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Biological Factors Associated with Poor Prognosis in Type 2 Diabetic Patients with COVID-19 in Pointe Noire

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Abstract **Original Research Article**

Introduction: There has been growing interest in the biological interactions between diabetes and COVID-19, particularly because of the serious implications associated with the coexistence of these two medical conditions. ***Objective***: The aim of this study was to identify poor biological prognostic factors in type 2 diabetic patients with COVID-19 in Pointe-Noire. ***Methods***: We recruited a total of 206 participants for this study. Detailed information on age, gender, and health status of participants was collected from medical records. Biomarkers were quantified from blood samples and sars cov-2 virus was identified using the PCR technique on nasopharyngeal swabs. ***Results***: The mean age was 56.33 ± 12 years with extremes ranging from 30 to 82 years and the majority of patients were male (70%), with a sex ratio of 2.37. Multivariable analysis showed that poor prognosis was significantly influenced by 14 biological parameters NPC: OR 1,09(1.09-1.10) p<0.001, BPNC: OR 1,72(1.70-1.74) p<0.001, Lympho: OR1,09(1.08-1.09) p<0.001, Mono: OR 1,07(1. 07-1.08) p<0.001, VS: OR 1,91(1.84-1.97) p<0.001, GOT: OR 1,10(1.06-1.15) p<0.001, DDI: OR 1,01(1.01-1.01) p<0. 001, Na+ : OR 515(383-694) p<0.001 Creat: OR 19.1(15.5-23.4) p<0.001, AU: OR 1.52(1.41-1.63) p<0.001, APTT: OR2 1.67(1.33-2. 09) p<0.001, TG/hdl: OR2 1.78(1.48-2.13) p<0.001, CK-MB: OR 1.37(1.17-1.59) p<0.001, Ct-Egene: OR 113.2(64.12-221.15) p<0.001. ***Conclusion*:** This study showed that poor prognosis was significantly influenced by NPC, BPNC, Lympho, Mono, ESR, GOT, DDI, APTT, Na+ Creat, AU, TCA, TG/hdl, CK-MB, Ct-Egene indicative of multivisceral failure in COVID-19 positive type 2 diabetics.

Keywords: Biological factors, type 2 diabetes, poor prognosis, covid-19.

INTRODUCTION

Type 2 diabetes (T2DM) is a chronic disease characterised by insulin resistance and pancreatic beta-cell dysfunction, leading to chronic hyperglycemia (Tenenbaum *et al*., 2018). Complications of T2DM can affect many organs and systems in the body, and people with the disease have an increased risk of developing cardiovascular disease, kidney failure, retinopathy, among other complications (Doumbia, 2019; Redjem and Douichine, 2022).

COVID-19, caused by SARS-CoV-2, is an infectious disease that has led to a global pandemic since 2019. Symptoms of infection vary widely, from no symptoms to severe or fatal illness (De Greef *et al*., 2020).

The presence of diabetes has been identified as an independent factor associated with a poor prognosis in recent coronavirus infections, such as severe acute respiratory syndrome (SARS-CoV-1) in 2003 (Yang JK *et al*., 2006), and Middle East respiratory syndrome

(MERS-CoV) in 2012 (Alraddadi BM *et al*., 2016). Very soon after the onset of the SARS-CoV-2 coronavirus 2019 (COVID-19) pandemic, comorbidities, including diabetes, again emerged as associated with severe forms of COVID-19. People with diabetes mellitus are associated with an increase in the severity and mortality of the infection compared with people without diabetes: 2.12 times mortality, 2.45 times severe COVID-19, 4.64 times ARDS and 3.33 times disease progression (J. Jing Yanga *et al*., 2020). Acute metabolic complications such as diabetic ketoacidosis and hyperosmolarity are common either in new cases of diabetes or in known diabetics. Factors influencing the prognosis of the infection include poor glycemic control aggravated by COVID-19-induced insulin resistance, co-morbidities such as obesity and hypertension, and the presence of cardiovascular and renal complications. In addition, the "cytokine storm" can induce multi-visceral failure in diabetics. (Rachid Malek *et al*., 2020).

The interaction between diabetes and COVID-19 represents a crucial area of research, particularly with regard to the mechanisms by which diabetes can aggravate the symptoms of the disease. By integrating this research, it becomes essential to explore in depth the biomedical implications of the relationship between diabetes and COVID-19 in order to better guide prevention and treatment strategies.

The aim of this study was to identify the biological factors associated with poor prognosis in Congolese type 2 diabetic patients with COVID-19.

MATERIAL AND METHOD

- Study Population

We conducted a descriptive cross-sectional study with prospective data collection. The study took place from September 2021 to August 2022, a period of 12 months. The study population consisted of D2T patients with COVID-19 hospitalized at the Guenin and Louise Michel clinics and the Adolphe Sicé General Hospital in Pointe-Noire.

Clinical survey: Data such as age, sex, clinical outcome were collected from medical records.

Biological survey:

Laboratory analyses were performed in the Biomedical Analysis Laboratory HDL of the Polyclinic Foundation Marie Madeleine Gombes in Pointe noire.

1) Sampling:

- Blood samples were taken in EDTA, heparinised and citrated tubes and stored at -20°C until use.
- Nasopharyngeal swabs were taken using the virus collections and transport kit type citoswab (W/3ML VTM) supplied by CITOTEST LABWARE MANUFACTURING CO. LTD Haimen city 226100, China.

2) **Blood biomarker analysis:**

The Cobas C 311 automatic biochemistry analyzer (Roche Diagnostics, HITACHI, Germany) was used for biochemical analyses: Fasting blood glucose (Glees); Glycated hemoglobin (HbA1c);Creatinine (Creat);Urea; Uric acid (AU); Lactate dehydrogenase (LDH); D-dimers (DDI); Ultra-sensitive C-reactive protein (CRP us); Transaminases (GOT,GPT); Gamma Glutamyl Transferase (GGT); Lipid profile (TC, TG, HDL, LDL); Blood ionogram (Na+, K+ and Cl-); Creatine phosphokinase(CPK); Creatine phosphokinase-MB (CPK-MB); Lactate dehydrogenase (LDH).

The Sysmex XP-300 instrument was used to perform the following blood counts: white blood cell (WBC), neutrophilic polymorphonuclear cell (NPC), eosinophilic polymorphonuclear cell (EPNC), basophilic polymorphonuclear cell (BPNC), lymphocyte (lympho), monocyte (mono): Haemoglobin (Hb) and Platelets (Plqt).

Hemostasis tests were performed using the Stago - STart® Hemostasis Analyzer: Activated partial thromboplastin time (APTT) and Prothrombin rate (PT). Sedimentation Rate (ESR): was carried out using the westerngreen method.

3. Molecular Analysis

a) Extractions

We extracted RNA from nasopharyngeal secretions using the Total RNA Purification Insert PI12200-37 kit, Norgen Biotek Corp (CANADA) in accordance with the manufacturer's recommendations.

b) Amplifications

The extracted RNAs were subjected to PCR using the Covid-19 TaqMan RT-PCR Kit (E/RdRP genes) from Norgen Biotek Corp (CANADA).

Procedure:

- First step: Mix preparation

- 10µl molecular biology water (nuclease free water)
- 1.5 µl Enzyme
- 3.5 µl ddH2O
- 5µl total RNA

- Second step: programming of the Mic thermocycler: total duration 1H36 min 18 sec

The amplification parameters were as follows: initial reverse transcriptase at 50°C for 20 minutes, then denaturation at 95°C for 03 minutes followed by 45 cycles of denaturation at 95°C for 15 seconds and 30 seconds of hybridization at 58°C.

- Choice of fluorochromes and targets:
- FAM (E-gene)
- HEX (Internal Control)

- Result is expressed as E-gene Ct: Cut of target E SARSCOV2 gene

Ethical Considerations

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved under number 125/CERS/FMMG-2021/PNR by the Health Research Ethics Committee (CERS) of the Marie Madeleine Gombes Foundation in Pointe Noire.

Statistical Analysis

The categorical data are expressed in numbers (percentage). The $\chi 2$ test was used to compare categorical data. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were conducted using SPSS software (version 26.0; IBM).

RESULTS

Table 1 shows that the study population consisted of 206 T2DM subjects, 70% (145) of whom were male and 30% (61) female. The mean age was 56.33 ± 12 years, with extremes ranging from 30 to 82 years. The clinical course showed that only 26% of our population had died.

Table 2 shows significant changes in biomarkers, mainly in subjects with a poor prognosis. There was also a statistically significant difference ($p<0.05$) in 23 out of 34 biomarkers between cured and deceased subjects.

The biological data for the univariable and multivariable analyses were integrated into a multiple logistic regression model to obtain the results shown in Table 3, where poor prognosis was significantly influenced by 14 parameters: PNN, PNB, Lympho, Mono, VS, GOT, DDI, Na+, Creat, AU, TCA, TG/hdl, CK-MB, Ct-Egene, compared between the cured and deceased groups.

Table 1: Description of the study population

Variables	Number (n)	Frequency (%)
Gender		
Male	145	70
Female	61	30
Clinacal course		
Cured	160	73,78
Died	46	26,21

Table 2: Biological profile of the study population

Characteristic	Cured,	Died,	Difference	95% CI	p
	N = 160	N = 46			
WBC (x103/mm3)	10,270 ±7,095	13,145 ±8,888	-2,876	-5,295, -456	0.020
Hb(g/dL)	12.66 ±2.21	11.71 ±2.01	0.94	0.35, 1.5	0.002
NPC (x103/mm3)	8,340 ±6,607	11,135 ±8,464	-2,795	-5,089, -501	0.017
EPNC (/mm3)	33 ±54	57 ±66	-23	-42, -5.4	0.011
BPNC (/mm3)	31 ±54	44 ±71	-14	-33, 5.4	0.2
Lympho(x103/mm3)	1,257 ±646	1,287 ±668	-30	-220, 160	0.8
Mono(x103/mm3)	524 ±346	635 ±418	-111	-226, 3.4	0.057
Plqte(x103/mm3)	226,964 ±123,665	255,512 ±140,110	-28,548	-67,523, 10,428	0.15
ESR(/mm3)	35 ±31	69 ±45	-35	-70	<0.001
CRP(mg/L)	170 ±82	265 ±110	-95	-189	<0.001
GLY(g/L)	2.26 ±0.94	2.87 ±1.12	-0.61	-0.92, -0.30	<0.001
HBA1c (%)	7.87 ±1.85	9.98 ±1.86	-2.1	-2.6, -1.6	<0.001
GPT(U/L)	47 ±20	80 ±55	-33	-66	<0.001
GOT(U/L)	58 ±30	75 ±31	-17	-26, -8.4	<0.001
GGT(U/L)	48 ±31	61 ±28	-13	-21, -4.6	0.003
LDH(U/L)	268 ±150	390 ±142	-122	-243	<0.001
DDI(µg/L)	1,898 ±1,611	5,310 ±4,095	-3,412	-4,440, -2,384	<0.001
TP(sec)	86 ±12	76 ±17	9.1	4.6, 14	<0.001
TCA (%)	29 ±8	28 ±8	0.13	-2.2, 2.5	>0.9
Na^+ (mmol/L)	139.2 ±5.9	139.1 ±4.3	0.11	-1.3, 1.5	0.9
K^+ (mmol/L)	4.28 ±0.65	4.70 ±0.88	-0.42	-0.66, -0.19	<0.001
CL^- (mmol/L)	101.8 ±3.9	101.2 ±4.1	0.53	-0.63, 1.7	0.4
Créat(mg/L)	12 ±5	21 ±18	-8.6	-13, -4.1	<0.001
Urée(g/L)	0.45 ±0.54	0.67 ±0.57	-0.22	-0.38, -0.06	0.009
AU(mg/L)	51 ±14	51 ±14	0.43	-3.6, 4.5	0.8
CholT(g/L)	2.18 ±0.54	2.18 ±0.40	0.01	-0.12, 0.13	>0.9
HDL(g/L)	0.45 ±0.20	0.48 ±0.40	-0.03	-0.13, 0.08	0.6
TG(g/L)	1.77 ±0.96	1.89 ±1.26	-0.12	-0.46, 0.22	0.5
CHOLT/hdl	6.1 ±3.6	7.5 ±4.8	-1.3	-2.6, -0.04	0.044
TG/hdl	4.5 ±3.6	7.4 ±8.3	-2.9	-5.0, -0.80	0.007
CPK(U/L)	71 ±33	119 ±94	-48	-97	<0.001
CKMB(U/L)	1 ±1	8 ±14	-7.1	-11, -3.7	<0.001
SPO2 (%)	93 ±4	87 ±7	5.8	3.9, 7.7	<0.001
Ct-E gene	26.8 ±5.0	18.2 ±3.5	8.6	7.4, 9.7	<0.001

Table 3: Univariate and multivariate logistic regression analysis of risk factors where death is the explanatory variable

Characteristic	univariable			Multivariable		
	OR[2]	95% CI	p	OR[2]	95% CI[2]	p
WBC	1.00	1.00, 1.00	0.071	0.92	0.91, 0.92	<0.001
Hb	0.78	0.66, 0.90	0.001	0.00	0.00, 0.00	<0.001
NPC	1.00	1.00, 1.00	0.059	1.09	1.09, 1.10	<0.001
EPNC	1.01	1.00, 1.01	0.027	0.87	0.86, 0.89	<0.001
BPNC	1.00	1.00, 1.01	0.2	1.72	1.70, 1.74	<0.001
Lympho	1.00	1.00, 1.00	>0.9	1.09	1.08, 1.09	<0.001
Mono	1.00	1.00, 1.00	0.056	1.07	1.07, 1.08	<0.001
Plqte	1.00	1.00, 1.00	0.14	1.00	1.00, 1.00	<0.001
ESR	1.02	1.01, 1.03	<0.001	1.91	1.84, 1.97	<0.001
CRP	1.01	1.01, 1.01	<0.001	0.71	0.70, 0.72	<0.001
GLY	1.87	1.38, 2.60	<0.001	0.00	0.00, 0.00	<0.001
HbA1c	2.00	1.61, 2.60	<0.001	0.91	0.49, 1.72	0.8
GPT	1.02	1.01, 1.03	<0.001	1.00	0.96, 1.05	0.9
GOT	1.02	1.01, 1.03	<0.001	1.10	1.06, 1.15	<0.001
GGT	1.01	1.00, 1.03	0.011	0.85	0.80, 0.89	<0.001
LDH	1.01	1.00, 1.01	<0.001	0.95	0.95, 0.96	<0.001
DDI	1.00	1.00, 1.00	<0.001	1.01	1.01, 1.01	<0.001
Na^+	0.98	0.92, 1.04	0.5	515	383, 694	<0.001
K^+	1.93	1.28, 2.97	0.003	0.77	0.33, 1.80	0.5
CL^-	0.96	0.88, 1.04	0.4	0.00	0.00, 0.00	<0.001
Créat	1.09	1.04, 1.15	<0.001	19.1	15.5, 23.4	<0.001
Urée	1.92	1.10, 3.53	0.028	0.00	0.00, 0.00	<0.001
AU	1.00	0.98, 1.02	0.9	1.52	1.41, 1.63	<0.001
CholT	0.83	0.43, 1.61	0.6	0.00	0.00, 0.00	<0.001
HDL	1.24	0.42, 3.60	0.7			
TG	1.15	0.85, 1.56	0.4			
TP	0.95	0.93, 0.98	<0.001	0.92	0.86, 0.99	0.024
TCA	1.00	0.96, 1.04	>0.9	1.67	1.33, 2.09	<0.001
Cholt/hdl	1.08	1.00, 1.16	0.058			
TG/hdl	1.11	1.04, 1.20	0.004	1.78	1.48, 2.13	<0.001
CPK	1.01	1.01, 1.02	<0.001	0.84	0.83, 0.86	<0.001
CKMB	2.48	1.45, 4.90	0.004	1.37	1.17, 1.59	<0.001
SPO2	0.83	0.77, 0.89	<0.001	0.00	0.00, 0.00	<0.001
Ct-Egene	0.58	0.45, 0.70	<0.001	119,181	64,119, 221,527	<0.001

DISCUSSION

COVID-19, caused by the SARS-COV-2 coronavirus, has led to a pandemic and has had a major impact on public health worldwide (Huang *et al*., 2020). Pointe-Noire, a coastal city in the Republic of Congo, has not been spared from this health crisis. Among the populations affected by COVID-19, T2DM patients were identified as a high-risk group due to the increased complications and mortality observed.

In our study, men predominated 145 (70%) compared with women 61 (30%), with a sex ratio (M/F) of 2.37. These data are consistent with several studies conducted worldwide (Louhaichi S *et al.*, 2020; Ketfi A *et al.*, 2020). This male predominance is thought to be due to the cumulative effect of risk factors for the severity of COVID-19, such as smoking, in the male population compared with the female population (Plaçais L *et al*., 2020).

The mean age of the participants was 56.33 ± 12 years. These results are consistent with those published in the study conducted by Wang *et al*., in 2020 and Chen *et al*., in 2019. On the other hand, the Guan *et al*., study found a mean age of 47 years lower than our study. The mean age observed in our study shows that T2DM is a disease of adults despite the relative youth of the population.

The clinical course showed 26.21% of deaths in our study population. A WHO analysis revealed that COVID-19 is four times more lethal in people with diabetes in Africa than it is in non-diabetic Africans (Ipouma *et al*., 2021). Worldwide epidemiological data shows that patients aged between 50 and 64 were 25 times more likely to suffer complications (CDC, 2020), as well as increased severity and mortality.

Multivariable analysis shows that poor prognosis is significantly influenced by 14 biological

parameters in this study PNN, PNB, Lympho, Mono, ESR, DDI, TCA, CK-MB, GOT, Na+, Creat, AU, TG/hdl and Ct-Egene:

Our results on inflammatory and infectious markers: NPC: OR 1,09 IC 95% (1.09-1.10) p<0.001, BPNC OR 1,72(1.70-1.74) p<0.001, Lympho OR 1, 09 IC 95% (1. 08-1.09) p<0.001, Mono OR 1,07 IC 95% (1.07-1.08) p<0.001 and ESR OR 1,91 IC 95% (1.84-1.97) corroborate with those of several studies (Wu C *et al*., 2020; Lu J, Hu S, Fan R, *et al*., 2020; Chen M *et al*., 2020) where they have been designated as predictive of severe forms and/or death.

Hemostasis data, DDI OR 1, 01 95% CI (1.01-1.01) p<0.001 and APTT OR 1, 67 95% CI (1.33-2.09) p<0.001 show that alterations in hemostasis and the resulting state of hypercoagulability are associated with a significant increase in thrombotic complications and a poor prognosis (Li Z *et al*., 2020). The excessive inflammatory response induced by the presence of SARS-COV-2 in the body. This inflammatory response in turn induces disseminated intravascular coagulation (DIC). This state of "hypercoagulability", essentially involving a marked rise in D-dimer levels, is associated with an accumulated risk of death. (Mezalek Z. Tazi *et al*., 2021).

CK-MB OR 1, 37 95% CI (1.17-1.59) p<0.001 and GOT OR 1, 10 95% CI (1.06-1.15) p<0.001, their disruption is a sign of multi-organ failure in the context of COVID-19. Studies suggest that higher levels of CK-MB may be linked to more severe cases of COVID-19 and could be associated with complications such as liver damage and pneumonia. Elevated levels of CK-MB may also be associated with an increased risk of mortality in patients with COVID-19 (Jia-Sheng Yu *et al*., 2020). The increase in GOT, a tissue enzyme (heart, liver, lungs, kidneys, etc.) has been described as a factor associated with severe forms of COVID-19 in the work of Chen M *et al*., 2020.

Our results of Na^+ OR 515 95% CI (383-694) p<0.001, Creat OR 19, 1 95% CI (15, 5-23.4) p<0.001, UA OR 1, 52 95% CI (1.41-1.63) p<0.001 and TG/hdl OR 1.78(1.48-2.13) p<0. 001, justify that disturbances in sodium and creatinine levels, uric acid and metabolic balance in diabetic patients with COVID-19 may have prognostic implications. COVID-19 can have an impact on renal function, leading to acute kidney injury and disturbances in electrolyte levels (Benedetti C *et al*., 2020).

Our results on viral load, Ct-Egene: OR 113.2(64.12-221.15) p<0.001 indicate that the viral load of COVID-19 can indeed have an impact on clinical prognosis. Studies show that a higher viral load in the lungs at the time of ventilation is correlated with an increased risk of death (Gagandeep Brar *et al*., 2020).

COVID-19 can cause cardiovascular complications or deterioration of coexisting cardiovascular disease through direct or indirect mechanisms, including viral toxicity, renin-angiotensin-aldosterone system (RAAS) deregulation, endothelial cell damage and thrombo-inflammation, cytokine storm and oxygen supply (Rachid Malek *et al*., 2020).

CONCLUSION

This study showed that poor prognosis was significantly influenced by NPC, BPNC, Lympho, Mono, ESR, GOT, DDI, APTT, Na+ Creat, AU, TCA, TG/hdl, CK-MB, Ct-Egene indicating multivisceral failure in COVID-19 positive Congolese type 2 diabetics.

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