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Direktor: Prof. Dr. Thomas Walther

EXPRESSION OF CIRCULATING MICRO-RNAS IN PATIENTS BEFORE AND AFTER AAA REPAIR

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Xinji Tan

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Dekan: Prof. Dr. Stefan Zeuzem

Referent/in: Prof. Dr. Thomas Schmitz-Rixen

Korreferent/in: Prof. Dr. Wesley Abplanalp

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ZUSAMMENFASSUNG

Das Abdominale Aortenaneurysma (AAA) ist die häufigste Form eines Aortenaneurysmas, das als eine Erweiterung der Bauchaorta von 3.0 cm oder mehr definiert ist. Die Behandlung erfolgt bei Erreichen eines kritischen Durchmessers oder bei Symptomatik, wobei man zwischen der offenen chirurgische Therapie (OSR) und der endovaskulären Aneurysma-Reparatur (EVAR) unterscheidet. Technisch gesehen wird das erkrankte Segment der Aorta bei der OSR vollständig durch eine Prothese ersetzt, während es bei EVAR durch einen Stentgraft minimalinvasiv von intravasal ausgeschaltet wird. Die EVAR ist eine weniger invasive Behandlung als die offene Operation und zeigt eine niedrigere Frühmortalitätsrate, obwohl die langfristigen Vorteile von EVAR gegenüber OSR noch unklar sind. Studien haben eine höhere Reinterventionsrate für die endovaskuläre Therapie gezeigt, die Langzeitmortalität gleicht sich im Laufe der Zeit für beide Verfahren an.

Endoleaks, insbesondere das Typ II Endoleak (T2EL), ist eine häufige Komplikation nach EVAR. Laut Forschung entwickeln 16-28% der Patienten nach EVAR ein T2EL, das fast drei Viertel aller Endoleak-Typen ausmacht. Etwa 30-50% der T2EL verschwinden während der Nachbeobachtung spontan, einige können jedoch zu Aneurysmasackvergrößerung und demnach sekundäre Intervention bei den Patienten mit sich bringen. Da es in Anwesenheit von Endoleaks zur sekundären Aneurysmarupturen kommen kann, ist es entscheidend, Endoleaks nach EVAR zu überwachen.

Offene arterielle Gefäßabgänge im Bereich des Stentgrafts sowie Vasa Vasorum wurden als potenzielle Quellen für den Blutfluss bei T2EL identifiziert. Die Mechanismen der biologischen Veränderungen oder Remodeling des Aneurysma-Sacks nach der Reparatur sind jedoch immer noch nicht klar, obwohl sie als wichtig für die Entwicklung von Endoleaks angesehen werden. Leider ist es nicht möglich, Gewebeproben von der

Aortenwand bei Patienten zu erhalten, die sich einer EVAR unterzogen haben.

MicroRNAs (miRNAs) sind eine Klasse kleiner einsträngiger nicht-kodierender RNAs, die die Expression von Ziel-Messenger-RNA (mRNA) hemmen. miR-29b/29c, miR-155 und miR-15a sind miRNAs, die mit der Regulation von extrazellulären Matrixkomponenten (ECM), Entzündungen und Proliferation in Verbindung stehen. Alle vier miRNAs wurden als Biomarker für AAA identifiziert, nicht nur im Aneurysmengewebe, sondern auch als zirkulierende miRNAs im Blut. Es ist jedoch immer noch unbekannt, ob sie die biologischen Veränderungen nach AAA-Reparatur widerspiegeln können. Daher führten wir eine prospektive Studie durch, um die Veränderungen im Ausdruck von zirkulierendem miR-29b, miR-29c, miR-155 und miR-15a vor (T0), 3 Tagen (T1) und 3 Monaten (T2) nach AAA-Reparatur zu untersuchen.

Insgesamt wurden 39 Patienten für diese Studie rekrutiert, von denen 17 durch OSR und 22 durch EVAR behandelt wurden. Vier Patienten schieden im Verlauf aufgrund der Covid-19-Pandemie aus. Es wurden keine signifikanten Veränderungen im Ausdruck von miR-29b, miR-29c, miR-155 und miR-15a gefunden. Im Vergleich OSR und EVAR konnten keine offensichtlichen Unterschiede in der Expression der miRNAs gezeigt werden. Die T1-Expression von miR-15a war jedoch signifikant niedriger bei Patienten ohne Endoleak nach EVAR im Vergleich zu denen, die nach EVAR einen Endoleak entwickelten und denen, die durch OSR repariert wurden. Leider hielten diese Unterschiede nicht bis zur T2-Nachverfolgung an, und es wurden keine weiteren Unterschiede unter diesen Patienten festgestellt.

Zusammenfassend handelt es sich bei miR-15a um ein miRNA, dass sich signifikant bei AAA-Patienten verändert. Diese Studie zeigt, dass die Expression von zirkulierendem miR-15a bei Patienten ohne Endoleak drei Tage nach EVAR niedriger ist als bei denen, die nach EVAR einen Endoleak entwickelten und bei denen, die sich einer OSR

unterzogen. Die Ergebnisse legen nahe, dass miR-15a als möglicher Indikator für ein frühes Endoleak nach EVAR sein könnte.

SUMMARY

Abdominal aortic aneurysm (AAA) is the most common type of aortic aneurysm, which is defined as a dilation of the abdominal aorta over 3.0 cm or more. Surgical repair is the golden standard for the treatment of AAA, in which open surgical repair (OSR) and endovascular aneurysm repair (EVAR) are the main approaches. Technically speaking, the lesion segment of aueurysm is completely replaced by a graft during OSR, while in EVAR, the lesion is insulated by a stentgraft. EVAR is a less invasive treatment than OSR and shows a lower early mortality rate, although the long-term advantages of EVAR over OSR remain inconclusive.

Endoleak, especially the type II endoleak (T2EL), is a common complication after EVAR. According to research, 16-28% of the patients develop a T2EL after EVAR, and it accounts for nearly three in four of all types of endoleaks. Around 30-50% of the T2EL resolved spontaneously during the follow-up, however, it still causes a secondary intervention in many patients. Therefore, it is critical to monitor endoleaks after repair.

Patent aortic branches in the stent-overlapped area and vasa vasorum have been identified as potential sources of blood flow in T2EL. However, the mechanisms of biological changes or remodeling of the aneurysm sac after the repair are still not clear, but they have been considered to play an important role in the development of endoleaks. Unfortunately, it is impossible to obtain a tissue sample of the aortic wall in patients who underwent EVAR.

MicroRNAs (miRNAs) are a class of small single-stranded non-coding RNAs that inhibit the expression of target message RNA (mRNA). miR-29b/29c, miR-155, and miR-15a are miRNAs associated with regulating extracellular matrix (ECM) components, inflammation, and proliferation, respectively. All four miRNAs have been identified as

biomarkers of AAA, not only in aneurysm tissue but also extracellular as circulating miRNAs. However, it is still unknown whether they can reflect the biological changes after AAA repair. Thus, we conducted a prospective study to investigate the changes in expression of circulating miR-29b, miR-29c, miR-155, and miR-15a before (T0), 3 days (T1), and 3 months (T2) after AAA repair.

A total of 39 patients were recruited for this study, 17 of whom were repaired by OSR and 22 of whom were repaired by EVAR. Four patients failed the T2 follow-up due to the Covid-19 pandemic. No significant changes were found in the expression of miR-29b, miR-29c, miR-155, and miR-15a. There were also no obvious differences between OSR and EVAR. However, the T1 expression of miR-15a was significantly lower in patients without endoleak after EVAR than in those who developed endoleak after EVAR and those who were repaired by OSR. Unfortunately, these differences did not persist to the T2 follow-up, and no other differences were found among these patients.

In summary, miR-15a is a miRNA that significantly changes in AAA patients. This study demonstrates that the expression of circulating miR-15a is lower in patients without endoleak three days after EVAR, compared to those who had endoleak after EVAR and those who underwent OSR. The results suggest that miR-15a might be involved in the early aortic remodeling after EVAR as an indicator of endoleak.

1. INTRODUCTION

Aortic aneurysms cause a related global death rate of 2.49-2.78 per 100,000 individuals[1]. As the most common form of aortic aneurysms, abdominal aortic aneurysm (AAA) is described as the dilatation or enlargement of the abdominal segment of the infrarenal aorta. The definition of AAA recommended by the European Society of Vascular Surgery (ESVS) is that the maximum diameter (in anterior-posterior or transverse planes) of the enlarged abdominal aorta is 3.0 cm or more[2]. Under this criterion, the diameter for an aneurysmal aorta is considered as over 2.0 times of standard deviation of the mean diameter of humans or over at least 1.5 times the expected normal infrarenal diameter of the patient self[2].

1.1 Prevalence and Incidence

Approximately 2.1-5.3% of the world population may suffer from AAA[3-6], and the prevalence rate for a certain group is diverse in different ages, genders, races ethnicities, and geographic locations.

The prevalence of AAA is increasing with age, which is commonly occurred in patients over the age of 65[6-8]. The estimated global burden of AAA is increased from 2.02-21.85 per 100,000 individuals in persons aged <50 years old to 123.52-725.66 in persons aged 50-65 years old, and to 1,229.12-3,002.78 in persons aged >65 years old[9]. In addition, men hold a 4-6 times higher prevalence than women[6]. The screening study, which enrolled 485,636 participants in the UK, showed that the annual incidence of AAA in women was 1.1% per 10,000 persons and in men was 6.5% per 10,000 persons[8]. Similar trends have been found in the Asian states. The incidence rate of AAA was over 29.7 per 100,000 person-years for men >60 years old and over 8.6 per 100,000 person-years for women >60 years old[10]. As for race, caucasians hold a significantly higher rate of

prevalence than asians[11]. In the Aneurysm Detection and Management (ADAM) study, a cross-sectional screening study that investigated 73,451 veterans aged 50-79, smoked white men over the age of 65 showed the highest rate of AAA among all participants[5,12]. The population-based study from Norway reported the highest prevalence for men with AAA. In total 8.9% of the men in this study were diagnosed with AAA, and the prevalence was over 14.1% for the men >65 years old[6].

1.2 Risk Factors for AAA

The most important risk factors of AAA are increasing age, male gender, smoking history, and family history[6-8,12]. The risk of AAA increased by 40% every 5 years after 65 years old, which is significantly higher in men than women by around 6 times[13]. The evidence of smoking on the risk of AAA is concrete, although its mechanism is still under research. Compared with the patient who never smoked, current smokers have an increased risk of AAA by 7.6 folds, while ex-smokers have a 3.0-fold higher risk[14]. Both duration of smoking and the consumption of cigarettes per day were associated with the increased risk[14,15]. Family history is also an important risk factor for AAA, which increased the risk by 1.93-4.77 times[12,16]. In the prospective study, around 3.3-25% of the siblings of the AAA patients had been found with AAA, simultaneously[17-20].

Besides, hypertension[5,7,15,16], atherosclerosis[21], hyperlipidemia[7,15,16], diabetes mellitus[5,7,16], and comorbid other cardiovascular diseases (coronary artery disease[5,7], cerebrovascular diseases[5], or other vascular aneurysms[5]) were correlated with AAA, although evidence of these correlations were inconsistent[22,23]. Interestingly, as a traditional risk factor for cardiovascular diseases, diabetes mellitus has shown a protective effect on AAA. Patients with diabetes mellitus not only held a lower rate of prevalence of AAA[24,25] but also had a lower aneurysm growth rate[26] and a lower rupture rate[27]. In addition, several studies have reported that height[5], obesity[28], alcohol consumption[29,30],

and socioeconomic factors[31] were associated with the development of AAA.

Research on the family history of AAA provided evidence that genetic factors played an important role in the development of AAA. The heritability analysis from twin studies showed that 70-77% of the total phenotype variance could be explained by the genetic effects and 23-30% of the variance was caused by the non-shared environment effects[32,33]. Several AAA-associated genetic loci and single nucleotide polymorphisms (SNPs) have been reported from genome-wide association studies (GWASs), which are mainly involved in the pathophysiological process like inflammation, lipid metabolism, extracellular matrix (ECM) remodeling, and vascular development[34].

1.3 Natural History

Around 57% of the sub-aneurysm aorta, identified as the aorta diameter of 2.5-2.9 cm, would become AAA within 5 years[35]. Over half of the patients who had an over 4.0 cm initial AAA diameter reached the criteria of surgical repairment within 5 years[36]. Most of the AAA grow linearly, and some AAA expand staccato, exponentially, or indeterminately[37]. The AAA growth rate is diverse in different baseline AAA diameters. The growth rate of AAA in 3.0 cm of diameter is 1.03-1.85 mm/year, and the rate is increased by approximately 0.5-0.59 mm/year for each increase in 0.5 cm of diameter[38,39]. Smoking is an important risk factor for AAA. The growth rate of the current smoker is 0.35 mm/year faster than the former smoker or the person who never smoked[40]. Diabetes shows a protective effect on the growth of AAA, which holds a 0.51 mm/year slower rate than the patient without diabetes[40]. There is a theory that this protective effect of diabetes is contributed by the utilization of metformin in those patients[41,42].

The risk of rupture for AAA is also increasing with the increase of aneurysm diameter, which is around 0.3 per 100 person-years for those with a diameter of 3.0-3.9 cm to 1.5

for the diameter of 4.0-4.9 cm, and to 6.5 for the diameter of 5.0-5.9 cm[43]. The reported rupture rate for AAA is diverse in different sexes, which is almost 4 times higher in women than men[38,40]. For men, the rupture rate of AAA sized in 3.0-5.5 cm is ranged from 0.5 to 6.4 per 1,000 person-years. As for women, the rate is from 2.2 to 29.7 per 1,000 person-years[38]. Another important risk factor for the rupture of AAA is smoking, which increased the risk by over 2.0 times[38,40]. In addition, aging and high blood pressure have been shown positively associated with the risk of rupture[40].

1.4 Pathogenesis

1.4.1 Atherosclerosis

Atherosclerosis aortic aneurysm is the most common form of AAA. Thus, there is a close relationship between AAA and atherosclerosis. The conventional opinion considers the development of AAA as a pathological response of the aorta to atherosclerosis. When the atherosclerotic plaque or intraluminal thrombosis developes, the intraluminal hemodynamic forces (such as shear stress) change and cause alteration of phenotypes of endothelium and vascular smooth muscle cells (VSMCs) and remodeling of the ECM[44]. Through this mechanism, the expanded aorta compensatory maintaines the luminal dimension. However, when this positive remodeling is excessive, the AAA develops[45]. Another theory believes that the development of AAA and atherosclerosis are independent of each other[46-48], although they shared similar environmental and genetic risk factors.

1.4.2 Inflammation

Traditional opinion believes that inflammation only exists in inflammatory AAA, which only represents 3-10% of AAA and characterizes by the thickening of the aortic wall and

adhesion of the peri-aneurysm tissues[49]. However, current studies have found concrete evidence that inflammation is not only crucial in inflammatory AAA but also in atherosclerotic AAA[50]. Hence, the pathological degradation of the aortic wall in AAA is believed to arise from an immune dysregulation, in which various inflammatory cells and their products play important roles.

Macrophages, especially monocyte-differentiated macrophages, play an important role in the early stage of AAA[51]. After receiving the biological signal, the circulating monocytes migrate to the injured aortic wall and onward differentiate into two subtypes of macrophages through the macrophage polarization[52]. The classically activated macrophages (M1 macrophages) are mainly located in the adventitia of the aortic wall, which would promote inflammation[52]. In contrast, the alternatively activated macrophages (M2 macrophages) are predominant in intraluminal thrombus and play an anti-inflammatory role during AAA[52]. During the progression of AAA, the polarization of macrophages was shifted from M1 dominance toward M2 dominance[53].

Neutrophils are one of the most crucial cells in inflammation, which are significantly increased in AAA[54]. The neutrophils act their functions through phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs)[55,56]. There are three important granules in neutrophils, including azurophilic granule, specific (secondary) granule, and gelatinase (tertiary) granule, which contain abundant enzymes and proteases[56]. NETs were covered with various proteases, antimicrobial molecules, and toxic molecules[55]. The exposed proteases, such as matrix metalloproteases (MMPs), directly destroy the normal structure of the aortic wall[51,57]. NETs could also build communications between neutrophils with other immune cells and modulate the inflammatory microenvironments[51,57]. In addition, the net-like structure of NETs promotes the capture of blood cells in the lumina, which may contribute to thrombosis[51,57].

Dendritic cells (DCs), mast cells, and natural killer (NK) cells also take part in the innate immune response of AAA[58-60], which give rise to T cells proliferation and activation, leukocytes adhesion and migration, VSMCs apoptosis and downregulation of its viability, and aortic matrix degradation[51].

T lymphocytes are the predominant infiltrated adaptive immune cells in AAA tissue, in which $CD4^+$ T cells are the majority subpopulation[61]. $CD4^+$ T cells consist of helper-1 T (T_h1) cells, T_h2 cells, T_h17 cells, T_h22 cells, regulatory T (T_{reg}) cells, and follicular helper T (T_{fh}) cells[62,63]. T_h1 cells and T_h2 cells modulate AAA mainly by secreting T_h1 cytokines (IFN-γ, IL-2, TNF-β) and T_h2 cytokines (IL-4, IL-5, IL-6, and IL-10), which are associated with the activity of macrophages, VSMCs apoptosis, collagen synthesis, and MMPs secretion[51,64]. The balance of T_h1/T_h2 cytokines is important in matrix remodeling after allografted aortic transplantation[65]. T_h17 cells promote inflammation and interact with T_{reg} cells by secreting IL-17, IL-17F, IL-21, and IL-22[66,67]. IL-17 is the main cytokine that originated from T_h17 cells, and it is overexpressed in the aortic tissue of AAA patients[68]. T_{reg} cells are an important subgroup of $CD4^+$ T cells, which is characterized by the expression of forkhead box protein 3 (FOXP3) and could suppress inflammatory reactions during the AAA[51]. The proportion of T_{reg} cells is decreased in the peripheral blood of AAA patients[69], and the expansion of T_{reg} cells in the AAA mice model significantly against the development and progression of AAA by decreasing the infiltration of immune cells and the expression of proinflammatory cytokines, increasing the anti-inflammatory cytokines, and suppressing the apoptosis and oxidative stress[70,71]. In addition, $CD8^+$ T cells[72] and gamma-delta TCR^+ T cells[73] were also increased in the aortic tissue of AAA patients.

Few studies have investigated the function of B lymphocytes in AAA, however, as an important type of adaptive immune cell, it has been found to increase during the disease[74]. Similar to the T cells, B cells are predominantly located around the vasa vasorum,

especially in the adventitia of the aneurysm[61]. The main function of B cells is to secrete immunoglobulins (IgG and IgM), besides, they can also produce various cytokines (IL-6, IL-10, and TNF-α) and MMPs[75]. The levels of IgG1, IgG2, and IgG3 are increased in AAA[76], which activates the complement C3 components through three pathways and eventually results in aortic wall destruction and AAA development[75]. There is a special subtype of AAA named "IgG4-related inflammatory AAA", which is characterized by a higher number of $IgG4^+$ plasma cells infiltration and elevated concentration of serum IgG4[77]. Unlike the common autoimmune disorders, which are associated with the activation of T_h1 cells and T_h17 cells, IgG4-related diseases are mainly related to the activation of T_h2 cells and T_{reg} cells and result in tissue fibrosis[78].

1.4.3 Genetics and Epigenetics

The third type of theory of AAA pathogenesis emphasizes the importance of genetic and epigenetic factors during AAA development. As mentioned above, the heritability studies have shown that 70-77% of the total phenotype variance in AAA could be explained by the genetic effects and only 23-30% was caused by the non-shared environment effects[32,33]. Mendelian syndromes are caused by single-gene mutation, which generally affects the aortic root, ascending aorta, and thoracic aorta, but it has also been found in patients with AAA. Marfan and Marfan-like syndromes are the most common type in AAA patients with the Mendelian syndrome[79], which is caused by the mutation of the FBN1 gene and (or) TGF-β receptor genes (TGFBR1, TGFBR2, and TGFBR3)[80]. In addition, the mutation of the TGF-β signaling axis (TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2, and SMAD3) would also contribute to another Mendelian syndrome, called Loeys-Dietz syndrome (LDS)[80]. Moreover, AAA has been reported in patients with vascular Ehlers-Danlos syndrome (caused by COL3A1 mutations) and aneurysm-osteogenesis syndrome (caused by COL1A1 and COL1A2 mutations) in which the mutations were related to the ECM component[81].

With the arising utilities of GWAS, many non-mendelian syndrome-relevant genes, like SNPs, have been identified in the past years. Several SNPs have been found associated with ECM components and MMPs, which affect the structural remodeling of the aorta. For example, rs3025058 for MMP-3[82-84], rs3827066 for MMP-9[83], and rs2252070 for MMP-13[82] are positively associated with the risk of AAA, in contrast, rs2071307 (encoding ENL)[82,85] and rs243865 (encoding MMP-2)[82] are negatively associated with the risk of AAA.

Several genes that encode inflammatory components have been found associated with AAA. IL-10 is an immune-regulating cytokine, which could suppress the inflammatory response during AAA[86]. rs1800896 is an SNP located in the IL10 gene, and the rs1800896 major (A) allele is associated with the increased risk of AAA by downregulating the level of plasma IL-10[87,88]. Another inflammation-related SNP is rs2228145, which is a non-synonymous variant in the IL6R gene and leads to the substitution of alanine with asparagine at amino acid position 358. rs2228145 is associated with the decreased risk of the development of AAA[89]. Moreover, rs10757278 has been identified as associated with several cardiovascular diseases including AAA, which encodes CDKN2A and CDKN2B[90].

Hyperlipidemia is marked as a risk factor for AAA, and several SNPs have been identified as associated with lipid metabolism. rs6511720 is located in the LDLR gene, which is negatively associated with the risk of AAA[91]. rs1466535 is an SNP in the LRP1 gene, which increases the binding of LDL to LDLR and promotes the development of AAA[92]. rs7025486 was found in the DAB2IP gene, which is associated with the increased risk of AAA[93]. Of note, DAB2IP is a member of the Ras-GTPase activating proteins (RasGAPs), which could not only regulate lipid droplet homeostasis by inhibiting the activity of RAB40C (a lipid trafficking protein)[94] but also promote cell apoptosis by upregulating

the ASK1-JNK pathway and downregulating the PI3K-Akt pathway[95].

In addition, several SNPs were identified as correlated to cell adhesion (rs7635818 tagged in CNTN3[96]) and vascular development (rs1795061 tagged in SMYD2[97], rs2836411 tagged in ERG[97]), there are also associated with the AAA. However, considering the technical limitation of GWAS, the exact relationships between these SNPs and AAA should be confirmed by more research.

Epigenetic modification is described as the heritable phenotype changes without the alterations in DNA sequences, like DNA methylation, histone modifications, and post-transcriptional regulation of non-coding RNAs (microRNA and lncRNA)[80]. microRNAs (miRNAs) are a class of small single-stranded non-coding RNAs that in a length of 18-21 nucleotides and inhibit the target message RNA (mRNA) expression by assembling into RNA-induce silence complex (RISC)[98]. miR-29 family, including miR-29b and miR-29c, is the most important set of miRNAs that promote the AAA formation by regulating ECM conponents[99,100]. miR-181b[101] and miR-205[102] are also associated with the turnover of ECM in AAA, and both inhibit the expression of the same gene, TIMP3. miR-195 is another identified miRNA that regulates the expression of ECM protein and MMPs[103]. The plasma level of miR-195 has been found not only associated with the presence and aortic diameter of AAA[103] but also with the rapidity of aneurysm growth[104].

miR-155 is a significant miRNA that exerts a regulator in the context of AAA[105], given its versatile capacity to modulate a diverse range of inflammatory cells[106-108]. miR-24 suppress the survival and activities of macrophages by targeting the CHI3L1 gene, thereby inhibiting inflammation during AAA[109]. Another inflammation-related miRNA is miR-33, which targets the ABCA1 gene and the ABCG1 gene and takes part in the cholesterol metabolism of macrophages[110]. miR-33 has also been shown to suppress the proliferation of VSMCs in grafted veins by targeting the BMP3 gene[111].

Moreover, miR-15a, a tumor suppressor in several cancers[112-114], has been shown to possess the ability to modulate VSMCs apoptosis by targeting CDKN2B in AAA[115]. Similarly, miR-145 and miR-143 have been shown to regulate the phenotype of VSMCs[116] and the communication between VSMCs and endothelial cells (ECs)[117,118], thereby stabilizing the aneurysm.

lncRNAs are another class of non-coding RNA that are over 200 nucleotides in length. Compared with miRNA, lncRNA holds a poorly conserved nucleotide sequence between species, and it has a diverse mode of action in regulating gene expression[98]. Increased H19 promotes apoptosis and against the proliferation and migration of smooth muscle cells (SMCs) by regulating the expression of hypoxia-induced factor-1 alpha (HIF-1α), thereby causing the dilation of the aorta[119]. Moreover, SENCR[120] and SMILR[121] have been also demonstrated associated with the migration and proliferation of SMCs, and both of them have been considered to have a potential role in AAA. Inc-HLTF-5 has been shown positively correlated with the aortic diameter and MMP-9 level in the thoracic aortic aneurysm (TAA)[122]. AK056155 has been found involved in the development of Loeys-Dietz syndrome through the AKT/PI3K pathway[123]. Furthermore, A meta-analysis of GWAS of AAA identified Linc00540 as a disease-specific risk locus[97], and this lncRNA has been verified in a meta-analysis based on another population[124].

With the arising attention on circular RNAs (circRNAs) in the past years, several circRNAs have been found associated with AAA, such as circ000595[125], circ101238[126], and circ0021001[127]. However, the function of these cicRNAs is obliged to be verified by more research.

1.5 Treatment

The pharmacologic treatment for AAA is based on two concerns: reducing the cardiovascular risk and stabilizing the aneurysm. The use of statins, β-blockade, antiplatelet therapy, or blood pressure control has been shown to improve the survival of patients with AAA[2,128]. Unfortunately, no medicine has been shown to effectively attenuate the clinical progression of AAA[128]. Thus, after an aneurysm meets the threshold, a surgical repair would be the only remedy. According to the current guideline from the ESVS, the aneurysm repair is recommended for 1) the male patient with a maximum aneurysm diameter of 5.5 cm (or for the female patient with a diameter of 5.2 cm), 2) the patient who develops symptomatic AAA, or 3) the patient who has a rapid aneurysm growth (>1 cm/year)[2].

To date, two types of surgical repairs are widely used for the treatment of AAA. Open surgical repair (OSR) for AAA has been practiced since the 1950s[129]. The operation could be performed through a trans-abdominal or retroperitoneal approach[130-133]. Endovascular aneurysm repair (EVAR) was first reported in 1991[134], which is a less invasive method compared to OSR. With the development in technique, EVAR has become the most frequent treatment for AAA. In Germany, the use of EVAR is currently more than four times higher than OSR in patients with intact AAA[135]. However, because of anatomic limitations (e.g., hostile aortic anatomy), OSR is still important in clinical practice. Technically, the aneurysm sac would be completely replaced by a graft during OSR, resulting in the cessation of perfusion within the sac. Whereas, during EVAR, a stent would be placed in the aneurysm sac to relieve the direct intraluminal pressure on the aortic wall. As a result, the aneurysm sac persists, albeit with a tendency to shrink due to lacking perfusion.

Of note, three important long-term multicenter randomized controlled trials (RCTs) have been conducted to investigate the differences between OSR and EVAR for AAA repair.

The Endovascular Aneurysm Repair trial-1 (EVAR-1) was reported in 2004, which recruited 1,082 AAA patients aged over 60-year-old in the UK. The EVAR-1 trial showed that both 30-day mortality (4.7% vs 1.7%, $p<0.001$) and in-hospital mortality (6.2% vs 2.1%, $p<0.001$) were significantly higher in the OSR group than in the EVAR group[136]. The long-term follow-up showed that both all-cause mortality and aneurysm-related mortality were lower in the EVAR group than the OSR group within the first 6 months after repair, but the EVAR group held a higher reintervention rate within the first 4 years[137,138]. Besides, the total mortality after 8 years was significantly higher for EVAR, and it was mainly attributed to a higher secondary aneurysm rupture[137]. The Open Versus Endovascular Repair (OVER) trial recruited 881 patients from the US veterans affairs medical centers, which showed that the perioperative mortality (death within 30-day postoperatively or during the hospitalization) was lower for EVAR than for OSR (0.5% vs 3.0%, $p=0.004$)[139], and this benefit of EVAR persisted until 3 years after the repair[140], after that, no difference in overall survival during the long-term follow-up up to 14 years[140,141]. In contrast, the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, which recruited 345 AAA patients with an aneurysm diameter ≥5.0 cm, showed that no significant differences were found between the OSR group and the EVAR group in both short-term and long-term mortality[142-144]. Whereas the short-term rate of moderate and severe systematic complications was higher after OSR[142], and the rate of secondary procedure in this trial was higher in the EVAR group, which is mainly because of the aneurysm-related indications[144]. A large-scale propensity-score-matching-based study, which identified 39,966 matched pairs of AAA patients, showed that the survival rate was higher for EVAR in the first 3 years of follow-up and the difference was gone after that time[145]. Nevertheless, EVAR held a higher aneurysm-related reintervention rate during the 8 years of follow-up[145].

1.6 Endoleaks

Endoleaks are described as the presence of persistent blood flow outside of the stent graft but within the aneurysm sac after the AAA repair[146]. Around 30% of the patients developed endoleak after EVAR[147-149], which is significantly associated with postoperative aneurysm growth but does not affect survival[147,150]. A long-term analysis showed that 86.4% of the AAA patients who underwent EVAR for 2 years were free from endoleaks, whereas 68.3% for 10 years, and 48.6% for 14 years[151].

1.6.1 Classification

Generally, endoleaks are classified into five types: type I endoleak (T1EL), type II endoleak (T2EL), type III endoleak (T3EL), type IV endoleak (T4EL), and endotension (T5EL). According to the time endoleak occur, it could also be classified as early/primary endoleak (within the first 30 days after repair) and late/secondary endoleak (during the follow-up)[2]. Moreover, some studies have defined an endoleak that persists for over 6 months as a persistent endoleak[152].

1.6.1.1 Type I endoleak (T1EL)

T1EL is the blood flow caused by the inadequate seal at the proximal (Type Ia, T1aEL) or the distal (Type Ib, T1bEL) end of the stent graft, or the iliac occluder (Type Ic, T1cEL). Around 1.9-4.0% of the patients have T1EL after repair[148,151,153], which is significantly associated with postoperative aneurysm sac growth and rupture[154]. The hostile neck anatomy is generally defined as the aneurysm neck length ≤15 mm (length of the aortic segment from the inferior border of the renal artery to the superior border of the aneurysm sac) and with one or more following events: 1) infrarenal aneurysm neck angle >60 degrees (the angle between long-axis of aneurysm and long-axis of aneurysm neck); 2)

aneurysm neck diameter >28 mm; 3) neck thrombus or calcification over 50% of the area of the cross-section (or with >2 mm thickness); 4) reverse taper morphology (gradual neck dilation >2 mm)[155,156]. Patients with hostile neck anatomy have a higher risk of T1EL[155,157-159], especially a higher risk of T1aEL[156,160-162]. In contrast, the presence of T1bEL is related to the tortuous iliac artery and a large diameter of the common iliac artery[163], and an extensive distal sealing length appears to reduce the risk of late T1bEL[164].

1.6.1.2 Type II endoleak (T2EL)

T2EL, the most frequent endoleak, represents the retrograde blood flow that comes from one (Type IIa, T2aEL) or more (Type IIb, T2bEL) aortic side branches[2], which occurred in around 16-28% of patients who underwent EVAR[165,166] and accounts for three-quarters of all endoleaks[147]. Approximately 30-50% of the T2EL resolved spontaneously during the follow-up, and the rest of them require secondary intervention[147,167]. T2EL is significantly associated with aneurysm sac growth[168], but long-term follow-up showed that T2EL did not change the all-cause mortality and aneurysm-related mortality[169,170].

Patent inferior mesenteric artery, lumbar arteries, accessory renal artery, or median sacral artery are the most common aortic branches involved in T2EL[171,172], and vasa vasorum have been considered another source of endoleak[173,174]. The number and the size of side branches are the most important risk factors for T2EL, in addition, anticoagulation therapy and the burden of thrombus in the aneurysm may also be risk factors[171,172]. Besides the anatomic factors, inflammation has been proven not only related to the development and progression of AAA but also plays an important role in endoleaks. Patients with systematic inflammatory diseases (such as allergic rhinitis, osteoarthritis, gout, and rheumatoid arthritis) have been shown to have more T2EL and late aneurysm sac expansion[175]. Meanwhile, several studies showed that the systematic inflammatory response after the repair (e.g., post-implantation syndrome) gave a protective effect to

reduce the risk of T2EL[176,177].

1.6.1.3 Type III endoleak (T3EL)

T3EL is attributed to the secondary structural failure of the graft, for which type IIIa (T3aEL) is caused by component disconnection (a result of migration and angulation of the stent graft) and type IIIb (T3bEL) is caused by fabric disrupture[2]. The incidence of T3EL is between 3% to 12% in the old generation of stent grafts, and with the arising use of the new generation of stent grafts, the incidence is significantly decreased[178]. However, considering T3EL increased the risk of postoperative aneurysm rupture by nearly 9 times[179], reintervention is strongly necessary.

1.6.1.4 Type IV endoleak (T4EL)

T4EL refers to the blood flow penetrated from the porous stent graft[2]. Compared to T3EL, the stent graft in T4EL is intact. Chronic wear, deformation of the stent graft, and chronic exposure to the pulsatile forces might be possible mechanisms for T4EL[180]. 0.4-3% of patients developed T4EL after the aneurysm repair[147,151], and it is far less frequent with the current generation of stent grafts. T4EL is less possible to cause the rupture since its blood flow is low and would generally disappear spontaneously[181].

1.6.1.5 Endotension (T5EL)

Endotension refers to the enlargement of an aneurysm sac after the repair but failed to detect any type of endoleaks[2], in some studies, it was also called the type V endoleak (T5EL)[182]. The reported incidence of endotension ranged from 0.46% to 6.89%[182]. Unfortunately, the mechanism of endotension is still unclear, but it may be attributed to the limitation of sensitivity of current imaging techniques[183], pressure transmission

through the graft wall[184], aneurysm sac hygroma caused by hyperfibrinolysis of thrombus[185], and infections[186].

1.6.2 Surveillance

Stent-graft-related endoleaks (T1EL and T3EL) can be life-threatening complications since they are the main causes of postoperative aneurysm rupture[187]. According to the current suggestion from the ESVS guideline (*Figure 1*), treatment should be taken once T1EL or T3EL have been observed during the follow-up[2]. In contrast, for T2EL and endotension, treatment is only considered when the diameter of the aneurysm sac increases over 10 mm[2] during observation.

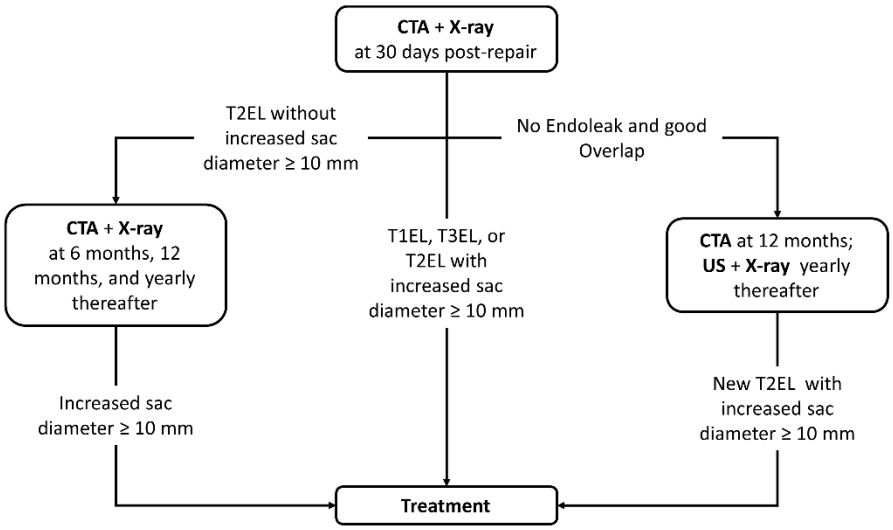


Figure 1. Surveillance protocol for endoleak after AAA repair as suggested by the ESVS guideline.

Digital subtraction angiography (DSA), color-doppler ultrasonography (CDUS), contrast-enhanced ultrasonography (CEUS), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) are the most frequently used techniques in the detection of endoleaks, while plain radiography is generally used to assess device migration, stent fracture, and modular disconnection[2]. CTA is the gold standard for postoperative surveillance after AAA repair, and it is considered the best method for endoleak detection[2] since it not only offers a high temporal and spatial resolution in anatomy but is also crucial for further clinical decision-making[188]. CDUS is a widely used imaging test for primary surveillance, which is less expensive, easy to perform, and without radiation. In contrast, CEUS offers higher sensitivity than CDUS without losing the advantages of ultrasonography, and some research showed that CEUS is as accurate as CTA in endoleak detection[189,190]. MRA is another applicable technique used in the follow-up of AAA patients, postoperatively. MRA provides a similar, and even better, accuracy as CTA in the endoleak detection[190], meanwhile, it hosts advantages like freedom of radiation exposure and renal function friendly.

In addition, several non-imaging techniques have been evaluated for the detection of endoleaks. For instance, aortic aneurysm sac pressure could be measured through an implantable pressure transducer (implanted at the time of repairment), which provides a long-term immediate evaluation of sac hemodynamics. Several studies showed that aortic aneurysm intrasac pressure measurements are feasible and reliable for the detection of endoleaks[191,192].

1.7 Aim of the Study

miRNAs have been proven to be significantly associated with the development and progression of AAA. However, the biological information of aneurysms after the repair

is scarce, and no research has investigated the expression of miRNAs in patients with postoperative endoleaks. Moreover, it seems completely impossible to obtain aneurysm tissue after successful EVAR for a study of postoperative aortic remodeling. Hence, the primary purpose of the present study is to investigate the changes in the expression of selected circulating miRNAs in AAA patients before and after repair, and the secondary purpose is to find out their differences in patients with or without endoleak.

2. MATERIALS AND METHODS

2.1 Study Design

This AAA repair was conducted at the Department of Vascular and Endovascular Surgery of the University Hospital Frankfurt of the Goethe University (Frankfurt am Main, Germany), and the samples were measured at Max-Plank- Institute of Heart and Lung Disease (Bad Nauheim, Germany). The ethical approval was obtained from the University Hospital Ethics Committee of Goethe University Frankfurt (Geschäftsnummer 396/18). Prior to the participation, all patients provided written informed consent in accordance with the applicable ethical guidelines.

Based on the observed difference from the literature[193], to compare the expression levels of miRNAs before and after AAA repair, a minimum required sample size of 30 was calculated using an assumed effect size of 1.25 with a statistical power (1-β) of 0.90 and a significance level (α) of 0.05. To account for the possibility of loss to follow-up, approximately 40 patients requiring AAA repair were prospectively recruited for the present study. Inclusion and exclusion criteria for the present study were as following:

Inclusion criteria:

1) age ≥18 years old;

2) patients were diagnosed with AAA and reached the indication for surgical repair according to the recommendation from the ESVS;

3) infrarenal or juxtarenal AAA.

Exclusion criteria:

1) age <18 years old;

2) women of childbearing age;

3) history of a prior operation on the aorta;

4) concomitant with a second aneurysm (thoracic, femoral, visceral, or popliteal);

5) malignancy;

6) peripheral arterial disease (PAD);

7) connective tissue disease.

All patients were treated by either EVAR or OSR and were subjected to a 3-month follow-up (*Figure 2*). Decision-making for the type of operation was done by the treating surgeon upon clinical and anatomical criteria and not part of the study. Preoperative baseline characteristics including age, sex, blood pressure, heart rate, smoking history, comorbidities, and medication history were documented, along with the type of repair, presence of intra- and postoperative endoleaks, and other perioperative complications. Blood samples were collected at three time points: before the operation (T0), at the 3-day (T1), and at the 3-month (T2) post-repair. The expression levels of miR-15a, miR-29c-3p, miR-29b, and miR-155 of the collected samples were quantified.

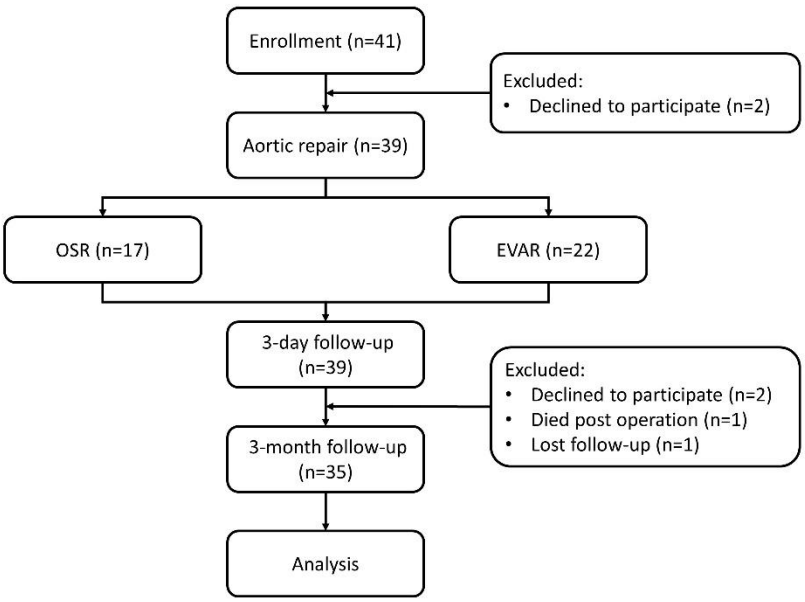


Figure 2. The workflow diagram for patient allocation and follow-up.

2.2 Plasma Preparation

In total 10 ml of whole blood was taken from the patient's vein and collected into two 5 ml blood sample tubes containing ethylenediaminetetraacetic acid (EDTA). Samples with macroscopic hemolysis were excluded. The first centrifugation was taken at 3,000 r/min for 10 min at room temperature using Hettich® Rotanta/AP (Andreas Hettich GmbH, Germany) immediately after withdrawal and the supernatants were carefully removed and transferred to a new tube. The second centrifugation was performed at 13,000×g for 10 min at 4°C using Thermo Scientific™ Fresco™ Microcentrifuge (Thermo Fisher Scientific Inc., the United States) to remove residual blood cells. Plasma was then stored at −80°C until further processing.

2.3 Total RNA Extraction

Frozen plasma was thawed at room temperature. The total RNA extraction was used by

the miRNeasy Serum/Plasma Advanced Kit (Qiagen, Germany) according to the manufacturer's instructions. Briefly, 50 µl plasma was blended with 15 µl buffer RPL and 3.5 µl cel-miR-39 (Qiagen, Germany) and incubated at room temperature for 3 min. 5 µl buffer RPP was then added into the reaction tube and incubated at room temperature. After 3 min of incubation, the mixture was centrifugated at 12,000×*g* for 3 min. The supernatant (around 60 µl) was mixed with 60 µl isopropanol and transferred to an RNeasy® UCP MinElute® spin column. The spin column was centrifugated for 5 sec at 8,000×*g*, and the flow-through was discarded. In the same way, the spin-column was then washed with 700 µl buffer RWT (centrifugated for 15 sec at 8,000×*g*), 500µl buffer RPE (centrifugated for 15 sec at 8,000×*g*), and 500 µl 80% ethanol (centrifugated for 2 min at 8,000×*g*), step by step. Finally, the 20 µl RNase-free water was used to carry the extracted total RNA (incubated for 1 min and centrifugated for 1 min at 13,000×*g*). All isolated total RNA was utilized to synthesize the complementary DNA (cDNA), immediately.

2.4 Synthesis of cDNA

cDNA was synthesized using miRCURY LNA™ RT Kit (Qiagen, Germany) by reverse transcription according to the manufacturer's instructions. Reverse transcription was carried out in a 10 µl solution that contained 2 µl miRCURY RT Reaction Buffer (5× concentrated), 5 µl RNase-free water, 1 µl miRCURY RT Enzyme Mix (10× concentrated), and 2 µl total RNA template. After being mixed on ice gently, the reaction mixtures were incubated in SensoQuest Labcycler (SensoQuest GmbH, Germany) followed by 42°C for 60 min and 95°C for 5 min, and then cooled down to 4°C. The part of the final cDNA products proceeded to the quantitative real-time-polymerase chain reaction (qPCR) directly and the remainder was stored at −20°C.

2.5 PCR Amplification

All samples were analyzed in triplicates. The PCR amplification was carried out using miRCURY LNA™ SYBR® Green PCR Kits (Qiagen, Germany) and following the manufacturer's protocol of miRCURY LNA™ miRNA PCR Assays. First, 10 µl cDNA was diluted to 1:30 by 290 µl RNase-free water. Then, blended 3 µl diluted cDNA with 5 µl miRCURY LNA SYBR® Green Master Mix, 1 µl resuspended PCR primer mix, and 1 µl RNase-free water. In total 10 µl reaction mix was dispensed into PCR plate wells, and centrifuged at room temperature. PCR amplification was carried out on a Bio-Rad® CFX96™ Real-Time PCR detection system (Bio-Rad Laboratories, the United States). The PCR program was initiated at 95°C for 2 min, then followed by 40 cycles of 95°C for 10 sec and 56°C for 60 sec. cel-miR-39 (Qiagen, Germany) has been added to samples during the RNA extraction as a spike-in control.

2.6 Statistical Analysis

All statistical analyses were conducted in SPSS for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA) or GraphPad, version 9.0.0 (GraphPad Software, San Diego, CA, USA). The continuous variables with normal distribution are presented as mean and standard deviation (SD), and the continuous variables with non-normal distribution are presented as median and interquartile range. Categorical data were presented as numbers (percentages). Differences between cohorts were compared by t-test or Mann-Whitney u-test (for continuous variables) and by Chi-square test or Fisher's exact test (for categorical variables). For multiple categorical variables, the Bonferroni post-hoc-test was used to compare the differences at each level of the variable.

Due to missing data during the follow-up period, miRNA expression comparisons between patients who underwent OSR and EVAR were analyzed using a mixed model

followed by Sidak's post hoc test. To assess the differences in miRNA expression between patients after OSR and those with or without endoleak after EVAR, a one-way ANOVA was conducted for data with residuals following a Gaussian distribution. For data that did not meet the assumption of Gaussian distribution, a nonparametric test was utilized.

3. RESULTS

In total 41 patients were eligible to meet our inclusion criteria from 2019 to 2022, two patients withdrew consent to participate in the study after inclusion and before the aortic repair (*Figure 2*). Until the present report, thirty-nine patients had aneurysm repair and completed the 3-day follow-up, in which 17 patients were repaired by OSR and 22 patients were repaired by EVAR. Thirty-five patients completed their 3-month follow-up. During this time, probably due to the influence of the Covid-19 pandemic, nine patients had a delayed 3-month follow-up (Median month for delay: 3 [1, 5]), two patients withdrew consent for follow-up in the subsequent study for personal reasons, and one patient was lost to the follow-up. One patient died before his T2 follow-up.

After the aneurysm repair, 10 (25.6%) patients developed an endoleak. Nine endoleaks were onset at T1 and one at T2, and three patients had persistent endoleak during the 3 months follow-up. All endoleaks were T2EL and were diagnosed after EVAR. Significant reductions in aneurysm diameter were observed in both patients with and without endoleak (*Figure 3*). Besides, no differences in baseline characteristics and postoperative complications were found between patients who underwent OSR and EVAR (*Table 1*).

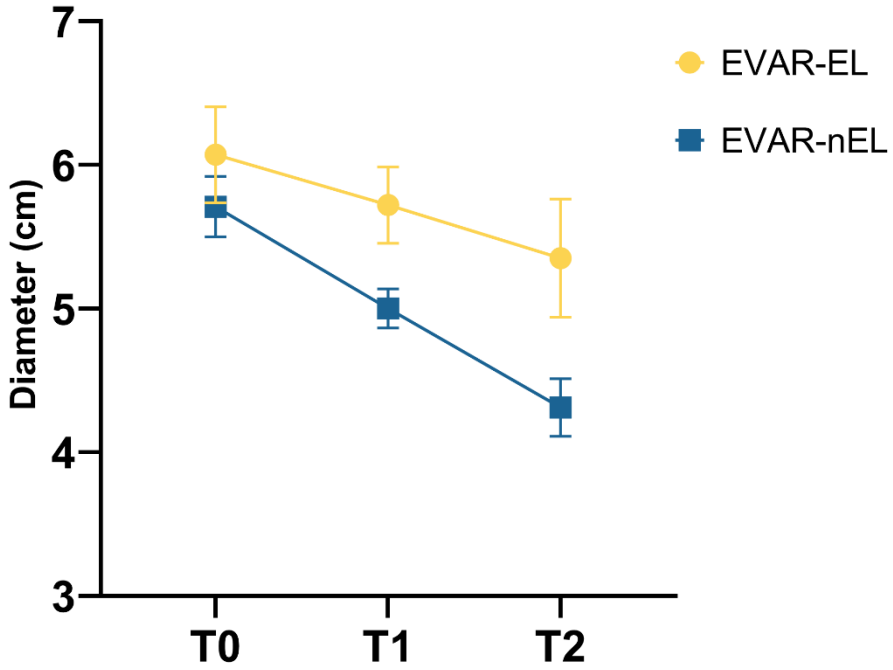


Figure 3. Change in aneurysm diameter between patients who developed endoleak and those who did not after EVAR. (EL: endoleak; nEL: no endoleak)

Table 1. Preoperative baseline characteristics and postoperative complications between patients with OSR and EVAR at the first 3 months post-operation.

Parameters	**OSR**	**EVAR**	***p*-value**
No.	17	22	
Age, yrs	71.71±6.77	73.50±9.36	0.510
Sex, n (%)			
Men	14 (82.4)	20 (90.9)	0.636
Women	3 (17.6)	2 (9.1)	
Systolic BP, mmHg	130.09±16.13	131.56±11.36	0.783
Diastolic BP, mmHg	73.00±9.49	77.86±5.79	0.133
Pulses, n	69.11±9.06	68.00±12.90	0.826

Diameter, cm	6.46±1.37	5.87±0.89	0.113
Comorbidity, n (%)			
CHD	8 (47.1)	9 (40.9)	0.701
CKD	1 (5.9)	4 (18.2)	0.363
DM	1 (5.9)	2 (9.1)	>0.999
HLD	2 (11.8)	3 (13.6)	>0.999
HTN	12 (70.6)	19 (86.4)	0.261
COPD	2 (11.8)	1 (4.5)	0.570
PAD	1 (5.9)	2 (9.1)	>0.999
Others	2 (11.8)	5 (22.7)	0.438
Smoking history, n (%)			
Non-smoker	3 (21.4)	4 (30.8)	0.850
Current smoker	4 (28.6)	3 (23.1)	
Former smoker	7 (50.0)	6 (46.2)	
Medication history, n (%)			
ACEI	6 (35.3)	8 (36.4)	0.945
Beta-blocker	7 (41.2)	10 (45.5)	0.789
CCB	3 (17.6)	2 (9.1)	0.636
Statins	9 (52.9)	14 (63.6)	0.501
Diuretics	6 (35.3)	8 (36.4)	0.945
PPI	4 (23.5)	10 (45.5)	0.157
Antiplatelets	12 (70.6)	15 (68.2)	0.872
VKA	0 (0)	0 (0)	/
Anticoagulants	0 (0)	4 (18.2)	0.118
L-Thyroxine	2 (11.8)	1 (4.5)	0.570
NSAIDs	0 (0)	0 (0)	/

Opioids	0 (0)	0 (0)	/
Metformin	1 (5.9)	0 (0)	0.436
Insulin	0 (0)	0 (0)	/
Other antidiabetics	1 (5.9)	0 (0)	0.436
SSRIs	1 (5.9)	0 (0)	0.436
SNRIs	0 (0)	0 (0)	/
MAOIs	0 (0)	0 (0)	/
Others	5 (29.4)	7 (31.8)	0.872
T1 Complications			
Endoleaks	0 (0)	9 (40.9)	0.003
Thromboembolism	1 (5.9)	0 (0)	0.436
Reoperation	0 (0)	0 (0)	/
Bleeding	0 (0)	0 (0)	/
Pneumonia	0 (0)	0 (0)	/
MI	0 (0)	0 (0)	/
Kidney failure	1 (5.9)	1 (4.5)	>0.999
Others[*]	4 (23.5)	6 (27.3)	0.791
T2 Complications			
Endoleaks	0 (0)	4 (20.0)	0.119
Thromboembolism	0 (0)	0 (0)	/
Reoperation	0 (0)	1 (5.0)	>0.999
Bleeding	0 (0)	1 (5.0)	>0.999
Pneumonia	0 (0)	0 (0)	/
MI	0 (0)	0 (0)	/
Kidney failure	0 (0)	0 (0)	/

*Others**	2 (13.3)	0 (0)	0.176

BP, Blood pressure; CHD, Coronary heart disease; CKD, Chronic kidney disease; DM, Diabetes mellitus; HLD, Hyperlipidemia; HTN, Hypertension; COPD, Chron ic obstructive pulmonary disease; PAD, Peripheral arterial disease; ACEI, Angiot ensin-converting-enzyme inhibitor; CCB, Calcium channel blocker; PPI, Proton p ump inhibitor; VKA, Vitamin K antagonist; NASIDs, Non-steroidal anti-inflammat ory drugs; SSRIs, Selective serotonin reuptake inhibitors; SNRIs, Serotonin–norep inephrine reuptake inhibitors; MAOI, Monoamine oxidase inhibitor; OSR, Open s urgical repair; EVAR, Endovascular aneurysm repair; MI, Myocardial infarction;

** Other complications include constipation, blood transfusion, arrhythmia, deliri um, chyloabdomen, anaphylactic reaction, paresthesia, subfebrile temperature, p ost-implantation syndrome, or infection.*

The plasma expression of miR-155, miR-15a, miR-29b, and miR-29c in patients who underwent OSR and EVAR were shown in *Figure 4*. No significant differences were found in these four miRNAs between OSR and EVAR. Additionally, the expressions were changed insignificantly during the follow-up from T0 to T2.

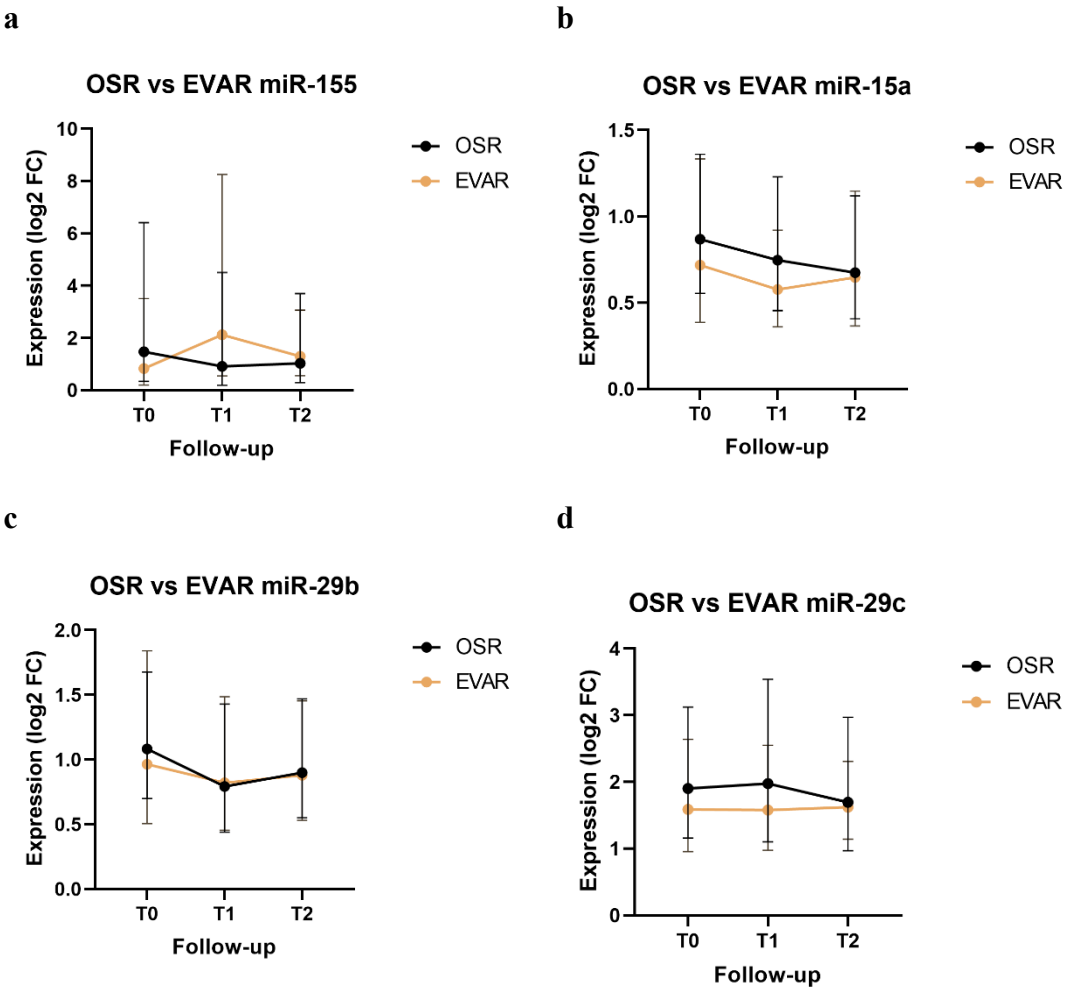
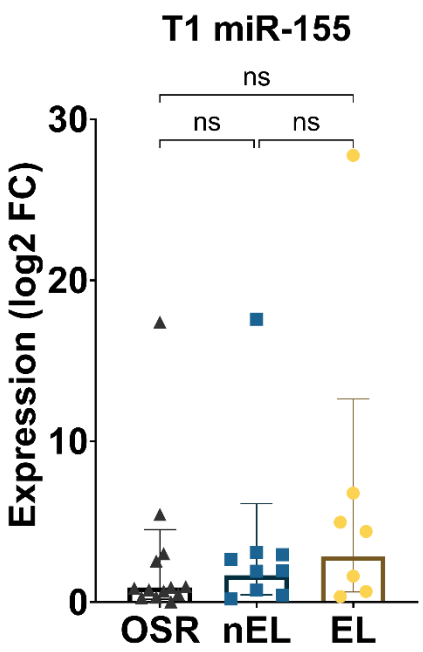


Figure 4. Differences in expression levels of miR-155, miR-15a, miR-29b, and miR-29c between patients underwent OSR and EVAR. **a**) No significant difference in the expression pattern of miR-155 between OSR and EVAR (p_{Time}=0.2252, $p_{Treatment}$=0.8912, $p_{Time \times Treatment}$=0.1450); **b**) No significant difference in the expression pattern of miR-15a between OSR and EVAR (p_{Time}=0.1022, $p_{Treatment}$=0.4400, $p_{Time \times Treatment}$=0.3619); **c**) No significant difference in the expression pattern of miR-29b between OSR and EVAR (p_{Time}=0.0760, $p_{Treatment}$=0.9729, $p_{Time \times Treatment}$=0.9637); **d**) No significant difference in the expression pattern of miR-29c between OSR and EVAR (p_{Time}=0.5680, $p_{Treatment}$=0.1116, $p_{Time \times Treatment}$=0.7483).

Patients who did not develop endoleak after 3 days of EVAR had a lower T1 expression of miR-15a than those who either developed endoleak after EVAR or underwent OSR, whereas no difference was found between the latter two groups (*Figure 5a*). No other differences were found at the T1 follow-up between each group. Moreover, no significant differences were found at the T2 follow-up between each group (*Figure 5b*).

a



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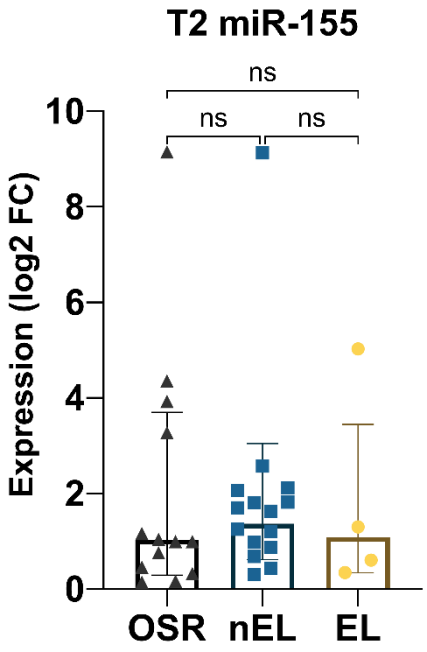

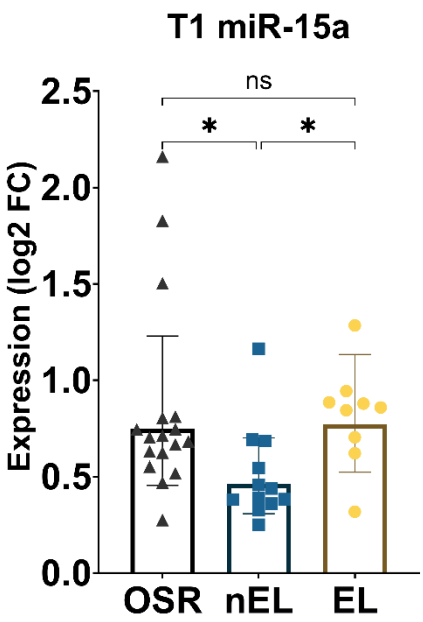
T1 miR-15a
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ns
*
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OSR
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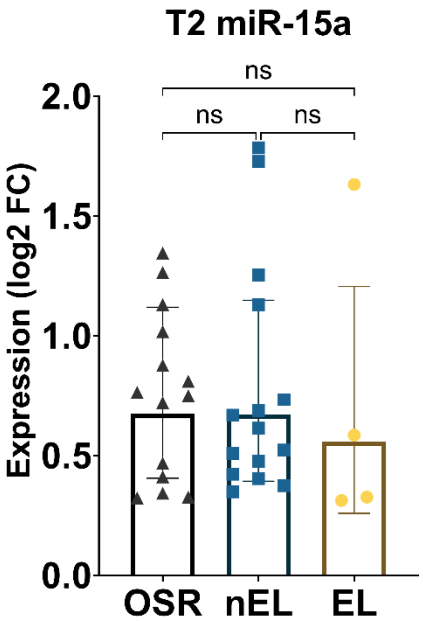
T2 miR-15a
Expression (log2 FC)
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OSR
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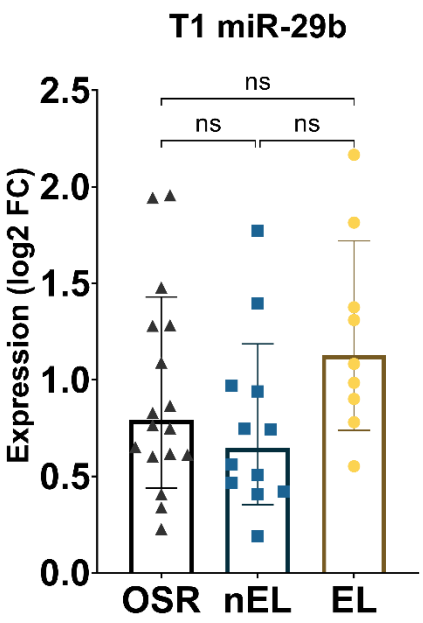
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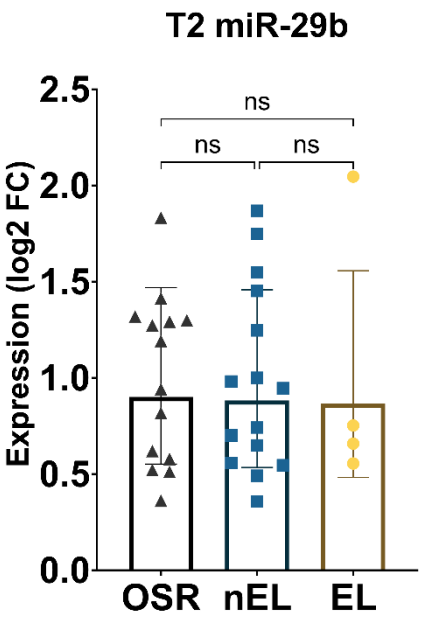
T2 miR-29b
Expression (log2 FC)
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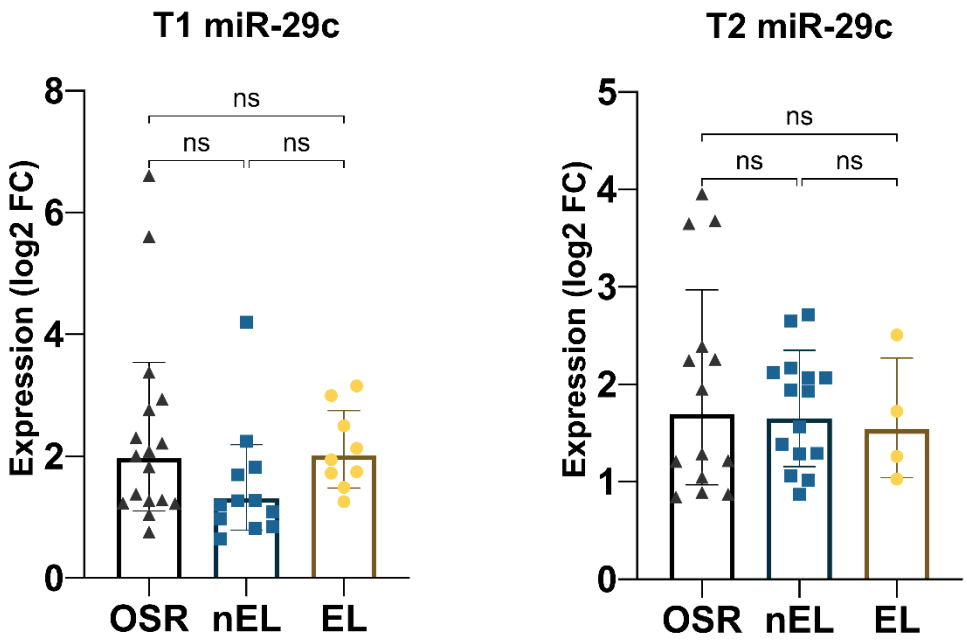

Figure 5. Plasma expression levels of miR-155, miR15a, miR-29b, and miR-29c at 3 days (T1) and 3 months (T2) after OSR and after EVAR with and without Endoleak. **a**) Expression levels at T1. The expression levels of miR-15a were significantly higher in patients after OSR than in those without endoleak after EVAR (p<0.05), but no significant difference when compared to patients with endoleak after EVAR. No statistical differences in the levels of miR-155, miR-29b, and miR-29c between each group. **b**) Expression levels at T2. No significant differences in the levels of miR-155, miR-15a, miR-29b, and miR-29c between each group.

4. DISCUSSION

Aortic remodeling after AAA repair is crucial for the surgical outcome, as early aneurysm sac shrinkage after EVAR has been considered a surrogate marker of repair success[194,195]. In general, the dilated aneurysm sac could be excised or sewn up over the graft (as we did in the present study) during OSR. Conversely, after the EVAR, the lesion is bypassed using a stent, leading to a subsequent shrinkage of the aneurysm sac. However, the

understanding of the biological processes involved in postoperative aortic remodeling is limited. Therefore, in this study, we conducted a prospective investigation to examine the expression of circulating miR-155, miR-15a, miR-29b, and miR-29c in patients before and after AAA repair.

Brujin et al.[196] exploratory investigated the histology of the aortic wall in patients with failed endovascular repair of AAA. Compared to the primary aneurysm wall (tissue from elective open repair), the aortic wall after repair showed more fibrosis, less inflammation, less calcification, and less atherosclerotic burden. In addition, after the repair, there was a neovascularization in the aneurysm intima and a large number of tertiary lymphoid organs-like structures in the adventitia. Similarly, Mengus et al.[197] analyzed the aneurysm wall in patients who underwent failed EVAR repair (with persistent T2EL), and the results showed that the dilated aneurysm wall appears to have significant intima/media thinning, altered ECM composition, and less inflammation. On the contrary, this study showed less fibrosis and neovessel formation in the intima/media layer compared to Brujin's. In addition, aortic calcification[198] and unorganized aneurysm sac thrombus[199] are also related to the failure of aneurysm shrinkage after EVAR.

MMPs contribute to aortic remodeling through their ability to degrade components of ECM and some non-matrix substrates[200]. MMP-9 is an important member of MMPs, the plasma level of which has been shown to accurately detect endoleaks after AAA repair in some research[201,202]. The meta-analysis verified that the high level of plasma MMP-9 concentrations demonstrated an endoleak in 3 months postoperatively, although there is no difference in 1 month after the repair[203]. Moreover, Wang et al.[204] showed that the plasma level of TNF-α converting enzyme (TACE) and Notch1 concentrations could be used to detect the presence of endoleaks with an AUC of 0.930 [CI95%: 0.883-0.978, p<0.01]. However, the diagnostic function of circulating biomarkers was not coherent. Moxon et al.[205] tested the level of circulating MMP-9, osteoprotegerin, D-dimer,

homocysteine, and C-reactive protein in patients who underwent elective EVAR, and the results showed that none of these four biomarkers were associated with the endoleaks.

Non-coding RNAs, especially miRNAs, have been also proven to play a significant role in AAA pathology[98]. Lyer et al.[105] reported a systematic review that included 15 studies from 2000 to 2016 and showed that miR-155 was upregulated in two tissue-based studies but controversial in blood-based studies (2 for upregulation and 1 for downregulation), whereas miR-29b was downregulated in two blood-based studies and diverse in two tissue-based studies. Moreover, three studies have reported the decreased expression of miR-15a and two studies have reported inconsistent expression of miR-29c in the circulating blood. Of these 15 studies, only two analyzed the samples from both tissue and blood, simultaneously. Kin et al.[206] screened the expression of tissue- and plasma-specific miRNAs in atherosclerotic AAA and showed that the fibrosis-related miRNA miR-29b, the inflammation-related miRNA miR-155, and the apoptosis-related miRNA miR-15a were significantly downregulated in plasma, whereas, miR-29b and miR-155 were upregulated in aneurysm tissue. A similar study reported by Biros et al.[193] showed that the expression of miR-155 was higher in the aneurysm body than in the neck, while it was 2.67-fold higher in patients with AAA compared to their sex- and age-matched healthy controls. Another study reported by Plana et al.[207] in 2020 showed that the expression of miR-29b-3p was decreased in AAA tissue, but there was no difference in the expression of miR-155-5p. However, in the present study, none of the above miRNAs changed significantly during the 3 months follow-up after repair by either OSR or EVAR, and we did not find any significant differences in these four miRNAs between patients who underwent OSR and those who underwent EVAR (*Figure 4*), although patients after 3 days of OSR showed a higher expression of miR-15a than those who did not develop endoleak after 3 days of EVAR (*Figure 5a*). Regarding EVAR specifically, apart from a lower expression of miR-15a at T1 follow-up in patients without endoleak after EVAR compared to those with endoleak, none of these four miRNAs demonstrated significant

differences at either T1 or T2 follow-up (*Figure 5*).

The miR-29 family hosts four members, miR-29a, miR-29b-1, miR-29b-2, and miR-29c, and they are transcripted from two clusters, the miR-29a/b-1 cluster and the miR-29b-2/c cluster[208]. In humans, the miR-29a/b-1 cluster is located on human chromosome 7 (7q32.3) and the miR-29b-2/c cluster is located on human chromosome 1 (1q32.2)[208]. The mature miR-29 family members shared the same seed sequence, AGCACC, which is conservative among species[208]. In humans, the miR-29 family is mainly highly expressed in the brain and heart tissue[209] as well as adaptive immune cells[210]. Bioinformatics revealed that the predicted targets of miR-29 were enriched at three biological processes (cellular processes and connective tissues, nervous and cardiovascular disease, and cancer and hematological functions) and at ten canonical signaling pathways (April signaling, IL-6 signaling, BAFF signaling, Glioma signaling, Axonal guidance signaling, TR/RXR activation, B-cell receptor (BCR) signaling, Intrinsic prothrombin activation pathway, PDGF signaling, and Estrogen-dependent breast cancer signaling)[211]. The miR-29 family has been validated to play an important role in the TGF-β-dependent pathway in the regulatory network of myocardial fibrosis (MF). miR-29 could target TGF-β2 and MMP2 to inactivate the TGF-β/Smad pathway to attenuate MF[212], while Smad3 would reduce the expression of miR-29 and exhibit a pro-fibrosis effect[213]. In addition, TGF-β1 was shown to activate the Notch pathway by increasing the related proteins[214], hence miR-29 might regulate the Notch pathway through the TGF-β/Smad pathway[215]. Tao et al.[216] showed that miR-29a participates in the inhibition of the MAPK pathway by targeting the VEGF-A. Hanping et al.[217] showed that the activation of AMPK inhibited the expression of hepatocyte nuclear factor 4 alpha (HNF-4α) and repressed the binding of HNF-4α to TGF-β1 promotor, and further downregulated TGF-β1 and upregulated miR-29. In addition, miR-29 has been shown directly targeted CDK2 to inhibit cardiac fibrosis[217]. Moreover, miR-29 could activate canonical and non-canonical Wnt pathways by downregulating their negative regulators[218,219]. In turn, the canonical Wnt pathway has

been shown to induce the transcription of miR-29a and formed a positive feedback loop with it[219]. Moreover, miR-29 has been found to inhibit DNA methylation by targeting DNA methyltransferases (DNMTs)[220,221].

miR-155 is regarded as an inflammation-related miRNA, which used to be identified as a B-cell integration cluster (BIC)[222,223]. In B cells, miR-155 has been verified to regulate ERK activation and cell proliferation by impairing the expression of SH2 domain-containing inositol 50-phosphatase 1(SHIP-1) and enhancing the sensitivity of BCR ligation[224,106]. miR-155 regulates the expression of cytokines in macrophages and DCs to promote inflammation. The expression of miR-155 has been shown to induce the increased production of TNF-α[225-227], IL-1β[225,226], IL-6[225], and IL-8[225] in macrophages. On the other hand, lacking miR-155 has been shown to decrease the expression of IL-12[228,229], IL-6[228,229], IL-1β[228,108], TNF-α[228-230], and IFN-α/β[230] in DCs, hence impairing the differentiation of Th17 cells and Th1 cells and consequently reducing the production of IFN-γ[228]. Moreover, several studies showed that the number of T_{reg} cells was reduced in miR-155-deficient mice[231,232], and the allergic model showed that the T-cell intrinsic miR-155 also played a crucial role in the Th2-mediated type 2 immunity by partially regulating S1pr1[233]. In $CD8^+$ T cells, the expression of miR-155 was upregulated in primary effector and effector memory T cells but downregulated in naive and central memory cells[107]. The deficiency of miR-155 impaired the effector T cell response to viral infection and skewed the differentiation preferably toward central memory T cells[234,235].

In the present study, the plasma miR-15a was significantly downregulated 3 days after successful EVAR (no endoleak), however, there was no difference at 3 months (*Figure 5*). miR-15a belongs to the miR-15 family, which is a set of miRNAs with a seed sequence AGCAGC that starts at their second nucleotide from the 5' end of the mature miRNA[236]. In addition, miR-103 and miR-107 hold the same seed sequence as the miR-15 family but start at the first nucleotide[236]. Hence, in many studies, they were examined together as the

miR-15/107 gene group. miR-15a is associated with many cardiovascular diseases. miR-15a has been verified as a target of KLF4, which could inhibit the proliferation of VSMCs and ECs by upregulating miR-15a[237]. The expression level of miR-15a is increased not only in ECs[238] but also in circulating progenitor cells[239] during limb ischemia, which inhibits angiogenesis and migration by mediating Tie or VEGF-A/Akt-3, respectively. Moreover, recent research showed that miR-15a could facilitate the ferroptosis of cardiomyocytes under the regulation of Erg-1[240]. All this information indicates that reduced miR-15a is involved in the preservation of vascular homeostasis, and it probably sheds light on explaining the results in our study, where the patients without endoleak after EVAR had a significantly lower level of circulating miR-15a. However, it cannot explain why this difference disappeared at 3 months postoperatively. Furthermore, miR-15 acts as a tumor suppressor in many types of cancers, including B-cell chronic lymphocytic leukemia (CLL), mantle cell lymphomas, multiple myeloma, and prostate cancers[241]. BCL2 is one of the main targets of miR-15a, which has been identified in CLL to regulate cell cycle and cell apoptosis[112]. In prostate cancer, the decreased expression of miR-15a and miR-16 was significantly associated with the increased expression of BCL2, CCND1, and WNT3A, which was considered to affect the survival, proliferation, and invasion of cancer cells[113]. miR-15a has also been shown to regulate T-cell immunity[242,243] and fat metabolism[244,245], which may contribute to the disorder in coronary artery disease and type II diabetes mellitus[246,247].

Unfortunately, except for the lower expression of miR-15a at 3 days after successful EVAR, our study failed to yield any other significant results about the relationship between postoperative outcomes and the selected miRNAs, it remains unclear how aneurysm wall changed after the AAA repair. To the greatest challenge, due to endovascular repair it is impossible to obtain a sample of AAA tissue from patients who have had endovascular AAA repair. In addition, even if the blood-derived markers could reflect the systemic changes to a certain degree, they are difficult to capture the biological

changes at the lesion site. Thus, further research is needed to find out an optimal solution to overcome these challenges. Of course, our study has other limitations that must be taken into consideration. Due to the Covid-19 pandemic, the enrollment and follow-up of our patients were severely impacted as some refused to continue participating in the study after recruitment or failed to comply with the strict follow-up schedule. Further, the sex distribution of our study population is unbalanced due to the different prevalence of AAA in males and females, therefore, further large-scale research is necessary.

5. CONCLUSION

The evidence of aortic remodeling after AAA repair is limited, therefore we conducted a study to investigate how circulating miR-155, miR-15a, miR-29b, and miR-29c change in AAA patients repaired by either OSR or EVAR, as these miRNAs have been identified as significantly altered in AAA. However, the present study shows that none of the above miRNAs showed significant changes during the 3 months of follow-up. Patients without endoleak after EVAR had a lower expression level of miR-15a than patients with endoleak after EVAR or patients who underwent OSR at T1 of follow-up. Whereas no other differences were found between each group at either T1 or T2 of follow-up. Our study is an exploration of the field of postoperative aortic remodeling in AAA, but to achieve a comprehensive understanding, further large-scale research and mechanistic investigation are needed.

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SCHRIFTLICHE ERKLÄRUNG

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Expression of circulating microRNAs in patients before and after AAA repair

in der *FrankfurtZentrum der Chirurgie, Klinik für Herz- und Gefäßchirurgie* unter Betreuung und Anleitung von *Prof. Dr. Thomas Schmitz-Rixen* mit Unterstützung durch *Prof. Dr. Kerstin Troidl* und *Dr. Daphne Gray* ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht*. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

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(Ort, Datum) (Unterschrift)

*) im Falle des Nichtzutreffens entfernen