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ORIGINAL ARTICLE

Pediatric Patients Hospitalized with Myocarditis: A Multi-Institutional Analysis

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Abstract The objective of this study was to identify the patient, institutional, and utilization characteristics associated with outcome in hospitalized pediatric patients with myocarditis. This was a nonconcurrent cohort study of all consecutive pediatric discharges from the 35 academic children's hospitals that are members of the Pediatric Health Information System (PHIS): patients from birth through age 21 years discharged from participating hospitals between January 1, 2005, and December 31, 2005. Patient-level, institution-level, and utilization variables were examined. A total of 427,615 patients were discharged, and 216 (0.05%) were diagnosed with myocarditis. Common etiologies were idiopathic (82%), related to other diseases (6%), and bacterial or viral (3%). Myocarditis patients required considerable support including intravenous immunoglobulin (IVIG; 49.1%), milrinone (45%), epinephrine (35%), mechanical ventilation (25%), extracorporeal membrane oxygenation (7%), and cardiac transplantation (5%). Even in patients with extreme illness scores, IVIG use did not impact survival ($P = 0.67$). Overall survival of myocarditis patients was 92%. Myocarditis patients who died presented with a higher severity of illness and required frequent use of extracorporeal membrane oxygenation and other ICU therapies. In conclusion, pediatric patients with myocarditis have considerable variability in their presentations and outcomes, use more resources, and die more often than children with other diagnoses. Attempts at using characteristics that uniformly predict illness severity or survival were not successful. Despite increased use in the sickest patients, IVIG conferred no survival advantage.

Keywords Myocarditis · Survival · Children · Severity of illness · Intensive care unit · Extracorporeal membrane oxygenation · Intravenous immunoglobulin

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Myocarditis is an inflammatory condition of the myocardium characterized by leukocyte infiltration and subsequent fibrosis and necrosis. Although myocarditis is rare, occurring in 0.05% of children, it causes significant morbidity and mortality, with long-term sequelae including chronic congestive heart failure (CHF), cardiomyopathy, and death [3, 5, 10, 19, 22, 24, 30].

Although most cases of myocarditis are preceded by a viral or flu-like illness, the spectrum of presentation is

broad and ranges from acute fulminant myocarditis characterized by the sudden onset of severe CHF and cardiogenic shock [1, 3, 6, 9, 10, 17, 18, 22] to an indolent onset with progression of symptoms resulting in CHF. Patients with acute fulminant myocarditis are critically ill, requiring prolonged intensive care unit (ICU) stays [1, 9, 18, 28] and, occasionally, extracorporeal membrane oxygenation (ECMO) [4, 8, 31]. Care for these patients is directed at respiratory and hemodynamic support while the diagnostic workup for myocarditis is completed [2, 11, 12].

Prior studies of pediatric myocarditis are limited to small cohorts or single-institution case series. Therefore, the purpose of this study was to use a multi-institutional dataset of discharges from freestanding academic childrens' hospitals to characterize pediatric patients hospitalized with myocarditis and determine the characteristics associated with mortality so that earlier opportunities for intervention might be identified.

Patients and Methods

Dataset

The Pediatric Health Information System (PHIS) dataset was used for these analyses. This dataset is available for the years 1997–2007 and represents detailed hospital-based inpatient information on all discharges ($n = 427{,}615$) from 35 independent, academic, freestanding, childrens' hospitals in the United States (PHIS). The participating institutions are affiliated with the Child Health Corporation of America (Shawnee Mission, KS) and supply demographic, diagnostic, and utilization data for purposes of internal and external benchmarking. They are heterogeneous with respect to geographic location, bed number, and average daily census. Data are submitted to the PHIS and tested for reliability and validity before inclusion. The data warehouse function for the PHIS is managed by Solucient, LLC (Evanston, IL).

Data Checks

The hospitals submit discharge-level data on a monthly basis from their internal data systems using a standardized discharge abstract. These data include the hospital identifier, medical record number, and admission and discharge dates, age, race, gender, payer, and up to 21 diagnoses and procedures. The data are then assigned an All Patient Refined Diagnostic Related Group (APR-DRG) severity level (3 M Center, St. Paul, MN). The medical record numbers, billing numbers, physician identifications, and Zip Codes are encrypted to protect the identity of the patients and assure compliance with federal regulations. These data are then subjected to a number of reliability and validity checks before being processed. If a hospital's quarterly data are unacceptable according to these limits, all of its quarterly data are rejected; however, these data can be resubmitted and re-evaluated for inclusion at a later time (Solucient). During the study period, all data from each of the participating institutions met the reliability and validity thresholds and were included for analysis.

Participant Inclusion and Exclusion

All consecutive pediatric discharges, from birth through age 21 years, from participating hospitals between January 1, 2005, and December 31, 2005, were included in this study. The unit of analysis for this investigation was the individual discharge. Readmissions of individual patients were considered separate admissions for the purpose of these analyses.

Study Design

Definitions

Discharges were surveyed for an ICD 9 procedure code indicative of myocarditis (defined by ICD 9 codes 391.2, 422, 422.0, 422.9, 429.0, 422.90–422.93, 074.23, 398.0, 032.82, 036.43, 093.82, 130.3). From the group of patients who had myocarditis, procedures and medications were determined by the presence of an ICD 9 diagnosis code corresponding to ECMO (39.65), heart transplantation (37.51), cardiac pacing (37.7), arterial catheters (89.61), central venous catheters (89.62), Swan Ganz catheters (89.64), mechanical ventilator use (96.04, 96.71, 96.72), cardiac catheterization (37.21, 37.22, 37.23), or myocardial biopsy (37.25) and medication use. The primary outcome measure of this study was survival.

Variables

We determined the association of myocarditis survival with the following independent variables obtained directly from existing data elements in the PHIS dataset or derived from PHIS data elements: (1) patient characteristics, (2) utilization characteristics, and (3) hospital characteristics. For each discharge with myocarditis, the demographic and utilization variables were identified. Patient-level variables included age, race, gender, payer, diagnosis, disposition, and survival. The utilization variable was length of stay (LOS). Institution-level variables included geographic location, bed size, and average daily census.

The severity variable represents a relative severity score that is derived by encoding age, diagnostic, and procedural codes into a computerized algorithm known as the All

Patient Refined Diagnostic Related Group (APR-DRG). This variable stratifies severity and risk of mortality into one of four levels based on the degree of coding. Generally, risk-of-mortality measures aim to predict mortality after accounting for clinical attributes at the patient level. As a result, the APR-DRG is now a standard for benchmarking inpatient severity of illness, hospital performance, and hospital quality.

Statistical Analyses

Results are given as representative rates to allow ease of comparison among and between groups and to allow the computation of odds ratios (OR's). The chi-square test was used for comparison of nominal data. Length-of-stay data may not be Gaussian in distribution. Therefore, a non-parametric test, the Mann–Whitney rank sums test was used for these comparisons. Stepwise multiple logistic regression analysis was performed to adjust for differences in case mix among myocarditis patients and to determine their association with outcomes. In all instances, a *P*-value of 0.05 was used as the significance level. Statistical analyses were performed using SAS (SAS Inc., Cary, NC). The study used deidentified data and was granted an exempt status from the Institutional Review Board.

Results

During the study period there were a total of 427,615 discharges from the participating institutions, of which 216 (0.05%) were diagnosed with myocarditis. Table 1 reports the baseline characteristics of survivors versus nonsurvivors with myocarditis. Children with myocarditis who survived had similar characteristics compared to children who died. There was no statistically significant difference in patient age, gender, hospital size, or insurance payer. Patients with myocarditis who died had higher severity-of-illness scores.

Ages of children hospitalized with myocarditis were evenly distributed, with approximately 53% of children being <5 years of age and 47% being ≥5 years of age (Table 1). There was no significant difference in the proportion of males (56.5%) versus females (43.5%) with myocarditis ($P = 0.064$). The majority of myocarditis patients were Caucasian (63.6%), with another large proportion of patients being African American (24.4%). Private (42.6%) or government (34.7%) insurance was the predominant insurance payer.

A total of 115 (53.2%) patients with myocarditis had a severity score of major or extreme (Table 1), and consistent with this finding, myocarditis patients were often admitted to the ICU ($N = 116$; 53.7%). The average hospital LOS was 14.4 days and the mortality rate was 7.8%.

Patients with myocarditis who died presented with severity of illness rated as either major ($n = 7$; 41.2%) or extreme ($n = 10$; 58.8%). There was a significant relationship between severity and mortality score when stratified by severity level ($P = 0.0001$). Using multiple logistic regression analysis of patient demographic factors associated with outcome, only severity of illness was statistically significant (OR = 7.84; 95% CI = 2.36, 26.04) (Table 2).

Children with myocarditis often required multiple invasive procedures and significant pharmacologic support (Table 3). Eighty-one (37.5%) patients required mechanical ventilation, including 64 (32.2%) of the patients who survived. Cardiac catheterization and myocardial biopsy were performed in 18.9% and 18.0% of patients, respectively. A total of 670 microbiologic cultures were performed on these children (mean, 3 cultures/patient) with 56% having bacterial cultures (either aerobic or anaerobic) and 88% having viral cultures performed. Pharmacologic therapy was widely used, including intravenous immunoglobulin (IVIG; 45.4%), inotropes, and antiarrhythmic medications (Table 3). Milrinone ($n = 97$; 44.9%) and epinephrine ($n = 76$; 35.2%) were used most often for vasoactive support.

Overall, the use of IVIG was not associated with severity (all *P*'s = NS) (Table 4). However, when evaluated by individual severity scores, there was a trend toward more frequent use of IVIG in patients with extreme severity scores ($n = 27$; 27.6%; $P = 0.06$). Despite the trend toward increased use in the sickest patients, IVIG did not confer a survival advantage regardless of the patient's severity of illness (P = NS). Of the seven patients with a major severity score who died, two received IVIG (6.9%), compared to five patients who did not receive IVIG (12.8%; OR = 0.5; $P = 0.4$) (Table 4). Four of twenty-seven patients (14.8%) with extreme severity scores who died received IVIG, compared to 6 of 20 patients (30%) with the same score who died but did not receive IVIG therapy (OR = 0.4, $P = 0.2$) (Table 4). Importantly, when analyzing the same patients with extreme severity scores, IVIG did not have any impact on mortality ($P = 0.22$) (Table 4).

Discussion

The purpose of this study was to improve the understanding of outcomes for patients diagnosed with myocarditis to determine if risk factors for mortality could be identified. While pediatric myocarditis presents with significant morbidity and mortality, the prevalence is rare, the diagnosis remains challenging [5, 19, 23, 27], and large multi-institutional studies are lacking. This study provides a multi-institutional analysis of children diagnosed with

Table 1 Demographic characteristics of patients with myocarditis

Variable	Survived ($N = 199$)		Died ($N = 17$)		Odds ratio[a]	P-value[a]
	n	%	*n*	%		
Age						
0–30 days	11	5.5%	1	5.9%	1.1	NS
31–365 days	32	16.1%	1	5.9%	0.3	NS
1–5 years	62	31.2%	8	47.1%	2.0	NS
6–12 years	32	16.1%	6	35.3%	2.8	NS
13–18 years	61	30.7%	1	5.9%	0.1	NS
19–21 years	1	0.5%	0	0.0%	0.0	NS
Gender						
Female	116	58.3%	6	35.3%	0.4	NS
Male	83	41.7%	11	64.7%	2.6	NS
Race						
Caucasian	122	61.3%	11	64.7%	1.2	NS
African American	47	23.6%	4	23.5%	1.0	NS
Asian	4	2.0%	0	0.0%	0.0	NS
American Indian	1	0.5%	0	0.0%	0.0	NS
Other	18	9.1%	2	11.8%	1.3	NS
Principal insurance						
Government	69	34.7%	6	35.3%	1.0	NS
Private	83	41.7%	9	52.9%	1.6	NS
Self pay	2	1.0%	0	0.0%	0.0	NS
Other	45	22.6%	2	11.7%	0.5	NS
Geographic region						
Northeast	18	9.0%	3	17.7%	2.2	NS
Southeast	12	6.0%	1	5.9%	1.0	NS
Mid Atlantic	35	17.6%	1	5.9%	0.3	NS
Mountain	4	2.0%	0	0.0	0.0	NS
New England	5	2.5%	0	0.0	0.0	NS
Pacific	35	17.6%	1	5.9%	0.3	NS
South Atlantic	27	13.6%	2	11.8%	0.8	NS
Northwest	22	11.1%	3	17.7%	1.7	NS
Southwest	41	20.6%	6	35.3%	2.1	NS
Severity score						
Minor	48	24.1%	0	0.0	0.0	<0.05
Moderate	53	26.6%	0	0.0	0.0	<0.05
Major	61	30.7%	7	41.2%	1.6	NS
Extreme	37	18.6%	10	58.8%	6.3	<0.05
ICU admit	106	53.3%	10	58.8%	1.3	NS

Note: *NS* nonsignificant

[a] Comparing survival vs. death

myocarditis at freestanding childrens' hospitals. Severity of illness at presentation was the only demographic characteristic associated with outcome in children with myocarditis. In addition, this study was unable to detect any survival advantage for myocarditis patients who received IVIG, a common treatment strategy.

Despite a rigorous attempt to more clearly define patient and institutional characteristics associated with survival in hospitalized children with myocarditis, these data suggest considerable variation in both presentation and outcome. We were unsuccessful in finding specific patient or hospital characteristics associated with outcome. The lack of

Table 2 Results of multiple logistic regression analysis for pediatric patients hospitalized with myocarditis and patient-level factors associated with survival

Demographic	Odds ratio	95% CI
Age	1.73	(0.93,3.21)
Gender	1.89	(0.52,6.87)
Race	0.45	(0.14,1.44)
Ethnicity	1.03	(0.46,2.29)
Severity score	7.84	(2.36,26.04)
Principal insurance	0.50	(0.25,0.99)

Note: *CI* confidence interval

well-defined clinical characteristics in this population highlights the ongoing diagnostic and clinical challenges associated with this illness. Endomyocardial biopsy (EMB) is often inaccurate because of patchy involvement of the myocardium; however, endomyocardial biopsy is more likely to be positive when performed within 72 h of presentation [6]. Newer diagnostic modalities such as MRI have shown promise for diagnosing myocarditis and should be considered in patients in whom the diagnosis is suspected [13, 20, 26], because they may be helpful in guiding early therapy and management.

Severity of illness was found to be a significant predictor of mortality upon initial hospital presentation. The severity of illness represented by our patient population is consistent with that in prior studies. In a study of children with acute fulminant myocarditis in France, 100% of the children required ICU admission [1]. Lee et al. reviewed 35 biopsy-positive cases of myocarditis, and 66% of the patients were admitted to the ICU [18]. However, despite

Table 3 Care requirements of patients with myocarditis

Variable	Total ($N = 216$)		Survived ($N = 199$)		Died ($N = 17$)		Odds ratio[a]	P-value[a]
	n	%	n	%	n	%		
Procedure								
ECMO	16	7.4%	9	4.5%	7	41.2%	14.8	<0.05
Heart transplant	4	1.9%	4	2.0%	0	0.0	0.0	NS
Need for pacing	6	2.8%	6	3.0%	0	0.0	0.0	NS
Arterial line	6	2.8%	5	2.5%	1	5.9%	2.4	NS
Central venous catheter	3	1.4%	3	1.5%	0	0	0.0	NS
Swann Ganz catheter	3	1.4%	3	1.5%	0	0	0.0	NS
Ventilator	81	37.5%	64	32.2%	17	100%	–	0.95
Cardiac catheterization	41	19.0%	36	18.1%	5	29.4%	1.9	NS
Myocardial biopsy	39	18.1%	36	18.1%	3	17.7%	1.0	NS
Other	171	79.2%	154	77.4%	17	100%	–	–
Medication								
Milrinone	97	44.9%	85	42.7%	12	70.6%	3.2	<0.05
Epinepherine	76	35.2%	64	32.2%	12	70.6%	5.1	<0.05
Dopamine	73	33.8%	61	30.7%	12	70.6%	5.4	<0.05
Lidocaine	93	43.1%	81	40.7%	12	70.6%	3.5	<0.05
IVIG	98	45.4%	92	46.2%	6	35.3%	0.6	NS

Note: *ECMO* extracorporeal membrane oxygenation, *NS* nonsignificant, *IVIG* intravenous immunoglobulin

[a] Comparing survival vs. death

Table 4 Mortality and IVIG use

Severity group	IVIG ($N = 98$)		No IVIG ($N = 118$)		Odds ratio	95% CI	P-value
	Died, n	Survived, n	Died, n	Survived, n			
Minor	0 (0.0%)	18 (100.0%)	0 (0.0%)	30 (100.0%)	–	–	
Moderate	0 (0.0%)	24 (100.0%)	0 (0.0%)	29 (100.0%)	–	–	
Major	2 (6.9%)	27 (93.1%)	5 (12.8%)	34 (87.2%)	0.5	(0.09,2.8)	0.43
Extreme	4 (14.8%)	23 (85.2%)	6 (30.0%)	14 (70.0%)	0.4	(0.10,1.70)	0.22

Note: *IVIG* intravenous immunoglobulin, *CI* confidence interval

initial clinical presentation, long-term follow-up studies have demonstrated that patients with acute fulminant myocarditis have favorable long-term survival [1, 9, 11, 17, 22]. Therefore, despite an increased likelihood of death early in their illness trajectory, patients with an acute fulminant presentation should be managed aggressively.

Despite the lack of proven efficacy, nearly half of the patients in our study received IVIG, demonstrating continued widespread use of immunosuppression in this patient population. This finding is consistent with the widely described use of this therapy [7, 14, 16, 21]. In a prospective trial of high-dose γ-globulin for children with myocarditis, Drucker and colleagues found improved recovery of left ventricular function, but no statistically significant improvement in survival, compared to a historical cohort of patients who did not receive IVIG [7]. Currently, there are no prospective, randomized, controlled trials demonstrating the efficacy of IVIG in this patient population, and our study confirms that there is a lack of appreciable survival advantage with IVIG use. Given the cost and potential side effects of this therapy, additional prospective studies are necessary to clearly delineate clinical benefit of high-dose IVIG in the treatment of pediatric myocarditis.

ECMO has been efficacious in the support of children with myocarditis [4, 8, 31], and our study continues to demonstrate the role of mechanical cardiac support in the treatment of these patients. However, ECMO should only be considered after routine supportive therapies have failed. Recently, other mechanical support modalities have been used to manage cases of pediatric myocarditis. Pulsatile paracorporeal support systems in pediatrics are being used more frequently to support children with myocarditis, and an improvement in outcomes for children with acute viral myocarditis has been documented in multiple single-center reports [15, 25, 29]. Hetzer and colleagues have demonstrated a significant increase, from 35 to 68%, in the use of ventricular assist devices in patients discharged from the hospital or bridged to transplant in two time frames, from 1990 to 1998 and from 1998 to 2004 [15].

There are important limitations to this study. First, the data were derived from a large administrative database that depends on the accuracy of coding by the participating hospitals. While the data are useful for analyzing the demographics and resource utilization for a population of patients, they cannot be used to draw inferences or make clinical decisions for individual patients. Second, using an administrative dataset limits the availability of routine culture and myocardial biopsy data. In addition, postmortem data are not available, making it likely that the incidence of myocarditis may be underestimated. It is also possible that the administrative dataset underestimates the number of procedures required by each patient and the severity of illness since it is not based on physiologic indexes. Finally, we used a single calendar year of data because our primary outcome of interest was survival at hospital discharge. However, using a single calendar year of data limits the time for evaluation of therapies such as IVIG which might be best evaluated over longer time periods. Nonetheless, the use of survival as a primary outcome measure allowed us the opportunity to move beyond surrogate markers of efficacy such as echocardiographic parameters or functional status and focus on other important clinical outcomes. These data do, however, provide a *multi-institutional* perspective of the demographics, patient care requirements, and outcomes of pediatric patients hospitalized with myocarditis free from the biases associated with single-institution studies.

Conclusion

The variation of presentation in children with myocarditis made the identification of unique patient characteristics associated with outcome difficult. Attempts at using characteristics that uniformly predict illness severity or survival in this cohort were not successful. Nonetheless, when myocarditis is suspected, early clinical suspicion should be high and the management should be aggressive. These data further highlight the need for additional multicenter studies using IVIG and other immunosuppressive agents for treating this patient population. While definitive and rapid diagnosis is important, there remain challenges in using diagnostic tools like MRI, and further investigations into easier and more accurate methods of diagnosis are needed.

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