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SERUM KERATIN 1 AND TMAP IN CARDIAC FUNCTION PROGNOSIS OF ACUTE HEART FAILURE (AHF)

SERUMSKI KERATIN 1 I TMAP U PROCENI PROGNOZE SRČANE FUNKCIJE KOD AKUTNE SRČANE INSUFICIJENCIJE (AHF)

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Summary

Background: To explore the relationships between serum TMAP (Tumour metastasis-associated peptide) and KRT1(Keratin 1) levels and the cardiac function classification and prognosis of patients with acute heart failure (AHF).

Methods: From January 2022 to January 2025, 428 patients with acute heart failure (AHF) admitted to this hospital composed the AHF group. Among them, 162 patients had NYHA cardiac function classification grade II, 166 grade III, and 100 grade IV. The control group consisted of 100 more healthy volunteers who had physical examinations at the same hospital during the same time period. After the AHF patients received relevant treatments according to the guidelines and were discharged, a 6-month follow-up was conducted. Patients with a poor prognosis were those who were readmitted due to heart failure or cardiac death; patients with a positive prognosis were those who were not. Each study participant's serum levels of KRT1 and TMAP were determined using the enzyme-linked immunosorbent assay (ELISA). Patients with AHF were given baseline data. The relationship between cardiac function classification in AHF patients and serum TMAP and KRT1 levels was examined using Spearman's correlation analysis. Factors associated with a poor prognosis in individuals with AHF were examined using multivariate logistic regression. The capacity of serum TMAP and KRT1 levels to predict a bad prognosis in AHF patients was examined using receiver operating characteristic (ROC) curves. Comparisons of the area under the

Kratak sadržaj

Uvod: Cilj je bio da se ispita povezanost serumskih nivoa peptida povezanog sa metastazom tumora (TMAP) i keratina 1 (KRT1) sa klasifikacijom srčane funkcije i prognozom kod pacijenata sa akutnom srčanom insuficijencijom (AHF)

Metode: U grupu AHF uključeno je 428 pacijenata sa akutnom srčanom insuficijencijom hospitalizovanih u našoj ustanovi u periodu od januara 2022. do januara 2025. godine. Prema klasifikaciji srčane funkcije Njujorškog kardiološkog udruženja (NYHA), 162 pacijenta su bila svrstana u II klasu, 166 u III klasu, a 100 u IV klasu. Kontrolnu grupu je činilo 100 zdravih ispitanika koji su tokom istog perioda obavili rutinske sistematske preglede. Nakon primene terapije u skladu sa važećim smernicama i otpusta iz bolnice, svi pacijenti sa AHF praćeni su tokom šest meseci. Pacijenti kod kojih je tokom perioda praćenja došlo do ponovne hospitalizacije zbog srčane insuficijencije ili do smrti usled srčanih uzroka svrstani su u grupu sa nepovoljnom prognozom, dok su ostali pacijenti svrstani u grupu sa povoljnom prognozom. Serumski nivoi KRT1 i TMAP su određivani metodom enzimski povezanog imunosorbentnog testa (ELISA). Prikupljeni su početni klinički podaci svih pacijenata. Spirmanova korelaciona analiza je korišćena za procenu povezanosti između serumskih nivoa TMAP i KRT1 i NYHA klasifikacije srčane funkcije. Multivarijantna logistička regresiona analiza primenjena je radi identifikacije faktora povezanih sa nepovoljnom prognozom kod pacijenata sa AHF. Prediktivna vrednost serumskih nivoa TMAP i KRT1 za nepovoljnu prognozu

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curve (AUC) were conducted using the DeLong test.
Results: Serum TMAP levels were greater in the AHF group than in the control group (P<0.05), and serum KRT1 levels were lower in the AHF group than in the control group (P<0.05). The serum TMAP level increased with increasing cardiac function classification (F trend = 109.195, P trend < 0.001). Conversely, as heart function categorisation increased, the serum KRT1 level dropped (F trend = 223.564, P trend < 0.001). According to Spearman correlation analysis, the cardiac function classification in AHF patients was positively connected with the serum TMAP level (rs=0.711, P<0.001) and inversely correlated with the serum KRT1 level (rs=-0.722, P<0.001). TMAP, KRT1, and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) levels, along with NYHA cardiac function classification, varied significantly (P<0.05) between the groups with poor and favourable prognoses. Elevated NT-pro BNP levels, elevated TMAP levels, and NYHA cardiac function classification grade IV were found to be independent risk factors for a poor prognosis in AHF patients (P<0.05), while elevated KRT1 levels were found to be an independent protective factor against a poor outcome in AHF patients (P<0.05), according to multivariate logistic regression analysis. The areas under the curve (AUCs) for serum TMAP and KRT1 alone and jointly were 0.782, 0.792, and 0.880, respectively, for predicting a poor prognosis in AHF patients, as determined by ROC analysis. The AUC of the combination of the two was greater than that of the single prediction of serum TMAP and KRT1 (Z=3.956, 3.642; P<0.001).
Conclusion: Serum TMAP levels are elevated in patients with AHF, whereas KRT1 levels are decreased. Both factors are related to patients' cardiac function classification and prognosis. Combined serum TMAP and KRT1 levels have relatively high predictive efficacy for poor prognosis in patients with AHF.

Keywords: acute heart failure, tumour metastasis-associated peptide, keratin 1, n-terminal precursor, b-type natriuretic peptide, cardiac function

procenjena je analizom ROC krivih, dok su razlike između površina ispod krive (AUC) upoređivane primenom DeLong testa.
Rezultati: Serumski nivoi TMAP su bili značajno viši u grupi sa AHF nego u kontrolnoj grupi (P<0,05), dok su serumski nivoi KRT1 bili značajno niži (P<0,05). Nivoi TMAP su progresivno rasli sa pogoršanjem NYHA klase srčane funkcije (F za trend = 109,195; P za trend < 0,001), dok su nivoi KRT1 odgovarajuće opadali (F za trend = 223,564; P za trend < 0,001). Spirmanova korelaciona analiza je pokazala da je NYHA klasifikacija srčane funkcije pozitivno korelisala sa serumskim nivoima TMAP (rs=0,711; P<0,001), a negativno sa serumskim nivoima KRT1 (rs=-0,722; P<0,001). Između grupa sa nepovoljnom i povoljnom prognozom su utvrđene statistički značajne razlike u serumskim nivoima TMAP, KRT1 i N-terminalnog pro-B-tip natriuretskog peptida (NT-proBNP), kao i u NYHA klasifikaciji srčane funkcije (sve vrednosti P<0,05). Multivarijantna logistička regresiona analiza je pokazala da su povišeni nivoi NT-proBNP, povišeni nivoi TMAP i NYHA IV klasa nezavisni faktori rizika za nepovoljnu prognozu kod pacijenata sa AHF (sve vrednosti P<0,05), dok su povišeni nivoi KRT1 predstavljali nezavisni zaštitni faktor (P<0,05). Analiza ROC krive pokazala je da su AUC vrednosti za TMAP, KRT1 i njihovu kombinaciju u predviđanju nepovoljne prognoze iznosile 0,782, 0,792 i 0,880. Kombinovani model pokazao je značajno bolju prediktivnu sposobnost u odnosu na svaki biomarker pojedinačno (Z=3,956 i 3,642; oba P<0,001).
Zaključak: Pacijenti sa akutnom srčanom insuficijencijom imaju povišene serumske nivoe TMAP i snižene serumske nivoe KRT1. Oba biomarkera su usko povezana sa statusom srčane funkcije i kliničkom prognozom. Kombinovana procena serumskih nivoa TMAP i KRT1 pokazuje dobru prediktivnu vrednost za nepovoljnu prognozu kod pacijenata sa AHF.

Ključne reči: akutna srčana insuficijencija, peptid povezan sa tumorskom metastazom, keratin 1, N-terminalni pro-B-tip natriuretski peptid, srčana funkcija

Introduction

Heart failure (HF) is a collection of intricate clinical syndromes that are brought on by aberrant cardiac structure and/or function for a variety of reasons, leading to ventricular diastole and/or systole dysfunction. It is a serious symptom of the majority of cardiovascular illnesses and their ultimate stage (1). Acute heart failure (AHF) refers to a clinical syndrome in which symptoms and signs of heart failure occur or worsen rapidly and mainly includes acute decompensated heart failure (ADHF) and new-onset AHF. It is characterised by a sudden onset and severe condition, with a rehospitalisation rate of approximately 50% within 6 months after discharge (2, 3). Therefore, timely assessment of the condition and prognosis of AHF patients is very important. TMAP is an inflammatory peptide that can promote vascular endothelial injury, the inflammatory response, and oxidative stress by regulating vascular function and inflammatory and oxidative stress signals (4, 5). KRT1 is a transmembrane protein with anti-inflammatory, antioxidant, and antifibrotic effects (6, 7). Research has demonstrated that oxidative stress, cardiac fibrosis, endothelial dysfunction, and the inflammatory response are important factors in the onset and progression of heart failure (8, 9). Thus, TMAP and KRT1 serum levels were measured in individuals with acute heart failure (AHF) in this investigation, and their effects on cardiac function classification and AHF prognosis were analysed. This study's objective was to provide a guide for improving the prognosis of AHF patients.

Materials and Methods

Preparation before experimental testing (serum samples)

1) Blood collection: For patients with acute heart failure, 3 millilitres of venous blood was collected within 24 hours after admis-

sion. The healthy control group also collected venous blood simultaneously. All blood samples were collected using vacuum blood collection tubes containing anticoagulants to ensure they were free of contamination and met testing requirements.

2. Sample processing: After collection, the blood samples were allowed to stand at room temperature for 30 minutes to allow for complete blood coagulation. Then, they were placed in a 4 °C centrifuge at 3000 rpm for 10 minutes. The centrifugal radius was strictly controlled at 10 centimetres to ensure complete separation of serum from blood cells.
3. Serum separation: After centrifugation, carefully aspirate the clear upper layer of serum, avoiding aspiration of blood cells. Use sterile EP tubes for sample packaging. The volume of each sample should be determined in accordance with the testing requirements to ensure sufficient sample volume for subsequent tests.

4) Sample preservation: The separated serum samples are immediately stored in an ultra-low-temperature freezer at -80 °C. Repeated freezing and thawing should be avoided to prevent biological activity in the samples. All samples are uniformly tested after complete collection to ensure consistent experimental conditions.

Principle of biochemical testing

The levels of TMAP and KRT1 in serum were measured by enzyme-linked immunosorbent assay (ELISA), a technique based on the principle of specific binding between antigens and antibodies, enabling quantitative analysis through enzymatically catalysed colour development reactions.

Before the experiment began, all reagents were brought to room temperature. Then, a standard series was prepared, and blank, standard, and sample wells were set up. Each sample was tested in duplicate to ensure the reliability of the results. During the detection process, the specific primary antibody was first added to bind to the target protein in the sample, followed by the addition of an enzyme-labelled secondary antibody to form an immune complex. The sample was incubated at 37 °C for sufficient time to promote complete binding in the antigen-antibody reaction. The washing steps effectively removed unbound antibodies, and the enzyme substrate was then added for colour development. The colour intensity was proportional to the concentration of the target protein.

Finally, the absorbance was measured at 450 nm using a Multiskan FC microplate reader (Thermo Scientific). The concentrations of TMAP and KRT1 in the samples were calculated from the standard curve. The entire detection process strictly controlled intra-assay variation within 5%, ensuring the accuracy and reliability of the detection results and providing a reliable laboratory basis for the prognosis assessment of cardiac function in patients with acute heart failure.

Measurement of serum TMAP and KRT1 levels

For patients with acute heart failure (AHF), 3 millilitres of venous blood was collected within 24 hours of admission, and venous blood from healthy controls was collected simultaneously as a control. All blood samples were collected using vacuum blood collection tubes containing coagulants, and were left at room temperature for 30 minutes before centrifugation at 3000 rpm for 10 minutes (with a centrifugal radius of 10 cm) at 4 °C. The upper layer of serum was carefully separated and aliquoted into sterile EP tubes. All serum samples were immediately stored at -80 °C in an ultra-low-temperature freezer to avoid repeated freezing and thawing. All samples were collected and tested uniformly after the completion of sample collection.

Serum TMAP and KRT1 levels were determined using enzyme-linked immunosorbent assay (ELISA). The experimental procedures were carried out strictly in accordance with the instructions of the reagent kits. The TMAP detection kit was provided by Wuxi Donglin Technology Development Co., Ltd. (lot number: DLR-SALb-Hu), and the KRT1 detection kit was provided by Shanghai Xiguo Biotechnology Co., Ltd. (lot number: XG-H103839). During detection, the reagent kits were brought to room temperature. A standard series was prepared, blank, standard, and sample wells were set up, and each sample was tested in duplicate. After adding the primary and secondary antibodies, incubation was performed at 37 °C, followed by washing and adding the chromogenic agent. The absorbance was measured at 450 nm using a microplate reader (Multiskan FC, Thermo Scientific). All tests were completed within the same batch, with intra-batch differences controlled to within 5%, ensuring the accuracy and reliability of the test results.

Relevant reagent information

TMAP Assay Kit:

- Manufacturer: Wuxi Donglin Technology Development Co., Ltd.
- Product batch number: DLR-SALb-Hu.

- Kit components: Includes a 96-well pre-coated plate, standard series, primary antibody, secondary antibody, enzyme-labelled antibody, substrate solution, and stop solution.
- Detection principle: Based on the double-antibody sandwich ELISA method, specific antibodies capture the TMAP protein in the serum; the enzyme-labelled secondary antibody binds; and finally, a colour reaction is used for quantitative detection.

KRT1 Assay Kit:

- Manufacturer: Shanghai Guo Biotechnology Co., Ltd.
- Product batch number: XG-H103839.
- Kit components: Includes pre-coated plate, standard series, specific antibody, enzyme conjugate, washing buffer, chromogenic agent, and termination solution.
- Detection principle: Utilises a competitive ELISA method. The labelled antibody competes with the KRT1 in the sample for binding to the solid-phase antibody. The intensity of colour development is inversely proportional to the concentration of KRT1.

Other reagents and consumables:

- Blood collection tube: A vacuum blood collection tube containing EDTA anticoagulant.
- Centrifuge tube: Sterile EP tube, 1.5 mL specification.
- Washing buffer: PBS solution containing 0.05% Tween-20.
- Colour development substrate: TMB (3,3′,5,5′-tetramethylbenzidine) solution.

Other biochemical indicators and marker detection methods

- Detection of heart failure markers: NT-proBNP is measured by chemiluminescent immunoassay. The test is conducted using the Roche Diagnostics Cobas e411 fully automatic immunoanalyzer and the corresponding reagent kit (batch number 178765), with the detection range being 5–35000 pg/mL. The test is completed within 2 hours after sample collection, and strict adherence to standard operating procedures is ensured to guarantee the accuracy and reliability of the test results.
- Detection of myocardial injury markers: Cardiac troponin I (cTnI) is detected using electrochemiluminescence immunoassay, with Beckman Coulter Access 2 analyser and the corresponding reagent kit (batch number 123456), with a detection sensitivity of 0.01 ng/mL; Creatine kinase isoenzyme (CK-MB) is detected by the inhibition method, using Hitachi 7600 automatic biochemical analyser, with a detection range of 0–200 U/L.
- Myocardial enzyme profile test: It includes creatine kinase (CK), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST). All of these are detected using the rate method, using the Beckman AU5800 automatic biochemical analyser. The test is carried out strictly in accordance with the standard operating procedures to ensure the accuracy and reproducibility of the test results. All indicators are completed within 4 hours after sample collection to avoid the influence of sample degradation on the results.

Statistical analysis

Data analysis was performed using SPSS 28.0; an independent-samples t-test was used to compare the two groups, and results are reported as $\bar{x}\pm s$ for normally distributed data. Several groups were compared using one-way analysis of variance; multiple groups were compared pairwise using the least significant difference (LSD) test; and the trend in changes in serum TMAP and KRT1 levels across various cardiac function grades was examined using the linear trend test in variance analysis.

Measurement data with a skewed distribution were reported as M (P25, P75), and the Mann-Whitney U test was used to compare the two groups. The Wilcoxon signed-rank test was used to compare rank data, and count data, which are represented as percentages and the number of instances, were compared using the χ^2 test. The relationship between blood TMAP and KRT1 levels and cardiac function grade in individuals with AHF was examined using Spearman correlation analysis. Factors predicting a poor prognosis in individuals with AHF were examined using multivariate logistic regression. The efficacy of serum TMAP and KRT1 levels to predict poor prognosis in AHF patients was examined using receiver operating characteristic (ROC) curves. The DeLong test was used to compare the area under the curve (AUC) at $\alpha=0.05$. A difference was deemed statistically significant if P was less than 0.05.

Results

Serum TMAP and KRT1 levels between the AHF and control groups

Serum TMAP levels were greater in the AHF group than in the control group (P<0.05). However, the control group's KRT1 level was lower (P<0.05), see *Table I*.

Compared with the healthy control group, patients with acute heart failure show significant differences in serum TMAP and KRT1 levels. The serum TMAP level of patients with acute heart failure shows an increasing trend, while the KRT1 level shows a decreasing trend. This indicates that TMAP and KRT1 may play important roles in the pathophysiological process of acute heart failure and may be closely related to the cardiac function status.

Comparison of serum TMAP and KRT1 levels and linear trend test results in patients with AHF of different cardiac function grades

Serum TMAP and KRT1 levels varied significantly across cardiac function categories, as determined by a one-way ANOVA (F=5 4.792 and 120.086, respectively; both P<0.001). The linear trend test indicated that serum TMAP levels increased with increasing cardiac function grade (F trend =109.195, P trend < 0.001), whereas serum KRT1 levels decreased with increasing cardiac function grade (F trend = 223.564, P trend < 0.001).

Subsequent pairwise comparisons showed that patients with cardiac function grade II had significantly lower serum TMAP levels than patients with grades III and IV (P<0.05). Patients with grade III had significantly lower serum KRT1 levels than patients with grade IV (P<0.05); Patients with cardiac function grade II had a considerably higher blood KRT1 level than patients with grades III and IV (P<0.05). In contrast, patients with grade III had a significantly higher serum KRT1 level than those with grade IV (P<0.05; see *Table II*).

Correlations between serum levels of TMAP and KRT1 in AHF patients and cardiac function classification

Spearman correlation analysis revealed that the serum TMAP level in AHF patients was positively correlated with cardiac function classification (rs=0.711, P<0.001), whereas the serum KRT1 level was negatively correlated with cardiac function classification (rs=-0.722, P<0.001).

Comparison of baseline data and serum TMAP and KRT1 levels between the poor-prognosis group and the good-prognosis group

The patient follow-up rate was 100%. During the follow-up period, 144 patients had a poor prognosis (poor-prognosis group), and 284 patients had a good prognosis (good-prognosis group), for

Table I Comparison of serum TMAP and KRT1 levels between the AHF group and control group ($\bar{x}\pm s$, pg/mL).

Group	n	TMAP (pg/mL)	KRT1 (pg/mL)
AHF group	428	429.82±110.94	429.82±110.94
Control group	100	272.61±75.87	775.24±188.27
t		11.962	-12.478
P		<0.001	<0.001

Table II Comparison and linear trend test results of serum TMAP and KRT1 levels in AHF patients with different concentric functional grades ($\bar{x}\pm s$, pg/mL).

Cardiac function classification	n	TMAP (pg/mL)	KRT1 (pg/mL)
Level II	162	304.69±91.36	525.03±77.68
Level III	166	376.16±86.34	403.25±69.47
Level IV	100	471.11±87.81	320.00±84.26
F		54.792	120.086
P		<0.001	<0.001
F Trend		109.195	223.564
P Trend		<0.001	<0.001

Table III Comparison of baseline data and serum levels of TMAP and KRT1 between poor prognosis group and good prognosis group [n (%) or $\bar{x}\pm s$ or M (P 25, P 75)].

Group	n	Gender (Male/Female)		Age (years)	AHF type		NYHA cardiac function classification		
					ADHF	Newly issued AHF	Level II	Level III	Level IV
Poor prognosis group	144	80 (55.56)	64 (44.44)	69.68±9.65	110 (76.39)	34 (23.61)	10 (6.94)	54 (37.50)	80 (55.56)
Good prognosis group	284	144 (50.70)	140 (49.30)	65.83±9.43	180 (63.38)	104 (36.62)	152 (53.52)	112 (39.44)	20 (7.04)
$x^2/t/Z$		0.454		2.818	3.704		8.402		
P		0.505		0.008	0.057		<0.001		

Group	n	Comorbidity					History of smoking	Have a history of drinking alcohol	Blood pressure (mmHg)	
		Diabetes	Hypertension	Stable Coronary Heart Disease	Atrial fibrillation	Hyperlipidaemia			Systolic blood pressure	Diastolic pressure
Poor prognosis group	144	54 (37.50)	110 (76.39)	70 (48.61)	68 (47.22)	48 (33.33)	36 (25.00)	28 (19.44)	141.42± 19.19	84.54± 15.52
Good prognosis group	284	72 (25.35)	210 (73.94)	132 (46.48)	80 (28.17)	70 (24.65)	58 (20.42)	48 (16.90)	138.01± 15.39	82.28± 14.53
$x^2/t/Z$		3.397	0.154	0.080	7.660	1.808	0.587	0.215	1.401	1.053
P		0.068	0.690	0.761	0.009	0.172	0.448	0.649	0.164	0.298

Group	n	LVEF (%)	NT-proBNP (pg/mL)	Medication status			
				Insulin	Sodium glucose cotransporter 2 inhibitor	Metformin	Beta blockers
Poor prognosis group	144	48.26±4.33	3263.39 (2725.02, 4214.94)	24 (6.67)	22 (15.28)	12 (8.33)	78 (54.17)
Good prognosis group	284	50.98±6.55	2440.68 (1677.16, 3141.40)	32 (11.27)	22 (7.75)	12 (4.23)	144 (50.70)
$x^2/t/Z$		-3.6403	5.432	1.228	2.931	0.849	0.222
P		<0.001	<0.001	0.261	0.080	0.351	0.635

Group	n	Medication status				TMAP (pg/mL)	KRT1 (pg/mL)
		Renin angiotensin system inhibitor	Aldosterone receptor antagonist	Loop diuretics	Statins		
Poor prognosis group	144	70 (48.61)	18 (12.50)	84 (58.33)	48 (33.33)	445.36± 96.47	352.33± 92.86
Good prognosis group	284	100 (35.21)	48 (16.90)	174 (61.27)	70 (24.65)	333.77± 94.63	469.26± 98.07
$x^2/t/Z$		3.586	0.713	0.175	1.808	8.104	-8.394
P		0.051	0.403	0.672	0.172	<0.001	<0.001

Table IV Multivariate logistic regression investigation of the variables influencing AHF patients' poor prognosis.

Factor	β	SE	Wald x^2	P	OR	OR 95% CI
Age	0.020	0.025	0.627	0.428	1.020	0.971~1.072
NYHA Cardiac Function Classification						
Level III	0.531	0.547	0.942	0.332	1.701	0.582~4.973
Level IV	1.934	0.589	10.790	0.001	6.917	2.181~21.915
Combined atrial fibrillation	0.215	0.472	0.209	0.648	1.240	0.492~3.125
LVEF	-0.053	0.038	1.923	0.166	0.948	0.879~1.022
NT-proBNP	0.001	0.000	10.264	0.001	1.001	1.000~1.001
Salusin	0.013	0.003	21.709	<0.001	1.013	1.007~1.018
KRT1	-0.011	0.003	18.890	<0.001	0.990	0.984~0.994

Table V Predictive efficacy of serum TMAP and KRT1 for poor prognosis in AHF patients.

Indicator	AUC	AUC 95%CI	P	Optimal truncation value	Sensitivity (%)	Specificity (%)	Youden index
TMAP	0.782	0.721~0.845	<0.001	402.51 pg/mL	68.09	75.38	0.4344
KRT1	0.792	0.732~0.854	<0.001	383.20 pg/mL	88.82	57.07	0.4597
Two joint projects	0.880	0.830~0.929	<0.001	-	86.14	77.49	0.6351

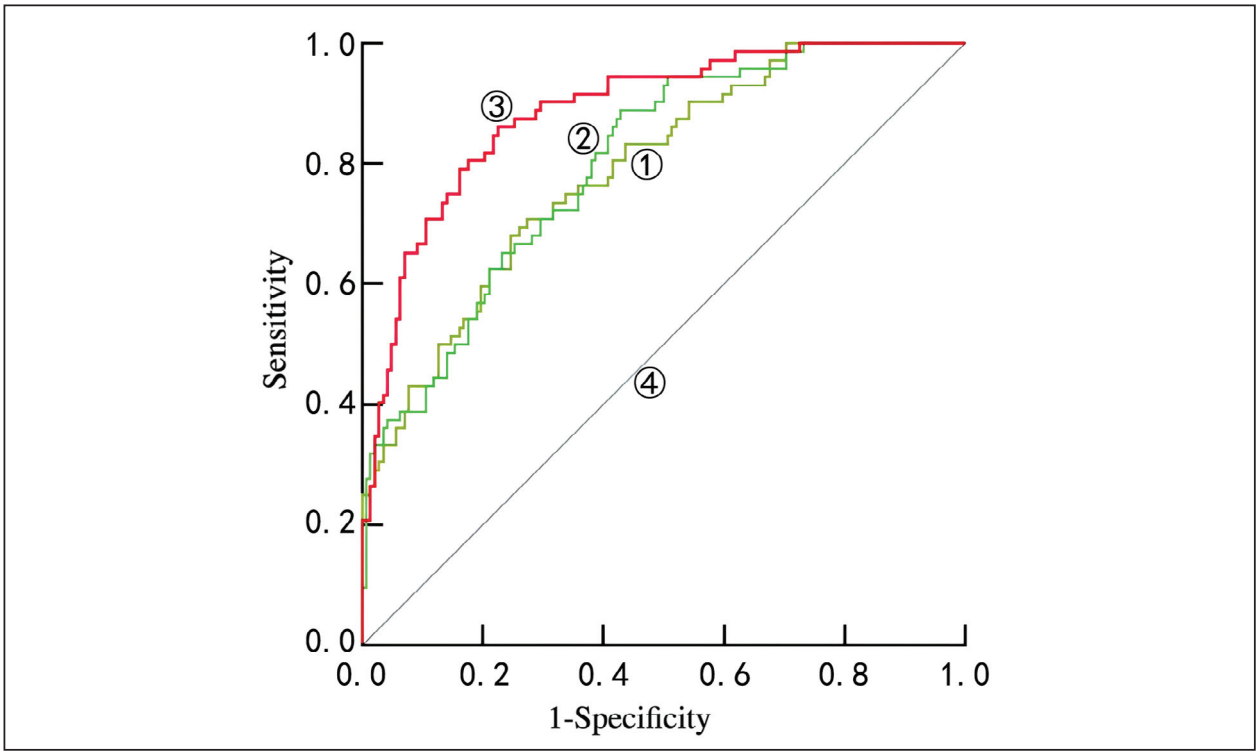

Figure 1 Serum TMAP and KRT1 ROC curves for predicting a bad prognosis in AHF patients.
①: TMAP; ②: KRT1; ③: Joint testing; ④: Baseline.

a poor-prognosis rate of 33.67%. There were statistically significant differences in age, NYHA cardiac function classification, and the proportions of patients with combined atrial fibrillation, LVEF, NT-proBNP, TMAP, and KRT1 levels between the groups with poor and excellent prognoses ($P<0.05$; see *Table III*).

Multivariate logistic regression investigation of the variables influencing the poor prognosis of acute heart failure patients

Using the dependent variables of AHF patients' prognosis (bad prognosis = 1, excellent prognosis = 0), age (input in original value), and NYHA cardiac function classification (grade II=1, grade III=2, grade IV=3), the presence of atrial fibrillation (yes = 1, no = 0), the presence of LVEF (input in original value), NT-proBNP (input in original value), TMAP (input in original value). KRT1 (input in original value) was the independent variable utilised in the multivariate logistic regression analysis. While elevated NT-proBNP and TMAP levels were identified as independent risk factors for bad prognosis in AHF patients ($P<0.05$), elevated KRT1 levels were revealed to be an independent protective factor for poor prognosis in AHF patients ($P<0.05$), see *Table IV*.

Serum TMAP, serum KRT1 and their combination for predicting poor prognosis in patients with acute heart failure

The prognosis status of AHF patients (poor prognosis = 1, good prognosis = 0) was used as the dependent variable, and serum TMAP and KRT1 levels were used as the independent variables to produce a receiver operating characteristic (ROC) curve. The AUCs for serum TMAP and KRT1, separately and together, were 0.782, 0.792, and 0.880, respectively, for predicting a poor prognosis in AHF patients. The AUC of the combined prediction of the two items was greater than that of the individual prediction of serum TMAP and KRT1 ($Z=3.956$, 3.642; $P<0.001$), see *Table V* and *Figure 1*.

Discussion

AHF is characterised by an acute-onset or exacerbation of abnormal cardiac function (left or right ventricle), resulting in a sharp decline in myocardial contractility and a sudden increase in cardiac load. The main clinical manifestations include acute reduction in cardiac output, increased pressure in the peripheral and pulmonary circulations, insufficient tissue and organ perfusion, systemic congestion, pulmonary congestion/pulmonary oedema, etc. In severe cases, it may also lead to cardiogenic shock and acute respiratory failure (10–13). Unlike the significant progress made in the treatment of chronic heart failure in recent years, AHF is a highly heterogeneous syndrome. Its pathophysiological mechanism remains unclear. Currently, treatment focuses mainly on alleviating short-term symptoms and stabilising the patient's hemodynamic status, with no specific treatment methods. This leads to a poor prognosis, especially for severe AHF patients (14, 15). Currently, clinical assessment of AHF prognosis relies mainly on NT-proBNP/BNP. Still, many influencing factors exist, and new markers, such as soluble tumour growth factor beta receptor 2, lactose agglutinin 3, and cystatin C, remain controversial (16, 17). Therefore, further exploration of biomarkers for predicting the prognosis of AHF is necessary.

Endothelial dysfunction, the inflammatory response, oxidative stress, and myocardial fibrosis play important roles in the development and progression of heart failure. Endothelial dysfunction caused by various factors can reduce vascular dilation ability and affect tissue and organ perfusion, thereby aggravating ischemic damage to the myocardium and other organs; the inflammatory response and oxidative stress can damage myocardial cells, induce myocardial apoptosis and fibrosis, affect cardiac function and accelerate ventricular remodelling, thereby promoting the occurrence and development of heart failure (18, 19). TMAP is an endogenous bioactive peptide expressed in tissues such as the hypothalamus, heart and kidneys. The enzymatic cleavage of the precursor protein prosalusin generates it. It can be secreted into the blood by vascular smooth muscle cells, macrophages and other tissue cells. It can stimulate cell proliferation, promoting aberrant vascular smooth muscle cell proliferation and triggering signalling pathways linked to oxidative stress and inflammation (20). For instance, in rat models of heart failure brought on by myocardial infarction, TMAP is upregulated. By reducing reactive oxygen species production, TMAP knockdown can improve vascular and cardiac function and attenuate cardiovascular remodelling in heart failure rats (21). TMAP is upregulated in rat models of heart failure induced by spontaneous hypertension, and silencing TMAP can inhibit the activity of the mitogen-activated protein kinase (MAPK)/nuclear factor- B (NF- B) inflammatory signalling pathway and downregulate the level of reactive oxygen species, thereby improving cardiac and vascular function in heart failure rats (22). In rats with hypertrophic cardiomyopathy, TMAP downregulation can also inhibit myocardial fibrosis by reducing oxidative stress, thereby improving cardiac function (23).

TMAP levels in the serum are useful in predicting the development of chronic heart failure. Nevertheless, it is still unknown how serum TMAP levels affect the state and prognosis of individuals suffer-

ing from acute heart failure (AHF). Elevated serum TMAP levels are risk factors for poor prognosis in AHF patients, indicating that elevated serum TMAP levels are related to cardiac function classification and poor prognosis (24). The possible reasons for these findings are as follows: as a bioactive peptide, TMAP can promote abnormal proliferation of vascular smooth muscle cells, leading to vascular remodelling and endothelial dysfunction, further increasing cardiac load, elevating cardiac function, and worsening the prognosis of AHF patients. TMAP can enhance the release of proinflammatory cytokines and reactive oxygen species, exacerbating the inflammatory response and oxidative stress damage to myocardial cells, aggravating ventricular remodelling, and deteriorating cardiac function, thereby increasing the risk of a poor prognosis in AHF patients (25–27).

Serum KRT1 levels decreased in patients with AHF, and the decrease was greater as the cardiac function grade increased. An increase in serum KRT1 levels was a protective factor against a poor prognosis in AHF patients, suggesting that decreased serum KRT1 levels are associated with cardiac function grade and prognosis (28). The possible mechanisms include the following: KRT1 can reducing the release of proinflammatory cytokines and reactive oxygen species, alleviating damage to the inflammatory response and oxidative stress to the myocardium, and improving the cardiac function and prognosis of patients with AHF (29); moreover, KRT1 can inhibit Wnt/ -catenin signalling, inhibiting the proliferation of cardiac fibroblasts and myocardial fibrosis, and improving ventricular remodelling, thereby improving the cardiac function classification and prognosis of patients with AHF (30). The combination of serum TMAP and KRT1 is more effective at predicting the prognosis of patients with AHF, and clinical assessment of AHF progression can be performed by measuring serum TMAP and KRT1 levels.

However, due to the single-centre design of this study, selection bias may have occurred. The molecular mechanisms underlying changes in TMAP and KRT1 were not analysed in depth, making it impossible to establish their causal relationships with clarity. Moreover, the follow-up period was relatively short, preventing a comprehensive assessment of the long-term prognostic impact of TMAP and KRT1 on patients with acute heart failure. In the future, multicentre studies are needed to conduct experimental verification, thereby enhancing the credibility of the research and its clinical guidance value.

Conclusion

Patients with AHF have higher serum TMAP levels, whereas KRT1 levels are decreased. Both factors are related to the cardiac function classification and the prognosis of AHF patients. When these two signs are combined, the prognosis of AHF patients can be more accurately predicted.

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Conflict of interest statement

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

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