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Outcomes of Patients with Heart Failure followed in a Cardiological Setting to Parakou from 2016 to 2020

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Abstract

Introduction: Heart failure (HF) is a serious pathology whose evolution is made of episodes of acute decompensation, rhythmic and thromboembolic complications, causes of iterative hospitalizations and death. The objective of this study was to describe the outcomes of patients followed for heart failure in a cardiological setting in Parakou from 2016 to 2020. Methods: This was a longitudinal, descriptive and analytical retrospective study of heart failure patients followed in consultation and/or hospitalization over a period of 5 years (October 2016 to July 2020) in cardiology units of Parakou. The outcome of HF was assessed by the NYHA symptomatic stage, rehospitalization, complications and death. Epidata 3.1 fr and SPSS 21 software were used for data processing and analysis. Results: Of the 4902 cardiovascular admissions, 453 cases of HF (9.24%) were observed. At the onset of care, 51.50% of patients were at NYHA stage IV and 69.46% had left ventricular systolic dysfunction. During the follow-up period, there was a symptomatic improvement in the first 06 months but at one year of follow-up, 45.28% of the subjects were seen with a deteriorated stage. At one year of follow-up, the rehospitalization rate was 23.58%. The complications noted were arrhythmias in 8.32% of cases. The mortality rate was 30.37%. Advanced age > 60 years, Charlson score ≥ 3 , hypokalemia and poor adherence to treatment were the factors associated with unfavorable outcomes. Conclusion: HF is associated with significant morbidity and mortality. This highlights the importance of its prevention, its better etiological research and patient's therapeutic education.

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Keywords

Heart Failure, Outcomes, Mortality, Associated Factors, Parakou

1. Introduction

Heart failure (HF) is the inability of the heart to ensure the necessary blood flow for the body's metabolic needs in all circumstances and/or at the cost of increased filling pressures [1] [2] [3]. It represents a very serious pathology with symptoms likely to significantly affect the quality of life of patients [1] [3] [4]. Its outcome is made up of episodes of acute decompensation, rhythmic and thromboembolic complications and non-cardiovascular problems which are causes of iterative hospitalizations. Gerber et al. reported that the rate of rehospitalization after the first episode of cardiac decompensation was 1.3 per person-year between 2000 and 2010 in Olmsted County [5]. According to Mosterd et al., atrial fibrillation (AF), a higher body mass index (BMI), and higher glycated haemoglobin (HbA1c), as well as a low estimated glomerular filtration rate (eGFR) are strong predictors of heart failure hospitalizations [2]. Sliwa et al., in their analysis of the Sub-Saharan Africa Survey on Heart Failure (THESUS HF) registry, found that the main predictors of either re-admission or death during HF were a history of malignancy and severe lung disease, admission systolic blood pressure, heart rate and signs of congestion (rales), kidney function, and echocardiographic ejection fraction [6]. This explains the high mortality of HF which varies from 15% to 20% at one year for hospitalized patients and from 5 to 10% for outpatients [7]. In Parakou, located in northern Benin in 2016, Sossou et al. observed a rehospitalization rate of 18% and a mortality rate of 37.20% at one year of follow-up [8]. This observation made at the beginning of cardiological activities in this area has prompted several remedial actions. This involved the organization of various awareness-raising activities on cardiovascular diseases to promote therapeutic compliance, the improvement of the technical platform, and the implementation of beta-blockers for medical treatment. After five years of practice, we wanted to reassess the current evolutionary profile of patients in order to contribute to improving the management of this pathology.

2. Methods

2.1. Framework, Type and Period of Study

It was a longitudinal, retrospective, descriptive and analytical study conducted at the cardiology department of the Departmental University Hospital of Borgou-Alibori (CHUD-B/A) and at the Septentrional Cardiology Clinic (CCS). At the time of the study, these two centers were the only functional cardiology units in the city of Parakou, located 450 km from Cotonou, and the economic capital of Benin. Data were collected from the files of patients consulted or hospitalized in those centers between January 1, 2016 and June 30, 2020.

2.2. Study Population

The study focused on heart failure patients followed in consultation and/or hospitalization units in these two centers. We proceeded to the systematic recruitment of patients with heart failure, having an accessible medical file and consenting to participate in the study. We excluded patients with incomplete medical records, patients who could not be reached (by telephone or after physical research) or those whose follow-up information was not available.

2.3. Variables of Interest

The main variable of the study was the outcome of HF assessed by the symptomatic evolution, rehospitalization for HF, the occurrence of complications and death. The functional capacity of patients has been classified into four stages according to the New York Heart Association (NYHA) [9]. The complications studied were arrhythmias, stroke, venous thromboembolic disease and hemodynamic complications (acute or subacute decompensation). The other variables were socio-demographic data (age, sex, profession), cardiovascular risk factors (arterial hypertension, diabetes, obesity, dyslipidemia, smoking, alcoholism), characteristics of heart failure at the onset of management (severity of symptoms according to the NYHA, underlying heart disease, left ventricular dysfunction, elements of poor prognosis of heart failure, nature of treatment, therapeutic compliance). The Charlson score [10] was used to assess comorbidities.

2.4. Data Collection

Patients with a diagnosis of HF were identified from hospitalization and consultation registers. Their medical records were searched in the archives. The evolutionary data were collected trimester by trimester from the analysis of these files. The patients or their relatives were contacted by phone call in order to be able to complete certain evolving data. Those we could not reach were considered lost to follow-up.

2.5. Statistical Analysis

The data analysis was carried out with the Stata version 15 software. The search for an association between the variable "Rehospitalization" and the different independent variables was made using the simple and multiple logistic regression method. Modeling according to the univariate and multivariate Cox regression model was used to identify the factors associated with death in heart failure patients. The Kaplan-Meier method was used to estimate instantaneous survival probabilities.

2.6. Ethical Considerations

This study was conducted in conformity with the principles of the Helsinki's declaration. All administrative authorizations were obtained before accessing the patients' medical records. Data were treated anonymously and confidentially and

were only used for the purpose of this study.

3. Results

During the study, 4902 patients were seen in a cardiological setting in Parakou. This included 453 cases of heart failure. The hospital prevalence of heart failure was therefore 9.24%. We excluded 53 patients because their files were unexploitable (**Figure 1**). The analysis therefore focused on 400 patients and the participation rate was 88%.

3.1. General Characteristics of the Sample

The mean age was 56.26 ± 16.45 years with extremes of 8 and 105 years. There was a male predominance (52%) with a sex ratio of 1.08. The main cardiovascular risk factor found was arterial hypertension (HTA) with a frequency of 54.25%. The comorbidities identified were mainly hepatic dysfunction (29.50%), renal failure (22.25%) and hyperuricemia (21.75%). According to the Charlson score, 4.75% had no comorbidities. These characteristics are showed in **Table 1**.

3.2. Initial Characteristics of Heart Failure

At the onset of management, 51.50% of the subjects had functional capacity at stage IV of the pathology and 39.75% were at stage III. Cardiac ultrasound was performed in 370 patients (92.50%). Left ventricular systolic dysfunction was present in 69.46%. The underlying heart diseases were divided according to morphology and according to the cause. According to morphology, it was mainly dilated heart disease (63.75%). According to the cause; probable ischemic

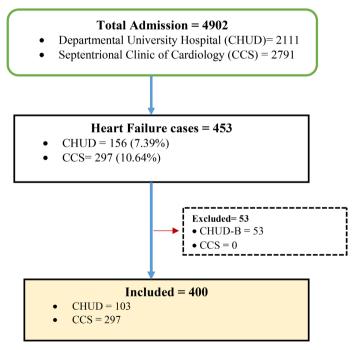


Figure 1. Flow chart showing the selection of heart failure patients received in a cardiology setting in Parakou from 2016 to 2020, for outcomes study.

Table 1. Distribution of heart failure patients received in a cardiological setting in Parakou from 2016 to 2020 according to their general characteristics (N = 400).

	Effectif $(N = 400)$	Pourcentage (%)	
Sociodemographic characteristics			
Age			
<40	74	18.50	
[41 - 60]	166	41.50	
>60	160	40.00	
Sex			
Male	208	52.00	
female	192	48.00	
Occupation			
Public workers	37	09.25	
Private workers	320	80.00	
Students	11	02.75	
Retired	32	08.00	
Cardiova	ascular risk factors		
Arterial hypertension	217	54.25	
Obesity	75	18.75	
Tabacco use	62	15.50	
Diabetes	61	15.25	
Dyslipidemia	52	13.00	
Alcoholism	6	01.50	
Co	omorbidities		
Hepatic dysfunction	118	29.50	
Kidney disease	89	22.25	
Hyperuricemia	87	21.75	
Gastric ulcer disease	73	18.25	
Atrial fibrillation	29	07.25	
Chronic lung disease	25	06.25	
Cerebrovascular disease	32	08.00	
Malignancy	11	02.75	
Human Immunodeficiency Virus	4	01.00	
Rheumatoid arthritis	3	00.75	
Leukaemia	1	00.25	
Charlson's score			
0	19	04.75	
1 - 2	204	51.00	
≥3	177	44.25	

heart disease (57.25%), hypertensive heart disease (25.25%) and valvular heart disease (13.50%) were the most observed (**Table 2**).

Table 2. Distribution of heart failure patients received in a cardiological setting in Parakou from 2016 to 2020 according to characteristics of the disease.

	Effectif	Pourcentage (%)
Functional capacity according to New York H	leart Association o	lassification $(N = 400)$
Class 1	2	00.50
Class 2	33	08.25
Class 3	159	39.75
Class 4	206	51.50
Ejection Fraction classification $(N = 370)$		
Reduced (<40%)	257	69.46
Middle Reduced (40% - 49%)	31	08.38
Preserved (≥50%)	82	22.16
Types of cardiac injuries (N = 400)		
Dilated cardiopathy	255	63.75
Hypertrophic cardiopathy	61	15.25
Restrictive cardiopathy	2	00.50
Organic valvulopathy	54	13.50
Chronic péricarditis	1	00.25
Suspected or confimed aetiology (N = 400)		
Coronary heart disease	229	57.25
Hypertensive cardiopathy	101	25.25
Peripartum cardiomyopathy	20	05.00
Chronic pulmonary heart disease	11	02.75
Congenital heart disease	5	01.25
Post tuberculosis pericarditis	1	00.25
Chronic rheumatic heart disease	32	08.00
Degenrative valvulopathy	9	02.25
Post endocarditis valvulopathy	11	02.75
Poor prognostic factors (N = 299)		
Tachycardia	211	70.56
Arterial hypotension	26	08.69
Hypokalemia	113	44.48
Hyponatremia	92	30.76
Anemia	66	22.07

The main pharmacological classes used were loop diuretics (94.25%), ACE inhibitors (61%), angiotensin 2 receptor antagonists (21.50%), beta-blockers (57.25%), anti-aldosterones (42%) and digitalis (14%). However, 6.5% of patients required amine (dobutamine or dopamine). Iron was prescribed for 20.25% and anxiolytics for 9%. The majority of patients (72%) had poor therapeutic compliance. Therapeutic features of patients are presented in **Table 3**.

Table 3. Distribution of heart failure patients received in a cardiological setting in Parakou from 2016 to 2020 according to their treatments.

	Effectif $(N = 400)$	Pourcentage (%)	
Symptomatic therapy			
Loop diuretic	377	94.25	
thiazidic	223	55.75	
Molsidomine	88	22.00	
Digoxine	56	14.00	
Dobutamine	18	04.50	
Dopamine	8	02.00	
Prognostic therapy			
Lifestyle	324	81.00	
RAAS inhibitors	330	82.50	
Beta-blockers	229	57.25	
MRA	168	42.00	
Other therapy			
Antithrombotics	323	80.75	
Antibiotics	151	37.75	
Iron	81	20.25	
Anti-malaria	66	16.50	
Antiarrhythmics	39	09.75	
Analgesics	34	08.50	
Potassium supplementation	358	89.50	
Hypouricemics	54	13.50	
Statins	40	10.00	
Anxiolytics	36	09.00	
Therapeutic observance			
Good	112	112 28.00	
Bad	288	72.00	

RAAS = Renine Angiotensine Aldosterone System; MRA = Mineralocorticoid Receptor Antagonist.

3.3. Follow-Up of Patients

Of the 400 patients included in the study, 51 were completely lost to follow-up. The **Figure 2** shows the point at each period of follow-up.

3.3.1. Outcome of Heart Failure

• Symptoms

Regarding to symptoms, we noted a progressive increase in the rate of asymptomatic patients (NYHA class 1) in the first two trimesters of follow-up. Between the second and third trimester, the proportion of asymptomatic patients began to drop, while that of patients at NYHA class 2 rose. In the fourth trimester, the number of patients at class 3 and 4 (congestive heart failure) gradually increased at the expense of patients at class 1 and 2 (Figure 3).

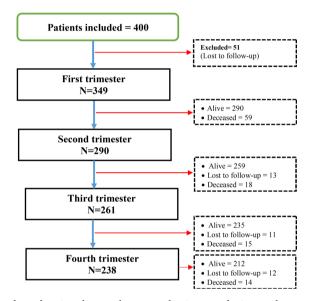


Figure 2. Flow chart showing the numbers at each trimester during twelve months follow-up of heart failure patients received in a cardiology setting in Parakou from 2016 to 2020.

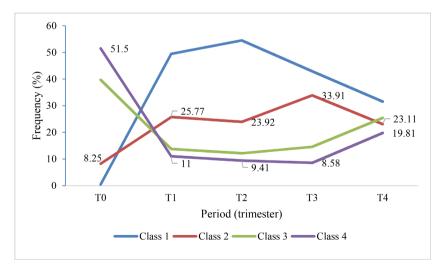


Figure 3. Distribution of heart failure received in a cardiological setting in Parakou from 2016 to 2020 according to the evolution of the NYHA class.

• Rehospitalization

The frequency of rehospitalization for heart failure during follow-up decreased gradually from 18.62% (at 03 months) to 13.14% (at 09 months). But at 12 months, it rose up to 23.58%. **Figure 4** shows the evolution of the frequency of rehospitalization during follow-up.

Mortality

During the 12-month follow-up, 106 patients had died. The mortality of heart failure at 12 months in a cardiological setting to Parakou was therefore 30.37%. The probability of survival varied from 99.4% (Day 1) to 68.62% (Day 365). **Figure 5** presents the Kaplan-Meier estimate of the survival curve for heart failure patients seen in a cardiology setting in Parakou from 2016 to 2020.

• Factors associated with death

In univariate analysis, factors associated with death in these patients were a

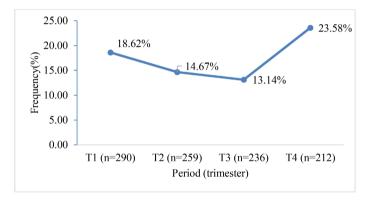


Figure 4. Distribution of heart failure received in a cardiological setting in Parakou from 2016 to 2020 according to the evolution of the frequency of rehospitalization.

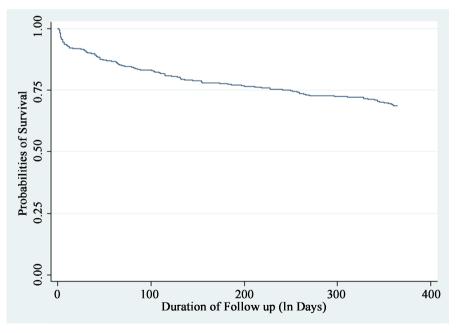


Figure 5. Kaplan-Meier estimate of the survival curve of heart failure patients seen in a cardiology setting in Parakou from 2016 to 2020.

Charlson score \geq 3 (p < 0.001), NYHA class 3/4 (p = 0.032), Systolic blood pressure < 90 mmHg (p = 0.029) and liver dysfunction (p < 0.001). These data are presented in **Table 4**.

Table 4. Univariate analysis of factors associated with death in heart failure patients treated in a cardiological setting in Parakou from 2016 to 2020.

	Occurrence	Occurrence of death		
	Yes	No	OR [IC95%]	p-value
Age				0.052
8 - 40	18 (29.51)	43 (70.49)	1.34 [0.76 - 2.38]	
41 - 60	35 (23.33)	115 (76.67)	1	
>60	53 (38.41)	85 (61.59)	1.68 [1.09 - 2.58]	
Sex				0.381
Male	48 (28.74)	119 (71.26)	1.18 [0.80 - 1.73]	
Female	58 (31.87)	124 (68.13)	1	
Charlson's score				< 0.001
0	1 (6.25)	15 (93.75)	1	
1 - 2	34 (19.54)	140 (80.46)	3.48 [0.47 - 25.45]	
≥3	71 (44.65)	88 (55.35)	9.41 [1.30 - 67.79]	
Functional capacity/New	York Heart Asso	ciation classif	ication	0.032
Class 1/2	4 (12.50)	28 (97.50)	1	
Class 3/4	102 (32.18)	215 (67.82)	2.98 [1.10 - 8.11]	
Blood pressure				0.029
<90 mmHg	12 (52.17)	11 (47.83)	1.80 [0.96 - 3.34]	
90 - 119 mmHg	61 (31.44)	133 (68.56)	1	
≥120 mmHg	33 (25.00)	99 (75.00)	0.71 [0.46 - 1.09]	
Hypokalemia				0.778
Yes	32 (32.65)	66 (67.35)	1.06 [0.70 - 1.60]	
No	74 (29.72)	175 (70.28)	1	
Hepatic dysfunction				< 0.001
Yes	49 (45.79)	58 (54.21)	2.11 [1.44 - 3.10]	
No	57 (24.26)	178 (75.74)	1	
Coronary heart disease				0.611
Yes	65 (31.71)	140 (68.29)	1.10 [0.74 - 1.63]	
No	41 (28.47)	103 (71.53)	1	
Therapeutic observance				0.670
Good	27 (26.21)	76 (73.79)	1	
Bad	66 (28.33)	167 (71.67)	1.10 [0.70 - 1.72]	

The risk of death was 1.56 times (RR = 1.56; CI95% = [1.01 - 2.40]; p = 0.042) higher in patients aged over 60 years. Patients with a Charlson score of 3 or more were 8.67 times (RR = 8.67; 95% CI = [1.20 - 62.66]; p = 0.032) more likely to die than those with a score of less than 3 (**Table 5**).

Regarding survival over time, in the first trimester, survival was significantly poor in patients under 40 years old, whereas in the fourth trimester, it was rather poor in patients over 60 years old (Figure 6).

Similarly, the more comorbidity the patient had, the worse the survival over time, with a significant difference (Figure 7).

4. Discussion

This longitudinal retrospective study was initiated to assess the evolutionary

Table 5. Multivariate model of the factors associated with death in heart failure patients treated in a cardiological setting in Parakou from 2016 to 2020.

	Adjusted RR [IC 95%]	p-value
Age		
8 - 40	1.36 [0.76 - 2.43]	0.298
41 - 60	1	
>60	1.56 [1.01 - 2.40]	0.042
Charlson's score		
0	1	
1 - 2	3.87 [0.52 - 28.36]	0.183
≥3	8.67 [1.20 - 62.66]	0.032

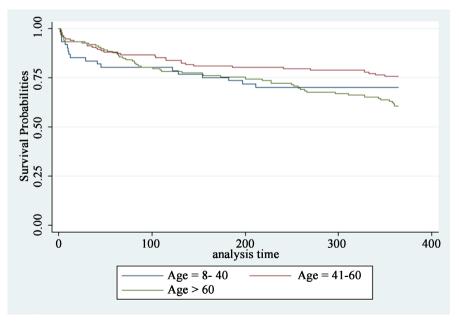


Figure 6. Kaplan-Meier estimate of the survival curve according to age of heart failure patients treated in a cardiological setting in Parakou from 2016 to 2020.

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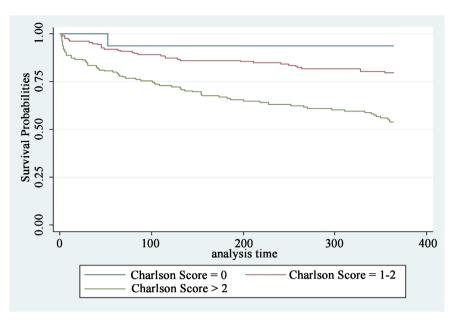


Figure 7. Kaplan-Meier estimate of the survival curve according to the Charlson score of heart failure patients followed in a cardiological setting in Parakou from 2016 to 2020.

profile of patients followed for heart failure in a city in northern Benin. It allowed us to find out that HF represents 9.24% of cardiology admissions in Parakou. At twelve months of follow-up, the readmission rate was 23.58% and a mortality rate of 30.37%. The factors of poor prognosis observed are the age greater than 60 years and the existence of comorbidities. These data from a city where cardiology activity is still embryonic deserve to be analyzed.

4.1. Hospital Frequency of Heart Failure

In our study, heart failure accounted for 9.24% of cardiology admissions. This rate is close to the 14.28% found by Affangla *et al.* in Thiès (Sénégal) [11] and the 11,8% reported by van Riet *et al.* in his systematic review [12]. However, this proportion can reach 50% when focusing on patients hospitalized in a cardiology setting [13] [14]. These data sufficiently show that heart failure is very common and is responsible for a high rate of hospitalization. In developed countries, the progression of heart failure is linked to the aging of the population and to major technological advances allowing better management of cardiovascular pathologies and better survival. When in poor countries like Benin, the high frequency of heart failure is the consequence of late diagnosis and insufficient management of the various cardiovascular pathologies. Thus, in these regions, patients are younger with more severe heart failure [15].

4.2. Age of Patients

In our study, the mean age was 56.26 ± 16.45 years. Sossou *et al.* observed, in 2016 in Parakou, a mean age of 54.73 ± 17.77 years [8]. In Niger, Abdoulaye *et al.* reported a mean age of 55.05 years [14]. In Gabon in 2016, it was 55.8 ± 17 years [16]. Heart failure patients in Africa are therefore younger than those in

developed countries where the average age varies between 60 and 70 years depending on the series [17] [18].

4.3. Initial Characteristics of Heart Failure

Patients on admission were mostly in NYHA class 3 (39.75%) or NYHA 4 (51.50%) heart failure. Similar data have been reported by other studies [1] [6] [15] [19] [20]. Systolic dysfunction was the most encountered echocardiographic abnormality in our work, with a proportion of 69.46%. Sossou *et al.* reported that 67.38% of patients in his series had systolic dysfunction [8]. This predominance of left ventricular systolic dysfunction has been reported by other African authors [11] [14] [16] [21]. As for the underlying heart disease, it was usually a dilated heart disease (63.75%) of probable ischemic origin (57.25%). Knowing that myocardial ischemia at the dilation stage is the result of a natural evolution of atherosclerosis, we can deduce that our patients are seen, generally late, with severe cardiac involvement [22]. This severity of heart failure in these patients is reinforced by the existence of several comorbidities and elements of poor prognosis. Faced with this severity of heart failure at initial diagnosis, symptomatic evolution and patient survival depend profoundly on therapeutic compliance.

In our study, 70% of subjects had bad compliance to treatment. This result is close to the 74.5% and 88.4% reported respectively by Yayehd *et al.* in Togo and N'cho-Mottoh *et al.* in Ivory Coast [23] [24]. These high rates of therapeutic non-compliance in heart failure patients are partly linked to the problem of access to medications in our country where the costs of care are borne exclusively by the patients and where the guaranteed minimum interprofessional salary is very low. Universal medical coverage should help improve medication compliance for our patients.

4.4. Evolution of Heart Failure

At the first two trimesters, an improvement in symptoms was noted, but this rate gradually declined. At one year of follow-up, 45.28% of the subjects were seen with a deteriorated NYHA class. Feldman *et al.* made a similar observation by revealing that at 12 months of follow-up, 37.3% of cases were reviewed with a deteriorated class [25]. Sossou *et al.* also reported a progressive deterioration of symptoms according to the NYHA class of their subjects after one year of follow-up [8]. This could be explained by the therapeutic non-compliance shown by patients with heart failure.

In our study, 23.58% of subjects were rehospitalized for heart failure at 12 months. This rate is close to 28% reported by Gnaba *et al.* in Ivory Coast [26]. It appears from these observations that HF is a very recurrent pathology.

The mortality linked to heart failure was 30.37%. Adoubi *et al.*, in Ivory Coast reported a rate of 31.8% [27]. This mortality was 32.7% for Parada *et al.* [13]. In 2016, Sossou *et al.* reported mortality of 37.20% at one year of follow-up [8].

This slight regression in the mortality of heart failure in Parakou remains to be confirmed and could be a reflection of the improvement in the management of heart failure. Indeed since 2016, molecules improving the prognosis of heart failure are available in this environment and increasingly used. For example, beta-blockers were used only by 7.88% in 2016 compared to 57.25% in 2020 [8]. In addition, the technical platform of the cardiology department has been improved and several awareness-raising activities on cardiovascular diseases are organized. In 2016, Parakou represented the only cardiology center in the northern region of the country. This is no longer the case in 2020; thus facilitating access to cardiology services. Despite these advances, heart failure remains grafted with a heavy mortality as we report in this study.

4.5. Factors of Poor Prognosis

Therapeutic noncompliance was correlated with rehospitalization for heart failure in this study (RR = 4.50; 95% CI = [2.48 - 8.14]; p < 0.001). This could be explained by the fact that compliance with treatment in black African heart failure patients is still strongly influenced by traditional therapy [23]. It is important in our context to continue to insist on raising awareness of patients and their entourage in order to avoid the use of these traditional therapies, which often cause renal and hepatocellular insufficiency, factors of poor prognosis in heart failure [7] [15] [25].

Patients over 60 years in our study were 1.56 times more at risk of death than others. This has been reported by many authors in the literature [28] [29]. The prognosis of heart failure remains severe in the elderly. After a first episode of hospitalization for heart failure, 40% of patients are at risk of being rehospitalized at one year with a mortality of 41% at three years [30]. Aging is accompanied by an increase in connective tissue deposits in the media and the adventitia of the arteries; which decreases vascular elasticity and left ventricular outflow impedance [31] [32]. In addition to cardiac aging, there are comorbidities in the form of chronic pathologies or acute intercurrent episodes which precipitate decompensation and death in these subjects.

Heart failure is a serious chronic disease often associated with comorbidities. A Charlson score ≥ 3 is significantly correlated with mortality in this study. Adoubi in Ivory Coast [27] and Conde-Martel in Spain [17] reported the same result. The presence of these comorbidities complicates management and worsens the prognosis of heart failure. Optimal treatment is sometimes limited in the presence of renal or hepatic impairment, requiring adjustment of dosages and exposing to the risk of overdose. Treatment of associated pathologies also increases the risk of drug interactions. Death in heart failure, especially in the presence of comorbidities, sometimes occurs as a result of an extracardiac complication [16].

5. Conclusion

In Parakou, the outcomes of patients followed for heart failure are characterized

at one year by high rehospitalization and high mortality. The factors of poor prognosis observed are the age greater than 60 years and the existence of comorbidities. These data will help us improve our heart failure management strategies.

Limitations of the Study

The main limitation of this work is its retrospective design. Indeed, we had to exclude 53 patients for incomplete and unexploitable files. In the files used, there were several missing data. Also, the evolutionary aspects such as the evaluation of symptoms and therapeutic compliance were limited to what was recorded in the medical records by different doctors. Finally, the rate of patients lost to follow-up at each deadline was high. This does not allow for a precise evaluation of patient outcomes. Thus, the rehospitalization and particularly the mortality reported in this paper may have been underestimated. Despite these observation biases, the results of this study constitute important data on heart failure in Benin.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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