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The importance of microRNAs in Endocarditis Associated with *Staphylococcus aureus*

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***Abstract*— Prosthetic valve endocarditis is a rare microbial infection but a dangerous complication of cardiac valve replacement surgical treatment. This study aims to figure out the genotype of *Staphylococcus aureus* isolated from patients with PVE by multilocus sequence typing (MLST). The study included 117 patients who were diagnosed with prosthetic valve endocarditis during the period of January to September 2023 at Heart Center Hospital in Al-Nasiriya city, Iraq. From each patient, blood (5 ml) were collected and cultured on differential and selective media, to isolate *Staphylococcus aureus* that identified according to standard methods and then confirmed the identification by using the API-20 Staph system and by PCR using mecA gene. . As well as detection of microRNA -15 and microRNA-24 as a biomarker of *Staphylococcus aureus* Prosthetic valve endocarditis the detection the levels of microRNA -15 and microRNA-24 by Real-Time PCR. The results showed that out of (117) studied specimens, there was 25 (11.52%) of them had given growth, while only 21 (84.00%) of them were gram-positive bacteria, and only 14 (66.67%) of them were identified as *Staphylococcus aureus*, and most of them were MRSA infections with a rate 11 (78.57%), which have been more confirmed by detection of mecA gene. The results of miR-15 and miR-24 expression showed the mean fold change of microR-15 level in patients was lower than in control groups (3.89) versus (4.97). Whereas the mean fold change of miR-24 level in patients was (19.11), which was higher than that of control groups (12.92).**

In conclusion, it has been shown the essential role of MiRNAs as bacterial infections biomarkers.

Keywords*— *Prosthetic valve endocarditis (PVE), Staphylococcus aureus microRNA

I. INTRODUCTION

Prosthetic valve endocarditis (PVE) is one type of infective endocarditis (IE), it accounts for 20% of all endocarditis cases [1]. PVE classified traditionally into two periods (early and late) depending on the diversity of microbiological profile for each period [2]. Prosthetic tap endocarditis affected through *Staphylococcus aureus* is a plain contagion, by a death rate up to 50% a year [3]. *Staphylococcus aureus* are Gram positive cocci with a diameter ranging from 0.5 to 1.5 µm, non-spore forming, non-motile, facultative an aerobes ,produce catalase and coagulase enzyme [4, 5]. The proportion of PVE cases due to methicillin-resistant *Staphylococcus aureus* (MRSA) has increased in recent decades, reaching more than 15% of cases of *Staphyllococcus aureus* PVE [6]. *Staphylococcus aureus* especially MRSA strains is one of the main etiologies of community and hospital acquired bacterial infections. The management of MRSA infections is difficult by using traditional antibiotics such as beta-lactams. Furthermore, both MRSA and Methicillin sensitive *Staphllococcus aureus* (MSSA), has developed resistance to different antibiotics categories involving aminoglycosides, tetracyclines, fluoroquinolones, macrolides, amphenicols, and sulfonamides which are used to treat humans infections and showed multidrug resistant pattern [7,8]. Different agents participate in the development of *Staphylococcus aureus* PVE which involve the existence of virulence genes that encode factors such as adhesive proteins, exoprotein, toxins,Clumping Factor A which have a role in distinguishing microbial surface component recognizing adhesive matrix molecules (MSCRAMMs) that contribute to the binding and colonization microRNAs (miRNAs) are a pool of non-protein coding small RNAs with a length of around 20-22 nucleotides, the role of miRNAs includes the regulation of gene expression at post-transcriptional level [9]. More than 2,600 microRNAs actively regulate diverse biological methods, for example development, multiplying, cell differentiation, and apoptosis. Any change in microRNA expression could result in deficient cellular functioning and decline gene regulation, which clarifies the part of mi RNA in illness pathogene [10]. Pathogens encoded miniRNA that used intended for the existence and amplifying of pathogens in the host either by interfere with different physiological processes or modify crowde quipment for their personal advantage by altering mRNA expression pattern [11]. The microRNAs, considered as reliable biomarkers in several diseases [12], and different miRNAs such as microR-15 and miniR-24 require been initiate to have a critical role as a biomarkers in response against *Staphylococcus aureus* contagions in individuals and mouse copies[13,14]

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II. PATIENT AND METHOD

Subjects and Samples Collection: After obtaining approval by the Ethics Committee from College of Science, University of Al-Qadisiyah, this study was performed. The study included 117 patients who were diagnosed with Prosthetic valve endocarditis during period of January to September 2023, from Heart Center Hospital in Al-Nasiriyah city, Iraq. From each patient, 5 ml of blood sample were collected using transport medium (Blood culture Bottle) and transferred to laboratory.

Identification of *Staphylococcus .aureus* Isolates *:* Totally models were marked conferring to typical systems on distinguishing and improvement mass media (BloodAgar (Accumix /India), Manitol Salt Agar (Biomark /India) and MacConkey Agar (HiMedia /India) to detect *Staphylococcus aureus* and then keep warm aerobical by 37 °C for over nieght [15].

Microbial societies were detected firstly giving to its morphological characteristic as soon as develop on the media mentioned above, and include colony character, surface, dye, and upper hand as well as other properties such as its ability to ferment lactose and pigments production [15].

Microscopic investigation was complete by transporting single clean single colony via disinfected ring to a microscopic slip, fixed by using dry heat and stained with Gram stain [15]. The Identification was established by using API Staph System (BioMérieux /France) and Vitek-2 system (BioMérieux /France).

Quantitative Real-Time PCR (qPCR) for miRNA:Its used microRNAs as biomarkers in *Staphylococcus aureus* PVE and estimation miRNA 15 and miRNA24 as biomarker in *Staphylococcus aureus* prosthetic Valve endocarditis

A. STATISTICAL ANALYSIS

The data was displayed as Mean SD. The statistical analysis was conducted using the LSD method, with a significant threshold of P 0.05. Version 22 of the SPSS program (SPSS, Chicago, USA) was used.

III RESULT and DISCUSSION

In this study, out of (117) studied specimens, only 25 (11.52%) of them had given growth, while only 21 (84.00%) of them were gram-positive bacteria, and only 14 (66.67%) of them were *Staphylococcus aureus*.

Different culture characteristics of Gram-positive bacteria, such as colony form, hemolytic type, and pigmentation, were used to identify bacterial isolates. Round, convex, and 1-4 mm in diameter with a strong border, *Staphylococcus aureus* colonies on blood agar often exhibit a light to golden yellow pigment, whereas *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* colonies display either brilliant yellow or white [16]. Pigmentation isn't usually a dependable trait, though. *Staphylococcus aureus* typically exhibits obvious β-hemolytic zones on blood agar, but *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* are nearly invariably nonhemolytic [17].

On mannitol salt agar, coagulase positive in staphylococcus aureus products creamy groups and adjacent yellow medium. Coagulase negative show figure (1) and staphylococcus spp. produces bloods collections and no color change of the phenol pink pointer [18]. These morphological and microscopical examinations are the main characteristics of staphylococcus aureus as mentioned by [19].

A **B**

Fig. 1: This image shows *S. aureus* on the blood agar (A) and on the mannitol salt agar (B)

After all (21/25) isolates were stained with Gram stain, microscopic analysis was performed to see how the isolates responded to the stain, the cells appeared as gram-positive cocci, mostly grouped in irregular clusters that resembled grapes. The results showed among these 14 isolates were previously identified as *Staphylococcus aureus* by manual Identification as show API in figure (2),show the table (2) and show table (1) for API 20. Because Staphylococcus aureus has a dense, powerfully cross-link covering of peptidoglycan (20 - 80 nm) that tricks the major stain-mordant complex in the cell wall, the bacteria is gram-positive (21).

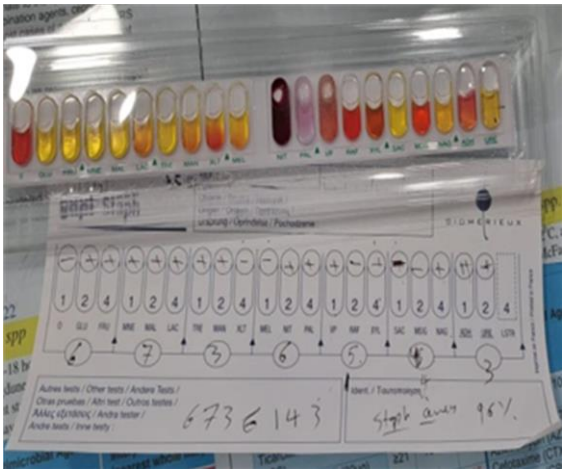

Fig. 2: The numerical profile in Api 20 system, The test positive, *Staphylococcus aureus*.

Table : 1 : The result of API 20 staph test

No.	Biochemical test	Results	No.	Biochemical test	Results
1	Negative control (O)	-	11	Nitrates to nitrites (NIT)	+
2	Positive control (GLU)	+	12	Alkaline phosphatase (PAL)	+
3	D-Fructose (FRU)	+	13	VogesProskauer (VP)	+
4	D-Mannose (MNE)	+	14	Raffinose (RAF)	-
5	D-Maltose (MAL)	+	15	Xylose (XYL)	-
6	D-Lactose (LAC)	+	16	Sucrose (SAC)	+
7	D-Trehalose (TRE)	+	17	Methyl-Alfa D-Glucopyranoside (MDG)	-
8	D-Mannitol (MAN)	+	18	N-Acetyl-Glucosamine (NAG)	+
9	Xylitol (XLT)	-	19	Arginine Dihydrolase (ADH)	+
10	D-Melibiose (MEL)	-	20	Urease (URE)	+

Table 2: Fold change (FC) of miRNA-15 in patients and control

HKG		Gene of Interest				Calculation		
Sample	CT	Sample	CT-Gene	CT-REF	Avg. CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta Ct}$
Normal Ref 1	31.81	Control 1	28.12	30.77	29.445	-2.365	-2.365	5.2
Normal Ref 2	31.34	Control 2	26.19	30.45	28.32	-3.02	-3.02	8.1
Normal Ref 3	30.76	Control 3	25.32	30.33	27.825	-2.935	-2.935	7.6
Normal Ref 4	30.14	Control 4	27.43	30.52	28.975	-1.165	-1.165	2.2
Normal Ref 5	31.62	Control 5	30.32	31.38	30.85	-0.77	-0.77	1.7
Patient Ref 1	28.77	Patient 1	25.76	28.37	27.065	-1.705	-1.705	3.3
Patient Ref 2	29.21	Patient 2	27.12	26.41	26.765	-2.445	-2.445	5.4
Patient Ref 3	28.98	Patient 3	26.81	29.13	27.97	-1.01	-1.01	2.0
Patient Ref 4	27.55	Patient 4	28.75	29.32	29.035	1.485	1.485	0.4
Patient Ref 5	29.37	Patient 5	24.19	28.41	26.3	-3.07	-3.07	8.4

The exact diagnosis of isolates was performed using the VITEK-2 system to complete the rest of the tests and experiments on those isolates. The existing marks presented that out of 21 examples were gram-positive bacteria, and only 14 (66.67%) of them were *Staphylococcus aureus.* The use of the Vitek-2 system to confirm the diagnosis of traditional biochemical tests is due to its Great feeling and specificity for the complete identification of *Staphylococcus aureus* isolates.

These can explain the finding that the patients were having antibiotic therapy in the last three days as a treatment for another infection and they were unwilling to give a proper history of their antibiotic administration [24].

MicroRNAs as biomarkers in *Staphylococcus aureus*

Comparison of fold change of microRNA-15 among study groups.As presented in the Table (2).

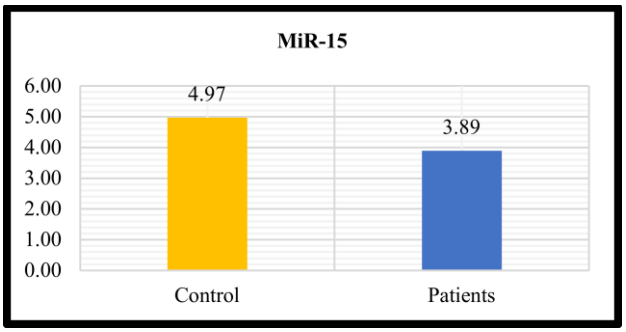

FIG. 3: Fold change (FC) of MiR-15 in patients and control groups

This finding was in accordance with a study by [20,21] which linked the micrRNA-15 family to bacterial infection in both people and mice. In response to gene pathways. In patients compared to control groups, miR-15 showed a decreased fold change (FC), while miR-24 exhibited an increased FC. While, the results of the current study were differed from what showed in independent study by [22,23]

that now *Staphylococcus aureus* contagion, raised stages of miRNA-15, miRNA-24, miRNA-128, miRNA-223, miRNA-142, and miRNA-155 remained noticed. Also, differ from what reported by [24-29] and [13].Where all found that patients who had an *Staphylococcus aureus* infection had higher amounts of miRNA-15, miRNA-24, miRNA-128, miRNA-223, miRNA-142, and miRNA-155. A lot of new studies has shown that miRNAs play a part in how *Staphylococcus aureus* infections start in humans and mice [27-29],[13]. Figure (3), the mean fold change (FC) of miRNA-15 level in patients was (3.89) which was lower than that of control groups (4.97).

It demonstrated the role of microRNA in the host's defense against bacterial infections. *Staphylococcus aureus* cells can alter the expression of microRNAs in the cells of the host. Moreover, research has discovered that *Staphylococcus aureus* can stimulate the production of miRNA-15 through the activation of responsive 2 species (ROS). Therefore, the triggering of miRNA-15b-5p after *Staphylococcus aureus* infection can hinder the process of wound healing. This, in turn, promotes the continuous inflammatory state associated with this condition [29].

This finding correspond with study of [30] which found that miniRNA-23a, miniRNA-23b, miniRNA-24, miniRNA-195, & miniRNA-214 showed greater than before levels during cardiac hypertrophy and induced hypertrophic development in cardiomyocytes. These reviews demonstrated that only certain particular miRNAs had a fundamental role in regulating cardiac hypertrophy programs.(24) examined the presence of MicroRNA-24 molecules, which regulate bone formation, in the blood of patients with osteomyelitis and in good physical shape individuals. In addition, the researchers quantified the amount of miniRNA-24 in *Staphylococcus aureus* infected mouse osteoblastic cells (MC3T3-E1). In previous studies [31-32] analyzed the expression of microRNA-24 using a method ,it is quantitative real-time polymerase chain reaction (qRT-PCR). A luciferase reporter test revealed that miniRNA-24 molecules regulate the chitinase-3-like1 (CHI3L1) gene(24) discovered that miniRNA-24 molecules attach to the 30' untranslated region (UTR) of CHI3L1 mRNA and prevent its production, which is associated to several signaling pathways. Therefore, the decrease in microRNA-24 fragments container eliminate the suppression of CHI3L1 production, which discovered that the CHI3L1 gene translates a 38-kD a glycoprotein that is not naturally created but is stimulated in various inflammatory situations, cancer illnesses, and tissue remodeling processes. The records indicated that the regulation of CHI3L1 concerning miniRNA-24 can have a substantial impact on antibacterial responses and infection.

The CHI3L1 gene is a direct goal of microRNA-24 and represses the production of CHI3L1 mRNA, which could have antibacterial properties. The high levels of miniRNA-24 causes decreased the levels of CHI3L1 during *Staphylococcus. Aureus* infuction, which helped the bacteria stay alive. Also, increasing miR-24 made the effects of *Staphylococcus. aureus* on MC3T3-E1 cells ineffective, while decreasing miR-24 made the effects effective. Hence, it is likely that innovative treatments for infections could utilize miR-24 molecules as a specific target for medication. These facts offer a unique and comprehensive understanding of the role of miRNAs in *Staphylococcus aureus* infections. Gaining a comprehension of this infection is crucial for the advancement of innovative therapies [14].

lately, researchers have been studying microRNAs in different infectious diseases as potential targets for therapy and as indicators for diagnosis [22,23]. This is because microRNAs tragedy a central part in regulating the formation of immune cells, hematopoiesis, immune responses, autoimmunity, and inflammation [33]. The microRNAs regulate both pro- and anti-inflammatory processes and undergo synthesis in various cells and organs [34]. Experiments involving the manipulation of gene activity have uncovered increasingly significant roles for these microRNAs in the field of cardiac biology. The over expression of certain up regulated microRNAs in hypertrophic hearts induces cardiac myocyte hypertrophy. In contrast, the decrease in expression of certain micro RNAs in hypertrophic hearts inhibits the enlargement of cardiac muscle cells [35] as shown in table (3) and figure (4).

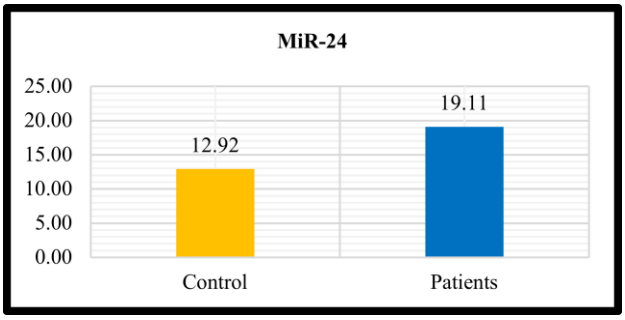

Fig. 4: below, the fold change (FC) of microRNA-24 in patients was (19.11) which was higher than that of control groups (12.92).

the fold change (FC) of miR-24 in patients was (19.11) which was higher than that of control groups (12.92).Researchers have recently investigated the comprehension of microRNA in *staphylococcus aureus* infections. Currently, research has shown the evolutionary importance of microRNA biogenesis and function process through numerous interactions between proteins and RNA, as well as between proteins themselves. This indicates that microRNAs serve a critical role due to its association with human illnesses [36], [23]. Associated the dysregulation of miRNA is an expression to the development of immunological, cardiovascular, and neurological complications, as well as cancer. Several diseases rely on microRNAs, as reliable biomarkers [12].

IV. CONCLUSION

In summary, prosthetic valve endocarditis (PVE) associated with *Staphylococcus aureus* is a serious, life-threatening complication of valve replacement, from a fold change in miRNA-15 and miRNA-24 levels, it has been confirmed from their role in PVE disease development

Table :3. Fold change (FC) of miRNA-24 in Patients and Control groups

HKG		Gene of Interest			Calculation			
Sample	CT	Sample	CT-Gene	CT-REF	Avg. CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta Ct}$
Normal Ref 1	31.81	Control 1	23.05	31.81	27.43	-4.38	-4.38	20.8
Normal Ref 2	31.34	Control 2	24.37	31.34	27.855	-3.485	-3.485	11.2
Normal Ref 3	30.76	Control 3	25.75	30.76	28.255	-2.505	-2.505	5.7
Normal Ref 4	30.14	Control 4	23.59	30.14	26.865	-3.275	-3.275	9.7
Normal Ref 5	31.62	Control 5	23.41	31.62	27.515	-4.105	-4.105	17.2
Patient Ref 1	29.81	Patient 1	22.52	26.81	24.665	-5.145	-5.145	35.4
Patient Ref 2	27.32	Patient 2	21.43	25.32	23.375	-3.945	-3.945	15.4
Patient Ref 3	27.82	Patient 3	23.59	26.82	25.205	-2.615	-2.615	6.1
Patient Ref 4	29.21	Patient 4	23.42	25.21	24.315	-4.895	-4.895	29.8
Patient Ref 5	28.61	Patient 5	25.31	25.61	25.46	-3.15	-3.15	8.9

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CONFLICT OF INTEREST

The authors declared that there was nothing different with interests

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