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.

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Effect of heart failure on the outcome of COVID-19 — A meta analysis and systematic review

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ABSTRACT

Background: Several comorbidities have been associated with an increased risk of severity and mortality in coronavirus disease 2019 (COVID-19), including hypertension, diabetes, cerebrovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.
Purpose: In this systematic review and meta-analysis, we attempted to investigate the association between heart failure (HF) and poor outcome in patients with COVID-19.
Methods: We performed a systematic literature search from PubMed, EuropePMC, SCOPUS, Cochrane Central Database, and medRxiv with the search terms, "Heart failure" and "COVID-19". The outcome of interest was mortality and poor prognosis (defined by incidence of severe COVID-19 infection, admission to ICU, and use of ventilator) in patients with preexisting heart failure with coronavirus disease.
Results: We identified 204 potential articles from our search, and 22 duplicates were removed. After screening of the titles and abstracts of the remaining 182 articles we identified 92 potentially relevant articles. We excluded 74 studies due to the following reasons: four studies were systematic reviews, two studies were meta-analyses, three articles were literature reviews, and 65 articles did not report on the outcome of interest. Finally, we included the remaining 18 studies in our qualitative synthesis and meta-analysis. There were 21,640 patients from 18 studies. HF was associated with hospitalization in COVID19 HR was 2.37 [1.48, 3.79; $p < 0.001$], high heterogeneity [I^2, 82%; $p < 0.001$]. HF was associated with a poor outcome demonstrated by an OR of 2.86 [2.07; 3.95; $p < 0.001$] high heterogeneity [I^2, 80%; $p < 0.001$]. Patient with preexisting HF was associated with higher mortality OR of 3.46 [2.52, 4.75; $p < 0.001$] moderately high heterogeneity [I^2, 77%; $p < 0.001$].
Conclusion: Patients with heart failure are at increased risk for hospitalization, poor outcome, and death from COVID-19. A significant difference in mortality between patients with and without heart failure was observed, patients with heart failure having a higher mortality.

1. Introduction

The coronavirus disease 2019 (COVID-19) has caused significant morbidity and mortality to date, with the number of new cases and deaths continue to rise at an alarming rate [1]. Although most cases of COVID-19 are asymptomatic or mild in severity, a minority of patients experience more severe symptoms of COVID-19 along with its complications, such as acute respiratory distress syndrome (ARDS), coagulopathy, multiple organ failure (MOF), and death. A number of comorbidities have been associated with an increased risk of severity and mortality in COVID-19 patients, including hypertension, diabetes, cerebrovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease [2-6]. Individuals with preexisting cardiovascular diseases have been shown to have poor outcomes with COVID 19 [7,8]. Study from Chinese center of disease control on 72,314 cases reported a case fatality rate of 10.5% for patients with preexisting cardiovascular disease, but no specific data on mortality on heart failure [9].

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Due to looming possibility of poor drug compliance and other complications related to disruption in medical services, the number of patients with new or decompensated heart failure may increase [10].

Currently, the plausible mechanisms for SARS-CoV-2 (severe acute respiratory syndrome 2) to infect human cells include binding to the angiotensin-converting enzyme 2 (ACE2) receptor and inducing hyperinflammation or cytokine storm. A high expression of ACE2 receptor is commonly found in patients with heart failure [7,8]. In this systematic review and meta-analysis, we wanted to investigate the association between heart failure with poor outcome in patients with COVID-19.

2. Methods

2.1. Search and selection criteria

We performed a systematic search of the literature on PubMed, EuropePMC, SCOPUS, Cochrane Central Database, and medRxiv for preprint studies with the search terms, "Heart Failure" and "COVID-19". After the removal of duplicates, the abstracts were screened by two independent authors (EY and RP). Irrelevant articles were excluded. The inclusion criteria for this study were studies that studied patients with preexisting HF comorbidity with COVID-19 infection. The outcome of interest was mortality and poor prognosis (defined by incidence of severe COVID-19 infection, admission to ICU, and use of ventilator) in patients with preexisting heart failure with coronavirus disease. This systematic search conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.2. Data extraction

Data extraction was carried out by EY, RP, MAL, and IH using a standardized form containing the following details: author name, year of publication, study design, and sample size.

2.3. Statistical analysis

This meta-analysis was conducted using Review Manager (RevMan) v5.3 (Cochrane Collaboration) software. Hazard ratio (HR) and odds ratio (OR) with 95% confidence interval (CI) were used as pooled measures for dichotomous data. Heterogeneity was assessed using Inconsistency Index (I^2) ranging from 0 to 100%. Statistically significant heterogeneity was defined as an I^2 value above 50% or $p < 0.05$. The Mantel–Haenszel method was used to determine OR, and the generic inverse variance method was used to determine HR. Random effects models were implemented for analyses with significant heterogeneity. Sensitivity analyses were done to test statistical robustness of pooled results, to see whether there is significant change in pooled results by exclusion of studies, and to single out studies with high heterogeneity. Meta-analysis of prevalence was done by pooling of events of HF per total patients using the meta-analysis of proportion. Small-study effects and the risk of publication bias were assessed qualitatively using funnel plot analysis and quantitatively using regression-based Egger's test.

3. Results

We extracted 204 potential articles from our search, and 22 duplicates were removed. After the titles and abstracts of the remaining 182 articles were screened we obtained 92 potentially relevant articles. We excluded 74 studies due to the following reasons: four studies were systematic reviews, two studies were meta-analyses, three articles were literature reviews, and 65 articles did not report on the outcome of interest. Finally, we included the remaining 18 studies in our qualitative synthesis and meta-analysis. There were 21,640 patients from 18 studies. The majority of study subjects are males ranging from 54.7% to 85%, with only two studies reported male subjects being minorities, (45.1% on study by Caraballo C et al. and 44.3% on study by Ji W et al.) (Table 1, Fig. 1).

3.1. Risk of hospitalization in patients with preexisting heart failure

Three studies reported a statistically significant difference in the risk of hospitalization in COVID19 patients with preexisting heart failure. The pooled HR was 2.37 [1.48, 3.79; $p < 0.001$], with moderately high heterogeneity between studies [I^2, 82%; $p < 0.001$]. Sensitivity analysis was performed, excluding the study by Petrilli et al., yielded HR 1.88 [1.36, 2.62; $p < 0.001$] with moderate heterogeneity between studies [I^2, 65%; $p = 0.09$] (Fig. 2).

3.2. Heart failure and poor outcome

Statistically significant differences in composite poor outcomes were reported in 15 studies. HF was associated with a poor outcome demonstrated by an OR of 2.86 [2.07; 3.95; $p < 0.001$] with high heterogeneity between studies [I^2, 80%; $p < 0.001$]. Sensitivity analyses were performed. Exclusion of the studies by Argenziano et al., Caraballo et al., Ji W et al., Paranjpe et al., Reilev et al., and Yanover et al. yielded an OR of 2.56 [2.17, 3.03, $p < 0.001$] with low heterogeneity between studies [I^2, 0%; $p = 0.55$] (Fig. 3).

3.3. Pooled HR of mortality in patients with coronavirus disease 2019 with preexisting heart failure

Seven studies reported a statistically significant difference in mortality between patients with COVID-19 with and without preexisting HF. The pooled HR was 1.70 [1.44, 2.02; $p < 0.001$] with moderate heterogeneity between studies [I^2, 59%; $p = 0.02$]. Sensitivity analysis was performed, excluding the study by Cummings which yielded an HR of 1.70 [1.57, 1.83; $p < 0.001$] with a low heterogeneity between studies [I^2, 9%; $p = 0.36$] (Fig. 4).

3.4. Comparison of mortality in patients with coronavirus disease 2019 accompanied with preexisting heart failure and without heart failure

Fourteen studies reported a statistically significant difference in mortality between patients with COVID-19 accompanied with and without preexisting heart failure. Pooled events yielded an OR of 3.46 [2.52, 4.75; $p < 0.001$] with moderately high heterogeneity between studies [I^2, 77%; $p < 0.001$]. Sensitivity analyses were performed, excluding the studies by Caraballo et al., Ji W et al., Rossi et al., and Yanover et al. which yielded OR of 2.77 [2.40, 3.20; $p < 0.001$] with low heterogeneity between studies [I^2, 0%; $p = 0.73$] (Fig. 5).

3.5. Incidence of new-onset heart failure in patients with coronavirus disease 2019

Three studies reported a statistically significant difference in incidence of new-onset HF in hospitalized patients with COVID-19. Pooled results yielded an OR of 11.67 [6.96, 19.56; $p < 0.001$] with moderate heterogeneity between studies [I^2, 44%; p0.17]. Sensitivity analysis was performed, excluding the study by Chen et al. which yielded an OR of 8.24 [4.59, 14.78; $p < 0.001$] with low heterogeneity between studies [I^2, 0%; $p < 0.96$] (Fig. 6).

3.6. Meta-analysis of prevalence

Sixteen studies were available for meta-analysis to determine the pooled prevalence of heart failure among patients with COVID-19; the meta-analysis revealed a pooled prevalence of heart failure of 9% (7–12%) (Fig. 7).

Table 1
Studies included in Meta Analysis

Author, year	Study design	Outcome of interest	Samples	Outcome vs no outcome	Male	Overall age	HF	Outcome/total HF vs No HF	HF outcome vs no outcome	New Onset HF	HR
Inciardi RM 2020	Observational, prospective cohort	Mortality	53	19 vs 34	85%	68 ± 12	21/53	12/21 vs 7/32	12/19 vs 9/26	N/A	N/A
Chen T 2020	Retrospective	Mortality	274	113 vs 161	62%	62.0 (44.0–70.0)	1/274	1/1 vs 112/273	1/113 vs 0/161	41/83 vs 3/94	N/A
Petrilli 2020	Retrospective	Critical illness	2729	990 vs 1739	61.3%	63 (51–74)	349/2729	189/349 vs 801/2380	189/990 vs 160/1739	N/A	HR mortality 1.77 (1.43 to 2.20)
	Retrospective	Hospitalization	2729	N/A	61.3%	63–51-74	N/A	N/A	N/A	N/A	4.56 [2.59, 8.04]
Yin W 2020	Retrospective	Mortality	112	52 vs 60	68.7%	66.00 (56.00–76.00)	2(1.8%)	2/2 vs 50/110	2/52 vs 0/60	N/A	N/A
Zhou F	Retrospective	Mortality	191	54 vs 137	62%	56·0 (46·0–67·0)	44 (23%)	N/A	N/A	28/54 vs 16/137	N/A
Baker KF 2020	Retrospective	mortality	316	81 vs 235	54.7	75 (60–83)	11	20/45 vs 61/271	20/81 vs 23/210	N/A	OR 2.67 [1.36–5.19], $p = .004$
Cummings MJ	Retrospective	Mortality	257	86/257 (33%)	66%	62 (51–72)	49/257 (CVD)	N/A	N/A	N/A	Univariate 0.62 (0.33–1.17) Multivariate 0.69 (0.34–1.42)
Caraballo C	Retrospective	Mortality	206 COVID positive	34 vs 172	45.1%	78 (65–87)	36/206	3/36 vs 31/136	3/34 vs 33/172	N/A	???
Heng GE	Retrospective	Mortality	51	12 vs 39	72.5%	70 (58–79)	4/51	4/4 vs 35/47	0/20 vs 4/31	N/A	N/A
		Severity	51	20 vs 31	72.5%	70 (58–79)	4/51		1/20 vs 3/31	N/A	N/A
Garibaldi BT 2020	Retrospective	Mortality	747	113 vs 634	53.2%	63 (49, 75)	127 (15.3%)	33/127 vs 80/634	33/113 vs 67/634	N/A	N/A
Ebinger JE	Retrospective	Severity (ICU care)	442	77 vs 365	58%	52.7 ± 19.7	49 (11%) (prior MI or HF)	18/49 vs 59/393	18/ 77 vs 31/365	N/A	Univariate 1.72 (0.96,3.09) 0.07 Multivariate 0.56 (0.27,1.18) 0.13
Liao X	Retrospective	Mortality/ventilator support	81	10 vs 71	63%	50.0 (39.0–65.0)	4 (4.9%	1/4 vs 9/77	1/10 vs 3/71	N/A	N/A
Ji W	Retrospective	Severity	5172	293 vs 4879	44.3%	42 (18–100)	217 (4.2)	44/217 vs 249/4955	44/293 vs 173/4879	N/A	(Odds ratio range 1.562–1.730)
Paranjpe I	Retrospective	Mortality	1078	310 vs 768	58.1%	Dead 75 (64–85) Alive 59 (45–72)	117/1078	64/117 vs 246/961	64/310 vs 53/768	N/A	N/A
Rossi PG	Retrospective	Hospitalization	2653	217 vs	61.9%	51–81	96/1075	N/A	N/A	N/A	HR 1.6, 95% CI 1.2 to 2.1
		Mortality	1292	217 vs 1075	800 (61.9%)	51–81	139/1292	43/137 vs 174/2516	43/217 vs 96/1075	N/A	HR 2.3, 95% CI 1.6 to 3.2
Yanover C	Retrospective	Critical care/death	4353	173 vs 4180	56.5%	35 [22–54]	30/4353	11/30 vs 162/4323	11/173 vs 19/4180	N/A	N/A
Argenziano MG	Retrospective	ICU Care (SEVERE COVID)	850	236 vs 614	59.6%	63.0 (50.0–75.0)	91/850	N/A	24/236 vs 67/614	18/236 vs 6/614	N/A
Reilev M	Retrospective	Hospitalization	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.2 (1.7–2.9) (age adjusted)
	Retrospective	Mortality	2090	524 vs 1566	57%	82 (75–89)	218/2090	98/204 vs 426/1886	98/524 vs 120/2090	N/A	1.7 (1.3–2.2) (age adjusted)

3.7. Publication bias

Regression-based Egger's test showed no indication of small-study effects for Heart Failure and Poor Outcome ($p = 0.852$), Pooled HR of mortality in patients with coronavirus disease 2019 with preexisting heart failure ($p = 0.640$), and Comparison of mortality in patients with coronavirus disease 2019 accompanied with preexisting heart failure and without heart failure ($p = 0.555$). There was an indication of small-study effects for Risk of hospitalization in patients with preexisting heart failure ($p = 0.035$) and Incidence of new-onset heart failure ($p < 0.001$). The number of included studies were <10 for risk of hospitalization in patients with preexisting heart failure, Pooled HR of mortality in patients with coronavirus disease 2019 with preexisting heart failure, and incidence new onset heart failure, thus, the results were less reliable. Analysis using funnel plot generated asymmetrical result for Heart Failure and Poor Outcome (Fig. 8A), and Comparison of mortality in patients with coronavirus disease 2019 accompanied with preexisting heart failure and without heart failure (Fig. 8B), with Fig. 8A showing somewhat less asymmetry compared to Fig. 8B. Based on Cochrane collaboration recommendation we only performed funnel plot analysis in meta-analysis involving more than 10 studies.

4. Discussion

In this meta-analysis, we observed an association between HF and poor outcome in patients with COVID-19, a higher risk of death and

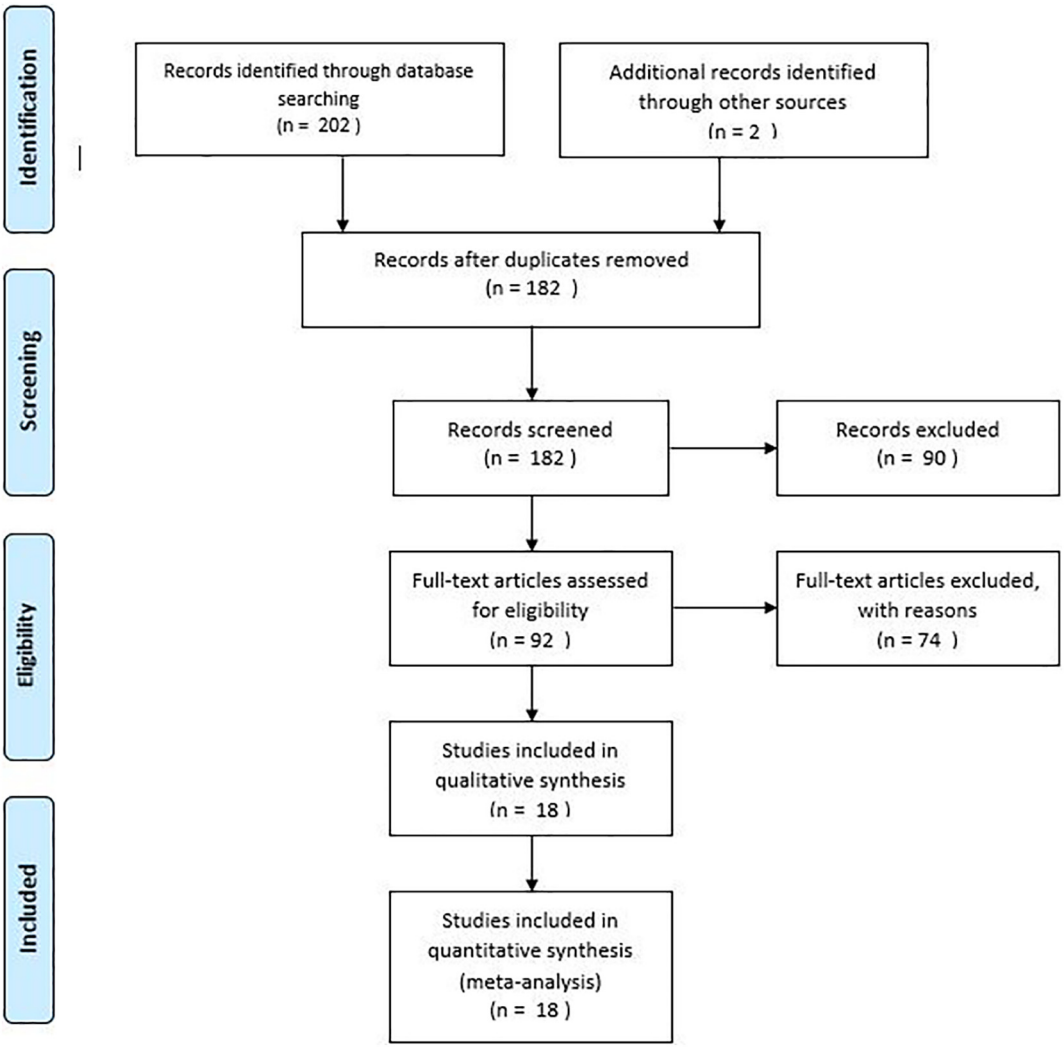

Fig. 1. PRISMA diagram.

hospitalization in those with preexisting HF, and higher mortality in those with preexisting HF compared to patients without HF.

As with other types of pneumonia, preexisting cardiovascular diseases, including HF, are risk factors for poor prognosis during and after the course of pneumonia [11]. The effect of an infective organism on the myocardium can cause non-ischemic cardiac injury. The systemic inflammatory response, which is particularly excessively elevated in COVID-19, can also result in kidney injury and impair sodium and water metabolism, which may precipitate the worsening of HF [12].

Recent studies on the role of ACE2 in COVID-19 infection have reported that ACE2 levels are 50% higher in male patients with HF [13-15]. This finding explains the higher risk of poor prognosis, hospitalization, and death in this population in the event of occurrence of COVID-19. In this meta-analysis, the majority of the studies had higher number of male patients than female patients.

In patients with coexisting HF and diabetes, who are in a pro-inflammatory state, the membrane-bound ACE2 protein can be cleaved by ADAM17, resulting in the release of ACE2 into the interstitium and blood circulation [16]. This inflammatory response, which occurs in COVID-19 as an elevated immune response [17,18] might also explain the increase in mortality in patients with COVID-19 accompanied with HF. The excessive inflammatory response and oxidative stress in these patients predispose them to a more severe clinical course of COVID-19 [19]. This phenomenon is particularly significant in patients with

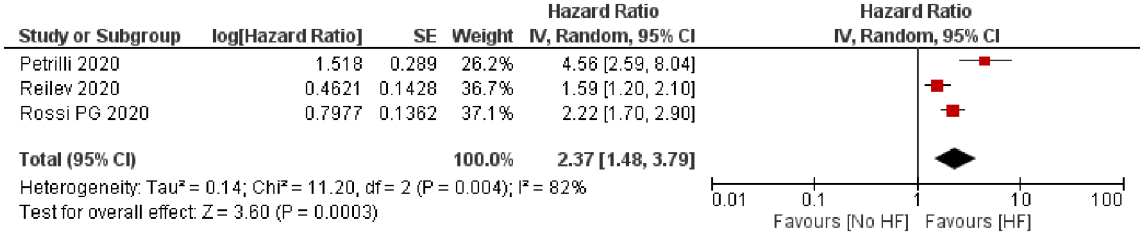

Fig. 2. Meta analysis, risk of hospitalization in patients with pre-existing heart failure.

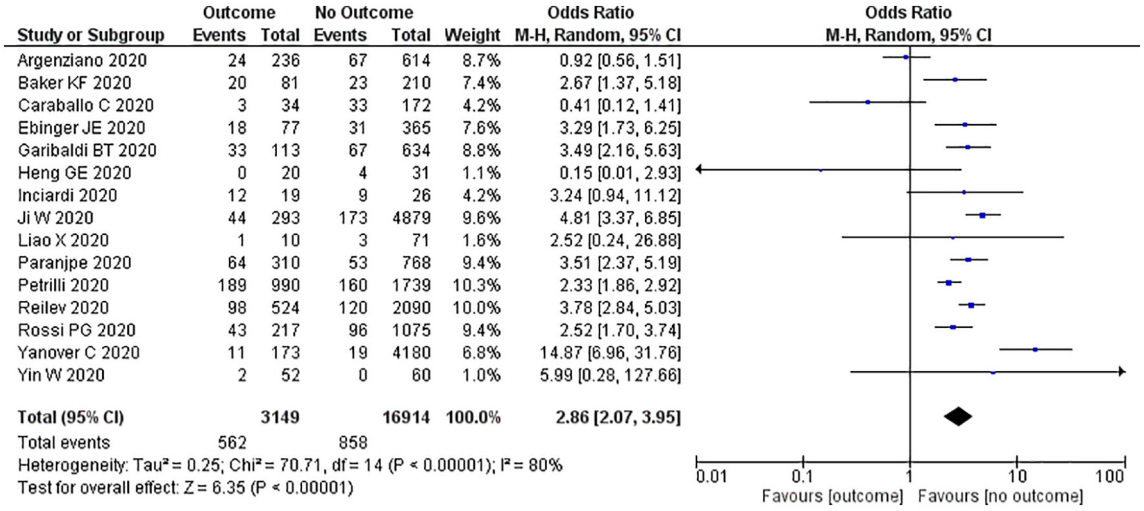

Fig. 3. Meta analysis, heart failure and poor outcome.

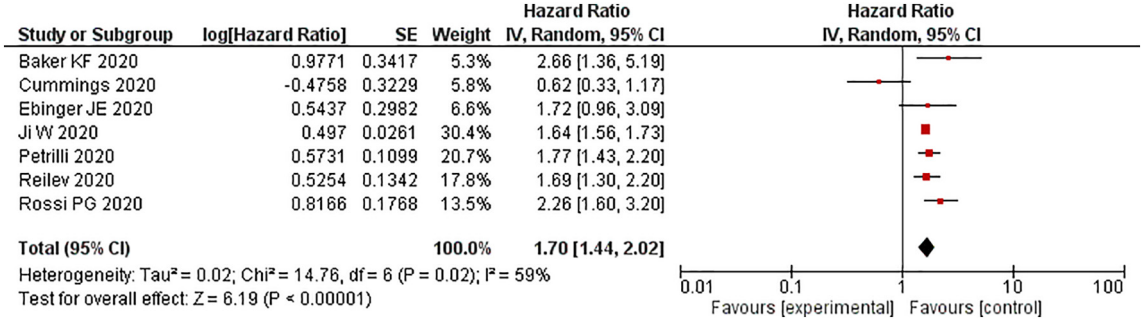

Fig. 4. Meta analysis, pooled HR of mortality in COVID19 patients with pre-existing heart failure.

preexisting HF since these patients suffer from decreased circulatory and physiological reserves. Older patients with HF commonly suffer from multiple comorbidities, deterioration in function of multiple organ systems, and functional decline [20,21].

ACE2 is an enzyme involved in the RAAS pathway; however, it differs from ACE in not being capable of converting angiotensin I into angiotensin II. Furthermore, as opposed to the vasoconstrictor property of angiotensin type 1 receptors, ACE2 via the ACE-2 receptors cleaves angiotensin II into angiotensin 1–7, which has vasodilatory properties [22].

Based on these explanations, it is easy for us to conclude regarding the dangers of upregulation of ACE2 as in patients being treated with renin-angiotensin system blockers (RASB). One study has even proposed ceasing administration of RASB in patients with COVID-19 on

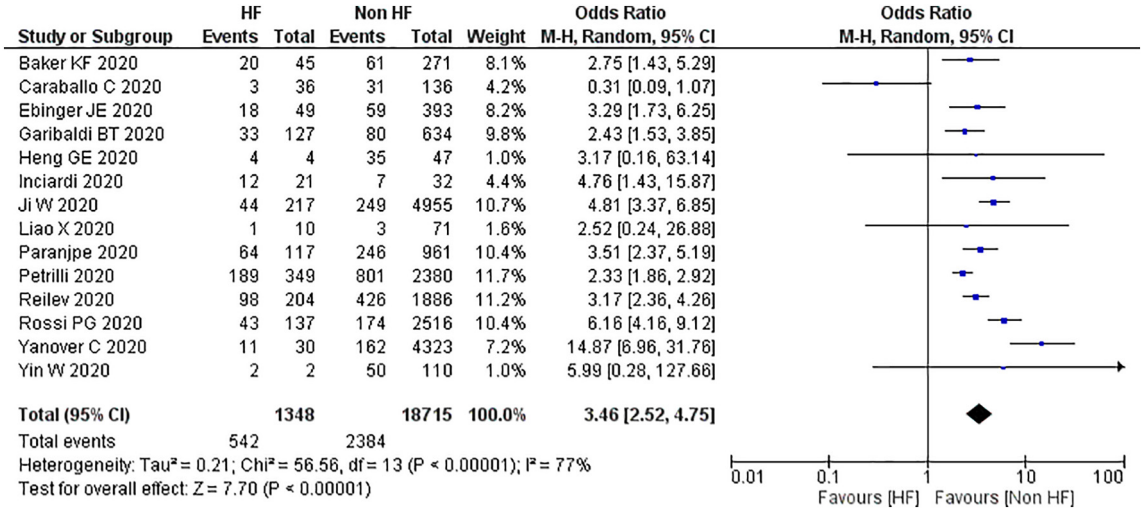

Fig. 5. Meta analysis, mortality in COVID19 patients with pre-existing heart failure compared to nonheart failure patients.

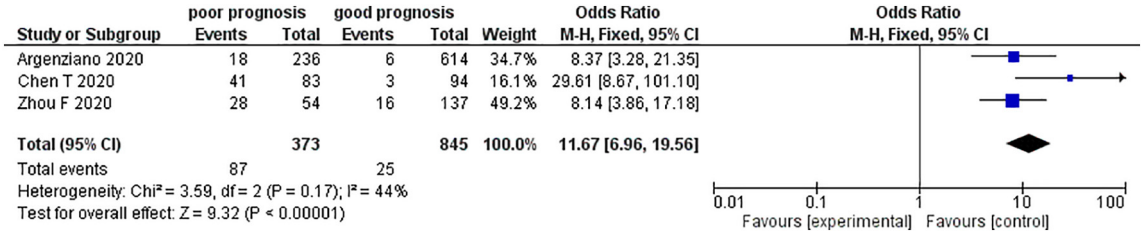

Fig. 6. Meta analysis, incidence of new-onset heart failure in COVID19 patients.

these drugs [23]. However, this does not seem to be the case, and several other authors have questioned this hypothesis [24-27]. The rationale for this rebuttal is based upon several in vitro studies, which revealed that upon entry into alveolar cells using membrane-bound ACE-2 receptors, SARS-CoV-2 downregulates the expression and causes internalization of ACE2 receptors. The result of this process is a decrease in angiotensin-II to angiotensin (1–7) conversion and an increase in the availability of angiotensin II to bind to the AT1 receptor. This induces cellular inflammation, oxidative stress, vasoconstriction, fibrosis, and aldosterone activation, which may eventually lead to lung injury [28-32]. The use of RASB may serve as a protective measure against lung injury by the inhibition of angiotensin II synthesis using ACEIs and blockade of AT1R by ARBs. This would result in a skew of the RAAS towards angiotensin (1–7) and its subsequent interaction with Mas-receptors, which may minimize the risk of lung injury [29,33].

The result of this meta-analysis is similar to that of previous studies in which patients with preexisting heart HF demonstrated an elevated risk of poor outcome, hospitalization, and death [31–49] [34] [35-41] [42-50] [51,52].

Compared to other diseases, based on our pooled results, patients with HF suffering from SARS-CoV-2 infection have a threefold increased risk of in-hospital mortality compared to patients with HF who develop influenza, OR 3.46 [2.52, 4.75; $p < 0.001$] vs. OR 1.15 [1.03, 1.30; $p = 0.02$] and OR 1.66 [1.44–1.91; $p < 0.001$] [53,54]. However, when compared to patients infected with Middle East respiratory syndrome coronavirus (MERS-CoV), patients with preexisting HF who developed COVID-19 had a lower risk of mortality [OR 3.46; 2.52, 4.75; $p < 0.001$ vs OR, 12.981; 1.324, 127.313; $p = 0.025$] [55].

Studies have shown a poorer prognosis in patients with HF who develop influenza [53,54]. As a result of the decreased physiological reserve, influenza virus infection in patients with HF is associated with a severe course and significant hemodynamic compromise, which often requires cardiac support [56]. Influenza vaccination in these patients is associated with a reduced risk of all-cause and cardiovascular death, furthermore receiving >1 influenza vaccine is associated with 18% reduction in both all-cause and cardiovascular death (all-cause death: 0.82; 95% CI,0.81–0.84; $p < 0.001$; cardiovascular death: 0.82; 95% CI, 0.81–0.84; $p < 0.001$), in the event of influenza infection, patients with heart failure may fail to cope with the increased metabolic demand which is caused by the infection itself, as a result, decompensation or exacerbation in heart failure symptoms may occur [57]. Patients with HF are currently classified as a high-priority group to be vaccinated with

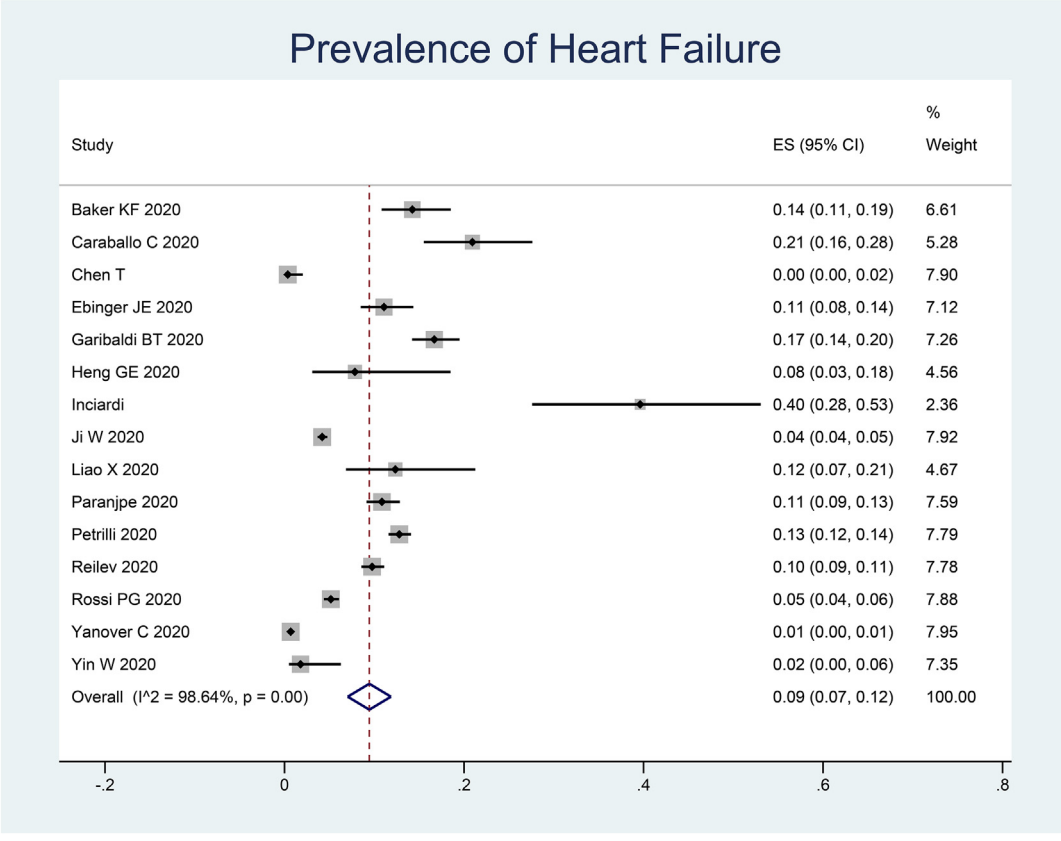

Fig. 7. Meta prevalence of heart failure patients in study population.

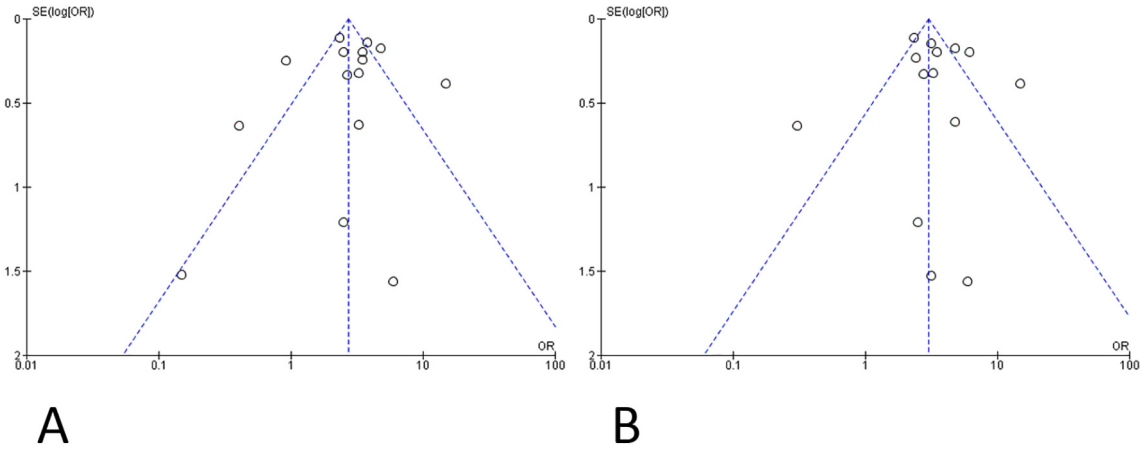

Fig. 8. A. Funnel plot analysis, heart failure and poor outcome. B. Funnel plot analysis, comparison of mortality in patients with coronavirus disease 2019 accompanied with preexisting heart failure and without heart failure.

the influenza vaccine [58]. Based on these findings, once an effective vaccine for SARS-CoV-2 infection becomes available, patients with HF should be prioritized to be vaccinated even in case of COVID-19.

We observed some limitations of this meta-analysis, such as the use of preprint studies included in this meta-analysis. Additionally, several studies have been conducted in the same cities/regions, posing a risk of subject overlap. Data regarding the difference between new-onset and worsening of HF in patients in the studies was rarely available. Data regarding staging of HF was also rarely found. Additionally, in patients with HF suffering from a severe course of COVID-19 infection, data regarding the use of vasopressors and inotropic agents as well as the incidence of cardiogenic shock was lacking.

5. Conclusion

In conclusion, patients with HF are at increased risk for poor outcomes such as hospitalization, and death from COVID-19. A significant difference in mortality between patients with and without HF was observed, those with HF showing higher mortality rates. These findings probably stem from the reduced physiological reserves in patients with HF. Mortality of patients with HF accompanied with SARS-CoV-2 infection is higher than that of patients with influenza, but lower than that of patients with MERS-CoV. Thus, if SARS-CoV-2 vaccine becomes available, patients with HF should be prioritized to be vaccinated.

CRediT authorship contribution statement

Emir Yonas: Conceptualization, Formal analysis, Methodology, Writing - original draft, Project administration. **Idrus Alwi:** Writing - review & editing. **Raymond Pranata:** Writing - review & editing, Formal analysis, Methodology. **Ian Huang:** Writing - review & editing. **Michael Anthonius Lim:** Writing - review & editing. **Eddy Jose Gutierrez:** Writing - review & editing. **Muhammad Yamin:** Writing - review & editing. **Bambang Budi Siswanto:** Writing - review & editing. **Salim S. Virani:** Conceptualization, Writing - review & editing.

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Declaration of competing interest

The authors of this manuscript has no conflict of interest.

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