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Original Research Article

# MiRNA expression affects survival in patients with obstructive sleep apnea and metastatic colorectal cancer

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ABSTRACT

*Introduction:* The relationship between obstructive sleep apnea (OSA) and cancer has been recognized for some time now. However, little is known about the mechanisms by which sleep apnea promotes tumorigenesis and the impact of OSA on survival after cancer diagnosis. In the last few years, research has focused on the exploration of different biomarkers to understand the mechanisms underlying this relationship and miRNAs, non-coding single strands of about 22 nucleotides that post-transcriptionally regulate gene expression, have emerged as possible actors of this process.

The aim of the study was to evaluate the impact of OSA on survival of metastatic colorectal cancer (mCRC) patients based on the expression of specific miRNAs.

*Methods:* The expression of 6 miRNAs, respectively miR-21, miR-23b, miR-26a, miR-27b, miR-145 and miR-210, was analyzed by qRT-PCR in patients' sera. Response to first-line therapy, Kaplan-Meier curves of overall and progression-free survival were used to evaluate survival in mCRC patients with and without OSA stratified for the expression of miRNAs.

*Results:* The expression of miR-21, miR-23b, miR-26a and miR-210 was significantly upregulated in mCRCs with OSA compared to no OSA. In mCRC patients with OSA and increasing expression of miR-21, miR-23b, miR-26a and miR-210 risk of progression after first-line therapy was higher and both overall and progression-free survival were significantly worst. Conversely, as miR-27b and miR-145 expression increased, the life expectancy of patients diagnosed with OSA and mCRC improved markedly.

*Conclusions:* This study highlights the relevance of specific miRNAs on OSA in mCRCs and their significance as non-invasive biomarkers in predicting the prognosis in patients with mCRC and OSA.

## 1. Introduction

Obstructive sleep apnea (OSA) is a chronic disease characterized by recurrent episodes of partial or complete obstruction of the upper airways during sleep. The consequent reduction in air flow often leads to serious alterations in gaseous exchanges with oxyhemoglobin desaturation and recurrent awakenings from sleep. Poor restful sleep contributes to the pathogenesis of daytime sleepiness, while repeated desaturation may contribute to the cognitive impairment often observed in these patients [1].

The most immediate nocturnal physiopathological consequences of OSA are fragmented sleep, increased respiratory effort, intermittent hypoxia and hypercapnia. These changes can, in turn, lead to systemic and pulmonary arterial hypertension, increased incidence of cardiovascular and cerebrovascular disease, cardiac arrhythmias and increased cancer incidence, progression and mortality [2–5].

In the last few years, evidence has accumulated that alterations in sleep architecture and continuity can promote or modulate many diseases, including cancer. Specifically, the link between OSA and cancer, considered as the possibility that being affected by OSA could lead to an

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increased risk of developing cancer, is currently much studied [6]. Numerous studies have evaluated this possibility and the first results of research seem to favor this hypothesis [7,8]. However, there remains a correlation yet to be studied and explored.

To date, there are few studies evaluating the impact of sleep apnea on survival after cancer diagnosis [9]. In recent years, microRNAs (miRNAs) have emerged as promising biomarkers for the diagnosis, prognosis, and treatment response prediction of various types of cancers. Their presence in biological fluids has also aroused great interest in their use as non-invasive biomarkers for the early diagnosis of cancer [10].

miRNAs are small (~22 nucleotide) single-stranded noncoding RNAs that down-regulate post-transcriptional gene expression by base pairing with the 3′ untranslated regions (3′UTR) of their target messenger RNAs (mRNAs) [11]. Several studies have demonstrated that miRNAs are key regulators of many physiological cellular mechanisms including growth, differentiation, proliferation, apoptosis, angiogenesis, and pathological processes such as inflammation and recovery after ischemia and hypoxic conditions [12].

Furthermore, recent studies have evaluated the role of miRNAs in intermittent hypoxia [13] and in OSA [14].

To date, colorectal cancer (CRC) represents one of the most common types of cancer and the second leading cause of cancer deaths [15]. An association between sleep deprivation and an increased risk of developing colorectal cancer has been observed [16] and our group previously reported that OSA worsen prognosis in mCRC [9]. These data highlight how insufficient sleep duration can become a public health problem, causing not only obesity, diabetes and coronary heart disease, but also cancer.

Based on the above considerations, our aim was to identify the impact of OSA on survival (overall and progression-free survival, OS and PFS) after diagnosis of mCRC based on the expression of selected miRNAs, respectively miR-21, miR-23b, miR-26a, miR-27b, miR-145 and miR-210, induced by hypoxia and known for their role in the development and progression of various forms of cancer.

## 2. Materials and methods

### 2.1. Population

27 subjects with a diagnosis of metastatic colorectal cancer (mCRC) were consecutively enrolled at the Oncology Unit of the "Policlinico of Foggia" and, subsequently, evaluated for the presence of OSA. In addition, 13 healthy controls were enrolled to evaluate differences in miRNA expression.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Policlinico of Foggia, Italy (approval number 26/CE/2023).

Written informed consent was obtained from all participants.

Patients' baseline characteristics are reported in Table 1.

**Table 1**
Patients' baseline characteristics.

| Patients, n | CRC PATIENTS | HEALTHY CONTROL |
|---|---|---|
| | 27 | 13 |
| *Demographic data* | | |
| sex, % male | 62 % | 61.5 % |
| age, years | 69.2 ± 9.3 | 62.5 ± 6.8 |
| BMI, kg/m$^2$ | 24.7 ± 3.2 | 25.6 ± 3.4 |
| *Nocturnal respiratory data* | | |
| $SpO_2$ mean, % | 93.7 ± 2.3 | 92.4 ± 2.6 |
| TS90, % | 9.5 ± 17.9 | 11.4 ± 27.5 |
| ODI, events·h$^{-1}$ | 6.9 ± 6.2 | 6.6 ± 7.0 |
| AHI, events·h$^{-1}$ | 6.6 ± 6.1 | 3.9 ± 1.8 |

Data are reported as mean ± SD.
BMI: body mass index; $SpO_2$: oxygen saturation; TS90: total sleep time with $SpO_2$ <90 %; ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index.

OSA was diagnosed at the diagnosis of mCRC, before starting first-line chemotherapy. All patients underwent clinical assessment, respiratory functional tests and nocturnal cardiorespiratory monitoring at the time of diagnosis. Main data collected were as follows: apnea-hyponea index (AHI), average $SpO_2$, time with $SaO_2$ lower than 90 % (T90), and oxygen desaturation index (ODI). OSA was defined as AHI >5.

According to the OSA presence, subjects were divided into 2 groups: i) patients with either OSA and cancer (ONCO-OSA) and patient with cancer. First-line therapy was based on FOLFOX or FOLFIRI regimen combined with bevacizumab or selected anti-EGFR monoclonals based on RAS/BRAF mutational status. **Human fasting sera were collected at the diagnosis of mCRC, prior to initiating first-line therapy via venous draw. After clotting at room temperature for at least 1 h, the samples were centrifuged at a maximum speed of 1300 g for 10 min. Aliquots were promptly prepared to ensure sample stability and stored at −80°C until use.** All subjects were followed up for between 40 and 50 months.

The prognostic importance of OSA was investigated in the ONCO-OSA group to establish a correlation between OSA and response to first-line therapy according to RECIST criteria, cancer-specific survival.

### 2.2. RNA isolation

Total RNA was extracted by using TRIzol™ Reagent (Thermo Fisher Scientific, Waltham, MA, USA), according to the manufacturer's protocol. Concentration and quality of the eluted RNA were measured using NanoDrop™ 2000 Spectrophotometer (Thermo Fisher Scientific). RNA purity was evaluated with the absorbance ratio A260/280.

### 2.3. RNA reverse transcription and miRNA expression through qRT-PCR

Total RNA was reverse-transcribed by using TaqMan MicroRNA RT kit (Thermo Fisher Scientific), according to the manufacturer's protocol. The resulting cDNA was used for detecting miRNA expression by quantitative real-time polymerase chain reaction (qRT-PCR) by using TaqMan miRNA assay (Thermo Fisher Scientific) on CFX96 Touch Real-Time PCR Detection System instrument (Bio-Rad Laboratories, Inc). RNU6B was used as endogenous control [17]. miRNA's expression was calculated using the comparative $2^{-\Delta\Delta Ct}$ method [18].

Table 2 shows miRNA sequences used.

### 2.4. Statistical analysis

Comparisons between groups were performed by Mann-Whitney or Kruskal-Wallis test. Data are presented as mean ± standard deviations (SD) or median ± range, depending on the normality of values.

Response to therapy was evaluated according to RECIST criteria. Disease control rate (DCR) was defined as

the sum of patients with stable or responding disease after first-line therapy. Survival data were assessed by the Kaplan–Meier methods. Progression-free survival (PFS) was defined as the time from inclusion to the date of first documentation of progression or date of last follow-up. Overall survival (OS) was defined as the time from diagnosis or from the start of treatment during which patients are still alive. Kaplan-Meier curves are step curves where each step represents an outcome measure. Time is plotted on the x-axis, and probability of survival is plotted on the y-axis. Patients were subdivided according to median miRNA expression. Results were considered significant when p values were $\leq$0.05.

Statistical analysis was performed using GraphPad Prism software (version 9.0, GraphPad Software).

## 3. Results

### 3.1. Population

OSA was diagnosed in 10/27 (37 %) patients (Table 3). No significant differences were observed in the distribution of OSA according to age, gender, and body mass index (BMI).

### 3.2. MIRNAs expression

The expression of miR-21, miR-23b, miR-26a and miR-210 was significantly higher in ONCO-OSA patients than in non-OSA patients with cancer and healthy controls (Fig. 1). miR-27b and miR-145, on the other hand, appeared reduced in ONCO-OSA patients compared to cancer patients (Fig. 1). No significant differences were found for miR-27b and miR-145 between ONCO-OSA and controls.

### 3.3. Response to therapy and survival

The relationship between OSA and DCR, PFS after first-line therapy, and cancer-specific mortality was evaluated in the ONCO-OSA cohort of patients (Fig. 2). Overall, 3 (30 %) patients achieved a response to first-line therapy and 4 (40 %) a disease stabilization, whereas 3 (30 %) patients had a disease progression. Interestingly, the expression of miRNAs miR-21, miR-23b, miR-26a and miR-210 was significantly higher in patients who progressed after first-line therapy compared to patients with disease control (Fig. 2), whereas no correlation was observed between the expression of miR-27b and miR-145 and response to first-line therapy.

In the ONCO-OSA group, Kaplan-Meier curves showed reduced survival with increasing expression of miR-21, miR-23b, miR-26a and miR-210. This is true both considering the overall and the progression-free survival. In detail, almost all 4 of these miRNAs showed a significant difference based on miRNA expression both considering OS and PFS, except miR-26a and miR-210 (Fig. 3).

On the contrary, patients with elevated levels of miR-27b and miR-145 showed a higher probability of survival considering both OS and PFS (Fig. 3).

However, for the non-OSA patient group with colorectal cancer, there were no differences in survival based on the expression of the various miRNAs studied, except for the PFS of the miR-210 and the OS of the miR-27b (Fig. 4).

## 4. Discussion

Recent studies have shown that obstructive sleep apnea contributes to increased cancer incidence and mortality; however, the mechanisms by which OSA promotes carcinogenesis, to date, remain largely unknown [19]. Three possible main mechanisms could be involved in the relationship between OSA and cancer. Hypoxia could increase the expression of a transcription factor (HIF-1) involved in angiogenesis and resistance to therapies. Hypoxia could also modulate the cells of the immune system, hampering anti-tumor responses and promoting some pro-tumor activities. Finally, sleep disturbance could alter circadian rhythms that are now known to be important for the expression of genes involved in cell proliferation and DNA repair [14,20]. Nonetheless, there is still much work to be done in this regard. The impact of sleep apnea on survival after cancer diagnosis remains also unknown [21].

Numerous studies have demonstrated a growing interest in exploring new biomarkers to better understand the mechanisms underlying the relationship between OSA and cancer [20]. However, there are few studies that link all these aspects: sleep apnea, cancer, survival and biomarkers.

In fact, as far as we know, this is the first study showing that cancer patients and sleep apnea show a more unfavorable cancer survival than non-OSA patients in relation to the expression of specific biomarkers, the microRNAs.

The results of this study suggest that the expression of miR-21, miR-23b, miR-26a and miR-210 is higher in ONCO-OSA patients than in non-OSA cancer patients and healthy controls. Noteworthy, both overall and progression-free survival depend on the expression of these miRNAs in the ONCO-OSA group and this correlated with resistance to first-line therapy in case of their upregulation. In detail, miR-21 and miR-23b are two miRNAs known for being overexpressed in different types of tumors [22,23] and, recently, numerous studies have demonstrated their altered expression in patients with sleep apnea [24]. In many patients affected by neoplasms, high concentrations of miR-21 and miR-23 have been found, which have the function of stimulating the expression of oncogenes (e.g. mTOR) and inhibiting the expression of tumor suppressor genes (e.g. PTEN) [22,23]. In addition, these same miRNAs are altered in response to low oxygen levels [25], through a mechanism dependent on the hypoxia-inducible factor, a condition that makes them excellent potential biomarkers for OSA.

miR-26a is also a hypoxia-induced miRNA whose expression appears to be upregulated during cell differentiation [26]. Numerous studies have demonstrated its involvement in various types of tumors and, to date, we know that many of its target genes are involved in important cellular processes such as proliferation, differentiation, apoptosis, invasion and metastasis [27].

Finally, miRNA-210, whose expression is induced by hypoxia, also targets many genes encoding proteins that play key roles in proliferation control, DNA and RNA binding and repair, differentiation, development

**Table 3**
OSA distribution in mCRC patients.

| Patients, n (%) | ONCO-OSA | CRC PATIENTS | p-value |
|---|---|---|---|
| | 10 (37 %) | 17 (63 %) | |
| *Demographic data* | | | |
| sex, % male | 60 % | 52.9 % | 0.1608 |
| age, years | 66.5 ± 10.5 | 70.8 ± 8.4 | 0.1040 |
| BMI, kg/m$^2$ | 25.8 ± 4.1 | 24.1 ± 2.5 | 0.1191 |
| *Nocturnal respiratory data* | | | |
| $SpO_2$ mean, % | 92.5 ± 2.5 | 94.4 ± 1.9 | **0.0113*** |
| TS90, % | 15.8 ± 25.2 | 4.4 ± 8.9 | **0.0064**** |
| ODI, events·h$^{-1}$ | 13.5 ± 7.3 | 3.4 ± 3.4 | **<0.0001**** |
| AHI, events·h$^{-1}$ | 14.4 ± 7.4 | 2.7 ± 1.4 | **<0.0001**** |

Data are reported as mean ± SD and were analyzed using Mann-Whitney test. p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.
BMI: body mass index; $SpO_2$: oxygen saturation; TS90: total sleep time with $SpO_2$ <90 %; ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index.

**Table 2**
miRNAs sequence.

| *Assay Name:* | *Assay ID* | *Species* | *miRNA Sequence* |
|---|---|---|---|
| RNU6B | 001093 | human | CGCAAGGATGACACGCAAATTCGTGAAGCGTTCCATATTTTT |
| hsa-miR-21-5p | 000397 | human | UAGCUUAUCAGACUGAUGUUGA |
| hsa-miR-23b-5p | 002126 | human | UGGGUUCCUGGCAUGCUGAUUU |
| hsa-miR-26a-5p | 000405 | human | UUCAAGUAAUCCAGGAUAGGCU |
| hsa-miR-27b-5p | 002174 | human | AGAGCUUAGCUGAUUGGUGAAC |
| hsa-miR-145-5p | 002278 | human | GUCCAGUUUUCCCAGGAAUCCCU |
| hsa-miR-210-3p | 000512 | human | CUGUGCGUGUGACAGCGGCUGA |

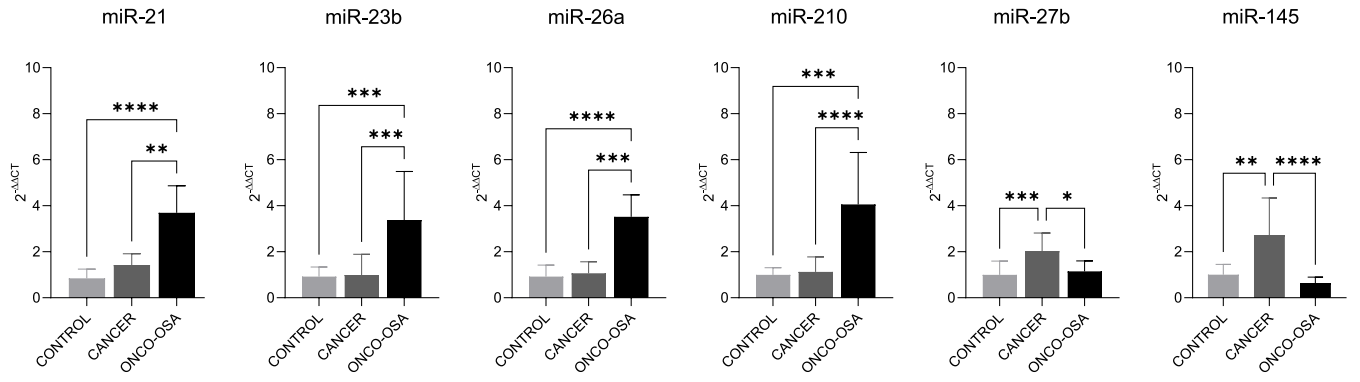


**Fig. 1.** miRNA expression in patients and healthy subjects Quantitative real-time PCR analysis of differentially expressed microRNAs in ONCO-OSA compared to no-OSA mCRCs patients and healthy controls.RNU-6B was used as endogenous control. Comparisons between groups were performed by Kruskal-Wallis test.Data are reported as mean ± SD. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.

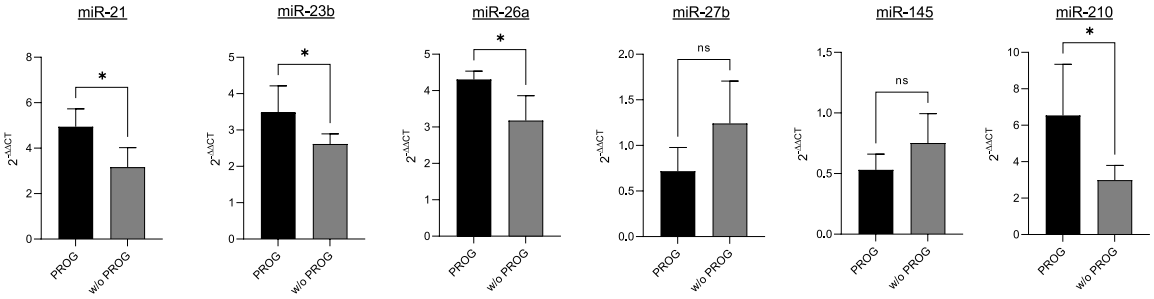


**Fig. 2.** Response to first-line therapy and miRNA expression ONCO-OSA patients were subdivided according to progression or disease control. Comparisons between groups were performed by Kruskal-Wallis test. Data are reported as mean ± SD. *p ≤ 0.05. PROG: with disease progression; w/o PROG: without disease progression.

and apoptosis [28]. Moreover, miRNA-210 is strongly overexpressed in many tumors [29].

For all the miRNAs, therefore, our results are consistent with previous studies showing a higher expression of these miRNAs in patients with OSA and some cancer types [30]. Interestingly, our observation provides significant survival data in a cohort of mCRC patients undergoing first-line therapy. Indeed, it emerges that the greater the expression of these miRNAs in patients with sleep apnea, the worse their chance to achieve a response to therapy and improve survival, both in terms of overall and progression-free survival. It is relevant that in the no-OSA cohort the expression of the same miRNAs does not provide any survival difference, this suggesting a link between OSA, miRNA expression and survival differences.

On the other hand, miR-145 and miR-27b show instead a marked antitumor activity, acting on different signaling pathways [31,32]. Their down-regulation has been observed in several tumor types demonstrating their role in the inhibition of tumor cell proliferation and migration [33,34]. Several studies have also highlighted their involvement in hypoxic conditions [12]. In our study, these two miRNAs did not show significant differences between non-OSA cancer patients and OSA-ONCO patients. A difference in expression was found only between cancer patients and healthy controls. On the other hand, the data on survival in ONCO-OSA patients are surprising. Indeed, based on our results, it would appear that the greater the expression of these two miRNAs, the greater the chances of survival. Where instead the expression is lower, both the overall and the progression-free survival are worse.

## 5. Limitations of the study

The rarity of the combination of OSA and metastatic colorectal cancer (mCRC) makes our clinical study based on a small population of patients with OSA and mCRC (n = 10).

Nonetheless, we observed statistically significant variations in miRNAs expression, indicating that the variations are sufficiently strong to be detected in this small cohort.

Moreover, a careful review of the literature led to the selection of miRNAs. It has been proven by previous studies [12,35] that the selected microRNAs (miR-21, miR-23b, miR-26a, miR-27b, miR-145 and miR-210) play a key role in the development and progression of various forms of cancer, including mCRC.

Surely, further studies on more patients and additional miRNAs will be required to confirm our results.

## 6. Conclusions

Our study represents a proof of concept that selected miRNAs, known to be induced by intermittent hypoxia associated with OSA, are upregulated in mCRC patients with OSA, thus demonstrating their role in tumorigenesis and confirming the relationship between OSA and colorectal cancer. In fact, our data support the hypothesis that these miRNAs could play a fundamental role in the mechanism of OSA, worsening the progression of CRC.

Furthermore, survival data suggest that the increased expression of certain hypoxia-inducible oncogenic miRNAs (miR-21, miR-23b, miR-26a and miR-210) correlated with reduced response to therapy and worst overall and progression-free survival in OSA colorectal cancer patients. Conversely, the increased expression of hypoxia-inducible tumor suppressor miRNAs (miR-27b and miR-145) correlates with improved life expectancy. However, it is important to underline that these data are preliminary since the study has been conducted on a small cohort of mCRC patients and this is due to the rare combination of OSA and CRC that makes difficult to enroll patients in this group. Thus, further studies are needed in a larger cohort of mCRCs with OSA to

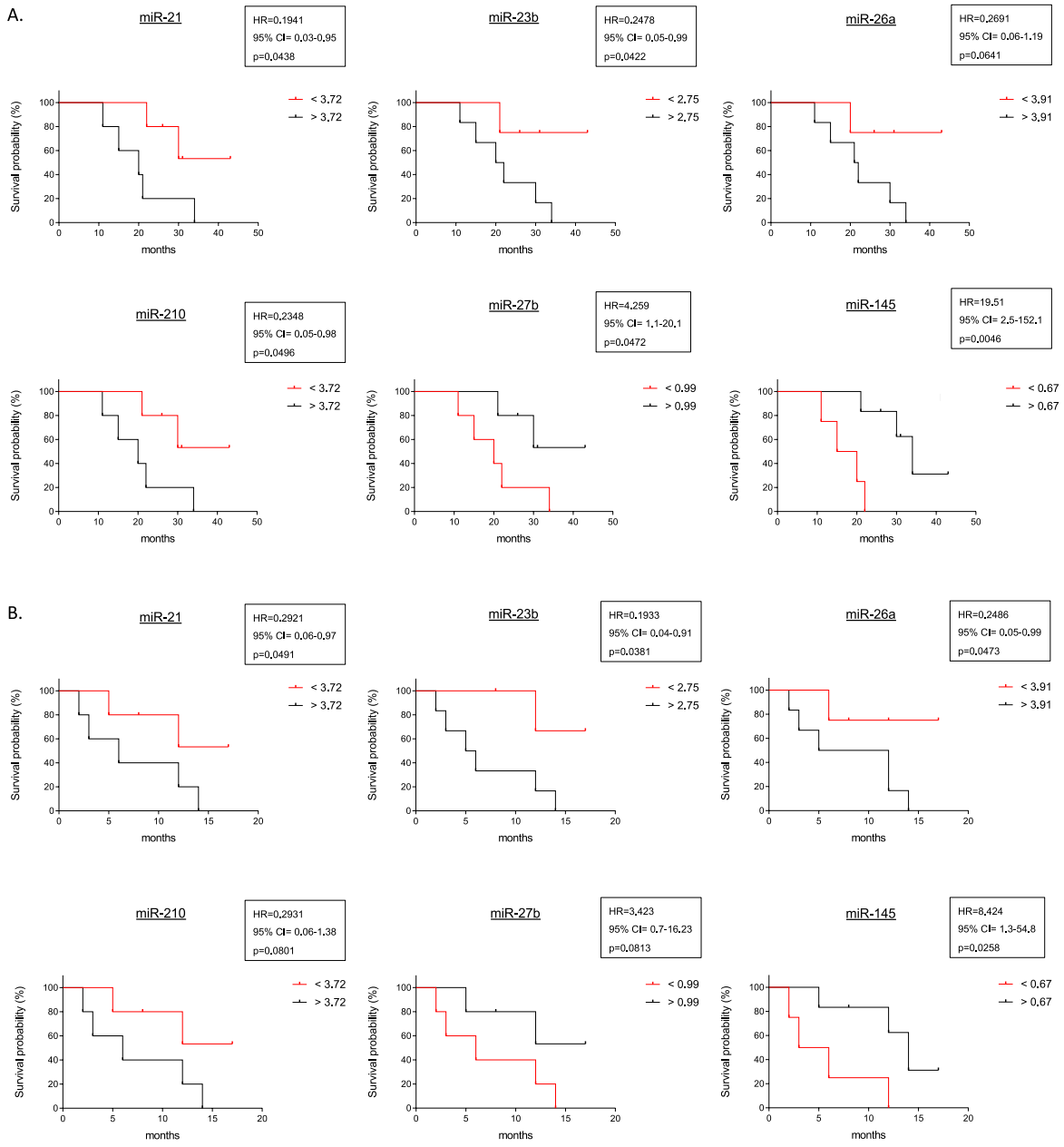


**Fig. 3.** Kaplan–Meier overall (A) and progression-free (B) survival curves in ONCO-OSA patients according to miRNA's expression A. Overall Survival B. Progression Free Survival HR: Hazard Ratio; 95 % CI: 95 % Confidence Interval. *p $\leq$ 0.05. Patients were subdivided according to median miRNA expression. Time is plotted on the x-axis, and probability of survival is plotted on the y-axis.

confirm our observations.

Overall, these data provide an excellent starting point for introducing miRNAs into clinical practice as useful non-invasive biomarkers for diagnosis, prognosis and progression assessment in cancer patients affected by sleep apnea and colorectal cancer.

## Ethics approval and informed consent

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Policlinico Riuniti of Foggia (approval number 26/CE/2023). Informed consent was obtained from all subjects involved in the study.

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## CRediT authorship contribution statement

**Piera Soccio:** Writing – original draft, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Giorgia Moriondo:** Writing – original draft, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Giulia Scioscia:** Resources, Methodology. **Pasquale Tondo:** Formal analysis. **Giuseppina Bruno:** Methodology. **Guido Giordano:** Resources. **Roberto Sabato:** Formal analysis. **Maria Pia Foschino Barbaro:** Supervision, Project administration. **Matteo**

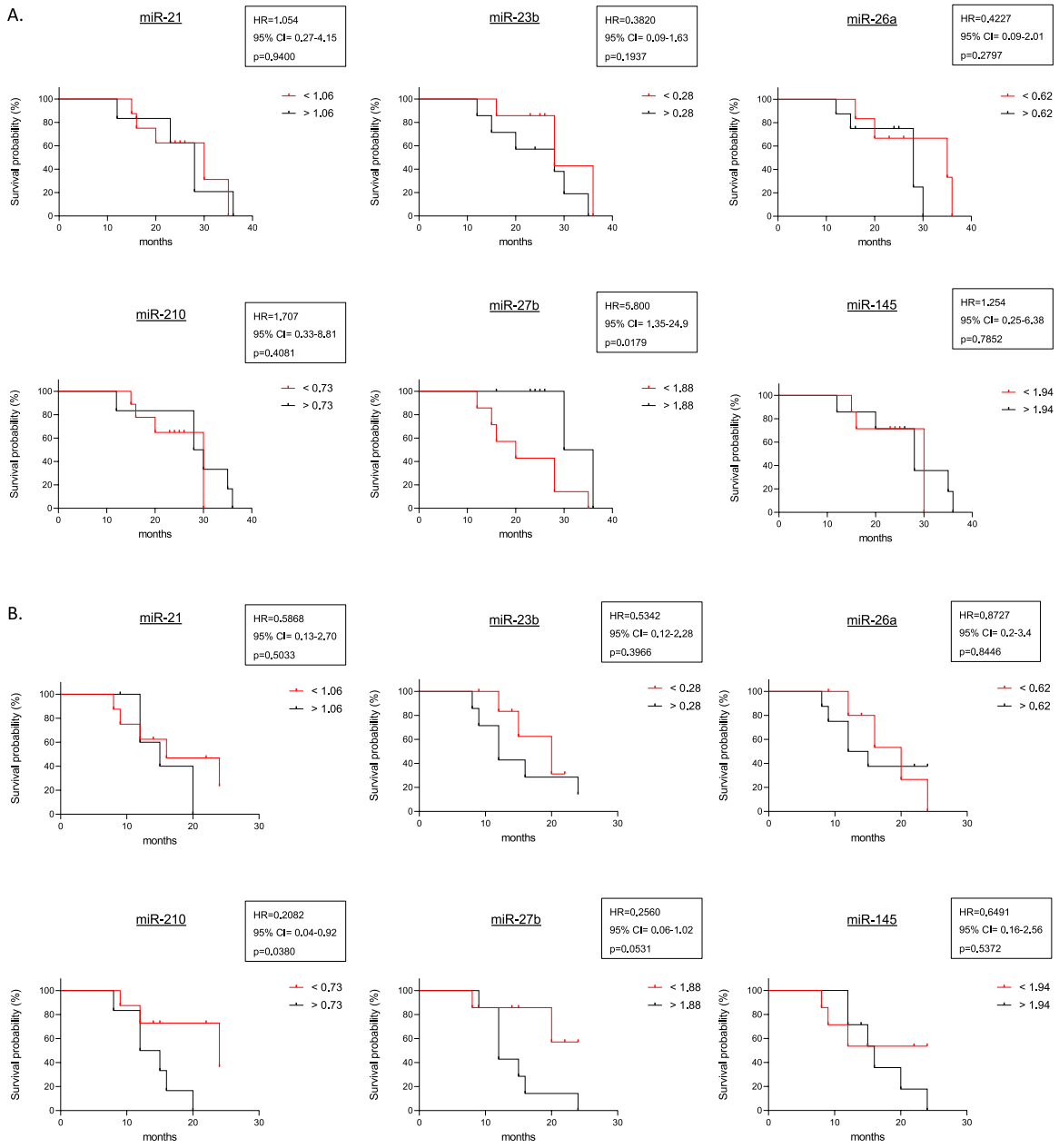


**Fig. 4.** Kaplan–Meier overall (A) and progression-free (B) survival curves in CRC patients according to miRNA's expression A. Overall Survival B. Progression Free Survival HR: Hazard Ratio; 95 % CI: 95 % Confidence Interval. *p $\leq$ 0.05.Patients were subdivided according to median miRNA expression. Time is plotted on the x-axis, and probability of survival is plotted on the y-axis.

**Landriscina:** Writing – review & editing, Writing – original draft, Resources, Project administration, Data curation. **Donato Lacedonia:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

## ABBREVIATIONS

| | |
|---|---|
| AHI | apnoea–hypopnoea index |
| BMI | body mass index |
| HIF-1 | hypoxia inducible factor 1 |
| mCRC | metastatic colorectal cancer |
| miRNAs | microRNAs |
| ODI | oxygen desaturation index |
| OS | overall survival |
| OSA | obstructive sleep apnea |
| PFS | progression-free survival |
| SpO2 | oxygen saturation |
| TS90 | total sleep time with SpO2 <90 % |

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