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Research Article

Factors Associated with Cardiovascular Complications and Mortality in Patients with Covid-19 Treated at Care Sites in Benin between 2020 and 2021

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Abstract

Introduction: COVID-19 is a viral infectious disease caused by SARS-CoV-2. Mortality from this disease is significant in subjects with cardiovascular comorbidity. The objective of this work was to study the factors associated with cardiovascular complications and mortality in patients treated for COVID-19 in Benin between 2020 and 2021.

Methods: The study was descriptive cross-sectional with an analytical aim and took place from March 16, 2020 to June 30, 2021 in the Epidemic Treatment Centers of Benin. Patients with COVID-19 confirmed by PCR or imaging were included. Data were collected from medical records, entered with the KoboCollect application and processed with SPSS 21 software. The level of significance was set at 5%.

Results: Of the 1265 patients, the main cardiovascular comorbidities found were hypertension (45.2%), diabetes (24.3%), obesity (11.2%), stroke (5 .5%) and heart disease (4.4%). The evolution was simple with recovery in 83.5% of patients. Cardiovascular complications were observed in 20.1% of cases. The mortality rate was 16.5%. The factors associated with cardiovascular complications were age ≥ 50 years (p=0.013), history of stroke (p=0.003) and severity of COVID-19 (p< 0.001). The factors associated with mortality were the severity of the case (p< 0.001), the existence of comorbidities such as cancer (p=0.012), chronic renal failure (p< 0.001) and decompensation of pre-existing heart disease (p=0.019).

Conclusion: Cardiovascular complications and mortality related to COVID-19 are more observed in patients with cardiovascular comorbidity, renal failure or cancer. Preventive actions should be more rigorous in the latter.

Keywords: Cardiovascular complications; Mortality; Comorbidity; COVID-19; Benin

Introduction

Emerging in Wuhan city (Hubei province, China) in December 2019, the SARS-CoV-2 infection has rapidly spread worldwide, becoming a pandemic responsible for numerous deaths. SARS-CoV-2 is the second coronavirus which can cause the severe acute respiratory syndrome. The disease due to this coronavirus is called COVID-19 [1].

The SARS-Cov-2 interacts with the cardiovascular system on several levels. On one hand, it increases the mortality in patients suffering from cardiovascular diseases and on another hand it causes direct damage to the layers of the heart [2]. Indeed, regarding patients with COVID-19, *Farhat Sameh Ben* reported in October 2021, that higher mortality rates in patients with cardiovascular diseases (10.5%), diabetes (7.3%) and hypertension (HTN) (6%) compared to the overall mortality rate which did not exceed 2.3% [3].

According to Shi and *al,* Greater proportions of patients with cardiac injury required noninvasive mechanical ventilation (38 of 82 [46.3%] vs 13 of 334 [3.9%]; P < .001) or invasive mechanical ventilation (18 of 82 [22.0%] vs 14 of 334 [4.2%]; P < .001) than those without cardiac injury. Complications were more common in patients with cardiac injury than those without cardiac injury and included acute respiratory distress syndrome (48 of 82 [58.5%] vs 49 of 334 [14.7%]; P < .001), acute kidney injury (7 of 82 [8.5%] vs 1 of 334 [0.3%]; P < .001), electrolyte disturbances (13 of 82 [15.9%] vs 17 of 334 [5.1%]; P = .003), hypoproteinemia (11 of 82 [13.4%] vs 16 of 334 [4.8%]; P = .01), and coagulation disorders (6 of 82 [7.3%] vs 6 of 334 [1.8%]; P = .02) and patients with cardiac injury had higher mortality than those without cardiac injury (42 of 82 [51.2%] vs 15 of 334 [4.5%]; P < .001) [4].

In Benin, as of February 2021, national statistics reported 4,625 confirmed cases of COVID-19, of which 3,781 recovered. There were 732 hospitalized patients including 66 severe cases and 56 deaths recorded to that date. According to data from the Benin Ministry of Healthhypothesied that these severe cases were mainly recorded among ageing people (aged over 60 years)with comorbidities [5].

We then report from this work which aimed to study the risk factors for cardiovascular complications and mortality among

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patients with COVID-19 treated at care sites in Benin between 2020 and 2021.

Patients and Methods

This study took place in the three Epidemic Treatment Centres (ETC) in Benin (Allada, former police school in Cotonou, Army Training Hospital in Parakou (HIA)) over of 16 months from March 16, 2020 to June 30, 2021.

This was a descriptive and analytical cross-sectional study with retrospective data collection.

We included in the study patients hospitalized in one of the ETCs for COVID-19 and with an available medical file. The diagnosis of COVID-19 was retained in all hospitalized patients with a positive Polymerase Chain Reaction (PCR) and/or radiological or CT images characteristic of COVID-19. In Benin laboratories, PCR or RT-PCR (reverse transcriptase polymerase chain reaction) is the detection of the viral genome (RNA) in the upper airways according to the Berlin protocol [6]. In imaging, this involved the demonstration of bilateral ground-glass patterns in the peripheral, posterior and basal sub-pleural areas [7,8].

Suspicious unconfirmed patients who did not have a positive PCR; a characteristic chest CT scan, or those who benefited from a sanitary evacuation were excluded.

Cardiovascular complications and death were the dependent variables studied in patients hospitalized for COVID-19. Cardiovascular complications were: pericarditis, myocarditis, acute coronary syndrome, cardiac arrhythmias, heart failure, pulmonary embolism and cardiogenic shock. These different pathologies were identified according to the classic diagnostic criteria. Death was retained by a medical doctor in the presence of a prolonged and irreversible cardiac arrest.

The other variables studied were: clinical recovery, socio-demographic characteristics (age, sex, and occupation), the severity of the case (simple case, moderate case, and severe case), the patient's cardiovascular background, and other chronic non-cardiovascular pathologies (HIV, cancer, chronic respiratory disease, sickle cell disease, and chronic renal failure). The case was said to be simple when the patient suffering from COVID-19 had no comorbidities and presented neither dyspnoea nor a clinical condition requiring specific assistance. The case was said to be moderate when the patient suffering from COVID-19 had comorbidity (hypertension, diabetes, asthma, etc.) but presented neither dyspnoea nor a clinical condition requiring specific assistance. COVID-19 was classified as severe when the patient presented with dyspnoea or a clinical condition requiring respiratory support. This respiratory assistance could be oxygen therapy by nasal cannula (severe grade 1), high concentration mask (severe grade 2), non-invasive ventilation or orotracheal intubation (severe grade 3) [9]. The cardiovascular background was assessed based on cardiovascular risk factors (smoking, dyslipidaemia, general obesity, hypertension, diabetes and age) and pre-existing cardiovascular conditions (stroke, coronary disease and the various documented heart diseases). A patient was said to have clinical recovered if, after hospitalisation and put on treatment, there is a regression of symptoms with two consecutive negative PCR test results [10].

Cardiovascular manifestations during COVID-19 sought were pericarditis, myocarditis, acute coronary syndrome, cardiac arrhythmias, heart failure, pulmonary embolism, cardiogenic shock and decompensation of pre-existing heart disease. Each of these diagnoses was confirmed by a cardiologist based on the appropriate and recommended clinical and paraclinical investigations. On each ETC, there was at least one cardiologist and, the various recommendations of the European Society of Cardiology served as references for the decisions on cardiovascular care for each patient.

The medical records of eligible hospitalized patients on the three ETCs were systematically identified and analysed. The data collected was entered using Kobocollect software, edited and processed with SPSS 21 French version software.

The qualitative variables were described as proportions, and the quantitative variables were expressed as means ± standard deviation or median with an interquartile range according to the normality of the distribution.

In univariate analysis, the percentages were compared with Karl Pearson's uncorrected Chi-square ($\chi 2$) test, or Fisher's exact test depending on the case, and the means with the Student's t-test. In multivariate analysis, we performed a binary logistic regression using Wald's "step-down" method. The association between the identified factors and the variable of interest was determined by the odds ratio (OR) and its 95% confidence interval.

The initial regression model included variables with a level of significance of $p < 0.20$ and forced variables ($p>0.20$) established in the literature as being risk factors for complications or death.

A threshold of $p < 0.05$ was used to retain the significant risk factors in the final models.

Results

During the period of our study, 1265 patients were selected out of the 1375 patients admitted to the three ETCs in Benin. Figure 1 shows the patient selection.

Sociodemographic Characteristics of Patients

The median age of the patients was 51 years (IQR: 35; 64). Among them, 713 (56.4%) were male thus, a sex ratio of 1.29.

The sociodemographic characteristics of the patients are presented in (Table 1).

Case Severity

Of the 1265 patients, 313 (24.7%) were simple (uncomplicated) cases; 365 (28.9%) were moderate cases; 587 (46.4%) were severe cases (grade 1: 18.1%; grade 2: 14.7% and grade 3: 13.6%).

Cardiovascular Profile

Concerning the risk factors and pre-existing cardiovascular conditions found, hypertension was 45.2%, diabetes at 24.3%, general obesity was 11.2% and stroke was 5.5%.

Among the 1265 patients, 227 (22.7%) had at least one cardiovascular risk factor.

Pre-existing heart disease was found in 4.4% of patients. It was dilated heart disease in 12.5% of cases. Ischemic cardiomyopathy

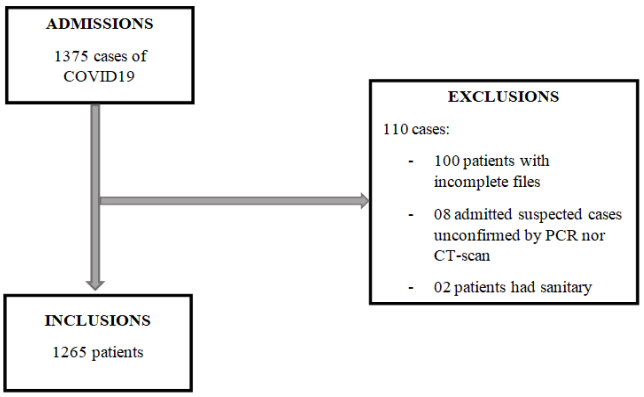

Figure 1: Flowchart showing the selection of patients for the study of factors associated with cardiovascular complications and mortality in patients with COVID-19 and treated at the three Epidemic Treatment Centres in Benin between 2020 and 2021.

Table 1: Distribution of patients with COVID-19 treated at the Epidemic Treatment Centres in Benin during the period from March 16, 2020 to June 30, 2021 according to sociodemographic characteristics (N=1265).

Sociodemographic characteristics	Total (N=1265)	Percentage (%)
Age (years)		
< 50	603	47.7
≥ 50	662	52.3
Sex		
Male	713	56.4
Female	552	43.6
Occupation		
Private employees and civil servants	430	34.0
Self-employed	631	49.9
Retired	129	10.2
Students/Pupils	63	5.0
Religious	12	0.9

accounted for 41.07% of heart diseases and hypertensive heart disease for 28.6% of cases.

Pulmonary embolism, new-onset heart failure, cardiac arrhythmia, and decompensation of pre-existing heart disease were the most observed cardiovascular manifestations. Concerning pulmonary embolism, 122 patients (9.64%) had been clinically suspected and treated as such and 89 had been confirmed by CT angiography, hence, 7% of the study population. We also found 9 cases of cardiogenic shock, 6 cases of the acute coronary syndrome, 4 cases of myocarditis and 2 cases of pericarditis. Table 2 presents the risk factors, pre-existing cardiovascular diseases and the cardiovascular manifestations found.

Non-Cardiovascular Chronic Pathologies

The most represented chronic non-cardiovascular pathologies were chronic respiratory diseases in 5.5% of cases, chronic renal failure in 5.3% of cases, HIV in 2.9% of cases and cancer in 2.0 % of cases.

Table 2: Distribution of COVID-19 patients treated at the three Epidemic Treatment Centres in Benin during the period from March 16, 2020 to June 31, 2021 according to risk factors and pre-existing cardiovascular diseases and cardiovascular manifestations (N=1265).

	Total (N=1265)	**Percentage** (%)
Risk factors		
Age ≥ 50 years	662	52.3
Hypertension	572	45.2
Diabetes	307	24.3
General Obesity	142	11.2
Dyslipidaemia	20	1.6
Smoking	15	1.2
Pre-existing cardiovascular diseases		
Stroke (Cerebrovascular accident)	70	5.5
Heart disease	56	4.4
Atrial fibrillation	8	0.5
Cardiovascular manifestations		
Pulmonary embolism	211	16.6
De novo heart failure*	50	3.2
Cardiac arrhythmias	45	3.6
Decompensation of a pre-existing heart disease	18	1.4
Cardiogenic shock	9	0.7
Acute coronary syndrome	6	0.5
Myocarditis	4	0.3
Pericarditis	2	0.2

*Isolated left heart failure (04); congestive (46)

Table 3: Factors associated with cardiovascular complications of COVID-19 in patients hospitalized in ETCs in Benin during the period from March 16, 2020 to June 31, 2021 (N = 1265).

	Univariate		**Multivariate**	
	ORb [CI 95%]	***P-value***	**ORa [CI 95%]**	***P-value***
Age (years)		*< 0...001*		*0.013*
< 50	1		1	
≥ 50	1.27 [1.20-1.34]		1.59 [1.10-2.29]	
Type of cases		*< 0.001*		*< 0.001*
Simple	1		1	
Moderate	2.50 [0.97-6.42]		2.14 [0.82-5.58]	
Severe 1	19.42 [8.23-45.82]		16.34 [6.78-39.42]	
Severe 2	38.62 [16.37-91.12]		32.01 [13.26-77.26]	
Severe 3	53.60 [22.65-126.86]		42.28 [17.24-103.70]	
Cancer		*0.607*		*0.070*
Yes	0.75 [0.26-2.22]		2.80 [0.92-8.51]	
No	1		1	
Stroke (CVA)		*0.213*		*0.003*
Yes	0..65 [0..33-1..29]		3..09 [1.48-6..48]	
No	1		1	
Heart disease		*0.003*		*0.074*
Yes	1.88 [0.76-4.63]		1.77 [0.5-3.29]	
No	1		1	

Table 4: Factors associated with death from COVID-19 in patients hospitalized at the three Epidemic Treatment Centres in Benin during the period from March 16, 2020 to June 31, 2021 (N=1265).

	Univariate			Multivariate	
	ORb [CI 95%]	*P-value*		**ORa [CI 95%]**	*P value*
Age (years)		*< 0.001*			*0.702*
< 50	1			1	
≥ 50	1.18[1.12-1.24]			1.09[0.69-1.69]	
Type of cases		*< 0.001*			*< 0.001*
Simple	1			1	
Moderate	2.50 [0.97-6.42]			1.03 [1.03-62.43]	
Severe 1	19.42 [8.23-45.82]			23.52 [3.11-177.76]	
Severe 2	38.62 [16.37-91.12]			106.31 [14.50-779.74]	
Severe 3	53.60 [22.65-126.86]			448.67 [61.24-3287.40]	
Cancer		*0.607*			*0.012*
Yes	0.75 [0.26-2.22]			3.81 [1.35-10.76]	
No	1			1	
Chronic renal failure		*< 0.001*			*< 0.001*
Yes	3.60 [2.75-4.70]			8.00 [4.00-15.99]	
No	1			1	
Decompensation of a pre-existing heart disease		*< 0.001*			*< 0.001*
Yes	3.28 [2.03-5.30]			4.11 [1.27-13.35]	
No	1			1	

In-Hospital Evolution of Patients with COVID-19

Recovery without sequelae was observed in 83.5% of cases.

Cardiovascular complications were recorded in 20.1% of patients. The death occurred in 16.5% of patients.

Factors Associated with Cardiovascular Complications in Patients Hospitalized with COVID-19

Age ≥ 50 years, disease severity (ranging from simple to severe cases) and stroke were independent predictors of the occurrence of cardiovascular complications from COVID-19 when adjusted for other variables ($p < 0,05$).

Table 3 presents factors associated with cardiovascular complications in univariate and multivariate analyses.

Case severity, cancer, chronic renal failure, and decompensation of pre-existing heart disease were associated with death in patients hospitalized with COVID-19 (p-value < 0.05). Indeed, all other things being equal, the risk of death changed significantly according to the severity of the cases ($p<0.001$). The risk of death was 3.81 times higher in subjects with, for example, cancer. Table 4 presents the factors associated with the death of patients hospitalized with COVID-19 in univariate and multivariate analyses.

Discussion

This study was initiated to assess cardiovascular morbidity and mortality among patients with COVID-19 hospitalised and treated in Benin. Taking into account all the cases received in the three ETCs in Benin, we believe that our sample is representative of the cases of COVID-19 treated in hospital settings in Benin. Indeed, at the advent of the COVID-19 pandemic, Benin took the option of gathering all cases requiring hospital care in three ETCs created for this purpose. Thus, all cases of COVID-19 are systematically referred to one of these ETCs. The ETC of Parakou takes into account cases from the North region, the one of Allada takes cases from the Centre and the South and the ETC of Cotonou, cases from the South.

These ETCs are led by a multidisciplinary medical team made up of resuscitators, cardiologists, infectiologists and general practitioners who are present there on a permanent basis. When necessary, other medical specialists intervene to give advice. In order to refine the diagnoses and the therapeutic decisions of the cases managed on these sites, a national staff is set up and meets three times a week through the Microsoft Teams software. During these staff meetings, other national and international specialists give their opinions on the management of each patient. All of these precautions guarantee the quality of the data we have collected from the patients' medical files.

At the end of this work, we observed that 22.7% of patients had at least one cardiovascular risk factor. Pulmonary embolism, heart failure and arrhythmia were the main cardiovascular manifestations presented by patients during COVID-19. The mortality rate was 16.5%. Case severity, cancer, chronic renal failure and decompensation of a pre-existing heart disease were the predictors of death among patients hospitalized for COVID-19 in Benin. Although COVID-19 is a recent disease, the speed of its spread and its lethality have prompted the publication of a multitude of data from different regions of the world. It is therefore necessary to analyse the Beninese situation in relation to this rich literature.

The Age of the Patients

In our study, the median age of the patients was 51 years (35; 64).; *Grasselli et al.* in Italy in 2020 observed a higher mean age of 63 years [11]. This age difference could be explained by the fact that the life expectancy of the Italian population is higher than that of Africa.

Pre-Existing Cardiovascular Risk Factors and Diseases

Arterial hypertension is the most common cardiovascular risk factor in our study, found in 45.2% of cases. This history of hypertension was observed in 49% of patients in Italy in 2020 [11], and 37.2% of cases in China the same year [12].

Diabetes was found in 24.3% of patients. This frequency is similar to that of *Du et al.*, and *Huang et al.* in China in 2020, which were respectively 22.4% and 20% [12,13]. Diabetes is thus, the second most common cardiovascular risk factor after hypertension in patients hospitalized for COVD-19.

The history of stroke was reported in 5.5% of our patients. This observation corroborates the 5.3% found by *Shi et al.* in China in 2020 [14] and the 5.1% found by *Zhou et al.* in the same country, and during the same year [15].

Concerning pre-existing heart diseases, they were found in 4.4% of patients. This frequency is similar to the 4.3% published by *Guo et al.* in China in 2020 [16], but lower than the 9.7% reported by *Kumar et al.* in India in 2020 [17]. This difference could be explained by their larger sample sizes, but also by the disparity of the diagnostic tools available depending on the setting. Indeed, the cardiology technical platform in Benin is sparse and the exploration of heart disease is limited to clinic examination, electrocardiogram and cardiac echo-Doppler. Thus, some asymptomatic heart diseases go unnoticed and only reveal themselves when complications or other acute illnesses occur [18]. This usually unrecognized cardiovascular background often affects the evolution of intercurrent conditions such as COVID-19 [16,19,20].

The Evolution of Patients with COVID-19

At the end of our study, the clinical recovery rate was 83.5%. This frequency is higher than the 71% and 77% respectively found by *Zhou et al.* and *Guo et al.* in China in 2020 [15,16]. This difference could be explained by the fact that the majority of patients admitted to intensive care in their studies had died compared to our study. Also, the fact that the proportion of severe cases in their studies was higher than ours. Indeed, in our study, severe COVID-19 cases were found in 46.4% of patients, against 62.3% found in the series of *Zhou et al.*

Frequency of Cardiovascular Complications and Mortality

Cardiovascular complications were present in 20.1% of patients. Pulmonary embolism ranked first with a frequency of 16.6%. *Planquette et al.* in France [21] and *Whyte et al.* in England [22] in 2020 reported lower frequencies than ours; 5.6% and 5.4% of cases respectively. This disparity could be explained by the systematic non-confirmation by CT angiography of some of our cases which unfortunately remain suspected cases of pulmonary embolism. In fact, the respiratory symptoms that constitute the main warning signs of pulmonary embolism were also the key manifestations of COVID-19 [23,24]. Only a multislice pulmonary CT angiography could provide diagnostic accuracy [7,8,24]. Unfortunately, this examination was not permanently available during the study period.

The pathogenic mechanisms involved in cardiovascular damage are multiple and make it possible to understand the frequent association between COVID-19 and pulmonary embolism. Indeed, the COVID-19 virus is responsible for hyper-inflammation accounting for diffuse activation of coagulation, both in the arterial and venous beds [26]. Faced with most situations of respiratory distress and strong clinical suspicion, the patients in our series received substantial anticoagulant treatment in case of impossibility to confirm pulmonary embolism. The cases, related to the severity of the infectious or inflammatory involvement of the lung parenchyma and not to the thromboembolism complications, might have been detected if angioscan had been systematically performed [7].

Heart failure was found in 3.2% of patients during their hospitalization and was more frequent in patients with advanced age. *Wang L et al.* [27] and *Zhou et al.* [15] in China in 2020 found significantly higher frequencies of 17.4% and 23% respectively. This difference could be explained by the high proportion of patients with underlying heart disease in their studies. Indeed, the presence of heart disease was found in 4.4% of patients in our study. This proportion is lower than the 15.7% found by *Wang L et al.* Patients with pre-existing heart disease are at higher risk of developing heart failure from COVID-19, which is a decompensating factor.

The mortality rate was 16.5% in our study. This rate is close to the 19% and 20.3% found by *Wang L et al.* in China in 2020 [27] and *Rosenthal et al.* in the United States in 2020 [28]. *Ferrando et al.* in Spain in 2020, on the other hand, found a rate of 31% [29]; this high frequency could be explained by the inclusion of patients only in intensive care in their studies, therefore cases of extreme severity or involving several damages.

Risk Factors for Death of Patients with COVID-19 in Benin between 2020 and 2021

After multivariate analysis, the factors associated with death among patients hospitalized for COVID-19 were; the severity of the case (CI [3.11-3287.40]; p< 0.001); the co-existence of cancer (ORa 3.81; CI [1.35-10.76]; p=0.012), chronic renal failure (ORa 8.00; CI [4.00-15.99]; p< 0.001) and the decompensation of pre-existing heart disease (ORa 4.11; CI [1.27-13.35]; p=0.019). Other studies have found risk factors different from those found in our study. *Zhou et al.* in China in 2020 found in multivariate analysis that risk factors of mortality were; older age (CI [1.03-1.17]; p = 0.0043), a high SOFA (Sepsis Organ Failure Assessment) score (CI [2.61-12.23]; p <0.0001) and D-dimers greater than 1 g/ml on admission (CI [2.64-128.55]; p = 0.0033) [15]. *Rosenthal et al.* in the United States in 2020 found in multivariate analysis that advanced age was the risk factor most strongly associated with mortality (P < 0.001). The risks of death were 16.2 times higher in hospitalized patients aged 80 years or older, than in those aged 18-34 years (age ≥ 80 years vs 18-34 years: odds ratio [OR], 16.20 95% CI, 11.58-22.67; P < 0.001) [28]. *Ouedraogo et al.* in Burkina Faso in 2020 also found advanced age (age ≥ 65 years) (HR: 2.3; CI (1.2-4.3); p=0.011) as a risk factor for death [30]. This difference compared to the factors found in our study could be explained on one hand by the fact that our patients are of younger age and on the other hand by the availability of D-dimers in the screening of patients from the day of admission in the study by *Zhou et al* [15].

Limits and Weaknesses of the Study

Due to the retrospective nature of this work, some data, particularly the one on the evolution of patients, were not found in all of the files, which did not allow a precise analysis, thus reducing the power of our results. Also, the lack of systematic performance of some of the paraclinical examinations in certain clinical situations may have contributed to the underestimation of some cardiovascular complications of COVID-19. For example, D-Dimers or CT angiography were not performed in certain patients with suspicious signs of pulmonary embolism. Similarly, the dosage of troponins I in the presence of suspected myocarditis and acute coronary syndrome and the coronary angiography and cardiac MRI were not systematic.

Thus, the diagnosis of acute coronary syndromes and myocarditis remains imprecise [31,32]. These common complications of COVID-19 are then, probably underestimated in our work.

Despite these limitations, this study provided important data on COVID-19 and cardiovascular disease in a low-income country like Benin.

Conclusion

The evolution of patients with COVID-19 is burdened with significant mortality, but also influenced by the presence of risk factors and/or pre-existing cardiovascular conditions, and/or direct cardiovascular manifestations due to this disease. This study identified factors associated with cardiovascular complications and death in patients with COVID-19 in Benin.

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