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Original Research Article

Factors related to the death of diabetic patients with COVID-19 hospitalized in Joseph Raseta Befelatanana University Hospital in Antananarivo, Madagascar

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ABSTRACT

Background: Diabetes mellitus is associated with severe and even fatal forms of COVID-19. The objective of this study was to identify the factors linked to the death of COVID-19 diabetic patients in order to improve their care.
Methods: An analytical cross-sectional study was carried out in the endocrinology department of the Joseph Raseta Befelatanana University Hospital Center, Antananarivo, Madagascar. It has concerned all the cases of COVID-19 diabetics (162 patients) recorded from April 2020 to July 2021 (16 months).
Results: In our study, the case fatality rate of COVID-19 in diabetics was 14.49%. Significant factors related to death, after univariate analysis, were: vascular complications including nephropathy (OR=4.74), neuropathy (OR=5.38) and ischemic heart disease (OR=3.9), presence of other comorbidities (OR=9.02), dyspnea (OR=4.60), seizures (OR=6.22) or alertness disorder (OR=4.35), lower oxygen saturation (p=0.04), pleurisy (OR=4.67), signs of cardiac decompensation (OR=3.46), an elevated mean blood sugar level (p<0.001), leukocytosis (p=0.02) and thrombocytopenia (p<0.001), impaired renal function (p=0.02) and pleurisy on chest imaging (OR=5.29).
Conclusions: Death factors in diabetics with COVID-19 can be diverse. They do not only include the cardiovascular complications of the diabetes, but also a worse clinical respiratory presentation on the admission, a higher inflammatory syndrome, and a greater imbalance of blood sugar during the hospitalization.

Keywords: COVID-19, Death, Diabetes mellitus, Risk factors

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndromee Coronavirus 2 (SARS-COV$_2$) that appeared in China in December 2019 has claimed many victims to date.[1,2] Indeed, in September 2021, the WHO had recorded 222,208,048 confirmed cases worldwide, including 4,593,097 deaths.[2]

In Madagascar, the first cases were reported on 21 March 2020.[3] On 07 September 2021, we had 42,884 confirmed cases of COVID-19 and 957 deaths.[2]

Some studies have shown that mortality got higher with age, in masculine gender, and/or people with comorbidities including diabetes or cardiovascular, renal, respiratory diseases. Actually, diabetes mellitus is

associated with severe, rapidly worsening, even fatal forms of COVID-19.[5] Among the causes, from a pathophysiological point of view; diabetes, through chronic hyperglycemia, exacerbates inflammation caused by infection by releasing especially tumor necrosis factor alpha (TNF alpha) and interleukin 10 (IL_{10}).[6] In addition, microangiopathies related to diabetes in the pulmonary capillaries, by glycosylation of collagen from lung tissue, increase susceptibility to lung infections.[7]

Diabetes mellitus began to be screened in more and more people in Madagascar. The Association of Diabetes in Madagascar (AMADIA) recensed 37,000 Malagasy diabetics in 2019. The WHO recensed 6% of diabetics in the Malagasy population in 2016 which does not include the not declared ones.[8]

Diabetes mellitus is cited as one of the most frequent death risk factors during COVID-19. Meanwhile, among diabetics with COVID-19, in the literature, the presence of microvascular complications before admission, long-term anticoagulation, the complaint of dyspnea, high levels of C-reactive protein (CRP) and aspartate aminotransferase (AST) and hyperleukocytosis were significantly associated with death.[9]

However, only a few studies concerning this association between COVID-19 and diabetes have been carried out in Madagascar, to our knowledge. We then conducted this study to determine the factors related to the death of our diabetic patients with COVID-19.

METHODS

This was a retrospective cross-sectional study. This study was carried out in the endocrinology department of the Joseph Raseta Befelatanana University Hospital Center (CHUJRB). The study was carried out between 01 April 2020 and 31 July 2021 (16 months).

Selection criteria of the patients

Patients had to be over 15 years old, and hospitalized for COVID-19 confirmed either by the polymerase chain reaction (PCR) of the nasopharyngeal swab or by chest CT showing images in favor of $SARS\text{-}COV_2$ pneumonitis according to the radiological criteria of COVID-19 infection.

In addition, they had to be diabetics known or discovered during hospitalization by two fasting blood sugar ≥126 mg/dl, glycated hemoglobin (HbA1C) ≥6.5% or signs of hyperglycemia with a random blood sugar ≥200 mg/dl.

Exclusion criteria

Patients transferred and those discharged against medical advice were excluded.

Procedure

Our sample of patients for the study was exclusive. That is to say, we recensed all the patients with diabetes mellitus and COVID-19 hospitalized in the study place during the study period. There were 162 patients included. Among them, one hundred and thirty-eight (138) patients were retained for the study.

We divided the patients in two groups: the deceased and the survivors.

In each group, we recorded: socio-demographic data- the average age, the sex ratio, smoking, ethylism and decoction; clinical data- the type of diabetes, the duration of diabetes, the microvascular and macrovasular complications of diabetes, comorbidities, pre-hospital treatment, clinical symptoms on admission; biological data- the result of the complete blood count, CRP, serum creatinine, D-dimers, ultrasensitive troponin, HbA_1C, blood glucose at admission, minimal blood glucose, maximal blood glucose, mean blood glucose during the hospitalization; radiological data- interstitial syndrome, alveolar syndrome, bronchial syndrome, cavitary syndrome, pleurisy and extent of lung involvement; therapeutic data- oxygen therapy, corticosteroid therapy, azithromycin, amoxicillin, amoxicillin clavulanic acid, third generation cephalosporin, heparinotherapy.

We compared those data in deceased and surviving patients, in order to highlight which characteristic were linked to death.

To respect ethical principles, we respected the privacy of the patients. We used then a coding system to identify them.

Statistical analysis

The statistical analysis consisted in a description and comparison of the distribution of patients according to each variable studied in the 2 groups in order to draw the particularities in the deceased. The data were analyzed by Epi-Info® software version 7.2.2.6. The odds ratio (OR) was used as an association measure. It was retained as significant when it belonged to the 95% confidence interval (95% CI) and when value 1 did not belong to this interval. Statistical tests (Chi square, Fischer, ANOVA, and Mann-Whitney/Wilcoxon) were selected as significant for a p value <0.05.

RESULTS

Among the one hundred and sixty-two (162) diabetic patients hospitalized for COVID-19 included, one hundred and thirty-eight (85.18) were selected for the final comparative study, divided into 20 deaths (n_1) and 118 survivors (n_2) giving a case fatality rate of 14.49%.

Table 1: Distribution of patients by socio-demographic characteristics (N=138).

Characteristics	N (%)		OR	CI at 95%	P value
	Deceased (n_1=20)	Survivors (n_2=118)			
Average age (years)	61.65±9.96	58.5±11.17			0.23
Sex-ratio (M/F)	1.85 (13/7)	1.03 (60/58)	0.71	0.38-1.33	0.24
Smoking	1 (5)	13 (11.02)	0.45	0.06-3.28	0.69
Ethylism	3 (15)	11 (9.32)	1.60	0.49-5.26	0.43
Decoction	0 (0)	8 (6.78)	0	ND	0.60

ND: Not defined.

Table 2: Distribution of patients by the type of diabetes and its complications, comorbidities and pre-hospital treatments (N=138).

Characteristics	N (%)		OR	CI at 95%	P value
	Deceased (n_1=20)	Survivors (n_2=118)			
Type					
Type 2	19 (95)	110 (93.22)	1.38	0.16-11.69	0.76
Type 1	0 (0)	6 (5.08)	0	ND	0.59
Secondary	1 (5)	2 (1.69)	3.05	0.26-35.34	0.37
Duration					
Inaugural	3 (15)	23 (19.44)	0.72	0.20-2.70	0.76
Average duration of pre-existing diabetes (months)	112.71±79.83	92.23±107.15			0.45
Complications					
Microangiopathy	18 (90)	59 (50)	9	2-40.53	<0.001
Nephropathy	16 (80)	54 (45.76)	4.74	1.49-15.03	0.005
Neuropathy	8 (40)	13 (11.02)	5.38	1.86-16.61	<0.001
Retinopathy	5 (25)	17 (13.28)	1.98	0.64-6.16	0.23
Macroangiopathy	16 (80)	41 (34.75)	7.51	2.35-23.95	<0.001
Ischemic stroke	1 (5)	7 (5.60)	0.83	0.09-7.17	1.00
POAD	0 (0)	2 (1.69)	0	ND	1.00
Ischemic heart disease	12 (60)	30 (27.78)	3.9	1.45-10.48	0.005
Comorbidities					
All-round comorbidities	19 (95)	80 (67.8)	9.02	1.16-69.94	0.01
High blood pressure	17 (85)	83 (70.34)	2.39	0.66-8.68	0.18
Dyslipidemia	4 (20)	28 (23.73)	0.80	0.25-2.60	1.00
CKD	6 (30)	11 (9.32)	4.17	1.22-13.04	0.009
Heart disease	8 (40)	34 (28.81)	1.65	0.62-4.38	0.31
Stroke	2 (10)	8 (6.78)	1.53	0.30-7.78	0.64
Asthma	1 (5)	3 (2.54)	2.01	0.20-20.42	0.47
COPD	1 (5)	3 (2.54)	2.01	0.20-20.42	0.47
Tuberculosis	2 (10)	3 (2.54)	4.25	0.66-27.27	0.15
Liver disease	0 (0)	7 (5.93)	0	ND	0.59
Cancers	1 (5)	1 (0.85)	6.16	0.37-102.68	0.27
Pre-hospital treatment					
No antidiabetic drugs	5 (25)	38 (32.20)	0.73	0.28-1.89	0.52
Metformin	3 (15)	32 (27.12)	0.47	0.13-1.73	0.40
Sulphonylurea	6 (30)	47 (39.83)	0.65	0.23-1.80	0.40
DPP4 inhibitors	1 (5)	0 (0)	0	ND	0.14
Insulin	10 (50)	42 (35.59)	1.81	0.70-4.70	0.22
RAAS blockers	7 (35)	48 (40.68)	0.78	0.29-2.11	0.63
Calcium channel blockers	10 (50)	29 (24.58)	3.07	1.16-8.11	0.02
Beta-blockers	3 (15)	9 (7.63)	2.13	0.52-8.69	0.38
Diuretics	4 (20)	16 (13.56)	1.59	0.47-5.38	0.49
Central acting antihypertensive drugs	1 (5)	1 (0.85)	6.15	0.37-102.68	0.27

Continued.

Characteristics	N (%)		OR	CI at 95%	P value
Antiplatelet agent	2 (10)	5 (4.24)	2.51	0.45-13.93	0.27
Statin	1 (5)	8 (6.78)	0.72	0.08-6.12	1.00

POAD: Peripheral occlusive artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ND: not defined; DPP4: dipeptidyl peptidase-4; RAAS: renin angiotensin aldosterone system.

Regarding the socio-demographic characteristics, an older age was not significantly related to death even if he deceased were slightly older than survivors with respective average ages of 61.65±9.96 year sold and 58.5±11.17 years old respectively (p=0.23). Despite a more important sex ratio (men/women) in deceased, gender was not either a factor of death (Table 1).

Regarding comorbidities associated with diabetes, having at least one comorbidity was a risk factor of death (OR=9.02; 95% CI=1.16-69.94; p=0.01). Among the comorbidities, having a chronic renal failure (CKD) was the one which was associated to death (CKD) (OR=4.17; 95% CI=1.33-13.04; p=0.009). There were other more frequent comorbidities but they were not related to death: high blood pressure (OR=2.39; 95% CI=0.66-8.68; p=0.18), heart disease (OR=1.65; 95% CI=0.62-4,38; p=0.31) chronic obstructive pulmonary disease (COPD) (OR=2.01; 95% CI=0.20-20.42; p=0.47), asthma (OR=2.01; 95% CI=0.20-20.42; p=0.47), tuberculosis (OR=4.25; 95% CI=0.66 -27.27; p=0.15) and cancers (OR=6.16 95% CI=0.37-102.68; p=0.27) (Table 2) .

Concerning the characteristics of the diabetes, the type and the duration before the COVID-19 were not risk factors of death (Table 2). However, the notion of microangiopathy was significantly related to death (OR=9; 95% CI=2-40.53; p<0.001). Among these microangiopathies, the statistically significant ones were nephropathy (OR=4.74; 95% CI=1.49-15.03; p=0.005) and neuropathy (OR=5.38; 95% CI=1.86-16.61; p=0.0008). In addition, macroangiopathies were also related to death (OR=7.51; 95% CI=2.35-23.95; p=0.0001). The statistically significant macroangiopathy was ischemic heart disease (OR=3.9; 95% CI=1.45-10.48; p=0.005) (Table 2).

Table 3: Distribution of patients by clinical characteristics at admission (N=138).

Characteristics	N (%)		OR	CI at 95%	P value
	Deceased (n_1=20)	Survivors (n_2=118)			
Asthenia	18 (90)	101 (85.59)	1.51	0.32-7.13	1.00
Anorexia	6 (30)	49 (41.53)	0.60	0.22-1.68	0.33
Weight loss	1 (5)	13 (11.02)	0.42	0.05-3.44	0.69
Fever	11 (55)	58 (49.15)	1.26	0.49-3.27	0.63
Cough	15 (75)	69 (58.47)	2.13	0.73-6.25	0.16
Dyspnea	12 (60)	29 (24.58)	4.60	1.71-12.36	0.001
Chest pain	3 (15)	15 (12.71)	1.21	0.31-4.63	0.77
Anosmia, ageusia	0 (0)	7 (5.93)	0	ND	0.59
Cyanosis	0 (0)	2 (1.69)	0	ND	1.00
Rhinorrhea	2 (10)	24 (20.34)	0.43	0.09-2.01	0.36
Sore throat	0 (0)	8 (6.78)	0	ND	0.60
Headaches	3 (15)	25 (21.19)	0.65	0.18-2.42	0.76
Seizures	5 (25)	6 (5.08)	6.22	1.69-22.91	0.002
Alertness disorders	7 (35)	13 (11.02)	4.35	1.47-12.87	0.005
Functional impotence	1 (5)	6 (5.08)	0.98	0.11-8.62	1.00
Abdominal pain	0 (0)	19 (16.10)	0	ND	0.07
Diarrhea	2 (10)	24 (20.34)	0.43	0.09-2.01	0.36
Nausea, vomiting	2 (10)	19 (16.10)	0.58	0.72-2.70	0.74
Externalized hemorrhage	2 (10)	7 (5.93)	1.76	0.34-9.16	0.62
Arthralgia, myalgia	5 (25)	27 (22.88)	1.12	0.37-3.37	0.83
Duration of symptom progression (days)	11.9±7.11	15.64±8.92			0.08
Average oxygen saturation	85.9±9.36	90.43±6.70			0.04
Signs of respiratory distress	7 (35)	24 (20.34)	2.11	0.76-5.97	0.15
Condensation syndrome	13 (65)	77 (65.25)	0.99	0.37-2.67	0.98
Bronchial syndrome	1 (5)	4 (3.39)	1.5	0.16-14.15	0.55
Fluid pleural syndrome	4 (20)	6 (5.08)	4.67	1.19-18.35	0.04
Cardiac decompensation	6 (30)	13 (11.02)	3.46	1.13-10.57	0.02

Continued.

Characteristics	N (%)		OR	CI at 95%	P value
Meningeal syndrome	2 (10)	2 (1.69)	6.44	0.85-48.67	0.10
Neurological deficit	1 (5)	6 (5.08)	0.98	0.11-8.62	1.00
Dehydration	7 (35)	22 (18.64)	2.35	0.84-6.57	0.09
Signs of DVT	1 (5)	5 (4.24)	1.19	0.13-10.75	1.00

DVT: Deep vein thrombose

Regarding the pre-hospital treatment of patients, taking antidiabetic drugs regardless of the molecule had no significant association with death. For antihypertensive therapy, calcium channel blocker intake was related to death (OR=3.07; 95% CI=1.16-8.11; p=0.02) (Table 2).

Clinically, none of the general signs were death risk factors. The functional signs which were related to death were: dyspnea (OR=4.60; 95% CI=1.71-12.36; p=0.001), seizures, OR=6.22; 95% CI=1.69-22.91; p=0.002) and alertness disorder (OR=4.35; 95% CI=1.47-12.87; p=0.005). Regarding the respiratory examination, a lower average oxygen saturation was another death risk factor (p=0.04), and also the presence of fluid pleural effusion (OR=4.67; 95% CI=1.19-18.35; p=0.04). Unfortunately, it could not have been distinguished if the pleurisy was exudative or transudative because most of the patients could not afford the realization of the analysis. Among extrapulmonary signs, the presence of signs of cardiac decompensation was a death factor (OR=3.46; 95% CI=1.13-10.57; p=0.02) (Table 3). Biologically, the risk factors related to death were: a higher leukocyte level (p=0.02) and a lower platelet count (p<0.001), a worse renal status (p=0.02). Regarding CRP, it had returned higher for deceased patients but without significant difference (p=0.73). The level of D-dimers of the deceased versus the survivors were also not significantly different in both groups (p=0.23). In addition, HbA_1C was lower in the deceased, but it was not correlated with outcome (p=0.21) (Table 4).

Table 4: Distribution of patients by biological test results (N=138).

Characteristics	Deceased (n_1=20)	Survivors (n_2=118)	P value
Leukocytes (gm/l)	16.65±8.99 for 19 patients	10.68±5.7 for 115 patients	0.02
Lymphocytes (gm/l)	1.52±1.20 for 15 patients	1.73±1.14 for 95 patients	0.53
Hemoglobin (gm/dl)	11.67±3.95 for 19 patients	14.18±7.83 for 115 patients	0.08
Platelet (gm/l)	208.58±113.12 for 19 patients	339.14±140.55 for 115 patients	<0.001
CRP (mg/l)	71.03±67.07 for 19 patients	60.25±64.39 for 108 patients	0.73
Serum creatinine (µmol/l)	280±440.70 for 19 patients	135.7±134.64 for 112 patients	0.02
Estimated GFR (ml/min/1.73 m²)	53.53±33.52	73.32±34	0.02
D-dimers (ng/ml)	3167.75±3886.22 for 8 patients	3114.59±8087.41 for 61 patients	0.23
ultrasensitive troponin (ng/ml)	122±142.76 for 4 patients	27.37±42.76 for 43 patients	0.06
HbA_1c ()	7.72±0.87 for 5 patients	9.41±2.89 for 46 patients	0.21
Blood glucose at admission (g/l)	2.83±1.05	2.79±1.14	0.91
Minimal blood glucose (gm/l)	1.35±0.47	1.06±0.39	0.004
Maximal blood glucose (gm/l)	4.57±1.05	3.62±1.49	0.001
Mean blood glucose (gm/l)	3.14±0.71	2.20±0.63	<0.001

GFR: Glomerular filtration rate; HbA1c: glycated hemoglobin

Table 5: Distribution of patients by radiological examination results (N=138).

Characteristics	Deceased (n_1=20)	Survivors (n_2=118)	P value
Interstitial syndrome	15 (75)	77 (65.25)	1.6
Alveolar syndrome	5 (25)	22 (18.64)	1.45
Bronchial syndrome	4 (20)	12 (10.17)	2.21
Cavitary syndrome	3 (15)	2 (1.69)	10.23
Pleurisy	5 (25)	7 (5.93)	5.29
Extent of lung involvement	35.91±28.44%	35.59±24.12%	

Table 6: Distribution of patients by hospital treatment for COVID-19 (N=138).

Characteristics	Deceased (n_1=20)	Survivors (n_2=118)	P value
Oxygen therapy	17 (85)	73 (61.86)	3.49
Corticosteroid therapy	13 (65)	90 (76.27)	0.58
Azithromycin	12 (60)	88 (74.58)	0.51

Continued.

Characteristics	Deceased (n_1=20)	Survivors (n_2=118)	P value
Amoxicillin	0 (0)	2 (1.69)	0
Amoxicillin clavulanic acid	4 (20)	12 (10.17)	2.20
Third generation cephalosporin	16 (80)	79 (66.95)	1.97
Heparinotherapy	13 (65)	101 (85.59)	0.31

Regarding glycemic figures, mean blood glucose levels during hospital stay was related to death (p<0.001) (Table 4).

On chest CT scan, interstitial syndrome characterized by frosted glass opacity was most found in both groups, so, it was not related to death (OR=1.6; 95% CI=0.54-4.70; p=0.002). The mean extent of lesions was also approximately equal between the two groups and was therefore not correlated with patient outcome (p=0.97). Meanwhile, the cavitary syndrome (OR=10.23; 95% CI=1.59-65.16; p=0.02) and fluid pleural effusion syndrome (OR=5.29; 95% CI=1.48-18.78; p=0.005) were statistically related to death (Table 5).

Therapeutically, the need of oxygen therapy (OR=3.49; 95% CI=0.97-12.59; p=0.07), corticosteroid therapy (OR=0.58; 95% CI=0.21-1.59; p=0.28) and azithromycin (OR=0.51; 95% CI=0.19-1.27; p=0.18) were not death risk factors. However, a less prescription of heparin therapy was related to the issue (OR=0.31; 95% CI=0.11-0.90; p=0.02) (Table 6).

Regarding the length of hospitalization, it was not either indicated as a death risk factor (p=0.08).

DISCUSSION

The COVID-19 case fatality rate in diabetics found in our study was 14.49%. The French CORONADO study found a higher case fatality rate of 20.6%, as well as a study conducted at a major medical center in New York that recorded 33.31% of deaths among diabetics.[9,10] Their high case fatality rate could be explained by the difference in the periods studied. Their studies were carried out in 2020, when the disease was just beginning and there were not yet enough studies or enough experience with its management. In addition, we can also note the difference in terrain including the greater frequency of other comorbidities including especially obesity in their patients.[9,10]

Despite a more advanced mean age and a male predominance in deceased, age and gender were not related to death in our study, contrary to what has been found in several studies including CORONADO in France, and in other studies carried out in the United Kingdom.[9,11] These studies explain that the older the age is, the more the risk of death is multifactorial, due to comorbidities. And, concerning the male predominance of COVID-19 death in diabetics, the role of the converting enzyme receptor (ACE_2) found three times more in men than in women has been suggested.[12] The discrepancy of our results with theirs could be explained by the small size of our sample compared to theirs. We found that the presence of at least one other comorbidity all combined was significantly linked to death. These comorbidities could decompensate or worsen and lead to an adverse outcome for COVID-19 patients. Therefore, it is imperative to look for them in each diabetic patient admitted for COVID-19 and we must not forget to stabilize them in addition to the treatment of the infection. In our study, the CKD was a death risk factor. Indeed, CKD leads to an alteration of the immune system, by a dysfunction of T and B lymphocytes, making patients more prone to having a chronic inflammatory state and more susceptible to complications related to infection.[13] In addition, CKD, due to the decrease in both nephrotic capital and renal self-regulation, also predisposes to acute renal failure or acute kidney injury (AKI). Patients with CKD, especially if they develop AKI during their COVID-19, are at a greater risk of death than those without CKD. According to the literature, the relative risk of death for a patient in case of stage III AKI during COVID-19 is 3.8 times higher than the risk of the patient with stage III AKI without COVID-19.[14]

Our results are in agreement with those of the CORONADO study who had objectified a correlation between microangiopathy, macroangiopathy and mortality.[9] The presence of microangiopathy as retinopathy, nephropathy or neuropathy that are explored in diabetic patients, reflect the state of all microvessels alterations of the diabetic patient. The pulmonary capillaries could present also a microangiopathy, favouring the development of the lung infection and desaturation. This hypothesis had been tested in mice in which alveolar capillary lesions and interstitial fibrosis in the lungs were found.[15,16] Moreover, these vascular complications could also decompensate during COVID-19. In addition, for our country, given the socio-economic situation of the Malagasy population, health check-ups including screening for diabetes and these complications are carried out only during hospitalization. Most of the time, these complications would then only be found at an advanced stage and they would worsen the patient's prognosis because of their decompensation that the infection could induce. These diabetic macroangiopathies and microangiopathies are to be carefully sought by a rigorous clinical examination and paraclinical examinations if necessary because their management is an integral part of the treatment to prevent a poor outcome.

Our study did not consider the antidiabetic treatments as related to death. However, several studies had found lower mortality in patients taking metformin at admission, including the CORONADO study (OR=0.59; CI 95%=0.42-0.84), as well as a Chinese study conducted by Luo et al with a mortality rate of 2.5% in patients taking metformin compared to 12.3% in those who were not, with p=0.01.[9,17] Scheen reported from different studies the mechanisms of action of metformin causing a better prognosis including a better glycemic balance, a decrease in weight and insulin resistance, an anti-inflammatory action, the activation of phosphorylation of ACE_2 which will inhibit the penetration of the virus.[18] This superiority of metformin to limit deaths was not found in our study, probably because of the slightest frequency of prescription of this molecule in our patients. It may be related to complications already present, contraindicating the prescription.

For other treatments associated with antidiabetic drugs, our study found that calcium channel blocker prescriptions were related to death. In fact, for diabetic patients, renin angiotensin aldosterone system (RAAS) blockers are the first-line antihypertensives for better cardiovascular protection.[19] The deleterious or beneficial effect of converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor antagonists (ARBs II) during COVID-19 remains a highly controversial topic. However, studies tend to show that there is no reason to interrupt treatment with these molecules even in case of $SARS\text{-}COV_2$ infection, and that they may even be beneficial by blocking ACE_2 which is the $SARS\text{-}COV_2$ receptor.[9,20] We can then deduce that patients treated by calcium channel blockers had a more severe hypertension using dual calcium channel blocker therapy and RAAS blockers, or severe complications, contraindicating the use of RAAS blocker such as renal failure which is the most common comorbidity in our deceased patients.

Regarding clinical signs, the notion of dyspnea, seizures and alertness disorder as well as lower oxygen saturation in the ambient air, and the presence of fluid pleural effusion syndrome were positively associated with death. This positive association with dyspnea was found in both the Coronado et al study, and the Chinese study.[9,21] Dyspnea can be multifactorial: pulmonary, metabolic and especially cardiovascular etiologies. It was the most frequent sign found in deceased diabetic patients testifying to the importance of lung involvement, reflected by the significantly lower oxygen saturation with an average of 85% in our deceased patients versus 90% in our surviving patients.

In addition, pleurisy was positively correlated with death. It could be reactive to lung infection or be related to cardiac decompensation or other comorbidity decompensating with an edematous or anasarca condition. Regarding neurological signs during COVID-19, it has been established that the presence of an alteration in neurological status is more objectified in severe forms. Seizures and confusion were more common in our deceased patients. According to Meippel et al, these neurological symptoms are mainly related to a specific encephalopathy associated with COVID-19, cerebral infarctions and more rarely to encephalitis, causing a poor prognosis.[22] Regarding biological examinations, as death risk factors, a significantly higher average white blood cell count and a significantly lower average platelet count, were objectified to the complete blood count. Similar results were found by the CORONADO study.[9] These results would suggest the presence of a greater inflammatory response to COVID-19 infection as well as a greater frequency of bacterial superinfection in the deceased.[21] In addition, thrombocytopenia is often considered an indicator of sepsis severity, which would also appear to be the case during $SARS\text{-}COV_2$ infection.

As mentioned above, chronic renal failure was the comorbidity related to death. Therefore, a worse renal status was also a death factor. Furthermore, this kidney function could deteriorate even more acutely during the course of infection. Regarding CRP and D-dimer levels, in our study, they were not correlated with death. However, they were death factors in the CORONADO study and the study conducted in China.[9,21] In fact, D-dimers are one of the main biological sign of thrombo-embolic events which makes it logically a death factor for several studies.[23] Unfortunately, our results were not really representative of the general population concerning this item. First, the realization of biological analysis, especially D-dimers was not possible for most of the patients due to financial issues. Then, for those who could do them, the moment of realization was different. Some did their analysis earlier after admission, and some did it later.

A higher average blood sugar during hospitalization was a death risk factor. Li et al had found that blood glucose on admission was a predictor of mortality. From a blood sugar level of 4 mmol/l, there would be a 1.17-fold increase in the risk of mortality for every 1 mmol/l (0.18 gm/l) of blood sugar. This indicates the need to balance blood sugar levels as quickly as possible during hospitalization to reduce risk.[24] For our deceased patients, by referring to the average blood glucose levels, we can deduce that blood glucose during hospitalization remained high in the deceased patients. In fact, this chronic hyperglycemia is reported to exacerbate inflammation by increasing the release of tumor necrosis factor α (TNFα) and interleukin (IL)-10. Besides, it also causes an imbalance in immune system.[6] That contributed to the poor outcome. Regarding the glycemic balance reflected by HbA_1C, it was not associated with death in our study. The same was true for studies carried out in Europe and China.[9,21] Yet in the Open safely study, the higher the HbA_1C was, the greater the risk of death was.[25] The mean HbA_1C is difficult to interpret in our study because only few patients had been able to perform the dosage. Moreover, there are several factors that can make

the interpretation of this dosage erroneous including: blood transfusion, hemoglobinopathies, anemia, acidosis, and renal failure.[26]

Concerning the pulmonary radiological examination, the presence of fluid effusion was positively correlated with death as previously described in the clinic. In addition, the extent of chest CT lesions was not related to the death of COVID-19 diabetic patients. In fact, CT scan was done at the admission whereas the lung lesions could progress during the hospitalization. Besides, the causes of death were not limitated in respiratory distress.

Therapeutically, a less use of heparin therapy was a death factor. According to the literature, there is a high risk of venous thromboembolic disease in COVID-19.[27] And other authors had also found an increased risk of venous thromboembolic diseases in diabetics.[28] These arguments could justify the best prognosis in patients on anticoagulants in our study. Moreover, in the Malagasy protocol, we need to prescribe anticoagulation for people with desaturation, which means with a severe COVID-19. Those who did not receive that treatment were then exposed to a worse outcome. In addition, in China, a greater proportion of deceased patients received corticosteroid therapy compared to survivors.[21] Glucocorticoids have a hyperglycemic effect, while hyperglycemia increases the risk of death.[24,29] However, the difference was not found in our study given the size of our sample, but also probably the difference in molecules used. In fact, the corticosteroid therapy of our patients was exclusively dexamethasone while the recommendations in developed countries as cited in the recovery study suggested different molecules including dexamethasone, hydrocortisone, prednisolone, and methylprednisolone.[30]

It must be recognized that our study had several limitations. First of all, the study place involved only one department while several cases of COVID-19 in diabetics were hospitalized in other places, in addition to those who were followed on an outpatient or at home. Second, a lot of data, especially paraclinical data, were not available due to a lack of resources, especially financial, to carry them out.

CONCLUSION

The present study identified the different characteristics that differed between diabetic patients with COVID-19 who died and who survived. Thus, in order to improve management, we suggest always looking for the comorbidities associated with diabetes in these patients with COVID-19 and treating them well, but not only treating infection and glycemic disorders. The same applies to the vascular complications of diabetes, which should also always be detected and treated. In addition, the clinical examination of patients must be complete and thorough since COVID-19 can have multisystemic manifestations. But still, the availability of the necessary paraclinical examinations in public hospitals should be improved and their access for all the financial categories should be facilitated. Finally, we must not forget that COVID-19 is a disease leading to thrombosis that seems to be favored by the diabetic terrain according to the literature. So, we must not only treat the infection but we must prevent and treat these thromboembolic events.

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