

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038976
Article Type:	Original research
Date Submitted by the Author:	31-Mar-2020
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
Keywords:	Epidemiology < INFECTIOUS DISEASES, Coronary heart disease < CARDIOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Tian Gu¹, MS, Qiao Chu², Ph.D., Zhangsheng Yu³, Ph.D., Botao Fa³, MS, Anqi Li⁴, MS, Lei Xu⁵, MD, Ruijun Wu⁴, Ph.D., Yaping He², 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 (hypeyr@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 \pm 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 estimation, 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.

1
2
3 **limitations:** Publicly reported data does not contain patient clinical test results, which restricted
4 further investigation on the association between comorbidity-related clinical index and mortality.
5
6
7

8 9 **Introduction**

10
11 Since the first report of Coronavirus Disease 2019 (COVID-19) in December 2019 in
12 Wuhan, Hubei Province, China, the novel virus infection has rapidly spread to other cities in
13 China, and has now been detected in 186 countries and locations internationally [1]. On March
14 11th, 2020, the World Health Organization declared COVID-19 a pandemic, and has called for
15 aggressive actions from all countries to fight the disease. Current research has indicated that
16 COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a beta-
17 coronavirus similar to the severe acute respiratory syndrome-coronavirus (SARS-CoV) in the
18 genetic sequence [2]. Epidemiological evidence suggests that initially reported cases in China
19 had a history of exposure to the Huanan seafood market [3-4]. With the escalated spread of the
20 infection, there has been clear evidence of human to human transmission [5-6]. The most
21 common symptoms include fever, dry cough and fatigue [5-8], with presence of asymptomatic,
22 yet contagious cases [9].
23
24
25
26
27
28
29
30
31

32 According to the COVID-19 situation reports of WHO, as of March 29th, 2020, the
33 infection has caused 81,445 confirmed cases in mainland China, including 3,300 deaths.
34 Internationally, a total of 601,020 confirmed cases have been reported from 186 countries
35 outside of China, including 28,747 deaths. Considering the global public health threat posed by
36 COVID-19, unraveling the prognostic factors for patients, especially the risk factors of mortality
37 associated with COVID-19, has important implications for clinical practice and is urgently
38 warranted.
39
40
41
42
43

44 Studies have indicated that severe cases tend to be older in age [6, 8] and are more likely
45 to have had pre-existing medical conditions, including but not limited to hypertension [3, 6, 8],
46 diabetes [6, 8], cardiovascular diseases [3, 6, 8, 10-12], cerebrovascular diseases [6], chronic
47 obstructive pulmonary disease (COPD) [3, 8], cancer [13], and digestive diseases [14], in
48 comparison to non-severe cases [3, 6, 8-15].
49
50
51

52 Recently, scholarly attention focuses on identifying the risk factors for death from
53 COVID-19. Some evidence suggests that pre-existing medical conditions are likely death risk
54
55
56
57
58
59
60

1
2
3 factors for COVID-19. For example, a study based on 72,314 cases in China indicated that the
4 case-fatality rate (CFR) tends to be higher among those with older age, and having pre-existing
5 cardiovascular disease, diabetes, and hypertension compared to all the patients [9]. Similarly, by
6 conducting logistic regression on odds of in-hospital death among 54 diseased patients and 137
7 recovered patients in Wuhan City, Hubei Province, Zhou et al. [16] found that older age, higher
8 Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1ug/ml at hospital
9 admission were associated with increased odds of in-hospital death. Chen et al. (2020) found that
10 pre-existing hypertension and other cardiovascular complications were more common among
11 diseased patients than recovered patients (unpublished data).
12
13
14
15
16
17
18

19 However, several gaps remain in the understanding of risk factors for mortality of
20 COVID-19. First, most current research on pre-existing comorbidities of COVID-19 was based
21 on univariate comparison, which did not account for important confounders such as age and
22 gender [17-20]. Second, no studies have investigated the hazard of the identified risk factors over
23 time, or the probability of survival at a given time. Under the rapidly changing pandemic
24 situation, it is crucial to provide timely survival-time guidance for implementing the targeted
25 treatment to the high-risk patients in clinical practice. Third, most existing studies on mortality
26 risk factors were focused on patients diagnosed in Wuhan, Hubei Province, with little
27 understanding about the mortality risk factors outside of Hubei Province. The risk factors are
28 likely different inside and outside of Hubei Province, since current research has found that the
29 clinical symptom severity [5] and the fatality-case rate [9, 21] to be higher in Hubei Province
30 (the center of outbreak) than cities outside of Hubei Province in China. Fourth, no studies thus
31 far have taken into account the pandemic stage when evaluating mortality risk factors. It has
32 been found that average daily attack rate in China was different before and after January 11th
33 2020, since non-pharmaceutical interventions were taken by the government before this date
34 [22]. The change of pandemic stage may also influence the risk factors for fatality associated
35 with COVID-19.
36
37
38
39
40
41
42
43
44
45
46
47

48 To fill the above research gaps in the existing literature about the mortality risk factors for
49 COVID-19, the present study conducted a nested case-control (NCC) study, aiming to evaluate
50 the risk of the common pre-existing comorbidities (hypertension, coronary heart disease,
51 diabetes and etc.) for mortality associated with COVID-19 in mainland China outside of Hubei
52 Province. NCC, also called risk set sampling, has been widely used in studying the fatal disease
53
54
55
56
57
58
59
60

1
2
3 risk effect in large pharmacoepidemiologic studies [23-28] and risk prediction in pandemic
4 influenza A (H1N1) 2009 (pH1N1) [29]. NCC is cost-effective in data collection, and is
5 especially suitable for research on the death risk of diseases such as COVID-19, where the
6 number of event-free people largely exceeds those who experienced events [30]. To attain this
7 goal, we employed survival analysis on 275 publicly reported confirmed cases, adjusting for age,
8 gender and the change in the pandemic stage in China (i.e., before and after January 11th, 2020).
9

14 **Method**

17 **Study Design and Rationale**

18 This study performed survival analysis under a nested case-control (NCC) design to
19 assess the roles of common comorbidities (cardiocerebrovascular, endocrine and respiratory
20 disease, etc.) in predicting mortality for COVID-19, among patients in mainland China outside of
21 Hubei Province. The study period was from December 18th, 2019, when the first laboratory-
22 confirmed case was announced in China, till March 8th, 2020.
23
24
25
26

27 The study cohort was defined as all the publicly reported confirmed COVID-19 patients
28 outside of Hubei Province in mainland China between the study period. During this period, 112
29 deaths outside of Hubei Province were reported by the National Health Committee of China, and
30 18 were excluded from the present study due to missingness of important clinical information. A
31 total of 408 publicly reported laboratory-confirmed COVID-19 cases (94 deaths and 314
32 survivors) were initially collected. The data collection procedure was blinded to patient
33 comorbidity information. All deaths were included as cases, and each case was matched with up
34 to three controls on gender and age \pm 1 year old (94 cases and 181 controls). The sample
35 distribution across all 32 province-level regions in mainland China is presented in
36 Supplementary Table S1.
37
38
39
40
41
42
43

44 **Data Collection Procedure**

45 We routinely searched for daily news and public health reports on confirmed COVID-19
46 cases in all areas in mainland China outside of Hubei Province. Patients' clinical and
47 comorbidity characteristics were recorded and doubly confirmed by
48 national/provincial/municipal health commission websites, the official COVID-19 data reporting
49 websites in China. Follow-up time was defined as the duration from the date of disease onset till
50 the end of observation on March 8th or when the participant died, whichever came first. For each
51
52
53
54
55
56
57
58
59
60

1
2
3 eligible patient, we followed local reports to update their survival status until the end of follow-
4 up time.
5

6 As illustrated in Figure 1, the inclusion criterion was publicly reported COVID-19 patients
7 who had complete information on basic demographics (age, gender and region), disease onset
8 date--the first time a patient became symptomatic, and history of comorbidities (include but not
9 limited to hypertension, cardiovascular disease, diabetes and respiratory diseases) were included
10 in the analysis. Asymptomatic patients were not included in this study. In addition, we defined
11 “comorbidity-free patients” as those who were specifically described as “no pre-existing medical
12 condition/comorbidity” on the national/provincial/municipal health commission websites.
13
14

15
16
17 In the following three steps, we used the No. 261 patient in the sample as an example to
18 introduce the dynamic tracking method we used to identify any missing dates:
19
20

21
22 **Step 1.** Conducting an internet search on confirmed cases on baidu.com, the largest search
23 engine in China, using keywords “confirmed COVID-19 cases report” and “pre-existing
24 comorbidities.” A search result pertained to one confirmed case reported on the website of
25 Municipal Health Commission of Binzhou (Shandong Province) on February 17th,
26 described as “*the 15th confirmed case: 30-year-old male without pre-existing morbidities,*
27 *who lives in the neighborhood of Xincun Village. This patient was diagnosed positive on*
28 *February 16th and is being treated with precaution in Bincheng hospital.*” We recorded
29 age, gender, region and comorbidity-free for this patient.
30
31

32
33 **Step 2.** We then determined the onset date of this patient based on another announcement
34 on the same website. In this announcement titled “*Possible exposure locations and times of*
35 *the 15th confirmed case,*” it says, “*the patient was symptomatic on February 14th.*”
36
37

38
39 **Step 3.** Finally, we confirmed the event status of this patient as discharged on March 3rd,
40 by following the updates on this website.
41
42
43
44
45

46 **Statistical Analysis**

47
48 Analyses were performed in R 3.6.2 (R Foundation for Statistical Computing). Baseline
49 clinical characteristics were shown as mean (SD), median (range), or number (%), with a
50 comparison of characteristics in subjects stratified by case and control via t-test for continuous
51 variables and chi-squared or Fisher’s exact test for binary variables.
52
53
54
55
56
57
58
59
60

1
2
3 In order to utilize the time-to-event information under the NCC design, the inverse
4 probability weighting Cox proportional hazard regression model was employed [32]. The
5 matching between cases and controls, and relative weights were simultaneously obtained via
6 KMprob function in multipleNCC R package [31], by specifying the Kaplan-Meier type weights
7 with additional matching on gender and age ± 1 year old. Only survivors were assigned weights,
8 since all cases (deaths) were included as designed with a weight of one. Those survivors with
9 sampling probabilities of zero were considered as “fail to match” and excluded from the study.

10
11 The total number of comorbidities was defined as the summation of comorbidities,
12 ranging from zero to four or above. Kaplan-Meier curve was plotted to check the proportional
13 hazard assumption and the Pearson correlation test was used to rule out the multicollinearity
14 concern before fitting any model. Univariate weighted Cox models were performed for each
15 comorbidity. The multivariate weighted Cox model was used to determine if pre-existing
16 comorbidity yielded prognostic hazard information. We included those comorbidities that were
17 marginally significant ($p < 0.1$) in the univariate analysis to the multivariate model. Other than the
18 common risk factors (age and gender), the multivariate model also adjusted for early period of
19 pandemic (after vs. before January 11th, 2020 when no-intervention was taken by the
20 government) [22]. Although matching was based on age and gender, we adjusted for the
21 matching covariates, since the matching was broken with inverse probability weighting [32]. A
22 separate multivariate model was built by using the total number of pre-existing comorbidities as
23 an ordinal predictor, adjusting for the same covariates. Hazard ratios (HRs) from the weighted
24 Cox model were reported along with 95% confidence intervals (CIs) and p-values. Sensitivity
25 analysis was performed using multivariate logistic regression to provide estimated odds ratio
26 (ORs), which includes the same covariates as the multivariate weighted Cox model.

27
28 Weighted Cox model-based survival estimates were plotted for an example patient profile
29 (65-year-old female with no other comorbidities) to compare the survival probability over time
30 with and without CHD. The log-rank test was used to compare the median survival difference.

31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 **Results**

52 53 **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, χ^2 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

1
2
3 an estimated HR of around 2.0, respectively. Similar results were observed by using unweighted
4 logistic regression in a sensitivity analysis (Supplementary Table S2).

5
6 The overall median follow-up was 40 days, during which 94 deaths were observed.
7
8 Figure 2 shows the estimated survival probability over 70 days for an example patient profile
9 with and without CHD (65-year-old female with no other comorbidities). For such patient
10 profile, having pre-existing CHD led to a significantly shorter survival probability over time,
11 compared to those without CHD ($p < 0.001$). For those with CHD, the estimated 30-day survival
12 probability was 0.53 (95% CI [0.34-0.82]), with an estimated 34 days' median survival time. On
13 the other hand, the estimated 30-day probability was 0.85 (95% CI [0.79-0.91]) for those without
14 CHD, with the corresponding median survival time over 70 days.

21 Discussion

22
23 In this paper, we used survival analysis to estimate the fatal risk of pre-existing
24 comorbidities in COVID-19, based on publicly reported confirmed cases and adjusted for the
25 confounding effect of age, gender, and early period of the pandemic when no-intervention was
26 taken. There were three major findings: First, a history of comorbidities significantly increased
27 the death risk of COVID-19: one additional pre-existing comorbidity led to an estimated 40%
28 increase of death risk ($p < 0.001$). Second, after adjusting for confounders, CHD was the only
29 significant risk factor for COVID-19 mortality. Patients with CHD had a 200% higher risk of
30 mortality in COVID-19, compared to patients without CHD ($p < 0.001$). For a patient profile (65-
31 year-old female without other comorbidities), the estimated median survival times for those with
32 CHD was 34 days, while it was over 70 days for those without CHD ($p < 0.001$). Third, older age
33 was associated with increased death risk. Specifically, every 5-year increase in age was
34 associated with a 20% increased risk of mortality ($p < 0.001$).

35
36 To our best knowledge, the present study is the first to provide substantial statistical
37 evidence to show the effect of CHD in predicting mortality for COVID-19. This result is
38 consistent with previous studies that found higher case-fatality rate among patients with
39 cardiovascular disease [9, 15]. It is worth pointing out that the existing studies [9, 16] that
40 investigate prognostic factors for death used chi-square tests or univariate logistic regression that
41 does not control for potential confounders. In contrast, by conducting weighted Cox proportional
42 hazard regression models, our study used time-to-event outcomes, which offers more survival-
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 time-related information to help guide the clinical intervention and more statistical power to
4 detect risk factors [33-34].

5
6 Previous studies have indicated that cardiovascular events following pneumonia may
7 increase the risk of mortality [35-41], which explained our findings from the point view of
8 pathophysiological mechanisms. One potential mechanism underlying the association between
9 pneumonia and cardiovascular events is inflammation [38]. Specifically, the inflammatory
10 reaction following pneumonia can result in plaque instability and damage in the blood vessels,
11 where evidence of elevated local inflammation in the atherosclerotic coronary arteries following
12 acute systemic infections have been shown in many studies [38, 40]. Thus, infections may result
13 in heightened loading imposed on cardiomyocytes, and lead to sympathetic hyperactivity,
14 ischemia, which may increase the risk of arrhythmia and heart failure in COVID-19 patients with
15 pre-existing CHD [37].

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

26
27 The design of excluding patients from Hubei Province was based on the concerns of
28 unknown confounders caused by insufficient medical resources in the epicenter. CDC's report
29 has pointed out that the rapidly increasing number of infections could easily crash the health care
30 system by exceeding its maximum capacity [42]. Therefore, analyzing patient data outside of
31 Hubei Province can avoid the competing death risk caused by insufficient health care resources,
32 and reveal the true underlying impact of pre-existing comorbidities on COVID-19 mortality [44].

33
34 One limitation of the present study lies in the nature of publicly reported data.
35 Researchers have pointed out that severe cases may be over-represented in publicly reported data
36 [45]. Nevertheless, we have managed to reduce the potential bias caused by severe case over-
37 representation, through the appropriate matching between cases and controls in NCC design. The

1
2
3 auto-matching procedure via statistical program also prevented the possibility of tendentiously
4 selecting survivors with comorbidity-free history during data collection. Since NCC design is
5 favored in our situation where the risk factor data and event of interest can be identified
6 opportunistically from publicly reported confirmed cases [30], NCC was the optimal choice,
7 given the restricted availability of public data.
8
9

10
11
12 Given the limited understanding of the prognostic factors for COVID-19, more research,
13 potentially prospective studies, are needed to investigate the mechanism by which pre-existing
14 CHD may influence the survival probability among patients with COVID-19. In addition, further
15 investigation is suggested on the association between comorbidity-related clinical index and
16 mortality based on patient clinical test results.
17
18

19
20 In conclusion, our findings provided preliminary yet strong evidence supporting the
21 association between pre-existing CHD and mortality risk for patients with COVID-19. Based on
22 our findings, close monitoring, extra care, and early medical intervention are needed for patients
23 with pre-existing CHD, to reduce the mortality risk associated with COVID-19.
24
25
26

27 28 **Footnotes**

29 30 **Author Contributions**

31
32 TG conducted the analysis, interpreted the data, drafted the article and rechecked the
33 transcribed manuscript. QC conducted literature review and drafted the article. ZY guided and
34 supervised the statistical analysis. BF helped with data analysis. AL helped data collection,
35 management, and quality check. LX provided clinical support and interpretation of the results.
36 RW collected, pre-processed and managed data, and conducted preliminary data analysis. YH
37 guided and supervised the research process, and provided funding support. All authors critically
38 revised the manuscript for intellectual content, approved the final draft, and agree to
39 accountability for all aspects of the work.
40
41
42
43
44
45
46

47 48 **Conflict of Interest**

49
50 The authors have no affiliations with or involvement in any organization or entity with
51 any financial or non-financial interest in the subject matter or materials discussed in this
52 manuscript.
53
54
55
56
57
58
59

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.

Funding

This project was funded by the National Natural Science Foundation of China (No. 71874111), Shanghai Municipal Health Bureau Foundation (No. 201740116) and Shanghai Jiao Tong University Scientific and Technological Innovation Funds (YG2020YQ01, YG2020YQ06).

Data sharing statement

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

Word count

3220

Reference

- [1] Coronavirus disease 2019 (COVID-19) Situation Report – 62. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46_2
- [2] Lu R., Zhao X., Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-74.
- [3] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506.

- 1
2
3 [4] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of
4 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**:
5 507-13.
6
7
8 [5] Xu X, Wu X, Gao J, et al. Clinical findings in a group of patients infected with the 2019
9 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*
10 2020; **368**: m606.
11
12
13 [6] Wang D, Hu B, Hu C *et al.* Clinical characteristics of 138 hospitalized patients with 2019
14 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061–1069.
15
16
17 [7] Zhang J-J, Dong X, Cao Y-Y et al. Clinical characteristics of 140 patients infected with
18 SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **00**: 1– 12.
19
20
21 [8] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in
22 China. *N Engl J Med* 2020. [Epub ahead of print].
23
24
25
26 [9] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus
27 disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the
28 Chinese Center for Disease Control and Prevention. *JAMA* 2020. [Epub ahead of print].
29
30
31 [10] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19
32 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020.
33 [Epub ahead of print].
34
35
36 [11] Shi S, Qin M, Shen Bo, et al. Association of Cardiac Injury with Mortality in Hospitalized
37 Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020. [Epub ahead of print].
38
39
40 [12] Liu J, Tu C, Zhu M, et al, Exploring the Law of Development and Prognostic Factors of
41 Common and Severe COVID-19: A Retrospective Case-Control Study in 122 Patients with
42 Complete Course of Disease. *Lancet* 2020 [Epub ahead of print].
43
44
45 [13] Liang W, Guan W, Chen R, *et al.* Cancer patients in SARS-CoV-2 infection: a nationwide
46 analysis in China. *The Lancet Oncology*.2020; **21**: 335-7.
47
48
49 [14] Mao R, Liang J, Shen J, *et al.* Implications of COVID-19 for patients with pre-existing
50 digestive diseases. *The lancet Gastroenterology & hepatology* 2020. [Epub ahead of print].
51
52
53 [15] Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease
54 2019 outbreak in China. *J Clin Med* 2020; **9**: 575.
55
56
57
58
59
60

- 1
2
3
4
5 [16] Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients
6 with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020. [Epub ahead
7 of print]
8
9
10 [17] Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic
11 review, *Stroke* 2009; **40**: 1082-90.
12
13 [18] Camp P G , Goring S M . Gender and the diagnosis, management, and surveillance of
14 chronic obstructive pulmonary disease. *Ann AmThorac Soc* 2007; **4**: 686-691.
15
16 [19] Tchkonja T, Kirkland JL. Aging, cell senescence, and chronic disease: emerging therapeutic
17 strategies. *JAMA* 2018; **320**: 1319–20.
18
19 [20] Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old medicine:
20 Role of chronic inflammation. *Prev Med* 2012; **54**: S29-S37.
21
22 [21] Chinese COVID-19 Outbreak Distribution System. Available at
23 <http://2019ncov.chinacdc.cn/2019-nCoV/>
24
25
26 [22] Wang C, Li L, Hao X, *et al*. Evolving Epidemiology and Impact of Non-pharmaceutical
27 Interventions on the Outbreak of Coronavirus Disease 2019 in Wuhan, China. [MedRxiv
28 ahead of print]
29
30 [23] Azoulay L, Dell'Aniello S, Gagnon B, *et al*. Metformin and Incidence of Prostate Cancer in
31 Patients with Type 2 Diabetes. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 337–344.
32
33 [24] Schlienger RG, Fedson DS, Jick SS, *et al*. Statins and the risk of pneumonia: a population-
34 based, nested case-control study. *Pharmacotherapy* 2007; **27**: 325–332.
35
36 [25] Lipscombe LL, Levesque LE, Gruneir A, *et al*. Antipsychotic drugs and the risk of
37 hyperglycemia in older adults without diabetes: a population-based observational study. *Am*
38 *J Geriatr Psychiatry* 2011; **19**: 1026-1033.
39
40 [26] Lipscombe LL, Gomes T, Levesque LE, *et al*. Thiazolidinediones and cardiovascular
41 outcomes in older patients with diabetes. *J Am Med Assoc* 2007; **298**: 2634–2643.
42
43 [27] Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with
44 cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005;
45 **142**: 481–489.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5 [28] Cerfolio RJ, Bryant AS. Survival and outcomes of pulmonary resection for non-small cell
6 lung cancer in the elderly: A nested case-control study. *Ann Thorac Surg* 2006; **82**: 424-430.
7
- 8 [29] Khandaker G, Rashid H, Zurynski Y, *et al.* Nosocomial vs community-acquired pandemic
9 influenza A (H1N1) 2009: a nested case-control study. *J Hosp Infect* 2012; **82**:94–100.
10
11
- 12 [30] Langholz, B. and Clayton, D. Sampling Strategies in Nested Case-Control
13 Studies. *Environ Health Persp* 1994; **102**: 47–51.
14
15
- 16 [31] Stoer N and Samuelsen S. multipleNCC. Weighted Cox-Regression for Nested Case-Control
17 Data. R package version 1.2-2.2020. Available at [https://CRAN.R-](https://CRAN.R-project.org/package=multipleNCC)
18 [project.org/package=multipleNCC](https://CRAN.R-project.org/package=multipleNCC)
19
20
- 21 [32] Stoer N and Samuelsen S. Inverse probability weighting in nested case-control studies with
22 additional matching - a simulation study. *Stat Med* 2013;**32**, 5328-5339.
23
24
- 25 [33] George B, Seals S and Aban I. Survival analysis and regression models. *J NuclCardiol* 2014;
26 **21**: 686–694.
27
28
- 29 [34] Annesi I, Moreau T and Lellouch J. Efficiency of the logistic regression and Cox
30 proportional hazards models in longitudinal studies. *Stat Med* 1989; **8**: 1515–1521.
31
32
- 33 [35] Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of
34 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**:
35 507-13.
36
37
- 38 [36] Tralhão A and Póvoa P. Cardiovascular Events After Community-Acquired Pneumonia: A
39 Global Perspective with Systematic Review and Meta-Analysis of Observational Studies, *J*
40 *Clin Med* 2020, **9**: 414.
41
42
- 43 [37] Kirchhof P, Benussi S, Kotecha D, *et al.* 2016 ESC Guidelines for the management of atrial
44 fibrillation developed in collaboration with EACTS. *Eur. Heart J* 2016; **37**: 2893–2962.
45
46
- 47 [38] Libby P. Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy. *N.*
48 *Engl. J. Med* 2013; **368**: 2004–2013
49
50
- 51 [39] Madjid M, Vela D, Khalili-Tabrizi H, *et al.* Systemic infections cause exaggerated local
52 inflammation in atherosclerotic coronary arteries: Clues to the triggering effect of acute
53 infections on acute coronary syndromes. *Tex. Heart Inst. J* 2007, **34**:11–18.
54
55
56
57
58
59
60

- 1
2
3 [40]Mauriello A, Sangiorgi G, Fratoni S, et al. Diffuse and Active Inflammation Occurs in Both
4 Vulnerable and Stable Plaques of the Entire Coronary Tree A Histopathologic Study of
5 Patients Dying of Acute Myocardial Infarction. *J Am Coll Cardiol* 2005; **45**: 1585–1593.
6
7
8 [41]Zhu J, Zhang X, Shi G, et al. Atrial fibrillation is an independent risk factor for hospital-
9 acquired pneumonia. *PLoS ONE*. 2015; **10**: e0131782.
10
11
12 [42]Corrales-Medina VF, Musher DM, Shachkina S, et al. Acute pneumonia and the
13 cardiovascular system. *Lancet* 2013; **381**: 496-505.
14
15
16 [43]Qualls N, Levitt A, Kanade N, et al. Community mitigation guidelines to prevent pandemic
17 influenza - United States, 2017. *MMWR Recomm Rep*. 2017; **66**: 1–34.
18
19
20 [44]Ji Y, Ma Z, Peppelenbosch MP, et al. Potential association between COVID-19 mortality
21 and health-care resource availability. *Lancet Glob Health*. 2020. [Epub ahead of print].
22
23
24 [45]Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019
25 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann*
26 *Intern Med* 2020. [Epub ahead of print].
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

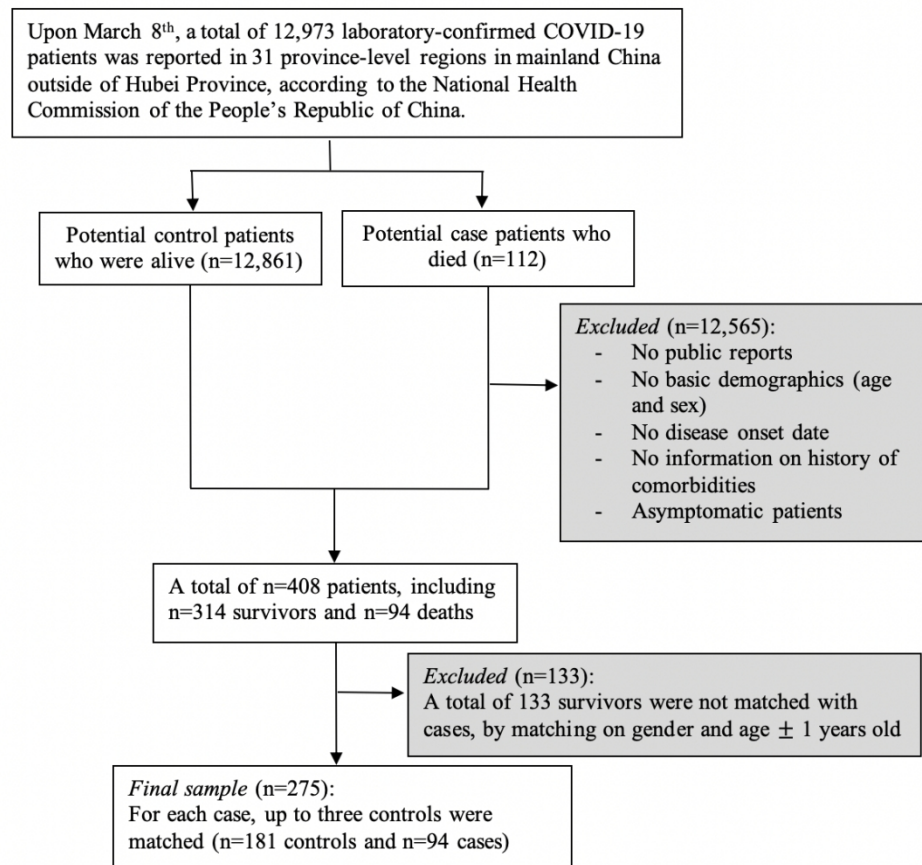


Figure 1: Patient flow diagram detailing included subjects and exclusion criteria

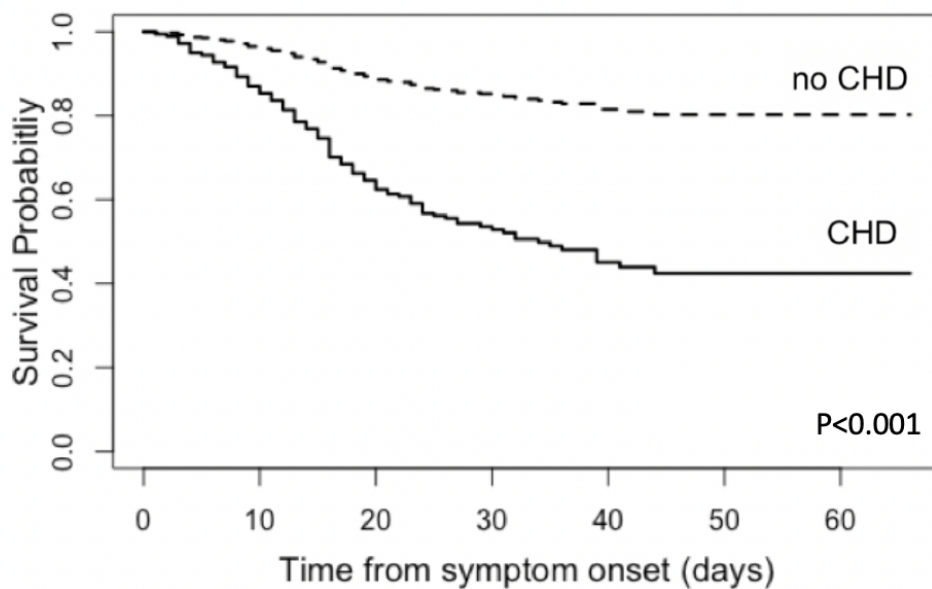


Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for an example patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) 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 $p < 0.05$

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038976.R1
Article Type:	Original research
Date Submitted by the Author:	19-Jun-2020
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
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Coronary heart disease < CARDIOLOGY, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Tian Gu, MS¹; Qiao Chu, PhD²; Zhangsheng Yu, PhD³; Botao Fa, MS³; Anqi Li, MS⁴; Lei Xu, MD⁵; Ruijun Wu, PhD⁴; Yaping He, PhD²

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 ([hypecyr@sina.com](mailto:hypcyr@sina.com)).

28 Abstract

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

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

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

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

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

43 **Results:** Of the 94 cases, the median age was 72.5 years old (IQR=16), and 59.6% were male,
44 while in the control group the median age was 67 years old (IQR=22) and 64.6% were male.
45 Adjusting for age, gender, and early period of outbreak, poor health conditions were associated
46 with a higher risk of COVID-19 mortality (HR of comorbidity score, 1.31 [95% CI: 1.11-1.54];
47 $p=0.001$). The estimated mortality risk in patients with pre-existing CHD was three times of
48 those without CHD ($p<0.001$). The estimated 30-day survival probability for a profile patient
49 with pre-existing CHD (65-year-old female with no other comorbidities) was 0.53 (95% CI,
50 0.34-0.82), while it was 0.85 (95% CI, 0.79-0.91) for those without CHD. Older age was also
51 associated with increased death risk: every 1-year increase in age was associated with a 4%
52 increased risk of mortality ($p<0.001$).

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

59 **Strengths and limitations of this study**

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

69 **Introduction**

70 Since the first report of Coronavirus Disease 2019 (COVID-19) in December 2019 in
71 Wuhan, Hubei Province, China, the novel virus infection has rapidly spread to other cities in
72 China, and has now been detected in 186 countries and locations internationally [1]. On March
73 11th, 2020, the World Health Organization declared COVID-19 a pandemic, and has called for
74 aggressive actions from all countries to fight the disease. Current research has indicated that
75 COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a beta-
76 coronavirus similar to the severe acute respiratory syndrome-coronavirus (SARS-CoV) in the
77 genetic sequence [2]. Epidemiological evidence suggests that initially reported cases in China
78 had a history of exposure to the Huanan seafood market [3]-[4]. With the escalated spread of the
79 infection, there has been clear evidence of human to human transmission[5]-[6]. The most
80 common symptoms include fever, dry cough and fatigue [5]-[8], with presence of asymptomatic,
81 yet contagious cases [9].

82 According to the COVID-19 situation reports of WHO, as of June 13th, 2020, the
83 infection has caused 83,132 confirmed cases in mainland China, including 4,634 deaths.
84 Internationally, a total of 7.41 million confirmed cases have been reported from 186 countries
85 outside of China, including 418,000 deaths. Considering the global public health threat posed by
86 COVID-19, unraveling the prognostic factors for patients, especially the risk factors of mortality
87 associated with COVID-19, has important implications for clinical practice and is urgently
88 warranted.

1
2
3 89 Studies have indicated that severe cases tend to be older in age [6], [8] and are more
4
5 90 likely to have had pre-existing medical conditions, including but not limited to hypertension [3],
6
7 91 [6], [8], diabetes [6] [8], cardiovascular diseases [3], [6], [8], [10]-[12], cerebrovascular diseases
8
9 92 [6], chronic obstructive pulmonary disease (COPD) [3], [8], cancer [13], and digestive diseases
10
11 93 [14], in comparison to non-severe cases [3], [6], [8]-[15].

12 94 Recently, scholarly attention focuses on identifying the risk factors for death from
13
14 95 COVID-19. Some evidence suggests that pre-existing medical conditions are likely death risk
15
16 96 factors for COVID-19. For example, a study based on 72,314 cases in China indicated that the
17
18 97 case-fatality rate (CFR) tends to be higher among those with older age, and having pre-existing
19
20 98 cardiovascular disease, diabetes, and hypertension compared to all the patients [9]. Similarly, by
21
22 99 conducting logistic regression on odds of in-hospital death among 54 diseased patients and 137
23
24 100 recovered patients in Wuhan City, Hubei Province, Zhou et al. [16] found that older age, higher
25
26 101 Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1ug/ml at hospital
27
28 102 admission were associated with increased odds of in-hospital death. Chen et al. (2020) found that
29
30 103 pre-existing hypertension and other cardiovascular complications were more common among
31
32 104 diseased patients than recovered patients (unpublished data).

33
34 105 However, several gaps remain in the understanding of risk factors for mortality of
35
36 106 COVID-19. First, most current research on pre-existing comorbidities of COVID-19 was based
37
38 107 on univariate comparison, which did not account for important confounders such as age and
39
40 108 gender [17]-[20]. Second, no studies have investigated the hazard of the identified risk factors
41
42 109 over time, or the probability of survival at a given time. Under the rapidly changing pandemic
43
44 110 situation, it is crucial to provide timely survival-time guidance for implementing the targeted
45
46 111 treatment to the high-risk patients in clinical practice. Third, most existing studies on mortality
47
48 112 risk factors were focused on patients diagnosed in Wuhan, Hubei Province, with little
49
50 113 understanding about the mortality risk factors outside of Hubei Province. The risk factors are
51
52 114 likely different inside and outside of Hubei Province, since current research has found that the
53
54 115 clinical symptom severity [5] and the fatality-case rate [9], [21] to be higher in Hubei Province
55
56 116 (the center of outbreak) than cities outside of Hubei Province in China. Fourth, no studies thus
57
58 117 far have taken into account the pandemic stage when evaluating mortality risk factors. It has
59
60 118 been found that average daily attack rate in China was different before and after January 22nd
119 2020, since non-pharmaceutical interventions were taken by the government before this date

1
2
3 120 [22]. The change of pandemic stage may also influence the risk factors for fatality associated
4
5 121 with COVID-19.

6
7 122 To fill the above research gaps in the existing literature about the mortality risk factors
8
9 123 for COVID-19, the present study conducted a nested case-control (NCC) study, aiming to
10
11 124 evaluate the risk of the common pre-existing comorbidities (hypertension, coronary heart
12
13 125 disease, diabetes and etc.) for mortality associated with COVID-19 in mainland China outside of
14
15 126 Hubei Province. NCC, also called risk set sampling, has been widely used in studying the fatal
16
17 127 disease risk effect in large pharmacoepidemiologic studies [23]-[28] and risk prediction
18
19 128 in pandemic influenza A (H1N1) 2009 (pH1N1) [29]. NCC is cost-effective in data collection,
20
21 129 and is especially suitable for research on the death risk of diseases such as COVID-19, where the
22
23 130 number of event-free people largely exceeds those who experienced events [30]. To attain this
24
25 131 goal, we employed survival analysis on 275 publicly reported confirmed cases, adjusting for age,
26
27 132 gender and the change in the pandemic stage in China (i.e., before and after January 11th, 2020).

26 133 **Method**

29 134 **Study Design and Rationale**

30
31 135 This study performed survival analysis under a nested case-control (NCC) design to
32
33 136 assess the roles of common comorbidities (cardiocerebrovascular, endocrine and respiratory
34
35 137 disease, etc.) in predicting mortality for COVID-19, among patients in mainland China outside of
36
37 138 Hubei Province. The study period was from December 18th, 2019, when the first laboratory-
38
39 139 confirmed case was announced in China, till March 8th, 2020.

40
41 140 The study cohort was defined as all the publicly reported confirmed COVID-19 patients
42
43 141 outside of Hubei Province in mainland China between the study period. During this period, 112
44
45 142 deaths outside of Hubei Province were reported by the National Health Committee of China, and
46
47 143 18 were excluded from the present study due to missingness of important clinical information. A
48
49 144 total of 448 publicly reported laboratory-confirmed COVID-19 cases (94 deaths and 354
50
51 145 survivors) were initially collected. To avoid selection bias due to intentionally collecting patient
52
53 146 with certain pre-existing comorbidities, two authors independently collected, compared and
54
55 147 reviewed the full text of each case report. Following the typical NCC design setting where all
56
57 148 events are included and a certain numbers of control are matched with replacement, all deaths
58
59 149 were included as cases, and each case was matched with up to three controls on gender and age

1
2
3 150 ± 1 year old (94 cases and 181 controls). The sample distribution across all 32 province-level
4 151 regions in mainland China is presented in Supplementary Table S1.

6 152 **Data Collection Procedure**

8 153 We routinely searched for daily news and public health reports on confirmed COVID-19
9 154 cases in all areas in mainland China outside of Hubei Province. Patients' clinical and
11 155 comorbidity characteristics were recorded and doubly confirmed by
13 156 national/provincial/municipal health commission websites, the official COVID-19 data reporting
15 157 websites in China. Follow-up time was defined as the duration from the date of disease onset till
16 158 the end of observation on March 8th or when the participant died, whichever came first. For each
18 159 eligible patient, we followed local reports to update their survival status until the end of follow-
20 160 up time. Pre-existing comorbidities were recorded based on the description of case reports.

22 161 As illustrated in Figure 1, the inclusion criterion was publicly reported COVID-19 patients
23 162 who had complete information on basic demographics (age, gender and region), disease onset
25 163 date--the first time a patient became symptomatic, and history of comorbidities (include
27 164 hypertension, CHD, cardiac failure, cerebral infarction, diabetes, chronic bronchitis, COPD,
28 165 renal failure, hepatic and history of surgery) were included in the analysis. Asymptomatic
30 166 patients were not included in this study. In addition, we defined "comorbidity-free patients" as
32 167 those who were specifically described as "no pre-existing medical condition/comorbidity" on the
34 168 national/provincial/municipal health commission websites.

36 169 In the following three steps, we used the No. 213 patient in the sample as an example to
37 170 introduce the dynamic tracking method we used to identify any missing dates:

39 171 **Step 1.** Conducting an internet search on confirmed cases on baidu.com, the largest search
41 172 engine in China, using keywords "confirmed COVID-19 cases report" and "pre-existing
43 173 comorbidities." A search result pertained to one confirmed case reported on the website of
44 174 Municipal Health Commission of Binzhou (Shandong Province) on February 17th,
46 175 described as "*the 15th confirmed case: 30-year-old male without pre-existing morbidities,*
48 176 *who lives in the neighborhood of Xincun Village. This patient was diagnosed positive on*
49 177 *February 16th and is being treated with precaution in Bincheng hospital.*" We recorded
51 178 age, gender, region and comorbidity-free for this patient.

1
2
3 179 **Step 2.** We then determined the onset date of this patient based on another announcement
4 on the same website. In this announcement titled “*Possible exposure locations and times of*
5 180 *the 15th confirmed case,*” it says, “*the patient was symptomatic on February 14th.*”
6 181

7
8 182 **Step 3.** Finally, we confirmed the event status of this patient as discharged on March 3rd,
9 by following the updates on this website.
10 183
11 184

13 185 **Statistical Analysis**

15 186 Analyses were performed in R 3.6.2 (R Foundation for Statistical Computing) through
16 RStudio version 1.2.5042. Data and code are available online at GitHub
17 187 (https://github.com/GuTian-TianGu/COVID-19_NCCstudy). Baseline clinical characteristics
18 188 were shown as mean (SD), median (range), or number (%), with a comparison of characteristics
19 189 in subjects stratified by case and control via the non-parametric Mann–Whitney U test for
20 190 continuous variables and chi-squared or Fisher’s exact test for binary variables.
21 191

22 192 In order to utilize the time-to-event information under the NCC design, the inverse
23 193 probability weighting Cox proportional hazard regression model was employed [32]. The
24 194 matching between cases and controls, and relative weights were simultaneously obtained via
25 195 KMprob function in multipleNCC R package [31], by specifying the Kaplan-Meier type weights
26 196 with additional matching on gender and age ± 1 year old. Only survivors were assigned weights,
27 197 since all cases (deaths) were included as designed with a weight of one. A total of 113 survivors
28 198 (mean age 46.5) with sampling probabilities of zero were considered as “fail to match” and
29 199 excluded from the study, mainly due to younger age than cases. A majority of the excluded
30 200 patients were from Shandong Province (38.1%) due to relatively high representation of the
31 201 sample (detailed information of excluded survivors is available online at Github). In a sensitivity
32 202 analysis adjusting for Shandong Province (results not shown here), we observed the consistent
33 203 results as the main analysis.
34 204

35 205 The comorbidity score was defined as the summation of nine comorbidities that have
36 206 been specifically mentioned in relation to COVID-19 outcomes (CHD, hypertension, cardiac
37 207 failure, cerebral infarction, chronic bronchitis, COPD, diabetes, renal failure and history of
38 208 surgery), ranging from zero to nine. Kaplan-Meier curve was plotted to check the proportional
39 209 hazard assumption and the Pearson correlation test was used to rule out the multicollinearity
40 210 concern before fitting any model. Univariate weighted Cox models were performed for each
41 211
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 210 comorbidity. The multivariate weighted Cox model was used to determine if pre-existing
4
5 211 comorbidity yielded prognostic hazard information. We included those comorbidities that were
6
7 212 marginally significant ($p < 0.1$) in the univariate analysis to the multivariate model. Other than the
8
9 213 common risk factors (age and gender), the multivariate model also adjusted for early period of
10
11 214 pandemic (after vs. before January 22nd, 2020 when no-intervention was taken by the
12
13 215 government) **Error! Reference source not found.** Although matching was based on age and
14
15 216 gender, we adjusted for the matching covariates, since the matching was broken with inverse
16
17 217 probability weighting [32]. A separate multivariate model was built by using the comorbidity
18
19 218 score as a continuous predictor, adjusting for the same covariates. Hazard ratios (HRs) from the
20
21 219 weighted Cox model were reported along with 95% confidence intervals (CIs) and p-values.
22
23 220 Sensitivity analysis was performed using multivariate logistic regression to provide estimated
24
25 221 odds ratio (ORs), which includes the same covariates as the multivariate weighted Cox model.

26
27 222 Weighted Cox model-based survival estimates were plotted for an example patient profile
28
29 223 (65-year-old female with no other comorbidities) to compare the survival probability over time
30
31 224 with and without CHD. The log-rank test was used to compare the median survival difference.

32 225 **Results**

33 226 **Sample Description**

34 227 Table 1 summarizes patient demographics and pre-existing medical conditions. Results
35
36 228 are presented for all patients in the study ($n=275$), as well as for cases ($n=94$) and controls
37
38 229 ($n=181$), respectively. Patients were 24-94 years old ($\text{Mean}_{\text{age}} = 66.4$, $\text{SD}_{\text{age}} = 14.5$). The average
39
40 230 age tended to be older in the case group (70.7 years old) than in the control group (64.2 years
41
42 231 old). Median ages were similar to mean ages in both groups. A majority (62.9%) of the patients
43
44 232 were male. Overall, 25.5% of the total patients had clinical symptoms associated with COVID-
45
46 233 19 before January 11th, 2020. A relatively small proportion of the total sample had COPD, renal
47
48 234 failure, history of surgery and hepatic failure (4.4%, 4.4%, 3.6% or 1.1%). Among all pre-
49
50 235 existing comorbidities with over 5% of the total sample, hypertension was the most common
51
52 236 (39.6%), followed by diabetes (26.2%), CHD (14.5%), cardiac failure (8%), cerebral infarction
53
54 237 (6.9%) and chronic bronchitis (6.9%). Patients in the case group had more CHD ($p < 0.001$) and
55
56 238 more cerebral infarction ($p = 0.05$), compared to those in the control group. The mean comorbidity

239 score was 1.22 (SD=1.21) in the overall sample, whereas 1.6 (SD=1.32) in the case and 1.02
240 (SD=1.10) in the control group ($p<0.001$).

241

242 **Model Results**

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

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

252 In a separate model using comorbidity score as predictor, we observed that higher
253 comorbidity score was associated with higher mortality risk in both unadjusted and adjusted
254 models ($p=0.009$ and $p=0.03$, respectively). All pre-existing comorbidities had HR over one in
255 the univariate model, of which CHD had the largest hazard ratio (HR) of 4.2 ($p<0.001$), followed
256 by cerebral infarction (HR=2.9, $p=0.004$), COPD (HR=2.6, $p=0.01$), renal failure (HR=2.3,
257 $p=0.09$), cardiac failure (HR=1.9, $p=0.1$), history of surgery (HR=1.7, $p=0.34$), hypertension
258 (HR=1.4, $p=0.17$), diabetes (HR=1.1, $p=0.61$) and chronic bronchitis (HR=1.1, $p=0.55$), but not
259 all statistically significant. After adjusting for age, gender, and early period of pandemic in
260 China, CHD was the only comorbidity that yielded a significant death risk: COVID-19 patients
261 with pre-existing CHD had an estimated 2.9 times death risk of those without CHD. In addition,
262 cerebral infarction, COPD, and renal failure all had an estimated HR of around 2.0, respectively.
263 Similar results were observed by using unweighted logistic regression in a sensitivity analysis
264 (Supplementary Table S2).

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

1
2
3 270 0.53 (95% CI [0.34-0.82]), while on the other hand, this number was 0.85 (95% CI [0.79-0.91])
4
5 271 for those without CHD.
6
7 272

8 273 **Discussion**

9
10 274 In this paper, we used survival analysis to estimate the fatal risk of pre-existing
11 275 comorbidities in COVID-19, based on publicly reported confirmed cases and adjusted for the
12 276 confounding effect of age, gender, and early period of the pandemic when no-intervention was
13
14 277 taken. There were three major findings: First, poor health condition was associated with higher
15 278 death risk of COVID-19. Second, after adjusting for confounders, CHD was the only significant
16
17 279 risk factor for COVID-19 mortality. Patients with pre-existing CHD was 3.11 times more likely
18
19 280 of death, compared to those without ($p<0.001$). For a patient profile (65-year-old female without
20
21 281 other comorbidities), the estimated 30-day survival probability for those with CHD was 0.53,
22
23 282 while it was 0.85 for those without CHD ($p<0.001$). Third, older age was associated with
24
25 283 increased death risk. Specifically, every 1-year increase in age was associated with a 4%
26
27 284 increased risk of mortality ($p<0.001$).
28

29 285 To our best knowledge, the present study is the first to provide substantial statistical
30
31 286 evidence to show the effect of CHD in predicting mortality for COVID-19. This result is
32
33 287 consistent with previous studies that found higher case-fatality rate among patients with
34
35 288 cardiovascular disease [9], [15]. It is worth pointing out that the existing studies [9], [16] that
36
37 289 investigate prognostic factors for death used chi-square tests or univariate logistic regression that
38
39 290 does not control for potential confounders. In contrast, by conducting weighted Cox proportional
40
41 291 hazard regression models, our study used time-to-event outcomes, which offers more survival-
42
43 292 time-related information to help guide the clinical intervention and more statistical power to
44
45 293 detect risk factors [33][34].
46

47 294 Previous studies have indicated that cardiovascular events following pneumonia may
48
49 295 increase the risk of mortality [35]-[41], which explained our findings from the viewpoint of
50
51 296 pathophysiological mechanisms. One potential mechanism underlying the association between
52
53 297 pneumonia and cardiovascular events is inflammation [38]. Specifically, the inflammatory
54
55 298 reaction following pneumonia can result in plaque instability and damage in the blood vessels,
56
57 299 where evidence of elevated local inflammation in the atherosclerotic coronary arteries following
58
59 300 acute systemic infections have been shown in many studies [38][40]. Thus, infections may result
60

1
2
3 301 in heightened loading imposed on cardiomyocytes, and lead to sympathetic hyperactivity,
4
5 302 ischemia, which may increase the risk of arrhythmia and heart failure in COVID-19 patients with
6
7 303 pre-existing CHD [37].

8 304 Given the limited understanding of the prognostic factors for COVID-19, more research,
9
10 305 potentially prospective studies, are needed to investigate the mechanism by which pre-existing
11
12 306 CHD may influence the survival probability among patients with COVID-19. From the clinical
13
14 307 point of view, early evaluation of patient medical history is necessary to implement early
15
16 308 medical interventions and decrease the mortality risk. We suggest monitoring the dynamic heart
17
18 309 rate for patients with pre-existing CHD. For those severe-symptomatic patients who had pre-
19
20 310 existing heart ischemia and abnormal heart function, early medical intervention may be needed
21
22 311 [41].

23 312 Furthermore, our results indicated that the hazard of COVID-19 death was significantly
24
25 313 higher in patients at older ages. Adjusting for others, every 5-year increase in age was associated
26
27 314 with a 22% increased risk of death, similarly to what was found in previous studies [8][9], [16].
28
29 315 Alongside the evidence of prognostic risk in CHD, we suggest that extra care is needed for those
30
31 316 with CHD, especially for elderly patients.

32 317 Previous studies yielded mixed results regarding gender differences in mortality risk of
33
34 318 COVID-19. Some studies found male sex was associated with higher death risk of COVID-19
35
36 319 [42], whereas other studies did not find gender to be a significant factor predicting the mortality
37
38 320 risk of COVID-19 [43][44]. In the current study, gender was not a significant mortality risk
39
40 321 factor for COVID-19. It calls more future research to further our understanding of gender
41
42 322 difference in the outcome of COVID-19 and the underlying mechanism.

43 323 The design of excluding patients from Hubei Province was based on the concerns of
44
45 324 unknown confounders caused by insufficient medical resources in the epicenter. CDC's report
46
47 325 has pointed out that the rapidly increasing number of infections could easily crash the health care
48
49 326 system by exceeding its maximum capacity [45]. Therefore, analyzing patient data outside of
50
51 327 Hubei Province can avoid the competing death risk caused by insufficient health care resources,
52
53 328 and reveal the true underlying impact of pre-existing comorbidities on COVID-19 mortality [46].

54 329 It is worth noting that the data were collected when COVID-19 was spreading rapidly in
55
56 330 China, and the health authorities and researchers had limited understanding of the incubation
57
58
59
60

1
2
3 331 period, modes of viral transmission and effective treatment. Whether our findings can be
4
5 332 generalized to later epidemic phases warrant future research.

6 333 One limitation of the present study lies in the nature of publicly reported data.
7
8 334 Researchers have pointed out that severe cases may be over-represented in publicly reported data
9
10 335 [47]. Nevertheless, we have managed to reduce the potential bias caused by severe case over-
11
12 336 representation, through the appropriate matching between cases and controls in NCC design. The
13
14 337 auto-matching procedure via statistical program also prevented the possibility of tendentiously
15
16 338 selecting survivors with comorbidity-free history during data collection. In addition, NCC design
17
18 339 is favored in our situation where the risk factor data and event of interest can be identified
19
20 340 opportunistically from publicly reported confirmed cases [30]. Therefore, NCC was the optimal
21
22 341 choice, given the restricted availability of public data. Moreover, due to the lack of information
23
24 342 of treatment in the health reports published by the local health commission websites, we did not
25
26 343 include treatment information into analysis, which may produce confounding effects. It calls for
27
28 344 future research to investigate the mortality risk effect of pre-existing comorbidities by adding
29
30 345 treatment as a covariate in the model. Lastly, we were not able to verify the missing at random
31
32 346 assumption of the 18 missing deaths (9 from Heilongjiang, 5 from Henan, 3 from Beijing, and 2
33
34 347 from Hunan) as well as the survivors.

35 348 In conclusion, our findings provided preliminary yet strong evidence supporting the
36
37 349 association between pre-existing CHD and mortality risk for patients with COVID-19. Based on
38
39 350 our findings, close monitoring, extra care, and early medical intervention are needed for patients
40
41 351 with pre-existing CHD, to reduce the mortality risk associated with COVID-19.

42 352
43 353
44 354
45 355
46 356
47 357
48 358
49 359
50 360
51 361
52
53
54
55
56
57
58
59
60

1
2
3 **362 Footnotes**
4

5 **363 Author Contributions**

6
7 364 TG conducted the analysis, interpreted the data, drafted the article and rechecked the transcribed
8
9 365 manuscript. QC conducted literature review and drafted the article. ZY guided and supervised
10
11 366 the statistical analysis. BF helped with data analysis. AL helped data collection, management,
12
13 367 and quality check. LX provided clinical support and interpretation of the results. RW collected,
14
15 368 pre-processed and managed data, and conducted preliminary data analysis. YH guided and
16
17 369 supervised the research process, and provided funding support. All authors critically revised the
18
19 370 manuscript for intellectual content, approved the final draft, and agree to accountability for all
20
21 371 aspects of the work.
22

23 **373 Conflict of Interest**

24 374 The authors have no affiliations with or involvement in any organization or entity with any
25
26 375 financial or non-financial interest in the subject matter or materials discussed in this manuscript.
27

28
29 **377 Ethics Approval**

30
31 378 The data published in news reports and websites were open to the public and free of identifiers.
32
33 379 The study was approved by Shanghai Jiao Tong University Public Health and Nursing Medical
34
35 380 Research Ethics Committee (SJUPN-202001).
36

37
38 **382 Patient and Public Involvement**

39
40 383 This study used publicly reported patient-level data. All data were available online to the public.
41
42 384 No patient recruitment was involved in the study design, and no personal information can be
43
44 385 identified from the data.
45

46
47 **387 Funding**

48
49 388 This project was funded by the National Natural Science Foundation of China (No. 71874111),
50
51 389 Shanghai Municipal Health Bureau Foundation (No. 201740116) and Shanghai Jiao Tong
52
53 390 University Scientific and Technological Innovation Funds (YG2020YQ01, YG2020YQ06).
54

55 **392 Data sharing statement**
56
57
58
59
60

1
2
3 393 Raw data is available at GitHub https://github.com/GuTian-TianGu/COVID-19_NCCstudy.git.

4
5 394

6
7 395 **Exclusive Licence**

8 396 I, the Submitting Author has the right to grant and does grant on behalf of all authors of the
9
10 397 Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive
11
12 398 licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has
13
14 399 agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US
15
16 400 Federal Government officers or employees acting as part of their official duties; on a worldwide,
17
18 401 perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd (“BMJ”) its licensees and
19
20 402 where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the
21
22 403 Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in
23
24 404 our licence.

25
26 405

27 406 The Submitting Author accepts and understands that any supply made under these terms is made
28
29 407 by BMJ to the Submitting Author unless you are acting as an employee on behalf of your
30
31 408 employer or a postgraduate student of an affiliated institution which is paying any applicable
32
33 409 article publishing charge (“APC”) for Open Access articles. Where the Submitting Author
34
35 410 wishes to make the Work available on an Open Access basis (and intends to pay the relevant
36
37 411 APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence
38
39 412 – details of these licences and which Creative Commons licence will apply to this Work are set
40
41 413 out in our licence referred to above.

42
43 414

44
45 415 **Word count**

46
47 416 3506

48
49 417

50
51 418

52
53 419

54
55 420

56
57 421

58
59 422

60
61 423

Reference

- [1] Coronavirus disease 2019 (COVID-19) Situation Report – 62. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46_2
- [2] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H *et al*. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-74.
- [3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506.
- [4] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-13.
- [5] Xu Xiao-Wei, Wu Xiao-Xin, JiangXian-Gao, Xu Kai-Jin, Ying Ling-Jun, Ma Chun-Lian *et al*. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020; **368**: m606.
- [6] Wang D, Hu B, Hu C *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061–1069.
- [7] Zhang, J-J, Dong, X, Cao, Y-Y *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **00**: 1– 12.
- [8] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. [Epub ahead of print].
- [9] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020. [Epub ahead of print].
- [10] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020. [Epub ahead of print].

- 1
2
3 461 [11]Shi, S., Qin, M., Shen, Bo. et al. Association of Cardiac Injury with Mortality in
4 462 Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020. [Epub ahead
5 463 of print].
6 464
- 7 465 [12]Liu, J. , Tu, C. , Zhu, M. , Wang, J. , Yang, C. , Liu, W. and Xiong, B., Exploring the Law
8 466 of Development and Prognostic Factors of Common and Severe COVID-19: A
9 467 Retrospective Case-Control Study in 122 Patients with Complete Course of Disease. *Lancet*
10 468 2020 [Epub ahead of print].
11 469
- 12 470 [13]Liang W, Guan W, Chen R, Wang W, Li J, Xu K *et al.* Cancer patients in SARS-CoV-2
13 471 infection: a nationwide analysis in China. *The Lancet Oncology*.2020; **21**: 335-7.
14 472
- 15 473 [14]Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H *et al.* Implications of COVID-19 for
16 474 patients with pre-existing digestive diseases. *The lancet Gastroenterology & hepatology*
17 475 2020. [Epub ahead of print].
18 476
- 19 477 [15]Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease
20 478 2019 outbreak in China.*J Clin Med* 2020; **9**: 575.
21 479
- 22 480 [16]Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for
23 481 mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.
24 482 *Lancet* 2020. [Epub ahead of print]
25 483
- 26 484 [17]Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic
27 485 review, *Stroke* 2009; **40**: 1082-90.
28 486
- 29 487 [18]Camp P G , Goring S M . Gender and the diagnosis, management, and surveillance of
30 488 chronic obstructive pulmonary disease. *Ann AmThorac Soc* 2007; **4**: 686-691.
31 489
- 32 490 [19]Tchkonia T, Kirkland JL. Aging, cell senescence, and chronic disease: emerging therapeutic
33 491 strategies. *JAMA* 2018; **320**: 1319–20.
34 492
- 35 493 [20]Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old medicine:
36 494 Role of chronic inflammation. *Prev Med* 2012; **54**: S29-S37.
37 495
- 38 496 [21]Chinese COVID-19 Outbreak Distribution System. Available at
39 497 <http://2019ncov.chinacdc.cn/2019-nCoV/>
40 498
- 41 499 [22]Wang, C. et al. Association of Public Health Interventions with the Epidemiology of the
42 500 COVID-19 Outbreak in Wuhan, China. *JAMA*. 2020;323(19):1915–1923.

- 1
2
3 501
4 502 [23] Azoulay L, Dell'Aniello S, Gagnon B, *et al.* Metformin and Incidence of Prostate Cancer in
5 503 Patients with Type 2 Diabetes. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 337–344.
6 504
7
8 505 [24] Schlienger RG, Fedson DS, Jick SS, Jick H, Meier CR. Statins and the risk of pneumonia: a
9 506 population-based, nested case-control study. *Pharmacotherapy* 2007; **27**: 325–332.
10 507
11
12 508 [25] Lipscombe LL, Levesque LE, Gruneir A, *et al.* Antipsychotic drugs and the risk of
13 509 hyperglycemia in older adults without diabetes: a population-based observational study. *Am*
14 510 *J Geriatr Psychiatry* 2011; **19**: 1026-1033.
15 511
16
17 512 [26] Lipscombe LL, Gomes T, Levesque LE, *et al.* Thiazolidinediones and cardiovascular
18 513 outcomes in older patients with diabetes. *J Am Med Assoc* 2007; **298**: 2634–2643.
19 514
20
21 515 [27] Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with
22 516 cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005;
23 517 **142**: 481–489.
24 518
25
26 519 [28] Cerfolio RJ, Bryant AS. Survival and outcomes of pulmonary resection for non-small cell
27 520 lung cancer in the elderly: A nested case-control study. *Ann Thorac Surg* 2006; **82**: 424-430.
28 521
29
30 522 [29] Khandaker G, Rashid H, Zurynski Y, *et al.* Nosocomial vs community-acquired pandemic
31 523 influenza A (H1N1) 2009: a nested case-control study. *J Hosp Infect* 2012; **82**:94–100.
32 524
33
34 525 [30] Langholz, B. and Clayton, D. Sampling Strategies in Nested Case-Control
35 526 Studies. *Environ Health Persp* 1994;**102**: 47–51.
36 527
37
38 528 [31] Stoer, N. and Samuelsen, S. multipleNCC. Weighted Cox-Regression for Nested Case-
39 529 Control Data. R package version 1.2-2.2020. Available at [https://CRAN.R-](https://CRAN.R-project.org/package=multipleNCC)
40 530 [project.org/package=multipleNCC](https://CRAN.R-project.org/package=multipleNCC)
41 531
42
43 532 [32] Stoer, N. and Samuelsen, S. Inverse probability weighting in nested case-control studies
44 533 with additional matching - a simulation study. *Stat Med* 2013;**32**, 5328-5339.
45 534
46
47 535 [33] George B, Seals S, Aban I. Survival analysis and regression models. *J NuclCardiol* 2014;
48 536 **21**: 686–694.
49 537
50
51 538 [34] Annesi I, Moreau T, Lellouch J. Efficiency of the logistic regression and Cox proportional
52 539 hazards models in longitudinal studies. *Stat Med* 1989; **8**: 1515–1521.
53 540
54
55
56
57
58
59
60

- 1
2
3 541 [35] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical
4 542 characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a
5 543 descriptive study. *Lancet* 2020; **395**: 507-13.
6 544
7
8 545 [36] Tralhão A, Póvoa P. Cardiovascular Events After Community-Acquired Pneumonia: A
9 546 Global Perspective with Systematic Review and Meta-Analysis of Observational Studies, *J*
10 547 *Clin Med* 2020, **9**: 414.
11 548
12
13 549 [37] Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., Castella,
14 550 M., Diener, H.C., Heidbuchel, H., Hendriks, J. *et al.* 2016 ESC Guidelines for the
15 551 management of atrial fibrillation developed in collaboration with EACTS. *Eur. Heart J*
16 552 2016; **37**: 2893–2962.
17 553
18
19 554 [38] Libby, P. Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy.
20 555 *N. Engl. J. Med* 2013; **368**: 2004–2013
21 556
22
23 557 [39] Madjid, M., Vela, D., Khalili-Tabrizi, H., Casscells, S.W., Litovsky, S. Systemic infections
24 558 cause exaggerated local inflammation in atherosclerotic coronary arteries: Clues to the
25 559 triggering effect of acute infections on acute coronary syndromes. *Tex. Heart Inst. J* 2007,
26 560 **34**:11–18.
27 561
28
29 562 [40] Mauriello, A., Sangiorgi, G., Fratoni, S., Palmieri, G., Bonanno, E., Anemona, L., Schwartz,
30 563 R.S., Spagnoli, L.G. Diffuse and Active Inflammation Occurs in Both Vulnerable and Stable
31 564 Plaques of the Entire Coronary Tree A Histopathologic Study of Patients Dying of Acute
32 565 Myocardial Infarction. *J Am Coll Cardiol* 2005; **45**: 1585–1593.
33 566
34
35 567 [41] Zhu J., Zhang X., Shi G., Yi K., Tan X. Atrial fibrillation is an independent risk factor for
36 568 hospital-acquired pneumonia. *PLoS ONE*. 2015; **10**: e0131782.
37 569
38
39 570 [42] Li X, Xu S, Yu M, *et al.* Risk factors for severity and mortality in adult COVID-19
40 571 inpatients in Wuhan [published online ahead of print, 2020 Apr 12]. *J Allergy Clin Immunol*.
41 572 2020. doi:10.1016/j.jaci.2020.04.006
42 573
43
44 574 [43] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality
45 575 of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*.
46 576 2020. doi: 10.1016/S0140-6736(20)30566-3
47 577
48
49 578 [44] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-
50 579 19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*.
51 580 2020; **46**(5):846-848.
52 581
53
54
55
56
57
58
59

1
2
3 582 [45] Qualls, N., Levitt, A., Kanade, N., *et al.* Community mitigation guidelines to prevent
4 583 pandemic influenza - United States, 2017. *MMWR Recomm Rep.* 2017; **66**: 1–34.

5 584
6 585 [46] Ji, Y., Ma, Z., Peppelenbosch, MP., Pan Q. Potential association between COVID-19
7 586 mortality and health-care resource availability. *Lancet Glob Health.* 2020. [Epub ahead of
8 587 print].

9 588
10 589 [47] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, *et al.* The Incubation Period
11 590 of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases:
12 591 Estimation and Application. *Ann Intern Med* 2020. [Epub ahead of print].
13 592

14 593 **Correspondence**

15 594 Address offprint requests to Dr. Wu at School of Social Development, East China Normal
16 595 University, 500 Dongchuan Rd., Shanghai 200241, China (rjwu@re.ecnu.edu.cn), or Dr. He at
17 596 College of Public Health, Shanghai Jiao Tong University School of Medicine, South Chongqing
18 597 Rd., No. 227, Shanghai 200025, China (hypcyr@sina.com), respectively.
19 598

20 599

21 600

22 601

23 602

24 603

25 604

26 605

27 606

28 607

29 608

30 609

31 610

32 611

33 612

34

35

36

37

613 **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, χ^2 test, or Fisher's exact test, as appropriate.

Bold: statistically significant using threshold $p < 0.05$

614

615

616

617

618

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

Characteristic	Univariate		Multivariate		Multivariate		P Value	
	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 $p < 0.05$.

619

620

621

622

623

624

1
2
3 625
45 626 **Figure 1:** Patient flow diagram detailing included subjects and exclusion criteria
6 6277
8 628 **Figure 2:** Estimated survival probability over time from the adjusted Cox proportional hazard
9
10 629 model for an example patient profile (65-year-old female without CHD [dashed line] or with
11 630 CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability
12 631 was 0.53 (95% CI [0.34-0.82]) for patients with pre-existing CHD, while 0.85 (95% CI [0.79-
13 632 0.91]) for those without ($p<0.001$). CHD=coronary heart disease.
14
15
16
17 633

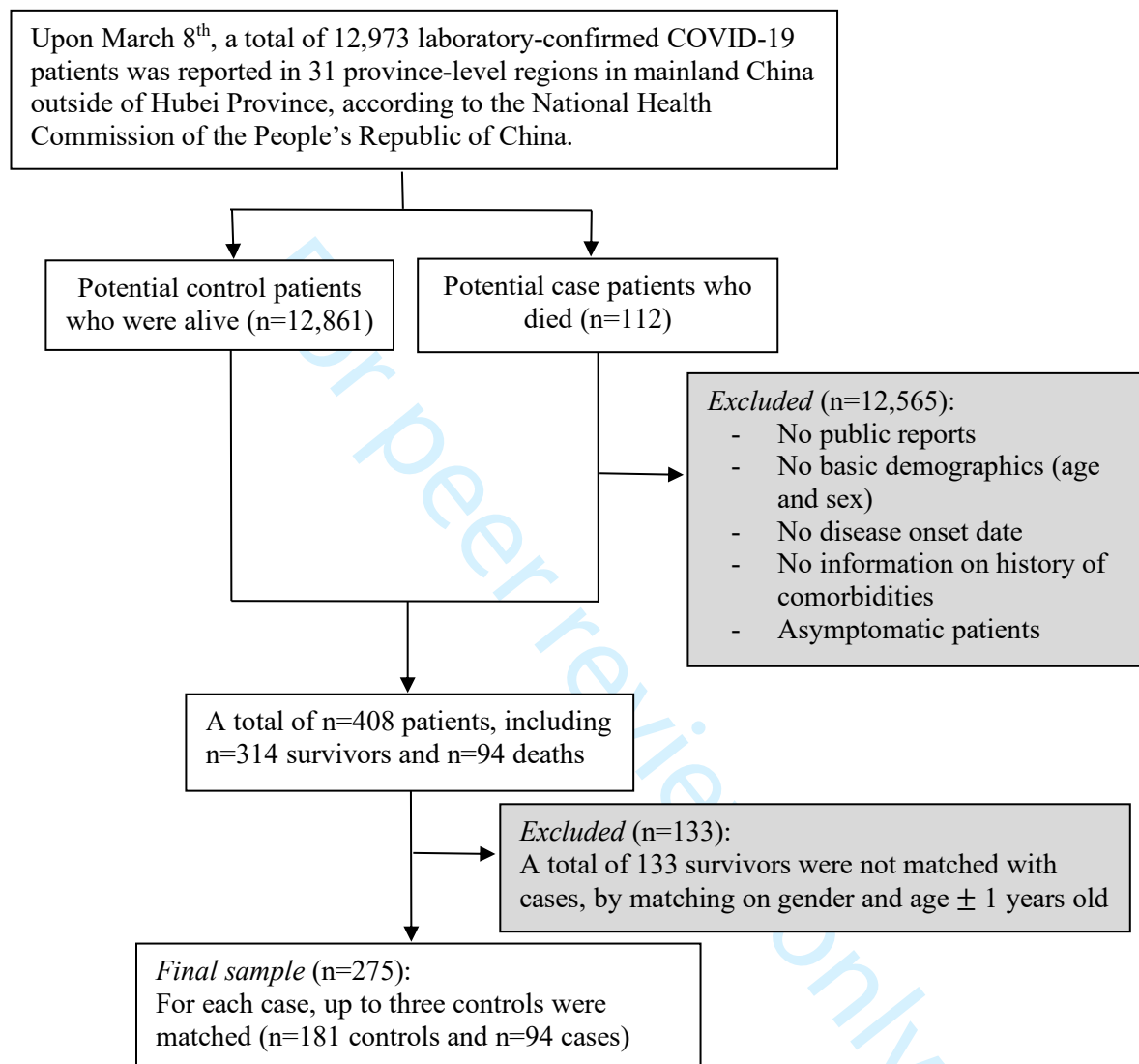


Figure 1: Patient flow diagram detailing included subjects and exclusion criteria

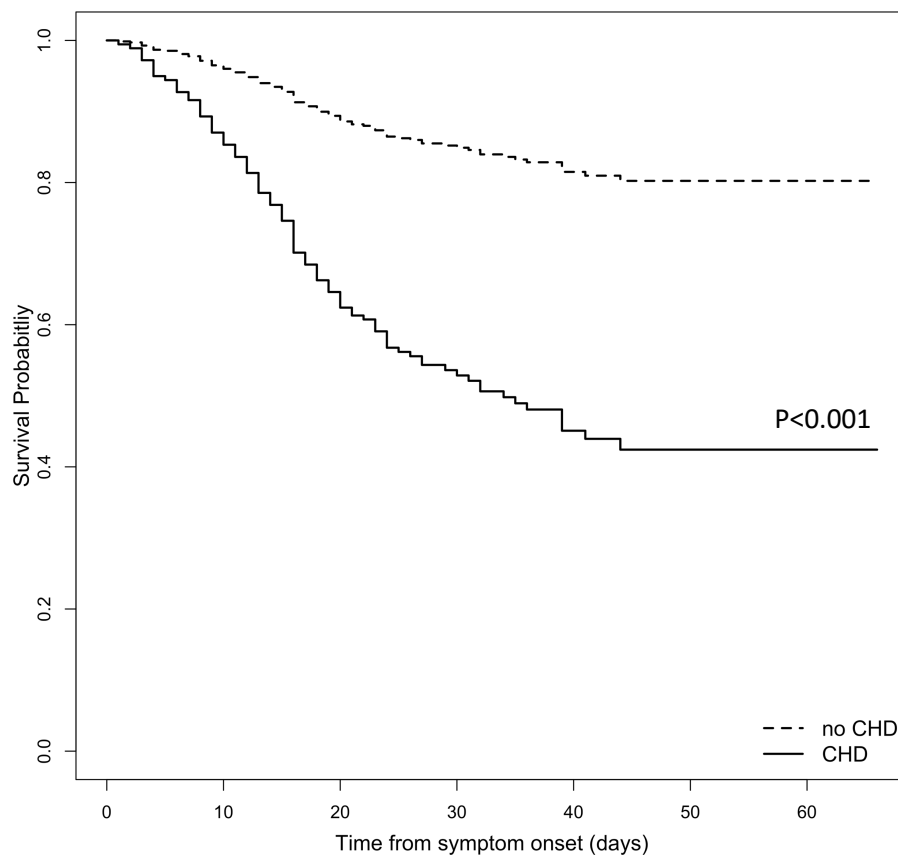


Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for an example patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) 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
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 $p < 0.05$

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038976.R2
Article Type:	Original research
Date Submitted by the Author:	07-Aug-2020
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
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Coronary heart disease < CARDIOLOGY, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Tian Gu, MS¹; Qiao Chu, PhD²; Zhangsheng Yu, PhD³; Botao Fa, MS³; Anqi Li, MS⁴; Lei Xu, MD⁵; Ruijun Wu, PhD⁴; Yaping He, PhD²

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

Key words:

Epidemiology, Survival Analysis, Coronary Disease

Word count

3585

33 Abstract

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

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

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

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

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

48 **Results:** Of the 94 cases, the median age was 72.5 years old (IQR=16), and 59.6% were male,
49 while in the control group the median age was 67 years old (IQR=22), and 64.6% were male.
50 Adjusting for age, gender, and the early period of the outbreak, poor health conditions were
51 associated with a higher risk of COVID-19 mortality (hazard ratio of comorbidity score, 1.31
52 [95% confidence interval (CI): 1.11-1.54]; $p=0.001$). The estimated mortality risk in patients
53 with pre-existing coronary heart disease (CHD) was three times that of those without CHD
54 ($p<0.001$). The estimated 30-day survival probability for a profile patient with pre-existing
55 CHD (65-year-old female with no other comorbidities) was 0.53 (95% CI, 0.34-0.82), while
56 it was 0.85 (95% CI, 0.79-0.91) for those without CHD. Older age was also associated with
57 increased mortality risk: Every 1-year increase in age was associated with a 4% increased
58 risk of mortality ($p<0.001$).

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

61

62

63

64

65

66 **Strengths and limitations of this study**

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

76 **Introduction**

77 Since the first report of coronavirus disease 2019 (COVID-19) in December 2019 in
78 Wuhan, Hubei Province, China, the novel virus infection has rapidly spread to other cities in
79 China and has now been detected in 186 countries and locations internationally [1]. On March
80 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic and has
81 called for aggressive actions from all countries to fight the disease. Current research has
82 indicated that COVID-19 is caused by severe acute respiratory syndrome coronavirus 2
83 (SARS-CoV-2), a beta-coronavirus similar to the severe acute respiratory
84 syndrome coronavirus (SARS-CoV) in its genetic sequence [2]. Epidemiological evidence
85 suggests that the initial reported cases in China had a history of exposure to the Huanan
86 seafood market [3]-[4]. With the escalated spread of the infection, there has been clear
87 evidence of human-to-human transmission [5]-[6]. The most common symptoms include
88 fever, dry cough, and fatigue [5]-[8], and there are asymptomatic yet contagious cases [9].

89 According to the COVID-19 situation reports of WHO, as of June 13, 2020, there
90 were 83,132 confirmed cases in mainland China, including 4,634 deaths. Internationally, a
91 total of 7.41 million confirmed cases and 418,000 deaths have been reported from 186
92 countries outside of China. Considering the global public health threat posed by COVID-19,
93 unraveling the prognostic factors for patients, especially the risk factors of mortality
94 associated with COVID-19, has important implications for clinical practice and is urgently
95 warranted.

96 Studies have indicated that in severe cases, patients tend to be older in age [6], [8] and
97 are more likely to have had pre-existing medical conditions, including but not limited to
98 hypertension [3], [6], [8], diabetes [6],[8], cardiovascular diseases [3], [6], [8], [10]-[12],

1
2
3 99 cerebrovascular diseases [6], chronic obstructive pulmonary disease (COPD) [3], [8], cancer
4 [13], and digestive diseases [14], in comparison to those with non-severe cases [3], [6], [8]-
5 100 [15].
6 101
7

8 102 Recently, scholarly attention has focused on identifying the risk factors for death from
9 COVID-19. Some evidence suggests that pre-existing medical conditions are likely risk
10 103 factors for death from COVID-19. For example, a study based on 72,314 cases in China
11 104 indicated that the case-fatality rate (CFR) tends to be higher among those who are older in
12 105 age and who have pre-existing cardiovascular disease, diabetes, and/or hypertension[9].
13 106 Similarly, by conducting logistic regression on odds of in-hospital deaths among 54 diseased
14 107 patients and 137 recovered patients in Wuhan City, Hubei Province, Zhou et al. (2020) [16]
15 108 found that older age, higher Sequential Organ Failure Assessment (SOFA) score, and D-
16 109 dimer greater than 1ug/ml at hospital admission were associated with increased odds of in-
17 110 hospital death. Chen et al. (2020) found that pre-existing hypertension and other
18 111 cardiovascular complications were more common among diseased patients than recovered
19 112 patients [4].
20 113

21 114 However, several gaps remain in the understanding of risk factors for mortality of
22 115 COVID-19. First, most current research on pre-existing comorbidities of COVID-19 was
23 116 based on univariate comparison, which did not account for important confounders such as
24 117 age and gender [17]-[20]. Second, no studies have investigated the hazard of the identified
25 118 risk factors over time or the probability of survival at a given time. Under the rapidly
26 119 changing pandemic situation, it is crucial to provide timely survival-time guidance for
27 120 implementing the targeted treatment to the high-risk patients in clinical practice. Third, most
28 121 existing studies on mortality risk factors were focused on patients diagnosed in Wuhan,
29 122 Hubei Province, with little understanding about the mortality risk factors outside of Hubei
30 123 Province. The risk factors are likely different inside and outside of Hubei Province since
31 124 current research has found the clinical symptom severity [5] and the CFR [9], [21] to be
32 125 higher in Hubei Province (the center of outbreak) than in cities outside of Hubei Province in
33 126 China. Fourth, no studies thus far have taken into account the pandemic stage when
34 127 evaluating mortality risk factors. It has been found that the average daily infection rate in
35 128 China was different before and after January 22, 2020, since non-pharmaceutical
36 129 interventions were taken by the government before this date [22]. The change of time in the
37 130 pandemic stage may also influence the risk factors for fatality associated with COVID-19.
38 131

39 132 To fill the above research gaps in the existing literature about the mortality risk
40 factors for COVID-19, the present study was conducted using a nested case-control (NCC)

1
2
3 133 study, which aimed to evaluate the risk of the common pre-existing comorbidities
4 (hypertension, CHD, diabetes, etc.) for mortality associated with COVID-19 in mainland
5 134 China outside of Hubei Province. NCC, also called risk set sampling, has been widely used in
6 135 studying fatal disease risk effect in large pharmacoepidemiological studies [23]-[28] and risk
7 136 prediction in pandemic influenza A (H1N1) 2009 (pH1N1) [29]. NCC is cost-effective in
8 137 data collection and is especially suitable for research on the mortality risk of diseases such as
9 138 COVID-19, where the number of event-free people largely exceeds those who are
10 139 symptomatic [30]. To attain this goal, we employed survival analysis on 275 publicly
11 140 reported confirmed cases, adjusting for age, gender, and the change in the pandemic stage in
12 141 China (i.e., before and after January 22, 2020).
13 142

143 **Method**

144 **Study Design and Rationale**

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

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

163 **Data Collection Procedure**

164 We routinely searched for daily news and public health reports on confirmed COVID-
165 19 cases in all areas in mainland China outside of Hubei Province. Patients' clinical and

1
2
3 166 comorbidity characteristics were recorded and doubly confirmed by
4
5 167 national/provincial/municipal health commission websites, the official COVID-19 data
6
7 168 reporting websites in China. Follow-up time was defined as the duration from the date of
8
9 169 disease onset until the end of observation on March 8, 2020, or when the participant died,
10
11 170 whichever came first. For each eligible patient, we followed local reports to update their
12
13 171 survival status until the end of follow-up time. Pre-existing comorbidities were recorded
14
15 172 based on the descriptions in case reports.

15 173 As illustrated in Figure 1, the inclusion criteria were publicly reported COVID-19
16
17 174 patients who had complete information on basic demographics (age, gender, and region),
18
19 175 disease onset date (the first time they became symptomatic), and the history of comorbidities
20
21 176 (including hypertension, coronary heart disease (CHD), cardiac failure, cerebral infarction,
22
23 177 diabetes, chronic bronchitis, COPD, renal failure, and history of surgery). Asymptomatic
24
25 178 patients were not included in this study. In addition, we defined “comorbidity-free patients”
26
27 179 as those who were specifically described as “no pre-existing medical condition/comorbidity”
28
29 180 on the national/provincial/municipal health commission websites.

29 181 In the following three steps, we used patientno. 213 in the sample as an example to
30
31 182 introduce the dynamic tracking method we used to identify any missing dates.

32
33 183 **Step 1.** We conducted an internet search on confirmed cases on baidu.com, the largest
34
35 184 search engine in China, using the keywords “confirmed COVID-19 cases report” and
36
37 185 “pre-existing comorbidities.” A search result pertained to one confirmed case reported
38
39 186 on the website of the Municipal Health Commission of Binzhou (Shandong Province)
40
41 187 on February 17, described as “*the 15th confirmed case: 30-year-old male without pre-*
42
43 188 *existing morbidities, who lives in the neighborhood of Xincun Village. This patient was*
44
45 189 *diagnosed positive on February 16th and is being treated with precaution in Bincheng*
46
47 190 *hospital.*” We recorded the age, gender, and region of this patient and that he was
48
49 191 comorbidity-free.

48 192 **Step 2.** We then determined the onset date of COVID-19 in this patient based on
49
50 193 another announcement on the same website. In this announcement titled “*Possible*
51
52 194 *exposure locations and times of the 15th confirmed case,*” it says, “*the patient was*
53
54 195 *symptomatic on February 14th.*”

55 196 **Step 3.** Finally, following the updates on the website, we confirmed the event status of
56
57 197 this patient as discharged on March 3, 2020.

58 198 **Statistical Analysis**

59
60

1
2
3 199 Analyses were performed in R 3.6.2 (R Foundation for Statistical Computing) through
4
5 200 RStudio version 1.2.5042. Data and codes are available online at GitHub
6
7 201 (https://github.com/GuTian-TianGu/COVID-19_NCCstudy). Baseline clinical characteristics
8
9 202 were shown as mean (SD), median (range), or number (%), with a comparison of
10
11 203 characteristics in subjects stratified by case and control via the non-parametric Mann–
12
13 204 Whitney U test for continuous variables and chi-squared or Fisher’s exact test for binary
14
15 205 variables.

15 206 In order to utilize the time-to-event information under the NCC design, the inverse
16
17 207 probability weighted Cox proportional hazard regression model was employed [31]. The
18
19 208 matching between cases and controls and relative weights were simultaneously obtained via
20
21 209 KMprob function in multipleNCC R package [32] by specifying the Kaplan-Meier type
22
23 210 weights with additional matching on gender and age ± 1 year old. Only survivors were
24
25 211 assigned weights since all cases (deaths) were included as designed with a weight of one. A
26
27 212 total of 113 survivors (mean age 46.5) with sampling probabilities of zero were considered
28
29 213 “fail to match” and excluded from the study, mainly due to younger age than cases. A
30
31 214 majority of the excluded patients were from Shandong Province (38.1%) due to the relatively
32
33 215 high representation of the sample (detailed information of excluded survivors is available
34
35 216 online at GitHub). In a sensitivity analysis adjusting for Shandong Province (results not
36
37 217 shown here), we observed the consistent results as the main analysis.

36 218 The comorbidity score, ranging from zero to nine, was defined as the summation of
37
38 219 nine comorbidities that have been specifically mentioned in relation to COVID-19 outcomes
39
40 220 (CHD, hypertension, cardiac failure, cerebral infarction, chronic bronchitis, COPD, diabetes,
41
42 221 renal failure, and history of surgery). The Kaplan-Meier curve was plotted to check the
43
44 222 proportional hazard assumption, and the Pearson correlation test was used to rule out the
45
46 223 multicollinearity concern before fitting any model. Univariate weighted Cox models were
47
48 224 performed for each comorbidity. The multivariate weighted Cox model was used to
49
50 225 determine if pre-existing comorbidity yielded prognostic hazard information. We included
51
52 226 those comorbidities that were marginally significant ($p < 0.1$) in the univariate analysis to the
53
54 227 multivariate model. Other than the common risk factors (age and gender), the multivariate
55
56 228 model also adjusted for the early period of the pandemic (after vs. before January 22, 2020,
57
58 229 when no intervention was taken by the government) [22]. Although matching was based on
59
60 230 age and gender, we adjusted for the matching covariates since the matching was broken with
61
62 231 inverse probability weighting [31]. A separate multivariate model was built by using the
63
64 232 comorbidity score as a continuous predictor, adjusting for the same covariates. Hazard ratios

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

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

241 Results

242 Sample Description

243 Table 1 summarizes patient demographics and pre-existing medical conditions. Results are
244 presented for all patients in the study (n=275) as well as for cases (n=94) and controls
245 (n=181), respectively. Patients were 24-94 years old (Mean_{age}=66.4, SD_{age}=14.5). The
246 average age tended to be older in the case group (70.7 years old) than in the control group
247 (64.2 years old). Median ages were similar to mean ages in both groups. A majority (62.9%)
248 of the patients were male. Overall, 25.5% of the total patients had clinical symptoms
249 associated with COVID-19 before January 22, 2020. A relatively small proportion of the total
250 sample had COPD, renal failure, history of surgery, and hepatic failure (4.4%, 4.4%, 3.6%,
251 and 1.1%, respectively). Among all pre-existing comorbidities with over 5% of the total
252 sample, hypertension was the most common (39.6%), followed by diabetes (26.2%), CHD
253 (14.5%), cardiac failure (8%), cerebral infarction (6.9%), and chronic bronchitis (6.9%).
254 Patients in the case group had more CHD (p<0.001) and more cerebral infarction (p=0.05)
255 than those in the control group. The mean comorbidity score was 1.22 (SD=1.21) in the
256 overall sample and 1.6 (SD=1.32) in the case and 1.02 (SD=1.10) in the control group
257 (p<0.001).

258 Model Results

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

262 Table 2 presents the results of univariate and multivariate weighted Cox models.
263 Older age was associated with significantly higher risk of death with similar magnitude in
264 univariate and multivariate models. In the adjusted model, every 1-year increase in age was
265 associated with an estimated 4% higher risk of death (p<0.001). No significant hazard

1
2
3 266 difference was found between male and female patients. Disease infection during the early
4
5 267 no-intervention period was associated with a higher risk of death but was not statistically
6
7 268 significant.

8
9 269 In a separate model using the comorbidity score as a predictor, we observed that a
10
11 270 higher comorbidity score was associated with a higher mortality risk in both unadjusted and
12
13 271 adjusted models ($p=0.009$ and $p=0.03$, respectively). All pre-existing comorbidities had an
14
15 272 HR over 1 in the univariate model, of which CHD had the largest HR of 4.2 ($p<0.001$),
16
17 273 followed by cerebral infarction (HR=2.9, $p=0.004$), COPD (HR=2.6, $p=0.01$), renal failure
18
19 274 (HR=2.3, $p=0.09$), cardiac failure (HR=1.9, $p=0.1$), history of surgery (HR=1.7, $p=0.34$),
20
21 275 hypertension (HR=1.4, $p=0.17$), diabetes (HR=1.1, $p=0.61$), and chronic bronchitis (HR=1.1,
22
23 276 $p=0.55$), but not all were statistically significant. After adjusting for age, gender, and the
24
25 277 early period of the pandemic in China, CHD was the only comorbidity that yielded a
26
27 278 significant mortality risk: COVID-19 patients with pre-existing CHD had an estimated 2.9
28
29 279 times higher risk of death than those without CHD. In addition, cerebral infarction, COPD,
30
31 280 and renal failure all had an estimated HR of around 2.0. Similar results were observed by
32
33 281 using unweighted logistic regression in a sensitivity analysis (Supplementary Table S2).

34
35 282 The overall median follow-up was 40 days, during which 94 deaths were observed.
36
37 283 Figure 2 shows the estimated survival probability over 70 days for a sample patient profile
38
39 284 with and without CHD (65-year-old female with no other comorbidities). For such a patient
40
41 285 profile, having pre-existing CHD led to a significantly shorter survival probability over time
42
43 286 compared to those without CHD ($p<0.001$). For those with CHD, the estimated 30-day
44
45 287 survival probability was 0.53 (95% confidence interval [CI] [0.34-0.82]); on the other hand,
46
47 288 this number was 0.85 (95% CI [0.79-0.91]) for those without CHD.

48 289 **Discussion**

49
50 290 In our research, based on publicly reported confirmed cases and adjusted for the
51
52 291 confounding effect of age, gender, and the early period of the pandemic when no intervention
53
54 292 was taken, we used survival analysis to estimate the fatality risk of pre-existing comorbidities
55
56 293 in COVID-19. There were three major findings: First, poor health condition was associated
57
58 294 with higher mortality risk of COVID-19. Second, after adjusting for confounders, CHD was
59
60 295 the only significant risk factor for COVID-19 mortality. Patients with pre-existing CHD were
296
297 3.11 times more likely to die than those without CHD ($p<0.001$). For one patient profile (65-
298
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

1
2
3 299 was 0.53. Third, older age was associated with an increased risk of death. Specifically, every
4
5 300 1-year increase in age was associated with a 4% increased risk of mortality ($p<0.001$).

6 301 To the best of our knowledge, the present study is the first to provide substantial
7
8 302 statistical evidence showing the effect of CHD in predicting mortality for COVID-19. This
9
10 303 result is consistent with previous studies that found higher CFR among patients with
11
12 304 cardiovascular disease [9], [15]. It is worth pointing out that the existing studies [9], [16] that
13
14 305 investigate prognostic factors for death used chi-square tests or univariate logistic regression
15
16 306 that does not control for potential confounders. In contrast, by conducting weighted Cox
17
18 307 proportional hazard regression models, our study used time-to-event outcomes, which offer
19
20 308 more survival-time-related information to help guide the clinical intervention and more
21
22 309 statistical power to detect risk factors [33][34].

23 310 Previous studies have indicated that cardiovascular events following pneumonia may
24
25 311 increase the risk of mortality [4], [35]-[40], which explained our findings from the viewpoint
26
27 312 of pathophysiological mechanisms. One potential mechanism underlying the association
28
29 313 between pneumonia and cardiovascular events is inflammation [37]. Specifically, the
30
31 314 inflammatory reaction following pneumonia can result in plaque instability and damage in
32
33 315 the blood vessels. Evidence of elevated local inflammation in the atherosclerotic coronary
34
35 316 arteries following acute systemic infections has been shown in many studies [37][39]. Thus,
36
37 317 infections may result in heightened loading that is imposed on cardiomyocytes and lead to
38
39 318 sympathetic hyperactivity or ischemia, which may increase the risk of arrhythmia and heart
40
41 319 failure in COVID-19 patients with pre-existing CHD [36].

42 320 Given the limited understanding of the prognostic factors for COVID-19, more
43
44 321 research, including potentially prospective studies, is needed to investigate the mechanism by
45
46 322 which pre-existing CHD may influence the survival probability of patients with COVID-19.
47
48 323 From the clinical point of view, early evaluation of a patient's medical history is necessary to
49
50 324 implement early medical interventions and decrease the mortality risk. We suggest
51
52 325 monitoring the dynamic heart rate for patients with pre-existing CHD. For those severe
53
54 326 symptomatic patients who had pre-existing heart ischemia and abnormal heart function, early
55
56 327 medical intervention may be needed [40].

57 328 Furthermore, our results indicated that the risk of death from COVID-19 was
58
59 329 significantly higher in older patients. Adjusting for others, every 1-year increase in age was
60
330 associated with a 4% increased risk of death, which is similar to what was found in previous
331 studies [8][9], [16]. Alongside the evidence of prognostic risk in CHD, we suggest that extra
332 care is needed for those with CHD, especially for elderly patients.

1
2
3 333 Previous studies yielded mixed results regarding gender differences in mortality risk
4
5 334 of COVID-19. Some studies found male sex was associated with a higher risk of death from
6
7 335 COVID-19 [41], whereas other studies did not find gender to be a significant factor
8
9 336 predicting the mortality risk of COVID-19 [10], [16]. In the current study, gender was not a
10
11 337 significant mortality risk factor for COVID-19. More research is needed to further our
12
13 338 understanding of gender differences in the outcome of COVID-19 and underlying
14
15 339 mechanisms.

15 340 The design of excluding patients from Hubei Province was based on the concerns of
16
17 341 unknown confounders caused by insufficient medical resources in the epicenter. CDC's
18
19 342 report has pointed out that the rapidly increasing number of infections could easily crash the
20
21 343 health care system by exceeding its maximum capacity [42]. Therefore, analyzing patient
22
23 344 data outside of Hubei Province avoided the competing mortality risk caused by insufficient
24
25 345 health care resources and revealed the true underlying impact of pre-existing comorbidities
26
27 346 on COVID-19 mortality [43].

27 347 This study has several limitations. It is worth noting that the data were collected when
28
29 348 COVID-19 was spreading rapidly in China and the health authorities and researchers had
30
31 349 limited understanding of the incubation period, modes of viral transmission, and effective
32
33 350 treatment. Whether our findings can be generalized to later epidemic phases warrants future
34
35 351 research. One limitation of the present study lies in the nature of publicly reported data.
36
37 352 Researchers have pointed out that severe cases may be overrepresented in publicly reported
38
39 353 data [44]. Nevertheless, we have managed to reduce the potential bias caused by severe case
40
41 354 overrepresentation by appropriately matching the cases and controls in the NCC design.
42
43 355 Following the NCC design, we allowed the controls to be matched with cases on age \pm 1
44
45 356 year old instead of the exact matching, which caused the significant age difference between
46
47 357 two groups (Table 1). Thus, we adjusted for the matching covariates in all the models to
48
49 358 address this [31]. The auto-matching procedure via the statistical program also prevented the
50
51 359 possibility of tendentiously selecting survivors with comorbidity-free history during data
52
53 360 collection. In addition, NCC design is favored in our situation where the risk factor data and
54
55 361 event of interest can be identified opportunistically from publicly reported confirmed cases
56
57 362 [30]. Therefore, NCC was the optimal choice, given the restricted availability of public data.
58
59 363 Moreover, due to the lack of information of treatment in the health reports published by the
60
364 local health commission websites, we did not include treatment information into analysis,
365 which may produce confounding effects. It calls for future research to investigate the
366 mortality risk effect of pre-existing comorbidities by adding treatment as a covariate in the

1
2
3 367 model. Lastly, we were not able to verify the missing at random assumption of the 18 missing
4
5 368 deaths (four from Heilongjiang, five from Henan, five from Beijing, two from Hunan, one
6
7 369 from Liaoning and one from Yunnan) as well as the survivors.

8 370 In conclusion, our findings provided preliminary yet strong evidence supporting the
9
10 371 association between pre-existing CHD and mortality risk for patients with COVID-19. Based
11
12 372 on our findings, close monitoring, extra care, and early medical intervention are needed for
13
14 373 patients with pre-existing CHD to reduce the mortality risk associated with COVID-19.

15 374
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 375 **Footnotes**

4
5 376 **Author Contributions**

6 377 TG conducted the analysis, interpreted the data, drafted the article, and rechecked the
7
8 378 transcribed manuscript. QC conducted the literature review and drafted the article. ZY guided
9
10 379 and supervised the statistical analysis. BF helped with data analysis. AL helped with
11
12 380 literature review, data collection, management and the data quality check, and was
13
14 381 responsible for reference organization. LX provided clinical support and interpretation of the
15
16 382 results. RW collected, preprocessed and managed data, and conducted preliminary data
17
18 383 analysis. YH guided and supervised the research process and provided funding support. All
19
20 384 authors critically revised the manuscript for intellectual content, approved the final draft, and
21
22 385 agreed to accountability for all aspects of the work.
23

24

24 387 **Conflict of Interest**

25 388 The authors have no affiliations with or involvement in any organization or entity with any
26
27 389 financial or nonfinancial interest in the subject matter or materials discussed in this
28
29 390 manuscript.
30

31 391

32 392 **Ethics Approval**

33 393 The data published in news reports and websites were open to the public and free of
34
35 394 identifiers. The study was approved by Shanghai Jiao Tong University Public Health and
36
37 395 Nursing Medical Research Ethics Committee (SJUPN-202001).
38

39 396

40 397 **Patient and Public Involvement**

41 398 This study used publicly reported patient-level data. All data were available online to the
42
43 399 public. No patient recruitment was involved in the study design, and no personal information
44
45 400 can be identified from the data.
46

47 401

48 402 **Funding**

49 403 This project was funded by the National Natural Science Foundation of China (No.
50
51 404 71874111), Shanghai Municipal Health Bureau Foundation (No. 201740116), and Shanghai
52
53 405 Jiao Tong University Scientific and Technological Innovation Funds (YG2020YQ01,
54
55 406 YG2020YQ06).
56

57 407
58
59
60

1
2
3 4084
5 **409 Data sharing statement**6
7 410 Raw data are available at GitHub: [https://github.com/GuTian-TianGu/COVID-](https://github.com/GuTian-TianGu/COVID-19_NCCstudy.git)
8 [19_NCCstudy.git](https://github.com/GuTian-TianGu/COVID-19_NCCstudy.git).9
10 41211
12 **413 Exclusive Licence**13
14 414 I, the Submitting Author has the right to grant and does grant on behalf of all authors of the
15 415 Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive
16 416 licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has
17 417 agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for
18
19 418 US Federal Government officers or employees acting as part of their official duties; on a
20 419 worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd (“BMJ”)
21
22 420 its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the
23
24 421 Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all
25
26 422 rights, as set out in our licence.
27
28

29 423

30
31 424 The Submitting Author accepts and understands that any supply made under these terms is
32
33 425 made by BMJ to the Submitting Author unless you are acting as an employee on behalf of
34
35 426 your employer or a postgraduate student of an affiliated institution which is paying any
36
37 427 applicable article publishing charge (“APC”) for Open Access articles. Where the Submitting
38
39 428 Author wishes to make the Work available on an Open Access basis (and intends to pay the
40
41 429 relevant APC), the terms of reuse of such Open Access shall be governed by a Creative
42
43 430 Commons licence – details of these licences and which Creative Commons licence will apply
44
45 431 to this Work are set out in our licence referred to above.

46 432

47 **433 Word count**48 434 3585
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 4354 436 **Reference**

- 5 437 [1] Coronavirus disease 2019 (COVID-19) Situation Report – 62.
6 438 [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46_2)
7 439 [62-covid-19.pdf?sfvrsn=f7764c46_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46_2)
8 440
- 9 441 [2] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H *et al*. Genomic characterisation and
10 442 epidemiology of 2019 novel coronavirus: implications for virus origins and receptor
11 443 binding. *Lancet* 2020; **395**:565-74. doi: 10.1016/S0140-6736(20)30251-8
- 12 444 [3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y *et al*. Clinical features of patients infected
13 445 with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**:497-506. doi:
14 446 10.1016/S0140-6736(20)30183-5
- 15 447 [4] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y *et al*. Epidemiological and clinical
16 448 characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a
17 449 descriptive study. *Lancet* 2020; **395**:507-13. doi: 10.1016/S0140-6736(20)30211-7
18 450
- 19 451 [5] Xu Xiao-Wei, Wu Xiao-Xin, Jiang Xian-Gao, Xu Kai-Jin, Ying Ling-Jun, Ma Chun-
20 452 Lian *et al*. Clinical findings in a group of patients infected with the 2019 novel
21 453 coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*
22 454 2020; **368**:m606. doi: 10.1136/bmj.m606
23 455
- 24 456 [6] Wang D, Hu B, Hu C *et al*. Clinical characteristics of 138 hospitalized patients with 2019
25 457 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; **323**:1061–9. doi:
26 458 10.1001/jama.2020.1585. Online ahead of print.
27 459
- 28 460 [7] Zhang, J-J, Dong, X, Cao, Y-Y *et al*. Clinical characteristics of 140 patients infected with
29 461 SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730– 41. doi: 10.1111/all.14238
30 462
- 31 463 [8] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX *et al*. Clinical characteristics of
32 464 coronavirus disease 2019 in China. *N Engl J Med* 2020; **382**:1708-1720. doi:
33 465 10.1056/NEJMoa2002032
34 466
- 35 467 [9] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus
36 468 disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from
37 469 the Chinese Center for Disease Control and Prevention. *JAMA* 2020. [Epub ahead of
38 470 print]. doi:10.1001/jama.2020.2648
39 471
- 40 472 [10] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to
41 473 COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive*
42 474 *Care Med* 2020; **46**:846-8. doi: 10.1007/s00134-020-05991-x
43 475

- 1
2
3 476 [11]Shi, S., Qin, M., Shen, Bo. et al. Association of Cardiac Injury with Mortality in
4
5 477 Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5** :802-
6
7 478 810. doi: 10.1001/jamacardio.2020.0950
8 479
- 9 480 [12]Liu, J. , Tu, C. , Zhu, M. , Wang, J. , Yang, C. , Liu, W. and Xiong, B., Exploring the
10 481 Law of Development and Prognostic Factors of Common and Severe COVID-19: A
11 482 Retrospective Case-Control Study in 122 Patients with Complete Course of Disease.
12 483 *Lancet* 2020. Available at SSRN 3555209.
13 484
- 14 485 [13]Liang W, Guan W, Chen R, Wang W, Li J, Xu K *et al.* Cancer patients in SARS-CoV-2
15 486 infection: a nationwide analysis in China. *The Lancet Oncology*.2020;**21**:335-7. doi:
16 487 10.1016/S1470-2045(20)30096-6
17 488
- 18 489 [14]Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H *et al.* Implications of COVID-19 for
19 490 patients with pre-existing digestive diseases. *The lancet Gastroenterology & hepatology*
20 491 2020;**5**:425-7. doi: 10.1016/S2468-1253(20)30076-5
21 492
- 22 493 [15]Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus
23 494 disease 2019 outbreak in China.*J Clin Med*2020;**9**:575. doi: 10.3390/jcm9020575
24 495
- 25 496 [16]Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for
26 497 mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort
27 498 study. *Lancet* 2020. doi: 10.1016/S0140-6736(20)30566-3
28 499
- 29 500 [17]Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic
30 501 review, *Stroke* 2009; **40**: 1082-90. doi: 10.1161/STROKEAHA.108.540781
31 502
- 32 503 [18]Camp P G , Goring S M . Gender and the diagnosis, management, and surveillance of
33 504 chronic obstructive pulmonary disease. *Ann AmThorac Soc*2007;**4**:686-691. doi:
34 505 10.1513/pats.200706-081SD
35 506
- 36 507 [19]Tchkonia T, Kirkland JL. Aging, cell senescence, and chronic disease: emerging
37 508 therapeutic strategies. *JAMA* 2018;**320**:1319–20. doi: 10.1001/jama.2018.12440
38 509
- 39 510 [20]Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old
40 511 medicine: Role of chronic inflammation. *Prev Med* 2012;**54**:S29-S37. doi:
41 512 10.1016/j.ypmed.2011.11.011
42 513
- 43 514 [21]Chinese COVID-19 Outbreak Distribution System. Available
44 515 at<http://2019ncov.chinacdc.cn/2019-nCoV/>
45 516
46 517
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 518 [22]Pan A, Liu L, Wang C, *et al.* Association of public health interventions with the
4 519 epidemiology of the COVID-19 outbreak in Wuhan, China. *JAMA*. 2020; 323: 1915-
5 520 23. doi:10.1001/jama.2020.6130
6 521
7 522 [23]Azoulay L, Dell'Aniello S, Gagnon B, *et al.* Metformin and Incidence of Prostate Cancer
8 523 in Patients with Type 2 Diabetes. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:337–344.
9 524 doi:10.1158/1055-9965
10 525
11 526 [24]Schlienger RG, Fedson DS, Jick SS, Jick H, Meier CR. Statins and the risk of pneumonia:
12 527 a population-based, nested case-control study. *Pharmacotherapy* 2007; **27**: 325–32.
13 528 doi:10.1592/phco.27.3.325
14 529
15 530 [25]Lipscombe LL, Levesque LE, Gruneir A, *et al.* Antipsychotic drugs and the risk of
16 531 hyperglycemia in older adults without diabetes: a population-based observational
17 532 study. *Am J Geriatr Psychiatry* 2011;**19**:1026-33. doi: 10.1097/JGP.0b013e318209dd24
18 533
19 534 [26]Lipscombe LL, Gomes T, Levesque LE, *et al.* Thiazolidinediones and cardiovascular
20 535 outcomes in older patients with diabetes. *J Am Med Assoc* 2007;**298**:2634–43. doi:
21 536 10.1001/jama.298.22.2634
22 537
23 538 [27]Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with
24 539 cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern*
25 540 *Med* 2005;**142**:481–9. doi:10.7326/0003-4819-142-7-200504050-00113
26 541
27 542 [28]Cerfolio RJ, Bryant AS. Survival and outcomes of pulmonary resection for non-small
28 543 cell lung cancer in the elderly: A nested case-control study. *Ann Thorac Surg*
29 544 2006;**82**:424-30. doi:10.1016/j.athoracsur.2006.02.085
30 545
31 546 [29]Khandaker G, Rashid H, Zurynski Y, *et al.* Nosocomial vs community-acquired
32 547 pandemic influenza A (H1N1) 2009: a nested case-control study. *J Hosp Infect* 2012;
33 548 **82**:94–100. doi:10.1016/j.jhin.2012.07.006
34 549
35 550 [30]Langholz, B. and Clayton, D. Sampling Strategies in Nested Case-Control
36 551 Studies. *Environ Health Persp*1994;**102**: 47–51. doi: 10.1289/ehp.94102s847
37 552
38 553 [31]Stoer, N. and Samuelsen, S. Inverse probability weighting in nested case-control studies
39 554 with additional matching - a simulation study. *Stat Med*2013;**32**, 5328-39. doi:
40 555 10.1002/sim.6019
41 556
42 557 [32]Stoer, N. and Samuelsen, S. multipleNCC. Weighted Cox-Regression for Nested Case-
43 558 Control Data. R package version 1.2-2.2020. Available at [https://CRAN.R-](https://CRAN.R-project.org/package=multipleNCC)
44 559 [project.org/package=multipleNCC](https://CRAN.R-project.org/package=multipleNCC)
45 560
46 561

- 1
2
3 562 [33]George B, Seals S, Aban I. Survival analysis and regression models. *J*
4 563 *NuclCardiol*2014;**21**:686–94. doi: 10.1007/s12350-014-9908-2
5 564
- 6 565 [34]Annesi I, Moreau T, Lellouch J. Efficiency of the logistic regression and Cox
7 566 proportional hazards models in longitudinal studies. *Stat Med* 1989; **8**: 1515–21. doi:
8 567 10.1002/sim.4780081211
9 568
- 10 569 [35]Tralhão A, Póvoa P. Cardiovascular Events After Community-Acquired Pneumonia: A
11 570 Global Perspective with Systematic Review and Meta-Analysis of Observational Studies,
12 571 *J Clin Med* 2020;**9**:414. doi:10.3390/jcm9020414
13 572
- 14 573 [36]Kirchhof, P.,Benussi, S., Kotecha, D.,Ahlsson, A.,Atar, D.,Casadei, B., Castella,
15 574 M.,Diener, H.C.,Heidbuechel, H., Hendriks, J. *et al.* 2016 ESC Guidelines for the
16 575 management of atrial fibrillation developed in collaboration with EACTS. *Eur. Heart*
17 576 *J*2016;**37**:2893–962. doi: 10.1093/eurheartj/ehw210
18 577
- 19 578 [37]Libby, P. Mechanisms of Acute Coronary Syndromes and Their Implications for
20 579 Therapy. *N. Engl. J. Med* 2013;**368**:2004–13. doi: 10.1056/NEJMra1216063
21 580
- 22 581 [38]Madjid, M., Vela, D., Khalili-Tabrizi, H.,Casscells, S.W.,Litovsky, S. Systemic
23 582 infections cause exaggerated local inflammation in atherosclerotic coronary arteries:
24 583 Clues to the triggering effect of acute infections on acute coronary syndromes. *Tex. Heart*
25 584 *Inst. J* 2007; **34**:11–8. pmid: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1847934/>
26 585
- 27 586 [39]Mauriello, A.,Sangiorgi, G.,Fratoni, S., Palmieri, G.,Bonanno, E.,Anemona, L., Schwartz,
28 587 R.S.,Spagnoli, L.G. Diffuse and Active Inflammation Occurs in Both Vulnerable and
29 588 Stable Plaques of the Entire Coronary Tree A Histopathologic Study of Patients Dying of
30 589 Acute Myocardial Infarction. *J Am Coll Cardiol*2005;**45**:1585–93. doi:
31 590 10.1016/j.jacc.2005.01.054
32 591
- 33 592 [40]Zhu J., Zhang X., Shi G., Yi K., Tan X. Atrial fibrillation is an independent risk factor
34 593 for hospital-acquired pneumonia. *PLoS ONE*. 2015;**10**:e0131782. doi:
35 594 10.1371/journal.pone.0131782
36 595
- 37 596 [41]Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19
38 597 inpatients in Wuhan. *J Allergy Clin Immunol*. 2020; **146** :110-8.
39 598 doi:10.1016/j.jaci.2020.04.006
40 599
- 41 600
- 42 601 [42]Qualls, N., Levitt, A., Kanade, N., *et al.* Community mitigation guidelines to prevent
43 602 pandemic influenza - United States, 2017. *MMWR Recomm Rep*. 2017;**66**:1–34.
44 603 doi:10.15585/mmwr.rr6601a1
45 604
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 605 [43] Ji, Y., Ma, Z., Peppelenbosch, MP., Pan Q. Potential association between COVID-19
4 606 mortality and health-care resource availability. *Lancet Glob Health*. 2020; **8** :e480.
5 607 doi:10.1016/S2214-109X(20)30068-1
6 608

7
8 609 [44] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation
9 610 Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed
10 611 Cases: Estimation and Application. *Ann Intern Med* 2020; **172**:577-82.
11 612 doi:10.7326/M20-0504
12
13

14 613
15 614

16 615 **Correspondence**

17
18 616 Address offprint requests to Dr. Wu at School of Social Development, East China Normal
19 617 University, 500 Dongchuan Rd., Shanghai 200241, China (rjwu@re.ecnu.edu.cn), or Dr. He
20 618 at College of Public Health, Shanghai Jiao Tong University School of Medicine, South
21
22 619 Chongqing Rd., No. 227, Shanghai 200025, China (hypcyr@sina.com), respectively.
23
24
25 620

621

622 **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, χ^2 test, or Fisher's exact test, as appropriate.

Bold: statistically significant using threshold $p < 0.05$

623

624

625

626

627

628

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

Characteristic	Univariate		Multivariate				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 $p < 0.05$.

629

630

631

1
2
3 632
4

5 633 **Figure 1:** Patient flow diagram detailing included subjects and exclusion criteria
6 634

7
8 635 **Figure 2:** Estimated survival probability over time from the adjusted Cox proportional hazard
9
10 636 model for an example patient profile (65-year-old female without CHD [dashed line] or with
11 637 CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability
12 638 was 0.53 (95% CI [0.34-0.82]) for patients with pre-existing CHD, while 0.85 (95% CI [0.79-
13 639 0.91]) for those without ($p<0.001$). CHD=coronary heart disease.
14
15
16 640

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

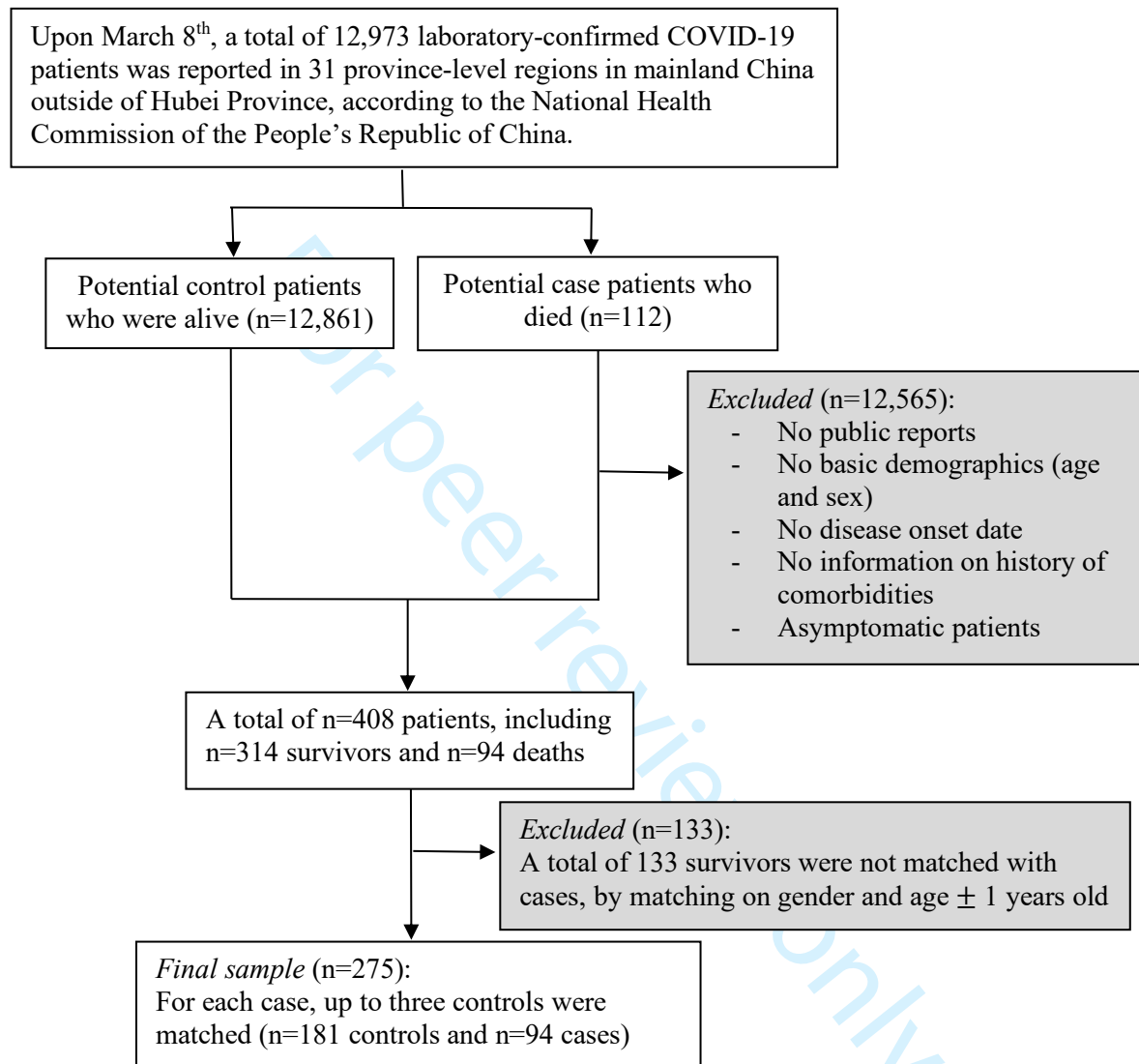


Figure 1: Patient flow diagram detailing included subjects and exclusion criteria

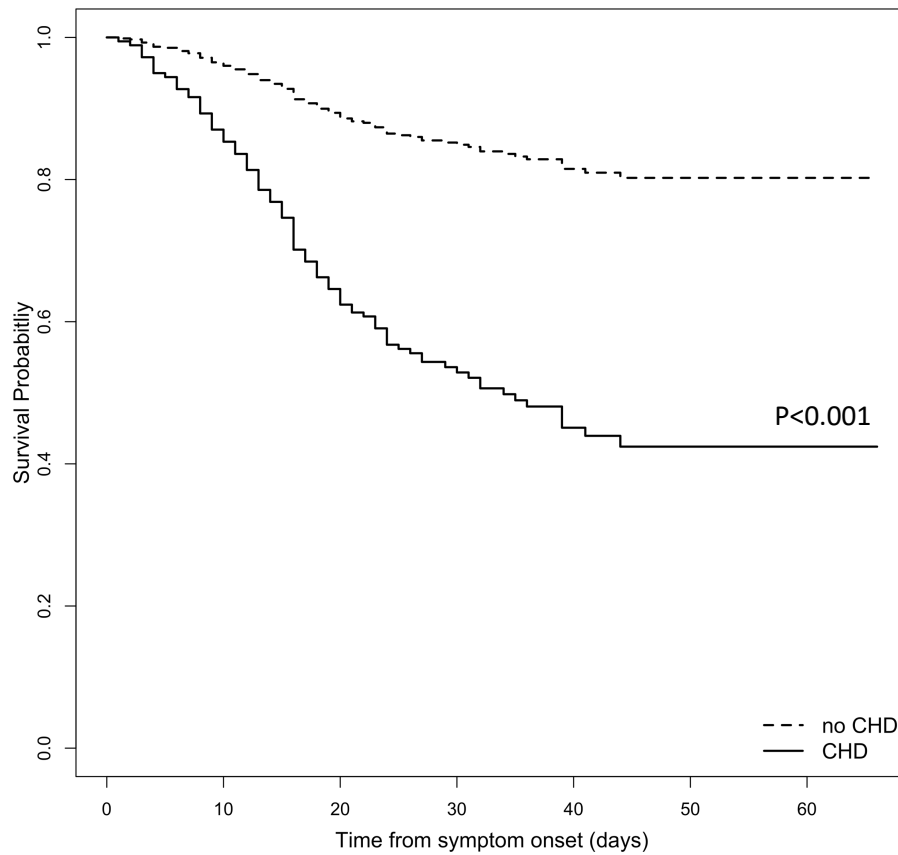


Figure 2: Estimated survival probability over time from the adjusted Cox proportional hazard model for a sample patient profile (65-year-old female without CHD [dashed line] or with CHD [solid line], who had no other comorbidities). The estimated 30-day survival probability was 0.53 (95% CI [0.34-0.82]) 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 $p < 0.05$