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COVID-19 and diabetes: a retrospective cohort study in a tertiary care hospital in Antananarivo Madagascar.

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ABSTRACT

Introduction: The management of COVID-19 is still difficult in poor countries due to insufficient infrastructure and technical platform, while it is major health problem. Diabetes is one of risk of severity of COVID-19. In that context, our study aimed to describe diabetic patients with COVID-19 and to analyze the factors of death in these patients. **Methods**: This was a retrospective study during twelve month in 2021. **Results:** We collected 94 patients with a mean age of 58 ± 11 years. Our population presented a severe form of COVID-19 with a mean oxygen saturation level (SpO_2) on admission of 87% ±12.8, a mean blood glucose level of 14 ± 6.5 mmol/L. Thirty-one patients (97%) had glycated hemoglobin test above 6.5%. Twenty-six out of thirty-seven (70%) of the diabetics had lung damage greater than 25% predominantly 15 (58%) extensive damage, 7 (27%) severe and 4 (15%) critical. Sixty-nine (73%) was known diabetics and 25 (27%) were newly diagnosed diabetics at the time of hospitalization for COVID-19. The mortality rate was 20.2% (n=19). Factors associated with mortality were age ≥ 70 years 37% vs 10% (OR 4.1 [1.2-14.2] 95% CI; p= 0.02); SpO_2 on admission ≤ 90% 74% vs 41% (OR 4.1 [1.3-12.7] 95% CI; p= 0.01); hyperosmolar coma 32% vs 3% (OR 15.5 [1.8-85.2] 95% CI; p< 0.001). **Conclusion** Diabetes is a risk factor of the severity even in all COVID-19 patients. This highlights and strongly recommends the necessity of screening diabetes in all patients with COVID-19 to improve their management and to prevent the damage induced.

Keywords : COVID—19; Diabetes; Madagascar; Mortality.

INTRODUCTION

Since the first case of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection in Wuhan in December 2019, the causative agent of COVID-19 (coronavirus disease 2019), this remains a global issue [1]. It is responsible for significant morbidity and mortality worldwide in hospitals. Diabetes is one of the significant predictors of morbidity and mortality during SARS-CoV-2 infection [2]. The result of meta-analyses showed that diabetes increases mortality and severity of SARS-CoV-2 infection by a factor two compared to non-diabetic patients [3]. Furthermore, there is a bidirectional relationship between COVID-19 and diabetes. On the one hand, diabetes is associated with an increased risk of the severe form of COVID -19. On the other hand, cases of incident diabetes and its severe acute metabolic complications can be observed during the course of the SARS-CoV-2 infection [2-4]. Given the damage caused by the combination of COVID-19 and diabetes, a good management of COVID-19 is therefore necessary especially in low-income countries with poor technical platform to improve the prognosis of the disease. In that context, this study aims to describe the clinical characteristics and management of diabetic patients hospitalized with COVID-19 and to evaluate the factors associated to the mortality of the patients.

METHODS

This was a retrospective cohort study. It took place in the Infectious Diseases Department of University Hospital of Befelatanana, a reference center for the management of COVID-19 patients. This department manages the largest COVID-19 patients locating in the capital of Madagascar, the most populated city.

We enrolled diabetic patients hospitalized for COVID-19 over twelve-month period from 1 April 2020 to 31 March 2021. We included all patients hospitalized for COVID-19, known diabetics or newly discovered diabetics with a positive nasopharyngeal COVID-19 polymerase chain reaction (PCR) or GeneXpert COVID-19 or a Computed Tomography scan in favour of COVID-19 associated or not with a compatible clinical presentation. We excluded all incomplete files that could not be used. The data collection was carried out anonymously by establishing question-

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naires and registered in electronics records.

The variables taken into account were the patients' characteristics such as: demographic characteristics, clinical characteristics: pulse oxygen saturation (SpO_2), mean oxygen saturation, known and newly discovered diabetic patients status, clinical forms of COVID-19, complicated forms of diabetes, treatments received, oxygen flow, insulin therapy, corticosteroid therapy, anticoagulant, the mean blood glucose level, glycated hemoglobin level and the severity of the infection involvement on chest CT scan. The diagnosis of Covid-19 is based on a positive Polymerase Chain Reaction (PCR) or a positive COVID-19 GeneXpert, or a negative nasopharyngeal COVID-19 PCR with chest CT involvement consistent with Covid-19. Diabetes is defined according to the criteria proposed by the World Health Organization: a blood glucose level > 1.26 g/l (7.0 mmol/l) after 8-hour of fasting and checked twice; or the presence of diabetic symptoms (polyuria, polydipsia, weight loss) associated with a blood glucose level (on venous plasma) > 2 g/l (11.1 mmol/l); or a blood glucose level (on venous plasma) > 2 g/l (11.1 mmol/l) 2 hours after an oral glucose load of 75 g glycated hemoglobin higher than 6.5. The severity form of COVID-19 was defined according to the severity form established by the World Health Organization (WHO). The CT involvement was classified according to the percentage of lung involvement into: minimal involvement less than 25%, mild 25-50%, severe 50-75% and critical more than 75%. The different complications of diabetes were:

- Ketoacidosis coma defined by confusion with a Glasgow score of less than 11/15, capillary hyperglycemia higher than 7 mmol/l, a state of metabolic acidosis with Kussmaul respiration, ketonuria and glucosuria on urine dipstick.
- Hyperosmolar coma defined by a coma with a Glasgow score lower than 11/15, global dehydration with dryness of the mucous membranes and skin folds, hyperglycemia with positive glucosuria on the urinary strip and negative ketonuria.
- Hypoglycemic coma is a coma with a blood sugar level below 0.5g/l (3 mmol/L).

Statistical analysis

Qualitative variables will be represented by proportions and quantitative variables as means or median. The comparison of qualitative variables will be done by the chi² test or the Fischer exact test. Quantitative variables will be compared by the Mann-Whitney-Wilcoxon test. The strength of the association between the dependent variable and the independent variables was measured using the Odds Ratio (OR) and their 95% confidence interval (95% CI). Univariate then multivariate analysis of factors associated with mortality among diabetic patients were performed using logistic regression. A p-value <0.05 will be considered as a significance threshold. Statistical analysis will be performed with Epi info© 7.2.2 software.

Ethics Consideration

We got authorization to use medical folders archived in the Infectious Diseases Department at the University Hospital of Befelatanana. As retrospective studies do not fall within the framework of the law of 7 May 2004 on experiments on the human person, the ethics approval was waived.

RESULTS

Four hundred and twenty-eight patients were hospitalized with COVID-19. Diabetics represented 24% (n= 103). Ninety-four patients (22%) were included and 9 (2%) were excluded due to incomplete medical records. The figure 1 shows the flowchart of the patient.

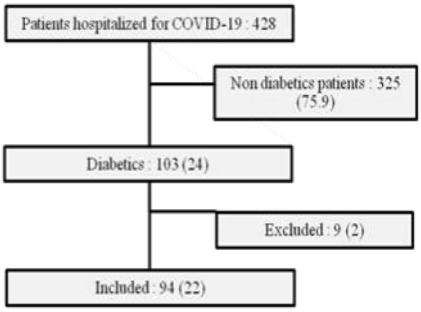

Figure 1 : Flowchart

The mean age was 58 ± 11 years, the youngest was 32 years and the oldest 78 years. Men predominated (59%) in the study population with a sex ratio of 1.4. The majority of those included were in the tertiary professional sectoring (61% n=57). Table I showed the clinical and paraclinical characteristic of patients. Seventy-seven of the included (82%) had other risk factors for COVID-19 severity in addition to diabetes and the mean number was 2.5 ± 1 severity factors (table I). The other most common severity factors among diabetics in order of frequency were: hypertension (68% n=64), age above 60 years (49% n=46) and smoking (11% n=10).

The mean duration of symptoms before hospitalization was 10.2 ± 6.2 days. The mean pulse oxygen saturation (SpO_2) in admission was 87% ±12.8. In contrast, the mean of the lowest SpO_2 of patients during hospitalization was 83.1% ± 13.5.

The mean blood glucose level on admission was 14 ± 6.5 mmol/l. Thirty-two patients (97%) had a glycated hemoglobin level more than 6.5%. Chest scans were performed in 43 patients (57%). The chest CT image was in favour of COVID-19 in 37 patients (86%), and 5 patients (12%) had early lung fibrosis. Twenty-six out of thirty-seven (70%) had lung involvement of more than 25% on the thoracic CT scan, of which 15 (41%) had extensive involvement, 7 (19%) severe and 4 (11%) critical (table I).

According to the form of severity of COVID-19, the

majority were diagnosed with severe form (45% n= 42), and then critical form (30% n=28). Sixty-nine (73%) was known diabetics and 25 (27%) were newly diagnosed diabetics during hospitalization for COVID-19. Almost all patients (97=91) had a blood glucose disorder during hospitalization and thirty-two 32 (34%) had at least acute metabolic complication of diabetes including diabetic ketoacidosis (27% n=25), hyperosmolar coma (10% n=9) and hypoglycemia (4% n=4). The other diagnoses of the patients are summarized in table I. Seventy-eight (83%) patients received insulin therapy: rapid acting insulin was the most commonly used, administered in 66 patients (70%); followed by intermediate acting insulin, used in 23 patients (25%); and long-acting insulin, used in 21 patients (22%). The remaining patients (17% n=16) were receiving oral and diabetics drugs. The majority (80%) were on oxygen therapy during their hospitalization. The average oxygen flow rate was 10.1 ± 5.7 L/min with a maximum flow rate of 25 l/min. Corticosteroid therapy was used in 76 patients (81%) with a mean dosage of 15.4 ± 11 mg dexamethasone equivalent per 24 hours. The mean time of use of corticosteroid was 8.8 ± 5.2 days. Seventy-six (81%) patients were on enoxaparin anticoagulation, the majority of which was curative 55 (72%). The length of stay varied between 1 day to 38 days and the average duration was 11 days ± 7.3 days (table I).

The mean SpO_2 at discharge was 94.3% ± 5. The table II shows the characteristics of dead patients. The mortality rate in the diabetic population was 19 (20%), there was no correlation between diabetes history (known diabetics, newly discovered diabetics) and mortality (p= 0.16) (Table III). The mean length of stay of the dead patients was 8.1 ± 5.7 days (table II). Table II summarizes the diagnosis of death of our patients which was predominated by acute respiratory distress. The factors associated to the mortality were described on table III. On univariate analysis, the factors associated to the mortality were age ≥ 70 years 36.6% vs 10.1% (OR 4.1 [1.2-14.2] 95% CI; p= 0.02); SpO_2 on admission ≤ 90% 73.7% vs 40.6% (OR 4.1 [1.3-12.7] 95% CI; p= 0.01); hyperosmolar coma 31.6% vs 2.9% (OR 15.5 [1.8-85.2] 95% CI; p< 0.001). And after multivariate analysis, SpO_2 on admission ≤ 90% and hyperosmolar coma were the two factors associated to the mortality in diabetic patients with COVID-19 (table III).

DISCUSSION

Our study highlights the relation between diabetes and severe form of COVID-19 the majority of patients with severe (45%) or critical forms (30%) with a mean SpO_2 of 87.3% ±12.8. We found that 69 (73%) were known diabetics and 25 (27%) were newly diagnosed diabetics during hospitalization for COVID-19.The length of stay was 11 days; the average oxygen flow rate was 10.1 ± 5.7 l/min with a maximum flow rate of 25 l/min.

Table I: Characteristics of patients

Characteristics	Patients n = 94	Percentage (%)
Mean age	58.1 +/- 10.6	-
Male gender	55	59
Female gender	39	41
Other risk factors of severity	77	82
Mean lenght of evolution of symptoms (days)	10.2 +/- 6.2	-
Mean of oxygen saturation level (%)	87.0 +/- 12.8	-
Mean of blood glucose level (mmol/l)	14.0 +/6 6.5	-
Glycated hemoglobin level > 6.5%	31	97
Chest scan realized	43	57
Chest scan in favor of COVID-19	37	86
Early fibrosis	5	12
Involvement > 25%	26	70
Extensive involvement	4	41
Severe involvement	7	19
Critical involvement	4	11
Severe form	42	45
Critical form	28	30
Number of patients known diabetic	69	73
Incident diabetes	25	27
Ketoacidosis coma	25	27
Hyperosmolar coma	9	10
Hypoglycemia	4	4
Insulin therapy ***Immmediate-acting insulin*** ***Long-acting insulin***	78 23 21	83 22 17
Oral antidiabetics	16	17
Oxygen therapy	75	80
Average oxygen flow (ml/mn) ***Max***	10.1 +/- 5,7 25	-
Corticosteroid therapy	76	81
Average dosage of corticosteroid	15.4 +/- 11	-
Average lenght corticosteroid (days)	8.8 +/- 5.2	-
Anticoagulants	76	81
Average lenght of stay (days)	11.0 +/- 7.3	-

Table II: Characteristics of dead patients

Characteristics	Patients n = 19	Percentage (%)
Average lenght of evolution of symptoms	11.4 +/- 8.4	-
Average lenght of stay	8.1 +/- 5.7	-
Diagnosis of death		
Acute respiratory distress	9	47
Ketoacidosis coma	8	42
Hyperosmolar coma	6	32
Digestive haemorrhage	5	26
Cardiac decompensation	3	16
Stroke	2	10
Shock	2	10

Our population represented 22% of patients hospitalized with Covid-19 and was a young population with a mean age of 58.5 years and predominantly male. Although diabetes has been associated with worse outcomes, there is no evidence at present that the risk of Covid-19 is higher in people with diabetes. A meta-analysis of 12 studies describing data from 2,108 Chinese patients with COVID-19 reported a diabetes prevalence of 10.3% [2], which was similar to the national prevalence of 10.9% reported in 2013 [3]. An Italian study of 146 patients with confirmed SARS-CoV-2 infection at the University Hospital of Padova found a similar pattern. The prevalence of diabetes in these patients was around 8.9% (mean age 65 years)[4]. There may not be more diabetics among COVID-19 patients and a diabetic patient would not be at greater risk of contracting the disease than a non-diabetic according to the Chinese and Italian data.

Table 3: Factors associated to the mortality

Factors	Patient outcome		Univariate analysis		Multivariate analysis	
	Dead n=19; %	Alive n=75; %	OR [IC95%]	p	OR [IC95%]	p
Male gender	12 (63)	43 (59)	1.2 [0.4—3.3]	0,39	-	-
Age ≥ 70 years old	6 (31)	7 (10)	4.1 [1.2—14]	0,01	-	-
Incident diabetes	3 (16)	22 (32)	0.4 [0.1—1.5]	0.16	-	-
2 or more COVID-19 severity factors	17 (90)	54 (78)	2.4 [0.5—11]	0,50	-	-
History of high blood pressure	14 (74)	45 (65)	1.5 [0.5—4.6]	0,25	-	-
History of stroke	2 (10)	1 (2)	8.0 [0.7—93]	0,60	-	-
Duration of evolution	7 (37)	28 (41)	0.9 [0.3—2.4]	0.39	-	-
Oxygen saturation on admission ≤ 90%	14 (74)	28 (41)	4.1 [1.3—12]	0.01	3.4 [1.0—11]	0.04
Diabetic ketoacidosis	8 (42)	16 (23)	2.4 [0.8—7.0]	0.06	-	-
Hyperosmolar coma	6 (32)	2 (3)	15 [2.8—85]	0.0001	11 [2.3—53]	0.003
Diagnosis of bacterial infection	4 (21)	18 (26)	0.8 [0.2—2.6]	0.65	-	-
Use of an anticoagulant	15 (79)	56 (81)	0.9 [0.2—3.1]	0.8	-	-

In Madagascar, Razafimahatratra et al. have estimated 43.5% the seroprevalence of Covid-19 in blood donor's Malagasy patient [5]. This is quite similar to our result but estimates that the risk of Covid-19 is independent of diabetes.

The risk of developing a severe form was described in our study as the study population had a mean saturation of 87.3%, which is a severe form of the disease. Diabetes and like any other cardiovascular disease is one of the most common co-morbidities giving a severe form of Covid-19 infection. Our study is in line with what has been reported in the literature including a Chinese meta-analysis including 1527 patients showing that the most prevalent cardiovascular metabolic co morbidities with COVID-19 were hypertension (17.1%, 95% CI 9.9-24.4%) and cardiovascular disease (16.4%, 95% CI 6.6-26.1%), followed by diabetes (9.7%, 95% CI 6.9-12.5%) [6]. In this report, patients with diabetes or hypertension had twice the risk of critical illness or intensive care unit (ICU) admission. Our population was a predominantly young population with a mean age of 58.5 years, the youngest at 32 years, the oldest at 78 years, whereas it has been described those severe forms of the disease occur mainly in older people. Indeed, this relationship between diabetes and severe forms of COVID-19 is also due to a statistical association: the most severe forms or deaths are mainly seen in patients over 65 years of age, a population in which the prevalence of diabetes is high. It should be remembered that about a quarter of people over 75 have type 2 diabetes [7]. This means that severe forms of the disease affect not only the elderly but also young people. This can be explained by the demographic characteristics of the Malagasy popula-

tion which is predominantly young. In comparison with the literature, there is heterogeneity in the reported patient population: 3 Chinese studies reported the median age of hospitalized patients was between 47-56 years with narrow interquartile ranges of 43-60 in the Wu et al study, 35-58 in the Guan et al study, 46-67 in the Zhou et al study [8]. Nevertheless, it has also been pointed out that advanced age alone does not explain the factors of severity. A French retrospective observational study of ninety-seven patients with an average age of 52 years showed in univariate analysis that the factors associated with the passage to the intensive care unit were age (OR=1.03, IC95% [1.003 ; 1.058] p=0.05), male sex (OR=3.79, CI95% [1.55; 9.56] p=0.004), a history of hypertension (OR=2.67, CI95% [1.10 ; 6.89], p=0.03), as well as lymphopenia<1000c/mm3 (OR=6, 95% CI [2.45; 15.55] p<0.001) and CRP>100mg/L (OR=4.74, 95% CI [1.96; 12.03] p<0.001). In multivariate analysis, CT involvement greater than 50% of the parenchyma (OR=6.3 95% CI [2.08; 20.9] p=0.001), CRP>100mg/L (OR=4.2 95% CI [1.7 ; 10.8] p=0.002), and lymphopenia<1000c/mm3 (OR=5.3, 95% CI [2.1; 14.3] p<0.001) were associated with an age-independent risk of ICU admission [9].

Most of our patients were diagnosed with a severe form (45% n=42), and a critical form (30% n=28) with a blood glucose disorder. In univariate analysis, hyperosmolar coma was defined among factors associated with mortality. Almost all of the patients had a blood glucose disorder, and some patients presented complications such as ketoacidosis coma or hyperosmolar coma.We noted that a sizeable proportion of our diabetic patients (27%) were newly diagnosed as diabetics during hospitalization for COVID-19. Diabetes is known to be linked with several defects in immunity; it promotes increased synthesis of pro-inflammatory cytokines, oxidative stress, and stimulates adhesion molecules that mediate tissue inflammation [10]. Furthermore, some in vitro studies have shown that exposure of lung epithelial cells to high concentrations of glucose significantly increases influenza virus infection and replication, indicating that hyperglycemia may increase also in vivo SARS-COV 2 replications [11]. Angiotensin-converting enzyme 2 (ACE2) has been identified as a major receptor for SARS-COV 2 [12]. ACE2 is widely expressed in the airways, heart, kidneys, intestines, brain neurons, endothelium of arteries and veins, immune cells and pancreas [13]. A Chinese study comparing 39 SARS-CoV 2 patients without prior diabetes, who did not receive steroid treatment, with 39 matched healthy siblings showed that 20 of the 39 SARS-CoV 2 patients developed diabetes during hospitalization. As ACE2 are strongly expressed in pancreatic islets cells, it has been suggested that SARS-CoV 2 may have damaged the pancreatic islets cell and caused acute insulin-dependent diabetes [12,13].

Therefore, although further evidence is needed, it is plausible that SARS-CoV-2 may cause alterations in glucose metabolism that may complicate the pathophysiology of pre-existing diabetes or lead to new disease mechanisms. That means that pancreatic damage may also be present in COVID-19 patients, which may lead to diabetes explaining the high proportion of diabetic patients newly discovered during hospitalization. These pathophysiological mechanisms, indeed, explain the occurrence of severe forms in our patients and the incidental discovery of diabetes in some patients. Thus, systematic screening for diabetes is essential during the course of COVID-19, by prescribing systematically capillary blood glucose and glycated hemoglobin level, in order not to miss development of diabetes in these patients as this improves their management.

Regarding treatment, the treatment followed the national protocol and the updated recommendations on the management of COVID-19. The case fatality rate was 20%, which is not negligible, despite the treatment. The length of hospital stay was between 1-38days. Indeed, a retrospective cohort reported that diabetic complications had no effect on mortality but affect in the length of hospitalization [14].

In our study, there was no correlation between hyperglycemia and mortality. But in other study, the impact of hyperglycemia at the time of admission on prognosis was demonstrated in a single-center Italian study of 387 patients admitted for COVID-19 in Lombardy (Italy), 90 of whom had diabetes, with hyperglycemia being an independent predictor of mortality (adjusted hazard ratio [aHR] = 1.22 [CI95%: 1.04-1.44] per mmol/L) [15]. This association was not found in the CORONADO cohort, where the relationship between hyperglycemia on admission and risk of adverse outcome leading to death was no longer significant after multivariate analysis [16]. Finally, a retrospective data from a Chinese observational study of 7337 COVID-19 patients, 13% of whom were diabetic, supported a relationship between "correct" glycemia control during hospitalization (variability between 3.9 and 10 mmol/L versus > 10 mmol/L) and reduced mortality [17].

This study is limited as it was a retrospective monocentric study. But it has been able to give us insight of the difficulty of the management of COVID-19 especially in diabetic patients.

This study showed that diabetes is one of the risk factors for progression to severe disease or death in COVID-19 patients. Thus, diabetes screening should be routinely included in the management of the Covid-19 patient to improve their management. Screening allows for assessment of the patient's condition and early identification of patients at higher risk of mortality. Healthcare workers should pay special attention to diabetes during Covid-19 for a better management of patients.

CONCLUSION

Our study showed that diabetes is associated with a severe form of COVID-19 even in young patients.

Hyperosmolar coma and $SpO_2 \leq 90\%$ on admission are significantly associated to the mortality in diabetic patients with COVID-19. Thus, diabetes is considered as a factor of morbidity and mortality which should be screened in every COVID-19 patients to improve their management and prognosis. We highlight that diabetes should not be missed in COVID-19 patients. An early detection should be done during every hospitalization by prescribing capillary blood glucose and a glycated hemoglobin level in all Covid-19 patients. This measure should be included in the Covid-19 response for a better management of this disease.

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