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Short Communication

# The changing landscape of cardiac co-morbidities and in-hospital cardiac complications mediating Covid-19 mortality between 2020 and 2021☆

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ABSTRACT

*Background:* Cardiac co-morbidities and in-hospital cardiac complications significantly contribute to COVID-19 mortality. However, their influence on mortality between 2021 and 2020 may differ due to the availability of vaccines, different viral strains, and therapeutic advancements.
*Methods:* We performed a retrospective chart review and individual patient analysis of all COVID-19 associated in-patient deaths in 2020 ($n = 346$) and 2021($n = 527$) in a large Minneapolis health system. Cause of death was adjudicated by at least two health care providers, including one cardiologist.
*Results:* Patients who died in 2021 were younger, of similar race/ethnicity, and body mass index compared to 2020. In 2021, 24 % of the cohort was full or partially vaccinated, while none were vaccinated in 2020. Patients who died in 2021 had significantly fewer cardiovascular co-morbidities and major adverse cardiovascular events prior to COVID-19 infection, resulting in significantly fewer in-hospital cardiac adverse events compared to patients who died in 2020, including myocardial infarction, stroke, and atrial fibrillation. In contrast, patients in 2021 had significantly higher rates of venous thromboembolic events.
*Conclusion:* Patients who died from COVID-19 in 2021 had significantly fewer cardiovascular co-morbidities and in-hospital cardiovascular complications compared to patients who died in 2020. Sixteen percent of patients stipulated as dying from COVID-19 actually die from other causes.

## 1. Introduction

Cardiac co-morbidities and in-hospital cardiac complications contribute significantly to COVID-19 mortality [1]. However, their influence on mortality between 2021 and 2020 may differ due to availability of vaccines, viral strains and therapeutics. Novel mutations of SARS-CoV-2 spike proteins in 2021resulting in the predominant Delta variant, influenced the incidence of severe COVID-19 infection [2]. Additionally, 2021 resulted in mass vaccination against SARS-CoV-2 and advancements in the management of severe COVID-19. These changes are of specific interest, as it has been speculated that vaccination status and SARS-CoV-2 variants may independently influence COVID-19 outcomes in clinical trials [3]. Thus, we investigated whether the incidence of pre-existing cardiac morbidities and rate of in-hospital cardiac complications altered COVID-19 mortality between 2020 and 2021. The present study performed a retrospective chart review and individual patient analysis of all patients who died with a COVID-19 diagnosis during their terminal hospitalizations in 2020 and 2021 in the largest metropolitan Minneapolis-St. Paul health system.

## 2. Methods

All patients who died with an active International Classification of Diseases (10th revision) COVID-19 diagnosis between March 19, 2020

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. JT, TB, and MD contributed to conception and design of the study. TB, MD, AA, and SO organized the database. BO performed the statistical analysis. TB, MD, and JT wrote the first draft of the manuscript. TB, MD, and JT wrote sections of the manuscript. All authors read and approved the submitted version.

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and December 31, 2021 in the metropolitan hospitals of Allina Health were identified. Clinical characteristics, cardiac co-morbidities, and in-hospital cardiac complications of 1034 patients who died with COVID-19 in 2020 ($n$ = 420) and 2021 ($n$ = 614) were extracted from the electronic health record. To reduce heterogeneity in what defines severe COVID-19, only patients who died primarily from COVID-19 were included in the study. Each cause of death was adjudicated as a primary or non-primary COVID-19 death by two health care practitioners, including one cardiologist. Patients were stipulated as primarily dying from COVID-19 if they had a positive COVID-19 test, chest x-ray or computed tomography imaging consistent with COVID-19, and suffered from progressive respiratory failure. Of 1034 patients that died with COVID-19, 346 (2020) and 527 (2021) patients were deemed to have died primarily from COVID-19 and were used for this analysis.

### 2.1. Statistical methods

Continuous variables are summarized with the median and inter-quartile range or mean and standard deviation and compared across years using the Wilcoxon rank sum test or unpaired $t$-test, respectively. Categorical variables are summarized with count and percentage and compared across years using Chi-squared test or Fisher's exact test where noted. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Review Board of Allina Health.

## 3. Results

Within our study population, the in-hospital mortality rate from COVID-19 was similar between 2020 and 2021 (1.21 vs 1.44 deaths/day). Compared to 2020, patients who died from COVID-19 in 2021 were younger (69 vs 76 years; $p < 0.01$) with similar distributions of sex, race, and body mass index (BMI). In 2021, 24 % of the cohort received full or partial vaccination while none were vaccinated in 2020. Patients who died primarily from COVID-19 in 2021 had lower rates of pre-existing cardiovascular co-morbidities as well as COPD (22 vs. 28 %), chronic kidney disease (34 vs. 46 %), and sleep apnea (22 vs. 30 %) (all $p < 0.05$) (Table 1).

Patients who died in 2021 had significantly fewer cardiovascular risk factors including hypertension (69 vs 84 %), smoking (9.5 vs 57 %), diabetes (40 vs 50 %) and dyslipidemia (65 vs 75 %) compared to 2020 (all $p < 0.005$) (Table 1). In 2021, lower rates of cardiac co-morbidities and risk factors resulted in significantly fewer troponin-positive (> 0.04 ng/mL) patients on admission (51 vs. 64 %; $p < 0.001$) and fewer in-hospital cardiac adverse events including atrial fibrillation/flutter. Patients who died in 2021 had lower rates of arterial thromboembolic events (ATE) including stroke and myocardial infarction (MI) compared to 2020 ($p < 0.035$) (Table 2). In contrast, patients who died in 2021 had significantly higher rates of venous thromboembolism (VTEs), including pulmonary embolism (PE) and deep vein thrombosis (DVT) despite more aggressive anticoagulation ($p < 0.001$). Sub-group analysis revealed unvaccinated patients who died from COVID-19 in 2021 were younger than their vaccinated counterparts (67.6 vs 74.3 years; p < 0.001). However, the rate of VTE was not affected by vaccination status (25.3 vs. 18.8 %; $p = 0.82$) or sex. Approximately 67 % of all subjects received intravenous steroids, 114 patients received monoclonal antibody therapy (Tocilizumab =91) and 75 patients received convalescent plasma.

A total of 161 COVID-positive patients who were stipulated as dying from COVID-19 primarily died from other causes including cardiovascular disease ($n$ = 48), sepsis ($n$ = 28), stroke (n = 28), pneumonia ($n$ = 15), and cancer ($n$ = 10) and were not included in the final analysis.

## 4. Discussion

The present study reveals several interesting findings regarding cardiovascular factors that contributed to COVID-19 mortality in 2020

**Table 1**
Cardiac co-morbidities during the terminal hospitalization of patients who died primarily of COVID-19 in the Allina Health System between 2020 and 2021.

| | All primary COVID-19 deaths 2020–21 ($N$ = 873) | 2020 primary COVID-19 deaths ($n$ = 346) | 2021 primary COVID-19 deaths ($n$ = 527) | $P$-value |
|---|---|---|---|---|
| Age at admission (n) | 72 (63, 81) | 76 (68, 83) | 69 (61, 78) | **<0.001**[b] |
| - 18–55 | 99 (11 %) | 20 (5.8 %) | 79 (15 %) | **<0.001**[a] |
| - 56–65 | 170 (19 %) | 47 (14 %) | 123 (23 %) | |
| - 66–75 | 253 (29 %) | 100 (29 %) | 153 (29 %) | |
| - 76–85 | 222 (25 %) | 106 (31 %) | 116 (22 %) | |
| - >85 | 129 (15 %) | 73 (21 %) | 56 (11 %) | |
| Body mass index | 30 (25, 35) | 30 (26, 36) | 29 (25, 35) | 0.21[b] |
| - Obese (n) | 403 (48 %) | 174 (50 %) | 229 (46 %) | 0.23[a] |
| Hypertension (n) | 656 (75 %) | 290 (84 %) | 366 (69 %) | **<0.001**[a] |
| Smoking (n) | 247 (28 %) | 197 (57 %) | 50 (9.5 %) | **<0.001**[a] |
| Hx of CAD (n) | 356 (41 %) | 154 (45 %) | 202 (38 %) | 0.069[a] |
| Hx of dyslipidemia | 604 (69 %) | 260 (75 %) | 344 (65 %) | **0.002**[a] |
| Diabetes (n) | 386 (44 %) | 173 (50 %) | 213 (40 %) | **0.005**[a] |
| COPD (n) | 215 (25 %) | 98 (28 %) | 117 (22 %) | **0.040**[a] |
| CKD (n) | 341 (39 %) | 160 (46 %) | 181 (34 %) | **<0.001**[a] |
| Hx of dialysis (n) | 61 (7.0 %) | 14 (4.0 %) | 47 (8.9 %) | **0.006**[a] |
| Pulmonary HTN (n) | 178 (20 %) | 69 (20 %) | 109 (21 %) | 0.79[a] |
| Sleep apnea | 221 (25 %) | 103 (30 %) | 118 (22 %) | **0.014**[a] |
| Hx of MI | 153 (18 %) | 86 (25 %) | 67 (13 %) | **<0.001**[a] |
| Hx of CABG | 84 (9.6 %) | 31 (9.0 %) | 53 (10 %) | 0.59[a] |
| Hx of PCI | 132 (15 %) | 80 (23 %) | 52 (9.9 %) | **<0.001**[a] |
| Hx of stroke/TIA | 149 (17 %) | 77 (22 %) | 72 (14 %) | **<0.001**[a] |
| Hx of CHF | 229 (26 %) | 115 (33 %) | 114 (22 %) | **<0.001**[a] |
| Hx of PVD/PAD | 175 (20 %) | 87 (25 %) | 88 (17 %) | **0.002**[a] |
| Hx of A-Fib/A-Flutter | 239 (27 %) | 126 (36 %) | 113 (21 %) | **<0.001**[a] |

[a] Pearson's Chi-squared test.
[b] Wilcoxon rank sum test.

**Table 2**
Rate of adverse events during the terminal hospitalization of patients who died primarily of COVID-19 in the Allina Health System between 2020 and 2021.

| | All primary COVID-19 deaths 2020–21 ($N$ = 873) | 2020 primary COVID-19 deaths (n = 346) | 2021 primary COVID-19 deaths ($n$ = 527) | P-value |
|---|---|---|---|---|
| MI (n) | 70 (8.0 %) | 36 (10 %) | 34 (6.5 %) | **0.035**[a] |
| CVA (n) | 106 (12 %) | 77 (22 %) | 29 (5.5 %) | **<0.001**[a] |
| DVT/PE (n) | 162 (19 %) | 35 (10 %) | 127 (24 %) | **<0.001**[a] |
| Shock (n) | 335 (38 %) | 109 (32 %) | 226 (43 %) | **<0.001**[a] |
| - Cardiogenic | 37 (4.2 %) | 9 (2.6 %) | 28 (5.3 %) | 0.052[a] |
| - Septic | 213 (24 %) | 65 (19 %) | 148 (28 %) | **0.002**[a] |
| A-Fib/A-Flutter (n) | 295 (34 %) | 151 (44 %) | 144 (27 %) | **<0.001**[a] |
| V-Fib/V-Tach (n) | 74 (8.5 %) | 31 (9.0 %) | 43 (8.2 %) | 0.68[a] |
| AKI (n) | 555 (64 %) | 207 (60 %) | 348 (66 %) | 0.062[a] |
| Dialysis/CRRT (n) | 123 (14 %) | 45 (13 %) | 78 (15 %) | 0.46[a] |
| Peak troponin (IQR, ng/mL) | 0.05 (0.02, 0.19) N = 654 | 0.07 (0.03, 0.22) N = 235 | 0.04 (0.01, 0.17) $N$ = 419 | **<0.001**[b] |
| Elevated troponin (n, >0.04 ng/mL) | 364 (56 %) $N$ = 654 | 151 (64 %) $N$ = 235 | 213 (51 %) N = 419 | **<0.001**[a] |

[a] Pearson's Chi-squared test.
[b] Wilcoxon Rank Sum Test.

and 2021. State-level data from the Minnesota Department Health shows that COVID-19 accounted for 11 % of all deaths in 2020 (5926 COVID-19 deaths/52,342 total deaths) and 9.6 % of all deaths in 2021 (4955 COVID-19 deaths/51,640 total deaths). Our data suggests that in 2021, the relative rate of hospital deaths from COVID-19 significantly declined in the elderly but increased in younger patients < 55 years old (5.8 % of deaths among patients in 2020 vs 15 % in 2021). This may be explained by the significantly greater number of patients who died from COVID-19 outside the hospital in nursing homes in 2020 (3176 of 5926 COVID-19 deaths) compared to 2021 (1321 of 4955 COVID-19 deaths) [4] resulting in fewer elderly and vulnerable patients left to die in 2021. A second factor that may have influenced our results is the introduction of vaccines. The decline in elderly mortality in 2021 may be secondary to the concerted effort to offer early vaccination to this group as 85 % of seniors were vaccinated by April 2021 in Minnesota [4].

Data from the NCATS N3C Data Enclave suggests vaccination for COVID-19 is associated with freedom from Major Adverse Cardiovascular Events (MACE) [5]. Although vaccinated individuals were significantly older than their unvaccinated counterparts at time of in-patient death from COVID-19 in 2021, our study found no significant differences in rates of ATE and VTE during terminal hospitalization for COVID-19 between these groups, nor between males and females. Future studies should assess the specific role of vaccination in addition to any sex differences both clinically and mechanistically on COVID-19 morbidity and mortality.

Changes in SARS-CoV-2 variants occurring between 2020 and 2021 may have also influenced our findings. In Minnesota, the principal ancestral SARS-CoV-2 strain in 2020 transitioned to the Alpha variant beginning in 2021 followed by the Delta variant in June 2021and Omicron by year's end [4]. The inflammatory and pro-thrombotic effects of SARS-CoV-2 could be influenced by individual variants as supported by several studies demonstrating that susceptibility to clotting and clinical events such as pulmonary embolism may vary by the strain of SARS-CoV-2 [6]. Additionally, a 28-study meta-analysis assessing predictors and mortality risk of VTEs in patients with COVID-19 suggested no significant association between VTEs and prophylactic or therapeutic anticoagulation therapy [7]. These factors may have contributed to the significant increase in VTEs observed for patients who died in 2021 despite heightened awareness of prophylactic anticoagulation use throughout the pandemic (Table 2).

To our knowledge, this is the first clinical study using individual patient data to investigate how temporal changes in SARS-CoV-2 variants and vaccination status between 2020 and 2021 may influence cardiovascular complications among patients with severe COVID-19 infection. These factors were recently speculated to be confounders of clinical trials with COVID-19 related outcomes, and thus are of specific clinical interest. However, our findings come with limitations as a preliminary, retrospective cohort study with a moderate sample size although it does represent a significant fraction of all deaths in the State of Minnesota between 2020 and 2021.

In conclusion, the influence of cardiovascular risks factors and in-hospital cardiac complications on COVID-19 mortality significantly declined between 2020 and 2021despite an increase in the rate of VTEs. These changes may be attributed in part, to the development of vaccines and shifts in viral strain between 2020 and 2021. Additionally, we observed that a significant fraction of patients who were stipulated as dying from COVID-19 died primarily from other causes.

## Ethical statement

This study was approved by the Institutional Review Board of Allina Health and The Minneapolis Heart Institute Foundation and followed the ethical guidelines of research as described in the Helsinki document.

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## CRediT authorship contribution statement

**Thomas R. Basala:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Marissa E. Dulas:** Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Alexis Albers:** Data curation, Methodology. **Sara D. Olson:** Data curation, Methodology. **Brynn Okeson:** Data curation, Formal analysis, Methodology. **Jay H. Traverse:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100351.

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