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ORIGINAL RESEARCH

Expression Characteristics of Soluble sCD13 in Wet Age-Related Macular Degeneration and Its Diagnostic Value and Correlation Study

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Objective: This study explored the level of soluble CD13 (sCD13) and its correlation with angiogenic factors, evaluating the predictive efficacy of sCD13 in wet age-related macular degeneration (wAMD).

Methods: 200 patients were included (58 in Non AMD group, 42 in Early AMD group, and 100 in wAMD group). Detailed routine and ophthalmologic examinations were performed on all subjects, and the central retinal thickness (CRT) and ganglion cell-inner plexiform layer (GCIPL) were determined. The concentration of sCD13 was compared. The correlation of sCD13 with PDGF, hsCRP and IL-8 was analyzed. ROC curves were plotted and the diagnostic value of sCD13 was assessed by area under the curve (AUC).

Results: The sCD13 concentration of patients in the wAMD group (20.41 ± 5.86 U/mL) was higher. Age, history of smoking, CRT, hsCRP and IL-8 were higher in the wAMD group, while mean GCIPL, BCVA, and PDGF were lower. sCD13 was positively correlated with hsCRP (r = 0.505) and IL-8 (r = 0.193) and negatively correlated with PDGF (r = −0.241). sCD13 had predictive efficacy in distinguishing wAMD from non AMD and early AMD, with AUC values of 0.74 and 0.61, respectively ($P < 0.05$).

Conclusion: sCD13 concentration in the affected eyes of wAMD patients is abnormally elevated and associated with elevated serum hsCRP and IL-8 levels and decreased PDGF. These results suggest that elevated sCD13 may promote the development of wAMD, emphasizing the importance of early control of sCD13 levels.

Keywords: age-related macular degeneration, soluble CD13, retinal pigment epithelium, diagnosis

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment in the aging population. Early and intermediate stages of AMD are characterized by the deposition of lipids and proteins between the retinal pigment epithelium (RPE) and Bruch's membrane (BM).[1] Advanced AMD is typically characterized by choroidal neovascularization (CNV) and/or geographic atrophy (GA), the main causes of rapid vision loss.[2] Wet AMD (wAMD), also known as exudative or neovascular AMD, is the most common form of advanced AMD, presenting with more severe clinical manifestations. The formation of neovascularization leads to hemorrhage and fluid leakage from the inner retina or subretinal space, which can eventually progress to subretinal fibrosis (SRFi), causing permanent vision loss.[3] Angiogenesis refers to the process of forming new blood vessels from the existing vascular system, playing a detrimental role in certain diseases that progress from benign to metastatic phenotypes.[4] At present, it is well-accepted that regulating vascular growth is an effective means of limiting or controlling the development and spread of disease.

The most common causative factors of wAMD are vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF are key factors regulating choroidal neovascularization (CNV) formation in wAMD. Compared with healthy control patients, VEGF levels are significantly higher and PDGF levels are lower in

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wAMD patients.[5] Currently, many drugs are used to treat wAMD on the concept of anti-PDGF and VEGF. In clinical practice, anti-VEGF agents (such as ranibizumab and aflibercept) have become the cornerstone of wAMD treatment. By competitively binding to VEGF and blocking its signaling pathway, they delay the progression of choroidal neovascularization (CNV) and improve visual acuity. However, most of these treatments cannot fundamentally improve patients' conditions.[6] Approximately 30%-40% of patients exhibit poor treatment response, and long-term repeated injections may trigger complications such as retinal atrophy and elevated intraocular pressure. These therapies fail to fundamentally reverse RPE cell damage and the imbalance in the inflammatory microenvironment. Therefore, identifying novel biomarkers and therapeutic targets related to inflammation regulation and angiogenesis represents a critical direction for breakthroughs in current wAMD research.

Soluble CD13 (sCD13) is a widely expressed membrane-bound metalloproteinase typically present in various human tissues and plasma in soluble or membrane-bound forms. It primarily hydrolyzes proteins and oligopeptides at N-terminal amide bonds via membrane-bound type II metalloproteinase activity.[7] It is involved in pleiotropic functions, including enzymatic cleavage of peptides, antigen presentation, and signal transduction, ultimately mediating downstream biological phenomena such as cell adhesion, proliferation, and motility.[8] sCD13 has been mostly used to study the effects in controlling tumor growth and metastasis. Previous studies have demonstrated that CD13 is highly expressed in breast, pancreatic, and lung cancer tissues and promotes malignant progression of tumors.[9,10] Under the stimulation of vascular growth factors, vascular endothelial cells within the tumor vasculature are activated and express the cell-surface peptidase sCD13/APN, while sCD13 expression promotes angiogenesis and tumor growth.[11] Therefore, modulation of sCD13 expression is an emerging therapy for angiogenesis-related diseases. sCD13 participates in the inflammatory cascade following retinal injury by regulating macrophage recruitment and proinflammatory cytokine release. Chronic inflammation is a key initiating factor for CNV formation in wAMD. A recent study indicates that CD13, expressed by vascular cells, may play a role in angiogenesis.[12] We hypothesize that sCD13 may mediate its role in retinal inflammation and angiogenesis by influencing the VEGF pathway.[13] Current research on sCD13 and wAMD remains significantly limited. First, existing literature predominantly focuses on sCD13's role in tumors or systemic diseases, with extremely limited studies specifically addressing wAMD. Second, while studies have suggested associations between sCD13 and angiogenesis/inflammation, its specific mechanisms in wAMD remain poorly understood, particularly lacking correlations with key angiogenesis/inflammation factors. Given these research gaps, investigating sCD13 level changes during wAMD progression offers a novel perspective.

sCD13 may be an influencing factor for CNV and SRFi in the macular region in wAMD. Exploring the changes in its specific level and its correlation with angiogenic factors, and evaluating the predictive efficacy of sCD13 on wAMD may confer new research targets and ideas.

Materials and Methods

Research Patients

A total of 200 subjects aged 50 to 83 years who visited or underwent physical examinations at the ophthalmology department of Huanggang Central Hospital between March 2020 and June 2023 were selected. Based on the AMD Clinical Classification System,[14] subjects were categorized into the Non-AMD group (58 cases), Early AMD group (42 cases), and wAMD group (100 cases). Inclusion Criteria for the Non-AMD group: (1) Participants undergoing routine health examinations at our hospital during the same period, with no history of ocular diseases or symptoms such as blurred vision or decreased visual acuity; (2) Normal ophthalmic examination findings (visual acuity, intraocular pressure, slit-lamp examination, fundus examination), with no AMD-related lesions detected by FFA/ICGA/OCT; (3) Age between 50 and 83 years; (4) No participation in other clinical studies within the past month. Inclusion criteria for the Early AMD group: Patients diagnosed with early AMD based on FFA/ICGA/OCT findings and meeting diagnostic criteria; patients with unilateral initial onset who have not undergone relevant treatment. Inclusion criteria for the wAMD group: (1) unilateral eye meets the diagnostic criteria of wAMD confirmed by professional ophthalmologists; (2) unilateral onset of the disease for the first time without relevant treatment. All subjects had complete clinical and pathological data, and had not participated in any other clinical trials within one month prior to admission. Exclusion

criteria for the three groups: (1) patients with ocular diseases other than wAMD; (2) patients with a history of eye trauma or those who have undergone eye surgery; (3) patients with diabetic retinal disease, macular hole, and high myopia; (4) patients with unclear fundus disease; (5) patients who were breastfeeding and pregnant; (6) patients with other diseases that may cause retinal and macular degeneration; (7) patients with allergy to fluorescein sodium; (8) patients with liver disease, hypertension, and severe inflammation within 1 month prior to treatment. This study followed the STORBE statement. This study was approved by the Ethics Committee of Huanggang Central Hospital (No.201902HG-13) and written informed consent was provided by all patients prior to the study start. All patients and their families fully understood the content of this study and voluntarily participated, demonstrating good compliance.

Diagnostic Methods

All subjects were required to undergo fluorescein fundus angiography and indocyanine green angiography. Briefly, the presence or absence of periorbital hyperpigmentation and pigmentation irregularities were evaluated within a grid with a radius of 3000 μm, centered on the fovea. A graded classification was used to estimate the amount of hyperpigmentation within the grid. GA was defined as an area of atrophy greater than 175 μm with well-defined margins and observable CNV. CNV was considered to be present if stereoscopic examination showed subretinal fluid, exudates, hemorrhages, and/or scar tissue in the macular area of the fundus.

Grouping Criteria

Diagnosis was made on the basis of clinical examination and using a clinical classification system for AMD that was methodologically established by 26 AMD experts.[14] This standardized clinical classification system is based on the evaluation of lesions within two disc diameters of the fundus fossa. Participants were classified based on characteristics observed in the affected eye. If the pigment deposition in the affected eye was ≤ 63 μm or irregular, with no CNV or GA detected on FFA/ICGA examination and normal retinal structure, the participant was assigned to the Non-AMD group. For Early AMD, there were accumulations of lipids and proteins (hyalomoedema) located between the RPE and BM, manifesting as either medium-sized drusen (63–125 μm in diameter) or large drusen (exceeding 125 μm) in the affected eyes. The predominant type was soft drusen (with blurred borders, gray or yellow in color, prone to progressing to CNV) or hard drusen (with well-defined borders, appearing as white dots, progressing more slowly). However, there was no CNV, no GA, subretinal fluid, or hemorrhage. If the affected eye exhibits CNV, characterized by abnormal vascular leakage into the subretinal or RPE during the contrast phase, or fibrovascular pigment epithelial detachment, with or without subretinal or choroidal neovascularization, it is classified into the wAMD group.[15]

A total of 58 cases were ultimately included in the Non-AMD group, 42 cases in the Early AMD group, and 100 cases in the wAMD group. There were no statistically significant differences in age or gender ratio among the three groups ($P > 0.05$).

General Information and Indicators

General information was collected, including gender, age, history of smoking, history of alcohol consumption, history of hypertension, history of diabetes mellitus, and comorbidity of hyperlipidemia. The best corrected visual acuity (BCVA) of the three groups was measured using Topcon KR-8900 computerized optometry. BCVA was assessed using a standard eye chart positioned 5 cm from the patient, with results expressed in logarithms of the minimum angle of resolution (LogMAR). BCVA measurements were recorded on the LogMAR scale, where finger counting, hand motion, light perception, and no light perception were assigned LogMAR values of 1.9, 2.3, 2.7, and 3.0, respectively.[16]

Optical Coherence Tomography (OCT) Examination

Frequency-domain OCT was performed on the macular area of eyes of wAMD patients by an experienced examiner using an OCT scanner (Spectralis HRA+OCT, Heidelberg). The scanning mode was set to a horizontal linear scan of 512×128 macular center concave with an axial resolution of 5 μm and a scanning speed of 26,000 scans/second. The outer boundary of the retinal nerve fiber layer and the outer boundary of the macular inner plexiform layer were identified by three-dimensional imaging. Macular central retinal thickness and ganglion cell-inner plexiform layer (GCIPL) were automatically measured. All

automated segmentation results underwent independent manual verification by two ophthalmologists with over five years of experience in diagnosing and treating retinal diseases. Should segmentation errors occur—such as confusion between the RNFL and GCIPL boundaries or fluid interference with layer identification—the two physicians jointly consult to manually adjust the segmentation. Measurement values were recorded only after confirming accurate layer identification, thereby minimizing systematic errors.

Laboratory Tests

Fasting elbow venous blood (5 mL) was drawn from each patient and centrifuged. Serum VEGF, PDGF, IL-8 and sCD13 levels were measured by a microplate reader (SwAMDctra Max iD3) and ELISA kits (Shanghai Xinfan Biological Technology, China). Serum C-reactive protein (hsCRP) levels were measured by biochemical analyzer (Cobas C501, Roche, Switzerland) and immunoturbidimetric assay (Beijing Bangding Biomedicine Company). Triacylglycerol (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using a fully automated biochemical analyzer (AU680, Beckman coulter; Shanghai, China).

Statistical Methods

SPSS 26.0 software was used for data analysis. Measurement information conforming to normal distribution was expressed as mean ± standard deviation (SD) and subjected to one-way ANOVA test. Measurement information with skewed distribution was expressed as [M (P25, P75)], and comparisons among the 3 groups were made using the Kruskal–Wallis *H*-test. Count data were expressed as frequency or cases (%), and comparisons were performed using the chi-square test. Correlations between variables were analyzed using Pearson correlation analysis. ROC curves were plotted, and area under the curve (AUC) was calculated. $p < 0.05$ was considered as a statistically significant difference.

Results

Clinical General Data of Patients in Groups

Age, history of smoking, central retinal thickness (CRT), hsCRP, IL-8 and sCD13 were higher while mean GCIPL, BCVA and PDGF were lower in the wAMD group than in the Non AMD and Early AMD groups (all $P < 0.05$). Patients in the Non AMD group were aged between 65–74 years with a mean age of (69.78 ± 4.71) years. There were 26 males and 32 females with a BMI of (27.50 ± 4.12) kg/m^2, and 25 patients with a history of smoking. Patients in the Early AMD group were aged between 65–74 years with a mean age of (70.4 ± 4.56) years. There were 20 males and 22 females, with a BMI of (27.35 ± 3.23) kg/m^2 and 22 patients with a history of smoking. The age of the patients in the wAMD group was between 68 and 83 years old, with a mean age of (75.80 ± 7.33) years. There were 52 males and 48 females, with a BMI of (27.41 ± 3.92) kg/m^2, and 62 patients with a history of smoking. VEGF, blood glucose, lipid metabolism indexes (TC, TG, LDL-C, HDL-C), and FBS were not statistically significant (all $P > 0.05$) (Table 1).

Elevated sCD13 Is Associated with wAMD in Patients Over 73 Years of Age

Patients were sub-divided into < 73 years old and ≥ 73 years old. In patients < 73 years of age, sCD13 concentrations in the Non AMD, Early AMD and wAMD groups were 14.82 ± 4.01 U/mL, 15.38 ± 4.39 U/mL and 14.77 ± 2.66 U/mL,

Table 1 Comparison of Clinical General Data of Patients in Non AMD Group, Early AMD Group and wAMD Group

Characteristics	Non AMD (n = 58)	Early AMD (n = 42)	wAMD (n = 100)	*P* value
Male no.	26 (44%)	20 (47%)	52 (52%)	0.854
Age (year)	69.78 ± 4.71	70.40 ± 4.56	75.80 ± 7.33	< 0.001
BMI (kg/m^2)	27.50 ± 4.12	27.35 ± 3.23	27.41 ± 3.92	0.981
Right eyes	32 (55%)	20 (47%)	48 (48%)	0.384

(*Continued*)

Table 1 (Continued).

Characteristics	Non AMD (n = 58)	Early AMD (n = 42)	wAMD (n = 100)	*P* value
Comorbidity				
Hyperlipidemia	18 (31%)	22 (52%)	43 (43%)	0.425
Hypertension	16 (28%)	13 (31%)	10 (10%)	0.098
Diabetes	26 (44%)	24 (57%)	51 (51%)	0.123
History of drinking	17 (29%)	18 (43%)	35 (35%)	0.64
History of smoking	25 (43%)	22 (52%)	62 (62%)	0.027
Blood Glucose (mg/dL)	109.80 ± 12.00	112.73 ± 17.51	115.22 ± 16.58	0.11
BCVA (LogMAR)	0.37 ± 0.03	0.79 ± 0.08	1.13 ± 0.27	< 0.001
CRT (μm)	178.00 ± 27.95	279.28 ± 45.88	491.23 ± 159.82	< 0.001
Mean GCIPL (μm)	81.95 ± 6.82	78.22 ± 4.02	72.73 ± 5.73	< 0.001
hsCRP (mg/L)	3.40 ± 0.75	3.71 ± 1.03	4.43 ± 0.99	< 0.01
Serum PDGF (pg/mL)	140.17 ± 43.58	133.81 ± 22.15	103.60 ± 27.91	< 0.001
Serum VEGF (pg/mL)	577.85 ± 336.29	569.22 ± 217.25	551.38 ± 461.84	0.911
TC (mmol/L)	4.29 ± 0.32	4.31 ± 0.52	4.37 ± 0.28	0.348
TG (mg/dL)	126.00 (96,186.00)	127.50 (96.50,162.13)	128.00 (98.50,158.75)	0.104
LDL-C (mmol/L)	2.73 ± 0.12	2.75 ± 0.28	2.78 ± 0.63	0.804
HDL-C (mmol/L)	1.51 ± 0.07	1.50 ± 0.08	1.49 ± 0.05	0.158
IL-8 (μg/L)	12.32 ± 3.65	14.88 ± 3.49	17.07 ± 4.24	<0.001
sCD13 (U/mL)	15.77 ± 4.84	17.98 ± 5.29	20.41 ± 5.86	< 0.001

Notes: Measurement information conforming to normal distribution is expressed as mean ± standard deviation (SD). Qualitative information was expressed as N (%). When data did not conform to normal distribution, they were expressed as M (Q25 to Q75). Continuous variables that met the normality test were tested using the One-way ANOVA test or the Kruskal–Wallis *H*-test. Categorical variables were tested using the chi-square test.

Abbreviations: AMD, age-related macular degeneration; wAMD, wet age-related macular degeneration; BCVA, Best Corrected Visual Acuity; l; CRT, central retinal thickness; GCIPL, ganglion cell-inner plexiform layer; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; hsCRP, high sensitive C-reactive protein; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IL-8, Interleukin-8.

respectively. There was no statistically significant difference in comparison of the 3 groups ($P > 0.05$). In patients aged ≥ 73 years, sCD13 concentrations were 19.30 ± 5.32 U/mL, 20.34 ± 4.98 U/mL and 23.06 ± 5.04 U/mL in the Non AMD, Early AMD, and wAMD groups, respectively. sCD13 was significantly higher in the wAMD group compared with the Non AMD and Early AMD groups ($P = 0.032$ and 0.029) (Figure 1).

Correlation Analysis of sCD13 with hsCRP, IL-8, and PDGF

Pearson analysis results in Figure 2 showed that sCD13 showed a moderate positive correlation with hsCRP levels ($r = 0.505$, $P < 0.05$), suggesting strong synergistic trends in their changes within wAMD patients (Figure 2B). Weak correlations were also observed between sCD13 and IL-8 ($r = 0.193$, $P < 0.05$) and PDGF ($r = -0.241$, $P < 0.05$) (Figure 2A–C). Although statistically significant, the strength of these correlations was limited.

Predictive Value of sCD13 in Patients Developing wAMD

ROC curves were plotted with the wAMD group as a positive sample and the Non AMD group or Early AMD group as a negative sample. The results were shown in Tables 2, 3 and Figure 3. When distinguishing between the Non-AMD group and the wAMD group, the AUC for sCD13 was 0.737, with a 95% confidence interval (CI) of 0.659 to 0.815 ($P < 0.05$), indicating that sCD13 possesses good predictive efficacy for both groups (Figure 3A). When distinguishing the Early AMD group from the wAMD group, the AUC of sCD13 was 0.610 with a 95% CI of 0.510–0.711 ($P < 0.05$), indicating relatively lower predictive efficacy for these two groups (Figure 3B). When the cut-off value was taken as sCD13 > 18.17 U/mL, the sensitivity for predicting wAMD was 65.00% and the specificity was 77.59%. When the cut-off value was taken as sCD13 > 16.37 U/mL, the sensitivity of predicting wAMD was 73.00% and the specificity was 47.62%.

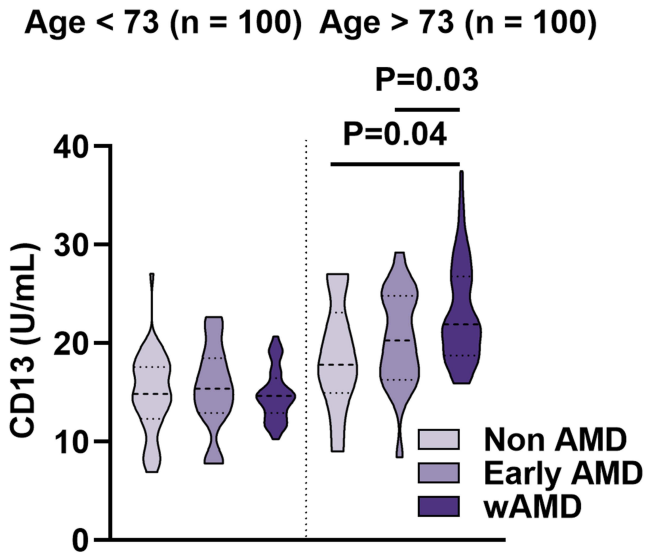

Figure 1 sCD13 expression in patients with < 73 years old and ≥ 73 years old.
Notes: Error bars represent SD. $P < 0.05$ indicates statistically significant differences.

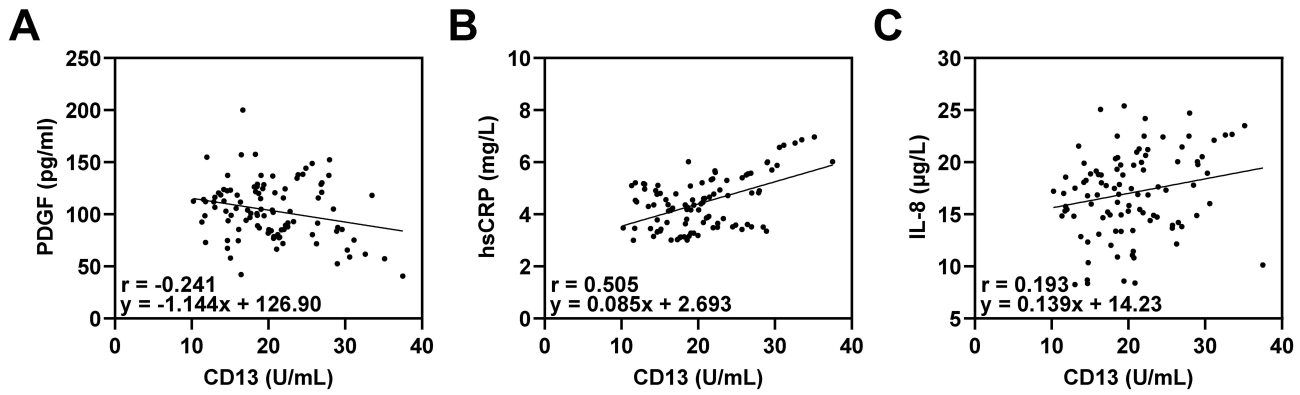

Figure 2 Pearson correlation analysis of sCD1 with hsCRP, IL-8, and PDGF. (**A**–**C**) Correlation between sCD13 and hsCRP, IL-8, and PDGF. According to correlation coefficient grading standards, absolute values of r_s between 0.1 and 0.3 indicate weak correlation, 0.3 to 0.6 indicate moderate correlation, and > 0.6 indicate strong correlation. Positive correlations are represented by positive values, while negative correlations are represented by negative values. All *P*-values are adjusted *P*-values (corrected using the FDR procedure), with $P < 0.05$ indicating statistically significant differences.

Discussion

Although wAMD is less prevalent than dry AMD, it accounts for 90% of severe vision loss due to AMD. The pathogenesis of wAMD is often associated with numerous factors such as age, smoking, diet, genetics, oxidative stress, chronic inflammation, hemodynamic abnormalities, etc. The pathological changes are mainly manifested as neovascularization activation in the RPE layer, CNV, and localized exudation, hemorrhage, and scarring of the retina, which can

Table 2 Predictive Value of sCD13 for the Development of wAMD in Patients with Non AMD

Indices	Cut-off	Sensitivity (%)	Specificity (%)	*P* value
sCD13	18.17	65	77.59	< 0.001

Note: The value of CD13 in predicting the occurrence of wAMD in Non AMD patients was assessed using ROC.
Abbreviations: AMD, age-related macular degeneration; wAMD, wet age-related macular degeneration.

Table 3 Predictive Value of sCD13 for the Development of wAMD in Patients with Early AMD

Indices	Cut-off	Sensitivity (%)	Specificity (%)	*P* value
sCD13	16.37	73	47.62	0.038

Note: The value of CD13 in predicting the occurrence of wAMD in patients with Early AMD was assessed using ROC.
Abbreviations: AMD, age-related macular degeneration; wAMD, wet age-related macular degeneration.

lead to symptoms of vision loss and, in severe cases, blindness.[17] Common therapeutic agents are anti-VEGF drugs, which provide competitive binding to VEGF-A, thus blocking the binding of the latter to its cognate receptors (VEGF-1 and VEGF-2), thereby preventing vascular endothelial cell proliferation and delaying CNV and improving vision.[18,19] However, the overall efficacy of the drugs remains questionable. This suggests an urgent need to explore new research targets and therapeutic ideas, in order to develop new strategies for therapeutic interventions. This study showed that sCD13 levels were abnormally elevated in the wAMD group compared with the Non AMD and Early AMD groups, and sCD13 was significantly correlated with hsCRP, IL-8, and PDGF.

In cancer research, sCD13 is considered to be shed from tumor cells and/or the endothelial cells lining tumor blood vessels. Elevated levels of sCD13 can be detected in tumor interstitial fluid and malignant effusions, potentially serving as a biomarker for cancer diagnosis and prognosis.[20,21] wAMD primarily affects the outer layer of the retina. This leads to a loss of photoreceptors, a decrease in visual function and a thinning of the outer nuclear layer due to the formation of vitreous warts caused by the accumulation of lipoproteins in the BM, as well as by mechanisms such as RPE damage caused by toxic intermediates and the triggering of apoptosis.[22,23] OCT has been used to examine the retinal pigmentation.[24] CRT is the average thickness of the retina between the inner and outer boundaries of a 1 mm area in the center of the macula, which is an important indicator of the degree of macular edema.[25–27] The inner retinal layer may be involved in the onset and progression of wAMD through a mechanism of neuronal apoptosis induced by transneuronal degeneration, leading to thinning of the GCIPL.[27] Mean GCIPL thickness is the average of the GCIPL thickness in each sector of the retinal macula, reflecting the apoptosis and loss of ganglion cells in the retinal macula[28,29] A previous study on AMD neuropathy confirms that GCIPL thinning in AMD patients is closely associated with localized retinal inflammatory activity. Inflammatory factors such as IL-8 can directly cause GCIPL thinning by inducing ganglion cell apoptosis and disrupting neural synaptic connections. This provides a mechanistic basis for the association between sCD13 and GCIPL alterations observed in this study.[30] High levels of inflammatory factors such as IL-8 in the circulation may also migrate by promoting an inflammatory response, thereby damaging the macular GCIPL structure and inducing retinal neuronal degeneration and apoptosis, leading to a thinning of

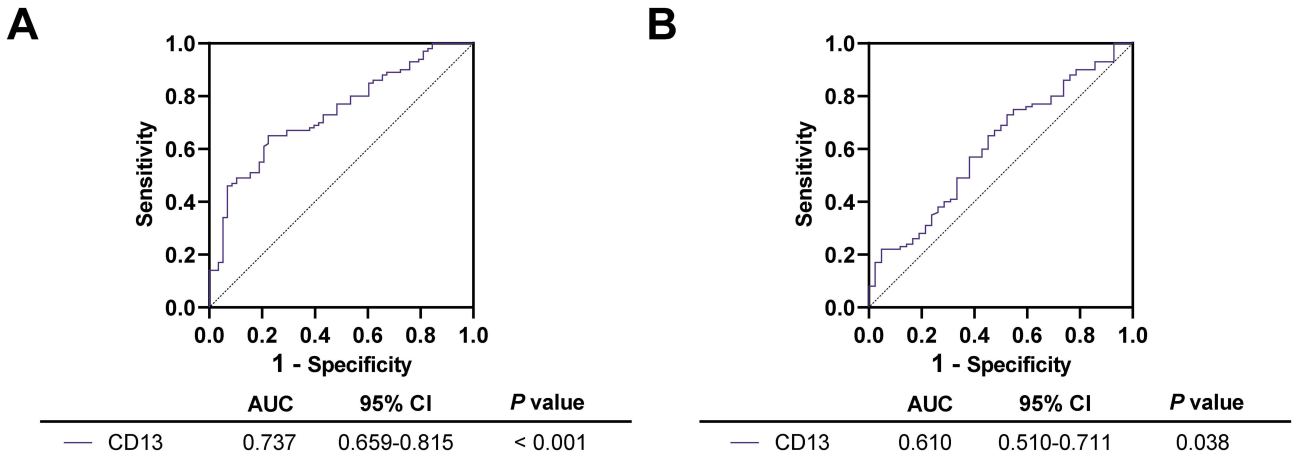

Figure 3 ROC curves of the diagnostic value of sCD13 in wAMD. (**A**) Predictive performance of sCD13 in distinguishing non-AMD from wAMD; (**B**) Predictive performance of sCD13 in distinguishing early AMD from wAMD. AUC denotes area under the ROC curve; 95% CI denotes 95% confidence interval; cut-off denotes optimal cutoff value.

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GCIPL.[31,32] This suggests that sCD13 may contribute to GCIPL thinning through inflammation-mediated indirect damage. Inflammation may not only indirectly affect retinal inner layer structures via complex signaling networks but also directly damage RPE cells. In cancers and inflammatory diseases such as rheumatoid arthritis and systemic sclerosis, sCD13 serves as a key pro-inflammatory mediator. By binding to the bradykinin receptor B1, sCD13 activates G protein-coupled receptor signaling pathways, promoting monocyte migration and inflammatory cytokine secretion, ultimately amplifying the local inflammatory microenvironment.[33,34] Literature has reported that elevated serum IL-8 levels are associated with wAMD.[35,36] In the present study, hsCRP and IL-8 were higher in the wAMD group than in the Non AMD and Early AMD groups. This indicates an enhanced inflammatory response surrounding the lesion, accompanied by abnormal release of hsCRP, IL-8, and VEGF. These substances disrupt the retinal barrier and vascular endothelium, leading to increased vascular permeability and allowing fluid to accumulate in the macular region and triggering edema.[37,38] The vitreomembranous area harbors abundant inflammatory cells,[39] indicating that high inflammatory activity is a key feature of AMD progression. Our findings revealed that sCD13 exhibits weak correlations with IL-8 and PDG, and moderate correlation with hsCRP. This suggests that sCD13 may participate in AMD progression by regulating the intensity of inflammatory responses within the vitreomembranous area. However, it must be explicitly stated that despite statistical significance, the weak correlations between sCD13 and IL-8/PDG cannot infer that sCD13 modulates these factors to influence wAMD pathogenesis. It is certain that wAMD development results from the synergistic action of multiple pathways, including inflammatory responses (eg, mediated by hsCRP and IL-8) and abnormal angiogenesis (eg, regulated by PDGF). However, some studies disagree with the results of the present study, and the correlation between wAMD and cytokine levels such as IL-6 and IL-8 is weak.[40] Therefore, the pathological mechanisms of wAMD and the core regulatory role of sCD13 require further investigation through in vivo and in vitro experiments.

In the setting of localized inflammation and underlying ischemia, choroidal angiogenesis begins to go unregulated, which can lead to an imbalance between VEGF and PEDF.[41] VEGF acts specifically on vascular endothelial cells, contributing to endothelial cell proliferation, induction of neoangiogenesis, and increased vascular leakage.[42,43] In contrast, blocking VEGF expression leads to vascular remodeling and regression of immature neovascularization. In addition, VEGF maintains ocular vascular integrity and is present in pericytes of ocular retinal capillaries, retinal pigment epithelial cells, and retinal endothelial cells. PDGF regulates the survival and function of pericytes of the retina, and blocks angiogenic stimulation induced by VEGF.[44] Under normal conditions, ocular tissues have low levels of VEGF and high levels of PDGF. When ischemia, hypoxia, and inflammation are present, VEGF expression is significantly increased and PDGF appears to be decreased, thus inducing the formation of pathological neovascularization.[45] VEGF is considered to be the most promising target for the treatment of choroidal and retinal neovascularization. The results of the present study showed that VEGF was higher in the wAMD group than in the Non AMD and Early AMD groups, suggesting that hypoxic or ischemic signaling alters the expression of genes related to angiogenesis, and the body compensates by increasing VEGF and promoting neoangiogenesis. sCD13 is expressed on the surface of tumor cells and plays a key role in regulating tumor cell metastasis and metabolism, as it activates angiogenic peptides, which play a key role in regulating tumor growth and metastasis.[8,11,46] Angiogenesis is a typical feature of wAMD. In the present study, sCD13 was higher in wAMD group than Non AMD group and Early AMD group. sCD13 elevated expression may be a direct response to hypoxic and ischemic environment with complementary functions in angiogenesis. ROC curves for diagnosing the Non-AMD group and the wAMD group, as well as those for diagnosing the Early AMD group and the wAMD group, both demonstrated the predictive efficacy of sCD13. Furthermore, sCD13 exhibited higher predictive value in distinguishing between Non-AMD and wAMD. wAMD represents the late neovascular form of AMD, essentially progressing from the pathological basis of Early AMD. This pathological continuity means some early AMD patients already exhibit mild inflammation or vascular activation, increasing the overlap in sCD13 expression between the Early AMD and wAMD groups. This ultimately reduces sCD13's predictive efficacy for both groups. This further illustrates the blurred pathological boundary between early AMD and wAMD, making it difficult for sCD13 to clearly distinguish between them. Therefore, while the findings of this study preliminarily confirm that sCD13 may serve as an important biomarker for early diagnosis, intervention, and prevention of vision loss in wAMD, it must be emphasized that in clinical practice, sCD13 cannot be used as the sole basis for diagnosing wAMD. It must be combined with imaging examinations such as OCT, FFA/ICGA, and others.

There are some limitations of this study. As a cross-sectional survey and due to the limitation of sample size, this study can only prove that there are some correlations between wAMD and age, history of smoking, CRT, hsCRP, IL-8,

mean GCIPL, BCVA, and PDGF levels, and it needs to be further determined by a large number of investigations or experiments. Also, this study was a single-center study and the sample size of the included studies was relatively small. The conclusions may be subject to bias from unmeasured confounders, as the study did not further control for potential confounding factors (such as smoking history and underlying medical conditions) using propensity score matching or multivariate regression models. Future research should employ methods like propensity score matching and multivariate analysis to conduct multicenter, large-sample studies for further validation. This approach would more comprehensively eliminate confounding and validate the robustness of the core findings.

Conclusion

In summary, sCD13 concentrations are abnormally elevated in the affected eye of wetAMD patients and correlate with increased serum hsCRP and IL-8 levels as well as decreased PDGF levels. This finding holds certain auxiliary value for diagnosing wAMD, particularly in distinguishing non-AMD from wAMD. This provides a reference for analyzing the clinical progression of wAMD. However, the regulatory role of sCD13 in wAMD pathology remains unclear at present, necessitating its clinical application in conjunction with imaging examinations. Future studies should further investigate the clinical relevance of sCD13 in individual patients to provide a clinical basis for predicting and preventing the onset and progression of wAMD.

Data Available

Data is available from the corresponding author on request.

Ethics Statement

The present study was approved by the Ethics Committee of Huanggang Central Hospital (No.201902HG-13) and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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