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Contents

Monthly Volume 15 Number 9 September 26, 2023

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

CASE REPORT

World Journal of Cardiology

Monthly Volume 15 Number 9 September 26, 2023

Contents

ABOUT COVER

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MINIREVIEWS

Real-time cardiovascular magnetic resonance-guided radiofrequency ablation: A comprehensive review

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Abstract

Cardiac magnetic resonance (CMR) imaging could enable major advantages when guiding in real-time cardiac electrophysiology procedures offering high-resolution anatomy, arrhythmia substrate, and ablation lesion visualization in the absence of ionizing radiation. Over the last decade, technologies and platforms for performing electrophysiology procedures in a CMR environment have been developed. However, performing procedures outside the conventional fluoroscopic laboratory posed technical, practical and safety concerns. The development of magnetic resonance imaging compatible ablation systems, the recording of high-quality electrograms despite significant electromagnetic interference and reliable methods for catheter visualization and lesion assessment are the main limiting factors. The first human reports, in order to establish a procedural workflow, have rationally focused on the relatively simple typical atrial flutter ablation and have shown that CMR-guided cavotricuspid isthmus ablation represents a valid alternative to conventional ablation. Potential expansion to other more complex arrhythmias, especially ventricular tachycardia and atrial fibrillation, would be of essential impact, taking into consideration the widespread use of substrate-based strategies. Importantly, all limitations need to be solved before application of CMR-guided ablation in a broad clinical setting.

Key Words: Interventional cardiac magnetic resonance; Image-guided ablation; Substrate ablation; Cavotricuspid isthmus; Catheter ablation; Tracking

Core Tip: Technologies and platforms for performing electrophysiology procedures in a cardiac magnetic resonance (CMR) environment have been developed and several human studies have demonstrated that CMR-guided catheter ablation is feasible for typical atrial flutter ablation. Expansion to other more complex arrhythmias, especially ventricular tachycardia and atrial fibrillation, would be of essential impact, taking into consideration the widespread use of substrate-based strategies. Importantly, several limitations need to be solved before application of CMR-guided ablation in a broad clinical setting. This article reviews the clinical implementation of real-time CMR-guided catheter ablation and discusses the potential benefits, challenges and future perspectives of this approach in the treatment of cardiac arrhythmias.

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INTRODUCTION

Cardiovascular magnetic resonance (CMR) has progressively evolved to become an important tool in imaging for cardiac arrhythmias and its implementation is increasingly used[1-3]. By enabling cardiac visualization with augmented temporal and spatial resolution and detailed tissue characterization, CMR imaging identifies both atrial and ventricular arrhythmogenic substrates[1-3]. Accurate scar tissue characterization has been shown to enable prediction of catheter ablation outcome[3], selection of ablation targets for substrate-based procedures[4,5] and identification of gaps in previous ablation lines[5-7]. Moreover, magnetic resonance (MR) imaging may facilitate ablation by providing a detailed anatomical description as pulmonary venous drainage pattern while pre-procedural imaging has also been used for image integration[8,9]. Recent innovations permit visual assessment through a variety of approaches including late gadolinium enhancement, T1 and T2 mapping.

Increased attempts have been performed to use CMR for the guidance of invasive procedures[10]. CMR-imaging could enable major advantages when guiding in real-time cardiac electrophysiology (EP) procedures offering high-resolution anatomy, arrhythmia substrate, and ablation lesion visualization in the absence of ionizing radiation. Scar tissue characterization has a high correlation with the electroanatomic maps (EAM) obtained during the ablation procedures while CMR provides delimitation within the entire myocardial thickness compared with endocardial or epicardial surface electroanatomic maps alone[11,12]. Over the last decade, technologies and platforms for performing electrophysiology procedures in a CMR environment have been developed. To date, human reports on interventional CMR are limited to typical atrial flutter ablation as several limitations have not permitted a routine clinical use.

The aim of this article is to review the clinical implementation of real-time CMR-guided catheter ablation and to discuss the challenges and limitations in this early stage of this approach as well as the potential benefits and the future perspectives in the treatment of cardiac arrhythmias.

TECHNICAL ASPECTS

Performing procedures in a CMR environment and outside the conventional fluoroscopic laboratory posed technical, practical and safety concerns[13]. A number of limiting factors should be overcome as the development of magnetic resonance imaging (MRI) compatible ablation systems, the recording of high-quality electrograms despite significant electromagnetic interference and reliable methods for catheter visualization and lesion assessment.

Interventional CMR suite

To transform the pre-existing magnetic resonance imaging environment into an interventional cardiac MRI suite, all standard EP (recording system, displays and catheters) and anesthetic instruments should be replaced with non-ferromagnetic alternatives to avoid potential risks and adverse incidences of both patient and health care personnel (Figure 1)[13]. Ferromagnetic instruments that cannot be replaced, as the non-MRI compatible radio frequency (RF) generators should therefore positioned outside the scanner room (Figure 1E)[13,14]. Communication between the operators and the radiologist at the MRI console may be facilitated by a compatible wireless communication system.

Additionally, modifications are probably required to the electrical installation to comply with safety guidelines that include to a touch-voltage less than 10 mV, isolation transformers for all wall power outlets, and a 'protected earth' connection for every device[13].

Patient preparation, including femoral vein access and possible intubation, is performed in an adjacent zone outside the scanner room[13]. Importantly, a detailed procedural workflow should have been established for the safe

Figure 1 Full transformation of the pre-existing magnetic resonance imaging environment into an interventional cardiac magnetic resonance imaging suite. A: Pre-existing diagnostic magnetic resonance imaging (MRI) scanner room; B: Pre-existing diagnostic MRI control room; C: Transformed interventional cardiac magnetic resonance (iCMR) suite; D: Transformed iCMR control room. E: The non-MR compatible RF generator including cooling-pump positioned in the iCMR control room. EP, electrophysiological; iCMR, interventional cardiac MRI. Citation: Bijvoet GP, Holtackers RJ, Smink J, Lloyd T, van den Hombergh CLM, Debie LJBM, Wildberger JE, Vernooy K, Mihl C, Chaldoupi SM. Transforming a pre-existing MRI environment into an interventional cardiac MRI suite. *J Cardiovasc Electrophysiol* 2021; 32: 2090-2096 [PMID: 34164862 DOI: 10.1111/jce.15128]. Epub 2021 Jul 4. Copyright © 2021 The Authors. *Journal of Cardiovascular Electrophysiology* published by Wiley Periodicals LLC. (Reproduced with permission)[13].

performance of the procedure and recognition and management of potential complications. Notably, CMR enables an early recognition of complications as pericardial effusion.

Catheter visualization

Catheter location in conventional EAM systems is visualized using magnetic-based sensing or impedance-based tracking and displayed on approximate geometries of cardiac chambers[15]. MR conditional diagnostic and ablation catheters are similar in appearance and function to conventional catheters, but include proprietary components to reduce MR-induced heating[16]. MR conditional catheters were initially created using a polyether block amide plastic body, copper wires and platinum electrodes[17] while the currently approved ablation catheter incorporates gold tip electrodes for energy delivery, recording of electrograms and pacing (Figure 2). During CMR-guided electrophysiology procedures, there are two methods of catheter visualization and intra-procedural guidance, active and passive catheter tracking.

Passive catheters are discerned by local susceptibility artifacts that are induced by para- or ferromagnetic materials placed near the tip of the catheter[18-20]. Optimized imaging protocols using a steady-state free precession imaging sequence at frame rates of 4-8 frames per second provide an adequate temporal resolution[18-20]. However, passive tracking permits a single plane real-time visualization[18,20]. Therefore, manipulation of the catheter requires a continuous manual selection of the appropriate image plane and a constant communication between the operator and the radiologist at the MR imaging console being time-consuming and prone to localization errors.

In contrast to passive tracking that is based on local susceptibility artifacts, active tracking uses integrated receiver lumenless solenoid micro-coils at the tip of the catheter to determine its location (Figure 2)[16,21,22]. These micro-coils act as point-source detectors of MR signals. Locating these coils is accomplished by acquiring the MR signal in the presence of applied magnetic field gradient and identifying the position of the most intense frequency-domain signal[16,22]. The main advantage of this technique is that enables automation of the tracking of the catheter for the localization of its position controlling the MRI scan plane in real-time (Supplementary material and Video). Moreover, high spatial resolution is provided using tracking rates up to 50 frames per second[16].

Electrogram fidelity in the MRI environment

Distortion of the electrograms within the magnetic field can make interpretation of both the surface electrocardiogram (ECG) and intra-cardiac electrograms (EGMs) unreliable[14,23,24]. Although hardware development over recent years has enabled ECG and EGMs acquisitions during MRI examination, interpretation and analysis of waveforms is limited. Signals are severely distorted during MRI scans due to the effects of magnetohydrodynamic (MHD) voltages, RF pulses and fast-switching gradient magnetic fields (Figure 3)[23,24].

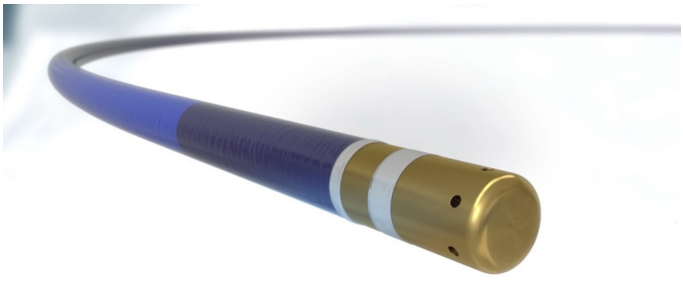

Figure 2 9 Fr. bipole irrigated-tip ablation catheter with two magnetic resonance receive coils in the distal end for active magnetic resonance tracking. (Reproduced with permission from https://imricor.com).

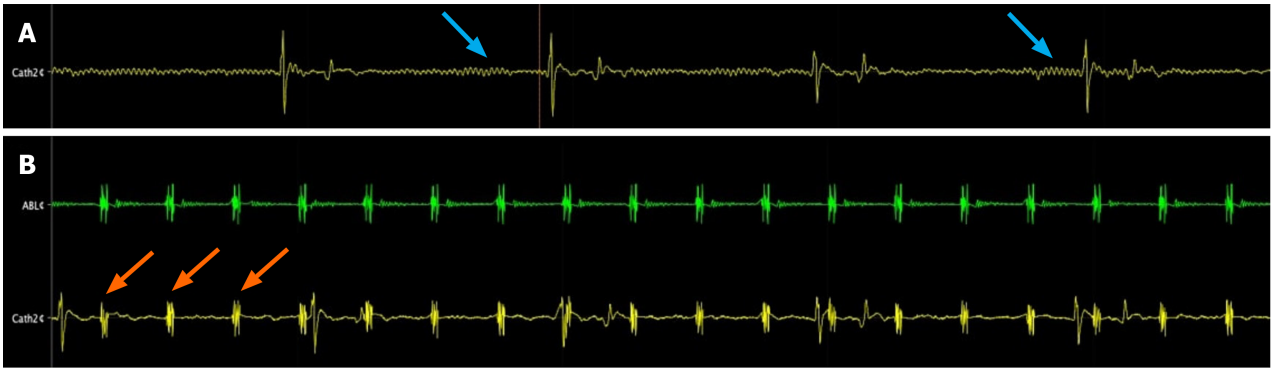

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Figure 3 Distortion of the electrograms within the magnetic field. A: Baseline noise of intra-cardiac electrograms recorded with the coronary sinus catheter (blue arrows indicate the maximally distorted signal); B: Gradient-induced artifacts that cause high frequency peaks during magnetic resonance scanning (orange arrows). ABLc: Ablation catheter; CATH2c: Coronary sinus catheter.

The MHD (or magnetofluid dynamic) effect is a result of the static magnetic field and the movement of charge carriers that induces a voltage across the blood vessels[23,24]. This induced voltage superimposes on the signals and appears primarily during the S-T phase of the cardiac cycle as it has been related to the blood ejection through the aortic arch which is perpendicular to the magnetic field and coincides with the occurrence of the T-wave of the ECG. The RF pulses (64-128 MHz) and the fast-switching gradients (33-50 mT/m, 20-100 T/m/s), which are required for MRI, both disturb the signals because of the voltages induced on the electrodes, wires and patient's body.

Passing electrograms through several levels of filtering limited the noise on EGMs, in a previous study[25]. In detail, low-pass RF filters to reduce the 64-MHz RF signal from the MRI scanner were combined with a series of active filters (a low pass filter of 300 Hz, a high-pass filter of 30 Hz and a 60-Hz notch filter) to reduce gradient signal-induced noise[23]. For low-pass filtering, the highest-quality EP signals was obtained at the frequency of 120 Hz despite lower peak-to-peak signal amplitude[26]. Algorithms that overcome the limitations of state-of the-art methods and enable suppression of MR gradient artifacts and improve signal denoising quality have also been described including adaptive noise cancellation and non-linear Bayesian filtering[23,27].

Signal distortion should be taken into consideration especially for interpretation of EGMs after previous ablation attempts as double potentials (for typical flutter ablation) or abnormal potentials of low-amplitude as late potentials (for ventricular tachycardia ablation), although previous reports have presented detection of these ambiguous electrograms [21,28,29]. Moreover, as interpretation of surface ECG leads recording (that are usually connected to the recorder for rhythm monitoring and early detection of complications) may be impeded, additional monitoring should be used as pulse waveform.

Ablation lesion assessment

Lesions of radiofrequency catheter ablation can be visualized with CMR imaging[30,31]. The failure to create contiguous and durable transmural lesions has been held largely responsible for high recurrence rates[8,9]. Changes in tissue electrical impedance, electrode tissue contact and delivered power during conventional ablation techniques may not strongly correlated with the actual lesion size[32]. Electrical isolation may also be observed despite the presence of gaps in myocardial tissue after ablation that can be identified with MRI[6,7]. Thus, real-time lesion imaging is attractive as it could assess the ablation results and potentially provide a procedural endpoint.

Imaging with T2 mapping detects inflamed edematous tissue (Figures 4 and 5)[33]. However, T2-derived edema also corresponds to reversible lesions and is poorly correlated to long-term outcome as edema subsides progressively leading to electrical reconnections[34]. Several studies have reported on the extent of post-ablation T2-weighted signal that is greater in extent than delayed enhancement and overlaps with the areas of irreversible injury[30,31].

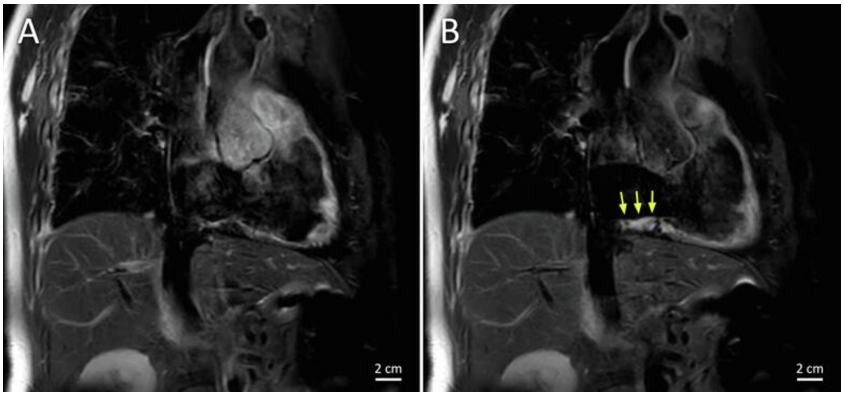

Figure 4 Imaging with T2 mapping detects inflamed edematous tissue. A and B: T2-weighted magnetic resonance images of the cavotricuspid isthmus in the RAO view before (A) and after (B) ablation showing edema in the ablation lesions, indicated by the yellow arrows. Citation: Bijvoet GP, Holtackers RJ, Nies HMJM, Mihl C, Chaldoupi SM. The role of interventional cardiac magnetic resonance (iCMR) in a typical atrial flutter ablation: The shortest path may not always be the fastest. *Int J Cardiol Heart Vasc* 2022; 41: 101078. [PMID: 35800043 DOI: 10.1016/j.ijcha.2022.101078]. Copyright © 2022 The Authors. Published by Elsevier B.V. (Reproduced under the terms of the Creative Commons CC-BY license)[44].

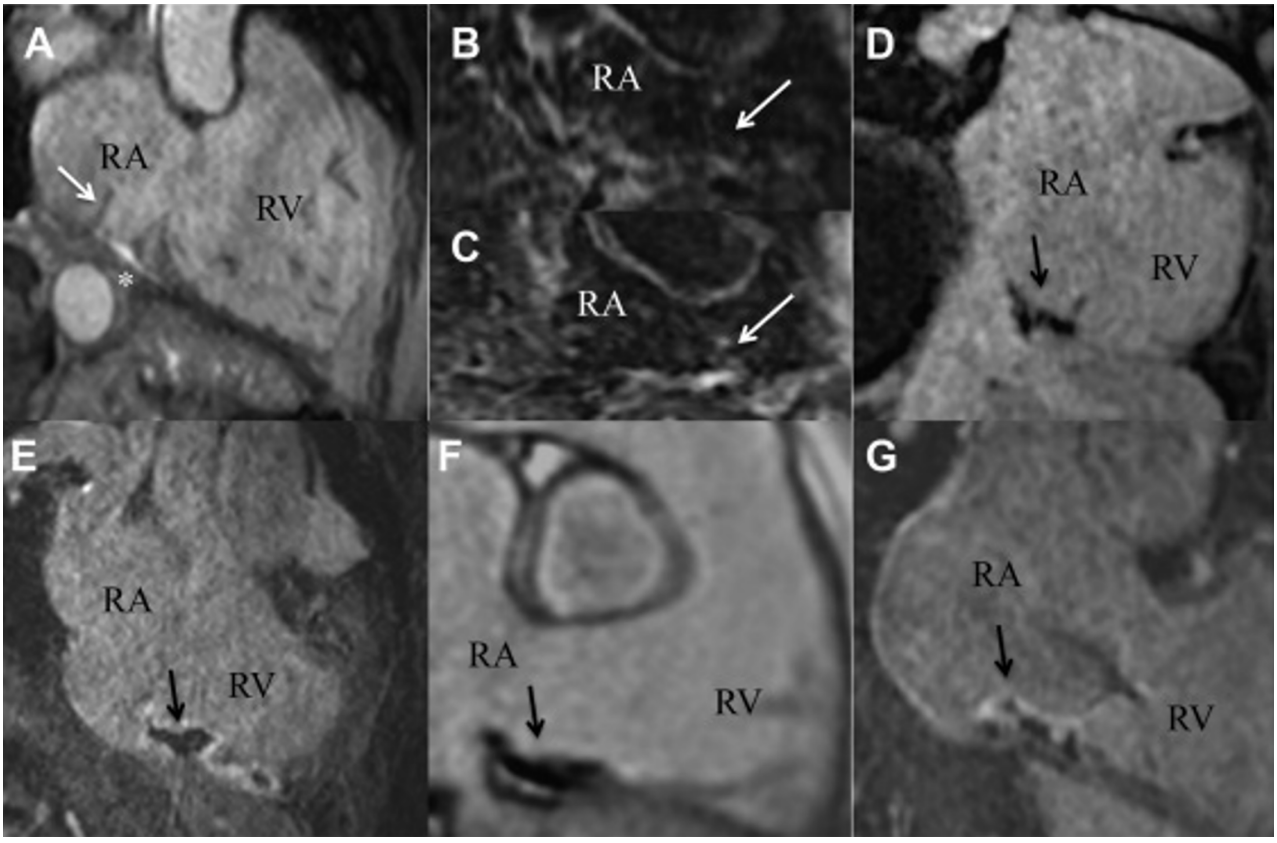

Figure 5 Acute lesion after radiofrequency ablation of the right cavotricuspid isthmus. A: Balanced steady-state free precision sequence image of the cavotricuspid isthmus (CTI) immediately after ablation. White asterisk indicates pericardial effusion. White arrow indicates a prominent eustachian valve; B and C: T2-weighted images preablation (B) and postablation (C) showing signal intensity enhancement of the isthmus line (white arrows); D: Noncontrast enhanced T1-weighted image of the CTI depicts acute necrotic lesions as signal intensity loss (black arrow); E: Postcontrast early enhancement image shows hypoenhanced myocardium localized at the CTI, known as a microvascular obstruction as an acute ablation lesion sign; F: Phase-sensitive inversion recovery image depicts acute ablation lesion in terms of black, hypoenhanced myocardium; G: Postcontrast late gadolinium enhancement images led to partially enhanced radiofrequency ablation lesions (white edge) with black necrotic core (black arrow). Citation: Ulbrich S, Huo Y, Tomala J, Wagner M, Richter U, Pu L, Mayer J, Zedda A, Krafft AJ, Lindborg K, Piorkowski C, Gaspar T. Magnetic resonance imaging-guided conventional catheter ablation of isthmus-dependent atrial flutter using active catheter imaging. *Heart Rhythm O2*. 2022; 3: 553-559 [PMID: 36340492 DOI: 10.1016/j.hroo.2022.06.011]. Copyright © 2022 Heart Rhythm Society. Published by Elsevier Inc. (Reproduced under the terms of the Creative Commons CC-BY license)[40].

Late contrast-enhancement is used to detect lesion necrosis and T1-weighted imaging is thought to reflect true procedural success determining reversibility of lesions (Figure 5)[33]. However, the use of gadolinium-based techniques has significant disadvantages related to wash-in and wash-out kinetics of this contrast agent[35]. Late contrast-enhanced imaging demonstrates higher contrast-to-noise ratio between normal myocardium tissue and the lesion. However, edematous tissues as well as previous fibrotic areas can also become enhanced, impeding identification of gaps between lesions. Furthermore, estimation of complete delayed enhancement is time-consuming. Measurements during the initial phase of contrast void overestimate the transmural extent of lesions while regions of micro-vascular obstruction acquired approximately 26 min after contrast administration to accurately predict the chronic lesion volume in a previous report [30,36]. Finally, repeated injections of gadolinium-based agents in a single session is limited by clinical restrictions in their dosage, as well as effects on imaging from accumulated contrast agent.

In this way, there has been interest in the development of intrinsic (non-contrast)-based methods for ablation lesion assessment[30]. Imaging with non-contrast-enhanced T_1-weighted pulse sequence with long inversion time was demonstrated to produce images of ablation lesions with readily visible contrast between the lesion core and normal myocardium and improved image quality for visualization of both lesions and anatomy (Figure 5)[30]. Importantly, unlike contrast-enhanced imaging, in which enhancement pattern changes over time, non-contrast based techniques can be repeated multiple times during a procedure.

MR thermometry is a technique for the monitoring of thermal treatments that utilizes the temperature dependent proton resonant frequency shift that occurs in water molecules[37]. MR thermometry has been shown to provide a direct assessment of ablation lesion extend in the myocardium[37]. The dimensions of the thermal lesions measured on thermal dose images were correlated with T1-weighted images acquired immediately after the ablation and at gross pathology in an animal study, although prediction of the lesion durability remains unclear[37].

Procedural workflows for real-time CMR-guided ablation of the cavotricuspid isthmus (CTI) have been proposed[21,38,39]. Pre-ablation balanced steady-state free precession three dimensions (3D) whole heart (bSSFP-3DWH) sequences without contrast provide the anatomy of cardiac cavities and large thoracic vessels with a selected acquisition window in ventricular diastole. Segmentation techniques may be used to derive the right atrial contour of this acquisition for integration into a navigation system. As a baseline for post-ablation imaging, T2- weighted images are also acquired prior to ablation. For guidance of the ablation catheter, the optimal planes are selected for the visualization of the CTI. A four-chamber view depicts the tricuspid valve and the distance to the interatrial septum while a long axis view the entire CTI length[38]. Views similar to the standard fluoroscopy views may also be used[39]. During active tracking, a dedicated sequence permits detection of the tip of the catheter and enables its manipulation along the CTI. A catheter is also placed into the coronary sinus for pacing maneuvers in order to verify isthmus block. For post-procedural imaging, the above-mentioned methods have been described. Imaging with non-contrast-enhanced T1-weighted pulse sequence with long inversion time can be performed multiple times in case of identified gaps. Gadolinium may also be administered in the end of the procedure for lesion assessment.

CLINICAL IMPLEMENTATION OF CMR-GUIDED ABLATION

Over the last two decades, substantial progress has been achieved in real-time CMR-guided electrophysiology studies and ablation procedures. In Tables 1 and 2, reported animal and human studies are presented. Following successful experimental reports, several human studies have demonstrated that CMR-guided catheter ablation is feasible without fluoroscopic guidance and enables the concurrent visualization of the targeted anatomical structure and substrate as well as the ablation lesion. The first human reports, in order to establish a procedural workflow, have rationally focused on typical atrial flutter ablation taking into consideration the relatively simple access to the right atrium and CTI[18,21,28,38,40].

Cavotricuspid isthmus dependent atrial flutter ablation

Reports of conventional radiofrequency catheter ablation of CTI-dependent atrial flutter have revealed a high acute success rate up to 95% and a low recurrence rate[41,42]. Moreover CTI-ablation is a relatively safe procedure with low risk of complications. However, difficult cases of initial failed ablation and persistent CTI conduction are occasionally encountered. A complex isthmus anatomy has been considered as a cause of failure to achieve a complete ablation line [43]. Isthmus pouches that are frequently present, a prominent Eustachian ridge and large pectinate muscles may impede catheter stability and navigation to target sites leading to poor tissue contact and low RF energy delivery (Figures 5A and 6). CMR-guidance provides visualization of these anatomical obstacles and enables the optimal target ablation line selection taking also into consideration the length and thickness of the lateral, medial and septal CTI portion[44].

Despite initial difficulties due either to technical issues or to unachievable procedural endpoint and requirement of ablation completion under fluoroscopic guidance[18,21,28], the most recent and larger studies have shown that CMR-guided CTI ablation represents a valid alternative to conventional ablation with an acute success rate of 93% to 100%[38,40]. Procedural times were comparable with fluoroscopy-guided treatment with similar results with regards to direct procedural success and short-term follow-up in a comparative study[38]. A steep learning curve was also demonstrated with a small number of procedures needed to achieve a level of competency and a meaningful gradual reduction of procedural duration[38].

Future perspectives

To date, no human studies have evaluated the use of real-time CMR-guided ablation apart from procedures performed

Table 1 Published animal studies on real-time cardiac magnetic resonance guided ablation

Ref.	*n*	Subject	Cardiac chamber/site	Procedure type
Lardo *et al*[31], 2000	6	Mongrel dog	RV apex	Ablation
Nazarian *et al*[25], 2008	10	Mongrel dog	RA, His bundle, RV	EP study
Nordbeck *et al*[60], 2009	8	Swine	RA, RV, AV node	Ablation
Hoffmann *et al*[61], 2010	20	Swine	CTI	Ablation
Nordbeck *et al*[62], 2011	9	Swine	CTI	Ablation
Vergara *et al*[63], 2011	6	Swine	RA, LA	Ablation
Ranjan *et al*[6], 2011	7	Mongrel dog	RA	Ablation
Ganesan *et al*[64], 2012	11	Sheep	PV, CTI	Ablation
Grothoff *et al*[65], 2017	14	Swine	RA, LA, AV node	Ablation
Krahn *et al*[33], 2018	12	Swine	LV	Ablation
Mukherjee *et al*[58], 2018	6	Swine	LV epicardium	Ablation
Chubb *et al*[21], 2017	5	Swine	CTI	Ablation
Lichter *et al*[53], 2019	8	Canine	PV, SVC, focal	(Cryo)ablation

AV: Atrioventricular; CTI: Cavotricuspid isthmus; EP: Electrophysiology; LA: Left atrium; PV: Pulmonary veins; SVC: Superior vena cava; RV: Right ventricle; RA: Right atrium.

Table 2 Published human studies on real-time cardiac magnetic resonance guided ablation

Ref.	*n*	Cardiac chamber/site	Procedure type
Nazarian *et al*[25], 2008	2	RA	EP study
Sommer *et al*[20], 2013	5	RA	EP study
Grothoff *et al*[18], 2014	10	CTI	Ablation
Hilbert *et al*[28], 2016	6	CTI	Ablation
Chubb *et al*[21], 2017	10	CTI	Ablation
Paetsch *et al*[38], 2019	30	CTI	Ablation
Ulbrich *et al*[40], 2022	15	CTI	Ablation

CTI: Cavotricuspid isthmus; EP: Electrophysiology; RA: Right atrium.

for typical atrial flutter. Broadening the application in the field of ventricular tachycardia (VT) would be of essential impact considering the widespread use of substrate-based strategies in VT ablation[45-47]. In the context of structural heart disease, surviving myocardium within areas of scar provide a substrate for reentry circuits[48]. Substrate-based ablation strategies have been shown to be as equally effective as activation mapping, which is often limited by haemodynamic instability and non-inducibility[49]. Even substrate ablation based only on the integration of pre-procedural CMR has been shown to be feasible and efficient while recent studies have shown improved VT recurrence-free survival compared to standard ablation[50,51]. Importantly, the information obtained from the CMR shows the wall distribution of the scar within the entire myocardial thickness[11]. Therefore, implementation of real-time CMR-guidance could increase the efficacy of VT ablation contributing also to deciding on the optimal approach during the procedure (endocardial, epicardial or combined). The VISABL-VT, a prospective, single-arm, multi-center trial will investigate the safety and efficacy of RF ablation of ventricular tachycardia associated with ischemic cardiomyopathy in the CMR environment (ClinicalTrials.gov Identifier: NCT05543798).

Towards the application of CMR-guided ablation in the field of atrial fibrillation, an MRI-compatible cryoablation system has been developed by removing all ferromagnetic components (as the circular mapping catheter) of a commercially available cryoballoon, implementing a compatible steering mechanism for balloon deflection and placing the console for the system outside the scanner room[52]. A recent animal study has shown that the real-time CMR-guided cryoablation of the pulmonary veins is feasible and provides the ability to visualize the freeze-zone formation during the freeze cycle[53]. Pulmonary vein reconnection has been reported as the main cause of arrhythmia recurrence and thus, durable isolation has been a key determinant of clinical outcome in patients undergoing catheter ablation for atrial fibril-

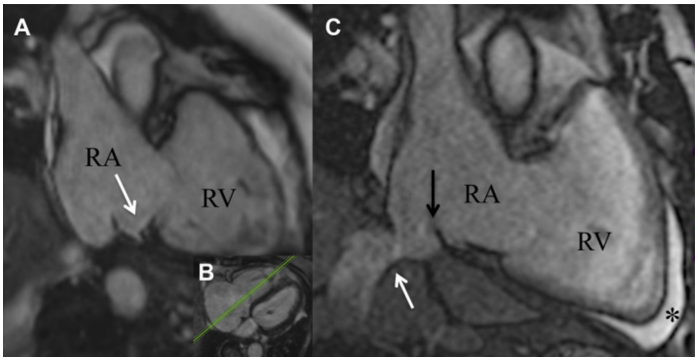

Figure 6 Isthmus pouches that are frequently present, a prominent Eustachian ridge and large pectinate muscles may impede catheter stability and navigation to target sites leading to poor tissue contact and low radio frequency energy delivery. A and B: Septal pouch (*white arrow*) of the cavotricuspid isthmus in a balanced steady-state free precision sequence image [as visualized in the transversal plane (B)]; C: Kinking of the vena cava inferior junction in the right atrium (*white arrow*) and a eustachian valve (*black arrow*) was found. Anterior to the right ventricular apex, a pre-existing pericardial effusion was located (*asterisk*). Citation: Ulbrich S, Huo Y, Tomala J, Wagner M, Richter U, Pu L, Mayer J, Zedda A, Krafft AJ, Lindborg K, Piorkowski C, Gaspar T. Magnetic resonance imaging-guided conventional catheter ablation of isthmus-dependent atrial flutter using active catheter imaging. *Heart Rhythm O2* 2022; 3: 553-559 [PMID: 36340492 DOI: 10.1016/j.hroo.2022.06.011]. Copyright © 2022 Heart Rhythm Society. Published by Elsevier Inc. (Reproduced under the terms of the Creative Commons CC-BY license)[40].

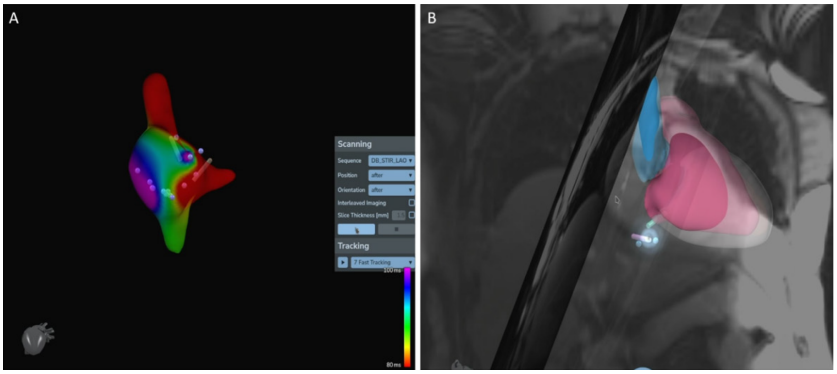

Figure 7 Electroanatomic mapping systems compatible for use inside a magnetic resonance scanner have been developed. A: 3D electroanatomical activation mapping; B: Integration with real-time cardiac magnetic resonance imaging planes. (Reproduced with permission from https://imricor.com).

lation[54]. It has also been demonstrated that electrical isolation may be observed due to local tissue architecture and/or anisotropy despite the presence of gaps in myocardial tissue and the recovery of conductivity can potentially lead to arrhythmia recurrence[6]. MRI has been shown to be able to identify gaps in ablation lines[54] while a report using real-time MR thermometry and thermal dosimetry demonstrated a strong correlation between thermal lesion and post-ablation T1-w images as well as with measurements at gross pathology[37]. Although further investigation is warranted, if MRI is able to assess lesion quality and durability, real-time CMR-guidance could improve effectiveness of catheter ablation.

However, several limitations should be solved before an extended application of CMR-guided ablation including the requirement of compatible tools as defibrillators and trans-septal needles, the scarce clinical data and safety concerns posed by performing procedures with high complication rate outside the conventional environment. Custom-made actively tracked needles (incorporated a receiver antenna) have been described to enable transseptal puncture under real-time CMR guidance[55]. Recently, a deflectable intracardiac MRI-compatible guiding-sheath was developed to accelerate imaging during CMR-guided electrophysiological interventions while real-time CMR-guided pericardiocentesis using commercially available passive access titanium needles has also been described[56,57].

EAM systems compatible for use inside an MR scanner have been developed (Figure 7)[58,59]. The achievement of active tracking opened up all the strengths of fast EAM, including activation and voltage mapping[21]. Integration with real-time imaging of cardiac anatomy, arrhythmia substrate and ablation lesions permits a combination of electro-physiological and anatomic information. However, further innovation of these tools may be warranted in order to be comparable to the conventional mapping systems including signal fidelity and modules for correction of annotation.

CONCLUSION

Real-time CMR-guided ablation could offer a number of benefits including not only radiation-sparing procedures, but also evaluation of cardiac anatomy and substrate as well as assessment of ablation lesion formation, although further research is warranted for confirming the above-mentioned potential advantages. The feasibility of CMR-guided CTI ablation has already been demonstrated and potential expansion to other more complex arrhythmias, especially ventricular tachycardia and atrial fibrillation, would be of essential impact. However, several limitations need to be solved before application of CMR-guided ablation in a broad clinical setting, including signal fidelity and compatible tools, while innovations in EAM integration could enable the combination of the advantages of conventional electrophysiological and substrate-based approaches.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Remdesivir, dexamethasone and angiotensin-converting enzyme inhibitors use and mortality outcomes in COVID-19 patients with concomitant troponin elevation

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Abstract

BACKGROUND

There are indications that viral myocarditis, demand ischemia, and renin-angiotensin-aldosterone system pathway activation play essential roles in troponin elevation in coronavirus disease 2019 (COVID-19) patients. Antiviral medications and steroids are used to treat viral myocarditis, but their effect in patients with elevated troponin, possibly from myocarditis, has not been studied.

AIM

To evaluate the effect of dexamethasone, remdesivir, and angiotensin-converting enzyme (ACE) inhibitors (ACEI) on mortality in COVID-19 patients with elevated troponin.

METHODS

Our retrospective observational study involved 1788 COVID-19 patients at seven hospitals in Southern California, United States. We did a backward selection Cox multivariate regression analysis to determine predictors of mortality in our study population. Additionally, we did a Kaplan Meier survival analysis in the subset of patients with elevated troponin, comparing survival in patients that received dexamethasone, remdesivir, and ACEI with those that did not.

RESULTS

The mean age was 66 years (range 20-110), troponin elevation was noted in 11.5% of the patients, and 29.9% expired. The patients' age [hazard ratio (HR) = 1.02, $P < 0.001$], intensive care unit admission (HR = 5.07, $P < 0.001$), and ventilator use (HR = 0.68, $P = 0.02$) were significantly associated with mortality. In the subset of patients with elevated troponin, there was no statistically significant difference in survival in those that received remdesivir (0.07), dexamethasone ($P = 0.63$), or ACEI ($P = 0.8$) and those that did not.

CONCLUSION
Although elevated troponin in COVID-19 patients has been associated with viral myocarditis and ACE II receptors, conventional viral myocarditis treatment, including antiviral and steroids, and ACEI did not show any effect on mortality in these patients.

Key Words: Coronavirus disease 2019; Troponin elevation; Remdesevir; Ace inhibitor; Steroids

Core Tip: Myocarditis from direct viral injury or related to angiotensin-converting enzyme (ACE) II downregulation with subsequent hyperactivity of the renin-angiotensin-aldosterone system plays an essential role in troponin elevation in coronavirus disease 2019 (COVID-19) patients. However, the effect of antiviral medications and steroids used to treat viral myocarditis has not been well-studied in patients with elevated troponins, which this study sought to address. We found no significant difference in survival rates in COVID-19 patients with elevated troponin that received remdesivir, dexamethasone, or ACE inhibitors *vs* those that did not. The implication for practice is that treatment with various medications that could be beneficial in viral myocarditis did not show any mortality benefit in our study for COVID-19 patients with troponin elevation.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection continues to have a devastating global impact, with over 640 million confirmed infections, including 6.6 million deaths worldwide as of December 3, 2022[1]. The virus's predilection for the pulmonary system is a well-studied effect of its pathogenicity, evidenced in the 2003 outbreak in Southern China. Cardiac involvement has also been a widely observed sequela of the COVID-19 infection, conferring a worse prognosis on those with underlying cardiovascular disease[2,3]. Several studies have discussed the usefulness of measuring cardiac troponins (cTn) as a measure of myocardial injury and also as a method to stratify at-risk individuals. Myocardial injury is defined as an elevation in cTn above the 99% of the upper reference limit (URL). It is considered acute if there is a subsequent rise and/or fall of cTn values[2,4].

Recent literature has revealed the cytopathic, inflammatory, and thrombotic effects of COVID-19 suggesting the important role of inflammatory markers in disease progression and severity[5,6] Particularly important is the correlation of the severity of the hyper-inflammatory response with a higher level of cTn, increasing the risk of mortality and complications in patients[2,7-9]. In addition, elevated C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, immunoglobulin G-induced protein 10, chemokine ligand 3 and tumor necrosis factor in COVID-19 patients, have been associated with cardiac injury and increased mortality[2,7-10].

Several mechanisms of myocardial injury leading to troponin elevation have been postulated. One such mechanism is direct virus-induced myocardial injury leading to myocarditis. In the initial phase, the virus facilitates its damage to the myocardium by direct lysis of cardiac myocytes[11]. This is typically followed by an intensified T-cell response, leading to further immune mediated myocyte injury and ventricular dysfunction[11]. Since 2005, it has been known that the SARS-CoV virus infects cells through the angiotensin-converting enzyme (ACE) II receptor. ACE II receptors are highly expressed in vascular endothelium, cardiac pericytes, and alveolar cells, which has lent support to this proposed mechanism of myocardial damage[11,12]. This observation has now sparked interest in evaluating whether medications such as ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) would benefit or harm those infected with SARS-CoV-2. In addition, SAR-CoV-2's indirect effects on the cardiovascular system have been studied extensively concerning ACE II downregulation leading to activation of the renin-angiotensin-aldosterone system (RAAS)[11]. Furthermore, ACE II catalyzes the conversion of angiotensin II to angiotensin I, a process that directly opposes the innate immune system's subsequent release of proinflammatory cytokines, vasoconstriction, pro-oxidants, pro-proliferative and profibrotic actions[11]. As such, there is interest in examining if inhibition of the ACE II enzyme with widely used antihypertensives, including ACEI and ARBs, would benefit COVID-19 patients as it stimulates the innate immune system, thus facilitating a more robust response to combat the underlying infection.

In summary, there are indications that viral myocarditis, demand ischemia, and RAAS pathway activation play essential roles in troponin elevation in COVID-19 patients. Antiviral medications and steroids are used to treat viral myocarditis, but their effect in patients with elevated troponin, possibly from myocarditis, has not been studied. Additionally, there is a lack of studies on the impact of ACEI use in patients with elevated troponin. Therefore, this

multicenter retrospective study aims to evaluate the effect of dexamethasone, remdesivir, and ACEI on mortality in COVID-19 patients with elevated troponin.

MATERIALS AND METHODS

We conducted a multicenter retrospective observational study at seven hospitals in Southern California, United States. The study enrolled 1788 consecutive COVID-19 patients admitted to the seven hospitals between March 2020 and August 2021 who had a troponin test on admission. All patients were confirmed to have COVID-19 infection through a positive polymerase chain reaction nasopharyngeal swab. We extracted relevant deidentified patient data using a SQL program from the electronic medical record, which included: Age, race, gender, comorbidities, date of hospital admission, date of discharge, laboratory results on admission, medications they received while on admission, heart rate, and disposition at discharge. Our primary outcomes were the predictors of troponin elevation in COVID-19 patients and the effect of dexamethasone, remdesivir, and ACEI on mortality in COVID-19 patients with elevated troponin. Elevated cTn diagnostic of myocardial infarction is when the levels exceed the 99th percentile of a normal, healthy reference population (URL). This value is determined for each specific troponin assay with appropriate quality control in each laboratory[13]. Based on our laboratory assay, a troponin I (cTnI) level above 0.4 ng/mL was considered elevated for our study.

We performed a univariate analysis of the independent variables, including patients' age, gender, race, length of hospital stay, comorbidities, the medication patients received while in the hospital, and laboratory results using means and percentages. Furthermore, we performed a bivariate analysis of the relationship between troponin elevation and different study variables using chi-square and *t*-test, with a *P* value of 0.05 considered significant. We then did a backward selection logistic regression to determine the factors associated with troponin elevation. Additionally, we did a backward selection Cox multivariate regression analysis using mortality as a dependent variable. For the logistic and Cox regression analysis, we initially included statistically significant or biologically plausible variables from the bivariate analysis, such as patients' age, sex, body mass index, comorbidities, intensive care unit (ICU) admission, and mechanical ventilation, as independent variables in the multivariate model. The effect was expressed in odds and hazard ratios (HRs) for the logistic and Cox regression, respectively. Hypothesis testing was done using a two-sided test, and an alpha value of 0.05 indicated statistical significance.

In the second phase of our analysis, we did the Kaplan Meier survival analysis in the subset of patients with elevated troponin comparing survival in patients that received dexamethasone, remdesivir, and ACEI with those that did not. Statistical analysis was done using IBM SPSS version 27. The WIRB-Copernicus Group institutional review board approved the study.

RESULTS

Descriptive statistics

Tables 1 and 2 show the descriptive statistics of continuous and categorical variables of the study population, including length of stay, age, body mass index (BMI), and gender. The mean age was 66 years and ranged from 20-110 years, and 58% were males. Patients' race was categorized into white, Asian, black, and others, with 64.4%, 6.1%, 4.5%, and 24.9%, respectively. The patients had underlying comorbidities, including hypertension (42.3%), diabetes (19.2%), chronic kidney disease (CKD) (24%), and congestive heart failure (CHF) (18.8%). The patients received different medications while on admission, including dexamethasone (68.2%), remdesivir (50.9%), and ACEI (19.4%). Troponin was elevated in 11.5% of the study subjects and 29.9% of the total study population expired.

Bivariate analysis

In the bivariate analysis of continuous variables, length of hospital stay ($P = 0.007$), CRP ($P < 0.001$), lactate dehydrogenase (LDH) ($P < 0.001$), ferritin ($P = 0.03$), creatine phosphokinase (CPK) ($P = 0.01$), platelet count ($P = 0.02$), white blood cell count ($P < 0.001$), potassium ($P < 0.001$) and total bilirubin were significantly associated with troponin elevation. Patients with elevated troponin were more likely to have increased inflammatory markers, including CRP, LDH, ferritin, and CPK. The length of stay was also higher in patients with elevated troponin. There was no difference in age, BMI, and oxygen saturation in patients with or without elevated troponin (Table 3).

In the bivariate analysis of categorical variables, mortality ($P < 0.001$), ventilator use ($P < 0.001$), ICU admission ($P < 0.001$), CKD ($P < 0.001$), and CHF ($P < 0.001$) were significantly associated with elevated troponin. Patients with elevated troponin were more likely to die, be admitted to ICU, or be placed on a ventilator. Additionally, those with CHF or CKD were more likely to have elevated troponin (Table 4).

Multivariate analysis

In the multivariate logistic regression analysis, elevated levels of LDH [odd ratio (OR) = 1, $P = 0.004$], underlying CHF (OR = 2.7, $P < 0.001$), and ICU admission (OR = 3.6, $P < 0.001$) were independently associated with elevated troponin. Additionally, in the Cox regression multivariate analysis, age (HR = 1.02, $P < 0.001$), ICU admission (HR = 5.07, $P < 0.001$), and ventilator use (HR = 0.68, $P = 0.02$) were significantly associated with mortality. However, Troponin elevation (HR = 1.25, $P = 0.1$) was not independently associated with mortality after adjusting for age, comorbidities like CHF, ICU admission, and inflammatory markers (Tables 5 and 6).

Table 1 Descriptive statistics of continuous variables

	n	Minimum	Maximum	Mean	SD
Length of stay	1788	1	117	11.77	11.73
Age	1788	20	110	66.36	16.36
Body mass index	1741	14.14	83.12	30.07	8.69
C-reactive protein	1575	0.05	54.38	14.60	9.57
Lactate dehydrogenase	1384	55	8180	487.45	525.15
Ferritin	1240	5.1	47560.8	1038.56	2187.49
Troponin	1788	0.01	32.78	0.49	2.41
Creatine phosphokinase	979	10	88961	755.30	4495.43
Platelet	1786	37	1176	328.47	138.68
White blood cell count	1787	2.4	80.7	16.12	9.05
Potassium	1513	2.70	8.50	4.82	0.84
Total bilirubin	1780	0.2	27.8	1.01	1.16

Subgroup analysis

In the Kaplan-Meier survival analysis of the subset of 205 patients with elevated troponin, the median survival in patients that received remdesivir (18 d) was higher than those that did not (14 d). However, this was not statistically significant (P = 0.07) (Figure 1A). Similarly, the median survival in patients receiving dexamethasone (16 d) was higher than in those not (14 d), but this was not statistically significant (P = 0.63) (Figure 1B). Finally, the median survival in patients on ACEI (16 d) was the same as those without (P = 0.8) (Figure 1C).

Furthermore, we did a Kaplan Meier analysis in the subset of patients with elevated concomitant troponin, CPK, and LDH, which would be expected in patients with significant myocarditis. However, similar to our analysis in those with elevated troponin, we found no difference in mortality between those that received dexamethasone (P = 0.88), ACEI (P = 0.83), or remdesivir (P = 0.93) and those that did not in this sub-group of patients.

DISCUSSION

COVID-19 has been reported to cause direct myocardial injury and myocarditis in some patients[14,15]. COVID-19 patients with myocarditis have increased troponin and non-specific ST-segment and T-wave changes. Echocardiogram typically shows global hypokinesis and pericardial effusion[14]. Thus, myocarditis mimics acute coronary syndrome, but the coronary arteries are usually normal on coronary angiogram. The gold standard for diagnosing myocarditis is histopathology of endomyocardial biopsy, an invasive procedure not often performed in clinical practice. Cardiac magnetic resonance imaging (MRI) is often used to diagnose myocarditis[14,16]. Antiviral medications, intravenous immunoglobulins, and immunosuppressants such as steroids and azathioprine have been used in treating viral myocarditis with limited evidence of benefit[16]. In our study, we did not do cardiac MRI to determine the proportion of patients with elevated troponin that have myocarditis. However, our Kaplan Meier analysis did not show any statistically significant difference in mortality in patients with elevated troponin who received steroids and those that did not. The role of steroids in myocarditis caused by COVID-19 is unclear, and the lack of steroid efficacy on mortality in patients with elevated troponin in our study could suggest that steroids may not play any significant role in COVID-19 induced myocarditis. However, we do not know the proportion of patients in our study with myocarditis, and the role of steroids in COVID-19 myocarditis needs to be further investigated.

Furthermore, studies have suggested a possible relationship between increased viral load and myocardial injury in COVID-19 patients. For example, in a study of hospitalized COVID-19 patients, those with detectable viremia were significantly more likely to have elevated troponin and myocardial injury than those without viremia[17]. Although another study did not find any relationship between the initial viral load and the incidence of myocardial injury in hospitalized COVID-19 patients, high viral load and myocardial injury were independent predictors of in-hospital mortality [18]. Remdesivir, a viral RNA polymerase inhibitor, significantly reduced the median recovery time of COVID-19 patients compared to placebo in the adaptive, randomized controlled Adaptive COVID-19 Treatment Trial-1 study[19]. However, there is limited data on how Remdesivir impacts cardiac injury. In the Kaplan-Meier survival analysis of the subset of patients with elevated troponin in our study, the median survival in patients that received remdesivir (18 d) was higher than those that did not (14 d). However, this was not statistically significant (P = 0.07). The lack of statistical significance could be due to our sub-group analysis being underpowered to detect a difference.

SARS-CoV-2 binds to the ACE II receptor (ACE II), which is highly expressed in the lungs and myocardium, and this has been postulated as a mechanism through which the virus causes direct damage to cardiac cells[20]. ACEI have been shown to upregulate the expression of ACE II in lung cells in animal studies. The mechanism is unclear but is possibly

Table 2 Descriptive analysis of categorical variable

	Frequency	Percent
Gender		
Female	749	41.9%
Male	1039	58.1%
Race		
Asian	109	6.1%
Black	81	4.5%
White	1152	64.4%
Others	446	24.9%
Expired		
No	1254	70.1%
Yes	534	29.9%
Ventilator use		
No	1352	75.6%
Yes	436	24.4%
Intensive care unit		
No	1328	74.3%
Yes	460	25.7%
Remdesivir		
No	853	49.1%
Yes	883	50.9%
Dexamethasone		
No	568	31.8%
Yes	1220	68.2%
Angiotensin converting enzyme inhibitor		
No	1441	80.6%
Yes	347	19.4%
Diabetes mellitus		
No	1444	80.8%
Yes	344	19.2%
Hypertension		
No	1032	57.7%
Yes	756	42.3%
Chronic kidney disease		
No	1355	76.0%
Yes	427	24.0%
Acute kidney injury		
No	1588	88.8%
Yes	200	11.2%
Congestive heart failure		
No	1451	81.2%
Yes	337	18.8%

Chronic obstructive pulmonary disease		
No	1678	93.8%
Yes	110	6.2%
Bradycardia		
No	823	46.0%
Yes	965	54.0%
Troponin elevation		
No	1583	88.5%
Yes	205	11.5%

Table 3 Bivariate analysis of the relationship between continuous variables and troponin elevation

	Troponin elevation	*n*	Mean	SD	*P* value
Length of stay	0	1583	11.46	11.44	0.007
	1	205	14.16	13.52	
Age	0	1583	66.14	16.49	0.08
	1	205	68.13	15.29	
Body mass index	0	1540	30.11	8.62	0.64
	1	201	29.80	9.20	
Oxygen on admission	0	1415	94.47	6.27	0.27
	1	187	94.20	6.69	
C-reactive protein	0	1393	14.23	9.50	< 0.001
	1	182	17.47	9.70	
Lactate dehydrogenase	0	1236	447.71	363.69	< 0.001
	1	148	819.34	1165.85	
Ferritin	0	1099	956.44	1859.08	0.03
	1	141	1678.58	3844.02	
Creatine phosphokinase	0	863	586.10	4245.13	0.01
	1	116	2014.03	5913.58	
Platelet	0	1582	331.24	138.55	0.02
	1	204	307.00	138.15	
WBC	0	1583	15.66	8.97	< 0.001
	1	204	19.76	8.88	
Potassium	0	1341	4.78	0.83	< 0.001
	1	172	5.07	0.92	
Total bilirubin	0	1577	0.95	0.83	0.004
	1	203	1.46	2.48	

WBC: White blood cell.

through decreasing angiotensin II, leading to indirect upregulation of ACE II[21,22]. Thus, there have been concerns that the use of ACEI in patients with COVID-19 will increase the risk of lung and myocardial injury. However, some human studies did not support the hypothesis that ACEI use increases ACE II expression and the risk of lung and myocardial injuries in COVID-19 patients[23]. Furthermore, the Kaplan-Meier analysis in our study showed no difference in survival in patients with elevated troponin who received ACEI and those who did not, suggesting that the use of ACEI should not be withheld even in patients with elevated troponin.

Table 4 Bivariate analysis of the relationship between categorical variables and troponin elevation

Variable	Troponin elevation		*P* value
	No	Yes	
Gender			
Male	918 (88.4%)	121 (11.6%)	0.78
Female	665 (88.8%)	84 (11.2%)	
Race			
Asia	96 (88.1%)	13 (11.9%)	0.38
Black	72 (88.9%)	9 (11.1%)	
White	1030 (89.4%)	122 (10.6%)	
Others	385 (86.3%)	61 (13.7%)	
Expired			
Yes	415 (77.7%)	119 (22.3%)	< 0.001
No	1168 (93.1%)	86 (6.9%)	
Ventilator			
Yes	334 (76.6%)	102 (23.4%)	< 0.001
No	1249 (92.4%)	103 (7.5%)	
Intensive care unit			
Yes	354 (77.0%)	106 (23.0%)	< 0.001
No	1229 (92.5%)	99 (7.5%)	
Diabetes mellitus			
Yes	314 (91.3%)	30 (8.7%)	0.08
No	1269 (87.9%)	175 (12.1%)	
Hypertension			
Yes	677 (89.6%)	79 (10.4%)	0.25
No	906 (87.8%)	126 (12.2%)	
Chronic kidney disease			
Yes	354 (82.9%)	73 (17.1%)	<0.001
No	1223 (90.3%)	132 (9.7%)	
Congestive heart failure			
Yes	279 (82.8%)	58 (17.2%)	< 0.001
No	1304 (89.9%)	147 (10.1%)	
Chronic obstructive pulmonary disease			
Yes	96 (87.3%)	14 (12.7%)	0.67
No	1487 (88.6%)	191 (11.4%)	
Bradycardia			
Yes	853 (88.4%)	112 (11.6%)	0.84
No	730 (88.7%)	93 (11.3%)	
Use of Remdesivir			
Yes	789 (89.4%)	94 (10.6%)	0.28
No	748 (87.7%)	94 (12.3%)	
Use of dexamethasone			
Yes	1069 (87.6%)	151 (12.4%)	0.08

No	514 (90.5%)	54 (9.5%)

Table 5 Logistic regression on predictors of increased troponin elevation

	B	SE	Wald	df	Sig	Exp (B)	95%CI for EXP (B)	
							Lower	Upper
Lactate dehydrogenase	0.000	0.000	8.091	1	0.004	1.000	1.000	1.001
Congestive heart failure	0.991	0.239	17.170	1	0.000	2.694	1.686	4.305
Intensive care unit	1.278	0.232	30.359	1	0.000	3.591	2.279	5.659
Constant	-3.154	0.194	264.436	1	0.000	0.043		

95%CI: 95% confidence interval; df: Degree of freedom; SE: Standard error; Sig: Significance.

Table 6 Cox regression analysis showing predictors of mortality in coronavirus disease 2019 patients

	B	SE	Wald	df	Sig	Exp (B)	95%CI for Exp (B)	
							Lower	Upper
Age	0.022	0.004	26.460	1	0.000	1.022	1.014	1.031
Ventilator use	-0.378	0.157	5.830	1	0.016	0.685	0.504	0.931
Intensive care unit admission	1.624	0.164	97.657	1	0.000	5.074	3.677	7.003
Troponin	0.219	0.133	2.705	1	0.100	1.245	0.959	1.616

95%CI: 95% confidence interval; df: Degree of freedom; SE: Standard error; Sig: Significance.

In our study, elevated levels of LDH (OR = 1, P = 0.004), underlying CHF (OR = 2.7, P < 0.001), and ICU admission (OR = 3.6, P < 0.001) were independently associated with elevated troponin. This finding is similar to former studies that showed that elevated troponin, increased age, and co-morbidities are predictors of ICU admission[24]. This was further collaborated by a meta-analysis of 23 studies that showed that patients with elevated troponin had a significantly increased risk of severe disease and ICU admission [risk ratio (RR) = 5.57, 95%confidence interval (95%CI): 3.04 to 10.22, P < 0.001; RR = 6.20, 95%CI: 2.52 to 15.29, P < 0.001][25]. Furthermore, our study showed that elevated troponin was associated with CHF, similar to previous studies that showed that patients with troponin elevation were older, with more co-morbidities[26].

In our study, there was increased mortality in patients with troponin elevation (HR = 1.25, P = 0.1), although this was not statistically significant at a P value of 0.05. The lack of statistical significance could be related to the fact that our study was underpowered to detect a difference. It could also be that patients in our study differ from those in previous studies. For example, while the proportion of patients in our study with elevated troponin was 11%, a meta-analysis of prior studies has shown an average of 31% (range 23%-38%)[27], 22.9%[28], and 27% (range 9%-51%)[29]. Studies have found that elevation of high-sensitivity troponin and traditional troponin assays are associated with increased mortality in COVID-19 patients[27-31]. Patients with elevated troponin had significantly increased odds of death than those with normal troponin independent of elevation in inflammatory markers and cardiovascular co-morbidities[27-31].

Our study has several limitations. Firstly, in the subgroup analysis, we dealt with a small sample size which may limit the overall power of the study. Secondly, troponin was assessed on admission and was not monitored for the duration of the patient's hospital stay, which may impact the lack of association observed between troponin elevation and mortality. Thirdly, in the analysis between ACEI use and troponin elevation, our data only reflects patients placed on an ACEI during their hospital stay. We did not stratify patients on whether they were on the medication previously, and it is possible some patients on ACEI at home might not have been started on it in the hospital. This might have resulted in a misclassification bias and affected the study outcome. Finally, this research is an observational study, and there might have been unmeasurable variables that might have confounded the study outcome. Also we did not conduct cardiac MRI to confirm out findings of myocarditis but based that on inferential analysis.

CONCLUSION

Although elevated troponin in COVID-19 patients has been associated with viral myocarditis, conventional viral myocarditis treatment, including steroids and antiviral, did not affect mortality in these patients. In addition, previous

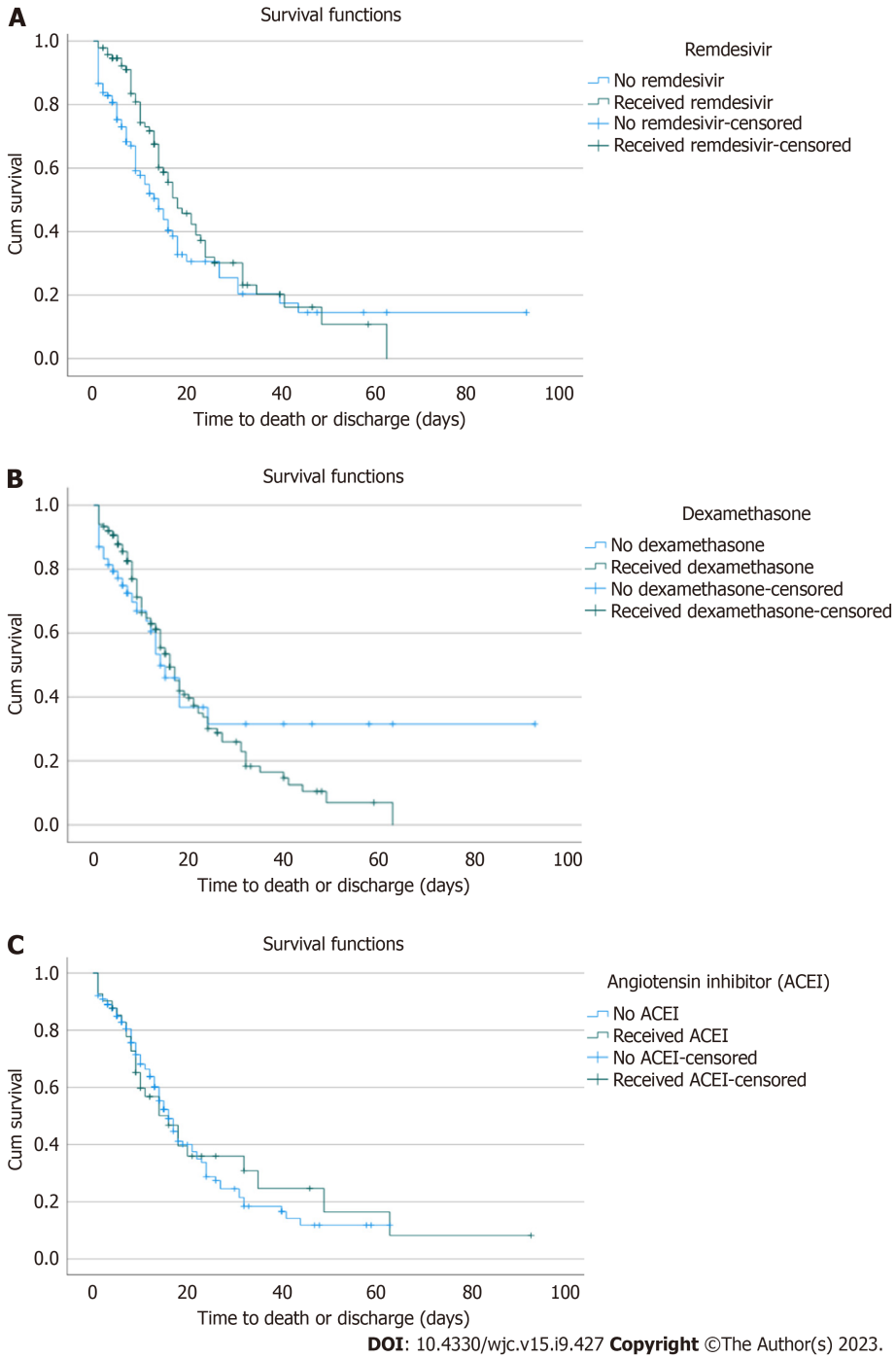

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Figure 1 Kaplan Meier. A: Remdesivir use and mortality in patients with troponin elevation; B: Dexamethasone use and mortality in patients with troponin elevation; C: Angiotensin-converting enzyme inhibitors use and mortality in patients with troponin elevation. ACEI: Angiotensin-converting enzyme inhibitors.

studies have suggested a possible association between COVID-19 viral load and myocardial injury; however, we found no statistically significant difference in survival in patients with elevated troponin treated with remdesivir and those that were not. Furthermore, our study suggested that ACEI should not be withheld even in patients with elevated troponin because it did not negatively or positively affect survival.

ARTICLE HIGHLIGHTS

Research background

Several studies have proposed that troponin elevation seen in coronavirus disease 2019 (COVID-19) patients is due to an interplay between viral myocarditis, demand ischemia and renin-angiotensin-aldosterone system pathway activation. This creates the hypothesis that the use of steroids, antivirals and angiotensin-converting enzyme inhibitors (ACEI) in

patients with COVID-19 infection and troponin elevation would impact mortality outcomes.

Research motivation

The COVID-19 pandemic has had a monumental global impact and resulted in several deaths worldwide. The motivation of this study was to analyze if the use of the steroids, antivirals and ACEI would improve survival in patient with COVID-19 infection and troponin elevation.

Research objectives

Our main objective was to analyze any differences in mortality in our subjects, in the hopes of adding to existing knowledge and creating a standardized treatment protocol in patients with COVID-19 and troponin elevation.

Research methods

Our study design was a retrospective observational study consisting of 1788 COVID-19 patients at seven hospitals across Southern California. To determine the predictors of mortality in our subjects, we did a backward selection cox multivariate regression analysis. Furthermore, to analyze survival in the subset of patients with troponin elevation we did a Kaplan Meier analysis comparing those that received treatment with steroids, remdesivir and ACEI and those that did not.

Research results

Though the beneficial role of steroids in the treatment of COVID-19 has been established, our study did not show any statistically significant difference in mortality in patients with elevated troponin who received steroids and those that did not. Therefore, the role of steroids in myocarditis caused by COVID-19 is still unclear and needs further investigation. On the other hand, our study showed improved survival in COVID-19 patients with elevated troponin that received remdesivir, although this was not statistically significant.

Research conclusions

Although the mechanism of troponin elevation in COVID-19 patient has been linked to viral myocarditis and renin-angiotensin-aldosterone system activation, the novel treatments of these subsequent pathologies including steroids, remdesivir and ACEI showed no significant survival benefit in our study. This creates the theory that there are other mechanisms at play guiding this complex interaction.

Research perspectives

Although our study did not show a statistically significant mortality benefit with the use of steroids and remdesivir, our sub-group analysis was limited by a small sample size, so further studies on the effect of remdesivir in the sub-set of COVID-19 patients with elevated troponin using a larger population will be beneficial.

FOOTNOTES

Author contributions: Umeh CA, Maoz H, Obi J, Dakoria R, Patel S, Maity G and Barve P conceptualized and revised the study design; Umeh CA analyzed the data; Maoz H, Umeh CA, Obi J, Dakoria R, Patel S, and Maity G, wrote the first draft of the paper; Barve P and Umeh CA, reviewed and revised the paper; Maoz H led and coordinated the research and writing of the manuscript; Barve P and Umeh CA supervised the project; all authors have read and approved the final manuscript.

Institutional review board statement: The WIRB-Copernicus Group (WCG) institutional review board (IRB) approved the study. IRB approval number: 13410516.

Informed consent statement: Our study was a retrospective observational study which used medical records for data acquisition and analysis and thus does not require informed consent from subjects.

Conflict-of-interest statement: None to declare.

Data sharing statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Immediate in-hospital outcomes after percutaneous revascularization of acute myocardial infarction complicated by cardiogenic shock

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Abstract

BACKGROUND

Cardiogenic shock (CS) is a life-threatening complication of acute myocardial infarction with high morbidity and mortality rates. Primary percutaneous coronary intervention (PCI) has been shown to improve outcomes in patients with CS.

AIM

To investigate the immediate mortality rates in patients with CS undergoing primary PCI and identify mortality predictors.

METHODS

We conducted a retrospective analysis of 305 patients with CS who underwent primary PCI at the National Institute of Cardiovascular Diseases, Karachi, Pakistan, between January 2018 and December 2022. The primary outcome was immediate mortality, defined as mortality within index hospitalization. Univariate and multivariate logistic regression analyses were performed to identify predictors of immediate mortality.

RESULTS

In a sample of 305 patients with 72.8% male patients and a mean age of 58.1 ± 11.8 years, the immediate mortality rate was found to be 54.8% (167). Multivariable analysis identified Killip class IV at presentation [odds ratio (OR): 2.0; 95% confidence interval (CI): 1.2-3.4; $P = 0.008$], Multivessel disease (OR: 3.5; 95%CI: 1.8-6.9; $P < 0.001$), and high thrombus burden (OR: 2.6; 95%CI: 1.4-4.9; $P = 0.003$) as independent predictors of immediate mortality.

CONCLUSION
Immediate mortality rate in patients with CS undergoing primary PCI remains high despite advances in treatment strategies. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality. These findings underscore the need for aggressive management and close monitoring of patients with CS undergoing primary PCI, particularly in those with these high-risk characteristics.

Key Words: Acute myocardial infarction; Cardiogenic shock; Primary percutaneous coronary intervention; Mortality; Predictors

Core Tip: Cardiogenic shock (CS) is a severe form of acute myocardial infarction (AMI) associated with low blood pressure, poor organ perfusion, and high mortality rates. Overall, primary percutaneous coronary intervention (PCI) plays a crucial role in the management of patients with CS by improving blood flow to the heart, restoring cardiac function, and reducing mortality rates. However, the success of primary PCI depends on several factors, including the timeliness of treatment, the skill and experience of the operators performing the procedure, and the patient's overall health status. Therefore, it is essential to identify high-risk patients and provide timely appropriate treatment to achieve the best outcomes. Therefore, we conducted a retrospective analysis of 305 patients with CS complicated AMI undergone primary PCI at our center. It has been observed the immediate mortality rate was unacceptably high at 54.8% with cardiac arrest followed by renal failure, multi-organ dysfunction, sepsis, hypoxic brain injury and cerebrovascular accident as a cause of mortality. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality in multivariable analysis.

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INTRODUCTION

The prevalence of myocardial infarction is estimated to vary by age group, with reported rates of 3.8% among individuals under 60 years of age and a higher prevalence of 9.5% among those aged 60 years and above. Within the context of acute myocardial infarction (AMI), a critical complication known as cardiogenic shock (CS) emerges as a life-threatening concern[1]. This condition stands as the leading cause of mortality associated with AMI, with reported incidence rates ranging from 5% to 15%[2,3]. CS is a medical emergency that occurs when the heart is unable to pump enough blood to meet the body's needs. It can be caused by a variety of conditions, including myocardial infarction (heart attack), cardiomyopathy, and valvular heart disease[3]. Management of CS involves identifying and treating the underlying cause and providing supportive care to stabilize the patient's condition[4]. In AMI, CS is a life-threatening complication with a high morbidity and mortality rate[5]. Primary percutaneous coronary intervention (PCI) has emerged as the preferred reperfusion strategy in patients with AMI and CS[6]. The main goal of primary PCI in patients with CS is to restore blood flow to the affected area of the heart, which can help to improve cardiac function and reduce mortality rates[4]. Compared to other revascularization strategies, such as thrombolysis or medical therapy alone, primary PCI has been shown to be more effective in restoring blood flow and improving outcomes in patients with CS[7].

Patients with CS are at risk of developing several in-hospital complications, which include; acute kidney injury (AKI) as a result of reduced kidney perfusion due to a decreased cardiac output and low blood pressure[8], arrhythmias such as atrial fibrillation and ventricular tachycardia[9], pulmonary edema due to excessive fluid administration or impaired cardiac function[10], and multi-organ failure due to impaired perfusion to vital organs as a result of prolonged hypotension and decreased cardiac output[10]. Additionally, invasive procedures such as PCI can increase the risk of bleeding complications[11], catheter-related bloodstream infections, and ventilator-associated pneumonia[12]. Also, CS is associated with an increased risk of thromboembolic events, as patients with reduced cardiac output and immobility are at increased risk of developing deep vein thrombosis and pulmonary embolism[10]. The development of these complications can further worsen the prognosis of patients with CS. Therefore, close monitoring and prompt management of these complications are essential in improving patient outcomes.

The management of CS requires a multidisciplinary approach involving cardiology, critical care, and interventional teams. Clinical precautions in the management of CS include several essential considerations. Firstly, early identification and diagnosis of CS is crucial, as early interventions have been shown to improve survival rates[13]. Therefore, healthcare providers should be vigilant for signs and symptoms of CS, such as hypotension, tachycardia, and decreased urine

output. Secondly, revascularization procedures such as PCI and coronary artery bypass grafting are essential in managing CS caused by myocardial infarction[6]. Early revascularization can restore blood flow to the heart muscle and prevent further damage. Thirdly, the use of inotropes and vasopressors should be carefully titrated to avoid complications such as arrhythmias and excessive vasoconstriction[14]. Adequate fluid resuscitation is necessary to maintain blood pressure and cardiac output, but excessive fluid administration can lead to pulmonary edema and worsen CS[14]. Fourthly, mechanical circulatory support devices such as intra-aortic balloon pump (IABP) and extracorporeal membranous oxygenation (ECMO) may be necessary in refractory cases of CS[15]. However, these devices have risks and complications, such as bleeding and infection, which should be carefully monitored and managed[16]. Finally, closely monitoring hemodynamic parameters such as blood pressure, heart rate, and cardiac output is essential to guide management and assess response to therapy[16]. Patients with CS require close attention and frequent assessments to identify and manage any complications that may arise.

The management of patients with CS undergoing primary PCI has evolved significantly over the last few decades. Despite these advances, the mortality rate in this patient population remains high[17]. There is a need to identify factors associated with poor immediate outcomes after primary PCI in patients with CS to help identify high-risk patients and guide treatment decisions[13]. Understanding the predictors of mortality and other immediate outcomes after primary PCI in patients with CS can also provide valuable insights for further refining the management of these patients. Therefore, this study aimed to investigate the immediate mortality rate in patients with CS undergoing primary PCI and identify mortality predictors.

MATERIALS AND METHODS

This retrospective analysis was conducted at the largest tertiary care cardiac hospital in Karachi, Pakistan, after approval from the institutional ethical review committee (ERC/46/2022). For this analysis, the de-identified data were extracted from the hospital records for the consecutive patients with CS who underwent primary PCI at our institution between January 2018 and December 2022. Patients with missing information on study variables were excluded from the analysis, and patients who did not undergo primary PCI were also excluded.

The primary outcome was immediate mortality, defined as mortality within index hospitalization. Baseline demographics, clinical characteristics, and procedural data were collected. Data regarding the hospital course of the patients were also extracted, which included IABP placement, intubation, temporary pacemaker, inotropic support, and in-hospital complications such as sepsis, renal dysfunction, cardiac arrest, cerebrovascular accident, hypoxic brain injury, and multi-organ dysfunction.

Data regarding demographics, clinical characteristics, procedural, and hospital course were compared between the two groups of patients based on immediate survival status with the help of an independent sample t-test/Mann-Whitney U test or Chi-square test/Fisher exact test. Univariate and multivariable binary logistic regression analyses were performed to identify predictors of immediate mortality. All the variables with P value < 0.20 in the univariate analysis were included in the multivariable analysis[18]. All the statistical analyses were formed with the help of IBM SPSS version 21, and $P < 0.05$ was the set criteria for statistical significance.

RESULTS

A total of 305 patients were included, of which 222 (72.8%) were male, and the mean age of the study sample was 58.1 ± 11.8 years. Most patients were in Killip class IV, 186 (61.0%), at the time of presentation. The immediate mortality rate was found to be 54.8% (167). The mean age was 59.4 ± 12.0 *vs* 56.5 ± 11.5; $P = 0.031$, Killip IV at presentation was 68.3% *vs* 52.2%; $P = 0.004$, and diabetes was present in 54.5% *vs* 41.3%; $P = 0.022$ among expired and survived patients, respectively (Table 1).

The multivessel disease was observed in 90.4% *vs* 68.1%; $P < 0.001$, high thrombus burden (grade ≥ 4) in 85.6% *vs* 67.4%; $P < 0.001$, bifurcations lesion in 29.9% *vs* 16.7%; $P = 0.007$, intraluminal defect in 89.8% *vs* 81.9%; $P = 0.045$, need of temporary pacemaker was for 60.5% *vs* 1.4%; $P < 0.001$, need of intubation for 78.4% *vs* 2.2%; $P < 0.001$, need of inotropic support was 76.0% *vs* 1.4%; $P < 0.001$, need of IABP was 48.5% *vs* 21.7%; $P < 0.001$, and left ventricular dysfunction was observed in 91.0% *vs* 75.4%; $P < 0.001$ among expired and survived patients, respectively (Table 2).

Multivariate analysis identified Killip class IV at presentation [odds ratio (OR): 2.0; 95% confidence interval (CI): 1.2-3.4; $P = 0.008$], Multivessel disease (OR: 3.5; 95%CI: 1.8-6.9; $P < 0.001$), and high thrombus burden (OR: 2.6; 95%CI: 1.4-4.9; $P = 0.003$) as independent predictors of immediate mortality (Table 3).

A 12.0% (20/167) of the total deaths were deaths on the catheterization table. Cardiac arrest was the most common cause of death observed in 95.8% (160/167). Among other causes, renal failure was observed in 25.1% (42/167), multi-organ dysfunction in 19.8% (33/167), sepsis in 18.0% (30/167), hypoxic brain injury in 6.6% (11/167), and cerebrovascular accident in 0.6% (1/167) patient.

DISCUSSION

CS is a severe complication of AMI associated with low blood pressure, poor organ perfusion, and high mortality rates.

Table 1 Distribution of demographics and clinical characteristics patients with cardiogenic shock stratified by immediate outcome after primary percutaneous coronary intervention

	Total	Immediate outcome		*P* value
		Mortality	Survived	
Total (*n*)	305	167	138	
Gender				
Male	222 (72.8)	114 (68.3)	108 (78.3)	0.051
Female	83 (27.2)	53 (31.7)	30 (21.7)	
Age (years)	58.1 ± 11.8	59.4 ± 12	56.5 ± 11.5	0.031
Body mass index (kg/m^2)	25.7 ± 2.9	25.6 ± 2.9	25.9 ± 3	0.346
Underweight	2 (0.7)	2 (1.2)	0 (0.0)	0.470
Healthy	150 (49.2)	84 (50.3)	66 (47.8)	
Overweight	131 (43)	71 (42.5)	60 (43.5)	
Obese	22 (7.2)	10 (6)	12 (8.7)	
Killip Class				
III	119 (39)	53 (31.7)	66 (47.8)	0.004
IV	186 (61)	114 (68.3)	72 (52.2)	
Known risk factors				
Diabetes	148 (48.5)	91 (54.5)	57 (41.3)	0.022
Hypertension	181 (59.3)	95 (56.9)	86 (62.3)	0.336
Smoke	80 (26.2)	40 (24)	40 (29)	0.320
Family history	8 (2.6)	4 (2.4)	4 (2.9)	0.784
Dyslipidemia	7 (2.3)	4 (2.4)	3 (2.2)	0.898
Chest pain to ER (min)	240 (120-360)	210 (120-360)	240 (120-360)	0.718
ER to lab time (min)	55 (39-76)	55 (35-70.11)	55 (40-80)	0.337
Total ischemic time (min)	285 (190-415)	280 (180-413)	287 (200-440)	0.672
ST depression in AVR	56 (18.4)	33 (19.8)	23 (16.7)	0.487

ER: Emergency room; AVR: Augmented vector right.

Overall, primary PCI plays a crucial role in managing patients with CS by improving blood flow to the heart, restoring cardiac function, and reducing mortality rates. However, the success of primary PCI depends on several factors, including the timeliness of treatment, the skill and experience of the operators performing the procedure, and the patient's overall health status. Therefore, it is essential to identify high-risk patients and provide timely and appropriate treatment to achieve the best outcomes. Therefore, we conducted a retrospective analysis of 305 patients with CS-complicated AMI who had undergone primary PCI at our center. It has been observed the immediate mortality rate was unacceptably high at 54.8%, with cardiac arrest followed by renal failure, multi-organ dysfunction, sepsis, hypoxic brain injury, and cerebrovascular accident as a cause of mortality. In multivariable analysis, Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality.

Despite advancements in the therapeutic and technical management of CS, the rate of adverse events remains unacceptably high. Studies have reported varying mortality rates in-hospital, short-term, and long-term depending on the definition of CS and follow-up duration. Similar to our study, Hayıroğlu *et al*[5] surveyed 319 CS complicated ST-elevation myocardial infarction (STEMI) patients treated with primary PCI and reported a high in-hospital mortality rate of 61.3%. This study found several predictors of in-hospital mortality, including final thrombolysis in myocardial infarction flow, chronic kidney disease, left ventricular ejection fraction, tricuspid annular plane systolic excursion, blood urea nitrogen level, lactate level, and plasma glucose level. Similarly, other studies, including Wang *et al*[19] and Backhaus *et al*[13], reported 65.3% and 37%-50% in-hospital mortality rates, respectively. The use of IABP has decreased over the years, and improvements in therapeutic management, such as increased use of drug-eluting stents, prasugrel, and ticagrelor, have resulted in better long-term prognosis for these patients[13]. Kawaji *et al*[20] conducted a registry-based study on 466 STEMI patients with CS and reported high 30-d, one-year, and five-year mortality rates of 25.4%,

Table 2 Distribution of angiographic and procedural characteristics patients with cardiogenic shock stratified by immediate outcome after primary percutaneous coronary intervention

	Total	Immediate outcome		*P* value
		Mortality	Survived	
Total (*n*)	305	167	138	
Number of involved vessels				
Single vessel disease (SVD)	56 (18.4)	15 (9)	41 (29.7)	< 0.001
Two vessel disease (2VD)	80 (26.2)	43 (25.7)	37 (26.8)	
Three vessel disease (3VD)	145 (47.5)	100 (59.9)	45 (32.6)	
Left main (LM)	2 (0.7)	1 (0.6)	1 (0.7)	
LM + SVD	2 (0.7)	0 (0)	2 (1.4)	
LM + 2VD	7 (2.3)	2 (1.2)	5 (3.6)	
LM + 3VD	13 (4.3)	6 (3.6)	7 (5.1)	
Infarct related artery				
Left anterior descending artery	191 (62.6)	106 (63.5)	85 (61.6)	0.917
Right coronary artery	78 (25.6)	42 (25.1)	36 (26.1)	
Left circumflex	31 (10.2)	17 (10.2)	14 (10.1)	
Left main	5 (1.6)	2 (1.2)	3 (2.2)	
Only LHC done	17 (5.6)	12 (7.2)	5 (3.6)	0.177
Only POBA	32 (10.5)	19 (11.4)	13 (9.4)	0.579
Lesion length (cm)	20 (15-26)	20 (15-26)	20 (15-26)	0.948
Bifurcations lesion	73 (23.9)	50 (29.9)	23 (16.7)	0.007
Side branch	57 (18.7)	37 (22.2)	20 (14.5)	0.087
Pre-procedure TIMI flow				
0	290 (95.1)	152 (91)	138 (100)	0.005
I	8 (2.6)	8 (4.8)	0 (0.0)	
II	6 (2)	6 (3.6)	0 (0.0)	
III	1 (0.3)	1 (0.6)	0 (0.0)	
Post-procedure TIMI flow				
0	14 (4.6)	9 (5.4)	5 (3.6)	0.124
I	9 (3)	7 (4.2)	2 (1.4)	
II	39 (12.8)	26 (15.6)	13 (9.4)	
III	243 (79.7)	125 (74.9)	118 (85.5)	
Tissue Myocardial Perfusion				
0	20 (6.6)	10 (6)	10 (7.2)	0.731
I	18 (5.9)	11 (6.6)	7 (5.1)	
II	62 (20.3)	37 (22.2)	25 (18.1)	
III	205 (67.2)	109 (65.3)	96 (69.6)	
Thrombus grading				
G0-No	8 (2.6)	2 (1.2)	6 (4.3)	0.003
G1-Possible	14 (4.6)	7 (4.2)	7 (5.1)	
G2-Small	8 (2.6)	1 (0.6)	7 (5.1)	
G3-Moderate	39 (12.8)	14 (8.4)	25 (18.1)	

G4-Large	55 (18)	32 (19.2)	23 (16.7)	
G5-Total	181 (59.3)	111 (66.5)	70 (50.7)	
Intraluminal defect	263 (86.2)	150 (89.8)	113 (81.9)	0.045
Export catheter use	138 (45.2)	62 (37.1)	76 (55.1)	0.002
Needed temporary pacemaker	103 (33.8)	101 (60.5)	2 (1.4)	< 0.001
ER	8 (7.8)	8 (7.9)	0 (0.0)	0.806
Cath lab	85 (82.5)	83 (82.2)	2 (100)	
CCU	10 (9.7)	10 (9.9)	0 (0)	
Needed intubation	134 (43.9)	131 (78.4)	3 (2.2)	< 0.001
ER	30 (22.4)	30 (22.9)	0 (0)	0.397
Cath lab	60 (44.8)	59 (45)	1 (33.3)	
CCU	44 (32.8)	42 (32.1)	2 (66.7)	
Needed inotropic support	129 (42.3)	127 (76)	2 (1.4)	< 0.001
ER	74 (57.4)	74 (58.3)	0 (0.0)	0.065
Cath lab	35 (27.1)	33 (26)	2 (100)	
CCU	20 (15.5)	20 (15.7)	0 (0.0)	
Needed IABP	111 (36.4)	81 (48.5)	30 (21.7)	< 0.001
LV dysfunction	256 (83.9)	152 (91)	104 (75.4)	< 0.001
Ejection fraction (%)	30 (30-40)	30 (30-40)	35 (30-45)	0.014

LV: Left ventricular; LHC: Left heart cath; TIMI: Thrombolysis in Myocardial Infarction; POBA: Plain old balloon angioplasty; IABP: Intra-aortic balloon pump; ER: Emergency room; CCU: Coronary care unit.

Table 3 Clinical predictors of immediate mortality after primary percutaneous coronary intervention of patients with cardiogenic shock

	Univariate		Multivariable	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Female	1.7 (1.0-2.8)	0.052	1.8 (1.0-3.3)	0.059
Age (years)	1.0 (1.0-1.0)	0.032	1.0 (1.0-1.0)	0.257
Killip class IV	2.0 (1.2-3.1)	0.004	2.0 (1.2-3.4)	0.008
Diabetes mellitus	1.7 (1.1-2.7)	0.022	1.5 (0.9-2.5)	0.126
Hypertension	0.8 (0.5-1.3)	0.337	-	-
Smoker	0.8 (0.5-1.3)	0.320	-	-
Total ischemic time ≥ 4 h	1.0 (0.6-1.7)	0.870	-	-
Multivessel disease	4.4 (2.4-8.3)	< 0.001	3.5 (1.8-6.9)	< 0.001
Bifurcations lesion	2.1 (1.2-3.7)	0.008	1.7 (0.8-3.5)	0.169
Side branch	1.7 (0.9-3.1)	0.090	0.9 (0.4-2.1)	0.839
Thrombus grade ≥ 4	2.9 (1.6-5.0)	< 0.001	2.6 (1.4-4.9)	0.003
Intraluminal defect	2.0 (1.0-3.8)	0.048	1.2 (0.6-2.6)	0.655
Left ventricular dysfunction	3.3 (1.7-6.4)	< 0.001	2.2 (0.8-6.3)	0.146
Ejection fraction (%)	1.0 (0.9-1.0)	0.002	1.0 (1.0-1.0)	0.542

OR: Odds ratio; CI: Confidence interval.

38.7%, and 51.4%, respectively.

Additionally, the identification of clinical predictors of mortality can help guide treatment decisions and improve patient outcomes. Our study identified Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) as independent predictors of immediate mortality. Several clinical predictors of mortality in patients with CS have been identified in the literature, including age: Advanced age is a significant predictor of mortality in patients with CS[21]. Older patients have more comorbidities and are at higher risk of complications. The severity of shock: The degree of hemodynamic compromise, measured by the cardiac index, central venous pressure, and mean arterial pressure, is strongly associated with mortality[21]. AKI: AKI is a common complication in patients with CS and is associated with increased mortality[8]. Delayed revascularization: Delayed revascularization, defined as a time to revascularization of more than 24 h, is associated with increased mortality in patients with CS due to myocardial infarction[22]. Elevated lactate levels: Elevated lactate levels indicate tissue hypoxia and are a marker of poor prognosis in patients with CS[23]. Presence of comorbidities: Patients with preexisting comorbidities such as diabetes, hypertension, and chronic kidney disease have a higher risk of mortality[24]. Use of mechanical circulatory support: Mechanical circulatory support devices such as IABP and ECMO are associated with increased mortality, likely due to the severity of illness in patients requiring these interventions[25].

Further research is necessary to oversee and manage patients with STEMI complicated by CS. To achieve this, some researchers have proposed risk stratification scoring systems that have demonstrated good predictive value for the risk stratification of 30-d mortality[19,26,27]. Along with reperfusions, multidisciplinary management of CS patients is mandatory to improve outcomes. Several studies have reported a significant increase in the incidence of CS complicating STEMI, with one study reporting an incidence of 9% in 2006, which rose to 16% over ten years[13]. Similarly, an analysis of a United States nationwide database found that the incidence of STEMI complicated by CS increased from 6.5% to 10.1% between 2003 and 2010[28]. As a result, targeted research efforts are required to improve outcomes for these high-risk patients. While emergency revascularization of the culprit artery is the only proven effective method thus far, evidence for other supportive and medical therapies is unsatisfactory, and the use of IABP has shown no clinical benefit; however, the use of ECMO and Impella may yield better outcomes[29].

Certain limitations of the study need to be acknowledged. It was a single center-based retrospective study with a relatively small sample; hence, the generalizability of study findings may be limited.

CONCLUSION

In conclusion, immediate mortality rates in patients with CS undergoing primary PCI remain high despite advances in treatment strategies. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality. Such predictors can help guide treatment decisions and risk stratification in patients with CS. These findings underscore the need for aggressive management and close monitoring of patients with CS undergoing primary PCI, particularly those with these high-risk characteristics.

ARTICLE HIGHLIGHTS

Research background

Cardiogenic shock (CS) is a life-threatening complication of acute myocardial infarction with high morbidity and mortality rates.

Research motivation

The management of CS requires a multidisciplinary approach involving cardiology, critical care, and interventional teams. Early identification and diagnosis of CS is crucial, as early interventions have been shown to improve survival rates.

Research objectives

This study aimed to investigate the immediate mortality rates in patients with CS undergoing primary percutaneous coronary intervention (PCI) and identify mortality predictors.

Research methods

We conducted a retrospective analysis of 305 patients with CS who underwent primary PCI and immediate mortality rate was analyzed.

Research results

In a sample of 305 patients, the immediate mortality rate was found to be 54.8% with Killip class IV at presentation, multivessel disease, and high thrombus burden as independent predictors of immediate mortality.

Research conclusions

Immediate mortality rate in patients with CS undergoing primary PCI remains high despite advances in treatment

strategies. Killip class IV at presentation, multivessel disease, and high thrombus burden (grade ≥ 4) were identified as independent predictors of immediate mortality.

Research perspectives

These findings underscore the need for aggressive management and close monitoring of patients with CS undergoing primary PCI, particularly in those with these high-risk characteristics.

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FOOTNOTES

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the National Institute of Cardiovascular Diseases (NICVD), Karachi.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors have no conflict of interest to disclose.

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Observational Study

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

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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, arrythmias, 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 arrythmias, 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

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 arrythmias, 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.

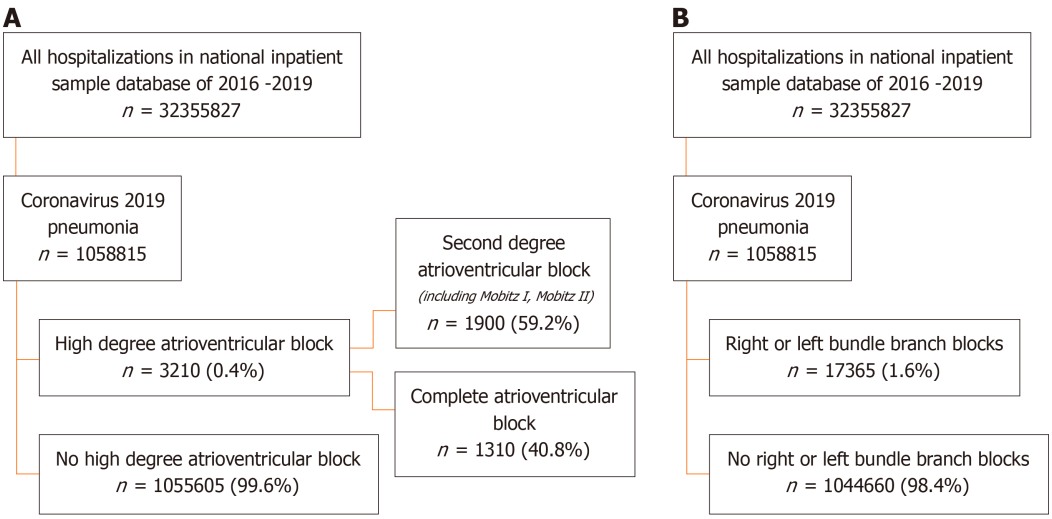

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Figure 1 Study population and stratification process. A: Coronavirus disease 2019 (COVID-19) pneumonia hospitalizations stratified by patients with and without high degree atrioventricular blocks; B: COVID-19 pneumonia hospitalizations stratified by 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 infraction (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 multivariant 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 (*n* = 3210/0.4%)	No high degree atrioventricular block (*n* = 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 (*n* = 17365/1.6%)	No bundle branch blocks (*n* = 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	*P* 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

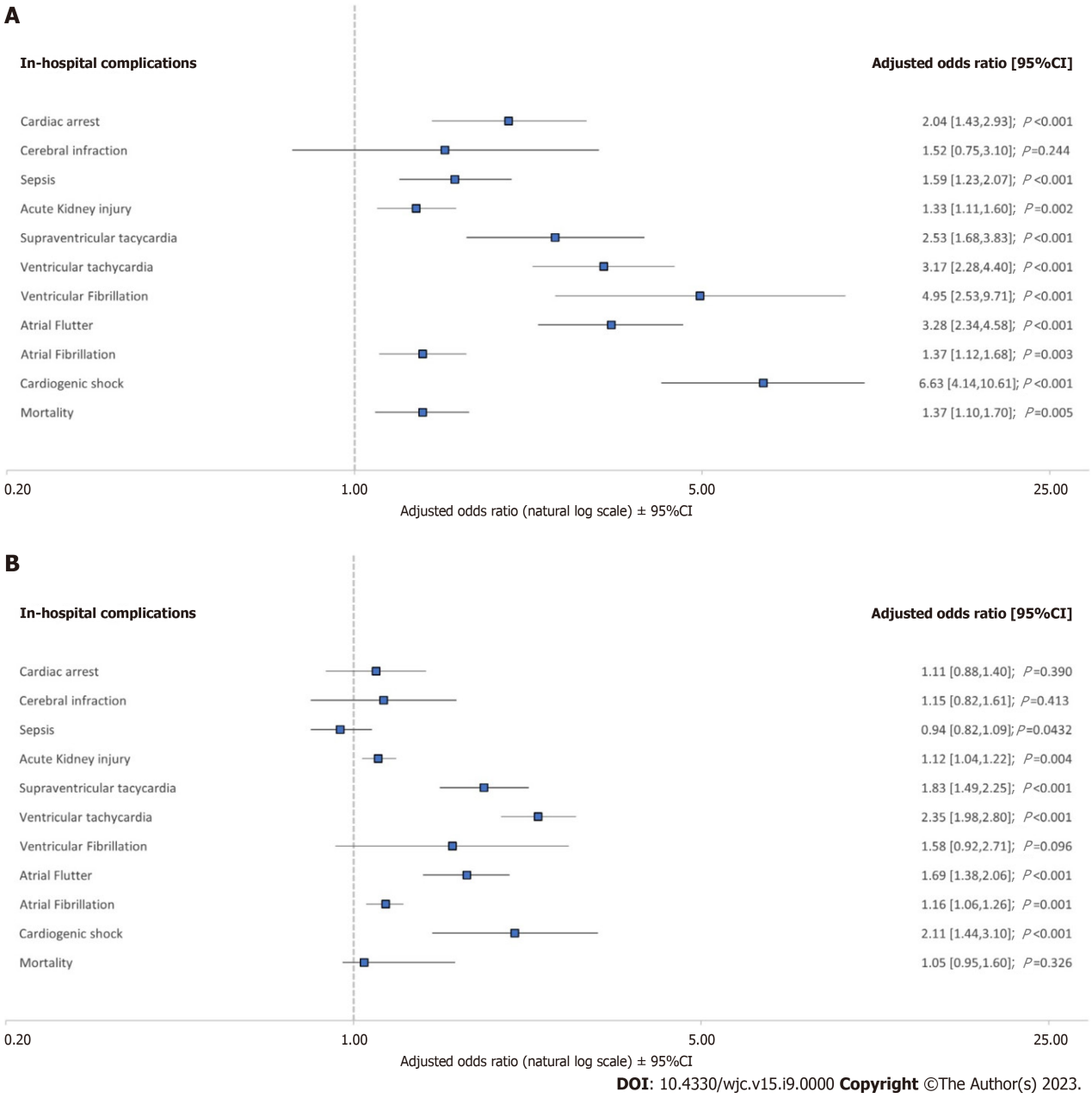
Table 5 Univariate regression analysis demonstrating absolute value of outcomes of interest in encounters with coronavirus disease 2019 and with high grade atrioventricular block or bundle branch blocks without pacemakers, *n* (%)

In-hospital outcomes Rates	High degree atrioventricular block (*n* = 3210)	All bundle branch blocks without pacemaker (*n* = 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.

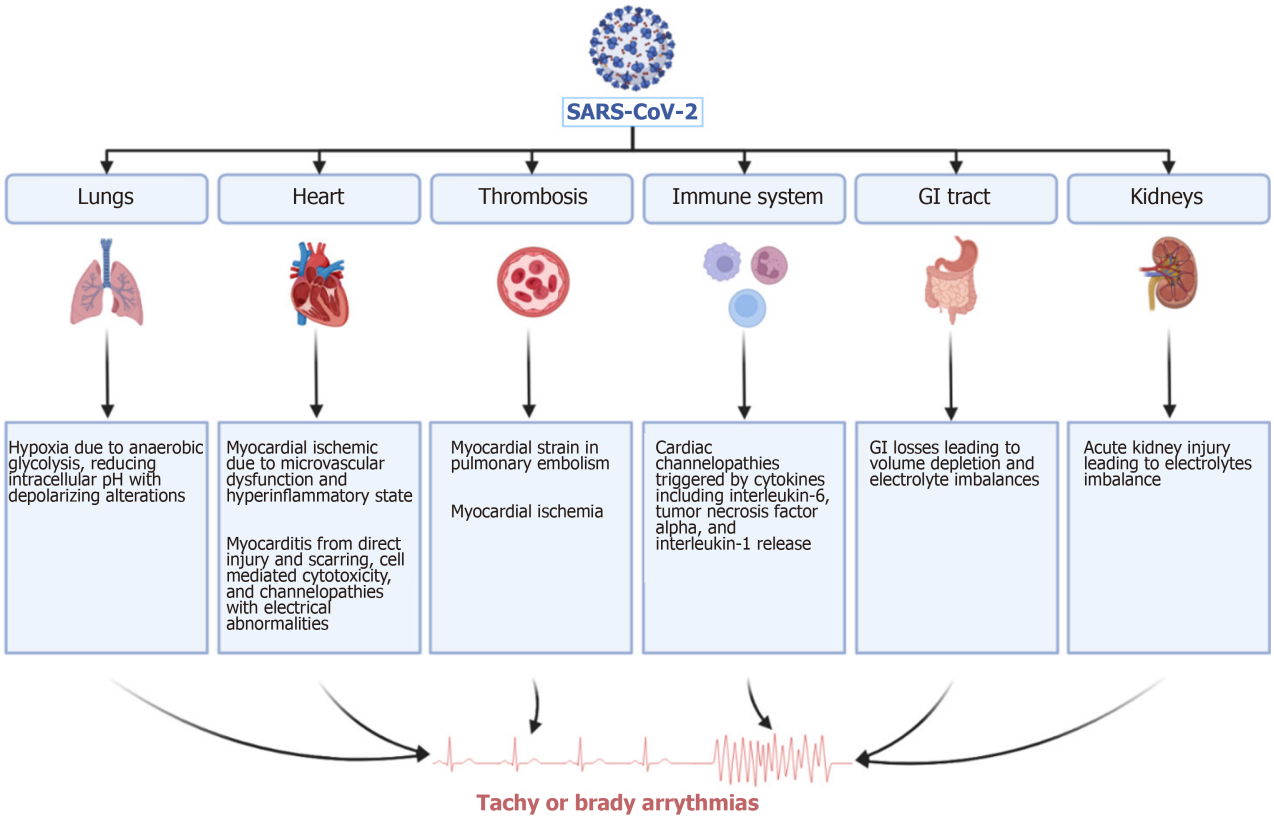


DOI: 10.4330/wjc.v15.i9.0000

Figure 2 Multivariant 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



DOI: 10.4330/wjc.v15.i9.448

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 contributary 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 arrythmias 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, multivariant 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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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment through HCUP. For more information, please visit https://hcup-us.ahrq.gov/nisoverview.jsp.

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Data sharing statement: The data used in this study is accessible online at https://www.hcup-us.ahrq.gov.

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CASE REPORT

Variant of Wellen's syndrome in type 1 diabetic patient: A case report

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Abstract

BACKGROUND

Wellen's syndrome is a form of acute coronary syndrome associated with proximal left anterior descending artery (LAD) stenosis and characteristic electrocardiograph (ECG) patterns in pain free state. The abnormal ECG pattern is classified into type A (biphasic T waves) and type B (deeply inverted T waves), based on the T wave pattern seen in the pericodial chest leads.

CASE SUMMARY

We present the case of a 37-year-old male with history of type 1 diabetes mellitus (T1DM), gastroparesis, mild peripheral artery disease and right toe cellulitis on IV antibiotics who presented to the emergency department with nausea, vomiting and abdominal pain for 3 d and as a result couldn't take his insulin. Noted to have fasting blood sugar 392 mg/dL. Admitted for diabetic gastroparesis. During the hospital course, the patient was asymptomatic and denied any chest pain. On admission, No ECG and troponin draws were performed. On day 2, the patient became hypoxic with oxygen saturation 80% on room air, intermittent mild right-sided chest pain which he attributed to vomiting from his gastroparesis. Initial ECG done was significant for Biphasic T wave changes in leads V2 and V3 and elevated high sensitivity troponin. Patient was transitioned to cardiac intensive care unit and cardiac catheterization performed with result significant for extensive coronary artery disease.

CONCLUSION

This case highlights an exceptional manifestation of Wellen's syndrome, wherein the right coronary artery and circumflex artery display a remarkable 100% constriction, alongside a proximal LAD stenosis of 90%-95%. Notably, this

occurrence transpired in a patient grappling with extensive complications arising from T1DM. Moreover, it underscores the utmost significance of promptly recognizing the presence of Wellen's syndrome and swiftly initiating appropriate medical intervention.

Key Words: Wellens's syndrome; Biphasic T waves; Deeply inverted T waves; Precordial leads; Left anterior descending artery; Pseudo-normalization; Right coronary artery; Left circumflex artery; Case report

Core Tip: When a patient exhibits atypical symptoms preceding chest pain and displays distinct T wave abnormalities on the electrocardiogram, it is crucial to seek immediate cardiology intervention. This entails conducting emergent cardiac catheterization to evaluate the presence of proximal stenosis in the left anterior descending artery, or in rare instances, the right coronary artery and left circumflex artery. Such stenosis can lead to the development of ischemic cardiomyopathy if left untreated. Acting promptly and carefully monitoring the characteristic T wave patterns, alongside normal or minimally elevated cardiac biomarkers, contributes to improved mortality prognosis.

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INTRODUCTION

Wellen's syndrome is a distinctive condition characterized by distinct alterations in the ST-T waves in the precordial leads, indicating an obstruction in the proximal left anterior descending coronary artery[1]. This syndrome has been observed in individuals experiencing unstable angina, as well as those with atypical presentations devoid of acute chest pain. If left untreated, Wellen's syndrome can cause myocardial infarction and necrosis in the anterior wall of the heart. The hallmark features of Wellen's syndrome are biphasic T waves (type A in 25% of cases) or deeply inverted T waves (type B in 75% of cases) in V2-V3, which can extend to V1-V6 and often involve the proximal anterior left anterior descending artery (LAD). Nevertheless, research has demonstrated that this syndrome is not confined solely to the proximal anterior LAD, as similar changes have been reported in the right coronary artery (RCA) and circumflex artery [2]. The correlation between T wave changes in precordial leads and the heightened risk of developing anterior wall myocardial infarction, despite medical intervention, was first elucidated by de Zwaan *et al*[3] in 1982. The diagnostic criteria for Wellen's syndrome encompass a history of angina, deeply inverted or biphasic T waves in the precordial leads, normal or slightly elevated serum cardiac enzymes, absence of precordial Q waves, minimal or isoelectric ST segment elevation (less than 1 mm), and the presence of the specific electrocardiograph (ECG) pattern during pain-free states[4]. Risk factors associated with Wellen's syndrome include diabetes mellitus, arterial hypertension, metabolic syndrome, hypercholesterolemia, smoking, and a family history of premature heart disease, all of which are present in our patient. This case report, accompanied by a review of the existing literature, emphasizes the critical importance of early recognition of Wellen's syndrome, not only in relation to the proximal LAD, but also its involvement in both the RCA and circumflex artery.

CASE PRESENTATION

Chief complaints

A 37-year-old man with chief complaint of nausea, vomiting, abdominal pain for 3-day duration associated with diarrhea.

History of present illness

The patient arrived at the emergency department with complaints of abdominal pain, characterized as burning, non-radiating and constant, 7/10 in severity, which he attributed to his gastroparesis as he has had multiple admissions with gastroparesis flares. Patient has a past medical history of type 1 diabetes, diabetic gastroparesis, major depression, anxiety, smoking (1 pack per week), 1 g of marijuana consumption and right 4th toe cellulitis recently treated with IV antibiotics. Admits to intermittent depressive episode; during which he stops taking his medication including insulin but denied suicidal ideation and intent.

History of past illness

Diabetic gastroparesis, type 1 diabetes mellitus, peripheral artery disease, and right toe cellulitis on antibiotics.

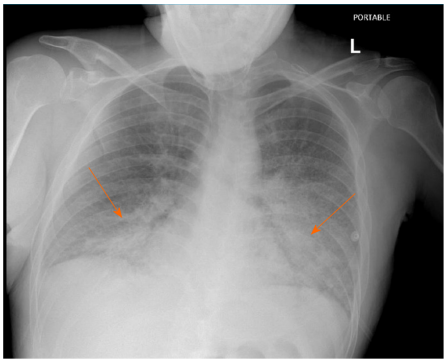

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Figure 1 Chest X Ray consistent with acute pulmonary Edema. Indicating bat wing opacities, interstitial edema, increased cardiothoracic ration and cephalization of pulmonary vessesl.

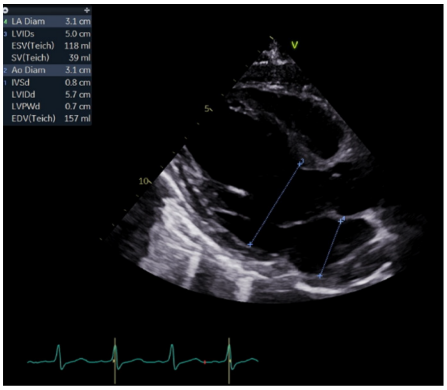

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Figure 2 Electrocardiogram indicative of ejection fraction less 20%. Moderately dilated left ventricle and left atrium.

Personal and family history

A noteworthy familial background of cardiovascular disease is documented, encompassing the father, parental uncle, and grandfather, each of whom underwent double bypass surgeries. The father's bypass operation was performed at the relatively young age of 40.

Physical examination

In the physical exam the abdomen was non-distended, tenderness on palpation of the 4 quadrants, positive bowel sounds, no organomegaly appreciated. The blood pressure on admission was 129/99 with heart rate of 124 bpm. Chest symmetry with respiration, no crackles or wheezing noted and normal vesicular breath sounds. Normal S1, S2 and no pathological murmur heard. The patient was euvolemic, and no bilateral lower extremity edema was noted.

Laboratory examinations

Urine toxicology is positive for marijuana. Given the atypical presentation, high sensitivity troponin was not ordered. Uncontrolled diabetes, Hyperlipidemia and hypoxia noted (Table 1).

Imaging examinations

Patient was admitted for diabetic gastroparesis, bedside point of care ultrasound; was significant for inferior vena cava (IVC) dilation and Kerley B lines. A chest X ray was ordered, which shows acute pulmonary edema (Figure 1). Given acute and sudden onset of hypoxia, echocardiogram (ECHO) was ordered (Figure 2), after notable elevation in cardiac enzyme (elevated high sensitivity troponin). The first electrocardiogram (EKG) was then ordered (Figure 3).

FURTHER DIAGNOSTIC WORK-UP

The patient underwent a treatment regimen that involved the administration of 3 L of normal saline, along with medications such as Benadryl, famotidine, Zofran, and IV fluids at a rate of 125 mL/h. Additionally, the patient received Reglan 10 mg every 8 h and pantoprazole. On the second day at 6:00 pm, the patient experienced a drop in oxygen

Table 1 Consistent with hypoxia from arterial blood gas, elevated troponin and uncontrolled diabetes

Hematology	Values	Chemistry	Values
WBC	17.00	High sensitivity troponin	12072.1
Hemoglobin	13.7	LDH	472
Hematocrit	40.3	TSH	0.810
MCV	95.1	T4	1.27
MCH	32.3	Hemoglobin A1C	10.9
RDW	12.1	Sodium	138
Platelet count	256	Potassium	4.1
Neutrophil	79.4	Chloride	105
Lymphocytes	13.3	CO_2 level	23
Monocytes	7.0	Blood urea nitrogen	21
EOS count	0.1	Creatinine	1.05
Basophils	0.2	GRF estimation	> 60
Nucleated RBC	0	LDL	127
RBC	4.2	HDL	44
Procalcitonin	0.07	Total cholesterol	184
		Calcium	
		Arterial blood gas	
		pH	7.40
		pCO_2	46
		O_2	64
		HCO_3	28.5

EOS: Eosinophil; GRF: Ground reaction force; HDL: High density lipoprotein; LDH: Lactate dehydrogenase; LDL: Low density lipoprotein; MCH: Melanin-concentrating hormone; MCV: Mean corpuscular volume; pH: Potential of hydrogen; pCO_2: Partial pressure of CO_2; RBC: Red blood cells; RDW: Red blood cell distribution width; TSH: Thyroid stimulating hormone; WBC: White blood cell count.

saturation, reaching the mid-80s while breathing room air. To address this, the patient was placed on a venti-mask at 50% oxygen concentration. During the examination, the patient acknowledged experiencing mild and intermittent right-sided chest pain, attributing it to vomiting and noting a history of similar pain during gastroparesis flares over the past 5 years. The patient denied any previous history of heart disease. A point-of-care ultrasound at the bedside revealed notable dilation of the IVC and the presence of Kerley B lines. Chest X-ray was ordered, which confirmed the diagnosis of acute pulmonary edema (Figure 1). Given the sudden onset of hypoxia, further investigations were initiated, including laboratory tests and an EKG (Figure 2). The patient received a 40 mg dose of furosemide and was subsequently continued on furosemide 40 mg every 12 h. To alleviate anxiety, the patient was given a STAT dose of alprazolam 0.25 mg orally. Following these measures, an initial EKG was ordered, along with a high sensitivity troponin test (Figure 3). Later that day, a cardiology consultation was sought, and an ECHO was performed. The ECHO revealed a moderately dilated left ventricle with a severely reduced ejection fraction of less than 20%. The left atrium was also found to be moderately dilated (Figure 2). The cardiologist was informed about the clinical findings and the elevated troponin levels. As a result, the acute coronary syndrome (ACS) protocol was initiated. The patient received a heparin drip following a loading dose of aspirin 81mg and a statin 80 mg, both given immediately. The patient was transferred to the cardiac center for coronary angiographic catheterization and right heart catheterization. The results of these procedures indicated the presence of extensive disease in the LAD, with stenosis extending to both the RCA and circumflex artery (Figure 4).

FINAL DIAGNOSIS

Conclusion of the cardiac coronary angiogram report indicated the following: Dominance: Right dominant; left main: Mild luminal irregularities less than 30%; left another decending artery: Min lad: 90% stenosis; distal lad: 95% stenosis; diagonal 1: 90% stenosis; circumflex artery: Ostial circ: 100 % stenosis; and RCA: Prox rca: 100% stenosis.

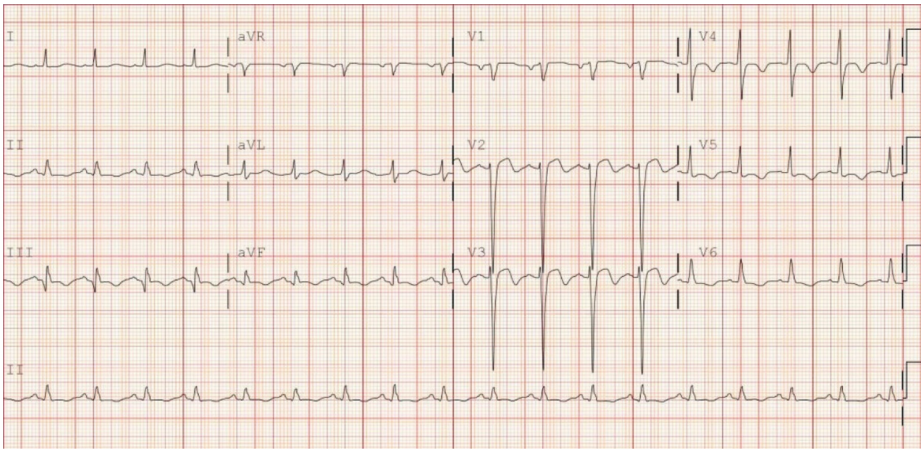

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Figure 3 Electrocardiogram showing Biphasic T wave inversion on V2-V3. T wave inversion in V4-V5.

TREATMENT

Following the placement of an intra-aortic balloon pump in the cardiac laboratory center, the patient was promptly transferred to the intensive care unit. In this setting, the patient's treatment regimen included the immediate initiation of aspirin 81 mg, ticagrelor 180 mg given STAT, followed by 90 mg every 12 h. Additionally, a nitroglycerin drip and 80 mg of atorvastatin were administered. The cardiologist recommended transferring the patient to a tertiary center for urgent coronary artery bypass graft (CABG) surgery given significant coronary artery lesions. On January 23, 2023, the patient underwent quadruple CABG, and a subsequent bedside ECHO revealed no evidence of pericardial effusion. Upon improvement, the patient was discharged with a medication regimen consisting of spironolactone 25 mg, metoprolol succinate 25 mg, aspirin 81 mg, atorvastatin 80 mg, valsartan 40 mg, and dapagliflozin 5 mg once a day.

OUTCOME AND FOLLOW-UP

Follow up in Cardiology clinic 1 wk post discharge from the tertiary center after contrary bypass graft. Notable significant improvement of symptoms with improved functional capacity and activities of daily living.

DISCUSSION

Wellen's syndrome was first described in 1982 by de Zwaan *et al*[3] as proximal LAD T- wave syndrome in the process of evaluating subgroup of patients with unstable angina during a stable and pain-free period[5]. Our patient presents with no chest pain, but abdominal pain, which he attributed to his recurrent gastroparesis. Wellen's syndrome was then discovered to be associated with significant critical occlusion of the LAD with a characteristic presentation distinctive to abnormal T wave changes in precordial leads in patients with suspected ACS. The electrocardiographic manifestation of Wellen's syndrome is characterized by 2 patterns; pattern A has biphasic T waves in V2-V3 (25%), and pattern B has symmetric and deeply inverted T waves in precordial chest leads (75%)[5,6]. In this case report, the patient presented on EKG with biphasic T wave in V2-V3 (Figure 2). These T wave changes signifies severe myocardial dysfunction or ischemia, although patients have been known to exhibit this syndrome during a pain free period at the time EKG is taken and have normal or minimally elevated cardiac enzymes, the prognosis of its event represents high risk of extensive anterior wall myocardial infarction within time of presentation[7]. Wellen's syndrome can also be a pre-coronary infarction stage that can lead to detrimental ACS. The concept of occlusion and reperfusion in the EKG sequence of Wellen's syndrome likely involves sudden complete occlusion of the LAD causing transient anterior ST segment elevation myocardia injury, leading to chest pain and diaphoresis stage not captured on EKG. Second stage then involves re-perfusion of the LAD likely secondary to spontaneous clot lysis leading to resolution of the chest pain with improvement in ST elevation and the appearance of biphasic or inverted T wave morphology[8]. Although Wellen's syndrome is known to involve mostly the LAD the syndrome is not limited to the anterior leads. The precordial T wave changes can be seen in the inferior or lateral leads with RCA or circumflex artery occlusion as noted in many studies and events in our case presentation. Diagnostic criteria of Wellen's syndrome includes[9]: Isoelectric or minimally elevated (< 1 mm) ST segment elevation; no precordial Q waves; deeply inverted or biphasic T waves in V2-V3 but may extend to V1-6; ECG pattern present in pain free state; preserved precordial R wave progression; recent history of angina; and normal or elevated serum cardiac markers.

Wellen's syndrome is often not an acute process as it can develop over days or weeks especially seen in people with risk factors (smoking, hypertension, diabetes and metabolic syndrome *etc*.). Although the syndrome is a temporary

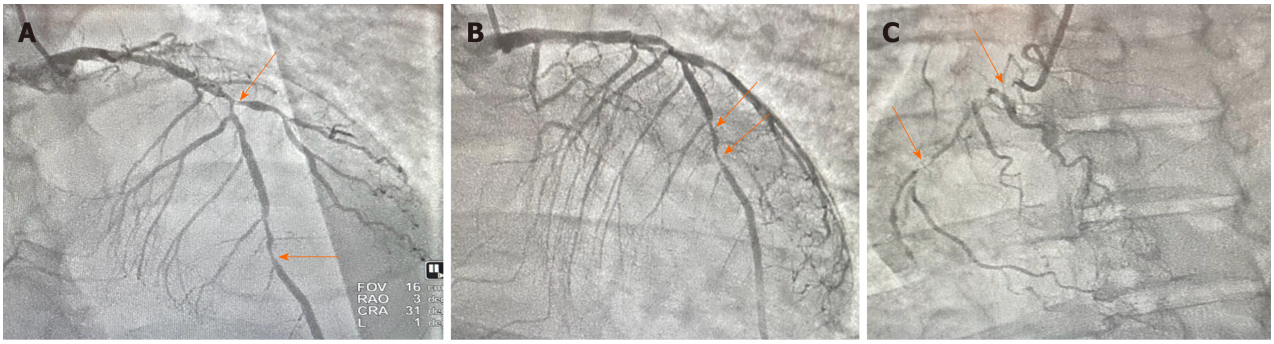

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Figure 4 Coronary angiography report. A to C: Coronary angiogram report consistent with severe triple vessel disease with stenosis in left anterior descending artery (A), left circumflex artery (B) and right coronary artery (C).

obstruction of the culprit coronary artery (pre-infarction state), LAD or artery involved can re-occlude at any time and the first EKG seen is normalization of the T wave called pseudo-normalization after which the T wave becomes upright and prominent; thus sign of hyper acute ST-elevation myocardial infarction during which the patient complains of chest pain that is associated with other symptoms of ACS[10]. Sometimes Wellen's syndrome can manifest in normal coronaries following an episode of vasospasm seen in cases of cocaine abuse, however, it is still appropriate to rule out thrombus formation or coronary thrombosis with angiogram during presentation given the syndromes risk of leading to sever and extensive anterior wall myocardial infarction and possible death. The phenomenon of re-occulsion and re-perfusion was likely experienced by our patient, however given the history of uncontrolled diabetes with complications, his presentation prior to hospital admission maybe masked during occlusion stage given the result of extensive coronary stenosis found on cardiac angiogram (Figure 4).

It is well known fact that uncontrolled diabetes can lead to cardiovascular disease. Its pathophysiology is linked to hyperglycemic state leading to an increase in oxidative stress, which results in micro and macrovascular complications. Persistent elevation in blood sugar can cause an overproduction of superoxide by the mitochondrial electron transport chain leading to complications seen in diabetic patients. The activation of superoxide overproduction pathway leads to increase generation of nitric oxide due to uncoupled state of endothelial nitric oxide synthase (NOS) and inducible NOS. All which leads to deoxyribonucleic acid (DNA) damage due to the formation of the strong oxidant peroxynitrite[11]. DNA damage causes rapid activation of poly (adenosine diphosphate-ribose) polymerase, depleting the intracellular concentration of its substrate nicotinamide adenine dinucleotide, and slowing the rate of glycolysis, electron transport, and adenosine-triphosphate formation and thus causing acute endothelial dysfunction[12]. Hyperglycemic state is an inflammatory state as it induces surge of inflammatory cytokines (such as C reactive protein, interleukin interleukin (IL)-6, IL-8 tumor necrosis factor-α, and endothelin-1and as result contribute to plaque instability. Accumulation of these inflammatory cytokines leads to endothelial injury and hypercoagulability increasing the risk for cardiovascular event. In clotting cascade, the quantity of clotting factors, including glycation and oxidation is affected during hyperglycemic state increasing the risk of thrombosis[13]. Patients with type 1 diabetes are on insulin regimen for glycemic control. Hyperinsulinemia can lead to an increase in hepatic synthesis on prothrombic factors leading to thrombotic state.

Cardiac autonomic neuropathy (CAN) is the most common complication seen in type I diabetic patients. Poor glycemic control is the risk factor of CAN with prevalence approximately 20%, increases with age and a known predictor of cardiovascular morbidity and mortality in type 1 diabetes[14]. Type 1 diabetes is thought to be caused by an autoimmune reaction that destroys the beta cells of the pancreas. The same immunological factors are seen affecting the sympathetic ganglia leading to cardiac sympathetic dysfunction[15]. All these pathologies can also be seen in patients with type 2 diabetes. In correlation to our patient, who presented with uncontrolled and complicated diabetes as such has increased risk of CAN and arthrosclerosis. Our patient presented with Wellen's syndrome, but the diagnosis was late given that patient delayed medical evaluation for cardiac disease, as he believed that all his symptoms of intermittent chest discomfort were due to prolonged vomiting and gastroparesis flares.

CONCLUSION

Wellen's syndrome emphasizes the need for serial EKGs in patients with cardiovascular risk factors, as critical stenosis may be detected and require invasive interventions. This case report highlights the extensive nature of Wellen's syndrome, involving occlusion in the LAD, RCA, and circumflex arteries. It demonstrates that Wellen's syndrome extends beyond proximal LAD disease and presents distinct EKG changes. Clinicians face diagnostic challenges due to atypical presentations, delaying ACS identification. Thus, it is vital for clinicians to identify Wellen's syndrome on EKGs and evaluate high-risk patients regardless of atypical symptoms.

FOOTNOTES

Author contributions: Obi MF contributed to manuscript writing, editing and data analysis; Namireddy V contributed to editing; Gale DB and Noel C contributed to data collection; Gargiulo P, Sharma M and Hyun C contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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