ORIGINAL RESEARCH

Pericardial effusion among children: Retrospective analysis of the etiology and short-term outcome in a referral center in the south of Iran

Nima Mehdizadegan¹ | Hamid Mohammadi¹ | Hamid Amoozgar² | Samira Pournajaf¹ | Mohammad Reza Edraki¹ | Amir Naghshzan¹ | Mohammad Nima Yazdani²

Correspondence

Hamid Mohammadi, Department of Pediatrics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

Email: mohammadi219@gmail.com

Abstract

Background and Aims: We reinvestigated the causes, symptoms, and management of childhood pericardial effusion (PE) and its gradual changes during recent years in a referral pediatric cardiology center in the south of Iran.

Methods: We retrospectively analyzed the profile of PE patients who were under 18 years old from 2015 to 2020. The patient's demographic, clinical, and paraclinical information was extracted and analyzed using SPSS software.

Result: In general, 150 out of 63,736 admitted patients (0.23% of the total pediatric admissions) were diagnosed with PE (male/female 1:1.17). The median age was 3.25 years (range:\ 2 days to 18 years; interquartile range: 9.5), and 50% of them were under 3 years of age. 32.6% had moderate to severe PE. Most patients presented with acute symptoms (68%) and respiratory problems, as the most common symptoms (30.6%). Tamponade signs were presented in 2% (n = 3) of the patients, and 80.7% (n = 121) were in a stable hemodynamic condition. In total, renal failure (22%) and parapneumonic effusion were the leading etiologies. Viral (7%) and bacterial (5%) pericarditis were the seventh and eighth causes; however, in severe cases, renal failure (22%) and bacterial pericarditis (14%) were dominant. In total, 14.1% (n = 21) of the patients needed pericardiocentesis that increased to 78.3% (n = 18) in severe cases. Only 6% had persistent PE for more than 3 months.

Conclusion: Childhood PE is mostly a result of renal failure and noninfectious causes. True pericarditis cases are not common, except in severe cases. It is more common in less than 3-year-old patients, and chronicity is rare. Severe cases had a high chance of pericardiocentesis, but other cases were mainly managed by treatment of the underlying causes.

KEYWORDS

pericardial effusion, pericardiocentesis, pericarditis, tamponade

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¹Department of Pediatrics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

²Neonatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

1 | INTRODUCTION

Pericardial effusion (PE) is related to many underlying etiologies. Idiopathic pericarditis accounts for 37% to 68% of inpatient admissions for PEs or acute pericarditis in children. 1-3 The pericardial sac typically contains less than 50 ml of serous fluid, and additional fluid accumulation constitutes a pathologic PE.4 Various underlying conditions and diseases can also cause PE, but bacterial pericarditis has been a major cause for many years. The other causes of PE include hypothyroidism, chylous pericardium, and hemopericardium.⁵⁻⁷ Moreover, autoimmune diseases, collagen-vascular diseases, radiation, myocardial infarction, noxious substances, malignancies, metastases, and renal failure might lead to PE.^{1,8,9} Depending on the amount and speed of fluid accumulation, the symptoms are variable from asymptomatic to severely symptomatic. 10,11 The symptomatic cases present with different symptoms including shortness of breath or difficulty breathing (dyspnea), feeling of discomfort while breathing in the supine position (orthopnea), cough, mild fever, palpitations, and chest pain which is usually behind the sternum or on the left side of the chest. 10,11

Rapid accumulation of large amounts of fluid in the pericardial space leads to tamponade and its related symptoms. ^{12,13} In many cases, the cause is evident or can be suggested from the history and previously obtained diagnostic tests. In cases where the etiology is not clear, additional diagnostic tests should be performed, such as pericardiocentesis. Meanwhile, the electrocardiographic, radiographic, and echocardiographic changes could confirm the diagnosis. ^{14,15}

Many studies have been conducted in various centers world-wide to determine the prevalence of PE in different areas, its common causes, prevention, and management protocols. 16,17 In addition, in recent years, with the change in the prevalence of infectious diseases, the etiology of PE has changed. This is somewhat related to the local epidemiology of the disease that may result in different etiologic lists in different areas. Therefore, we aimed to re-evaluate our cases at a referral pediatric cardiology center in the south of Iran.

2 | METHODS

This retrospective study was conducted at Nemazi Hospital affiliated with Shiraz University of Medical Sciences; we included patients with PE from March 2015 to March 2020. Based on our local pediatric databases, the records of all patients under 18 years old with PE in their echocardiographic evaluation were extracted. Inclusion criteria were age less than 18 years and PE in echocardiography. Patients with an incomplete record who were not on the call were excluded.

A researcher-made checklist was used to collect the patients' information including demographic variables, common clinical symptoms, results of laboratory tests, pericarditis etiology, duration of hospitalization, received medications, and treatment outcomes. The cause of PE was classified into infectious disease, autoimmunity, chylous, posttrauma, malignancies, structural heart disease, postcardiac

operation, renal failure, constrictive pericarditis, myocarditis, and cardiomyopathy-related disease, and pericarditis. Some causes with less than two cases were categorized as miscellaneous.

The amount of PE was divided into four categories in the echocardiographic view as follows:

- · Minimal: Pericardial fluid was barely observed.
- Mild: Pericardial fluid was seen in the long axis view only during systole.
- Moderate: Pericardial fluid was observed in both systole and diastole
- Severe: Pericardial fluid surrounded the heart (both the right and left ventricles).

The presence or absence of pleural fluid, either unilaterally or bilaterally, was determined along with echocardiography. Clinical symptoms included acute (less than 2 weeks from initial symptoms) or gradual onset of symptoms. Hemodynamic stability, concomitant tests, and pericardiocentesis were performed. Treatment outcomes were also explained. Persistent PE for more than 3 months was considered a chronic case.

2.1 | Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 16). Continuous data including age, hospitalization duration, and laboratory analysis were presented as median and range for non-normally distributed data and mean for normally distributed ones. We used one-sample Kolmogorov–Smirnov to analyze the distribution of data in these variables. To compare the mean and frequency of the variables among PE severity groups, we used the Mann–Whitney U-test for continuous variables (age, hospitalization duration) and the χ^2 test (sex, presentation, and etiologies) for categorical variables. Multivariate logistic regression analysis was used to explore the association of etiology, patient age, effusion size, and drainage with recurrence or development of chronic effusion. A two-sided p-value less than 0.05 was considered statistically significant. ¹⁸

3 | RESULTS

3.1 Demographic data

According to the medical records reviewed, 63,736 patients were admitted to the pediatric wards of Nemazi Hospital. Finally, 150 patients were diagnosed with PE and included in this study. Based on these data, the rate of PE in hospitalized pediatric patients was about 0.23%.

Out of 150 patients, 54% were male (n = 81) and 46% were female (n = 69). Age distribution was not normally distributed (one-sample Kolmogorov–Smirnov, p < 0.001) and most of the

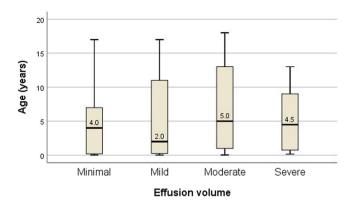


FIGURE 1 Age distribution across different pericardial effusion volumes. The median of each case is inserted. It was not statistically different across groups (p = 0.303).

TABLE 1 Sex distribution was not statistically different among patients with various amounts of pericardial effusion

	Effusion	volume				
	Minimal	Mild	Moderate	Severe	Total	p Value
Sex						
Male(n)	20	34	16	11	81	0.267
Female (n)	10	37	10	12	69	
Total	30	71	26	23	150	

patients were under 3 years of age. The median age of patients was 3.25 years (interquartile range [IQR]: 9.5) ranging from early birth neonate to 18 years; 38.5% (n = 57) of them were under 1 year and 50% (n = 75) were under 3 years old. Figure 1 displays the age distribution across four PE severity groups (p-value: 0.30). The median age of the patients with severe PE was 4.5 (IQR: 8.3) years. 47.8% (n = 11) were male and 52.2% (n = 12) were female (Table 1).

3.2 | Clinical presentations

Clinical symptoms were acute in 68% (n = 102). Respiratory symptoms such as shortness of breath, respiratory distress, and cyanosis were the most common symptoms of PE (Table 2). In this study, a report of the Kusmal sign or "paradoxical pulse" was not identified in the patients' records.

Almost 80.7% of patients (n = 121) were hemodynamically stable at the time of admission, but 29 patients were unstable. Interestingly, the amount of PE effusion did not increase the rate of unstable hemodynamic state, and the prevalence of hemodynamic instability did not differ across different PE volumes (p = 0.918; Table 3). In general, 69.4% (n = 102) of the patients presented with acute symptoms (less than 2 weeks) and this increased up to 95.5% (n = 21) in severe cases; the difference was statistically significant (p = 0.012) (Table 3). The chance of acute presentation significantly increased among severe cases. During echocardiography, pleural effusion was detected in 30%

TABLE 2 Common symptoms in patients with pericardial effusion

Symptoms	Count	Percent
Fever	26	21.5
Chest pain	4	3.3
Abdominal pain	2	1.7
Respiratory (tachypnea, distress, cyanosis, dyspnea)	37	30.6
Cough	10	8.3
Edema	23	19.0
Arrhythmia	3	2.5
Nausea, vomiting, poor feeding	5	4.1
Decreased LOC, shock	6	5.0
Others, underlying disease manifestation	5	4.1

(n = 45) of the patients. The co-occurrence of pleural effusion in severe PE was 39.1% (nine patients).

3.3 | Para-clinical evaluation

The highest erythrocyte sedimentation rate (ESR) was related to autoimmune causes, bacterial pericarditis, and renal failure patients, but the difference was not statistically significant (p = 0.06) due to a wide range of ESR. Other lab data were not diagnostic for a special diagnosis, except high blood urea nitrogen (Bun) for renal failure cases that was expected. Interestingly, mean ESR was significantly lower in unstable patients versus stable ones (16.9 ± 12.1 vs. 46.5 ± 32.4 ; p = 0.001).

Paracentesis data were limited to 21 cases and Table 5 showed no significant difference between different etiologies. If we had less than two cases in a specific etiology that underwent pericardiocentesis, we did not include their data in this table. Only triglyceride in chylopericardium showed a statistically higher mean, as compared to other etiologies (p < 0.010). Lactate dehydrogenase (LDH) was higher in bacterial and especially in malignancy cases, but the difference was not statistically significant due to small case numbers.

3.4 Etiology

As to etiology, renal failure (22%; n = 33 cases) was the leading cause of PE in this study, and the second most common etiology was para-pneumonic effusion. Pericarditis settled in the seventh and eighth sites, and a few patients presented with chylopericardium (Table 4 and Figure 2). Other categories included causes with a total number of two or less, such as tuberculosis (two cases), leishmaniasis, respiratory distress syndrome cases, metabolic disorder, post-cardiopulmonary rescucitation cases, unknown

TABLE 3 Effusion volume and distribution of different variables

	Effusion volume							
	Minimal (A)	Mild (B)	Moderate (C)	Severe (D)	Total			
Sex								
Male (n) (%)	20 (66.7%)	34 (47.9%)	16 (61.5%)	11 (47.8%)	81 (54.0%)			
Female (n) (%)	10 (33.3%)	37 (52.1%)	10 (38.5%)	12 (52.2%)	69 (46.0%)			
Presentation								
Acute (n) (%)	23 (76.7%)	43 (61.4%)	15 (60.0%)	21*B, C (95.5%)	102 (69.4%)			
Gradual (n) (%)	7 (23.3%)	27 ^D (38.6%)	10 ^D (40.0%)	1 (4.5%)	45 (30.6%)			
Hemodynamic								
Stable (n) (%)	25 (83.3%)	58 (81.7%)	20 (76.9%)	18 (78.3%)	121 (80.7%)			
Unstable (n) (%)	5 (16.7%)	13 (18.3%)	6 (23.1%)	5 (21.7%)	29 (19.3%)			
Pericardiocentesis								
Yes	0 (0%)	0 (0%)	3(11.5%)	18**A,B,C (78.3%)	21 (14.1%)			
No	29 (100%)	71 (100%)	23 (88.5%)	5 (21.7%)	128 (85.9%)			
Total number (%)	29 (19.3%)	71 (47.3%)	26 (17.3%)	24 (16.0%)	150 (100%)			

Note: The results are based on two-sided tests. For each significant pair, the key of the category with the smaller column proportion appears in the category with the larger column proportion. Other rows were not statistically significant. *p*-value across sex group (0.30) and across hemodynamic group (0.918).

^{**}Significance level for upper case letters (B, C, D) < 0.001.

	Case number and % of					
	total c	ases	WBC	ESR	CRP	BUN
1 Renal failure	33	22%	10,813 ± 6547	56 ± 37	33 ± 50	64 ± 32
2 Parapneumonic effusion	16	11%	10,486 ± 5348	27 ± 22	71 ± 68	9 ± 6
3 Postcardiac surgery	14	9%	12,710 ± 3965	46 ± 38	57 ± 55	9 ± 4
4 Structural heart disease	12	8%	15,780 ± 13,942	35 ± 45	29 ± 23	18 ± 18
5 Malignancy	12	8%	8263 ± 6533	43 ± 38	45 ± 56	14 ± 11
6 Myocarditis or cardiomyopathies	11	7%	11,413 ± 4592	4	3	11
7 Acute viral pericarditis	11	7%	11,364 ± 8114	39 ± 30	39 ± 55	15 ± 13
8 Bacterial pericarditis	7	5%	11,700 ± 3585	61 ± 35	90 ± 55	12 ± 6
9 Autoimmune	4	3%	7475 ± 4406	71 ± 36	66 ± 54	18 ± 10
10 Trauma ^a	3	2%	11,700	31	27	8
11 Liver cirrhosis ^a	3	2%	12,600	34	27	21
12 Constrictive pericarditis ^a	2	1%	9600	12	6	20
13 Chylopericardium ^a	2	1%	12,700	25	4	8
14 Other	20	13%	8042 ± 4647	35 ± 27	44 ± 56	13 ± 13
p Value across groups			0.506	0.064	0.145	<0.001 ^b

Abbreviation: CRP, C-Reactive Protein.

TABLE 4 Comparison of laboratory variables in different etiologies

^{*}Significance level for upper case letters (B, C, D): 0.012.

^aDue to the small number of cases, only mean value is presented.

 $^{^{\}mathrm{b}}$ Significance p-value.

 TABLE 5
 Pericardiocentesis analysis in different etiologies

	Pericardiocentesis lab data							
Etiology (case number)	LDH (mg/dl)	Protein (mg/dl)	WBC	Lymph (%)	PMN (%)	Triglyceride (mg/dl)	Cholesterol (mg/dl)	
Bacterial pericarditis (5)	1174.5 ± 468.8	6.1 ± 0.1	1310	46.0 ± 59.4	54.0 ± 59.4	60.0	84.0 ± 4.2	
Autoimmune (2)	1276.5 ± 713.5	5.2 ± 1.8	2450	45.0 ± 7.1	55.0 ± 7.1	44.0	94.0 ± 0.0	
Chylopericardium (2)	357.0 ± 212.1	8.4 ± 4.7	955	85.0 ± 19.8	15.0 ± 19.8	2072.5 ± 361.3*	88.0 ± 50.9	
Malignancy (2)	3642.5	3.7 ± 0.4	6405	3.0 ± 2.8	52.0 ± 60.8	170.0	87.0 ± 0.0	
Postcardiac surgery (4)	544.0 ± 0.0	4.0 ± 0.0	4000	27.0 ± 0.0	68.0 ± 0.0	20.0	53.0 ± 0.0	
Myocarditis or cardiomyopathies (3)	581.7 ± 339.6	2.9 ± 0.7	103 ± 55	19.7 ± 17.5	47.3 ± 40.5	14.5	25.0 ± 0.0	
Total	1120.5	4.6 ± 2.5	1923	38.9 ± 33.2	45.8 ± 35.3	503.1	75.4 ± 30.7	
p Value	0.743	0.254	0.740	0.242	0.866	0.010	0.716	

Note: Standard deviation was not present in non-normal distributed data. Abbreviation: PMN, polymorphonuclear leukocyte.

cases, and so forth. Figure 3 shows the percentage of moderate to severe effusion based on each etiology. It is clearly shown that 100% (n = 7) of bacterial cases presented with moderate to severe effusion and this decreased to 33% (n = 11) for renal failure cases.

3.5 | Therapeutic interventions

Out of 150 patients, 14.1% (n = 21) underwent pericardiocentesis, 85% of whom were in the severe category. Only three cases fulfilled the tamponade criteria with unstable conditions, and the others partially fulfilled the criteria. The median hospitalization stay was 14 days (range: 1–75 days; IQR: 14).

In this study, 4% of cases (n = 6) had PE (chronic PE) for more than 3 months, and three of them underwent pericardiectomy or pericardial window due to persistent chylopericarium (one case) and constrictive pericarditis (two cases). Non steroidal anti-inflammatory drug, alone or combined with colchicine or steroid, was used in 7.1% of patients (n = 10). One case used colchicine, and two cases used prednisolone for persistent PE. We excluded the patients who received corticosteroids for underlying diseases. Among all cases, 79% (n = 114) recovered with supportive care and underlying disease management. As it was expected, no one with less than moderate effusion needed pericardiocentesis. Therefore, most cases of PE finally had a cure, and the chronic cases with more than 3 months of persistent effusion were not common in our study.

4 | DISCUSSION

Relatively, there are few data points to guide the management of PE in children. Therefore, there is a need to follow a practical pathway for diagnosing PE to avoid missing specific etiologies that require targeted therapies and prevent unnecessary extensive diagnostic work-ups. 1.6.10

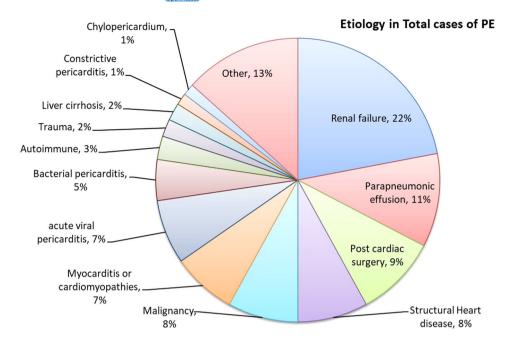
Using HIS from 2015 to 2020, we described the PE causes, symptoms, and management results in our referral center in the south of Iran. During this period, 150 patients with PE were admitted. Therefore, 0.23% of pediatric hospitalized cases had PE, the severe cases of which account for 15% of the total. Similar studies in Bangladesh and Nigeria showed similar prevalence (in a shorter time period) with different etiologies that skewed to the infectious causes. ¹⁹ The rate of tamponade in their studies was 0.2%. ^{19,20} Kuhn et al., in a duration of 20 years, reported 116 patients with large and 365 ones with moderate PE. ^{12,19,20} They used different methodologies and did not present a prevalence, but their etiologies shifted to noninfectious causes.

Almost all similar studies did not find any sex difference in PE, and there was a wide range of diseases from 1 day to 18 years of age; the tendency to lower age was dominant and other studies have also confirmed it. 1,3 In spite of different methodologies resulting in different rates of PE, tamponade is not a common complication and 14.1% (n = 21) of all PE patients need pigtail insertion. This rate sharply increased to 78.3% (n = 18) in severe cases. None of the cases with less than moderate effusion needed intervention, and this is similar to other studies. 1

The respiratory symptoms were the most common symptom in our study in both groups (Table 2). After that, fever, edema, and cough were the most common symptoms. This is consistent with other studies.²¹ Even in moderate to severe cases, the majority of patients were hemodynamically stable, and only one in every five patients presented with an unstable status at the time of admission (Table 3). Due to the possibility of overlooking this pathology in the context of stable patients, the finding should be addressed to the emergency department physicians. Clinicians should pay closer attention to acute symptoms and not discharge patients who have stable hemodynamics.

According to the Etiology Table and in comparison with other studies, PE causes were obviously geographically and socioeconomically

^{*}Significant p-value (0.01).



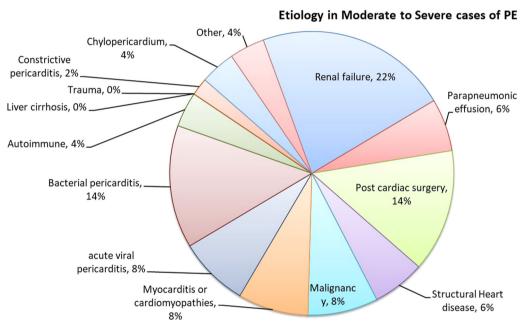


FIGURE 2 Pericardial effusion etiologies in all cases (upper chart) versus moderate to severe cases (lower chart).

dependent (Table 4 and Figures 2 and 3). In high-income countries, etiologies tend to be noninfectious, while in low-income or crowded countries infectious causes, such as bacterial pericarditis and tuberculosis, are dominant. 1,2,9,16,19,20 This study found that in our country renal failure was the major cause of PE rather than infection, a trend more consistent with high health status. The second category of the cause was parapneumonic, followed by structural heart disease and surgical complications by these conditions. Interestingly, pericarditis (both viral and bacterial) is not on the list of top five causes of PE in our study. Depending on the approach and categorization, autoimmune diseases may have a different level in various studies. 10,19,20 For example, some

of our renal failure cases had lupus nephritis, and it was difficult to distinguish the exact etiology (renal failure overloading or lupus serositis); however, we classified them as renal failure cases. In contrast to Kuhn et al.'s report, we had a few cases (four cases) of pure autoimmune disease with PE. This fact and different prevalence rates of autoimmune disease in each setting may change the status of autoimmune causes as an etiology of PE. An older report from Iran with small case numbers report more autoimmune cases who presented with PE.²² Roodpyma et al. did not include renal failure, trauma, and CHD cases in their study; they focused on pericardial disease. In fact, they evaluated the causes of pericarditis. In that study, after more than

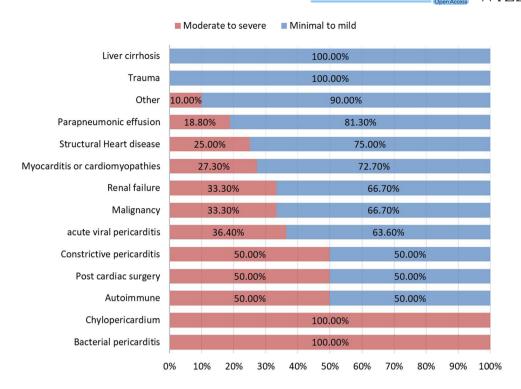


FIGURE 3 Pericardial effusion (PE) severity by etiology. The degree of PE is divided into two categories (minimal to mild PE, and moderate to severe PE) and the proportions of each category are reported in percent for each cause of PE.

20 years, the purulent pericarditis lost the first position in the list of pericarditis causes and moved to the eighth position after autoimmune, malignancy-related, and viral pericarditis in our study in the same country. This change was indicated in some other studies as well. 8.12,14,16,22 However, this etiology list was revised when we considered moderate to severe cases. We observed a considerable number of bacterial pericarditis cases in moderate to severe status, which was next to renal failure and in the same status as the postcardiac surgery cases (Figure 3).

In general, supportive care and treatment of underlying causes is the main step in the treatment of PE. About 14.1% (n = 21) of all cases needed pericardiocentesis; all of them had moderate to severe PE. The chance of pericardiocentesis sharply increased in severe cases (Table 3). Compared to other studies, we did more pericardiocentesis. Although it may be related to different policies and monitoring setups, over-conservative management should be considered. 1,22,23 The most common drug used by our patients, as in other studies, was nonsteroid antiinflammatory drugs. We had only three cases of colchicine and steroid in recurrent and chronic cases; this is less than that of other studies.²³ Both of these cases finally had pericardiectomy. Recurrence of pericarditis can be seen in both children and adults.^{24,25} Higher recurrence rates have been observed in patients with a history of corticosteroid use in the initial episodes of pericarditis. 24,25 Recommendations for colchicine use in children are sparse^{26,27}; also, due to the small number of chronic and recurrent cases in this study, we are unable to discuss this section.

5 | LIMITATIONS

The retrospective gathering of data was the main limitation of the study. The small number of recurrent or persistent cases was another limitation of this study. Due to small pericardiocentesis cases and their distribution among seven etiologies, the pericardiocentesis data were not conclusive.

6 | CONCLUSION

Generally, noninfectious diseases and, on top of them, renal failure were the leading causes of PE in our region. In severe cases, the chance of infectious disease increases. In contrast to older studies, TB pericarditis is rare in the new era. Most PE cases are hemodynamically stable even in severe cases. Except for severe cases who have high chance of pericardiocentesis, other patients usually respond to treatment of the underlying disease. Persistent PE for more than 3 months is not a common complication in pediatric age groups.

AUTHOR CONTRIBUTIONS

Nima Mehdizadegan: Conceptualization; funding acquisition; writing —review & editing. Hamid Mohammadi: Conceptualization; formal analysis; writing—original draft. Hamid Amoozgar: Conceptualization; funding acquisition. Samira Pournajaf: Funding acquisition; writing—original draft. Mohammad Reza Edraki: Writing—review & editing. Amir Naghshzan: Writing—review & editing. Mohammad Nima

Yazdani: Writing—review & editing. All authors have read and approved the final version of the manuscript and had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

TRANSPARENCY STATEMENT

The article authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

ETHICS STATEMENT

This retrospective study was approved by the Local Ethics Committee of Shiraz University of Medical Sciences and registered with the code of IR.SUMS.MED.REC.1399.559. It was exempted from the informed consent form of patients and no sensitive or private patient data, such as name or their address field, was used in this study.

DATA AVAILABILITY STATEMENT

Data are available on request from the corresponding author.

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