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ORIGINAL ARTICLE

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Prevalence of frequent premature ventricular contractions and left-ventricular systolic dysfunction in patients receiving Holter monitoring

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Abstract

Background: Premature ventricular contractions (PVCs) are frequently observed with left ventricular (LV) systolic dysfunction, although the prevalence of these associated conditions in the general population remains unknown.

Objective: We sought to understand the prevalence of frequent PVCs (defined PVCs > 5%) and high burden PVCs (defined PVCs > 10%) and LV systolic dysfunction in patients receiving ambulatory Holter monitors (HM).

Methods: A prospective multicenter (eight US medical centers) cross-sectional study collected demographic and PVC burden data from consecutive patients undergoing 24-h, 48-h, and 14-day HM (July 2018–June 2020). Left ventricle ejection fraction (LVEF) data was collected if obtained within 6 months of HM. Four PVC burden

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groups were analyzed (<1%, 1%–5%, 5.1%–10%, and >10% burden) and stratified by normal LVEF (≥50%) or presence LVEF < 50%.

Results: The prevalence of PVC burden of 5.1%–10% and >10% was 4% and 5%, respectively in the population undergoing HM ($n = 6529$). Age was significantly different between PVC groups ($p < .001$). In those with LVEF assessment ($n = 3713$), the prevalence of LVEF < 50% and both LVEF < 50% and PVC > 5% was 16.4% and 4.2%, respectively. The prevalence of PVC > 5% and PVC > 10% in patients with LVEF < 50% was 26% and 16%, respectively. PVC > 5% were more prevalent in older, male, and Caucasians ($p < .001$). Females had a lower prevalence of PVC > 5% than males (6% vs. 11%; $p < .001$), but not among those with LVEF < 50% (24% vs. 26%, $p = .10$).

Conclusion: PVC > 5% and PVC > 10% and LVEF < 50% are prevalent in patients undergoing HM. PVC > 5% are associated with older age. Females have a lower prevalence of PVC > 5% than males but similar combined PVC > 5% and LVEF < 50%. ClinicalTrial.gov identifier: NCT03228823.

KEYWORDS
ambulatory ECG monitoring, cardiomyopathy, heart failure, premature ventricular contractions, sex differences

1 | INTRODUCTION

A high burden of premature ventricular contractions (PVCs) may be associated with the development of cardiomyopathy (CM) and heart failure, referred to as PVC-induced cardiomyopathy (PVC-CM).[1,2] However, the presence of PVCs in an abnormal heart can represent a mere consequence of the underlying (unrelated) CM ("bystander PVCs"), or as mentioned, it may represent the main etiology of the newly diagnosed CM (i.e., PVC-CM), or a secondary mechanism that worsens the original ventricular dysfunction ("superimposed PVC-CM").[1,2] Although several studies have tried to elucidate some of its pathophysiological mechanisms and risk factors,[1–3] this clinical entity still faces several unmet clinical needs. Currently, a PVC burden (percentage of PVCs) greater than 15% is considered a strong predictor for the development of PVC-CM.[1,2] However, there is no clear consensus of the PVC burden required to produce invariably "deleterious effects" to the heart.[1–4] Undoubtedly, this distinction has treatment implications. Furthermore, it is unclear what the prevalence of frequent PVCs (>5% burden), high PVC burden (>10%) and PVC-CM is in the general population. The first step would be to estimate the prevalence of frequent PVCs with and without LV systolic dysfunction in a cohort of patients undergoing ambulatory Holter monitors. The purpose of this study was to understand the prevalence of LV systolic dysfunction and frequent PVCs and describe their demographic profiles in consecutive patients receiving ambulatory ECG monitors.

2 | METHODS

Each participating center obtained ethics approval by either central or local Institutional review board, based on their central or local regulatory requirements. This is a prospective multicenter cross-sectional study of 8 major US medical centers that provided data on consecutive patients undergoing ambulatory ECG Holter monitors, ranging from 24 h up to 14 days, between July 2018 through June 2020 regardless of clinical indication. Demographic data and PVC burden were obtained from each ambulatory ECG monitor, including 24-h, 48-h, and 14-day monitors. Assessment of LV function by any imaging modality (multi-gated acquisition [MUGA] scan, echocardiography, cardiac magnetic resonance imaging [MRI]) was collected only if obtained within 6 months of Holter placement. Patients with missing demographic information ($n = 321$) were excluded from this study. The data that support the findings of this study will be available from the corresponding author upon reasonable request.

Analysis was stratified by PVC burden into four different groups (<1%, 1%–5%, 5.1%–10% and >10% burden). Frequent PVCs were defined as PVC burden greater than 5%, mid-burden between 5.1% and 10%, and high burden if frequency exceeded 10%. Patients with LVEF assessment were divided in 2 groups either normal (≥50%) or systolic dysfunction (<50%). PVC burdens were compared among different durations of ambulatory ECG monitors (i.e., 24-h, 48-h and 2-week).

The Veteran population is known to be primarily comprised of an older male population. Since one of the eight medical centers was a Veteran Medical Center, an additional analysis was performed after excluding the Veteran cohort to better assess the demographics in different PVC burden groups in the civilian cohort. *For analysis purposes*, *"general study cohort"* includes all ambulatory Holter data, *whereas "civilian"* cohort refers to the data excluding the *Veteran cohort*. Self-reported gender, race and ethnicity was collected from the patient's chart. This information was gathered to assess for potential differences in PVC burden and LV systolic dysfunction prevalences between these categorical variables.

2.1 | Statistics

Data is reported as mean+/−SD or frequency and percentage. Pearson chi-squared tests or ANOVA were used to compare the PVC burden across each demographic variable. PVC burden was compared between males and females, separately by LVEF, using a proportional odds ordinal logistic regression with sex, LVEF, and their interaction. A $p < .05$ was considered statistically significant. SAS V9.4 (Cary) was used for all data management and calculations.

3 | RESULTS

Eight centers across the US provided a total of 6529 patients with ambulatory Holter monitors. Table 1 summarizes the demographics, LVEF, and Holter duration in the general study cohort receiving ambulatory monitors by different PVC groups. The prevalence of PVC burden between 5.1% and 10% and greater than 10% was 4% and 5%, respectively (Table 1, Figure 1A). The mid- (5.1%–10%) and high-burden (>10%) PVC groups were older (63.8 ± 15.1 and 63.7 ± 15.1 years, respectively) compared to those with burden <5% (59.5 ± 18 and 57.9 ± 17.6 years for 1%–5% and <1% PVC burden, respectively, Figure 1B). Frequent PVCs (>5% burden) were more prevalent in male patients ($p < .001$, Table 1, Figure 1C). Moreover, males constituted a greater percentage of patients in the mid- and high-burden PVC groups (63% and 68% males in the mid-burden (5%–10%) and high-burden (>10%) PVCs (Figure 1D).

3.1 | PVC burden and LVEF assessment

A total of 3713 patients had LVEF assessed within 6 months of Holter monitoring. Imaging modalities for EF assessment included echocardiogram, ($n = 3625$, 96%), MUGA ($n = 63$, 2%) and cardiac MRI ($n = 65$, 2%). Of these patients, 610 (16.4%) had LVEF <50% and 157 (4.2%) had both LVEF <50% and PVC burden greater than 5%. Notably, LVEF was significantly lower in the PVC burden of 6%–10% and >10%, compared to lower PVC burdens (Table 1). Males were more likely to have had LVEF assessment than females (58% vs. 55%, $p = .013$). Moreover, 29% and 21% of females and 23% and 15% of males did not have LVEF assessment within 6 months of ambulatory Holter monitoring, despite frequent PVCs (>5%) or high burden PVCs (>10%), respectively.

TABLE 1 Demographics and Holter duration in the general study cohort receiving ambulatory Holters ($n = 6529$).

		PVC Burden				
	Total	**<1%**	**1%–5%**	**6%–10%**	**>10%**	***p* value**
Patients (*n*, %)	**6529**	4576 (70)	1368 (21)	259 (4)	326 (5)	
Age (mean, SD)	58.8 (17.6)	57.9 (17.6)	59.5 (18.0)	63.8 (15.1)	63.7 (15.1)	<.001
LVEF (mean, SD)*	57.0 (10)	58.2 (9.1)	56.4 (11.1)	51.0 (13.2)	50.6 (12.6)	<.001
Gender						<.001
Female (*n*, %)	3170 (49%)	2287 (72)	678 (21)	84 (3)	121 (4)	
Male (*n*, %)	3359 (51%)	2289 (68)	690 (21)	175 (5)	205 (6)	
Race						<.001
Other (*n*, %)	848 (13)	679 (80)	110 (13)	23 (3)	36 (4)	
Black (*n*, %)	1639 (25)	1119 (68)	388 (24)	62 (4)	70 (4)	
White (*n*, %)	4042 (62)	2778 (69)	870 (21)	174 (4)	220 (5)	
Ethnicity						<.001
Hispanic (*n*, %)	331 (5)	270 (82)	43 (13)	7 (2%)	11 (3%)	
Non-Hispanic (*n*, %)	6198 (95)	4306 (69)	1325 (21)	252 (4%)	315(5%)	
Holter duration~						<.001
24-h (*n*, %)	1501 (23)	921 (61)	380 (25)	85 (6)	115 (8)	
48-h (*n*, %)	1994 (30)	1240 (62)	584 (29)	67 (3)	103 (5)	
14-day (*n*, %)	2310 (47)	1831 (79)	307 (13)	90 (4)	82 (4)	

Note: (*) LVEF available for 3713 patients; (~) Holter duration was not provided in 724 subjects.

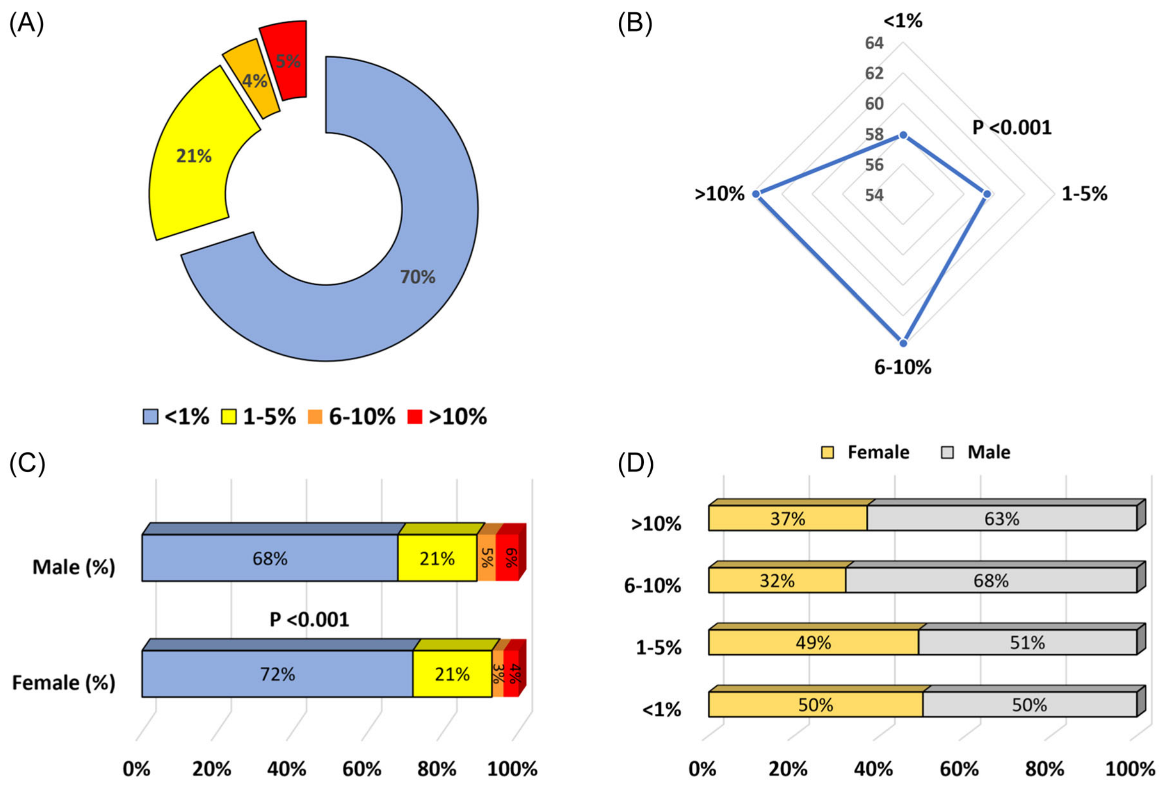

FIGURE 1 Demographics based on PVC burden groups in the General study cohort receiving ambulatory Holter monitors. (A) Total PVC prevalence of 9% in mid-burden (5%–10%) and high-burden (>10%) PVCs. (B) Mean age is higher in those with mid- and high-burden PVC groups. (C) Frequent PVCs (>5% burden) has a higher prevalence in male than female (11 vs. 7%). (D) While gender distribution is equal in PVC groups less than 5%, almost 2/3 of patients are male in the mid- and high-burden PVCs groups.

Table 2 summarizes the demographics in the general study cohort receiving ambulatory Holter monitors with LVEF <50% based on different PVC groups. Males had a higher PVC burden in the cohort with preserved LVEF (odds ratio [OR] = 1.53, 95% confidence interval [CI]: 1.09, 2.16), but not with LVEF <50% (OR = 1.15, 95% CI = 0.98, 1.34). Females had a lower prevalence of frequent PVC burden (>5%) than males regardless of LVEF (7% vs. 11%; $p < .001$, Table 1). However, prevalence was similar between female and males among those with LVEF < 50% (24% vs. 26%, $p = .10$; Table 2).

In patients with LVEF <50%, the prevalence of PVC burden greater than 5% and 10% in patients was 26% and 16%, respectively (Figure 2A). No age difference was found in patients with LVEF <50%, across different PVC groups ($p = .9$, Figure 2B). Despite the general study cohort having similar sex distribution (49% female vs. 51% male), 74% of patients with LVEF <50% were males. Yet, frequent PVC burden (>5%) was similar in both sexes with LVEF <50% (24% females; 26% males) (Table 2, Figure 2C).

3.2 | PVC burden based on length of ECG ambulatory monitor

The shorter ambulatory ECG Holter monitors (24- and 48-h) had a higher percentage of patients with PVC burden greater than 5% compared to those with 14-day monitors (Table 1). This trend was opposite in patients with LVEF < 50% that was driven primarily by PVC burden >10% (24-h, 48-h and 14-day Monitors of 10%, 17% and 27%, respectively, Table 2), The mean (SD) age of patients wearing a 24-h-, 48-h-, and 14-day Holter monitors were 55.0 (19.0), 54.4 (17.8), and 64.6 (14.5), respectively. While only 21% of patients ($n = 923$) in the civilian cohort had a 14-day Holter monitor, 98% of Veterans received a 14-day monitors ($n = 1387$) (Supporting Information S1: Table S1 and Table S3).

3.3 | PVC burden in civilians

Online Supporting Information S1: Table S1 summarizes the demographics in the civilian cohort ($n = 5111$, excluding VA cohort) receiving ambulatory Holter monitors stratified by different PVC burden groups. The majority of ambulatory Holters were performed in females compared to males (58% vs. 42%, $p < .001$). The prevalence of PVC burden of 5.1%–10% and greater than 10% remained unchanged from the general study cohort with a higher prevalence in older and male patients. Similar to the general study cohort, LVEF was significantly lower in the PVC burden of 6%–10% and >10%. Despite females undergoing more Holters, they had a lower prevalence of frequent (>5%) and high PVC burden (>10%) than males

TABLE 2 Demographics in the general study cohort receiving ambulatory Holters with LVEF < 50% (*n* = 610, 9.3%).

	Total	PVC Burden <1%	1–5%	6–10%	>10%	*p* value
Patients (*n*, %)	**610**	286 (47)	167 (27)	58 (10)	99 (16)	
Age (mean, SD)	64.3 (14)	64.3 (13.5)	64.3 (15.0)	63.0 (14.0)	65.0 (14.1)	.864
LVEF (mean, SD)	36.4 (10.2)	36.9 (10.2)	36.7 (10.1)	33.7 (10.1)	35.8 (10.1)	.210
Gender						.025
Female (*n*, %)	159 (26)	90 (57)	32 (20)	12 (8)	25 (16)	
Male (*n*, %)	451 (74)	196 (43)	135 (30)	46 (10)	74 (16)	
Race						.053
Other (*n*, %)	38 (6)	25 (66)	5 (13)	1 (3)	7 (18)	
Black (*n*, %)	204 (34)	97 (48)	58 (28)	24 (12)	25 (12)	
White (*n*, %)	368 (60)	164 (45)	104 (28)	33 (9)	67 (18)	
Ethnicity						.285
Hispanic (*n*, %)	19 (3)	12 (63)	2 (11)	1 (5)	4 (21)	
Non-Hispanic (*n*, %)	591 (97)	274 (47)	165 (27)	57 (11)	95 (16)	
Holter duration~						<.001
24-h (*n*, %)	279 (49)	154 (55)	69 (25)	29 (10)	27 (10)	
48-h (*n*, %)	127 (22)	52 (41)	42 (33)	11 (9)	22 (17)	
14-day (*n*, %)	159 (28)	48 (30)	51 (32)	17 (11)	43 (27)	

Note: (~) Holter duration was not provided in 45 subjects.

(7% and 4% vs. 12% and 7%, respectively). Online Supporting Information S1: Table S2 presents the demographics in the civilian cohort receiving ambulatory Holters with LVEF < 50% (*n* = 404) based on different PVC groups. The prevalence of PVC burden greater than 5% and 10% in patients with LVEF < 50% was 24% and 16% (Table S2), respectively, which is similar to the general study cohort (Table 2).

3.4 | PVC burden in veterans

Online Supporting Information S1: Table S3 summarizes the Veteran (noncivilian) cohort receiving ambulatory Holters, which is older in age than the civilian cohort (64.9 vs. 57.1%). Females consisted of only 13% of all Veterans. Only 4% (*n* = 7; Table S3) and 20% (*n* = 2; Table S4) of female Veterans had frequent PVCs (>5% burden) and frequent PVCs with LVEF < 50%, respectively, when compared to 7% and 27% in the civilian cohort (Table S1 and S2).

4 | DISCUSSION

Arrhythmias (i.e., PVCs, atrial fibrillation, and PVCs) have emerged as a frequent cause of nonischemic cardiomyopathy and heart failure.[2] PVC-CM is primarily characterized by LV systolic dysfunction, LV dilatation, eccentric hypertrophy, electrophysiological remodeling and interstitial fibrosis.[1,3,5–9] Oftentimes, frequent, or high burden PVCs are either underdiagnosed or disregarded as the culprit of cardiomyopathy.[1,10] In this context, understanding the prevalence and coexistence of these two conditions (frequent/high PVC burden and LV systolic dysfunction) in patients receiving ambulatory Holter monitors would help clinicians to understand the potential relevance and promote their detection and further work-up. Moreover, it provides the needed background to launch further clinical trials of PVCs with and without LV dysfunction.

Our study found that frequent (>5%) and high-burden (>10%) PVCs are often present in patients (9% and 5%, respectively; Table 1) undergoing ambulatory ECG monitoring and those with LV systolic dysfunction (26% and 16%, respectively; Table 2). Males have a higher prevalence of frequent PVCs (>5% burden) than females, even among those with LV systolic dysfunction. Nonetheless, 15% of males and 21% of females in our study did not have LVEF assessment to rule out PVC-CM despite a documented high-burden PVCs (>10%). While the mechanism(s) of PVC-CM are being elucidated,[3,11–13] the diagnosis of PVC-CM can be confirmed only when PVC suppression is achieved and LV function restored.[1,2]

Few studies have addressed the incidence of PVCs, but none have addressed the incidence of frequent or high burden PVCs. The Olmstead County study reported a crude incidence of overall

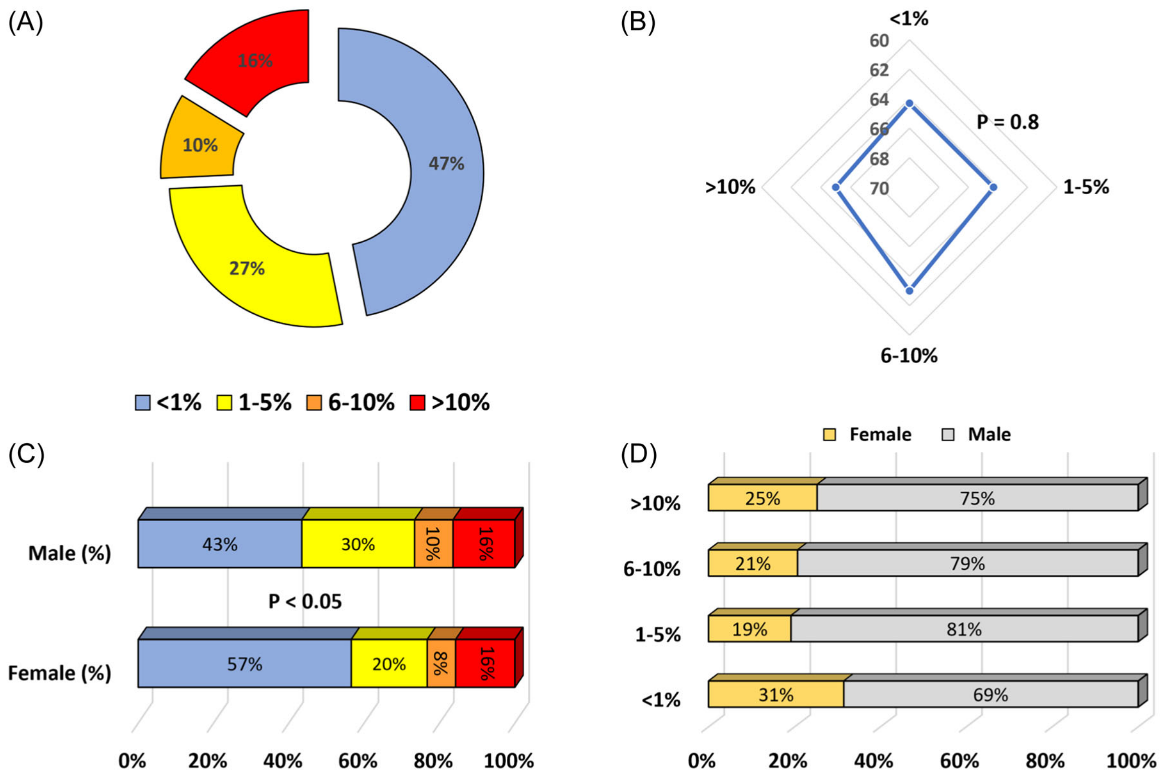

FIGURE 2 Demographics based on PVC burden groups in patients receiving ambulatory Holter monitors with cardiomyopathy (LVEF < 50%). (A) Total PVC prevalence of 26% in mid-burden (5%–10%) and high-burden (>10%) PVCs. (B) Mean age is similar across all PVC groups. (C) Frequent PVCs (>5% burden) has a higher prevalence in male than female (29 vs. 26%). (D) Majority of patients with cardiomyopathy are males across all PVC groups.

idiopathic ventricular arrhythmias (VA), idiopathic ventricular tachycardia (VT), symptomatic PVCs, and VA-associated CM of 48.1, 13.9, 31.9 and 2.3 per 100,000, respectively from 2005 to 2013.[14] However, rates of incidence of idiopathic VA, VT, and PVCs were higher (58.1, 16.3, 39.4, respectively) (2011-2013),[14] which may be reflective of the increased surveillance with ambulatory Holter monitors. A recent study using the Korean healthcare database demonstrated a 0.04% incidence of PVCs in the general population.[15] In contrast, the prevalence of PVCs has been reported in several studies to vary from 1% to 4% in patients undergoing 10-second 12-lead ECGs to 75% in patients with a 24- or 48-h ambulatory ECG monitoring.[2] More specifically, a prevalence of 48% of >1000 PVCs per 24 h has been reported in patients with systolic HF NYHA class II and III.[16] Agarwal et. al. reported a PVC prevalence of 0.2% in 16.8 million hospitalized patients with 1.2% developing systolic HF.[17] Moreover, diagnosis of PVCs predicted incident systolic HF, which was most pronounced in younger patients without comorbidities supporting PVC-CM likely as a significant etiology.

4.1 | Ambulatory holters and frequent PVCs by sex

While women underwent more ambulatory ECG monitors (58%, Supporting Information S1: Table S1) in the civilian cohort, we found that males had a greater prevalence of frequent and a high-burden PVCs when compared to women (12% vs. 7%, respectively). However, most studies of PVC suppression due to frequent PVCs include a higher percentage of female patients.[18,19] This is likely explained by the referral bias of symptomatic patients to clinical studies of PVC suppression (either radiofrequency ablation or antiarrhythmic drugs [AADs]). In the Olmsted County study, women had a higher incidence of symptomatic PVCs than men (46.2 vs. 20.5 per 100,000, respectively).[14] This is consistent with our data, and we speculate that in our civilian cohort, females more frequently underwent ambulatory Holters than men, due to a higher prevalence of symptoms/palpitations. Moreover, our study found that females receiving ambulatory ECG Holter monitor were less likely to have LVEF assessment than their male counterparts, despite having frequent PVCs. We cannot explain this finding, but similar to coronary artery disease, we hypothesize that females complaining of palpitations undergo echocardiographic evaluation less often than men. Finally, males had a higher PVC burden than women in the cohort with preserved LVEF (OR = 1.53), but this sex difference was not seen in patients with LVEF < 50% (OR = 1.15), suggesting that sex differences may no longer be relevant in the presence of LV dysfunction.

4.2 | LV systolic dysfunction and PVCs

Recent data suggests that PVC suppression can not only improve LV systolic function, but more importantly it can improve survival in patients with PVC-CM.[4,6,20] However, the prevalence of frequent and high burden PVCs and CM and its demographics in these populations remain unclear. Our study reports the prevalence of LVEF < 50% and frequent PVCs (>5%) recognizing sex differences with different PVC burdens (Table 2, Figure 2) and the lack of LVEF assessment in patients at risk of developing PVC-CM (>10% burden).

In contrast to the general study cohort (Table 1), the length of ambulatory ECG Holter monitors in the general study cohort with LVEF <50% (Table 2) showed a higher percentage of patients with PVC burden greater than 10% in 14-day ECG monitors compared to shorter (24- and 48-h). This is consistent with prior publication[10] reporting a minimal 7-day Holter monitor to adequately identify high burden PVCs. Moreover, the older age in 14-day Holter monitor in the general study cohort is likely driven by primarily by a higher number of Veterans likely based on institutional preference for longer ambulatory ECG Holter monitors.

The risk of PVC-induced CM is considered present if daily PVC burden or count is greater than 10% or around 10,000, respectively.[1,2,10] Consequently, 15% of patients in our study (99 of 610 patients receiving Holters with LV dysfunction had a PVC burden >10%, Table 2) could potentially have a PVC-CM diagnosis. Based on a diagnosis of PVC-CM in 29% of Veterans with frequent PVCs (>10 PVCs per hour; median and mean daily PVCs of 2,800 and 6,600, respectively) and cardiomyopathy reported in the CHF-STAT (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure) study,[4] we could speculate that at least 28 patients (29% out of 99 subjects with CM and PVC > 10%) may have had a diagnosis of PVC-CM. However, this could be even higher (46 out of 99) since other studies also support that patients with PVC burdens as low as 4% (4000 daily PVCs) may also develop PVC-CM and a potentially increased mortality.[1,4,21,22] The high prevalence of PVCs >5% in our study supports the recommendation that all patients with a newly diagnosed or worsening CM should undergo an ambulatory Holter monitoring to exclude frequent and high PVC burden. Its detection may offer a possibility of identifying a treatable and reversible condition that would not only prevent further unnecessary interventions such as the implantation of cardiac implantable defibrillators but also potentially improve survival.[1,2] For instance, Panela et al.[23] found that assessing and ablating frequent PVCs in patients with LV systolic dysfunction, eliminated the need for an implantable cardioverter-defibrillator (ICD) in 64% of subjects at 6 months. Current guidelines recommend PVC suppression (Class I) only with PVC burden greater than 15% and periodic monitoring of PVCs and LV systolic function (class IIa) in patients with frequent, asymptomatic PVCs and normal LV function.[24] Consideration should also be given to amending current guidelines to obtain ambulatory ECG monitor screening for high PVC burden before ICD or cardiac resynchronization therapy implantation.

4.3 | Limitations

This study was limited to demographic data of ambulatory Holter monitors. Thus, it cannot provide any information regarding associated comorbidities, symptoms or outcomes. LV systolic dysfunction in this cohort may not have been attributed by PVCs but other causes alone or in combination. The prevalence of PVC-CM cannot be addressed in this study since that would have required reversibility of LV dysfunction after PVC suppressive therapies (e.g., antiarrhythmic drugs, ablation). The potential for selection bias may be present in some comparisons. Finally, the prevalence and findings of this study are a snapshot, limited only to those with an indication for ambulatory ECG Holter but not the general population, likely representing a probable indication for Holter during study period. However, as there were no formal exclusion criteria, all patients undergoing Holter monitoring were included. Future prospective studies are recommended to overcome these limitations.

5 | CONCLUSIONS

The prevalence of frequent (PVC > 5%) and high-burden (PVC > 10%) in the general study cohort undergoing ambulatory Holter monitoring was high (9% and 5%, respectively) and more common in older men. Frequent PVCs were particularly common in patients with LVEF < 50% (~25%) with a similar prevalence between men and women. Female patients were less likely to undergo assessment of LVEF than men. Given the high prevalence, healthcare providers should consider obtaining monitors to assess PVC burden in patients with LV systolic dysfunction and evaluate LV function in all patients with frequent PVCs.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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