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Observational Study

Outcomes in patients with COVID-19 and new onset heart blocks: Insight from the National Inpatient Sample database

Sami J Shoura, Taha Teaima, Muhammad Khawar Sana, Ayesha Abbasi, Ramtej Atluri, Mahir Yilmaz, Hasan Hammo, Laith Ali, Chanavuth Kanitsoraphan, Dae Yong Park, Tareq Alyousef

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a worldwide health crisis since it first appeared. Numerous studies demonstrated the virus's predilection to cardiomyocytes; however, the effects that COVID-19 has on the cardiac conduction system still need to be fully understood.

AIM

To analyze the impact that COVID-19 has on the odds of major cardiovascular complications in patients with new onset heart blocks or bundle branch blocks (BBB).

METHODS

The 2020 National Inpatient Sample (NIS) database was used to identify patients admitted for COVID-19 pneumonia with and without high-degree atrioventricular blocks (HDAVB) and right or left BBB utilizing ICD-10 codes. The patients with pre-existing pacemakers, suggestive of a prior diagnosis of HDAVB or BBB, were excluded from the study. The primary outcome was inpatient mortality. Secondary outcomes included total hospital charges (THC), the length of hospital stay (LOS), and other major cardiac outcomes detailed in the Results section. Univariate and multivariate regression analyses were used to adjust for confounders with Stata version 17.

RESULTS

A total of 1058815 COVID-19 hospitalizations were identified within the 2020 NIS

database, of which 3210 (0.4%) and 17365 (1.6%) patients were newly diagnosed with HDAVB and BBB, respectively. We observed a significantly higher odds of in-hospital mortality, cardiac arrest, cardiogenic shock, sepsis, arrhythmias, and acute kidney injury in the COVID-19 and HDAVB group. There was no statistically significant difference in the odds of cerebral infarction or pulmonary embolism. Encounters with COVID-19 pneumonia and newly diagnosed BBB had a higher odds of arrhythmias, acute kidney injury, sepsis, need for mechanical ventilation, and cardiogenic shock than those without BBB. However, unlike HDAVB, COVID-19 pneumonia and BBB had no significant impact on mortality compared to patients without BBB.

CONCLUSION

In conclusion, there is a significantly higher odds of inpatient mortality, cardiac arrest, cardiogenic shock, sepsis, acute kidney injury, supraventricular tachycardia, ventricular tachycardia, THC, and LOS in patients with COVID-19 pneumonia and HDAVB as compared to patients without HDAVB. Likewise, patients with COVID-19 pneumonia in the BBB group similarly have a higher odds of supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, acute kidney injury, sepsis, need for mechanical ventilation, and cardiogenic shock as compared to those without BBB. Therefore, it is essential for healthcare providers to be aware of the possible worse predicted outcomes that patients with new-onset HDAVB or BBB may experience following SARS-CoV-2 infection.

Key Words: In-patient outcomes; Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019, High degree atrioventricular blocks; Bundle branch blocks; Retrospective observational study

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Core Tip: This is the first and largest retrospective observational study based on the 2020 National Inpatient Sample database that illustrates the outcomes of patients with coronavirus disease 2019 (COVID-19) who developed new onset high degree atrioventricular blocks (HDAVB) or bundle branch blocks (BBB). We observed significantly higher rates of inpatient outcomes of interest in patients admitted for COVID-19 pneumonia and the secondary diagnosis of HDAVB or BBB compared to patients who did not. Several reports in the literature described worse outcomes experienced by this patient population. We conclude that elderly patients, whites, and males with common co-morbid conditions, hospitalized for COVID-19 pneumonia and HDAVB, seem to be at a significantly increased risk of developing cardiac complications and have a significantly increased risk of inpatient mortality, necessitating a need for preventative strategies, such as the use of temporary pacemakers or cardiac rhythm monitoring techniques.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has significantly impacted global health and the world's economy[1,2]. The virus primarily targets the respiratory system, but it also elicits a robust systemic immune response, otherwise known as "cytokine storm", leading to multi-organ dysfunction[2,3]. Although much of the focus has been on the acute respiratory distress syndrome caused by the virus, it is crucial for providers to understand the complex interplay between COVID-19 and the cardiovascular system[4,5].

Research has demonstrated that individuals with pre-existing cardiovascular disease are at a significantly higher risk of developing life-threatening SARS-CoV-2 infections and increased case fatality rates. Additionally, COVID-19 has been associated with a myriad of cardiovascular complications, including arrhythmias, acute coronary syndromes, myocarditis, acute heart failure, pericarditis, cardiac tamponade, takotsubo cardiomyopathy, cor-pulmonale, cardiogenic shock, and pulmonary embolism[3,6]. These cardiovascular complications can significantly impact short and long-term mortality associated with COVID-19[7].

Of those hospitalized with COVID-19 pneumonia, 14.1% of patients experience a cardiovascular complication, with arrhythmia incidence rates ranging between 6.9-10.3%[3,8-13]. While tachyarrhythmias are the most commonly cited arrhythmias, bradyarrhythmias still represent 12% of all arrhythmias that can develop in COVID-19 affected patients[13, 14]. Bradyarrhythmias can increase mortality rates, particularly in cases of new onset atrioventricular blocks. However, there is currently a lack of large-scale database analyses regarding hospital outcomes, trends, and demographics of bradyarrhythmias in patients with COVID-19.

To address this gap in knowledge, this review focuses on major cardiovascular complications in COVID-19 patients, with an emphasis on bradyarrhythmias due to high-degree atrioventricular blocks (HDAVB) (of which 1900 patients (59.2%) developed second degree atrioventricular block and 1310 (40.8%) developed complete atrioventricular block) in patients who did not have a prior permanent pacemaker or other implantable cardiac devices such as implantable cardioverter-defibrillator (ICD).

MATERIALS AND METHODS

Study design and data sources

This study is a retrospective cohort analysis of admissions for COVID-19 patients in 2020 using the National Inpatient Sample (NIS) database. The NIS database is the largest publicly available all-payer inpatient healthcare database, maintained by the Agency for Healthcare Research and Quality. It was designed to assess all hospitalizations in non-federal acute care hospitals across the United States, excluding rehabilitation and long-term acute care hospitals, through a weighted probability sampling method. Data was collected from billing records submitted by hospitals to statewide data organizations, representing almost 97% of the United States (US) population. The NIS database then stratifies these hospitalizations according to bed size, teaching status, urban/rural locations, and geographic location. A sample of 20% of all hospitalizations in each stratum is collected, pooled, and weighted to ensure that it accurately represents the entire US population.

The NIS database contains patient and hospital-level information, including primary diagnosis, secondary diagnosis, primary payer type, median household income, hospital teaching status, geographic region, hospital bed size, and urban/rural location. All diagnoses are coded using the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS).

In this database, diagnoses are divided into a single primary diagnosis and secondary diagnoses. The principal diagnosis represents the main reason for hospitalization, while secondary diagnoses include any other ICD-10 codes associated with the hospitalization. The NIS has previously been used to estimate the burden of cardiovascular diseases.

It is worth noting that this study's manuscript is exempt from Institutional Review Board (IRB) approval since it uses de-identified data. The data used in this study is accessible online at <https://www.hcup-us.ahrq.gov>.

Inclusion criteria and study variates

Note to reader: Although High Degree Atrioventricular Block is defined as “≥ 2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles with evidence for some atrioventricular conduction”[15] by the American Heart Association, the term High Degree Atrioventricular Block (HDAVB) throughout the entirety of the manuscript will represent patients with Mobitz I, Mobitz II and Complete heart block only. We chose to use this abbreviation to avoid word redundancy.

This retrospective cohort study focuses on adult patients aged 18 years or older who were hospitalized with COVID-19 pneumonia during the year 2020. We identified the study population by combining multiple ICD-10-CM codes, including U07.1, J12.82, U100, U49, U50, and U85, based on a literature review of similar validated studies on COVID-19, bundle branch blocks and heart blocks which included Mobitz type one, Mobitz type two and complete heart block. We further stratified the population based on the presence or absence of HDAVB without a pacemaker (I44.1, I44.2) or BBB without a pacemaker (I44.7, I45.19, I45.10) using ICD-10 codes.

Patients with prior permanent pacemakers and other intra-cardiac devices were excluded to ensure that analyzed patients had not been previously diagnosed with heart blocks and had no devices placed for this reason.

Demographic characteristics such as age, sex, race, medical insurance status, and mean household income, as well as hospital characteristics such as hospital bed size, location, and teaching status, were included as study variables. Comorbidity burden was assessed using the Charlson comorbidity index, which was adjusted for population-based research.

The study population and the stratification process are outlined in [Figure 1](#).

Clinical outcomes and definitions

The primary outcome of our analysis was to examine the mortality rate in COVID-19 pneumonia patients who had newly diagnosed HDAVB or BBB (without permanent pacemaker). In addition, we also analyzed secondary outcomes such as mean length of stay (LOS), mean total hospital charges (THC), and adjusted odds of inpatient morbidities including but not limited to cardiac arrest, respiratory failure, ventricular and supraventricular arrhythmia, acute kidney injury, and cerebral infarction.

To conduct our statistical analyses, we utilized STATA® (StataCorp, College Station, TX) version 17. The Healthcare Cost and Utilization Project (HCUP) offers year-based discharge weights, which were utilized to quantify weighted nationwide estimates. We used Fisher's exact test or Chi-square test to compare categorical variable proportions and an independent sample *t*-test to compare means of continuous data. We calculated unadjusted odds ratio (OR) using univariate regression analysis for every outcome. With significance of each univariate screen set to *P* value < 0.2, we selected variables to conduct multivariable logistic regression analysis adjusting for possible confounders. Other essential variables, based on literature review, were also included in the model. We used logistic regression analysis for binary or categorical outcomes and linear regression analysis for continuous outcomes. Two-tailed *P* values and a threshold of 0.05 were used to determine statistical significance.

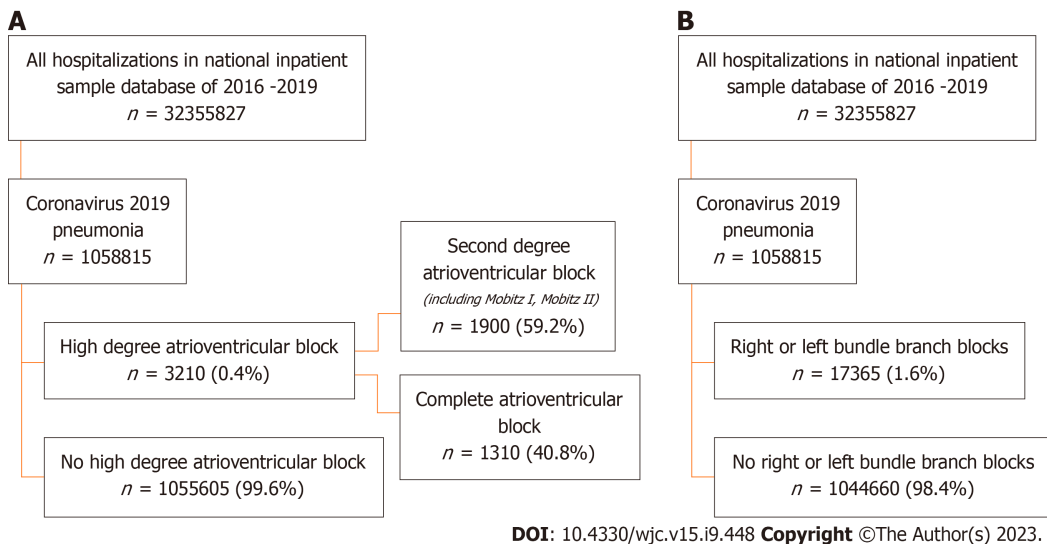


Figure 1 Study population and stratification process. A: Coronavirus disease 2019 (COVID-19) pneumonia hospitalizations stratified by patients with and without high degree atrioventricular blocks; B: COVID-19 pneumonia hospitalizations stratified by patients with and without right and left bundle branch blocks.

Ethical considerations

Our manuscript is exempt from IRB approval, as NIS is a de-identified national administrative database and readily available online at <https://www.hcup-us.ahrq.gov>. Based on that and according to HCUP guidelines, our study did not require Institutional Review Board of Cook County Health's approval.

RESULTS

According to the 2020 NIS database, out of 1058815 COVID-19 pneumonia hospitalizations, 3210 (0.4%) patients had newly diagnosed HDAVB without a pacemaker, while 17365 (1.6%) had newly diagnosed right or left BBB without a pacemaker (Figures 1 and 2). The mean age of COVID-19 patients with and without HDAVB were 72 and 64 years, while COVID-19 patients with and without BBB had a mean age of 72.5 and 64 years, respectively ($P < 0.001$ for both).

Compared to COVID-19 patients without HDAVB or BBB, COVID-19 patients with newly diagnosed HDAVB or BBB were more likely to be white (58% vs 52%, $P = 0.0359$; 62% vs 52%, $P = 0.0359$), be male (66.5% vs 52.7%, $P < 0.001$; 60.6% vs 52.7%, $P < 0.001$), have governmental insurance (82% vs 67%, $P < 0.001$; 79.5% vs 67%, $P < 0.001$), and be treated in large bed size hospitals (50.8% vs 45.4%, $P = 0.0286$; 46.8% vs 45.4%, $P = 0.025$) respectively.

In terms of underlying comorbidities, patients with COVID-19 pneumonia with newly diagnosed HDAVB or BBB were more likely to have complicated diabetes mellitus (55% vs 30%, $P < 0.001$; 43% vs 30.8%, $P < 0.001$), chronic kidney disease (33% vs 19%, $P < 0.001$; 29% vs 19%, $P < 0.001$), congestive heart failure (34% vs 15%, $P < 0.001$; 32% vs 15%, $P < 0.001$), prior myocardial infarction (17% vs 7%, $P < 0.001$; 17.5% vs 7%, $P < 0.001$), history of cerebrovascular accidents (5% vs 4%, $P = 0.0223$; 6% vs 4%, $P < 0.001$), peripheral vascular disease (10% vs 4.5%, $P < 0.001$; 10% vs 4.4%, $P < 0.001$), and a higher number of comorbid conditions in general (Charlson index ≥ 3) compared to COVID-19 patients without HDAVB or BBB.

COVID-19 patients with HDAVB or BBB as compared to COVID-19 patients without were less likely to be female (43.5% vs 47.2%, $P < 0.001$; 39.4% vs 47.3%, $P < 0.001$), to be African-American (18% vs 19%, $P = 0.0359$; 14% vs 19%, $P = 0.0359$), to be Hispanic (17% vs 21%, $P = 0.0359$; 15% vs 21%, $P = 0.0359$), and have private insurance (17% vs 21%, $P = 0.0359$; 15% vs 21%, $P = 0.0359$), and were less likely to have hypertension (32% vs 41%, $P < 0.001$; 37% vs 41%, $P < 0.001$) (Tables 1 and 2).

Multi-variant regression analysis

On multivariate regression analysis of encounters with COVID-19 and newly diagnosed HDAVB without pacemakers as demonstrated in Figure 2A, they were found to have a longer mean LOS of 2.28 d [95% confidence interval (CI): 1.49-3.07, $P < 0.001$], higher mean THC of \$33801 (95%CI: 17314 -50261, $P < 0.001$), higher adjusted odds (aOR) of mortality (aOR: 1.36, 95%CI: 1.1-1.69, $P = 0.005$), cardiac arrest (aOR: 2.04, 95%CI: 1.42-2.92, $P < 0.001$), atrial fibrillation (aOR: 1.36, 95%CI: 1.12-1.68, $P = 0.003$), atrial flutter (aOR: 3.27, 95%CI: 2.33-4.58, $P < 0.001$), ventricular fibrillation (aOR: 4.95, 95%CI: 2.52-9.71, $P < 0.001$), supraventricular tachycardia (aOR: 2.53, 95%CI: 1.68-3.82, $P < 0.001$), ventricular tachycardia (aOR: 3.16, 95%CI: 2.27-4.4, $P < 0.001$), acute kidney injury (aOR: 1.33, 95%CI: 1.11-1.6, $P = 0.002$), sepsis (aOR: 1.59, 95%CI: 1.22-2.06, $P < 0.001$), mechanical ventilation (aOR: 1.41, 95%CI: 1.08-1.84, $P = 0.011$), and cardiogenic shock (aOR: 6.62, 95%CI: 4.14-10.6, $P < 0.001$), compared to those without HDAVB.

Meanwhile, patients with COVID-19 and BBB without pacemakers as demonstrated in Figure 2B had an increased odds of atrial fibrillation (aOR: 1.15, 95%CI: 1.05-1.26, $P = 0.001$), atrial flutter (aOR: 1.68, 95%CI: 1.37-2.06, $P < 0.001$), supraventricular tachycardia (aOR: 1.83, 95%CI: 1.48-2.5, $P < 0.001$), ventricular tachycardia (aOR: 2.35, 95%CI: 1.97-2.8, P

Table 1 Baseline demographics and comorbid condition rate of patients admitted for coronavirus disease 2019 pneumonia with and without high degree atrioventricular block without a pacemaker, *n* (%)

	Study group	Control group	P value
	High degree atrioventricular block (<i>n</i> = 3210/0.4%)	No high degree atrioventricular block (<i>n</i> = 1058815/99.6%)	
Age (year), mean	72	64	< 0.001
Gender			< 0.001
Female	1075 (33.5)	498545 (47.2)	
Male	(66.5)	(52.7)	
Ethnicity			0.0359
White	1862 (58)	550584 (52)	
Black	578 (18)	201175 (19)	
Hispanic	482 (15)	211763 (21)	
Other	225 (7)	84705 (8)	
Chronic kidney disease	1084 (33)	205000 (19)	< 0.001
Hypertension	1030 (32)	437190 (41)	< 0.001
Congestive heart failure	1095 (34)	162930 (15)	< 0.001
Government insured	2555 (82)	673794 (67)	< 0.001
Private insured	480 (15)	292190 (29)	< 0.001
Self-pay	80 (2.6)	35875 (3.6)	0.1828
Poor socioeconomic status	550 (17)	168015 (16)	
Hospital region			0.0144
Northeast	550 (17)	186650 (17.6)	
Midwest	925 (29)	245190 (23.2)	
South	1225 (38)	441800 (42)	
West	510 (16)	181964 (17.2)	
Hospital bed size			0.0286
Small	770 (24)	270620 (25.6)	
Medium	810 (25.2)	304920 (29)	
Large	1630 (50.8)	480065 (45.4)	
Charlson index			< 0.001
0	385 (12)	296468 (28)	
1	642 (20)	296468 (28)	
2	578 (18)	169410 (16)	
3	1605 (50)	296468 (28)	
Median household income			0.0418
First quartile	931 (29)	359997 (34)	
Second quartile	995 (31)	296468 (28)	
Third quartile	738 (23)	232939 (22)	
Fourth quartile	546 (17)	169410 (16)	
Myocardial infarction	570 (17)	77240 (7)	< 0.001
Peripheral vascular disease	320 (10)	47355 (4.5)	< 0.001
Cerebrovascular disease	185 (5)	42075 (4)	0.0223

Dementia	570 (17)	116035 (11)	< 0.001
Chronic obstructive lung disease	875 (27)	247225 (23.4)	0.0244
Rheumatoid arthritis	65 (2)	30120 (3)	0.2037
Peptic ulcer disease	20 (0.6)	4625 (0.4)	0.4797
Mild liver disease	95 (3)	36275 (3.4)	0.5039
Diabetes mellitus	680 (21)	262850 (25)	0.0311
Diabetic complications	1790 (55)	327870 (30)	< 0.001
Hemiplegia or paraplegia	50 (1.5)	16690 (1.5)	0.9732
Renal disease	2220 (70)	421060 (40)	< 0.001
Cancer	260 (8)	57440 (5.4)	0.0371
Moderate/severe liver disease	45 (1.4)	15855 (1.5)	0.9051
Metastatic cancer	210 (6.5)	49170 (4.6)	0.3633
AIDS	60 (1.9)	13980 (1.3)	0.6272

Student's *t*-test and Chi-square test were used to compare the baseline characteristics accordingly, and the resulting *P* values are shown. AIDS: Acquired immunodeficiency syndrome.

< 0.001), acute kidney injury (aOR: 1.12, 95%CI: 1.03-1.21, *P* = 0.004), sepsis (aOR: 1.59, 95%CI: 1.22-2.06, *P* < 0.001), mechanical ventilation (aOR: 1.22, 95%CI: 1.08-1.39, *P* = 0.001), and cardiogenic shock (aOR: 2.11, 95%CI: 1.44-3.08, *P* < 0.001), than those without BBB without pacemaker but with a similar odds of mortality (aOR: 1.05, 95%CI: 0.95-1.16, *P* = 0.326).

Univariate regression analysis

On univariate regression analysis of encounters with COVID-19 and HDAVB as demonstrated in Table 3, they were found to have a longer mean LOS of 3.07 d (95%CI: 2.32-3.84, *P* < 0.001), higher mean THC of \$40692 (95%CI: 24708-56674, *P* < 0.001), increased odds of mortality (aOR: 2.18, 95%CI: 1.8-2.64, *P* < 0.001), cardiac arrest (aOR: 2.78, 95%CI: 2-3.86, *P* < 0.001), atrial fibrillation (aOR: 2.46, 95%CI: 2.1-2.9, *P* < 0.001), atrial flutter (aOR: 5.45, 95%CI: 4-7.42, *P* < 0.001), ventricular fibrillation (aOR: 6.33, 95%CI: 3.27-12.27, *P* < 0.001), supraventricular tachycardia (aOR: 3.39, 95%CI: 2.31-4.96, *P* < 0.001), ventricular tachycardia (aOR: 4.75, 95%CI: 3.05-6.46, *P* < 0.001), acute kidney injury (aOR: 1.73, 95%CI: 1.47-2.03, *P* < 0.001), sepsis (aOR: 1.85, 95%CI: 1.44-2.39, *P* < 0.001), mechanical ventilation (aOR: 1.72, 95%CI: 1.33-2.22, *P* < 0.001), and cardiogenic shock (aOR: 8.75, 95%CI: 5.61-13.63, *P* < 0.001), as compared to those without HDAVB.

Encounters with COVID-19 and with BBB without pacemaker as demonstrated in Table 4 had an increased odds of mortality (aOR: 1.63, 95%CI: 1.42-1.89, *P* < 0.001), atrial fibrillation (aOR: 2.12, 95%CI: 1.88-2.40, *P* < 0.001), atrial flutter (aOR: 2.32, 95%CI: 1.7-3.17, *P* < 0.001), supraventricular tachycardia (aOR: 2.22, 95%CI: 1.64-2.99, *P* < 0.001), ventricular tachycardia (aOR: 4.09, 95%CI: 3.24-5.14, *P* < 0.001), acute kidney injury (aOR: 1.71, 95%CI: 1.53-1.9, *P* < 0.001), sepsis (aOR: 1.81, 95%CI: 1.52-2.26, *P* < 0.001), mechanical ventilation (aOR: 1.67, 95%CI: 1.38-2.23, *P* < 0.001), and cardiogenic shock (aOR: 3.29, 95%CI: 2.04-5.31, *P* < 0.001), than those without BBB without pacemaker.

Absolute values of outcomes such as mortality amongst other outcomes of interest comparing both groups (HDAVB and BBB) can be found in Table 5.

DISCUSSION

This analysis is the most comprehensive and updated study to date that examined newly diagnosed HDAVB and BBB in SARS-CoV-2 positive patients who have not previously received a permanent pacemaker. Several cases in the literature suggesting poor predicted outcomes in this patient population have been described.

Our analysis uncovered several significant findings in patient demographics and major clinical outcomes, summarized in Tables 1 and 2, respectively.

We found that patients with COVID-19 and newly diagnosed HDAVB had a significantly higher odds of inpatient mortality and cardiac arrest. Furthermore, COVID-19 patients with either HDAVB or BBB had a significantly higher odds of cardiac arrest, cardiogenic shock, sepsis, acute kidney injury, and requirement for ventilatory support. Additionally, they had higher total hospital charges and a longer length of stay compared to patients without HDAVB or BBB. Furthermore, we observed a higher burden of atrial flutter, atrial fibrillation, supraventricular tachycardias, and ventricular tachycardias in patients with HDAVB or BBB without pre-existing pacemakers. Patients with COVID-19 and newly diagnosed HDAVB or BBB may have higher mortality rates and adverse clinical outcomes due to a higher burden of co-morbidities, such as chronic kidney disease, diabetes mellitus, and heart failure[7,16]. These conditions may increase the risk of complications and make it difficult for patients to recover from the virus. The increased burden of arrhythmias

Table 2 Baseline demographics and comorbid condition rate of patients admitted for coronavirus disease 2019 pneumonia with and without bundle branch block without a pacemaker, *n* (%)

	Study group	Control group	P value
	All bundle branch blocks without pacemaker (<i>n</i> = 17365/1.6%)	No bundle branch blocks (<i>n</i> = 1044660/98.4%)	
Age (year), mean	72.5	64	< 0.001
Gender			< 0.001
Female	6845 (39.4)	492775 (47.3)	
Male	(60.6)	(52.7)	
Ethnicity			0.0359
White	10766 (62)	543223 (52)	
Black	2431 (14)	198485 (19)	
Hispanic	2952 (17)	219378 (21)	
Other	1216 (7)	83573 (8)	
Chronic kidney disease	5005 (29)	201080 (19)	< 0.001
Hypertension	6390 (37)	431830 (41)	< 0.001
Congestive heart failure	5470 (32)	158555 (15)	< 0.001
Government insured	13360 (79.5)	662990 (67)	< 0.001
Private insured	3065 (18.2)	289605 (29.3)	< 0.001
Self-pay	385 (2.3)	35570 (3.6)	< 0.001
Poor socioeconomic status	3290	165275	
Hospital region			< 0.001
Northeast	3885 (22.4)	183315 (17.6)	
Midwest	4725 (27.2)	241390 (23.2)	
South	6160 (35.4)	436866 (42)	
West	2595 (15)	179880 (17.2)	
Hospital bed size			0.0025
Small	3900 (22.4)	267490 (25.6)	
Medium	5345 (30.8)	300385 (29)	
Large	8120 (46.8)	473575 (45.4)	
Charlson index			< 0.001
0	2952 (17)	292505 (28)	
1	3646 (21)	292505 (28)	
2	3299 (19)	147145 (16)	
3	7466 (43)	292505 (28)	
Median household income			< 0.001
First quartile	5088 (29.3)	355184 (34)	
Second quartile	4705 (27.1)	292505 (28)	
Third quartile	4202 (24.4)	229825 (22)	
Fourth quartile	3334 (19.2)	147145 (16)	
Myocardial infarction	3035 (17.5)	74775 (7)	< 0.001
Peripheral vascular disease	1530 (9)	46145 (4.4)	< 0.001
Cerebrovascular disease	1045 (6)	41215 (4)	< 0.001

Dementia	2835 (16)	113770 (11)	< 0.001
Chronic obstructive lung disease	4300 (25)	243800 (23.4)	0.0592
Rheumatoid arthritis	495 (3)	29690 (3)	0.9993
Peptic ulcer disease	60 (0.4)	4585 (0.4)	0.4011
Mild liver disease	670 (3.8)	35700 (3.4)	0.1675
Diabetes mellitus	4005 (23)	259525 (25)	0.0137
Diabetic complications	7420 (43)	322240 (30.8)	< 0.001
Hemiplegia or paraplegia	320 (1.8)	16420 (1.6)	0.3728
Renal disease	10370 (60)	412910 (39.5)	< 0.001
Cancer	970 (5.6)	56730 (5.4)	0.7950
Moderate/Severe liver disease	240 (1.4)	15660 (1.5)	0.7335
Metastatic cancer	840 (4.8)	48540 (4.6)	0.8478
AIDS	210 (1.2)	13830 (1.3)	0.8074

Student's *t*-test and Chi-square test were used to compare the baseline characteristics accordingly, and the resulting *P* values are shown. AIDS: Acquired immunodeficiency syndrome.

Table 3 A Univariate regression analysis of encounters with coronavirus disease 2019 and with high grade atrioventricular block without pacemakers

High degree atrioventricular block without pacemakers	Adjusted OR	95%CI	<i>P</i> value
Mortality	2.18	1.80-2.64	< 0.001
Cardiac arrest	2.78	2.00-3.86	< 0.001
Atrial fibrillation	2.46	2.10-2.90	< 0.001
Atrial flutter	5.45	4.00-7.42	< 0.001
Ventricular fibrillation	6.33	3.27-12.27	< 0.001
Supraventricular tachycardia	3.39	2.31-4.96	< 0.001
Ventricular tachycardia	4.75	3.05-6.46	< 0.001
Acute kidney injury	1.73	1.47-2.03	< 0.001
Sepsis	1.85	1.44-2.39	< 0.001
Mechanical ventilation	1.72	1.33-2.22	< 0.001
Cardiogenic shock	8.75	5.61-13.63	< 0.001

in patients with HDAVB or BBB could be due to the effect of the virus on the heart's electrophysiology. Previous studies suggested that SARS-CoV-2 can cause myocarditis, which may lead to arrhythmias and other cardiac complications[17, 18].

A retrospective study that included 756 COVID-19 patients demonstrated a 2-fold increase in the risk of death in the presence of atrioventricular block[7]. Multiple underlying mechanisms behind the development of atrioventricular block in COVID-19 patients have been postulated but incompletely understood. Inflammatory mediated injury to the myocardial cells and the intrinsic cardiac conduction system whether at the supra-Hisian or infra-Hisian level and severe hypoxia seem to be the main driving triggers to the development of heart blocks in COVID-19 patients[19]. Other possible underlying mechanisms mostly observed in patients with myocarditis due to COVID-19 are caused by the interruption of the electrical impulse generation or propagation throughout the cardiac conduction system[18]. Other suggested mechanisms in the literature are illustrated in Figure 3. It is also pertinent to mention that the use of hydroxychloroquine and azithromycin in year 2020 and the use of atrioventricular blocking agents such as beta blockers, which can prolong QTc interval and delay conduction at the level of the atrioventricular node, respectively, may have exaggerated the incidence of arrhythmias particularly in COVID-19 patients[20]. Therefore, to prevent the unnecessary over-utility of permanent pacemakers in these patients, it is imperative to re-evaluate this patient population for indications of permanent pacemaker placement after their recovery[21].

Our results suggest that patients with COVID-19 pneumonia who developed new-onset HDAVB or BBB without the presence of prior pacemakers and with concomitant positive SARS-CoV-2 results on admission, regardless of symptom

Table 4 Univariate regression analysis of encounters with coronavirus disease 2019 and with bundle branch block without pacemakers

Right or left bundle branch blocks without pacemaker	Adjusted OR	95%CI	P value
Mortality	1.63	1.42-1.89	< 0.001
Cardiac arrest	1.43	1.04-1.97	0.026
Atrial fibrillation	2.12	1.88-2.40	< 0.001
Atrial flutter	2.32	1.70-3.17	< 0.001
Ventricular fibrillation	2.31	1.11-4.82	0.024
Supraventricular tachycardia	2.22	1.64-2.99	< 0.001
Ventricular tachycardia	4.09	3.24-5.14	< 0.001
Acute kidney injury	1.71	1.53-1.90	< 0.001
Sepsis	1.81	1.52-2.26	< 0.001
Mechanical ventilation	1.67	1.38-2.23	< 0.001
Cardiogenic shock	3.29	2.04-5.31	< 0.001

Table 5 Univariate regression analysis demonstrating absolute value of outcomes of interest in encounters with coronavirus disease 2019 and with high grade atrioventricular block or bundle branch blocks without pacemakers, *n* (%)

In-hospital outcomes Rates	High degree atrioventricular block (<i>n</i> = 3210)	All bundle branch blocks without pacemaker (<i>n</i> = 17365)
Mortality	665 (21.3)	2952 (17.0)
Cardiac arrest	175 (5.6)	504 (2.9)
Atrial fibrillation	172 (5.5)	799 (4.6)
Atrial flutter	209 (6.7)	538 (3.1)
Ventricular fibrillation	44 (1.4)	87 (0.5)
Supraventricular tachycardia	150 (4.8)	555 (3.2)
Ventricular Tachycardia	222 (7.1)	799 (4.6)
Sepsis	365 (11.6)	1233 (7.1)
Mechanical ventilation	324 (10.4)	1528 (8.8)
Cardiogenic shock	103 (3.3)	174 (1.0)
Pulmonary embolism	106 (3.4)	521 (3.0)
Acute kidney injury	1298 (41.6)	5956 (34.3)
Cerebrovascular accidents	50 (1.6)	191 (1.1)

severity, consisted of an older population with a higher comorbidity burden, as evidenced by a higher prevalence of chronic kidney disease, diabetes mellitus, and heart failure. Hypertension, however, was less commonly observed in patients who developed HDAVB. The absence of hypertension in patients who developed HDAVB could be due to the fact that hypertension is a risk factor for other types of heart disease, such as coronary artery disease and heart failure, which may have masked the association with HDAVB in this study. White race and male gender were associated with a higher risk for developing HDAVB compared to other races and female gender. This higher incidence of HDAVB in white and female patients could be related to differences in genetic susceptibility or hormonal factors. However, further research is required to confirm this hypothesis.

Previous studies have shown that older age, male gender, and diabetes mellitus were associated with a higher risk of atrioventricular block. Additionally, a population-based cohort study established a longitudinal increase in the risk of atrioventricular blocks with each 20 mg/dL increase in fasting blood glucose level[22].

We also report a higher odds of tachyarrhythmias in patients with HDAVB as compared to patients without HDAVB. Given the higher burden of co-morbidities and older age in the former, the likelihood of fibrosis in the cardiac conduction system is high, which can lead to the development of HDAVB. Given these findings, it is understandable that higher mortality and major adverse cardiovascular events were more commonly observed in patients with a higher comorbidity burden.

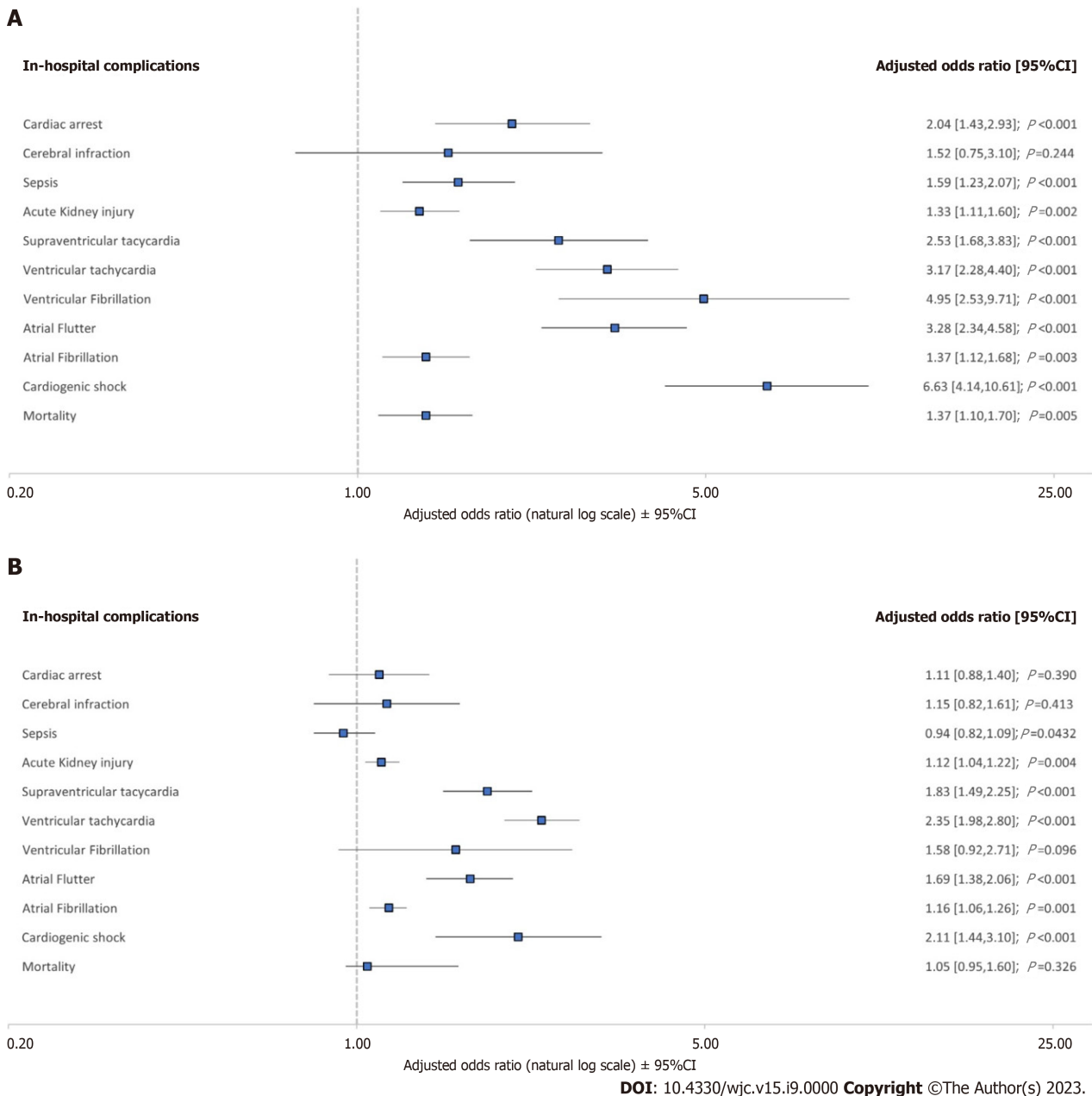


Figure 2 Multivariate regression analysis. A: Outcomes in patients with coronavirus disease 2019 (COVID-19) pneumonia who developed high degree atrioventricular block without permanent pacemaker; B: Outcomes in patients with COVID-19 pneumonia who developed bundle branch block without permanent pacemaker.

Moreover, patients with heart failure are more likely to be on atrioventricular nodal blocking agents precipitating heart blocks as well. HDAVB has been reported with COVID-19 though the incidence is rare and limited to case reports and series. The nature of HDAVB associated with COVID-19 is mostly regarded as transient with spontaneous recovery (incidence and percentages might add reliability) with mere observation[19,23] but has been treated with permanent pacemakers[24-26] and rarely with ablation as well[27].

Several studies have highlighted the association between COVID-19 infection and worse clinical outcomes in patients with new-onset bundle branch blocks. A meta-analysis encompassing 2539 hospitalized COVID-19 patients revealed a higher prevalence of LBBB among those experiencing unfavorable clinical outcomes[28]. Another meta-analysis comprising 1580 patients with COVID-19 infection demonstrated a mortality risk associated with LBBB, indicating its potential as a predictive marker[29]. Similarly, a meta-analysis involving 1904 COVID-19 patients revealed a significantly increased risk of short-term mortality in those with right bundle branch block (RBBB)[30]. Our own study further confirms a high risk of mortality in COVID-19 pneumonia patients with secondary diagnoses of new-onset bundle branch blocks and no prior intracardiac devices. The observed association between COVID-19 infection and new-onset BBB in our study opens up new avenues for understanding potential myocardial injury mechanisms in this context. Acute BBB may signify acute myocardial injury, possibly arising from various etiologies, including COVID-induced ischemic heart disease, inflammation or myocarditis, medication-related side effects, and electrolyte imbalances. Recognizing these potential mechanisms is crucial in guiding appropriate management strategies for these patients, especially those with

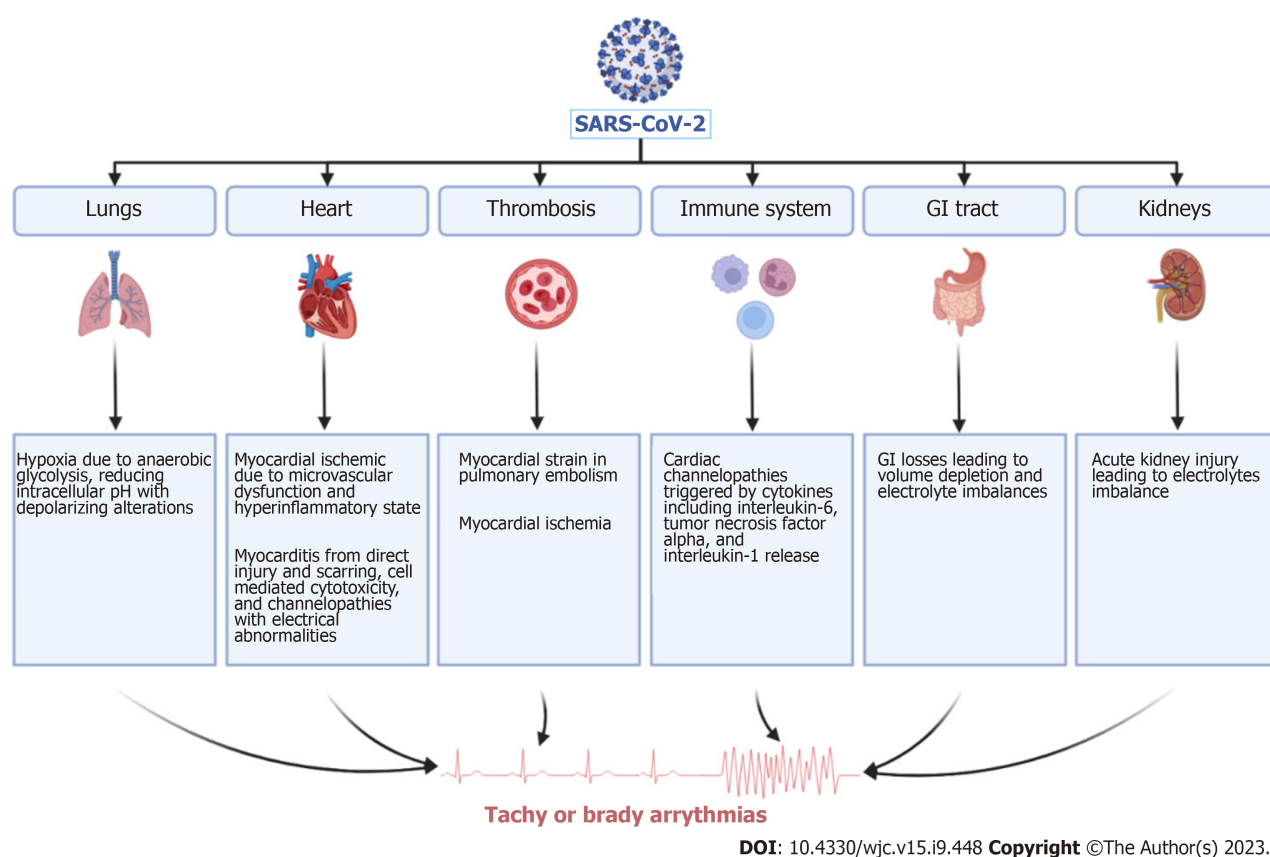


Figure 3 Underlying mechanisms behind the development of atrioventricular block in coronavirus disease 2019 patients. GI: Gastrointestinal; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

significant cardiovascular comorbidities.

Study limitations

Despite several significant findings, our study has several limitations as well. Since its a NIS based study, the limitations of database analysis apply here as well. The diagnosis depends on the ICD-10 coding and may not be representative of the actual real-world figures given the potential for human errors. The NIS database is limited in the use of therapeutic medications that the patients are on and therefore confounders with use of atrioventricular nodal blockers cannot be mitigated. Therefore, due to the unavailability of such data, we were unable to estimate medication effect on the development of HDAVB in our study. Thus, our results may underestimate the contributory effect of those medications on the development of HDAVB. It is pertinent to mention the use of hydroxychloroquine in the year 2020 which can prolong QTc and may have exaggerated the incidence of arrhythmias particularly in COVID-19 patients.

To ensure that all the patients admitted with COVID-19 pneumonia had a secondary diagnosis of new onset HDAVB, we decided to exclude patients with pacemakers or other intracardiac devices which may suggest a prior diagnosis of HDAVB. It is worth noting that due to the possibility that some patients without prior pacemakers may have had undiagnosed asymptomatic atrioventricular heart blocks prior to the diagnosis of COVID-19, those patients cannot be identified nor can be excluded.

CONCLUSION

As SARS-CoV-2 continues to loom with potential for future resurgence, there is a dire need for long term observational studies to better recognize patients at risk of developing fatal arrhythmias such as HDAVB or BBB and to validate management strategies. We conclude that elderly patients, whites, and males with underlying diabetes, chronic kidney disease, congestive heart failure, prior myocardial infarction, history of cerebrovascular accidents, or peripheral artery disease admitted for COVID-19 pneumonia who develop new onset HDAVB are at least six times more likely to develop cardiogenic shock and three times more likely to develop ventricular tachycardia or ventricular fibrillation and have a significantly increased risk of inpatient mortality. Meanwhile, patients who developed new onset BBB had an at least two times increased risk of developing cardiogenic shock and ventricular tachycardia compared to patients who did not develop BBB, albeit without significant increase in inpatient mortality.

Therefore, it is crucial for healthcare providers to recognize the potential for worse outcomes in patients with COVID-19 who develop new HDAVB or right or Left BBB, given their significant co-morbidities and predicted worse outcomes.

By identifying the disease process early in its course, through monitoring techniques and temporary pacemakers, it may be possible to initiate treatment early and prevent the development of adverse outcomes in high-risk patients.

Finally, the management of COVID-19 has evolved over time, including the use of different medications with varying cardiac effects. This evolution may impact the incidence and severity of bradyarrhythmias. Therefore, our dataset from 2020 may not be fully representative of the current situation.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) tremendously impacted patients worldwide. While most research has focused on the virus's effects on the respiratory system, we set to understand the impact that the virus has on the cardiac conductive system. Research has strongly suggested that COVID-19 has a predilection to cardiac tissue. Fewer studies, however, have looked into the effect of the virus on the cardiovascular conductive system. With the availability of pacemakers, cardiac monitoring techniques, and the increasing burden of cardiac arrhythmias triggered by COVID-19, there is a dire need for new studies to establish this association on a larger patient population.

Research motivation

By identifying the gaps in the literature, and with the emergence of case reports and series reported about this topic, we acknowledged the need for large scale studies to draw statistically significant conclusions which could give rise to new interventions that could possibly mitigate life threatening cardiovascular outcomes in high risk patients.

Research objectives

The aim of our study was to analyze the impact that COVID-19 had on the odds of major cardiovascular complications in patients with newly diagnosed heart blocks and bundle branch blocks on a large patient sample. Our analysis was successful in measuring the cardiovascular impact caused by this virus with significance of our results supported by our large sample of patients and patient selection process. We included only patients with new onset high degree atrioventricular blocks or bundle branch blocks, presumed to be triggered by COVID-19 or its treatment. Regardless of causality, which was not the aim of our study, we demonstrated the large burden of serious and life-threatening complications inflicting our patient population. Therefore, our results may suggest that high-risk patients may benefit from early use of temporary pacemakers to mitigate the negative impact coronavirus has on patients with newly diagnosed heart blocks and bundle branch blocks.

Research methods

Using the 2020 National Inpatient Sample database, we selected our patient population of interest, which included all patients hospitalized for COVID-19 pneumonia as the primary diagnosis, utilizing ICD-10 codes. To conduct our statistical analysis, we utilized STATA® (StataCorp, College Station, TX, United States) version 17. We further stratified our sample into patients who had a secondary diagnosis of either high degree atrioventricular blocks or bundle branch blocks. We excluded patients with prior pacemakers using ICD-10 procedure codes. Inpatient mortality was our primary outcome of interest while secondary outcomes included significant cardiac and noncardiac outcomes. Finally, multivariate and univariate regression analyses were conducted on both patient groups.

Research results

Our analysis demonstrated that patients with coronavirus 2019 pneumonia and newly diagnosed high degree atrioventricular blocks had a significantly increased odds of inpatient mortality, cardiac arrest, life-threatening tachyarrhythmias, need for mechanical ventilation, and cardiogenic shock. Patients with COVID-19 pneumonia and newly diagnosed bundle branch blocks experienced no significant increase in mortality on multivariate regression analysis however had similar other outcomes.

Research conclusions

Our study identified high risk groups or patients prone to poor clinical outcomes. Elderly white males with common medical co-morbidities such as diabetes, chronic kidney disease, and peripheral artery disease who were hospitalized for COVID-19 pneumonia and developed high degree atrioventricular block or bundle branch blocks experienced worse clinical outcomes, and thus may benefit from temporary pacemaker placement or long term cardiac monitoring techniques. However, additional research is required to establish clear benefit from the utility of temporary pacemakers or continuous cardiac monitoring techniques on the outcomes experienced in this patient population. Although we identified the increased odds of possibly fatal complications experienced by this patient population, we were unable to measure the contribution of medications used during our patients' hospitalizations due to the limitations of the National Inpatient Sample database. Furthermore, we have no available data to discern the outcomes of these patients following their discharge. This information would be crucial in determining the predicted course of disease in these patients.

Research perspectives

Future research with different methodology should focus on comparing outcomes of patients admitted with COVID-19 pneumonia with newly diagnosed heart blocks secondary to the virus and undergo temporary pacemaker placement to

controls who do not. This will help draw conclusions and establish guidelines that can standardize the approach and utility of temporary pacemakers in high risk patients.

FOOTNOTES

Author contributions: Shoura SJ and Alyousef T contributed to resources and conceptualization; Shoura SJ, Abbasi A, Ali L, Kanitsoraphan C, and Alyousef T contributed to supervision and project administration; Shoura SJ, Atluri R, and Alyousef T contributed to data selection; Shoura SJ, Teaima T, Sana MK, Abbasi A, and Alyousef T contributed to investigation; Shoura SJ, Teaima T, Sana MK, Atluri R, Yilmaz M, Hammo H, Ali L, Kanitsoraphan C, and Alyousef T contributed to validation; Shoura SJ, Abbasi A, Yilmaz M, Hammo H, and Alyousef T contributed to visualization; Shoura SJ, Teaima T, Sana MK, Abbasi A, Yilmaz M, Hammo H, and Alyousef T contributed to writing the original draft; Shoura SJ, Teaima T, and Sana MK contributed to table and figure creation; Shoura SJ, Teaima T, Sana MK, Abbasi A, Atluri R, Yilmaz M, Hammo H, Park DY, Ali L, Kanitsoraphan C, and Alyousef T contributed to manuscript review and editing; Shoura SJ, Teaima T, and Sana MK contributed to literature review; Shoura SJ and Alyousef T contributed to methodology; Atluri R contributed to software and formal analysis; Yilmaz M and Hammo H contributed to writing the second draft and final manuscript polishing; all authors have read and approved the final manuscript.

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