0.09	NA	NA	NA	NA	2.02 (0.81-5.07)	0.13
History of surgery	1.71 (0.6-5.1)	0.34	NA	NA	NA	NA	NA	NA

HR=hazard ratio;
CHD=coronary heart disease;
COPD=chronic obstructive pulmonary disease;
Bold: statistically significant using threshold p<0.05.

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

Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for an example patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) for patients with pre-existing CHD, while 0.85 (95% CI [0.79-0.91]) for those without ($p<0.001$). CHD=coronary heart disease.

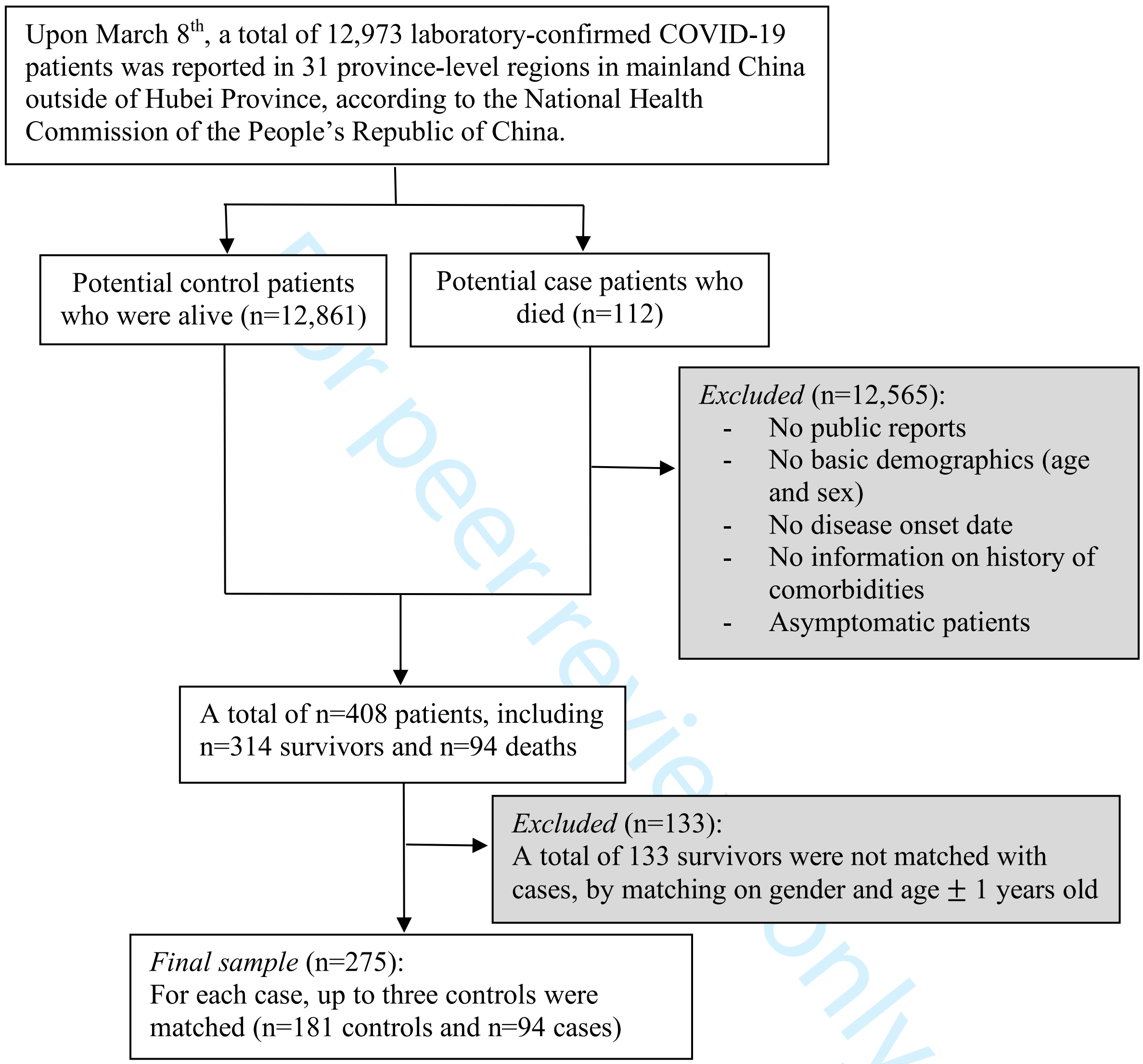
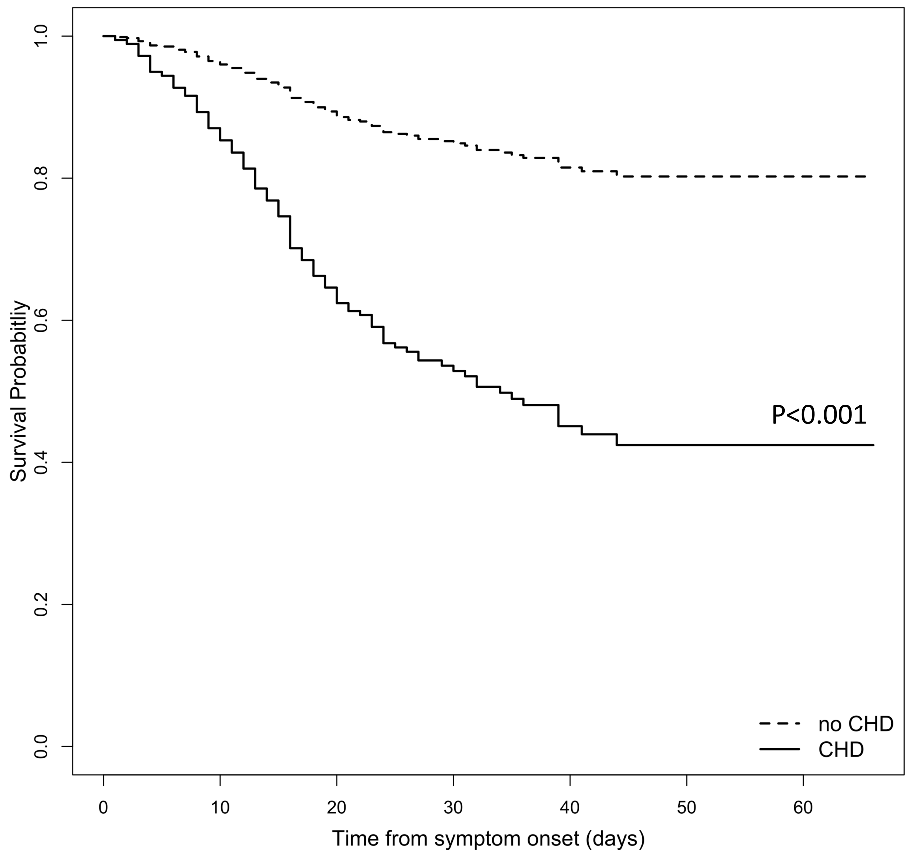


Figure 1: Patient flow diagram detailing included subjects and exclusion criteria



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Supplementary Table S1. Sample distribution across all 32 province-level in mainland China

Province	Survivors		Deaths	
	National total n	Sample n (%)	National total n	Sample n (%)
Guangdong	1343	9 (0.67)	8	8 (100.00)
Henan	1265	7 (0.55)	22	17 (77.30)
Zhejiang	1205	10 (0.83)	1	1 (100.00)
Hunan	1003	15 (1.50)	4	2 (50.00)
Anhui	981	9 (0.92)	6	6 (100.00)
Jiangxi	932	3 (0.32)	1	1 (100.00)
Shandong	692	66 (9.54)	6	6 (100.00)
Jiangsu	618	13 (2.10)	0	0 (100.00)
Chongqing	576	0 (0.00)	6	6 (100.00)
Sichuan	535	4 (0.75)	3	3 (100.00)
Heilongjiang	475	6 (1.26)	13	9 (69.20)
Beijing	425	3 (0.71)	8	3 (37.50)
Shanghai	339	3 (0.88)	3	3 (100.00)
Hebei	312	6 (1.92)	6	6 (100.00)
Fujian	294	2 (0.68)	1	1 (100.00)
Guangxi	250	2 (0.80)	2	2 (100.00)
Shaanxi	239	6 (2.51)	1	1 (100.00)
Yunnan	171	3 (1.75)	2	1 (50.00)
Hainan	163	5 (3.07)	6	6 (100.00)
Guizhou	144	2 (1.39)	2	2 (100.00)
Tianjin	132	4 (3.03)	3	3 (100.00)
Shanxi	131	2 (1.53)	0	0 (100.00)
Liaoning	125	0 (0.00)	1	0 (0.00)
Gansu	123	1 (0.81)	2	2 (100.00)
Jilin	92	1 (1.09)	1	1 (100.00)
Xinjiang	76	0 (0.00)	3	3 (100.00)
Neimenggu	73	2 (2.74)	1	1 (100.00)
Ningxia	75	0 (0.00)	0	0 (100.00)
Hubei*	NA	NA	NA	NA
Total	12698	275 (2.17)	112	94 (83.9)

*Hubei Province was excluded from this study

Supplementary Table S2: Results from unweighted logistic regression

	Multivariate					
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.0 (1.0-1.1)	**0.03**	1.0 (1.0-1.1)	**0.007**	1.0 (1.0-1.1)	**0.05**
Male	1.1 (0.6-1.7)	0.98	1.1 (0.6-1.8)	0.87	1.0 (0.5-1.7)	0.89
Before 01/11/2020	1.7 (0.9-3.1)	0.09	1.6 (0.9-2.9)	0.12	1.7 (0.9-3.1)	0.09
Comorbidity Score	1.12 (1.09-1.72)	**0.007**	NA	NA	NA	NA
CHD	NA	NA	3.3 (1.6-6.9)	**0.002**	3.4 (1.7-7.4)	**0.001**
Cerebral infarction	NA	NA	NA	NA	2.5 (0.9-7.0)	0.08
COPD	NA	NA	NA	NA	2.5 (0.7-9.4)	0.14
Renal failure	NA	NA	NA	NA	1.9 (0.5-7.0)	0.30

OR=odds ratio; CHD=coronary heart disease; COPD=chronic obstructive pulmonary disease.

Bold: statistically significant using threshold $p<0.05$

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History of coronary heart disease increased the mortality rate of COVID-19 patients: a nested case-control study

Tian Gu, MS[1]; Qiao Chu, PhD[2]; Zhangsheng Yu, PhD[3]; Botao Fa, MS[3]; Anqi Li, MS[4]; Lei Xu, MD[5]; Ruijun Wu, PhD[4]; Yaping He, PhD[2]

Author affiliations:

1. Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA
2. School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
3. Department of Bioinformatics and Biostatistics, Shanghai Jiao Tong University, Shanghai, China
4. School of Social Development, East China Normal University, Shanghai, China
5. Department of Cardiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Corresponding authors:

Prof. Ruijun Wu: School of Social Development, East China Normal University, 500 Dongchuan Rd., Shanghai 200241, China
Phone: +86 (021) 62235782
Fax: +86 (021) 62604330
rjwu@re.ecnu.edu.cn

Prof. Yaping He: College of Public Health, Shanghai Jiao Tong University School of Medicine, South Chongqing Rd., No. 227, Shanghai 200025, China
Phone: +86 (021) 63846590*776494
Fax: +86 (021) 33310986
hypcyr@sina.com

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Abstract

Objective: Evaluate the risk of pre-existing comorbidities on COVID-19 mortality, and provide clinical suggestions accordingly.

Setting: A nested case-control design using confirmed case reports released from the news or the national/provincial/municipal health commissions of China between December 18, 2019, and March 8, 2020.

Participants: Patients with confirmed SARS-CoV-2 infection, excluding asymptomatic patients, in mainland China outside of Hubei Province.

Outcome measures: Patient demographics, survival time and status, and history of comorbidities.

Method: A total of 94 publicly reported deaths in locations outside of Hubei Province, mainland China, were included as cases. Each case was matched with up to three controls, based on gender and age ± 1 year old (94 cases and 181 controls). The inverse probabilityweighted Cox proportional hazard model was performed, controlling for age, gender, and the early period of the outbreak.

Results: Of the 94 cases, the median age was 72.5 years old (IQR=16), and 59.6% were male, while in the control group the median age was 67 years old (IQR=22), and 64.6% were male. Adjusting for age, gender, and the early period of the outbreak, poor health conditions were associated with a higher risk of COVID-19 mortality (hazard ratio of comorbidity score, 1.31 [95% confidence interval (CI): 1.11-1.54]; p=0.001). The estimated mortality risk in patients with pre-existing coronary heart disease (CHD) was three times that of those without CHD (p<0.001). The estimated 30-day survival probability for a profile patient with pre-existing CHD (65-year-old female with no other comorbidities) was 0.53 (95% CI, 0.34-0.82), while it was 0.85 (95% CI, 0.79-0.91) for those without CHD. Older age was also associated with increased mortality risk: Every 1-year increase in age was associated with a 4% increased risk of mortality (p<0.001).

Conclusion: Extra care and early medical interventions are needed for patients with pre-existing comorbidities, especially CHD.

Strengths and limitations of this study

(i) Since we used data outside of the epicenter of the outbreak in mainland China, we avoided the competing mortality risk caused by insufficient health care resources; (ii) the study controlled for the confounding effects of age, gender, and the early period of the pandemic, which were, in general, not considered in the existing literatures; (iii) the survival-time-related statistical results can help guide the early clinical intervention to reduce mortality; (iv) the lack of medical test results in the publicly reported data restricted further investigation on the association between comorbidity-related clinicalindex and mortality; and (v) the missing at random assumption could not be verified.

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 11, 2020, the World Health Organization (WHO) 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 beta-coronavirus similar to the severe acute respiratory syndromecoronavirus (SARS-CoV) in its genetic sequence [2]. Epidemiological evidence suggests that the initial 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]-[8], and there are asymptomatic yet contagious cases [9].

According to the COVID-19 situation reports of WHO, as of June 13, 2020, there were 83,132 confirmed cases in mainland China, including 4,634 deaths. Internationally, a total of 7.41 million confirmed cases and 418,000 deaths have been reported from 186 countries outside of China. 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 in severe cases, patients 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], [10]-[12], cerebrovascular diseases [6], chronic obstructive pulmonary disease (COPD) [3], [8], cancer [13], and digestive diseases [14], in comparison to those with non-severe cases [3], [6], [8]-[15].

Recently, scholarly attention has focused on identifying the risk factors for death from COVID-19. Some evidence suggests that pre-existing medical conditions are likely risk factors for death from COVID-19. For example, a study based on 72,314 cases in China indicated that the case-fatality rate (CFR) tends to be higher among those who are older in age and who have pre-existing cardiovascular disease, diabetes, and/or hypertension[9]. Similarly, by conducting logistic regression on odds of in-hospital deaths among 54 diseased patients and 137 recovered patients in Wuhan City, Hubei Province, Zhou et al. (2020) [16] found that older age, higher Sequential Organ Failure Assessment (SOFA) score, and D-dimer greater than 1ug/ml at hospital admission were associated with increased odds of in-hospital death. Chen et al. (2020) found that pre-existing hypertension and other cardiovascular complications were more common among diseased patients than recovered patients [4].

However, several gaps remain in the understanding of risk factors for mortality of COVID-19. First, most current research on pre-existing comorbidities of COVID-19 was based on univariate comparison, which did not account for important confounders such as age and gender [17]-[20]. Second, no studies have investigated the hazard of the identified risk factors over time or the probability of survival at a given time. Under the rapidly changing pandemic situation, it is crucial to provide timely survival-time guidance for implementing the targeted treatment to the high-risk patients in clinical practice. Third, most existing studies on mortality risk factors were focused on patients diagnosed in Wuhan, Hubei Province, with little understanding about the mortality risk factors outside of Hubei Province. The risk factors are likely different inside and outside of Hubei Province since current research has found the clinical symptom severity [5] and the CFR [9], [21] to be higher in Hubei Province (the center of outbreak) than in cities outside of Hubei Province in China. Fourth, no studies thus far have taken into account the pandemic stage when evaluating mortality risk factors. It has been found that the average daily infection rate in China was different before and after January 22, 2020, since non-pharmaceutical interventions were taken by the government before this date [22]. The change of time in the pandemic stage may also influence the risk factors for fatality associated with COVID-19.

To fill the above research gaps in the existing literature about the mortality risk factors for COVID-19, the present study was conducted using a nested case-control (NCC) study, which aimed to evaluate the risk of the common pre-existing comorbidities (hypertension, CHD, diabetes, etc.) for mortality associated with COVID-19 in mainland China outside of Hubei Province. NCC, also called risk set sampling, has been widely used in studying fatal disease risk effect in large pharmacoepidemiological studies [23]-[28] and risk prediction in pandemic influenza A (H1N1) 2009 (pH1N1) [29]. NCC is cost-effective in data collection and is especially suitable for research on the mortality risk of diseases such as COVID-19, where the number of event-free people largely exceeds those who are symptomatic [30]. To attain this goal, we employed survival analysis on 275 publicly reported confirmed cases, adjusting for age, gender, and the change in the pandemic stage in China (i.e., before and after January 22, 2020).

Method

Study Design and Rationale

This study performed survival analysis under an NCC design to assess the roles of common comorbidities (cardiocerebrovascular, endocrine, and respiratory disease, etc.) in predicting mortality for COVID-19 among patients in mainland China outside of Hubei Province. The study period was from December 18, 2019, when the first laboratory-confirmed case was announced in China, to March 8, 2020.

The study cohort was defined as all the publicly reported confirmed COVID-19 patients outside of Hubei Province in mainland China during the study period. During this period, 112 deaths outside of Hubei Province were reported by the National Health Committee of China, and 18 were excluded from the present study due to the missingness of important clinical information. A total of 448 publicly reported laboratory-confirmed COVID-19 cases (94 deaths and 354 survivors) were initially collected. To avoid selection bias due to intentionally collecting patients with certain pre-existing comorbidities, two authors independently collected, compared, and reviewed the full text of each case report. Following the typical NCC design setting where all events are included and a certain number of controls are matched with replacements, all deaths were included as cases, and each case was matched with up to three controls on gender and age $\pm$ 1 year old (94 cases and 181 controls). The sampledistributionacross all 32 province-level regions in mainland China is presented in Supplementary Table S1.

Data Collection Procedure

We routinely searched for daily news and public health reports on confirmed COVID-19 cases in all areas in mainland China outside of Hubei Province. Patients' clinical and comorbidity characteristics were recorded and doubly confirmed by national/provincial/municipal health commission websites, the official COVID-19 data reporting websites in China. Follow-up time was defined as the duration from the date of disease onset until the end of observation on March 8, 2020, or when the participant died, whichever came first. For each eligible patient, we followed local reports to update their survival status until the end of follow-up time. Pre-existing comorbidities were recorded based on the descriptions in case reports.

As illustrated in Figure 1, the inclusion criteria were publicly reported COVID-19 patients who had complete information on basic demographics (age, gender, and region), disease onset date (the first time they became symptomatic), and the history of comorbidities (including hypertension, coronary heart disease (CHD), cardiac failure, cerebral infarction, diabetes, chronic bronchitis, COPD, renal failure, and history of surgery). Asymptomatic patients were not included in this study. In addition, we defined "comorbidity-free patients" as those who were specifically described as "no pre-existing medical condition/comorbidity" on the national/provincial/municipal health commission websites.

In the following three steps, we used patientno. 213 in the sample as an example to introduce the dynamic tracking method we used to identify any missing dates.

Step 1. We conducted an internet search on confirmed cases on baidu.com, the largest search engine in China, using the keywords "confirmed COVID-19 cases report" and "pre-existing comorbidities." A search result pertained to one confirmed case reported on the website of the Municipal Health Commission of Binzhou (Shandong Province) on February 17, described as "*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 the age, gender, and region of this patient and that he was comorbidity-free.

Step 2. We then determined the onset date of COVID-19in this patient based on 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, following the updates on the website, we confirmed the event status of this patient as discharged on March 3, 2020.

Statistical Analysis

Analyses were performed in R 3.6.2 (R Foundation for Statistical Computing) through RStudio version 1.2.5042. Data and codes are available online at GitHub (https://github.com/GuTian-TianGu/COVID-19_NCCstudy). Baseline clinical characteristics were shown as mean (SD), median (range), or number (%), with a comparison of characteristics in subjects stratified by case and control via the non-parametric Mann–Whitney U test for continuous variables and chi-squared or Fisher's exact test for binary variables.

In order to utilize the time-to-event information under the NCC design, the inverse probability weighted Cox proportional hazard regression model was employed [31]. The matching between cases and controls and relative weights were simultaneously obtained via KMprob function in multipleNCC R package [32] by specifying the Kaplan-Meier type weights with additional matching on gender and age $\pm$ 1 year old. Only survivors were assigned weights since all cases (deaths) were included as designed with a weight of one. A total of 113 survivors (mean age 46.5) with sampling probabilities of zero were considered "fail to match" and excluded from the study, mainly due to younger age than cases. A majority of the excluded patients were from Shandong Province (38.1%) due to the relatively high representation of the sample (detailed information of excluded survivors is available online at GitHub). In a sensitivity analysis adjusting for Shandong Province (results not shown here), we observed the consistent results as the main analysis.

The comorbidity score, ranging from zero to nine, was defined as the summation of nine comorbidities that have been specifically mentioned in relation to COVID-19 outcomes (CHD, hypertension, cardiac failure, cerebral infarction, chronic bronchitis, COPD, diabetes, renal failure, and history of surgery). The Kaplan-Meier curve was plotted to check the proportional hazard assumption, and the Pearson correlation test was used to rule out the multicollinearity concern before fitting any model. Univariate weighted Cox models were performed for each comorbidity. The multivariate weighted Cox model was used to determine if pre-existing comorbidity yielded prognostic hazard information. We included those comorbidities that were marginally significant ($p<0.1$) in the univariate analysis to the multivariate model. Other than the common risk factors (age and gender), the multivariate model also adjusted for the early period of the pandemic (after vs. before January 22, 2020, when no intervention was taken by the government) [22]. 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 comorbidity score as a continuous predictor, adjusting for the same covariates. Hazard ratios

(HRs) from the weighted Cox model were reported along with 95% CIs and p-values. Sensitivity analysis was performed using multivariate logistic regression to provide estimated odds ratio (ORs), which included the same covariates as the multivariate weighted Cox model.

Weighted Cox model-based survival estimates were plotted for a sample patient profile (65-year-old female with no other comorbidities) to compare the survival probability over time with and without CHD. The log-rank test was used to compare the median survival difference.

Results

Sample Description

Table 1 summarizes patient demographics and pre-existing medical conditions. Results are presented for all patients in the study (n=275) as well as for cases (n=94) and controls (n=181), respectively. Patients were 24-94 years old ($Mean_{age}$=66.4, SD_{age}=14.5). The average age tended to be older in the case group (70.7 years old) than in the control group (64.2 years old). Median ages were similar to mean ages in both groups. A majority (62.9%) of the patients were male. Overall, 25.5% of the total patients had clinical symptoms associated with COVID-19 before January 22, 2020. A relatively small proportion of the total sample had COPD, renal failure, history of surgery, and hepatic failure (4.4%, 4.4%, 3.6%, and 1.1%, respectively). Among all pre-existing comorbidities with over 5% of the total sample, hypertension was the most common (39.6%), followed by diabetes (26.2%), CHD (14.5%), cardiac failure (8%), cerebral infarction (6.9%), and chronic bronchitis (6.9%). Patients in the case group had more CHD (p<0.001) and more cerebral infarction (p=0.05) than those in the control group. The mean comorbidity score was 1.22 (SD=1.21) in the overall sample and 1.6 (SD=1.32) in the case and 1.02 (SD=1.10) in the control group (p<0.001).

Model Results

Results of the Pearson correlation test showed no significant correlations with the presence of comorbidities of interest, and the assumption of the proportional hazard was not violated.

Table 2 presents the results of univariate and multivariate weighted Cox models. Older age was associated with significantly higher risk of death with similar magnitude in univariate and multivariate models. In the adjusted model, every 1-year increase in age was associated with an estimated 4% higher risk of death (p<0.001). No significant hazard difference was found between male and female patients. Disease infection during the early no-intervention period was associated with a higher risk of death but was not statistically significant.

In a separate model using the comorbidity score as a predictor, we observed that a higher comorbidity score was associated with a higher mortality risk in both unadjusted and adjusted models (p=0.009 and p=0.03, respectively). All pre-existing comorbidities had an HR over 1 in the univariate model, of which CHD had the largest HR of 4.2 (p<0.001), followed by cerebral infarction (HR=2.9, p=0.004), COPD (HR=2.6, p=0.01), renal failure (HR=2.3, p=0.09), cardiac failure (HR=1.9, p=0.1), history of surgery (HR=1.7, p=0.34), hypertension (HR=1.4, p=0.17), diabetes (HR=1.1, p=0.61), and chronic bronchitis (HR=1.1, p=0.55), but not all were statistically significant. After adjusting for age, gender, and the early period of the pandemic in China, CHD was the only comorbidity that yielded a significant mortality risk: COVID-19 patients with pre-existing CHD had an estimated 2.9 times higher risk of death than those without CHD. In addition, cerebral infarction, COPD, and renal failure all had an estimated HR of around 2.0. Similar results were observed by using unweighted logistic regression in a sensitivity analysis (Supplementary Table S2).

The overall median follow-up was 40 days, during which 94 deaths were observed. Figure 2 shows the estimated survival probability over 70 days for a sample patient profile with and without CHD (65-year-old female with no other comorbidities). For such a patient profile, having pre-existing CHD led to a significantly shorter survival probability over time compared to those without CHD (p<0.001). For those with CHD, the estimated 30-day survival probability was 0.53 (95% confidence interval [CI] [0.34-0.82]); on the other hand, this number was 0.85 (95% CI [0.79-0.91]) for those without CHD.

Discussion

In our research, based on publicly reported confirmed cases and adjusted for the confounding effect of age, gender, and the early period of the pandemic when no intervention was taken, we used survival analysis to estimate the fatality risk of pre-existing comorbidities in COVID-19. There were three major findings: First, poor health condition was associated with higher mortality risk of COVID-19. Second, after adjusting for confounders, CHD was the only significant risk factor for COVID-19 mortality. Patients with pre-existing CHD were 3.11 times more likely to die than those without CHD (p<0.001). For one patient profile (65-year-old female without other comorbidities), we saw an estimated 30-day survival probability of 0.85 (p<0.001). However, for those with CHD, the 30-day survival probability was 0.53. Third, older age was associated with an increased risk of death. Specifically, every 1-year increase in age was associated with a 4% increased risk of mortality (p<0.001).

To the best of our knowledge, the present study is the first to provide substantial statistical evidence showing the effect of CHD in predicting mortality for COVID-19. This result is consistent with previous studies that found higher CFR among patients with cardiovascular disease [9], [15]. It is worth pointing out that the existing studies [9], [16] 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 models, our study used time-to-event outcomes, which offer more survival-time-related information to help guide the clinical intervention and more statistical power to detect risk factors [33][34].

Previous studies have indicated that cardiovascular events following pneumonia may increase the risk of mortality [4], [35]-[[40], which explained our findings from the viewpoint of pathophysiological mechanisms. One potential mechanism underlying the association between pneumonia and cardiovascular events is inflammation [37]. Specifically, the inflammatory reaction following pneumonia can result in plaque instability and damage in the blood vessels. Evidence of elevated local inflammation in the atherosclerotic coronary arteries following acute systemic infections has been shown in many studies [37][39]. Thus, infections may result in heightened loading that is imposed on cardiomyocytes and lead to sympathetic hyperactivity or ischemia, which may increase the risk of arrhythmia and heart failure in COVID-19 patients with pre-existing CHD [36].

Given the limited understanding of the prognostic factors for COVID-19, more research, including potentially prospective studies, is needed to investigate the mechanism by which pre-existing CHD may influence the survival probability of patients with COVID-19. From the clinical point of view, early evaluation of a patient's medical history is necessary to implement early medical interventions and decrease the mortality risk. We suggest monitoring the dynamic heart rate for patients with pre-existing CHD. For those severe symptomatic patients who had pre-existing heart ischemia and abnormal heart function, early medical intervention may be needed [40].

Furthermore, our results indicated that the risk of death from COVID-19 was significantly higher in older patients. Adjusting for others, every 1-year increase in age was associated with a 4% increased risk of death, which is similar to what was found in previous studies [8][9], [16]. Alongside the evidence of prognostic risk in CHD, we suggest that extra care is needed for those with CHD, especially for elderly patients.

Previous studies yielded mixed results regarding gender differences in mortality risk of COVID-19. Some studies found male sex was associated with a higher risk of death from COVID-19 [41], whereas other studies did not find gender to be a significant factor predicting the mortality risk of COVID-19 [10], [16]. In the current study, gender was not a significant mortality risk factor for COVID-19. More research is needed to further our understanding of gender differences in the outcome of COVID-19 and underlying mechanisms.

The design of excluding patients from Hubei Province was based on the concerns of unknown confounders caused by insufficient medical resources in the epicenter. CDC's report has pointed out that the rapidly increasing number of infections could easily crash the health care system by exceeding its maximum capacity [42]. Therefore, analyzing patient data outside of Hubei Province avoided the competing mortality risk caused by insufficient health care resources and revealed the true underlying impact of pre-existing comorbidities on COVID-19 mortality [43].

This study has several limitations. It is worth noting that the data were collected when COVID-19 was spreading rapidly in China and the health authorities and researchers had limited understanding of the incubation period, modes of viral transmission, and effective treatment. Whether our findings can be generalized to later epidemic phases warrants future research. One limitation of the present study lies in the nature of publicly reported data. Researchers have pointed out that severe cases may be overrepresented in publicly reported data [44]. Nevertheless, we have managed to reduce the potential bias caused by severe case overrepresentation by appropriately matching the cases and controls in the NCC design. Following the NCC design, we allowed the controls to be matched with cases on age $\pm$ 1 year old instead of the exact matching, which caused the significant age difference between two groups (Table 1). Thus, we adjusted for the matching covariates in all the models to address this [31]. The auto-matching procedure via the statistical program also prevented the possibility of tendentiously selecting survivors with comorbidity-free history during data collection. In addition, NCC design is favored in our situation where the risk factor data and event of interest can be identified opportunistically from publicly reported confirmed cases [30]. Therefore, NCC was the optimal choice, given the restricted availability of public data. Moreover, due to the lack of information of treatment in the health reports published by the local health commission websites, we did not include treatment information into analysis, which may produce confounding effects. It calls for future research to investigate the mortality risk effect of pre-existing comorbidities by adding treatment as a covariate in the model. Lastly, we were not able to verify the missing at random assumption of the 18 missing deaths (four from Heilongjiang, five from Henan, five from Beijing, two from Hunan, one from Liaoning and one from Yunnan) as well as the survivors.

In conclusion, our findings provided preliminary yet strong evidence supporting the association between pre-existing CHD and mortality risk for patients with COVID-19. Based on our findings, close monitoring, extra care, and early medical intervention are needed for patients with pre-existing CHD to reduce the mortality risk associated with COVID-19.

Footnotes

Author Contributions

TG conducted the analysis, interpreted the data, drafted the article, and rechecked the transcribed manuscript. QC conducted the literature review and drafted the article. ZY guided and supervised the statistical analysis. BF helped with data analysis. AL helped with literature review, data collection, management and the data quality check, and was responsible for reference organization. LX provided clinical support and interpretation of the results. RW collected, preprocessed and managed data, and conducted preliminary data analysis. YH guided and supervised the research process and provided funding support. All authors critically revised the manuscript for intellectual content, approved the final draft, and agreed to accountability for all aspects of the work.

Conflict of Interest

The authors have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethics Approval

The data published in news reports and websites were open to the public and free of identifiers.The study was approved by Shanghai Jiao Tong University Public Health and Nursing Medical Research Ethics Committee (SJUPN-202001).

Patient and Public Involvement

This study used publicly reported patient-level data. All data were available online to the public. No patient recruitment was involved in the study design, and no personal information can be identified from the data.

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Data sharing statement

Raw data are available at GitHub: https://github.com/GuTian-TianGu/COVID-19_NCCstudy.git.

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Correspondence

Address offprint requests to Dr. Wu at School of Social Development, East China Normal University, 500 Dongchuan Rd., Shanghai 200241, China (rjwu@re.ecnu.edu.cn), or Dr. He at College of Public Health, Shanghai Jiao Tong University School of Medicine, South Chongqing Rd., No. 227, Shanghai 200025, China (hypcyr@sina.com), respectively.

Tables and Figures

Table 1. Patient Characteristics, stratified by survival status*

	Overall (N=275), n (%)	**Case (deaths) (N=94), n (%)**	**Control (survivors) (N=181), n (%)**	**P Value †**
Matching variables				
Age				
Mean (SD)	66.4 (14.5)	70.7 (13.3)	64.2 (14.7)	**<0.001**
Median (IQR)	68.0 [22]	72.5 [16]	67.0 [22]	-
Male	173 (62.9)	56 (59.6)	117 (64.6)	0.49
Other covariates				
Before 01/22/2020	70 (25.5)	27 (28.7%)	43 (23.8)	0.52
History of surgery	10 (3.6)	4 (4.3)	6 (3.3)	0.74
Cardiocerebrovascular diseases				
Hypertension	109 (39.6)	42 (44.7)	67 (37.0)	0.27
CHD	40 (14.5)	25 (26.6)	15 (8.3)	**<0.001**
Cardiac failure	22 (8.0)	10 (10.6)	12 (6.6)	0.35
Cerebral infarction	19 (6.9)	11 (11.7)	8 (4.4)	**0.05**
Endocrine diseases				
Diabetes	72 (26.2)	26 (25.4)	46 (27.7)	0.80
Respiratory diseases				
Chronic bronchitis	19 (6.9)	7 (7.4)	12 (6.6)	1.00
COPD	12 (4.4)	7 (7.4)	5 (2.8)	0.14
Other diseases				
Renal failure	12 (4.4)	6 (6.4)	6 (3.3)	0.38
Hepatic failure	3 (1.1)	3 (3.2)	0 (0)	0.07
Comorbidity score				
Mean (SD)	**1.22 (1.21)**	**1.60 (1.32)**	**1.02 (1.10)**	**<0.001**

CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease.

*Mean (standard deviation) is reported for the continuous variables and the counts (%) for categorical variables. p values were calculated by the Mann–Whitney U test, $\chi 2$ test, or Fisher's exact test, as appropriate.

Bold: statistically significant using threshold p<0.05

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	HR (95% CI)	P Value
Age	1.05 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**	1.0 (1.0-1.1)	**<0.001**	1.04 (1.02-1.06)	**<0.001**
Male	0.76 (0.5-1.2)	0.24	1.1 (0.7-1.7)	0.74	1.1 (0.7-1.7)	0.71	0.997 (0.62-1.60)	0.99
Before 01/22/2020	1.12 (0.7-1.8)	0.66	1.3 (0.8-2.1)	0.29	1.2 (0.7-1.9)	0.48	1.21 (0.74-1.98)	0.45
Comorbidity Score	1.50 (1.27-1.75)	**<0.001**	1.31 (1.11-1.54)	**0.001**	NA	NA	NA	NA
Cardiocerebrovascular								
CHD	4.19 (2.5-7.1)	**<0.001**	NA	NA	2.9 (1.7-4.9)	**<0.001**	3.01 (1.82-4.98)	**<0.001**
Hypertension	1.37 (0.9-2.2)	0.17	NA	NA	NA	NA	NA	NA
Cardiac failure	1.85 (0.9-3.9)	0.10	NA	NA	NA	NA	NA	NA
Cerebral infarction	2.86 (1.4-5.8)	**0.004**	NA	NA	NA	NA	1.90 (0.94-3.8)	0.07
Respiratory								
Chronic bronchitis	1.05 (0.4-2.5)	0.55	NA	NA	NA	NA	NA	NA
COPD	2.61 (1.2-5.6)	**0.01**	NA	NA	NA	NA	1.85 (0.89-3.85)	0.10
Endocrine								
Diabetes	1.14 (0.7-1.9)	0.61	NA	NA	NA	NA	NA	NA
Others								
Renal failure	2.30 (0.9-6.0)	0.09	NA	NA	NA	NA	2.02 (0.81-5.07)	0.13
History of surgery	1.71 (0.6-5.1)	0.34	NA	NA	NA	NA	NA	NA

HR=hazard ratio;
CHD=coronary heart disease;
COPD=chronic obstructive pulmonary disease;
Bold: statistically significant using threshold p<0.05.

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

Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for an example patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) for patients with pre-existing CHD, while 0.85 (95% CI [0.79-0.91]) for those without (p<0.001). CHD=coronary heart disease.

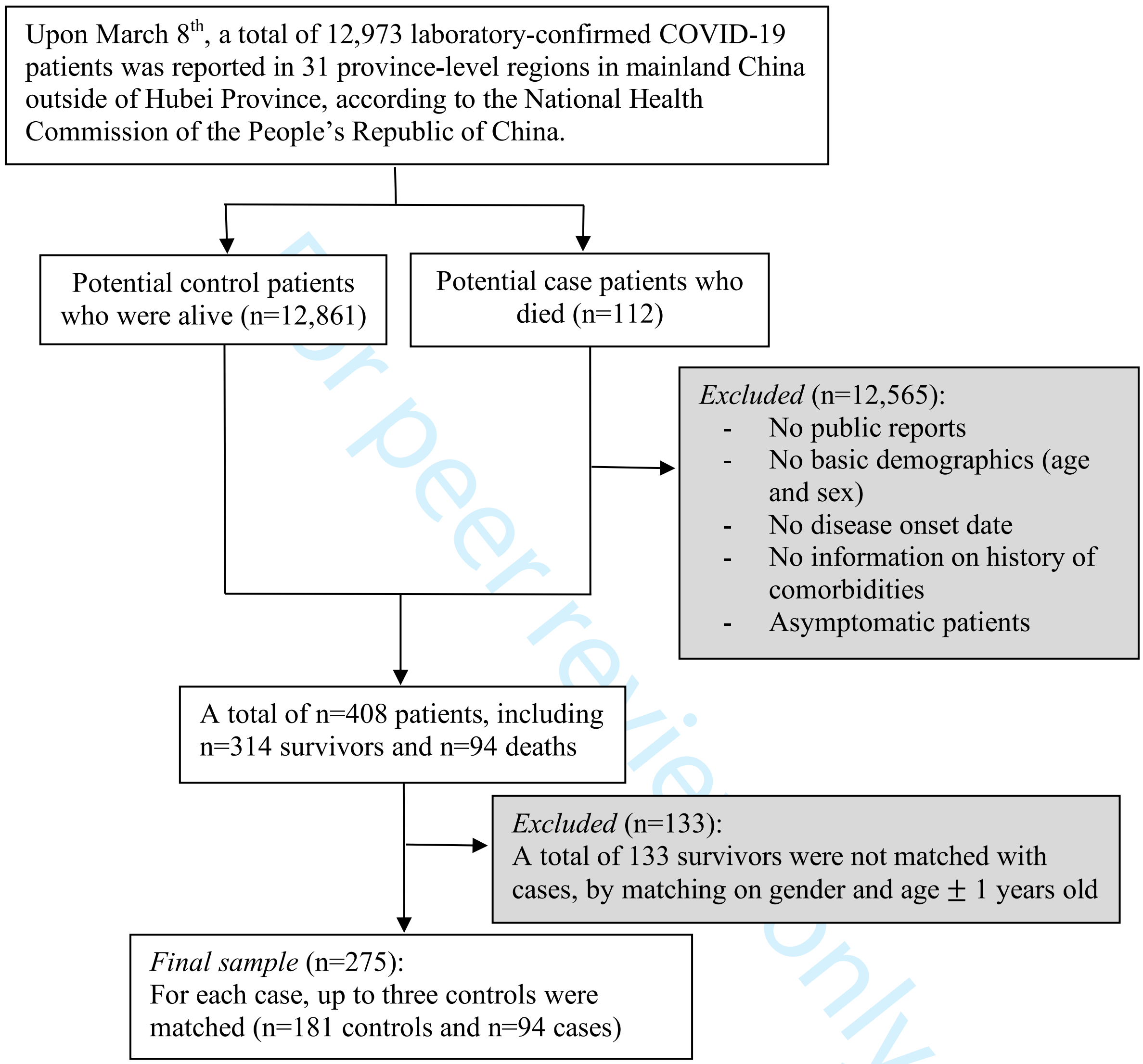

Figure 1: Patient flow diagram detailing included subjects and exclusion criteria

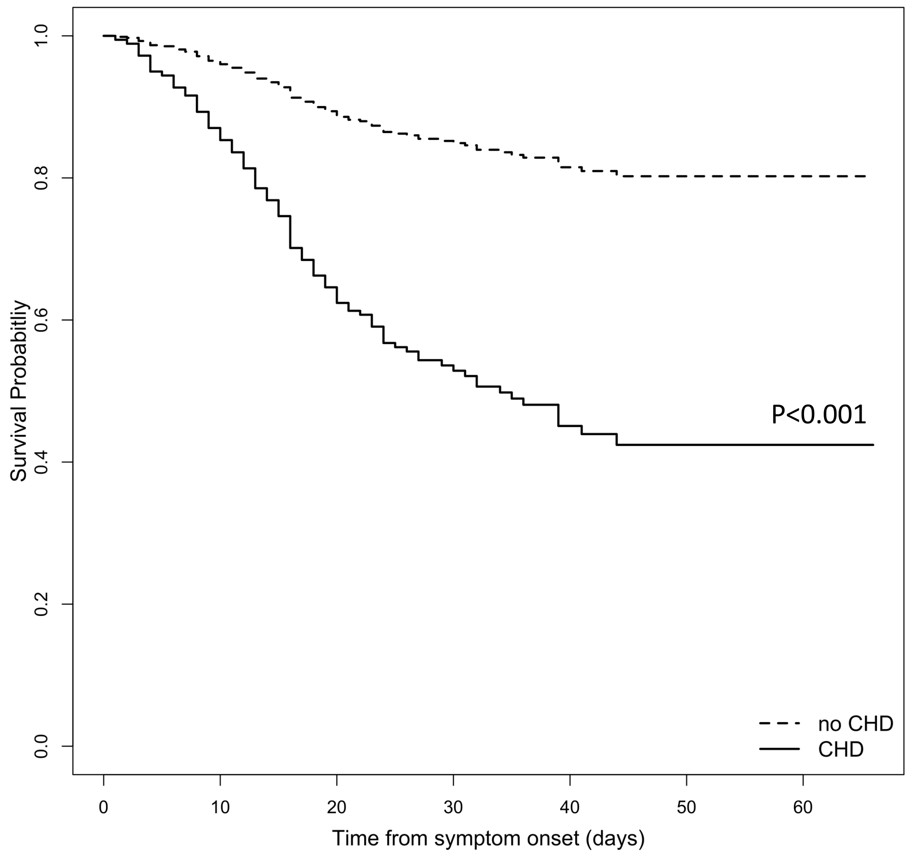

Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for a sample patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) for patients with pre-existing CHD, while 0.85 (95% CI [0.79-0.91]) for those without (p<0.001). CHD=coronary heart disease.

Supplementary Table S1. Sample distribution across all 32 province-level in mainland China

Province	Survivors		Deaths	
	National total n	Sample n (%)	National total n	Sample n (%)
Guangdong	1343	9 (0.67)	8	8 (100.00)
Henan	1265	7 (0.55)	22	17 (77.30)
Zhejiang	1205	10 (0.83)	1	1 (100.00)
Hunan	1003	15 (1.50)	4	2 (50.00)
Anhui	981	9 (0.92)	6	6 (100.00)
Jiangxi	932	3 (0.32)	1	1 (100.00)
Shandong	692	66 (9.54)	6	6 (100.00)
Jiangsu	618	13 (2.10)	0	0 (100.00)
Chongqing	576	0 (0.00)	6	6 (100.00)
Sichuan	535	4 (0.75)	3	3 (100.00)
Heilongjiang	475	6 (1.26)	13	9 (69.20)
Beijing	425	3 (0.71)	8	3 (37.50)
Shanghai	339	3 (0.88)	3	3 (100.00)
Hebei	312	6 (1.92)	6	6 (100.00)
Fujian	294	2 (0.68)	1	1 (100.00)
Guangxi	250	2 (0.80)	2	2 (100.00)
Shaanxi	239	6 (2.51)	1	1 (100.00)
Yunnan	171	3 (1.75)	2	1 (50.00)
Hainan	163	5 (3.07)	6	6 (100.00)
Guizhou	144	2 (1.39)	2	2 (100.00)
Tianjin	132	4 (3.03)	3	3 (100.00)
Shanxi	131	2 (1.53)	0	0 (100.00)
Liaoning	125	0 (0.00)	1	0 (0.00)
Gansu	123	1 (0.81)	2	2 (100.00)
Jilin	92	1 (1.09)	1	1 (100.00)
Xinjiang	76	0 (0.00)	3	3 (100.00)
Neimenggu	73	2 (2.74)	1	1 (100.00)
Ningxia	75	0 (0.00)	0	0 (100.00)
Hubei*	NA	NA	NA	NA
Total	12698	275 (2.17)	112	94 (83.9)

*Hubei Province was excluded from this study

Supplementary Table S2: Results from unweighted logistic regression

	Multivariate					
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.0 (1.0-1.1)	**0.03**	1.0 (1.0-1.1)	**0.007**	1.0 (1.0-1.1)	**0.05**
Male	1.1 (0.6-1.7)	0.98	1.1 (0.6-1.8)	0.87	1.0 (0.5-1.7)	0.89
Before 01/11/2020	1.7 (0.9-3.1)	0.09	1.6 (0.9-2.9)	0.12	1.7 (0.9-3.1)	0.09
Comorbidity Score	1.12 (1.09-1.72)	**0.007**	NA	NA	NA	NA
CHD	NA	NA	3.3 (1.6-6.9)	**0.002**	3.4 (1.7-7.4)	**0.001**
Cerebral infarction	NA	NA	NA	NA	2.5 (0.9-7.0)	0.08
COPD	NA	NA	NA	NA	2.5 (0.7-9.4)	0.14
Renal failure	NA	NA	NA	NA	1.9 (0.5-7.0)	0.30

OR=odds ratio; CHD=coronary heart disease; COPD=chronic obstructive pulmonary disease.

Bold: statistically significant using threshold $p<0.05$