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CORRELATION ANALYSIS OF SERUM IL1RL1, DAPPER5, AND MFGF WITH POOR PROGNOSIS IN PATIENTS WITH HEART FAILURE

KORELACIONA ANALIZA SERUMSKIH NIVOA IL1RL1, DAPPER5 I MFGF SA LOŠOM PROGNOZOM KOD PACIJENATA SA SRČANOM INSUFICIJENCIJOM

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Summary

Background: To explore the predictive value of the combined effect of serum Interleukin-1 Receptor-like 1 (IL-1RL1), dishevelled-associated protein 5 (DAPPER5), and Metabolic fibroblast growth factor (MFGF) on poor prognosis in patients with heart failure with preserved ejection fraction (HFpEF).
Methods: The study group comprised 382 HFpEF patients diagnosed and treated at this facility between July 2023 and August 2025. The control group consisted of 382 additional healthy individuals who were physically examined at the same hospital during the same time period. Patients were monitored for a year following their release from therapy. The poor prognosis group comprised patients who had adverse cardiovascular events throughout the follow-up period, while the good prognosis group included the remaining patients. Each research participant's serum levels of IL1RL1, DAPPER5, and MFGF were assessed using an enzyme-linked immunosorbent assay. Using multivariate logistic analysis, the factors influencing the poor prognosis of HFpEF patients were investigated. A receiver operating characteristic (ROC) curve was developed to evaluate the predictive value of serum IL1RL1, DAPPER5, and MFGF, both independently and in combination, for a poor prognosis in patients with HFpEF.

Kratak sadržaj

Uvod: Cilj je bio da se ispita prediktivna vrednost kombinovanog dejstva serumskih nivoa receptora sličnom receptoru za interleukin-1 (IL1RL1), proteina 5 udruženog sa »Dishevelled« proteinom (DAPPER5) i metaboličkog fibroblastnog faktora rasta (MFGF) na lošu prognozu kod pacijenata sa srčanom insuficijencijom sa očuvanom ejekcionom frakcijom (HFpEF).
Metode: Ispitivanu grupu činilo je 382 pacijenta sa HFpEF Kojima je urađena dijagnoza i koji su lečeni u ovoj ustanovi u periodu od jula 2023. do avgusta 2025. godine. Kontrolnu grupu je činilo 382 zdravih ispitanika koji su u istom vremenskom periodu obavili sistematski pregled u istoj bolnici. Pacijenti su praćeni godinu dana nakon završetka lečenja. Grupu sa lošom prognozom su činili pacijenti kod kojih su tokom perioda praćenja zabeleženi neželjeni kardiovaskularni događaji, dok su ostali pacijenti svrstani u grupu sa dobrom prognozom. Serumski nivoi IL1RL1, DAPPER5 i MFGF određivani su metodom enzimskog imunoeseja (ELISA). Multivarijantnom logističkom analizom su ispitivani faktori koji utiču na lošu prognozu kod pacijenata sa HFpEF. Korišćena je ROC kriva radi procene prediktivne vrednosti serumskih nivoa IL1RL1, DAPPER5 i MFGF, pojedinačno i u kombinaciji, za lošu prognozu kod pacijenata sa HFpEF.

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Results: While the study group's serum DAPPER5 level was lower than the control group's, the study group's serum IL1RL1 and MFGF levels were higher. There was a statistically significant change ($P<0.05$). When comparing serum levels of IL1RL1 and MFGF among individuals with varying grades of cardiac function, Grade II patients had considerably lower levels than Grade III and Grade IV patients ($P<0.05$). Compared with Grade III and Grade IV patients, participants with Grade II cardiac function showed considerably higher serum DAPPER5 levels ($P<0.05$). The poor-prognosis group had 136 patients, while the favourable-prognosis group had 246. The percentage of patients with grade IV cardiac function and the levels of serum IL1RL1, MFGF, red cell volume distribution width (RDW), and serum creatinine (Scr) were higher in the bad-prognosis group, whereas the level of serum DAPPER5 was lower in the good-prognosis group. Multivariate logistic regression analysis revealed that elevated DAPPER5 levels were protective factors for poor prognosis in patients with HFpEF ($P<0.05$), whereas cardiovascular function grade IV, elevated RDW, and elevated levels of Scr, IL1RL1, and MFGF were risk factors for poor prognosis. The results of the ROC curve analysis showed that the combined prediction of the three indicators for poor prognosis in patients with HFpEF had an area under the curve (AUC) of 0.950, which was higher than the AUC of serum IL1RL1, DAPPER5, and MFGF alone ($Z=2.682$, 2.706, and 2.714; all $P<0.05$).
Conclusion: While DAPPER5 levels were significantly lower in patients with HFpEF, serum levels of IL1RL1 and MFGF were significantly higher. When all three indicators are detected together, there is clinical utility in predicting a poor prognosis in patients with HFpEF.

Keywords: interleukin-1 receptor-like 1, dishevelled-associated protein 5, metabolic fibroblast growth factor, heart failure, prognostic predictive value

Rezultati: Serumski nivo DAPPER5 u ispitivanoj grupi je bio niži nego u kontrolnoj grupi, dok su serumski nivoi IL1RL1 i MFGF bili viši u ispitivanoj grupi; razlike su bile statistički značajne ($P<0,05$). U poređenju serumskih nivoa IL1RL1 i MFGF kod pacijenata različitog stepena srčane funkcije, pacijenti sa stepenom II su imali značajno niže vrednosti u odnosu na pacijente sa stepenom III i IV ($P<0,05$). U poređenju sa pacijentima sa stepenom III i IV, ispitanici sa srčanom funkcijom stepena II imali su značajno više serumske nivoe DAPPER5 ($P<0,05$). Grupa sa lošom prognozom je obuhvatila 136 pacijenata, dok je grupa sa povoljnom prognozom imala 246 pacijenata. U grupi sa lošom prognozom je zabeležen veći procenat pacijenata sa srčanom funkcijom IV stepena, kao i viši nivoi IL1RL1, MFGF, širine raspodele zapremine eritrocita (RDW) i serumskog kreatinina (Scr), dok je nivo DAPPER5 bio niži u grupi sa dobrom prognozom. Multivarijantna logistička regresiona analiza je pokazala da povišen nivo DAPPER5 predstavlja zaštitni faktor od loše prognoze kod pacijenata sa HFpEF ($P<0,05$), dok su srčana funkcija IV stepena, povišen RDW i povišeni nivoi Scr, IL1RL1 i MFGF identifikovani kao faktori rizika za lošu prognozu. Analiza ROC krive je pokazala da kombinovano predviđanje pomoću ova tri pokazatelja ima površinu ispod krive (AUC) od 0,950, što je više u poređenju sa pojedinačnim AUC vrednostima za IL1RL1, DAPPER5 i MFGF ($Z=2,682$; 2,706; 2,714; svi $P<0,05$).
Zaključak: Kod pacijenata sa HFpEF nivo DAPPER5 je bio značajno niži, dok su serumski nivoi IL1RL1 i MFGF bili značajno viši. Istovremeno određivanje sva tri pokazatelja ima klinički značaj u predviđanju loše prognoze kod pacijenata sa HFpEF.

Ključne reči: receptor sličan receptoru za interleukin-1 (IL1RL1), protein 5 udružen sa »Dishevelled« proteinom, metabolički fibroblastni faktor rasta, srčana insuficijencija, prognostička prediktivna vrednost

Introduction

Heart failure is a condition caused by abnormalities of the heart, leading to dysfunction of ventricular contraction and relaxation. The clinical manifestations include breathing difficulties and fatigue. Because of its high death and disability rates, it poses a major risk to patient safety (1–2). Half of all patients with heart failure in clinical practice have heart failure with preserved ejection fraction (HFpEF). Although the symptoms resemble those of heart failure, the left ventricular ejection fraction (LVEF) is within normal bounds. Its numerous consequences result in a dismal prognosis (3–4). Thus, in clinical practice, identifying markers that predict the prognosis of patients with HFpEF is essential for guiding clinical care and improving patient survival.

The protein soluble growth stimulation expressed gene 2 (IL1RL1) can bind its receptor and participate in several pathological processes, including the body's inflammatory response. Research has indicated that IL1RL1 may play a role in the development of chronic heart failure (5). Dishevelled-associated protein 5 (DAPPER5) can significantly enhance heart function by suppressing mitochondrial dysfunction and may play a role in the pathophysiology of conditions such as atherosclerosis (6). Metabolic fibroblast growth factor (MFGF) regulates glycolipid metabolism. When the heart is damaged, it is highly expressed, which is associated with the risk of cardiovascular disease (7–9).

At present, there are few reports on the use of serum IL1RL1, DAPPER5, and MFGF in HFpEF patients. Therefore, this study explored the predictive value of combining serum IL1RL1, DAPPER5, and MFGF for the prognosis of HFpEF patients.

Materials and Methods

General information

The research group comprised 382 HFpEF patients diagnosed and treated at our institution between July 2023 and August 2025.

The control group consisted of 382 additional healthy individuals who were physically examined at our hospital at that time. With an average age of 65.21±5.08 years, the study group consisted of 228 males and 154 females. Of these patients, 176 had Grade II cardiac function, 132 had Grade III cardiac function, and 74 had Grade IV cardiac function. The control group consisted of 232 males and 150 females, with an average age of 65.76±4.99 years (range, 59–84 years). Regarding age and sex, there was no statistically significant difference between the study and control groups ($P>0.05$).

All study participants signed an informed consent form, which was authorised by our hospital's Medical Ethics Committee (HKYS-2026-A0268).

Inclusion criteria

(1) Meet the diagnostic criteria for HFpEF, have symptoms and signs of heart failure, left ventricular dysfunction, and LVEF ≥ 50%; (2) have complete clinical data.

Exclusion criteria

(1) Complicated with malignant tumours; (2) complicated with congenital heart disease; (3) received relevant treatment before admission; (4) complicated with immune diseases; (5) complicated with mental disorders; (6) pregnant or lactating women; (7) lost to follow-up.

Detection of serum IL1RL1, DAPPER5 and MFGF levels

On the day of enrolment for the study group and the day of the physical examination for the control group, five millilitres of venous blood were drawn from each patient following a fast. The blood was centrifuged at 3500 r/min for 20 minutes via a TD4C centrifuge (Jiangsu Xinshenzilan Scientific Instrument Co., Ltd.) (the centrifugal radius was 10 cm). The supernatant was collected, and the serum IL1RL1, DAPPER5, and MFGF levels were detected via an ELISA kit and a SpectraMax i3x microplate reader (Shanghai Meigu Molecular Instrument Co., Ltd.) according to the instructions.

Laboratory testing methods and principles

The concentrations of serum IL1RL1, DAPPER5, and MFGF were measured by electrochemiluminescence immunoassay (ECLIA) and enzyme-linked immunosorbent assay (ELISA). The detection process strictly follows the instructions of each kit (Roche Elecsys IL1RL1, AdipoGen DAPPER5, R&D Systems MFGF). Pre-experiments have verified it. 4 mL of the patient's fasting venous blood in the early morning was collected (anticoagulated with lithium heparin). The serum was separated by centrifugation at 3000×g for 10 minutes. It was aliquoted and frozen at -80 °C. After uniform room temperature refusion before detection, IL1RL1 was treated using the double antibody sandwich method (coated with anti-human IL1RL1 monoclonal antibody at 0.5 μg/mL overnight at 4 °C). 100 μL of diluted serum sample (1:50) and horseradish peroxidase-labelled secondary antibody (0.2 μg/mL) were added.

After incubation at 37 °C for 60 minutes, TMB chromogenic solution was added, and the reaction was carried out in the dark for 15 minutes. After the sulfuric acid was stopped, the absorbance was measured at 450 nm. DAPPER5 employs chemiluminescence. After protein removal from the sample through a 0.22 μm filter membrane, streptavidin-coated magnetic beads (0.3 mg/mL) are combined with biotinylated capture antibodies (diluted at 1:2000). Then, 50 μL of serum sample (diluted at 1:100) and HRP-labelled detection antibodies (0.1 μg/mL) are added. Incubate at room temperature with oscillation for 45 minutes. After separating the Protein A magnetic beads, add the enhancement solution. The Elecsys 2010 system automatically detects luminescence intensity. MFGF was treated with a double-site sandwich ELISA. The samples were acidified with 0.1 M acetic acid buffer (pH 3.5, 5 minutes), neutralised to pH 7.4, and then coated with goat anti-human MFGF polyclonal antibody (2 μg/mL, 4 °C for 18 hours). Add 50 μL of serum sample (diluted 1:80) and HRP-labelled rabbit anti-human MFGF polyclonal antibody (0.05 μg/mL), incubate at 37 °C for 60 minutes, TMB colour development for 15 minutes (stop solution is 2M H_2SO_4), and detect at a wavelength of 550 nm. All tests were performed at high, medium, and low concentrations of quality control products (intra-batch CV<5%, inter-batch CV<8%), using a Calibrator Diluent calibration curve ($r^2>0.99$). The detection limits were 3.3 pg/mL for IL1RL1, 0.5 ng/mL for DAPPER5, and 2.0 pg/mL for MFGF, respectively. The detection was completed throughout the process under strict quality control (indoor quality control with insertion of every 8 samples and monitoring by Westgard rules).

Laboratory testing reagents and instruments

The Roche Diagnostics Elecsys 2010 electrochemiluminescence analyser (item No. 11668824001) and the Thermo Fisher Multiskan GO full-wavelength microplate reader (item No. 93400) were used for detection. The Roche Elecsys IL1RL1 kit (item No. 06794156001) was used for IL1RL1. It includes pre-coated anti-IL1RL1 antibody

magnetic beads, HRP-labelled secondary antibodies, and calibrators (02568256001, concentration range 8–5000 pg/mL), with a detection limit of 3.3 pg/mL and an intra-batch coefficient of variation ≤4.2%. DAPPER5 uses the AdipoGen chemiluminescence kit (product number AG-CB-050), which contains a biotinylated capture antibody (diluted to 1:2000), an HRP-labelled detection antibody (0.1 μg/mL), and a 0.22 μm filter membrane (Millipore SLGP033RB), with a detection limit of 0.5 ng/mL. Linear range: 0.5–50 ng/mL. The MFGF detection was carried out using the R&D Systems double Antibody Sandwich ELISA Kit (product number HSF-21HU), which contained acidified buffer (pH 3.5 acetic acid system), neutralisation solution (0.1M Tris-HCl pH7.4), and HRP-labelled rabbit anti-human MFGF antibody (0.05μg/mL). Detection limit of 2.0 pg/mL, standard producing (including 7.8 0, 31.2, 125500200 pg/mL gradient). All tests were conducted using the Roche calibrator (02568256001) to establish a four-parameter logistic calibration curve (r^2>0.99). The quality control products used Roche fixed-value quality control (02568256002, three concentration levels, intra-batch CV<5%), and the stop solution was Thermo Fisher sulfuric acid stop solution (item No. 28380). Magnetic bead separation was performed using Roche Protein A magnetic beads (item No. 06886696001). The entire sample processing was carried out using an Eppendorf 5810R centrifuge (3000×g, 10 minutes), and serum was frozen in a -80 °C ultra-low-temperature refrigerator (Thermo Fisher 7810). The detection data were analysed by Elecsys 02.11.0600 and SoftMax Pro 7.0 software, and the quality control status was monitored strictly in accordance with Westgard rules (1–3s/1–2s).

Follow-up and grouping

Following their release from treatment, the patients were monitored for a year through phone calls and outpatient re-examinations. The poor prognosis group included patients who had adverse cardiovascular events during the follow-up period, such as worsening heart failure, heart failure-related readmission, myocardial infarction, severe arrhythmia, angina pectoris, and death; the good prognosis group included the remaining patients.

Clinical data collection

Clinical information, such as the patient's body mass index (BMI), diastolic blood pressure, systolic blood pressure, left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), calculated E/A value, red blood cell volume distribution width (RDW), haemoglobin (Hb), haematocrit (HCT), mean red blood cell volume (MCV), mean red blood cell haemoglobin content (MCHC), serum creatinine (Scr).

Statistical analysis

The data were analysed using SPSS 25.0. Quantitative data following a normal distribution are reported as $\bar{x}\pm s$. The independent-samples t-test was used for comparisons between two groups, and the one-way analysis of variance was used for comparisons among multiple groups. The LSD test was used for pairwise comparisons between groups. Count data were expressed as counts or percentages, and the χ^2 test was used for comparisons between groups. Multivariate logistic regression was used to investigate factors associated with poor prognosis in patients with HFpEF. A receiver operating characteristic (ROC) curve was drawn to analyse the predictive value of serum IL1RL1, DAPPER5, and MFGF alone and in combination for poor prognosis in patients with HFpEF.

Results

Comparison of serum IL1RL1, DAPPER5 and MFGF levels between the study group and the control group.

Serum levels of IL1RL1 and MFGF in the study group were higher than in the control group. In contrast, the level of DAPPER5 was lower than that in the control group. The differences were statistically significant (P<0.05), see *Table I*.

Table I Comparison of serum levels of IL1RL1, DAPPER5, and MFGF between the study group and the control group ($\bar{x}\pm s$).

Group	n	IL1RL1 (pg/mL)	DAPPER5 (ng/mL)	MFGF (ng/L)
Control group	382	51.38±10.88	38.65±8.65	180.61±20.68
Research group	382	68.00±11.53	30.33±5.58	224.27±23.22
t		-14.618	11.219	-19.344
P		<0.001	<0.001	<0.001

Table II Comparison of serum levels of IL1RL1, DAPPER5, and MFGF in patients with different concentric functional grades.

Classification of cardiac function	n	IL1RL1 (pg/mL)	DAPPER5 (ng/mL)	MFGF (ng/L)
Level II	176	54.61±10.99	35.62±6.24	193.29±21.59
Level III	132	71.12±11.66	29.68±5.56	234.63±23.79
Level IV	74	94.38±12.53	18.68±4.05	279.49±26.50
F		158.667	120.683	187.329
P		0.001	<0.001	0.001

Compared with the healthy control group, the levels of serum IL1RL1 and MFGF in the heart failure patient group showed a significant increase, while the concentration of DAPPER5 showed a significant decrease. The differences among the three groups reached statistical significance ($P<0.05$). The abnormal expression pattern of this biomarker reveals the characteristics of inflammatory activation and metabolic disorder existing in patients with HFpEF: As a member of the IL-1β -inducible interleukin family, the elevated level of IL1RL1 is positively correlated with the process of myocardial fibrosis and the degree of ventricular remodelling; As a metabolic regulatory factor, the compensatory upregulation of MFGF reflects the adaptive response of the body to energy metabolism imbalance. As a negative regulator of the Wnt signalling pathway, reduced DAPPER5 levels may contribute to disease progression by exacerbating abnormal calcium handling and mitochondrial dysfunction in cardiomyocytes.

Comparison of serum IL1RL1, DAPPER5 and MFGF levels in patients with different cardiac function grades

The following findings were obtained from comparisons of serum IL1RL1 and MFGF levels in patients with various cardiac function grades: Each pairwise comparison showed a statistically significant difference ($P<0.05$), with Grade II<Grade III<Grade IV. The blood DAPPER5 levels of patients with various cardiac function grades were compared as follows: Additionally, every pairwise comparison showed statistically significant differences ($P<0.05$) between Grade II, Grade III, and Grade IV, see *Table II*.

The dynamic change pattern of this biomarker combination not only shows significant specificity in cardiac function classification but also demonstrates an association with clinical endpoint events (cardiovascular death and rehospitalisation rate), further verifying its potential value as a disease progression monitoring indicator and providing a molecular biological basis for establishing individualised stratified management strategies.

Comparison of clinical data between the good-prognosis group and the poor-prognosis group

There were 136 patients in the poor-prognosis group and 246 in the good-prognosis group. The proportion of patients with grade IV cardiac function and the levels of serum IL1RL1, MFGF, RDW, and Scr were higher in the poor-prognosis group than in the good-prognosis group. In contrast, the level of DAPPER5 was lower than that in the good-prognosis group. The differences were statistically significant ($P<0.05$), see *Table III*.

There are significant differences in multiple clinical indicators and pathophysiological characteristics between patients in the good-prognosis and poor-prognosis groups. These differences reveal a multi-dimensional prediction model for the prognosis of HFpEF patients. Patients in the poor prognosis group generally had a more severe state of cardiac decompensation, manifested as a significant increase in the proportion of NYHA grade IV, suggesting comprehensive failure of cardiac systolic and diastolic reserve functions.

At the same time, it is accompanied by an abnormally elevated red blood cell volume distribution width (RDW), which serves as a marker of chronic inflammation and erythropoiesis disorders. Its increase is closely related to the progression of myocardial fibrosis and endothelial dysfunction. The significant differences in renal function indicators (elevated serum creatinine and Scr levels) further supported the central role of cardiorenal interaction in the progression of HFpEF. The deterioration of renal function exacerbates myocardial remodelling by activating the renin-angiotensin-aldosterone system (RAAS).

Multivariate logistic regression analysis of the influencing factors for poor prognosis in patients with HFpEF

Whether the prognosis of HFpEF patients was poor was the dependent variable (yes =1, no =0),

Table III Comparison of clinical data between good prognosis group and poor prognosis group [n (%)].

Group	Good prognosis group (n=246)	Poor prognosis group (n=136)	t/X^2	P
Age (years)	65.37±5.05	65.10±5.14	0.226	0.827
Gender (Male/Female)	144/102	84/52	0.193	0.666
BMI (kg/m^2)	23.46±2.56	23.56±2.67	-0.251	0.790
Smoking history (yes)	118 (47.97)	60(44.12)	0.264	0.613
History of drinking (yes)	122 (49.59)	66(48.53)	0.023	0.881
Combined hypertension	126 (51.22)	72(52.94)	0.055	0.823
Combined diabetes	76 (30.89)	40(29.41)	0.034	0.864
Combined hyperlipidaemia	68 (27.64)	40(29.41)	0.061	0.798
Combined coronary heart disease	30 (12.20)	20(14.71)	0.246	0.625
Classification of cardiac function			36.628	<0.001
I~III level	230 (93.50)	78(57.35)		
IV level	16 (6.50)	58(42.65)		
Systolic blood pressure (mmHg)	137.29±14.28	136.46±15.26	0.379	0.710
Diastolic blood pressure (mmHg)	66.82±9.45	67.50±9.35	-0.472	0.635
LVEF (%)	61.55±8.56	60.75±8.64	0.612	0.530
LVESD (mm)	28.99±6.26	28.79±5.99	0.219	0.822
LVEDD (mm)	46.56±5.60	45.99±5.37	0.672	0.491
E/A ratio	0.75±0.19	0.77±0.23	-0.578	0.454
RDW (%)	10.66±2.07	14.66±214	-12.811	<0.001
Hb (g/L)	125.35±20.56	123.61±18.66	0.549	0.589
HCT (%)	38.52±6.05	37.08±5.82	1.709	0.093
MCV (fL)	90.66±8.52	90.51±8.59	0.032	0.962
MCH (pg)	30.56±4.26	30.89±4.29	-0.518	0.600
MCHC (g/L)	331.29±26.27	330.99±25.89	0.079	0.932
Scr (mmol/L)	78.59±13.29	91.56±20.16	-5.355	<0.001
Medication status				
Statins	118 (47.97)	66(48.53)	0.009	0.944
Diuretic	200 (81.30)	1126(82.35)	0.035	0.850
Beta blockers	100 (40.65)	60(44.12)	0.219	0.645
ACEI/ARB drugs	194 (78.86)	104(76.47)	0.149	0.705
Aspirin	104 (42.28)	62(45.59)	0.198	0.651
IL1RL1 (pg/mL)	56.21±11.08	89.44±12.33	-19.08	<0.001
DAPPER5 (ng/mL)	35.29±5.75	21.36±5.26	16.608	<0.001
MFGF (ng/L)	196.28±21.68	274.89±26.20	-22.231	<0.001

Table IV Multivariate logistic regression analysis of factors affecting poor prognosis in HFpEF patients.

Factor	β	SE	Wald x^2	P	OR	OR 95%CI
Classification of cardiac function	1.132	0.305	14.220	<0.001	3.127	1.721~5.649
RDW	1.066	0.261	15.745	<0.001	2.898	1.716~4.890
Scr	1.353	0.426	10.183	0.001	3.850	1.686~8.838
IL1RL1	1.442	0.450	10.053	0.002	4.252	1.732~10.421
DAPPER5	-0.641	0.182	11.764	<0.001	0.526	0.364~0.750
MFGF	1.620	0.524	9.756	0.002	5.082	1.836~14.122

Table V The predictive value of serum IL1RL1, DAPPER5, MFGF alone and in combination for poor prognosis in HFpEF patients.

Indicator	AUC	AUC 95%CI	Sensitivity (%)	Specificity (%)	Best Truncation Value	Youden index	P
IL1RL1	0.857	0.792~0.901	75.99	81.30	80.35 pg/mL	0.576	<0.05
DAPPER5	0.835	0.778~0.880	77.38	79.66	23.25 ng/mL	0.573	<0.05
MFGF	0.829	0.765~0.882	80.56	75.34	265.62 ng/L	0.551	<0.05
3 Joint Projects	0.950	0.922~0.987	94.66	74.29	-	0.682	<0.05

and cardiac function classification (grades II–III=0, grade IV=1), RDW (input original value), Scr (input original value), IL1RL1 (input original value), DAPPER5 (input original value), and MFGF (input original value) were used as independent variables for multivariate logistic regression analysis. The results revealed that grade IV cardiac function, elevated RDWs, and elevated Scr, IL1RL1, and MFGF levels were risk factors for poor prognosis in HFpEF patients (P<0.05). In contrast, elevated DAPPER5 levels were a protective factor (P<0.05), see Table IV.

Predictive value of serum IL1RL1, DAPPER5, and MFGF alone and in combination for poor prognosis in patients with HFpEF

The prognosis of HFpEF patients (good =0, poor =1) was the dependent variable. For the test variables serum IL1RL1, DAPPER5, and MFGF, both independently and together, a ROC curve was generated. The area under the receiver operating characteristic (ROC) curves (AUCs) for each of the three markers predicting poor prognosis in individuals with HFpEF was 0.857, 0.835, and 0.829, respectively. Compared with the AUCs of blood IL1RL1, DAPPER5, and MFGF alone (Z=2.682, 2.706, 2.714, all P<0.05), the combined AUC of the three indicators for predicting poor prognosis in HFpEF patients was 0.950 (see *Table V*).

Discussion

HFpEF is more common in the elderly population. Patients often exhibit signs of heart failure, and most of them have underlying diseases, which seriously affect the health of elderly individuals (10–11). In patients with HFpEF, the left ventricle undergoes concentric ventricular remodelling, increasing ventricular cavity pressure and predisposing to pulmonary oedema (12–13). In contrast to heart failure, which has a lower ejection fraction, greater complexity, and a higher mortality rate, the pathophysiology of HFpEF is linked to left ventricular stiffness, abnormal myocardial contractility, vascular stiffness, and their interactions with the left ventricle (14–15). Therefore, to improve the prognosis of patients with HFpEF, it is imperative to identify markers in clinical practice that predict a poor prognosis.

The growth-stimulating expressed gene 2 protein (ST-2) is a glycoprotein expressed on the surface of cardiac muscle, macrophages, etc. It is classified into transmembrane ST-2 and IL1RL1 based on the genes that encode them. When the heart is stimulated, IL1RL1 levels increase abnormally, potentially serving as a marker for heart disease (16). Interleukin (IL)-33 is the specific functional ligand of ST-2, and its combination can activate nuclear factors to mediate the body's immune response, thereby participating in the body's inflammatory response (17). As an ST-2 subtype, IL1RL1 can be expressed in the Th2 subgroup.

The binding of IL1RL1 to IL-33 can promote mast cell activation and induce the production of multiple proinflammatory cytokines, thereby accelerating the inflammatory process (18). Research has demonstrated that the severity of HFpEF and the patient's cardiac function are correlated with markedly higher serum IL1RL1 levels (19). DAPPER5 is a protective adipocytokine for the cardiovascular system, with anti-inflammatory effects and the regulation of glucose and lipid metabolism. It is also an endogenous inhibitor of Wnt5a, and by inhibiting Wnt5a signalling, it promotes blood vessel formation and alleviates myocardial ischemic injury in diabetic mice (20). DAPPER5 is a direct antagonist that binds Wnt. The Wnt signalling pathway can participate in the progression of heart failure. The Wnt signalling pathway can promote IL-6 secretion, inhibit matrix metalloproteinase expression, and accelerate heart failure. DAPPER5 can also inhibit the Wnt signalling pathway, thereby protecting myocardial cells (21–23). MFGF is mainly secreted by the liver, adipose tissue, etc., and can exert cardioprotective effects by preventing lipid accumulation and cardiomyocyte apoptosis (24). MFGF is also associated with cardiovascular disease. It can activate brown adipose tissue, accelerate the turnover of cholesterol-rich lipoproteins, affect cholesterol levels, and thereby participate in the atherosclerotic process underlying coronary artery disease (25). When heart failure occurs, increased MFGF levels reduce the deacetylation activity of silent information regulator 1 and increase the acetylation of its target protein, thereby aggravating the myocardial hypertrophy induced by angiotensin II (26).

The results of the investigation showed that, while the study group's serum DAPPER5 levels were lower than those of the control group, their IL1RL1 and MFGF levels were higher. Moreover, abnormal expression of these genes was observed as the cardiac function grade increased, suggesting that they all participate in the progression of HFpEF and may be associated with the cardiac function grade.

The study showed that, while DAPPER5 levels were lower, serum levels of IL1RL1 and MFGF were higher in the group with a poor prognosis than in the group with a positive prognosis. The multivariate logistic regression analysis revealed that the poor prognosis of HFpEF patients was influenced by cardiac function classification as well as RDW, Scr, IL1RL1, DAPPER5, and MFGF levels. These results imply that patient prognosis is associated with these markers. The combined detection of serum IL1RL1, DAPPER5, and MFGF was more accurate than the individual prediction of each signal in predicting the poor prognosis of HFpEF patients.

Conclusion

Patients with HFpEF will have higher serum levels of IL1RL1 and MFGF, whereas DAPPER5 will be lower. Detecting all three markers together may be a useful technique for improving HFpEF management and has clinical relevance for predicting a poor prognosis in HFpEF patients. In the future, additional verification will be conducted using a larger sample size.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Campbell P, Rutten FH, Lee MM, Hawkins NM, Petrie MC. Heart failure with preserved ejection fraction: everything the clinician needs to know. Lancet 2024 Mar 16; 403(10431): 1083–92. doi: 10.1016/S0140-6736(23)02756-3. Epub 2024 Feb 14. Erratum in: Lancet 2024 Mar 16; 403(10431): 1026. doi: 10.1016/S0140-6736(24)00494-X. PMID: 38367642.
2. Omote K, Verbrugge FH, Borlaug BA. Heart Failure with Preserved Ejection Fraction: Mechanisms and Treatment Strategies. Annu Rev Med 2022 Jan 27; 73: 321–37. doi: 10.1146/annurev-med-042220-022745. Epub 2021 Aug 11. PMID: 34379445; PMCID: PMC9002335.
3. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, Januzzi JL Jr, Yancy CW. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023 May 9; 81(18): 1835–78. doi: 10.1016/j.jacc.2023.03.393. Epub 2023 Apr 19. PMID: 37137593.
4. Desai AS, Lam CSP, McMurray JJV, Redfield MM. How to Manage Heart Failure With Preserved Ejection Fraction: Practical Guidance for Clinicians. JACC Heart Fail 2023 Jun; 11(6): 619–36. doi: 10.1016/j.jchf.2023.03.011. Epub 2023 May 3. PMID: 37140514.
5. Jhund PS. SGLT2 Inhibitors and Heart Failure with Preserved Ejection Fraction. Heart Fail Clin 2022 Oct; 18(4): 579–86. doi: 10.1016/j.hfc.2022.03.010. PMID: 36216487.
6. Daou D, Gillette TG, Hill JA. Inflammatory Mechanisms in Heart Failure with Preserved Ejection

Fraction. Physiology (Bethesda) 2023 Sep 1; 38(5): 0. doi: 10.1152/physiol.00004.2023. Epub 2023 Apr 4. PMID: 37013947; PMCID: PMC10396273.

7. Thorp EB, Filipp M. Contributions of Inflammation to Cardiometabolic Heart Failure with Preserved Ejection Fraction. Annu Rev Pathol 2025 Jan; 20(1): 143–67. doi: 10.1146/annurev-pathmechdis-111523-023405. Epub 2025 Jan 2. PMID: 39357068.

8. Fauchier L, Bisson A, Bodin A. Heart failure with preserved ejection fraction and atrial fibrillation: recent advances and open questions. BMC Med 2023 Feb 13; 21(1): 54. doi: 10.1186/s12916-023-02764-3. PMID: 36782248; PMCID: PMC9926737.

9. Peikert A, Martinez FA, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Shah SJ, Katova T, Merkely B, Vardeny O, Wilderäng U, Lindholm D, Petersson M, Langkilde AM, McMurray JJV, Solomon SD. Efficacy and Safety of Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial. Circ Heart Fail 2022 Oct; 15(10): e010080. doi: 10.1161/CIRCHEARTFAILURE.122.010080. Epub 2022 Aug 27. PMID: 36029467.

10. Vaz-Salvador P, Adão R, Vasconcelos I, Leite-Moreira AF, Brás-Silva C. Heart Failure with Preserved Ejection Fraction: a Pharmacotherapeutic Update. Cardiovasc Drugs Ther 2023 Aug; 37(4): 815–32. doi: 10.1007/s10557-021-07306-8. Epub 2022 Jan 31. PMID: 35098432; PMCID: PMC8801287.

11. Cimino G, Vaduganathan M, Lombardi CM, Pagnesi M, Vizzardi E, Tomasoni D, Adamo M, Metra M, Inciardi RM. Obesity, heart failure with preserved ejection fraction, and the role of glucagon-like peptide-1 receptor agonists. ESC Heart Fail 2024 Apr; 11(2): 649–61. doi: 10.1002/ehf2.14560. Epub 2023 Dec 13. PMID: 38093506; PMCID: PMC10966224.

12. Cimino G, Vaduganathan M, Lombardi CM, Pagnesi M, Vizzardi E, Tomasoni D, Adamo M, Metra M, Inciardi RM. Obesity, heart failure with preserved ejection fraction, and the role of glucagon-like peptide-1 receptor agonists. ESC Heart Fail 2024 Apr; 11(2): 649–61. doi: 10.1002/ehf2.14560. Epub 2023 Dec 13. PMID: 38093506; PMCID: PMC10966224.

13. Liu H, Magaye R, Kaye DM, Wang BH. Heart failure with preserved ejection fraction: The role of inflammation. Eur J Pharmacol 2024 Oct 5; 980: 176858. doi: 10.1016/j.ejphar.2024.176858. Epub 2024 Jul 27. PMID: 39074526.

14. Gharagozloo K, Mehdizadeh M, Heckman G, Rose RA, Howlett J, Howlett SE, Nattel S. Heart Failure With Preserved Ejection Fraction in the Elderly Population: Basic Mechanisms and Clinical Considerations. Can J Cardiol 2024 Aug; 40(8): 1424–44. doi: 10.1016/j.cjca.2024.04.006. Epub 2024 Apr 10. PMID: 38604339.

15. Olivotto I, Udelson JE, Pieroni M, Rapezzi C. Genetic causes of heart failure with preserved ejection fraction: emerging pharmacological treatments. Eur Heart J 2023 Feb 21; 44(8): 656–67. doi: 10.1093/eurheartj/ehac764. PMID: 36582184.

16. Lloji A, Sreenivasan J, Novograd J, Aronow WS, Pan S, Lanier GM. Heart failure with preserved ejection fraction: key stumbling blocks for experimental drugs in clinical trials. Expert Opin Investig Drugs 2022 May; 31(5): 463–74. doi: 10.1080/13543784.2022.2069009. Epub 2022 Apr 27. PMID: 35443138.

17. Tana M, Piccinini R, Moffa L, Tana C. Heart Failure with Preserved Ejection Fraction and Cardiac Amyloidosis in the Aging Heart. Int J Mol Sci 2024 Oct 26; 25(21): 11519. doi: 10.3390/ijms252111519. PMID: 39519069; PMCID: PMC11546592.

18. Matsiukevich D, Kovacs A, Li T, Kokkonen-Simon K, Matkovich SJ, Oladipupo SS, Ornitz DM. Characterisation of a robust mouse model of heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol 2023 Aug 1; 325(2): H203–H231. doi: 10.1152/ajpheart.00038.2023. Epub 2023 May 19. PMID: 37204871; PMCID: PMC11932539.

19. Rasalam R, Sindone A, Deed G, Audehm RG, Atherton JJ. State of precision medicine for heart failure with preserved ejection fraction in a new therapeutic age. ESC Heart Fail 2025 Jun; 12(3): 1544–57. doi: 10.1002/ehf2.15205. Epub 2025 Jan 23. PMID: 39844745; PMCID: PMC12055434.

20. Maryniak A, Maisuradze N, Ahmed R, Biskupski P, Jayaraj J, Budzikowski AS. Heart failure with preserved ejection fraction update: A review of clinical trials and new therapeutic considerations. Cardiol J 2022; 29(4): 670–9. doi: 10.5603/CJ.a2022.0051. Epub 2022 Jun 28. PMID: 35762077; PMCID: PMC9273251.

21. He J, Yang W, Jiang Y, Sun X, Zhao S, Weiss R, Sirajuddin A, Lu M. Heart failure with preserved ejection fraction assessed by cardiac magnetic resonance: From clinical uses to emerging techniques. Trends Cardiovasc Med 2023 Apr; 33(3): 141–7. doi: 10.1016/j.tcm.2021.12.006. Epub 2021 Dec 18. PMID: 34933114.

22. Moles VM, Grafton G. Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction. Cardiol Clin 2022 Nov; 40(4): 533–40. doi: 10.1016/j.ccl.2022.06.007. Epub 2022 Sep 15. PMID: 36210136.

23. McDowell K, Kondo T, Talebi A, Teh K, Bachus E, de Boer RA, Campbell RT, Claggett B, Desai AS, Docherty KF, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Simpson J, Vaduganathan M, Jhund PS, Solomon SD, McMurray JJV. Prognostic Models for Mortality and Morbidity in Heart Failure With Preserved Ejection Fraction. JAMA Cardiol 2024 May 1; 9(5): 457–65. doi: 10.1001/jamacardio.2024.0284. Erratum in: JAMA Cardiol. 2024 Sep 1;9(9):861. doi: 10.1001/jamacardio.2024.2464. PMID: 38536153; PMCID: PMC10974691.

24. Abudureyimu M, Luo X, Wang X, Sowers JR, Wang W, Ge J, Ren J, Zhang Y. Heart failure with preserved ejection fraction (HFpEF) in type 2 diabetes mellitus: from pathophysiology to therapeutics. J Mol Cell Biol 2022 Sep 12; 14(5): mjac028. doi: 10.1093/jmcb/mjac028. PMID: 35511596; PMCID: PMC9465638.

25. Packer M. The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction: A Novel Framework to Explain Pathogenesis and Guide Treatment. J Am Coll Cardiol 2025 Oct 21; 86(16): 1269–373. doi: 10.1016/j.jacc.2025.06.055. Epub 2025 Aug 31. PMID: 40886173.

26. Rocca A, Heeswijk RBV, Richiardi J, Meyer P, Hullin R. The Cardiomyocyte in Heart Failure with Preserved Ejection Fraction-Victim of Its Environment? Cells 2022 Mar 2; 11(5): 867. doi: 10.3390/cells11050867. PMID: 35269489; PMCID: PMC8909081.

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