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Délai diagnostique de l'insuffisance cardiaque chez l'enfant : mesure, conséquences et déterminants

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TABLE DES MATIERES

Délai diagnostique de l'insuffisance cardiaque chez l'enfant : mesure, conséquences et déterminants, l'étude DIACARD.

INTRODUCTION GENERALE

L'insuffisance cardiaque (IC) est un syndrome causé par une anomalie structurelle et/ou fonctionnelle du cœur, conduisant à une diminution du débit cardiaque et/ou une augmentation des pressions intracardiaques. Chez l'enfant, l'IC peut débuter par une phase asymptomatique, détectable par l'échographie transthoracique, utilisée à la fois pour le diagnostic positif et la recherche étiologique (1).

L'IC de l'enfant peut débuter en anténatal et être présente à la naissance, ou se développer plus tard dans l'enfance (2). On distingue deux étiologies principales : les cardiopathies congénitales (CC) et les cardiomyopathies et myocardites (CM). Les CC sont plus fréquentes chez le nouveau-né, avec une incidence d'environ 8 pour 1000 naissances vivantes et sont responsables de 55% des transplantations avant l'âge d'un an (3)(4)(5). Les CM dominent les étiologies de l'enfant plus âgé, leur incidence est d'environ 1,1 pour 100 000 entre la naissance et 18 ans (6). En excluant les CC, l'incidence des nouveaux épisodes d'IC en pédiatrie est d'environ 0,87 pour 100 000 avec une mortalité à 1 an autour de 18 % (7). L'IC de l'enfant est donc une pathologie rare et grave, dont le diagnostic est difficile à établir, surtout lorsque les médecins y sont peu confrontés dans leur pratique courante. Cette épidémiologie particulière pose ainsi la question du délai diagnostique de l'IC de l'enfant, qui correspond au temps écoulé entre l'apparition des premiers signes d'IC et le moment du diagnostic. La littérature contient peu d'études sur le délai diagnostique de l'IC, et il n'a pas encore été étudié chez l'enfant à notre connaissance.

En médecine adulte, un retard au diagnostic d'IC n'est pas associé à une augmentation de la mortalité ni du nombre d'hospitalisations, mais à une durée de séjour plus longue (8).

Le délai diagnostique a cependant été étudié dans de nombreuses autres pathologies pédiatriques, avec des associations au pronostic variables. Dans les traumatismes crâniens non accidentels de l'enfant, un délai diagnostique entre 6 et 12 heures est associé à une évolution péjorative, comparé aux délais plus courts ou plus longs (9). Dans les accidents vasculaires cérébraux ischémiques de l'enfant, le pronostic est fortement lié au délai diagnostique, car celui-ci conditionne l'accès à un traitement optimal, notamment la thrombolyse (10). En cardiopédiatrie, concernant la maladie de Kawasaki, un délai médical prolongé (temps entre le premier contact médical et le diagnostic) est associé à une augmentation du risque d'anévrysme des artères coronaires. L'idée la plus largement répandue est qu'un délai diagnostique long est associé à une évolution péjorative. Cependant, le délai diagnostique dépend de nombreux facteurs : médicaux, liés à la pathologie en cause ou encore aux caractéristiques du patient. En 2012, Brasme et al ont montré que c'est l'histologie de la tumeur qui est le plus liée au devenir de l'enfant, et dans le cadre des tumeurs cérébrales, un délai diagnostique long est le signe d'une maladie moins agressive qui est associée à un meilleur pronostic (11).

Puisque 80 % des enfants chez qui est découverte une atteinte du muscle cardiaque sont diagnostiqués avec des signes sévères d'IC et qu'environ un tiers décède ou nécessite une transplantation cardiaque dans l'année, nous faisons l'hypothèse qu'un diagnostic tardif pourrait être associé à un pronostic péjoratif (7). Le but de cette étude est de mesurer le délai diagnostic de l'IC chez l'enfant, d'analyser la relation entre le délai et le devenir (conséquences) et d'identifier les caractéristiques associées à ce délai (déterminants).

TITLE PAGE

Time to diagnosis of new-onset heart failure in children with no known heart disease: measure, consequences and determinants, the DIACARD study.

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ABSTRACT

Introduction: Heart failure (HF) in children is a severe condition which diagnosis can be difficult. Time from first symptoms to diagnosis, called time to diagnosis (TTD) is related to prognosis in several diseases. The aim of this study is to assess TTD of new-onset HF in children, and study its consequences and determinants.

Material and methods: We conducted a retrospective monocentric observational study between 2007 and 2016. We included all children under 16 years old with new-onset HF confirmed by echocardiography and no known heart disease. Two junior doctors assessed TTD independently. Analyses were stratified on HF etiologies: congenital heart diseases (CHD) and cardiomyopathies and myocarditis (CM).

Results: Among the 624 eligible patients, 117 were analyzed (60 CHD and 57 CM). Overall median TTD (interquartile range) was 3.3 days (1.0-21.2); it was 2.2 days (0.6-16.5) among CHD and 5.0 days (2.0-28.1) among CM. One-year mortality was 17%, one-year neuro-motor sequel rate was 18%. Low birth weight was independently associated with one-year death for all patients (aOR 0.24, 95% CI: 0.08-0.68). In CM, a TTD above the median (5 days) was independently associated with one-year survival (aOR 0.09, 95% CI 0.01-0.87). Clinical severity at first day of symptoms was an independent determinant of short TTD for all patients (aHR 3.39, 95% CI 2.01-5.72). In CM, older children had a significantly longer TTD (aHR 0.09, 95% CI 0.02-0.41 for 4^{th} quartile of age compared to 1^{st} quartile). Diagnosis of myocarditis was an independent determinant of short TTD in CM (aHR 26.50, 95% CI: 4.80-146.31), and hospital-doctor diagnosis in CHD (aHR 6.08, 95% CI 1.25-29.54).

Conclusion: In children with new-onset HF, median TTD is short. Our study does not confirm the widespread idea that a long TTD leads to poor outcome. Conversely, long TTD is associated with survival in cardiomyopathies.

KEYWORDS

Diagnosis delay, cardiomyopathy, myocarditis, congenital heart disease, cardiogenic shock.

ABBREVIATIONS

95% CI: 95 % Confidence interval

aHR: Adjusted hazard ratio

ALCAPA: Abnormal left coronary artery from pulmonary artery

aOR: Adjusted odds ratio

CHD: Congenital heart diseases

CKD: Chronic kidney disease

CM: Cardiomyopathies and myocarditis

DCM: Dilated cardiomyopathy

ECMO: Extracorporeal membrane oxygenation

EF: Ejection fraction

HCM: Hypertrophic cardiomyopathy

HF: Heart failure

HR: Hazard ratio

ICD: International classification of diseases

ICU: Intensive care unit

IQR: Interquartile range

LOS: Length of stay

LVEF: Left ventricular ejection fraction

OR: Odds ratio

PIMII: Pediatric index of mortality II

PVR: Pulmonary vascular resistances

SF: Shortening fraction

TTD: Time to diagnosis

VAD: Ventricular assisting device

1. INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality leading to a decreased cardiac output and/or elevated intra-cardiac pressures at rest or during stress. HF can begin with an asymptomatic phase that can be detected by transthoracic echocardiography which is the also key-exam to diagnose the underlying cause (1).

HF in children can begin antenatally and be present at birth or develop at any child age (2). Congenital heart diseases (CHD) account for 55% of transplantations in infants aged less than 1 year, whereas cardiomyopathies are the most common cause in older children (5). CHD incidence is about 8 per 1000 children live births whereas the pediatric incidence of heart muscle diseases including cardiomyopathies is about 1.1 per 100,000 children younger than 18 years old (3)(4)(6). Excluding CHD, it has been shown that the pediatric incidence of new-onset heart failure is 0.87 per 100 000 (7). This relatively rare condition is therefore hard to diagnose with little experience of primary care practitioners. In adults, delay in diagnosis was not associated with increased mortality or all-cause readmissions but was associated with a longer length of stay (LOS) (8). There are however limited data on time to diagnosis (TTD) of HF in children.

TTD and its association with prognosis have been recurrently studied among children in different diseases. Long TTD has shown to be associated with poor prognosis in some pediatric diseases. In pediatric abuse-related fractures, TTD between 6 and 12 hours is associated with poor outcome (9). In stroke, prognosis is deeply linked to TTD to apply the appropriate treatment including thrombolysis (10). In cardio-pediatrics, in Kawasaki disease, a delay in diagnosis by physicians is associated with a higher risk of coronary artery aneurysms. Despite the strong *a priori* that delayed diagnosis is responsible for poor outcome, some data are against this thought. Brasme et al. have shown that histology of some pediatric solid tumor is much more influent on children than parental or medical factors with delayed diagnosis frequently

associated with less aggressive tumors and better outcomes in central nervous system tumors (11).

Knowing that more than 80% of children with new-onset heart muscle disease are diagnosed in a state of severe symptomatic HF and that one third die or require transplantation within one year, we hypothesize that late diagnosis can be associated with poor outcome in children (7). The aim of the present study is to measure TTD, to assess its consequences on health outcomes and to define its determinants in children with new-onset HF with no known heart disease.

2. MATERIAL AND METHODS

We conducted a retrospective monocentric observational study and reported it in accordance with REST guidelines for studies on TTD (11).

2.1 POPULATION

The source population was composed of all children addressed to or consulting in outpatient unit, pediatric accident & emergency ward, cardio-pediatric unit or intensive care unit for a suspected diagnosis of HF. We retrospectively included all patients aged less than 16 years old and admitted in the Nantes university hospital from January 2007 to December 2016 for a diagnosis of HF. Data were obtained by searching for the keywords “heart failure”, “cardiogenic shock”, “cardiomyopathy” and “myocarditis” in the Nantes university hospital database which includes all diagnoses coded by physicians depending on the international classification of diseases (ICD-10). Data were crossed with a surgical database including patients with cardiac transplantation, ventricular assisting device (VAD) and extracorporeal membrane oxygenation (ECMO). Patients with an antenatal diagnosis of HF including hydrops were excluded because of a poorly defined TTD. Patients having a specific screening program or with a known CHD at HF diagnosis were also excluded from analysis.

2.2 DEFINITIONS AND DIAGNOSIS PROCEDURE

First HF symptoms are different depending on child age with firstly feeding difficulties and respiratory signs in infants, and dyspnea in older children (12). Hepatomegaly is a major clinical sign and the protocol of the Nantes university hospital is to systematically realize an electrocardiogram, chest X-rays and heart ultrasonography in case of dyspnea and hepatomegaly. HF diagnosis was confirmed by transthoracic echocardiography with evidence of systolic dysfunction with reduced left ventricular ejection fraction (LVEF) under 55% and/or diastolic dysfunction with arguments for increased filling pressure. Eventually, HF was diagnosed by the attending cardio-pediatrician based on history, clinical symptoms and signs, and echocardiographic evidence of HF caused by CHD, heart muscle or pericardial disease. The period between the first HF symptoms and the date of diagnosis was called TTD, expressed in days. This period was divided into a patient interval, defined as the period between the date of first HF symptoms and the date of first medical consultation, and a physician interval, the period between the date of first medical consultation and the date of diagnosis. The moment of the diagnosis was when the first diagnostic transthoracic echocardiography was realized by an experienced cardio-pediatrician. Two junior doctors including one specialized in cardio-pediatrics first assessed TTD independently. Arbitrarily, “morning” was defined as 8am, “midday” 12am, “afternoon” 3pm, “evening” 8pm and “night” midnight. “During the beginning of the month” was defined as the 5^{th}, “the middle” 15^{th} and “the end” 25^{th} day. Degree of agreement between the different assessors was evaluated and potential disagreements could be secondly resolved by the implication of a third experienced expert doctor. The two assessors were blinded for final outcome at the first evaluation of TTD. Data were collected from each medical file in the Nantes university hospital.

2.3 DATA COLLECTION

2.3.1 Patient characteristics

We collected sociodemographic data (child age at first symptoms, gender, family postcode), details of medical history (birth weight, weight at diagnosis, known chronic disease) and whether the patient was already hospitalized or at the maternity when first HF symptoms occurred.

2.3.2 Characteristics of the HF episode

We collected the date and hour of first symptoms, first medical consultation, admission in hospital, admission in intensive care unit (ICU) (when appropriate) and of diagnosis. We also collected the number of consultations until diagnosis, first-doctor-consulted specialty and center, HF symptoms and their day of first appearance, HF physical signs including hepatomegaly and their day of first appearance, cardiac enlargement and signs of overload on chest X-ray, echocardiography results including left and right ventricular function, thickness and diameter, and the presence or not of an intra-cardiac thrombus. Exact positive diagnosis was noted: myocarditis, dilated, hypertrophic, restrictive cardiomyopathy. Etiology was determined: infectious, idiopathic, familial, metabolic, neuromuscular, ischemic, due to arrhythmia, or to vascular shunt. Congenital malformations were classified using the nomenclature of the international pediatric and congenital cardiac code. If the child was admitted in ICU, severity at admission was assessed using pediatric index of mortality II (PIMII) score and blood gas analysis including pH and lactates. Medical treatment and need for resuscitation from cardiac arrest during first hospitalization were noted.

2.3.3 Outcomes

Data collection included day of death, ECMO, VAD or heart transplantation, LOS of first hospitalization, number of catheter or surgical procedures, number of readmissions including readmissions for HF, and presence of neuro-motor sequels one and five years after diagnosis.

Primary health outcome was one-year death. Secondary health outcome was LOS. A long LOS was defined as above 10 days, in line with literature (13).

2.4 STATISTICAL ANALYSIS

TTD was measured as a median with interquartile range (IQR, first and third quartile). Agreement between the 2 assessors was measured using Spearman correlation coefficient. Associations between TTD and health outcome ("consequences study") were studied through univariate analyses with chi-square or Fisher's exact test, Mann-Withney or Kruskal Wallis tests and then through multivariate analyses with logistic regression. Potential confounding factors taken into account for the "consequence study" were: birth weight, severity signs, TTD and etiology of heart disease. The linearity of the association between TTD and health outcome was tested and TTD was transformed in polynoma and categorized in case of deviance to linearity. A long TTD was defined as above the median. Determinants of TTD were studied through Cox model as TTD is a censored variable. Analysis of determinants was stratified on etiology because of different physiopathology and epidemiology: CHD or cardiomyopathies and myocarditis (CM) (7). The potential determinants of TTD studied were: age at first symptom, comorbidities, first-consulted-doctor specialty and center, first symptom or sign including severity signs, etiology of CM when applicable.

Statistical analyses were performed with Stata v15 (Statacorp, Texas, USA). Results were presented as number (percentage), median (IQR), or odds ratio (OR) with 95% confidence interval (95% CI). A p-value<0.05 was considered as 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 through ward display.

3. RESULTS

3.1 POPULATION CHARACTERISTICS

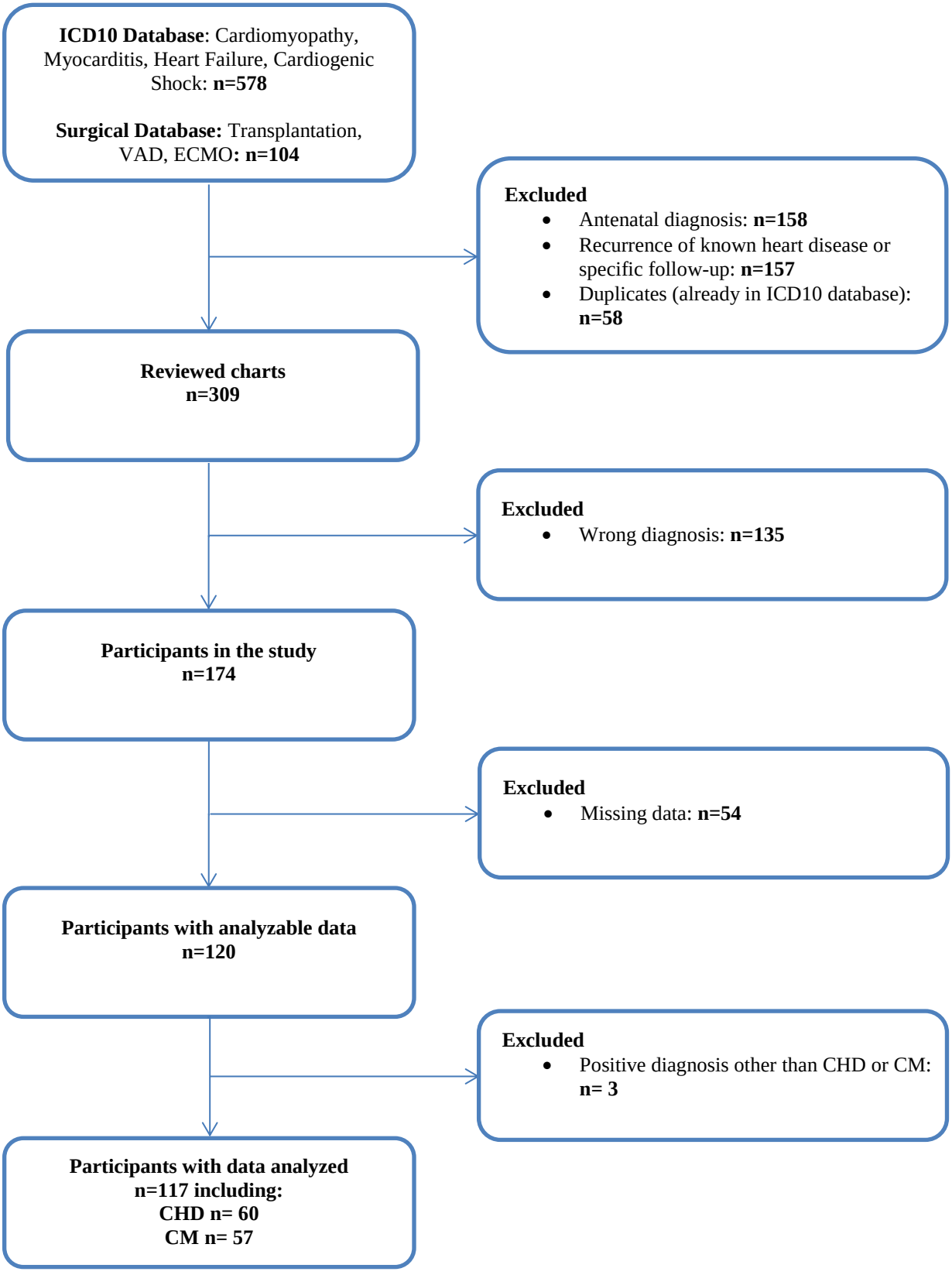


Figure 1: Flow chart (ICD: International classification of diseases, VAD: ventricular assist device, ECMO: extracorporeal membrane oxygenation, CHD: congenital heart disease, CM: cardiomyopathies and myocarditis).

3.1.1 Incidence of HF in the studied area

Taking into account the 3 children with acute coronary syndrome or pericardial tamponade, 32.2% of our children came from Loire-Atlantique area with a children population in this area in 2015 of about 292 100 (14). Excluding wrong diagnosis, we had 174 children, among them 54 were not analyzed because of missing data, that is 17.4 child per year including 5.60 child per year in Loire-Atlantique. The incidence of new-onset HF in children was hence 1.92 per 100 000 and the incidence of new-onset HF due to heart muscle disease in children was 0.91 per 100 000 as 47.5% of children had cardiomyopathies and myocarditis.

3.1.2 Description of the studied population

One hundred and seventeen patients between 0 and 16 years old were analyzed, 96 children were under 1 year old (82.9%). We identified and compared 2 groups of diseases: CHD, and CM also called heart muscle diseases (7). Three patients had different pathologies (one with acute coronary syndrome and two with pericardial tamponade) and were excluded from analysis because of a very small number of cases (Figure 1).

Table 1 shows the main etiologies of HF. Dilated cardiomyopathies (DCM) including myocarditis represented 49 children (86% of all CM). Among them, 18 (37%) were secondary to: arrhythmia (16 (33%) including at least 1 His tachycardia and 1 ectopic atrial tachycardia), ischemia (1 (2%), abnormal left coronary artery from pulmonary artery (ALCAPA)) or vascular shunt (1 (2%), intra-hepatic shunt). Primary causes were mainly considered infectious or inflammatory including myocarditis (12 (24.5%)), or idiopathic (12 (24.5%)). Other primary etiologies were familial (5 (10%), including 1 mixed phenotype of DCM and hypertrophic cardiomyopathy (HCM)), metabolic (1 (2%)) or neuromuscular (1 (2%), congenital myopathy). Among cases of infectious or inflammatory DCM including myocarditis, 5 (42%) had documented viral infection (enterovirus, 2 B19 Parvovirus and 2 HHV6 including 1 co-infection, influenza B virus) and 2 (17%) were associated with Kawasaki syndrome. HCM

accounted for 10.5% (including 1 metabolic HCM: disorder of fatty-acid metabolism) and restrictive cardiomyopathy 3.5% of all CM. Among CHD, coarctation of the aorta with or without aortic arch hypoplasia was from far the leading cause, followed by left-to-right shunts (including ventricular septal defects, persistent arterial duct and atrial septal defects) and cyanogen neonatal emergencies including total abnormal venous return and transposition of the great arteries. Coronary malformations especially ALCAPA, which one case presented as a DCM, and severe aortic stenosis were also common causes of new-onset HF.

Table 1: Detailed etiologies of heart failure among the 117 patients

	Total
Congenital Heart Diseases (CHD), n (%)	60 (51.3)
Congenital anomaly of great arteries including arterial duct, n (%)	29 (24.8)
Congenital anomaly of a ventricle or the ventricular septum, n (%)	6 (5.2)
Congenital anomaly of mediastinal vein, n (%)	6 (5.2)
Congenital anomaly of an atrioventricular or ventriculoarterial connection, n (%)	5 (4.3)
Congenital anomaly of coronary arteries, n (%)	4 (3.4)
Congenital anomaly of a ventriculo-arterial valve or adjacent regions, n (%)	4 (3.4)
Congenital anomaly of an atrium or atrial septum , n (%)	3 (2.6)
Congenital anomaly of an atrioventricular valve or atrioventricular septum, n (%)	2 (1.7)
Functionally univentricular heart , n (%)	1 (0.9)
Cardiomyopathies and myocarditis (CM), n (%)	57 (48.7)
Dilated cardiomyopathy, n (%)	40 (34.2)
Myocarditis, n (%)	9 (7.7)
Hypertrophic cardiomyopathy, n (%)	6 (5.1)
Restrictive cardiomyopathy, n (%)	2 (1.7)

Table 2 shows the characteristics, first symptoms and initial care of the 117 children with HF diagnosis. For TTD evaluation, 45.4% of values were different between the 2 analyzers. Spearman correlation coefficient was r= 0.94 (95% CI 0.90 - 0.96, p<0.001). After discussion, all values were uniformed. The CHD and CM groups were significantly different for age at first symptoms (p <0.001), weight at diagnosis (p<0.001), nature of first symptom or sign (p=0.002), first doctor consulted (p=0.001), in-hospital diagnosis (p <0.001) and patient interval (p=0.003) but not significantly different for TTD (p= 0.09). Physician interval contributed to 33.8% (IQR 6.3-100.0) of TTD for 104 children with available data. Excluding in-hospital diagnosis, physician interval was not significantly modified (data not shown) and median patient interval increased to 3.0 (1.0-14.0); it was 8.0 (1.0-28.0) in CHD and 2.0 (1.0-9.3) in CM (p=0.197).

The alert symptoms or signs were general symptoms (i.e., poor feeding, asthenia, weight stagnation) for 57 children (48.7%). Hepatomegaly was never found as an isolated first sign leading to HF diagnosis. However, during the first HF episode, dyspnea was the leading symptom and hepatomegaly was palpated at some point after diagnostic suspicion for 65 children (55.6%). Fifty-seven children (48.7%) had severe signs during the first day of symptoms. Sixty children (55.6% of children with available data) consulted at least two times before diagnosis. The first doctor consulted was a general practitioner in 24 cases (22.4%) and first consulted doctors were hospital workers in 72 cases (67.3%). Nantes university hospital was the first consulted center for 25 patients (23.3%). First symptoms of the HF episode occurred during hospitalization in 31 cases among newborns (57 %) versus 4 among children aged more than 28 days (10%), $p<0.001$.

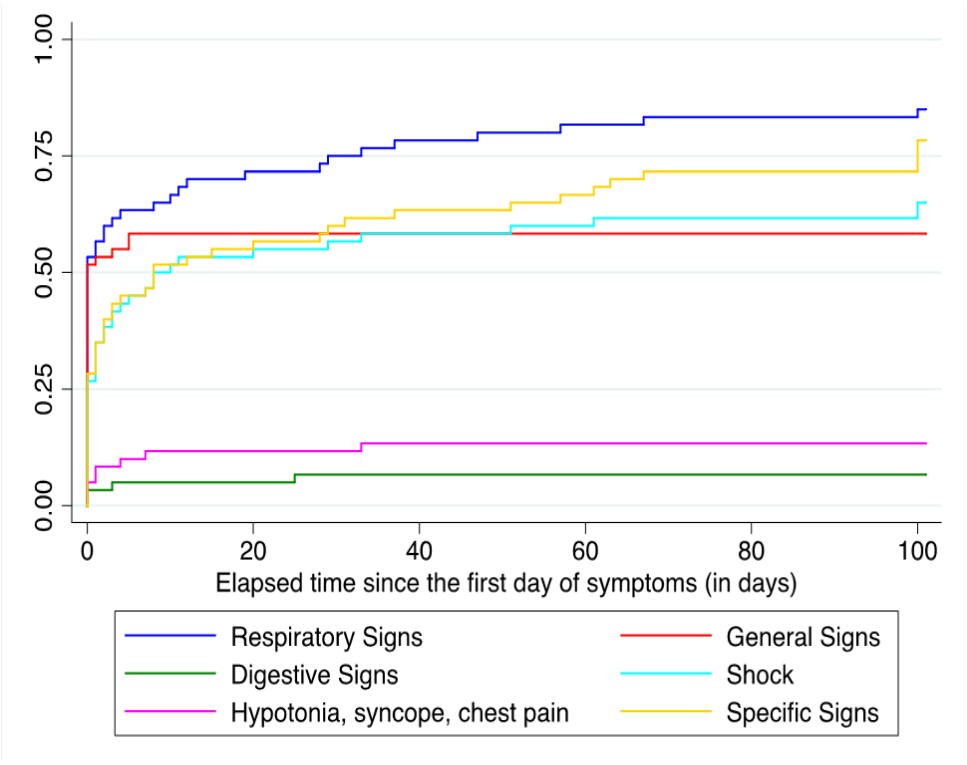
Figure 2 details, by HF etiology, the cumulative proportion of children with a specific group of clinical signs from the onset of HF (i.e., time from the first detected and reported symptom). Digestive signs, syncope, and chest pain were more frequent in CM: 15 (26%) versus 4 (7%) children ($p<0.001$) for digestive signs, 14 (25%) versus 8 (13%) children ($p=0.03$) for hypotonia, syncope and chest pain. The order of the 4 frequent groups of clinical signs in CHD was: respiratory signs, specific HF physical signs, signs of shock and general signs. In CM, these 4 groups of signs were as frequent. Respiratory signs were not significantly more frequent in CHD than in CM: 51 (85%) versus 44 (77%) children ($p=0.13$) whereas general signs were more frequent in CM than in CHD: 44 (77%) versus 35 (58%) children ($p<0.001$). Timing of the different groups of signs was different. In both groups, all children had general signs within the first 5 days whereas signs of shock and HF specific signs could appear later. Progression of disease was faster in CM and few children developed any new symptoms after 1 month in CM and 2 months in CHD. Fifty-four children (95%) had serious signs on the day of diagnosis in CM and 51 children (85%) in CHD ($p=0.127$).

Table 2: Characteristics, first symptoms and initial management of the 117 children diagnosed with HF

	Total	**CHD**	**CM**
Total, n	117	60	57
Sex ratio (M/F)	1.02	1.22	0.84
Age at First Symptoms (days), median (IQR) (n=120)	25 (6 - 146)	8 (1-20.3)	99 (27-804)
Age ≤ 28 days, n (%)	64 (54.7)	48 (80)	16 (28)
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)
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)
Medical history, n (%)	6 (5.1)	3 (5)	3 (5)
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)
First symptom or sign, n			
Respiratory sign[1], n (%)	35 (29.9)	23 (38)	12 (21)
Growth failure, n (%)	23 (19.7)	15 (25)	8 (14)
Feeding difficulties, n (%)	22 (18.8)	10 (17)	12 (21)
Fatigue, n (%)	12 (10.3)	0 (0)	12 (26)
Hemodynamic sign[2], n (%)	8 (6.8)	5 (8)	3 (5)
Syncope or hypotonia, n (%)	6 (5.1)	2 (3)	4 (7)
Digestive sign, n (%) (including vomiting, abdominal pain and ascitis)	5 (4.3)	1 (2)	4 (7)
Abnormal auscultation, n (%) (including heart murmur and gallop)	5 (4.3)	4 (7)	1 (2)
Chest pain, n (%)	1 (0.9)	0 (0)	1 (2)
First doctor consulted, n	106	56	50
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)
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)
Number of consultations until diagnosis, median (IQR) (n=108)	2 (1-2)	2 (1-2)	2 (1-2)
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)
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)

[1]Respiratory signs included dyspnea, cyanosis, signs of respiratory distress, tachypnea and sweating.
[2]Hemodynamic signs included abnormal color of the skin, oligoanuria, tachycardia, bradycardia and cardiac arrest
CHD : congenital heart disease, CM : cardiomyopathies and myocarditis, M: male, F: female, IQR: interquartile range, CKD: chronic kidney disease, ICU: intensive care unit, HF: heart failure, ICU: intensive care unit, Patient interval: time to first consultation, Physician interval: time from first consultation to diagnosis

A) CHD



B) CM

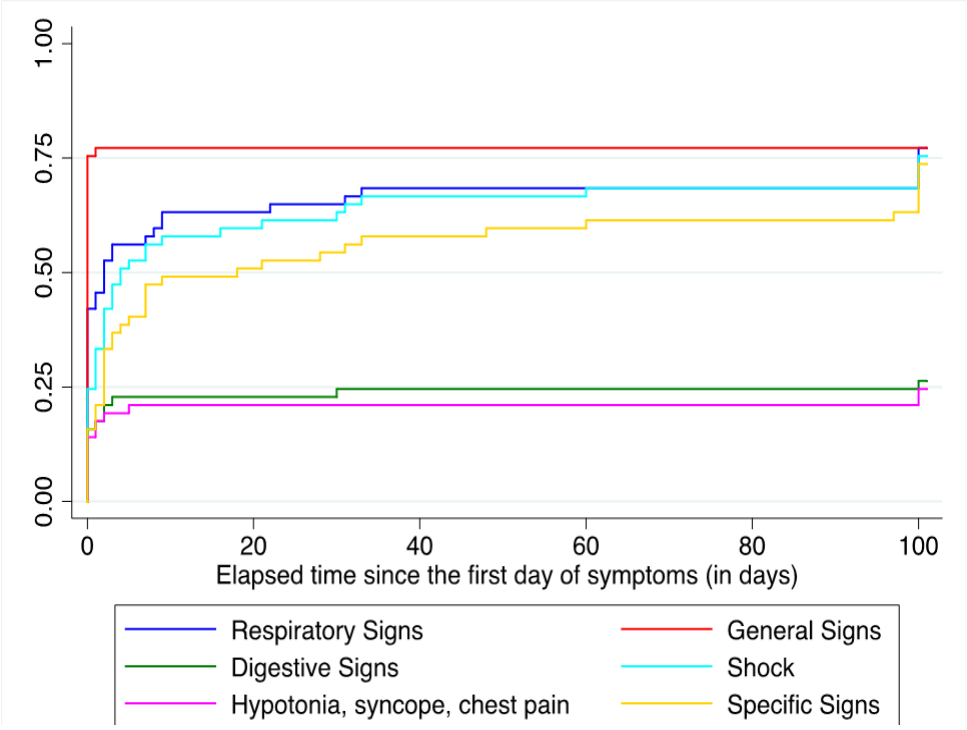


Figure 2: Development of clinical features depending on time from onset of heart failure (first detected and reported symptom) among the 117 patients for A) congenital heart diseases (CHD) and B) cardiomyopathies and myocarditis (CM).

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 ascitis.
Signs of shock: abnormal color of the skin, marbling, cold extremities, prolonged recoloration time, non or less palpable pulse, oligoanuria, hypotension, tachycardia, bradycardia and/or cardiac arrest.
Specific heart failure signs: hepatomegaly, jugular turgescence, hepato-jugular reflux, oedema and/or abnormal auscultation including pulmonary crackles, heart murmur and 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 3 shows radiographic and biological findings, hospital care characteristics and outcomes of the first episode of HF. On echocardiography, left ventricular end diastolic diameter Z-score was reported for 28 patients (median Z-score 2.68 (0.57 - 3.90)). Left ventricular ejection fraction (EF) was reported for 43 patients (median EF 30.0% (20.0% - 41.0%)) and left ventricular shortening fraction (SF) for 22 patients (median SF 23.8% (15.0% - 28.0%)). Cardiac thrombus was found for 3 children (2.6%) and only in patients with dilated cardiomyopathy and EF at 20% or below. Ninety-three children (79.5%) were hospitalized in ICU. Fifteen children (12.8%) died during first hospitalization. Among them, median PIM II was 16.9% (3.8 - 47.0) for 4 children with available data. Median PIM II of children who survived after first hospitalization was 3.9% (1.7 - 13.4) for 55 children with available data (p=0.218). Patients with CHD had at least one surgery or catheterism more frequently (p <0.001) and had a longer first LOS (p=0.008) than patients with CM. Thirty-seven children with CHD (79%) versus 22 children with CM (46%) had a long first LOS (p=0.001). Median TTD was 2.13 days (0.90 - 8.29) in children with no readmission versus 7.90 days (2.07 - 59.09) in children with at least 1 all-cause readmission (p=0.013). Among 110 children with available data, 43 children with CHD (78%) survived free of death, transplantation, VAD and/or ECMO and 43 children with CM (78%) (p=1.000). No child with CHD was implanted with VAD nor transplanted compared with 7 children with CM (12.3%, p=0.005).

Table 3: Radiographic, biological, hospital care findings and one-year outcomes (CHD: congenital heart disease, CM: cardiomyopathies and myocarditis, IQR: interquartile range, HF: heart failure, ECMO: extracorporeal membrane oxygenation, VAD: ventricular assisting device).

	Total	**CHD**	**CM**
Radiographic Findings			
Cardiac Enlargement, n (%) (n= 103)	89 (86.4)	48 (89)	41 (84)
Cardio-Thoracic Index, median (IQR) (n= 85)	0.64 (0.59-0.67)	0.64 (0.60-0.69)	0.63 (0.58-0.66)
Overload Signs, n (%) (n=87)	75 (86.2)	40 (85)	35 (88)
Biological Findings			
Acidosis*, n (%) (n = 78)	34 (43.6)	17 (45)	17 (43)
Lactates (mmol/l), median (IQR) (n=91)	2.9 (1.9-7.9)	3.1 (1.9-8.4)	2.9 (1.9-7)
Hyperlactacidemia (lactates > 2.4 mmol/L), n (%)	55 (60.4)	27 (57)	28 (64)
Hospital Care Characteristics			
Resuscitation For Cardiac Arrest, n (%) (n= 117)	17 (14.5)	6 (10)	11 (19)
At least 1 Surgery Or Catheter procedure, n (%) (n= 111)	65 (58.6)	52 (93)	13 (23)
At least 1 All-Cause Readmission at last follow-up, excluding deaths during first hospitalization, n (%) (n= 99)	52 (53)	25 (51)	27 (54)
At least 1 Readmission for HF at last follow-up, excluding deaths during first hospitalization, n (%) (n= 98)	27 (28)	15 (32)	12 (24)
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)
One-Year Death, n (%) (n=110)	19 (17.3)	11 (20)	8 (15)
One-Year ECMO, n (%) (n=110)	17 (15.4)	10 (18)	7 (13)
One-Year VAD, n (%) (n=110)	4 (3.6)	0 (0)	4 (7)
One-Year Transplantation, n (%) (n=110)	5 (4.5)	0 (0)	5 (9)
One-Year Neuromotor Sequels, n (%) (n= 61)	11 (18.0)	8 (28)	3 (9)
Moderate Sequels, n (%)	7 (11.4)	6 (21)	1 (3)
Severe Sequels, n (%)	4 (6.6)	2 (7)	2 (6)

*For venous samples: pH<7.35, for capillary and arterial samples: pH<7.29 for ages ≤21days and pH<7.36 for ages ≥22days), laboratory thresholds.

3.2 OUTCOMES

Median age at death for all children was 105 days (19-575), it was lower in CHD: 20 days (8.5-107), with 91% aged under 6 months old (all but one).

Table 4a shows univariate and multivariate analysis of factors associated with one-year death for all 117 children. Low birth weight was strongly associated with death on multivariate analysis: aOR 0.24 (95% CI 0.08-0.68), p=0.007. This association persisted when adjusting

further on medical history including prematurity: aOR 0.21 (95% CI 0.05-0.96), p=0.044. Low birth weight (OR 0.24, 95% CI 0.06-0.97), young age at first symptoms (OR 0.85, 95% CI 0.73-1.0), and serious signs at first day (OR 13.2, 95% CI 1.55 – 111.0) were associated with one-year death for CHD only on univariate analysis (table 4b, appendix). No gender difference was found. TTD was dichotomized around the median. A long TTD was associated with better survival for CM on multivariate analysis (aOR 0.09, 95% CI 0.01-0.87) (table 4c, appendix).

Table 4a: Factors associated with one-year-from-diagnosis death for all 117 children with new-onset heart failure (OR: odds ratio, aOR: adjusted odds ratio, 95% CI: 95% confidence interval, TTD: time to diagnosis, CHD: congenital heart disease, CM: cardiomyopathies and myocarditis).

	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 at first day	2.76	(0.96-7.91)	0.058	2.17	(0.51-9.18)	0.291
TTD (days)	0.99	(0.97-1.01)	0.258			
TTD > 3.3 days (median of TTD)	0.27	(0.09-0.81)	**0.019**	0.59	(0.13-2.66)	0.492
Etiology CHD (compared with CM)	1.47	(0.54-3.99)	0.451	1.30	(0.34-4.96)	0.702

On multivariate analysis, low birth weight was also associated with long LOS for all children: aOR 0.18 (95% CI 0.05-0.67) (table 5). CHD diagnosis was associated with long LOS in comparison with CM: aOR 7.49 (95% CI 2.04 - 27.51). TTD was not associated with long LOS. No significant association with long LOS was found by pathology.

Table 5: Factors associated with long length of stay (>10 days) for the 95 children with new-onset heart failure and available data excluding deaths during first hospitalization (OR: odds ratio, aOR: adjusted odds ratio, 95% CI: 95% confidence interval, TTD: time to diagnosis, CHD: congenital heart disease, CM: cardiomyopathies and myocarditis).

	Univariate analysis			**Multivariate analysis**		
	OR	**95% CI**	**p**	**aOR**	**95% CI**	**p**
Birth weight (kg)	0.24	(0.07-0.78)	**0.018**	0.18	(0.05-0.67)	**0.010**
Serious signs at first day	1.18	(0.51-2.73)	0.697	0.48	(0.11-1.94)	0.304
TTD (days)	1.00	(0.99-1.00)	0.391			
TTD > 3.3 days (median of TTD)	0.55	(0.23-1.28)	0.164	0.69	(0.18-2.62)	0.581
Etiology CHD (compared with CM)	4.37	(1.78-10.76)	**0.001**	7.49	(2.04-27.51)	**0.002**

3.3 DETERMINANTS OF TTD

Tables 6a and 6b show determinants of TDD for CHD and CM subgroups respectively. On multivariate analysis, the existence of serious signs at first day was a determinant of short TTD for both subgroups (aHR 3.88, 95% CI 1.61-9.38 and 2.27, 95% CI 1.03-5.01 respectively), whereas age was a determinant of TTD only in CM (aHR 0.09, 95% CI 0.02-0.41) for 4th quartile of age compared with 1st quartile. Non-hospital first consulted doctor was a specific determinant of long TTD in CHD even when adjusting further on in-hospital diagnosis (aHR 0.10, 95% CI 0.03-0.36) and the presence of serious signs at first day also remained a determinant: aHR 3.01 (95% CI 1.14-7.94), p=0.026. Diagnoses of HCM or myocarditis were specific determinants of short TTD in CM (aHR 3.80, 95% CI 1.02-14.19 and 26.50, 95% CI 4.80-146.31 respectively).

Table 6a: Determinants of short time to diagnosis for the 60 children with congenital heart disease and new-onset heart failure (HR: hazard ratio, aHR: adjusted 95% CI: 95% confidence interval, CKD: chronic kidney disease, ICU: intensive care unit).

	Univariate analysis			**Multivariate analysis**		
	HR	**95% CI**	**p**	**aHR**	**95% CI**	**p**
Age at first symptoms in days (compared with 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 at first day	6.60	(3.37-12.93)	**<0.001**	3.88	(1.61-9.38)	**0.003**
First consulted doctor (compared with 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**

Table 6b: Determinants of short time to diagnosis for the 57 children with cardiomyopathies and myocarditis (CM) and new-onset heart failure (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).

	Univariate analysis			**Multivariate analysis**		
	HR	**95% CI**	**p**	**aHR**	**95% CI**	**p**
Age at first symptoms in days (compared with 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 at first day	3.39	(1.83-6.27)	**<0.001**	2.27	(1.03-5.01)	**0.043**
First consulted doctor (compared with 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 (compared with 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

For all children, determinants of TTD are shown in Table 6c (appendix). On univariate analysis, factors associated with short TTD were : age at first symptoms divided into quartiles and compared to 1st quartile (HR 0.44, 95% CI 0.26-0.74 for 2nd quartile; HR 0.27, 95% CI 0.16-0.47 for 3rd quartile and HR 0.16, 95% CI 0.9-0.3 for 4th quartile), presence of serious signs at first day (HR 4.74, 95% CI 3.04-7.4) and maternity doctor as the first consulted practitioner (HR 4.11, 95% CI 2.33-7.28). Birth weight was not associated with TTD (HR 0.90, 95% CI 0.62-1.32). On multivariate analysis, age at first symptoms of more than 4 months remained conversely associated with short TTD (aHR 0.23, 95% CI 0.08-0.68 compared to 1st quartile) whereas the presence of serious signs at first day was a determinant of short TTD (aHR 3.39, 95% CI 2.01-5.72).

4. DISCUSSION

Our study was, to our knowledge, the first to assess specifically TTD in pediatric new-onset HF with no known heart disease. The median TTD was short with 3.3 days for all HF, 2.2 days for CHD and 5 days for CM. A long TTD was associated with a better outcome in univariate analysis but this paradoxical association disappeared after adjustment on severity. Low birthweight appeared to be the only studied factor independently associated with risk of death. For both CM and CHD, the presence of severity signs was associated with a short TTD. For children with CM, older children had longer TTD compared to children in the first quartile (aged less than 27 days). For children with CHD, TTD was longer when the child consulted first a non-hospital practitioner after the onset of symptoms even when adjusted on age at first symptoms.

TTD varies widely among pediatric pathologies : 22 hours of median TTD in strokes (10), 60 days in brain tumors (15) and 14 weeks for Ewing's sarcoma (11). Median patient interval was 1 day, or 3 days excluding in-hospital diagnosis in our study. This brief TTD can explain the absence of association with outcome because of too few patients with long TTD. It is also shorter than in adult literature on HF diagnosis delay where median patient interval ranged from 3 to 7 days (8). In 2012, Johansson et al found a median prehospital interval (time from first symptoms to admission) of 3 days in adult HF, this interval was shorter in patients with severity signs as in our study (16).

Physician interval was not significantly different between children with CHD and CM whereas patient interval was longer in children with CM. This was largely explained by in-hospital diagnosis which significantly modified patient interval. Moreover, older age at first symptoms was a determinant of long TTD in CM as reported in cancers (11). Several studies in children found that non-specific signs were also determinants of long TTD in cancers or missed diagnosis in HF (11)(17). When we analyzed the kinetics of first symptoms (Figure 2),

it appeared that non-specific signs were frequent and early in CM. Considering these non-specific signs as the onset of the disease may have contributed to lengthen TTD. This could explain why TTD tend to be longer in CM compared to CHD. The kinetics of the symptoms in CM may also reflect less aggressive diseases leading to longer TTD. Older age as a determinant of long TTD can then be explained by a lower worrying of parents with older children and by non-specific general signs associated with older age. As a consequence, early CM diagnosis is not easy in children older than 3 months (the age above which the quartiles of age were significantly associated with TTD) and parents should be encouraged consulting especially in the case of general signs, a child "who is not as usual". Physicians are encouraged to closely repeat examinations as different groups of signs including HF specific signs can be delayed and appear successively within the first hours and days from the onset of disease as found here. The presence of serious signs at first day was a strong determinant of short TTD which is appropriate as diagnosis procedures have to be set faster in case of signs of shock. However, in CHD, TTD was longer when first consulted doctor was a liberal practitioner and this association remained after adjustment on age at first symptoms. This result suggests that medical care is influenced by the doctor's specialty and, importantly, knowledge of CHD among liberal practitioners should be improved as, although rarely diagnosed on HF signs, CHD are frequent and can be life-threatening (18)(19). Initial presentation to the primary care provider has also shown its association with missed diagnosis at first presentation in new-onset systolic HF in children with no known heart disease and 49% of these children were missed at first presentation (17). In our study, 55.6% consulted at least two times before diagnosis.

Low birth weight was strongly associated with one-year mortality on multivariate analysis. A study has already shown that preterm birth was associated with a higher risk of death for newborns with CHD after adjusting on intrauterine growth restriction (20). However, even when adjusting on past medical history of prematurity, low birth weight remained predictive of death in our study. Birth weight seemed to be more strongly associated with one-

year mortality in CHD than in CMD. In CHD, weight at the time of surgery of less than 2.4 kg has shown to be an independent risk factor for death in children younger than 6 months old (21). Genetic and metabolic disorders could also have an impact on survival but our small effective limited this analysis. Among children with CM who died, with available data on birth weight, 3 children out of 5 (60%) had a probable genetic or metabolic disease. Conversely, among children with CHD who died, with available data on birth weight, only 1 child out of 11 (9%) had a genetic disease. Genetic and metabolic diseases are known to be associated with low birth weight and worse outcome (22)(23)(24). Low birth weight was also associated with a long initial LOS on multivariate analysis. A study reported that age under 1 year old was associated with long LOS in children with medical complexity (13). We report that low birth weight is predictive of long LOS in children with new-onset HF. We did not show any association between TTD and LOS. This result in children is different from what has been observed in adults for whom a long TTD has been associated with a long LOS but not with mortality in HF (25). However, pathologies are different in children. In particular, CM are rarely ischemic.

Our study was comprehensive for the area of Loire-Atlantique. Indeed, all children in this area are referred to Nantes university hospital in case of need for cardiac-specialized intensive care unit. The incidence of new-onset HF in children was 1.92 per 100 000 and the incidence of new-onset HF due to heart muscle disease in children was 0.91 per 100 000. This result is consistent with literature where the reported incidence of heart muscle disease was 0.87 per 100 000 in the United Kingdomand Ireland in 2003 (7). Nevertheless, there could have been rare undiagnosed cases if death occurred before diagnosis especially leading to unexpected infant death. However, in case of cardiac cause, arrhythmia is often the trigger with channelopathies being the leading cause and not HF (26).

We excluded heart diseases diagnosed before HF appearance to limit the recruitment bias that may have reduced TTD due to a closer follow-up. In antenatal diagnosis, the exact onset of symptoms is often unclear with also planned follow-up after birth. We had 31% missed data because the exact moment of first symptoms and/or diagnosis echocardiography was not defined. This could have influenced results too. Determining TTD can be difficult on retrospective data. Qualitative reports of the moment during the day or the month can also induce a classification bias. However, hours were defined *a priori* depending on the phrases used. First symptoms were not always related to HF because of another preceding condition: these symptoms were then not taken into account. Eventually, the primary outcome was evaluated on 110 patients, that is 6.0% of children lost from follow-up leading to a limited attrition bias. As survival was defined from diagnosis, a longer TTD would have falsely decreased survival in case of lead time bias (27). However, survival was assessed at 1 year with a median TTD of 3.3 days which was very short in comparison with the period of study. Moreover, we showed that a long TTD was associated with increased survival in CM. So at worse, lead time bias would have falsely decreased this association. Finally, we assessed TTD as a quantitative variable but it may be interesting to complete this analysis with a qualitative analysis to define diagnosis delay rather than TTD. Indeed, we arbitrarily considered TTD above median as diagnosis delay but in some cases where first symptoms were not specific to HF, TTD may have been overestimated.

5. CONCLUSION

In this retrospective study on 117 children with new-onset heart failure, we showed that median TTD was short and that severity signs were well recognized, particularly by specialized physicians, and lead to early diagnosis. Our initial hypothesis that TTD was too long and lead to over-mortality was not confirmed by our results. Low birthweight appeared as strongly associated with risk of death. TTD of CM tended to be longer than for CHD maybe due to less specific symptoms at beginning. This should incite physicians to provide monitoring instructions to family caregivers and repeat examinations in children with non-specific symptoms. This study should now be completed by qualitative analyses to assess the optimality of TTD (i.e. whether TTD was adequate considering the symptoms presented) and also the optimality of treatment. Such an evaluation of the optimality of care by experienced physicians could be an interesting work in order to target points of the diagnosis and treatment procedure that could be improved. Moreover, this study reports the epidemiology of new-onset HF in Loire-Atlantique, which is consistent with literature for incidence and mortality. The need to stratify analyses by etiology lowered the number of cases and enlarged confidence intervals. Furthermore, some interesting outcomes such as transplantation, VAD or sequels were not analyzed because of a too small number of cases. Adding cases to this database would improve the statistical power of the analyses and lead to more robust and precise conclusions.

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APPENDIX

Table 4b: Factors associated with one-year-from-diagnosis death for the 60 children with new-onset heart failure due to congenital heart disease (OR: odds ratio, aOR: adjusted odds ratio, 95% CI: 95% confidence interval, TTD: time to diagnosis, CKD: chronic kidney disease).

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p**	**aOR**	**95% CI**	**p**
Age at first symptoms (days)	0.85	(0.73-1.00)	**0.047**	0.88	(0.76-1.02)	0.078
Gender (female compared with male)	1.31	(0.34-4.95)	0.686			
Birth weight (kg)	0.24	(0.06-0.97)	**0.046**	0.16	(0.02-1.09)	0.061
Medical history of prematurity or CKD	9.55	(0.78-117.07)	0.077			
Serious signs at first day	13.16	(1.55-111.88)	**0.018**	3.84	(0.27-54.93)	0.321
TTD (days)	0.97	(0.92-1.02)	0.258			
TTD > 2 days (median of TTD)	0.19	(0.04-0.84)	**0.028**	0.77	(0.10-5.85)	0.798

Table 4c: Factors associated with one-year-from-diagnosis death for the 57 children with new-onset heart failure due to cardiomyopathies and myocarditis (OR: odds ratio, aOR: adjusted odds ratio, 95% CI: 95% confidence interval, TTD: time to diagnosis, CKD: chronic kidney disease).

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p**	**aOR**	**95% CI**	**p**
Age at first symptoms (years)	1.06	(0.90-1.25)	0.453			
Gender (female compared with male)	0.44	(0.09-2.08)	0.303			
Birth weight (kg)	0.25	(0.06-1.10)	0.067	0.14	(0.02-1.08)	0.059
Medical history of prematurity or CKD	3.21	(0.26-40.31)	0.366			
Serious signs at first day	0.74	(0.16-3.47)	0.706	0.21	(0.01-3.07)	0.258
TTD (days)	1.00	(0.98-1.01)	0.554			
TTD > 5 days (median of TTD)	0.13	(0.01-1.10)	0.061	0.09	(0.01-0.87)	**0.038**

Table 6c.: Determinants of short time to diagnosis for all 117 children with new-onset heart failure (HR: hazard ratio, aHZ: adjusted hazard ratio, 95% CI: 95% confidence interval, CKD: chronic kidney disease, ICU: intensive care unit, CHD: congenital heart disease, CM: cardiomyopathies and myocarditis).

	Univariate analysis			**Multivariate analysis**		
	HR	**95% CI**	**p**	**aHR**	**95% CI**	**p**
Age at first symptoms in days (compared with 1st quartile)						
2nd quartile (6-25)	0.44	(0.26-0.74)	**0.002**	0.75	(0.34-1.65)	0.469
3rd quartile (25-146)	0.27	(0.16-0.47)	**<0.001**	0.45	(0.17-1.20)	0.110
4th quartile (146-5716)	0.16	(0.09-0.30)	**<0.001**	0.23	(0.08-0.68)	**0.007**
Medical history of prematurity or CKD	2.11	(0.91-4.87)	0.082	1.55	(0.35-6.87)	0.562
Serious signs at first day	4.74	(3.04-7.40)	**<0.001**	3.39	(2.01-5.72)	**<0.001**
First consulted doctor (compared with emergency doctor)						
ICU doctor	2.97	(0.89-9.88)	0.076	2.47	(0.42-14.76)	0.323
Non-hospital practitioner	0.72	(0.45-1.16)	0.175	0.81	(0.46-1.44)	0.474
Maternity doctor	4.11	(2.33-7.28)	**<0.001**	1.62	(0.78-3.39)	0.199
Other hospital doctor	1.65	(0.68-3.97)	0.265	2.14	(0.86-5.35)	0.103
Etiology CHD (compared with CM)	1.36	(0.94-1.96)	0.106	0.74	(0.41-1.34)	0.321

CONCLUSION GENERALE

Dans cette étude rétrospective analysant 117 cas pédiatriques de découverte d'insuffisance cardiaque, nous avons trouvé un délai diagnostic médian relativement court. La reconnaissance rapide des signes de gravité, notamment par les médecins entraînés, a probablement permis un diagnostic précoce. Notre hypothèse initiale d'un délai trop long menant à un impact péjoratif sur la mortalité n'a donc pas été confirmée par ces résultats. Le faible poids de naissance était le facteur le plus fortement associé au risque de décès. Le délai diagnostic des CM avait tendance à être plus long que celui des CC, possiblement du fait de premiers symptômes d'IC peu spécifiques, rendant le diagnostic plus difficile à évoquer. Il serait donc intéressant pour les médecins, en cas de signe aspécifique, d'informer et d'éduquer les familles sur la reconnaissance des signes d'alerte de l'IC ainsi que de répéter les examens cliniques.. Cette étude devrait ensuite être complétée par une analyse qualitative afin d'évaluer l'optimalité du délai diagnostique (adéquation entre le délai et les symptômes présentés) ainsi que du traitement. Une telle évaluation, réalisée par des médecins expérimentés, pourrait être intéressante afin de cibler les étapes de la prise en charge pouvant être améliorées. Cette étude décrit également l'épidémiologie des cas de découverte d'IC de l'enfant dans le département de Loire-Atlantique, en accord avec la littérature pour l'incidence et la mortalité. En raison de la stratification des analyses, le nombre de sujets dans chaque groupe était relativement faible et les intervalles de confiance assez larges. De plus, d'importants facteurs de morbidité (transplantation cardiaque, pose d'un système d'assistance ventriculaire et séquelles neuromotrices) n'ont pas pu être étudiés en raison d'un trop faible nombre de cas. Implémenter la base de données avec de nouveaux sujets permettrait donc d'améliorer la puissance statistique et de préciser les conséquences du délai diagnostique.

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RESUME

Introduction : L'insuffisance cardiaque (IC) de l'enfant est une pathologie rare et potentiellement grave. Les conséquences et les déterminants du délai entre les premiers symptômes et le moment du diagnostic, appelé délai diagnostique de l'IC (DD), n'ont jamais été étudiés chez l'enfant.

Matériel et méthodes : Notre étude rétrospective monocentrique observationnelle entre 2007 et 2016 a inclus les enfants de 0 à 16 ans hospitalisés au CHU de Nantes pour la découverte d'une IC, avec diagnostic étiologique de cardiopathie congénitale (CC) ou cardiomyopathie (CM) confirmé par échocardiographie.

Résultats : Parmi les 624 patients éligibles, 117 ont été analysés (60 CC et 57 CM). Le DD médian était de 3,3 jours (1,0-21,2). Les signes généraux étaient les plus fréquents initialement. La mortalité à 1 an de l'épisode d'IC était de 17% et le taux de séquelles de 18%. Un faible poids de naissance était indépendamment prédictif de la mortalité à 1 an pour les CC et les CM. Pour les CM, un DD supérieur à la médiane (5 jours) était associé à une meilleure survie à 1 an. La présence de signes de gravité le premier jour des symptômes était indépendamment associé à un DD plus court pour les CC et les CM. Les autres déterminants d'un délai court étaient l'âge jeune et le diagnostic de myocardite pour les CM, un médecin hospitalier comme premier médecin consulté pour les CC.

Conclusion : L'idée répandue qu'un délai long serait associé à un pronostic péjoratif n'est pas vérifiée par cette étude dans l'IC de l'enfant, le contraire est même retrouvé pour les CM.

MOTS-CLES

Délai diagnostique, cardiomyopathie, myocardite, cardiopathie congénitale, choc cardiogénique.