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The Potential Roles of CHI3L1 in Failed Autologous Arteriovenous Fistula in End-Stage Renal Disease

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Autologous arteriovenous fistula (AVF) is commonly placed for hemodialysis treatment. Recent studies show that increased baseline serum level of Chitinase-3-like protein 1 (CHI3L1) is independently associated with a higher risk of the early failure of forearm AVFs. However, the changes and mechanisms of CHI3LI in local vascular tissues of failed AVF have not be revealed. This study aims to conduct the expression and mechanism of CHI3L1 in vascular tissues from patients. Immunoreactivity of CHI3L1, matrix metalloproteinase 2 (MMP-2) and vascular endothelial growth factor-A (VEGF-A) were detected in vascular tissues collected from nine patients with AVF surgery. Due to the significant stenosis clinically, six of the nine patients received arteriovenous fistula reconstruction. The expression differences of CHI3L1 between the initial vascular tissues and failed AVF are significant ($P < 0.05$). Failed AVF due to stenosis shows intraluminal thrombus, collagen fiber rupture, fibrous connective tissue hyperplasia, tube wall thickening, neovascularization, scattered inflammatory cell infiltration in the tunica media as well as high CHI3L1 expression level, and the expression of MMP-2 ($r = 0.9022$, $P = 0.0139$) and VEGF-A ($r = 0.8355$, $P = 0.0393$) was positively correlated with CHI3L1. CHI3L1 expression in vascular tissues possibly plays an important role in AVF failure. MMP-2 and VEGF-A may participate in venous stenosis with CHI3L1.

Keywords: autologous arteriovenous fistula; chitinase-3-like protein 1; hemodialysis; renal replacement therapy
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Introduction

End-stage renal disease (ESRD) refers to the eventual outcome of the continuous progression of chronic kidney disease (CKD). At this stage, the loss of most kidney function is irreversible, and the available treatments are limited. The renal replacement therapy is needed, such as renal transplantation or dialysis. Hemodialysis is a common type of renal replacement therapy. In recent years, the prevalence of CKD is increased, and the burden of CKD is growing rapidly around the world (Lv and Zhang 2019). In 2017, the global average prevalence of CKD is 9.1%, which represents an increase of 29% compared to that of 1990. In the same year, 697.5 million patients with CKD are recorded globally. There are about 434.3 million adults suffering from the CKD in Asia until 2022, where the patients with advanced CKD is nearly 65.6 million. Most of CKD patients are from China and India, whose patient number are 159.8 million and 140.2 million, respectively (Liyanage et al. 2022). According to the China Hemodialysis Registration System (CNDRS), there were 690,000 hemodialysis patients in China in 2020. Autologous arteriovenous fistula (AVF) is commonly placed for hemodialysis treatment, which is associated with lower mortality and infection rates compared to indwelling central venous catheters and grafts (Ravani et al. 2013a, b). However, the fail-

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ure and obstacles of AVF often limit the applications in clinical settings in general. It is demonstrated that the primary patency of AVFs is only 64% at one year, and 21% of fistulas were abandoned without coming into use (Bylsma et al. 2017). In the view of the large hemodialysis population, resolution of AVF failure and obstacles has gained a hot focus of research currently.

Chitinase-3-like protein 1 (CHI3L1) is a secretory glycoprotein (molecular weight 40 kDa). As a member of the chitinase family, it has been discovered as a heparin-binding protein that binds to chitin-like oligosaccharides (Zhao et al. 2020), acting as a marker of inflammation in different diseases. Recent studies have shown that increased baseline serum CHI3L1 levels is independently associated with a higher risk of the early failure of forearm AVFs, and the association between base line CHI3L1 concentrations and AVF failure is stable and robust (Liang et al. 2021). Therefore, CHI3L1 has a significant potential biomarker of AVF failure in ESRD patients. The serum CHI3L1 levels are related to the AVF failure, yet the expression of CHI3LI in local vessels remains unclear. The present study detects the expression of CHI3L1 in venous tissues from patients undergoing AVF surgery, evaluates its clinical significance and explores the possible mechanism of CHI3L1 in AVF failure.

Materials and Methods

Patients and tissue samples

Specimens were collected from 9 patients undergoing AVF surgery in April 2022 at the Hemodialysis Unit, the First Affiliated Hospital of Xi'an Medical University (Xi'an, Shaanxi, China). All subjects had signed informed consents for specimen collection for the purposes of this study before undergoing the operations. Among them were 7 males and 2 females within the age range of 29-70 years. The study was approved by the institutional review board of Xi'an Medical University (No. XYYFY2022LSKY-016).

Inclusion criteria were: (1) Patients were ≥ 18 years of age; (2) Definitive diagnosis of CKD [the glomerular filtration rate estimated by the CKD epidemiology collaboration (CKD-EPI) formula is less than 15 ml/min/1.73 m^2] regular hemodialysis treatment; 3) No obvious surgical contraindications such as acute infection, heart failure, myocardial infarction, acute stroke, gastrointestinal bleeding, etc.; (4) No malignant tumor or severe liver disease; (5) Complete clinical data. Exclusion criteria were: (1) Transferred to peritoneal dialysis; (2) Allogenic kidney transplantation; (3) The functional status of the patient's AVF could not be known during follow-up. All the patients underwent preoperative clinical assessment with ultrasound imaging by a vascular sonographer who measured the vessel size and other variables (including distensibility, vessel wall thickness, and resistance index) to evaluate the suitability of vessels for AVF access creation or re-anastomosis surgery.

Six of the 9 patients received arteriovenous fistula reconstruction due to clinically significant stenosis. Clinically significant stenosis was defined as the inability to achieve the prescribed dialysis blood pump flow rate in at least two consecutive hemodialysis sessions and any one of the following criteria on ultrasound: (1) AVF with blood flow rate < 400 mL/min; (2) The ratio of venous access pressure to main arterial pressure > 0.55; (3) Peak systolic velocities of ≥ 500 cm/sec; and (4) ≥ 50% reduction in luminal diameter in comparison with the adjacent vessel (Wo et al. 2017; Huang et al. 2021). All specimens were obtained from the pruning process of the venous anastomotic site, and no venous tissue samples were obtained from other normal vessels or locations in the field.

Hematoxylin and eosin (H&E) staining

The fixed tissues were dehydrated with gradient alcohol, embedded in paraffin, and sliced into pathological sections. The dried slices were immersed in xylene I/II/III in sequence for 10 min each, then in absolute ethanol, 95%, 80%, and 70% ethanol for 7 min each, and washed with water for 5 min. The slices were stained in hematoxylin for 5 min, then washed with water for 5 min. The slices were differentiated by 1% hydrochloric acid in alcohol for 5 s and rinsed with water for 1 min, counterstained with 1% eosin for 10 s and then washed for 1 min. They were immersed in 70%, 80%, 95% and absolute ethanol each for 2 min, then immersed in xylene I/II for 5 min each. Finally, once the sections were naturally dried, they were sealed with neutral gum and then browse with digital slices (PANNORAMIC MIDI, Jinan, China).

Immunohistochemistry

Formalin-fixed and paraffin-embedded tissues were cut into serial sections with a thickness of 4 μm. Sections were stained with hematoxylin and eosin (H&E) for histological examination. The paraffin sections were deparaffinized and rehydrated. Then, the sections were placed in citrate buffer (pH 6.0) for 10 min and washed with phosphate-buffered saline (PBS). After blocking with 3% bovine serum albumin (BSA) solution for 30 min at room temperature, the sections were incubated with CHI3L antibody 1 (1:200, ab77528, Abcam, Cambridge, UK), MMP-2 antibody (1:400, GB11130, Servicebio, Wuhan, China) and VEGF-A antibody (1:300, GB14165, Servicebio) overnight at 4°C. The sections were washed with PBS and then incubated with the secondary antibodies for 1 h at room temperature. The sections were then stained with 3, 3′-diaminobenzidine tetrahydrochloride for 10 min and counterstained with hematoxylin, dehydrated and mounted. Light yellow or brownish-yellow particles in the cytoplasm or nucleus indicated positive cells, and the integrated optical density (IOD) value was obtained by Aipathwell software (Servicebio).

Statistical analysis

GraphPad 8.3.0 (GraphPad, San Diego, CA, USA) software was used for data analysis. The data were expressed as mean ± standard deviation (SD). For baseline

characteristics, the significance of differences in continuous variables between the failed group and the functional group were tested using t-test or Wilcoxon rank-sum test. Categorical variables were compared with the use of the chi-squared test or Fisher's exact test where appropriate. Comparisons for two non-normal distribution groups were performed using the Mann-Whitney test of variance. Correlation analyses were carried out using Pearson's correlation. In this study, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 9 patients were included in this study and categorized into two groups. Six of the 9 patients who received arteriovenous fistula reconstruction due to clinically significant stenosis, were grouped into AVF reconstruction group, also known as AVF failure group. The other three are the initial AVF group, and have initiated dialysis via central venous catheters before the first angioplasty of arteriovenous fistula. Table 1 presents the clinical data of all patients. Patients of two groups did not differ significantly in terms of sex, age and other basic clinical information.

Pathological changes in the vein tissues from AVF of ESRD patients

The pathological changes in the vein tissues are shown in Figs. 1 and 2. H&E staining showed no obvious fibrous connective tissue hyperplasia and inflammatory cell infiltration in the initial group, and endothelial cell shedding in the intima can be observed (Fig. 1). Compared with the initial AVF group, the AVF reconstruction group showed intraluminal thrombus, collagen fiber rupture, fibrous connective tissue hyperplasia, tube wall thickening, neovascularization and scattered inflammatory cell infiltration in the tunica media (Fig. 2A-D). Pathological features were graded according to the four-level grading system of subjective (Table 2). Furthermore, the pathologic score of the AVF reconstruction group was higher than that of the initial AVF group (6.50 ± 1.76 vs. 0.33 ± 0.58, $P < 0.05$), showed in Fig. 2E.

Immunohistochemistry

The expression of CHI3LI, MMP-2 and VEGF-A by immunohistochemistry staining showed in Fig. 3, positive staining showed brownish-yellow granules. The difference of positive area rate of CHI3L1 between the initial AVF and the AVF reconstruction group was statistically significant (0.44 ± 0.05 vs. 0.61 ± 0.08, $P < 0.05$). Compared with the initial AVF group, significantly higher expression levels of CHI3LI, MMP-2 and VEGF-A were observed in the AVF reconstruction group (Fig. 4A-C). A positive correlation was found between the expression levels of CHI3L1 and MMP-2 in the all samples ($r = 0.9383$, $P < 0.001$, Fig. 5A), there was also a positive correlation between the expression levels of CHI3L1 and MMP-2 in the AVF reconstruction group ($r = 0.9022$, $P < 0.05$, Fig. 5B). In the all samples, a positive correlation was observed between the expression levels of CHI3L1 and VEGF-A ($r = 0.8956$, $P < 0.005$, Fig. 6A), and the expression levels of CHI3L1 were positively correlated with VEGF-A in the AVF reconstruction group (r

Table 1. Baseline characteristics of enrolled participants according to the status of the autologous arteriovenous fistula (AVF).

	Total	AVF reconstruction group	Initial AVF group	*P*-value
Number (%)	9	6 (66.7)	3 (33.3)	–
Age (years)	54.44 ± 14.12	58.17 ± 5.85	44 ± 22.60	0.17
Male (n, %)	7 (77.8)	5 (55.6)	2 (22.2)	> 0.9999
Cause of kidney disease (n, %)				0.23
Chronic glomerulonephritis	0 (0)	0 (0)	0 (0)	
DKD	3 (0.33)	1 (16.7)	2 (66.7)	
Others	6 (0.67)	5 (83.3)	1 (33.3)	
Hypertension (n, %)	6 (0.67)	5 (83.3)	1 (33.3)	0.23
Diabetes (n, %)	3 (0.33)	1 (16.7)	2 (66.7)	0.23
Hemoglobin (g/L)	100.56 ± 16.76	105.17 ± 12.59	91.33 ± 23.16	0.27
Serum albumin (g/L)	34.38 ± 5.33	35.43 ± 6.11	32.27 ± 3.23	0.44
Calcium (mmol/L)	2.15 ± 0.12	2.19 ± 0.83	2.08 ± 0.15	0.17
Phosphorus (mmol/L)	1.37 ± 0.43	1.49 ± 0.41	1.12 ± 0.40	0.25
Uric acid (μmol/L)	312 ± 149.76	326.83 ± 160.42	282.33 ± 152.97	0.70
Creatinine (μmol/L)	646.67 ± 248.12	634.92 ± 244.95	670.17 ± 308.24	0.86

Data are shown as n (%) or mean ± SD.
DKD, diabetic kidney disease.

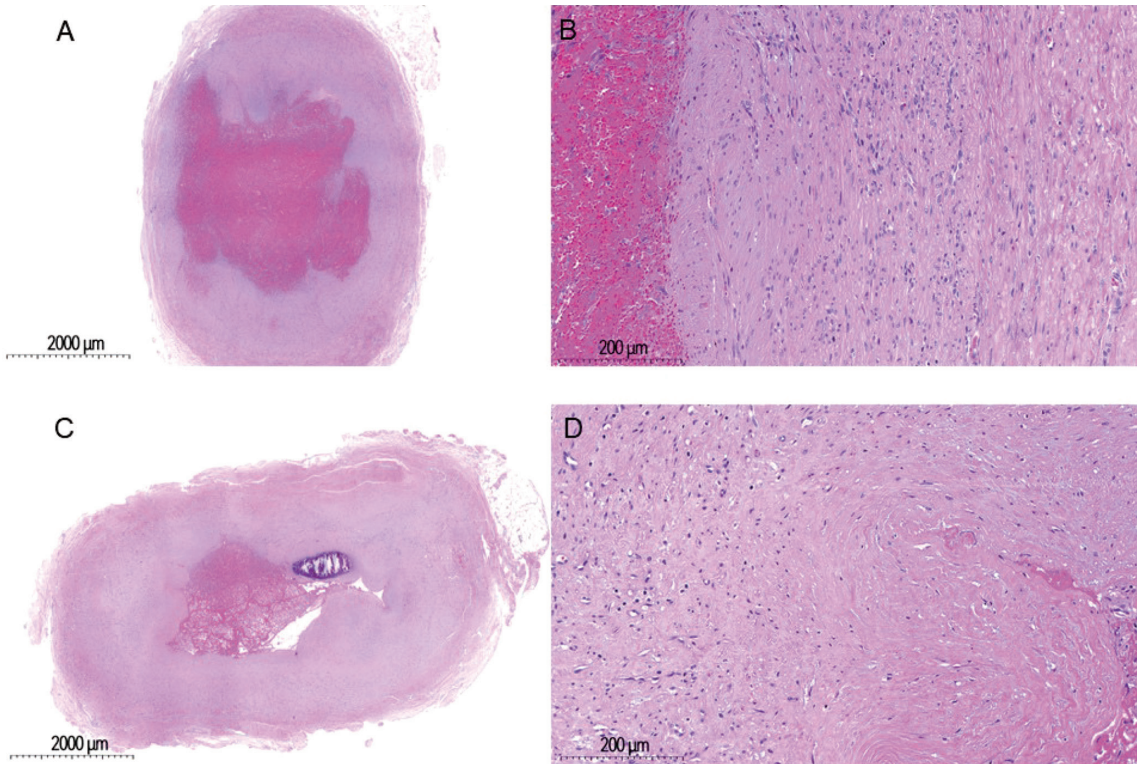

Fig. 1. Representative hematoxylin and eosin (H&E) staining of vein tissues in the autologous arteriovenous fistula (AVF) reconstruction group.
Changes in venous tissue of failed AVF due to stenosis by H&E staining. Representative sections showing intraluminal thrombus, collagen fiber rupture, fibrous connective tissue hyperplasia, tube wall thickening, neovascularization and scattered inflammatory cell infiltration. Sections were collected from 2 different patients. (A) and (C) H&E staining in venous tissue of failed AVF (× 20). (B) and (D) H&E staining in venous tissue of failed AVF (× 200). Scale bars are 500 μm and 50 μm, respectively.

= 0.8335, $P < 0.05$, Fig. 6B).

Discussion

Compromised vascular access is a common cause of hospitalization in patients receiving maintenance hemodialysis and it remains an important clinical problem (Gil Giraldo et al. 2020). Reliable clinical biomarkers predicting AVF failure is still lacking. In a recent systematic review and meta-analysis comprising thirteen studies with a combined population of 1,512 subjects, 48 biomarkers were assessed and no significant association between any of the assessed routine circulating biomarkers and AVF failure was observed (Morton et al. 2016; Wang et al. 2022). Previous studies have shown that the ESRD patients had a higher level of serum CHI3L1 (Tatar et al. 2017) compared to the healthy controls. Elevated serum CHI3L1 levels can even independently predict all-cause mortality in ESRD patients (Lorenz et al. 2018; Nielsen et al. 2018). The correlation between CHI3L1 and the AVF failure also makes sense in the population of ESRD patients. As previously described, the prospective observational cohort study of 109 ESRD patients have shown that the increased baseline serum level of CHI3L1 is associated with higher risk of the failure of forearm AVFs (Liang et al. 2021). Vascular non-thrombotic stenosis is the most common cause of AVF failure. Stenosis can be located in any part of the vascular access, but it is most common at the venous end and the anastomosis of the internal fistula. The main pathological basis is venous intima hyperplasia (Vazquez-Padron et al. 2021), which is composed of endothelial cells, vascular smooth muscle cells (SMCs), macrophages, fibroblasts, myofibroblasts and a large amount of extracellular matrix (ECM), while CHI3L1 is expressed by different types of cells including SMCs, macrophages, and neutrophils (Yeo et al. 2019). Thus, it is supposed that CHI3L1 might also have an impact on the failure of AVF in ESRD patients, apart from the molecular mechanisms already demonstrated by several studies, such as inflammation, uremia, hypoxia, and sheer stress, which are responsible for the AVF failure (Brahmbhatt et al. 2016).

Although serum CHI3L1 is a promising marker of AVF failure, there is no sufficient experimental research about CHI3L1 expression in AVF failure. In particular, the expression of CHI3L1 protein in failed AVF tissues has not been reported. In this study, it is evaluated that the expression of CHI3L1 in venous tissues of failed AVF due to non-thrombotic stenosis, and the positive correlations between the levels of CHI3L1 and MMP-2 or VEGF-A have been found.

It is shown that the expression levels of CHI3L1,

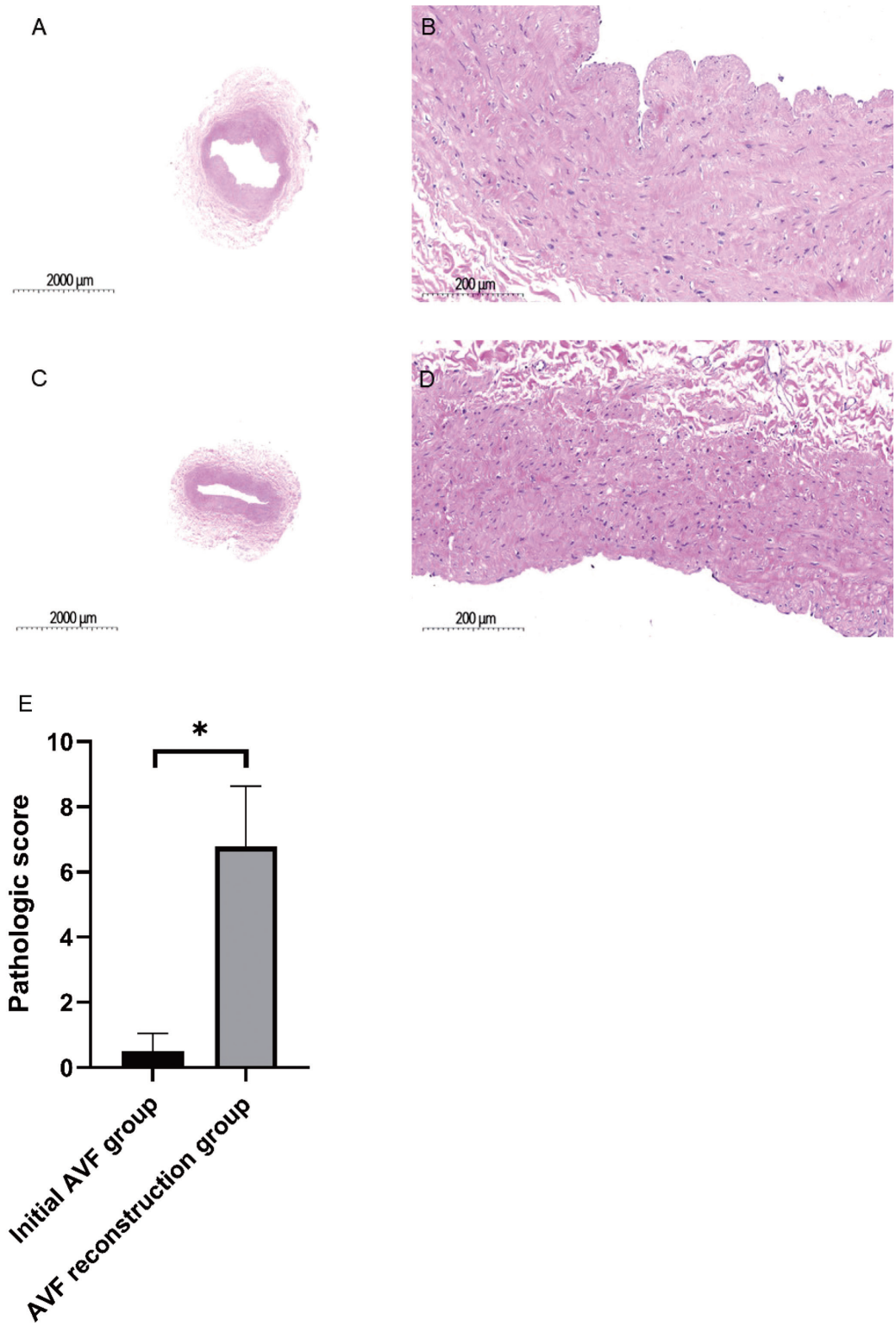

Fig. 2. Hematoxylin and eosin (H&E) staining of venous tissues in the initial autologous arteriovenous fistula (AVF) group and the pathologic score of the AVF reconstruction group and the initial AVF group.
H&E staining showed no obvious fibrous connective tissue hyperplasia and inflammatory cell infiltration in the venous tissue of the initial AVF group. Sections were collected from 2 different patients. (A) and (C) H&E staining in venous tissue of the initial AVF (× 20). (B) and (D) H&E staining in venous tissue of the initial AVF (× 200). (E) The pathologic score of the AVF reconstruction group (shown in Fig. 1) was higher than that of the initial AVF group (shown in Fig. 2A-D) (6.50 ± 1.76 vs. 0.33 ± 0.58, mean ± SD, $P < 0.05$).

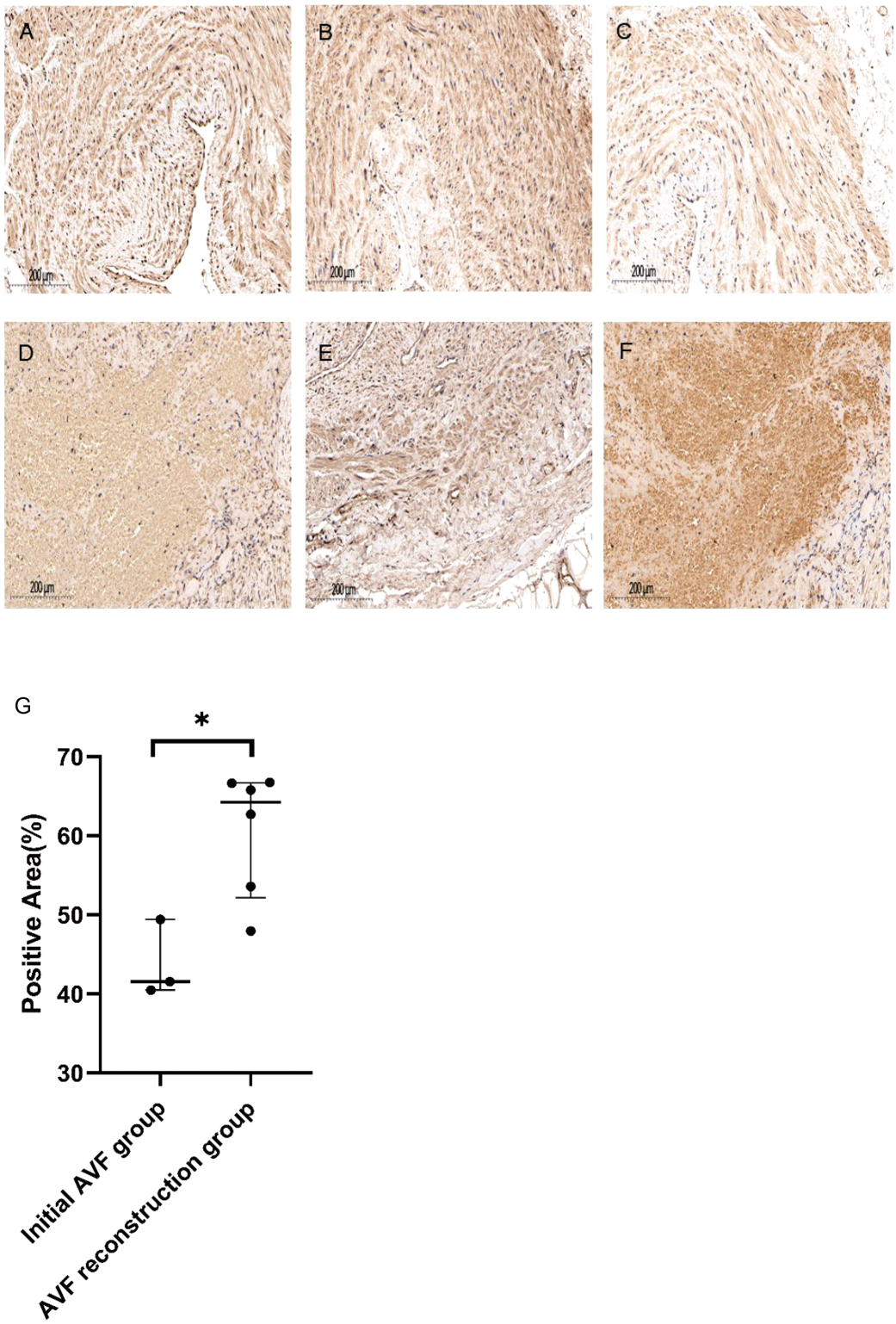

Fig. 3. Representative immunohistochemical staining of CHI3LI, MMP-2 and VEGF-A in venous tissues. Sections were collected from 3 different patients. (A) CHI3L1 expression in venous tissue of the initial AVF (× 200). (B) MMP-2 expression in venous tissue of the initial AVF (× 200). (C) VEGF-A expression in venous tissue of the initial AVF (× 200). (D) CHI3L1 expression in venous tissue of the AVF reconstruction group (× 200). (E) MMP-2 expression in venous tissue of the AVF reconstruction group (× 200). (F) VEGF-A expression in venous tissue of the AVF reconstruction group (× 200). (G) The positive area rate of CHI3L1 in the AVF reconstruction group and the initial AVF group. Data are expressed as median with interquartile range. The difference of positive area rate of CHI3L1 between the initial AVF and the AVF reconstruction group was statistically significant (0.44 ± 0.05 vs. 0.61 ± 0.08, mean ± SD, $P < 0.05$).

Table 2. Four-level grading system of subjective.

Grade	Description
0	In the study condition, the tissue was considered normal.
1	The change is just outside the normal range.
2	The lesion can be observed but is not severe.
3	The lesions are obvious.
4	The lesions are very severe (the lesions have taken up the entire tissue and organ).

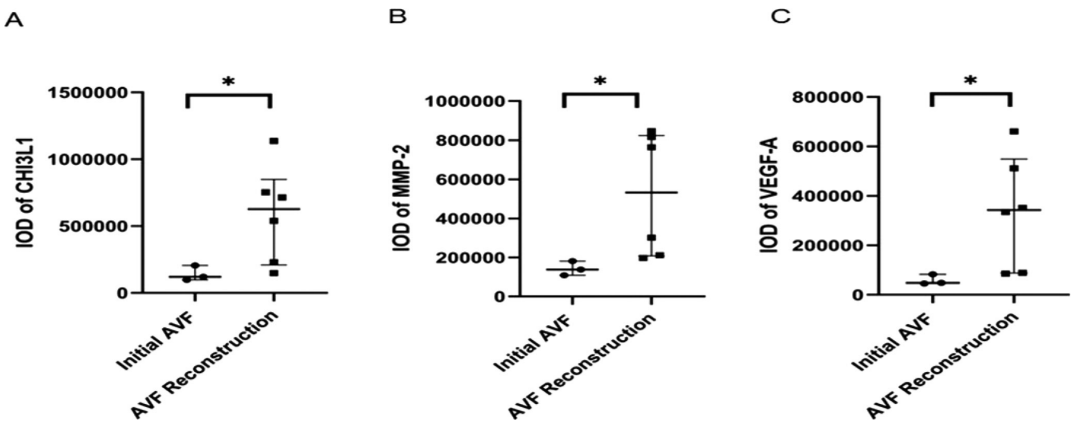

Fig. 4. Immunohistochemistry analysis of the CHI3L1, MMP-2, and VEGF-A expression levels.
The integrated optical density (IOD) value was obtained by Aipathwell software. Data are expressed as median with interquartile range. *$P < 0.05$. (A) Relative level of CHI3L1. (B) Relative level of MMP-2. (C) Relative level of VEGF-A.

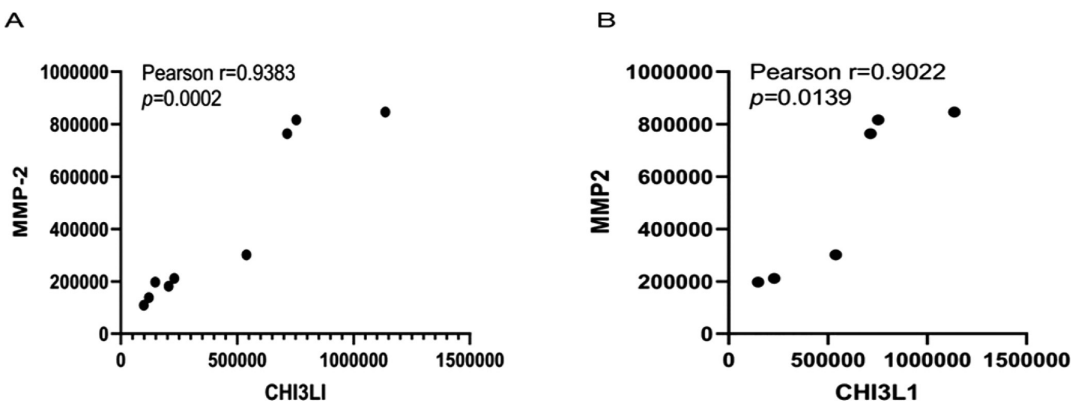

Fig. 5. Correlation between CHI3L1 and MMP-2.
(A) The correlation between CHI3L1 and MMP-2 in all tissue samples (n = 9). (B) The correlation between CHI3L1 and MMP-2 in the AVF reconstruction group (n = 6).

MMP-2 and VEGF-A were higher in the venous tissue of AVF reconstruction patients compared to the initial AVF initial group. The pathological characteristics shows that more fibrous connective tissue hyperplasia, lumen stenosis and inflammatory cell infiltration are observed in the AVF reconstruction group. The important role of matrix metalloproteinases (MMPs) in the process of AVF maturation has been proven, and MMPs are risk factors for cardiovascular diseases (Bassiouni et al. 2021). MMP-2 is a member of the MMP family and it can be secreted by SMC, mediating SMC proliferation and migration (Maybee et al. 2022). This mechanism has been clearly involved in the occurrence and development of atherosclerosis (Tao et al. 2021). The proliferation of SMCs and the migration of SMCs from the adventitia to the intima are the main causes of intimal hyperplasia. Therefore, MMP-2 may be involved in the occurrence of AVF failure. Studies have shown that MMP-2 correlates with the severity of intimal thickening, which may be used as a biomarker of the vascular remodeling underlying AVF stenosis (Nadolski et al. 2018). VEGF-A is one of the most potent angiogenic factors (Al Kawas et al. 2022). It plays a major role in vascular remod-

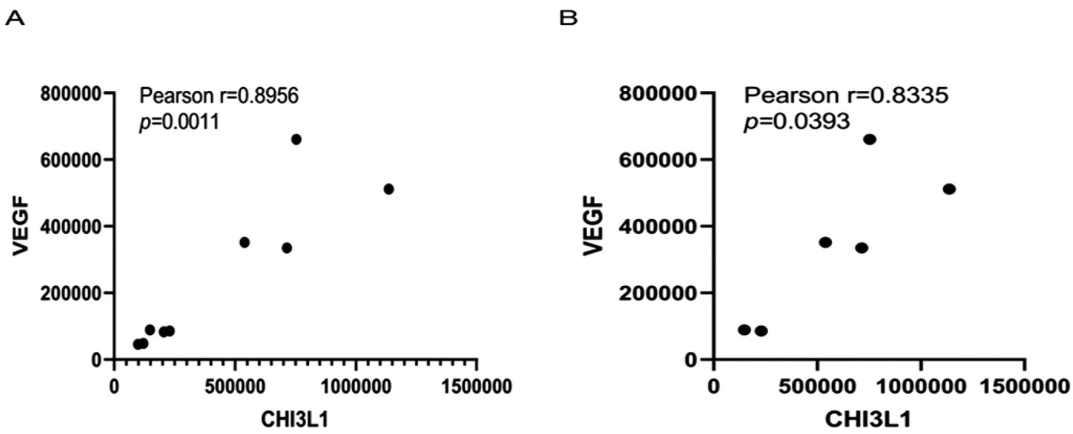

Fig. 6. Correlation between CHI3L1 and VEGF-A.
(A) The correlation between CHI3L1 and VEGF-A in all tissue samples (n = 9). (B) The correlation between CHI3L1 and VEGF-A in the AVF reconstruction group (n = 6).

eling, and it is involved in the pathogenesis of arterial stenosis, vein bypass grafts, and venous neointimal hyperplasia associated with hemodialysis vascular access. Previous studies on animal models have confirmed that the VEGF-A expression is increased at the venous stenosis site of arteriovenous fistula for hemodialysis (Yang et al. 2014).

MMP-2 is regulated by a variety of signaling pathways. The phosphoinositide 3-kinase (PI3K)/AKT pathway is a critical pathway that increases the expression level of MMP-2 (Park et al. 2020) and allows CHI3L1 to exert biological effects. CHI3LI affects tumor angiogenesis, cell proliferation and migration and it is associated with increased glucose uptake in skeletal muscles via the PI3K/AKT signaling pathway (Rusak et al. 2016; Kwak et al. 2020). This study showed that the expression levels of CHI3L1 are positively correlated with MMP-2 in the samples of the AVF reconstruction group. It is speculated that CHI3L1 up-regulates MMP-2 expression through the PI3K/AKT signaling pathway, and it is involved in the occurrence and development of arteriovenous fistula stenosis. Further experimental studies on the mechanism of CHI3L1 are required.

VEGF-A plays an essential role in vascular remodeling. Previous studies have demonstrated that the expression of VEGF-A in stenotic samples collected from patients with failed hemodialysis vascular access has increased (Misra et al. 2010). A recent study shows that the reduction of VEGF-A can reduce intimal hyperplasia and abnormal vascular remodeling (Huang et al. 2021). Furthermore, the expression of VEGF in the venous tissues of patients with AVF failure was significantly up-regulated compared with the control group, which was consistent with the results of the proposed study. H&E staining in the AVF reconstruction group showed neovascularization, which further confirmed that VEGF-A might play a role in AVF failure. It is reported that CHI3L1 small interfering RNA could reduce the expression level of VEGF-A in endometrial cancer HEC-1A cells (Chen et al. 2021). The expression of CHI3L1 was positively correlated with VEGF-A in the samples of this study, suggesting that VEGF-A may be one of the targets of CHI3L1 in AVF failure.

In conclusion, the overexpression of CHI3L1 in local tissues provides further evidence for serum CHI3L1 as a biomarker of AVF failure. However, the limited sample size is a limitation of this study. In addition, the elevation of CHI3L1 expression on local tissues might respond to abnormal systemic conditions, in which patients are more likely to form AVF failure. The involvement of CHI3L1 in AVF failure caused by regulating MMP-2 and VEGF-A needs to be confirmed by further *in vitro* experiments. Further research on CHI3L1 will help to provide a new aspect for AVF failure.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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