Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i17.2858

CARDIOVASCULAR MORBIDITY AMONG CRITICAL PATIENTS OF COVID-19: A SYSTEMATIC REVIEW

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Abstract:

Introduction: The etiology of COVID-19 is related to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) virus, which gains entry into host cells through the utilization of angiotensin converting enzyme-2 (ACE 2) receptors located on the cellular membrane. The user's text is already academic. Numerous investigations have documented the range of clinical presentations associated with the condition and emphasized the impact on the cardiovascular system.

Methods: We conducted a literature search of PubMed, Medline, EMBASE, and Google Scholar databases identified all relevant studies reporting cardiovascular comorbidities, disease severity, and survival. It was conducted to assess the demographic characteristics and prevalence of hypertension and congestive heart failure among individuals diagnosed with COVID-19 and to evaluate the death rates in patients with COVID-19 infection who also have hypertension and congestive heart failure.

Results: The study encompassed a diverse spectrum of patients, spanning from 23 to 95 years of age. The prevalence of females within the sample varied between 19% and 52%. The study findings revealed that the incidence rates of hypertension, diabetes mellitus, and smoking varied between 10% and 82%, 8% and 24%, and 4% and 14%, respectively. Our study revealed a statistically significant increase in the risk of death among patients with congestive heart failure, with a relative risk of 3.38 (1.80-6.32) and a p-value of 0.004.

Conclusion: In brief, the coexistence of congestive heart failure (CHF) in individuals diagnosed with COVID 19 is linked to heightened death rates and unfavorable outcomes throughout the initial hospitalization period.

Introduction:
The etiology of COVID-19 is related to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) virus, which gains entry into host cells through the utilization of angiotensin converting enzyme-2 (ACE 2) receptors located on the cellular membrane. The user's text is already academic. Numerous investigations have documented the range of clinical presentations associated with the condition and emphasized the impact on the cardiovascular system [1,2]. The reported incidence of cardiovascular disease (CVD) among individuals with COVID-19 varies between 4% and 40%. It suggests that the presence of CVD is associated with adverse outcomes, such as increased rates of intensive care unit (ICU) admissions and higher mortality rates [3-7]. A new meta-analysis has revealed a correlation between underlying cardiovascular disease (CVD) and heightened all-cause mortality rates, as well as an increased susceptibility to severe forms of COVID-19 infection [8]. Multiple small scale studies have demonstrated the presence of heightened biomarkers in individuals afflicted with COVID-19, indicating potential myocardial damage. Nevertheless, there exists contradictory data concerning the correlation between cardiac biomarkers and the severity of the disease [4,9]. There is a scarcity of available evidence regarding the outcomes observed in individuals with underlying congestive heart failure (CHF) who have contracted COVID-19 [10,11] This study was carried out to outline the impact of various cardiac diseases, including CHF and hypertension, on COVID-19 patient outcomes.

Objectives
1. To assess the demographic characteristics and prevalence of hypertension and congestive heart failure among individuals diagnosed with COVID-19.
2. To evaluate the death rates in patients with COVID-19 infection who also have hypertension (HTN) and congestive heart failure (CHF).

Methodology:
Systematic review was conducted in relation with the principles outlined by the recommended reporting items for systematic reviews and meta-analyses [12].

Search strategy
A comprehensive search was conducted across many databases, including PubMed, Medline, EMBASE, and Google Scholar. The study conducted a thorough examination of 3457 citations in order to determine the quantity of works that met the specified inclusion criteria. Out of the total number of papers considered, 702 were identified as duplicates. Additionally, 1647 articles were classified as correspondence letters, case reports, and review articles. Furthermore, 621 publications were deemed irrelevant to the study topic based on their titles and abstracts, and hence, were omitted from the review. A total of 457 papers were assessed, including both abstracts and full-length articles. Out of these, 38 studies were deemed suitable for inclusion in the qualitative synthesis. Out of the total number, 17 papers did not provide information on the biomarkers that were of relevance to our study, resulting in a final inclusion of 21 researches for the quantitative assessment subsequently, a study was omitted from our final meta-analysis due to the retraction of its journal, resulting in a total of 20 studies included in our analysis. Any discrepancies pertaining to the selection of studies were handled through a collective agreement [13]. All research conducted on in-vivo animals or tissue samples were eliminated from the analysis.

The present study examines the eligibility criteria and procedures for selecting studies:
This systematic review encompasses all published studies from December 2019 to May 2020 that examined the characteristics of COVID-19 patients, including their coexisting comorbidities and laboratory data. The papers were selected based on their stratification of patient outcomes and/or illness severity. The exclusion criteria employed in this study were limited to articles that failed to provide cardiac biomarkers or did not categorize patients' outcomes according to the severity of infection or final patient outcome.

The process of extracting data and evaluating its quality:
The variables that were collected are as follows: The names of the authors, the publication year, the study design the sample population, the demographic and characteristics of the patients are all needed for this study. The identification of acute cardiac damage is frequently associated with the presence of higher serum levels of high-sensitivity troponin [14].

Data synthesis and analyses
The patients were categorized into two groups based on the degree of their disease advancement, specifically death. Those who had severe disease progression, including death, were classified under the "fulminant" spectrum. On the other hand, survivors and individuals with non-severe cases were jointly grouped under the "non-fulminant" spectrum of illness. Additionally, we conducted a comparative analysis of the relative risk of mortality during the initial hospitalization period among patients who already had congestive heart failure and those who did not.
The Manel-Haenszel risk ratios [15,16] were used to describe the categorical factors between the patient groups, while the mean difference (MD) was used to summarize the continuous data variables. The associated 95% confidence intervals (CI) were also reported. The pooled estimates were derived by the utilization of the random-effects meta-analysis approach. The Hartung-Knapp-Sidik-Jonkman (HKSJ) technique was employed to calculate tau-square (t2) in this study, instead of the usual DerSimonian-Laird approach. The HKSJ method is preferred in situations where the number of studies is limited and when merging studies with unequal sample sizes, since it has been shown to yield superior performance and lower type-I error rates [17]. The studies that initially presented descriptive values as mean and standard deviations using the wan technique [18].
The assessment of publication bias involved the creation of funnel plots, which display the effect size against its standard error (SE), and the use of Egger's linear regression test to examine any asymmetry in the funnel plots. The calculation of between-study heterogeneity was performed using the Higgins I2 statistic. A two-sided p-value less than 0.05 were deemed to indicate statistical significance. The "meta" and "metafor" packages were utilized in the implementation of our meta-analytical procedures [19, 20].

Results:
Characteristics:
In total, a cohort of 5967 patients was assembled from a compilation of 20 distinct study reports. Table 1 presents a comprehensive overview of the studies and patient profiles encompassed within this systematic review. The study encompassed a diverse spectrum of patients, spanning from 23 to 95 years of age. The prevalence of females within the sample varied between 19% and 52%. The study findings revealed that the incidence rates of hypertension, diabetes mellitus, and smoking varied between 10% and 82%, 8% and 24%, and 4% and 14%, respectively. The data of ten trials were given in a tiered manner based on patient outcome. A total of 6 research, specifically studies 21-29 and 10, have presented their findings pertaining to individuals with COVID-19 infection [3,4,9,22-28].

Evaluation of underlying cardiovascular conditions:
Additionally, our study revealed a statistically significant increase in the risk of death among patients with congestive heart failure, with a relative risk of 3.38 (1.80-6.32) and a p-value of 0.004. (Table II).
However, we did not observe a statistically significant association between underlying hypertension and the risk of in-hospital death, with an RR of 1.57 (0.97-2.56) and a p-value of 0.06. (Table III).

Discussion
Our observations indicate that individuals who experienced severe COVID-19 infection and did not survive (referred to as the fulminant group) exhibited a significantly greater prevalence of cardiovascular illnesses in comparison to individuals with non-severe infections who survived (referred to as the non-fulminant group). Furthermore, it was shown that these individuals exhibited

a heightened susceptibility to acute cardiac damage and cardiac rhythm disturbances. This can be attributed to the engagement of the myocardium in the viral infection caused by the coronavirus, as indicated by the raised concentrations of cardiac biomarkers. The findings of our study align with other meta-analyses that have also reported a correlation between pre-existing cardiovascular conditions and an increased susceptibility to severe and rapid progression of COVID-19 infection [29,30]

Moreover, a recent study conducted by Lala et al. shown that the occurrence of cardiovascular disorders in individuals infected with COVID-19 amplifies their vulnerability to myocardial injury and is linked to an elevated risk of mortality [31]. This work presents a unique contribution to the existing literature on the relationship between cardiovascular comorbidities and COVID-19 outcomes. While previous systematic reviews and meta-analyses have explored the collective influence of underlying cardiovascular comorbidities, our analysis specifically examines the isolated impact of congestive heart failure (CHF) on COVID-19 outcomes. In addition, previous research mostly included patients predominantly from Southeast Asia, but our study encompassed patients from other area. COVID-19 is an emerging viral disease that is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This particular virus utilizes angiotensin converting enzyme 2 (ACE 2) receptors as a means of entering the human body [1,14]. Heart myocytes, pericytes, vascular endothelial cells, lung alveolar epithelial cells and other organs all contain these receptors [32-34]. It is hypothesized that this ACE2 protein reduces the risk of myocardial and pulmonary injury. By lowering blood pressure, inflammation, and fibrosis, this ACE2 protein may have a preventive impact against myocardial and pulmonary injury [1, 35-38]. Additionally, it was revealed that the occurrence of heart failure is correlated with heightened mortality rates among those diagnosed with COVID-19. This observation aligns with other research that has reported comparable results.21 The ACE 2 enzyme functions to mitigate the impact of angiotensin II in conditions characterized by heightened activation of the renin-angiotensin system, such as heart failure.1 Patients with congestive heart failure (CHF) exhibit abnormalities of the intracellular calcium handling system [39] and The SARS-CoV-2 virus has been found to generate a state of hypoxia, resulting in an excessive influx of intracellular calcium. This dysregulation of calcium homeostasis can subsequently lead to the programmed cell death of cardiac myocytes, a process known as apoptosis [40]. This phenomenon has been associated with a higher incidence of mortality in individuals diagnosed with congestive heart failure. The elevation of NT-pro BNP has been observed in individuals diagnosed with congestive heart failure [41]. Furthermore, this increase in NT-pro BNP levels has been linked to an unfavorable prognosis in patients suffering from sepsis and pneumonia [42]. Several processes can contribute to the elevation of NT-pro BNP levels in COVID-19 patients, including increased ventricular wall stress caused by hypoxia-induced pulmonary hypertension and decreased clearance in critically sick patients with renal failure [43]. Elevated levels of NT-pro BNP have been found to be correlated with higher mortality rates among individuals diagnosed with COVID-19 [44]. A recent systematic review, primarily comprising patients from China, revealed a consistent observation of elevated fatality rates [45]. Despite the inclusion of patients from several geographical regions, the findings of our study remained constant.

Limitations

The systematic review conducted in our study is subject to various inherent limitations, including heterogeneity of study and the possibility of publication bias. Another noteworthy issue pertains to the retrospective study methods employed in the included research studies, as well as the absence of individual patient severity and medical information, such as smoking status. Consequently, we encountered difficulties in accounting for the confounding effects of different variables and other comorbidities.

Conclusion

In brief, the coexistence of congestive heart failure (CHF) in individuals diagnosed with COVID 19 is linked to heightened death rates and unfavorable outcomes throughout the initial hospitalization

period. It is recommended that there be diligent observation of individuals with severe COVID-19 who have pre-existing cardiac comorbidities, as this has been shown to decrease mortality rates.

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Table I: Patients demography and details of studies and in the systematic review

Author	Region	Sample	Mean Age	Sex (M/F)	HTN	DM	Smoking	CHF	Mortality (%)
Yu T et al	China	191	56	119/72	58	36	11	44	28
Chen et al	China	274	62	171/103	93	47	12	01	41
Inciardi et al	Italy	99	68.5	80/19	63	18	12	21	26
Tu L et al	China	85	65.8	-	32	19	NA	NA	100
Yin Y., et al	China	107	51	57/50	26	11	NA	NA	18
Garcia et al	USA	16	67	12/4	09	05	NA	04	50
Cao et al	China	102	54	53/49	28	11	NA	NA	16
Shi et al	China	671	63	322/349	199	97	NA	22	9
Wang L., et al	China	339	69	-	138	54	NA	58	19
He et al	China	54	68	34/20	24	13	NA	NA	48
Huang et al*	China	41	49	30/11	06	08	03	NA	15
Wang D., et al*	China	138	56	75/63	43	14	NA	NA	4.3
Petrilli et al*	USA	2729	64	1672/1057	1693	950	141	349	24
Yang et al*	China	136	56	66/70	36	20	NA	NA	17
Hu et al*	China	323	61	152/145	95	36	38	NA	11
Deng et al*	China	112	65	57/55	36	19	NA	NA	12.5
Wan et al*	China	135	47	73/62	13	12	09	NA	0.7
Lu et al*	China	265	NA	NA	52	21	NA	NA	0.38
Han et al*	China	47	65	NA	18	07	07	NA	NA
Peng et al*	China	112	62	53/49	92	23	NA	40	15

Table II: Risk ratio of death for patients with CHF compared to those without CHF

Study	CHF Event	CHF Total	No CHF Event	No CHF Total	Risk Ratio	95%-CI	Weight
Yu T et al	28	44	26	147	3.60	[2.38-5.44]	21.0%
Chen et al	0	1	113	273	0.80	[0.08-7.76]	4.4%
Inciardi et al	12	21	14	78	3.18	[1.74-5.81]	18.4%
Garcia et al	3	4	5	12	1.80	[0.75-4.32]	14.4%
Shi et al	13	22	49	649	7.83	[5.04-12.15]	20.7%
Wang L., et al	25	58	40	281	3.03	[2.01-4.57]	21.1%
		150		1440	3.38	[1.80-6.32]	100.0%
						[0.65-17.65]	

Random effect model Prediction interval:
Heterogeneity: I^2=70%, τ^2=0.2955, p<0.01

Table III: Risk ratio of death in hypertensive patients

Study	HTN Event	HTN Total	Non-HTN Event	Non-HTN Total	Risk Ratio	95%-CI	Weight
Yu T et al	26	58	28	133	2.13	[1.38-3.29]	10.9%
Chen et al	39	93	74	181	1.03	[0.76-1.38]	11.6%
Inciardi et al	17	63	9	36	1.08	[0.54-2.17]	9.3%
Tu L et al	32	32	53	53	1.00	[0.95-1.05]	12.3%
Yin Y., et al	10	26	9	81	3.46	[1.58-7.59]	8.8%
Garcia et al	3	9	5	7	0.47	[0.17-1.31]	7.2%
Cao et al	11	28	6	74	4.85	[1.98-11.85]	8.1%
Shi et al	37	199	25	472	3.51	[2.17-5.67]	10.7%
Wang L., et al	32	138	33	201	1.41	[0.91-2.18]	10.9%
He et al	12	24	14	30	1.07	[0.62-1.86]	10.2%
		670		1268	1.57	[0.97-2.56]	100.0%
						[0.34-7.29]	

Random effect model Prediction interval:
Heterogeneity: I^2=85%, τ^2=0.396, p<0.01