Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Meta-analysis of Cardiovascular Events and Related Biomarkers Comparing Survivors Versus Non-survivors in Patients With COVID-19

Saeed Shoar, M.D.[a], Fatemeh Hosseini, M.D.[b], Mohammad Naderan, M.D.[c], and Jawahar L. Mehta, M.D., Ph.D.[d,*]

Since the emergence of the coronavirus disease 19 (COVID-19), a number of studies have reported the presence of cardiovascular diseases in affected patients and linked them with a higher risk of mortality. We conducted an online search in Medline/PubMed to identify original cohorts comparing data between survivors and non-survivors from COVID-19. The presence of cardiovascular events and related biomarkers were compared between the 2 groups. Data on 1,845 hospitalized patients with COVID-19 were pooled from 12 comparative studies. The overall mortality rate in relation to COVID-19 was 17.6%. Men aged > 50 years old were more likely to die from COVID-19. Significant co-morbidities contributing to mortality were hypertension, diabetes mellitus, smoking, a previous history of cardiovascular disease including chronic heart failure, and cerebrovascular accidents. A significant relationship was observed between mortality and patient presentation with dyspnea, fatigue, tachycardia, and hypoxemia. Cardiovascular disease-related laboratory biomarkers related to mortality were elevated serum level of lactate dehydrogenase, creatine kinase, brain natriuretic peptide, and cardiac troponin I. Adverse cardiovascular disease-related clinical events preceding death were shock, arrhythmias, and acute myocardial injury. In conclusion, severe clinical presentation and elevated biomarkers in COVID-19 patients with established risk factors can predict mortality from cardiovascular causes. Published by Elsevier Inc. (Am J Cardiol 2020;135:50−61)

As the pandemic of coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2), is evolving, an increasing number of studies are pointing to the relationship of cardiovascular disease with mortality in hospitalized patients.[1−5] Most previously published studies on this subject consist of small-to-large series of patients who had or developed cardiovascular events as a result of infection with SARS-CoV-2. However, few studies have compared the presence of cardiovascular disease risk factors, its manifestations, and related laboratory parameters with regard to mortality in patients with COVID-19. We performed a systematic analysis of the literature to compare these parameters between survivors and nonsurvivors of COVID-19.

Methods

A systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[6] and performed in compliance with the Meta-analyses Of Observational Studies in Epidemiology Checklist.[7] Two independent researchers performed the literature review, screened the articles, and obtained the full text of the eligible studies.

An electronic search was performed in Medline/PubMed to identify studies with original data on mortality in patients with COVID-19. A combination of the following keywords was used: “COVID-19” or “SARS-CoV-2” or “SARS CoV-2” or “2019 novel coronavirus” or “2019-nCoV” and “mortality” or “death” or “died” or “die”. Due to a high volume of preprint publication on this topic, we limited our online database search to the Medline/PubMed. The title and abstract of articles were screened for relevancy and the full text of relevant studies was reviewed for eligibility.

Original studies in adult patients with COVID-19 comparing the demographics, clinical characteristics, radiologic findings, or laboratory parameters between survivors and non-survivors were eligible for inclusion if available in English language full-text. Eligible articles were included into meta-analysis if data on variables of interest were extractable in crude numbers for both the survivor and non-survivor groups. Case report, review articles, modeling studies, and commentaries were excluded.

The main end point of this systematic review was to compare cardiovascular disease risk factors, its manifestations, and related laboratory parameters between COVID-19 survivors and non-survivors. Cardiovascular disease risk factors included gender, hypertension, dyslipidemia, diabetes, and a previous history of cardiovascular disease, including heart failure and cerebrovascular events. Clinical presentations pertient to the cardiovascular system included shortness of breath, tachycardia, and other vital signs

[a]Department of Clinical Research, ScientificWriting Corporation, Houston, TX; [b]Department of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [c]Department of Medicine, Tehran University of Medical Sciences, Tehran, Iran; and [d]Department of Medicine (Cardiology), Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, AR. Manuscript received July 15, 2020; revised manuscript received and accepted August 17, 2020.

This study did not receive any grant or financial support in any forms.

*Corresponding author: Tel 501-296-1426.

E-mail address: arheartdoc@gmail.com (J.L. Mehta).

0002-9149/Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2020.08.044

instability. The cardiovascular disease-related laboratory biomarkers included cardiac troponin I (CTnI), brain natriuretic peptide (BNP) or proBNP, lactate dehydrogenase (LDH), and creatine kinase (CK).

Review Manager (RevMan. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform meta-analysis of the extracted data in this systematic review. Data on variables of interest was extracted from at least 2 eligible studies to perform the quantitative analysis. An odds ratio (OR) was calculated as the prevalence of a potential risk factor in the non-survivor group compared with the survivor group. A mean difference (MD) was a weighted difference in the mean of a continuous variable between the 2 groups. If enough data was available, the laboratory parameters were analyzed both as a continuous variable, that is, their average serum levels, and as a categorical variable, that is, the reported value as elevated or positive. Mantel-Haenszel statistical method was applied using a random-effects analysis model. Statistical significance was set at $p < 0.05$.

Results

Figure 1 shows the PRISMA flowchart of our systematic literature review, article screening, and study selection.

A total of 12 studies were included encompassing 3,257 hospitalized patients with COVID-19 who either died from the SARS-CoV-2 infection, discharged from the hospital, or continued to remain under observation between December 20, 2019 and March 15, 2020.[8–19] Death from COVID-19 occurred in 574 patients, whereas 1,271 patients survived and were discharged from the hospital (Table 1). These 1,845 patients constituted the population of our meta-analysis. The mortality rate ranged from 11.3%[19] to 61.5% [16] with a pooled average of 17.6%.

Meta-analysis of data showed that non-survivors were generally men (OR= 2.1, $p < 0.0001$), aged > 50 years (OR 8.7, $p < 0.00001$), with established comorbidities including hyperlipidemia (OR = 44.1, $p = 0.0005$), smoking (OR = 13.5, $p = 0.0009$), hypertension (OR = 2.6, $p < 0.00001$), and diabetes mellitus (OR = 1.7, $p = 0.03$). Non-survivors had a history of chronic cardiovascular disease (OR = 2.7, $p = 0.0004$), including chronic heart failure (OR = 27.8, $p < 0.0001$) or cerebrovascular disease (OR = 4.4, $p = <0.00001$), and a respiratory condition (OR = 3.4, $p = 0.006$) (Table 2 and Figure 2).

In terms of clinical presentation at admission, presence of hypoxemia (MD = −12 % hemoglobin saturation, $p < 0.00001$), a higher heart rate (MD = 5.4 beats/minute, $p = 0.04$), dyspnea (OR = 4.8, $p < 0.0001$), and fatigue (OR = 1.4, $p = 0.04$) were associated with death from COVID-19 (Table 2).

Mortality from COVID-19 was preceded by acute respiratory distress syndrome (OR = 122.0, $p < 0.0001$), circulatory shock (OR = 53.1, $p = 0.001$), arrhythmias (OR = 22.4, $p = 0.02$), and acute cardiac injury (OR = 20.0, $p < 0.0001$) (Table 2 and Figure 2).

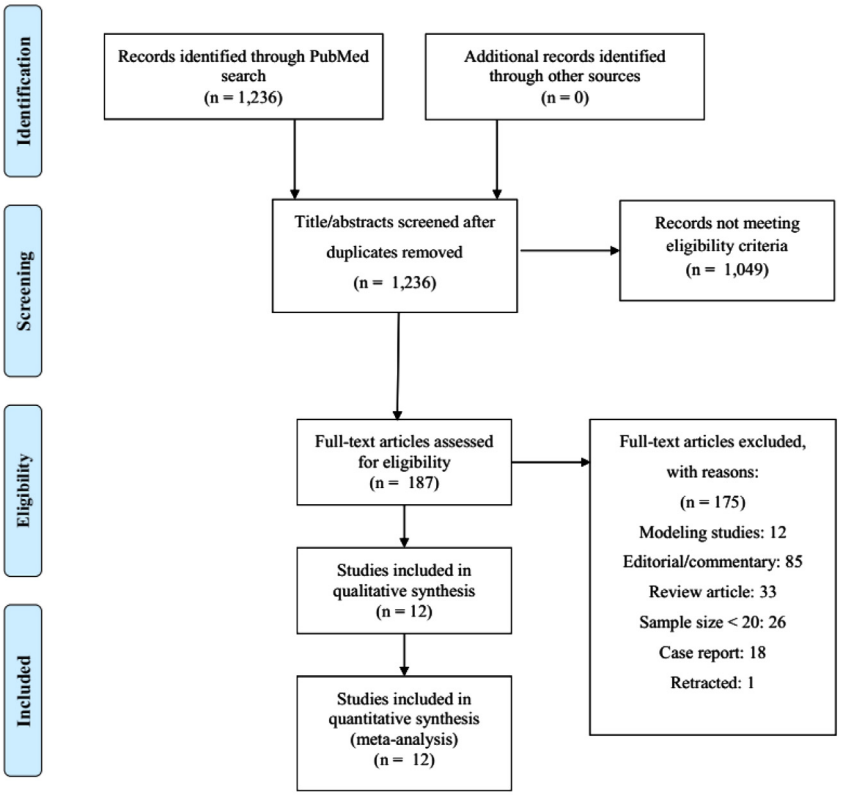


Figure 1. PRISMA flowchart demonstrating our literature review and study selection.

Table 1
Characteristics of studies included in this systematic review

	First Author (Reference #)	City	Sample Size	Date of Last Discharge	Mortality Rate
1	Cao (8)	Wuhan	102	02/15/2020	16.7 %
2	Chen (9)	Wuhan	799	02/28/2020	14.1 %
3	Chen (10)	Wuhan	203	02/20/2020	12.8 %
4	Deng (19)	Wuhan	964	02/21/2020	11.3 %
5	Du (11)	Wuhan	179	N/A	11.7 %
6	Li (12)	Wuhan	25	03/3/2020	20 %
7	Tang (13)	Wuhan	183	02/13/2020	11.5 %
8	Wang (14)	Wuhan	339	03/05/2020	19.2 %
9	Yan (15)	Wuhan	193	N/A	56 %
10	Yang (16)	Wuhan	52	02/9/2020	61.5 %
11	Yuan (17)	Wuhan	27	N/A	37 %
12	Zhou (18)	Wuhan	191	N/A	28.3%

All studies were published in 2020.
N/A = Not available.

Table 2
Factors associated with mortality from COVID-19 in the meta-analysis of comparative studies

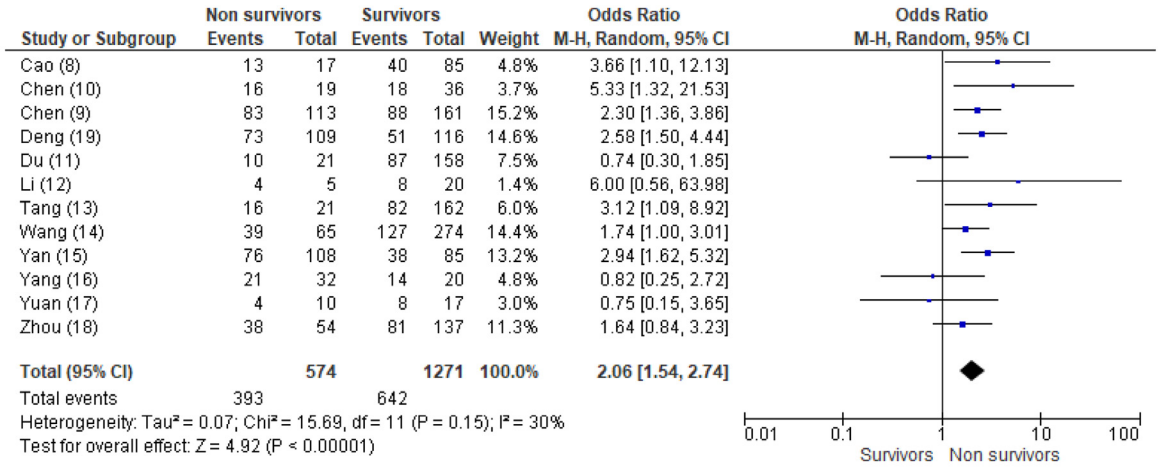
Variable	OR [95% CI]	Heterogeneity (I^2)	p
Age > 50 years	8.7 [5.1, 14.9]	0%	<0.00001
Men	2.1 [1.5, 2.7]	30%	<0.00001
Hyperlipidemia	44.1 [5.2, 374.4]	0%	0.0005
Chronic heart failure	27.8 [6.3, 122.9]	0%	< 0.0001
Current smoker	13.5 [2.9, 63.5]	75%	0.0009
Chronic respiratory diseases	3.4 [1.4, 8.1]	43%	0.006
Any cardiovascular diseases	2.7 [1.6, 4.8]	29%	0.0004
Hypertension	2.6 [1.9, 3. 7]	39%	< 0.00001
Diabetes	1.7 [1.0, 2.8]	47%	0.03
Heart rate at admission, mean difference in beats/minute	5.3 [0.2, 10.5]	58%	0.04
Dyspnea	4.8 [2.4, 9.7]	74%	< 0.0001
Fatigue	1.4 [1.0, 1.8]	0%	0.04
Partial arterial O2 pressure to the fraction of inspired O2 at admission, mean difference in PaO2:FiO2	−54.9 [−87.9, −22.0]	76%	0.001
Transcutaneous pulse oximetry, mean difference in % hemoglobin saturation	−12.00 [−12.5, −11.5]	0%	< 0.00001
Brain natriuretic peptide or pro-brain natriuretic peptide, mean difference in pg/ml	721.7 [657.0, 786.4]	0%	< 0.00001
Lactate dehydrogenase, mean difference in U/L	214.1 [133.9, 294.4]	98%	< 0.00001
Creatine kinase, mean difference in U/L	56.1 [11.2, 101.1]	97%	0.01
Cardiac troponin I, mean difference in pg/ml	18.7 [−3.4, 40.8]	99%	0.10
Elevated serum level of cardiac troponin I	25.5 [7.2, 90.7]	44%	< 0.00001
Elevated level of lactate dehydrogenase	11.8 [1.3, 105.8]	90%	0.03
Elevated level of creatine kinase	2.3 [1.04, 5.1]	2%	0.04
Acute respiratory distress syndrome	122.01 [69.96, 212.79]	0%	< 0.00001
Shock	53.10 [4.67, 603.89]	85%	0.001
Arrhythmia	22.4 [1.8, 283.6]	90%	0.02
Acute myocardial injury	20.3 [7.8, 53.3]	71%	< 0.00001
Acute heart failure	3.2 [0.3, 30.1]	89%	0.3

Variables are presented as odds ratio, unless mentioned otherwise, i.e. mean difference

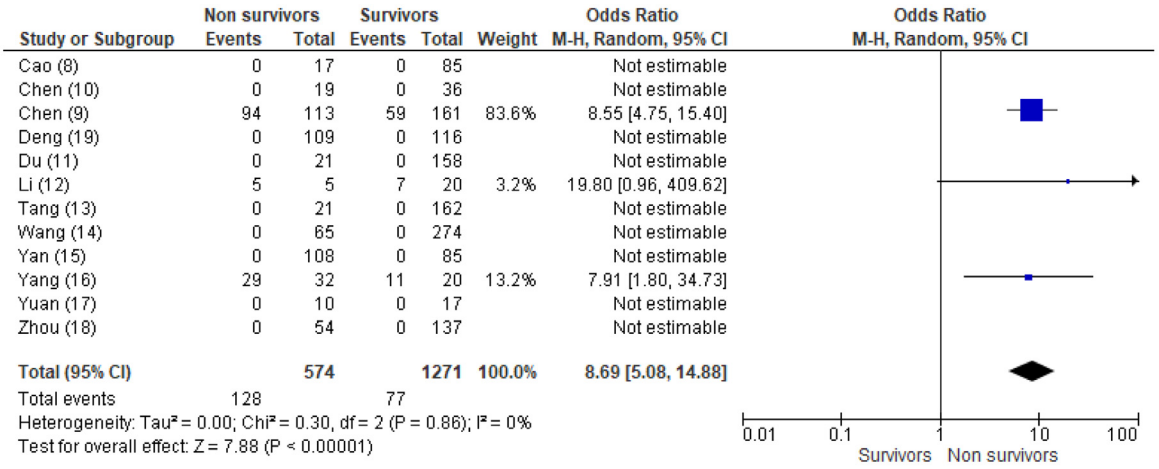
Mortality from COVID-19 infection was associated with elevation of cardiovascular disease-related laboratory biomarkers such as cardiac troponin I (OR = 25.5, p = <0.0001), LDH (OR = 11.8, p = 0.03), and CK (OR = 2.3, p = 0.04) (Table 2 and Figure 2). Additionally, serm level of BNP or pro-BNP was significantly elevated in the non-survivor group compared to the survivr group.

A meta-analysis was also performed on available data for 4 major therapeutic modalities provided to COVID-19 patients. These included antiviral treatment, antibiotics, corticosteroid administration, and mechanical ventilation. Of these, corticosteroid administration (OR = 3.3, p =0.001) and mechanical ventilation (OR = 9.07, p = 0.02) were used more commonly in non-survivors than in survivors (Figure 3).

Male gender



Age > 50 years



Comorbidity: Smoking status.

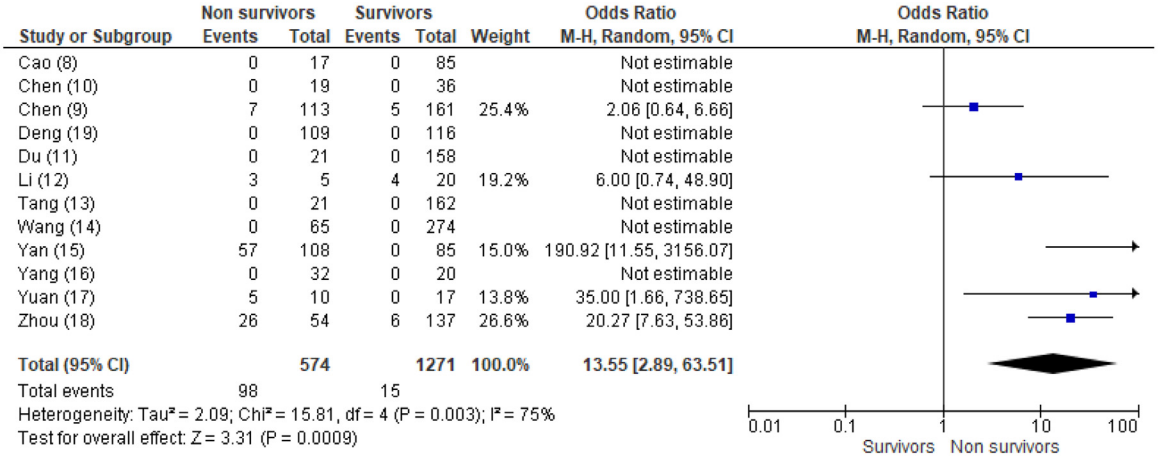
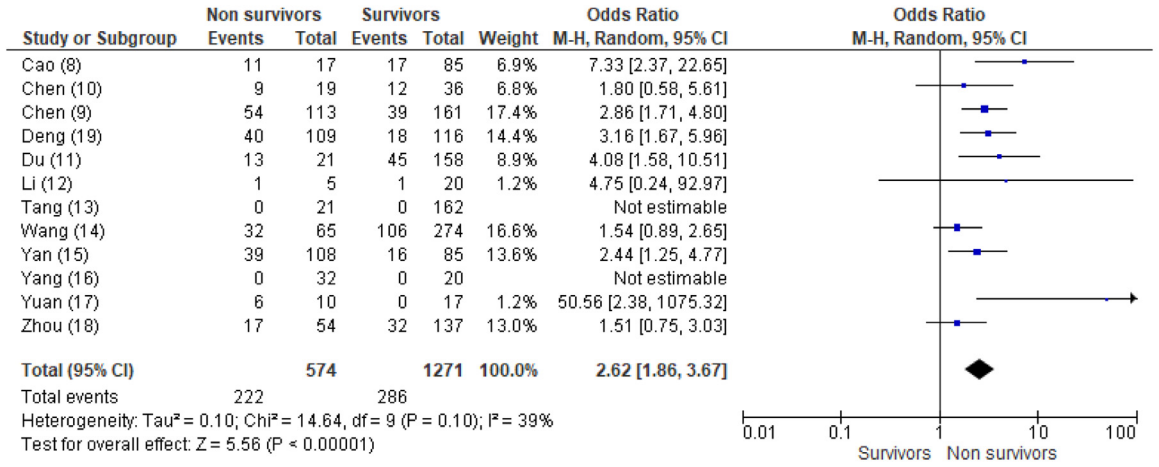
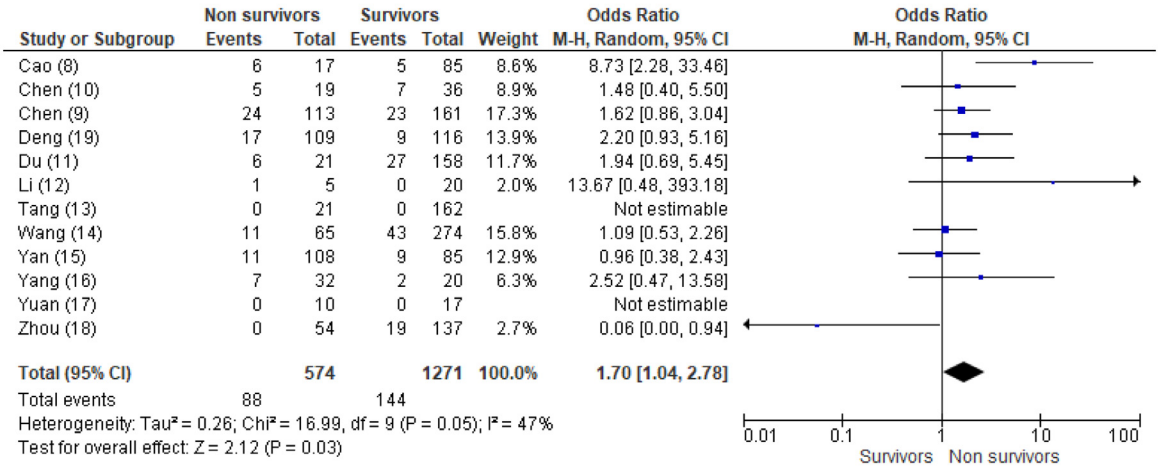


Figure 2. Forest plots demonstrating pooled analysis of cardiovascular system involvement in patients with COVID-19. The meta-analysis estimated a mean difference and 95% confidence interval for the continuous variables and an odds ratio and 95% confidence interval for the categorical variables. Mantel-Haenszel statistical method using a random-effects model was utilized for all of the analysis.

Comorbidity: Hypertension.



Comorbidity: Diabetes



Comorbidity: Hyperlipidemia

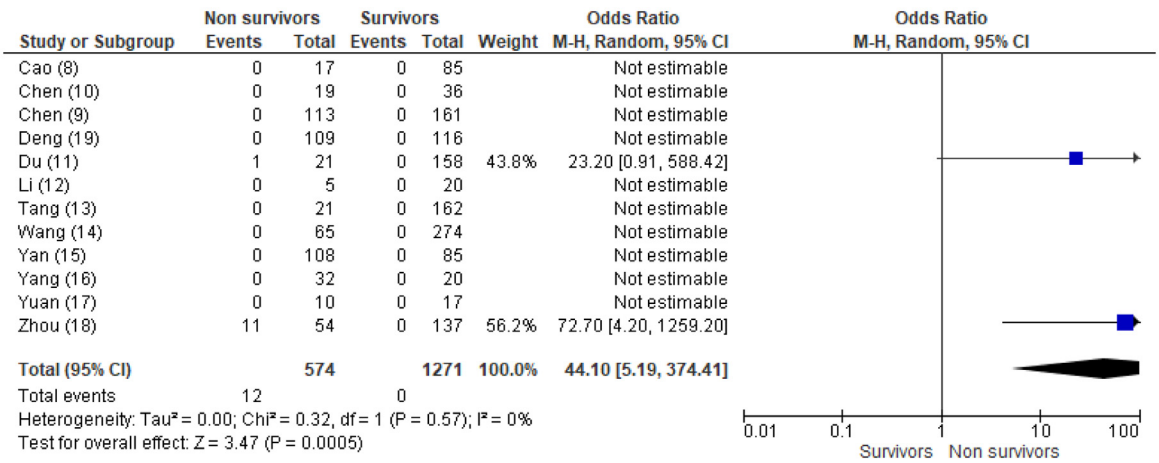
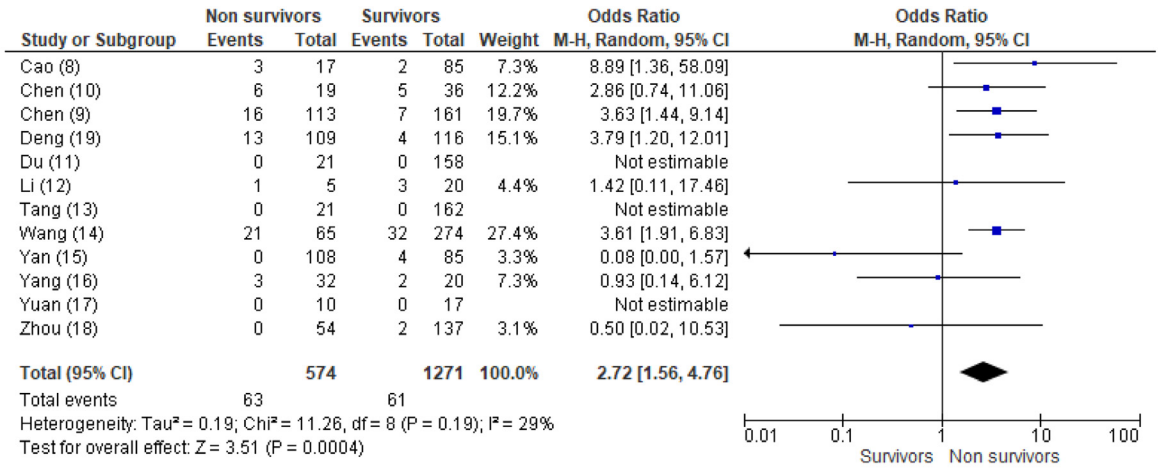
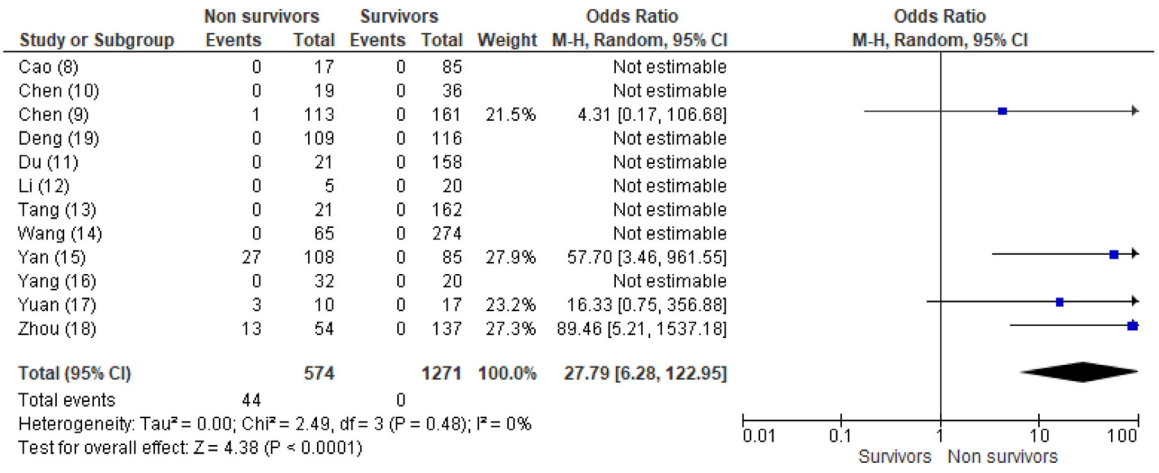


Figure 2. Continued

Comorbidity: Cardiovascular diseases



Comorbidity: Chronic heart failure.



Comorbidity: Chronic respiratory diseases

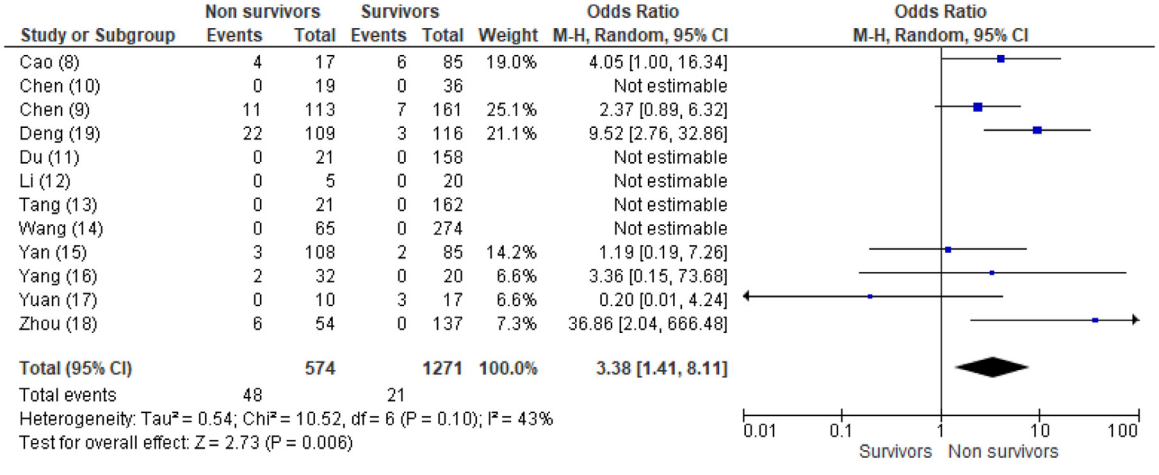
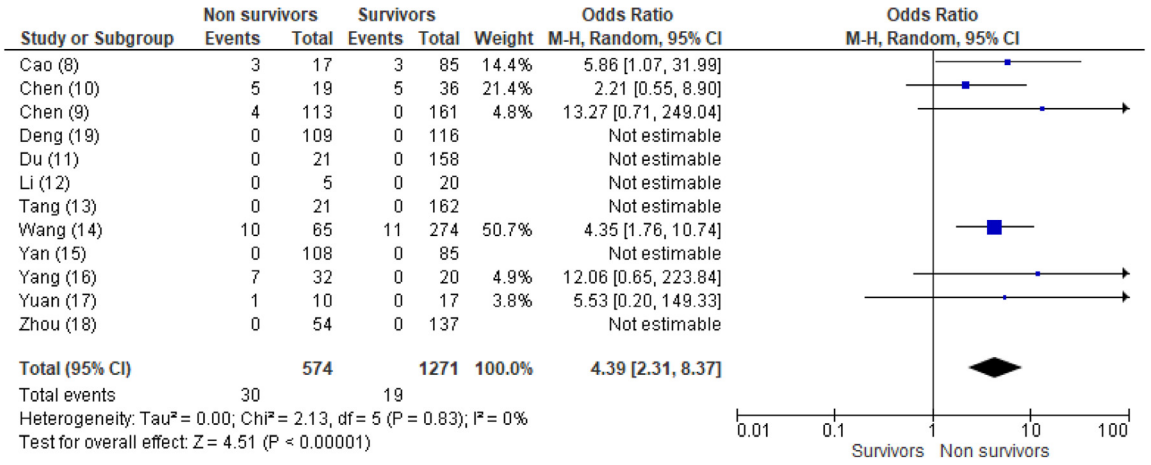
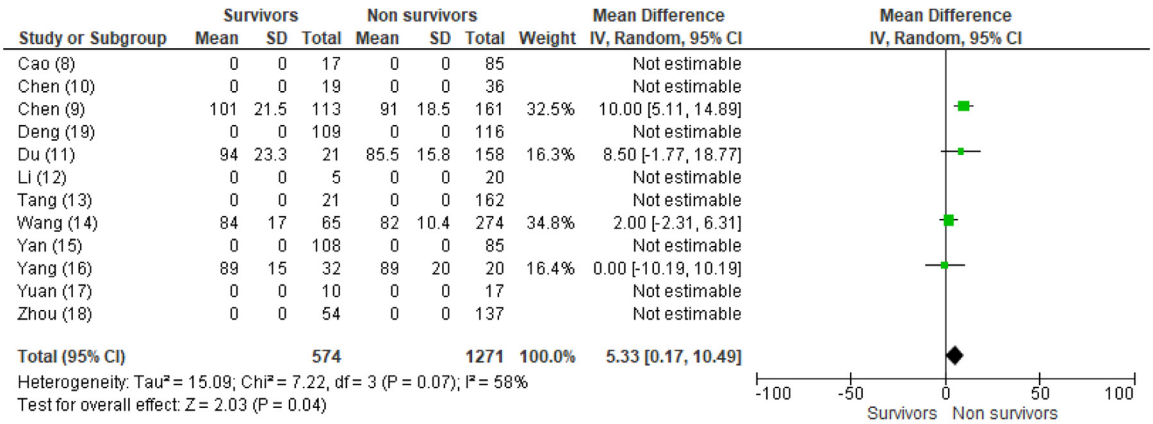


Figure 2. Continued

Comorbidity: Cerebrovascular diseases



Mean difference in heart rate at admission, beats/minute



Elevated creatine kinase as a predictor of mortality

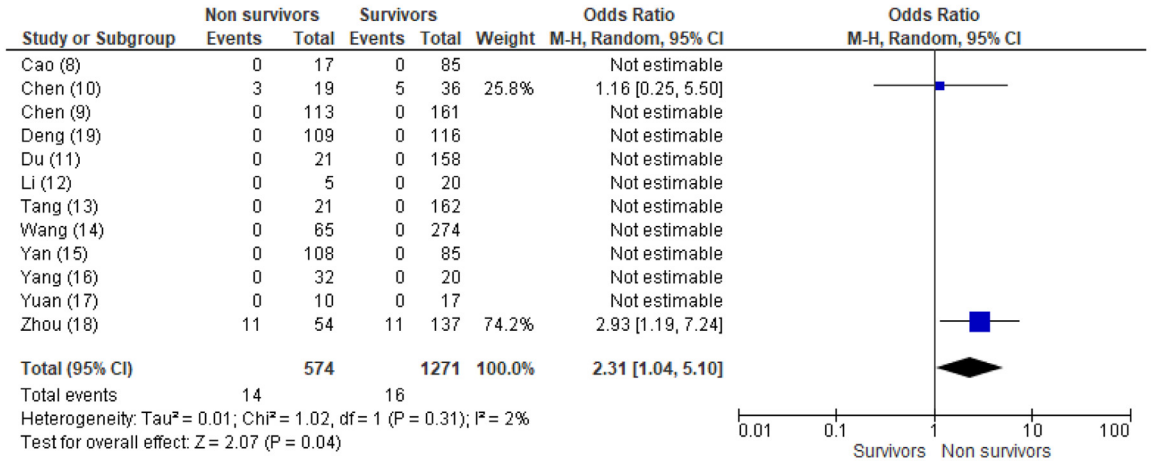
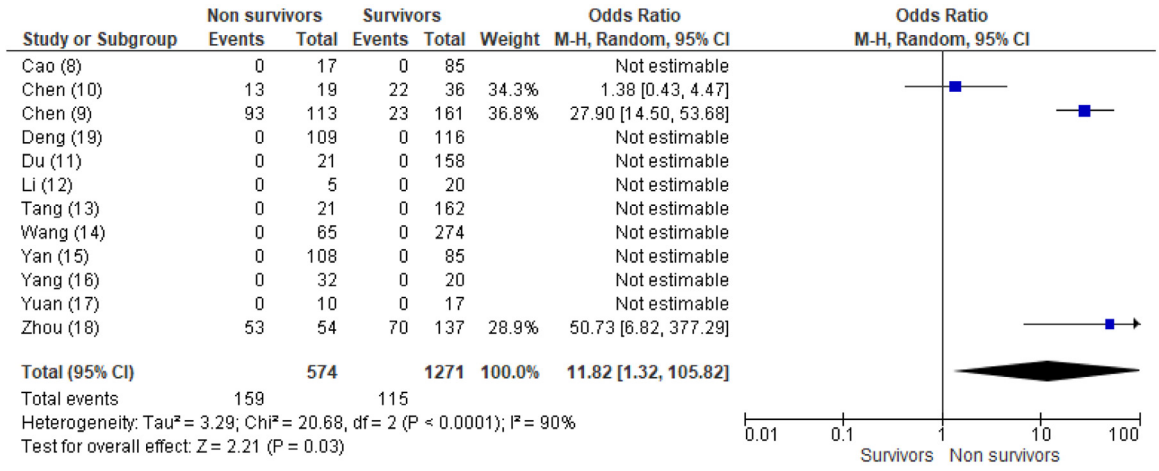
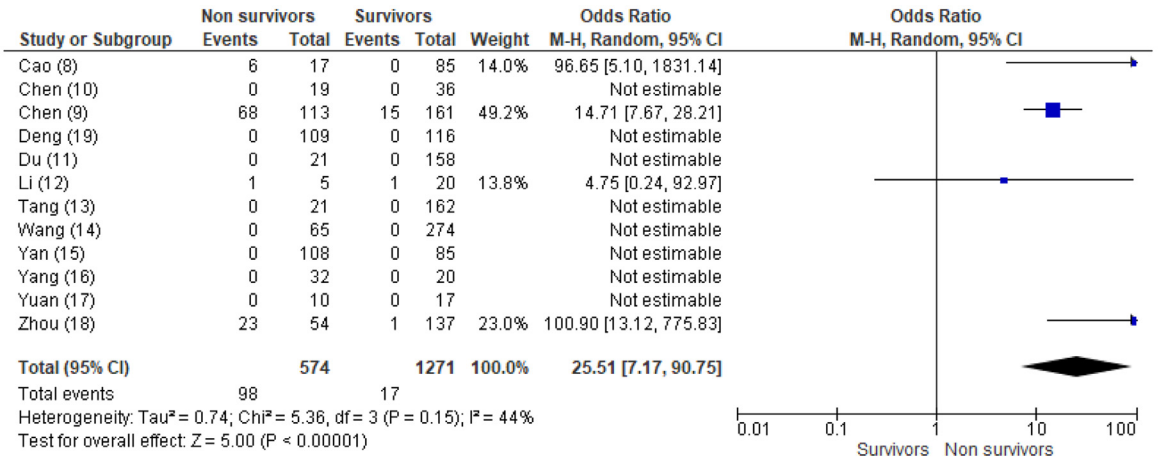


Figure 2. Continued

Elevated LDH as a predictor of mortality



Elevated cardiac troponin I (CTnI) as a predictor of mortality



Elevated brain natriuretic peptide (BNP) or proBNP as a predictor of mortality

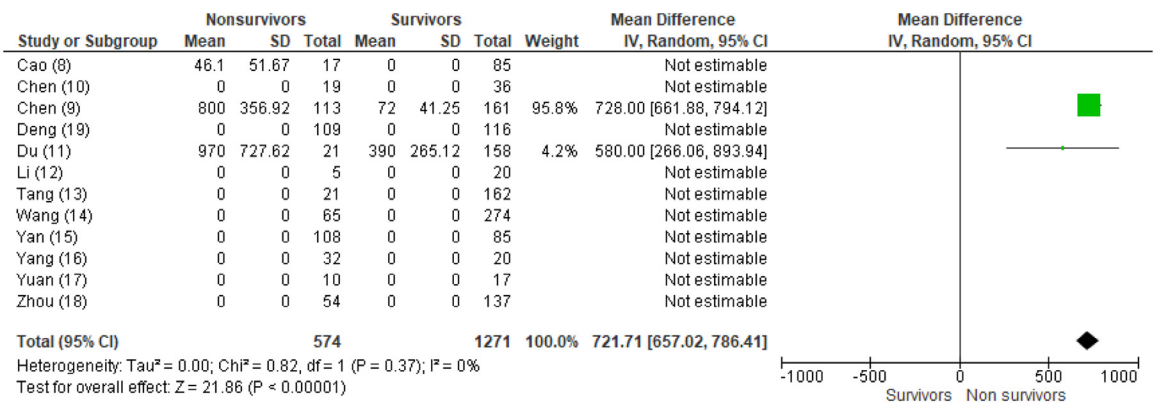
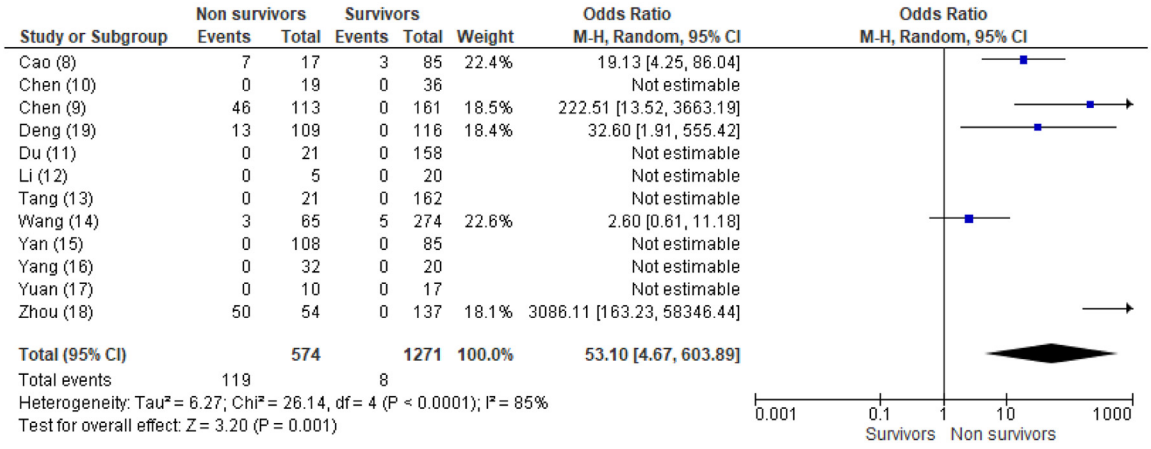
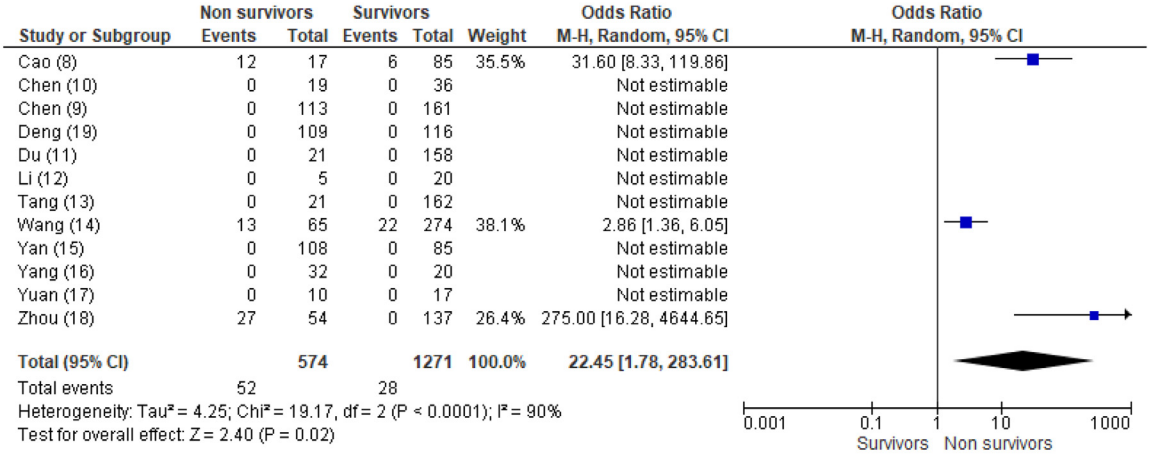


Figure 2. Continued

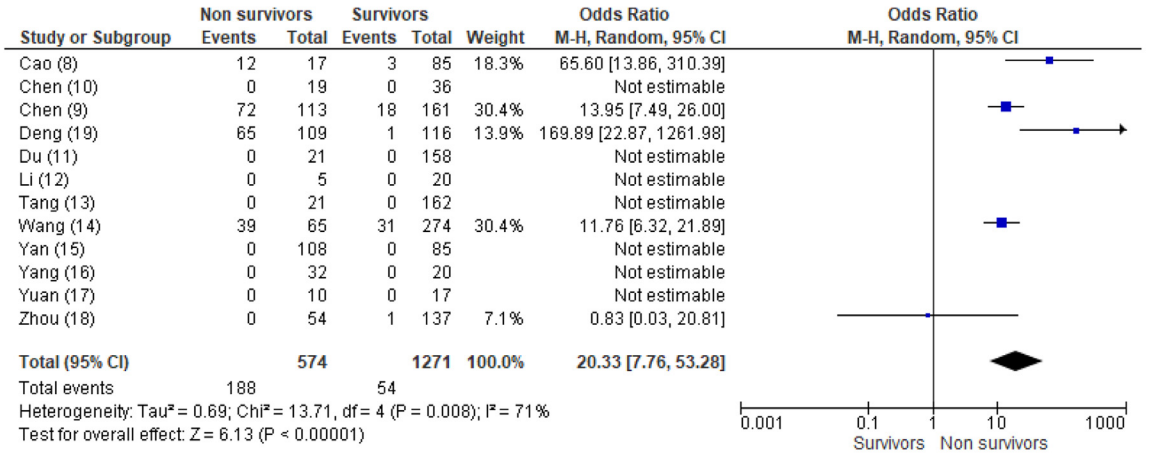
Development of shock as a predictor of mortality



Development of arrhythmia as a predictor of mortality



Development of acute myocardial injury as a predictor of mortality



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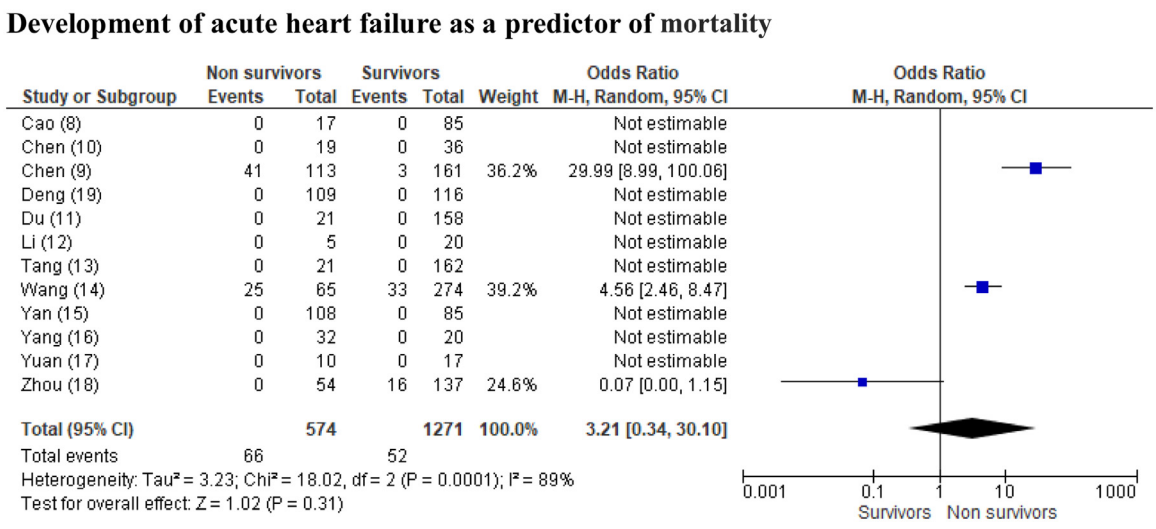


Figure 2. Continued

Discussion

Our meta-analysis of comparative studies in hospitalized patients with COVID-19 shows that patients who died had a significant involvement of cardiovascular system. Non-survivors had preponderance of cardiovascular disease risk factors - male gender, older than 50 years, a history of dyslipidemia, smoking, hypertension, and diabetes. They also had a significant past history of a preexisting cardiovascular condition, including chronic heart failure and cerebrovascular accident. At presentation, they had a high prevalence of hypoxemia, higher heart rate, dyspnea, and fatigue suggesting cardiovascular system instability. While in the hospital, non-survives had a significant increase in serum level of laboratory biomarkers such as cardiac troponin I, LDH, BNP or proBNP, and CK, suggesting new myocardial injury or worsening of a pre-existing heart disease. Not surprisingly, non-survivors had clinical evidence of cardiovascular system instability as manifested by the presence of shock, cardiac arrhythmias, and acute respiratory distress.

In a large series of hospitalized patients with COVID-19 in New York City, Lala et al[5] showed that elevated troponin I level was significantly associated with coronary artery diseases, atrial fibrillation, and heart failure. These authors suggested a 3-fold increase in the mortality rate with troponin-I elevation to 3-times above the upper reference limit.

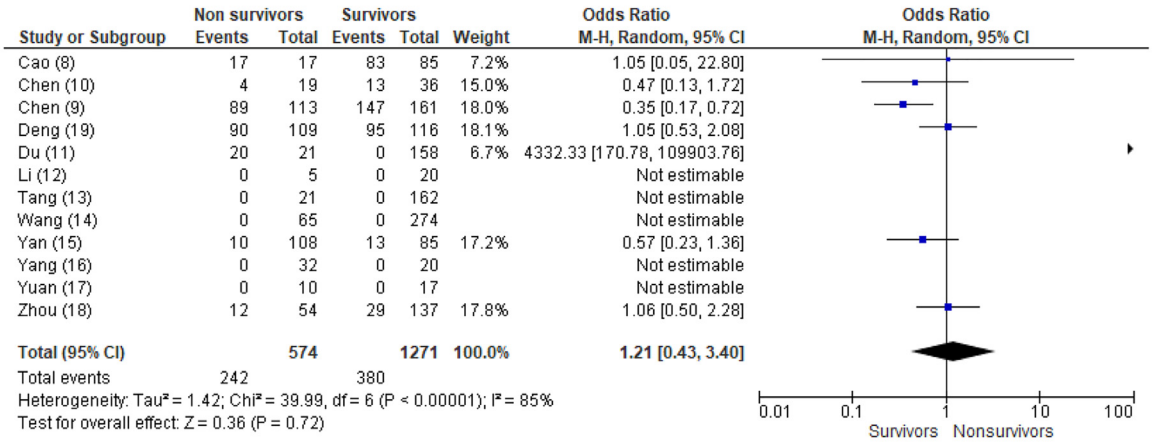
In an attempt to develop a risk prediction model, Liang et al[20] used the retrospective data of the National Health Commission of China to identify independent predictors of mortality in COVID-19 patients. The validated results showed that an abnormality on chest radiography, older age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, a history of cancer, neutrophil-to-lymphocyte ratio, LDH, and direct bilirubin remained independent predictors of death.

Chen et al.[4] compared cardiovascular system variables in a small number of severely sick (39 cases) and critically sick (15 cases) COVID-19 patients, and found that diabetes, significant leukocytosis, elevated level of inflammatory elements (interleukin-6, C-reactive protein, erythrocyte sedimentation rate, D-dimer, and procalcitonin), elevated markers of myocardial injury (CK-MB, troponin-I, myoglobin, and proBNP), hypotension and tachycardia at admission, atrioventricular block, pericardial effusion, and right heart block were more prevalent in critically-ill patients.

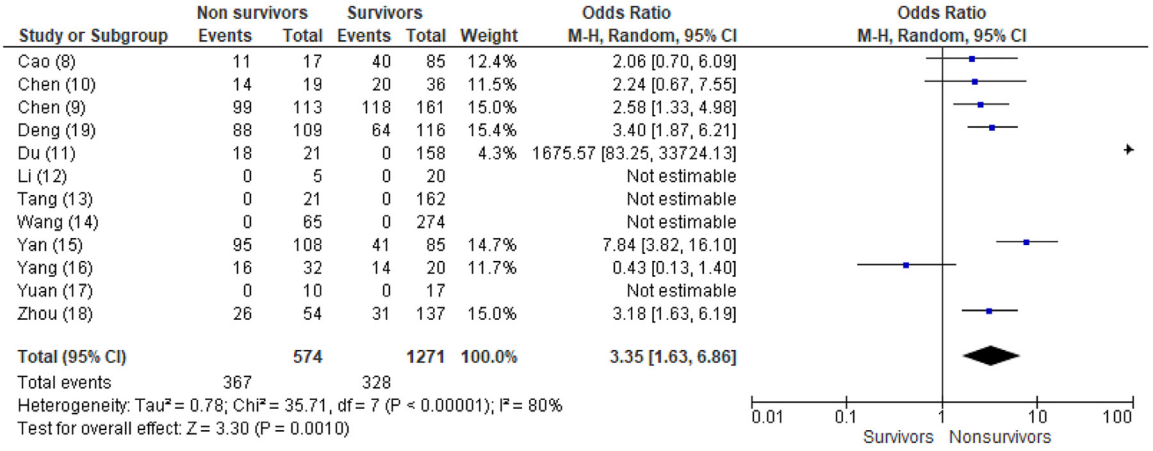
Our study showed that cardiovascular disease risk factors, its manifestations, and related laboratory biomarkers were powerful predictors of death in COVID-19 patients. Our meta-analysis including several large and small studies confirmed the hypothesis that cardiovascular system instability predicts mortality in COVID-19 patients. Unfortunately, the included studies did not provide sufficient data on the type of cardiac arrhythmia. Also, due to the limited number of events for each subgroup analysis, some variables did not reach a statistical significance of which an acute heart failure is a major one. Although studying the efficacy of various therapeutic modalities was beyond the scope of our meta-analysis, non-survivors had a tendency to receive more aggressive treatment such as mechanical ventilation and corticosteroid administration. However, none of these therapeutic modalities seemed to improve the survival in patients with COVID-19.

In conclusion, this meta-analysis of comparative studies highlights the pivotal role of cardiovascular system instability in predicting mortality in patients with COVID-19. A careful consideration of history of cardiovascular disease and its risk factors, attention to signs and symptoms at presentation and during hospitalization, and related laboratory parameters should alert the clinicians toward the high-risk patient.

Antiviral treatment in non-survivors vs. survivors.



Corticosteroid treatment in non-survivors and survivors.



Antibiotic use in non-survivors and survivors.

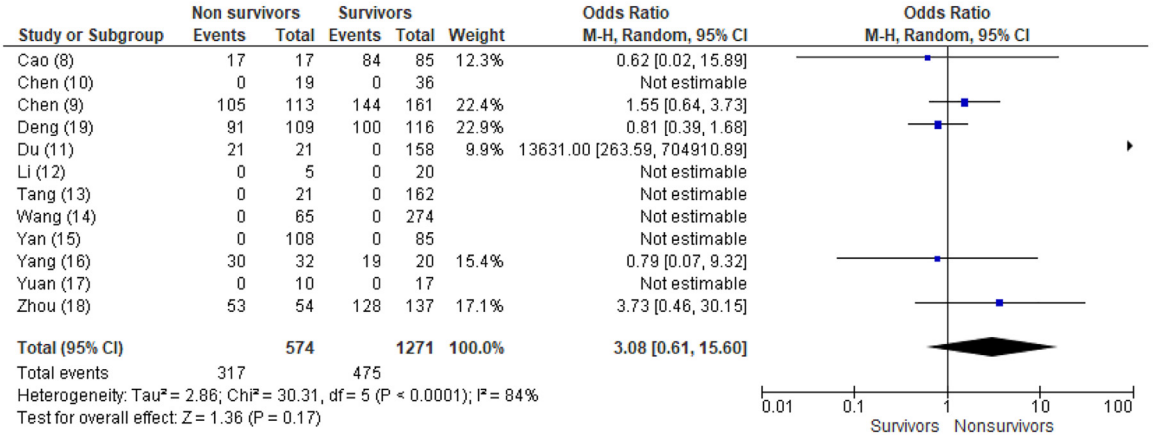


Figure 3. Forest plots demonstrating the effect of major therapeutic options given to the patients with COVID-19. The meta-analysis estimated odds ratio and 95% confidence interval for 4 major treatment modalities. Mantel-Haenszel statistical method using a random-effects model was utilized for all analyses.

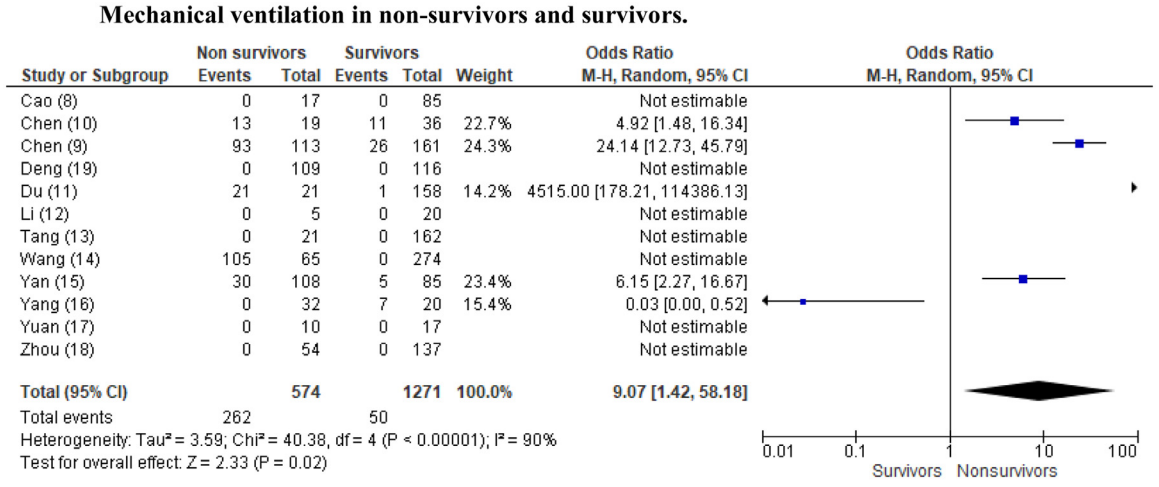


Figure 3. Continued

Conflict of Interests Statement

All authors have no conflict of interests to disclose.

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