

ORIGINAL ARTICLE

Pericardial effusion in children admitted with juvenile idiopathic arthritis: A multicenter retrospective cohort study from the pediatric health information system

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ABSTRACT

Objectives: This study aimed to determine if the presence of a pericardial effusion is associated with adverse outcomes among children admitted with juvenile idiopathic arthritis.

Patients and methods: The multicenter, retrospective cohort study was conducted with 4,332 patients (1,554 males, 2,778 females; median age: 12 years; IQR, 7, 15 years) using the Pediatric Health Information System. Data from hospital admissions between January 1, 2004, and September 15, 2015, were obtained for patients with an International Disease Classification, Ninth Revision code for juvenile idiopathic arthritis. Pericardial effusion was the primary predictor variable; the outcomes of interest were length of stay, hospital costs, and readmission within 90 days. Multivariate models were created to evaluate associations between pericardial effusion and adverse outcomes. We also analyzed factors associated with increased odds of having pericardial effusion in juvenile idiopathic arthritis.

Results: One hundred twenty (3%) patients had a code for pericardial effusion. Children with pericardial effusion had a longer median length of stay (7 days (IQR 3-12) vs. 3 days (IQR 2-6), p<0.001), higher median costs (\$17,688 (IQR 8,657-40,623) vs. \$8,456 (IQR 4,865-16,302), p<0.001), and greater rates of readmission (22% vs. 15%, p=0.045). Multivariate analysis demonstrated no significant association between pericardial effusion and outcomes of interest. Black race and male sex were associated with increased odds of having pericardial effusion.

Conclusion: Pericardial effusion is rare among children admitted with juvenile idiopathic arthritis but is associated with significant morbidity; its presence may be a marker of disease severity. Black children and males admitted with juvenile idiopathic arthritis warrant special consideration and may benefit from screening echocardiography.

Keywords: Juvenile idiopathic arthritis, juvenile rheumatoid arthritis, pericardial effusion, tamponade.

Juvenile idiopathic arthritis (JIA) represents a group of inflammatory diseases of unknown etiology with various manifestations. JIA is characterized by arthritis lasting at least six weeks and disease onset before 16 years of age.¹⁻³ Extra-articular manifestations occur in various subtypes of JIA, particularly in the systemic subtype. These manifestations include fever, skin rash, hepatomegaly, splenomegaly, lymphadenopathy, uveitis, and serositis.^{4,5} Additionally, multiple

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cardiovascular manifestations have also been reported.^{6,7} JIA can involve all cardiac structures, including the endocardium, myocardium, pericardium, valves, coronary vessels, and the conduction system. Of these, the pericardium is most frequently implicated.⁶ Pericardial effusions (PCEs) and pericarditis have been reported to occur in 4-36% of patients with JIA and occur more commonly in children with the systemic form of the disease.8-11 PCE may occur at any time in the course of the disease but is usually accompanied by a systemic exacerbation.¹² In case reports or small single-center studies, patients with JIA and PCE tend to have mild to no clinical symptoms, and the effusions usually do not require pericardiocentesis.⁶ In one series of 55 patients with JIA, 20 (36%) had echocardiographic evidence of PCE. Of those, zero had reported symptoms, four had cardiac friction rubs, and zero required treatment with pericardiocentesis.⁸ Rarely, however, significant effusions resulting in cardiac tamponade have been reported.¹²⁻¹⁴

Pericardial effusion is a finding common to many autoimmune and rheumatologic conditions.¹⁵⁻²⁰ Its presence has been shown to be associated with increased morbidity in pediatric patients with systemic lupus erythematosus and Kawasaki disease.^{21,22} However, the outcomes of patients with JIA and PCE have not been reported in a multicenter cohort. Hence, we performed a retrospective cohort study to delineate the characteristics of children admitted with JIA and PCE and determine the impact of PCE on their outcomes. Given PCE's associations with adverse outcomes in other inflammatory disorders, we hypothesized that PCE is associated with a longer length of stay (LOS), higher hospital cost, and greater risk of readmission among children admitted with JIA.

PATIENTS AND METHODS

The multicenter, retrospective cohort study was conducted with 4,332 patients (1,554 males, 2,778 females; median age: 12 years; IQR, 7 to 15 years) at the University of Arkansas for Medical Sciences and Arkansas Children's Research Insitute, using the Pediatric Health Information System (PHIS). Data were obtained from admissions between January 1, 2004, and September 30, 2015, to avoid overlap with the transition from the International Classification of Disease. Ninth Revision (ICD-9) to the 10th Revision. Patients were included if they were ≤ 18 years of age at the time of admission and had an ICD-9 code for JIA. Patients were excluded if they had congenital heart disease (except for those with patent ductus arteriosus or atrial septal defect) or if they underwent a cardiac procedure (except for pericardiocentesis). These exclusions were performed to eliminate cases of postoperative PCE. We dichotomized the sample based on the presence or absence of PCE, the primary predictor variable. Patients carrying a diagnostic code for PCE were assigned to the PCE group; patients without a diagnosis of PCE were assigned to the No PCE group. The primary outcomes were LOS, adjusted hospital costs, and readmission at 90 days. Hospital costs were adjusted for 2010 dollars to correct for inflation. For patients with multiple admissions, the first admission was used to define readmissions.

The PHIS is a pediatric inpatient administrative database comprised of data from 49 pediatric hospitals in the USA participating in the Children's Hospital Association. Data from the PHIS include deidentified, detailed information on hospitalized children's demographics, diagnoses, procedures, medications, and outcomes. The database has ongoing, multistep quality assurance measures in place; data are accepted from participating hospitals only when classified errors in a given quarter occur less frequently than a criterion threshold of 2%.

Statistical analysis

Data were analyzed using the statistical software R v3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) for summary statistics and statistical testing, and SAS 9.4 (SAS Institute Inc, Cary, North Carolina, USA) for modeling. Univariate analysis was used to compare groups for demographic features, clinical characteristics, and outcomes. Descriptive statistics were expressed as median with interquartile ranges (IQRs) for continuous variables and as percentages (count) for categorical variables. The distributions of continuous variables were compared between groups using the Kruskal-Wallis test, and the proportions of categorical variables were

Characteristic	All (n=4,332) Mean (%) or Median (IQR)	No PCE (n=4,212) Mean (%) or Median (IQR)	PCE (n=120) Mean (%) or Median (IQR)	<i>p</i> †
Admission quarter				0.32
First quarter	1,176 (27)	1,150 (27)	26 (22)	
Second quarter	1,117 (26)	1,082 (26)	35 (29)	
Third quarter	1,021 (24)	996 (24)	25 (21)	
Fourth quarter	1,018 (23)	984 (23)	34 (28)	
Admission age (year)	12 (7, 15)	12 (12, 15)	9 (5, 14)	< 0.001
Male	1,554 (36)	1,496 (36)	58 (48)	0.004
Race				0.002
White	3056 (73)	2983 (74)	73 (62)	
Black	518 (12)	491 (12)	27 (23)	
Other	596 (14)	579 (14)	17 (15)	
Median household income (\$2010)	44,164 (34,561, 57,912)	44,174 (34,588, 57,789)	42,757 (33,993, 60,479)	0.82
Principal payer				0.06
Commercial	2,031 (47)	1,979 (47)	52 (43)	
Governmental	1,847 (43)	1,798 (43)	49 (41)	
Self-pay/other	413 (10)	394 (9)	19 (16)	
Intensive care unit	432 (10)	386 (9)	46 (38)	< 0.001
Mechanical ventilation	149 (3)	129 (3)	17 (14)	< 0.001
Infectious disease	634 (15)	597 (14)	37 (31)	< 0.001
Hypothyroidism	83 (2)	82 (2)	1 (1)	0.38
Neoplastic disease	140 (3)	137 (3)	3 (2)	0.65
Renal disease	23 (1)	22 (1)	1 (1)	0.64
Rheumatic heart disease	8 (<1)	6 (<1)	2 (2)	< 0.001
Anemia	803 (19)	755 (18)	48 (40)	< 0.001
Methotrexate	317 (7)	304 (7)	13 (11)	0.13
Ibuprofen	738 (17)	685(16)	53 (44)	< 0.001
Indomethacin	158 (4)	133 (3)	25 (21)	< 0.001
Etanercept	75 (2)	70 (2)	5 (4)	0.04
Tocilizumab	37 (1)	33 (1)	4 (3)	0.003
Infliximab	58 (1)	56 (1)	2 (2)	0.75
Rituximab	19 (<1)	17 (<1)	2 (2)	0.04
Intravenous immunoglobulin	96 (2.)	83 (2)	13 (11)	< 0.001
Mortality	22 (<1)	19 (<1)	3 (3)	0.002
Length of stay (days)	3 (2, 6)	3 (2, 6)	7 (3, 12)	< 0.001
Adjusted total cost (\$2015)	8,585 (4,920, 16,712)	8,456 (4,865, 16,302)	17,688 (8,657, 40,623)	< 0.001
Readmission within 30 days of discharge‡	412 (10)	395 (9)	17 (14)	0.08
Readmission within 90 days of discharge‡	658 (15)	632 (15)	26 (22)	0.045

†: P-values are obtained from comparison of two groups (No PCE and PCE) using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables; † Individuals with missing readmission data were assumed to have no readmission.

compared using the chi-square test. P-values were obtained by comparing the PCE and No PCE groups using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables.

performed Multivariate analysis was using generalized linear models to evaluate for associations between PCE and the three primary outcomes. The presence of PCE was also analyzed as a dependent variable to determine if any patient characteristics were associated with a greater likelihood of having PCE when admitted with JIA. Covariates in the multivariate model were PCE, race, discharge year, admission age, sex, median household income, infectious disease, neoplastic disease, renal disease, hypothyroidism, anemia, intensive care admissions, mechanical ventilation, and the use of the following medications: methotrexate, ibuprofen. indomethacin. etanercept. or intravenous immunoglobulin (IVIG). Median household income was adjusted to 2010 dollars. Binomial distribution and logit link were used for the two binary outcomes: PCE and readmission

by 90 days. Quasi-Poisson distribution and log link were employed for adjusted hospital costs and LOS. Firth's bias-reduced, penalized likelihood approach was used when the sample size was small, as was the case for readmissions. Models for LOS and readmission were fitted only among those alive to initial discharge. Adjusted odds ratios (aOR) were reported with 95% confidence intervals (CIs). A *p*-value <0.05 was considered statistically significant.

RESULTS

One hundred twenty (3%) patients involved in the study had PCE. Table 1 shows the characteristics of the entire cohort and compares those with PCE to those without PCE. Patients with PCE tended to be younger (median age 9.0 years [IQR: 5.8-14.0]) than those without PCE (12.0 years [IQR: 7.0-15.0]), p<0.001. More children with PCE were male (48% vs. 36%, p=0.004). Whites comprised a greater percentage of the entire cohort (73% vs. 12% Black and 14% Other); however, there was a greater percentage

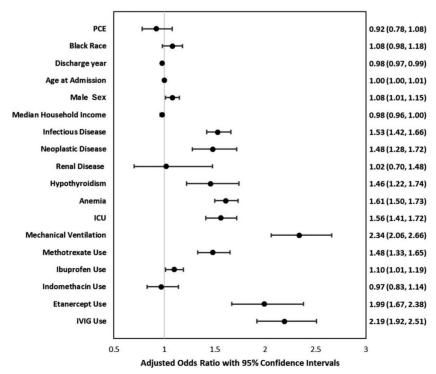


Figure 1. Multivariate model for LOS.

LOS: Longer length of stay; PCE: Pericardial effusions; ICU: Intensive care unit; IVIG: Intravenous immunoglobulin.

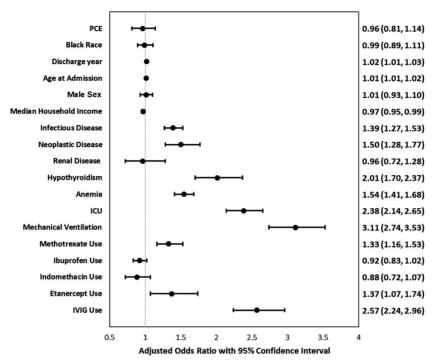


Figure 2. Multivariate model for adjusted hospital costs. PCE: Pericardial effusions; ICU: Intensive care unit; IVIG: Intravenous immunoglobulin.

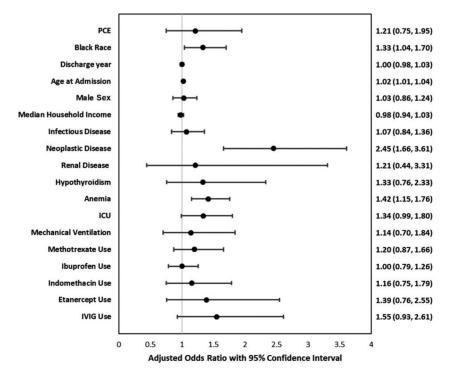


Figure 3. Multivariate model for readmission within 90 days. PCE: Pericardial effusions; ICU: Intensive care unit; IVIG: Intravenous immunoglobulin.

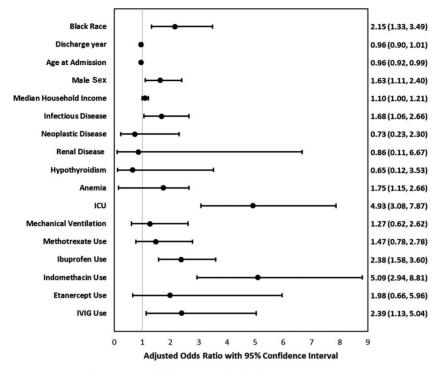


Figure 4. Multivariate model for pericardial effusion. ICU: Intensive care unit; IVIG: Intravenous immunoglobulin.

of Black patients in the PCE group compared to the No PCE group (23% vs. 12%, p=0.002). Patients with PCE had a statistically significant association with the following: intensive care unit admission, mechanical ventilation, infectious disease, rheumatic heart disease, anemia, and the use of certain medications, including ibuprofen, indomethacin, etanercept, tocilizumab, and rituximab.

Regarding outcomes in the univariate analysis, patients with PCE tended to have a longer LOS than those without PCE (7 days [IQR: 3-12] vs. 3 days [IQR: 2-6], p<0.001). Median adjusted hospital costs were higher for the PCE group (\$17,688 [IQR: 8,657-40,623]) compared to the No PCE group (\$8,456 [IQR: 4,865-16,302], p<0.001). Patients in the PCE group were more frequently readmitted within 90 days of discharge than those in the No PCE group (22% vs. 15%, p=0.045). There were no significant differences between groups for discharge year, admission month, median household income, or principal payer. Finally, mortality was higher in the PCE group (3%) compared to the No PCE group (0%), p<0.001, although overall mortality was low (1% of the total cohort).

Multivariate analysis demonstrated no significant association between PCE and the three outcomes of interest: LOS, adjusted hospital costs, and readmission by 90 days. In the model for LOS (Figure 1), variables associated with the highest likelihood of a longer LOS included mechanical ventilation (aOR=2.34 [95% CI 2.06-2.66], p<0.001), IVIG use (aOR=2.19 [95% CI 1.92-2.51], p<0.001), and etanercept use (aOR=1.99 [95% CI: 1.67-2.38], p<0.001). Figure 2 demonstrates the multivariate model for adjusted hospital costs. The greatest probability of higher costs was associated with mechanical ventilation (aOR=3.11 [95% CI 2.74-3.53], p<0.001), IVIG use (aOR=2.57 [95% CI 2.24-2.96], p<0.001), and intensive care admission (aOR=2.38 [95% CI 2.14-2.65], p<0.001). The model for readmission by 90 days is shown in Figure 3. The odds of readmission were highest in patients with neoplastic disease (aOR=2.45 [95% CI 1.66-3.61], p<0.001), anemia

(aOR=1.42 [95% CI 1.15-1.76], p=0.001), and the Black race (aOR=1.33 [95% CI 1.04-1.70], p=0.023).

Multivariate analysis for factors associated with the presence of PCE is shown in Figure 4. Multiple factors were associated with an increased odds of having PCE: indomethacin use (aOR=5.09 [95% CI 2.94-8.81], p<0.001), intensive care admission (aOR=4.93 [95% CI 3.08-7.87], p<0.001), ibuprofen use (aOR=2.38 [95% CI 1.58-3.60], p<0.001), the Black race (aOR=2.15 [95% CI 1.33-3.49], p=0.002), and male sex (aOR=1.63 [95% CI 1.11-2.40], p=0.014).

DISCUSSION

In this study of 4,332 pediatric patients with JIA admitted to tertiary pediatric hospitals across the USA, there were three prominent findings. First, PCE was relatively rare, occurring in less than 3% of subjects. Second, PCE was associated with all three adverse outcomes, although not after controlling for other selected variables. Third, both the male sex and Black race were independently associated with PCE as well as adverse outcomes in the multivariate analysis. These findings suggest that PCE is a marker of disease severity and that further consideration of how Black children and males admitted with JIA are managed.

The present study is the largest to date to examine PCE in children with JIA. Our findings were consistent with other studies that showed a low incidence of cardiovascular disease among children with JIA.7 Additionally, we found that PCE was associated with all three adverse outcomes (LOS, hospital costs, and readmission at 90 days), although not after controlling for other variables; these data suggest that PCE is part of more severe disease presentation in children admitted with JIA. This was also supported by the fact that mortality was higher in the PCE group, although mortality in the entire cohort was low (<1%). This is consistent with other studies of other pediatric inflammatory processes, namely systemic lupus erythematosus and Kawasaki disease, which demonstrated higher rates of adverse outcomes among patients with PCE.^{21,22}

There were also notable effects on the outcomes of interest according to sex. In the full analytic sample, there were more females admitted with JIA than males (64% female vs. 36% male). This female preponderance is not surprising, given that the prevalence of JIA is higher in females than males.²³ However, we found that there was a predilection for PCE in males admitted with JIA, and in multivariate analysis, male sex was associated with longer LOS. The underlying cause of these findings is not entirely clear. Given that the presence of PCE itself was not associated with longer LOS, the longer LOS in males could indicate that males tend to have more severe illness or slower recovery than females admitted with JIA. This would not be surprising as other sex differences in JIA-related complications have been previously reported.²⁴ Further research is needed to fully explain the cause of these findings; nevertheless, clinicians should have a higher index of suspicion for PCE in males with JIA.

Another notable finding in the present study was the relationship between race and adverse outcomes. Though there were significantly more White children than Black children in our cohort, there was a higher percentage of Black children with PCE than those without PCE. In multivariate analyses, the Black race was independently associated with an increased likelihood of having PCE and readmission within 90 days. However, Black race was not associated with differences in LOS or costs. Prior studies have demonstrated that features of JIA are different in Black children than other races: Black children with JIA tend to have the systemic subtype of JIA and increased disease activity compared to other races.^{24,25} This may explain why PCE and readmission were more common in Black children in our cohort. The present data suggest that special attention should be made to evaluate effusions in Black children and take measures at discharge to prevent readmission.

This study had several limitations. Its retrospective design precluded determination of causation. JIA subtypes, as defined by the International League of Associations for Rheumatology (ILAR), were unable to be included as ICD-9 diagnosis codes reflect an earlier classification system and do not

correlate well with current ILAR subtypes. Corticosteroids were not included in the treatment data presented in Table 1. There were also limitations unique to the PHIS database. Patients were identified using ICD-9 codes, which are dependent on billing physicians and hospital coders. The PHIS lacks granularity that may otherwise be available in a retrospective chart review. Additionally, temporality is difficult or impossible to determine from the PHIS. The PHIS only provides diagnostic codes for a given admission but not the time of onset of a specific condition. For example, the date on which a diagnosis of JIA was made cannot be determined from the PHIS, and therefore, the time between JIA diagnosis and any of the studied outcomes is not known. Furthermore, in relying on diagnostic codes for a given admission, it was not possible to exclude potential patients who received care at more than one participating center. The PHIS does not contain data from diagnostic studies (imaging, laboratory, or otherwise), and therefore, data on the size or location of the PCE were not available. Finally, data on clinical decision making are not present.

In conclusion, children admitted with JIA and PCE seem to have more severe disease manifestations than those without PCE. Pericardial effusion is significantly more common in Black children and male children with JIA. The Black race is associated with higher rates of readmission, and male sex is associated with longer LOS. These findings suggest demographic differences in JIA phenotypes in these groups and support the need for further research into this disease and its cardiac manifestations.

Ethics Committee Approval: This study was reviewed by the Institutional Review Board of the University of Arkansas for Medical Sciences which confirmed that no ethical approval is required as it was deemed non-human subject research. (date 24.01.2019, no: 261894). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: It consisted of a retrospective review of de-identified patient information, and informed consent was not obtained.

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

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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