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Predicting factors for unresolved premature ventricular complexes in healthy children

Seongjin Choi[1], Jae Suk Baek[1*], Mi Jin Kim[1], Seulgi Cha[1] and Jeong Jin Yu[1]

Abstract

Background Premature ventricular complexes (PVCs) are generally benign in healthy children, but in some cases, a persistent high PVC burden may be observed, potentially related to ventricular tachycardia or left ventricular dysfunction. This study explores the natural history of PVCs in children with structurally normal hearts and identifies factors associated with unresolved PVCs.

Methods We retrospectively analyzed demographic and clinical data from children < 18 years of age with confirmed PVCs, including 12-lead electrocardiogram (ECG) and 24-h Holter monitoring data.

Results A total of 113 children (mean age 8.35 ± 5.28 years, 71 males [62.8%]) were included. The mean follow-up duration was 44.9 ± 44.8 months. PVC burden at initial diagnosis was 13.54 ± 12.53%. During follow-up, 44.2% of patients showed complete PVC improvement, 13.3% partial improvement, and 42.5% persistent. Older age at the initial onset and female sex were associated with unresolved PVCs (per 1-year increase: OR 1.09, 95% CI: 1.01–1.18, $P = 0.027$; females: OR 2.25, 95% CI: 1.00–5.06, $P = 0.050$).

Conclusion Older age at onset and female sex were predictors of unresolved PVCs in healthy children, highlighting the need for tailored monitoring for these subgroups, despite the generally favorable prognosis of PVCs.

Keywords Premature ventricular complexes, Pediatrics, Risk factors

Background

Premature ventricular complexes (PVCs) are a relatively common arrhythmia, as shown by a Holter monitoring study, which detected PVCs in up to 41% of children over 24 h [1]. PVCs can occur as an isolated phenomenon in otherwise healthy pediatric hearts, though they may also be indicative of underlying cardiac abnormalities. In pediatric patients with structurally normal hearts, PVCs are generally considered transient and resolve without intervention [2]. However, some PVC cases remain unresolved despite an initial diagnosis of benign PVCs. These patients, in particular those with a high PVC burden, may develop serious complications, such as ventricular tachycardia, cardiomyopathy, or even sudden cardiac death. Research in adult populations has shown that patients with a high burden of PVCs are more likely to have episodes of ventricular tachycardia (VT) or left ventricular (LV) dysfunction [3–5]. Similarly, recent pediatric studies indicated that a high PVC burden may lead to LV dysfunction in children [6–8]. Therefore, it is crucial to differentiate between potentially harmful PVCs that may lead to complications from benign PVCs that are likely to resolve spontaneously, enabling early intervention for high-risk cases. Achieving this requires identifying the factors that predict the PVC persistence in pediatric patients with structurally normal hearts [9].

This study aimed to investigate the natural course of PVCs in pediatric patients with structurally normal hearts and to identify factors associated with a lack

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of improvement. Additionally, this study focused on patients with a high burden of PVCs upon initial presentation, which may require additional intervention.

Methods

Patient selection

The study enrolled children < 18 years diagnosed with PVCs who visited Asan Medical Center between 1995 and 2021 and underwent serial 24-h Holter monitoring. A 24-h Holter monitoring was performed to evaluate symptoms such as chest discomfort or palpitations. In asymptomatic children, 24-h Holter monitoring was performed when PVCs were incidentally detected on 12-lead ECGs conducted due to irregular heartbeats found during routine health care examinations, or during preoperative workups for surgeries such as those in otolaryngology or orthopedics. We excluded patients with congenital heart disease, except those with a patent foramen ovale or minor atrial septal defects.

This study was approved by the Institutional Review Board (Approval No. 2020–0702). The requirement for informed consent was waived due to the retrospective nature of the study design.

Data collection

We conducted a retrospective review of electronic medical records to collect and collate data related to the patients' baseline characteristics, clinical symptoms, and signs, as well as several test results, including echocardiography, 12-lead electrocardiogram (ECG), 24-h Holter monitoring, and exercise stress test. Using sequential 12-lead ECG and 24-h Holter monitoring data, we assessed the initial PVC burden, PVC QRS duration, and morphology of the bundle branch block pattern.

Definition

The initial onset age refers to the age at which PVCs were diagnosed using 24-h Holter monitoring. PVC burden is the percentage of PVCs among total ventricular complexes recorded over 24 h. Improvement in PVCs, including complete and partial improvement, refers to a decrease in the PVC burden to less than half of the initial burden without treatment. Complete improvement is defined as a decrease to < 1%, while partial improvement applies to cases where PVC burden decreased but did not reach < 1%. Patients who showed no improvement or required treatment were classified as persistent.

High PVC burden was defined as ≥ 25% of the PVC burden. Although there is no clear single threshold cut-off for high PVC burden, two main studies have identified PVC burden > 16% and > 24% as markers for identifying patients at risk for PVC-induced cardiomyopathy [3, 10].

PVC QRS duration was measured from the beginning to the end of the predominant PVC QRS complex on a 12-lead ECG. The z-score was evaluated using age- and sex-specific z-scores and standard deviations outlined in the previous study on electrocardiogram standards for children and young adults [11].

The morphology of the bundle branch block pattern was determined based on the morphology of the QRS complex in lead V1: "right bundle branch block (RBBB)" for positive QRS and "left bundle branch block (LBBB)" for negative QRS.

PVCs were classified based on their origin as either outflow tract (OT) or non-outflow tract. Those with a prominent R-wave pattern in the QRS complex in leads II, III, and aVF were identified as having an outflow tract origin [12].

The echocardiographic results were used to exclude structural abnormalities. Data from a treadmill exercise stress test, which demonstrated suppression at faster heart rates, were also extracted to confirm the presence of benign PVCs.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables are summarized as frequency and percentage. Demographic data were categorized and compared by Pearson Chi-Square or Linear-by-Linear Association. Logistic regression analysis was used to elucidate the factors associated with the lack of improvement in PVCs, and a linear mixed model was used to compare PVC burden over time. $P < 0.05$ was considered significant, and analyses were performed using SPSS (version 21.0; SPSS, Inc., Chicago, Illinois, USA) and R version 4.3.2.

Results

Patients

A total of 113 children (71 male [62.8%]) were enrolled. The mean age at the diagnosis of PVC was 8.35 ± 5.28 years and the follow-up duration was 44.9 ± 44.8 months. 12 patients (10.26%, 4 chest discomfort, 4 palpitations, etc.) were symptomatic and 11 children (9.4%, 9 medical therapies, 2 radiofrequency catheter ablation) needed intervention. The mean age at PVC diagnosis for 11 (9.4%) treated patients was 9.63 ± 5.12 years. The primary indication for treatment was the presence of symptoms associated with a high PVC burden. Eight patients were initially treated with atenolol, of whom two showed improvement, while six did not. Among these six, four were switched to other medications (flecainide or another beta-blocker), but only one showed improvement. Two patients underwent

radiofrequency catheter ablation (RFCA) due to LV dysfunction.

Figure 1 shows the frequency and sex distribution of the study population according to initial onset age.

ECG

The heart rate, QRS axis, QRS width, and QTc interval were normal. The mean QRS duration of PVC was 111 ± 31 ms. The morphology of PVC was observed as an LBBB pattern in 61 (56%) patients and OT-origin morphology in 54 (58.7%).

24-h Holter monitoring

24-h Holter monitoring was conducted 4.8 ± 3.3 times per patient during a follow-up period. No additional findings were observed apart from PVCs during the Holter monitoring. All other parameters, including lower, upper, and mean rates, were within normal ranges. The initial PVC burden was 13.54 ± 12.53%. During the follow-up period, 50 patients (44.2%) experienced complete improvement of PVCs (Group CI), 15 patients (13.3%) showed partial improvement (Group PI), while 48 patients (42.5%) did not show improvement and continued to experience PVCs (Group P) (Table 1).

Factors associated with lack of improvement

Factors associated with PVC improvement included age at initial onset, sex, and PVC QRS duration. The likelihood of PVC improvement decreases with older age at initial onset. Figure 2 illustrates the proportion of patients with improved PVCs versus persistent PVCs, stratified by the age at initial onset. Improvement was observed in 83.3% of patients with onset before the age of 1 year, compared to only 45.5% in those with onset at 13 years or older. With each 1 year increase in the age of initial onset, the odds of persistent PVCs increased 1.08 times (95% Confidence interval (CI): 1.01–1.17, $P=0.033$). Additionally, the female sex was associated with a lack of improvement (sex, male: 63.4% [$N=45$], female: 47.6%% [$N=20$, OR: 2.25, 95% CI: 1.00–5.06, $P=0.050$]) in multivariate analysis. Additionally, longer QRS duration was associated with a lack of improvement (PVC QRS duration Z-score, < 3: 64.1% [$N=50$], ≥ 3: 41.2% [$N=14$, OR: 2.55, 95% CI: 1.12–5.82, $P=0.026$]) only in univariate analysis. There was no significant difference in the improvement

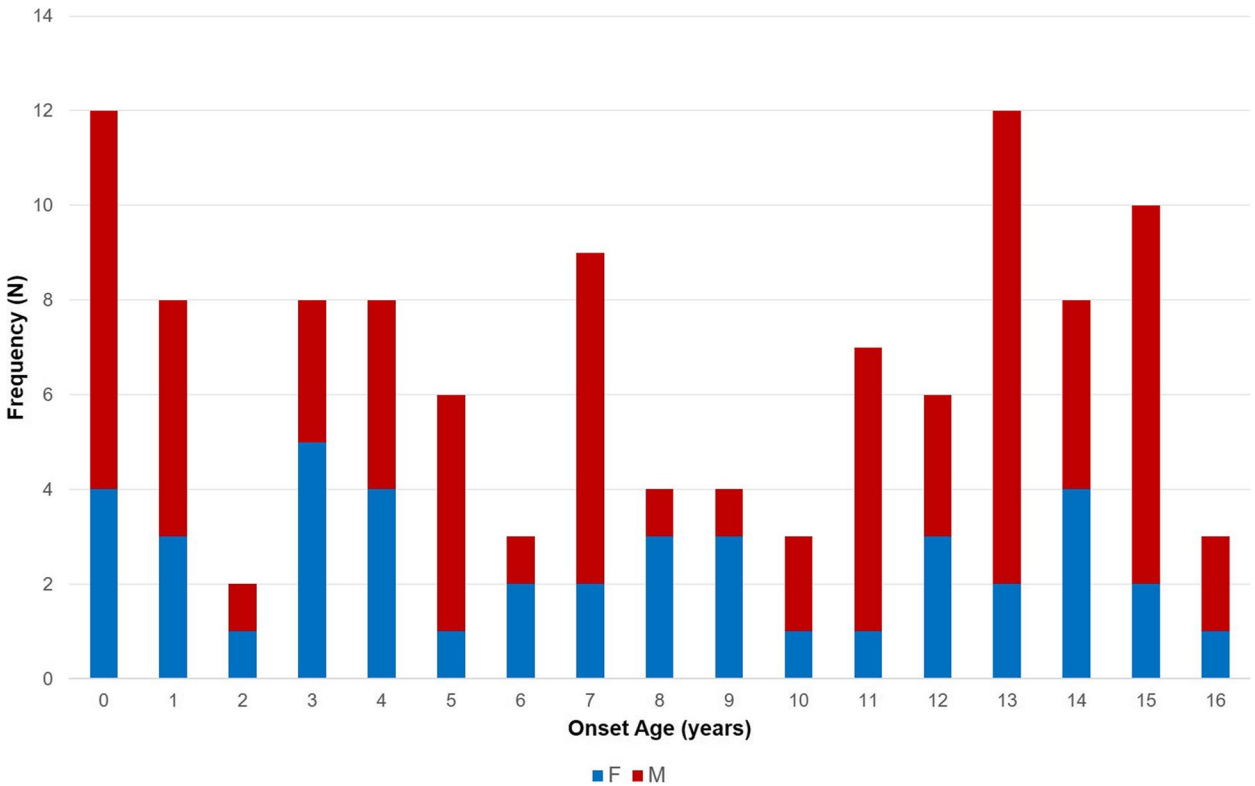

Fig. 1 Frequency and sex according to onset age. The onset age was defined as the age at which PVCs were diagnosed using 24-h Holter monitoring

Table 1 Demographic data (mean ± standard deviation)

	Total (*N* = 113)	Group I (*N* = 65)		Group P (*N* = 48)
		Group CI (*N* = 50)	Group PI (*N* = 15)	
Age of initial onset (years)	8.35 ± 5.28	7.07 ± 5.14	8.51 ± 5.83	9.63 ± 5.03
Male	71(62.8%)	32(62.7%)	15(88.2%)	24(53.3%)
ECG PVC characteristics				
PVC QRS duration (ms)	111 ± 31	102 ± 31	112 ± 32	120 ± 29
QRS Z-score	2.49 ± 2.26	1.92 ± 1.97	2.32 ± 2.32	3.14 ± 2.37
QRS Z-score ≥ 3 (n, %)	34(30.4%)	9(18.0%)	6(35.3%)	19(42.2%)
LBBB morphology (n, %)	61(56.0%)	27(57.4%)	9(52.9%)	25(55.6%)
Outflow tract morphology (n, %)	54(58.7%)	22(56.4%)	11(73.3%)	21(55.3%)
24-h Holter monitoring				
Initial PVC burden (%)	13.54 ± 12.53	8.97 ± 8.34	18.2 ± 11.63	16.84 ± 14.87
Follow-up period (months)	44.9 ± 44.8	42.2 ± 47.2	42.7 ± 37.0	48.4 ± 45.2
Number of Holter	4.8 ± 3.3	4.2 ± 2.0	4.3 ± 2.6	5.6 ± 4.2

ECG Electrocardiogram, *PVC* Premature ventricular complex, *LBBB* Left Bundle Branch Block, *Group I* improvement group, *Group CI* complete improvement group, *Group PI* partial improvement group, *Group P* persistent group

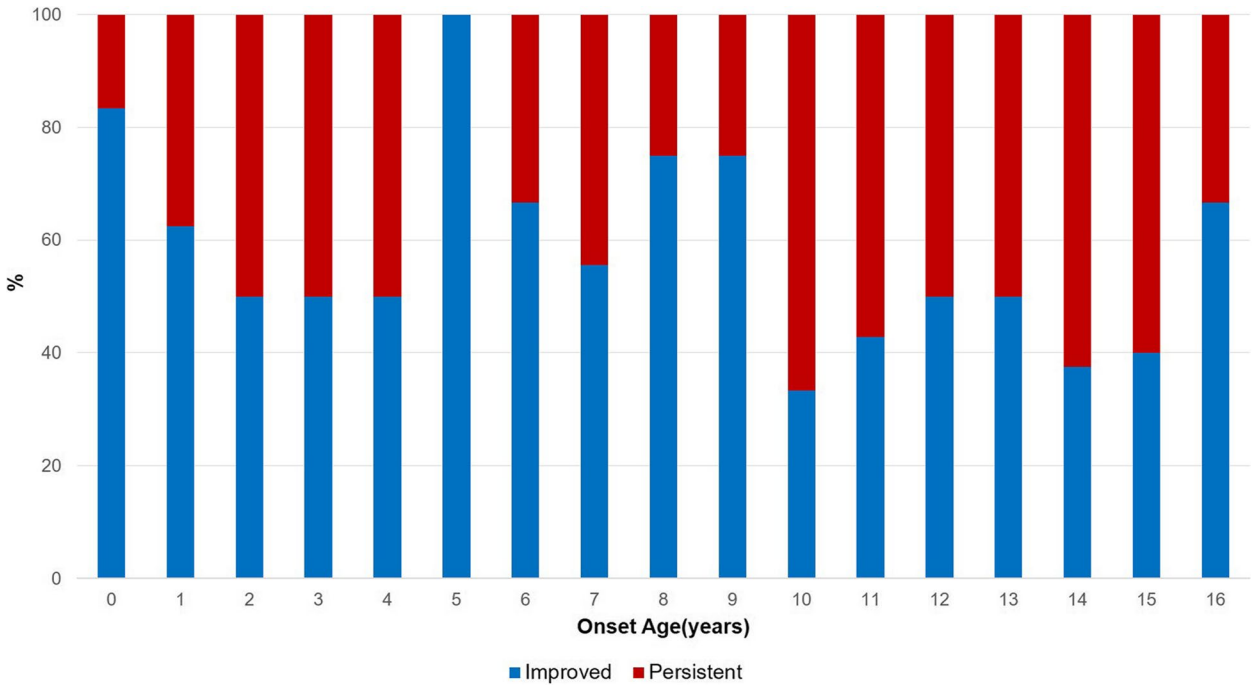

Fig. 2 Outcomes by initial onset age. The onset age was defined as the age at which PVCs were diagnosed using 24-h Holter monitoring and Improvement refers to a reduction in PVC burden by at least half compared to the initial level

of PVCs according to PVC morphology, origin, or initial PVC burden (Table 2).

Figure 3 depicts the changes in the PVC burden over time according to age group. This illustrates that the improvement in PVCs tended to slow in the older age group. When comparing the mean follow-up period until complete improvement, it was 5.8 months for children aged < 1 year, 42 months for children aged 1 to < 13 years, and 52 months for children aged ≥ 13 years. The change in PVC burden over time showed no significant difference between the < 1 year group and 1 to < 13 years group ($P = 0.183$). However, there were differences between the < 1 year group and

Table 2 Risk factors for persistent Premature ventricular complexes

	Group I (*N* = 65)	Group P (*N* = 48)	Univariate			Multivariate		
			OR	95% CI	*P* value	OR	95% CI	*P* value
Age of initial onset (years)								
Per 1 year			1.08	1.01–1.17	0.033	1.09	1.01–1.18	0.027
Sex								
Male	45(63.4%)	26(36.6%)	1.00			1.00		
Female	20(47.6%)	22(52.4%)	1.90	0.88–4.13	0.103	2.25	1.00–5.06	0.050
PVC QRS duration Z-score (*N* = 112)								
< 3	50(64.1%)	28(35.9%)	1.00			1.00		
≥ 3	14(41.2%)	20(58.8%)	2.55	1.12–5.82	0.026	1.90	0.79–4.57	0.151
PVC morphology (*N* = 109)								
RBBB	27(56.3%)	21(43.8%)	1.00					
LBBB	34(55.7%)	27(44.3%)	1.02	0.48–2.19	0.957			
PVC Origin (*N* = 92)								
Outflow tract	31(57.4%)	23(42.6%)	1.00					
Others	20(52.6%)	18(47.4%)	1.21	0.53–2.80	0.650			
Initial PVC burden (%)								
< 5	20(64.5%)	11(35.5%)	1.00					
5–25	36(60%)	24(40%)	1.21	0.49–2.98	0.675			
≥ 25	9(57.5%)	13(42.5%)	2.63	0.85–8.08	0.092			

PVC Premature ventricular complex, *Group I* complete or partial improvement group, *Group P* persistent group, *RBBB* Right Bundle Branch Block, *LBBB* Left Bundle Branch Block

the ≥ 13 years group ($P = 0.014$), as well as between the 1 to < 13 years group and the ≥ 13 years group ($P = 0.004$).

Outcome of patients with high PVC burden

Of the total 113 children, 22 children (19.5%) had an initial high burden of PVC (≥ 25%). The age at the PVC diagnosis was 8.67 ± 5.28 years and the PVC QRS duration was 135 ± 30 ms. The PVC morphology was observed as an LBBB pattern in 17/22 (77.3%) patients and as an OT origin in 18/21 (85.7%) patients. The initial PVC burden was 34.96 ± 8.45% and 24-h Holter monitoring was conducted 6.3 ± 4.6 times per patient during a follow-up period of 55 ± 59.8 months.

Among 22 patients, 9 (40.9%) demonstrated either complete or partial improvement (subgroup I), while 13 (59.1%) had persistent PVCs (subgroup P). There were no significant differences between the two subgroups in terms of age at diagnosis, sex, PVC QRS duration, PVC morphology, PVC origin, or initial PVC burden.

Among patients with a high PVC burden, six (27.2%) received medical therapy. Only one patient (4.5%) developed left ventricular dysfunction with an ejection fraction (EF) of 27% and required two RFCA procedures. After the second RFCA, the patient achieved PVC resolution and showed improvement with an EF of 50%.

Discussion

In this study, we investigated the natural course and factors associated with the lack of improvement in PVC burden among pediatric patients with a structurally normal heart using serial 24-h ECG monitoring. Distinguished from previous studies on this problem applying average-based analysis, we applied a per-patient time-series analysis and discovered new findings that a significant proportion of cases can remain unresolved despite the generally benign nature of PVCs. Furthermore, our study identified that the age at onset and sex were important factors related to unresolved PVCs. Specifically, patients with a later onset of PVCs were less likely to experience resolution, and female patients had a lower likelihood of improvement.

These findings have several clinical implications. First, PVCs do not improve and persist in about one-third of patients, which highlighting the need for close follow-up and careful monitoring even though the generally benign

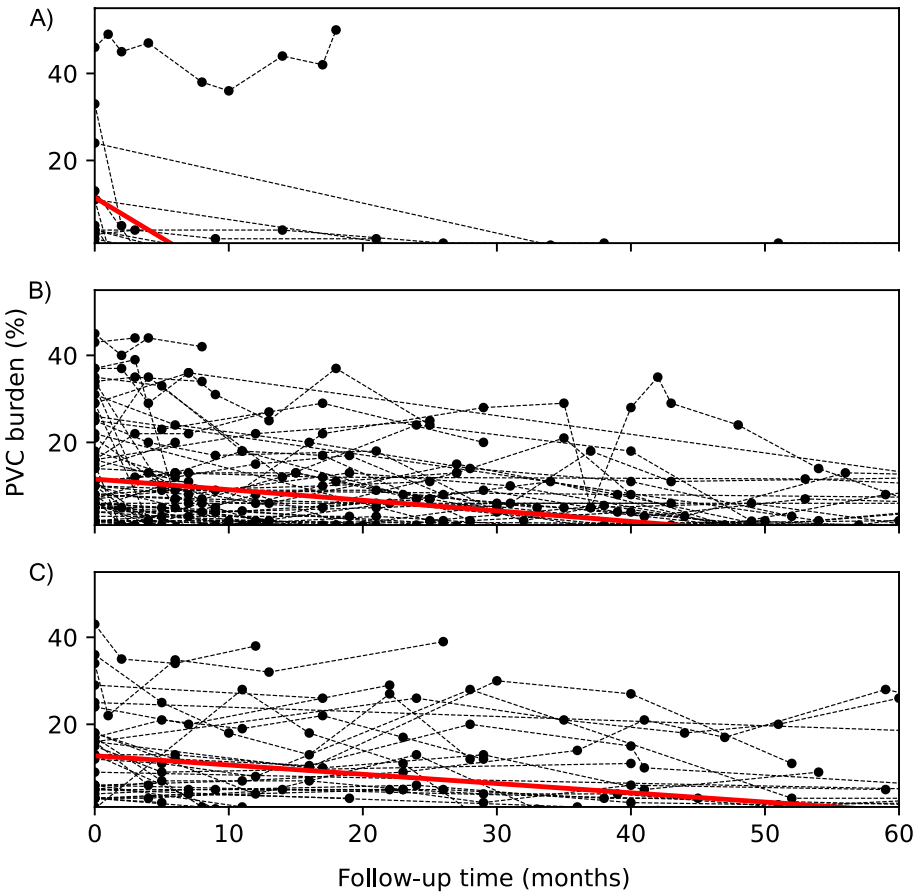

Fig. 3 Scatter plot of premature ventricular complex (PVC) burden (%) over time (months) by age group. The change in PVC burden over time showed a significant difference between the < 1 year group and the ≥ 13 years group ($P = 0.014$), as well as between the 1 to < 13 years group and the ≥ 13 years group ($P = 0.004$). However, there was no significant difference between the < 1 year group and the 1 to < 13 years group ($P = 0.183$). **A** < 1 year group. **B** 1 to < 13 years group. **C** ≥ 13 years group

nature of PVCs in children with structurally normal hearts. Second, a late onset of PVCs and female sex were higher risk for unresolved PVCs. Therefore clinicians should consider more vigilant monitoring and surveillance for these high-risk subgroups.

Initial onset age

PVCs in children with structurally normal hearts generally show a benign course and frequently disappear as the child grows older [2]. However, our study shows that an older age at initial onset was associated with a higher risk of persistent PVCs. Especially, for cases where the initial onset age was 13 years or older, more than half (54.5%, [$N = 18$]) had persistent PVCs during the follow-up period. Additionally, differences in PVC burden improvement over time were observed between age groups. (< 1 year vs ≥ 13 years [$P = 0.014$]; 1- < 13 years vs ≥ 13 years [$P = 0.004$]).

These findings may be attributed to changes in cardiac electrical properties and autonomic regulation during the transition from childhood to adolescence. Specifically, increased sympathetic nervous system activity and alterations in myocardial repolarization characteristics during puberty may contribute to this less favorable course [13, 14]. These results suggest a need for more vigilant and ongoing monitoring for PVCs that first manifest at an older age, given their lower likelihood of spontaneous resolution.

Sex

The importance of sex differences in electrophysiology began to be studied in the early twentieth century [14–16]. Sex differences are evident in many aspects of a wide range of cardiac arrhythmias, including incidence, characteristics, and outcomes [17]. Some sex-related differences in the origin of various idiopathic VTs have been reported. Right ventricular outflow tract VT is more prevalent in females, left ventricular septal VT is more prevalent in males, and left ventricular outflow tract VT is equally distributed [18]. But, it remains

unclear how sex affects the natural course of these ventricular arrhythmia including PVC. This study showed that females had less improvement of PVCs compared to males. Sex differences in the natural course of PVCs may be attributed to variations in ventricular electrophysiologic properties between men and women, such as longer QT intervals, ventricular action potential durations, and effective refractory periods in women [16, 19, 20].

PVC morphology and PVC QRS duration

PVC morphology does not seem to have a significant impact on the natural course of PVCs. Certainly, previous studies have concluded that PVCs with RBBB tend to disappear during childhood, based on the observation that the frequency of RBBB PVCs decreases with increasing age (1–3 years: 16.3 ± 4.2%, ≥ 16 years: 0.6 ± 1.4%, $P = 0.02$), whereas PVCs with LBBB maintain a constant frequency (1–3 years: 12.3 ± 21.4%, ≥ 16 years: 11.7 ± 5.5%) [21, 22]. However, our study found that improvement was not associated with PVC morphology.

Furthermore, we found that OT-origin PVCs were not a significant risk factor for persistent PVCs. This finding may seem contrary to a previous study, which reported that OT- orgin PVCs tend to increase with age [12]. The conclusion of that study was based on the observation that the frequency of PVCs with an LBBB morphology, characterized by a downward main QRS wave in lead V1 and a prominent R-wave pattern in leads II, III, and aVF, increased with age (-3 years: 15.1%, -6 years: 23.3%, -12 years: 45.6%, -18 years: 50.0%).

Our finding could suggest that the increase in OT-origin PVCs with age reflects the new onset of these PVCs rather than the persistence of OT-origin PVCs from childhood. Therefore, it would not be reasonable to consider our results as completely opposite to those of previous studies.

The other aspect of PVC morphology is that certain PVC patterns may be associated with ventricular dysfunction or specific cardiomyopathies. Although not a pediatric study, adult studies have recommended regular monitoring PVCs originating from the right ventricle (RV) because they are significantly associated with decreased LV EF with a lower burden than LV-origin PVCs and RV origin-PVCs could be an early symptom of arrhythmogenic right ventricular cardiomyopathy [23, 24].

In our study, the mean PVC QRS duration was 111 ± 31 ms, PVCs with shorter QRS duration were associated with improvement in PVC burden (Z-score, < 3: OR: 2.55, 95% CI: 1.12–5.82, $P = 0.02$) in univariate analysis. However, this association did not persist in multivariate analysis, suggesting that other factors may influence PVC QRS duration. One possible explanation is the influence of body surface area (BSA). The reference study derived z-scores based on age, sex, and BSA. However, since BSA data was not collected in this study, the accuracy of the z-scores may be limited.

PVC burden

In our study, even among patients with an initial high burden of PVC (> = 25%), almost half (9/22, 40.9%) showed improvement and only 1 patient (4.5%) developed left ventricular dysfunction. An adult study involving 174 patients undergoing ablation for frequent idiopathic PVCs found that 57 patients (33%) exhibited reduced left ventricular ejection [3]. In contrast, a pediatric study of 134 children found that none of 31 patients with PVC burden over 20% developed LV dysfunction and their condition resolved without medication or intervention, which aligns with our results [25]. For this reason, even though there is still no consensus on the PVC burden cutoff points for routine evaluation and management in children, it may be better to take a conservative approach rather than RFCA considering complications and progress in children [26, 27].

Limitation

This was a retrospective study conducted at a single center, with different follow-up intervals among patients. Additionally, since most patients were asymptomatic, it was uncertain how long the PVC had persisted before detection. Moreover, we included cases with a low burden of PVCs (< 1%), which was clinically insignificant. Lastly, the small sample size limits the generalizability of the findings.

Conclusion

Older age at onset and female sex were predictors of unresolved PVCs in healthy children. These findings indicate the need for careful, individualized long-term monitoring to manage potential risks in certain subgroups, despite the generally transient nature and good prognosis of PVCs in healthy children.

Abbreviations

CI	Confidence Interval
ECG	Electrocardiogram
EF	Ejection fraction
LBBB	Left bundle branch block
LV	Left ventricle or left ventricular
OR	Odds Ratio
OT	Outflow Tract
PVC	Premature ventricular complex
PVCs	Premature ventricular complexes
RBBB	Right bundle branch block
RFCA	Radiofrequency catheter ablation
RV	Right ventricle

VT Ventricular tachycardia

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Authors' contributions
Seongjin Choi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Visualization; Writing—original draft. Jae Suk Baek: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Visualization; Validation; Writing—review & editing. Mi Jin Kim: Investigation; Methodology; Resources; Supervision; Validation; Writing—review & editing. Seulgi Cha: Investigation; Methodology; Resources; Supervision; Validation; Writing—review & editing. Jeong Jin Yu: Investigation; Methodology; Resources; Supervision; Validation; Writing—review & editing.

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

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Board of Asan Medical Center (Approval No. 2020–0702). The requirement for informed consent was waived due to the retrospective nature of the study design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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