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Vascular endothelial growth factor-D plasma levels in fluid overload and cardiac function evaluation of elderly patients with cardiovascular disease

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Abstract

This study aimed to investigate the clinical significance of vascular endothelial growth factor (VEGF) subtypes and growth differentiation factor-15 (GDF-15) plasma levels in evaluating the fluid overload and cardiac function of elderly patients with cardiovascular disease. The plasma levels of VEGF-C, VEGF-D, and GDF-15 were measured using ELISA. Their correlations with N-terminal pro B-type natriuretic peptide (NT-Pro BNP) and echocardiography data were analyzed. 1. Higher plasma levels of VEGF-D and GDF-15 were observed in elderly patients with cardiovascular disease and heart failure($P < .01$). VEGF-D plasma levels were higher in patients with chronic heart failure than those with acute myocardial infarction ($P < .01$). VEGF-D plasma levels were positively correlated with amino-terminal pro-B type natriuretic peptide (NT-pro BNP) ($P < .001$). VEGF-D plasma levels were positively correlated with echocardiographic parameters, including left atrial diameter, left ventricular end-diastolic diameter and left ventricular ejection fraction, in patients with cardiovascular disease ($P < .01$). 2. VEGF-C plasma levels were higher in acute myocardial infarction group ($P < .05$). The plasma levels of VEGF-C were not correlated with either VEGF-D or NT-pro BNP plasma levels. VEGF-C plasma levels had no correlation with echocardiographic parameters. 3. GDF-15 plasma levels were positively correlated with sera biomarkers of cardiac injury (creatine kinase isoenzyme MB and cardiac troponin I). GDF-15 plasma levels were positively correlated with urinary biomarkers of tubular injury (N-acetyl-β-galactosidase and α1-microglobulin). Both GDF-15 and NT-pro BNP plasma levels were correlated with age, estimated glomerular filtration rate (eGFR), and nutritional biomarkers (albumin and hemoglobin plasma levels). VEGF-D plasma levels is a potential biomarker of fluid overload and cardiac function in elderly patients with cardiovascular disease. Age, nutrition, and kidney injury are factors influencing both GDF-15 and NT-pro BNP plasma levels in estimating cardiac function and fluid overload.

Abbreviations: AMI = acute myocardial infarction, CAD = coronary artery disease, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, GDF-15 = growth differentiation factor-15, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LAD = left atrial diameter, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, NT-pro BNP = amino-terminal pro-B type natriuretic peptide, VEGF = vascular endothelial growth factor.

Keywords: elderly, fluid overload, growth differentiation factor-15 (GDF-15), heart failure, vascular endothelial growth factor (VEGF)

1. Introduction

Heart failure, a major complication of cardiovascular diseases, is associated with a high risk of mortality and worsening renal function in patients with chronic kidney disease (CKD).[1,2] It is vital to identify high-risk patients with hypervolemia and heart failure to make early diagnosis and timely management. N-terminal pro-B-type natriuretic peptide (NT-pro BNP) is a well-recognized biomarker of heart failure and fluid overload, which is secreted in response to myocardial stretch from volume overload or pressure.[3,4] However, the clinical application of NT-pro BNP, with a molecular weight of 8.5 KD, is affected by both age and renal function.[5] Recent studies have reported that vascular endothelial growth factor (VEGF)-C or VEGF-D might be candidate biomarkers of fluid overload in hemodialysis patients.[6,7] VEGF-C/VEGF-D-VEGFR3 signaling pathways have been reported to participate

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each patient. The study protocol was approved by the Medical Ethical Review Committee of the Affiliated Hospital of Jiangnan University (Approval No. 20190105R).

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in lymphangiogenesis, which is involved in cardiac remodeling after ischemia–reperfusion injury.[8,9] Seraina et al observed that VEGF-D plasma levels were significantly associated with fluid overload in 2 independent hemodialysis patient cohorts but were unrelated to cardiac systolic function.[6] Sahutoglu et al reported VEGF-C plasma levels as a candidate biomarker of hypervolemia in patients with chronic kidney disease.[7]

Growth differentiation factor-15 (GDF-15), a cytokine belonging to transforming growth factor-β family, is significantly increased in response to cardiovascular injury, including pressure overload, heart failure, ischemia–reperfusion, and atherosclerosis.[10,11] However, GDF-15 is not expressed in the heart under normal physiological conditions.[10,11] In patients with systolic heart failure and chronic kidney disease, GDF-15 is more strongly associated with adverse outcomes than the conventionally used NT-pro BNP.[12,13] A clinical study showed that GDF-15 is a novel promising biomarker of heart failure with normal ejection fraction.[14]

Both cardiovascular disease (CVD) and CKD are great burdens for elderly patients.[15] Although the elderly have high morbidity and mortality from coronary artery disease,[16] there is still unknown about the clinical significance of VEGF-C, VEGF-D and GDF-15 in evaluating the fluid overload and cardiac function of elderly patients with cardiovascular disease, especially those complicated with renal insufficiency.

2. Materials and methods

2.1. Patient selection

2.1.1. The enrollment of elderly patients with cardiovascular disease. We enrolled elderly patients who were hospitalized in the affiliated hospital of Jiangnan University from January 2019 to December 2021. The inclusion criteria were as follows: 1. Age >65 years old; 2. Patients with coronary artery disease (CAD) were diagnosed by coronary angiography, which includes stable CAD and acute myocardial infarction (AMI). 3. Patients with non-CAD heart disease were diagnosed by coronary angiography and echocardiography, which includes hypertrophic cardiomyopathy, dilated cardiomyopathy, and hypertensive heart disease. Patients were excluded if they had congenital heart disease, concurrent sepsis, liver cirrhosis, malignant tumor, severe chronic obstructive pulmonary disease, Alzheimer disease, renal transplantation, dialysis, or surgery within 3 months.

2.1.2. Healthy controls. Twenty age- and sex-matched healthy controls from individuals who presented to the medical center were included in the study. They had no medical history of cardiovascular disease, kidney disease, cerebrovascular disease, lung disease, diabetes, liver disease or tumors.

2.2. Data collection

Medical and medication histories were recorded. The medical histories include hypertension, diabetes, atrial fibrillation, and the medication histories include aspirin, clopidogrel, ticagrelor, statins, beta-receptor blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, sacubitril/valsartan, dapagliflozin, digoxin, and diuretic drugs. The demographics and clinical biochemical parameters were recorded at admission, including echocardiographic parameters, blood urea nitrogen, plasma levels of creatinine, uric acid electrolytes, liver function, and lipid profile.

2.3. Detection of VEGF-D, VEGF-C, GDF-15, and NT-pro BNP plasma levels

VEGF-D, VEGF-C, GDF-15, and NT-pro BNP levels were measured in heparin plasma stored at −70 °C. VEGF-D, VEGF-C, and GDF-15 were measured using ELISA (R&D Systems, Minneapolis, MN) and had intra-assay coefficients of variation of 2.4%, 3.5%, and 1.8%, respectively. NT-pro BNP were measured using electrochemiluminescence.

2.4. Definitions

2.4.1. Coronary artery disease was defined according to the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions for percutaneous coronary intervention (ACCF/AHA/SCAI) 2011 guidelines.[17]

2.4.2. The definition of heart failure was in accordance with the 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure as follows: heart failure with preserved ejection fraction (HFpEF), left ventricular ejection fraction (LVEF) ≥ 50%; heart failure with mildly reduced ejection fraction (HFmrEF), LVEF 41–49%; heart failure with reduced ejection fraction (HFrEF), LVEF ≤ 40%.[18] In our study, we combined HFmrEF and HFrEF groups, according to previous published data from CRIC (Chronic Renal Insufficiency Cohort) Study.[3] Therefore, HFrEF was defined as LVEF < 50% with symptoms and HFpEF was defined as LVEF ≥ 50% with symptoms. LVEF was ascertained from echocardiograms performed during hospitalization for clinical purposes.

2.4.3. The definition of atrial fibrillation (AF) was in accordance with the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society (AHA/ACC/HRS) Task Force on Practice Guidelines.[19]

2.4.4. The definition of Renal insufficiency was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 using the formulation of CKD-EPI[20] (Chronic Kidney disease Epidemiology Collaboration).

2.5. Statistical analysis

Continuous data are expressed as mean ± standard deviation or median (interquartile range) and categorical data as percentages. Continuous data were compared among more than 3 groups using variance analysis and between 2 groups using the Independent Sample *t* test. Comparisons between groups were performed using the Kruskal–Wallis test and comparisons between 2 groups were performed using the Mann–Whitney *U* test for nonparametric data. Correlations between biochemical parameters were evaluated using a Pearson correlation test for continuous data and Spearman correlation test for nonparametric data. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL). Statistical significance was set at $P < .05$.

3. Results

3.1. The baseline characteristics of patients with cardiovascular disease (n = 94) are listed in Table 1

The average age was 76 ± 9 years, and male/female ratio was 63/31. The study included 41 elderly patients with cardiovascular disease and renal insufficiency.

3.2. VEGF-C, VEGF-D, and GDF-15 plasma levels in health controls and patients with cardiovascular disease

3.2.1. The comparison of VEGF-C, VEGF-D, and GDF-15 plasma levels between patients whose eGFR ≥ 60 mL/min·1.73 m^2 and patients whose eGFR < 60 mL/min·1.73 m^2 (as listed in Table 2). In age-matched healthy controls (n = 20), the average age was 75 ± 4years, and male/female ratio was 13/7. Healthy controls

had lower plasma levels of VEGF-D and GDF-15, but higher plasma levels of VEGF-C than patients with cardiovascular disease.

Patients with cardiovascular disease were divided into 2 groups according to their eGFR. There were higher plasma levels of VEGF-D, NT-pro BNP, and GDF-15, yet lower plasma levels of VEGF-C in patients with eGFR lower than 60 mL/min·1.73 m². Patients with lower eGFR had higher values of left atrial diameter (LAD). Patients with lower eGFR had higher systolic blood pressure, higher plasma levels of uric acid, and blood urea nitrogen, but lower plasma levels of albumin and hemoglobin than those with higher eGFR. Patients with lower eGFR were older than those with higher eGFR.

Table 1

The baseline clinical characteristics of patients with cardiovascular disease (n = 94) are listed in Table 1.

Clinical characteristics	
Medical history	**Case number(percentage)**
Smoking history	28(29.8%)
Hypertension	60(63.8%)
Diabetes	47(50%)
Cerebrovascular disease	19(20.2%)
Hyperuricemia	42(44.7%)
Microalbuminuria	52(55.3%)
Acute myocardial infarction	27(28.7%)
atrial fibrillation	24(25.5%)
Heart failure	68(72.3%)
Medication history	**Case Number(percentage)**
ACEI or ARBs	55 (58.5%)
Beta-receptor blocker	47(50.0%)
Sacubitril/valsartan	9 (9.6%)
Diuretics	51 (54.2%)
Dapagliflozin	11 (11.7%)
Digoxin	9 (9.6%)
Clinical parameters	
SBP (mm Hg)	138 ± 22
DBP (mm Hg)	77 ± 12
eGFR (mL/min·1.73 m²)	60 ± 25
Albumin (g/L)	38 ± 5
Hemoglobulin (g/L)	125 ± 25
NT-pro BNP (pg/mL)	3529 (660–11,340)
LVEF (%)	54 ± 11

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, NT-pro BNP = amino-terminal pro-B type natriuretic peptide, PCI = percutaneous coronary intervention, SBP = systolic blood pressure.

3.2.2. The comparison of VEGF-C and VEGF-D plasma levels among the HFpEF group (LVEF ≥ 50%), HFrEF group (LVEF < 50%), and normal cardiac function group (as shown in Table 3). Based on cardiac symptoms, echocardiographic imaging, and LVEF, patients with cardiovascular disease were divided into 3 groups: HFrEF (LVEF < 50%), HFpEF (LVEF ≥ 50%), and normal cardiac function (who had normal systolic and diastolic function without symptoms of heart failure)[3].

Higher plasma levels of VEGF-D, GDF-15, and NT-pro BNP were observed in HFrEF group than those in HFpEF group. The patients in HFrEF group had high values of left ventricular end-diastolic diameter (LVEDD) but lower left ventricular short axis shortening rate (LVFS) and LVEF than those in HFpEF group. There were no significant differences of age and eGFR between HFrEF group and HFpEF group.

Patients in normal cardiac function group had lower plasma levels of VEGF-D, GDF-15, and NT-proBNP than those in both HFrEF group and HFpEF group. There were lower values of LAD and LVEDD, yet higher LVEF and LVFS in normal cardiac function group. There was no significant difference of VEGF-C plasma levels among HFpEF group, HFrEF group, and normal cardiac function group. The patients in normal cardiac function group were younger than those in HFrEF group.

3.2.3. The comparison of VEGF-C, VEGF-D, and GDF-15 plasma levels among patients with different etiologies of cardiovascular disease (Table 4). The patients were divided into 3 groups according to the etiology of cardiovascular disease, including stable coronary artery disease group, AMI group, and non-CAD chronic heart failure group. The causes of non-CAD and chronic heart failure include hypertrophic

Table 2

The comparison of VEGF-C, VEGF-D and GDF-15 plasma levels between patients with cardiovascular disease whose eGFR were ≥ 60 mL/min·1.73 m² and patients whose eGFR were 60 mL/min·1.73 m².

Baseline characters	eGFR ≥ 60 mL/min(n = 53)	eGFR < 60 mL/min (n = 41)	*P*
VEGF-C(pg/mL)	2341 (1679–2848)	1463 (863–2047)	.000
VEGF-D(pg/mL)	701 (376–1215)	882 (475–1720)	.046
GDF-15 (pg/mL)	1151 (718–1823)	2256 (1162–3370)	.003
NT-pro BNP (pg/mL)	1500 (327–6216)	6850 (2035–13,167)	.004
CK-MB (u/L)	10 (6–27)	12 (7–17)	.884
CTnT (ng/mL)	32 (15–154)	86 (50–162)	.740
CTnI (ng/mL)	0.08 (0.01–1.03)	0.07 (0.03–0.82)	.434
LAD	44 ± 10	47 ± 6	.050
LVEDD	56 ± 9	56 ± 8	.772
LVEF	54 ± 11	52 ± 11	.391
LVFS	29 ± 7	28 ± 7	.654
Cholesterol (mmol/L)	3.4 ± 0.9	3.7 ± 1.0	.188
Low-density lipoprotein (mmol/L)	1.8 ± 0.6	2.0 ± 0.8	.077
Albumin (g/L)	40 ± 5	36 ± 5	.003
Magnesium (mmol/L)	0.8 ± 0.1	0.9 ± 0.1	.017
Sodium (mmol/L)	139 ± 4	137 ± 5	.011
Hemoglobulin (g/L)	133 ± 17	114 ± 29	.001
eGFR (mL/min·1.73 m²)	78 ± 14	37 ± 16	.000
Age (year)	72 ± 8	80 ± 9	.000

CTn = cardiac troponin, eGFR = estimated glomerular filtration rate, LAD = left atrial dimension, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVFS = left ventricular fractional shortening, NT-pro BNP = amino-terminal pro-B type natriuretic peptide, VEGF = vascular endothelial growth factor.

Table 3

The comparison of VEGF-C, VEGF-D and GDF-15 plasma levels among HFpEF group, HFrEF group and normal cardiac function group.

Baseline characters	HFrEF Patients(n = 38)	HFpEF (n = 30)	Normal cardiac function (n = 26)	Healthy controls (n = 20)
VEGF-C (pg/mL)	2048 (1379–2849)	1992 (1241–2504)	1847 (1383–2443)	3524 (2886–4221)
VEGF-D (pg/mL)	1213 (841–1499)*△△	831 (543–1289)△△	342 (216–527)	131 (88–348)**
GDF-15 (pg/mL)	2825 (1596–3964)**△△	1517 (956–1828)△△	737 (457–1041)	278 (184–382)
NT-pro BNP (pg/mL)	11,000(5294–20,632)**△△	2845 (1490–7571)△△	315 (37–661)	112 (36–412)**
CK-MB (U/L)	13 (7–28)	11 (7–25)	10 (6–16)	4.7 (4.0–10.9)
cTnT (ng/mL)	86 (47–337)△△	67 (22–551)△△	20 (10–76)	8 (5–14)
cTnI (ng/mL)	0.09 (0.04–1.57)△△	0.08 (0.04–5.59)△	0.01 (0.01–0.17)	0
LAD	49 ± 9△△	45 ± 7	42 ± 9	27 ± 4
LVEDD	61 ± 8**△△	54 ± 8△△	50 ± 5	45 ± 3
IVST	9.7 ± 1.8*	10.7 ± 2.2	10.2 ± 1.8	8.3 ± 0.5
LVPWT	9.1 ± 1.4**△	10.4 ± 1.8	10.0 ± 1.1	8.2 ± 0.4
LVEF	42 ± 6**△△	59 ± 7△△	63 ± 6	64 ± 3
LVFS	22 ± 6**△△	31 ± 5△△	34 ± 4	36 ± 4
Albumin (g/L)	37 ± 5△	38 ± 4	40 ± 5	46 ± 4
Sodium (mmol/L)	137 ± 5△	137 ± 5△	140 ± 3	140 ± 3
Magnesium (mmol/L)	0.87 ± 0.11	0.83 ± 0.11	0.85 ± 0.08	0.93 ± 0.11
Hemoglobulin (g/L)	117 ± 24△△	126 ± 28	134 ± 17	140 ± 5
eGFR (mL/min·1.73 m^2)	51 ± 23△△	61 ± 27	71 ± 21	91 ± 5
Age(year)	79 ± 9△△	75 ± 10	72 ± 9	72 ± 4

cTn = cardiac troponin, eGFR = estimated glomerular filtration rate, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, IVST = interventricular septum thickness, LAD = left atrial diameter, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVFS = left ventricular fractional shortening, LVPWT = left ventricular posterior wall thickness, NT-pro BNP = amino-terminal pro-B type natriuretic peptide, VEGF = vascular endothelial growth factor.

HFrEF group compared with HFpEF group:

*$P < .05$

**$P < .01$.

HFrEF and HFpEF groups compared to the normal cardiac function group:

△$P < .05$

△△$P < .01$.

cardiomyopathy, dilated cardiomyopathy, and hypertensive heart disease.

VEGF-C plasma levels were higher in AMI group than stable coronary artery disease group. Plasma levels of VEGF-D, GDF-15, and NT-pro BNP were higher in AMI group than those in stable coronary artery disease group. The patients in AMI group had higher values of LVEDD, yet lower LVEF and LVFS than those in stable coronary artery disease group. There was no significant difference of age and eGFR between the AMI group and stable coronary artery disease group.

Compared with AMI group, patients in non-CAD chronic heart failure group had higher plasma levels of VEGF-D, GDF-15, and NT-pro BNP, yet lower eGFR, lower plasma levels of hemoglobin, and albumin. There were higher values of LAD and interventricular septum thickness in non-CAD chronic heart failure group compared with AMI group. Patients in non-CAD heart failure group were older than those in AMI group.

3.3. Correlation analysis of VEGF-C, VEGF-D and GDF-15 and clinical data in patients with cardiovascular disease.

VEGF-D plasma levels were positively correlated with the plasma levels of NT-pro BNP and GDF-15 ($R = 0.514$, $P < .001$; $R = 0.673$, $P < .001$, respectively) in patients with cardiovascular disease. However, the plasma levels of VEGF-C had no correlation with either VEGF-D or NT-pro BNP plasma levels. In patients with cardiovascular disease, VEGF-D, NT-pro BNP, and GDF-15 plasma levels were positively correlated with the values of LAD ($R = 0.423$, $P < .001$; $R = 0.482$, $P < .001$; $R = 0.427$, $P < .001$,respectively) and LVEDD ($R = 0.350$, $P = .001$; $R = 0.357$, $P < .001$; $R = 0.350$, $P = .001$, respectively), yet negatively correlated with LVFS (r = –0.403, $P < .001$; r = –0.459, $P < .001$; r = –0.474, $P < .001$, respectively) and LVEF (r = –0.456, $P < .001$; r = –0.549, $P < .001$; r = –0.537, $P < .001$, respectively). Plasma levels of VEGF-C were not correlate with the above echocardiographic parameters. Neither VEGF-C nor VEGF-D plasma levels were correlated with plasma levels of sodium.

Plasma levels of VEGF-D, NT-pro BNP, and GDF-15 were all negatively correlated with eGFR (r = –0.369, $P < .001$; r = –0.504, $P < .001$; r = –0.448, $P < .001$, respectively). However, VEGF-C plasma levels were positively correlated with eGFR ($R = 0.386$, $P < .001$). Both NT-pro BNP and GDF-15 plasma levels were positively correlated with age ($R = 0.424$, $P < .001$; $R = 0.337$, $P = .001$, respectively). However, neither VEGF-C nor VEGF-D plasma levels were correlated with age.

The plasma levels of GDF-15 were positively correlated with both creatine kinase isoenzyme MB ($R = 0.304$, $P = .007$) and cardiac troponin I ($R = 0.347$, $P = .003$) sera levels. Plasma levels of GDF-15 were positively correlated with blood urea nitrogen ($R = 0.521$, $P < .001$), plasma uric acid ($R = 0.446$, $P < .001$), urinary N-acetyl-β-galactosidase ($R = 0.318$, $P = .025$), urinary albumin ($R = 0.582$, $P < .001$), and urinary α1-microglobulin ($R = 0.437$, $P = .001$). The plasma levels of GDF-15 and NT-pro BNP were negatively correlated with both albumin (r = –0.425, $P < .001$; r = –0.504, $P < .001$, respectively) and hemoglobin plasma levels (r = –0.344, $P = .001$; r = –0.474, $P < .001$, respectively).

4. Discussion

Recent studies have found that VEGF-C and VEGF-D might be biomarkers of fluid overload in patients with chronic kidney disease.[6,7] As NT-pro BNP is widely used in the evaluation of cardiac function and fluid overload in cardiovascular disease, we investigated the correlation among VEGF-C, VEGF-D and

Table 4

The comparison of VEGF-C, VEGF-D, and GDF-15 plasma levels among different etiology of patients with cardiovascular disease.

Baseline characters	Stable coronary artery disease(n = 31)	Non-CAD heart failure (n = 36)	AMI (n = 27)
VEGF-C (pg/mL)	1677 (1320–2381)*	2023 (1109–2672)	2150 (1630–2858)
VEGF-D (pg/mL)	344 (221–559)**,△△	1314 (1025–1828)**	637 (477–1012)
GDF-15 (pg/mL)	732 (478–1156)**,△△	3142 (1748–3953)**	1409 (969–2256)
NT-pro BNP (pg/mL)	328 (83–792)**,△△	10,840 (4464–20,948)**	4160 (1584–10,880)
CK-MB (u/L)	10 (6–16)**	12 (6–16)**	28 (15–71)
CTnT (ng/mL)	20 (11–64)**,△△	55 (33–102)**	470 (135–1803)
CTnI (ng/mL)	0.02 (0.01–0.09)**	0.06 (0.03–0.09)**	6.46 (0.84–23.88)
LAD	43 ± 8△△	50 ± 8**	42 ± 6
LVEDD	52 ± 7**,△△	57 ± 9	57 ± 8
IVST	10.2 ± 1.8*,△	10.9 ± 2.2**	9.2 ± 1.3
LVPWT	9.9 ± 1.1	9.9 ± 2.1	9.3 ± 1.0
LVEF	61 ± 7**,△△	48 ± 11	52 ± 9
LVFS	33 ± 5**,△△	26 ± 7	27 ± 6
Albumin (g/L)	39 ± 5**	37 ± 6**	38 ± 4
Low-density lipoprotein	1.7 ± 0.6*	1.8 ± 0.7*	2.3 ± 0.7
Sodium (mmol/L)	139 ± 3△	137 ± 6*	139 ± 3
Hemoglobulin (g/L)	127 ± 22△△	114 ± 30**	134 ± 16
eGFR(ml/min·1.73 m^2)	60 ± 29△△	55 ± 25*	67 ± 21
Age (year)	75 ± 10△	78 ± 9*	74 ± 9

AMI = acute myocardial infarction, CAD = coronary artery disease, cTn = cardiac troponin, eGFR = estimated glomerular filtration rate, IVST = interventricular septum thickness, LAD = left atrial diameter, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVFS = left ventricular fractional shortening, LVPWT = left ventricular posterior wall thickness, NT-pro BNP = amino-terminal pro-B type natriuretic peptide, VEGF = vascular endothelial growth factor.

Compared with AMI group:

*$P < .05$

**$P < .01$.

Stable coronary artery disease group compared with the non-CAD heart failure group:

△$P < .05$

△△$P < .01$.

NT-pro BNP plasma levels in elderly patients with cardiovascular disease.[5,8] We observed that NT-pro BNP plasma levels were closely correlated with age, biomarkers of nutrition, and eGFR, which limited their use in the assessment of cardiac function and fluid overload respectively, in elderly patients with renal failure.

We observed a significant positive correlation between VEGF-D and NT-pro BNP plasma levels in elderly patients with cardiovascular disease. Interestingly, similar to NT-pro BNP, VEGF-D plasma levels had significant correlation with echocardiographic parameters, including LAD, LVEDD, and LVEF. Besides, we observed that there were higher plasma levels of VEGF-D in non-CAD chronic heart failure group who also had higher values of LAD and LVEDD, compared with AMI group who had acute heart failure. Since there was no significant difference of LVEF between patients with AMI and those with chronic heart failure, higher plasma levels of VEGF-D might reflect higher fluid overload in elderly patients with chronic heart failure.

Researchers have reported that VEGF-D is associated with elevated pulmonary artery wedge pressure in chronic heart failure and elevated VEGF-D may alleviate chronic heart failure symptoms.[21] It is suggested that elevated plasma levels of VEGF-D might respond to compensatory neurohumoral regulation in patients with heart failure, especially those with chronic heart failure who had higher values of LAD and LVEDD. Interestingly, we observed that VEGF-D plasma levels were also correlated with LVEF in elderly patients with cardiovascular disease, which is different from Seraina study.[6] Since VEGF-D had no correlation with either age or nutritional biomarkers, it will be a better biomarker of cardiac function and fluid overload than NT-pro BNP in elderly patients.

In elderly patients with cardiovascular disease and renal insufficiency, the plasma levels of VEGF-C had no correlation with either VEGF-D or NT-pro BNP plasma levels, meanwhile had no correlation with echocardiographic parameters. It is suggested that VEGF-C might play a different role from that of VEGF-D in cardiovascular diseases. Animal model studies have reported that selective stimulation of cardiac lymphangiogenesis with VEGF-C reduces myocardial edema and fibrosis, leading to improved cardiac function following myocardial infarction.[8,9] In addition to regulating fluid balance, cardiac lymphatic vessels have vital functions in extravasated proteins and cholesterol transport, inflammation, and immune responses, which are speculated to be involved in cardiovascular diseases (including atherosclerosis, AMI, and heart failure).[8,9,22] We observed that there were higher plasma levels of VEGF-C in AMI group compared with stable coronary artery disease group, yet there was no significant difference of eGFR between the 2 groups. It is suggested that elevated VEGF-C may be involved in stimulating cardiac lymphangiogenesis to improve ischemic myocardial injury in AMI. In contrast to Sahutoglu reports, we did not observe a correlation between VEGF-C plasma levels and fluid overload in elderly patients with cardiovascular disease.[7]

Previous studies have reported that exogenous VEGF-C can delay the progression of chronic kidney disease in animal models, including obstructive nephropathy, diabetic nephropathy, and salt-sensitive hypertension-associated nephropathy.[23–25] Consistently, we observed that elderly patients with cardiovascular disease whose eGFR < 60 mL/min·1.73 m^2 had significantly lower plasma levels of VEGF-C. In addition, lower plasma levels of VEGF-C were observed in patients with cardiovascular disease and renal insufficiency in comparison with healthy controls. Since VEGF-C plasma levels had a positive correlation with eGFR, it suggested that insufficient endogenous VEGF-C might be related with the corresponding kidney injury.

Higher plasma levels of GDF-15 are associated with greater mortality and high incidence of cardiovascular events in patients.[4,26] We observed that GDF-15 plasma levels were significantly correlated with NT-pro BNP plasma levels and echocardiographic parameters in elderly patients with cardiovascular disease. We also observed a significant positive

correlation between GDF-15 plasma levels and sera biomarkers of myocardial injury, including creatine kinase isoenzyme MB and cardiac troponin I. Increased expression of GDF-15 was observed in human heart within hours after myocardial infarction, which remained elevation in the infarcted myocardium for several days.[10] It is suggested that higher plasma levels of GDF-15 in patients with cardiovascular disease may be a biomarker of ischemic myocardial injury. The clinical significance of GDF-15 in evaluating cardiac function and fluid overload in elderly patients with cardiovascular disease needs further research.

GDF-15 is a nephroprotective factor that is insufficiently upregulated in acute kidney injury and chronic kidney disease. The nephroprotective action of GDF-15 is associated with both downregulation of inflammation and upregulation of anti-inflammatory activity in tubular cells.[27] We also observed that GDF-15 plasma levels were positively correlated with eGFR and urinary biomarkers of tubular injury, including N-acetyl-β-galactosidase and α1-microglobulin. GDF-15 plasma levels might be a biomarker of tubular injury in elderly patients with cardiovascular disease and renal insufficiency. Besides, just the same as NT-pro BNP, GDF-15 also had positive correlation with age and nutritional biomarkers. Correspondingly, age, nutrition, and kidney injury are factors influencing both NT-pro BNP and GDF-15 plasma levels in estimating cardiac function and fluid overload of elderly patients.

4.1. Limitations

This was a clinical observational study with a small sample size. Large-scale clinical studies are needed to illustrate the clinical significance of VEGF-D plasma levels in evaluating the fluid overload and cardiac function of elderly patients with cardiovascular disease.

5. Conclusions

VEGF-D plasma levels is a potential biomarker of fluid overload and cardiac function in elderly patients with cardiovascular diseases. Age, nutrition, and kidney injury are factors influencing both GDF-15 and NT-pro BNP plasma levels in estimating cardiac function and fluid overload.

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References

[1] GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395:709–33.
[2] Beldhuis IE, Lam CSP, Testani JM, et al. Evidence-based medical therapy in patients with heart failure with reduced ejection fraction and chronic kidney disease. Circulation. 2022;145:693–712.
[3] Bansal N, Zelnick L, Go A, et al. Cardiac biomarkers and risk of incident heart failure in chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) Study. J Am Heart Assoc. 2019;8:e012336.
[4] Tummalapalli SL, Zelnick LR, Andersen AH, et al. Association of cardiac biomarkers with the Kansas City Cardiomyopathy Questionnaire in patients with chronic kidney disease without heart failure. J Am Heart Assoc 2020;9:e014385.
[5] Tzatzaki E, Spartalis M, Kamperidis V, et al. Association of brain natriuretic peptide and adrenomedullin plasma levels with left ventricular filling pressures in end-stage renal disease patients on hemodialysis. Eur Rev Med Pharmacol Sci. 2018;22:7945–51.
[6] von Moos S, Segerer S, Davenport A, et al. Vascular endothelial growth factor D is a biomarker of fluid overload in haemodialysis patients. Nephrol Dial Transplant. 2021;36:529–36.
[7] Sahutoglu T, Sakaci T, Hasbal NB, et al. Serum VEGF-C levels as a candidate biomarker of hypervolemia in chronic kidney disease. Medicine (Baltimore). 2017;96:e6543.
[8] Vieira JM, Norman S, Del Campo CV, et al. The cardiac lymphatic system stimulates resolution of inflammation following myocardial infarction. J Clin Invest. 2018;128:3402–12.
[9] Lammoglia GM, Van Zandt CE, Galvan DX, et al. Hyperplasia, de novo lymphangiogenesis, and lymphatic regression in mice with tissue-specific, inducible overexpression of murine VEGF-D. Am J Physiol Heart Circ Physiol. 2016;311:H384–94.
[10] Rochette L, Dogon G, Zeller M, et al. GDF15 and cardiac cells: current concepts and new insights. Int J Mol Sci. 2021;22:8889.
[11] Andersson J, Fall T, Delicano R, et al. GDF-15 is associated with sudden cardiac death due to incident myocardial infarction. Resuscitation. 2020;152:165–9.
[12] Claus R, Berliner D, Bavendiek U, et al. Soluble neprilysin, NT-proBNP, and growth differentiation factor-15 as biomarkers for heart failure in dialysis patients (SONGBIRD). Clin Res Cardiol. 2020;109:1035–47.
[13] Arkoumani M, Papadopoulou-Marketou N, Nicolaides NC, et al. The clinical impact of growth differentiation factor-15 in heart disease: a 2019 update. Crit Rev Clin Lab Sci. 2020;57:114–25.
[14] Chirinos JA, Orlenko A, Zhao L, et al. Multiple plasma biomarkers for risk stratification in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2020;75:1281–95.
[15] Li J, Liu F-H, Guo J, et al. Retrospective analysis of renal prognosis in elderly coronary artery disease patients complicated with renal insufficiency. Aging (Albany NY). 2021;13:22856–66.
[16] Dharmarajan K, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. Heart Fail Clin. 2017;13:417–26.
[17] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol. 2011;58:e44–122.
[18] McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44:ehad195.
[19] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1–76.
[20] Levey AS, Eckardt K-U, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
[21] Borné Y, Gränsbo K, Nilsson J, et al. Vascular endothelial growth factor D, pulmonary congestion, and incidence of heart failure. J Am Coll Cardiol. 2018;71:580–2.
[22] Liu X, De la Cruz E, Gu X, et al. Lymphoangiocrine signals promote cardiac growth and repair. Nature. 2020;588:705–11.
[23] Onions KL, Gamez M, Buckner NR, et al. VEGFC reduces glomerular albumin permeability and protects against alterations in VEGF receptor expression in diabetic nephropathy. Diabetes. 2019;68:172–87.
[24] Hasegawa S, Nakano T, Torisu K, et al. Vascular endothelial growth factor-C ameliorates renal interstitial fibrosis through lymphangiogenesis in mouse unilateral ureteral obstruction. Lab Invest. 2017;97:1439–52.
[25] Beaini S, Saliba Y, Hajal J, et al. VEGF-C attenuates renal damage in salt-sensitive hypertension. J Cell Physiol. 2019;234:9616–30.
[26] You AS, Kalantar-Zadeh K, Lerner L, et al. Association of growth differentiation factor 15 with mortality in a prospective hemodialysis cohort. Cardiorenal Med. 2017;7:158–68.
[27] Valiño-Rivas L, Cuarental L, Ceballos MI, et al. Growth differentiation factor-15 preserves Klotho expression in acute kidney injury and kidney fibrosis. Kidney Int. 2022;101:1200–15.