Research Article

Temporal Trend in Mortality from COVID-19 Associated with Cardiovascular Disease

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Abstract

Study Objective: The objective of this study is to investigate trends in all-cause mortality associated with co-morbid cardiovascular disease (CVD) throughout the consecutive waves of the COVID-19 pandemic.

Design: A retrospective cohort study was conducted on patients with COVID-19 infection. Multivariable logistic regression was used to investigate associations between co-existing CVD (defined as congestive heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease) and mortality, adjusting for age, sex, race, and comorbidities defined in the Charlson comorbidity index.

Setting: The study took place at Rush University System for Health, a tertiary care center in Chicago.

Participants: Patients greater than 18 years of age with a documented COVID-19 infection between March 2020 and September 2022.

Main Outcome Measures: The primary outcome was all-cause mortality.

Results: The study included 38651 participants (mean age 45 years, 57.6% female, 11.4% with co-existing CVD). All-cause mortality in COVID-19 patients was highest during the Delta wave and remained elevated until the late Omicron wave. Mortality associated with co-existing CVD increased during the early pandemic waves, decreased in the later waves, but remained elevated relative to the overall population. When adjusted for age, sex, and race, all-cause mortality was 2.3-fold higher in patients with co-existing CVD compared to those with non-CVD comorbidities (OR = 2.30, 95% CI 1.95 – 2.62; p < 0.001).

Conclusion: While overall mortality rates declined toward the later waves of the pandemic, all-cause mortality associated with CVD remained elevated compared to individuals without CVD.

Keywords: Cardiovascular, COVID-19, Temporal trends, Mortality

Introduction

The impact of Coronavirus disease 2019 (COVID-19) has touched millions of lives worldwide, causing downstream effects at the level of healthcare systems, communities, and patients. The COVID-19 pandemic has persisted for over three years, from March 2020 until the present day, with over twelve SARS-CoV-2 variants afflicting the globe. Consequently, we have had the opportunity to learn about the long-term effects of COVID-19

infections, examine temporal trends, and identify high-risk populations. Much of the research on COVID-19 mortality describes associations within a specific interval or wave of the pandemic. For example, retrospective studies and meta-analyses have repeatedly shown that advanced age and cardiovascular disease (CVD) are associated with worse overall morbidity and mortality outcomes in those infected with COVID-19 [1-4]. However, few studies have described the trends in COVID-19 mortality over time, starting from the emergence of the pandemic to the present day. A recent analysis of age-standardized death rates from 2010 to 2020 found that heart disease death rates declined by 9.8% from 2010 to 2019; however, death rates increased by 4.1% in 2020, coinciding with the advent of the pandemic [5]. Heart disease death rates in 2020 were even more pronounced among non-Hispanic Black adults, with an increase of 11.2%. Similarly, a cohort study by Sidney et al. noted an increase in risk-associated death from heart disease and stroke, with the highest risk observed in racial and ethnic minority groups, especially non-Hispanic Black and Hispanic individuals [6].

The etiology of this unfavorable trend is not well defined. Still, multiple theories include reduced access to preventive health care, psychosocial and economic factors, increased stress and anxiety, diminished physical activity, and a possible predisposition to CVD in those with prior COVID-19 infection. This study specifically investigates all-cause mortality associated with CVD through the sequential waves of the pandemic. It is important that trends associated with specific comorbidities, especially CVD, are detected as it has implications from not only a healthcare provider perspective but also from a public health and healthcare systems outlook.

Materials & Methods

Study Design

We performed a retrospective study among a cohort of patients who were under investigation for COVID-19 at Rush University System for Health from March 2020 to September 2022. We included patients greater than 18 years of age with a documented infection of COVID-19. We divided the pandemic into six distinct waves based on the predominant coronavirus variants and COVID-19 vaccine distribution. The study was approved by the Rush University Institutional Review Board (IRB) and exempt from informed consent.

Exposure

CVD was defined using the International Classification of Diseases (ICD)-10 codes: congestive heart failure (CHF), myocardial infarction (MI), cerebrovascular disease (CEVD), or peripheral vascular disease (PVD).

Outcomes

The primary outcome of this study is all-cause mortality, including both inpatient and outpatient deaths, as documented through a retrospective review of patients' electronic medical records. Inpatient deaths were defined as deaths associated with in-hospital admissions or emergency room visits; outpatient deaths were defined as deaths associated with out-of-hospital or patient vehicle encounters. The date of death was identified through a retrospective review of the patient record. The secondary outcome of this study is inpatient hospitalizations.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics. We assessed associations between co-existing CVD and mortality using multivariable logistic regression, adjusting for age, sex, race, CVD comorbidities defined in the Charlson comorbidity index (CHF, MI, CEVD, and PVD), and non-CVD comorbidities defined in the Charlson comorbidity index (dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, any malignancy [including lymphoma and leukemia, except malignant neoplasm of skin], moderate or severe liver disease, metastatic solid tumor, and AIDS/HIV) [7]. A p-value of $p < 0.05$ was used to determine statistical significance. Age-stratified analyses were conducted to identify differences in demographics and comorbidities across age groups (18-49 years, 50-69 years, and 70-90 years). All statistical analyses were performed using R4.1.2.

Results

Among 38,651 patients (mean age 45 years, 57.6% female, 11.4% with existing CVD comorbidities), 1,046 (2.7%) died. Across all waves of the pandemic, higher mortality was seen among individuals aged 70-90 (11.7%) and aged >90 (24.5%), men (3.5%), and persons with co-existing CVD comorbidities (12.2%) (**Table 1**). All-cause mortality in patients with COVID-19 was highest during the Delta wave (3.8% from June 2021 to December 2021) (**Table 2**) and remained elevated until the late Omicron wave (until March 2022). Mortality associated with co-existing CVD increased similarly through the early pandemic waves. Although decreasing in later waves, the mortality for patients with co-existing CVD remained elevated relative to the overall adult population (**Figure 1**). When adjusted for age, sex, and race, all-cause mortality was 2.3-fold higher in patients with co-existing CVD compared to those without any comorbidities as defined by the Charlson comorbidity index (OR = 2.30, 95% CI 1.95 – 2.62; p < 0.001) (**Figure 2a**). Further analysis stratified by age groups (adults with age <50 years, age 50-69, and age 70-90) indicate that co-existing CVD had a markedly increased risk of death amongst those <50 years of age (OR=8.26, 95% CI 5.42 – 12.55) (**Figure 2b**).

Further analyses were performed to evaluate the four

Table 1: Baseline characteristics of COVID-19-positive patients treated at Rush University System for Health from March 2020 to September 2022.

| Characteristic	N (%)	Death	No Death
	N=38651	N (%)	N (%)
		N=1046	N=37605
Age (years)			
18 - 49	23990 (62.1%)	125 (0.5%)	23865 (99.5%)
50-69	10540 (27.3%)	404 (3.8%)	10136 (96.2%)
70-90	3860 (10.0%)	453 (11.7%)	3407 (88.3%)
> 90	261 (0.7%)	64 (24.5%)	197 (75.5%)
Gender			
Female	22262 (57.6%)	475 (2.1%)	21787 (97.9%)
Male	16389 (42.4%)	571 (3.5%)	15818 (96.5%)
Race			
White	13008 (33.7%)	415 (3.2%)	12593 (96.8%)
Black or African American	11560 (29.9%)	316 (2.7%)	11244 (97.3%)
Asian or Other	1167 (3.0%)	32 (2.7%)	1135 (97.3%)
Undisclosed	12916 (33.4%)	283 (2.2%)	12633 (97.8%)
Comorbidity[a]			
CVD	4391 (11.4%)	535 (12.2%)	3856 (87.8%)
Myocardial infarction	1089 (2.8%)	165 (15.2%)	924 (84.8%)
Congestive heart failure	2120 (5.5%)	288 (13.6%)	1832 (86.4%)
Peripheral vascular disease	1593 (4.1%)	187 (11.7%)	1406 (88.3%)
Cerebrovascular disease	1836 (4.8%)	255 (13.9%)	1581 (86.1%)
Non-CVD	11784 (30.5%)	789 (6.7%)	10995 (93.3%)
Dementia	560 (1.4%)	99 (17.7%)	461 (82.3%)
Chronic pulmonary disease	4541 (11.7%)	228 (5.0%)	4313 (95%)
Rheumatic disease	606 (1.6%)	38 (6.3%)	568 (93.7%)
Peptic ulcer disease	250 (0.6%)	32 (12.8%)	218 (87.2%)
Mild liver disease	1434 (3.7%)	99 (6.9%)	1335 (93.1%)
Diabetes without chronic complication	3502 (9.1%)	208 (5.9%)	3294 (94.1%)
Diabetes with chronic complication	2089 (5.4%)	239 (11.4%)	1850 (88.6%)
Hemiplegia or paraplegia	202 (0.5%)	23 (11.4%)	179 (88.6%)
Renal disease	2253 (5.8%)	319 (14.2%)	1934 (85.8%)
Malignancy[b]	1825 (4.7%)	152 (8.3%)	1673 (91.7%)
Moderate or severe liver disease	199 (0.5%)	45 (22.6%)	154 (77.4%)
Metastatic solid tumor	505 (1.3%)	115 (22.8%)	390 (77.2%)
AIDS/HIV	142 (0.4%)	7 (4.9%)	135 (95.1%)

[a]CVD and non-CVD comorbidities are not mutually exclusive.

[b]Malignancy includes lymphoma and leukemia, except malignant neoplasm of skin.

Abbreviations: acquired immunodeficiency syndrome, AIDS; cardiovascular disease, CVD; human immunodeficiency virus, HIV.

Table 2: COVID-19 pandemic waves, hospitalization rates, and mortality rates of COVID-19 adult patients overall and with co-existing CVD.

Wave- Predominant COVID-19 Variant	Overall Adult Population			Adults With Co-Existing CVD		
	N	Hospitalization N (%)	Mortality N (%)	N	Hospitalization N (%)	Mortality N (%)
1: Wildtype+D614G (3/7/2020 – 3/20/2021)	21253	5901; 27.8%	627; 3.0%	2130	1142; 53.6%	297; 13.9%
2: Alpha (3/21/2021 – 6/19/2021)	1871	801; 42.8%	57; 3.0%	247	168; 68.0%	38; 15.4%
3: Delta (6/20/2021 – 12/11/2021)	3070	1259; 41.0%	118; 3.8%	372	229; 61.6%	56; 15.1%
4: Omicron BA.1 (12/12/2021 – 3/19/2022)	8236	2290; 27.8%	204; 2.5%	1028	552; 53.7%	119; 11.6%
5: Omicron BA.2 (3/20/2022 – 6/18/2022)	1750	469; 26.8%	18; 1.0%	232	119; 51.3%	12; 5.2%
6: Omicron BA.4/ BA.5 (6/19/2022 – (9/30/2022)	2471	797; 32.3%	22; 0.9%	382	184; 48.2%	13; 3.4%
Overall	38651	11517; 29.8%	1046; 2.7%	4391	2394; 54.5%	535; 12.2%
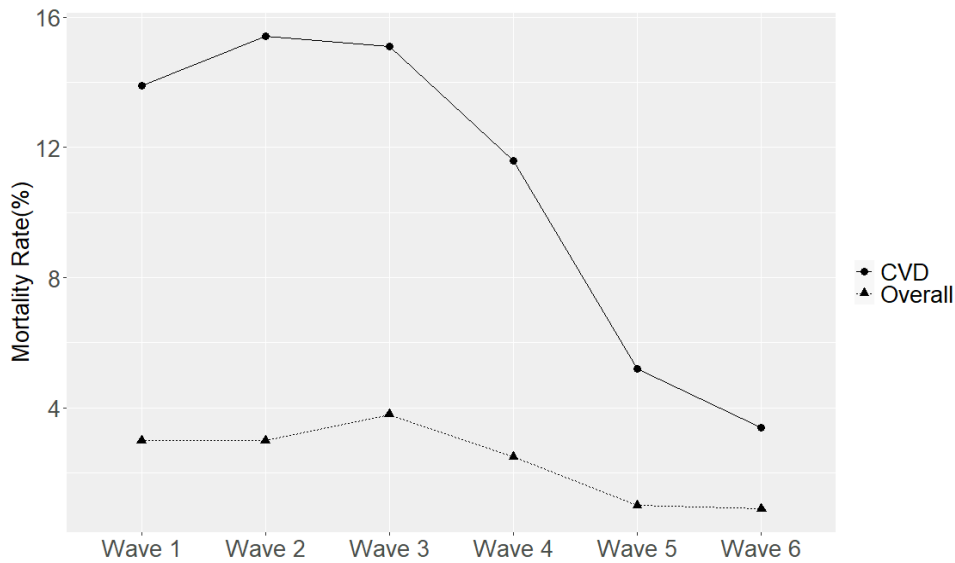
Figure 1: Mortality rate in each pandemic wave (Overall vs. co-existing cardiovascular disease).

CVD comorbidities in the Charlson index (CHF, MI, CEVD, and PVD). Mortality in patients with COVID-19 was highest during the Alpha wave for CEVD (18.4%), CHF (19.8%), and PVD (15.8%). For those with a history of MI, the highest mortality occurred during the initial Wildtype variant (18.2%) (**Figure 3, Table 3**), plateaued through Wave 2 – 4 but began rising again during Wave 6. In contrast, mortality in patients with co-existing CEVD, CHF, or PVD continued to decline over time. Hospitalizations associated with co-existing CVD

similarly peaked with the Alpha wave and generally declined with subsequent waves (**Figure 3, Table 3**).

Limitations

A limitation of this study is that this database could not determine if the mortality was due to the preexisting CVD in the patient or if it was due to the COVID-19 infection. Another limitation is that we used the date range to represent the COVID-19 variant, not the patients' actual viral infection.
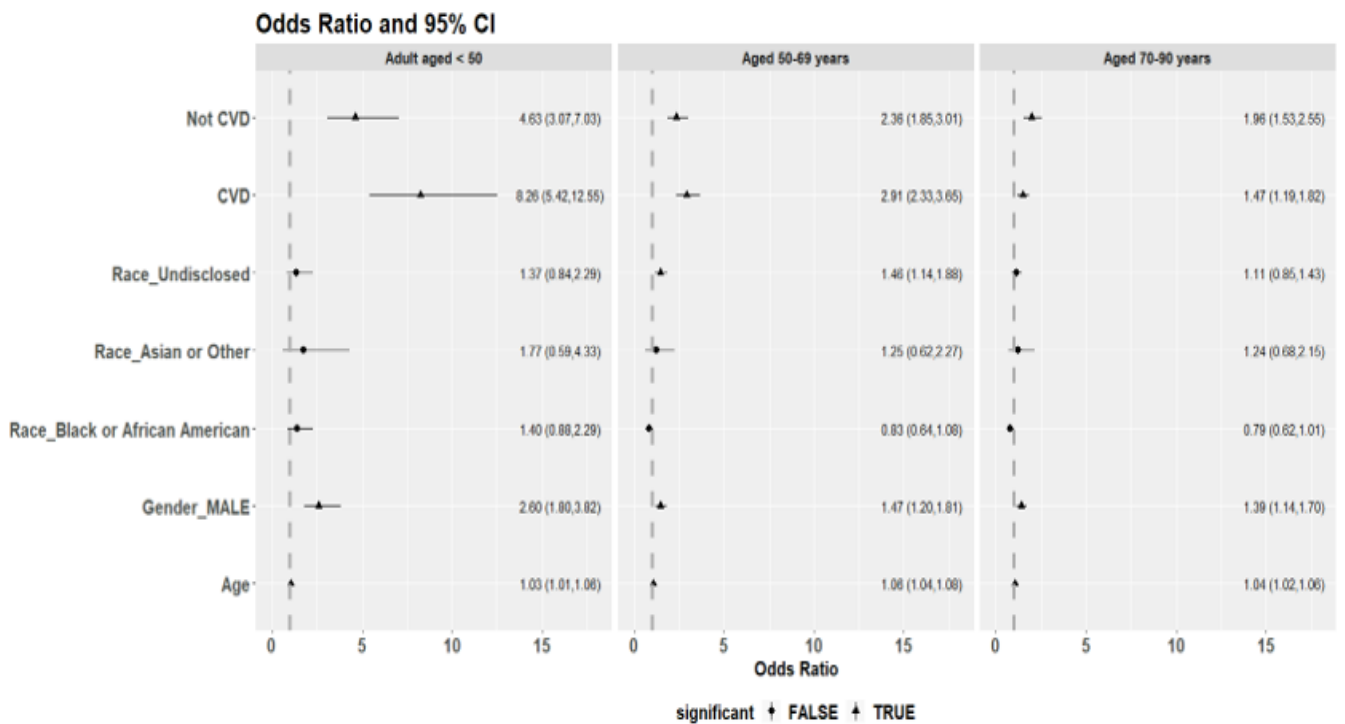

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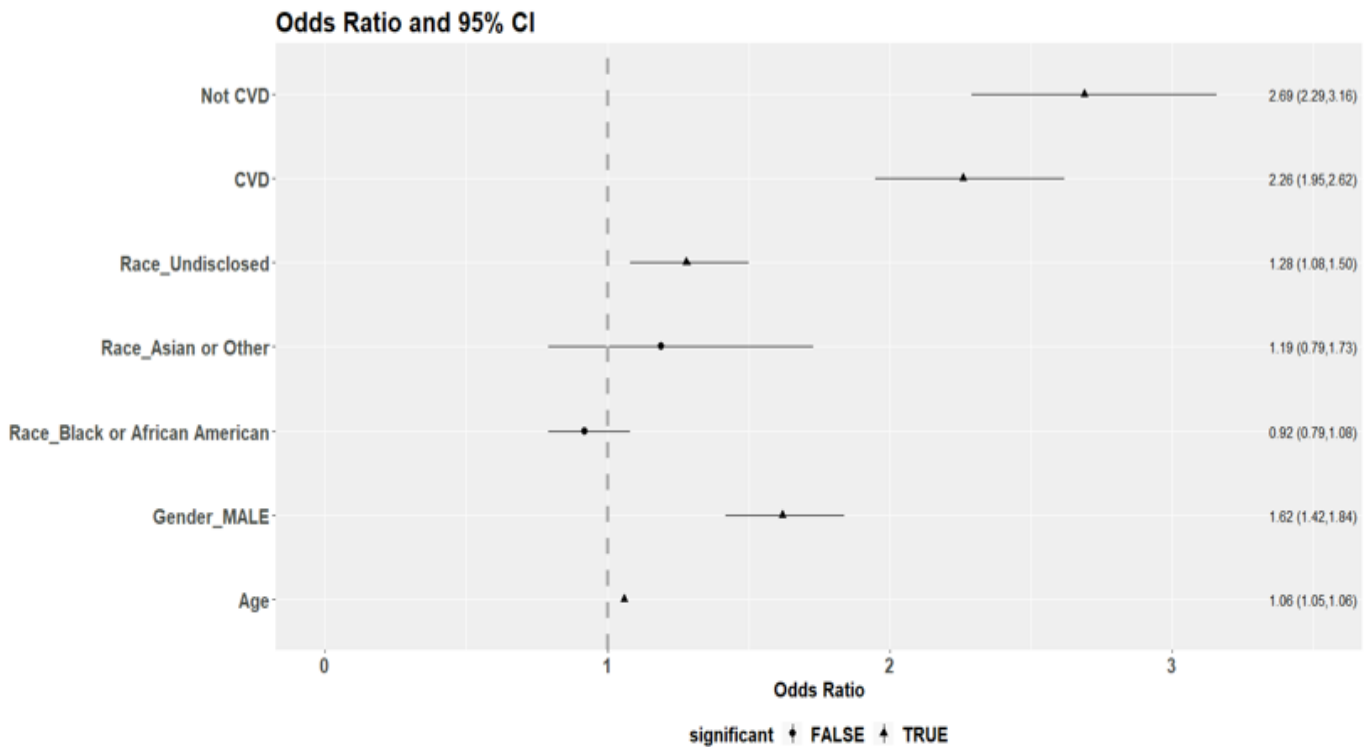
Figure 2: Multivariable logistic regression model for **(a)** overall mortality and **(b)** age-stratified mortality.

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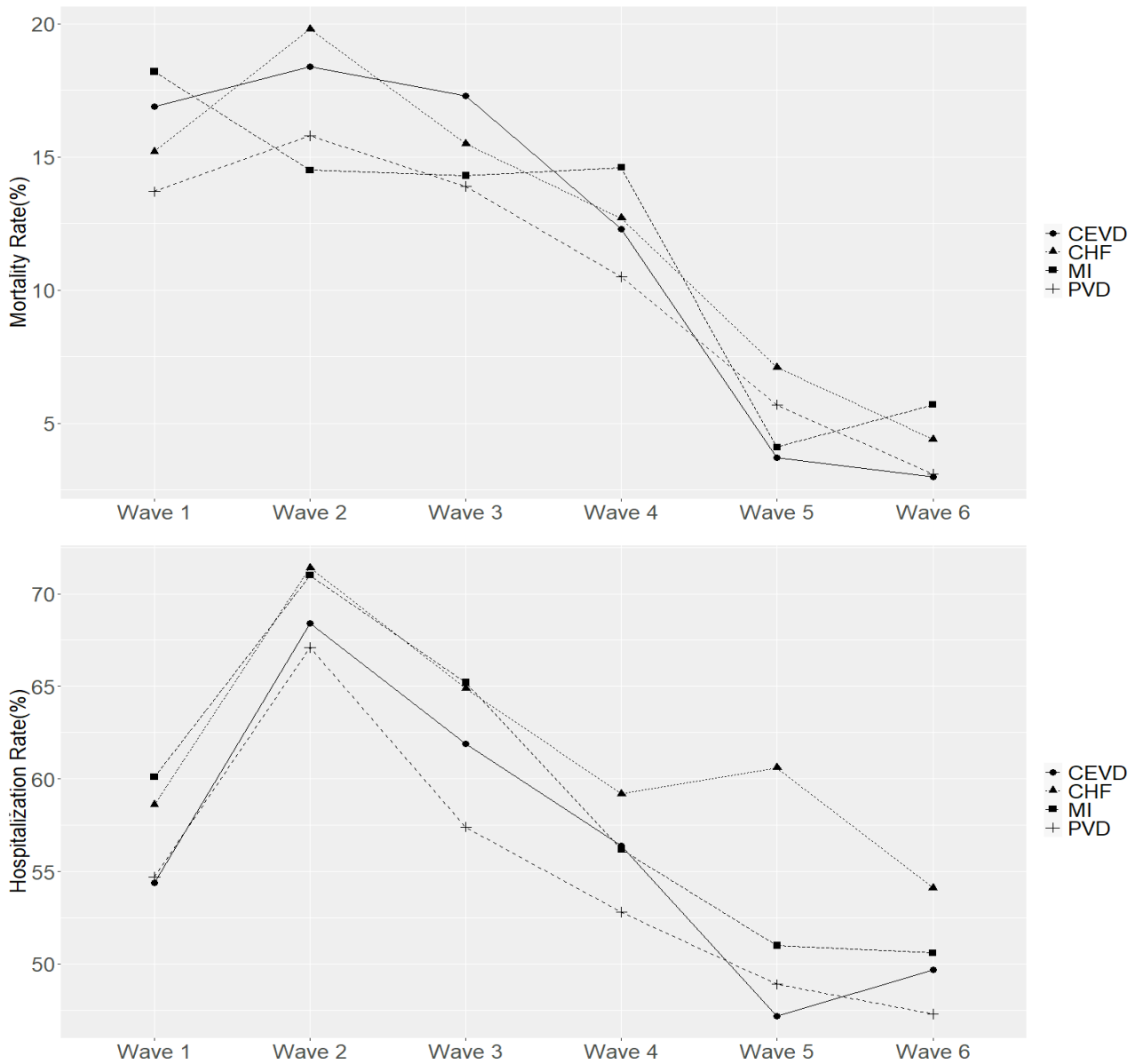
Figure 3: Mortality (top) and hospitalization (bottom) rate in each pandemic wave (Overall vs co-existing CVD).

Abbreviations: cerebrovascular disease, CEVD; congestive heart failure, CHF; myocardial infarction, MI; peripheral vascular disease, PVD.

Discussion

This retrospective cohort study highlights temporal trends in CVD-associated mortality compared to the general population of COVID-19 patients. While overall mortality rates declined toward the more recent waves of the pandemic with late Omicron variants predominating, all-cause mortality associated with CVD remained elevated compared to non-CVD-associated individuals. To our knowledge, this is the first study to report these findings and one of few studies that describe temporal trends during the pandemic. While a few papers illustrate CV mortality trends over the last decade, they did not specifically analyze patients with documented

COVID-19 infections [5, 6]. A study performed in Japan did look at temporal trends related to in-hospital COVID-19 mortality during three waves of the pandemic and noted a progressive decline in in-hospital mortality with each wave when adjusted for sex and age; however, they did not look at CVD associations [8]. It is well known that cardiovascular comorbidities are associated with increased morbidity and mortality due to COVID-19 [9]. However, whether individuals with prior COVID-19 infection are at increased risk of subsequent CVD events is still unclear. It has been suggested that patients with a prior COVID-19 infection are at increased risk of atrial fibrillation, venous thromboembolism, heart failure, and death; these events were noted particularly

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in patients who required hospitalization and more commonly in the early post-infection period within 30 days [10]. Similar findings were observed in a study by Wang et al., who noted a significantly higher 12-month risk of CVD in survivors of COVID-19 compared to non-infected controls [11].

There are no proven explanations for the increase in all-cause mortality in COVID-19 patients with associated CVD; however, the etiology is likely multifactorial. Probable factors include lack of access to or reluctance to seek healthcare during the pandemic, healthcare disparities in certain racial/ethnic and socioeconomic groups, hospital strain and limited healthcare resources, reduced physical activity, increased propensity for detrimental habits, and a potential predisposition to CVD in those with prior COVID-19 infection. The variations of mortality rates in patients with a history of MI suggest that the variants of COVID-19 may have different virulence in atherosclerotic disease. During the early waves of the pandemic, there was limited access to preventive health care and a shift toward telemedicine, which led to delays in detecting and treating cardiovascular conditions. A web-based survey of U.S. adults obtained in June 2020 revealed that 40.9% of adults avoided medical care due to COVID-19 concerns, with 12.0% avoiding urgent/emergent care and 31.5% avoiding routine care [12].

A recent study by Gotanda et al. describes a substantial decline in blood pressure monitoring during the early pandemic; they also found that blood pressure measurements in patients with chronic hypertension were significantly higher during the pandemic compared to pre-pandemic times [13]. Furthermore, there was a delay in care from the perspective of hospital systems, including deferral of elective procedures, such as outpatient coronary angiograms and percutaneous coronary interventions. There was even an estimated 38.0% reduction in STEMI activations during the early waves of the pandemic [14]. These factors likely propagated detrimental downstream cardiovascular sequelae such as congestive heart failure, MI, and cardiovascular mortality. Multiple psychosocial and behavioral factors likely contributed to the temporal rise in CVD-associated mortality observed during the pandemic. Quarantine periods and social distancing became essential practices to mitigate the spread of COVID-19 infection; however, a recent scoping review revealed that social isolation and loneliness are directly associated with increased mortality from coronary heart disease and stroke [15]. Due to lockdown and quarantine circumstances, many people were required to stay in their homes. Over time, the work culture for many occupations has transitioned to "work from home" conditions. As a result, less participation in physical activity, increased alcohol consumption, higher anxiety scores, increased weight gain, and higher rates of obesity have been observed [16, 17]. Further research is needed to explore the possible underlying mechanism(s) behind observed increases in cardiovascular conditions in patients with COVID-19. It would also be valuable to explore direct causes for the temporal rise in CVD-associated mortality, as well as identify other temporal trends in the COVID-19 population, as these would have significant public health implications.

References

1. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis. Aug 29 (2020): 104949.

2. Silverio A, Di Maio M, Citro R, et al. Cardiovascular risk factors and mortality in hospitalized patients with COVID-19: systematic review and meta-analysis of 45 studies and 18,300 patients. BMC Cardiovasc Disord. Jan 7 21 (2021): 23.

3. Li X, Guan B, Su T, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart. Aug 106 (2020): 1142-1147.

4. Mishra P, Parveen R, Bajpai R, Samim M, Agarwal NB. Impact of cardiovascular diseases on severity of COVID-19 patients: A systematic review. Ann Acad Med Singap. Jan 50 (2021): 52-60.

5. Woodruff RC, Tong X, Jackson SL, Loustalot FV, Vaughan AS. Abstract 9853: Trends in National Death Rates from Heart Disease in the United States, 2010–2020. Circulation 146 (2022): A9853-A9853.

6. Sidney S, Lee C, Liu J, Khan SS, Lloyd-Jones DM, Rana JS. Age-Adjusted Mortality Rates and Age and Risk-Associated Contributions to Change in Heart Disease and Stroke Mortality, 2011-2019 and 2019-2020. JAMA Netw Open. Mar 1 5 (2022): e223872.

7. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care Nov 43 (2005): 1130-9.

8. Endo H, Lee K, Ohnuma T, Watanabe S, Fushimi K. Temporal trends in clinical characteristics and in-hospital

mortality among patients with COVID-19 in Japan for waves 1, 2, and 3: A retrospective cohort study. J Infect Chemother. Oct 28 (2022): 1393-1401.

9. Sahni S, Gupta G, Sarda R, Pandey S, Pandey RM, Sinha S. Impact of metabolic and cardiovascular disease on COVID-19 mortality: A systematic review and meta-analysis. Diabetes Metab Syndr. Nov-Dec 15 (2021): 102308.

10. Raisi-Estabragh Z, Cooper J, Salih A, et al. Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank. Heart. Oct 24 (2022).

11. Wang W, Wang CY, Wang SI, Wei JC. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks. E Clinical Medicine Nov 53 (2022): 101619.

12. Czeisler M, Marynak K, Clarke KEN, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. MMWR Morb Mortal Wkly Rep. Sep 11 69 (2020): 1250-1257.

13. Gotanda H, Liyanage-Don N, Moran AE, et al. Changes in Blood Pressure Outcomes Among Hypertensive Individuals During the COVID-19 Pandemic: A Time Series Analysis in Three US Healthcare Organizations. Hypertension. Dec 79 (2022): 2733-2742.

14. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-Segment Elevation Cardiac Catheterization Laboratory Activations in the United States During COVID-19 Pandemic. J Am Coll Cardiol. Jun 75 (2020): 2871-2872.

15. Cené CW, Beckie TM, Sims M, et al. Effects of Objective and Perceived Social Isolation on Cardiovascular and Brain Health: A Scientific Statement from the American Heart Association. J Am Heart Assoc. Aug 16 11 (2022): e026493.

16. Restrepo BJ. Obesity Prevalence Among U.S. Adults During the COVID-19 Pandemic. Am J Prev Med. Jul 63 (2022): 102-106.

17. Flanagan EW, Beyl RA, Fearnbach SN, Altazan AD, Martin CK, Redman LM. The Impact of COVID-19 Stay-At-Home Orders on Health Behaviors in Adults. Obesity (Silver Spring). Feb 29 (2021;29(2):438-445. doi:10.1002/oby.23066