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REVIEW ARTICLES

Effects of underlying heart failure on outcomes of COVID-19; a systematic review and meta-analysis

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Background: The risk for worse outcomes of COVID-19 (Coronavirus 2019 disease) is higher in patients with cardiac conditions. In this study, we aim to investigate the risks of COVID-19-induced conditions in cases with underlying heart failure.

Methods: We systematically searched PubMed, Scopus, Ovid, ProQuest, Web of Science, and the Cochrane library, to collect the English language articles that investigated patients with underlying heart failure who get infected by COVID-19. The second version of comprehensive meta-analysis (CMA.2) software was used to conduct the meta-analysis.

Results: From 5997 publications, our eligibility criteria were met by 27 studies. Overall, outcomes investigated in all studies include but are not limited to mortality rate, length of hospitalization, need for Intensive care unit (ICU) admission, need for mechanical ventilation, and major cardiovascular conditions. Regarding mortality heart failure patients were more susceptible to death (OR:2.570, 95%CI: 2.085 to 3.169; p-value:<0.001). Also in heart failure patients, the risk of mechanical ventilation was higher (OR:1.707, 95%CI: 1.113 to 2.617; p-value: 0.014).

Conclusion: Pre-existing heart failure is associated with the increased risk of mortality and the need for mechanical ventilation while getting infected with COVID-19. Finding an answer to determine the risk of hospitalization, length of stay, readmission rate, and multiorgan failure is necessary for further development of preventive care and making a plan for providing optimal healthcare facilities for these patients.

Key words: COVID-19, heart failure, mechanical ventilation, mortality, comorbidity.

INTRODUCTION

COVID-19 (Coronavirus 2019 disease), caused by a coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread all over the globe since December 2019 [1]. The risk for critical illnesses and worse outcomes of COVID-19 has been seen to be higher in cases of conditions such as older age, obesity, diabetes mellitus, cerebrovascular disease, and cardiovascular diseases [2]. It has also been confirmed that COVID-19 affects various organs in the human body, including the heart [3–7]. COVID-19 causes or exacerbates complications like heart failure, myocarditis, arrhythmias, and acute myocardial infarction, especially in patients with previous coronary artery disease or heart failure. COVID-19 aggravates cardiac function through myocardial damage and worsens the patient's condition resulting in poorer outcomes [2, 8–10]. Mechanisms suggested are a disruption in the renin-angiotensin system caused by COVID-19 receptors and involvement of angiotensin-converting enzyme 2 (ACE2) and cytokine storm after left ventricular dysfunction in the acute phase of COVID-19 infection [2, 8].

Patients with cardiovascular diseases constitute a group with a great risk of morbidity and mortality due to underlying vulnerability and renal impairment [2, 11]. Although there was a considerable number of original articles studying this relation between the presence of underlying heart failure and consequent COVID-19 complications, there have not been sufficient reviews performed regarding the subject. In this study, we aim to further investigate the risks of COVID-19-induced conditions in cases with underlying heart failure to provide a wholesome review of studies conducted in this field.

MATERIAL AND METHODS

Search strategy

We systematically searched for studies available on PubMed, Scopus, Ovid, ProQuest, Web of Science,

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and the Cochrane library databases, from the oldest possible articles (which were published in 2019) up to September 2021 and updated via hand searching in February 2022. The main elements of the search were "COVID-19" and "Heart Failure". Our search was done accordingly using both the pre-determined database-specific searching terminology (MeSH and Ovid, etc.), and the synonym terms added manually. The detailed search strategy is mentioned in the **appendix 1**. Lastly, the reference lists of all identified reports and articles were also searched for additional studies.

Eligibility criteria and study selection

Our inclusion criteria were articles in the English language that studied patients with underlying heart failure who got infected by COVID-19. The exclusion criteria were papers that contain neither comparison between heart failure and control groups nor a calculated odds ratio or hazard ratio. The outcomes of interest were all possible complications developed in the heart failure group with COVID-19 infection.

The abstracts and full texts were evaluated by two distinct authors after duplicate removal.

Data extraction

Gathered papers were divided into three groups, then their data was extracted by three researchers individually. These data consisted of author name, publication year, study design, setting, sample size, male ratio, age (mean± standard deviation [SD]), COVID-19 diagnosis method, and various outcomes that each paper provided regarding the status of cases in both groups of heart failure cases and the control group.

Statistical analysis

The second version of comprehensive meta-analysis (CMA.2) software was used to conduct the meta-analysis. The analysis was carried out and presented through forest plots. Confidence intervals of 95% and a 0.05 threshold of significance for the p-value were used in the final analysis. The I^2 index was used to evaluate the result's heterogeneity. There was no significant heterogeneity in our meta-analysis even when using a p-value of 0.10 rather than the common level of 5% [12]. While assessing the heterogeneity using the I^2 method, values >50% are considered significant, and thereby we used random effect model estimates for these clinical and/or methodologic diversity. Otherwise, we used a fixed effect model. Additionally, funnel plots and Begg and Mazumdar rank correlation test for the mortality and mechanical ventilation outcomes were generated to assess the publication bias and the precision of the studies.

RESULTS

By searching electronic databases, hand searching, and checking the references of similar studies, there were 5,997 publications found to enroll in the initial phase. From these, 3,494 duplicates and 2,288 irrelevant papers (from 2,503 studies screened by their title/abstract) were removed. Full texts of 215 articles were reviewed, and eventually, our criteria mentioned above in the methods section were met by 27 studies. The search and selection process of this systematic review is demonstrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1).

All data gathered in this study are summarized in Table 1. Our results include the summary of 27 individual original studies conducted in this field. Outcomes measured in different studies vary according to their design and goal. Of these 27 articles, 13 articles exclusively compared COVID-19-related complications in heart failure versus non-heart failure patients (heart failure + COVID-19 group vs only the COVID-19 control group). In the remainder, specific outcomes in COVID-19 patients were mainly discussed based on their association with several comorbidities including heart failure and we obtained heart failure-related data.

Overall, outcomes investigated in all studies include the length of hospitalization, mortality rate, readmission rate, need for Intensive care unit (ICU) admission, multi-organ failure, septic shock rate, respiratory insufficiency rate, need for non-invasive ventilation, need for mechanical ventilation, need to intubation, need to tracheostomy, arrhythmia, major cardiovascular conditions, heart failure, acute myocardial infarction (MI), Acute respiratory distress syndrome (ARDS) or respiratory failure, cardiogenic shock, embolism, stroke, need to blood transfusion, need to heart transplantation, need to vasopressors, need to inotropes, acute kidney injury and need to dialysis and replacement therapies.

General outcomes

Regarding this category, length of hospitalization, mortality rate, readmission rate, need for ICU admission, multi-organ failure, septic shock rate, and a few others were evaluated.

Length of hospitalization was assessed in 5 studies, of any kind including ward, or ICU. There were overall 10 lengths of stay (LOS) values and 8 studies reported this outcome's comparisons out of which, 5 studies found a statistically significant difference.

Specifically, 1 out of 3 studies for ICU LOS, the only study for ward LOS, and 3 out of 6 studies for total hospital LOS reported a statistically significant association.

The mortality rate was assessed exclusively in 24 studies, in different formats including overall death, in-hospital or ICU mortality, 30-day or 60-day mortality, and etiological categories.

Overall, out of 37 mortality-related values, 16 studies found a statistically significant association between heart failure and

COVID-19-related mortality. Regarding delayed death (30-day or 60-day mortality), 2 out of 3 studies reported a significant relation.

The readmission rate was assessed in 3 studies, out of which, all of them reported a statistically significant linkage in this regard.

ICU admission rate was assessed in 11 studies with 13 related values, out of which, 4 reported a statistically significant association. The multiorgan failure rate was assessed in 2 studies, and for the rate of failure itself, both of them found a statistically significant association.

Sepsis and septic shock incidence rate were assessed in 3 studies, the results of which provided 1 statistically significant association in this regard.

The hospitalization rate was assessed in 3 studies out of which, 1 report seemed to be of a significant difference between the two groups.

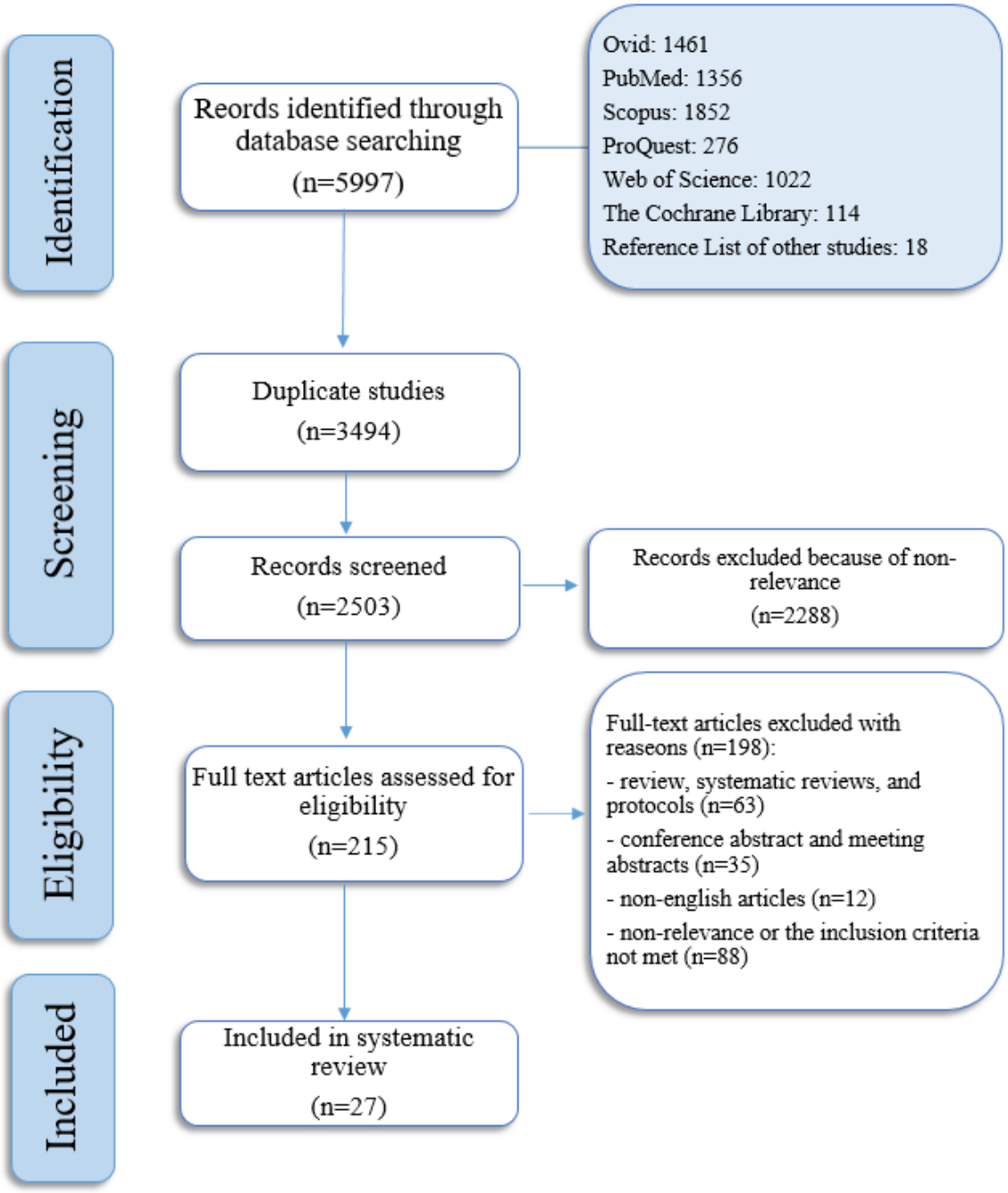

Fig. 1. PRISMA flow diagram.

Table 1
Data extraction table

Author(year)	Study design	Setting	Sample size (HF/ control)	Male ratio (HF/ control)	Mean age ± SD (HF/ control)	COVID-19 diagnosis	Outcome	Rate (in percent) or mean ± SD (HF/ control/P-value)
P. Llacer (2020) [26]	Retrospective observational	Spain	71 / 154	46 (65%) / 82 (53%)	76±13/ 65±17	PCR test	NIMV, n (%)	18(25.3%) / 33(21.4%) / 0.509
							Respiratory insufficiency, n (%)	56(78.9%)/ 106(68.8%)/ 0.123
							Length of stay, days	**11 (6–18)/ 8 (5–13) / 0.022**
							Death, n (%)	**27(38%)/ 25(16.2%)/ <0.001**
							Death or readmission, n (%)	**41(57.7%) / 37(24%) / <0.001**
M. Ruge (2020) [27] [values are reported after matching]	Retrospective cohort	USA	188/188	104 (55.3%) / 107 (56.9%)	63.54±16.03/ 64.11±15.70	PCR test or rapid test	In-hospital mortality Incidence (%)	14.4% / 13.8% / 0.88
							60-day mortality Incidence (%)	17.6% / 20.7% / 0.43
							Intubation Incidence (%)	28.2% / 28.7% / 0.91
							Need for tracheostomy Incidence (%)	4.8% / 4.3% / 0.80
							Need for ICU Incidence (%)	46.8% / 43.6% / 0.53
							Need for pressors Incidence (%)	27.7% / 28.2% / 0.91
							Need for inotropes Incidence (%)	5.3% / 2.7% / 0.18
							Readmitted Incidence (%)	**26.6% / 11.2% / <0.001**
							Major adverse cardiovascular events	27.7% / 22.3% / 0.23

Table 1 (*continued*)

Daniela Tomasoni (2020) [23]	Retrospective observational	Italy	90/602	66 (73.3%) / 415 (68.9%)	73.0±11.4 / 66.5±13.3	RT-PCR	Death, n (%)	Respiratory insufficiency	26 (70.2%) / 84 (66.6%) / 0.52
								Acute MI	0 (0%) / 4 (3.2%) / 0.24
								Pulmonary embolism	1 (2.7%) / 10 (7.9%) / 0.22
								Stroke	0 (0%) / 4 (3.2%) / 0.24
								Multiorgan failure	10 (27.0%) / 24 (19.0%) / 0.15
								overall	**37 (41.1%) / 126 (20.9%) / <0.001**
							Acute heart failure, n (%)		**26 (33.3%) / 24 (5.1%) / <0.001**
							Acute RV failure, n (%)		**6 (10.0%) / 5 (2.7%) / 0.016**
							STEMI, n (%)		1 (1.1%) / 10 (1.7%) / 0.69
							NSTEMI, n (%)		3 (3.8%) / 14 (3.0%) / 0.68
							Ventricular arrhythmia, n (%)		**5 (5.6%) / 3 (0.5%) / <0.001**
							Pulmonary embolism, n (%)		**2 (2.2%) / 50 (8.5%) / 0.040**
							Other thromboembolic events, venous or arterial, n (%)		4 (4.4%) / 57 (9.5%) / 0.12
							ARDS, n (%)		**7 (9.9%) / 92 (18.2%) / 0.08**
							Sepsis, n (%)		**16 (18.4%) / 52 (8.9%) / 0.006**
							Acute renal failure, n (%)		**18 (28.1%) / 54 (12.9%) / <0.001**
							Multiorgan failure, n (%)		**10 (15.9%) / 24 (5.8%) / 0.004**

Table 1 (*continued*)

Minkook Son (2020) [28]	Case Control	South Korea	317/884	136 (42.9%) / 382 (43.2%)	70.0±14.8 / 68.9±14.5	PCR amplification of viral E gene test as a screening test, and amplification of the RdRp region of the orf1b gene as a confirmatory test	Composite of complications	**114 (36.0%) / 202 (22.9%) / < 0.0001**
							Oxygen therapy	**90 (28.4%) / 161 (18.2%) / < 0.0001**
							Use of vasopressors	14 (4.4%) / 30 (3.4%) / 0.3274
							Admission for intensive care unit	14 (4.4%) / 25 (2.8%) / 0.3734
							Continuous renal replacement therapy	3 (1.0%) / 5 (0.6%) / 0.0897
							Extracorporeal membrane oxygenation	**1 (0.3%) / 0 (0%) / 0.0553**
							Death, %	**59 (18.6%) / 91 (10.3%) / < 0.0001**
M. Sokolski (2021) [29]	Retrospective cohort	Zurich, Switzerland	256/1026	145/256 (57%) / 601/1026 (59%)	76 [68–84] / 71 [61–80]	PCR test or a positive blood antigen test	Mechanical ventilation	54/253 (21%) / 157/949 (17%)
							Non-invasive ventilation	111/233 (48%) / 247/833 (30%) / < 0.001
							Respiratory failure	**160/254 (63%) / 490/1013 (48%) / < 0.001**
							Sepsis	43/236 (18%) / 148/897 (16%)
							Septic shock	23/235 (10%) / 86/897 (10%)
							Multi-organ failure	**60/237 (25%) / 139/900 (15%) / < 0.001**
							Renal replacement therapy	15/235 (6%) / 45/839 (5%)
							ICU	**85/254 (33%) / 216/1021 (21%) / < 0.001**
							ICU, length of stay, days	4 [0–8] (129) / 4 [0–14] (32)

Table 1 (*continued*)

							Length of hospital stay, days		12 [6–19] (143) / 11 [5–19] (706)
							In-hospital death		**92/256 (36%) / 231/1026 (23%) / < 0.001**
							Cardiac manifestations during hospitalization	Heart failure event	**110/240 (46%) / 76/910 (8%) / < 0.001**
								Acute coronary syndrome	13/240 (5%) / 26/910 (3%)
								Myocarditis	5/240 (2%) / 7/909 (1%)
								Ventricular arrhythmias	**8/238 (3%) / 10/899 (1%) / < 0.05**
								Pulmonary embolism	9/229 (4%) / 24/893 (3%)
								Other thromboembolic events	8/237 (3%) / 17/898 (2%)
Bin Saleh (2021) [19]	Retrospective cohort	Saudi Arabia	59 / 664	36/59 (61.0%) / 484/664 (72.9%)	68.7±11.56 / 60.0±14.89	RT-PCR test	In-hospital mortality, n (%)		**36 (64.3%) / 286 (44.6%) / <0.01**
							ICU mortality within 30 days, n (%)		**30 (54.5%) / 242 (39.0%) / 0.02**
							MV duration during ICU stay (days), median (IQR)		7.5 (3.00, 15.00) / 8.0 (3.00, 16.00) / 0.84
							ICU Length of Stay (days), median (IQR)		10.0 (7.00, 16.00) / 10.0 (6.00, 18.00) / 0.93
							Hospital Length of Stay (days), median (IQR)		18.0 (9.00, 28.00) / 17.0 (11.00, 25.00) / 0.63
							Complications during ICU stay	Acute kidney injury, n (%)	**30 (50.8%) / 178 (26.8%) / <0.01**
								Liver injury, n (%)	**14 (24.1%) / 63 (9.6%) / <0.01**

Table 1 (*continued*)

								Respiratory failure required mechanical ventilation, n (%)	46 (79.3%) / 451 (68.8%) / 0.09
								Thrombosis, n (%)	8 (14.0%) / 65 (10.0%) / 0.33
Murat (2021) [30]	Propensity score-matched	Eskişehir (Turkey)	240 / 240 (After propensity score-matched populations)	162 (67.5%) / 148 (61.7%) (After propensity score-matched populations)	73.3 ± 10.1 / 72.1 ± 9.74 (After propensity score-matched populations)	RT-PCR test	Death, n (%)		**94 (39.2%) / 37 (15.4%) / <0.001**
							Mechanical ventilation, n (%)		**101 (42.1%) / 37 (15.4%) / <0.001**
							Cardiogenic shock, n (%)		**117 (48.8%) / 28 (11.7%) / <0.001**
							Blood transfusion, n (%)		29 (12.1%) / 24 (10.0%) / 0.56
							Dialysis, n (%)		**36 (15.0%) / 15 (6.2%) / 0.003**
							Composite outcome, n (%)		**127 (52.9%) / 41 (17.1%) / <0.001**
							New onset arrhythmia, n (%)		**26 (10.8%) / 4 (1.7%) / <0.001**
							Length of stay ward, ±SD		**6.43 ± 6.39 / 7.68 ± 4.91 / <0.001**
							Length of stay in ICU, ±SD		**6.22 ± 8.80 / 3.71 ± 8.24 / <0.001**
							Total length of hospital stay, ±SD		12.7 ± 10.4 / 11.4 ± 8.92 / 0.118

Table 1 (*continued*)

Goyal (2021) [31]	Multivariable modified Poisson regression	US	979 / 7941	523 (53.4%) / 4426 (55.7%)	71.5±14.2 / 60.2±17.5	RT-PCR test, IgM antibody test or clinical diagnosis using hospital specific criteria	Admission to the intensive care unit, n (%)	**33.5% / 27.6% / <0.001**
							Mechanical ventilation, n (%)	22.4% / 20.5% / 0.18
							Shock (cardiogenic, distributive or mixed)	**15.7% / 11.6% / <0.001**
							Altered mental status	**19.9% / 9.4% / <0.001**
							In-hospital mortality	31.6% / 16.9% / -
Kuno (2020) [32]	Retrospective cohort	US	584 / 7854	Overall: 53.9%	Overall: 59 [43, 71]	PCR	Intubation, % (event/total)	14.6% (85/584) / 6.0% (474/7854) / RR (95% CI): 2.41 (1.94-2.99)
							Death, % (event/total)	34.2% (200/584) / 13.4% (1053/7854) / RR (95% CI): 2.55 (2.25-2.90)
Kyle Rumery (2021) [33]	Retrospective cohort	USA	6,148/ 24,903	94.3% / 84.8%	69.8 ± 13.3/ 57.0 ± 16.9	PCR	Post 30-day mortality, n (%)	**334 (5.4%)/ 383 (1.5%)/ <0.0001**
							Post 30-day readmission, n (%)	**1138 (18.5%)/ 2091 (8.4%)/ <0.0001**
Jesus Alvarez-Garcia (2020) [34]	Retrospective cohort	New York, USA	422/ 6,017	55.9%/ 55%	72.5 ± 13.3/ 62.9 ± 17.7	RT-PCR	ICU	**98 (23.2%)/1,000 (16.6)/ <0.001**
							LOS ICU, days	**5 (2–11)/ 7 (3–15)/ 0.057**
							ICU mortality	**72 (73.5%)/564 (56.4%)/0.001**
							LOS, days	**8 (4–13)/ 6 (3–12)/ <0.001**
							Intubation	**96 (22.8%)/ 717 (11.9%)/ <0.001**
							Still admitted	**0 (0.0)/ 228 (3.8)/ <0.001**
							In-hospital mortality	**169 (40.0%)/ 1,495 (24.9%)/ <0.001**

Table 1 (*continued*)

Laia C. Belarte-Tornero (2021) [35]	Cohort	Spain	43/86	48.8%/ 48.8%	80.3 ± 12.1)/ 80.4 ± 12.1	PCR	Intensive care unit admission	1 (2.3%)/ 6 (7.0%)/ 0.423	
							Advanced ventilatory support	4 (9.3%)/ 12 (14.0%)/ 0.450	
							Hospital length of stay, days	**17 (8–31)/ 10 (1–20)/ 0.023**	
							Clinical worsening during admission	14 (32.6%)/ 25 (29%)/ 0.749	
							Overall death	**22 (51.2%)/ 25 (29.1%)/ 0.014**	
							Overall CV death	**4 (9.3%)/ 0 (0%)/ 0.019**	
							Acute HF during admission	**9 (21%)/ 3 (3.5%)/ 0.004**	
							Oxygen support	35 (81.4%)/ 60 (69.8%)	P-value: 0.436
							High flow nasal cannula	0 (0)/ 1 (1.2%)/	
							Non-invasive ventilation	3 (7%)/ 5 (5.8%)/	
							Intubation and invasive ventilation	1 (2.3%)/ 6 (7%)	
Edimar Alcides Bocchi (2020) [25]	Retrospective case series	Brazil	16/-	68%/-	50 ± 16/-	PCR	Outcome during COVID-19		
							SARS (requiring invasive pulmonary mechanical ventilation)	8(50%)/ -	
							Non-invasive pulmonary ventilation	7(43.75%)/-	
							Supplemental oxygen by catheter	1(6.25%)/-	
							Severe ventricular arrhythmias	1(6.25)/-	
							Acute kidney injury	4(25%)/-	

Table 1 (*continued*)

							Death (from septic and cardiogenic shock)	4(25%)
							Outcome follow-up after COVID-19 recovery	
							Heart transplantation	2(12.5%)/-
							Total Death	3(18.75%)/-
							Death from mixed septic and cardiogenic shock	2(12.5%)/-
							Death from sustained ventricular tachycardia and cardiogenic shock	1(6.25%)/-
							Remain hospitalized in a rehabilitation programme	2(12.5%)/-
							Discharged to ambulatory care	5(31.25%)/-
							Waiting heart transplant	4(25%)/-
Inciardi RM (2020) [36]	Observational, prospective cohort	Italy	21 /78	80 (81%)	67 ± 12	PCR test	Mortality	12(57.1%)/14 (17.9%) There was a significant difference between dead and alive groups in HF (0.001)
Chen T 2020 [37]	Retrospective cohort	China	1/273	Overall: 171 (62%)	Overall: 62.0 (44.0–70.0)	RT-PCR	Mortality	1 (100%)/ 112 (41%)
Petrilli 2020 [24]	prospective cohort study	USA	349/2380	Overall: 61.3%	Overall: 63 (51–74)	RT-PCR	Critical illness (intensive care, mechanical ventilation, discharge to hospital care, or death)	189 (54.1%)/ 801 (33.6%)/ HF mortality hazard ratio (HR): 1.77 (1.43 to 2.20) / <0.001
								critical illness including VS adjusted OR: 1.93 (1.40 to 2.6) <0.001
								HR hospitalization: 4.56 [2.59, 8.04] <0.001

Table 1 (*continued*)

Yin Y 2020 [38]	Retrospective observational	China	2/110	Overall: 68.7%	Overall: 66 (56 -76)	RT-PCR	Mortality	2 (100%) / 50 (45.45%)/ 0.213 Survived non-HF patients had other complicating comorbidities (i.e. resembles other studies)
Baker KF 2020 [39]	Retrospective cohort	UK	45/271	Overall: 54.7%	Overall: 75 (60-83)	PCR	Mortality	**20 (24.7%)/ 81 (29.88%) / 0.004** **OR 2.67 [1.36–5.19], p = 0.004**
Caraballo C 2020 [40]	Retrospective cohort	USA	36/170	Overall: 45.1%	Overall: 78 (65–87)	PCR	Mortality	3 (8.3%)/ 31 (18.23%) / 0.15
Henge GE 2020 [41]	A prospective observational study	China	4/47	Overall: 72.5%	Overall: 70 (58–79)	RT-PCR	Mortality	0 (0%) / 12 (25.5%)/ 0.329
							Severity	Severely ill: 1 (25%)/ 19 (40.42%) Critically ill: 3 (75%)/ 28 (59.57%)
Garibaldi B 2020 [42]	Retrospective cohort	USA	100/647	Overall: 53.2%	Overall: 63 (49, 75)	Nucleic acid tests	Mortality	33 (33%)/ 80 (12.3%)
Liao X 2020 [43]	Retrospective cohort	China	4/77	Overall: 51 (63.0%) but in NR group: 4 (40.0%)	Overall: 50.0 (39.0-65.0) but in NR group: 76.0 (64.0-80.0)	RT-PCR	No recovery (Death or ventilator support)	1 (25%)/9 (11.6%)
Paranjpe I 2020 [44]	Retrospective case series	USA	117/961	Overall: 58.1%	mortality G: 75 (64-85) discharge G: 59 (45-72)	RT-PCR	Mortality	64(54.7%)/310 (28.7%)

Table 1 (*continued*)

Rossi PG 2020 [45]	Prospective cohort	Italy	137/2516	Overall: 50.1% (65.8% in death patients)	Mean age: 63.2	PCR	Mortality	43 (31.3%)/ 174 (6.9%) HR:2.3 (1.6–3.2)
							Hospitalization	96 (70.0%)/ 979 (38.9%) HR:1.6 (1.2–2.1)
Yanover C 2020 [46]	Retrospective cohort	Israel	30/4323	Overall: 55.5%	35 [22–54]	PCR	Complicated COVID-19 (Critical care/death)	11 (36.6%)/ 162 (3.7%)
								For ages>65y, the OR of cardiovascular disease (not specifically HF) with increased risk of complication**: 1.91 [1.22, 2.99] /p-value:0.032** In age>65y & sex (F) adjusted: **OR 2.76 [1.29, 5.85] 0.045**
Argenziano MG 2020 [47]	Retrospective case series	USA	102/898	Overall: 59.6%	Overall: 63.0 (50.0–75.0)	RT-PCR	Need for ICU care (severity)	24 (23.5%)/ 212 (23.6%)
Reilev M [48]	Retrospective cohort	Denmark	315/10807	57%	Overall PCR+: 48 (33–62) Hospitalized: 71 (56–80)	RT-PCR	30-day mortality	101 (32.0%)/ 476 (4.4%)
							Hospitalization	221 (70.1%)/2033 (18.8%) Age & sex adjusted OR: 2.6 (2.0–3.4)
							ICU care	15 (4.7%)/ 299 (2.7%) Age & sex adjusted OR: 1.8 (1.3–2.4)

PCR: Polymerase chain reaction; HF: Heart failure; OR: odds ratio; ICU: Intensive care unit; RT-PCR: Reverse transcription polymerase chain reaction; MI: myocardial infarction

Respiratory conditions and outcomes

Regarding this category, respiratory insufficiency rate, need for non-invasive ventilation, mechanical ventilation, intubation, tracheostomy, and a few others were evaluated.

The respiratory insufficiency incidence rate was assessed in 3 studies, one of which assessed respiratory failures leading to death, and from them, 1 study reported a statistically significant association.

The need for non-invasive ventilation including oxygen therapy and high flow nasal cannula was assessed in 5 studies, including 6 comparisons, out of which, 2 were statistically significant.

The need for advanced and invasive mechanical ventilation including intubation, tracheostomy, extracorporeal membrane oxygenation, and supplemental oxygen by catheter, was assessed in 11 studies. Two out of 10 reported comparisons between heart failure and the control group were statistically significant.

ARDS incidence rate was the other outcome assessed in only one individual study and does not seem to have a statistically significant association with pre-existing heart failure.

Cardiovascular conditions and outcomes

Regarding this category, arrhythmia, major cardiovascular conditions, heart failure, acute MI, cardiogenic shock, embolism, stroke, need for blood transfusion, need for heart transplantation, need for vasopressors, and inotropes need were evaluated.

The arrhythmia incidence rate was assessed in 4 studies, and there were reported comparisons, 2 of which were statistically significant.

Major cardiovascular conditions, heart failure, acute MI, and cardiogenic shock were assessed in 7 studies and 10 comparisons were conducted for these comparisons (1 for major adverse cardiovascular events, 3 for MI, 4 for heart failure, and 2 for cardiogenic shock), out of which, 6 were statistically significant (0 out of 1 for major adverse cardiovascular events, 0 out of 3 for MI, 4 out of 4 for heart failure, and 2 out of 2 for cardiogenic shock).

One of the 3 studies reporting a non-significant association for myocardial infarction incidence, assesses MI incidence in dead patients. Also, regarding cardiogenic shock, one of the 2 studies mentioned, reported a significant relation for shock incidence (not specifically cardiogenic type).

Renal conditions and outcomes

Regarding this category, acute kidney injury and the need for dialysis and replacement therapies were evaluated. One out of one study reported a significant association with acute kidney injury (AKI), and 1 out of 2 studies reported a significantly higher rate for dialysis and replacement therapy in patients with heart failure.

Meta-analysis

The meta-analysis was performed based on mortality and the need for mechanical ventilation. In mortality, reported in 20 studies, a significant difference was seen between heart failure and non-heart failure patients in which the heart failure group was more susceptible to death (OR:2.570, 95%CI: 2.085 to 3.169; p-value:<0.001) (Figure 2). About mechanical ventilation as an outcome, based on 6 groups, there was a significant difference between heart failure vs. non-heart failure groups, and in the heart failure patients, mechanical ventilation risk was higher (OR:1.707, 95%CI: 1.113 to 2.617; p-value: 0.014) (Figure 3). Results of Begg and Mazumdar rank correlation test detected no significant publication bias (p-values > 0.05) for neither of outcomes. Funnel plots can be accessed in appendix 2.

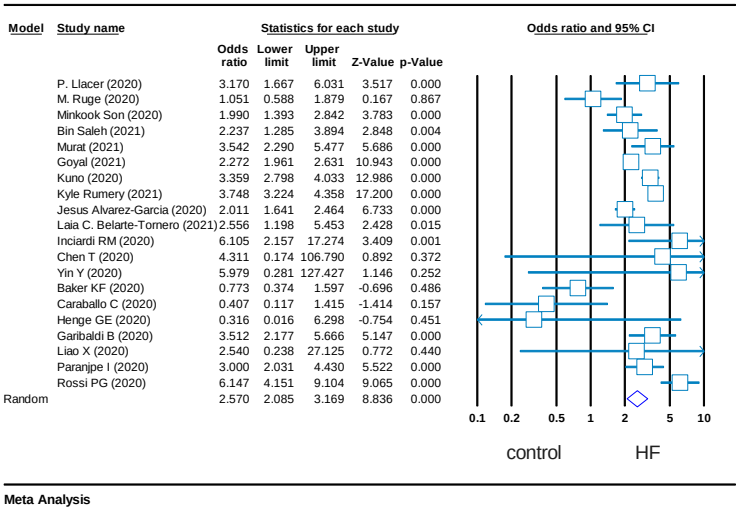

Fig. 2. Forest plot of mortality in COVID-19 patients. Squares indicate the mortality odds ratio in each study and diamond indicator shows the overall result. Horizontal lines demonstrate the 95% confidence intervals.

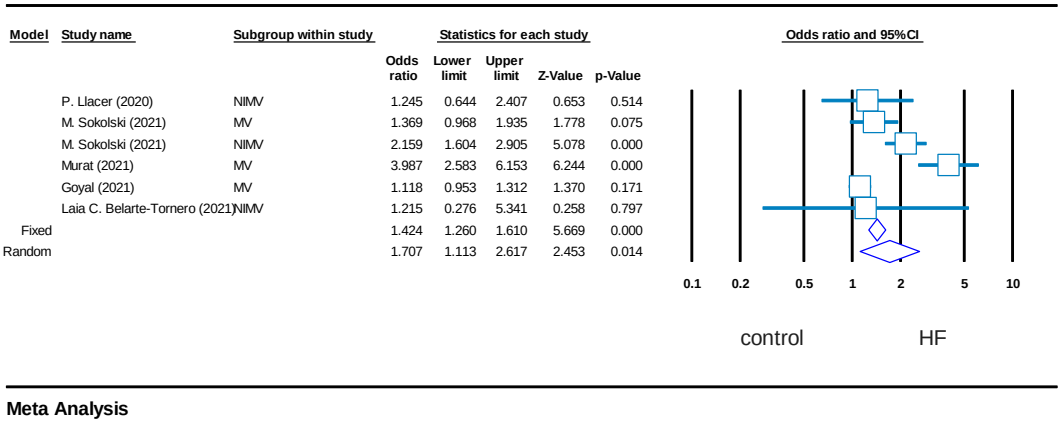

Fig. 3. Forest plot of mechanical ventilation in COVID-19 patients. Squares indicate the mechanical ventilation odds ratio in each study and diamond indicator shows the overall result. Horizontal lines demonstrate the 95% confidence intervals.

Table 2
Frequency of heart failure patients outcomes vs control group

Outcomes	Number of Studies	Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity			
		Point estimate (%)	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Mortality	20	2.570	2.085	3.169	8.836	<0.001	94.767	19	<0.001	79.951
MV	6	1.707	1.113	2.617	2.453	0.014	0.00	5	<0.001	86.902

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction

DISCUSSION

A meta-analysis of this study showed that pre-existing heart failure is associated with a higher mortality rate and increased risk for mechanical ventilation. But an analytically significant difference between heart failure vs non-heart failure group could not be obtained while assessing the other outcomes, which results from the insufficient number of studies and different methods of reporting.

Here in this review, we gathered almost all encountered debilitating complications related to COVID-19 infection in patients with preexisting heart failure rather than specifically poor prognosis and death, as studied in the previously conducted systematic review [13].

It has been proposed that the basic mechanism responsible for the severe complications including death as the worst-case scenario and poor prognosis, in SARS-CoV-2 infected patients with preexisting heart failure resembles the mechanisms which cause such outcomes in patients with a previous history of heart failure who acquired influenza or Middle East respiratory syndrome (MERS). These include non-ischemic myocardial injury, heightened levels of systemic inflammatory state, and consequent excess of oxidative stress, ARDS, thromboembolic events due to a hypercoagulable state, and water-electrolyte imbalance due to renal impairment which in the context of the reduced physiological reserve, leads to more hemodynamically unstable patients and higher mortality and complication rate [13–15]. Each of these contagious infections commonly manifests extrapulmonary complications either via direct invasion and toxicity of the virus or secondary to the cytokine storm, which aggravates the condition for patients with preexisting debilitating diseases such as heart failure [14, 16]. It's worth mentioning that the mortality rate in COVID-19 is higher than in influenza and lower than in MERS [13].

Angiotensin-converting enzyme 2 (ACE2) receptor, also known as the SARS-CoV-2 receptor, was studied for its important role in the pathogenesis of COVID-19 infection. This receptor was also used by SARS-CoV-1, responsible for the 2003 SARS outbreak, but with a much lower affinity of binding to the specific cells of several organs, especially the type 2 alveolar epithelial cells of the lower respiratory tract, myocardial cells of the heart, and proximal tubular and podocyte cells of the kidneys. SARS-CoV-2 also has tropism to particular neurological, pharyngeal, and gastrointestinal tract cells, and the tissue destruction of direct viral toxic effect is one of the suggested mechanisms for the multi-organ involvement and dysfunction in COVID-19 [16–18].

After the SARS-CoV-2 spike glycoprotein binds to the ACE2, the virus enters the cell and activates A disintegrin and metalloproteinase-17 (ADAM17) which via downregulation of the ACE2 expression. ACE2 contributes to angiotensin type 2 receptor (AT2R), and angiotensin 1–7 (Ang-(1–7))-mitochondrial assembly (MAS) receptor pathway to counteract the functions of the classic RAAS including vasoconstriction, inducing oxidative stress, inflammation, and fibrosis. It also respectively facilitates the production of Ang-(1-7) directly or indirectly from Ang II and I. Thus, lower ACE2 levels and higher ACE/ACE2 ratio [19] correlate with a higher Ang II to angiotensin type-1 receptor (AT1R) binding and consequent increased vascular permeability causing severe respiratory compromise. It has been mentioned that the pro-inflammatory condition due to coexisting heart failure and diabetes in a patient, eases the ADAM17 function in the cleaving of ACE2 and exacerbates the adverse effects of high Ang-II levels in a decreased circulatory reserve state [13, 17]. So based on the possible dual effect of ACE2 in COVID-19 patients, the use of the renin-angiotensin system blocker (RASB) drugs in patients with a previous history of heart failure should be adjusted, because they increase the risk of being infected but protect the infected patient against severe lung injuries which increase the need for mechanical ventilation, possible ICU admission, and mortality rate [13]. In addition, dysregulation of RAAS can be the promoting factor for diseases related to blood pressure and body volume disturbances [16].

Two other proposed mechanisms for extra-pulmonary presentations of COVID-19 are endothelial injury and its related susceptibility to thrombus formation and immune system dysregulation via exaggerated activation of the innate immune system in a T lymphocyte-depleted context. Endothelial damage occurs because of the direct cellular invasion or endothelialitis posing a prothrombotic state with fibrinolysis suppression, activation of complement systems, and potentiated thrombin construction. Interactions between platelets and neutrophils via the production of neutrophil extracellular traps (NETs) and fibrin, and spillover of the proinflammatory cytokines are associated with dramatic outcomes in COVID-19 patients. The role of hypoxia-induced factor-α (HIF-α) and hypoxia-induced hyperviscosity is also mentioned as a thrombosis propagation inducer [16]. All of these factors can worsen the heart failure-related hypercoagulable state resulting from decreased blood circulation and its endothelial shear stress, impaired platelet function, and increased levels of oxidative stress, TNF-α, and ACE1 activity which eventually leads to thromboembolic events and poor outcomes [20]. Despite the additive effect of the above-mentioned mechanisms in most of the critical complications, the contemplated underlying pathophysiology for acute kidney injury is a good example of the mixture of concomitant cytokine storm, endothelial dysfunction, and direct cellular effects of virus invasion [16].

Older age especially >65 and the male gender are more susceptible groups to complications and worse prognosis in COVID-19 cases as it's obvious from the extracted data table in this review. Old age is related to numerous medical comorbidities and risk factors, dysfunction in several body organs, senescent cells and age-related functional deficits in B and T immune cells [15, 21, 22]. Cell mitochondria in an old patient fail to robustly handle the reactive oxygen species, and when accompanied by hypoxia leads to the activation of the HIF-α/sirtuin pathway. Besides, these oxygen radicals destroy mitochondrial membranes releasing the damage-associated molecular pattern (DAMP) proteins that subsequently activate innate immunity, both of which contribute to the release of excessive mediators of inflammation, resultant higher metabolic demands and an increase in the risk of poor outcome in COVID-19 infection [13, 21]. On the other hand, it suggested that males are at higher risk of mortality and morbidity due to higher ACE2 expression levels and different composition and serum concentrations of the sex hormones compared to women [13, 22].

While comparing the current results with the previously conducted systematic review [13], both studies confirm that preexisting heart failure positively correlates with the increased death rate either in-hospital or ICU mortality. In contrast with the previous one, this study cannot conclude that the history of heart failure significantly affects the length of stay and hospitalization. Due to few studies assessing hospitallization and high heterogeneity in studies evaluating LOS, we suggest that more studies can help to put an end to this controversy. The need for mechanical ventilation was the other outcome of our paper that significantly correlates with the history of heart failure. A possible explanation for no change in the demand for mechanical ventilation assistance especially in resource-limited countries could be that the same limited numbers of ventilators were used to support all patients suffering from severe illnesses necessitating patient prioritization [23, 24]. Other results of our study which could have a significant correlation with previous heart failure history if the number of studies was higher are readmission rate, multi-organ failure, arrhythmia, major cardiovascular conditions, acute kidney injury, and pulmonary embolism.

We had limitations in our meta-analysis. Only English articles were included in this study and conference papers and unpublished proposals were excluded. The included studies have different study designs and sometimes different methods for COVID-19 confirmation which can affect the overall result. In almost all of our studies, participating heart failure patients had other comorbidities like diabetes, coronary artery disease, hypertension, etc., and were consuming related drugs which all could be mentioned as confounding factors with variable effects on patient outcome. The risk of patient overlap between studies conducted in the same regions should also be considered [13]. Changes that occur in the treatment

guidelines over the time of COVID-19 detection can also affect patient outcomes. Another important and at the same time, inevitable limitation is that our included articles did not study the SARS-CoV-2 infected patients with a previous history of heart failure who did not visit the hospital because they were asymptomatic or with mild symptoms, or they had a fear of being hospitalized [25].

CONCLUSION

Pre-existing heart failure accounts for the increased risk of mortality and the need for mechanical ventilation while getting infected with COVID-19. This primarily results from underlying abnormalities such as endothelial dysfunction or increased ACE1 level and also a significant decline in physiologic functions of important organs e.g., the heart, lungs, and kidneys, and the related deficient compensatory mechanisms which in a negative feedback cycle deteriorates the patient condition. But finding an answer to determine the risk of hospitalization, length of stay, readmission rate, and multiorgan failure is necessary for further development of preventive care and making a plan for providing optimal healthcare facilities.

Introducere: *Riscurile pentru complicații severe ale COVID-19 sunt mai mari la pacienții cardiaci. Scopul acestei meta-analize a fost de a investiga riscurile COVID-19 la pacienții cu insuficiență cardiacă pre-existentă.*

Metode: *Au fost căutate sistematic articole din bazele de date PubMed, Scopus, Ovid, ProQuest, Web of Science și Cochrane Library pentru articolele din limba engleză eligibile, ce au evaluat pacienții cu COVID-19 și insuficiență cardiacă pre-existentă. Softul CMA.2 a fost folosit pentru meta-analiză.*

Rezultate: *Din 5997 de publicații am inclus 27 de studii eligibile. Efectele urmărite au fost în principal mortalitatea, durata spitalizării, necesitatea de internare în secțiile de terapie intensivă, necesitatea ventilației mecanice. Referitor la mortalitate, pacienții cu insuficiență cardiacă au fost mai susceptibili să sufere acest eveniment (OR:2.57, 95%CI: 2.085 – 3.169; p<0.001). Totodată, riscul de ventilație mecanică a fost mai mare (OR:1.707, 95% CI 1.113 – 2.617; p=0.014).*

Concluzii: *Insuficiența cardiacă pre-existentă este asociată cu creșterea riscului de mortalitate și necesitatea ventilației mecanice odată cu infecția de COVID-19.*

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APPENDIX 1

Search Strategy of PubMed

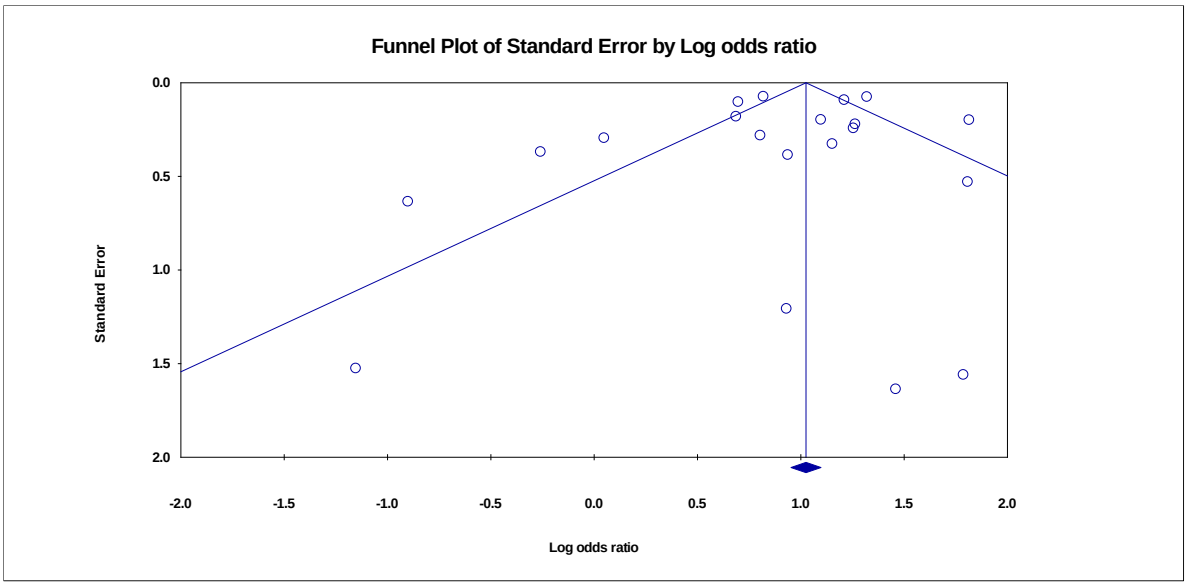
Search	Query	Items found
#1	Search: **("COVID-19"[Mesh]) OR "SARS-CoV-2"[Mesh]**	106,352
#2	Search: **(((((((COVID-19[Title/Abstract]) OR (COVID19[Title/Abstract])) OR (COVID 19[Title/Abstract])) OR (2019-nCoV[Title/Abstract])) OR (2019 nCoV[Title/Abstract])) OR (Coronavirus[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (SARS CoV 2[Title/Abstract])**	180,767
#3	Search: **(("COVID-19"[Mesh]) OR "SARS-CoV-2"[Mesh]) OR (((((((COVID-19[Title/Abstract]) OR (COVID19[Title/Abstract])) OR (COVID 19[Title/Abstract])) OR (2019-nCoV[Title/Abstract])) OR (2019 nCoV[Title/Abstract])) OR (Coronavirus[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (SARS CoV 2[Title/Abstract]))**	187,428
#4	Search: **"Heart Failure"[Mesh]**	131,082
#5	Search: **(("Heart Failure"[Title/Abstract]) OR ("Cardiac Failure"[Title/Abstract])) OR ("Myocardial Failure "[Title/Abstract])) OR ("Heart Decompensation"[Title/Abstract])**	201,330
#6	Search: **("Heart Failure"[Mesh]) OR ((("Heart Failure"[Title/Abstract]) OR ("Cardiac Failure"[Title/Abstract])) OR ("Myocardial Failure "[Title/Abstract])) OR ("Heart Decompensation"[Title/Abstract]))**	234,015
#7	Search: **((("COVID-19"[Mesh]) OR "SARS-CoV-2"[Mesh]) OR (((((((COVID-19[Title/Abstract]) OR (COVID19[Title/Abstract])) OR (COVID 19[Title/Abstract])) OR (2019-nCoV[Title/Abstract])) OR (2019 nCoV[Title/Abstract])) OR (Coronavirus[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (SARS CoV 2[Title/Abstract]))) AND (("Heart Failure"[Mesh]) OR ((("Heart Failure"[Title/Abstract]) OR ("Cardiac Failure"[Title/Abstract])) OR ("Myocardial Failure "[Title/Abstract])) OR ("Heart Decompensation"[Title/Abstract])))**	1,380

Search Strategy of Ovid

1	exp COVID-19/	106857
2	exp SARS-CoV-2/	83178
3	COVID-19.ti. or COVID-19.ab. or COVID19.ti. or COVID19.ab. or COVID 19.ti. or COVID 19.ab. or 2019-nCoV.ti. or 2019-nCoV.ab. or 2019 nCoV.ti. or 2019 nCoV.ab. or Coronavirus.ti. or Coronavirus.ab. or SARS-CoV-2.ti. or SARS-CoV-2.ab. or SARS CoV 2.ti. or SARS CoV 2.ab.	228819
4	1 or 2 or 3	234697
5	exp Heart Failure/	131126
6	"Heart Failure".ti. or "Heart Failure".ab. or "Cardiac Failure".ti. or "Cardiac Failure".ab. or "Myocardial Failure".ti. or "Myocardial Failure ".ab. or "Heart Decompensation".ti. or "Heart Decompensation".ab.	273245
7	5 or 6	310847
8	4 and 7	1561

APPENDIX 2

Funnel plot for mortality and Begg and Mazumdar analysis for publication bias assessment



Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-16.00000

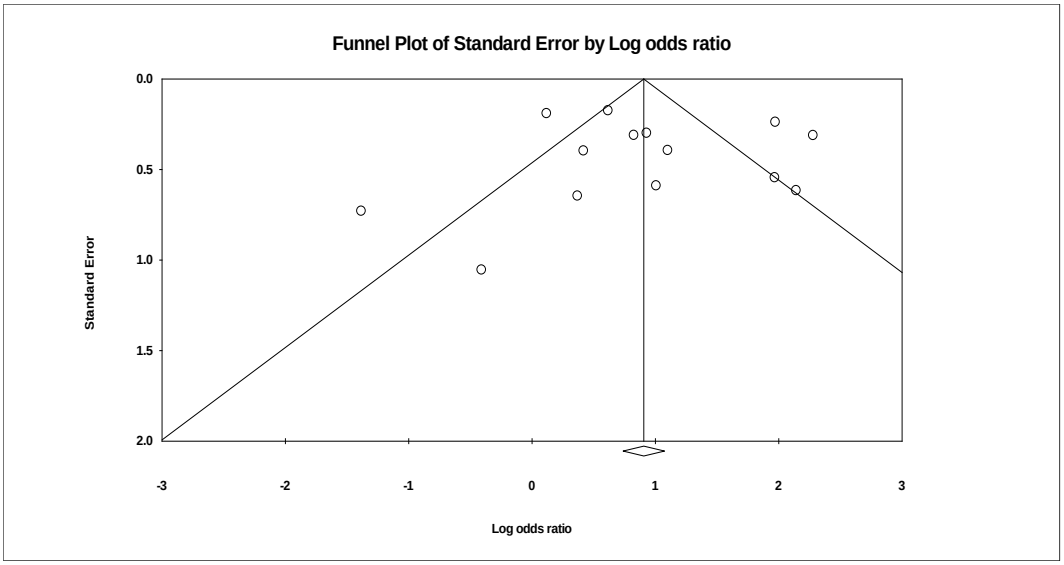
Kendall's tau without continuity correction

Tau	-0.08421
z-value for tau	0.51911
P-value (1-tailed)	0.30184
P-value (2-tailed)	0.60369

Kendall's tau with continuity correction

Tau	-0.07895
z-value for tau	0.48666
P-value (1-tailed)	0.31325
P-value (2-tailed)	0.62650

Funnel plot for mechanical ventilation and Begg and Mazumdar analysis for publication bias assessment



Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-5.00000
Kendall's tau without continuity correction	
Tau	-0.05495
z-value for tau	0.27372
P-value (1-tailed)	0.39215
P-value (2-tailed)	0.78430
Kendall's tau with continuity correction	
Tau	-0.04396
z-value for tau	0.21898
P-value (1-tailed)	0.41333
P-value (2-tailed)	0.82667