Title
Evaluation of Premature Ventricular Complexes (PVCs) during In-Hospital ECG Monitoring in the ICU

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Publication Date
2021

Peer reviewed|Thesis/dissertation

Evaluation of Premature Ventricular Complexes (PVCs) during In-Hospital ECG Monitoring in the ICU: Occurrence Rates, Associated Patient and Clinical Factors & their Association with Ventricular Tachycardia

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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Acknowledgments

I made it to the finish line of the PhD with the encouragement, support, and help of many. I thank my big family in Indonesia, my mother and father, Marlin, Petrus, Risal, and my two beautiful nephews, for their constant encouragement, love, and prayer, and for always being available to talk whenever I needed. To my buddies, Nick Collins and Casey Jones, I am eternally grateful the world brought us together.

During my time at UCSF, I met so many inspiring, brilliant people who generously shared their wisdom and knowledge to help me succeed. With deep gratitude, I thank my mentor Dr. Michele M. Pelter, PhD, RN, for her incredible mentorship, guidance, leadership, and support. I am also thankful for my dissertation committee: Dr. Xiao Hu, PhD, who served as my qualifying exam chair and who provided me the very first opportunity to explore the research path that eventually led me to the PhD program; Dr. Hildy Schell-Chaple, PhD, RN and Dr. Priya Prasad, PhD for sharing their expertise and guiding my dissertation.

I am grateful to Dean Catherine Gillis, PhD, RN, for believing in me and providing mentorship and funding support. I thank the faculty in the Nursing PhD program, particularly Dr. OiSaeng Hong, PhD, RN, FAAN, FAAOHN, Dr. Roberta S. Rehm, PhD, RN, FAAN, and Dr. Christine Miaskowski, PhD, RN, FAAN, for their mentorship. To my brilliant and inspiring cohort, thank you for your immense support and encouragement. To Dr. Steven Paul, PhD, thank you for providing me with the opportunity to assist in teaching his last biostatistics courses. I am also grateful to Dr. Thomas Hoffmann, PhD, for his amazing statistical support from the conception to completing my dissertation, and to my collaborators, Dr. Jessica K Zègre-Hemsey, PhD, RN, Cass Sandoval, MS, RN, CCN, CCNS, and Dr. Fabio Badilini, PhD, for their shared expertise in my research projects.

I am forever grateful for the generous funding support I received throughout the program: David W. Mortara Pre-Doctoral Fellowship Award (supported the first year), T.T. and

W.F. Chao Endowed Scholarship in Global Health Nursing (second year), Lloyd M. Kozloff Fellowship Award (third year), and ECG Monitoring Research Pre-Doctoral Fellowship from the School of Nursing Dean's Office (second – fourth year).

Finally, I thank my friends... Marty, Brian (who also read most of my manuscript drafts), Matt, Rebecca, Sam, Caitlyn, Bennett, The Kroes', Ci Vivy, UCSF Vocal Cords (2018 – 2020 cohort), and many others for sharing many moments with me.

Abstract

Evaluation of Premature Ventricular Complexes (PVCs) during In-Hospital ECG Monitoring in the ICU: Occurrence Rates, Associated Patient and Clinical Factors & their Association with Ventricular Tachycardia

Sukardi Suba

Significance: Early studies showed that premature ventricular complexes (PVCs) were associated with lethal arrhythmias (ventricular tachycardia (VT) and ventricular fibrillation (VF)) and death in patients with acute myocardial infarction (MI). However, the Cardiac Arrhythmia Suppression Trial (CAST) showed that treatment of PVCs with antiarrhythmics was associated with death. As a result, aggressive pharmacological treatment of PVCs was no longer standard practice. Nevertheless, continuous monitoring for PVCs remains routine care in the intensive care unit (ICU), mainly due to clinicians' fear of missing patients at risk for developing lethal arrhythmias. Although studies examining the significance of PVCs in outpatient settings exist, similar evidence is lacking in hospital settings, especially in the ICU.

Methods: We performed a literature review of the evidence of the diagnostic and prognostic significance of PVCs utilizing the frameworks for scoping review by Arksey and O'Malley and the Joanna Briggs Institute (JBI). We synthesized the results and described the significance of PVCs in patients with and without cardiac disease in the community and hospital settings. We evaluated occurrence rates of PVC alarms in 446 ICU patients and determined whether demographics (age, sex, race) and clinical characteristics (medical history, presence of PVC and atrial fibrillation on baseline 12-lead ECGs, serum potassium, ejection fraction, and primary diagnosis) were associated with six PVC types (i.e., isolated, bigeminy, trigeminy, couplet, R-on-T, and run PVC). Using logistic regression modeling, we determined if any of the six PVC types were associated with the occurrence of lethal arrhythmias (ventricular tachycardia and ventricular fibrillation), code blue, and death.

Results: Existing evidence largely examined the prognostic value of PVCs in the outpatient settings on several patient outcomes, such as left ventricular dysfunction, arrhythmia development, and mortality. Only three studies, done in the 1970s, evaluated the significance of PVCs in acute MI. Isolated PVCs were the most common type, accounting for 81.3% (646,666 out of 797,072 individual PVC alarms), and were concentrated in a small subgroup of patients. We found that none of the six PVC types were associated with VT events and death. Due to the small sample size, we could not determine a similar association for VF and code blue outcomes.
Conclusion: This dissertation represents current "real-world" clinical practice regarding PVC monitoring from a large time-series dataset during continuous ECG monitoring in the ICU. PVC monitoring was shown to be non-specific and likely not clinically meaningful, leading to an increased alarm burden and alarm fatigue. Therefore, the clinical team should strategize and develop different alarm strategies to minimize nuisance (i.e., true but not clinically significant) PVC alarms.

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Chapter 1

Introduction to Dissertation

In the 1960s, when electrocardiographic (ECG) monitoring was first introduced into the intensive care unit (ICU) setting, premature ventricular complexes (PVCs) were identified as one of the most commonly occurring arrhythmias among patients with myocardial infarction (MI).[1] It was generally accepted that PVCs in the setting of MI identified electrical instability of the heart or myocardial irritability, which might be a forewarning for a lethal ventricular arrhythmia.[1,2] Furthermore, it was believed that as the frequency of PVCs increased, there was an increased likelihood of subsequent ventricular tachycardia (VT) or ventricular fibrillation (VF).[1] Thus, the frequency of PVCs, or "ectopic beats," were considered an important prognostic determinant of lethal arrhythmias in acute MI.[1] Therefore, prompt treatment of PVCs could improve a patient's prognosis.[2] Based on these observations made some 40 years ago, it was concluded that it would be beneficial to incorporate PVC monitoring algorithms into future ECG monitoring devices.[1]

Interestingly, even though the suggested pathophysiology of PVCs for triggering malignant arrhythmias is somewhat speculative, two commonly cited mechanisms have been used describe how PVCs trigger malignant arrhythmias: non-uniform refractoriness and short coupling intervals.

Non-uniform Refractoriness. A short-long-short cycle of PVCs, as seen in torsade de pointes (TdP) along with QTc prolongation ("c" indicating the QT interval is *corrected* for heart rate), was the first described mechanism. In a study by Kay et al.,[3] TdP events were reviewed in 32 hospitalized patients, all of whom had a prolonged QTc (≥ 450 msec) using a baseline ECG. The investigators found that the mean QTc immediately prior to TdP, which was 590 msec, had increased from the baseline QTc of 450 msec. In addition to the progression of lengthening of the QTc, the investigators also found that there were PVCs with a short-long-

short ventricular cycle pattern just prior to the initiation of TdP. The TdP events in this study were determined to be induced by medication(s) and/or electrolyte abnormalities, specifically hypokalemia and hypomagnesemia.

In order to maintain a normal cardiac cycle, depolarization (i.e., excitation) and repolarization (i.e., refractory period or recovery of excitability) must have uniformity.[4] In situations where in particular when the refractory period is not uniform (i.e., *dispersion of refractoriness*) as can be seen with myocardial ischemia or cardiac sympathetic nerve stimulation,[4] a premature stimulus (such as PVCs) or a longer cycle length (as might be seen during ventricular pacing, or QT prolonging medications) makes the ventricles vulnerable to lethal arrhythmias like VT or TdP. Kay and colleagues posited that the combination of QTc prolongation along with a short-long-short cardiac cycle which is followed by a PVC created "temporal dispersion of refractoriness" and set up the perfect physiologic storm for TdP.[3(p815)] Thus, PVCs that occur with QTc prolongation can deteriorate (in some instances quickly) into TdP due to the non-uniform refractoriness of the myocardium brought about by medications and/or electrolyte disturbances.[3]

PVCs with a Short Coupling Intervals Trigger VF. Viskin et al. described the role that PVCs might play in the occurrence of idiopathic ventricular fibrillation (VF), especially in the absence of QTc prolongation.[5] This physiologic theory was based on an analysis of 12-lead ECGs in 32 patients with idiopathic VF, defined as: (1) ≥1 episode of a cardiac arrest with VF documented at the time of resuscitation; and (2) no evidence of heart disease based on physical examination, 12-lead ECG(s), echocardiogram, exercise stress test, and coronary angiography. The investigators showed that a PVC with a very short coupling interval (302 ± 52 msec) initiated all spontaneous VF events. The PVC occurred within 40 msec of the peak of the preceding T-wave, or the relative refractory period. The authors labeled this as the "supranormal" part of the refractory period, which is a vulnerable period of the cardiac cycle during dispersion of refractoriness of the myocardium leading to "reentrant waves" seen in VF.

This is similar to that described for TdP, although, in this case, QTc prolongation is absent. This particular physiologic mechanism is believed to be the most likely explanation for the occurrence of VF.[5,6] In clinical practice, this phenomenon is referred to as an R-on-T, with R representing the PVC. Clinicians responsible for ECG monitoring in the hospital setting are keenly aware of R-on-T type PVCs due to the potential for initiating lethal arrhythmias like VT and VF. [5,6]

However, in clinical practice today, it is somewhat problematic to generalize that these two mechanisms (non-uniform refractoriness[3] and short coupling intervals[5]) are the only contributors to lethal arrhythmias in all ICU patients. Nevertheless, these concepts provide important foundational understanding and may explain why clinicians and researchers believe that careful monitoring for PVCs in the ICU setting is an important predictor of lethal arrhythmias during continuous ECG monitoring.

Continuous ECG Monitoring for PVC and Alarm Fatigue

PVCs are commonly found in both outpatient and inpatient populations. Among outpatient populations, studies show that PVCs are associated with stroke,[7-9] atrial fibrillation (AF),[8,10] ventricular tachycardia (VT),[11,12] heart failure,[10,13-18] cardiomyopathy,[19] and mortality.[10,15,20-26] A meta-analysis among self-reported healthy adult populations also found that PVCs were associated with cardiac death.[27]

While a substantial body of evidence concerning the clinical significance of PVCs in the outpatient setting exists, this same evidence is lacking in the hospital setting. Of note, the study most often cited and applied to patients in the acute care setting is the landmark Cardiac Arrhythmia Suppression Trial (CAST), which was published in 1989.[28] The CAST study showed that treatment of PVCs with class Ic antiarrhythmic drugs (i.e., encainide, flecainide, and moricizine) was associated with more deaths compared to placebo; hence, aggressive treatment to suppress PVCs was not recommended. Interestingly, the CAST study enrolled

patients one week or later following acute myocardial infarction (MI), which would be well outside of an ICU stay by today's standards.[28]

The current in-hospital ECG practice standards for PVC monitoring from the American Heart Association provide some guidance regarding PVC monitoring during continuous ECG monitoring.[29] Of note, the authors identified that because PVCs are considered to be not immediately life-threatening, in the absence of other significant indications, continuous monitoring for PVCs may be considered but is not required (i.e., Class of Recommendation of IIb and Level of Evidence C). This was based on there not being established evidence from well-designed research studies and are rather based on expert opinion, case studies, or standard of care. Importantly, while there is a lack of evidence about the clinical value of continuous PVC monitoring, it is common practice for PVC alarms to be turned on (both inaudible and audible) during in-hospital ECG monitoring.[30-33]

Continuous ECG monitoring of PVCs in the ICU is problematic. In the UCSF Alarm Study,[30] PVCs were the most common alarm cited, accounting for 854,901 (33%) of over 2.5 million total alarms (**Figure 1**), which equated to 358 PVC alarms/bed/day. Therefore, PVC monitoring likely contributes to alarm fatigue, a condition where clinicians are desensitized to excessive numbers of alarms. Alarm fatigue has been cited as a significant contributing factor for alarm-related sentinel events that have led to extended hospitalization, permanent loss of function, and even death.[34,35] Alarm fatigue is now recognized as a significant patient safety hazard by several federal agencies and national organizations such as the Association for the Advancement of Medical Instrumentation (AAMI),[36] The Joint Commission,[35,37] Emergency Care Research Institute (ECRI),[38] American Association of Critical-Care Nurses (AACN),[39] and the Society of Critical Care Medicine (SCCM).[40] In fact, The Joint Commission has identified device alarm management as a National Patient Safety Goal that has been in place since 2014 and requires hospitals to make improvements to ensure that alarms on medical equipment are heard and responded to on time. Given the high number of PVC alarms, one can appreciate the

burden placed on nurses who must response to these alarms and determine if an action is required. Our research group has published a number of studies specific to arrhythmia alarms,[41-44] but has yet to examine PVC alarms, which has set the stage for this dissertation work.

PVCs could contribute to the alarm fatigue in the following ways: (1) over-monitoring for a condition that is ***not*** routinely treated; (2) high occurrence rates, particularly in some subsets of patients such as those with significant cardiac problems (e.g., heart failure or MI); and (3) lack of specificity about which type, if any, of PVCs might be relevant to monitor for. For example, ECG monitoring manufacturers have created alarm algorithms for several different PVC types (e.g., isolated, couplets, bigeminy, trigemini, R on T, run PVC, and number/hour). However, it is challenging for nurses to quickly identify if a particular PVC type occurs more often than another. Of note, there are no industry standards that have identified the type(s) of PVC alarms that should be available to clinicians, which means that the number and type of PVC alarms generated vary by manufacturer. This is important since it is not uncommon for hospitals to use two or more different ECG manufacturers in one hospital (e.g., emergency department, telemetry unit, ICU); hence, clinicians could become confused about PVC monitoring alarms depending upon the type of monitor available in each unit. Finally, most nurses responsible for making alarm adjustments are not always comfortable or skilled with adjusting alarm parameter settings.[45,46]

In addition, currently there are no standards to guide PVC alarm priority levels. For example, ECG monitors are designed with alarm priority-level sequencing such as, high priority (crisis), medium-priority (warning), low-priority (advisory), and inaudible text message alarms. The alarm priority level further corresponds to the sound of an alarm and action required when an alarm is generated. For instance, high priority level alarms typically produce higher pitched and more frequent alarm tones, whereas low level alarms are typically inaudible but flash a message on the bedside monitoring screen to alert the nurse to a potential problem (e.g., leads

off, isolated PVC). High priority alarms are typically “latching,” which means the nurse must acknowledge the alarm and physically push a button to turn it off. To date, however, there is no clear guidance on whether or not PVC alarms should be set as audible or message-type alarms. Furthermore, given the variety of PVC type alarms, perhaps one type should be audible and one inaudible. Of note, some monitoring manufacturers do not have the option to configure alarms as inaudible text message alerts, which creates substantial challenges for the ICU clinical team when deciding which alarms to turn on or off when selecting default monitor settings.

As mentioned, there is a lack of evidence regarding which, if any, of the multiple PVC types require close monitoring. For example, are R-on-T type PVCs more clinically relevant then isolated PVCs? In current clinical practice, it is common to see most, if not all, PVC types turned ‘on’ in default alarm settings, presumably because turning them off altogether might risk missing a PVC induced arrhythmia event. In addition, whether patient characteristics are associated with PVCs has not been examined. A better understanding of this could guide alarm management strategies. Lastly, there have been no hospital-based studies that have examined whether PVCs of all types (i.e., isolated, bigeminy, trigeminy, couplets, R-on-T, or run PVCs) are associated with lethal arrhythmias. Given that PVC could forewarn a lethal arrhythmia, especially in patients with acute MI or QT prolongation, identification of PVCs might help identify high risk patients.

Therefore, definitive evidence is needed regarding the clinical significance of PVCs among ICU patients. Findings from such an investigation could not only begin to address the alarm fatigue problem that PVCs create but help better define clinically significant PVC patterns. Both could influence future algorithm development and ultimately improve patient outcomes through more precise ECG monitoring. To date, no contemporary study has examined occurrence rates for various types of PVCs, whether any of these are more frequent by demographic, clinical history, or type of diagnosis, and whether a particular PVC type predicts VT or VF.

Purpose

This dissertation was designed to examine the significance of PVCs in adult ICU patients. Specifically, three distinct **aims** were examined and include: (1) a scoping review of the literature examining the diagnostic and prognostic significance of PVCs in patients with and without cardiac disease across different settings (community and hospital settings); (2) determine occurrence rates for PVC seven different types of PVCs (i.e., isolated, bigeminy, trigeminy, couplets, R-on-T, run PVC, and PVC/minute) in an ICU cohort; (3) determine if demographic and clinical characteristics are associated PVC occurrence rates by type; and (4) determine whether PVCs were associated with VT and/or VF.

Chapters two, three and four address the above study Aims. In Chapter #2, the results of the scoping review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review (PRISMA-ScR) format.[47] Chapter #3, is a secondary analysis using 797,072 individual PVC alarms data in 446 ICU patients included in the UCSF Alarm Study.[30] In this chapter, we examined the distribution of the seven PVC alarm types based on patients' demographic and clinical characteristics. Specifically, we examined whether patient demographics (age, sex, race), clinical characteristics (medical history, presence of atrial fibrillation and PVC on 12-lead ECGs, LVEF, and potassium level at ICU admission), and primary diagnosis were associated with PVC occurrence rates by PVC type. Finally, in Chapter #4, we examined whether any of the PVC types were associated with VT and/or VF, and adjusted for potential confounders. In this paper, we performed an exploratory analysis on whether PVCs were associated with code blue events and/or in-hospital mortality.

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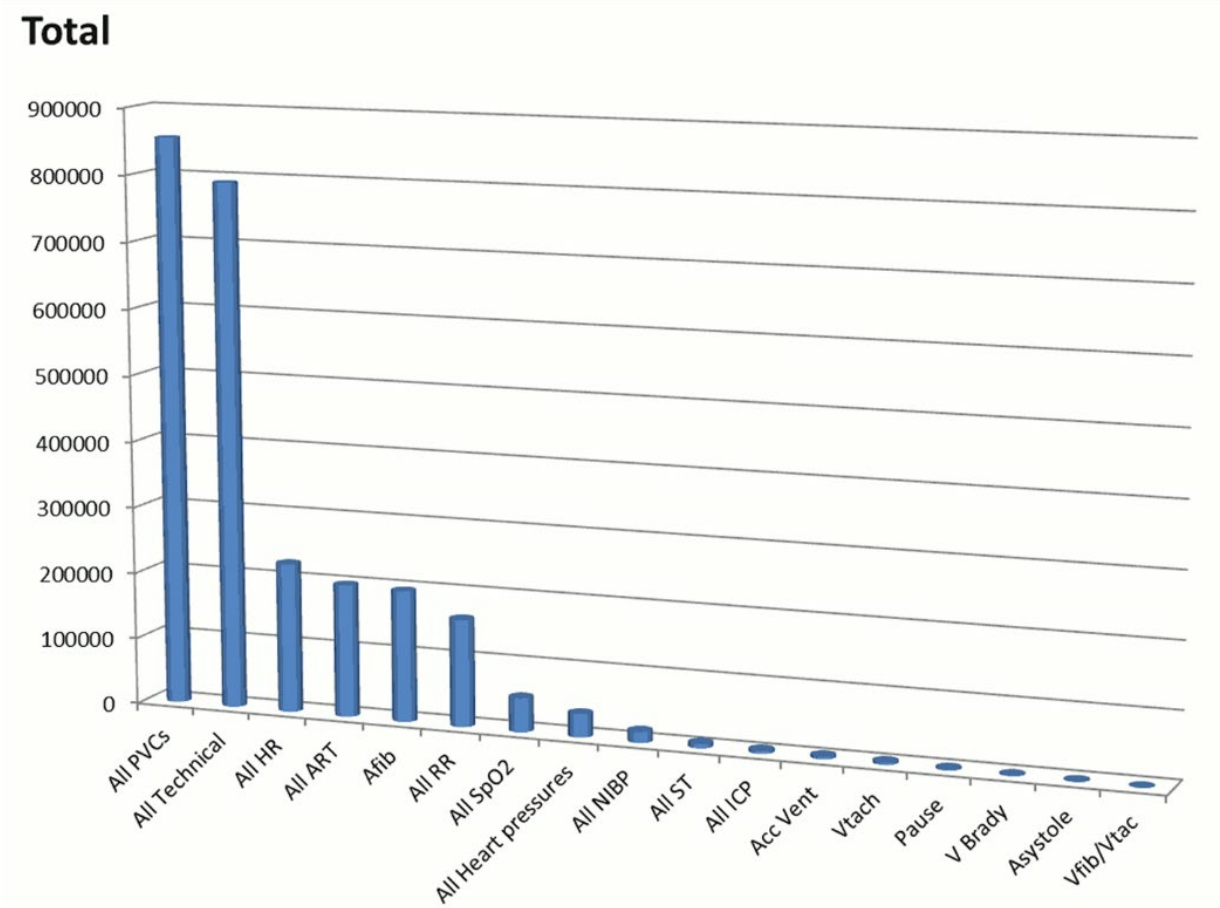

Figure 1.1 – Distribution of all unique clinical alarms during 31 days in the UCSF Alarm Study among 461 intensive care unit patients. Note that PVC alarms are the most frequently occurring alarm, accounting for 33.4% of the total 2,558,760 alarms (From: Drew et al.[30] under CC-BY 4.0 license)

Abbreviations: Acc Vent, accelerated ventricular rhythm; Afib, atrial fibrillation; HR, heart rate; ICP, intracranial pressure; NIBP, non-invasive blood pressure; PVCs, premature ventricular contractions; RR, respiratory rate; SpO_2, oxygen saturation; ST, ST-segment; V Brady, ventricular bradycardia; Vfib/Vtach, ventricular fibrillation/ventricular tachycardia; and Vtach, ventricular tachycardia.

Chapter 2

Diagnostic and Prognostic Significance of Premature Ventricular Complexes in Community and Hospital-Based Participants: A Scoping Review

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Abstract

Background. Although PVCs are not commonly treated in the hospital settings, particularly after the Cardiac Arrhythmia Suppression Trial (CAST) was published, there is still uncertainty about the significance of the PVCs concerning patient monitoring, evaluation, and management. Debates remain as to whether PVCs are simply a benign arrhythmia or serve as a risk marker for various cardiac diseases. This scoping review aims to evaluate published studies that have examined the diagnostic and prognostic significance of PVCs.

Methods. We utilized scoping review frameworks by Arksey and O'Malley and the Joanna Briggs Institute (JBI). We conducted a systematic search of the literature in 4 databases (CINAHL, Embase, PubMed, and Web of Science) from database inception to January 2020.

Results. We identified 71 relevant articles, with nearly all is observational, and 5 are secondary analysis of randomized trials. Three studies examined the diagnostic importance of PVCs' origin and QRS morphology in diagnosing acute myocardial ischemia (MI). The majority of studies examined the significance of PVCs' presence, frequency, burden, and QRS morphology on prognostic outcomes such as left ventricular dysfunction or heart failure, arrhythmias, ischemic heart diseases, and mortality.

Conclusions. Although early studies show the significance of PVCs in acute MI diagnosis, such finding has never been rigorously explored or validated. Evidence shows that PVCs are not entirely benign regarding an individual's prognosis, particularly in the community setting. However, the causal association cannot be established due to the studies available are observational.

Registration. This scoping review has been registered in the Open Science Framework (OSF), DOI: https://doi.org/10.17605/OSF.IO/GAVT2.

Keywords: arrhythmia, clinical significance, electrocardiography, premature ventricular complex, scoping review.

INTRODUCTION

Premature ventricular complexes (PVCs) are early depolarizations of myocardial cells that originate in the ventricle and are caused primarily by impulse formation disorder (enhanced automaticity or triggered activity)[1-3] or reentry mechanisms of myocardial tissues.[1, 4-6] In hospitalized patients, PVCs are one of the most common arrhythmias seen on either a 12-lead electrocardiogram (ECG) and/or during continuous ECG monitoring.[7-9] Among community-based participants enrolled in large cohort studies, the occurrence rate of PVCs is reported to be 1% to 4%,[10-12] and PVCs are more prevalent in individuals with structural heart disease (SHD), suggesting they may be a marker of cardiac pathology in some subjects.[13]

In the late 1960s, when ECG monitoring was first introduced in the hospital setting, PVCs were carefully monitored for and treated, particularly in patients with acute coronary syndromes, because PVCs were considered a potential precursor to more lethal arrhythmias (i.e., ventricular tachycardia [VT] and/or ventricular fibrillation [VF]).[14] After two decades of treating PVCs in hospitalized patients without empirical evidence, the landmark Cardiac Arrhythmia Suppression Trial (CAST)[15] tested the hypothesis that pharmacological suppression of PVCs would reduce the incidence of arrhythmic death in post-myocardial infarction (MI) patients. Surprisingly, preliminary data from the CAST study showed that pharmacologic suppression of PVCs using encainide or flecainide (class IC antiarrhythmics) was associated with increased mortality when compared with placebo.[15] This finding from the interim analysis led to early termination of the study and a shift away from routine aggressive treatment of PVCs in clinical practice. Interestingly, even though PVCs are not typically treated in the hospital setting, bedside ECG monitors used in both the intensive care and telemetry unit settings are often configured to monitor for PVCs. Not only is this considered potential over monitoring,[16, 17] but this practice can cause alarm burden to clinicians and thus, contribute to alarm fatigue.[7, 18] The practice standards for ECG monitoring in hospital settings indicate that the benefit of continuous PVC monitoring is less well-established (class: IIb), and unfortunately, there is a

paucity of literature regarding the potential relevance of PVCs among hospitalized patients (level of evidence: C).[17] Hence, guidance on how best to monitor and/or manage PVCs in hospitalized patients is mostly unknown.

In the outpatient setting, there is debate as to whether PVCs are generally benign or serve as a marker of risk for various cardiovascular diseases such as left ventricle (LV) dysfunction, cardiomyopathies or MI.[19, 20] Although published consensus and practice guidelines provide insights on the management of PVCs,[21-25] there is still a scarce data regarding the clinical importance of PVCs.

Three meta-analyses that examined community-based participants without known cardiac disease identified PVCs as a predictor of mortality.[13, 26, 27] In one meta-analysis, there was an association between the presence of PVCs and an increased risk for all-cause and cardiovascular mortality.[13] Another study showed that frequent PVCs were an independent risk factor for sudden and overall cardiac death.[26] Moreover, in patients undergoing exercise stress testing, the presence of PVCs was correlated with a higher risk for mortality.[27] While these meta-analyses show that PVCs were associated with an increased risk for all-cause and cardiovascular mortality, they included only outpatient and community-based participants without cardiac disease. Of note, this same evidence is lacking in other important groups such as hospitalized patients, asymptomatic patients with cardiac disease and/or patients with implantable cardioverter-defibrillator (ICD).

Therefore, there is a need to establish a clearer understanding of the diagnostic and prognostic implications of PVCs in both community and hospital settings and whether there are differences based on presence of underlying cardiac disease. This would not only help guide clinical practice (in- and out-patient), but shed light on whether PVCs are an important marker in patients at risk for the development of cardiac disease and/or adverse outcomes. The purpose of this scoping review was to evaluate published studies to date that have examined the

diagnostic and prognostic significance of PVCs across different care settings (i.e., community, hospital) and among various adult patient populations (i.e., with-, without heart disease).

METHODS

Our scoping review protocol has been registered in the Open Science Framework (OSF), DOI: https://doi.org/10.17605/OSF.IO/GAVT2, along with a published full-text.[28] This review followed the scoping review framework of Arksey and O'Malley[29] and the Joanna Briggs Institute (JBI) Methodology for Scoping Review.[30] This report was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review (PRISMA-ScR): Checklist and Explanation,[31] and can be found in **Supplement Table 2.A**. The methods of this scoping review followed the published protocol[28] with a few minor changes, which will be described below.

Eligibility. We included primary studies that collected quantitative data that were published in English. We included studies that met the Population, Concept, and Context (PCC) framework set forth by the JBI scoping review methodology (**Table 2.1**).[30] The gold standard test for diagnosing PVCs is the ECG;[25] therefore, all of the included studies used some type of ECG device/method to diagnose PVCs (e.g., standard 12-lead ECG, Holter, or bedside monitor).

Information Sources and Search Strategy. The preliminary search was done by SS with a pilot review and guidance on the content and review methodology from MMP. After both investigators were confident that the search and review process was well established, SS performed the literature search and selected the studies for inclusion with validation from MMP. Four electronic databases were searched: the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, PubMed, and the Web of Science Core Collection, and included publications with limitations on publication date. Once the electronic search had been completed, the reference lists for all the available articles were careful searched manually to

ensure there were no studies excluded. The detailed database search strategy is shown in **Supplement Table 2.B**.

Selection Process. The title for each study identified was exported into EndNote X8 (Clarivate Analytics, PA, USA) in order to identify and remove duplicates. These references were then exported to Microsoft Excel (version 2016; Microsoft, Redmond, WA) for a secondary duplicate screening process. The remaining list was carefully screened to ensure the established eligibility criteria were met. The first author (SS) conducted the screening, selection, and review process independently. The last author (MMP) provided oversight to ensure the established criteria were met for the selected studies and to ensure that the extracted data from the included studies was captured accurately. **Figure 2.1** is the PRISMA flow diagram detailing our process.[32]

Data Charting. A data extraction form was developed by SS and MMP.[28] Minor modifications to the data extraction form were made following a pilot study for the current review. For example, data on PVC criteria (e.g., simple, complex, or frequent PVCs) and the ECG annotation method were originally included on the data extraction form. However, after reviewing over half of the studies, we determined that the majority of studies did not report these data elements; hence, these variables were not extracted. The first author (SS) performed the data extraction process, with consultation from MMP whenever data were unclear.

Data Extracted and Synthesis of the Results. Data extracted for this scoping review included study characteristics (i.e., country of origin, year, aims, design, setting, patient population, sampling criteria/size, age, and sex), methodology (i.e., ECG method, follow-up period, and analysis), and key findings/outcomes. While we examined studies for ethnicity and race, very few provided these data. Because the purpose of this present review was to gather evidence on the prognostic and clinical significance of PVCs, only studies that performed statistical analyses were included in the scoping review. The data from the studies included in our review are presented in tables. We grouped the evidence primarily based on the setting

(outpatient versus hospital-based), presence or absence of cardiac disease(s) and outcomes. Key findings are synthesized and described in detail in the narrative text.

Critical Appraisal/Publication Bias. We did not perform a critical appraisal of the individual source evidence included in this review as initially planned because there was significant methodological heterogeneity across the studies. Nevertheless, since the goal of this review was to "map" the existing evidence regarding the significance of PVCs regardless of the methodological quality, a critical appraisal is not required. This is aligned with the PRISMA-ScR guidelines,[31] hence, our approach is within the guidelines of a well-designed review of the literature.

RESULTS

The literature search was conducted in January 2020, and resulted in a total of 10,063 titles from the four databases searched. Five additional titles were identified after searching the cited references. After a careful screening process using the outlined inclusion/exclusion criteria above, 71 articles were ultimately included in the scoping review (**Figure 2.1**). The characteristics of the 71 included studies are summarized in **Table 2.2**.

Study Characteristics

Location, Design and Setting*.* Of the 71 studies included, 39 (55%) were conducted in the United States (US), 16 (23%) from Asia (Japan, South Korea, Turkey, China, Taiwan, and Israel), 13 (18%) from Europe (Denmark, France, Germany, Italy, Poland, Romania, and United Kingdom), one (3%) from each Canada and Mexico. One study was a multi-national study including participants from the US, Canada, and Europe. Nearly all (n=66, 93%) were observational; and five (7%) were secondary analyses from randomized clinical trials including the: Multiple Risk Factor Intervention Trial (MRFIT);[38] Beta Blocker Heart Attack Trial (BHAT);[90, 94] Danish Verapamil Infarction Trial II (DAVIT II);[97] and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT).[80] Fifty (70%) of the studies were conducted in outpatient and/or ambulatory clinics. Several were secondary data

analyses from large community-based observational and/or epidemiological studies including the Tecumseh Community Health Study,[33] the Framingham Offspring Study,[43] Healthcare Cost and Utilization Project (HCUP),[74] the Atherosclerosis Risk in Communities (ARIC) Study,[45, 50, 54, 56, 57, 73] the Cardiovascular Health Study (CHS),[70, 73] the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study,[69] and the Third National Health and Nutrition Examination Survey (NHANES III).[67] A small number (n=18, 25%) were conducted in the hospital setting at varied locations including: cardiac catheterization and electrophysiology laboratory; coronary care unit; and non-ICU units. Three (4%) of the studies did not fall within the community/outpatient or hospital setting, two did not report study setting and one included both in- and outpatient settings.

Sampling Criteria. The study sample sizes ranged from <100 participants[44, 48, 55, 62, 66, 68, 83, 87, 88, 92, 101] to >16-million.[74] In the majority of the studies, data were obtained from medical records, while others collected data during clinic visits/hospital stay, and/or a combination of both locations. Several of the studies examined the significance of PVCs in a cohort of healthy adults who did not have a history of a cardiac disease(s). For example, the ARIC Study excluded participants not in a sinus rhythm and those with cardiac rhythm disorders such as Wolff-Parkinson-White (WPW) syndrome, atrial fibrillation (AF)/atrial flutter, wandering atrial pacemaker, and supraventricular tachycardia (SVT).[45, 50, 54, 56, 57, 73] In addition to rhythm disorders, several other secondary analyses using the ARIC Study database also excluded participants with heart failure (HF),[56] coronary heart disease (CHD),[54, 56, 57] or a history of stroke.[50, 54, 57] One study using the HCUP dataset excluded adults with both systolic and/or diastolic HF at enrollment, arrhythmogenic right ventricular dysplasia, paroxysmal ventricular tachycardia, and valvular heart disease.[74] Similarly, one study using the NHANES III dataset also excluded participants with known cardiovascular disease, ECG evidence of prior MI, paced rhythms, or AF.[67]

In contrast, several studies purposefully examined patients with known cardiac disease. Initial studies done in the 1970's and 1980's were focused on hospitalized patients with acute MI.[35, 83, 84, 86, 87, 89-92] However, beginning in the late 2000's, the focus shifted to patients with frequent PVCs referred for catheter ablation,[58-60, 72, 76] or patients with exercise induced-PVCs who later had a cardiac catheterization procedure.[46] Other studies investigated the significance of PVCs among patients with dual-chamber ICDs;[44, 79, 80, 101] or patients with palpitations, syncope, near-syncope who were referred for Holter recording due to these clinical problems.[61,71,75]

The mean age of the study samples included were primarily between 50 and 60 years old. Of the 71 studies included, in 34 (48%), men made up the majority of the sample and four studies (6%) included only male participants.[35, 37, 38, 41] A handful of the studies did not report demographics such as age (n=5; 7%) or sex (n=9; 13%). As mentioned previously, very few studies reported ethnicity or race. **Supplement Table 2.C** shows details of the sampling criteria.

ECG Data Collection Method used to Identify PVCs. The ECG method used to identify PVCs varied considerably across the studies, and in two studies the ECG method was not reported.[37, 74] Of the 71 studies, 30 (42%) used a Holter recorder, with varied recording times (6 to 48-hours); 15 studies (21%) used a standard 12-lead ECG; while 10 studies (14%) used a short duration ECG rhythm strip (2-minutes to 1-hour). In a handful of studies, other methods were used including; both a standard 12-lead and Holter recording, ICD device, and ECG data obtained during a diagnostic procedure such as cardiac mapping or stress test.

Key Findings

Diagnostic Value of PVCs Acute MI. Three studies examined the diagnostic importance of PVCs in the early phase of acute MI for identifying the location, or diagnosis of acute MI, specifically the origin (ventricle) and QRS morphology of the PVCs.[86-88] For example, one study showed that a right bundle branch block (RBBB) pattern PVC during the first 48 hours post-MI along with right axis deviation was correlated with anterior MI (anteroseptal and/or

anterolateral), whereas a RBBB pattern PVC and left axis deviation was associated with infero-posterior wall MI.[86] The QRS characteristics of the PVC, such as the duration of the Q-wave and/or Q/R ratio were found to have low sensitivity, high specificity and moderate positive predictive value (PPV) for identifying anterior, or inferior MI location.[87, 88] PVCs with a qR or qRS configuration also had low sensitivity but high specificity and PPV in the diagnosis of MI.[88] Details of the study results are provided in **Table 2.3**.

Prognostic Value of PVCs. The focus of the vast majority of the studies examined the prognostic value of PVCs. These studies look at a multitude of clinical outcomes (described below) from different settings (i.e., outpatient, community-based, and hospital based) among those with and without known cardiac disease. The details reported effects on the following prognostic outcomes: (1) SHD; (2) lethal arrhythmia; (3) AF and/or stroke; (4) IHD and other adverse outcomes; (5) all-cause mortality; and (6) cardiovascular mortality are described below.

Structural Heart Disease. Patients with frequent PVCs have a larger diameter of the left atrium (LA) and volume index compared to those without frequent PVCs.[62, 65] LA remodeling is important to examine because higher filling pressures in the LV impact the LA shape and volume due to increased filling pressure in the LA from the ventricle, which can indicate the presence of diastolic dysfunction and/or HF.[63] For example, one study showed that among patients with an extreme number of PVCs (>1,000/24-hour) with symptoms (palpitations or dyspnea), the odds of having a trapezoidal LA for was a 1.32 higher for each 10% increase in PVC frequency (odds ratio, OR, 1.32, 95% confidence interval, CI, 1.17 – 1.48).[63] This study also found that a high frequency of PVCs was associated with a higher LA volume.[63]

The presence of PVCs has also been associated with LV dysfunction. In patients followed for 5-years, the presence of PVCs measured from a baseline ECG was associated with 2.8-times greater odds of having a reduced LV ejection fraction (LVEF) as compared to patients without PVCs.[70, 73] PVC morphology has also been associated with a lower LVEF. For example, patients with a lower LVEF have PVCs that are either notched or have a wide shelved QRS,[93] or

have a greater coupling interval and longer PVC QRS duration.[64, 82] Studies show that there is a higher prevalence of LV dysfunction in patients with frequent PVCs (≥ 10 PVCs/hour or > 1,000 PVCs/day)[49, 103] or a high burden of PVCs (i.e., PVCs >30% of all beats/day),[60] indicating PVCs as a marker of LV dysfunction. One study reported that for each 1% incremental increase in the daily rate of PVCs, there was an increased risk of impaired LV relaxation (diastolic dysfunction) (OR 1.18, 95% CI 1.02 – 1.37).[48] Another study found that PVCs that originate from the right ventricle (RV) were associated with a lower LVEF when the PVC burden was at least 10%, while PVCs originating from the left ventricle (LV) were associated with a reduced LVEF when the PVC burden was at least 20%.[55] Finally, among patients with frequent PVCs who are asymptomatic, a 10% increase in PVC burden was found to be an independent predictor of an impaired LV function (OR 2.1, 95% CI 1.2 – 3.6).[58]

A number of studies found that PVCs were associated with the development of cardiomyopathy (CMP), so called PVC-induced CMP (PVC-CMP), and/or HF.[56, 68, 70, 71, 73-75] In patients referred for catheter ablation due to frequent idiopathic PVCs, those with a high PVC burden (>24% over 24-hour) were at increased risk for developing CMP.[51, 58, 59, 72] The QRS duration (width) of the PVCs had been found to be an independent predictor of PVC-CMP even when controlling for other important variables, such as a patient's symptom status, PVC origin, and PVC burden.[59, 66, 72] Several studies showed that wider QRS's increased the risk for PVC-CMP from 3% to 12%.[51, 59, 72] Data from large cohort studies (ARIC,[56, 73] CHS,[70, 73] and HCUP)[74] showed that there is an increased risk of incident HF (1.3- to 2-fold) when PVCs are present on either a 2-minute ECG rhythm strip or standard 12-lead ECG. In a sub-group analysis of individuals < 65 years of age without hypertension, diabetes mellitus (DM), CHD, or AF, there was a higher risk for incident HF compared to participants without PVCs (hazard ratio, HR, 6.5, 95% CI 5.5 – 7.7).[74] In patients referred for 24-hour Holter monitoring due to syncope, palpitations, or suspected arrhythmia, there was a 1.5-fold increase in the rate new-onset HF when multiform PVCs were present compared to no PVCs (HR 1.46, 95% CI 1.06 – 2.00).[71]

Finally, patients with a high PVC burden (≥ 20%) were found to have 3 times the odds of developing HF compared to the control group (OR 3.15, 95% CI 1.28 – 6.50).[68]

Lethal Arrhythmias. Several studies have examined the relationship between PVCs and the development of VT and/or VF.[36, 39, 44, 77, 79-81, 98, 101] In patients with frequent PVCs (> 6/minute), high PVC burden (≥ 10% of QRS's/24-hour) and/or couplets, there is an increased risk for VT (PVC burden OR=1.07, 95% CI 1.03 – 1.11; PVC couplets OR=33.98, 95% CI 11.53 – 100.19).[81] In post-MI patients and those admitted for rule-out cardiac diagnosis, longer QT dispersion of the PVCs, defined as the difference between maximum and minimum QT interval of the PVCs measured across the 12-leads, was associated with the occurrence of lethal arrhythmias.[39, 98] In a study in patients with exercise-induced PVCs (EiPVCs) followed for up to 14 years, there was an increased risk of VF/flutter and/or sustained VT in this patient group.[77] Another study showed that PVCs that occur in the late-period of exercise testing and/or frequent multiform PVCs were also associated with VT or VF.[36] In patients with reduced LV function or CMP, a high PVC burden (>10 /hour) increased the risk for VT/VF by 2.8-fold (HR 2.79, 95% CI 1.69 – 4.58).[80] In patients with an ICD, the frequency of PVCs was higher among those who developed VT/VF compared to those who did not develop VT/VF.[44, 79] One study examined R-on-T type PVCs in a group of patients with an ICD and found that this type of PVC rarely induced sustained VT. However, in the small number of patients in this study with sustained VT that were induced by an R-on-T, the PVCs were more likely to be polymorphic (positive and negative QRS's) and in patients with coronary artery disease (CAD).[101]

Atrial Fibrillation and Stroke. In large cohort studies, there was a 1.1- to 1.6-fold increased risk of developing AF when PVCs were present on an ECG recording,[50, 73] although only the study by Nguyen et al. that analyzed the association by taking into account the occurrences of premature atrial complex (PAC).[73] In one study that included patients with syncope, palpitations, or suspected arrhythmia, but who did not have a history of documented heart disease, the presence of multiform PVCs was associated with 1.5-times higher risk of

new-onset AF compared to those without PVCs (HR 1.5, 95% CI 1.06 – 2.26).[71] In two different community-based studies, researchers found an association between the presence of any PVCs (vs. absence of PVCs) and an increased risk for incident stroke at 6-year follow-up (HR 1.4, 95% CI 1.05 – 1.81)[69] and 15-year follow-up periods (HR 2.1, 95% CI 1.2 – 3.6).[50] A subsequent analysis in one of these studies showed that the occurrence of ≥ 4 PVCs/minute was associated with a higher risk of stroke (HR 2.06, 95% CI 1.24 – 3.42) when compared to patients who did not have PVCs.[50] Additionally, when comparing any PVCs vs. no PVCs, non-hypertensive individuals were at increased risk for thrombotic stroke of non-carotid origin (HR 3.48, 95% CI 1.74-6.95). Interestingly, this same association was not present among patients with hypertension (HR 1.21, 95% CI 0.58 – 2.53).[50] Similarly in a secondary analysis of a longitudinal study (13 years) using data from the ARIC study (n=14,493), participants with PVCs who were normotensive had a higher risk of ischemic stroke compared to hypertensive individuals with PVCs (HR 1.69, 95% CI 1.02 – 2.79).[57]

Among a group of patients without history of cardiac disease referred for 24-hour Holter monitoring for new cardiac symptoms (i.e., syncope, palpitations, suspected arrhythmia, and/or other clinical indication), those with multiform PVCs had an increased risk for transient ischemic attack at 10-years follow-up (HR 1.41, 95% CI 1.06 – 1.87).[71] In a 3.5-years of follow-up period, frequent PVCs, defined as >10% of the total number of beats over 24-hours, were associated with the occurrence of stroke-like symptoms (i.e., painless weakness, sudden numbness, “dead” feeling on one side of the body, sudden but painless loss of vision, and sudden loss of the ability to understand what people were saying) (OR 3.42, 95% CI 1.09 – 10.73).[99]

Coronary Heart Disease and Other Adverse Outcomes. Community based studies show that the presence of PVCs are correlated with a 1.2-fold increased risk for the development of ischemic/coronary heart disease over a 10 year follow-up period.[37, 54] Moreover, frequent PVCs (≥0.6 PVCs/hour) following MI were an independent predictor of CAD severity.[91] Similarly, PVCs during the recovery phase of a stress test also predicted myocardial ischemia

on myocardial perfusion imaging, adjusting for stress test scores and other significant clinical predictors (OR 1.27, 95% CI 1.04–1.56).[46]

In a 10-year follow-up study in patients with palpitations and syncope with suspected arrhythmia, the presence of >12 PVCs/day was found to increase a person's risk for cardiovascular-related hospitalization (crude HR 1.24, 95% CI 1.06 – 1.45).[75] In two separate studies, multiform PVCs (vs. no PVCs) were associated with all-cause hospitalization (HR 1.20, 95% CI: 1.06–1.35),[71] cardiovascular-related hospitalization (HR 1.29, 95% CI 1.03–1.61),[71] and a major adverse cardiovascular event or new/worsening HF (HR 3.05, 95% CI 1.39 – 6.70).[61] In a study that followed hospitalized patients with decompensated HF for up to 2 years, PVC burden (per 1% increase) was an independent risk factor for a cardiac event, such as ICD therapy, re-hospitalization, or death (HR 1.036; CI 1.005-1.068).[100] In a different analysis, patients with left bundle branch block (LBBB) type PVCs (negative QRS in lead V1) without axis deviation had a lower incidence of various cardiac diseases (i.e., hypertension, IHD, CMP, and/or valvular heart disease) than those with RBBB-type PVCs.[42] Finally, in a study of patients with frequent idiopathic PVCs who were referred for catheter ablation, presence of pleomorphic PVCs (i.e., multiple morphologies in at least three ECG leads) with a cut-off of ≥156 PVCs/24-hour was associated with a non-successful ablation outcome.[76]

All-Cause Mortality. In population-based studies that included between 3.5 and 13 years of follow-up, the presence of PVCs at enrollment was associated with an increased risk of all-cause mortality.[33, 34, 37, 45] In another community based study, ≥30 PVCs/hour during a 48-hour Holter recording was associated with all-cause mortality, or a first acute MI event (HR 2.46, 95% CI 1.29 – 4.68).[47] Among 1,139 participants from the CHS, individuals with frequent PVCs (upper versus lowest quartile) had a 1.31-fold increased risk of death during a median follow-up of 13 years.[70] When considering the potential mediation effect of HF, the presence of PVCs on a 12-lead ECG was associated with an increased risk for overall mortality during the 10-year follow-up period among ARIC Study participants (HR 1.5, 95% CI 1.3 – 1.8), but this was not

significant in CHS participants (HR 1.1, 95% CI 0.9-1.20).[73] Interestingly, in another study with a large sample size (n=7,504), the presence of PVCs at enrollment was an independent risk factor of mortality only among individuals aged 65 years or older (HR 1.36, CI 1.04 – 1.76).[67]

In a 1979 study, Rengo et al. showed that in 232 hospitalized patients followed for 30-months who had at least one PVC on a standard 12-lead ECG, those with a short coupling interval of <360 millisecond had a higher rate of sudden death.[85] Similarly, hospitalized patients who had PVCs on any resting ECG had a doubled of mortality (HR 2.0, 95% CI 1.1 – 2.8) over a 5.5-year follow-up period.[102] In other studies, PVCs during exercise stress testing were associated with mortality in patients without cardiovascular and/or valvular heart disease,[43] and in patients with known CAD or idiopathic CMP,[77] during the 14-year follow-up period. Moreover, among patients referred for single-photon emission computed tomography (SPECT), the presence of EiPVCs was a risk factor for mortality in patients with preserved (> 50%) LVEF (OR 2.17, 95% CI 1.09 – 4.34).[78] Multiform PVCs and >12 PVCs/day during a 24-hour Holter recording increased the risk of mortality by 1.5-fold among patients with syncope and palpitations where an arrhythmia was suspected over a 10-year follow-up period.[71, 75] Similarly, in patients with cardiac resynchronization therapy and a defibrillator (CRT-D), high PVC burden (>10 PVCs/hour) was associated with increased risk of HF and death (HR 2.76, p<0.001).[80]

Numerous studies have examined the association between PVCs and mortality in patients with MI.[35, 40, 83, 89, 90, 92, 94, 96, 97] In a study with only male participants with acute MI, the presence of complex PVCs vs. no complex (i.e., “early” PVC or R-on-T, run-PVCs, multiform PVC, or bigeminy) was associated with a higher risk of mortality (RR 1.9, p ≤ 0.01).[35] In patients with PVCs on a 12-lead ECG recorded at least 4 weeks post-MI, a PVC QT dispersion ≥100 millisecond was an independent predictor of mortality (HR 3.10, 95% CI 1.7 – 9.4).[40] In patients admitted to a coronary care unit for acute MI, several studies showed that PVCs were associated with an increased risk of death at both 1- and 2-year follow-up.[89, 90, 92, 94, 96] Two of these studies showed that the risk of mortality was nearly 2-fold in patients with a run of PVCs

(≥2 consecutive)[89] and 3.6-fold in patients with complex PVCs (i.e., couplets, multiform, run of PVCs, and R-on-T).[92] Those treated with thrombolytics who had ≥ 25 PVCs/hour had a higher risk of mortality as compared with those who had <25 PVCs/hour. Similarly, those treated without thrombolytics who had ≥ 10 PVCs/hour had a higher risk of mortality as compared with those who had< 10 PVCs/hour.[96]

Cardiovascular Mortality. In apparently healthy adult populations, the presence of PVCs at enrollment to the study was associated with 2- to 3.7-fold increased risk for cardiac death up to at least a 4-year follow-up period.[38, 47, 52, 54] In particular, frequent PVCs defined as ≥30/hour (vs. <30 PVCs/hour) significantly increased the risk for cardiovascular mortality (HR 2.85, 95% CI 1.16 – 7.0).[47] Similarly, frequent PVCs during exercise stress testing was associated with a higher risk of cardiovascular death over a 15 year follow-up time frame.[41, 43] In patients with clinical HF, the presence of PVCs increased the risk of cardiac death by 5.48-fold;[53] while high PVC burden (i.e., ≥40% in 60-days continuous monitoring) was associated with a higher risk of cardiac mortality in patients with a dual-chamber ICD (HR 3.29, 95% CI 1.72 – 6.28).[79] In the setting of MI, patients with PVCs had a 2.8-fold increased risk of sudden cardiac death as compared with those who did not have PVCs.[35]

DISCUSSION

To our knowledge, this is the first scoping review to map carefully the available evidence on the diagnostic and prognostic significance of PVCs across different care settings (community versus hospital) and patient populations (with and without heart disease). Our review, covering half a century (1969 to 2019), shows that numerous, predominantly observational studies have been published in the outpatient and/or community-based settings. These studies show that PVCs and its characteristics (e.g., frequency, burden, and morphology) are associated with adverse outcomes, although the spectrum of risk is quite varied. Among studies enrolling healthy adults, the presence of PVCs increased risk for AF, stroke, LA and LV dysfunction, IHD, and all-cause and cardiac mortality. Similar findings are also observed in patients with known

cardiac disease or symptoms suggestive of cardiac disease. Moreover, in these patients there is an associated risk between PVCs and arrhythmia events (i.e., sustained VT, VF, or sudden cardiac death) and hospitalization. Surprisingly, only a small number of studies have been performed in the acute care/hospital setting, which have focused primarily on the long-term risk for arrhythmias and mortality.

Three hospital-based studies from the early 1980s examined the diagnostic significance of PVCs in patients with acute MI. These studies were designed to better understand the occurrence of PVCs in the early phase of acute MI when ECG monitoring was relatively new in hospital settings. Interestingly, two of the studies compared whether PVCs were associated with the diagnosis of MI, comparing PVC morphology from a 12-lead ECG recording to findings during cardiac catheterization, and found poor sensitivity but higher specificity and positive predictive value for acute MI.[87, 88] Also, there is evidence to suggest that patients with PVC morphology of a qR or qRS configuration with a q-wave duration of at least 0.04 second on their ECG recording have a high probability of having an acute MI (86% PPV).[88] However, these studies are very dated, and the findings have never been rigorously explored, nor validated in a contemporary setting. Therefore, the idea of using PVCs to diagnose or exclude MI seems over-reaching. Surprisingly, there are no recent studies available validating the value of PVC morphology using continuous ECG monitoring given these data are readily available and ubiquitous in the hospital setting. Moreover, ECG monitors are configured to show and, in some cases, alarm for PVCs, yet there is very little evidence for this practice.

Early studies focused primarily on the association between PVCs and all-cause mortality and cardiovascular mortality, particularly among patients with acute MI, but after hospitalization.[104] Based on the significant association found in these studies, there was a growing concern that patients with PVCs would have a poor short-term prognosis. Therefore, researchers and clinicians investigated the feasibility of treating or suppressing PVCs in order to prevent adverse patient outcomes. The Cardiac Arrhythmia Pilot Study (CAPS), supported by

the National Heart, Lung, and Blood Institute, was the first study designed to test whether suppression of PVCs post-MI with antiarrhythmic drugs would improve survival rates.[104] The CAPS study was a double-blind RCT involving ten medical centers and 502 acute MI patients enrolled between 6 and 60 days post-MI who had at least 10 PVCs/hour. At a 12-month follow-up period, the study showed that encainide, flecainide, and moricizine, suppressed ventricular arrhythmias and were well tolerated by the study participants.[104] Based on these findings, these drugs were then selected for the much larger CAST study to test whether suppressing PVCs in patients with asymptomatic or mildly symptomatic ventricular arrhythmias would reduce the mortality rate.[15] Surprisingly, preliminary results from the CAST study showed a higher death rate from arrhythmias and non-fatal cardiac arrest (relative risk, RR, 3.6, 95% CI 1.7 – 8.5), as well as total mortality (RR 2.5, 95% CI 1.6 – 4.5) in the encainide and flecainide group compare to the placebo group.[15] Based upon these findings, aggressive treatment with anti-arrhythmia drugs was not recommended.[15, 105]

After the CAST study's preliminary report, researchers and clinicians began shifting their focus from the post-MI population to the general population of patients with and without cardiac disease. Studies across different settings (outpatient, community, and hospital based) show that among individuals who are healthy, patients with cardiac disease, or with idiopathic PVCs, the presence of PVCs and/or their characteristics (e.g., frequency, morphology, coupling interval, and QRS duration) on the 12-lead ECG or Holter recordings are associated to varying degrees with LA remodeling, LV dysfunction, IHD, HF, and mortality. Studies also show similar trends for the prognostic significance of PVCs and frequent PVCs during exercise stress testing. **Table 2.4** summarizes the prognostic significance of PVCs on varied outcomes measured based on the setting, patient population, and PVC criteria.

One particular finding of interest from this review is that the presence of PVCs is linked with AF[50, 71, 73] and ischemic stroke.[50, 57, 69] This is potentially pathophysiologically plausible given that PVCs occur when there is SHD present, particularly in the LV. Atrial stretch or remodeling

from LV pathology can lead to AF and this arrhythmia can cause blood clots associated with heightened risk of stroke. However, AF has been associated with atrial ectopy arising from the pulmonary veins, and only one study[73] did account for the degree of atrial ectopy when assessing the correlation between PVCs and AF. Also, studies[50, 57, 69] did not account for potential mediation by AF or the use of antiarrhythmics when examining the association between PVCs and incident stroke, potentially introducing a bias. In addition, it is worth noting that all of these studies were community based, rather than in the acute care setting. To our knowledge, there is currently no study examines whether PVCs might be correlated with new-onset AF or stroke during hospitalization.

Another particular finding of interest is that there is an association between PVCs and occurrences of lethal arrhythmias. Historically, this was one of the primary reasons for continuous monitoring for PVCs decades ago, and is still a main rationale as to why clinicians have heightened awareness and concern about the presence of PVCs captured during ECG monitoring in the acute care setting. However, published studies examined the correlation between PVCs and lethal arrhythmias only after years of follow-up. For example, in a study that included hospitalized patients after MI, the lethal arrhythmia events were measured after approximately 3 years of follow-up.[98] Among patients with ICD seen in the outpatient clinic, the long-term impact of PVCs on the ventricular arrhythmic events was examined at a median follow-up of 3.5 years.[44, 79] Evidence that could show the prognostic significance of PVCs on the occurrence of acute lethal arrhythmias *during hospitalization* is needed to support the current practice of continuous PVC monitoring. To date, literature that shows PVCs as a trigger of lethal arrhythmias is mainly from case reports or studies with limited participants.[106-110] Although the mechanisms of how PVCs trigger lethal arrhythmias in some patients remain unclear, it is generally agreeable that PVCs somewhat play an important role in the event of ventricular fibrillation,[25] until research shows otherwise. In particular, clinical experience has shown successful treatment for idiopathic VF by ablation of the PVCs triggering VF,[111] and in some

cases prevent the VF recurrence.[112, 113] Further research is required to examine whether such a mechanism is common in all ICU patient populations or occurs only in specific targeted patient populations, which eventually would guide optimal patient monitoring practices.

Recently, there is a growing interest in the significance of PVCs in predicting future incident HF, as shown by the growing number of studies on this issue. Unfortunately, to date, there is a lack of clinical trials to show whether PVCs cause LV dysfunction and HF and almost all of the available evidence comes from cross-sectional and longitudinal studies. Cross-sectional studies could only show that the PVCs might just be a manifestation of the extant of HF.[68, 82] Although, longitudinal studies might provide a better insight into the association between PVCs and LV dysfunction since PVCs are clearly present before incident HF or LV dysfunction at follow-up period.[56, 70, 73, 74] However, there could be factors other than PVCs that confound an individual's likelihood to develop HF or LV dysfunction that might not be captured in these studies. Nevertheless, such an association might have some predictive value that is worth further investigation. Interestingly, interventional studies show a significant LV improvement after radiofrequency catheter ablation of PVCs, particularly in patients with frequent PVCs.[114-117] Although it appears that PVCs were the cause for the LV dysfunction in these individuals, these studies were not aimed to determine the causal effect of PVCs on LV dysfunction. Therefore, such an interpretation could be biased. Nonetheless, data from these studies show the significant contribution of PVCs to the development of LV dysfunction, leading to HF.

Mortality has been one of the major outcomes of interest examined across studies in relation to PVCs since the 1980s. Our review shows evidence of the long-term prognostic value of PVCs on mortality among patients with and without cardiac disease, echoing and adding to the previously published meta-analyses data.[13, 26, 27] The association between PVCs and mortality, however, requires careful interpretation, especially when taking into consideration the follow-up period across available studies. As shown in the summary **Table 2.4**, in the

community/outpatient setting, the association between PVCs and mortality is measured after at least 2-years of follow-up. In the hospital setting, a similar association was also measured after only a year of follow-up. Moreover, the study population is limited to patients with MI. Although it might suggest that PVCs are a significant risk factor for mortality, the aforementioned studies only showed an association effect and not a causal. Importantly, currently there is no convincing data available to show that active treatment of PVCs in general outpatient settings reduces mortality. In the hospital and acute care units, however, the evidence is lacking to show the prognostic value of PVCs *during* hospitalization, which raises the similar question of the importance of continuously monitoring for PVCs, and whether there is a significant association between PVCs that occur in hospitalized patients and in-hospital death.

Although it is evident from this review that PVCs have diagnostic and prognostic value, it should be noted that other areas related to this topic that may benefit from further investigation. For example, as mentioned above, the significance of PVCs has not been evaluated in hospitalized patient populations other than patients with acute MI who were followed for over a year. This lack of evidence has important implications for in-hospital ECG monitoring. For example, patients with SHD, impaired LVEF or HF who are hospitalized and have continuous ECG monitoring are likely to generate high numbers of PVCs during ECG monitoring, which could create a high alarm burden and contribute to alarm fatigue in nurses and providers. One observational study collecting clinical alarms data including arrhythmias from physiologic bedside monitors reported that PVCs were the most prevalent arrhythmia type during continuous bedside ECG monitoring in a sample of 461 ICU patients.[7] Of over 2.5 million unique alarms in just 31-day period, there were 854,901 PVC alarms, accounting for 33% of the total alarms. However, what is not entirely understood is whether PVCs and their characteristics (e.g., PVC types, frequency, wide QRS, and other morphologies) during acute hospitalization identify high risk patients who would be treated differently and thus, should be carefully monitored for. Given that continuous ECG monitoring is utilized in a number of different hospital

settings, an evaluation regarding the relevance of PVCs, if any, in varied patient populations would be relatively simple to do and could be performed for large numbers of patients. It is also important to note that almost all of the included studies were observational; therefore, we are unable to determine if the relationship between PVCs and outcomes is causal.

Although studies included in this review provide tremendous information on the significance of PVCs, there is still much to learn about translating this knowledge into practice. There is still limited data available to guide clinical workflow for evaluation and management of PVCs; for example, the best approach for health providers when one encounters a patient with a PVC on their ECG or frequent PVCs. Finally, with the growing evidence on PVCs' potential predictive value, there is also a need for studies to determine optimal approaches to utilize the predictive value of PVCs and/or mitigate the adverse consequences of PVCs.

Limitations

We acknowledge that this review has limitations. First, we were unable to perform a critical appraisal or publication bias because of the significant between-study heterogeneity in designs, setting, patient population(s), ECG data collection method, analysis approach and outcomes of interest. However, because this was a scoping review, heterogeneity was expected as our goal was to describe the available evidence on this topic without paying strict attention to homogeneity across studies as one would do in a systematic review. This approach allowed us to examine this topic in a much broader way as we were able to examine PVCs across settings (community- and hospital-based) and in various patient populations (with- and without cardiac diseases). Second, we limited our search to studies published in English from four bibliographic databases. Therefore, it is possible we missed studies that have been published in other languages, or reports that are published outside of traditional peer-reviewed commercial publications (grey literature). To account for grey literature, we searched the reference lists of available articles included. Finally, as mentioned above, some of the studies included in this scoping review are dated, especially those from 1970s to 1990s. Therefore, the outcomes of

these studies, which might be influenced by the standard clinical management for PVCs available at the time, might not reflect the current patient population and/or management of PVCs. Nevertheless, these studies provided directions for areas on the topic that warrant further investigations.

CONCLUSION

In this scoping review, we found the evidence is unconvincing to support the diagnostic value of PVCs, particularly considering the very small number of studies available, all of which are dated and lack validation. However, evidence shows the prognostic value of PVCs across different care settings (community and hospital) and patient populations (with and without cardiac diseases). Furthermore, these studies show that PVCs are not entirely benign, with certain types of PVCs, their frequency, setting, and occurrence over the course of a person's life being associated with long-term adverse patient outcomes. The present scoping review highlights some research gaps, such as the varied ECG data collection methods used across studies and especially the limited utilization of continuous ECG data from bedside monitor; lack of available studies on hospitalized patients, specifically those in the acute or critical care units where PVC monitoring is widely used; and inconsistencies with regards to the research methods and patient selection across studies; all of which are important for future research examining the clinical significance of and best practices regarding PVCs..

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Table 2.1 – Population, Concept, and Context (PCC) eligibility criteria,[28] adapted from the Joanna Briggs Institute (JBI).[30]

Eligibility Component	Criteria
Participants	Adults 19 years of age or older who had PVCs diagnosed. Studies that examined exercise-induced PVCs (EiPVCs) were included if the procedure was performed during hospitalization or a clinic visit as part of a screening or diagnostic test.
Concept	The focus of this scoping review was to assess the diagnostic (i.e., identification of a specific condition or disease) and prognostic importance (i.e., patient outcomes) of PVCs. Studies that examined the combination of both PVCs and other arrhythmias were excluded. Finally, studies that assessed ECG features of PVCs (e.g., QRS duration, morphology) were included only if the study also examined the correlation of such features with patient outcomes.
Context	Studies conducted in both outpatient and inpatient settings were included. There were no exclusions based on geographical location or demographics (i.e., race, ethnicity, sex, etc.), or year of publication.

Table 2.2 – Characteristics of the studies included in the scoping review grouped by setting (community-based, outpatient, hospital).

Study	Country	Study Design	Patient Population*	Sample Size	Mean Age (± SD), years	Male, n (%)	ECG Data Collection of PVCs
Community-Based and Outpatient Clinic (by year earliest to most recent)							
Chiang 1969 [33]	US	Longitudinal epidemiological	Cardiac disease (+)	264	30+	NR	Single channel (duration unspecified)
Desai 1973 [34]	US	Observational	Cardiac disease (+/–)	1,037	Mean 60	640 (62%)	12-lead for ≥30 seconds
Ruberman 1977 [35]	US	Observational	History of MI	1,739	Range 35 - 74	1,739 (100%)	Single-lead for 1-hour
Boudoulas 1979 [36]	US	Observational	Cardiac disease (+)	339	Mean 52 (19 - 72)	223 (66%)	24-hour Holter
Rabkin 1981 [37]	Canada	Observational	IHD (–)	401	Predominantly 25 – 35	401 (100%)	NR
Abdalla 1987 [38]	US	Randomized prevention trial	Apparently healthy	15,481	46 ± 7	15,481 (100%)	2-minute lead I rhythm strip
Dabrowski 1998 [39]	Poland	Observational	Cardiac symptoms (+)	303	59 ± 14	215 (71%)	12-lead
Dabrowski 1999 [40]	Poland	Observational	Post MI	193	62 ± 10	161 (83%)	12-lead
Jouven 2000 [41]	France	Prospective observational	CHD (–)	6,101	48 ± 2	6,101 (100%)	Bipolar lead (V5 and V5R) per bicycle exercise test protocol
Hatanaka 2002 [42]	Japan	Observational	PVC (+), history of cardiac disease (–)	201	Mean 44	192 (96%)	12-lead
Morshedi-Meibodi 2004 [43]	US	Observational	Cardiac disease (–)	2,885	43 ± 10	1,385 (48%)	Leads V1 and V5 (during treadmill and recovery)
Carrim 2005 [44]	UK	Observational	ICD (+)	44	Mean 57	38 (86%)	ICD (duration unspecified)
Massing 2006 [45]	US	Observational	Cardiac disease (–)	15,070	54 ± 0.1	6,766 (45%)	2-minute leads V1, II, and V5 rhythm strip; and 12-lead
Meine 2006 [46]	US	Observational	Referred for stress test; cardiac disease (–)	2,828	Median 58 (50 – 67)	2,036 (72%)	12-lead
Sajadieh 2006 [47]	Denmark	Epidemiological survey	Apparently healthy	678	64 ± 7	398 (59%)	48-hour two-channel Holter
Topaloglu 2007 [48]	Turkey	Observational	Cardiac symptoms (+)	63	39 ± 9	19 (30%)	24-hour Holter
Niwano 2009 [49]	Japan	Observational	Frequent PVCs; cardiac disease (–)	239	43 ± 13	118 (49%)	Holter (duration unspecified)
Agarwal 2010 [50]	US	Observational	Cardiac disease (–)	14,783	54 ± 6	6,652 (45%)	2-minute leads V1, II, and V5 rhythm strip; and 12-lead
Baman 2010 [51]	US	Retrospective observational	Frequent PVC referred for ablation	174	48 ± 13	87 (50%)	24-hour Holter

Study	Country	Study Design	Patient Population*	Sample Size	Mean Age (± SD), years	Male, n (%)	ECG Data Collection of PVCs
Hirose 2010 [52]	Japan	Cohort	Cardiac disease (–)	11,158	55 ± 11	4,333 (39%)	12-lead
Le 2010 [53]	US	Observational	Cardiac disease (+)	352	64 ± 11	345 (98%)	12-lead
Cheriyath 2011 [54]	US	Observational	Cardiac disease (–)	14,574	54 ± 6	6,327 (43%)	2-minute leads V1, II, and V5 rhythm strip; and 12-lead
Munoz 2011 [55]	US	Observational	Frequent and symptomatic PVCs	70	42 ± 17	30 (43%)	24- to 48-hour Holter and 12-lead
Agarwal 2012 [56]	US	Observational	Cardiac disease (–)	13,486	54 ± 6	5,932 (44%)	2-minute leads V1, II, and V5 rhythm strip; and 12-lead
Ofoma 2012 [57]	US	Observational	Cardiac disease (–)	14,493	Mean 54	6,232 (43%)	2-minute leads V1, II, and V5 rhythm strip; and 12-lead
Yokokawa 2012a [58]	US	Observational	Frequent PVCs referred for ablation	241	48 ± 14	115 (48%)	24-hour Holter
Yokokawa 2012b [59]	US	Observational	Frequent PVCs referred for ablation	294	48 ± 14	137 (47%)	12-lead ECG (mapping procedure) and 24-hour Holter
Ban 2013 [60]	South Korea	Observational	Frequent PVCs underwent ablation	127	44 ± 13	50 (39%)	24-hour Holter and 12-lead
Ephrem 2013 [61]	US	Cohort	Cardiac symptoms (+)	222	55 ± 16	94 (43%)	24-hour three-channel Holter (unspecified)
Barutcu 2014 [62]	Turkey	Observational	Frequent PVCs; SHD (–)	80	Mean 47 (22 – 60)	34 (43%)	24-hour Holter
Cozma 2014 [63]	Romania	Cross-sectional	Cardiac disease (–)	121	43 ± 11.5	76 (63%)	24-hour Holter
Lee 2014 [64]	US	Observational	Cardiac disease (+/–)	1,589	61 ± 16	879 (55%)	24-hour Holter and 12-lead
Park 2014 [65]	South Korea	Observational	Frequent PVCs; SHD (–)	438	55 ± 15	144 (33%)	24-hour Holter
Pol 2014 [66]	US	Observational	Cardiac disease (+)	45	49 ± 15	17 (38%)	24-hour Holter and 12-lead
Qureshi 2014 [67]	US	Cohort	Cardiac disease (–)	7,504	59 ± 13	3,977 (53%)	12-lead
Yang 2014 [68]	US	Cross-sectional	High-burden PVC	66	64 ± 16	38 (58%)	24-hour Holter and 12-lead
Agarwal 2015 [69]	US	Observational	Baseline stroke (–)	24,460	64 ± 9	10,990 (45%)	12-lead
Dukes 2015 [70]	US	Cohort	Cardiac disease (–)	1,139	Median 70 (68 – 74)	482 (42%)	24-hour Holter
Lin 2015 [71]	Taiwan	Observational	Apparently normal hearts with symptoms	3,351	58 ± 19	1,910 (57%)	24-hour Holter
Bas 2016 [72]	US	Observational	Cardiac diseases (+/–)	107	50 ± 15	58 (54%)	24-hour Holter
Nguyen 2017 [73]	US	Cohort	Cardiac disease (–)	18,910	Range 49 – 80	NR	12-lead

Study	Country	Study Design	Patient Population*	Sample Size	Mean Age (± SD), years	Male, n (%)	ECG Data Collection of PVCs
Agarwal 2017 [74]	US	Longitudinal	Cardiac disease (–)	16,807,903	50 ± 19	7,091,590 (42%)	NR
Lin 2017 [75]	Taiwan	Observational	Apparently normal hearts with symptoms	5,778	63 ± 18	3,352 (61%)	24-hour three-channel Holter (unspecified)
Sheldon 2017 [76]	US	Observational	Frequent idiopathic PVCs referred for ablation	100	52 ± 15	53 (53%)	24-hour Holter
Aviles-Rosales 2018 [77]	Mexico	Observational	Cardiac disease (+)	1,442	56 ± 14	1,179 (82%)	Continuous 12-lead (treadmill and recovery)
Bière 2018 [78]	France	Observational	Probability of CAD	343	67 ± 12	235 (68.5%)	Continuous 12-lead (treadmill and recovery)
Li 2018 [79]	China	Observational	ICD (+)	416	Median 64 (55 – 73)	314 (76%)	ICD for 60-days
Ruwald 2018 [80]	US, Canada, Europe (multicenter)	Randomized controlled trial	CRT-D (+)	698	64 ± 10	520 (74%)	24-hour Holter
Su 2018 [81]	China	Observational	Cardiac diseases (+/–)	342	57 ± 15	153 (45%)	24-hour Holter
Altıntaş 2019 [82]	Turkey	Cross-sectional	Idiopathic PVC	341	Median 50 (38 - 60)	172 (50.4)	24-hour Holter and 12-lead

Study	Country	Study Design	Setting	Patient Population	Sample Size	Mean Age (± SD), years	Male, n (%)	ECG Data Collection of PVCs
In-Hospital (by year earliest to most recent)								
Schulze 1977 [83]	US	Observational	Non-ICU	AMI	81	Mean 56	61 (75%)	24-hour Holter
Moss 1979 [84]	US	Observational	CCU	AMI	940	54 ± 8	770 (82%)	6-hour Holter
Rengo 1979 [85]	Italy	Observational	Non-ICU	Cardiac disease (+/–)	232	Mean 64	155 (67%)	12-lead
Sclarovsky 1979 [86]	Israel	Observational	CCU	AMI	114	NR	NR	12-lead
Lichtenberg 1980 [87]	US	Observational	Cath	AMI	81	NR	NR	Leads I, aVF, V1 oscilloscopic recorder
Dash 1983 [88]	US	Observational	Cath	Cardiac disease (+)	58	NR	NR	2-minute multiple lead (unspecified)
Bigger 1984 [89]	US	Observational	CCU	Post MI	819	Under 70	NR	24-hour leads V1 and V5 Holter
Kostis 1987 [90]	US	Randomized controlled trial	CCU	AMI	1,640	NR	NR	24-hour two-channel Holter (unspecified)

Study	Country	Study Design	Setting	Patient Population	Sample Size	Mean Age (± SD), years	Male, n (%)	ECG Data Collection of PVCs
In-Hospital (by year earliest to most recent)								
Minisi 1988 [91]	US	Observational	Non-ICU	Post MI	128	55 ± 10	91 (71%)	24-hour Holter
Rasmussen 1988 [92]	Denmark	Observational	CCU	Post MI	51	Median 66 (24 - 89)	33 (65%)	24-hour two-channel Holter (unspecified)
Moulton 1990 [93]	US	Observational	Non-ICU	Cardiac disease (+)	100	60 ± 2	NR	12-lead
Wilson 1992 [94]	US	Randomized controlled trial	CCU	AMI	2,456	NR	NR	24-hour two-channel Holter (unspecified)
Fujimoto 1994 [95]	Japan	Observational	Non-ICU	Cardiac disease (+/–)	100	58 ± 16	59 (59%)	Holter (unspecified)
Statters 1996 [96]	UK	Observational	CCU	AMI	680	58 ± 9	537 (79%)	24-hour leads II and modified CM5 Holter
Vaage-Nilsen 1998 [97]	Denmark	Randomized controlled trial	Non-ICU	Post MI	250	60 ± 9	187 (75%)	12- to 24-hour Holter
Dabrowski 2000 [98]	Poland	Observational	Non-ICU	Post MI	148	61 ± 9	127 (86%)	12-lead
Im 2018 [99]	South Korea	Observational	Non-ICU	Cardiac disease (–)	373	60 ± 16	168 (45%)	24-hour Holter
Yamada 2019 [100]	Japan	Observational	Non-ICU	Cardiac disease (+)	435	65 ± 14	271 (62%)	24-hour Holter
Other Settings (by year earliest to most recent)								
Fries 2003 [101]	Germany	Observational	NR	ICD (+)	38	58 ± 14	33 (87%)	ICD (unspecified)
Engel 2007 [102]	US	Observational	Both In- and Outpatient	AF or paced rhythm (–)	45,401	56 ± 15	40,861 (90%)	12-lead
Kanei 2008 [103]	US	Observational	NR	Frequent PVCs; SHD (–)	108	50 ± 16	34 (31%)	24-hour Holter

***Patient Population:** (+) and (-) indicates whether the study populations do or do not have the listed criteria. For example, “cardiac disease (+)” means the study participants have cardiac disease, and “cardiac disease (+/-)” means the study includes participants with and without cardiac disease.

Abbreviations: 12-lead = standard 12-lead ECG; AF = atrial fibrillation; AMI = acute myocardial infarction; CAD = coronary artery disease; Cath = cardiac catheterization lab; CCU = coronary care unit; CHD = coronary heart disease; CRT-D = cardiac resynchronization therapy with defibrillator; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; NR = not reported; PVC = premature ventricular complex; SD = standard deviation; SHD = structural heart disease; UK = United Kingdom; US = United States.

Table 2.3 – Diagnostic value of PVCs during early phase of acute MI.

Study	Diagnostic Value	PVC Criteria	Notes
Sclarovsky 1979[86]	Location of MI	- RBBB pattern in V1 and RAD is indicative of anterior wall AMI. - RBBB pattern in V1 and LAD is indicative of infero-posterior wall AMI.	PVCs were considered acute when they appeared only during the first 48-hour of the acute phase of the infarction. Using standard 12-lead ECG, the origin of the PVCs was determined primarily based on right- versus left-bundle branch block pattern in V1 and axis deviation criteria in leads II, III, and aVF
Lichtenberg 1980[87]	Location of MI	- Lead V_1: a Q wave of ≥0.04 sec and a Q/R ratio >0.1 may detect anterior MI (sensitivity 0.36, specificity 0.87, and PPV 0.67). - Lead aVF: a Q wave of ≥0.02 sec may detect abnormal inferior wall motion (sensitivity 0.22, specificity 0.94, and PPV 0.70).	PVCs induced by catheter stimulation in lead V1 for the diagnosis of anterior wall MI, and lead aVF for the inferior wall MI
Dash 1983[88]	Diagnosis of MI	Morphologic analysis of PVC has 29% sensitivity but high specificity (97%) and PPV (86%) for the diagnosis of MI.	Pre-defined PVC criteria for MI diagnosis: a qR or qRS configuration with a q-wave duration of at least 0.04 second

Abbreviations: ECG = electrocardiogram; LAD = left axis deviation; MI = myocardial infarction; PPV = positive predictive value; PVC = premature ventricular complex; RBBB = right bundle branch block.

Table 2.4 – Prognostic significance of PVC based on settings, patient populations, and PVC criteria.

Setting	Patient Population*	PVC Criteria	Prognostic Outcome	Follow-Up (y)†
Outpatient	Without cardiac disease	Presence of any	- AF[50, 73]	10 – 15
			- Stroke[50, 57, 69]	6 – 15
			- LV dysfunction (decreased LVEF, HF)[56, 73, 74]	5 – 15
			- Ablation outcome (≥80% reduction of baseline PVC burden)[76]	5.6 mo
			- Develop IHD[37, 54]	10 – 14
			- Mortality (all-cause, sudden death, sudden cardiac)[38, 45, 52, 54, 67]	7.5 – 14
		Frequent/high burden	- LA dysfunction[63, 65]	NR
			- LV dysfunction (decreased LVEF, CMP, HF)[49, 51, 58-60, 68, 70, 82]	1.2 – 8
			- Mortality (all-cause mortality, cardiac death)[38, 47]	4.4 – 8
		During exercise testing	- Myocardial ischemia[46]	4.6
			- CV death[41, 43]	15 – 23
			- All-cause mortality[43]	15
	With cardiac disease or cardiac symptoms‡	Presence of any	- AF, TIA[71]	10
			- Arrhythmic events§[39]	2.2
			- HF[71, 75]	10
			- Hospitalization[71, 75]	10
			- Combined adverse outcomes (ACS, stroke, CHF, all-cause mortality)[61]	2
			- Mortality (all-cause, sudden death, sudden cardiac death)[33, 35, 40, 71, 75]	2 – 10
		Frequent/high burden	- LV dysfunction (decreased LVEF, CMP)[48, 55, 66]	8 mo
			- Arrhythmic events§[44, 79, 80]	2.2 – 2.8
			- Mortality (all-cause and CV)[79, 80]	2.2 – 2.8
		During exercise test	- Arrhythmic events§[36, 77]	14
			- Mortality (all-cause and CV)[53, 77, 78]	4.5 – 15
In-hospital	Without cardiac disease	High burden	- Stroke-like symptoms[99]	3.5
	With cardiac disease or cardiac symptoms*	Presence of any	- Decreased LVEF[93]	NR
			- Arrhythmic events§[98]	3.1
			- Mortality (all-cause, CV, sudden death)[83, 84, 90, 92, 94]	7 mo – 3 y
		Frequent	- CAD severity[91]	NR
			- Cardiac event (ICD therapy, re-hospitalization)[100]	2.3
			- Mortality[89, 96, 97]	1 – 1.8

* Without cardiac disease category includes apparently healthy individuals, without ischemic/structural heart disease, idiopathic PVCs

† Represents the range of mean/median years of follow-up period across studies for each prognostic outcome. References not reporting the follow-up period: [36, 44, 48, 55, 62, 63, 65, 82, 91, 93]. Details on follow-up period for all studies are available in Supplement Table 2.C.

‡ Cardiac symptoms = syncope, lightheadedness/near-syncope, dizziness, palpitations, angina, and/or dyspnea.
§Arrhythmia event: sustained VT, VF, or sudden cardiac death.

Note: studies with no details on settings, or studies that included participants with and without cardiac disease are not included in the table. Study setting grouping is similar to that in Table 2.

Abbreviations: ACS = acute coronary syndrome; AF = atrial fibrillation; CAD = coronary artery disease; CV = cardiovascular; CHF = congestive heart failure; CMP = cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; NR = not reported; PVC = premature ventricular complex; TIA = transient ischemic attack

Supplement Table 2.A – Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist for a scoping review examining the clinical and prognostic significance of premature ventricular contractions (PVCs) in adults across care settings.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4 – 6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6; Table 1
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6 – 7
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	7; Additional File 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7 – 8
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	8
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	8
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9; Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9 – 11; Table 2

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not Applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9 – 11; Additional File 3
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	11 – 19
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	19 – 26
Limitations	20	Discuss the limitations of the scoping review process.	26
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	27
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	29

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplement Table 2.B – Literature search strategy and results from four bibliographic databases.

Database	Query	Results
CINAHL	(MH "Premature Ventricular Contractions") *Filters: Abstract Available, Academic Journals, English.*	803
Embase	('heart ventricle extrasystole'/exp OR 'heart ventricle extrasystole') AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [clinical study]/lim	3,696
PubMed	premature ventricular contraction[MeSH] *Filters: Humans, English.*	1,750
Web of Science Core Collection	((premature ventricular contraction) OR (ventricular extrasystole) OR (ventricular extra systole) OR (premature ventricular beat)) *Filters: Document types (Articles), English.*	3,814

Supplement Table 2.C – Methodology and key findings of the included studies.

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
Chiang 1969 [33]	Determine the relationship of premature beats to the subsequent morbidity and mortality from CHD. Outcome variable:	General population with premature systoles on the ECG recording (Tecumseh Community Health Study)	6 year	Chi-square	Not provided	Incidence rate of sudden death among those with preexistent PVCs was higher compared to those without PVCs.
Desai 1973[34]	Define the effect on mortality of PVC present in a routine ECG and if there were different risks in the various subgroups within the total PVC population.	Patients with one or more PVC om standard 12-lead ECGs	3.5 years (3 - 4 years)	Not provided	Not provided	- The ratio of deaths in the PVC group compared to the control group was 1.6 to 1. - In patient with CVD, mortality rate was higher among those with PVC compared to those without PVC.
Ruberman 1977 [35]	Assess the role of PVCs in influencing mortality of coronary patients.	Male, insured, had had at least one myocardial infarction or angina	Up to 4 years (mean 24.4 months)	Peto-Pike chi-square; Cox's regression	Age ≥65, heart rate ≥90, duration of heart disease, treatment with diuretics, ST-segment depression, CHF, and complex PVCs.	- Presence of baseline complex PVCs was associated with higher risk of SCD (RR 2.8) and all-cause death (RR 1.9). - At the 3-year point, the cumulative probability for SCD was higher among men with R-on-T or runs compared with men with bigeminy or multiform PVCs (RR 2.3).
Schulze 1977 [83]	Evaluate the relative role of PVC and depressed LVEF following AMI in predicting mortality.	Patients who were discharged from Coronary Care Unit and were diagnosed with AMI. Exclusion: if MI occurred as a complication of surgery or catheterization; had documented malignancy or end-stage renal or hepatic disease; technical problems made completion of the study not feasible.	2 - 16 months (mean 7 months)	Unpaired t-test/chi-square; Life Table survival analysis	Not provided	Life table survival analysis showed that patients with PVC class III – V (Lown criteria) had higher sudden death rate compared to those with PVC class 0 – II.

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
Boudoulas 1979 [36]	Define the prevalence of PVC in ambulatory patients and the characteristics of PVCs predisposing to VT or VF.	Patients with more than occasional PVC (>1 /min) detected by exercise testing or 24-hr monitoring, who were suspected to have dysrhythmias and were referred for ambulatory monitoring and exercise testing to define the nature of dysrhythmias.	NR	Student t-test; chi-square	Not provided	- The frequency of VT/VF, or both, was greater in patients with late-PVC compared with early- and midcycle-PVC. - Patients with frequent multiform PVC had a greater frequency of VT or VF compared with patients with uniformed PVC.
Moss 1979 [84]	Explore the role of both simple and complex PVCs as they relate to sudden and nonsudden cardiac death throughout both the early and late posthospital phases of myocardial infarction.	Patients younger than 66 years of age who entered coronary care units with either definite or probable AMI and who survived hospitalization.	Average 36 months (1-60 months)	Wilcoxon-Breslow; Mantel-Haenszel	Age >55; education <10th grade; social class IV and V; history of cigarette smoking; NYHA class II, III, IV; history of angina; history of MI; posterior MI; anterior MI; LV dysfunction.	Complex PVCs were associated with increased cardiac death rate; but did not discriminate sudden from non-sudden death.
Rengo 1979 [85]	Assess if ECG patterns of PVCs were related to an increased risk of sudden death.	Patients with one or more PVCs on standard 12-lead ECG on hospital admission	30 months	Chi-square	Not provided	Patients with PVC coupling interval of <360 msec had a higher rate of sudden death compared to patients with coupling interval of >360 msec.
Sclarovsky 1979 [86]	Investigate the relationship between the ECG location of the AMI and the origin of the PVCs, and to study their prognosis in relation to serious arrhythmias.	Patients with AMI in whom the diagnosis of the origin of PVCs was obtained. Exclusion: receiving digitalis, beta-blockers, anti-arrhythmic drugs, diuretics, and those with electrolyte disturbances.	NR	Chi-square; Fisher's exact	Not provided	The origin of the acute PVCs was highly correlated with the location of AMI.
Lichtenberg 1980 [87]	Determine the validity of the PVC QR pattern in the diagnosis of MI	Patients undergoing cardiac catheterization	NR	Chi-square	Not provided	- PVC in V_1 with a Q ≥0.04 sec and a Q/R ratio >0.1 had a greater applicability in the detection of anterior MI (sens 0.36, spec 0.87, and predictive value 0.67).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
						- Presence of a wide Q PVC of ≥0.02 sec in aVF was correlated with abnormal inferior wall motion (sens 0.22, spec 0.94, predictive value 0.70).
Rabkin 1981 [37]	Examine the relationship between the occurrence and characteristics of PVCs and subsequent development of IHD in men without clinically apparent heart disease.	Individuals from community without clinical manifestation of ischemic heart disease who had ventricular ectopic beats.	10.8 ± 0.4 (± 1 SEM)	Chi-square; Fisher's exact; Life Table method	Age groups	Presence of PVCs was correlated with patient outcomes: total IHD (RR 1.80), MI (RR 1.43), sudden death (RR 4.18), coronary insufficiency or suspected MI (RR 1.93), and angina pectoris (RR 1.41).
Dash 1983 [88]	Evaluate the value of VPB analysis in the diagnosis of old MI.	Patients who undergone diagnostic cardiac catheterization and had PVCs on ECGs recorded the day before catheterization	NR	Chi-square with Yate's correction	Not provided	- Morphologic analysis of PVC had a low sensitivity (29%) but high specificity (97%) and predictive value (86%) for the diagnosis of MI. - Sinus beats analysis had higher sensitivity (52%) than PVC morphologic, but with similar specificity (97%) and predictive value (92%).
Bigger 1984 [89]	Define the interrelationships of frequency and repetitiveness of PVCs, LV dysfunction, and mortality.	Patients who had acute myocardial ischemia and were under 70 years of age. Exclusion: life-threatening comorbity; lived too far away from participating centers for follow up.	Average 22 months (12 - 36 months)	Laird-Oliver survivorship analysis	LVEF, PVC frequency categories, and PVC repetitiveness categories.	- Patients with PVC ≥3/hr had a higher risk for dying compared to those with PVC <1/hr (HR 2). - Patients with run PVC had a higher risk for dying compared to those with no repetitive PVC (HR 1.9). - ≥3 PVCs/hr was an independent predictor of higher risk for dying >6 months of MI (HR 3.7 vs HR 1.2 ≤6 months).
Abdalla 1987 [38]	Examine the relation between PVCs and the subsequent SCD in apparently healthy	Apparently healthy patients included in the Multiple Risk Factor Intervention Trial (MRFIT) without	7.5 years	Cox proportional hazard	Age, SBP, serum cholesterol level, and cigarette smoking	Presence of any PVC (RR 3.0 [95% conf. interval (CI) 1.3-7.3]), frequent PVCs (RR 3.8 [95% CI 1.4-10.9]), and frequent/complex PVCs (RR 4.2

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	middle-aged men (part of the Multiple Risk Factor Intervention Trial [MRFIT]).	previous history of myocardial infarction or DM, or ECG abnormalities other than PVCs.				[95% CI 1.6-10.7]) were significantly associated with SCD.
Kostis 1987 [90]	Define the usefulness of various definitions of ventricular ectopic activity in predicting the mortality rate among survivors of acute myocardial infarction.	Patients with a definite acute MI who had 24 hour ambulatory ECG 2 to 21 days after admission to a coronary care unit. Exclusion: history of severe congestive heart failure, bronchial asthma as an adult, marked bradycardia and life-threatening illness other than coronary artery disease, those who had or were likely to have aortocoronary bypass surgery and those who were taking or were likely to take a beta-adrenergic blocking agent (part of Beta Blocker Heart Attack Trial, BHAT).	25 months (12 to 40 months)	Student's t-test and logistic regression	Age, employed, current cigarette smoker, prior MI, diastolic BP, systolic BP, heart rate, hematocrit, serum cholesterol, elevated LDH, anteriorly located infarction, ST depression, major LV hypertrophy, cardiothoracic ratio, experienced complications during hospitalization, history of CHF, history of diabetes, beta-blocker use prior to the study period, antiplatelet use at entry, digitalis use at entry, antiarrhythmic drug use at entry, Holter characteristics from 24-hour Holter.	- Ventricular ectopic activities were significant predictors of mortality (adjusted OR ranging from 1.003 to 2.23). - Presence of multiform PVC was an independent predictor for atherosclerotic sudden death (OR 2.43). - Presence of a mean PVC ≥10/h was independently associated with atherosclerotic non-sudden death (OR 2.25) *NOTE:* Ventricular ectopic activities include PVC/hr, couplet/hr, and presence of mean PVC/hr >0, mean PVC/hr ≥10, and multiform PVCs.
Minisi 1988 [91]	Examine association between the extent of coronary artery disease and	Patients 6 days after MI. Exclusion: >74 years, women with childbearing potential, malignancies,	NR	Ordinal regression analysis	Not provided	- Both PVC frequency and LVEF were independently important predictors of CAD severity by

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	frequency of PVCs in survivors of MI	significant and/or potentially lethal organ system disorders (other than cardiac), severe hypertension (SBP ≥180 mm Hg or DBP ≥120 mm Hg), cardiogenic shock, significant non-CAD, glaucoma, and symptomatic urinary tract obstruction in males.				vessels stenosis and jeopardy score. - The median PVC frequency was 1/hr, 0.6/hr, and 6/hr in zero to one-, two-, and three-vessel CAD, respectively (zero to one- and two-V CAD vs three-V CAD p <0.01, one-V CAD vs two-V CAD p=NS)
Rasmussen 1988 [92]	Define patients at increased risk of death in the early phase after MI based on the ventricular ectopic activity in 24-hour ECG recordings.	Patients surviving initial stage of acute MI. Exclusion: atrial fibrillation and chronic treatment for ventricular dysrhythmias	20 - 27 months	Wald test; Kaplan-Meier survival analysis	Age, presence of PVC, and heart failure.	- All-cause mortality was significantly higher in the group with than in that without complex PVC. - Complex PVC was associated with increased risk of mortality (relative risks of 3.6).
Moulton 1990 [93]	Characterize the relationship between PVC morphology and myocardial disease state.	Consecutive patients undergoing cardiac catheterization, echocardiography, or nuclear ventriculography; have at least 1 PVC present on 12-lead ECG.	NR		Not provided	- Patients with type II PVC had significantly higher EDVI and lower EF compared to patients with type I PVC. - PVC QRS morphology (type I vs type II) could classify EDVI (> or ≤90 ml/m2) and LVEF (< or ≥50%), with sen 92%, spec 80%, and accuracy of 86%. *NOTE:* Type I PVC: QRS complexes with either smooth and uninterrupted contour or narrow (<40 msec) notches. Type II PVC: QRS that is wide (≥40 msec) notches or shelves.
Wilson 1992 [94]	Study the independent contribution of ventricular ectopic activity in predicting mortality (part of Beta Blocker Heart Attack Trial, BHAT)	Patient with definite AMI who had <2PVC/h. Exclusion: history of severe CHF, marked bradycardia, life-threatening illnesses other than CAD, those who had bronchial asthma as adults, those who had or	25 months (range 11 - 40 months)	Logistic regression	Age, employment status, smoking, prior myocardial infarction, diastolic blood pressure, hematocrit, elevated LDH, ST depression (on	Patients with an average of 0.5 or more but <1PVC/h had significantly increased mortality by 190% than patients who had no PVC at all, and by 95% than patients who had <0.5 PVC/h (p<0.001).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		were likely to have aortocoronary bypass surgery, patients who were taking or were likely to take beta blockers.			ECG), cardiothoracic ratio (from x-ray film), hospital complications, CRF, diabetes, beta-blocker use, anti-platelet use, antiarrhythmic drug use.	
Fujimoto 1994 [95]	Clarify the relationship between characteristics of their PVCs and the patients' prognosis.	Patients with frequent PVCs (>1,000 beats/day). Exclusion: patients with acute heart disease (acute MI, myocarditis or pericarditis) or sustained ventricular tachycardia	4 years	One-way ANOVA; unpaired t-test; chi-square	Not provided	- Lown grades 4a and 4b were more frequent in patients with underlying diseases who survived and those suffered cardiac death, compared to that in patients with idiopathic PVC and survived ($p<0.05$). - The mean coupling interval was significantly longer in those who suffered cardiac death than that in patients with idiopathic PVC and survived).
Statters 1996 [96]	Compare the predictive value of PVCs in survivors of AMI who have and have not received thrombolytic therapy.	Patients who were admitted to coronary care unit and diagnosed with AMI. Exclusion: patients who had noncardiac diseases likely to influence mortality, important nonischemic cardiac disease, or a history of cardiac surgery or permanent pacemaker insertion.	1 year	Kaplan-Meier; Wilcoxon-Breslow	Not provided	The highest VPC frequency for the dichotomy of patients into high- and low-risk groups for mortality was 25 VPCs/hour after thrombolysis, but 10 VPCs/hour for patients without thrombolysis.
Dabrowski 1998 [39]	Determine whether the evaluation of QT dispersion in PVC (QTd-V) may be used to identify patients at high risk of	Patients had at least one PVC on routine 12-lead ECG prior to 24h Holter recording, who complained syncope, dizziness, palpitations, and angina.	26 ± 19 months	Kaplan-Meier; cox proportional hazard	Qt dispersion in PVCs ≥100 ms, LVEF <40%, underlying heart disease, QRS duration of PVCs >150ms, and	- PVC-QT dispersion (QTd-V) was greater in patients with arrhythmic events than that in those without the events. - QTd-V ≥ 100ms and LVEF < 40% were independent predictors of arrhythmic events.

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	subsequent arrhythmic events.				complete bundle branch block	<u>*NOTE:*</u> Arrhythmic events: sustained ventricular tachycardia, ventricular fibrillation or sudden cardiac death.
Vaage-Nilsen 1998 [97]	Evaluate the prognostic implications of ventricular ectopy recorded by 24-h Holter monitoring following (in conjunction with a randomized trial [Danish Verapamil Infarction Trial II, DAVIT II).	Patients with AMI <76 years of age. Exclusion: patients with calcium antagonists or beta blockers for angina pectoris, hypertension, or arrhythmias; heart failure not controlled on furosemide, second- or third-degree AV block; hypotension or other severe diseases; additional exclusion for this study included permanent atrial fibrillation and treatment with antiarrhythmic drugs or digoxin.	615 – 1702 days	Kaplan-Meier; multivariate cox analysis	Age, previous AMI, history of angina pectoris, intermitten claudication, index AMI involving anterior and inferior or posterior wall, resting heart rate, left bundle-branch or IV block on ECG, and heart failure.	>10 VPCs/hr 1 week (HR 2.81, 95%CI 1.55-5.08) and 1 month (HR 3.13, CI 1.46-6.69) after acute MI independently predicted long-term mortality.
Dabrowski 1999 [40]	Evaluate whether dispersion of repolarization calculated from VPBs on a 12-lead ECG offers improved risk stratification in patients after myocardial infarction.	Patients had PVCs on a 12-lead ECG recorded at least 4 weeks post-MI	38 ± 17 months	Cox proportional hazard	Age ≥60 years, complete bundle branch block, LVEF <40%, JT dispersion ≥100 ms, QT dispersion ≥100 ms, and R on T index of PVCs <1.	- QTd-V (HR 3.89), JTd-V (HR 2.77), and "R-on-T" index of PVCs<1 (HR 1.89) were predictors of mortality (univariate analysis). - QTd-V ≥100 msec was an independent predictor of mortality (HR= 3.1041; 95% CI= 1.7–9.4).
Dabrowski 2000 [98]	Assess prognostic significance of QTd-V and QTd-S in post infarction patients with PVCs on a routine ECG.	Patients after MI who exhibited PVCs on a standard 12-lead ECG, referred for 24-hour ECG monitoring due to symptoms (syncope, dizziness, palpitations, and angina). Exclusion: treated with class I or III antiarrhythmic drugs at presentation, patients with	35 ± 17 months	Kaplan-Meier; cox proportional hazard	Age ≥60 years, time between MI - follow up <5 mo, LVEF <40%, QTd-S ≥100 ms, QTd-V ≥100 ms.	- QTd-V and QTd-S were significantly greater in patients with arrhythmic events than that without arrhythmic events. - Patients with QTd-V ≥100 msec had higher arrhythmic event rates compared with those with QTd-V <100 msec. - QTd-V ≥100 msec was an independent predictor of

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		atrial fibrillation or flutter, complete BBB, or pacemaker rhythm, and patients with unmeasurable QT intervals of sinus beats or PVCs in > ECG leads.				arrhythmic events (HR 4.27, 95%CI 2.4 - 11.1). *NOTE:* Arrhythmic events: sustained VT, VF, or sudden cardiac death.
Jouven 2000 [41]	Assess the long-term outcome for asymptomatic persons with exercise-induced PVC.	Men aged 42 to 53 years who gave consent to undergo ECG and physical examination and exercise test, and free of CHD. Exclusion: Exercise testing exclusion: if individuals had known or suspected cardiovascular disease of any grade or cause, a systolic blood pressure above 180 mmHg at rest, or any abnormality on 12-lead standard ECG at rest according to the Minnesota code.	23 years	ANOVA; logistic regression; cox proportional hazard	Age, body-mass index, heart rate at rest, systolic blood pressure, tobacco use, level of physical activity, presence or absence of diabetes, total cholesterol level, and presence or absence of PVDs before exercise and during recovery from exercise.	Occurrence of frequent PVC during exercise test independently associated with an increased risk of death from cardiovascular causes (RR 2.53, 95% CI 1.65-3.88)
Hatanaka 2002 [42]	Evaluate the relationship between PVC patterns on routine ECG and heart diseases.	Individuals who underwent clinical examination for heart disease and had one or more PVCs on routine 12-lead ECG. Exclusion: Based on medical history: subjects with atrial fibrillation (valvular heart disease, lone atrial fibrillation, ischemic heart disease, cardiomyopathy), conduction disturbance (AV block, LBBB, RBBB, Wolff-Parkinson-White syndrome), who were taking antiarrhythmic drugs or who showed poorly recorded ECG tracing.	NR	Chi-square with Bonferroni correction	Not provided	- Individuals with LBBB PVC morphology without axis deviation had a lower incidence of having heart disease than those with LBBB morphology with LAD, RBBB morphology with LAD and without axis deviation. - Asymptomatic individuals with the LBBB pattern without axis deviation had a lower incidence of heart disease than those with other PVC patterns.

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
Fries 2003 [101]	Determine the clinical significance of the R-on-T phenomenon in ICD recipients	Patients with ICD and had recorded spontaneous tachyarrhythmias	NR	Mann-Whitney U; chi-square	Not provided	R-on-T PVCs rarely induced sustained VT in patients with ICD. However, R-on-T VTs occurred particularly in patients with CAD and more often, the VTs are polymorphic.
Morshedi-Meibodi 2004 [43]	Assess prognostic impact of exercise-induced PVCs (EiPVCs) on a large, community-based sample of young to middle-aged men and women free of overt CVD.	Framingham Offspring Study participants who underwent routine treadmill test during their second examination (4 years after the initial examination). Exclusion: Individuals with any prevalent CVD, valvular heart disease, COPD, usage of cardiac glycoside or blocking agents, or presence of PVCs at rest.	15 years (SD not provided)	Cox proportional hazard	Age, hypertension, smoking, total/HDL cholesterol, diabetes, resting heart rate, peak heart rate, duration of exercise, and ischemic ST-segment response.	- EiPVC was associated with increased all-cause mortality rates (adjusted hazard ratio, 1.86 95% CI 1.24-2.79 for infrequent EiPVCs, and 1.71, 95% CI 1.18-2.49 for frequent versus none). - Frequent EiPVC was associated with >3-fold increased risk for cardiovascular death (HR, 3.45; 95% CI 1.69 - 7.07).
Carrim 2005 [44]	Examine relationship between mean frequency of PVCs and a predisposition to malignant ventricular arrhythmias in a group of patients who had received ICD devices.	Patients with an implantable cardioverter defibrillation (ICD) device for underlying ischemic or non-ischemic cardiac pathology, with available single and run PVC counts	NR	Mann-Whitney U; chi-square	Not provided	In patients with IHD, the frequency of single-PVC and run-PVC were significantly higher in those with VT/VF than that without VT/VF.
Massing 2006 [45]	Estimate the magnitude of PVC-associated risk for coronary heart disease and mortality among patients without history or clinical evidence of CHD at the time PVCs were detected.	Participants from general populations (ARIC Study) without CHD at the baseline. Exclusion: Participants with cardiac rhythm disturbances (WPW syndrome, AF/flutter, wandering atrial pacemaker, SVT).	>10 years	Proportional hazard	Age, race, gender, education, hypertension status, systolic blood pressure, diabetes status, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum potassium and magnesium levels,	Risk for fatal CHD and any death were higher among those with PVCs compared with those without PVCs, regardless of the presence of CHD at baseline (No CHD group: RR 2.14, 95%CI 1.46-3.13, RR 1.48, CI 1.25-1.75, respectively; with CHD group: RR 2.12, CI 1.39-3.22, 1.74, CI 1.28-2.36, respectively).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
					cardiac rate, and medication use.	
Meine 2006 [46]	Quantify the incidence of recovery PVCs and correlate this finding to mortality and presence of ischemia in patients referred for exercise stress testing.	Patients who underwent cardiac catheterization within 180 days of a treadmill stress test. Exclusion: Patients with any valvular or congenital heart disease or heart failure symptoms and currently not taking antiarrhythmic medications, and those with uninterpretable ECG due to a paced rhythm at rest.	Median 4.6 years (max 10 years)	Logistic regression; Kaplan-Meier; cox proportional hazard	History of hypertension, Charlson's co-morbidity, carotid bruits, cerebrovascular disease, peripheral vascular disease, diabetes, race, gender, third heart sound, age, sums stress, difference, and rest scores, previous coronary bypass, and 3-vesel CAD.	PVCs during recovery of stress test significantly predicted with myocardial ischemia (OR 1.27, 95% CI 1.04-1.56)
Sajadieh 2006 [47]	Evaluate the prognostic significance of VPCs in apparently healthy population.	Apparently healthy middle-aged and elderly population. Exclusion: 1) Manifest ischemic heart disease manifest ischemic (history of AMI, coronary revascularization, or angina pectoris; (2) manifest other cardiac diseases (CHF, valvular heart disease, congenital heart disease, atrial fibrillation or flutter, or medical treatment for any heart disease; (3) history of stroke; (4) left bundle branch block, significant Q waves, and ST depression 1.0 mm; and (5) other significant or life-threatening diseases (cancer, acquired immune deficiency syndrome,	53 months (51 - 55 interquartile)	Kaplan-Meier; cox proportional hazard	Age, gender, blood pressure, smoking, diabetes mellitus, total cholesterol, body mass index, physical activity level, and silent ischemia.	- Frequent PVC (≥30/h) was a significant predictor of combined event (HR 2.46, 95% CI 1.29 - 4.68) and CV events (HR 2.85, 95% CI 1.16 - 7.0). - Men with frequent PVCs of ≥30/hr (HR 3.15; 95% CI 1.57 - 6.30), and individuals with Framingham risk score of greater than average with frequent PVCs of ≥30/hr (HR 2.53; 95% CI 1.16 - 5.54), had higher risk for the combined events. *NOTE:* Combined events = all-cause mortality or first AMI; Cardiovascular events = CV death or AMI.

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		cirrhosis hepatis, renal insufficiency requiring dialysis, or chronic lung disease requiring home oxygen therapy).				
Engel 2007 [102]	Confirm the significance of PVCs and analyze the interaction between heart rate and PVCs.	Consecutive patients who obtained ECGs for any reason at the facility during study period. Exclusion: Patients with atrial fibrillation and paced rhythms.	5.5 years	Kaplan-Meier; cox proportional hazard	Age, gender, abnormal/normal ECG classification, and in- or outpatient status.	Presence of any resting PVCs was an independent predictor of mortality (HR 2.0; 95% CI 1.1–2.8) and CV mortality (RR 1.61, 95% CI 1.44–1.80).
Topaloglu 2007 [48]	Examine the effects of repetitive monomorphic PVCs on LV diastolic function.	Patients younger than 50 years of age who had symptoms of palpitations, dyspnea, or fatigue lasting for more than 1 year, in whom RVOT-PVCs (≥1000 ectopic beats/day) but with a normal LV systolic function. Exclusion: Significant obstructive CAD, presence of VT or atrial tachyarrhythmias, or history of thyroid disease, diabetes mellitus, and hypertension.	NR	Multiple logistic regression	Age, total PVC count, LVEF, LVEDd, and LVESd.	Each 1% increment in rate of daily PVCs was found to be associated with a 1.185 times increased risk of impaired LV relaxation (p=0.023).
Kanei 2008 [103]	Describe the prevalence and predictors of LV dysfunction in patients with frequent RVOT PVCs.	Patients with frequent (≥10 PVCs per hour) RVOT PVCs. Exclusion: Patients with sustained supraventricular tachycardia, atrial fibrillation, or a pacemaker; also with history of ischemic heart disease, structural heart disease, LV dysfunction with segmental wall motion abnormality on echocardiography, or with other apparent cause of LV	NR	Logistic regression	Not provided	There was a higher prevalence of LV dysfunction among patients with RVOT PVCs >10,000/24 hr compared to those with <1,000/24hr and those with 1,000-10,000/24h (p=0.02).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		dysfunction (i.e., alcohol, HIV).				
Niwano 2009 [49]	Clarify the prognostic significance of frequent PVCs in asymptomatic or less symptomatic patients with a normal LV function.	Patients with frequent PVCs (>1000 beats/day) originating from RVOT or LVOT without any detectable heart disease.	5.6 ± 1.7 years	One-way ANOVA	Age, initial LVEF, PVCs/day, and PVC grade.	- The PVC prevalence was negatively correlated ΔLVEF ($p<0.001$) and positively correlated with ΔLVDd ($p<0.001$). - PVC prevalence was an independent predictor of decrease LVEF by >6% (OR 85.4, $p<0.01$). - PVC prevalence cutoff point of 31,268 beats/day was significantly predicted LVEF reduction (AUC 0.724, sen 0.692, spec 0.929, $p<0.0001$).
Agarwal 2010 [50]	Examine the association between PVCs and incident stroke in middle-aged population.	Participants from general populations (ARIC Study). Exclusion: Participants with cardiac rhythm disturbances (WPW syndrome, AF/flutter, wandering atrial pacemaker, SVT, not sinus rhythm), and missing information on prevalent history of stroke.	15 years	Cox proportional hazard	Age, gender, race, smoking status, heart rate, serum magnesium, serum potassium, prevalent CHD, diabetes, hypertension, LDL lipids, and HDL lipids	- Among individuals with no major risk factors for stroke, presence of PVCs (vs without PVCs) was associated with incident stroke (HR 2.09, CI 1.21-3.58). - Any PVCs (vs no PVC) among non-hypertensive was associated with embolic stroke of non-carotid origin (HR 3.48; CI 1.74-6.95). - Frequency of ≥4 PVCs/min compared to no PVC was associated with incident stroke (HR 2.06, CI 1.24-3.42). - Risks for incident afib among those with any PVCs was higher than that in those with no PVCs (HR 1.56, 95% CI: 1.30, 1.87).
Baman 2010 [51]	Identify the critical PVC burden associated with cardiomyopathy.	Patients without coronary artery disease but with frequent PVCs referred for catheter ablation.	31 ± 20 months post ablation	ROC curve; proportional hazard	Not provided	- High PVC burden was independently associated with PVC-induced cardiomyopathy (HR 1.12, CI 1.08-1.16). - A PVC burden of >24% best separated patients with impaired as compared with preserved LV function (sensitivity 79%, specificity 78%, AUC 0.89).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
Hirose 2010 [52]	Investigate the association on PVCs and cardiac deaths in subjects without cardiovascular disease	Apparently healthy individuals who had baseline 12-lead ECG, without history of MI and stroke (Jichi Medical School (JMS) cohort study).	11.9 years (SD not provided)	Cox proportional hazard	Age, BMI, systolic BP, total cholesterol level, HDL-cholesterol, and blood glucose.	- In CV mortality, age-adjusted hazard ratios (HRs) with PVC were 3.73 (1.16-12.00) for male. - HRs adjusted for multiple variables: 3.98 (1.21-13.00) for male.
Le 2010 [53]	Study the prognostic value of rest PVCs in patients with clinical heart failure referred for exercise treadmill testing.	Patients referred for exercise testing following a clinical presentation of heart failure.	Median 6.2 years (range 5.5-6.7 years)	Kaplan-Meier; cox proportional hazard	Age, beta-blocker use, rest ECG findings, resting and peak HR, rest EF, maximal systolic BP, and exercise capacity.	The presence of rest PVC was associated with a 5.48-fold (HR 5.48, p=0.004) increased risk of CV mortality.
Cheriyath 2011 [54]	Investigate the prospective relation between baseline ectopy and clinical cardiac events in population-based individuals without any history of cardiac disease or stroke.	Participants from general populations (ARIC Study) without coronary heart disease and stroke at baseline.	Median 14 years	Kaplan-Meier; cox proportional hazard	Age, race, gender, education, smoking, BMI, LDL/HDL ratio, DM, hypertension, serum potassium, magnesium, HR, and use of heart rhythm medications.	- Fully adjusted model showed that presence of PVCs was significantly correlated with incident CHD (HR 1.24, 95%CI 1.02-1.50). - Fully adjusted model showed that presence of VPCs was significantly correlated with SCD and fatal CHD (HR [95%CI] 2.09 [1.22-3.56] and 2.18 [1.53-3.12], respectively).
Munoz 2011 [55]	Evaluate whether PVC characteristics are associated with LV systolic dysfunction.	Patients who underwent radiofrequency catheter ablation for frequent and symptomatic PVCs, and had no other identified cause for cardiomyopathy.	NR	Multivariate linear regression	History of palpitations, history of dizziness, PVC burden, nonsustained VT, PVC duration of ≥ 140 msec, fascicular PVCs, and multiform PVC.	- PVCs originating from the RV were associated with reduced LVEF at a PVC burden ≥10%. - PVCs originating from the LV were associated with reduced LVEF at a PVC burden ≥20%. - Independently significant predictors of a reduced LVEF: history of palpitations, presence of NSVT, PVC duration ≥140 msec, and nonfascicular PVCs.
Agarwal 2012 [56]	Examine whether the presence of PVCs on a 2-minute ECG recording is associated with	Participants from general populations (ARIC Study) without prevalent heart failure. Exclusion: Participants with prevalent	15.6 ± 3.8 years	Cox proportional hazard	Age, gender, race, study center, education level, diabetes, systolic blood pressure,	- Presence of PVCs was associated with the incident HF (HR 1.84 (CI 1.41-2.41). - After multivariate adjustment, the HR of HF among those with any

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	incident HF in individuals without prevalent heart failure.	HF, missing information about baseline CHD and incident HF, and cardiac rhythm disturbances (WPW syndrome, AF/flutter, wandering atrial pacemaker, SVT, not sinus rhythm).			hypertension medication intake, LDL and HDL cholesterol, BMI, current smoking, former smoking, pack-years of smoking, amount of ethanol use, heart rate, serum K+, serum Mg++.	VPCs versus no VPCs was 1.63 (1.36-1.96); remained significant after additional adjustment for LV mass (HR 1.59; 1.32-1.92) or medications (beta-blocker, anti-arrhythmic drugs, and calcium channel blockers); and after adjustment for incident CHD as a time-varying covariate (HR 1.71; 1.42-2.08).
Ofoma 2012 [57]	Evaluate the longitudinal relationship between premature cardiac contractions and incident ischemic stroke in general population.	Participants from general populations (ARIC Study). Exclusion: Participants with baseline history of stroke or coronary heart disease and individuals who developed subarachnoid or intracerebral hemorrhage during follow-up.	13 years	Cox proportional hazard	Age, race, gender, BMI, total cholesterol, diabetes, hypertension, smoking, and PAC/PVC predictor.	Among normotensives, multivariable adjusted risk analysis showed that having PVCs was associated with increased risk of incident ischemic stroke (HR 1.69, 95%CI 1.02-2.78).
Yokokawa 2012a [58]	Correlate the symptoms and symptom duration with the presence of cardiomyopathy in patients with frequent PVCs.	Symptomatic and asymptomatic patients with frequent PVCs referred for catheter ablation but without structural heart disease.	95 ± 73 months post ablation	Logistic regression	Gender, PVC burden, duration of symptoms, and presence/absence of symptoms.	PVC burden in asymptomatic patients was an independent predictor of impaired LV function (OR 2.1, 95% CI 1.2-3.6).
Yokokawa 2012b [59]	Determine the impact of the PVC QRS duration on reversible PVC-induced cardiomyopathy (rPVC-CMP).	Patients with frequent idiopathic PVCs referred for PVC ablation. Exclusion: Patients with cardiomyopathy preceding frequent PVCs, presence of delayed enhancement in cardiac MRI, evidence of structural heart disease, and patients with CAD, valvular heart disease, or hypertensive heart disease.	46 ± 33 months	Logistic regression; ROC curve	Male sex, PVC burden, QRS width, epicardial origin of PVC, and symptom duration.	- PVC-QRS width was predictive of rPVC-CMP (OR 1.03 for every 1-msec increase in QRS duration), independent of the PVC burden, symptom duration, sex, and PVC origin. - PVC-QRS cutoff width of ≥150 msec best separated patients with and without rPVC-CMP (AUC 0.66; sensitivity 0.80; specificity 0.52). - Epicardial PVC site of origin was independently associated with rPVC-CMP (OR 2.9; P=.04).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
						- PVC burden was predictive of rPVC-CMP (OR 1.04, p=.02). The PVC burden for developing rPVC-CMP is significantly lower in patients with a PVC-QRS width of ≥150 msec than in patients with a narrower PVC-QRS complex.
Ban 2013 [60]	Determine the ECG and electrophysiological characteristics of frequent PVC-mediated LV dysfunction.	Patient with frequent PVCs (burden >10%/day) with no significant structural heart disease. Exclusion: Patients with significant structural heart disease, including CAD, valvular heart disease, and congenital heart disease, and patients with spontaneous or inducible sustained VT.	14 ± 14 months	Logistic regression; ROC curve	Gender, LVEF, LVEDd, LVESd, class I antiarrhythmic drugs, amiodarone, PVC burden, non-sustained VT, and retrograde P wave.	- The mean PVC burden (31 ± 11 vs. 22 ± 10%, P<0.001) and the presence of a retrograde P-wave following a PVC (64.3 vs. 30.3%, P=0.001) were significantly greater in those with LV dysfunction than in those with normal LV function. - The cut-off PVC burden related to LV dysfunction was 26%/day (sens 70%, spec 78%). - Presence of retrograde P-wave following a PVC (OR 2.79, 95% CI 1.08–7.19, P=0.034) was independently associated with PVC-mediated LV dysfunction.
Ephrem 2013 [61]	Evaluate the prognostic significance of both PVC frequency and morphology revealed on continuous ambulatory ECG monitoring.	Symptomatic patients (palpitations, syncope, and lightheadedness/near-syncope) referred for outpatient 24-hour ambulatory ECG monitoring who had at least one PVC during 24-hour monitoring. Exclusion: Patients with ventricular couplets, triplets, or non-sustained VT.	Median 2.3 years (range 2.0-2.6)	Kaplan-Meier; cox proportional hazard	Age, gender, heart rate, history of CAD, HTN, DM, dyslipidemia, diastolic HF, systolic HF, MI, smoking, alcohol consumption, family history of CAD, and use of aspirin, clopidogrel, statin, beta-blocker, ACEI/ARB, or CCB.	Multiform PVCs were found to be a significant predictor of clinically adverse outcome independently of other covariates (HR 3.18, 95%CI 1.46-6.96), and remained significant after adjusting for CAD and prior MI (HR 3.05, 95%CI 1.39-6.70). *NOTE:* Clinically adverse outcome: major adverse CV event (ACS, stroke, or all-cause mortality), or CHF.
Barutcu 2014 [62]	Investigate the effects of PVCs on LA	Patients with frequent PVCs (>30 beats/hour) and	NR	Mann-Whitney U/t-	Not provided	- In patients with PVCs, LA dysfunction parameters LAd,

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	function in patients without structural heart disease.	without structural heart disease. Exclusion: Patients with LV hypertrophy, LVEF <55 % or right ventricular dysfunction, valvular heart disease (including mild mitral regurgitation), Grade 3–4 hypertension, uncontrolled hypertension and diabetes patients using insulin, history of AF, renal disease, COPD, malabsorptive disease, systemic diseases, liver disease, thyroid dysfunction, hyperprolactinemia, and Cushing's disease, as well as patients with endocrinopathy, patients with neoplastic or metabolic disease, and patients using corticosteroids were also excluded from this study.		test; chi-square/Fisher's exact; Spearman correlation		LAVI and LAa) and LVED and LVSD diameters were found to be significantly higher, but LVEF was lower than in patients without PVCs. - Global peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) were significantly lower; and time to peak longitudinal strain (TPLS) was significantly longer in the PVCs group. - Number of PVCs was positively correlated with TPLS, but negatively correlated with PALS and PACS.
Cozma 2014 [63]	Assess LA remodeling in patients with frequent PVCs and explore the relationship between the PVC burden and LA shape and size.	Consecutive patients referred to clinic for persistent symptomatic PVCs in excess of 1,000/24-hr Holter. Exclusion: Patients with evidence of structural heart disease; patients with hypertension for ≥5 years, persistent AF, sick sinus syndrome, CAD, significant comorbidities, and unexplained syncope.	NR	Logistic regression	Age, sex, mean blood pressure, LVEF, and the LV end-diastolic diameter.	Each 10% increase in PVCs was significantly associated with trapezoidal LA shape (OR 1.32, 95%CI 1.17-1.48).
Lee 2014 [64]	Investigate the relation of PVC burden, origin, QRS	Patients diagnosed with PVC.	3.4 years (SD 2.5)	Kaplan-Meier;	Age, gender, presence of heart disease, dilated	Greater coupling interval (OR 1.03, 95% CI 1.01-1.05) and PVC QRS

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	duration, and coupling interval with LV function and long-term survival in a large patient cohort with presence or absence of heart disease.			logistic regression	cardiomyopathy, symptoms of dizziness or palpitations, LV function, NSVT, heart rate, PVC origin, PVC coupling interval, PVC duration, antiarrhythmic drugs, flecainide, propafenone, and ACEI/ARB.	duration (OR 1.02 [1.01-1.03]) were predictive for LVEF <50%.
Park 2014 [65]	Investigate the impact of a high burden PVCs on early pathologic changes of cardiac performance in subjects with frequent PVCs and normal LVEF.	Patients with frequent PVCs (>10/h) without structural heart disease. Exclusion: Patients with congenital heart disease, LVEF of <55%, more than mild degree of valvular dysfunction, pericardial disease, ischemic heart disease, cardiomyopathies, uncontrolled thyroid dysfunction, a permanent pacemaker, or atrial fibrillation, or who were prescribed an antiarrhythmic drug, including β-blocker, within 6 months before enrollment.	NR	Multiple linear and logistic regressions	LA volume index, LVEF, and systolic mitral annulus velocity.	- There was independent association between frequent PVC and LAVI (OR 1.06, 95% CI 1.03–1.09) and LVEF (OR 0.92, 95% CI 0.89–0.96). - PVC burden was found to be an independent determinant of LAVI.
Pol 2014 [66]	Determine whether PVC QRS duration measured before the onset of CMP would be a useful predictor of the subsequent development of CMP.	Patients who underwent PVC ablation, had ≥10% PVC on preprocedural 24-hr Holter monitoring, and had PVC on ECG at least 6 month before ablation. Exclusion: Patients with structural or genetic heart disease, and pts with	Median 14 mo (IQR 8-32 mo)	Multivariate logistic regression	Longer PVC QRS duration, longer conducted QRS duration, LV site of origin, and non-outflow tract site of origin.	- Patients who developed PVC-induced CMP had significantly longer PVC QRS duration and sinus QRS duration. - Longer PVC QRS duration (OR 2.94 [for each 10-msec increase in the baseline PVC QRS], 95%CI 1.36-6.55) and a non–outflow tract site of PVC origin

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		history of sustained VT or sudden cardiac death.				(OR 14; 95% CI 1.55-126.84) were independent risk factors for LV dysfunction after multivariate analysis. - PVC QRS duration of ≥153 msec best predicted development of PVC-CMP (sens 82%, spec 75%).
Qureshi 2014 [67]	Examine the prognostic significance premature contractions detected by a single 12-lead ECG in subjects without known cardiovascular disease.	Patients from the National Health and Nutrition Examination Survey (NHANES) III aged at least 20 years with good quality of ECGs. Exclusion: Subjects with known CVD, ECG evidence of MI, paced rhythms, or atrial fibrillation.	13 ± 4 years	Kaplan-Meier; cox proportional hazard	Age, sex and race/ethnicity, smoking status, systolic blood pressure, body mass index, blood pressure medications, total cholesterol, diabetes mellitus, cancer and pulmonary disease (bronchial asthma and chronic obstructive pulmonary disease), electrocardiographic left ventricular hypertrophy, and corrected QT interval.	In individuals aged 65 years or older, presence of PVC was associated with all-cause mortality (HR 1.36, 95%CI 1.04-1.76).
Yang 2014 [68]	Determine predictors of high-burden PVCs and, among high-burden PVC patients, predictors of heart failure.	Patients had at least 20% PVCs burden.	NR	Multivariable logistic regression	Age, sex, hypertension, CAD, creatinine, previous MI, CABG, CHF, and first-degree family history of sudden death.	- High-burden PVC patients had a three-fold greater odds of HF (OR 3.15, 95%CI 1.28-6.50). - High-burden PVC patients had almost 10-fold greater odds of having a first-degree family history of sudden death (OR 9.97, 95%CI 1.78-60.8).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
Agarwal 2015 [69]	Examine whether PVCs detected by the more conventional short-term routine ECG are associated with increased risk of ischemic stroke.	REGARDS study community-based participants without incident hemorrhagic stroke, prevalent stroke or transient ischemic attack.	6 ± 2 years	Cox proportional hazard	Age, sex, race, geographic region, education level, prior heart disease, systolic blood pressure, use of antihypertensive medication, left ventricular hypertrophy by ECG, atrial fibrillation, diabetes, current smoking, and use of warfarin and aspirin	PVCs were associated with a 38% increased risk of ischemic stroke (HR 1.38, CI 1.05–1.81).
Dukes 2015 [70]	Determine whether PVC frequency ascertained using a 24-h Holter monitor is a predictor of a decrease in the LVEF, incident CHF, and death.	Patients from the CHS study who were randomly assigned to 24-h ambulatory ECG (Holter) monitoring during their initial assessment and who were part of the initial recruitment cohort. Exclusion: Patients without a normal LVEF, as determined by the baseline echocardiogram, or with prevalent CHF.	Median 13.7 years (range 8.0 - 18.2) for incident CHF; median f/u 15.2 years (range 9.6 - 18.4) for mortality	Cox proportional hazard	Age, sex, race, BMI, and history of hypertension, diabetes, CAD, beta-blocker use, Holter-based atrial fibrillation, and number of Holter-based VT episodes.	- Patients in the upper quartile of PVC frequency (vs lowest quartile) had 3-fold greater odds of a 5-year decrease in LVEF (OR 3.10; CI, 1.42 to 6.77), and a 48% increased risk of incident CHF (HR: 1.48; CI: 1.08 to 2.04) during a median follow-up of 13 years. - Patients in the upper quartile of PVC frequency (vs lowest quartile) had a 31% increased risk of death (HR: 1.31; CI 1.06 to 1.63) during a median follow-up of 13 years.
Lin 2015 [71]	Evaluate the prognostic significance of PVC polymorphism in patients with apparently normal hearts.	Patients who received 24-hour ECG monitoring due to palpitations, syncope, suspected arrhythmia, and clinical follow-up as clinically indicated, but otherwise with apparently normal hearts. Exclusion: Participants with prevalent	10 ± 1 years	Kaplan-Meier; cox proportional hazard	Age, sex, hypertension, DM, CKD, and usage of hypertensive medication.	- Patients with multiform PVC had an increased incidence of mortality (HR 1.642, 95% CI 1.327–2.031), hospitalization (HR: 1.196, 95% CI: 1.059–1.350), cardiovascular hospitalization (HR: 1.289, 95% CI: 1.030–1.613), new-onset heart failure (HF; HR: 1.456,

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		sustained or non-sustained ventricular tachycardia (defined as reported history of tachycardia on baseline 12-lead ECG or on baseline Holter monitoring), permanent pacemaker (confirmed as a reported history of permanent pacemaker at their first study encounter on baseline 12-lead ECG or on baseline Holter monitoring), HF (confirmed by physician report, discharge summary, and echocardiography report), previousmyocardial infarction (confirmed by physician report or review of medical chart), history of ablation, and valvular heart disease (confirmed by physician report or review of medical chart) were excluded. Patients with frequent PVC, more than 720 beats per day were also excluded.				95% CI: 1.062–1.997), transient ischemic accident (HR: 1.411, 95% CI 1.063–1.873), and new-onset atrial fibrillation (AF; HR: 1.546, 95% CI: 1.058–2.258) compared to the group without PVC. - Patients with multiform PVC had a higher rate of mortality (HR: 1.231, 95% CI: 1.033–1.468) and all cause-hospitalization (HR: 1.147, 95% CI: 1.025–1.283) compared with patients with uniform PVC.
Bas 2016 [72]	Assess the impact of circardian PVC variability on PVC-induced cardiomyopathy.	Patients with frequent PVCs referred for catheter ablation, with and without cardiomyopathy	3-6 months	Logistic regression	Asymptomatic status, PVC burden, QRS duration of PVCs, pleomorphic PVCs, male sex, interpolation, symptom duration, and interquartile coefficient of PVC variation.	- Compared to those without, patients with cardiomyopathy had a higher PVC burden, less variability in circadian PVC distribution (coefficient of variability, CoV), and more frequent interpolated PVCs. - Interquartile CoV cutoff value of ≤31% best distinguished patients with and without cardiomyopathy (AUC 0.74; sens 66%; spec 81%; P = .0001).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
						- PVC QRS duration (OR 1.086, 95% CI 1.014 - 1.16) and interquartile CoV <31% (OR 16.32, 95% CI 1.715 - 155.3) are independent predictors of PVC-induced cardiomyopathy.
Agarwal 2017 [74]	Examine interactions that might prove clinically useful in risk-stratifying patients with PVCs (large state-database, Healthcare Cost and Utilization Project [HCUP]). *NOTE: PVC diagnosis was based on ICD-9 code 427.69*	Patients from the Healthcare Cost and Utilization Project (HCUP) California database. Exclusion: Patients with prevalent systolic or diastolic HF at the baseline, arrhythmogenic RV dysplasia, paroxysmal VT, valvular heart disease, and those with HF diagnosis during the same visit as the first diagnosis as PVCs.	5 years	Kaplan-Meier; cox proportional hazard	Age, gender, race, annual household income, and presence of CAD, hypertension (HTN), DM and AF.	- Patients with PVCs exhibited an 80% excess risk of incidence systole HF (HR 1.8, 95% CI 1.8 – 1.9). - In younger patients aged <65 years (without HTN, DM, CAD, or AF), the diagnosis of PVCs increased the risk of incident HF by >6-fold (HR 6.5, 95% CI 5.5 – 7.7).
Lin 2017 [75]	Determine the predictive values of PVC frequency on mortality, CV hospitalization, and HF during long-term clinical follow-up.	Patients who were indicated for 24-hour Holter monitoring (palpitations, syncope, and clinical follow-up). Exclusion: Patients with sustained VT, permanent pacemaker, or history of catheter ablation.	10 years (SD 1)	ROC curve; Kaplan-Meier; cox proportional hazard	Age, sex, HTN, CAD, DM, previous MI, valvular heart disease, HF, and medication with ACEI/ARB or diuretics.	- Optimal cut-off for PVC/24hr for predicting all-cause mortality was 12 PVCs/day (sens 58.3%, spec 59.8%, AUC 59.6%). - A propensity score matched analysis found that PVC >12/day was associated with new-onset HF (crude HR 1.38, CI 1.10 – 1.74), and CV-cause hospitalization (crude HR 1.24, CI 1.06 – 1.45). - PVC >12/day was associated with increased risk for all-cause mortality (adjusted HR 1.49, 95%CI 1.28-1.59).
Nguyen 2017 [73]	Investigate whether atrial or ventricular ectopy on a standard 10-second 12-lead ECG is associated with an increased risk	Participants/patients from the CHS and ARIC studies. Exclusion: Participants/patients with poor data, artificial pacing, wandering atrial pacemaker, or missing	10 years (SD not provided)	Kaplan-Meier; cox proportional hazard	Age, sex, race, study site, hypertension, diabetes mellitus, myocardial infarction, coronary artery	- In univariate analysis, the presence of a PVC was associated with an increased risk of AF in the CHS participants (HR, 1.3, 95%CI, 1.1-1.6, p=0.007); with similar finding in

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	of incident AF, HF, and mortality.	ECG data, with additional exclusion criteria of prevalent HF and without baseline echocardiography for "myopathy" analyses.			disease, beta-blocker, atrial fibrillation, study site, and baseline LVEF.	ARIC cohort (HR, 1.9, 95%CI, 1.2-3.0, p=0.005). (). - After multivariable adjustment, there was 30% increased risk of incident HF in CHS participant (HR, 1.3; 95% CI 1-1.6), and 2-fold increased risk in ARIC study (HR 2.0, 95% CI 1.4 – 2.8). - There was an association between presence of a PVC with incident HF with systolic dysfunction (HR 1.8, 95% CI 1.2 – 2.5). - Over 5 years, a PVC on the baseline ECG was associated with approx. 3-fold greater odds of a reduction in LVEF (OR 2.8, 95% CI, 1.3-6.1).
Sheldon 2017 [76]	Compare clinical characteristics and outcomes of patients with pleomorphic vs monomorphic idiopathic PVCs.	Patients who were referred for ablation with a frequent idiopathic PVCs. Exclusion: Patients with structural heart disease or absence of adequate ambulatory ECG data, also those with myocarditis, infiltrative heart disease, prior MI, or definitive late gadolinium enhancement (LGE) on cardiac MRI.	5.6 months (median f/u for ambulatory ECGs)	Multivariate logistic regression	Not provided	A cutoff of ≥156 non-predominant PVCs over 24hr best differentiated successful from unsuccessful ablation procedures (AUC 0.64, sens 56%, spec 74%).
Aviles-Rosales 2018 [77]	Find associations between exercise-induced PVCs, the occurrence of life-threatening ventricular arrhythmias and all-cause mortality in patients with cardiovascular disease.	Patients with recognized CAD or idiopathic cardiomyopathy (ICM), who initially performed stress testing as a part of their routine CV evaluation, and did not have VT.	14 years	Kaplan-Meier; cox proportional hazard	Diagnosis of idiopathic cardiomyopathy or coronary artery disease, LVEF, digoxin, diuretic-espironolactone, antiarrhythmic, exercise tolerance, and life-threatening	Patients with EiPVC showed an increased long-term risk of mortality (RR 2.1; 1.2-3.4) and life-threatening arrhythmia combined outcome (LACO) (RR 2.81; 1.9-4.3).

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
					arrhythmia combined outcome.	
Bière 2018 [78]	Determine whether infrequent stress-induced right bundle-branch block morphology VE (SI-RBVE) provide prognostic information on CV outcomes.	Patients referred for SPECT	4.5 ± 1.3 years	Cox proportional hazard	Age, history of heart failure, peripheral arterial disease, scar, LVEF <50%, LVEF <50% + stress-induced right bundle branch block VE, and LVEF ≥50% + stress-induced right bundle branch block VE	- There was a higher proportion of all-cause mortality in patients with SI-RBVE (23.4% vs 14.0%, p=0.021). - There was an interaction between SI-RBVE and LVEF. In patients with LVEF >50%, SI-RBVE was an incremental risk factor for mortality (OR 2.17, 95% CI 1.09-4.34, p=0.028).
Im 2018 [99]	Evaluate the association of frequent PVCs>10% and stroke-like symptoms without a prior diagnosis of stroke or TIA.	Patients with or without documented PVCs, *and without* any history of cardiomyopathy or valvular or congenital or ischemic heart disease, hepatic or renal disease, acute cerebrovascular or cardiovascular events, major trauma or surgery, hyperthyroidism, uncontrolled hypertension, malignancy, connective tissue disease, acute/chronic inflammatory disease.	3.5 years	Kaplan-Meier; multivariate logistic regression	Age, atrial fibrillation, hypertension, LVH, E/E' (peak mitral flow velocity of the early rapid filling wave/early distolic mitral annulus velocity), mitral regurgitation grade, and NT-proBNP.	PVC>10% was found to be an independent risk factors for stroke-like symptoms without a prior diagnosis of stroke or TIA (OR 3.421, CI 1.092-10.726).
Li 2018 [79]	Evaluate the prognostic impact of baseline long-term continuous frequent PVC (CfPVC) burden among patients with an ICD.	Patients who had dual-chamber ICD capable of hourly PVC counting and home monitoring transmission, with daily average ventricular pacing percentage of <20%. Exclusion: Patients with single chamber device,	Median 43 months (34-53 months)	ROC curve; Kaplan-Meier; cox proportional hazard	Age, gender, BMI, indication for ICD implantation, ICM, Non-ICM, stroke, valvular disease, diabetes mellitus, paroxysmal atrial fibrillation, hypertension,	- CfPVC percentage ≥40% was an independent predictor of cardiac death (HR = 3.288; 95%CI = 1.720–6.283; p<0.001). - The best cut-off point of CfPVC percentage against ventricular arrhythmic events was 40% (AUC 0.703, p<0.001). This cut-off point means that the hourly

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		incapable of processing home monitoring, history of channelopathy and other inherited arrhythmias, and if they experienced outcomes during data collection period.			syncope, NYHA, LVEF, LVEDD, CfPVC percentage, and the use of amiodarone, β-blockers, ACEIs/ARBs and spironolactone.	mean PVC≥10 beats was accounted for 40% (24 days) of the 60-day monitor duration.
Ruwald 2018 [80]	Evaluate the association between 12-month ventricular ectopic burden and the risk of HF/death and malignant ventricular tachyarrhythmias in patients with cardiac resynchronization therapy with defibrillator (CRT-D) (from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)	Patients with CRT-D from the MADIT-CRT study who had undergone both pre-implant and 12-month 24-hour Holter monitoring. MADIT-CRT criteria: depressed LV function (LVEF < 30%), prolonged QRS duration (>130 ms), ischemic (NYHA class I/II), or non-ischemic (NYHA class I) cardiomyopathy and sinus rhythm at enrollement. Exclusion: Patients who, within 3 months prior to enrollment, had undergone CABG, PCI, or had experienced an MI, or if they, within 1 month prior to enrollment, had experienced atrial fibrillation.	2.23 ± 0.98 years	Kaplan-Meier; cox proportional hazard	Diabetes, left bundle branch block (LBBB) QRS morphology, male gender, hospitalizations 1 year prior to enrollment, glomerular filtration rate<60 ml/min/m2, and baseline LV end systolic volume index.	- High ectopic burden (>10 PVCs/hr) was associated with a significant 2.8 fold increased risk of HF/death (HR 2.76, p<0.001) and VT/VF (HR 2.79, p<0.001) compared to patients with low ectopic burden. - Patients with an unchanged high ectopic burden, and patients who experienced an increase in ectopic burden had a higher risk of HF/death and VT/VF, with 3-year cumulative incidences of 24%–25% (p<0.001, Kaplan-Meier curve). - Unchanged high PVC burden was associated with higher risk of HF/death (HR 2.9; CI 1.51 – 5.56) and VT/VF (HR 2.99; CI 1.66 – 5.37). - Increased PVC burden was associated with higher risk of HF/death (HR 2.97; CI 1.35 – 6.51) and VT/VF (HR 2.32; CI 1.09 – 4.97).
Su 2018 [81]	Explore the predictors for development of VT among patients with frequent PVCs.	Patients with frequent PVCs (>30 beats/hour; and PVCs ranged 746 - 47083/24 h). Exclusion: Pulmonary heart disease, severe dysfunction of kidney and liver, rheumatic	NR	Multiple stepwise logistic regression	Potassium level, PVC burden, LVEF, couplets, and alcohol consumption	Extensive PVC burden (OR 1.07; 1.032-1.108) and PVC couplets (OR 33.984; 11.526-100.199) are associated with the occurrence of VT.

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
		disease, and tumor, and receiving treatment of digitalis, quinidine, and tricyclic antidepressant.				
Altıntaş 2019 [82]	Evaluate the relationship between PVC burden and LV ejection fraction (LVEF).	Adults with idiopathic PVC of >1,000 PVC/24h. Exclusion: Patients with less than 24 hr and/ or inconclusive Holter recording, coronary artery disease (CAD), history of cardiac arrest, sustained VT, intracardiac defibrillator (ICD), second- or third-degree AV block, sick sinus syndrome, permanent cardiac pacemaker, known or suspected etiology of cardiomyopathies including, ischemic, restrictive, hypertrophic, diabetic, arrhythmogenic, and non-compaction before or on admission, genetic cardiac channelopathies, pericardial disease, myocarditis, all forms of atrial fibrillation, thyroid disorders, anemia, electrolyte disorders, chronic pulmonary disease, pulmonary hypertension, moderate-to-severe valvular heart disease, or pulmonary embolism.	NR	Proportional odds logistic regression; generalized additive model	Age, sex, PVC burden, antiarrhythmic drug use, interpolated PVC, polymorphic PVCs, circardian variability, sinus QRS duration, PVC QRS duration, PVC coupling interval, LVOT, and RVOT site of origin.	Increase in PVC burden (%), PVC QRS duration, and age are associated with decrease in LVEF. Decrease in LVEF become more prominent when PVC burden is >5%.
Yamada 2019 [100]	Validate the clinical significance of PVC burden on cardiac function, exercise capacity, and outcome in	Hospitalized patients with decompensated HF, excluding patients with ACS and receiving hemodialysis	Median 2.3 years	ROC curve; Kaplan-Meier; cox proportional hazard	Age, NYHA class III/IV, LVEF, Holter-based AF, diabetes, chronic kidney disease, anemia, receiving	- An increase of PVC burden (%/d) was associated with an increased risk of cardiac events (HR 1.036; CI 1.005-1.068). - The optimal cutoff value of PVC burden (high/low) for predicting

Authors	Study Aim	Sample Criteria	Follow-Up Period	Analysis Method	Variables in Multivariate/Max Adjusted Models	Key Findings
	hospitalized patients with HF.				devise therapy, and the use of amiodarone.	cardiac events at the 1-year follow-up was 0.145%/d (95% CI: 0.570-0.714, p < .001, sens 64.2%, spec 59.0%, AUC 0.64). *NOTE:* Cardiac events: ICD therapy, re-hospitalization due to worsening HF, or death.

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitors; ACS = acute coronary syndrome; AF = atrial fibrillation; AMI = acute myocardial infarction; ANOVA = analysis of variance; ARB = Angiotensin II receptor blockers; ARIC = Atherosclerosis Risk in Communities; AUC = area under the curve; BHAT = Beta Blocker Heart Attack Trial; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CHS = Cardiovascular Health Study; CI = confidence interval; CKD = chronic kidney disease; CMP = cardiomyopathy; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CRT-D = cardiac resynchronization therapy with defibrillator; CVD = cardiovascular disease; DAVIT II = Danish Verapamil Infarction Trial II; DBP = diastolic blood pressure; DM = diabetes mellitus; ECG = electrocardiogram; EDVI = end-diastolic volume index; HCUP = Healthcare Cost and Utilization Project; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; HR = hazard ratio; HR = heart rate; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; LA = left atrium; LAa, LAd = left atrium area, diameter; LAD = left axis deviation; LAVI = left atrium volume index; LBBB = left bundle branch block; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LV = left ventricular; LVEDd = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESd = left ventricular end systolic diameter; LVOT = left ventricular outflow tract; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MRFIT = Multiple Risk Factor Intervention Trial; MRI = magnetic resonance imaging; NHANES III = Third National Health and Nutrition Examination Survey; NR = not reported; NSVT = non-sustained ventricular tachycardia; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; PAC = premature atrial contraction; PCI = percutaneous coronary intervention; PVC = premature ventricular contraction; RBBB = right bundle branch block; REGARDS = Reasons for Geographic and Racial Differences in Stroke; ROC = receiver operating characteristic; RR = risk ratio; RV = right ventricular; RVOT = right ventricular outflow tract; SBP = systolic blood pressure; SCD = sudden cardiac death; SD = standard deviation; SEM = standard error of the mean; SHD = structural heart disease; SPECT = single-photon emission computed tomography; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachycardia.

Chapter 3

Occurrence Rates for Premature Ventricular Complexes and Associated Patient Characteristics during Intensive Care ECG Monitoring

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Acknowledgments: SS received a Predoctoral Fellowship from the UCSF School of Nursing for his doctoral studies. The alarm data were procured by the Center for Physiologic Research, University of California, San Francisco (UCSF) School of Nursing.

Funding: This study was funded by Lipps Research Fund (MMP) and Century Club Dissertation Award (SS), UCSF School of Nursing.

Abstract

Introduction: Premature ventricular complexes (PVCs) are considered not immediately life-threatening and generally do not require aggressive treatment. Nevertheless, continuous PVC monitoring remains a common practice in the intensive care unit (ICU). Understanding the specific PVC alarm types and their distribution among ICU patients could inform a more effective alarm management.

Aims: to determine the occurrence rates of PVC alarm types and patient factors associated with occurrence rates of PVCs during continuous ECG monitoring.

Methods: Secondary analysis using data from the UCSF Alarm Study. Seven PVC alarm types were examined: isolated PVC, couplet bigeminy, trigeminy, run PVC, R-on-T, and PVC/minute. Negative binomial and hurdle regression analyses were computed to examine the association between patient's characteristics and the occurrence rates of PVC types.

Results: Of the total 797,072 individual PVC alarms during 45,271.3 hours of ECG monitoring, isolated PVC accounted for 81.13% (*n* = 646,665), while R-on-T was the fewest (*n* = 2,321, 0.29%). All 446 patients had at least one PVC alarm, including six who had disproportionately larger alarm counts, contributing 40% (*n* = 320,342) of the total PVC alarms. Older age (IRR 1.04, 95% CI 1.03 – 1.05), male (IRR 1.94, 95% CI 1.40 – 2.84), and presence of PVCs on the baseline 12-lead ECG (IRR 2.85, 95% CI 1.83 – 4.30) were associated with higher rates of isolated PVCs. Only age was associated with a higher rate of bigeminy (IRR 1.04, 95% CI 1.02 – 1.06) and couplets (IRR 1.02; 95% CI 1.01 – 1.03), while hyperkalemia at ICU admission was associated with lower incidence rate of R-on-T (IRR 0.07, 95% CI 0.03 – 0.17).

Conclusion: Older age, male, and presence of PVCs on 12-lead ECGs at the baseline are independent predictors for higher rates of PVC alarms, particularly isolated PVCs, bigeminy, and couplets. A high proportion of PVC alarms are concentrated in a very small number of patients. Efforts aimed at reducing frequently occurring alarms like PVCs, which are not typically aggressively treated, as well as more thoughtful alarm management in select patients with

extreme numbers of PVC alarm could potentially reduce the risk for alarm fatigue and ultimately improve care experiences for both clinicians and patients.

INTRODUCTION

When electrocardiographic (ECG) monitoring was introduced into the intensive care unit (ICU) in the 1960s, premature ventricular complexes (PVCs) were identified as one of the most commonly occurring arrhythmias among patients with myocardial infarction (MI).[1] It was generally accepted that PVCs indicated electrical instability of the heart or myocardial irritability and might forewarn a lethal ventricular arrhythmia.[1,2] Furthermore, it was believed that as the frequency of PVCs increased, there was an increased likelihood of subsequent ventricular tachycardia (VT) or ventricular fibrillation (VF),[1] and therefore identification followed by prompt treatment with an antiarrhythmic medication(s) could thwart these events and improve a patient's prognosis.[2] Based on these observations made some 40 years ago, monitoring PVCs as an alarm condition was incorporated into in-hospital ECG monitoring devices.[1] However, findings from the 1989 Cardiac Arrhythmia Suppression Trial (CAST),[3] a large multi-site randomized control trial, changed aggressive pharmacologic PVC management practices. The CAST study examined whether suppression of PVCs with class IC antiarrhythmic drugs (i.e., encainide, flecainide, and moricizine) after acute MI would reduce sudden death. Of note, the study was terminated early because the data showed that treatment of PVCs with class IC antiarrhythmic drugs was associated with more deaths as compared to placebo.[3] As a result, aggressive pharmacological treatment of PVCs in hospitalized MI patients was no longer standard practice.

The most recently published 2017 American Heart Association ECG Practice Standards for In-hospital ECG Monitoring[4] grouped PVCs with non-sustained VT and assigned a Class of Recommendation IIb (usefulness is less well established) and Level of Evidence C (mainly based on expert opinion or standard of care). The rationale for these recommendations is based on evidence showing that these arrhythmias are not "immediately life-threatening," and in the absence of other indications for monitoring, continued monitoring may be "considered" but is not required.[4] Despite these recommendations, it is still a common practice to monitor for PVCs in

the hospital setting, which could be useful in some circumstances. For example, a PVC alarm(s) could alert the bedside nurse to a true clinical problem (e.g., increase in PVCs due to electrolyte imbalance), which could be treated to reduce the risk of developing a lethal arrhythmia. Moreover, the alarm setting for PVCs in bedside monitors can be configured as either audible or inaudible (text message alert on the monitor). In fact, monitoring manufacturers commonly have a variety of algorithms that identify several types of PVCs, such as isolated PVC, bigeminy, trigeminy, couplet, run PVC, number/minute, and R-on-T. While an alarm notification is clinically relevant in certain situations, our research group has found that PVCs are common. In a group of 461 ICU patients monitored during a one-month study period, PVCs were the most commonly occurring arrhythmia and accounted for 854,901 (33%) out of 2,588,760 unique alarms.[5] Given that PVCs are not routinely treated and the current recommendations for hospital-based monitoring state that PVC monitoring may be considered, it is unclear why this practice continues. Furthermore, the frequency with which PVCs occur contribute to alarm fatigue (desensitization, unsafe alarm adjustments) in nurses and providers; thus, increasing the risk of missing a true event(s), which threatens patient safety.[6-11]

There have been a handful of studies[12,13] and quality improvement projects[14-17] that have reported on PVC alarms during hospital-based monitoring. However, these studies were designed to examine the total number of <u>all</u> alarm types (PVCs pooled with all alarms) and test alarm reduction strategies aimed mostly at improving ECG signal quality and default settings. Therefore, there has not been a comprehensive and contemporary research study examining the specific types of PVC alarms, and whether demographic and/or patient clinical characteristics are associated with PVCs during continuous ECG monitoring.

Therefore, the purpose of this study that included 446 ICU patients with continuously recorded ECG data was threefold: (1) determine the number and type of PVC alarms for isolated couplets, bigeminy, trigeminy, run PVC (*"VT>2" based on the manufacturer's definition*), R-on-T, and PVC/minute; (2) determine the distribution of PVC alarm types by patient

demographics (i.e., age, sex, race/ethnicity) and clinical variables (i.e., medical history, diagnosis, 12-lead ECG, ejection fraction, and serum potassium); and (3) test whether demographic and/or clinical variables are associated with PVC alarm types.

MATERIALS AND METHODS

Study Design

This is a secondary data analysis from the University of California, San Francisco (UCSF) Alarm Study, a single-center, prospective observational study that collected all physiologic and clinical alarm data from 77 adult ICU bedside physiologic monitors during a 1-month study period in 2013.[5] Each of the 77 ICU beds (16 cardiovascular, 32 medical-surgical, and 29 neurological/neurosurgery) was equipped with a five lead ECG Solar 8000i monitor (version 5.4 software, GE Healthcare). A closed and secure data capture system connected all of the 77 monitors, including the central monitoring station, to a specialized CARESPACE Gateway (GE Healthcare), which allowed the physiologic data to securely pass to an external server for offline and retrospective analyses; hence, our data did not interfere with patient care, nor was it available for clinical decision making. The UCSF institutional review board approved this study with a waiver of informed consent. Our data capture system allowed us to collect data from consecutive ICU patients; hence, this study represents a comprehensive evaluation of PVC occurrence rates. We were also approved to collect demographic, clinical history, and current hospitalization variables of interest (detailed below) from the patients' electronic health records (EHRs).

Premature Ventricular Complexes Alarms

A total of seven PVC alarm types were examined as defined by the vendor as follows: (1) *isolated PVC* (single PVC); (2) *couplet* (two consecutive PVCs >100 beats per minute); (3) *bigeminy* (PVC alternates with a non-ventricular beat for ≥3 cycles); (4) *trigeminy* (PVC alternates with 2 non-ventricular beats for ≥3 cycles); (5) *run PVCs* (3-5 consecutive ventricular beats ≥100 beats/minute); (6) *R-on-T* (PVC falls on the ST or T wave portion of the previous

beat); and (7) *PVC/minute* (PVC count is ≥ a user-defined limit). For PVCs/minute, our hospital configured this alarm for ≥10 PVC/minute, which generates an alarm when this limit was exceeded regardless of the PVC type (isolated, couplets, etc.).

Patient Data

All demographic and clinical variables for the sample were collected from the EHR (Epic Cyberspace 2019, Madison, WI). Demographic data included age, sex, race, and ethnicity. Clinical variables collected included history of ischemic heart disease (IHD), heart failure (HF), primary percutaneous intervention (PCI [stent]), or coronary artery bypass graft (CABG) surgery, stroke, and atrial fibrillation. These variables were selected based on prior studies showing they are associated with PVCs.[18-20] Also collected were ICU admission variables, including PVC (any) and/or atrial fibrillation on a 12-lead ECG, serum potassium, ejection fraction, and primary diagnosis.

Definitions used for ICU Admission Variables

The presence of any or multiple PVCs, as well as atrial fibrillation, was determined by examining all 12-lead ECGs recorded within 24-hours of ICU admission. All 12-lead ECGs have been over-read by a board-certified cardiologist. If there were no ECGs obtained in the ICU during this time frame, a 12-lead ECG obtained in the emergency room or step-down/medical-surgical floor (transfer patients) within 24-hours prior to ICU admission was used. Left ventricular ejection fraction (LVEF) was obtained from an echocardiogram during hospitalization. If an echocardiogram was not available from the current admission, a recent echocardiogram (within 6 months) prior to admission was used. The numeric LVEF (%) and the categorical evaluation (i.e., preserved ≥ 50%; mid-range 41% - 49%; and reduced ≤ 40%) were obtained. The serum potassium level at ICU admission was also collected. In addition, we subdivided the serum potassium into categories for analysis: normal (3.8 - 5.1 mEq/L); hypokalemia (<3.8 mEq/L); and hyperkalemia (>5.1 mEq/L). Finally, the primary ICU diagnosis

was obtained and categorized into cardiovascular, medical-surgical, and neuro-neurosurgery diagnoses.

Statistical Analysis

The frequency of all seven PVC alarm types was tabulated. Mean, median, range, and interquartile ranges were calculated to describe the distribution of each PVC type across patient demographics and clinical characteristics. We report the PVC/minute type in our descriptive analysis to show its occurrence rate but did not include this PVC type in the patient and clinical characteristic analyses since this is a vendor-specific value that is selected by a hospital. Because it is common for some patients to have high numbers of PVCs while others may have only had one or no PVC, we examined PVC counts (total number of PVCs per patient) using modeling strategies that allowed us to account for excess zeros.

We examined the association of 16 variables for each of the six PVC types. For the counts of isolated PVC outcome, we conducted a negative binomial regression analysis using the R package *MASS v7.3.50*,[21] and tested coefficients with a nonparametric bootstrap (5,000 replicates), utilizing bias-corrected and accelerated (BCa) 95% confidence intervals (CIs).[22-24] For the counts of bigeminy, trigeminy, couplet, run PVC, and R-on-T PVC types, we conducted a hurdle regression analysis[25] using the R package *pscl v1.5.2*[26] to account for the excess zeros in these distributions. The hurdle model consisted of two components: (1) logistic regression for whether or not an individual had a PVC alarm, and (2) zero truncated negative binomial regression to model the counts of PVC alarms in individuals who had one or more of the PVC alarm. Coefficients from this hurdle model again were tested via a nonparametric bootstrap. We present first the univariate models of each of the factors against each PVC type. Results were considered ***significant*** if they reached ***p<.00052*** (to account for 96 multiple comparisons of the six PVC types by 16 potential demographic and clinical factors), and we also note when results meet *p<.05*. Finally, we conducted a stepwise regression model for each PVC type where we added one variable at a time into the model. Here, we used a bootstrap multiple imputation

approach (500 bootstraps, each bootstrap utilizing 20 multiple imputations)[27] to appropriately handle the missing data. All analyses were computed using R v3.4.1.[28]

RESULTS

PVC Alarm Distribution

A total of 446 ICU patients were included in this study. Demographics and clinical characteristics of the sample are detailed in **Table 3.1**. The mean age was 59.97 ± 17.03 years. There were approximately equal proportions of males (*n* = 244, 54.7%) and females (*n* = 202, 45.3%). Of the sample, 118 (26.5%) were Non-White, and 270 (60.5%) were White. When examining the 12-lead ECG within 24 hours of ICU admission, a small portion of the patients had PVCs (*n* = 24, 5.4%) and/or atrial fibrillation (*n* = 35, 7.8%). Of note, there was missing data in the sample for the following variables: baseline 12-lead ECG (*n* = 95, 21.3%); serum potassium (*n* = 4, 0.9%), and LVEF (*n* = 273, 61.2%).

There were 797,072 PVC alarms during 45,271.3 hours of ECG monitoring, or 17.6 PVC alarms/hour across the 77 beds in three units (**Table 3.2**). Of the total number of the alarms, the isolated PVC type accounted for 81.13% (*n* = 646,665), while R-on-T PVC type had the fewest (*n* = 2,321, 0.29%). **Table 3.3** shows the distribution of PVC alarm types based on the median and interquartile range in the 446 ICU patients against their demographic and clinical characteristics. Regarding patient characteristics, older, male patients had a higher median count of isolated PVCs. In addition, patients with a history of IHD, HF, PCI/CABG, stroke, or atrial fibrillation had a higher median count of both isolated PVCs and couplets than those without these clinical histories. Also, patients with a reduced LVEF had a higher median count of isolated PVCs (966 alarms) as compared to those with preserved (146 alarms) and mid-range LVEF (346 alarms). In patients with a cardiovascular diagnosis (*n* = 98; 22%), the median count of isolated PVCs and couplets were higher than that in those with other diagnoses. Alarm distribution based on the mean, minimum, and maximum count of PVC types is provided in **Supplement Table 3.A**.

All patients included had at least one PVC alarm. Ten patients had only one PVC alarm during an average of 25 hours of monitoring (nine had an isolated PVC, one had a couplet). There were 41 (9.2%) patients who were categorized as outliers (defined below) for one or more PVC type outcomes. In this group, there was a trend for older age (mean 65 years) and/or having a cardiac history, such as IHD and heart failure (**Table 3.4**). Six of the patients had disproportionately larger alarm counts, contributing 40% (*n* = 320,342) of 797,072 total PVC alarms (**Table 3.5**). One patient, in particular, had 153,347 alarms (19%), including 124,944 for isolated PVCs during 744 hours of monitoring. The patient was an 80-year old female with a significant history of diastolic HF, chronic atrial fibrillation, hypertension, and mitral valve replacement. Similarly, the patient with the second-largest PVC alarm count (*n*=54,287, 6.8%) had a history of tetralogy Fallot with pulmonary valve replacement.

Factors Associated with Occurrence Rates of PVCs

Results presented in the paper had outlier observations removed. We defined an outlier as an observation with a standardized residual from the negative binomial portion of the model ≥ 3, iterated until no outliers remained. The number of outlier patients for each PVC types was as follows: 21 isolated PVC (4.7% of the count model dataset), 11 bigeminy (6.4%), 13 trigeminy, (8.7%), 11 couplets (2.8%), 11 run PVC (3.5%), and 9 R-on-T (5.5%). Sensitivity analysis including these outlier observations, as well as with a standardized residual cutoff of 2.5 (number of outliers: 34 isolated PVC (7.6%); 17 bigeminy (9.9%); 18 trigeminy (12.1%); 35 couplets (8.8%); 21 run PVC (6.8%); and 14 R-on-T (8.6%)) are included in the Supplementary material (listed below).

Table 3.6 details the univariate regression analysis for PVC count outcomes with outliers removed (**Supplement Table 3.B** with outliers included; outliers ≥2.5 removed in **Supplement Table 3.C**; **Supplement Tables 3.D**, **3.E**, and **3.F** show the corresponding logistic model of the hurdle regression). A higher incidence of isolated PVC was associated with age (IRR 1.05, 95% CI 1.04 – 1.06), history of IHD (IRR 2.98, 95% CI 2.04 – 4.44), presence of PVCs on the

baseline 12-lead ECG (IRR 3.50, 95% CI 2.31 – 5.15), and cardiovascular diagnosis (IRR 2.05, 95% CI 1.39 – 3.05). As for bigeminy and couplets: age (bigeminy, IRR 1.04, 95% CI 1.02 – 1.06; couplets, IRR 1.02, 95% CI 1.01 – 1.03); and PVC(s) on the baseline 12-lead ECG (bigeminy, IRR 4.90, 95% CI 1.61 – 14.88; couplets, IRR 2.46, 95% CI 1.58 – 3.90) were significant factors.

In stepwise regression analyses, older age (IRR 1.04, 95% CI 1.03 – 1.05), male sex (IRR 1.94, 95% CI 1.40 – 2.84), and presence of PVCs on the baseline 12-lead ECG (IRR 2.85, 95% CI 1.83 – 4.30) were independent factors associated with higher incidence rates of isolated PVCs. Only age was associated with a higher incidence rate of bigeminy (IRR 1.04, 95% CI 1.02 – 1.06) and couplets (IRR 1.02; 95% CI 1.01 – 1.03), while hyperkalemia at ICU admission was associated with a lower incidence rate of R-on-T (IRR 0.07, 95% CI 0.03 – 0.17). Since LVEF data were available in only 173 patients (38.8%), this variable was excluded from the stepwise fits. Results from the stepwise regression analysis with outliers removed are presented in **Table 3.7** (**Supplement Table 3.G** with outliers included; outliers ≥2.5 removed in **Supplement Table 3.H**; **Supplement Tables 3.I**, **3.J**, and **3.K** show the corresponding logistic model of the hurdle regression).

DISCUSSION

This is the first comprehensive research study that has examined occurrence rates of PVCs in ICU patients with continuous ECG monitoring. The main findings of our study are as follows: (1) There were nearly 800,000 PVC alarms (18 per hour of monitoring) with the vast majority for isolated PVCs; (2) all of our ICU population had at least one PVC alarm; (3) R-on-T rarely occur, accounting for only 0.29% of the total number; (4) a small number of patients had most of the PVC alarms; and (5) PVCs are mostly concentrated in older, male, or patients who had PVC(s) present on a 12-lead ECG obtained within 24 hours of ICU admission.

Our study shows an extremely high number of PVC alarms generated during continuous ECG monitoring in the ICU. In the primary study, PVCs accounted for the vast majority of all of

the alarms generated (33% of over 2.5 million alarms). Our study builds on these findings[5] and others[16,17] by reporting the specific types of PVC alarms and associated patient characteristics. Because PVCs are typically configured in the bedside monitor as inaudible text message alarms that flash an alert on the monitor screen, many believe these types of alarms/alerts do not contribute to alarm fatigue. However, in a qualitative study exploring nurses' perceptions of clinical alarm, nurses reported that these types of flashing alerts do catch their attention, and they wonder if something is wrong with the patient and if an action/intervention is indicated.[29] Based upon these study findings and the very high number of PVC alarms we found, it is safe to assume that a nurse's attention is frequently diverted by flashing text messages associated with PVC alarms, and this potentially contributes to alarm fatigue. Interestingly, we found some instances where PVC alarms had been changed from an inaudible setting to a low-priority alarm level (one-beep alarm), which meant the PVC alarm(s) has been made audible. It is unclear why this setting adjustment occurred. Given the retrospective design of this study, we are unable to explain this finding. Regardless, our study shows that PVCs represent a major source of alarms (inaudible and audible) that contribute to the alarm burden in nurses. Future studies are needed to more fully examine the impact of inaudible text message alarms on alarm fatigue.

What remains unknown is whether monitoring for PVCs is clinically meaningful. For example, an R-on-T type PVC has been shown to be a precursor of VT and/or ventricular fibrillation,[30-32] and therefore, clinicians carefully monitor for these types of PVCs. In our study, we found that R-on-T type PVCs were uncommon, accounting for only 0.29 % of all of the PVC alarms. In clinical practice, clinicians commonly closely monitor for new-onset PVCs and/or more frequently occurring PVCs, which could signal electrolyte imbalances or ischemia and potential risk for lethal ventricular arrhythmias. However, current PVC alarm algorithms are not designed with these features (e.g., PVC trending or new-onset PVC(s)). More sophisticated PVC algorithms that could provide more clinically meaningful information could help identify high-risk patients who could benefit from pharmacological and/or electrolyte replacement to

reduce the potential for lethal arrhythmias. However, given the sheer volume of PVC alarms, as reported in this study, it is extremely challenging for nurses and/or providers to identify clinically important PVC patterns; rather, they are buried within all of the “noise” of frequent PVC alarms. Thus, there is a need for well-designed research studies including patient outcomes, to help identify PVC patterns associated with adverse outcomes (e.g., the occurrence of lethal arrhythmias or code blue) and to guide new algorithm development.

Prior studies examining arrhythmia alarms have found that alarms are often concentrated in a small number of patients.[5,33-35] Our findings, specific to PVC alarms, are similar. We found six patients who generated 40% of the total PVC alarms. In particular, one patient generated 153,347 (19%) PVC alarms during 744 hours of monitoring, including 124,944 alarms for isolated PVCs; hence this patient had constant PVC alarms. Further chart review showed that this patient had a history of mitral valve replacement. Mitral valve disease has been found to play an important role in the development of ventricular arrhythmias and PVCs.[36] However, the effectiveness of mitral valve replacement in reducing arrhythmia burden has been limited to case reports.[36-38] Therefore, this patient’s PVCs were likely persistent despite having the surgical procedure several years prior. Of note, this patient also had a history of chronic atrial fibrillation. It is possible that the large number of PVCs identified in this patient was actually due to Ashman’s phenomenon, a scenario where the algorithm misinterprets the wide single QRS complex as a PVC when in fact, it is an aberrantly conducted beat due to atrial fibrillation. Ashman phenomenon is commonly seen during atrial fibrillation and has a similar appearance of PVC on ECGs.[39,40] Therefore, some of the isolated PVCs in this patient might have been due to Ashman’s and not true PVCs, although we cannot state this with confidence since our PVC data were not annotated.

Intermittent ventricular pacing might also explain a high number of PVC alarms, as observed in one of the six patients with high PVC alarms. In our prior work, we have identified that the “PaceMode” feature is frequently not activated, which some manufacturers require to

turn on a filter for paced beats.[5,35,41] The PaceMode feature, when activated, will allow the monitor algorithm to detect pacer spikes, and thus, recognize paced rhythms when present. Of note, the PaceMode feature in this one particular patient had not activated throughout the 21-day stay in the ICU; hence, it is likely that many of the PVCs occurred during intermittent ventricular pacing. Some newer bedside monitors come with an algorithm that searches for a pacemaker; hence, this problem might be improved with this method.

Unfortunately, we did not find distinct patient and/or clinical characteristics to explain why some patients have high numbers of PVC alarms. The goal of this analysis was to help guide PVC alarm customization. For example, turning off the message alert for isolated PVC alarms in certain patients based on demographic and/or clinical characteristics who have high numbers of PVC alarms, and instead using PVCs/hour could reduce these types of alarms, while still providing an assessment of PVCs. However, changing this setting is an extra step for nurses, and there are no data on the safety of this practice. Nevertheless, it is clear that some patients have persistent, often isolated PVC alarms throughout their ICU stay, which suggests in some patients there should be a discussion between bedside nurses and providers about safe PVC alarm adjustments to reduce the potential for alarm fatigue. However, validation of optimal PVC alarm configurations (e.g., type, number), paired with patient outcomes data, is needed before solid recommendations can be implemented.

One consistent characteristic associated with PVCs during ICU ECG monitoring was the presence of PVC(s) on a baseline 12-lead ECG, specifically for isolated PVCs. Although the 12-lead ECG only provides a 10-second snapshot recording, the presence of PVCs on this test at ICU admission suggests that these patients may be prone to higher rates of PVC alarms. This finding is consistent with a prior study,[42] which may suggest PVCs in this situation are chronic and perhaps some patients tolerate the PVCs, even when frequent.[19] However, whether PVC frequency/burden is associated with acute adverse events in the ICU setting has not been investigated; hence, turning off PVC alarms in this patient group cannot be recommended. In

addition, given that all of these patients were presenting to the ICU for an acute illness, it is not safe to presume that the PVCs identified on the admission 12-lead ECG are chronic versus new, the latter of which could indicate a higher risk patient.

Surprisingly, although there was a trend for a history of IHD and/or HF to be associated with a higher rate of isolated PVCs, we did not find a significant association at the multiple comparisons corrected significance level of 0.00052. This is inconsistent with prior studies that found a history of MI and the severity of CAD were associated with frequent PVCs.[43,44] Furthermore, studies have found that in patients without CAD, left ventricular hypertrophy was associated with the frequency and complexity of PVCs.[45,46] We also found a trend suggesting that hypokalemia was associated with a lower incidence of run PVC, incongruent with prior studies.[47,48] In the Framingham Offspring Study, Tsuji et al. found that participants with a 0.46 mEq/L decrement in potassium had 1.27 times odds (95% CI 1.06 – 1.51) for having complex or frequent PVC as compared to participants without this drop in potasium.[48] However, our analysis showed that hyperkalemia was associated with a lower rate of R-on-T, although it is important to note the small sample size for this PVC type due to its infrequent occurrence. Interestingly, little is known about the relationship of hyperkalemia to PVC occurrence rates. However, one study shows that hyperkalemia causes velocity reductions in phase 0 of depolarization and a reduction in the height of action potential, resulting in non-excitable myocardial tissue;[49] thus, it is less likely for the ventricle to develop an arrhythmia.

Limitations

One limitation of this study is that the PVC alarms were not annotated as true/false; hence, the accuracy of the PVC events is unknown. However, these data represent commercially available algorithms; hence, our data represent real-world data that nurses and other clinicians experience at the bedside. We also do not know if the current monitoring algorithm missed any PVCs. However, in a recent review, the accuracy of PVC detection

algorithms was between 86% and 99%.[50] Of note, we did review the ECGs of the individual with the largest count of isolated PVCs and found that the PVC detection was accurate.

Another limitation is that our dataset contains outliers, which may substantially impact the count regression fits (we see minimal/negligible impact on the logistic regression for presence/absence of the dependent variable). Using a standardized cutoff of ≥3, the proportion of outliers ranged from 2.8% to 8.7% (and up to 12.1% for a lower cutoff of ≥2.5), depending on the PVC types, which may have influenced our ability to identify the association between demographics and clinical factors and the PVC types, and understand the true effect size. However, throughout our sensitivity analysis, we often found that those variables meeting Bonferroni's significance remained in the model regardless of the outlier treatment used. Nonetheless, our data show that a small group of patients have excessive PVC alarms that potentially contribute to alarm fatigue. Lastly, our study examined only one type of monitoring manufacturer in a single center. Thus, differences may exist with other manufacturers who have different types of PVC alarms and different alarm configurations in other institutions, which could influence alarm burden differences.

CONCLUSIONS

In the present study, we found that isolated PVCs were the most common among all PVC types alarms, while R-on-T type PVC were rare. Factors associated with a higher occurrence rate of isolated PVCs include older age, male sex, and presence of PVC(s) on a baseline 12-lead ECG. Older age is also associated with a higher incidence rate of bigeminy and couplets, whereas hyperkalemia is associated with a lower incidence rate of R-on-T. Efforts aimed at reducing frequently occurring alarms like PVCs, which are not typically aggressively treated or used routinely for clinical decision making, as well as more thoughtful alarm management in select patients with extreme numbers of PVC alarm, could potentially reduce the risk for alarm fatigue and ultimately improve care experiences for both clinicians and

patients. Ultimately, more sophisticated PVC algorithms tested using patient outcome data are needed to reduce nuisance PVC alarms.

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Table 3.1 – Demographic, past medical history, and baseline clinical characteristics upon ICU admission for ICU patients (N=446).

Characteristics	N (%)
Age, mean ± SD, year	59.97 ± 17.03
Sex	
Female	202 (45.3)
Male	244 (54.7)
Race	
Asian	76 (17)
Black or African American	34 (7.6)
Native Hawaiian or Pacific Islander	8 (1.8)
White	270 (60.5)
Unable or decline to state	58 (13)
Ethnicity	
Hispanic or Latino	49 (11)
Not Hispanic or Latino	390 (87.4)
Unable or decline to state	7 (1.6)
Past medical history	
Ischemic heart disease	72 (19)
Heart failure	44 (9.9)
PCI/stent/CABG	39 (8.7)
Stroke	37 (8.3)
Atrial fibrillation	46 (10.3)
Clinical characteristics at ICU admission [a]	
12-lead ECG	
PVCs present	24 (5.4)
Atrial fibrillation	35 (7.8)
Serum potassium mEq/L, mean ± SD	4.13 ± 0.75
Normal	*283 (63.5)*
Hyperkalemia	*34 (7.6)*
Hypokalemia	*125 (28)*
LVEF %, mean ± SD	57.86 ± 17.29
Preserved EF	*125 (28)*
Mid-range EF	*16 (3.6)*
Reduced EF	*32 (7.2)*
Primary ICU diagnosis	
Cardiovascular	98 (22)
Medical-surgical	178 (39.9)
Neurological	170 (38.1)

[a] The proportions, means, and standard deviations are calculated excluding patients with missing data as follows: 12-lead ECGs to determine presence of PVC and/or atrial fibrillation (n=95, 21.3%), serum potassium (n = 4, 0.9%), and baseline LVEF (n = 273, 61.2%). Serum potassium categories: normal (3.8 - 5.1 mEq/L), hypokalemia (<3.8 mEq/L), and hyperkalemia (>5.1 mEq/L). LVEF categories: preserved (≥ 50%), mid-range (41% - 49%), and reduced (≤ 40%) EF.

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 3.2 – Total PVC Alarms Distribution.

Alarm Type	Total # of Alarms (%)	Mean (Min-Max)	Median (Q_1, Q_3)	*n* Patients with Zero Count (%)
Isolated PVC	646,665 (81.13)	1,449.92 (0 – 124944)	108.5 (17.25, 653.5)	2 (0.45)
Couplet	43,907 (5.51)	98.44619 (0 – 11778	8 (3, 33)	47 (10.54)
Bigeminy	22,164 (2.78)	49.69507 (0 – 8035)	0 (0, 2)	275 (61.66)
Trigeminy	18,513 (2.32)	41.50897 (0 – 4898)	0 (0, 1)	297 (66.59)
Run PVC (VT>2)	12,595 (1.58)	28.23991 (0 – 3866)	2 (0, 8.75)	135 (30.27)
R-on-T	2,321 (0.29)	5.204036 (0 – 372)	0 (0, 1)	283 (63.45)
PVC/minute	50,907 (6.39)	114.1413 (0 – 7545)	6.5 (1, 53)	96 (21.52)

Table shows of 797,072 total premature ventricular complex (PVC) alarms, representing seven PVC types among 446 intensive care unit patients. The mean, lower quartile (Q_1), and upper quartile (Q_3) exclude zero counts.

Table 3.3 – Distribution of PVC types in 446 intensive care unit patients based on demographic and clinical characteristics using median and interquartile ranges.

Characteristics	Median (Q_1, Q_3)						
	Isolated PVC	Couplet	Bigeminy	Trigeminy	R-on-T	Run PVC	PVC/minute
Age Group, yr							
19 – 48	21.0 (4.8, 151.0)	3.0 (1.0, 16.2)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	1.0 (0.0, 4.0)	2.5 (0.0, 10.2)
49 – 61	82.5 (16.5, 530.5)	7.5 (3.0, 30.5)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (1.0, 6.0)	4.0 (1.0, 33.5)
62 – 73	205.5 (29.2, 1116.2)	14.5 (4.0, 44.8)	0.0 (0.0, 4.5)	0.0 (0.0, 3.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.8)	15.5 (1.0, 98.2)
74+	269.5 (72.8, 1530.2)	17.0 (5.2, 44.2)	1.0 (0.0, 9.8)	0.0 (0.0, 5.8)	0.0 (0.0, 1.0)	3.5 (1.0, 12.8)	21.0 (4.0, 135.2)
Sex							
Female	83.5 (17.2, 421.0)	8.0 (3.0, 31.8)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	2.0 (0.0, 10.0)	6.0 (1.0, 33.8)
Male	135.5 (17.8, 863.2)	8.0 (2.0, 33.2)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 6.2)	7.0 (1.0, 70.5)
Race							
Asian	124.5 (18.2, 615.8)	14.0 (4.0, 42.8)	0.0 (0.0, 3.5)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	3.0 (1.0, 14.0)	10.0 (1.0, 70.5)
Black or African American	182.5 (21.8, 813.8)	11.0 (3.0, 25.0)	0.0 (0.0, 2.0)	0.0 (0.0, 4.0)	0.0 (0.0, 2.0)	2.5 (1.0, 10.2)	11.0 (2.0, 54.2)
Native Hawaiian or Pacific Islander	188.0 (73.0, 626.0)	5.0 (3.5, 13.2)	0.0 (0.0, 3.2)	0.5 (0.0, 6.0)	0.0 (0.0, 0.2)	1.5 (0.0, 5.5)	8.5 (4.0, 60.0)
White	112.0 (15.2, 679.0)	8.0 (2.0, 31.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 8.0)	6.0 (1.0, 51.8)
Unknown or decline to state	81.0 (20.2, 422.0)	8.0 (3.0, 29.8)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 6.0)	5.5 (0.0, 36.8)
Ethnicity							
Hispanic or Latino	79.0 (19.0, 254.0)	8.0 (2.0, 30.0)	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	3.0 (0.0, 8.0)	6.0 (0.0, 28.0)
Not Hispanic or Latino	122.0 (17.0, 717.0)	8.0 (3.0, 35.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 9.0)	7.0 (1.0, 55.8)
Unknown or not reported	78.0 (43.0, 335.0)	6.0 (3.0, 14.0)	0.0 (0.0, 3.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.5)	0.0 (0.0, 1.5)	5.0 (1.5, 22.0)
Past medical history [a]							
IHD (-)	83.0 (14.0, 441.0)	7.0 (2.0, 27.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.0)	5.0 (1.0, 33.5)
IHD (+)	609.0 (100.5, 2451.5)	30.0 (8.0, 73.5)	1.0 (0.0, 13.0)	1.0 (0.0, 11.5)	0.0 (0.0, 1.0)	5.0 (1.0, 15.0)	45.0 (5.5, 182.5)
HF (-)	84.0 (14.0, 529.0)	8.0 (2.0, 29.8)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.0)	5.0 (1.0, 42.0)
HF (+)	853.5 (194.8, 2641.2)	26.5 (7.8, 155.0)	2.5 (0.0, 23.8)	1.5 (0.0, 19.8)	0.5 (0.0, 4.2)	7.0 (1.0, 19.0)	43.5 (9.2, 322.2)
PCI/Stent/CABG (-)	93.0 (15.0, 560.0)	8.0 (2.0, 30.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.0)	6.0 (1.0, 44.0)
PCI/Stent/CABG (+)	594.0 (139.5, 1795.0)	23.0 (7.0, 73.5)	1.0 (0.0, 6.0)	1.0 (0.0, 11.5)	0.0 (0.0, 1.0)	5.0 (1.0, 15.0)	38.0 (5.0, 146.5)
Stroke (-)	100.0 (15.0, 594.0)	8.0 (2.0, 30.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.0)	6.0 (1.0, 51.0)

Characteristics	Median (Q_1, Q_3)						
	Isolated PVC	**Couplet**	**Bigeminy**	**Trigeminy**	**R-on-T**	**Run PVC**	**PVC/minute**
Stroke (+)	347.0 (65.0, 1849.0)	32.0 (7.0, 66.0)	1.0 (0.0, 20.0)	1.0 (0.0, 16.0)	0.0 (0.0, 2.0)	6.0 (1.0, 18.0)	33.0 (4.0, 216.0)
Afib (-)	87.5 (14.0, 544.8)	8.0 (2.0, 29.2)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.0)	5.0 (1.0, 42.2)
Afib (+)	579.0 (145.0, 2522.0)	27.0 (7.5, 92.5)	3.0 (0.0, 17.5)	1.0 (0.0, 14.0)	0.0 (0.0, 1.8)	4.5 (1.0, 20.2)	41.0 (14.0, 283.2)
Characteristics at ICU admission [b]							
Baseline 12-lead ECG							
PVC absent on ECG	122.0 (23.0, 625.5)	8.0 (3.0, 32.5)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 9.0)	7.0 (1.0, 52.0)
PVC present on ECG	2670.5 (1247.0, 7077.8)	67.0 (24.5, 149.5)	11.5 (2.8, 287.0)	14.0 (1.8, 189.8)	1.0 (0.0, 5.2)	6.0 (3.0, 28.2)	216.5 (64.5, 410.8)
Afib absent on ECG	124.5 (22.8, 747.8)	8.5 (3.0, 35.0)	0.0 (0.0, 3.0)	0.0 (0.0, 1.2)	0.0 (0.0, 1.0)	2.0 (0.0, 9.0)	7.0 (1.0, 61.2)
Afib present on ECG	613.0 (182.5, 2415.0)	23.0 (6.0, 66.5)	1.0 (0.0, 7.0)	1.0 (0.0, 4.5)	1.0 (0.0, 4.0)	2.0 (1.0, 15.5)	20.0 (4.0, 260.0)
Normal serum potassium	100.0 (14.5, 624.5)	8.0 (2.0, 31.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 9.0)	6.0 (1.0, 54.0)
Hyperkalemia	152.0 (26.8, 624.0)	17.0 (3.8, 47.2)	0.0 (0.0, 2.8)	0.0 (0.0, 1.8)	0.5 (0.0, 1.0)	3.0 (1.0, 14.2)	14.0 (2.2, 53.2)
Hypokalemia	129.0 (24.0, 773.0)	10.0 (4.0, 31.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (1.0, 8.0)	7.0 (1.0, 46.0)
Preserved EF	146.0 (35.0, 774.0)	14.0 (4.0, 38.0)	0.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	3.0 (1.0, 9.0)	12.0 (2.0, 62.0)
Mid-range EF	345.5 (113.0, 2300.5)	24.5 (6.0, 51.2)	2.5 (0.8, 61.0)	0.5 (0.0, 3.5)	0.5 (0.0, 1.2)	10.0 (0.8, 12.0)	19.5 (2.8, 80.8)
Reduced EF	966.0 (180.8, 2349.5)	24.5 (5.5, 136.5)	1.5 (0.0, 16.2)	1.0 (0.0, 16.8)	0.5 (0.0, 9.5)	7.0 (1.0, 16.2)	73.5 (5.5, 345.0)
Primary admitting diagnosis							
Cardiovascular	343.0 (59.0, 1740.2)	16.0 (5.0, 64.2)	1.0 (0.0, 7.5)	0.5 (0.0, 9.8)	0.0 (0.0, 1.8)	4.5 (1.0, 15.8)	19.5 (2.2, 161.0)
Medical-surgical	87.5 (16.2, 599.5)	8.0 (3.0, 30.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	2.0 (0.0, 8.0)	6.0 (1.0, 36.8)
Neurological	56.0 (11.2, 432.2)	6.0 (1.0, 27.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 6.0)	4.0 (0.0, 37.5)

[a] Past medical history: (+) indicates “Yes”, (-) indicates “No”; a patient can have more than one medical history.

[b] The proportions, means, and standard deviations are calculated excluding patients with missing data (see **Table 1**).

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Table 3.4 – Demographic, past medical history, and baseline clinical characteristics upon ICU admission for outliers (standardized residual cutoff of 3; N = 41)

Characteristics	All Outliers (N=41)	N (%) for PVC Type					
		Isolated PVC (N = 21)	Bigeminy (N = 9)	Couplet (N = 11)	Trigeminy (N = 13)	Run PVC (N = 11)	R-on-T (N = 9)
Age, mean ± SD, year	64.78 ± 15.05	63.93 ± 17.17	70.22 ± 9.11	66.82 ± 19.01	68.85 ± 13.50	62.55 ± 15.38	64.33 ± 18.05
Sex							
Female	15 (36.6)	7 (33.3)	4 (44.4)	5 (45.5)	4 (30.8)	5 (45.5)	6 (66.7)
Male	26 (63.4)	14 (66.7)	5 (55.6)	6 (54.5)	9 (69.2)	6 (54.5)	3 (33.3)
Race							
Asian	7 (17.1)	1 (4.8)	2 (22.2)	2 (18.2)	1 (7.7)	3 (27.3)	4 (44.4)
Black or African American	6 (14.6)	3 (14.3)	0 (0.0)	0 (0.0)	2 (15.4)	1 (9.1)	1 (11.1)
Native Hawaiian or Pacific Islander	1 (2.4)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	23 (56.1)	13 (31.9)	6 (66.7)	8 (72.7)	8 (61.5)	7 (63.6)	4 (44.4)
Unable or decline to state	4 (9.8)	3 (14.3)	1 (11.1)	1 (9.1)	2 (15.4)	0 (0.0)	0 (0.0)
Ethnicity							
Hispanic or Latino	4 (9.8)	2 (9.5)	0 (0.0)	1 (9.1)	1 (7.7)	0 (0.0)	1 (11.1)
Not Hispanic or Latino	37 (90.2)	19 (90.5)	9 (100)	10 (90.9)	12 (92.3)	11 (100)	8 (88.9)
Unable or decline to state	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Past medical history							
IHD	15 (36.6)	8 (38.1)	4 (44.4)	5 (45.5)	7 (53.8)	4 (36.4)	2 (22.2)
HF	12 (29.3)	5 (2.8)	1 (11.1)	4 (36.4)	2 (15.4)	3 (27.3)	4 (44.4)
PCI/stent/CABG	6 (14.6)	3 (14.3)	2 (22.2)	2 (18.2)	2 (15.4)	1 (9.1)	1 (11.1)
Stroke	6 (14.6)	2 (9.5)	1 (11.1)	1 (9.1)	1 (7.7)	1 (9.1)	1 (11.1)
Atrial fibrillation	11 (26.8)	6 (28.6)	1 (11.1)	2 (18.2)	3 (23.1)	3 (27.3)	2 (22.1)
Clinical characteristics at ICU admission [a]							
12-lead ECG							
PVCs present	10 (24.4)	8 (38.1)	4 (44.4)	4 (36.4)	6 (46.2)	2 (18.2)	2 (22.2)
Atrial fibrillation	6 (14.6)	2 (9.5)	1 (11.1)	1 (9.1)	2 (15.4)	2 (18.2)	2 (22.2)
[Missing ECG data]	2 (4.9)	1 (4.8)	0 (0.0)	2 (18.2)	0 (0.0)	1 (9.1)	0 (0.0)
Serum potassium mEq/L, mean ± SD	4.32 ± 0.86	4.09 ± 0.42	4.22 ± 0.49	4.42 ± 0.82	4.09 ± 0.46	4.43 ± 0.86	4.89 ± 1.26
Normal	*27* (65.9)	*15* (71.4)	*7* (77.8)	*8* (72.7)	*10* (76.9)	*8* (72.7)	*5* (55.6)
Hypokalemia	*10* (24.4)	*6* (28.6)	*2* (22.2)	*2* (18.2)	*3* (23.1)	*2* (18.2)	*1* (11.1)
Hyperkalemia	*4* (9.7)	*0* (0.0)	*0* (0.0)	*1* (9.1)	*0* (0.0)	*1* (9.1)	*3* (33.3)
LVEF %, mean ± SD	43.10 ± 21.00	53.22 ± 25.15	46.67 ± 14.36	49.83 ± 28.44	57.25 ± 26.74	47.00 ± 20.96	36.67 ± 18.27
Preserved EF	*8* (19.5)	*6* (28.6)	*1* (11.1)	*3* (27.3)	*3* (23.1)	*2* (18.2)	*1* (11.1)
Mid-range EF	*1* (2.4)	*1* (4.8)	*1* (11.1)	*0* (0.0)	*0* (0.0)	*0* (0.0)	*0* (0.0)
Reduced EF	*11* (26.8)	*2* (9.5)	*1* (11.1)	*3* (27.3)	*1* (7.7)	*2* (18.2)	*5* (55.6)
[Missing]	*21* (51.2)	*12* (57.1)	*6* (66.7)	*5* (45.5)	*9* (69.2)	*7* (63.6)	*3* (33.3)

Characteristics	All Outliers (N=41)	N (%) for PVC Type					
		Isolated PVC (N = 21)	Bigeminy (N = 9)	Couplet (N = 11)	Trigeminy (N = 13)	Run PVC (N = 11)	R-on-T (N = 9)
Primary ICU diagnosis							
Cardiovascular	19 (46.3)	7 (33.3)	2 (22.2)	2 (18.2)	6 (46.2)	3 (27.3)	5 (55.6)
Medical-surgical	15 (36.6)	8 (38.1)	6 (66.7)	8 (72.7)	4 (30.8)	8 (72.7)	3 (33.3)
Neurological	7 (17.1)	6 (28.6)	1 (11.1)	1 (9.1)	3 (23.1)	0 (0.0)	1 (11.1)

[a] The proportions, means, and standard deviations are calculated excluding patients with missing data (see **Table 1**).

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 3.5 – Characteristics of six patients who generated the most PVC alarms.

Characteristics	Pt. #1	Pt. #2	Pt. #3	Pt. #4	Pt. #5	Pt. #6
Age	69	87	60	67	38	80
Sex	Female	Female	Male	Female	Female	Female
Race	White	White	White	White	White	Asian
Ethnicity	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino
Past medical history						
IHD	No	Yes	Yes	No	No	No
PCI/Stent/CABG	No	Yes	No	No	No	No
HF	No	No	No	No	No	Yes
Stroke	No	No	No	Yes	No	
Afib	No	No	No	Yes	No	Yes
At ICU admission						
PVC present	No	Yes	Yes	No	NA	Yes
Afib present	No	No	No	Yes	NA	Yes
Serum potassium (mEq/L)	5.1	4.1	4	4.1	4.5	4
LVEF (%)	No	No	0.83	No	0.73	No
Admission Diagnosis	Cervical cord compression with myelopathy	Dysphagia; squamous cell cancer	End-stage liver disease	Lung cancer	Hypoxemia	Right empyema; consideration for video-assisted thoracoscopic surgery
Note	-	-	-	Currently with demand pacemaker	History of tetralogy of Fallot; post pulmonary valve replacement	History of mitral valve replacement
Alarm Occurrences						
Isolated PVC	30198¶	20891¶	21476¶	19555	36044¶	124944¶
Bigeminy	3367¶	795¶	690	109	180	8035¶
Couplet	19	862¶	1131¶	1042	9254¶	11778¶
Trigeminy	1903¶	4898¶	376¶	62	402	2530¶
Run PVC	0	180¶	69	399¶	693¶	3866¶
R-on-T	3	5	0	80	169¶	23
PVC/minute	561	258	1889	1890	7545	2171
Total PVC	36051	27889	25631	23137	54287	153347
Monitoring hour	161.02	71.68	173.33	510.73	348.9	743.98

¶ denotes PVC types the patient was an outlier.

Abbreviations: Afib, atrial fibrillation; CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Table 3.6 – Univariate regression analyses (after standardized outliers ≥3 removed; **keeping outliers Supplemental Table 3.B, ≥2.5 removed Supplemental Table 3.C**) for counts of PVC outcomes. Cells display the incidence rate ratios (IRRs) for the counts of PVC type outcomes and 95% confidence interval (95% CI). *, P<.05; **, P<.00052. **Supplement Table 3.D, 3.E,** and 3.**F** shows the corresponding results of the logistic model, as part of the hurdle regression analysis.

Variable	Isolated PVC	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
Age	1.05 (1.04,1.06)**	1.04 (1.02,1.06)**	1.01 (.98,1.04)	1.02 (1.01,1.03)**	1.01 (1.00,1.02)	.98 (.96,1.00)
Male	1.72 (1.20,2.46)*	2.25 (.99,5.26)	1.70 (.75,4.22)	1.11 (.81,1.50)	.89 (.62,1.28)	.82 (.43,1.64)
Race: White	1.10 (.76,1.60)	1.21 (.53,2.86)	2.19 (1.01,5.26)	.87 (.64,1.19)	.80 (.55,1.15)	3.13 (1.53,6.23)*
Presence of clinical history						
IHD	2.98 (2.04,4.44)**	1.92 (.77,5.42)	.85 (.30,2.58)	1.68 (1.12,2.49)*	1.22 (.76,2.04)	.70 (.26,1.78)
HF	2.30 (1.51,3.89)*	.71 (.34,1.52)	1.22 (.46,3.94)	1.60 (1.03,2.63)*	1.52 (.88,2.80)	1.60 (.40,5.53)
PCI/stent/CABG	2.49 (1.49,4.32)*	.34 (.10,1.20)	1.28 (.34,4.81)	1.23 (.80,1.89)	1.22 (.65,2.46)	.41 (.13,1.18)
Stroke	1.79 (1.05,2.91)*	1.09 (.34,3.00)	1.29 (.37,4.81)	1.57 (.99,2.67)	1.36 (.81,2.24)	.98 (.35,2.64)
Atrial fibrillation	2.15 (1.40,3.62)*	2.25 (.95,5.05)	1.32 (.47,4.22)	2.03 (1.37,3.03)*	1.37 (.81,2.31)	1.33 (.44,4.57)
Clinical characteristics on ICU admission						
PVC on ECG	3.50 (2.31,5.15)**	4.90 (1.61,14.88)*	3.39 (.74,14.15)	2.46 (1.58,3.90)**	2.05 (1.11,3.67)*	1.07 (.35,3.46)
Atrial fibrillation on ECG	1.53 (.97,2.52)	.63 (.17,2.11)	.58 (.13,1.94)	1.46 (.90,2.47)	1.39 (.74,2.60)	1.18 (.35,4.14)
(log) Potassium	1.70 (.60,4.29)	12.06 (.74,249.64)	.56 (.03,9.03)	1.39 (.56,3.35)	2.80 (.99,7.92)	.02 (.00,.40)*
Hypokalemia	1.09 (.72,1.72)	.59 (.24,1.54)	2.17 (.84,6.62)	.99 (.71,1.40)	.64 (.45,.92)*	1.56 (.76,3.35)
Hyperkalemia	1.04 (.60,1.76)	1.35 (.34,4.10)	.29 (.09,.98)*	.77 (.49,1.36)	.80 (.46,1.78)	.06 (.02,.13)*
Mid-level/Reduced LVEF	2.10 (1.24,3.35)*	.90 (.27,2.80)	1.99 (.72,5.47)	1.38 (.83,2.32)	1.29 (.77,2.13)	2.11 (.72,6.23)
Neuro/neurosurgical diagnosis	.70 (.47,1.03)	.67 (.25,1.72)	.80 (.30,1.83)	.77 (.56,1.08)	.87 (.60,1.23)	.85 (.41,1.76)
Cardiovascular diagnosis	2.05 (1.39,3.05)**	.80 (.35,1.73)	.86 (.33,2.21)	1.70 (1.21,2.40)*	1.53 (1.05,2.26)*	1.14 (.52,2.86)

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Table 3.7 – Stepwise regression analyses (after standardized outliers ≥3 removed; **keeping outliers Supplemental Table 3.G, ≥2.5 removed Supplemental Table 3.H**) for counts of PVC outcomes. An empty cell indicates it is not in the final stepwise model. Cells display the incidence rate ratios (IRRs) for the counts of PVC type outcomes and 95% confidence interval (95% CI). *, P<.05; **, P<.00052. **Supplement Table 3.I, 3.J,** and 3.**K** shows the corresponding results of the logistic model, as part of the hurdle regression analysis.

Variable	Isolated PVC	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
(Intercept)	.22 (.09,.44)**	.00 (.00,.01)**	.00 (.00,.05)**	.07 (.04,.14)**	.06 (.05,.08)**	.00 (.00,.01)
Age	**1.04 (1.03,1.05)****	**1.04 (1.02,1.06)****	-	**1.02 (1.01,1.03)****		
Male	**1.94 (1.40,2.84)****		-			
Race: White	-	-	-	-	-	2.92 (1.66,5.70)*
History of IHD	1.75 (1.10,2.58)*	-	-	-	-	--
History of HF	2.06 (1.28,3.15)*	-	-	-	-	-
PVC on baseline ECG	**2.85 (1.83,4.30)****	5.70 (1.03,15.49)*		2.16 (1.34,3.46)*	2.18 (1.10,3.63)*	
Hypokalemia at baseline					.65 (.47,.88)*	
Hyperkalemia at baseline			.29 (.07,.74)*			**.07 (.03,.17)****
Cardiovascular diagnosis				1.74 (1.18,2.44)*	1.72 (1.15,2.58)*	

Abbreviations: ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PVC, premature ventricular complex.

Supplement Table 3.A – Distribution of PVC alarms in 446 ICU patients based on demographic and clinical characteristics based on mean and minimum/maximum range.

Characteristics	Mean [min, max]						
	Isolated PVC	Couplet	Bigeminy	Trigeminy	R-on-T	Run PVC	PVC/minute
Age group							
19 - 48	701.8 [1.0, 36044.0]	105.7 [0.0, 9254.0]	3.6 [0.0, 180.0]	17.5 [0.0, 854.0]	2.9 [0.0, 169.0]	13.0 [0.0, 693.0]	106.8 [0.0, 7545.0]
49 - 61	990.6 [0.0, 21476.0]	54.9 [0.0, 1967.0]	23.2 [0.0, 975.0]	16.1 [0.0, 549.0]	4.7 [0.0, 129.0]	23.7 [0.0, 1701.0]	81.7 [0.0, 1889.0]
62 - 73	1514.7 [0.0, 30198.0]	70.9 [0.0, 1942.0]	74.8 [0.0, 3367.0]	51.0 [0.0, 2630.0]	5.0 [0.0, 230.0]	29.7 [0.0, 1700.0]	112.6 [0.0, 1890.0]
74+	2730.2 [2.0, 124944.0]	171.6 [0.0, 11778.0]	102.9 [0.0, 8035.0]	86.7 [0.0, 4898.0]	8.5 [0.0, 372.0]	48.7 [0.0, 3866.0]	161.4 [0.0, 2954.0]
Sex							
Female	1697.4 [1.0, 124944.0]	147.6 [0.0, 11778.0]	69.0 [0.0, 8035.0]	55.1 [0.0, 4898.0]	7.7 [0.0, 372.0]	34.3 [0.0, 3866.0]	111.6 [0.0, 7545.0]
Male	1245.0 [0.0, 22081.0]	57.8 [0.0, 1967.0]	33.7 [0.0, 1596.0]	30.2 [0.0, 2630.0]	3.1 [0.0, 182.0]	23.2 [0.0, 1701.0]	116.2 [0.0, 2954.0]
Race							
Asian	2354.8 [0.0, 124944.0]	226.1 [0.0, 11778.0]	127.7 [0.0, 8035.0]	39.5 [0.0, 2530.0]	11.9 [0.0, 372.0]	87.7 [0.0, 3866.0]	94.2 [0.0, 2171.0]
Black or African American	1179.7 [1.0, 7233.0]	43.2 [0.0, 305.0]	9.3 [0.0, 114.0]	33.8 [0.0, 549.0]	4.9 [0.0, 108.0]	10.9 [0.0, 81.0]	109.6 [0.0, 806.0]
Native Hawaiian or Pacific Islander	602.6 [5.0, 2468.0]	16.1 [0.0, 72.0]	2.8 [0.0, 13.0]	6.5 [0.0, 37.0]	0.8 [0.0, 5.0]	5.8 [0.0, 27.0]	72.8 [0.0, 349.0]
Unknown or decline to state	629.3 [1.0, 5038.0]	28.5 [0.0, 323.0]	6.0 [0.0, 263.0]	21.3 [0.0, 854.0]	0.7 [0.0, 10.0]	4.7 [0.0, 36.0]	45.7 [0.0, 536.0]
White	1430.6 [0.0, 36044.0]	86.9 [0.0, 9254.0]	43.6 [0.0, 3367.0]	48.4 [0.0, 4898.0]	4.5 [0.0, 182.0]	19.4 [0.0, 1701.0]	136.2 [0.0, 7545.0]
Ethnicity							
Hispanic or Latino	615.8 [1.0, 6103.0]	31.1 [0.0, 323.0]	4.2 [0.0, 145.0]	20.2 [0.0, 854.0]	0.9 [0.0, 14.0]	5.5 [0.0, 36.0]	55.2 [0.0, 589.0]
Not Hispanic or Latino	1575.1 [0.0, 124944.0]	108.4 [0.0, 11778.0]	56.3 [0.0, 8035.0]	44.9 [0.0, 4898.0]	5.8 [0.0, 372.0]	31.6 [0.0, 3866.0]	123.1 [0.0, 7545.0]
Unknown or not reported	316.9 [4.0, 1380.0]	13.6 [0.0, 55.0]	2.0 [0.0, 8.0]	0.4 [0.0, 1.0]	0.6 [0.0, 3.0]	2.4 [0.0, 14.0]	28.6 [0.0, 148.0]
Past medical history							

Characteristics	Mean [min, max]						
	Isolated PVC	Couplet	Bigeminy	Trigeminy	R-on-T	Run PVC	PVC/minute
IHD (-)	1224.3 [0.0, 124944.0]	101.2 [0.0, 11778.0]	47.5 [0.0, 8035.0]	23.9 [0.0, 2530.0]	4.4 [0.0, 230.0]	30.2 [0.0, 3866.0]	94.8 [0.0, 7545.0]
IHD (+)	2641.6 [7.0, 22081.0]	84.1 [0.0, 862.0]	61.4 [0.0, 1596.0]	134.5 [0.0, 4898.0]	9.4 [0.0, 372.0]	17.8 [0.0, 181.0]	216.3 [0.0, 2954.0]
HF (-)	1008.3 [0.0, 36044.0]	68.3 [0.0, 9254.0]	33.3 [0.0, 3367.0]	36.5 [0.0, 4898.0]	3.8 [0.0, 230.0]	19.4 [0.0, 1701.0]	89.3 [0.0, 7545.0]
HF (+)	5484.5 [8.0, 124944.0]	374.1 [2.0, 11778.0]	199.4 [0.0, 8035.0]	87.1 [0.0, 2530.0]	18.1 [0.0, 372.0]	109.4 [0.0, 3866.0]	341.5 [1.0, 2954.0]
PCI/Stent/CABG (-)	1353.8 [0.0, 124944.0]	100.2 [0.0, 11778.0]	50.4 [0.0, 8035.0]	32.0 [0.0, 2630.0]	5.1 [0.0, 372.0]	29.6 [0.0, 3866.0]	103.2 [0.0, 7545.0]
PCI/Stent/CABG (+)	2453.3 [7.0, 22081.0]	80.5 [1.0, 862.0]	42.7 [0.0, 795.0]	140.9 [0.0, 4898.0]	6.0 [0.0, 182.0]	14.5 [0.0, 180.0]	228.0 [0.0, 2954.0]
Stroke (-)	1330.0 [0.0, 124944.0]	97.5 [0.0, 11778.0]	50.5 [0.0, 8035.0]	37.3 [0.0, 4898.0]	4.9 [0.0, 372.0]	28.5 [0.0, 3866.0]	99.9 [0.0, 7545.0]
Stroke (+)	2775.1 [9.0, 19555.0]	109.2 [1.0, 1042.0]	40.9 [0.0, 500.0]	88.2 [0.0, 2630.0]	8.6 [0.0, 182.0]	24.9 [0.0, 399.0]	271.4 [0.0, 1890.0]
Afib (-)	987.8 [0.0, 36044.0]	68.4 [0.0, 9254.0]	32.3 [0.0, 3367.0]	31.3 [0.0, 4898.0]	4.1 [0.0, 230.0]	19.2 [0.0, 1701.0]	88.8 [0.0, 7545.0]
Afib (+)	5468.0 [12.0, 124944.0]	359.8 [0.0, 11778.0]	200.7 [0.0, 8035.0]	129.9 [0.0, 2630.0]	14.4 [0.0, 372.0]	106.5 [0.0, 3866.0]	334.6 [0.0, 2954.0]
Characteristics upon ICU admission [a]							
Baseline 12-lead ECG**							
PVC absent on ECG	1069.2 [1.0, 30198.0]	53.4 [0.0, 1967.0]	28.9 [0.0, 3367.0]	26.2 [0.0, 2630.0]	5.0 [0.0, 372.0]	21.8 [0.0, 1701.0]	92.6 [0.0, 2954.0]
PVC present of ECG	9788.8 [288.0, 124944.0]	640.3 [3.0, 11778.0]	502.3 [0.0, 8035.0]	390.0 [0.0, 4898.0]	17.1 [0.0, 230.0]	182.1 [0.0, 3866.0]	417.1 [3.0, 2171.0]
Afib absent on ECG	1245.6 [1.0, 30198.0]	54.5 [0.0, 1967.0]	40.5 [0.0, 3367.0]	39.3 [0.0, 4898.0]	4.4 [0.0, 230.0]	21.0 [0.0, 1701.0]	102.7 [0.0, 2954.0]
Afib present on ECG	5455.7 [18.0, 124944.0]	445.7 [2.0, 11778.0]	248.3 [0.0, 8035.0]	157.5 [0.0, 2630.0]	18.6 [0.0, 372.0]	138.7 [0.0, 3866.0]	224.2 [0.0, 2171.0]
Normal serum potassium	1643.1 [0.0, 124944.0]	122.4 [0.0, 11778.0]	61.7 [0.0, 8035.0]	49.1 [0.0, 4898.0]	3.7 [0.0, 182.0]	32.5 [0.0, 3866.0]	117.6 [0.0, 7545.0]
Hyperkalemia	714.5 [3.0, 6103.0]	50.3 [1.0, 608.0]	17.4 [0.0, 277.0]	2.9 [0.0, 36.0]	20.0 [0.0, 372.0]	16.2 [0.0, 283.0]	86.1 [0.0, 832.0]
Hypokalemia	1254.3 [1.0, 22081.0]	59.6 [0.0, 1967.0]	32.7 [0.0, 1596.0]	36.1 [0.0, 2630.0]	4.6 [0.0, 129.0]	22.6 [0.0, 1701.0]	116.8 [0.0, 2954.0]
Preserved EF	1379.4 [1.0, 36044.0]	122.5 [0.0, 9254.0]	22.1 [0.0, 690.0]	17.3 [0.0, 549.0]	3.5 [0.0, 169.0]	16.4 [0.0, 693.0]	174.6 [0.0, 7545.0]
Mid-range EF	1597.7	38.9	57.5	5.8	2.4	8.8	93.7

Characteristics	Mean [min, max]						
	Isolated PVC	**Couplet**	**Bigeminy**	**Trigeminy**	**R-on-T**	**Run PVC**	**PVC/minute**
	[8.0, 6103.0]	[3.0, 131.0]	[0.0, 318.0]	[0.0, 45.0]	[0.0, 17.0]	[0.0, 23.0]	[1.0, 589.0]
Reduced EF	2247.9 [11.0, 15264.0]	95.9 [2.0, 608.0]	35.3 [0.0, 500.0]	28.3 [0.0, 509.0]	31.3 [0.0, 372.0]	22.8 [0.0, 283.0]	266.0 [0.0, 1539.0]
Primary admitting diagnosis							
Cardiovascular	1752.8 [0.0, 22081.0]	65.9 [0.0, 835.0]	24.2 [0.0, 500.0]	49.5 [0.0, 2630.0]	10.4 [0.0, 372.0]	15.1 [0.0, 210.0]	170.1 [0.0, 2954.0]
Medical-surgical	1989.0 [0.0, 124944.0]	187.6 [0.0, 11778.0]	85.2 [0.0, 8035.0]	56.2 [0.0, 4898.0]	4.9 [0.0, 169.0]	56.8 [0.0, 3866.0]	136.1 [0.0, 7545.0]
Neurological	710.9 [1.0, 30198.0]	23.9 [0.0, 305.0]	27.2 [0.0, 3367.0]	21.5 [0.0, 1903.0]	2.5 [0.0, 108.0]	5.9 [0.0, 82.0]	58.9 [0.0, 1105.0]

[a] The proportions, means, and standard deviations are calculated excluding patients with missing data: 12-lead ECGs for the presence of PVC and atrial fibrillation (n=95, 21.3%), serum potassium (n = 4, 0.9%), and baseline LVEF (n = 273, 61.2%). Serum potassium categories: normal (3.8 - 5.1 mEq/L), hypokalemia (<3.8 mEq/L), and hyperkalemia (>5.1 mEq/L). LVEF categories: preserved (≥ 50%), mid-range (41% - 49%), and reduced (≤ 40%) EF.

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Supplement Table 3.B – Univariate regression analyses for counts of PVC outcomes with **outliers (≥3) included**. Cells display the incidence rate ratios (IRRs) for the counts of PVC type outcomes and 95% confidence interval (95% CI). Pooled 6 PVC variable is included below and shows identical results with isolated PVC, of which making up 86% of the pooled data. *, P<.05; **, P<.00052.

Variable	Isolated PVC	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
Age	1.04 (1.02,1.06)**	1.09 (1.05,1.14)**	1.03 (.95,1.09)	1.02 (.98,1.04)	1.01 (.99,1.04)	1.02 (.97,1.06)
Male	1.52 (.88,2.48)	1.70 (.42,10.07)	.65 (.09,5.58)	.69 (.33,1.27)	1.03 (.45,2.27)	.28 (.07,.87)*
Race: White	1.28 (.78,2.04)	2.83 (.78,12.43)	1.81 (.30,11.82)	1.10 (.58,2.27)	.78 (.33,1.80)	.47 (.11,1.59)
Presence of clinical history						
IHD	3.25 (2.04,5.31)**	3.67 (.83,20.09)	4.31 (.78,28.79)	1.95 (1.00,3.82)*	1.66 (.69,4.48)	3.19 (.32,21.98)
HF	2.14 (1.24,3.77)*	.45 (.07,3.71)	.47 (.07,2.83)	2.70 (1.22,6.49)*	2.75 (.95,10.59)	8.85 (1.98,42.10)*
PCI/stent/CABG	2.30 (1.26,4.93)*	.91 (.05,5.05)	4.90 (.17,42.10)	1.64 (.70,4.48)	1.06 (.37,3.71)	.49 (.07,3.46)
Stroke	1.44 (.78,2.68)	.51 (.09,3.13)	.42 (.05,3.39)	1.18 (.60,2.48)	.73 (.36,1.53)	.68 (.14,3.63)
Atrial fibrillation	2.48 (1.45,4.28)*	.58 (.15,2.83)	.73 (.11,3.63)	2.23 (1.07,5.81)	2.12 (.72,8.67)	5.37 (.58,33.12)
Clinical characteristics on ICU admission						
PVC on ECG	6.72 (3.92,11.15)**	4.48 (.94,17.12)*	8.08 (1.37,64.72)*	6.49 (2.94,14.30)**	4.53 (1.08,17.99)*	2.01 (.21,10.28)
Atrial fibrillation on ECG	1.15 (.65,2.52)	.49 (.05,4.35)	.49 (.04,4.18)	2.03 (.81,7.17)	2.32 (.61,11.36)	4.76 (.54,35.52)
(log) Potassium	2.31 (.78,8.85)	1.76 (.00,3197.10)	.48 (.00,10097.06)	4.26 (1.15,36.97)	6.17 (.44,80.64)	20.29 (1.15,428.38)
Hypokalemia	.83 (.51,1.33)	1.78 (.15,14.88)	.40 (.08,1.62)	.58 (.31,.93)*	.63 (.25,1.78)	.52 (.14,1.61)
Hyperkalemia	.55 (.31,.94)*	.19 (.04,.71)*	.03 (.01,.13)**	.55 (.27,1.12)	.64 (.22,2.04)	8.33 (.78,45.15)
Mid-level/Reduced LVEF	1.57 (.89,2.81)	2.07 (.48,9.30)	.72 (.13,6.42)	1.09 (.38,2.46)	1.46 (.66,3.10)	15.49 (4.10,69.41)**
Neuro/neurosurgical diagnosis	.75 (.45,1.24)	.62 (.11,3.03)	.77 (.09,4.62)	.43 (.23,.72)*	.31 (.16,.55)**	.31 (.09,1.00)
Cardiovascular diagnosis	1.48 (.95,2.33)	.36 (.08,1.49)	.56 (.10,2.40)	1.01 (.56,1.68)	.90 (.45,1.75)	5.70 (1.63,22.87)*

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Supplement Table 3.C – Univariate regression analyses for counts of PVC outcomes with **outliers (≥2.5) excluded**. Cells display the incidence rate ratios (IRRs) for the counts of PVC type outcomes and 95% confidence interval (95% CI). *, P<.05; **, P<.00052.

Variable	Isolated PVC	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
Age	1.06 (1.05,1.07)**	1.03 (1.01,1.05)*	1.03 (1.00,1.05)*	1.03 (1.03,1.04)**	1.02 (1.01,1.03)**	.99 (.97,1.01)
Male	1.44 (1.01,2.06)*	2.13 (.97,4.22)*	1.06 (.50,2.26)	.91 (.70,1.17)	.85 (.63,1.17)	.55 (.30,1.05)
Race: White	1.07 (.75,1.52)	.87 (.40,1.96)	1.03 (.48,2.22)	.96 (.74,1.24)	.93 (.68,1.29)	2.75 (1.41,5.16)*
Presence of clinical history						
IHD	2.59 (1.77,3.71)**	1.01 (.43,2.33)	.89 (.38,2.14)	1.66 (1.23,2.27)*	.89 (.60,1.37)	.64 (.24,1.45)
HF	1.55 (1.04,2.29)*	1.25 (.62,2.68)	1.19 (.56,2.35)	1.41 (1.04,1.93)*	1.01 (.65,1.56)	.60 (.20,2.12)
PCI/stent/CABG	2.06 (1.27,3.31)*	.56 (.17,1.97)	1.02 (.37,2.83)	1.63 (1.11,2.40)*	.67 (.44,1.03)	.55 (.14,1.43)
Stroke	1.92 (1.14,3.18)*	1.23 (.40,3.42)	1.09 (.39,2.86)	1.38 (.98,2.04)	1.46 (.93,2.29)	1.34 (.48,3.67)
Atrial fibrillation	1.91 (1.31,2.84)*	1.72 (.76,3.71)	1.28 (.55,2.83)	1.74 (1.28,2.36)**	1.23 (.78,1.93)	.97 (.35,2.68)
Clinical characteristics on ICU admission						
PVC on ECG	4.29 (2.89,6.20)**	.76 (.28,2.13)	1.70 (.45,4.95)	2.30 (1.62,3.06)**	2.10 (1.15,3.53)*	.83 (.27,1.88)
Atrial fibrillation on ECG	1.87 (1.18,2.95)*	1.16 (.32,4.01)	.50 (.15,1.93)	1.32 (.92,1.99)	1.20 (.68,2.11)	.89 (.30,2.46)
(log) Potassium	2.32 (.97,5.55)	8.00 (.63,148.41)	2.04 (.17,28.50)	1.04 (.56,2.02)	1.19 (.53,2.66)	.01 (.00,.09)**
Hypokalemia	.92 (.63,1.36)	.74 (.31,1.79)	1.12 (.48,2.75)	1.02 (.77,1.34)	.79 (.58,1.11)	1.75 (.90,3.46)
Hyperkalemia	1.24 (.70,2.15)	1.34 (.33,4.22)	.47 (.17,1.56)	.90 (.63,1.34)	.70 (.46,1.01)	.08 (.03,.17)*
Mid-level/Reduced LVEF	1.80 (1.08,2.98)*	1.55 (.49,4.48)	3.46 (1.49,8.17)*	.96 (.63,1.52)	1.34 (.84,2.05)	1.54 (.58,3.90)
Neuro/neurosurgical diagnosis	.85 (.58,1.27)	.36 (.18,.84)*	1.71 (.79,3.56)	.85 (.65,1.14)	1.12 (.81,1.56)	1.05 (.52,2.00)
Cardiovascular diagnosis	1.73 (1.20,2.48)*	1.26 (.57,2.64)	1.06 (.50,2.14)	1.57 (1.19,2.06)*	1.08 (.79,1.54)	1.09 (.55,2.10)

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Supplement Table 3.D – Logistic regression analyses of presence/absence of PVC outcomes (**outliers ≥3 excluded**), as part of the hurdle regression model. Cells display odds ratios (ORs) and 95% CIs. Some models would not fit because there was not enough variation in the outcome for the model of the presence of the dichotomous covariate to fit, and so are left blank. *, P<.05; **, P<.00052.

Variable	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
Age	1.03 (1.01,1.04)**	1.03 (1.02,1.05)**	1.03 (1.01,1.05)*	1.03 (1.01,1.04)**	1.02 (1.00,1.03)*
Male	1.12 (.75,1.64)	1.25 (.84,1.91)	.97 (.52,1.80)	.76 (.51,1.17)	.92 (.62,1.38)
Race: White	.99 (.65,1.49)	.81 (.53,1.22)	1.12 (.58,2.13)	.74 (.48,1.12)	.77 (.52,1.14)
Presence of clinical history					
IHD	2.94 (1.73,5.10)**	2.86 (1.64,4.95)**		2.64 (1.34,5.47)*	1.19 (.70,2.01)
HF	2.94 (1.56,5.87)*	3.32 (1.70,6.69)*		1.96 (.89,5.10)	1.57 (.79,3.06)
PCI/Stent/CABG	2.44 (1.21,5.05)*	2.52 (1.21,5.16)*		3.22 (1.27,10.28)	1.38 (.69,2.80)
Stroke	2.97 (1.43,6.30)*	3.03 (1.49,6.23)*			1.35 (.63,2.77)
Atrial fibrillation	3.60 (1.80,6.96)**	2.54 (1.31,4.95)*		2.49 (1.10,6.69)	1.61 (.83,3.10)
Clinical characteristics on ICU admission					
PVC on ECG					2.42 (.95,6.69)
Atrial fibrillation on ECG	2.21 (1.04,4.90)*	1.82 (.85,3.78)		2.21 (.85,7.32)	3.10 (1.44,7.03)*
(log) Potassium	2.75 (.86,9.49)	1.84 (.49,6.42)	4.31 (1.25,21.98)*	.60 (.19,1.94)	1.04 (.28,3.82)
Hypokalemia	.85 (.55,1.32)	.91 (.58,1.47)	1.26 (.60,2.70)	1.75 (1.08,2.89)*	.96 (.61,1.48)
Hyperkalemia	1.39 (.65,2.86)	1.19 (.53,2.50)		1.72 (.71,4.57)	1.56 (.70,3.25)
Mid-level/Reduced LVEF	1.98 (.96,4.01)	1.81 (.89,3.63)		.77 (.34,1.87)	1.03 (.49,2.09)
Neuro/neurosurgical diagnosis	.64 (.43,.98)*	.71 (.46,1.11)	.43 (.22,.81)*	.49 (.32,.74)*	.69 (.47,1.07)
Cardiovascular diagnosis	2.67 (1.66,4.35)**	2.34 (1.45,3.82)*	2.57 (1.01,8.85)	2.07 (1.19,3.67)*	1.14 (.70,1.80)

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Supplement Table 3.E – Logistic regression analyses of presence/absence of PVC outcomes with **outliers (≥3) included**, as part of the hurdle regression model. Cells display odds ratios (ORs) and 95% CIs. Some models would not fit because there was not enough variation in the outcome for the model of the presence of the dichotomous covariate to fit, and so are left blank. *, P<.05; **, P<.00052.

Variable	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
Age	1.03 (1.02,1.04)**	1.03 (1.02,1.05)**	1.03 (1.01,1.05)*	1.03 (1.01,1.04)**	1.02 (1.00,1.03)*
Male	1.14 (.77,1.67)	1.30 (.87,1.96)	.97 (.50,1.79)	.77 (.51,1.18)	.88 (.60,1.32)
Race: White	1.03 (.70,1.51)	.83 (.56,1.25)	1.13 (.60,2.10)	.75 (.48,1.14)	.74 (.50,1.11)
Presence of clinical history					
IHD	3.06 (1.79,5.21)**	3.25 (1.93,5.58)**		2.75 (1.41,5.93)*	1.21 (.71,2.03)
HF	2.86 (1.45,5.42)*	3.29 (1.64,6.30)*		2.08 (.93,5.16)	1.85 (.99,3.49)
PCI/Stent/CABG	2.52 (1.29,5.00)*	2.54 (1.29,5.16)*		3.19 (1.25,9.78)	1.38 (.71,2.77)
Stroke	2.89 (1.41,5.81)*	2.89 (1.43,5.93)*			1.36 (.64,2.75)
Atrial fibrillation	3.46 (1.70,6.69)**	2.65 (1.38,5.05)*		2.62 (1.12,6.69)	1.68 (.89,3.10)
Clinical characteristics on ICU admission					
PVC on ECG					2.66 (1.07,6.82)
Atrial fibrillation on ECG	2.15 (1.06,4.71)*	1.85 (.90,3.90)		2.28 (.84,7.61)	3.22 (1.49,6.96)*
(log) Potassium	2.97 (.91,9.30)	1.79 (.49,6.36)	4.62 (1.24,24.78)*	.67 (.22,2.25)	1.42 (.42,5.05)
Hypokalemia	.82 (.54,1.26)	.90 (.57,1.42)	1.24 (.58,2.72)	1.72 (1.02,2.75)*	.92 (.58,1.40)
Hyperkalemia	1.29 (.60,2.68)	1.08 (.50,2.30)		1.72 (.73,4.48)	1.81 (.85,3.71)
Mid-level/Reduced LVEF	2.12 (1.08,4.48)*	1.77 (.92,3.60)		.80 (.35,1.90)	1.27 (.61,2.51)
Neuro/neurosurgical diagnosis	.63 (.42,.94)*	.68 (.45,1.04)	.41 (.22,.77)*	.46 (.31,.71)**	.66 (.44,.99)*
Cardiovascular diagnosis	2.56 (1.63,4.06)**	2.48 (1.57,3.94)**	2.55 (1.03,8.17)	2.08 (1.16,3.67)*	1.26 (.78,1.97)

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Supplement Table 3.F – Logistic regression analyses of presence/absence of PVC outcomes with **outliers (≥2.5) excluded**, as part of the hurdle regression model. Cells display odds ratios (ORs) and 95% CIs. Some models would not fit because there was not enough variation in the outcome for the model of the presence of the dichotomous covariate to fit, and so are left blank. *, P<.05; **, P<.00052.

Variable	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
Age	1.02 (1.01,1.04)**	1.03 (1.02,1.05)**	1.03 (1.01,1.05)*	1.03 (1.02,1.04)**	1.02 (1.01,1.03)*
Male	1.10 (.74,1.65)	1.21 (.80,1.82)	.95 (.50,1.76)	.77 (.51,1.14)	.89 (.59,1.34)
Race: White	.97 (.65,1.43)	.75 (.50,1.16)	1.13 (.60,2.06)	.76 (.49,1.16)	.75 (.49,1.12)
Presence of clinical history					
IHD	2.80 (1.62,4.85)**	2.89 (1.67,5.05)**		2.52 (1.29,5.37)*	1.18 (.67,2.05)
HF	3.10 (1.59,6.11)*	3.29 (1.69,6.75)*		1.83 (.81,4.53)	1.43 (.71,3.00)
PCI/Stent/CABG	2.55 (1.26,5.31)*	2.47 (1.24,5.21)*		3.00 (1.18,10.91)	1.43 (.69,2.94)
Stroke	2.94 (1.47,6.42)*	2.97 (1.39,6.17)*			1.40 (.66,2.86)
Atrial fibrillation	3.29 (1.66,6.69)*	2.51 (1.29,4.81)*		2.43 (1.06,6.62)	1.58 (.79,3.06)
Clinical characteristics on ICU admission					
PVC on ECG					2.31 (.89,6.42)
Atrial fibrillation on ECG	2.33 (1.10,5.00)*	1.74 (.79,3.82)		2.11 (.79,7.24)	3.06 (1.38,6.96)*
(log) Potassium	2.44 (.74,8.17)	2.00 (.49,7.32)	4.06 (1.10,19.30)	.54 (.17,1.81)	1.03 (.30,4.01)
Hypokalemia	.86 (.55,1.35)	.86 (.54,1.37)	1.28 (.60,2.69)	1.82 (1.13,3.00)*	.97 (.62,1.49)
Hyperkalemia	1.34 (.62,2.77)	1.24 (.54,2.65)		1.71 (.72,4.71)	1.62 (.73,3.56)
Mid-level/Reduced LVEF	2.02 (.98,4.06)	1.89 (.94,3.78)		.76 (.32,1.85)	.99 (.48,2.10)
Neuro/neurosurgical diagnosis	.62 (.41,.96)*	.75 (.49,1.16)	.43 (.23,.81)*	.50 (.33,.76)*	.71 (.46,1.08)
Cardiovascular diagnosis	2.75 (1.74,4.39)**	2.39 (1.50,3.90)**	2.48 (.99,7.77)	1.94 (1.10,3.49)*	1.15 (.70,1.83)

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.

Supplement Table 3.G – Stepwise regression analyses of count PVC outcomes with **outliers (≥3) included**. Cells display the incidence rate ratios (IRRs) for the counts of PVC type outcomes and 95% confidence interval (95% CI). An empty cell indicates it is not in the final stepwise model. *, P<.05; **, P<.00052.

Variable	Isolated PVC	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
(Intercept)	1.00 (.27,3.00)	.00 (.00,.00)**	.00 (.00,.00)**	.36 (.27,.51)**	.04 (.00,.10)	.00 (.00,.00)**
Age	1.03 (1.02,1.05)**	1.09 (1.05,1.14)**				
Male						.28 (.12,.70)*
History of IHD	1.97 (1.30,3.30)*					
History of HF	2.06 (1.21,3.63)*			1.98 (.93,3.53)*		9.30 (1.78,23.57)*
PVC on baseline ECG	4.56 (2.47,7.69)**		7.39 (.85,31.19)*	6.55 (2.59,11.82)**		
Hyperkalemia	.45 (.22,.83)*		.06 (.01,.21)**			
Neuro/neurosurgical diagnosis				.53 (.32,.80)*	.31 (.18,.59)**	

Abbreviations: ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PVC, premature ventricular complex.

Supplement Table 3.H – Stepwise regression analyses of count PVC outcomes with **outliers (≥2.5) excluded**. Cells display the incidence rate ratios (IRRs) for the counts of PVC type outcomes and 95% confidence interval (95% CI). An empty cell indicates it is not in the final stepwise model. *, P<.05; **, P<.00052.

Variable	Isolated PVC	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
(Intercept)	.13 (.07,.23)**	.00 (.00,.02)*	.00 (.00,.01)*	.03 (.02,.05)**	.02 (.01,.03)**	.68 (.00,9.12)
Age	1.05 (1.04,1.06)**	1.03 (1.02,1.05)**	1.03 (1.00,1.06)*	1.03 (1.02,1.04)**	1.02 (1.01,1.03)**	
Male	1.70 (1.22,2.36)*					
Race: White						2.49 (1.24,4.76)*
History of IHD	1.77 (1.18,2.65)*					
PVC on baseline ECG	3.08 (2.10,4.55)**			1.81 (1.30,2.52)*	1.71 (.97,2.55)*	
Atrial fibrillation on baseline ECG	1.78 (1.04,2.72)*					
Potassium (log)						.03 (.00,.24)*
Cardiovascular diagnosis				1.37 (1.08,1.75)*		
Neuro/neurosurgical diagnosis		.35 (.17,.71)*				

Abbreviations: ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease; PVC, premature ventricular complex.

Supplement Table 3.I – Logistic regression analyses of presence/absence of PVC outcomes (**outliers ≥3 excluded**), as part of the hurdle regression model. Cells display odds ratios (ORs) and 95% CIs. *, P<.05; **, P<.00052.

Variable	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
(Intercept)	.13 (.05,.33)**	.07 (.03,.15)**	2.17 (.79,6.30)	.54 (.23,1.22)	.21 (.08,.44)**
Age	1.02 (1.00,1.03)*	1.03 (1.01,1.04)**	1.03 (1.01,1.05)*	1.03 (1.01,1.04)**	1.01 (1.00,1.03)*
History of IHD	1.87 (1.05,3.42)*				
History of HF		2.48 (1.22,5.42)*			
History of stroke		2.28 (1.07,5.37)*			
History of Atrial fibrillation	2.02 (1.13,4.31)*				
Atrial fibrillation on baseline ECG					2.40 (1.40,5.21)*
Hypokalemia				1.72 (1.06,3.00)*	
Neuro/neurosurgical diagnosis			.43 (.24,.84)*	.49 (.31,.74)*	
Cardiovascular diagnosis	1.85 (1.15,3.16)*	1.68 (.99,2.69)			

Abbreviations: ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease.

Supplement Table 3.J – Logistic regression analyses of presence/absence of PVC outcomes with **outliers ≥3 included**, as part of the hurdle regression model. Cells display odds ratios (ORs) and 95% CIs. *, P<.05; **, P<.00052.

Variable	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
(Intercept)	.11 (.05,.25)**	.07 (.02,.14)**	2.21 (.82,7.39)	.57 (.23,1.22)	.23 (.11,.47)**
Age	1.02 (1.01,1.04)*	1.03 (1.02,1.04)**	1.03 (1.01,1.05)*	1.03 (1.02,1.04)**	1.01 (1.00,1.03)*
History of IHD	2.08 (1.20,3.71)*	2.02 (1.14,3.67)*			
History of HF		2.15 (1.06,4.90)*			
Atrial fibrillation on baseline ECG					2.67 (1.43,5.16)*
Hypokalemia				1.70 (1.10,2.97)*	
Neuro/neurosurgical diagnosis			.42 (.21,.80)*	.46 (.31,.72)*	
Cardiovascular diagnosis	1.92 (1.19,3.16)*	1.67 (1.01,2.72)*			

Abbreviations: ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease.

Supplement Table 3.K – Logistic regression analyses of presence/absence of PVC outcomes with **outliers (≥2.5) excluded**, as part of the hurdle regression model. Cells display odds ratios (ORs) and 95% CIs. *, P<.05; **, P<.00052.

Variable	Bigeminy	Trigeminy	Couplet	Run PVC	R-on-T
(Intercept)	.13 (.05,.30)**	.07 (.03,.17)**	1.92 (.70,5.75)	.48 (.23,1.10)	.19 (.09,.42)**
Age	1.02 (1.01,1.03)*	1.03 (1.01,1.04)*	1.03 (1.01,1.05)*	1.03 (1.02,1.04)**	1.02 (1.00,1.03)*
History of IHD		1.90 (1.09,3.35)*			
History of HF	2.24 (1.11,4.95)*	2.55 (1.13,5.47)*			
History of Stroke	2.25 (1.08,5.05)*	2.33 (1.14,5.10)*			
Atrial fibrillation on baseline ECG					2.46 (1.27,5.10)*
Hypokalemia				1.79 (1.09,3.00)*	
Neuro/neurosurgical diagnosis			.44 (.21,.79)*	.51 (.33,.75)*	
Cardiovascular diagnosis	2.09 (1.24,3.39)*				

Abbreviations: ECG, electrocardiogram; HF, heart failure; IHD, ischemic heart disease.

Chapter 4

Premature Ventricular Complexes are not Associated with Ventricular Tachycardia in the Intensive Care Unit

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Acknowledgments: SS received a Predoctoral Fellowship from the UCSF School of Nursing for his doctoral studies. The authors would like to thank the Center for Physiologic Research, University of California, San Francisco (UCSF) School of Nursing, for their assistance with PVC alarm data acquisition, and the UCSF Clinical and Translational Science Institute (CTSI; funding details below) and the UCSF Division of Hospital Medicine Data Core for their assistance with medication data acquisition.

Funding: This study was funded by Lipps Research Fund (MMP) and Century Club Dissertation Award (SS), UCSF School of Nursing. This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR001872. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Abstract

Introduction: While premature ventricular complexes (PVCs) during continuous electrocardiographic (ECG) monitoring can forewarn the occurrence of lethal arrhythmias (ventricular tachycardia [VT] and ventricular fibrillation [VF]), not all PVCs are not routinely treated. Importantly, PVC alarms are common and may contribute to alarm fatigue in clinicians. However, there is little research about the association of PVCs in the development of VT or VF; hence the benefit of continuous PVC monitoring as part of routine ECG monitoring in the ICU is largely unknown.

Aims: Examine whether PVCs, recorded during continuous ECG, monitoring were associated with the occurrence of VT or VF) in adult ICU patients.

Methods: Secondary data analysis in 445 ICU patients. Six PVC types (isolated, bigeminy, trigeminy, couplet, R-on-T, and run PVCs) were evaluated. Association between PVC types and the occurrence of VT or VF were examined using logistic regression.

Results: VT occurrence confounders identified were reduced left ventricular ejection fraction ($p=0.011$)) and cardiovascular diagnosis ($p<0.001$). In the unadjusted logistic regression model, isolated PVCs were associated with the occurrence of VT, but after adjusting for confounders, no association for any of the six PVC types and VT events. There were a small number of VF cases ($n=7$); therefore, statistical analysis was underpowered. All seven patients with VF had a cardiac diagnosis, all had at least one type of PVC, and six of the seven had VT prior to VF.

Conclusions: There is no association between PVCs and the occurrence of VT. We could not establish whether a similar association existed for VF due to the small number of patients with this arrhythmia. Continuous PVC monitoring appears non-specific for identifying patients at risk of developing VT and is likely to increase nurses' alarm burden and contribute to alarm fatigue. Configuration of PVC alarms for use during continuous ECG monitoring should be revisited.

INTRODUCTION

Early research studies done in the 1960s showed that premature ventricular complexes (PVCs) preceded lethal arrhythmias (i.e., ventricular tachycardia [VT] and ventricular fibrillation [VF]) in patients with acute myocardial infarction (MI).[1,2] Based on these findings, it was recommended that PVC monitoring be incorporated into future electrocardiographic (ECG) monitoring devices.[2] Subsequent studies that followed patients at least six months after acute MI also found that PVCs were associated with arrhythmic death.[3-5] Given these data, the Cardiac Arrhythmia Pilot Study (CAPS),[6,7] and later the Cardiac Arrhythmia Suppression Trial (CAST),[8] were conducted to test whether suppressing PVCs with antiarrhythmics improved survival in patients after an acute MI event. Interestingly, an interim data analysis of participants enrolled in the CAST study showed that patients treated with encainide and flecainide had a higher death rate than patients in the placebo group,[8] which changed the practice of aggressively treating PVCs.

Since the CAST Study, there have been a few hospital-based studies that have examined the association of PVCs and the development of VT/VF and *torsade de pointes* (TdP).[9-12] However, these studies are dated, included small numbers of patients, and focused primarily on patients with QT prolongation[9,10] or idiopathic VF;[11,12] hence, the findings have limited generalizability to hospitalized patient populations. More recent studies were conducted in primarily outpatient settings using longitudinal (±2 years) designs.[13-16] Therefore, there is limited evidence available to guide clinical practice on PVC monitoring in hospitalized patients.

The current Practice Standards for ECG monitoring in Hospital Settings assigned the following level of evidence to support PVC monitoring: Class IIb (may be considered) and Level of Evidence C (very limited populations evaluated).[17] This recommendation was made because PVCs (including nonsustained VT) are not typically immediately life-threatening, and in the absence of other indications (e.g., structural heart disease), ECG monitoring may be "considered" but is not required. Despite this recommendation, and the fact that not all PVCs

are treated (e.g., pharmacologic and/or electrolyte replacement), PVC monitoring is part of routine ECG monitoring in the intensive care unit (ICU). Nearly all contemporary ECG monitors incorporate algorithms to detect various PVC types (e.g., isolated, bigeminy, trigeminy, couplets, R-on-T, and run of PVC). Importantly, PVCs are the most common type of arrhythmia alarm during continuous ECG monitoring in the ICU. Of the 2,558,760 unique alarms, there were a total of 854,901 (33%) PVC alarms during a 31-day study period.[18] Other studies, while not as comprehensive, have found PVC alarms to be common as well.[19-22] Thus, PVC alarms are frequent and likely contribute to the alarm burden and fatigue among nurses and providers. However, because of the fear of missing a patient at risk for developing a lethal arrhythmia(s), there is hesitancy to simply turn off PVC alarms.[18] Also, no research has examined whether a specific type of PVC may be more clinically meaningful than another. Therefore, there is a need for a more in-depth understanding of the association of PVCs and the occurrence of VT and/or VF.

The purpose of this study was to determine if any of the following six types of PVCs were associated with the occurrence of VT or VF: (1) isolated; (2) bigeminy; (3) trigeminy; (4) couplet; (5) R-on-T; or (6) run of PVC. An exploratory aim of this study was to determine whether any of the six PVC types were associated with a code blue event and/or death.

METHODS

Study Design, Sample, and Setting

This study is a secondary analysis of 2013 data from the UCSF Alarm Study,[18] which was designed to determine the number and type of all physiologic monitor alarms (audible and inaudible) in a group of 461 adult ICU patients at a quaternary academic medical center. Fifteen out of 461 patients from the primary study were excluded because we could not verify the medical record number with the PVC alarms, and one patient was excluded because they had incessant VT (VT storm). Therefore, 445 patients were included in this study.

Three adult ICUs were included: cardiac (16 beds), medical-surgical (32 beds), and neurological/neurosurgery (29 beds). Each bed was equipped with a Solar 8000i monitor (version 5.4 software, GE Healthcare, Milwaukee, WI). A specially designed CARESCAPE Gateway system (GE Healthcare, Milwaukee, WI) allowed capture all of the physiologic data (e.g., ECG, waveform, and numeric vital signs) from each bedside monitor. The data capture was done in the background; therefore, the data collection did not interfere with patient care, nor was it available for clinical decision-making. The university's institutional review board (IRB) approved both the primary and current study with a waiver of patient consent because of the observational nature of the study. The data capture system allowed data collection from the monitors of all consecutive ICU patients admitted to the ICU during March 2013.

Electrocardiographic Data

The bedside ECG monitors recorded seven ECG leads: I, II, III, aVR, aVL, aVF, and V (V1 at our hospital). Six PVC types, specific to the monitors used, were collected for this study and included: (1) isolated PVC (single PVC); (2) bigeminy (PVC alternates with a non-ventricular beat for ≥3 cycles); (3) trigeminy (PVC alternates with 2 non-ventricular beats for ≥3 cycles); (4) couplets (two consecutive PVCs >100 beats per minute); (5) R-on-T (PVC lands on the ST or T wave portion of the previous beat); and (6) run PVCs (3 to 5 consecutive ventricular beats ≥100 beats/minute).

For this study, we included true VT and VF events that were annotated by four Ph.D. prepared nurse-scientists using a standardized protocol. All of the annotators had expertise in ECG interpretation and extensive clinical experience with bedside physiologic monitors. There was 95% agreement among the annotators (Cohen's Kappa score of 0.86).[18] A VT alarm was annotated as "true VT event" if met any of the following: ≥6 consecutive wide QRSs (ventricular beats) with a heart rate ≥100 beats/minute; simultaneous drop in arterial or pulmonary artery pressure; documentation of the VT event in the electronic health record (EHR); atrioventricular (AV) dissociation present throughout the wide QRS tachycardia in any of the seven ECG leads;

or in patients with a bundle branch block (right or left), the VT event QRS morphology is different than the patient's baseline rhythm. True VF was defined as follows: coarse flutter waves without QRS complexes; simultaneous drop in arterial or pulmonary artery pressure to near zero; or EHR documentation of cardiac arrest at the same time as the VF event.[18]

Patient and Clinical Data

Demographic and clinical variables for the sample were collected from the UCSF electronic health record (EHR) (Epic Cyberspace 2019, Madison, WI). Demographic data included age, gender, and race. The following clinical history was collected: ischemic heart disease (IHD), heart failure (HF), and percutaneous coronary intervention (PCI/stent), or coronary artery bypass graft (CABG) surgery. These variables were selected based on their association with VT/VF.[23] We also collected patients' left ventricular ejection fraction (LVEF) from an echocardiogram obtained during hospitalization. If an echocardiogram was not available from the current admission, an echocardiogram obtained within six months prior to ICU admission was used. In addition to the calculated LVEF (%), the categorical evaluation was also obtained (i.e., non-reduced LVEF ≥41%; and reduced LVEF ≤40%). Finally, all of the standard 12-lead ECGs (over-read by a board-certified cardiologist) obtained within 24-hours of ICU admission were used to determine the presence of PVCs.

Medications that could potentially prevent an arrhythmia (antiarrhythmic), provoke an arrhythmia (proarrhythmic), or had both properties (pro-antiarrhythmic) were also collected from the EHR. The medications for this analysis were defined according to the 2017 *Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society*.[23] Because PVCs are associated with triggering TdP (multi-focal VT) due to drug-induced QT prolongation, we also collected whether a patient received medication with these properties (CredibleMeds.org).[24]. We also obtained whether electrolyte replacement (magnesium and potassium) had been given. Finally,

patients were categorized by ICU diagnoses using the following: cardiovascular, medical-surgical, and neurological-neurosurgical diagnosis.

Group Comparisons in Patients with and without VT or VF

For the VT outcome analysis, the patients were grouped into two groups based on the absence (non-VT) or presence of VT (VT) using the following approach. In patients with a VT event(s), PVCs that occurred in the 24-hour period prior to the first VT event were examined. In the non-VT patients, the 24-hour period with a peak count of PVCs was used for comparison. We used this approach to examine whether PVCs were associated with VT or VF, which has been used in previous studies examining ECG changes prior to in-hospital cardiac arrest.[25,26] The two 24-hour periods (PVC counts prior to VT and peak PVC count during monitoring) were used to compare medications and electrolyte replacement. This same approach was used to examine VF.

Statistical Analysis

Descriptive statistics: Frequencies, means, and standard deviations were calculated to describe demographics, clinical characteristics, medications, and ICU diagnosis. Means, medians, and interquartile ranges were calculated to describe the six PVC types and their distributions.

Association of PVCs and VT or VF: Our primary goal was to test if PVCs were associated with VT and VF. To determine the association of PVCs and the VT occurrence, we conducted logistic regression, with PVCs as significant if they met a Bonferroni correction for the six PVCs of $P<0.0083$, and we noted *suggestive* associations meeting a $P<0.05$. Since the PVC counts data were highly skewed, we grouped patients based on the quartiles or tertiles (to prevent too small cell counts) with zero inflation (depending on the distribution) of each PVC type. These PVC categories were then used as covariates in the logistic model (described below).

We first examined the association between each of the PVC covariates to the occurrence of VT. We then sought to adjust these results for potential confounders (i.e., demographics, clinical history, and ICU clinical factors). We tested the association of each potential confounder with the occurrence of VT univariately, using a logistic regression model in R *v4.0.0*.[27] We then built a stepwise model (adding one variable at a time into the model) for VT occurrence by these potential confounders, including variables with P <0.1. To handle missing data of variables included in the stepwise model, we performed multiple imputations (using 50 multiple imputations with *mice* v3.8.0).[28] Finally, any confounders identified from the stepwise regression model related to the VT outcomes were then added as covariates in the logistic regression analyses testing for the association of PVCs to VT occurrence. We further conducted sensitivity analyses with the PVC distributions dichotomized (detailed in supplementary materials) instead of using quartiles or tertiles to explore whether PVC covariates were associated with VT occurrence. As for the VF outcome, however, there were very few cases (n=9). Therefore, we did not perform any statistical analysis. Instead, results are presented descriptively.

Association of PVCs to Code blue or Death: We additionally ran an exploratory analysis to test for an association between PVC covariates and in-hospital mortality (n=49). We further looked at code blue (n=11) cases. However, since there were so few cases, results on the code blue outcome are presented descriptively.

RESULTS

PVCs and the Occurrence of VT

The demographic and clinical characteristics of 445 ICU patients included in this study are presented in **Table 4.1**. Overall, the mean age of the sample was 60 ± 17 years, with approximately equal proportions between males (n=243, 54.6%) and females (n=202, 45.4%). The majority of the patients were white (n=269, 60.4%), and 118 (26.5%) were non-white. Of the sample, 58 (13%) were unable to state their race because of the acuity of their illness on

admission or declined. Most of the patients were admitted with a medical-surgical diagnosis (n=178, 40%), followed by neurological/neurosurgical diagnosis (n=170, 38.2%), then cardiac diagnosis (n=97, 21.8%). There were 24 patients (6.9%) who had PVC(s) present on a standard 12-lead ECG at ICU admission, and 31 (18%) had reduced LVEF (≤40%). A history of IHD was present in 71 patients (16%), PCI/CABG in 38 (8.5%), and HF in 44 (9.9%). Of the 445 patients, seven (1.6%) developed VF, 11 (2.5%) had a code blue event, and 49 (11%) died.

When comparing those without and with VT, the groups did not differ by mean age, race, gender, presence of PVC on baseline 12-lead ECG, or medications. A higher proportion of patients with VT had a cardiovascular diagnosis ($p<0.001$), reduced LVEF ($p<0.001$), history of IHD ($p=0.002$), PCI/CABG ($p=0.001$), and HF ($p<0.001$). Patients with VT events were more likely to have VF events (12.5% vs. 0.3%; $p<0.001$) and code blue events (14.6% vs. 1%; $p<0.001$) compared to those without VT events. However, there was no difference between the groups for death (18.8% vs. 10.1%; $p=0.07$).

Table 4.2 shows the distribution of the six PVCs types examined across all 445 patients. The most common PVC type was isolated (mean = 461.1, median = 51, range = 0 – 8,484), and the least common was R-on-T (mean = 2.2, median = 0, range = 0 - 356). There was no difference between the two groups (Non-VT vs. VT) when examining each of the six PVC types, except for the mean isolated PVCs (447.9 vs. 569.5, $p=0.031$) and run PVC (6.8 vs. 15.8, $p=0.032$).

Regression Analysis

The univariate logistic regression analysis (VT event outcome) identified a history of IHD ($p=0.003$), PCI/CABG ($p=0.002$), HF ($p<0.001$), reduced LVEF ($p=0.002$), and cardiovascular diagnosis ($p<0.001$) as potential VT outcome confounders. However, only reduced LVEF and cardiovascular diagnosis remained significant as confounders in the final stepwise model (**Table 4.3**).

Since the counts for each of the six PVC types were highly skewed, patients were grouped by quartiles or tertiles with zero inflation (depending on the distribution) for each PVC type (**Table 4.4**). These PVC categories were then used as covariates in the logistic regression model. **Table 4.5** shows the unadjusted and adjusted logistic regression models for the six PVC types examined. In both unadjusted and adjusted models, we found none of the six PVC types were associated with the occurrence of VT. These findings are also similar in the sensitivity analysis (**Supplement Table 4.A**).

PVCs and the Occurrence of VF

Since there were only seven patients with VF (1.6%), the study was underpowered to detect any effect that the PVC covariates may have had on a VF event. Descriptive statistics (demographics, clinical characteristics, and PVC distributions) in the seven patients are shown in **Table 4.6**. Among the seven patients, two were under 43 years of age (both females), and five were older than 62 (males). One of seven patients did not have a VT event(s) prior to VF; this one patient had nine VF events. The LVEF was not available in three patients. Of the remaining patients, three had reduced LVEF (one patient had 4% LVEF), and one preserved LVEF. All seven patients had a cardiovascular diagnosis and/or a history of arrhythmias (Pt. #3; supraventricular tachycardia). Four patients developed VF relatively soon after a VT event (four minutes to 14 hours). A code blue event occurred in two patients, and five died during their hospital stay.

None of the patients with VF events had PVCs on their admission standard 12-lead ECG, but all seven patients did have at least one type of PVC during continuous ECG monitoring in the ICU. Isolated PVCs were the most common type, and one patient had eight R-on-T PVCs and one isolated PVC. The total number of PVCs in the seven patients ranged from 27 to 2,201.

Exploratory Analysis: Code Blue Event and/or Death

We explored any potential association between PVCs and a code blue event or death. Like VF, only a small number of patients had a code blue event (n=11; 2.5%); hence, we were underpowered to detect a statistical effect of PVC covariates.

Table 4.7 shows the univariate and stepwise regression models of potential confounders for death, which occurred in 49 patients. We found older age (p=0.024), reduced LVEF (p=0.029), neuro/neurosurgical diagnosis (p=006), and magnesium replacement (p=0.015) as confounders in a stepwise logistic regression model. **Table 4.8** shows the unadjusted and adjusted regression models for the six PVC types for the outcomes of death. In the unadjusted logistic model, isolated PVCs and bigeminy were associated with death. However, after adjusting for the above confounders, there were no associations between PVC covariates and death.

DISCUSSION

This is the most contemporary hospital-based study to examine the association of six types of PVCs and the occurrence of VT, VF, and patient outcomes (i.e., code blue and/or death) in a group of 445 consecutive ICU patients. Our study's design allowed us to examine six different types of PVC in a 24-hr period prior to a VT event(s) and make comparisons to a group of patients with PVCs who did not have VT using carefully annotated data. When controlling for demographic, clinical characteristics, and medications, our study shows no associations between PVCs and the occurrence of VT and in-hospital death. Due to the small sample of patients with VF and/or a code blue event, we were unable to make statistical conclusions about the relationship of PVCs to these outcomes. Isolated PVCs were by far the most common type (mean 461; range 0 to 8,482), while R-on-T type was infrequent (mean 2, range 0 – 356) but occurred in 92 patients.

In a prior study, we found PVCs to be the most frequent arrhythmia alarm.[18] However, in this study, the specific type of PVCs were not reported, nor were associations of PVCs with

arrhythmias and/or patient outcomes. This present study builds on these findings by examining whether any of the six specific types of PVCs available in our bedside monitors were associated with VT events. From our analysis, we found that none of the six PVC types were associated with VT. Our data shows that careful monitoring of PVCs does not appear to help identify patients at risk for VT and likely contributes to alarm fatigue in clinicians, especially isolated type PVCs. While one could argue that PVC alarms (typically configured as inaudible text message alerts) do not cause alarm fatigue, the flashing message on the bedside monitor draws the nurses' attention to the monitor, and they wonder if there is a problem with the patient that needs to be solved.[29] These constant interruptions impact a nurse's workflow and are problematic given the sheer number of PVC alarms generated. Perhaps a more meaningful PVC alarm would be an alarm for new-onset PVCs, which might signal an acute physiologic change in a patient that warrants closer examination. Trend data on PVCs per hour could also potentially provide a meaningful tool to monitor PVCs without overwhelming clinicians with excessive alarms.

In general, clinicians carefully monitor for R-on-T type PVCs since they can trigger VT or VF in some cases,[18] particularly in patients who develop drug-induced QT-prolongation.[9,30] In our study, we found R-on-T PVCs were not associated with VT, although it is important to note the small number of patients with R-on-T. Our findings are similar to findings from two prior studies.[31,32] Chiladakis and co-workers examined 24-hr Holter recordings in acute MI patients treated with thrombolysis and found that R-on-T was rarely observed and they were not associated with ventricular tachyarrhythmias (VT and VF).[31] Likewise, Fries et al. found that R-on-T type PVCs in patients with an implanted cardioverter-defibrillator (ICD) rarely precipitated sustained VT. While R-on-T type PVCs rarely occurred in their sample, the investigators did find that VT events initiated by an R-on-T were more likely to lead to polymorphic VT as compared to non-R-on-T VTs.[32] Therefore, continuous monitoring for R-on-T PVCs, although they are infrequent, seems prudent and relevant in this context.

Moreover, from examining TdP events in 32 hospitalized patients with an acquired QT prolongation (caused by a medication(s) and/or electrolyte abnormalities), Kay et al.[9] found that progressive QTc lengthening just before a TdP event was frequently preceded by PVCs. In addition, the investigators also found a short-long-short pattern of R-R cycles initiated TdP events. This was defined as a short-coupled PVC, followed by a compensatory pause, then an R-on-T PVC that landed at the end of the T-wave of the preceding beat.[9] Applying this study's findings in the context of current ECG monitoring, an algorithm that could monitor for both R-on-T PVCs and the QT interval, or the short-long-short pattern, might potentially be an effective and more specific approach to identify patients at high risk of developing lethal arrhythmias. Of note, our hospital and many others currently configure R-on-T PVC alarms as inaudible text message alerts. This configuration is likely due largely to the high number of PVC alarms generated during continuous ECG monitoring. Prior to our study, it was unknown how often R-on-T type PVCs occurred in ICU patients and whether they were associated with VT and/or VF. While we found R-on-T PVCs were not associated with VT, our data represented only a small number of R-on-T events due its infrequent occurrence. A larger sample of patients with this type of PVC might help determine whether or not this alarm should be made audible. As for other PVC types (i.e., bigeminy, trigeminy, couplets, and run PVC), to our knowledge, our study is the first to examine these PVC types and the occurrence of VT in adult ICU patients. Similar to isolated PVCs and R-on-T, we found these PVC types were not associated with VT events.

In addition to examine the association between PVCs and VT, we also examined (albeit in a small sample of patients) whether PVCs were associated with VF, code blue, and/or death. Only seven patients had a VF event. In all but one, VT preceded these events. We were underpowered to examine the association of PVCs to VF, but all of these patients had at least one type of the six types of PVCs, with one having eight R-on-T PVCs. Given that six of the seven patients had VT prior to VF, clinicians should take note of VT events as they may signal high-risk patients who may have VF. Similarly, we only had small cases of code blue. A much

larger sample is needed to draw any conclusions. We did not find an association between PVCs and death. However, as with VF, this finding should be interpreted with caution because our sample was small.

Our study represents current “real-world” clinical practice regarding PVC monitoring from a large time-series dataset of continuous ECG monitors in three adult ICU types (cardiac, medical/surgical, neurologic). An important finding in our study is that PVCs were not associated with the occurrence of VT events. This finding aligns with the current Practice Standard for ECG monitoring in Hospital Settings, which identified that PVC monitoring should be considered but is not required since PVCs are not typically immediately life-threatening.[17] Importantly, this study provides a better understanding of a variety of PVC types identified during continuous ECG monitoring. While not as frequent as isolated PVCs, the need to closely monitor for bigeminy, trigeminy and run-PVCs may not be useful and leads to an excessive amount of PVC alarms that do not appear clinically meaningful. Future research is needed to identify algorithms with more unique characteristics (i.e., PVCs with QT intervals) that could identify patients at risk of developing lethal arrhythmias without burdening clinicians with unnecessary alarms.

Limitations

Several limitations needed consideration. First, PVC alarms used in this study were not annotated; thus, whether PVC events were true or false and if any PVC were missed (false negatives) is unknown. However, in a recent review evaluating PVC detection algorithms, it was reported that the accuracy of PVC detection was between 86% and 99%.[33] While our data were collected from a commercially available monitor, representing real-world PVC data, the findings of this study may not apply to different vendors. We used the count data of PVC covariates and did not analyze specific ECG characteristics (e.g., QT interval, prematurity index, or morphology), which would be important to explore in future work. We could not analyze the association between PVCs and VF due to the very small number of patients with this arrhythmia. However, these data show how infrequent this type of lethal arrhythmia is in adult

ICU patients. In addition, this study was conducted in a single center, using data from a single vendor; hence, there is a potential sampling bias. Our PVC alarm data were collected in March 2013. Since then, some hospitals in response to alarm fatigue have changed their practice of PVC monitoring. Nevertheless, our data help reaffirm this practice and may help guide other hospitals in making alarm configuration decisions. Finally, our analysis regarding in-hospital death was potentially biased due to the varied and delayed time between the 24-hr PVC count and the time of death among our sample. Several clinical factors could have confounded the associations during these periods, including the progression of lethal arrhythmias, medical procedures, medications, etc. Therefore, even though we found no associations, we cannot confidently determine whether PVCs were associated with death.

CONCLUSION

Of six types of PVCs examined during continuous ECG monitoring in the ICU, none were associated with the occurrence of VT. We could not establish whether a similar association exists between PVCs and VF due to the small sample size in this study. Continuous ECG monitoring for PVCs in the ICU setting to identify patients at risk of developing lethal arrhythmias is non-specific and may not be clinically meaningful. The sheer number of PVC alarms is likely to increase alarm burden in nurses and providers, which likely contributes to alarm fatigue. Therefore, current practices regarding continuous PVC monitoring need to be revisited. Future research on the progression of PVCs over time and specific ECG characteristics (e.g., coupling interval, QRS duration, and morphology) could provide meaningful information to guide algorithm development as to whether PVCs require close monitoring during continuous physiologic monitoring in the ICU.

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Table 4.1 – Demographic and clinical characteristics of 445 intensive care unit (ICU) patients with and without ventricular tachycardia.

Characteristics	Total (N=445) N (%)	Non-VT (N=397; 89%)	VT (N=48; 11%)	*p*-value [a]
Age, years, mean (SD)	60.0 (17.0)	60.1 (17.3)	58.7 (15.0)	0.584
Race				0.142
Asian	76 (17.1%)	71 (17.9%)	5 (10.4%)	
Black or African American	34 (7.6%)	28 (7.1%)	6 (12.5%)	
Native Hawaiian or Pacific Islander	8 (1.8%)	8 (2.0%)	0 (0.0%)	
Unknown (acute illness) or decline to state	58 (13.0%)	55 (13.9%)	3 (6.2%)	
White	269 (60.4%)	235 (59.2%)	34 (70.8%)	
Gender				0.583
Female	202 (45.4%)	182 (45.8%)	20 (41.7%)	
Male	243 (54.6%)	215 (54.2%)	28 (58.3%)	
Primary Diagnosis				**< 0.001**
Cardiovascular	97 (21.8%)	73 (18.4%)	24 (50.0%)	
Medical-surgical	178 (40.0%)	164 (41.3%)	14 (29.2%)	
Neurological	170 (38.2%)	160 (40.3%)	10 (20.8%)	
Presence of PVC on 12-lead ECG at ICU admission [b]	24 (6.9%)	23 (7.5%)	1 (2.3%)	0.209
Left ventricular ejection fraction (LVEF) [c]				**< 0.001**
Preserved (LVEF >40%)	141 (82.0%)	125 (86.2%)	16 (59.3%)	
Reduced (LVEF ≤40%)	31 (18.0%)	20 (13.8%)	11 (40.7%)	
Clinical history				
Ischemic heart disease	71 (16.0%)	56 (14.1%)	15 (31.2%)	**0.002**
PCI/CABG	38 (8.5%)	28 (7.1%)	10 (20.8%)	**0.001**
Heart failure	44 (9.9%)	31 (7.8%)	13 (27.1%)	**< 0.001**
Medications [d]				
Antiarrhythmic drugs	105 (23.6%)	95 (23.9%)	10 (20.8%)	0.633
Pro-arrhythmic drugs	233 (52.4%)	205 (51.6%)	28 (58.3%)	0.38
Pro/antiarrhythmic drugs	35 (7.9%)	32 (8.1%)	3 (6.2%)	0.66
Magnesium replacement	129 (29.0%)	117 (29.5%)	12 (25.0%)	0.519
Potassium replacement	194 (43.6%)	167 (42.1%)	27 (56.2%)	0.061
Adverse outcome				
Ventricular fibrillation	7 (1.6%)	1 (0.3%)	6 (12.5%)	**< 0.001**
Code blue	11 (2.5%)	4 (1.0%)	7 (14.6%)	**< 0.001**
In-hospital death	49 (11.0%)	40 (10.1%)	9 (18.8%)	0.07

[a] Chi-square test, except for variable *Age* (t-test). [b] Missing data in 95 patients (90 in non-VT group; 5 in VT group). [c] Missing data in 273 patients (252 in non-VT group; 21 in VT group). [d] Medications (antiarrhythmic, pro-arrhythmic, and pro/antiarrhythmic) and electrolyte replacement (magnesium and/or potassium) are compared between the groups using the 24-hours prior to the VT event (VT group) and during a 24-hour peak PVC count period (non-VT group).

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiograph; ICU, intensive care unit; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

Table 4.2 – Distribution of six types of premature ventricular complexes (PVCs) among 445 intensive care unit (ICU) patients with and without ventricular tachycardia.

PVC Type	Total (N=445)	Non-VT Group (N=397)	VT Group (N=48)	*p*-value*
Isolated PVC				**0.031**
Mean (SD)	461.1 (1111.7)	447.9 (1125.4)	569.5 (995.6)	
Median (Q1, Q3)	51.0 (13.0, 279.0)	45.0 (12.0, 255.0)	103.0 (27.5, 682.2)	
Min – Max	0.0 - 8482.0	0.0 - 8482.0	0.0 - 4879.0	
Bigeminy				0.232
Mean (SD)	19.8 (113.1)	19.0 (109.8)	25.7 (138.4)	
Median (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	
Min - Max	0.0 - 1596.0	0.0 - 1596.0	0.0 - 953.0	
Trigeminy				0.168
Mean (SD)	19.3 (146.8)	20.5 (155.2)	9.2 (24.2)	
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.2)	
Min - Max	0.0 - 2343.0	0.0 - 2343.0	0.0 - 139.0	
Couplet				0.175
Mean (SD)	23.6 (98.2)	20.4 (84.3)	50.0 (174.4)	
Median (Q1, Q3)	4.0 (1.0, 13.0)	4.0 (1.0, 13.0)	7.0 (2.0, 17.0)	
Min - Max	0.0 - 1274.0	0.0 - 1274.0	0.0 - 1145.0	
R-on-T				0.936
Mean (SD)	2.2 (18.6)	2.2 (19.5)	1.7 (6.7)	
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
Min - Max	0.0 - 356.0	0.0 - 356.0	0.0 - 45.0	
Run PVCs				**0.032**
Mean (SD)	7.8 (59.1)	6.8 (59.7)	15.8 (53.2)	
Median (Q1, Q3)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	2.0 (0.0, 5.0)	
Min - Max	0.0 - 1162.0	0.0 - 1162.0	0.0 - 300.0	

* Kruskal–Wallis test

Note: PVC counts are compared during 24-hr period prior to the VT event (VT group) and during 24-hr peak PVC counts (non-VT group).

Table 4.3 – Evaluation of demographic and clinical factors for potential confounders of a ventricular tachycardia (VT) event outcome. Results are first shown for a logistic model with each potential confounder included univariately, and second for a stepwise regression of the confounders. An empty cell indicates a variable is not in the final model.

Variable	Univariate Model		Stepwise Model	
	OR (95% CI)	***p-value***	**OR (95% CI)**	***p-value***
(Intercept)			0.062 (0.039, 0.098)	0.000
Age	0.995 (0.978, 1.01)	0.583	-	-
Gender: Female	0.844 (0.46, 1.55)	0.583	-	-
Race: White	1.67 (0.871, 3.22)	0.122	-	-
History of ischemic heart disease	**2.77 (1.41, 5.42)**	**0.003**	-	-
History of PCI/Stent/CABG	**3.47 (1.57, 7.68)**	**0.002**	-	-
History of heart failure	**4.39 (2.1, 9.14)**	**0.000**	-	-
Reduced LVEF	**4.3 (1.74, 10.6)**	**0.002**	**3.62 (1.37, 9.56) ***	**0.011**
PVC present on baseline 12-lead ECG	0.294 (0.0387, 2.23)	0.237	-	-
Primary diagnosis: neuro/neurosurgical	0.39 (0.189, 0.805)	0.011	-	-
Primary diagnosis: cardiovascular	**4.44 (2.39, 8.25)**	**0.000**	**3.42 (1.73, 6.76)**	**0.000**
Antiarrhythmic drugs	0.837 (0.402, 1.74)	0.634	-	-
Proarrhythmic drugs	1.31 (0.715, 2.4)	0.381	-	-
Drugs with pro- and antiarrhythmic properties	0.76 (0.224, 2.58)	0.661	-	-
Magnesium replacement	0.798 (0.401, 1.59)	0.52	-	-
Potassium replacement	1.77 (0.968, 3.24)	0.064	-	-

* Multiple imputations were performed to handle missing data for reduced LVEF variable (missing = 273).

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiograph; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PVC, premature ventricular complex.

Table 4.4 – Categorization of premature ventricular complex (PVC) covariates into tertiles or quartiles.

PVC Covariate	Quartiles Cut-off Points (n)			
	Group 1	**Group 2**	**Group 3**	**Group 4**
Isolated PVC	≤13 (118)	14-51 (106)	52-279 (110)	>279 (111)
Couplets	≤1 (122)	2-4 (106)	5-13 (108)	>13 (109)
Runs of PVC	≤0 (182)	>0, ≤1 (83)	2-5 (104)	>5 (76)
PVC Covariate	**Tertiles Cut-off Points (n)**			
	Group 1	**Group 2**	**Group 3**	
Bigeminy	≤0 (311)	1-3 (68)	>3 (66)	
R-on-T	≤0 (353)	>0, ≤1 (43)	>1 (49)	
Trigeminy	≤0 (338)	1-7 (57)	>7 (50)	

Table 4.5 – Association between premature ventricular complex (PVC) covariates and ventricular tachycardia (VT) outcome using logistic regression. *Logistic model adjusted for confounders identified in the stepwise fit (**Table 4.3**)**.** Sensitivity analysis of dichotomized PVC covariates is presented in **Supplement Table 4.A**.

PVC covariates	Unadjusted Model		Adjusted Model*	
	OR (95% CI)	Overall *p*	OR (95% CI)	Overall *p*
Isolated				
14 – 51	1.94 (0.682, 5.55)	**0.048**	1.85 (0.621, 5.49)	0.35
52 – 279	3.18 (1.2, 8.44)		2.48 (0.883, 6.95)	
>279	3.14 (1.18, 8.35)		1.69 (0.573, 5.01)	
Bigeminy				
1 – 3	1.61 (0.748, 3.49)	0.463	1.32 (0.564, 3.07)	0.82
>3	1.29 (0.564, 2.96)		1.07 (0.439, 2.62)	
Trigeminy				
1 – 7	0.889 (0.332, 2.38)	0.119	0.779 (0.276, 2.2)	0.472
>7	2.31 (1.06, 5.04)		1.6 (0.668, 3.85)	
Couplet				
2 – 4	0.936 (0.372, 2.35)	0.573	0.814 (0.3, 2.21)	0.943
5 – 13	1.5 (0.651, 3.47)		1.09 (0.435, 2.74)	
>13	1.49 (0.645, 3.43)		1.04 (0.419, 2.59)	
R-on-T				
>0, ≤1	0.192 (0.0257, 1.43)	0.051	0.176 (0.0221, 1.4)	0.115
>1	1.57 (0.687, 3.59)		1.02 (0.401, 2.59)	
Run PVCs				
>0, ≤1	1.03 (0.402, 2.62)	0.248	1.05 (0.386, 2.84)	0.515
2 – 5	1.88 (0.877, 4.01)		1.76 (0.769, 4.02)	
>5	1.88 (0.822, 4.32)		1.44 (0.581, 3.59)	

Table 4.6 – Seven patients with a ventricular fibrillation (VF) event. Shown are demographics, clinical characteristics, and the distribution of the six PVC types and total number of PVC.

Characteristics	Pt. #1	Pt. #2	Pt. #3	Pt. #4	Pt. #5	Pt. #6	Pt. #7
Age	63	63	68	78	42	40	80
Race	White	White	Asian	White	White	Black or African American	White
Gender	Male	Male	Male	Male	Female	Female	Male
Primary diagnosis	ACS; rule out demand ischemia	Aspiration w/ PEA arrest	Cholangio-carcinoma	AAA	Cardiac arrest with dissection of LAD and circumflex artery during emergency PCI	Right HF due to pulmonary HTN	Recurrent VT
LVEF	37%	35%	NO	NO	NO	60%	4%
Medical history	IHD, PCI/CABG, HF	HF, Atrial throm-bosis	NSVT; unspecified arrhythmia; SVT	IHD, PCI/CABG, coumadin for clotting of fistula	None	PCI/CABG, HF, heart murmur	IHD, PCI/CABG, HF, prior VT ablation
Medications [a]	Ondan-setron; Metoprolol Azithro-mycin	Propofol	None	Propofol; Metoprolol	Propofol	Ondansetron, Fluconazole, Potassium replacement	Amiodarone; Potassium replacement
PVCs on ICU admission ECG	No	No	No	No	No	No	No
PVC counts [b]							
Isolated PVC	96	16	1068	340	23	2072	915
Bigeminy	0	0	135	0	2	17	1
Trigeminy	0	0	33	0	0	5	31
Couplets	0	3	336	6	1	77	40
R-on-T	0	8	0	0	0	0	0
Runs of PVC	0	0	300	2	4	30	3
Total 6 PVC types	*96*	*27*	*1872*	*348*	*30*	*2201*	*990*
VT event(s)	Yes	Yes	Yes	Yes	Yes	No	Yes
Total VT events	9	2	3	6	2	0	4
Total VF events	24	8	1	20	4	9	3
Time from first VT to first VF[c]	0 day 2:48	0 day 14:29	0 day 0:19	0 day 0:04	2 days 7:25	1 day 10:48	1 day 22:08
Code blue	Yes	No	No	Yes	No	No	No
In-hospital death	Yes	Yes	Yes	No	Yes	No	Yes

[a] Medications include proarrhythmic, antiarrhythmic, and electrolyte replacements (potassium and magnesium) given during 24-hr prior to the first VT event (24-hr peak PVC counts for Pt. #6). [b] Counts represent total PVCs during 24-hr prior to the first VT event (24-hr peak PVC counts for Pt. #6). [c] Elapsed time shown in "days hours:minutes" format. For Pt. #6, elapsed time shown between end of peak PVC 24-hr period and the first VF event. **Abbreviations:** AAA, Abdominal aortic aneurysm; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; ECG, electrocardiograph; HF, heart failure; ICU, intensive care unit; IHD, ischemic heart disease; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; NO, not obtained; NSVT, non-sustained ventricular tachycardia; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; PVC, premature ventricular complex; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 4.7 – Evaluation of demographic and clinical factors for potential confounders of death outcome. Results are first shown for a logistic model with each potential confounder included univariately, and second for a stepwise regression of the confounders. An empty cell indicates it is not in the final model.

Variable	Univariate model		Stepwise model	
	OR (95% CI)	***p-value***	**OR (95% CI)**	***p*-value**
(Intercept)			0.044 (0.011, 0.175)	0.000
Age	**1.02 (1, 1.04)**	**0.037**	**1.02 (1.00, 1.04)**	**0.027**
Gender: Female	1.07 (0.592, 1.94)	0.818	-	-
Race: White	0.712 (0.392, 1.29)	0.264	-	-
History of ischemic heart disease	1.62 (0.785, 3.35)	0.192	-	-
History of PCI/Stent/CABG	1.59 (0.628, 4.01)	0.329	-	-
History of heart failure	1.95 (0.85, 4.48)	0.115	-	-
Reduced LVEF	**2.88 (1.18, 7.01)**	**0.020**	**2.83 (1.01, 7.89) ***	**0.049**
PVC present on baseline 12-lead ECG	1.28 (0.418, 3.93)	0.664	-	-
Primary diagnosis: neuro/neurosurgical	**0.282 (0.129, 0.617)**	**0.002**	**0.31 (0.135, 0.71)**	**0.006**
Primary diagnosis: cardiovascular	**2.33 (1.24, 4.38)**	**0.009**	-	-
Antiarrhythmic drugs	0.507 (0.221, 1.16)	0.109	-	-
Proarrhythmic drugs	0.859 (0.474, 1.56)	0.616	-	-
Drugs with pro- and antiarrhythmic properties	1.39 (0.512, 3.76)	0.521	-	-
Magnesium replacement	**0.518 (0.243, 1.1)**	**0.087**	**0.358 (0.157, 0.815)**	**0.015**
Potassium replacement	0.594 (0.317, 1.11)	0.104	-	-

* Multiple imputations were performed to handle missing data for reduced LVEF variable (missing = 273).

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiograph; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PVC, premature ventricular complex.

Table 4.8 – Association between PVC covariates and in-hospital mortality using logistic regression. *Logistic model adjusted for confounders identified in the stepwise fit (**Table 4.7**)**.** Sensitivity analysis of dichotomized PVC covariates is presented in **Supplement Table 4.B**.

PVC covariates	Unadjusted Model		Adjusted Model*	
	OR (95% CI)	Overall *p*	OR (95% CI)	Overall *p*
Isolated PVC				
14 – 51	4.7 (1.51, 14.6)	**0.005**	3.71 (1.11, 12.4)	0.144
52 – 279	3.49 (1.09, 11.2)		2.12 (0.604, 7.47)	
>279	5.52 (1.8, 16.9)		2.11 (0.565, 7.91)	
Bigeminy				
1 – 3	2.21 (1.03, 4.74)	**0.011**	1.67 (0.732, 3.8)	0.175
>3	2.81 (1.35, 5.83)		1.97 (0.877, 4.41)	
Trigeminy				
1 – 7	0.86 (0.321, 2.3)	0.132	0.561 (0.194, 1.62)	0.401
>7	2.24 (1.03, 4.87)		1.28 (0.523, 3.14)	
Couplets				
2 – 4	1.45 (0.578, 3.66)	0.263	1.23 (0.464, 3.27)	0.948
5 – 13	1.57 (0.634, 3.88)		1.13 (0.426, 3)	
>13	2.32 (0.988, 5.45)		1.3 (0.504, 3.36)	
R-on-T				
>0, ≤1	0.826 (0.28, 2.43)	0.901	0.755 (0.24, 2.37)	0.776
>1	1.12 (0.449, 2.81)		0.739 (0.267, 2.04)	
Runs of PVC				
>0, ≤1	1.03 (0.402, 2.62)	0.111	0.957 (0.357, 2.56)	0.436
2 – 5	1.59 (0.725, 3.49)		1.48 (0.638, 3.45)	
>5	2.51 (1.15, 5.51)		1.82 (0.77, 4.32)	

Supplement Table 4.A. Sensitivity analysis of the association between dichotomized PVC covariates and VT outcome. PVC covariates were dichotomized into the following: ≤51 isolated PVC (vs. >51); ≤0 bigeminy (vs. >0); ≤4 couplets (vs. >4); ≤0 R-on-T (vs. >0); ≤0 runs of PVC (vs. >0); and ≤0 trigeminy (vs. >0).

PVC Covariate	Unadjusted Model		Adjusted Model	
	OR (95% CI)	Overall *p*	OR (95% CI)	Overall *p*
Isolated PVC >51	**2.2 (1.17, 4.14)**	**0.012**	1.5 (0.744, 3)	0.256
Bigeminy >0	1.45 (0.779, 2.71)	0.246	1.2 (0.607, 2.38)	0.602
Couplets >4	1.54 (0.84, 2.83)	0.16	1.19 (0.618, 2.3)	0.598
R-on-T >0	0.873 (0.407, 1.87)	0.725	0.69 (0.3, 1.59)	0.358
Trigeminy >0	1.51 (0.784, 2.9)	0.228	1.2 (0.593, 2.43)	0.623
Runs of PVC >0	1.6 (0.841, 3.04)	0.144	1.43 (0.721, 2.85)	0.284

Supplement Table 4.B. Sensitivity analysis of the association between dichotomized PVC covariates and in-hospital mortality.

PVC Covariate	Unadjusted Model		Adjusted Model	
	OR (95% CI)	**Overall *p***	**OR (95% CI)**	**Overall *p***
Isolated PVC >51	**1.69 (0.923, 3.11)**	**0.089**	0.938 (0.457, 1.93)	0.861
Bigeminy >0	**2.5 (1.37, 4.56)**	**0.003**	1.84 (0.955, 3.56)	0.069
Couplets >4	1.6 (0.878, 2.93)	0.124	1.12 (0.574, 2.17)	0.747
R-on-T >0	0.982 (0.47, 2.05)	0.961	0.753 (0.336, 1.69)	0.492
Trigeminy >0	1.46 (0.76, 2.79)	0.256	0.952 (0.461, 1.97)	0.894
Runs of PVC >0	1.65 (0.872, 3.13)	0.123	1.42 (0.705, 2.85)	0.328

Chapter 5

Conclusions

The purpose of this dissertation research was to evaluate the significance of premature ventricular complexes (PVCs) in clinical practice, particularly during continuous electrocardiographic (ECG) monitoring in the adult intensive care unit (ICU).

Chapter 1 presented an overview of the significance of PVCs from early studies (1960s), particularly in patients surviving acute myocardial infarction (MI). These studies examined the identification of PVCs and their potential role in arrhythmic death.[1,2] These early studies led to studies that tested whether treating PVCs with antiarrhythmic drugs would reduce mortality. The first study, The Cardiac Arrhythmia Suppression Trial (CAST),[3] was designed to test this hypothesis. However, in an interim analysis (data safety monitoring) the study showed that patients who received treatment with class Ic antiarrhythmic drugs (i.e., encainide, flecainide, and moricizine) had a higher death rate than patients in the placebo group.[3] As a result, the study was stopped and aggressive treatment of PVCs was not recommended.[4] Despite this, continuous monitoring of PVCs in the hospital setting, including the ICU, remained a standard practice and continues to this day. However, PVC monitoring is problematic, particularly concerning the sheer number of PVC alarms with associated alarm burden that contributes to alarm fatigue. Because not all PVCs are treated aggressively, the benefit of continuous PVC monitoring needs further investigation. Therefore, this dissertation study was conducted to address the important issue pertaining to PVC alarms and their significance in the ICU setting.

In **Chapter 2**, we presented the results of a scoping review on the diagnostic and prognostic significance of PVCs in individuals with and without cardiac disease across care settings (community and in-hospital). We identified 71 relevant articles, the majority of which were observational. We found three studies that showed the diagnostic value of PVCs in acute

MI diagnosis, although similar findings have not been rigorously validated. Studies, most of which were in outpatient/community, showed the prognostic significance of PVCs' presence, frequency, burden, and QRS morphology on outcomes such as left ventricular dysfunction or heart failure, arrhythmias, ischemic heart diseases, and mortality. However, since the available studies were observational, the causal association could not be established.

Using data from the UCSF Alarm Study,[5] in **Chapter 3,** we showed that isolated PVCs were the most commonly occurring PVC type alarm, accounting for 81.3% of 797,072 individual PVC alarms. R-on-T type PVCs, which clinicians are generally most concerned about, were infrequent (*n* = 2,321; 0.29%). Patients who had a history of ischemic heart disease (IHD), heart failure, coronary revascularization procedures, stroke, or atrial fibrillation had a higher median count of both isolated PVCs and couplets than those without these clinical histories. Our analysis also showed that a small number of patients (outliers) contributed to a large proportion of the total PVC alarms. In addition, we identified that older age, male gender, and the presence of PVC(s) on a baseline 12-lead ECG were associated with a higher occurrence rate of isolated PVCs.

In **Chapter 4**, in the univariate analysis we found none of the six PVC types were associated with the occurrence of ventricular tachycardia (VT). Similarly, after adjusting for significant confounders in the multi-variate analysis (i.e., reduced left ventricular ejection fraction (LVEF) and cardiovascular diagnosis), there were no associations between PVCs and VT. We were unable to evaluate whether a similar association existed for VF outcome since there were a small number of cases (n=7). A chart review of the seven patients showed that all of the VF patients had significant cardiac problems and had at least one type of PVC.

Implications for Clinical Practice

Overall, this dissertation study provides valuable information about the available evidence regarding the significance of PVCs in community (most studies) and in-hospital settings (low number of studies). The scoping review highlighted the small number of hospital-

based studies. Also, this dissertation provides a thorough analysis of the distribution of seven PVC alarm types and examined demographic and clinical characteristics associated with PVCs. Importantly, we identified six outlier patients from the sample of 446 ICU patients who contributed to 40% of the nearly 800,000 PVC alarms. These six patients generated high numbers of PVC alarms throughout their ICU stay, calling into question the need to keep the PVC alarms on due to the risk of alarm fatigue in nurses. Unfortunately, due to the observational and retrospective nature of our data analysis we are unable to draw conclusions about this finding. Nevertheless, our finding underscores the importance of individualizing alarm management in some ICU patients, especially when patients have PVCs over days and do not have symptoms or arrhythmia events.

We did not find an association between PVCs and the occurrence of VT. However, we could not establish whether a similar association existed between PVCs and VF due to the small sample size in this study. Years ago, PVC algorithms were added to patient monitors because PVCs were believed to be a predictor of arrhythmic death.[1,2] Although studies in the outpatient/community setting have shown an association between PVCs and risk for long-term mortality,[6-8] to our knowledge, similar observation have not been extensively explored among ICU patient populations, or other hospitalized patients with ECG monitoring. Therefore, continuous ECG monitoring for PVCs in the ICU to identify patients at risk of developing lethal arrhythmias appears non-specific and thus, not clinically meaningful especially given the high numbers of PVC alarms generated. We did find that R-on-T type PVCs, while infrequent, were present in a patient with VF and therefore, may be useful to keep turned on.

Given the extremely high rate of PVC alarms generated especially for isolated PVCs, these types of alarm are likely to increase nurses' alarm burden and thus, contribute to alarm fatigue. While this this study was done at one location and used a specific ECG monitor vendor, our data calls into question the need to carefully monitor for every PVC and highlights the importance of re-thinking default settings in bedside monitor for PVCs. Critical care nurses are

particularly invested in the findings from this study, given that they are the professionals who are most often exposed to clinical alarms, and thus, alarm fatigue. Efforts aimed at reducing frequently-occurring alarms, like PVCs, which are not typically treated, could reduce the risk of alarm fatigue and may ultimately help provide evidence for better management of PVC alarms, improving care experiences for both clinicians and patients.

Recommendations for Future Research

Interventions testing alarm fatigue management strategies have focused primarily on arrhythmia alarm reduction (not PVCs) and most have used quality improvement approaches. Therefore, the next phase of intervention research should be well designed research studies that evaluate strategies to reduce excessive and unnecessary alarms and include patient outcomes to ensure these alarm adjustments are safe for patients. Although we found no association between PVCs and the occurrence of VTs, this study should be repeated to evaluate whether a time-series analysis would provide more meaningful information on whether PVCs over time are associated with lethal arrhythmias. Finally, an in-depth analysis of ECG characteristics (e.g., coupling interval, QRS duration, and PVC morphology) and their changes/progression over time could add to our understand of PVCs, which could help guide algorithm development.

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