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Burden of Renal Dysfunction and Neurologic Complications in Hospitalized Pediatric Heart Failure Unrelated to Congenital Heart Disease: A Multicenter Study

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Abstract: Objectives: Limited data are available on renal dysfunction and neurologic complications in heart failure in children, when the heart failure is not related to congenital heart disease (CHD) or cardiac surgery. This study used a multi-center database to describe pediatric heart failure (pHF)-related renal dysfunction, neurological complications, and outcomes in non-CHD patients. Methods: The Pediatric Health Information System (PHIS) database between 2004 and 2020 was used to analyze the prevalence of renal dysfunction and neurologic complications associated with pHF hospitalizations and their impact on outcomes. Results: Of the 5515 hospitalizations included in the study, renal dysfunction was identified in 1239 (22.5%), and neurologic dysfunction was diagnosed in 539 (9.8%). The diagnosis of renal or neurologic complications was associated with significantly higher use of ICU therapies, including mechanical ventilation, parenteral nutrition, and mechanical circulatory support. Patients with significant renal dysfunction were likely to receive kidney transplants in 3.1% of the cases. Neurologic complications were higher in patients with pHF who underwent heart transplantation (21.3% vs. 7.8%, $p < 0.001$). Patients with renal dysfunction and neurologic complications had significantly higher mortality rates than those without renal dysfunction (11.7% vs. 4.3%, $p < 0.001$) and neurologic complications (18.4% vs. 4.6%, $p < 0.001$). Conclusions: Renal dysfunction and neurologic complications are common, resulting in significantly higher utilization of ICU therapies and mortality rates during non-CHD-related pHF hospitalization. Neurologic complications associated with hospitalization for pHF are associated with a significantly higher mortality, which has been underemphasized in the literature. This study assesses the burden of these morbidities and highlights the importance of monitoring and managing renal and neurologic complications in pHF to improve outcomes.

Keywords: pediatric heart failure; renal dysfunction; neurologic complications; VAD; ECMO; mortality in pediatric heart failure; heart transplantation; kidney transplantation

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1. Introduction

Pediatric heart failure (pHF) is a serious and often life-threatening condition that affects children with congenital heart defects (CHD), cardiomyopathies, and other cardiac disorders. It can lead to a wide range of complications, including renal and neurologic dysfunctions. Although the overall incidence of HF is low in children compared to adults, pediatric cardiomyopathy and HF-related hospitalizations are associated with worse outcomes than adult hospitalizations and are twice as costly as in adults [1]. Costs of pHF are significant—in the order of USD 1 billion annually as per hospital charges for inpatient admissions alone in 2009 [2]. In a Pediatric Health Information System (PHIS) database study,

Shamszad et al. found a significant increase in the annual cardiomyopathy-related HF admissions during their 2005–2010 study period [3]. Heart failure-related hospitalizations occur in 11,000–14,000 children annually in the United States, with an overall mortality of 7% [4]. The most significant mortality risk occurred with extracorporeal membrane oxygenation (ECMO), acute renal failure, and sepsis [4]. Renal dysfunction is a common complication of HF in adults and children and determines the outcomes of HF hospitalization [5–7]. One study found that serum creatinine increased in 82% of children hospitalized with decompensated HF, and renal dysfunction worsened (defined as an increase in serum creatinine by $\geq$0.3 mg/dL during hospitalization) in 48% of patient hospitalizations [8]. Neurologic complications are common in children after CHD surgery and ventricular assist device (VAD) placement, which can arise from a variety of causes, including hypoxia, hypoperfusion, and thromboembolism in children with VAD [9–12]. However, neurologic complications associated with non-CHD pHF hospitalization are not adequately studied. Menteer et al. demonstrated focal gray matter volume loss in pediatric heart failure, which may coincide with multiple neurologic and psychological changes. However, the underlying mechanisms leading to the observed brain changes remain unclear [13]. Renal and neurologic complications are significant burdens during pHF admissions and highlight the importance of early diagnosis and treatment of pHF and close monitoring of patients for these potential complications [14].

In pHF related to CHD, there is a vast literature describing renal and neurologic complications associated with pHF hospitalizations after cardiac surgery; however, these comorbidities are not well-characterized in non-CHD pHF hospitalizations [15–17]. Our study aimed to analyze the burden of renal dysfunction and neurologic complications during pHF hospitalizations due to non-CHD, such as cardiomyopathies, acquired cardiovascular disorders such as myocarditis, Kawasaki disease, sepsis, and chemotherapy-induced cardiac dysfunction. Our hypothesis for this study was diagnosing renal dysfunction or neurologic complications is associated with significant mortality in children admitted for HF. For this purpose, we used the Pediatric Health Information System® (PHIS) database to obtain a large representative sample to study this hypothesis. With early recognition of the aforementioned complications through a multidisciplinary approach, healthcare providers can improve outcomes for pHF and minimize the impact of these morbidities on their health and quality of life.

2. Methods

Data for this study were obtained from the PHIS, a comparative pediatric database that includes clinical and resource utilization data for inpatient, ambulatory surgery, Emergency Department, and observation unit patient encounters for 51 children's hospitals in the United States [18]. The PHIS hospitals are 51 of the largest and most advanced children's hospitals in the United States and constitute the most demanding standards of pediatric service in America. The PHIS includes a unique patient identifier that permits the measurement of repeated hospitalizations for the same patient within the same hospital but not at different hospitals. The study was reviewed and approved by the PHIS review board. Our study included all non-CHD HF-related ICU hospitalizations in children aged $\leq$18 between 1 January 2004 and 31 December 2020. The diagnosis of non-CHD pHF was made using the discharge diagnosis of the International Classification of Diseases (ICD)-9/10 codes from the PHIS data registry (Appendix A). Briefly, renal dysfunction was defined using ICD codes N17.9, N18.5, and N18.6, while neurologic dysfunction was determined by the presence of ICD codes related to altered mental status (R41.82), stroke (161,163), seizures (R56.9), encephalopathy (G93.4), and weakness or paralysis (R53.1).

We excluded patients with CHD-related pHF and those with repeated admissions. The primary outcome analyzed was renal dysfunction and neurologic complications in hospitalized pHF patients. Our secondary outcomes included length of hospital stay (LOS), ICU LOS, use of vasoactive medications, ECMO or VAD, and heart transplantation.

The age ranges were defined as neonates (0–30 days), infants (≤1 year), children (1–12 years), and adolescents (12–18 years). All other procedural and diagnostic codes used in the descriptive and risk analysis are listed in Appendix B. Mechanical circulatory support (MCS) was defined as using ECMO or VAD (both temporary and durable). Vasoactive agents included calcium chloride, dobutamine, dopamine, epinephrine, milrinone, norepinephrine, phenylephrine, and vasopressin. Readmission was defined as any admission 24 h in duration occurring within 30 days of the most recent hospital discharge. Other data identifying ICU admissions, parenteral inotropic and vasoactive drugs (dopamine, dobutamine, milrinone, epinephrine, norepinephrine, vasopressin, and calcium chloride), mortality, patient demographics (age, sex, and race/ethnicity), LOS data, and hospital census region membership were obtained from the PHIS registry.

Statistical analysis: We reported the frequency count (percentage) of categorical variables and the mean and standard deviation (SD) for continuous variables. Given the unequal distribution of PHIS-participating hospitals within different census regions, all region-based data were subjected to region-weighted analysis. Continuous variables were analyzed using the Mann–Whitney U test because the data were not normally distributed. A two-tailed test of significance was used for all statistical analyses, and statistical significance was defined as $p < 0.05$. All analyses were performed using SPSS Statistics version 19 (IBM Corp., Armonk, NY, USA).

3. Results

A total of 17,227 pHF hospitalizations were observed during the study period (January 2004 to December 2020). Of these, 5515 pHF hospitalizations were included in the study after excluding 7265 hospitalizations with CHD, 3868 repeat hospitalizations, and 579 where coding data were unavailable. Renal dysfunction was identified in 1239 (22.5%) patients, and neurologic dysfunction was diagnosed in 539 (9.8%) patients. Renal dysfunction and neurologic complications were not counted when the same patient was admitted to the same hospital, and trends in renal dysfunction and neurologic complications were noted.

Table 1 describes the demographics, race, ethnicity, and renal dysfunction identified at the emergency department (ED) as high risk (ED Flag), identified as high risk during ICU admission (ICU flags), the need for mechanical ventilation, need for MCS (ECMO or VAD) support, need for total parenteral nutrition (TPN), need for dialysis, and need for heart and kidney transplantation. Outcomes in the form of mortality for admission were also tabulated. Renal dysfunction was noted in 1239 (22.5%) hospitalizations. Black race was a significant risk factor for the development of renal dysfunction. Patients with renal dysfunction were more likely to be admitted to the ICU and require mechanical ventilation, ECMO support, TPN, dialysis, VAD placement, heart transplantation, and kidney transplantation (all $p < 0.001$). Discharge mortality was higher for pHF hospitalization with renal dysfunction than those without (5.9% compared 11.7%, $p < 0.001$).

Table 2 describes the demographics, race, ethnicity and neurological impairemnet identified at ED as high risk (ED Flag), identified as high-risk during ICU admission (ICU flags), need for mechanical ventilation, need for MCS (ECMO or VAD) support, need for total parenteral nutrition (TPN), need for dialysis, need for heart and kidney transplantation and mortality in pHF patients. Neurologic complications were diagnosed in 539 (9.8%) of pHF hospitalizations. Unlike renal dysfunction, neurologic complications were seen in all three races and ethnicities ($p = 0.914$ and 0.54 for race and ethnicity, respectively). There was a female predominance in neurologic complications ($p = 0.022$). Patients with neurologic complications were significantly more likely to be admitted to the ICU, needing mechanical ventilation, ECMO support, TPN, dialysis, VAD placement, and heart transplantation (21% vs. 7.8%), all $p < 0.001$. Pediatric heart failure patients with neurologic complications had a discharge mortality of 18.4% compared to 4.6% ($p < 0.001$) for those without neurologic complications.

Table 1. Renal dysfunction associated with pediatric heart failure hospitalization and outcomes.

Parameter Total	No Renal Dysfunction N = 4276 (77.5%)	Renal Dysfunction N = 1239 (22.5%)	Total N = 5515	*p* Value
Sex				
Male	2382 (55.7%)	689 (55.6%)	3071 (55.7%)	0.952
Female	1894 (44.3%)	550 (44.4%)	2444 (44.3%)	
Race				
White	1877 (43.9%)	524 (42.3%)	2401 (43.5%)	**<0.001**
Black	727 (17%)	**336 (27.1%)**	1063 (19.3%)	
Asian	131 (3.1%)	50 (4%)	181 (3.3%)	
Other	1541 (36%)	329 (26.6%)	1870 (33.9%)	
Ethnicity				
Not Hispanic or Latino	3574 (83.6%)	1010 (81.5%)	4584 (83.1%)	0.087
Hispanic or Latino	702 (16.4%)	229 (18.5%)	931 (16.9%)	
ED flag	1618 (37.8%)	450 (36.3%)	2068 (37.5%)	0.331
ICU flag	2697 (63.1%)	947 (76.4%)	3644 (66.1%)	**<0.001**
Mechanical ventilation flag	1114 (26.1%)	594 (47.9%)	1708 (31%)	**<0.001**
ECMO flag	124 (2.9%)	166 (13.4%)	290 (5.3%)	**<0.001**
TPN flag	539 (12.6%)	404 (32.6%)	943 (17.1%)	**<0.001**
Dialysis	0 (0%)	389 (31.4%)	389 (7.1%)	**<0.001**
VAD placement	139 (3.3%)	88 (7.1%)	227 (4.1%)	**<0.001**
Heart transplant	316 (7.4%)	186 (15%)	502 (9.1%)	**<0.001**
Kidney transplant	0 (0%)	38 (3.1%)	38 (0.7%)	**<0.001**
Discharge mortality	182 (4.3%)	**145 (11.7%)**	327 (5.9%)	**<0.001**

ED = emergency department, ICU = intensive care unit, ECMO = extracorporeal membrane oxygenation, TPN = total parenteral nutrition, VAD = ventricular assist device. Bolded numbers indicated significant difference.

Table 2. Neurologic complications during pediatric heart failure hospitalization and outcomes.

Parameter Total	No Neurologic Issues N = 4976 (90.2%)	Neurologic Issues N = 539 (9.8%)	Total N = 5515	*p* Value
Sex				
Male	2796 (56.2%)	275 (51%)	3071 (55.7%)	**0.022**
Female	2180 (43.8%)	**264 (49%)**	2444 (44.3%)	
Race				
White	2160 (43.4%)	241 (44.7%)	2401 (43.5%)	0.914
Black	962 (19.3%)	101 (18.7%)	1063 (19.3%)	
Asian	162 (3.3%)	19 (3.5%)	181 (3.3%)	
Other	1692 (34%)	178 (33%)	1870 (33.9%)	
Ethnicity				
Not Hispanic or Latino	4141 (83.2%)	443 (82.2%)	4584 (83.1%)	0.544
Hispanic or Latino	835 (16.8%)	96 (17.8%)	931 (16.9%)	
ED flag	1891 (38%)	177 (32.8%)	2068 (37.5%)	**0.019**
ICU flag	3142 (63.1%)	443 (82.2%)	3644 (66.1%)	**<0.001**
Mechanical ventilation flag	1374 (27.6%)	334 (62%)	1708 (31%)	**<0.001**
ECMO flag	171 (3.4%)	119 (22.1%)	290 (5.3%)	**<0.001**
TPN flag	707 (14.2%)	236 (43.8%)	943 (17.1%)	**<0.001**
Dialysis	319 (6.4%)	70 (13%)	389 (7.1%)	**<0.001**
VAD placement	184 (3.7%)	43 (8%)	227 (4.1%)	**<0.001**
Heart transplant	387 (7.8%)	115 (21.3%)	502 (9.1%)	**<0.001**
Kidney transplant	36 (0.72%)	2 (0.37%)	38 (0.7%)	0.347
Discharge mortality	228 (4.6%)	99 (18.4%)	327 (5.9%)	**<0.001**

ED = emergency department, ICU = intensive care unit, ECMO = extracorporeal membrane oxygenation, TPN= total parenteral nutrition, VAD = ventricular assist device. Bolded numbers indicated significant difference.

4. Discussion

This is the first multi-institutional study to describe renal dysfunction and neurologic complications associated with pHF hospitalizations unrelated to congenital heart disease or cardiac surgery. We found that renal dysfunction was present in 22.5%, and neurologic

complications were in 9.8%, of pHF hospitalizations. Our findings complement a growing body of literature indicating that renal dysfunction and neurologic complications are responsible for increased mortality [4,15]. Shamszad et al. previously described that non-CHD pHF represented 12% of all ICU hospitalizations, had significant in-hospital comorbidity, a 20% transplantation rate, and 11% mortality [3]. A more recent study from the Pediatric Cardiac Critical Consortium also revealed that advanced decompensated HF in children due to CHD and non-CHD is characterized by high comorbidities and mortality [15].

Studies have indicated that the risk of poor outcomes is high when pHF is related to an underlying CHD [9,14,15,19]. However, obtaining a true sense of overall non-CHD pHF hospitalizations, clinical courses, and outcomes is extremely challenging because of complex heterogeneous etiologies. This heterogeneous non-CHD pHF is well-documented in recently concluded PANOROMA-HF trials, and etiologies include familial/genetic conditions, an inborn error of metabolism, neuromuscular disorder, left-ventricular (LV)-non-compaction, mitochondrial disorder, and chemotherapy-induced cardiomyopathy [20]. Thus, it becomes very challenging to accurately study the trajectory of pHF hospitalizations for each specific etiology, due to the need for the etiological granularity of the PHIS database. Therefore, we evaluated the overall burden of renal and neurologic morbidities and assessed their impact on pHF hospitalizations. Nevertheless, the discharge diagnosis utilized in our study is a simple but effective way to analyze the burden of renal and neurologic complications during hospitalization for pHF.

The burden of renal dysfunction and neurologic complications in pHF hospitalizations highlights the need to monitor and manage these patients closely. Optimal use of available therapies and risk-mitigation strategies is extremely important. Specifically, early recognition and treatment of neurologic complications is critical to prevent further neurologic damage and improve outcomes. Despite facing elevated mortality risks in adults, patients with HF with reduced LV ejection fraction and kidney disease are not optimally treated with evidence-based medical treatments, even at eGFR levels where such therapies are appropriate [21–23].

The pediatric HF risk prediction model, using pHF clinical data from the ACTION network and PHIS database at the time of listing for heart transplantation, showed that ECMO support (Odds Ratio, OR [OR] 6.3), VAD support (OR 1.3), ventilator support (OR 2.5), CHD (OR 2.3), and renal dysfunction (OR 2.3) increased the 30-day risk of mortality [19]. Also, Chen et al. [19]. reported that pediatric patients with renal dysfunction had extended hospital stays and were more likely to require mechanical ventilation, renal replacement therapy, and vasoactive medication in pHF hospitalization and had worse survival outcomes. The use of milrinone in these high-risk patients does not improve outcomes, despite minor improvements in renal function [21]. Many studies have highlighted the significant burden of renal dysfunction in adult patients with HF [22–24]. Our understanding of the underlying mechanism of renal dysfunction in HF in children is evolving [24,25]. Early diagnosis of cardiorenal syndrome will be essential in targeting therapies preemptively for renal dysfunction in HF. Commonly used HF therapies, such as ACE inhibitors, are associated with renal insufficiency [22]. However, the current data on SGLT2 inhibitors support the notion that therapeutic interventions could improve renal function and HF outcomes [26].

A higher rate of neurologic and neuropsychological comorbidities, namely ischemic stroke, structural brain alterations, cognitive impairment, sleep apnea, and possible side effects of HF medication, such as delirium or (intracerebral) hemorrhage, are documented in adults with chronic HF [27–29]. However, insufficient data are available in children, except for pHF related to CHD [10]. Our study will contribute to a more detailed discussion of this issue. The responses to neurologic events and treatment in the pediatric group may differ from those in the adult age group. Primary prevention methods should be the main approach in combating neurologic complications via the early identification of low cardiac output in pHF hospitalizations. This will prevent admission to ICU and may avoid ICU

delirium and psychosis during pHF hospitalization. Unlike renal dysfunction, commonly seen in boys of Black ethnicity, as demonstrated by the previous literature, our study shows neurologic complications are observed in girls and equally distributed in all ethnicities [30].

Interestingly, a study on hospitalized pHF patients from the 2019 Kid Inpatient Database (KID) showed that overall mortality was 6.31% in children aged <21 years, and there is a decreasing trend in mortality compared to the study by Rosanno et al., who noted a mortality rate of 7.3% among pHF admissions 10 years ago [4,31]. Sepsis of unspecified organisms, CHD (hypoplastic left heart syndrome), and acute respiratory failure are the most common principal diagnoses among hospitalized children with pHF. In their analysis from the KID database, which included pHF due to both CHD and non-CHD, Adebiyi et al. [31] found the causes of hospital mortalities in children <2 years were complex CHD and sepsis and unspecified organisms; in children between 2–12 years, the causes were acute-on-chronic systolic HF or acute-on-chronic combined systolic and diastolic HF due to cardiomyopathies; and in children between 13–20 years, the causes of hospital mortality were acute-on-chronic heart failure and acute respiratory failure.

In another study, hypotension, abnormally high liver enzyme levels, the need for mechanical ventilation, and the need for multiple inotropic drugs were statistically significant predictors of mortality in pediatric cardiomyopathies [15,32]. At the same time, age, sex, fractional shortening, ejection fraction, the presence of mitral regurgitation, mural thrombus, electrolyte disturbance, and arrhythmias did not predict or affect patients' outcomes [32]. In pediatric dilated cardiomyopathy patients, Weng et al. found that age at the initial diagnosis did not predict poor outcomes [33]. However, two other studies reported that patients >5 years at presentation had a higher risk of death or heart transplantation [34,35]. Miranda et al. reported that hospital mortality with HF-admission was highest below one year [36].

Any child with pHF requiring hospitalization is generally progressive and has a poor prognosis [37]. Pediatric HF is an evolving public concern, and increased awareness among pediatricians, funding agencies, and policymakers regarding the obstacles faced by pediatric patients with HF is critical to meeting the needs of this complex patient population [37]. Identifying high-risk profiles, improving our understanding of the renal dysfunction and neurological complications and preventive measures and prompt treatment are paramount in reducing pHF in-hospital mortality.

Strengths and Limitations: The PHIS data are retrospective and observational. The PHIS database contains detailed information regarding patient demographics, HF management during hospitalization, and outcomes. As the database includes data from multiple institutions, it allows for large-scale analyses of patient populations and the ability to identify areas to improve clinical care, enhance financial outcomes, improve clinical documentation, and perform research. One of the strengths of PHIS is that it can track patients across encounters within the same hospital, indicating the trend in renal dysfunction and neurologic status of the patients. A previous validation study found that the ICD-9/10 codes in the PHIS database have high specificity (few false positives) but lower sensitivity (some actual cases missed) [38] However, access to the database is restricted, and approval is required for researchers to use it for their studies. PHIS is a non-population-based database. Therefore, our results on the prevalence of renal dysfunction and neurologic complications may not be generalizable to the overall pHF population, or to other hospitalized pHF populations not admitted to freestanding children's hospitals not included in PHIS [39]. A second limitation is there is no granular data to classify into different etiologies of non-CHD pHF. Lastly, we did not risk stratifying renal dysfunction and neurological complications by age in this study.

5. Conclusions

Our analysis noted that renal dysfunction and neurologic complications occur in a significant proportion of pHF admissions. Those with renal and neurologic complications are significantly more likely to have higher complexity, higher use of intensive care therapies,

and three–four times higher mortality. A better understanding of these morbidities, the identification of modifiable factors, and better therapeutic strategies and multidisciplinary care are urgently needed to improve the overall outcomes of pHF hospitalization.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The study data is available on the PHIS registry.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. ICD-99/10-code for non-CHD or non-surgery-related heart failure diagnosis.

ICD-code	Diagnosis
150.1	Left ventricular failure
150.2	Unspecified congestive heart failure
150.21	Acute systolic failure
150.22	Chronic systolic heart failure
150.23	Heart failure requiring ventilator
150.3	Diastolic heart failure
150.4	Combined systolic and diastolic heart failure
150.8	Other heart failure
150.84	Heart failure with vasoactive medications
150.9	Acute decompensated heart failure
150.810	Heart failure with VAD

Appendix B

Table A2. ICD-9/10-code for complications associated with pHF hospitalization.

Z99.8	VA ECMO
T82.57	Mechanical complication of VAD
T82.898A	Specified complications of VAD
N17.9	Acute kidney injury
N18.5	Renal failure
N18.6	Dialysis in children with heart failure
Z94.1	Heart transplantation
Z94.0	Renal transplantation
R41.82	Altered mental status
161	Stroke (hemorrhagic)
163	Stroke (ischemic)
R56.9	Seizures
G93.4	Encephalopathy
R53.1	Weakness or paralysis

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