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# Measurement, consequences and determinants of time to diagnosis in children with new-onset heart failure: A population-based retrospective study (DIACARD study)☆

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ABSTRACT

*Background:* Time from first symptoms to diagnosis, called time to diagnosis, is related to prognosis in several diseases. The aim of this study was to assess time to diagnosis in children with new-onset heart failure (HF) and assess its consequences and determinants.
*Methods:* A retrospective population-based observational study was conducted between 2007 and 2016 in a French tertiary care center. We included all children under 16 years old with no known heart disease, and HF confirmed by echocardiography. With logistic regression used for outcomes and a Cox proportional-hazards model for determinants, analyses were stratified by HF etiology: congenital heart diseases (CHD) and cardiomyopathies/myocarditis (CM).
*Results:* A total of 117 children were included (median age [interquartile range (IQR)] 25 days (6–146), 50.4% were male, 60 had CHD and 57 had CM). Overall median (IQR) time to diagnosis was 3.3 days (1.0–21.2). The frequency of 1-year mortality was 17% and 1-year neuromotor sequel 18%. Death at 1 year was associated with low birth weight for all patients (adjusted odds ratio 0.24, 95% confidence interval [CI] 0.08–0.68) and time to diagnosis below the median with CM (0.09, 0.01–0.87) but not time to diagnosis above the median for all patients (0.59, 0.13-2.66). Short time to diagnosis was associated with clinical severity on the first day of symptoms for all patients (adjusted hazard ratio 3.39, 95% CI 2.01–5.72), and young age with CM (0.09, 0.02–0.41).
*Conclusions:* In children with new-onset HF presenting in our region, median time to diagnosis was short. Long time to diagnosis was not associated with poor outcome.

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## 1. Introduction

Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality leading to decreased cardiac output and/or elevated intracardiac pressure at rest or during stress [1]. HF is diagnosed upon characteristic symptoms and signs depending on the child age, although HF can begin antenatally [2]. Different investigations are used to confirm the diagnosis of HF including echography and biomarkers. Transthoracic echocardiography is a key examination to diagnose the underlying cause, guide treatment and determine prognosis [3].

The main etiologies of HF in children are congenital heart diseases (CHD) and cardiomyopathies: CHD account for 55% of heart transplantations in infants <1 year old, whereas cardiomyopathies are the most common cause in older children [4]. New-onset HF is a rare condition, with a pediatric incidence excluding CHD of 0.87/100,000, and clinical presentation is varied [5]. Diagnosis of HF can thus be difficult and a delay in diagnosis may lead to poor outcomes. In adults, a delay in diagnosis was not found associated with increased mortality or all-cause readmissions but was associated with longer length of hospital stay

*Abbreviation:* CHD, congenital heart diseases; CKD, chronic kidney disease; CM, cardiomyopathies/myocarditis; ECMO, extracorporeal membrane oxygenation; F, female; HF, heart failure; HR, hazard ratio; aHR, adjusted hazard ratio; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LVEF, left ventricular ejection fraction; M, male; NS, not significant; OR, odds ratio; aOR, adjusted odds ratio; patient interval, time from first symptoms to first consultation; physician interval, time from first consultation to diagnosis; VAD, ventricular assisting device.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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(LOS) [6]. However, we have limited data on time to diagnosis in children with HF.

Time to diagnosis and its association with prognosis have been recurrently studied in children with different diseases. Long time to diagnosis has been found associated with poor prognosis in some pediatric diseases. Diagnosis delay has occurred more often in children who have died from severe bacterial infections [7]. In pediatric abuse-related fractures, time to diagnosis of 6 to 12 h has been associated with poor outcome [8]. In stroke, prognosis is deeply linked to time to diagnosis in applying the appropriate treatment including thrombolysis [9]. In cardio-pediatrics, in Kawasaki disease, a delay in diagnosis by physicians is associated with increased risk of coronary artery aneurysms [10]. Despite the strong a priori concept that delayed diagnosis is responsible for poor outcome, some data argue against this idea. Brasme et al. have shown the histology of some pediatric solid tumors explains delayed diagnosis better than parental or medical factors: less aggressive tumors diagnosed late are associated with better outcomes in central nervous system tumors [11].

Knowing that >80% of children with new-onset heart muscle disease receive a diagnosis in a state of severe symptomatic HF and that one third die or require heart transplantation within 1 year, we have hypothesized that late diagnosis is associated with poor outcome in children [5]. The aim of the present study is to measure time to diagnosis, assess its consequences on health outcomes and define its determinants in children with new-onset HF with no known heart disease.

## 2. Methods

This was a retrospective monocentric observational study reported in accordance with REporting Studies on Time to diagnosis (REST) guidelines for studies of time to diagnosis [12].

### 2.1. Population

The source population was all children addressed or consulting in outpatient units, pediatric accident and emergency wards, cardio-pediatric units or intensive care units (ICUs) in the Nantes area for suspected HF. We retrospectively included all children <16 years old and admitted with a diagnosis of HF to Nantes University Hospital from January 2007 to December 2016. Nantes University Hospital is the reference center for pediatric cardiology for the administrative area of Loire-Atlantique. Children from adjacent administrative areas (Morbihan, Ille-et-Vilaine, Maine-et-Loire, Vendée) are also referred when surgery or intensive care is indicated ensuring the completeness of recruitment because of the local organization of care. Charts were identified by searching for the keywords “heart failure”, “cardiogenic shock”, “cardiomyopathy” and “myocarditis” in the Nantes University Hospital discharge database, which includes all diagnoses coded by physicians according to the *International Classification of Diseases* (ICD-10). Data were cross-checked with a surgical database including children with cardiac transplantation, ventricular assisting device (VAD) and extracorporeal membrane oxygenation (ECMO). Children with an antenatal diagnosis of HF including hydrops were excluded because of poorly defined time to diagnosis. Children from a specific screening program or with known heart disease at HF diagnosis were also excluded because they may have a shortened time to diagnosis, due to a known etiology, that may bias the results and limit their applicability. Charts were reviewed and children without diagnosis of HF (miscoding) or with missing data on time to diagnosis were eventually excluded.

### 2.2. Definitions and diagnosis procedure

First HF symptoms differ depending on the child's age: first feeding difficulties and respiratory signs in infants and dyspnea in older children [3]. Hepatomegaly is also a major clinical sign. The protocol of Nantes University Hospital during the study period was to routinely perform electrocardiography, chest X-rays and heart ultrasonography in case of respiratory signs or dyspnea and hepatomegaly. HF diagnosis was confirmed by an increase in NT-proBNP level and a transthoracic echocardiography with evidence of systolic dysfunction including left ventricular ejection fraction (LVEF) < 55% and/or diastolic dysfunction with arguments for increased filling pressure [3]. Echocardiography is indeed increasingly recommended for the diagnosis of severe cardiac diseases including acute heart failure [13]. Lung ultrasound was not usually employed to diagnose HF in Nantes University Hospital during the study period. Eventually, HF was diagnosed by the attending cardio-pediatrician on the basis of history, clinical symptoms and signs, biomarkers and echocardiography evidence of HF caused by CHD or heart muscle or pericardial disease.

The period between the first HF symptoms and the date of diagnosis was called time to diagnosis, expressed in days. This period was divided into a patient interval, defined as the period between the date of the first HF symptoms and the date of the first medical consultation, and a physician interval, the period between the date of first medical consultation and the date of diagnosis. The time of the diagnosis was arbitrarily defined as the time when the first diagnostic transthoracic echocardiography was performed by an experienced cardio-pediatrician. Two junior doctors (SB and DM), including one specialized in cardio-pediatrics, first assessed time to diagnosis independently. Arbitrarily, “morning” was defined as 0800 h, “midday” 1200 h, “afternoon” 1500 h, “evening” 2000 h and “night” 2400 h. “During the beginning of the month” was defined as the 5th day of the month, “the middle” the 15th day and “the end” the 25th day. Degree of agreement between the assessors was evaluated, and potential disagreements were resolved by a third experienced expert doctor. The two assessors were blinded to final outcome at first time to diagnosis evaluation.

### 2.3. Data collection

#### 2.3.1. Patient characteristics

We collected socio-demographic data (age at first symptoms, sex, and family postal code), details of medical history (birth weight, weight at diagnosis, and known chronic disease) and whether the patient was already hospitalized or at the maternity unit when the first HF symptoms occurred.

#### 2.3.2. Characteristics of the HF episode

We collected the date and hour of the first symptoms, first medical consultation, admission to the hospital, admission to the ICU (when appropriate) and diagnosis. We also collected the number of consultations until diagnosis; first-consulted-doctor specialty and center; HF symptoms and day of their first appearance; HF physical signs including hepatomegaly and day of their first appearance; cardiac enlargement and signs of overload on chest X-ray; echocardiography results including left and right ventricular function, thickness and diameter; and presence or not of an intracardiac thrombus. *Z*-scores were determined using the data from Pettersen et al. [14]. Exact positive diagnosis was noted: myocarditis and dilated, hypertrophic, restrictive cardiomyopathy. Congenital malformations were classified by using the nomenclature of the International Pediatric and Congenital Cardiac Code [15]. Biomarker levels including NT-proBNP and troponin T were collected and considered abnormal when ≥450 ng/L for NT-proBNP and ≥ 50 ng/L for troponin. If the child was admitted to the ICU, disease severity at admission was assessed by using pH and lactate level. Acidosis was defined as follows depending on laboratory thresholds: for venous samples, pH < 7.35, and for capillary and arterial samples, pH < 7.29 with age ≤ 21 days and pH < 7.36 with age ≥ 22 days. Hyperlactatemia was defined as lactate level > 2.4 mmol/L.

#### 2.3.3. Outcomes

Data collection included day of death, ECMO, VAD or heart transplantation, LOS of first hospitalization, number of readmissions including readmissions for HF, and presence of neuro-motor sequelae.

The primary health outcome was death at 1 year. The secondary health outcome was LOS. A long LOS was defined as >10 days, in line with the literature [16].

### 2.4. Statistical analysis

Time to diagnosis was described with median (interquartile range [IQR], first and third quartile). Agreement between the 2 assessors was measured with the Spearman correlation coefficient. Associations between time to diagnosis and health outcomes were studied by univariate analyses with chi-square or Fisher exact test, Mann-Whitney or Kruskal Wallis test, then multivariate analyses with logistic regression. Potential confounding factors analyzed were birth weight, severity signs, time to diagnosis and etiology of heart disease. Analysis of outcomes was secondarily stratified on etiology because of different pathophysiology and epidemiology: CHD or cardiomyopathies/myocarditis (CM) [5]. The linearity of the association between time to diagnosis and health outcome was tested, and time to diagnosis was transformed into a polynomial and categorized in case of deviance from linearity. A long time to diagnosis was defined as above the median. Determinants of time to diagnosis were studied with a Cox proportional-hazards model because time to diagnosis is a censored variable. Hazard ratios (HRs) obtained with this model expressed the instantaneous risk of a diagnosis (i.e., the higher the HR, the shorter the time to diagnosis). Analysis of determinants was also stratified on etiology: CHD or CM. The potential determinants of time to diagnosis studied were age at first symptoms, comorbidities, first-consulted-doctor specialty and center, first symptoms or signs including severity signs, and etiology of CM when applicable.

Incidence of new-onset HF in the Loire-Atlantique area was calculated by dividing the yearly mean number of participants in the study from the Loire-Atlantique area by the yearly mean official population of <16 years old in the area during the study period, that is 270,405 [17].

Statistical analyses were performed with Stata v15 (Statacorp, College Station, TX, USA). Results were presented as number (percentage), median (IQR), or odds ratio (OR) with 95% confidence interval (95% CI). $P < .05$ was considered statistically significant.

The protocol of this study was reviewed by the local ethics committee. Patients and family were informed of the Nantes University Hospital research activity by a display in the ward. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

## 3. Results

### 3.1. Patient characteristics

Among 624 eligible patients, 174 participated in the study after exclusion of 315 children with a known heart disease before the onset of HF and 135 children without HF as shown in Fig. A.1. The incidence of new-onset HF in children was 2.07/100000 (32.2% of included children were from the Loire-Atlantique area) and the incidence of new-onset HF due to CM in children was 0.98/100000 (47.5% of children had CM).

Table 1 shows the characteristics of the 117 children with an HF diagnosis after exclusion of 54 children without data on time to diagnosis and 3 children without CHD or CM. Median age (IQR) was 25 days (6–146). Age interval (min-max) was (0 day - 2 years old) in CHD and (0 day – 16 years old) in CM. Ninety-six (82.9%) children were under 1 year old. Six (5%) children were above 10 years old. The main etiologies of HF are presented in Table A.1. Among CHD, coarctation of the aorta with or without aortic arch hypoplasia was the leading cause (21 children, 35%).

**Table 1**
Characteristics, time to diagnosis and 1-year outcomes of children with a diagnosis of heart failure. n = 117.

| | Total (n = 117) | CHD (n = 60) | CM (n = 57) | p |
|---|---|---|---|---|
| Sex ratio (M/F) | 1.02 | 1.22 | 0.84 | NS |
| Age at first symptoms (days), median (IQR) | 25 (6–146) | 8 (1–20.3) | 99 (27–804) | <0.001 |
| Birth weight (kg), median (IQR) (n = 84) | 3.1 (2.8–3.5) | 3.1 (2.8–3.4) | 3.2 (2.8–3.5) | NS |
| Weight at diagnosis (kg), median (IQR) (n = 110) | 4.0 (3.2–6.5) | 3.3 (2.9–4.1) | 6.1 (4.0–11.8) | <0.001 |
| Medical history, n (%) | 6 (5.1) | 3 (5) | 3 (5) | NS |
| Prematurity, n (%) | 5 (4.3) | 3 (5) | 2 (3) | |
| CKD, n (%) | 1 (0.8) | 0 (0) | 1 (2) | |
| Distance to Nantes University Hospital (km), median (IQR) (n = 113) | 93 (40–135) | 93 (49–140) | 93 (28–126) | NS |
| First consulted doctor, n | 106 | 56 | 50 | 0.001 |
| Emergency doctor, n (%) | 36 (34.0) | 12 (20) | 24 (42) | |
| Non-hospital practitioner, n (%) | 35 (33.0) | 16 (29) | 19 (38) | |
| Maternity doctor, n (%) | 26 (24.5) | 22 (39) | 4 (8) | |
| Other hospital doctor (including ICU doctors), n (%) | 9 (8.5) | 6 (11) | 3 (6) | |
| In-hospital diagnosis, n (%) | 35 (29.9) | 28 (47) | 7 (12) | <0.001 |
| Patient interval (days), median (IQR) (n = 104) | 1.0 (0.0–7.0) | 0.0 (0.0–7.0) | 1.9 (0.2–7.0) | 0.003 |
| Number of consultations until diagnosis, median (IQR) (n = 108) | 2 (1–2) | 2 (1–2) | 2 (1–2) | NS |
| Physician interval (days), median (IQR) (n = 104) | 0.3 (0.1–1.3) | 0.3 (0.1–1.0) | 0.3 (0.1–2.0) | NS |
| Time to diagnosis (days), median (IQR) (n = 117) | 3.3 (1.0–21.2) | 2.2 (0.6–16.5) | 5.0 (2.0–28.1) | NS |
| First length of stay excluding deaths during first hospitalization (days), median (IQR) (n = 95) | 14 (8–22) | 17 (11–27) | 10 (6.5–15.5) | 0.008 |
| One-year death, n (%) (n = 110) | 19 (17.3) | 11 (20) | 8 (15) | NS |
| Age at death (days), median (IQR) | 105 (19–575) | 20 (8.5–107) | 881 (134–1711) | 0.003 |
| One-year ECMO, n (%) (n = 110) | 17 (15.4) | 10 (18) | 7 (13) | NS |
| One-year VAD, n (%) (n = 110) | 4 (3.6) | 0 (0) | 4 (7) | NS |
| One-year transplantation, n (%) (n = 110) | 5 (4.5) | 0 (0) | 5 (9) | NS |
| One-year neuromotor sequelae, n (%) (n = 61) | 11 (18.0) | 8 (28) | 3 (9) | NS |
| Moderate sequelae, n (%) | 7 (11.4) | 6 (21) | 1 (3) | NS |
| Severe sequelae, n (%) | 4 (6.6) | 2 (7) | 2 (6) | NS |

CHD: congenital heart diseases, CKD: chronic kidney disease, CM: cardiomyopathies/myocarditis, ECMO: extracorporeal membrane oxygenation, F: female, ICU: intensive care unit, IQR: interquartile range, M: male, NS: not significant, patient interval: time from first symptoms to first consultation, physician interval: time from first consultation to diagnosis, VAD: ventricular assisting device.

For time to diagnosis evaluation, 45.4% of values differed between the 2 assessors, but their distribution was correlated ($r = 0.94$, 95% CI 0.90–0.96, $p < .001$). After discussion, all values were uniform.

### 3.2. Characteristics of the HF episode

During the first HF episode, difficulty in breathing was noted in 78 (65.0%) children and hepatomegaly was clinically detected and reported at some point after the suspected diagnosis in 65 (55.6%). For children with available data, chest X-ray showed cardiac enlargement in 89 (86.4%) and overload signs in 75 (86.2%). Median (IQR) cardiothoracic index was 0.64 (0.59–0.67). Among children with available data, 53 of 57 (93%) had increased NT-proBNP and 56 of 70 (80%) increased troponin T. Median (IQR) NT-proBNP level was 34,199 ng/L (4907–42,459) and troponin T 177 ng/L (64–752). On echocardiography, median left ventricular end diastolic diameter z-score was 2.68 (0.57–3.90) for 28 children; median LVEF was 30.0% (20.0–41.0%) for 43. Three (2.6%) children had cardiac thrombus. These 3 patients had dilated cardiomyopathy and LVEF ≤20%. A total of 92 (78.6%) children were hospitalized in an ICU. Thirty-four of 78 (44%) children had acidosis, 55 of 91 (60%) hyperlactatemia. Fifteen children (12.8%) died during the first hospitalization. At last follow-up, 52 of 99 (53%) children with available data were readmitted to hospital at least once for any cause and 27 of 98 (28%) for HF. Excluding in-hospital diagnoses, median patient interval in days increased to 3.0 (1.0–14.0); it was 8.0 (1.0–28.0) with CHD and 2.0 (1.0–9.3) with CM ($p = .197$).

Fig. 1 details the cumulative proportion of children with a specific group of clinical signs from HF onset (i.e., time from the first detected and reported symptom) by HF etiology. Respiratory signs were not significantly more frequent with CHD than CM (51 [85%] vs 44 [77%] children, $p = .13$), whereas general signs were more frequent with CM than CHD (44 [77%] vs 35 [58%] children, $p < .001$). In both groups, general signs always occurred within the first 5 days, whereas shock signs and HF specific signs could appear later.

### 3.3. Outcomes

Table 2 shows univariate and multivariate analyses of factors associated with 1-year death for all 117 children. On multivariate analysis, long time to diagnosis was associated with better survival only with CM (adjusted OR [aOR] 0.09, 95% CI 0.01–0.87) (Table A.2), and low birth weight was associated with long LOS for all children (aOR 0.18, 95% CI 0.05–0.67) (Table A.3).

### 3.4. Determinants of time to diagnosis

Table 3 shows factors associated with time to diagnosis for children with CHD and CM. On multivariate analysis, for all children, risk of long time to diagnosis was associated with older age at first symptoms (> 4 months old, 4th vs 1st quartile) (adjusted HR [aHR] 0.23, 95% CI 0.08–0.68), whereas risk of short time to diagnosis was with the presence of serious signs on the first day (aHR 3.39, 95% CI 2.01–5.72) (Table A.4).

## 4. Discussion

### 4.1. Main results

This study is, to our knowledge, the first to specifically assess time to diagnosis in pediatric new-onset HF with no known heart disease. The median time to diagnosis was short, 3.3 days for all HF cases, 2.2 days with CHD and 5 days with CM. Long time to diagnosis was associated with better outcome on univariate analysis, but this paradoxical association disappeared after adjustment for disease severity. Low birth weight seemed the only factor independently associated with risk of death for all children. With both CM and CHD, short time to diagnosis was associated with the presence of severity signs. For children with CM, risk of long time to diagnosis was associated with older age (vs first quartile of life: <27 days). For children with CHD, risk of long time to diagnosis was associated with the child first consulting a non-hospital practitioner after symptoms onset, even when adjusted on age at first symptoms.

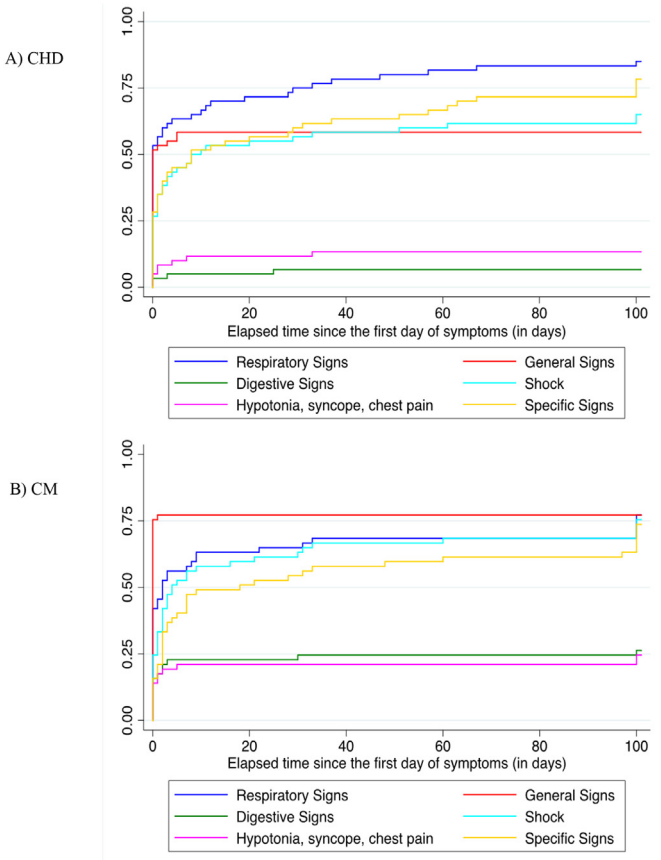



**Fig. 1.** Development of clinical features depending on time from onset of heart failure (first detected and reported symptoms) for A) congenital heart diseases (CHD) and B) cardiomyopathies/myocarditis (CM). n = 117. *Respiratory signs:* dyspnea, signs of respiratory distress, cyanosis, tachypnea, apnea, sweating and/or cough. *General signs:* feeding difficulties, growth failure and/or fatigue. *Digestive signs:* vomiting, abdominal pain and/or ascites. *Shock signs:* abnormal color of the skin, marbling, cold extremities, prolonged recoloration time, no or less palpable pulse, oligo-anuria, hypotension, tachycardia, bradycardia and/or cardiac arrest. *Specific heart failure signs:* hepatomegaly, jugular turgor, hepato-jugular reflux, edema and/or abnormal auscultation including pulmonary crackles, heart murmur and/or gallop. Signs appeared until 732 days from the first day of symptoms but time from onset in our graphs was limited to 100 days.

**Table 2**
Factors associated with 1-year-from-diagnosis death for all children with new-onset heart failure. n = 117.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p | aOR | 95% CI | p |
| Birth weight (kg) | **0.26** | **(0.09–0.70)** | **0.008** | **0.24** | **(0.08–0.68)** | **0.007** |
| Serious signs on first day | 2.76 | (0.96–7.91) | 0.058 | 2.17 | (0.51–9.18) | 0.291 |
| Time to diagnosis (days) | 0.99 | (0.97–1.01) | 0.258 | | | |
| Time to diagnosis >3.3 days (median) | **0.27** | **(0.09–0.81)** | **0.019** | 0.59 | (0.13–2.66) | 0.492 |
| Etiology CHD (vs CM) | 1.47 | (0.54–3.99) | 0.451 | 1.30 | (0.34–4.96) | 0.702 |

OR: odds ratio, aOR: adjusted odds ratio, 95% CI: 95% confidence interval, CHD: congenital heart diseases, CM: cardiomyopathies/myocarditis. Significant odds ratios are indicated in bold ($p<0.05$).

**Table 3**
Determinants of short time to diagnosis for the 60 children with congenital heart diseases (CHD) and new-onset heart failure and the 57 children with cardiomyopathies/myocarditis (CM) and new-onset heart failure.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | aHR | 95% CI | p |
| CHD | | | | | | |
| Age at first symptoms in days (vs 1st quartile) | | | | | | |
| 2nd quartile [1–8] | **0.46** | **(0.22–0.96)** | **0.038** | 1.11 | (0.46–2.65) | 0.821 |
| 3rd quartile (8–21.5) | **0.16** | **(0.07–0.37)** | **<0.001** | 3.48 | (0.66–18.46) | 0.143 |
| 4th quartile (21.5–335) | **0.10** | **(0.04–0.25)** | **<0.001** | 1.66 | (0.37–7.52) | 0.513 |
| Medical history of prematurity or CKD | 4.01 | (1.18–13.61) | **0.026** | 0.54 | (0.06–4.66) | 0.576 |
| Serious signs on first day | 6.60 | (3.37–12.93) | **<0.001** | **3.88** | **(1.61–9.38)** | **0.003** |
| First consulted doctor (vs emergency doctor) | | | | | | |
| ICU doctor | **6.95** | **(1.39–34.87)** | **0.018** | 5.38 | (0.47–61.81) | 0.176 |
| Non-hospital practitioner | **0.19** | **(0.07–0.50)** | **0.001** | **0.09** | **(0.02–0.31)** | **<0.001** |
| Maternity doctor | **4.19** | **(1.83–9.63)** | **0.001** | 2.80 | (0.78–10.13) | 0.116 |
| Other hospital doctor | **4.99** | **(1.44–17.27)** | **0.011** | **6.08** | **(1.25–29.54)** | **0.025** |
| CM | | | | | | |
| Age at first symptoms in days (vs 1st quartile) | | | | | | |
| 2nd quartile (27–99) | **0.41** | **(0.19–0.86)** | **0.019** | **0.56** | **(0.22–1.45)** | 0.233 |
| 3rd quartile (99–804) | **0.14** | **(0.06–0.33)** | **<0.001** | **0.11** | **(0.03–0.42)** | **0.001** |
| 4th quartile (804–5716) | **0.19** | **(0.08–0.46)** | **<0.001** | **0.09** | **(0.02–0.41)** | **0.002** |
| Medical history of prematurity or CKD | 1.54 | (0.47–5.06) | 0.478 | 0.72 | (0.05–9.72) | 0.802 |
| Serious signs on first day | **3.39** | **(1.83–6.27)** | **<0.001** | **2.27** | **(1.03–5.01)** | **0.043** |
| First consulted doctor (vs emergency doctor) | | | | | | |
| ICU doctor | 1.40 | (0.18–10.61) | 0.747 | 0.72 | (0.03–18.29) | 0.840 |
| Non-hospital practitioner | 1.04 | (0.56–1.93) | 0.911 | 0.85 | (0.39–1.87) | 0.688 |
| Maternity doctor | 2.89 | (0.96–8.76) | 0.060 | 2.48 | (0.60–10.17) | 0.208 |
| Other hospital doctor | 0.84 | (0.20–3.65) | 0.821 | 1.46 | (0.30–7.09) | 0.640 |
| Etiology of CM (vs DCM) | | | | | | |
| HCM | 2.17 | (0.89–5.28) | 0.089 | **3.80** | **(1.02–14.19)** | **0.047** |
| Myocarditis | **2.78** | **(1.27–6.12)** | **0.011** | **26.50** | **(4.80–146.31)** | **<0.001** |
| RCM | 0.43 | (0.10–1.79) | 0.245 | 1.92 | (0.19–19.65) | 0.581 |

HR: hazard ratio, aHR: adjusted hazard ratio, 95% CI: 95% confidence interval, CKD: chronic kidney disease, ICU: intensive care unit, DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, RCM: restrictive cardiomyopathy. Significant hazard ratios are indicated in bold ($p<0.05$).

### *4.2. Time to diagnosis in children with HF: interpretation*

Time to diagnosis varies widely among pediatric pathologies: median time to diagnosis is 22 h with stroke [9], 60 days with brain tumor [18] and 14 weeks with Ewing's sarcoma [11]. In our study, median patient interval was 1 day, or 3 days when excluding in-hospital diagnoses. This brief time to diagnosis can explain the lack of association with our outcome because of too few patients with long time to diagnosis. It was also shorter than for adults in the literature, with median patient interval ranging from 3 to 7 days [6]. In 2012, Johansson et al. found a median pre-hospital interval (time from first symptoms to admission) of 3 days with adult HF, this interval was shorter for patients with severity signs as in our study [19]. Physician interval did not significantly differ between children with CHD and CM, whereas patient interval was longer for children with CM. Excluding in-hospital diagnoses, patient interval did not significantly differ between children with CHD and CM.

### *4.3. Outcomes*

Low birth weight was strongly associated with 1-year mortality on multivariate analysis [20]. This element is of paramount importance as 96 (82.9%) children included in our study were <1 year old, in line with literature. Indeed, infants account for the greatest number of heart transplants [4]. In CHD, the majority of HF cases occur during the first year of life [21]. In CM, the greatest number of new-onset HF cases are diagnosed in infancy, as nearly half of the children are aged under 1 year old and 70% under 2 years old [5]. Moreover, preterm birth has been associated with increased risk of death for newborns with CHD after adjusting on intrauterine growth restriction [22]. However, even when adjusting on history of prematurity, low birth weight remained associated with death in our study. With CHD, weight < 2.4 kg at the time of surgery has been found an independent risk factor for death in children younger than 6 months [23]. Genetic and metabolic disorders could also affect survival, but our small sample limited this analysis [24]. Among children with CM who died, for 5 with available data on birth weight, 3 (60%) had a probable genetic or metabolic disease associated with low birth weight and worse outcome [25–27].

Low birth weight was also associated with a long initial LOS on multivariate analysis. One study reported longer LOS for children under 1 year old and with medical complexity including children with significant chronic disease or malformations in at least 2 organ systems [16]. Additionally, in isolated CHD (defined as CHD not associated with other malformations or syndromes) the proportion of low birth weight is lower than in all CHD suggesting that low birth weight is associated with medical complexity [28]. We showed for the first time that low birth weight is associated with long LOS and mortality in children with CHD and CM presenting with new-onset HF. Besides, we did not find any significant association between time to diagnosis and LOS. Conversely, in adults with HF, long time to diagnosis has been associated with a long LOS but not mortality [19]. However, pathologies are different in children, and CM is rarely ischemic.

### *4.4. Determinants of time to diagnosis*

Older age at first symptoms was a determinant of long time to diagnosis in CM, as reported in cancer [11]. Non-specific signs are also determinants of missed diagnosis in childhood HF [29]. Non-specific signs including general signs were frequent and early with CM in our study. The kinetics of symptoms with CM may also reflect less aggressive disease leading to longer time to diagnosis. Hence, rapid CM diagnosis is not easy in children older than 3 months (median age at diagnosis). Physicians are encouraged to closely repeat examinations because HF specific signs can be delayed, as we found.

The presence of serious signs on the first day was a strong determinant of short time to diagnosis, which is appropriate because diagnostic

procedures must be initiated faster with signs of shock. However, in CHD, time to diagnosis was longer when the first consulted doctor was a non-hospital practitioner and remained after adjustment on age at first symptoms. Initial presentation to the primary care provider was previously found associated with missed diagnosis at first presentation in new-onset systolic HF in children with no known heart disease [29]. These results suggest that knowledge of CHD among non-hospital practitioners could be improved. However, although CHD is frequent and can be life-threatening, it is very rarely diagnosed on HF signs [30] [31]. CHD is most often already known because the incidence of CHD is 8/1000 [32] [33], whereas the incidence of new-onset HF leading to a previously unknown diagnosis of CHD was only about 1/100000 in our study [34] [35].

### *4.5. Study strengths and limitations*

Our study was comprehensive for the area of Loire-Atlantique. Indeed, Nantes University Hospital is the cardio-pediatric referral center in the area. More than half of children with new-onset HF receive a diagnosis of CHD [21]. The incidence of new-onset HF due to heart muscle disease in children was 0.98/100000. This result is consistent with the literature, with the reported incidence 0.87/100000 in the United Kingdom and Ireland in 2003 [5].

The primary outcome was evaluated in 110 patients, with 6.0% of children lost to follow-up, for limited attrition bias [36]. Because survival was defined from diagnosis, a longer time to diagnosis would have falsely decreased survival in case of lead time bias. Nevertheless, survival was assessed at 1 year, with a median time to diagnosis of 3.3 days, which was very short as compared with the period of study. Also, a long time to diagnosis seemed associated with increased survival with CM. So, at worse, lead time bias would have falsely decreased this association. Importantly, the association found between long time to diagnosis and survival is probably linked to residual confusion, possibly due to the subtype of CM (in CMD: infectious, idiopathic, familial, metabolic, neuromuscular, ischemic, arrhythmic, associated with vascular shunt), as is found in pediatric cancers [11]. It could not be assessed in our study because of a limited sample size. We included all the children admitted into Nantes University Hospital as a first exploratory study because there is sparse pediatric data on this topic. The results encourage us to go further by including children from other University Hospitals.

We excluded heart disease diagnosed before HF appearance to limit the recruitment bias that may have reduced time to diagnosis due to a close follow-up [32]. In antenatal diagnosis, the exact onset of symptoms is often unclear with also planned follow-up after birth. As a consequence, among the 624 eligible children, only 174 (28%) were included in the study. Furthermore, 54 (31%) children had missing data because the exact moment of first symptoms and/or diagnostic echocardiography was not defined.

Finally, determining time to diagnosis can be difficult with retrospective data. Qualitative reports of the time during the day or the month can induce classification bias. However, hours were defined a priori depending on the phrases used in medical files. First symptoms were not always related to HF because of another preceding condition: these symptoms were not taken into account when they were not considered part of HF syndrome.

## 5. Conclusions

In this retrospective study of 117 children (of whom 96 were infants) with new-onset HF, median time to diagnosis was short and severity signs were well recognized, particularly by specialized physicians, and led to early diagnosis. Our initial hypothesis that time to diagnosis may be too long and leads to increased mortality was not confirmed by our results. Low birth weight seemed strongly associated with death. Risk of short time to diagnosis was associated with young age and diagnosis of myocarditis with CM, hospital doctor as the first consulted physician with CHD, and severity signs during the first day of symptoms with both CM and CHD. Our study is the first to report the incidence of new-onset HF in children with no known heart disease in a French area. Larger studies are needed to confirm these results, qualitatively assess diagnosis delay and optimality of care.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.06.007.

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