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ORIGINAL ARTICLE

MiR-34a-5p as a Diagnostic and Prognostic marker for Patients of Chronic Rhinosinusitis with Nasal Polyps

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ABSTRACT

Background*: Chronic rhinosinusitis with nasal polyps (CRSwNP) is considered a common disease in Ear, Nose, and Throat (ENT) practice that has a negative impact on quality of life, and also has a high relapse rate after endoscopic nasal surgery.* ***Objectives:*** *to detect the expression level of miR-34a-5p in CRSwNP patients and to assess its correlation with clinical and laboratory data.* ***Methodology****: This study is a controlled observational study that included 100 subjects (50 patients with CRSwNP and 50 healthy controls). Blood samples were drawn from all subjects. RNA extraction and detection of fold change of miR-34a-5p was performed using real-time PCR.* ***Results:*** *A significant down-regulation of the miR34a-5p marker in CRSwNP patients was detected. The median for the miR-34a5p marker was lower in patients suffering from facial pain and severe nasal obstruction. Patients with nasal polyps that were large enough to protrude outside the middle meatus had significantly lesser levels of the miR-34a-5p marker.* ***Conclusion:*** *The down-regulation of miR-34a-5p level may regulate the pathogenesis and development of nasal polyps in CRSwNP patients clarifying miR-34a-5p role as new a biomarker and suggesting future research giving the chance to innovation of a new drug to up-regulate the miR34a-5p to its normal expression level.*

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as the nasal and paranasal sinus mucosa inflammation for at least 12 successive weeks which causes rhinorrhea, nasal congestion, and hyposmia. Although many environmental, host, and genetic variables have been hypothesized, the majority's etiology is still unknown [1]. Different theories have been assumed for CRS pathophysiology. The initial theory was the fungus hypothesis, which postulated that CRS was caused by an overactive host inflammatory response to the ubiquitous airborne fungus Alternaria [2]. The second theory is the CRS microbiome theory, which postulates that inflammation is caused by a dysbiosis of the microbial population [3]. Also, viral infections could lead to the CRS development. Repeated infections may cause mucociliary stasis, and acquired ostiomeatal obstruction[4]. The host and environmental variables increasingly interact to cause one or more pathologic pathways, chronic inflammation: (endotypes) that result in the clinical presentations: (phenotype)[5]. Two CRS phenotypes are considered: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). CRSwNP is well recognized to be characterized by type 2 (T2) inflammation with prominent eosinophilia (endotype) and the inflammation in CRSsNP is highly heterogeneous. The association between an inflammatory endotype and clinical phenotype is not clear [6]. Tomassen et al, in a case-control study of CRS, pointed out that adopting clinically defined phenotypes would not accurately reflect the pathophysiologic of the disease diversity[7]. It is important to find reliable biomarkers that can forecast the disease onset and how well a patient will respond to the treatment [6].

MicroRNAs (miRNAs) are considered the bright spots of modern molecular biomedical research in addition to their biological, diagnostic, and therapeutic properties. MicroRNAs are short, naturally occurring RNA molecules that have an average length of 22 nucleotides. They are important for the post-transcriptional regulation of the expression of genes. Small amounts of particular miRNAs are crucial immune system regulators [8]. For instance, in adaptive immunity, members of the miR-17-92 family stimulate the differentiation of early B cells, whereas miR-150 suppresses the growth of early B cells. The antibody production, B-cell class switching, and the differentiation of Th1, Th2, and Th17 cells all depend on miR-155[9]. In CRS, several miRNAs show therapeutic promise. Zhang et al. reported that 31 different miRNAs were expressed differently in

eosinophilic CRSwNP. It appears to be involved in innate antiviral immunity [10].

Different miRNAs control the essential and acquired immune response through targeting IFNγ producer mRNA like miR-29b which plays a part in regulating Th1 differentiation in multiple sclerosis patients [11, 12].

The family of miR-34 includes three memberships, miR-34a, miR-34b, and miR-34c, set on chromosomes number 1 and 11. miR-34a is coded on chromosome number 1. The miR-34a is a crucial immune system regulator. It is abundantly expressed in immune cells. MiR-34a may inhibit B cell development. T cell activity may be increased as a result of miR-34a. Additionally, miR-34a controls various innate/adaptive immunological processes and the regulation of T cell [13].

Because miRNAs have tissue-specific expression patterns and are frequently altered in different diseases, they can be employed as diagnostic and prognostic tools. miRNAs may provide excellent biomarkers for various diseases because of their stability in addition to the comparative ease of study. miRNAs may hold enormous promise as brand-new therapy targets due to their crucial significance in various diseases and their function as master regulators in cellular pathways [14]. We aimed to detect the expression level of miR-34a-5p in CRSwNP patients and to assess its correlation with clinical and laboratory data.

METHODOLOGY

The present study was conducted during the period from January 2021 to June 2022. All the patients were recruited from the Otorhinolaryngology Outpatient Clinic of the Fayoum Surgical University Hospital. The objectives and procedures of the study were endorsed by the Fayoum University Ethics Committee NO: D234. Written consent was obtained from all participants after a clear explanation of the study's objectives. The study was a controlled observational study. It was performed by the Declaration of Helsinki.

One hundred individuals were divided into two groups. The case group comprised fifty patients admitted to the outpatient clinic having CRSwNP. The control group (with matched age and sex) included fifty healthy subjects presented with no evidence of allergic rhinosinusitis, CRSwNP, or any other nasal pathology.

The inclusion criteria included adults aged over eighteen, evidence of CRSwNP, and patients who were not treated with corticosteroids (topical or systemic) for four weeks minimum.

Excluded criteria: cases below eighteen years of age, patients with previous nasal surgery or pathology, immunocompromised patients such as diabetes mellitus, kidney failure, and diseases with known craniofacial abnormalities, congenital defects, or mental retardation, patients with cardiovascular, pulmonary, and metabolic diseases, and pregnant females.

Our patient's symptoms included:

Nasal obstruction, sneezing, rhinorrhea (clear or colored), itching of the nose, eyes, or palate, postnasal drip, facial pain/pressure, and the reduction or loss of smell. Each complaint was analyzed as follows: onset, course, and duration of symptoms, what increases symptoms and what decreases them, degree, and severity (mild – moderate – severe).

Clinical examination was done by nasal endoscope for assessment of: signs of chronic rhinosinusitis like nasal discharge, crust, and congested, pale bluish, and edematous nasal mucosa. Inferior turbinate hypertrophy was noted and classified accordingly into mild enlargement with no apparent obstruction (grade I), moderate obstruction (grade II), and severe with complete nasal cavity obstruction (grade III) [15].

The nasal septum deviation degree was also taken into consideration and classified into normal, mild (grade I), moderate (grade II), and severe deviation (grade III).

Nasal polyps' detection:

The Lund-Kennedy scale [16, 17] was recommended for endoscopic nasal polyps staging.

A Radiology CT scan of the nose and paranasal sinuses was obtained to clarify the detailed anatomy of paranasal sinuses and to detect the mucosal changes within the osteomeatal complex and/or sinuses. We used the Lund-Mackay system to stage our CT findings. The sinus position and degree of opacification are the key elements of the Lund-MacKay system: 0 indicates normal, 1 indicates partial opacification, and 2 indicates entire opacification[16, 17].

microRNA extraction and detection of fold change of miR-34a-5p using real- time PCR:

Three milliliters of peripheral venous blood were collected from each individual. After being collected in serum separator tubes, the samples were centrifuged for 10 minutes at 4000 Xg after being allowed to clot for 15 minutes. Before analysis, sera were separated and kept at -80 °C.

The sera were used for:

A. **RNA extraction:** this was done by using a miRNeasy mini kit and protocol for serum total RNA purification, with miRNA (Qiagen, Hilden, Germany). Samples of RNA were exposed to the assessment of RNA quantitation and purity by the NanoDrop® (ND)-1000 spectrophotometer (NanoDrop Technologies, Inc. Wilmington, USA).
B. **Reverse transcription** was carried out on total RNA in a final volume of 10 ul RT reactions using the miRCURY LNA RT Kit (cat. no. 339340) (Qiagen, Maryland, USA).
C. **Quantitative real-time PCR (qPCR) for Detection of miR 34a-5p:**

The real-time cycler (ThermoScientific™, PikoReal 24™ RealTime PCR System, Finland) was programmed and used for detecting miR 34a-5p. The miR-34a-5p serum expression levels were assessed by miR-16-5p

(an internal control) using ready-made miR-34a-5p primers. Catalog no. of miR-34a-5p is YP00204486 and its lot number is 201902080015–3, and the catalog no. of miR-16-5p is YP00205702 and its lot number is 201910040131-3.

ΔCt was calculated by subtracting the Ct values of miR-16-5p from those of target micro-RNAs. ΔΔCt was calculated by subtracting the ΔCt of the control samples from the ΔCt the samples of disease. The fold change in miR 34a-5p expression was calculated by the equation $2^{-\Delta\Delta Ct}$ **18**.

Statistical Analysis

Data were gathered, organized, and coded to make data manipulation easier, then double-entered into Microsoft Access. Data statistical analysis was performed by SPSS software version 16 running on Windows 7(SPSS, Inc., USA). For quantitative data, the median, the mean, the rang, and the standard deviation were calculated. The Kolmogorov–Smirnov test was utilized as a test of normality. The Mann–Whitney U test or Kruskal–Wallis test was performed to compare the 2 groups. Qualitative data were presented as numbers and percentages, and chi-square (× 2) was utilized as a test of significance. Spearman's correlation was utilized to test the association of quantitative variables. ROC curve evaluated the diagnostic performance of the biomarkers and the best cut-off point of the biomarkers was determined, Data were considered significant when $p < 0.05$.

RESULTS

Demographic and clinical data of the studied groups:

The patients group included 30 males and 20 females, whose ages ranged from 18 to 60 years (mean of 36.90 ± SD 11.04 years). The control group included 32 males and 18 females, with ages ranging from 22 to 64 years (mean of
39.78± 12.741 years). Among patients, 40 patients (80%) with severe nasal obstruction, 39 patients (78%) with hyposmia and 9 patients with anosmia (Table 1).

Table 1: Demographic and clinical data of the patients and control

	Cases (N=50)	Control (N=50)	P-value
Age /years	36.90± 11.04	39.78 ±12.741	0.230
Sex: **Male N (%)** **Female N (%)**	 30 (60) 20 (40)	 32 (64) 18 (36)	0.680
History of Asthma N (%)	7(14)	-	
Symptoms			
Nasal obstruction Mild to moderate N (%) Severe N (%)	 10(20) 40(80)		
Nasal discharge Mild N (%) Moderate to Severe N (%)	 11(22) 39(78)		
Itching Absent N(%) Present N(%)	 29(58) 21(42)		
Postnasal discharge Absent N(%) Present N (%)	 12(24) 38(76)		
Facial pain/pressure Absent N (%) Present N (%)	 11(22) 39(78)		
Smell disorders Normal **N** (%) Hyposmia N(%) Anosmia (%)	 2(4) 39(78) 9(18)		

Data are expressed as mean ± SD or N (%).

Endoscopic nasal Examination among patients: 40 patients (80%) had polyps protruding beyond the middle meatus filling the cavity of the nose and 10 patients (20%) had nasal polyps just present in the middle meatus (Table 2).

Table 2: Endoscopic nasal Examination data of the patients (N=50)

Variable	N (%)	
Nasal mucosa Congestion (%)	Pale blue	28 (56)
	Congestion	22 (44)
Inferior turbinate hypertrophy (%)	Mild to moderate	26 (52)
	Severe	24 (48)
Degree of deviated nasal septum (DNS) (%)	Normal to mild deviation	35 (70)
	Severe	15 (30)
Nasal polyp (%)	**1** Polyps in middle meatus only	10 (20)
	2 Polyps beyond middle meatus	40 (80)
Mucosal edema (%)	**1** Mild	13 (26)
	2 Severe	37 (74)
Nasal discharge (%)	**1** Clear, thin or mucoid discharge	24 (48)
	2 Thick colored discharge	26 (52)
Nasal crustations (%)	**0** No crustations	43 (86)
	1 Present	7 (14)

The nose and the paranasal sinuses Computed tomography among patients: Table 3 demonstrates that 43 patients (86%) had total opacification of the maxillary sinus while 46 patients (92%) had complete opacification of the osteomeatal complex.

Table 3: CT nose & PNS findings among the patients (N=50):

Variable		**N (%)**
Maxillary sinus	1 Partial opacification	7 (14)
	2 Complete opacification	43 (86)
Anterior ethmoid	1 Partial opacification	8 (16)
	2 Complete opacification	42 (84)
Posterior ethmoid	1 Partial opacification	18 (36)
	2 Complete opacification	32 (64)
Sphenoid sinus	0 No abnormality	6 (12)
	1 Partial opacification	16 (32)
	2 Complete opacification	28 (56)
Osteomeatal complex	1 Partially occluded	4 (8)
	2 Occluded	46 (92)

CT: Computed tomography **PNS**: Paranasal sinuses

miR-34a-5p expression in CRSwNP the patients and the control group: There was a statistically significant down-regulation of miR-34a-5p between the control and the patients group (P = 0.001).

Association between miR-34a-5p and clinical, endoscopic, and radiological findings among the patient's group: A significantly decreased level of marker (p-value <0.05) was observed with severe nasal obstruction. Moreover, patients with pain in their faces had significant down- regulation of miR-34a-5p (p-value <0.05) (Table 4).

Table 4: Relation between miR-34a-5p and clinical data in the patients group.

		miR-34a-5p Median (IQR)	P value
Gender (sex)	**Male**	$75*10^{-6}$ ($25*10^{-6}$- 0.239)	**0.008***
	Female	$88*10^{-5}$ ($59*10^{-6}$- 0.239)	
Asthma	**No**	$138*10^{-6}$ ($6*10^{-5}$- $72*10^{-4}$)	0.133
	Yes	$3*10^{-5}$($13*10^{-4}$- $17*10^{-4}$)	
Chronic diseases	**No**	$124*10^{-6}$ ($5*10^{-5}$- $3*10^{-3}$)	0.850
	Yes	0.337($8*10^{-6}$- 0.705)	
Nasal obstruction	**Mild to moderate**	0.0265($64*10^{-6}$-0.417)	**0.042***
	Severe	$10*10^{-5}$($3*10^{-5}$-$95*10^{-5}$)	
Itching	**Absent**	$14*10^{-5}$ ($6*10^{-5}$-0.073)	0.751
	Present	$122*10^{-6}$ ($33*10^{-6}$-$69*10^{-4}$)	
Nasal discharge	**Mild**	$8*10^{-5}$ ($6*10^{-5}$-0.0523)	0.725
	Moderate to severe	$1*10^{-5}$ ($3*10^{-5}$-$7*10^{-3}$)	
Postnasal discharge	**Absent**	$6*10^{-5}$ (0.026-0.284)	0.143
	present	$13*10^{-5}$ ($29*10^{-6}$-$84*10^{-5}$)	
Facial pain	**Absent**	$95*10^{-5}$ ($8*10^{-5}$-0.264)	**0.0009***
	present	$7*10^{-5}$ ($3*10^{-5}$-$56*10^{-5}$)	
Smell disorders	**Hyposmia**	$12*10^{-5}$ ($45*10^{-6}$-0.2659)	0.910
	Anosmia	$95*10^{-5}$ ($2*10^{-5}$-$7*10^{-3}$)	

Data are expressed as median (IQR) *Significant at P <0.05

In addition, our findings reported that patients who had nasal polys protruding beyond the middle meatus and filling the nasal cavity had significantly lesser levels of miR-34a-5p (p-value <0.05)

Also, significantly decreased levels of miR-34a-5p expression were detected in patients with nasal crusting with a P value <0.05 (Table 5).

Table 5: Relations between miR-34a-5p and nasal endoscopic examination among the patients:

		miR-34a-5p	
		Median (IQR)	**P value**
Nasal mucosa congestion	Pale blue	$91*10^{-6}$($35*10^{-6}$- $71*10^{-5}$)	0.118
	Congested	$21*10^{-5}$ ($55*10^{-6}$-0.271)	
Inferior turbinate hypertrophy	Mild to moderate	$4*10^{-4}$ ($3*10^{-5}$- 0.105)	0.303
	Severe	$7*10^{-5}$ ($5*10^{-5}$- $22*10^{-5}$)	
	Midline to mild deviation	$14*10^{-5}$ ($3*10^{-5}$-$72*10^{-4}$)	0.966
Degree of deviation	Severe	$8*10^{-5}$ ($4*10^{-5}$-$6*10^{-4}$)	
Polyp	**1** Polyps in middle meatus only	$98*10^{-5}$ ($1*10^{-5}$- 0.281)	**0.033***
	2 Polyps protruded beyond middle meatus	$79*10^{-6}$ ($3*10^{-5}$- $88*10^{-5}$)	
Mucosal Edema	**1** Mild	$25*10^{-5}$ ($8*10^{-5}$- 0.311)	0.163
	2 Severe	$8*10^{-5}$ ($4*10^{-5}$- $43*10^{-4}$)	
Nasal Discharge	**1** Thin clear or mucoid discharge	$14*10^{-6}$ ($6*10^{-5}$- $86*10^{-5}$)	0.985
	2 Colored thick discharge	$1*10^{-4}$ ($25*10^{-6}$- 0.076)	
Nasal Crusting	**0** Absent	$17*10^{-5}$ ($6*10^{-5}$- 0.120)	**0.001***
	1 Present	$16*10^{-6}$ ($6*10^{-6}$- $4*10^{-5}$)	

Data are expressed as median (IQR) *Significant at P <0.05

Patients who showed complete opacification of the maxillary, anterior ethmoid, and posterior ethmoid sinuses had significantly lower levels of miR-34a-5p with p-value <0.05 (Table 6).

Table 6: Relations between miR-34a-5p and CT findings among the patients:

		miR-34a-5p	
		Median (IQR)	**P value**
Maxillary sinus	Partial opacification	$0.259(6*10^{-5}$-0.331)	**0.039***
	Complete opacification	$1*10^{-4}$ ($3*10^{-}$-$95*10^{-5}$)	
Anterior ethmoids	Partial opacification	$0.130(24*10^{-5}$-0.589)	**0.020***
	Complete opacification	$9*10^{-5}$ ($29*10^{-6}$-$11*10^{-4}$)	
Posterior ethmoid	Partial opacification	$20*10^{-5}$ ($6*10^{-5}$-0.301)	**0.043***
	Complete opacification	$86*10^{-6}$ ($21*10^{-6}$-$57*10^{-4}$)	
Sphenoid	No or partial opacification	$15*10^{-5}$ ($6*10^{-5}$-0.112)	0.226
	complete opacification	$11*10^{-5}$ ($27*10^{-6}$-$57*10^{-4}$)	
Osteomeatal complex	Partially occluded	$81*10^{-4}$ ($6*10^{-5}$-$2*10^{-4}$)	0.717
	occluded	$12*10^{-5}$ ($34*10^{-7}$-0.105)	

Data are expressed as median (IQR), *Significant at P <0.05

MiR-34a-5p can be utilized to distinguish patients with CRSwNP from healthy control with a 94% sensitivity and 90.9% specificity with cutoff point = 0.22144 and a P-value <0.001 (highly significant considering they are biomarkers)

DISCUSSION

Chronic rhinosinusitis is the nasal and paranasal sinus inflammation that lasts for at least three months [19]. The life quality is adversely affected by CRS. The treatment for CRSwNP is costly since such disease usually resists medical treatment and also has a high relapse rate [20]. Consistent with the guidelines of EPOS [21], medical or surgical therapy of CRS should be relied upon the principles of evidence-based medicine. Management guidelines for CRS treatment based on the phenotype of patients. ENT physicians can quickly phenotype CRS patients according to the endoscopic examination and the severity of the disease. Clinical studies show that about 20.6% of the patients of CRSwNP require subsequent surgery for relapse in five years following original nasal endoscopic surgery. The CRSwNP relapse rate even reached 78.9 percent [22].

Around 4% of the universal population has CRSwNP, and men are more likely than women to obtain the disease [23], with the average age of clinical presentation in the fourth and fifth decade [24]. This was in agreement with our findings, which displayed that our patients group consisted of 30 men (60%) and 20 women (40%), whose ages ranged from 18 to 60 years (mean of 36.9 years).

Our findings in the current study reported that 80% of patients complain of severe nasal obstruction, and 78% with hyposmia, moreover by endoscopic and CT examination of paranasal sinuses, excess patients had polyps filling the nasal cavity. This is in agreement with a cohort study on 126 CRS patients done by Banjeri and colleagues who found that nasal obstruction and hyposmia were more significantly associated with CRSwNP patients and CRSwNP have more extensive sinus disease as measured through worse endoscopic and CT examination[25].

For the time being, the scientific community's task is to present concrete suggestions for the emergence of new biomarkers to create individualized treatment plans for different diseases. Over the last years, miRNAs have attracted scientific attention such as biomarkers in biopsies and treatment goals. miRNAs are single-stranded RNA molecules that control target messenger RNA expression in several diseases. Most cellular functions are managed by them as master post-transcriptional regulators, dysregulated expression of miRNAs may change specific cellular responses as well as assist in the emergence of different diseases. Additionally, it has been established that microRNAs perform an important part in inflammation control [26]. Some miRNAs play significant roles and have therapeutic promise in CRS, with miR-125b being the most often studied differentially expressed miRNA in research on CRS pathogenesis. Zhang et al., first employed miRNA microarray for examination of the expression profiles of miRNA in different phenotypes of CRS [10].

It was found a lot of interest in the relationship between microRNAs and the pathogenesis, relapse, miRNAs used as biomarkers, or treatment of CRSwNP. The potential influence of those is unknown at this time. We chose miR-34a-5p which has previously been associated with inflammation in other diseases, to examine the possible role of miRNA in immunological dysregulation associated with CRSwNP patients and control.

In the current work, a statistically significant difference between CRwNP patients and control was found with low mean miR-34a-5p among patients (P=<0.001) (down-regulation). Consistent with the research conducted Hou et al who discovered that individuals with obstructive sleep apnea-hypopnea syndrome have changed upper airway skeletal muscle tissue due to down-regulated miR-34a-5p [27]. Another study by Zhao et al. revealed that miR-34a was down-expressed in diabetic wounds inflammatory stage and this indicated that miR34a may inhibit the inflammation of wounds. The miR-34a anti-inflammatory property could be useful to hasten diabetic wound healing [28].

Our study revealed that the down-expression of miR-34a-5p had an association with the severity of the disease, in which the median for miR-34a-5p was lower in patients who suffered from severe nasal obstruction and facial pain. Patients who suffered from nasal polyps that were large enough to protrude outside the middle meatus had significantly decreased levels of the marker.

The title role of miR-34a-5p as a biomarker in separating patients from controls is shown in the present work by the ROC curve: miR-34a-5p was discovered to pose a sensitivity of 94% and a specificity of 90.9%, with a p-value of <0.001.

From the above findings, we suggested that the down-regulation miR 34a-5p level could be accountable for the appearance and the development of nasal polyps in CRSwNP patients and its effect in the complex pathogenesis of the illness, clarifying the role of miR-34a-5p as a new biomarker for CRSwNP in addition suggesting future research as new drugs to up-regulate the miR34a-5p level.

We recommended, studying the relation between miR-34a-5p and other anti-inflammatory markers especially type 2 markers like IL-13, IL-4, and IL-5 in chronic sinusitis patients.

CONCLUSION

MiR-34a-5p showed significant under-expression levels in CRSwNP patients. This emphasizes its role as a new biomarker for diagnosis and predicting prognosis of CRSwNP patients.

All authors have agreed to publish this paper in your journal and they confirm that this manuscript is not under publication in any journal.

No conflict of interest

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The present work was approved by the Ethics Committee of Fayoum University

Declarations:

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Authors' contributions

Sylvana N. Gaber, Mostafa M Ali, and Omayma O. Abdelaleem, wrote the manuscript, and contributed to the actual laboratory work. Sherif Guindi, Qotb Mohamed, and Mohammad bahi edited the manuscript.

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All methods were performed by relevant guidelines and regulations.

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