META ANALYSIS OF THE ASSOCIATION BETWEEN CARDIOVASCULAR DISEASES AND COVID-19

EPI 227 PROJECT

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ABSTRACT

Background: The COVID-19 pandemic has caused serious public health problems. The research of coronavirus has shown some relationships between cardiovascular diseases and COVID-19. In this case, this study is aimed to test if there is any statistically significant effect of cardiovascular diseases on the severe progression and mortality of patients with COVID-19.
Method: A comprehensive literature review and data extraction can be obtained in online database. The fixed effect model and random effects model can be utilized to estimate the risk ratio of the severe progression and death to COVID-19 patients. Then the subgroup analysis can be established to see if there is any significant heterogeneity between groups and finally to detect the publication bias.
Results: 28 studies can be included in the meta analysis, the random effects model show the high heterogeneity ($I^2 = 75\%, p < 0.01$) in this study with pooled risk ratio for both mortality and severe progression $3.03, 95\%$CI $[2.29, 4.02]$. The cardiovascular diseases are associated with increased mortality (pooled $RR = 3.29$ with 95% CI $[2.18, 4.97]$) and severe progression of COVID-19 (pooled $RR = 2.66$ with 95% CI $[1.81, 390]$). There is no between group heterogeneity and small-study effect.
Conclusion:The cardiovascular diseases are associated with an increased risk of severe progression and death among COVID-19 patients.

***K*eywords** Meta Analysis · COVID-19 · Cardiovascular Diseases

1 Introduction

Coronavirus disease, also called COVID-19, is an epidemic disease caused by a novel coronavirus. It has influenced serious public health emergency and many people are infected with the COVID-19 virus. By December 2020, it has more than 70 million cases around the world with 1.5 million deaths. However, the number of new cases and deaths is still increasing, which would intensify the burden of health care. For some of patients, especially for young people, the symptoms are mild or undetectable when they are infected by the coronavirus so that it is easy to spread around the world. Even if some patients are with no symptoms, many patients especially for the elder or people with underlying health problems would develop serious complications including acute myocardial infarction, myocardial injury, myocarditis, dysrhythmias, heart failure and venous thromboembolic events. [1, 2] A narrative review of the cardiovascular diseases and COVID-19 study [3] has shown that patients with underlying cardiovascular disease (CVD) would cause cardiac injury during the course of the illness, which would increase the risk of progression and death. However, those studies are mainly finished in the beginning of the coronavirus pandemic with small sample and less patients data. By December, many clinical trials in patients infected with COVID-19 virus has been conducted to share the clinical data with patients characteristics. In this meta analysis, we are supposed to estimate the association between cardiovascular diseases and the severe progression and mortality of COVID-19, based on the latest literature review and data analysis.

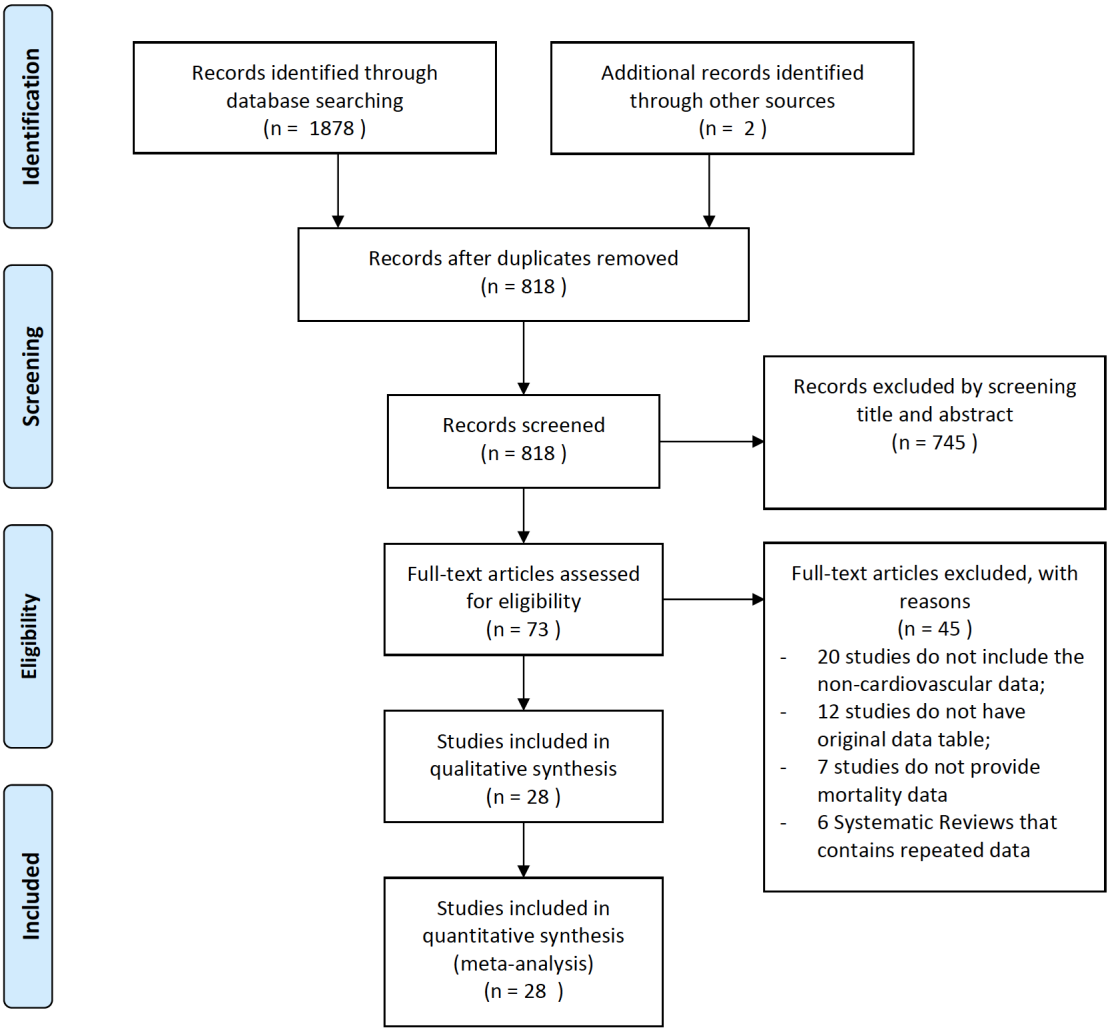

Figure 1: PRISMA Flowchart

2 Method

2.1 Search strategy and selection criteria

In this study, we applied a comprehensive literature search in PubMed, Embase and Google Scholar, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The searching strategy is to select the study from January 1, 2020 to December 10, 2020 without any language restriction using these advanced searching engines. The searching term contains: (1) (COVID-19) OR (SARS-CoV-2) AND (clinical trial); (2) (COVID-19) OR (SARS-CoV-2) AND (cardiovascular disease); (3) (COVID-19) OR (SARS-CoV-2) AND (cardiovascular disease) And (mortality); (4) (COVID-19) OR (SARS-CoV-2) AND (cardiovascular disease) And (severe). One individual researcher would search these terms to find appropriate papers and researches with double-checking to see if there is any conflict or misunderstanding. After removing the duplicate studies, the potential papers of associated with full texts and datasets would be evaluated with the inclusion criteria and exclusion criteria.
The inclusion criteria is: (i) Studies that contain the grouping information of cardiovascular diseases for patients with COVID-19; (ii) Studies that include the mortality of patients or definition of severe progression of patients with COVID-19. (iii) No preference of study designs. The exclusion criteria is to omit the duplicate reports, systematic review and the articles that only contains abstracts.

Table 1: Demographics of the included studies

Author	Ee	Ne	Ec	Nc	Events
Akbari [4]	2	25	11	415	Death
Bai T [5]	2	3	34	124	Death
Cao J [6]	3	5	14	97	Death
Chen T [7]	16	23	97	251	Death
Deng [8]	65	109	1	116	Death
Fu L [9]	2	16	32	184	Death
Guan WJ [10]	6	67	21	1029	Death
Lang W [11]	21	53	44	286	Death
Mo P [12]	14	85	1	70	Death
Shi S [13]	42	82	15	334	Death
Shi Y [14]	4	94	7	438	Death
Wang D [15]	9	36	11	102	Death
Goyal P [16]	7	141	19	290	Death
Wang Z [17]	5	14	3	55	Death
Wu C [18]	5	94	3	117	Death
Yang X [19]	3	32	2	20	Death
Yuan ML [20]	3	3	7	24	Death
Zhou F [21]	13	54	2	147	Death
Anwer S [22]	4	13	1	28	Severe
Huang C [23]	3	13	3	28	Severe
Li Q [24]	5	18	21	307	Severe
Liu JY [25]	1	1	16	60	Severe
Qin [26]	8	11	278	441	Severe
Wan S [27]	6	7	34	128	Severe
Gaurav A [28]	8	36	2	102	Severe
Bonow [29]	12	16	59	127	Severe
Zhang GQ [30]	13	22	42	199	Severe
Zheng X [31]	2	28	2	52	Severe

2.2 Data Extraction

The data can be extracted with these measures: author, year, number of events in cardiovascular group (Ee), number of events in non-cardiovascular group (Ec), number of patients in cardiovascular group (Ne), number of patients in non-cardiovascular group (Nc) and event type (death or severe progression). The events of interest are death and severe progression of COVID-19.
The definition of cardiovascular diseases in this meta-analysis were the historical cardiovascular (cardiac) disease or the co-morbidity cardiovascular diseases with COVID-19. The definition of severe progression of COVID-19 can be summarized from the included papers: (a) respiratory distress breaths per min is greater than 30; (b) the oxygen saturation at rest is lower than 93%; (c) the ratio of partial pressure of arterial oxygen (PaO2) to fractional concentration of oxygen inspired air (FiO2) $\leq$300 mmHg; (d) ICU events and (e) some other complications including respiratory failure, septic shock, and or multi organ dysfunction or failure. [4]

2.3 Statistical Analysis

The data are collected into Excel and are analyzed in R. The meta analysis for the binary outcome can be analyzed with risk ratio in (1) fixed-effect models (Mantel–Haenszel method) or (2) random-effect models if there is any significant heterogeneity between studies. The statistic I^2 and the corresponding p-value can be used to detect the heterogeneity issue. If there is any statistically significant heterogeneity problem for the results, then small-study effect analysis can be conducted to determine if the heterogeneity is from different event types. The subgroup difference can be test by random effects model with common estimate of τ^2. Here we define composite outcome as the patients is progressed serverely or dead, so we can calculate the risk ratio of the composite outcome. Then for subgroup analysis, we can calculate the pooled risk ratio by event type (severe progression and death). Finally, the publication bias can be detected by funnel plot and Begg and Mazumdar test.

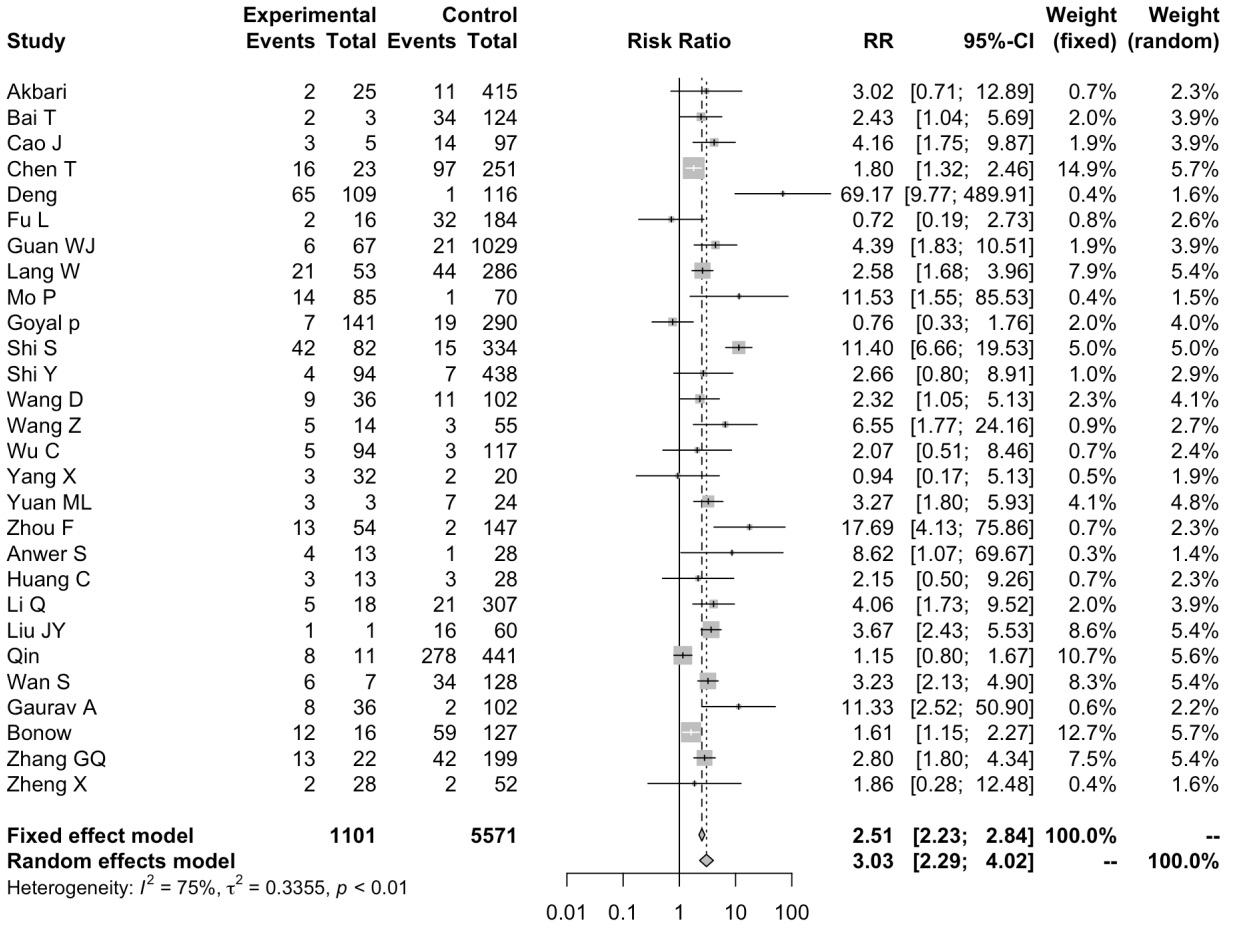

Figure 2: Cardiovascular Diseases and Composite Outcome

3 Results

3.1 Study Selection and Characteristics

Based on the previous searching strategy in Embase, PubMed and Gogle Scholar, total 1878 studies and 2 additional pre-printed articles were detected firstly. After removing the duplicated papers, 818 records were used to screen by the paper title. Then 745 papers were excluded, the rest 73 papers were used to check the full texts to see if they contain proper data. The PRISMA Flowchart in Figure 1 is shown to describe the selection details. 45 studies are excluded including 20 studies without non-cardiovascular data, 12 studies without original data, 7 studies without mortality data and 6 review studies that contain repeated datasets. Finally, 28 studies included in quantitative synthesis can be used to do meta analyze of the association between cardiovascular diseases and the death or the severe progression status on COVID-19.

In the 28 meta data from different studies (18 for mortality, 10 for severe progression), all of them are published in 2020 with sample size ranging from 27 to 1096. The details of the data are shown in Table 1. There is no empty cell in the table, which means the dataset is not too sparse.

3.2 Random Effects Model

Since the statistic I^2 for composite outcome is 75% with p-value lower than 0.01, which indicates strong heterogeneity. In this case, the random effect model can be used to relax the problem. From Figure 2, the cardiovascular diseases are associated with increased composite outcome (pooled $RR = 3.03$ with 95% CI $[2.28, 4.02]$). For different event types (severe progression and death), the results of subgroup study can be shown in Figure 3 and Figure 4. Since the

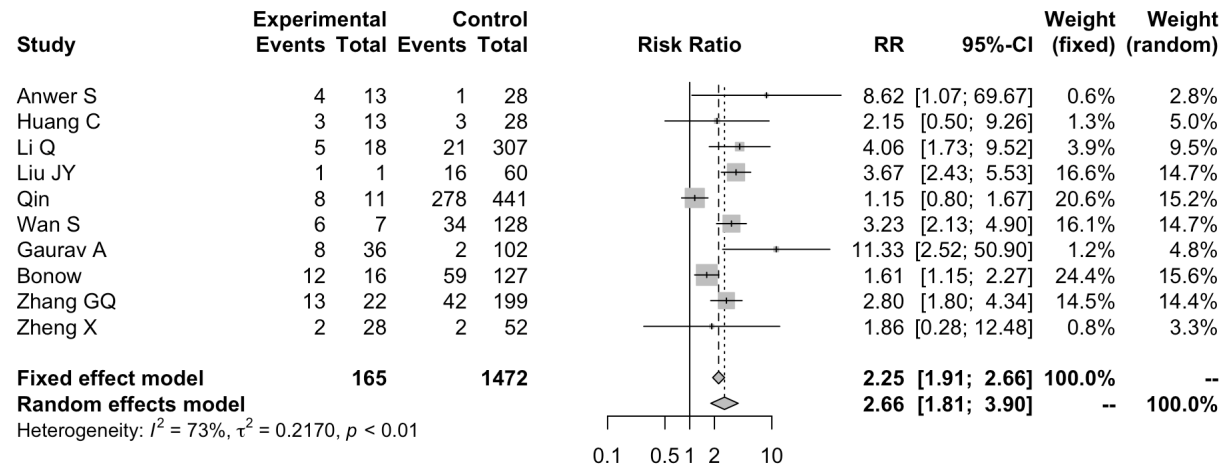

Figure 3: Cardiovascular Diseases and Severe Progression

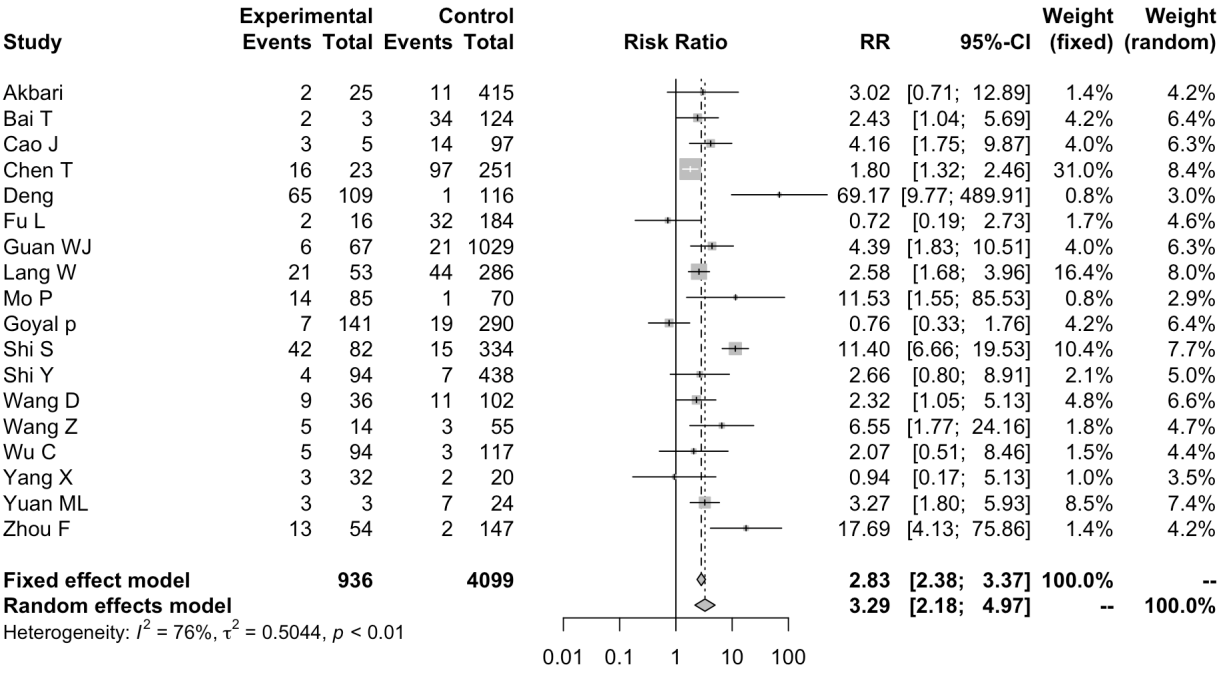

Figure 4: Cardiovascular Diseases and Mortality

high heterogeneity in the data ($I^2 = 73\%$ for severe progression group and $I^2 = 76\%$ for mortality group), the random effect model can be used to estimate the pooled risk ratio. The random effects model can show that the cardiovascular diseases are associated with increased mortality (pooled $RR = 3.29$ with 95% CI $[2.18, 4.97]$) and severe progression of COVID-19 (pooled $RR = 2.66$ with 95% CI $[1.81, 390]$).

3.3 Subgroup Difference

From the previous random effects model, the heterogeneity is significant between studies. The results of random effects model with common τ^2 show that the estimated common $\tau^2 = 0.3577$. And $Q_R^* = 0.31$ with p-value $0.5778 > 0.05$, which indicates that there is no significant difference between the 2 subgroups by event type. However, the within-in group difference is significant since $Q_R = 104.89$ with p-value smaller than 0.001.

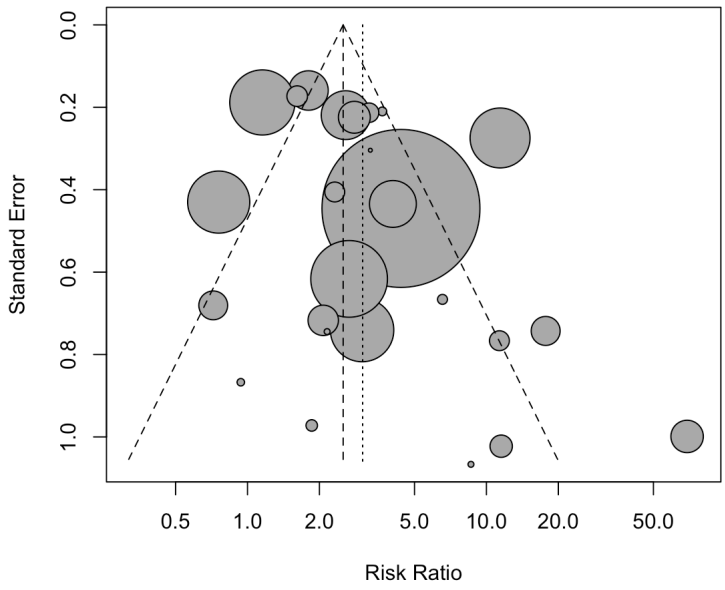

Figure 5: Funnel Plot: the larger sample size, the larger point

3.4 Publication Bias

The Funnel Plot in the Figure 5shows that the effects of cardiovascular diseases for large and small studies scatter around a common average effect symmetrically. The results of rank correlation test (Begg and Mazumdar test) show that the estimate of $z = 1.3434, p - value = 0.1791 > 0.05$. In this case, there is no significant small-study effects for the association between cardiovascular diseases and the mortality and severe progression of COVID-19.

4 Discussion

4.1 Conclusion

From the previous meta analysis, we can conclude that cardiovascular diseases are associated with an increased risk of severe progression and death among COVID-19 patients. This finding is consistent with the latest systematic review with 13 studies[32]. The pooled risk ratio by random effects model is relatively higher than the previous meta analysis. One possible reason is the increasing number of studies that can be selected into the meta analysis. In addition, there is no significant small-study effect in this meta analysis, which indicates that this conclusion is statistically confident. The pooled risk ratio for death group is relatively higher than the risk ratio for severe progression group, which might suggest that the co-morbidity or historical cardiovascular diseases would influence more for death than for severe progression of COVID-19. There is no significant subgroup difference across two event types, which means that the heterogeneity of this meta analysis might be from clinical baseline heterogeneity or other sources.

4.2 Limitation and Future Work

Since the high heterogeneity of the study cannot be interpreted by the between group difference, more studies can be done to detect the group difference. However, the meta analysis with 13 researches[32] has showed that there is no heterogeneity in the study. It would indicate that the new clinical trial would cause more heterogeneity results in the future. For further study, more studies along with other clinical characteristics are still needed to include in the meta analysis.

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