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**Original Research Article**

# Profile of MicroRNAs in Type 2 Diabetic Patients Positive for COVID-19 in Nasopharyngeal Secretions in Pointe-Noire

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**Abstract:** ***Introduction***: The COVID-19 pandemic has had a disproportionate impact on people with certain underlying conditions, including type 2 diabetes (T2D). It is therefore essential to identify biomarkers such as microRNAs allowing patient stratification and thus contributing to better care. ***Objective*:** This study aimed to analyze the profile of microRNAs in type 2 diabetic patients with COVID-19 in nasopharyngeal secretions in Pointe-Noire. ***Methods*:** We recruited a total of 206 participants for this study. Detailed information on participants' age, gender, body mass, and health status was collected from medical records. MicroRNAs were quantified from the nasopharyngeal samples using qPCR. The study consisted of researching 17 microRNAs. ***Results*:** The majority of patients were men (70.39%), aged 40 – 69 years (77.69%) and obese (66.02%). Severe symptoms (67%) of COVID-19 and comorbidities (57.77%) were more common. The area under the ROC curve (AUC) was calculated to analyse the prognostic performance of microRNAs associated with a COVID-19+DT2 microRNA hsa-miR-33a-5p (AUC 0.85; CI 0.75 to 0.95 and p<0.000) and hsa-miR-486-5p (AUC 0.93; CI 0.85 to 1.00 and p<0. 000) were significant predictors of mortality and three hsa-miR21-3p (AUC 0.90; CI 0.83 to 0.98 and p<0.000), miR33b-5p (AUC 0.83; CI 0.72 to 0.94 and p<0.000) and miR29a-5p (AUC 0.85; CI 0.76 to 0.94 and p<0.000) as biomarkers predicting cure. ***Conclusion***: This study showed that hsa-miR33a-5p, hsa-miR486-5p, hsa-miR21-3p, has-miR33b-5p and miR29a-5p in nasopharyngeal secretions with excellent discrimination could be used as prognostic biomarkers in subjects with covid-19 in the context of type 2 diabetes.

**Keywords:** COVID-19, Type 2 Diabetes, MicroRNA.



## INTRODUCTION

Type 2 diabetes (T2DM), also known as non-insulin-dependent diabetes, is the most common form of diabetes, accounting for around 90% to 95% of cases **(Zimmet *et al.*, 2001).** It usually develops in adults, but can also appear in children and adolescents **(Dabelea *et al.*, 2014)**. In T2DM, the body's cells become resistant to the action of insulin, meaning that they are unable to effectively use the insulin produced by the pancreas **(DeFronzo *et al.*, 2015).** In response to this insulin resistance, the pancreas may increase its insulin production to compensate, but at some stage it may no longer be able to maintain adequate insulin levels, leading to hyperglycemia.

Complications of T2MD can be serious and affect various organs and systems of the body, such as the eyes (diabetic retinopathy), kidneys (diabetic

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nephropathy), nerves (diabetic neuropathy), heart and blood vessels (cardiovascular disease), and feet (ulcers and amputations). T2DM presents a complex association with other medical conditions, such as covid-19 infection. Covid-19, caused by the coronavirus SARS-CoV-2, has caused a global pandemic and has significantly impacted public health globally **(Huang *et al.*, 2020).** A WHO analysis found that COVID-19 is four times more deadly among people with diabetes in Africa than it is for Africans without diabetes **(Ipouma *et al.*, 2021).**

Pointe Noire, a coastal town in the Republic of Congo, has not been spared this health crisis. Among the populations affected by covid-19, type 2 diabetic patients have been identified as a group at high risk of increased complications and mortality.

It is therefore essential to understand the specific molecular mechanisms linking T2DM and covid-19. It is therefore crucial to understand the distribution of microRNAs in this explosive cocktail.

MicroRNAs are defined as small single-stranded non-coding RNA molecules 21-23 nucleotides in length that bind to the target transcript in the 3' untranslated region (UTR), inhibiting protein translation and destabilizing their target messenger RNAs (mRNAs). MicroRNAs can regulate almost a third of the human genome and are widely implicated in multiple pathways, such as cell proliferation, cell death, cell proliferation and cell death, stress resistance and fat metabolism. Furthermore, evidence suggests that a gain or loss of function of one or more microRNAs is associated with the diagnosis, progression and prognosis of several diseases. Consequently, deregulated microRNAs, in addition to serving as biomarkers of disease **(Nicoletti, Ad *et al.*, 2022),** may constitute potential therapeutic targets enabling a better understanding of the signaling pathways involved and the pathogenesis of disease.

In this context, the identification of biomarkers allowing a better stratification of D2T patients infected with SARS-CoV-2 at risk of developing severe consequences is of paramount importance for personalised healthcare.

The aim of this study is to analyse the MicroRNA profile of covid-19 positive type 2 diabetic patients in nasopharyngeal secretions in Pointe Noire.

# 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, BMI, covid-19 symptoms and comorbidities 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. Samples**

Nasopharyngeal swabs were taken by gently pushing the swab deep into the nostril (as far as the nasopharynx: approximately half the length from the nose to the ear) and detaching as many cells as possible by scraping the inside of the nostril using the virus collections and transport kit type citoswab (W/3ML VTM) supplied by CITOTEST LABWARE MANUFACTURING CO., LTD Haimen city 226100, China.

**2. Extractions**

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

**3. Amplifications**

We used a set of 17 pairs of primers coding for microRNAs provided by NeoBiotech (Table I). The SYBR Green qPCR Master Mix Universal Amplification Kit (MedChemExpress USA) was used. The amplification parameters were as follows: Initial denaturation at 95°C for 30 seconds followed by 40 cycles of denaturation at 95°C for 10 seconds and 30 seconds of hybridization at 60°C. We then proceeded to melt curve by cycling at 95°C for 15 seconds, then 60 seconds at 60°C and 95°C for 15 seconds. Expression of each microRNA was performed in each sample in duplicate and the level was normalized to beta-2 globulin. We evaluated this expression using the Livak method with the formula Rq = 2^-(ΔΔCt) **(Schmittgen TD and Livak KJ, 2008)**. A positive value of relative quantification (Rq) corresponds to overexpression and a negative value to underexpression.

**Table I: Primer pairs used**

| | |
|---|---|
| hsa-miR-9-5p | **Forward** : TCT TTG GTT ATC TAG CTG TAT GA<br>**Reverse**: TCA TAC AGC TAG ATA ACC AAA GA |
| hsa-miR-15b-3p | **Forward**: TAG CAG CAC ATC ATG GTT TAC A<br>**Reverse**: TGT AAA CCA TGA TGT GCT GCT A |
| hsa-miR-21-3p | **Forward** : CAA CAC CAG TCG ATG GGC TGT<br>**Reverse**: ACA GCC CAT CGA CTG GTG TTG |
| hsa-miR-29a-5p | **Forward**: ACT GAT TTC TTT TGG TGT TCA G<br>**Amorces anti-sens** : GTG AAC ACC AAA AGA AAT CAG T |
| hsa-miR-30d-3p | **Forward**: CTTTCAGTCAGATGTTTGCTGC<br>**Reverse**: GCA GCA AAC ATC TGA CTG AAA G |
| hsa-miR-33a-5p | **Forward**: GTG CAT TGT AGT TGC ATT GCA<br>**Reverse**: TGC AAT GCA ACT ACA ATG CAC |
| hsa-miR-33b-5p | **Forward**: GTG CAT TGT AGT TGC ATT GCA<br>**Reverse**: TGC AAT GCA ACT ACA ATG CAC |
| hsa-miR-122-3p | **Forward**: AAC GCC ATT ATC ACA CTA AAT A<br>**Reverse**: TAT TTA GTG TGA TAA TGG CGT T |
| hsa-miR-126-5p | **Forward**: CAT TAT TAC TTT TGG TAC GCG<br>**Reverse**: CGC GTA CCA AAA GTA ATA ATG |
| hsa-miR-130a-5p | **Forward:** GCT CTT TTC ACA TTG TGC TAC T<br>**Reverse :** AGT AGC ACA ATG TGA AAA GAG C |
| hsa-miR-141-3p | **Forward**: TAA CAC TGT CTG GTA AAG ATG G<br>**Reverse**: CCA TCT TTA CCA GAC AGT GTT A |
| hsa-miR-486-5p | **Forward**: TCCTGTACTGAGCTGCCCCGAG<br>**Reverse**: CTC GGG GCA GTC CAG TAC AGG A |
| hsa-miR-203a-5p | **Forward**: GTG AAA TGT TTA GGA CCA CTA G<br>**Reverse**: CTA GTG GTC CTA AAC ATT TCA C |
| hsa-miR-221-3p | **Forward**: AGC TAC ATT GTC TGC TGG GTT TC<br>**Reverse**: GAA ACC CAG CAG ACA ATG TAG CT |
| has-miR-223-5p | **Forward**: CGT GTA TTT GAC AAG CTG AGT T<br>**Reverse**: AAC TCA GCT TGT CAA ATA CAC G |
| has-miR-375-5p | **Forward**: GCG ACG AGC CCC TCG CAC AAA CC<br>**Reverse**: GGT TTG TGC GAG GGG CTC GTC GC |
| hsa-let 7a-5p | **Forward**: TGA GGT AGG TAG GTT GTA TAG TT<br>**Reverse**: AAC TAT ACA ACC TAC TAC CTC A |
| beta 2 globuline | **Forward**: TCGCAACCTCAGGAACAGAC<br>**Reverse**: CAGGAAAGGGGGCTTAGTGG |

**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:** Categorical data are expressed as percentages. Analyses were performed using SPSS software (version 26.0; IBM).

# RESULTS

**1. Description of the Study Population (Table II):**

The study population consisted of 206 T2DM subjects with 70% (145) male subjects and 30% (61) female subjects. The sex ratio (M/F) was 2.37%. The most common age group was 40 to 69 years, with 77.67% (160). The most frequent symptoms were fatigue (97.57%), fever (97.08%), dyspnea (96.11%) and cough (91.26%). Over 50% of our study population had loss of smell, taste and anorexia. 67.0% of our patients had severe symptoms. Over 57% of patients had a co-morbidity, of which hypertension was present in 33%. And 66% of our population were overweight. The clinical course showed that only 26% of our population died.

**2. Quantification of MicroARNs (Table II and Fig1 and 2):**

The microRNAs, hsa-miR-33a-5p, hsa-miR-33b-5p, hsa-miR-203-5p, hsa-miR-223-5p were overexpressed in our entire study population and regardless of clinical outcome. And hsa-miR486-5p was overexpressed only in non-survivors.

The area under the ROC curve (AUC) was calculated to analyse the prognostic performance of microRNAs associated with COVID-19+dt2. Five microRNAs: hsa-miR33a-5p, hsa-miR-486-5p 486-5p, hsa-miR21-3p, miR33b-5p and miR29a-5p potentially discriminate between surviving and non-surviving cases with an AUC of 0.93, 0.85, 0.90, 0.83 and 0.85 respectively.

**Table II: Sociodemographic and clinical characteristics**

| Variables | Number | Frequency (%) |
|---|---|---|
| **Gender** | | |
| Male | 145 | 70,39 |
| Female | 61 | 29,61 |
| **Age range** | | |
| 30 - 39 years old | 18 | 8,74 |
| 40 - 69 years old | 160 | 77,67 |
| >over 70 | 28 | 13,59 |
| **Symptoms** | | |
| Dyspnoea | 198 | 96,11 |
| Fatigue | 201 | 97,57 |
| Couche | 188 | 91,26 |
| Fever | 200 | 97,08 |
| Diarrhoea | 21 | 10,19 |
| Loss of taste | 131 | 63,59 |
| Anorexia | 153 | 74,27 |
| Loss of sense of smell | 106 | 51,45 |
| **Severity of symptoms** | | |
| Moderate | 68 | 33,00 |
| Severe | 138 | 67,00 |
| **Comorbidity** | | |
| No comorbidity<br>With comorbidity | 87<br>119 | 42,23<br>57,77 |
| Hypertension | 68 | 33,00 |
| Cardiovascular disease<br>Chronic kidney disease | 14<br>18 | 6,80<br>8,74 |
| Chronic lung disease | 11 | 5,34 |
| Maladies Du Système Nerveux | 8 | 3,88 |
| **Body mass** | | |
| Normal | 70 | 33,98 |
| Overweight | 136 | 66,02 |
| **Clinical course** | | |
| Recovered | 160 | 73,78 |
| Died | 46 | 26,21 |

**Table III: Micro Arn expression profile.**

| Expression | T2DM-covid-19(+) Survivor | T2DM-covid19(+) no-Survivor |
|---|---|---|
| **Over-expression** | hsa-miR 33a | hsa-miR 33a |
| | hsa-miR 33b | hsa-miR 33b |
| | hsa-miR 203 | hsa-miR 203 |
| | hsa-miR 223 | hsa-miR 223 |
| | | hsa-miR 486 |
| **Under-expression** | hsa-miR 9 | hsa-miR 9 |
| | hsa-miR 15b | hsa-miR 15b |
| | hsa-miR 21 | hsa-miR 21 |
| | hsa-miR 29a | hsa-miR 29a |
| | hsa-miR 30d | hsa-miR 30d |
| | hsa-miR 122 | hsa-miR 122 |
| | hsa-miR 126 | hsa-miR 126 |
| | hsa-miR 130 | hsa-miR 130 |
| | hsa-miR 141 | hsa-miR 141 |
| | hsa-miR 221<br>hsa-miR 375 | hsa-miR 221<br>hsa-miR 375 |
| | hsa-miR 486 | hsa-let 7a |
| | hsa-let 7a | |

ROC analysis of MicroRNAs:

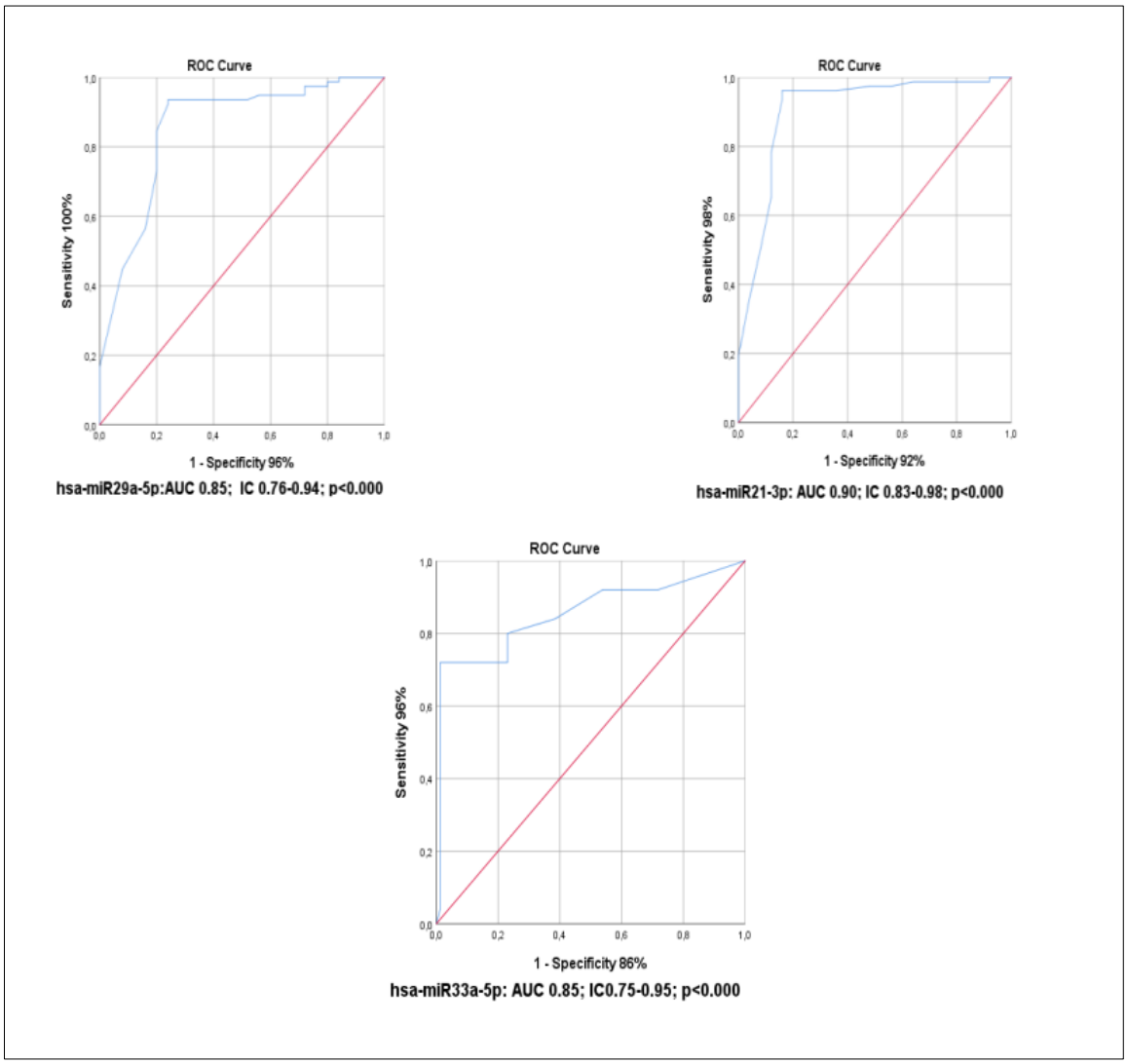


**Figure 1: ROC analyses of the microRNAs hsa-miR21-3p, miR33b-5p and miR29a-5p whose true positive state is cure**

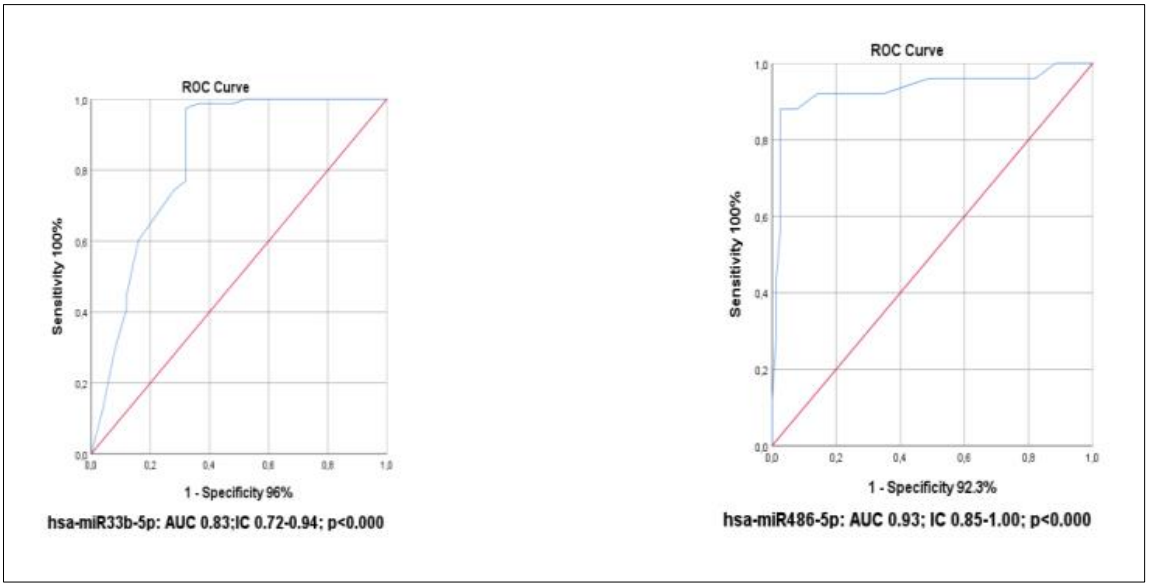


**Figure 2: ROC analyses of MicroRNAs: hsa-miR33a-5p and 486-5p the true positive state is death**

# DISCUSSION

MicroRNAs are small non-coding RNA molecules that play a crucial role in regulating gene expression **(Bartel *et al.*, 2009)**. Their irregular distribution has been associated with many diseases, including diabetes and viral infections. By analyzing microRNA expression profiles in these patients, we aim to identify specific microRNAs that may play a key role in the interaction between D2T and covid-19. These results could contribute to a better understanding of the molecular mechanisms involved and to the identification of predictive biomarkers and potential new therapeutic targets.

In our study, 70% of patients were male. Our results corroborate those of other authors in the literature. **Jin *et al.*, 2020; Luigi *et al.*, 2020** also observed a male predominance in cases of COVID-19 and T2DM.

Our results show that fever, fatigue, dyspnea and cough were the most frequent severe symptoms in over 91% of the study population. We also observed that in 67% of cases these symptoms were severe. Our results are in line with most studies in the literature indicating that diabetic patients are more likely to develop a severe form of COVID-19 as described in the study by **Hadjadj *et al.*, 2023 and Plaçais & Richier, 2020**.

In our study, over 57.77% of our population had comorbidities, 33% of whom were hypertensive. In agreement with literature data from studies by B**iswas and al. 2020; Kania *et al.*, 2023.** Our results confirm that hypertension is a major risk factor in T2DM. In this context, COVID-19 becomes an aggravating factor in the disease.

Most diabetic patients were obese (66.02%). This data is important because type 2 diabetes has been identified as a major risk factor in the severity of COVID-19 **(Huang, C *et al.*, 2020; Zhou, Y *et al.*, 2021; Simonnet, A *et al.*, 2020)**. Obesity is a known risk factor for type 2 diabetes and has also been associated with increased severity of covid-**19 (Simonnet, A *et al.*, 2020)**. Our results corroborate with the meta-analysis and systematic review conducted by **Sawadogo *et al.*, 2022**, which showed that obesity was an independent risk factor for severity of COVID-19, with an increased risk of hospitalization and death.

In relation to the clinical course, 26.21% of deaths were observed in our study population. These results corroborate those presented in **SITREP N°233 of 2022** concerning the 50-69 age group in the Republic of Congo. However, the WHO Africa report of 2021 **(IPOUMA *et al.*, 2021)** reports a case-fatality rate of around 10% in 13 African countries among diabetic subjects infected with SARS-COV-2. In contrast, **Fadini *et al.*, in 2020**, in a cohort of Italian T2-COVID-19 patients, reported a death rate of 35%. Worldwide epidemiological data show that patients aged between 50 and 64 have a 25-fold greater risk of complications (**CDC, 2020)**, as well as increased severity and mortality. This finding highlights the need for optimized prevention and management strategies for diabetic patients with COVID-19.

The results of microRNA quantification in our population show that only four (04) hsa-miR-33a-5p, hsa-miR-33b-5p, hsa-miR-203-5p, hsa-miR-223-5p were significantly up-regulated and twelve (12) hsa-miR-9-5p, hsa-miR-15b-3p, hsa-miR-21-3p hsa-miR-29a-5p , hsa-miR-30d-3p, hsa-miR-122-3p, hsa-miR-126-5p, hsa-miR-130-5p, hsa-miR-141-3p, hsa-miR-221-3p, hsa-miR-375-5p and hsa-let 7a-5p were significantly down-regulated regardless of clinical outcome except for hsa-miR-486-5p which was up-regulated in non-survivors.

Each of these microRNAs was implicated in the regulation of various cellular and physiological processes that could influence covid-19 infection and complications in type 2 diabetic subjects.

The value of miRNAs as predictive biomarkers in nasopharyngeal secretions was determined using the AUC of ROC curves. According to **Hosmer and Lemeshow, 2013** "0.5 = no discrimination; 0.5 to 0.7 = poor discrimination; 0.7 to 0.8 = acceptable discrimination; 0.8 to 0.9 = excellent discrimination; and > 0.9 = exceptional discrimination". Current research has found that hsa-miR33a-5p, hsa-miR486-5p, hsa-miR21-3p, miR33b-5p and miR29a-5p in nasopharyngeal secretions provide excellent discrimination for use as a predictive biomarker.

Interestingly, among all of them, two microRNAs hsa-miR-33a-5p (AUC 0.85; CI 0.75 to 0.95 and $p<0.000$) and hsa-miR-486-5p (AUC 0.93; CI 0.85 to 1.00 and $p<0.000$) proved to be significant predictors of mortality and three hsa-miR21-3p (AUC 0. 90; CI 0.83 to 0.98 and $p<0.000$), miR33b-5p (AUC 0.83; CI 0.72 to 0.94 and $p<0.000$) and miR29a-5p (AUC 0.85; CI 0.76 to 0.94 and $p<0.000$) as biomarkers predicting cure.

The results of the many studies often differ, sometimes significantly, in terms of sample preparation, material testing and molecular approach, techniques used for microRNA extraction, expression profiling, as well as severity of the patients evaluated and standardization strategies and statistical methods **(Abed *et al.*, 2023).**

# CONCLUSION

In this study, we examined the microRNA profile in COVID-19 positive type 2 diabetic patients in Pointe-Noire.

We observed that the majority of diabetic patients were overweight and had severe symptoms of COVID-19, with a higher proportion of comorbidities.

Our microRNA analysis identified hsa-miR33a-5p and hsa-miR486-5p as biomarkers predictive of death and hsa-miR21-3p, miR33b-5p and miR29a-5p as biomarkers predictive of recovery. However, further research is needed to elucidate the exact mechanisms by which these microRNAs influence the pathogenesis of COVID-19, particularly in type 2 diabetic patients.

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