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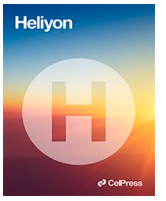

Research article

Prognostic value of a disintegrin and metalloproteinase Domain-8 in heart failure

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Background: Heart failure (HF) is a severe disease threatening people's health. The aim of this study is to find a significant biomarker inducive to predicting the prognosis of HF.
Methods: GSE135055 and GSE161472 datasets were reanalyzed for exploring key genes related to HF. This single-center, prospective, observational cohort study enrolled 298 patients with or without HF from the Cardiology Department of Zhongda Hospital. Levels of ADAM8 were measured using ELISA kits. Major adverse cardiovascular events (MACEs) were defined as the composite end points of the first occurrence of rehospitalization because of HF or cardiac-related death during one-year follow-up.
Results: (1) Bioinformatics analysis showed that ADAM8 was a key gene in HF via mainly regulating the mechanisms of extracellular matrix (ECM) organization. (2) Levels of ADAM8 were significantly increased in the HF group, compared to the non-failing (NF) group ($p < 0.001$), especially in patients with HFrEF ($p < 0.05$), and HFmEF ($p < 0.05$). The prevalence of HF in the high ADAM8 group (≧472.916 pg/mL) was significantly higher than in the low ADAM8 group (<472.916 pg/mL) (41.95 % vs 30.54 %, $p < 0.01$). (3) Correlation analysis revealed that ADAM8 was negatively correlated to the left ventricular ejection fraction (LVEF) ($r = -0.272$, $p < 0.001$). ROC analysis showed that the AUC of ADAM8 in predicting HF and predicting the MACE were 0.701 ($p < 0.0001$) and 0.683 ($p < 0.0001$), respectively. (4) Logistic and Cox regression both indicated that high ADAM8 expression can predict adverse prognosis of HF.
Conclusions: ADAM8 may be a risk factor for HF, especially in cases of HFrEF and HFmEF. High ADAM8 expression in plasma was related to the decreased heart function, and can predict the adverse prognosis of HF.

1. Introduction

Heart failure (HF) affects nearly 64 million people worldwide, representing a significant global health concern [1]. The prevalence of HF among the general adult population in developed countries ranges from 1 % to 2 %, and the total number of HF patients still continues to increase [1]. HF refers to a complex clinical condition characterized by symptoms and signs caused by abnormal cardiac structure or function leading to ventricular contraction or filling disorders [2]. The diagnosis of HF is on structural and/or functional

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abnormalities, complemented by objective evidence of elevated natriuretic peptide levels and/or the presence of cardiogenic pulmonary congestion/systemic circulation congestion [2]. The classification of chronic HF is mainly based on the left ventricular ejection fraction (LVEF). Specifically, LVEF ≤40 % is called HF with reduced ejection fraction (HFrEF), while LVEF 41 %–49 % is defined as heart failure with mildly reduced ejection fraction (HFmEF), LVEF ≥50 % is referred to as heart failure with preserved ejection fraction (HFpEF) [2].

ADAMs, formerly known as metalloproteinases/disintegrins/cysteine-rich (MDC) proteins, represent a family of zinc (Zn2+) dependent protein hydrolases [3]. The ADAMs family plays a role in vascular dysfunction and cardiovascular diseases, such as hypertension, atherosclerosis, coronary artery disease, myocardial infarction, HF, peripheral artery disease and hemangioma [4]. Similar to matrix metalloproteinases (MMPs), ADAMs have a signal peptide, pre-domain, and metalloproteinase-domain. In addition, ADAMs also have a disintegrin domain and a cysteine-rich domain similar to snake venom metalloproteinase (SVM). Furthermore, ADAMs have a highly variable region within the cysteine-rich domain, an additional epidermal growth factor (EGF)-like region, a transmembrane domain, and a cytoplasmic tail [3].

Compelling evidences has indicated that ADAMs exerted indispensable functions in the HF process. The levels of cardiac ADAM12 increased significantly in a mouse model of HF induced by arteriovenous fistula (AVF) [5]. ADAM17 has been shown to aggravate AngII-induced cardiac injury by cleaving ACE2 [6]. Furthermore, decreased expression of ADAM23 has been observed in HF human hearts and hypertrophic mouse hearts. Cardiac-specific ADAM23 knockout in mice resulted in increased cardiomegaly, fibrosis and dysfunction, while transgenic mice overexpressing ADAM23 exhibited reduced cardiomegaly under conditions of pressure overload [7].

Human ADAM8, also known as CD156, is located on chromosome 10q26.3 and is comprised of 824 amino acids [8]. The expression of ADAM8 was initially identified in macrophages, and subsequently in various cellular populations, including human B lymphocytes, dendritic cells, glia, human eosinophils and other cells [8]. Structurally, ADAM8 consists of an inhibitor prodomain (Pro), a metalloprotein domain (MP), a DIS-like (DIS), a cyclic-rich (Cys), and an EGF like domain (EGF), the transmembrane (TM) region, and the cyclic tail. Functionally, ADAM8 has been characterized as a protein hydrolase. It is capable of releasing the extracellular functional area of cell surface proteins, thereby modulating the functions of various cytokines and participating in the degradation of the ECM [9].

Recent studies have shown that ADAM8 also plays a role in cardiovascular diseases. The expression of ADAM8 has been associated with coronary artery disease (CAD), encompassing conditions such as atherosclerosis and myocardial infarction in mice and humans, particularly in endothelial cells and leukocytes. A correlation between ADAM8 expression and vascular disease markers VCAM-1, ICAM-1, TNF, IL-6 and CCL-2 was observed both in vivo and in vitro [10].

One of the main disputes raised by using ADAM8 as a predictive marker is specificity. In addition to cardiovascular diseases, ADAM8 has been implicated in pulmonary inflammation [11], asthma [12] and chronic obstructive pulmonary disease (COPD) [8]. In addition, ADAM8 plays an important role in invasive malignant tumors, including breast cancer, pancreatic cancer and brain cancer [13]. Increased expression of ADAM8 has been associated with tumor invasiveness and has predictive value for poor prognosis in cancer patients [14].

By bioinformatic analysis exploration of HF-related datasets, significant changes in ADAM8 expression in HF were observed. Here, we aimed to further explore the diagnostic and prognostic roles of ADAM8 in HF patients.

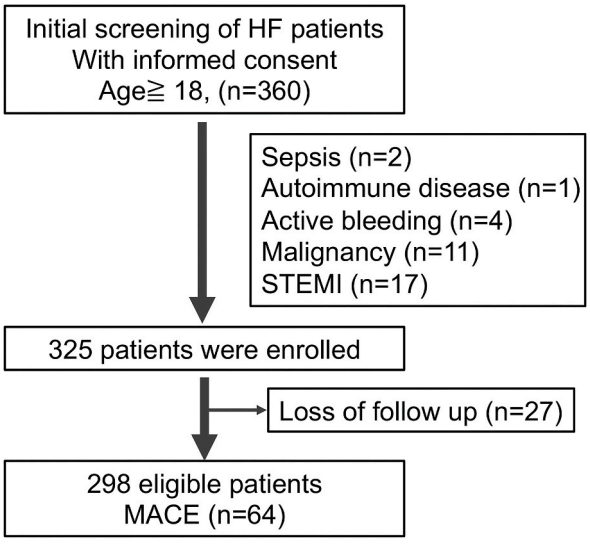

Fig. 1. Flow chart of patients enrolling.

2. METHODS

2.1. Bioinformatics

Two important datasets related to HF were downloaded from PubMed. GSE135055 dataset [15] included transcriptomic data of left ventricular heart tissue from 21 HF patients and 9 healthy donors. Age of HF patients and patients in the healthy group was 34.6 ± 15.9 and 41.7 ± 4.0 years respectively, and male percentages were 61.9 % and 100 %, respectively. The LVEF in the HF group was 27.6 ± 9.8. GSE161472 dataset [16] included mRNA profiles of left ventricular tissues from 10 non-failing (NF) donors and 12 HFrEF. The age of individuals in NF and HF groups was 44.5 ± 9.9 and 38.8 ± 13.0, respectively, and male percentages were 60 % and 58.33 %. Furthermore, the LVEF was 61.73 ± 15.06 % and 55.43 ± 16.10 % respectively. GEO2R was used to identify differentially expressed genes (DEGs) between healthy donors and HF patients. DEGs with $|logFC|>0.8$ and $adjp<0.05$ were used for pathway analysis. KEGG (Kyoto Encyclopedia of Genes and Genomes) database, a major public pathway-related database, was used for pathway enrichment analysis, which was performed using the OmicShare tools (www.omicshare.com/tools). GeneCards (https://www.genecards.org), PathCards (https://pathcards.genecards.org/) and Reactome (https://reactome.org/PathwayBrowser/) were used for analysis of important pathways. A Venn diagram was created by online tools for obtaining the intersection genes of two datasets (http://www.interactivenn.net/) [17].

2.2. Study design and enrollment patients

This is a single-center, prospective, observational cohort study. A total of 298 patients with suspected HF were enrolled from the Cardiology Department of Zhongda Hospital, Southeast University during July 2021 to April 2022 (Fig. 1). This study has been approved by IEC for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (2021ZDSYLL167-P01). All patients were diagnosed and received treatment following the recommendations outlined in the Chinese Heart Failure guidelines and 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF [2,18]. Suspected HF patients were first assessed for risk factors, HF symptoms and signs, and an abnormal electrocardiogram. Next, they underwent NT-proBNP/BNP testing and echocardiography examination. Based on the results, patients were diagnosed as either a non-HF or HF patients. HF was further classified into three categories: HFpEF (LVEF ≥50 %), HFmEF (LVEF 41 %–49 %), and HFrEF (LVEF ≤40 %). In total, 82 patients had no HF, and 121 patients were diagnosed as HFpEF, 50 patients as HFmEF, and 45 patients as HFrEF. According to the Guidelines for the Diagnosis and Treatment of Heart Failure in China, chronic HF was defined as N-terminal pro-BNP (NT-proBNP) levels ≥125 ng/mL or B-type natriuretic peptide (BNP) levels ≥35 ng/mL. Exclusion criteria were as follows: 1. Pregnant women; 2. patients with acute ST-elevated myocardial infarction, sepsis, a history of malignant tumors, autoimmune diseases, severe renal failure (estimated glomerular filtration rate<15 mL/min/1.73 m2 or patients receiving renal replacement therapy), or active bleeding; 3. Other severe diseases with an estimated lifespan of less than 1 year. The study adhered to the principles of Declaration of Helsinki and written informed consent was obtained from all participants. The demographic data, medical history, laboratory and echocardiography examination results at admission were collected. Variables included age, sex, smoking history, hypertension history, diabetes history, body mass index (BMI), systolic blood pressure (SBP), white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), platelet (Plt), albumin (ALB), aspartate transaminase (AST), lactic dehydrogenase (LDH), creatine kinase (CK), fasting plasma glucose (FPG), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), glycosylated hemoglobin (HbA1C), and LVEF. Major Adverse Cardiovascular Events (MACEs) were defined as the composite end points of first occurrence of rehospitalization because of HF or cardiac death during one-year follow-up. Telephone and electronic medical record system traceability were utilized to acquire follow-up information in this study.

2.3. Transthoracic echocardiography

Standard transthoracic echocardiography examination was conducted using the Vivid E9 equipment (GE Healthcare UK Ltd, Little Chalfont, UK). The left ventricular end diastolic and systolic volumes were measured through the Simpson's method and were indexed by the body surface area. Subsequently, the LVEF was calculated. Three measurements were taken for all variables and the average was recorded. Echocardiograms were reviewed by a single physician who did not have any knowledge of the other patient information.

2.4. ELISA

Human ADAM8 (A Disintegrin and Metalloprotease 8) ELISA Kits were purchased (E-EL-H0264c, Elabscience, China). Whole blood was collected into an anticoagulant tube containing EDTA-Na2, and subjected to centrifugation at 1000*g* at 2–8 °C for 15 min within 30 min after collection,. Blood plasma was prepared and sample testing was conducted according to the instructions provided with the ELISA kit instructions. In brief, 100 μL standard working solution or sample was added to the corresponding well, and incubated at 37 °C for 90 min. After discarding the supernatant, 100 μL biotinylated antibody working solution was added immediately, and plates were incubated at 37 °C for 1 h. The supernatant in the wells was then discarded, and the plate was washed three times. Next, 100 μL horse-radish peroxidase (HRP) enzyme conjugate working solution was added to each well, and plates were incubated at 37 °C for 30 min. Following another round of washing (five times), 90 μL of substrate solution was added to each well, and plates were incubated at 37 °C for about 15 min. Finally, 50 μL termination solution was added to each well and the plates were read using microplate reader at a wavelength of 450 nm.

2.5. Statistics

Statistical analysis was conducted using SPSS 23.0 version (IBM, USA), GraphPad Prism 8.0.1 version (GraphPad Software, USA), MedCalc statistical software version 19.0.7 (MedCalc Software bvba, Ostend, Belgium). Assuming an event rate of 25 % at 1 years, a power of 0.8, and a hazard ratio (HR) for the biomarker of 1.6, a sample size of 250 patients would be sufficient to meet the study's requirements, using PASS 15.0. Values with 2-tailed $P < 0.05$ were considered statistically significant. Continuous variables are presented as the mean ± standard deviation or median (interquartiles). Categorical variables are presented in numbers (percentages). The baseline characteristics of the two groups were compared by means of the independent *t*-test of normal distribution continuous variables, the Wilcoxon rank sum test was employed for non-normal distribution continuous variables, and the Chi-squared test for categorical variables. Based on the type and distribution of the variables, the $\chi 2$-test, one-way ANOVA, or Kruskal Wallis rank sum test were employed to evaluate differences. The missing values (10 %) were filled by the random forest method. Pearson and Spearman were used to analyze the linear correlation between ADAM8 and clinical variables according to the normality. Furthermore, Kaplan Meier (KM) analysis was performed to evaluate the time to the study endpoint, and the logarithmic rank trend test was used to evaluate the difference. The multivariate Cox proportional risk model and logistic regression model were used to analyze the impact of ADAM8 on the prognosis of HF.

3. Results

3.1. ADAM8 was identified as a key gene in HF by bioinformatics analysis

Bioinformatics analysis was conducted using the GSE135055 and GSE161472 datasets, which was comprised of left ventricular tissues from both normal individuals (NF donors) and patients with HF (Fig. 2A). Volcano plots showed 465 upregulated DEGs and 279 downregulated DEGs in GSE161472 dataset, and 1083 upregulated DEGs and 411 downregulated DEGs in GSE135055 dataset (Fig. 2A). KEGG analysis showed that ECM-receptor interaction was among the top 4 pathways in GSE135055 and GSE161472 datasets (Fig. 2B). The ADAMs family is known to be responsible for ECM degradation and organization (Fig. 2C). ADAM12/ADAMTSL1/ADAMTS2/ADAM19/ADAMTSL2/ADAMTS14/ADAM21/ADAMTS10/ADAMTSL5/ADAM8/ADAMTS7/ADAMTS19/ADAMTS15/ADAM11 were DEGs in GSE135055 dataset, and ADAMTS8/ADAMTS14/ADAM19/ADAM8 were DEGs in GSE161472 dataset. Venn diagram analysis showed that ADAMTS14, ADAM19, and ADAM8 were identified as key molecules found in the intersection GSE135055 and GSE161472 datasets (Fig. 2D). A comprehensive review of relevant publications indicated that ADAM8, likely plays a significant role in cardiovascular diseases. PathCards and Reactome analysis showed that ADAM8 mainly regulated the mechanisms of

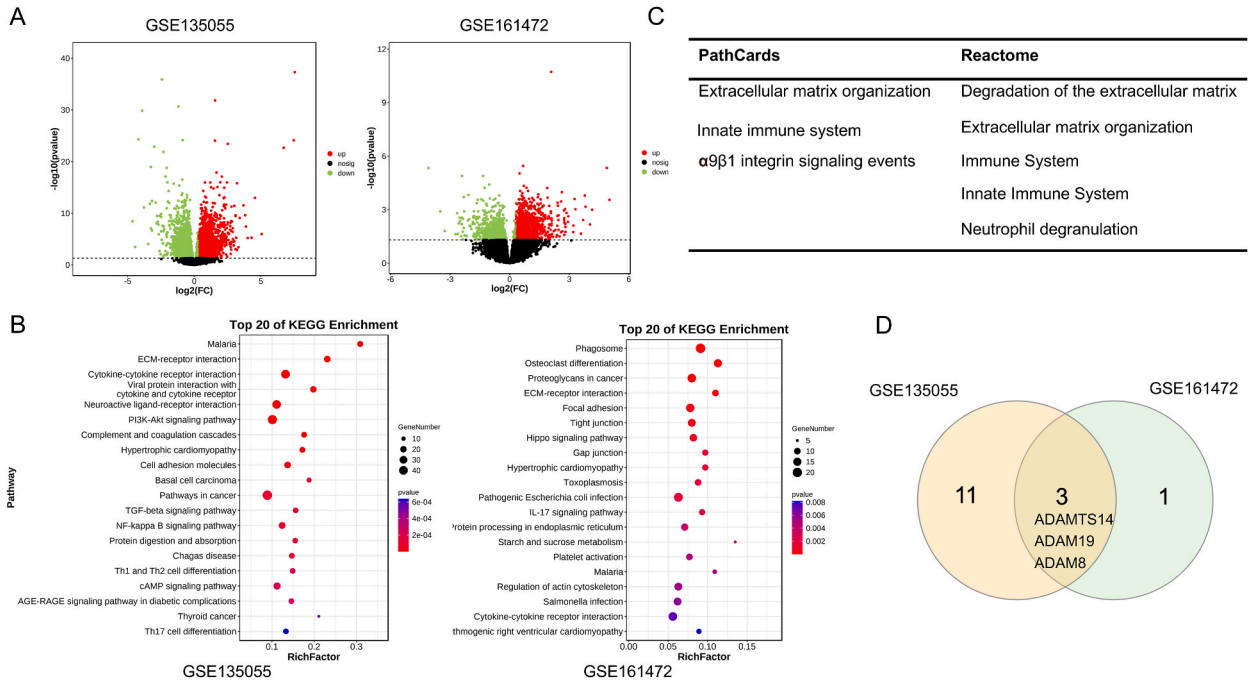

Fig. 2. Key genes exploring by bioinformatic analysis.
(A) Volcano plot showed DEGs between the GSE135055 and GSE161472 datasets. (B) KEGG analysis showed that ECM-receptor interaction was among the top 4 pathways in GSE135055 and GSE161472 datasets. (C) Pathcards and Reactome tools showed that the ADAM family is responsible for ECM organization. (D) Venn diagram analysis showed that ADAMTS14, ADAM19 and ADAM8 were identified as key molecules found in the intersection GSE135055 and GSE161472 datasets.

ECM degradation and organization. Therefore, ADAM8 emerges as a potentially important player in the context of HF. In fact, ADAM family interact with many specific genes. For example, substrates of ADAM8 include ECM molecules, receptors, ligands, adhesion molecules, and cytokines/chemokines, etc. ECM molecules include collagen I, fibronectin, and periostin. Receptors include TNFR1, LRP6, IL1RII, and CD23. Ligands include PSGL1. Adhesion molecules include CHL1, CD31, E-selectin, and L-selectin. Cytokines/chemokines include TNF-α/CXCL1 [13]. In this manuscript, we aim to validate the role of ADAM8 in heart failure patients, and do not explore the mechanisms of its interacted genes.

3.2. Characteristics of enrolled patients

According to the median of ADAM8 expression, patients were divided into a low ADAM8 group and high ADAM8 group according to the median of ADAM8 expression (472.916 pg/mL). Compared to the low ADAM8 group, the percentage of hypertension history was obviously elevated (68.456 %) in the high ADAM8 group ($p = 0.002$). In addition, the level of LVEF ($p = 0.001$) and Hb ($p = 0.001$) were lower in the high ADAM8 group. In contrast, the levels of Cr were significantly higher in the high ADAM8 group ($p = 0.023$) compared to the low ADM8 group (Table 1). The characteristics of patients with HFpEF, HFmEF, and HFrEF were presented in Table 2.

3.3. ADAM8 is highly expressed in patients with HF

The levels of ADAM8 were significantly increased in HF group (687.23 ± 539.04), compared to non-failing group (418.03 ± 219.96) ($p < 0.001$) (Fig. 3A). Compared to the control group (418.03 ± 219.96), plasma levels of ADAM8 were elevated in plasma of patients with HFrEF (852.63 ± 689.36) ($p < 0.05$), HFmEF (809.59 ± 638.51) ($p < 0.05$), and HFpEF (575.16 ± 388.21) ($p > 0.05$)

Table 1
Characteristics of enrolled patients. Data conforming to normal distribution are presented as mean ± standard deviation. The continuous data that do not conform to the normal distribution are presented quartiles. The categorical variable is expressed in frequency (percentage). Body Mass Index (BMI), Systolic Blood Pressure (SBP), White Blood Cells (WBC), Red Blood Cells (RBC), Hemoglobin (Hb), Platelet (Plt), Albumin (ALB), Aspartate Transaminase (AST), Lactic Dehydrogenase (LDH), Creatine Kinase (CK), Fasting Plasma Glucose (FPG), Blood Urea Nitrogen (BUN), Creatinine (Cr), Uric Acid (UA), Triglyceride (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), glycosylated hemoglobin (HbA1C).

Variables	Low ADAM8 group N = 149	High ADAM8 group N = 149	p value
Age (years)	67.600 ± 11.218	69.060 ± 10.828	0.253
Sex (Male)	93 (62.416 %)	85 (57.047 %)	0.345
Clinical characteristics			
Smoking history	40 (26.846 %)	43 (28.859 %)	0.672
Diabetes history	58 (38.926 %)	57 (38.255 %)	0.942
Hypertension history	76 (51.007 %)	102 (68.456 %)	0.002[b]
BMI (kg/m^2)	25.170 ± 4.476	25.483 ± 4.559	0.550
Heartrate	80.725 ± 16.7555	80.242 ± 18.0149	0.811
SBP (mmHg)	132.380 ± 22.306	130.050 ± 23.024	0.375
NYHA classification			
NYHA (I-II)	88 (59.060 %)	42 (28.188 %)	<0.001[c]
NYHA (III-IV)	61 (40.940 %)	107 (71.812 %)	
Laboratory examination			
WBC ($10^9/L$)	7.234 ± 5.505	7.179 ± 3.791	0.920
RBC ($10^9/L$)	5.419 ± 11.445	4.245 ± 0.701	0.212
Hb (g/L)	135.818 ± 23.215	126.859 ± 20.893	0.001[b]
Plt ($10^9/L$)	199.697 ± 62.967	203.121 ± 82.142	0.687
ALB (g/L)	39.083 ± 4.705	38.123 ± 4.574	0.075
AST (U/L)	20.00 (16.00, 30.50)	20.00 (16.00, 29.00)	0.722
LDH (U/L)	201.00 (171.00, 249.50)	211.00 (184.00, 263.00)	0.049[a]
CK (U/L)	77.00 (56.00, 116.50)	80.00 (57.50, 119.50)	0.406
FPG (mmol/L)	7.215 ± 5.606	7.029 ± 3.4398	0.731
BUN (mmol/L)	6.774 ± 6.373	7.845 ± 4.386	0.092
Cr (μmol/L)	81.383 ± 49.710	96.336 ± 62.508	0.023[a]
UA (μmol/L)	368.965 ± 145.954	394.242 ± 134.138	0.121
TG (mmol/L)	1.457 ± 1.021	1.363 ± 0.876	0.300
TC (mmol/L)	3.996 ± 1.171	3.854 ± 1.212	0.306
HDL-C (mmol/L)	1.196 ± 0.386	1.125 ± 0.285	0.071
LDL-C (mmol/L)	2.264 ± 0.833	2.208 ± 0.860	0.575
HbA1C (%)	6.766 ± 2.1313	6.797 ± 1.761	0.890
NT-proBNP (ng/L)	269.00 (76.00, 1770.00)	1490.00 (605.500, 4175.00)	<0.001[c]
D-dimer (ug/L)	230.000 (128.50, 611.50)	256.000 (132.50, 624.50)	0.927
LVEF (%)	61.727 ± 15.062	55.434 ± 16.099	0.001[b]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

Table 2
Characteristics of patients with heart failure. Data conforming to normal distribution are presented as mean ± standard deviation. The continuous data that do not conform to the normal distribution are presented quartiles. The categorical variable is expressed in frequency (percentage).

Variables	HFpEF N = 121	HFmEF N = 50	HFrEF N = 45	p value
Age (years)	72.560 ± 8.923	69.980 ± 11.847	67.930 ± 11.490	0.027*
Sex (Male)	66 (54.545 %)	30 (60.000 %)	33 (73.333 %)	0.090
Clinical characteristics				
NYHA (III-IV)	87 (71.901 %)	40 (80.000 %)	42 (93.333 %)	0.005**
Smoking history	32 (26.446 %)	14 (28.571 %)	13 (28.889 %)	0.933
Diabetes history	45 (37.190 %)	24 (48.980 %)	15 (33.333 %)	0.244
Hypertension history	88 (72.727 %)	35 (71.429 %)	32 (71.111 %)	0.972
BMI (kg/m^2)	25.064 ± 3.457	25.861 ± 5.727	24.165 ± 3.691	0.139
Heartrate	78.917 ± 19.160	84.840 ± 18.876	83.733 ± 17.318	0.108
SBP (mmHg)	133.380 ± 24.182	129.060 ± 22.351	124.670 ± 21.954	0.091
Laboratory examination				
FPG (mmol/L)	6.690 ± 2.692	8.404 ± 3.996	7.920 ± 4.573	0.007**
Cr (μmol/L)	88.950 ± 52.648	103.680 ± 66.441	97.800 ± 43.594	0.245
NT-proBNP (ng/L)	1170.00 (451.00, 2135.00)	2191.50 (1077.50, 4882.50)	3200.00 (1590.00, 7410.00)	<0.001***
Coronary artery lesions				
One vessel lesion	37 (30.579 %)	12 (24.000 %)	12 (26.667 %)	0.140
Two vessels lesion	13 (10.744 %)	8 (16.000 %)	5 (11.111 %)	
Three vessels lesion	29 (23.967 %)	21 (42.000 %)	11 (24.444 %)	
LVEF (%)	65.552 ± 7.546	45.696 ± 5.079	30.607 ± 6.062	<0.001***

Heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmEF), heart failure with preserved ejection fraction (HFpEF), Body Mass Index (BMI), Systolic Blood Pressure (SBP), Fasting Plasma Glucose (FPG), Creatinine (Cr).
*p < 0.05, **p < 0.01, ***p < 0.001.

(Fig. 3B). The study found no significant difference in ADAM8 expression levels between HFmEF and HFrEF. However, ROC analysis indicated that elevated levels of ADAM8 can predict HFpEF from other types of heart failure with a moderate accuracy (AUC = 0.609, 95%CI 0.533–0.686, p = 0.007). Therefore, while ADAM8 may not be useful in distinguishing between HFmEF and HFrEF, it may have a meaningful role in distinguishing HFpEF from other types of heart failure.

Based on the median value of ADAM8 (472.916 pg/mL), the patients were divided into two groups: a low ADAM8 group (<472.916 pg/mL) and a high ADAM8 group (≧472.916 pg/mL). The MACE prevalence in the low ADAM8 and high ADAM groups were 7.05 % (n = 21) and 14.43 % (n = 43), respectively (Fig. 3C). In the low ADAM8 group, the frequency of rehospitalization was 19 (6.38 %), and cardiac death was 2 (0.67 %). In the high ADAM8 group, the frequence of rehospitalization was 41 (13.76 %), and that of cardiac death was also 2 (0.67 %). The prevalence of HF in the high ADAM8 group (n = 125) was significantly higher than in the low ADAM8 (n = 91) group (41.95 % vs 30.54 %, p < 0.01) (Fig. 3D). Moreover, the prevalence of HFrEF, HfmEF, and HFpEF in the high and low ADAM8 groups were 9.40 % (n = 28) vs 5.70 % (n = 17), 11.74 % (n = 35) vs 5.03 % (n = 15), and 20.81 % (n = 62) vs 19.80 % (n = 59), respectively (Fig. 3D). Additionally, the LVEF in the high ADAM8 group was lower than in the low ADAM8 group (55.434 % ± 16.099 % vs 61.727 % ± 15.062 %, p < 0.001) and the median levels of NT-proBNP were significantly higher in the high ADAM8 group (1490) compared to the low ADAM8 group (269) (p < 0.001). To summarize, elevated levels of ADAM8 may be a risk factor for HF, especially in cases of HFrEF and HFmEF.

3.4. Correlation analysis of ADAM8

Pearson correlation analysis revealed several significant associations between ADAM8 levels and clinical variables. ADAM8 was positively correlated to age (r = 0.179, p = 0.002), FPG (r = 0.120, p = 0.038), BUN (r = 0.193, p = 0.001), Cr (r = 0.185, p = 0.001), UA (r = 0.24, p < 0.001), HbA1C (r = 0.114, p = 0.048), Left ventricular end diastolic dimension (LVDd) (r = 0.260, p < 0.001). Spearman analysis showed that ADAM8 was positively correlated to NT-proBNP (r = 0.394, p = 0.001) and negatively correlated to SBP (r = −0.126, p = 0.030), Hb (r = −0.175, p = 0.002), ALB (r = −0.152, p = 0.008), ApoA1 (r = −0.263, p < 0.001), LVEF (r = −0.272, p < 0.001) (Table 3).

3.5. ROC analysis of ADAM8 predicting the prevalence of HF and MACE

ROC analysis showed that the AUC of ADAM8 in predicting HF was 0.701 (z = 6.263, p < 0.0001). Similarly, the AUC of ADAM8 in predicting the MACE was 0.683 (z = 4.840, p < 0.0001). The AUC of joint detection of ADAM8 and NT-proBNP was 0.784. When comparing the individual performance of ADAM8 with other biomarkers, ADAM8 (0.701) exhibited a higher AUC than ALB (0.660) and CK (0.514), but lower than LDH (0.795) in predicting HF. Similarly, the AUC of joint detection of ADAM8 and NT-proBNP was 0.863 (Fig. 4A). ROC analysis showed that ADAM8 (0.683) had a higher AUC than ALB (0.610), CK (0.547) and LDH (0.638), but lower than NT-proBNP (0.796) in predicting MACE (Fig. 4B).

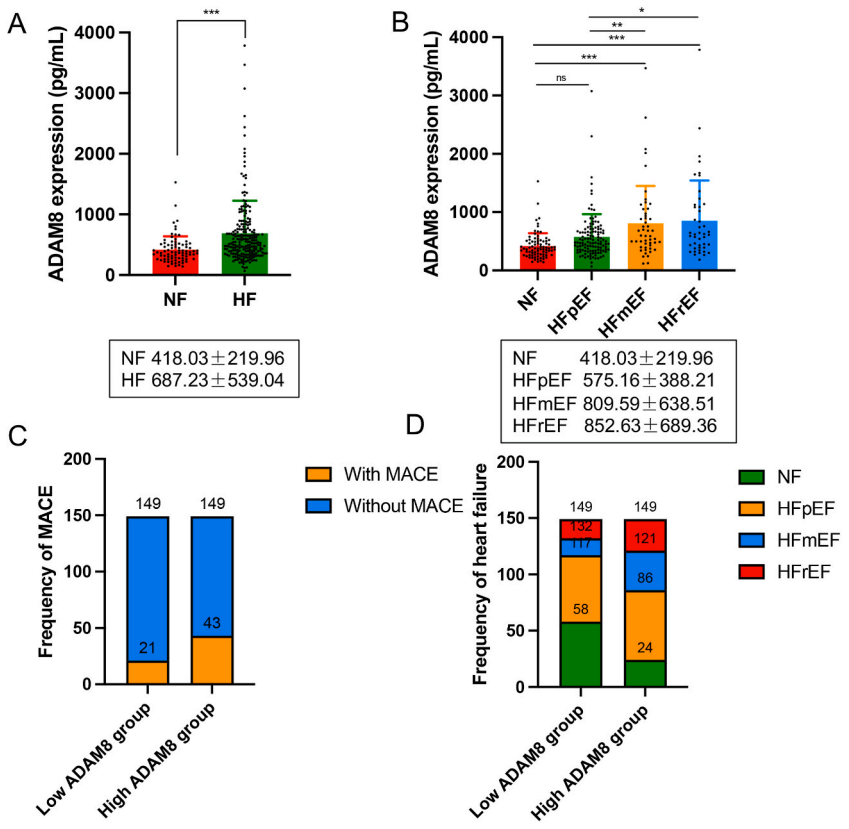

Fig. 3. ADAM8 is highly expressed in patients with heart failure.
(A) The levels of ADAM8 were significantly increased in heart failure group (687.23 ± 539.04), compared to NF group (418.03 ± 219.96) ($p < 0.001$). (B) ADAM8 was elevated in plasma of patients with HFrEF (852.63 ± 689.36) ($p < 0.05$), HFmEF (809.59 ± 638.51) ($p < 0.05$) and HFpEF (575.16 ± 388.21) ($p > 0.05$), compared to the control group (418.03 ± 219.96). (C) Based on the median value of ADAM8 (472.916 pg/mL), the patients were divided into two groups; the low ADAM8 group (<472.916 pg/mL) and the high ADAM8 group (≧472.916 pg/mL). The MACE prevalence in low ADAM8 and high ADAM groups were 7.05 % (n = 21) and 14.43 % (n = 43), respectively. (D) The prevalence of heart failure in the high ADAM8 group was significantly higher than in the low ADAM8 group (41.95 % vs 30.54 %, $p < 0.01$). The prevalence of HFrEF, HFmEF and HFpEF in the high and low ADAM8 groups were 9.40%vs 5.70 %, 11.74 % vs 5.03 %, and 20.81 % vs 19.80 %, respectively. NF: Non-failing group, HF: heart failure group, HFrEF: heart failure with reduced ejection fraction, HFmEF: heart failure with mildly reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction.

Table 3
Correlation analysis among ADAM8 and different variables. Pearson (for data conforming to normality) and Spearman analysis (for data not conforming to normality) were used.

Variables	r	P value	Variables	r	P value
ALB	−0.152	0.008**	LVEF	−0.272	<0.001***
FPG	0.120	0.038*	LVDd	0.260	<0.001***
BUN	0.193	0.001**	BMI	−0.020	0.729
UA	0.240	<0.001***	SBP	−0.126	0.030*
HbA1C	0.114	0.048*	NT-proBNP	0.394	<0.001***

Body Mass Index (BMI), Systolic Blood Pressure (SBP), Albumin (ALB), Fasting Plasma Glucose (FPG), Blood Urea Nitrogen (BUN), Creatinine (Cr), Uric Acid (UA), glycosylated hemoglobin (HbA1C), Left ventricular end diastolic dimension (LVDd), left ventricular ejection fraction (LVEF).
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

3.6. Logistic and Cox regression of the influence of ADAM8 on the prognosis of HF

Univariate logistic regression revealed that ADAM8 expression (≧472.916 pg/mL) was a significant predictor of HF (HR = 2.473, 95%CI = 1.382–4.424, p = 0.002). Important variables selected by clinical physicians such as sex, age, smoking history, diabetes history, hypertension history, BMI, Cr, TG and LDL-C, were included in a multivariate logistic regression. The "Enter" method showed that high ADAM8 expression (HR = 2.160, 95%CI = 1.123–4.158, p = 0.021), hypertension history (HR = 2.999, 95%CI =

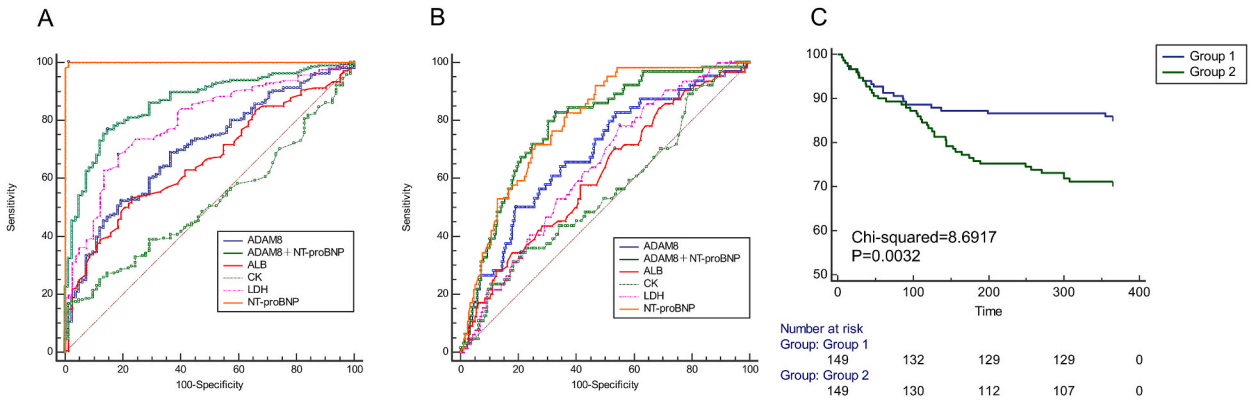

Fig. 4. ROC, Logistic and Cox regression of ADAM8 in predicting the occurrence of MACEs.
(A) ROC analysis showed that the AUC of ADAM8 in predicting heart failure was 0.701 (z = 6.263, p < 0.0001). The AUC of joint detection of ADAM8 and NT-proBNP was 0.863 (z = 16.298, p < 0.0001). The AUC of ALB (z = 4.875, p < 0.0001), CK (z = 0.412, p = 0.680), and LDH (z = 10.675, p < 0.0001) were 0.660, 0.514, and 0.795. (B) ROC analysis showed that the AUC of ADAM8 in predicting the MACE was 0.683 (z = 4.840, p < 0.0001). The AUC of joint detection of ADAM8 and NT-proBNP was 0.784 (z = 9.157, p < 0.0001). The AUC of ALB (z = 2.777, p = 0.0055), CK (z = 1.145, p = 0.252), LDH (z = 3.776, p = 0.0002), and NT-proBNP (z = 10.406, p < 0.0001) were 0.610, 0.547, 0.638, and 0.796. (C) KM analysis indicated that the prevalence of non-MACE in low ADAM8 group was significantly higher than in the high ADAM8 group (p = 0.0032).

1.430–6.291, p = 0.004), BMI (HR = 0.881, 95%CI = 0.799–0.970, p = 0.010), and NT-proBNP (HR = 1.000, 95%CI = 1.000–1.000, p = 0.004) were four important variables predicting MACE. Both "Forward LR" and "Backward LR" methods both showed that high ADAM8 expression (HR = 2.243, 95%CI = 1.198–4.199, p = 0.012), hypertension history (HR = 2.603, 95%CI = 1.293–5.238, p = 0.007), BMI (HR = 0.874, 95%CI = 0.797–0.958, p = 0.004), and NT-proBNP (HR = 1.000, 95%CI = 1.000–1.000, p = 0.005) were four important variables in predicting MACE (Table 4).

Univariate Cox regression analysis showed that high ADAM8 expression (≧472.916 pg/mL) was a significant predictor of HF (HR = 2.151, 95%CI = 1.280–3.615, p = 0.004). Subsequently, a multivariate Cox regression analysis was conducted, including important variables selected by clinical physicians such as sex, age, smoking history, diabetes history, hypertension history, BMI, Cr, TG and LDL-C. Using the "Enter" method, the results showed that high ADAM8 expression (HR = 1.735, 95%CI = 0.996–3.024, p = 0.052), hypertension history (HR = 2.461, 95%CI = 1.291–4.692, p = 0.006), BMI (HR = 0.911, 95%CI = 0.844–0.983, p = 0.016), and NT-proBNP (HR = 1.000, 95%CI = 1.000–1.000, p = 0.002) were four important variables with p < 0.1 in predicting MACE. "Forward LR" and "Backward LR" methods both showed that high ADAM8 expression (HR = 1.883, 95%CI = 1.107–3.203, p = 0.020), hypertension history (HR = 2.185, 95%CI = 1.176–4.061, p = 0.013), BMI (HR = 0.896, 95%CI = 0.834–0.963, p = 0.003), and NT-proBNP (HR = 1.000, 95%CI = 1.000–1.000, p = 0.002) were four important variables in predicting MACE (Table 5). KM analysis indicated that the prevalence of non-MACE in low ADAM8 group was significantly higher than in the high ADAM8 group (p = 0.0032) (Fig. 4C).

4. Discussion

ADAM8 plays critical roles in many pathophysiological processes, such as inflammatory responses and tumor invasion, by cleaving a variety of substrates, such as membrane binding molecules and ECM proteins. In this study, we found that ADAM8 was closely associated with an adverse prognosis of HF, regardless of the underlying causes of HF.

BNP or NT-proBNP is usually used for HF screening, as well as for evaluating the severity and prognosis of HF. However, data from the GUIDE-IT study indicated that compared to conventional treatment, NT-proBNP guided treatment did not significantly improve the prognosis of HFrEF [19]. Therefore, it is crucial to identify more effective biomarkers for the diagnosis and prognosis of HF. To further explore new biomarkers for HF, we used two GEO datasets to analyze and compare molecular differences of left ventricles between the control group and HF patients, and further identify ECM related mechanisms and ADAM family associated mechanisms in patients with HF.

The ECM is mainly a protein network structure composed of collagen I-IV, and fibronectin. The ECM can also participate in many biological reactions as signaling molecules. Imbalances in the ECM have been implicated in the development of numerous chronic diseases [20]. Both ADAM and ADAMTS belong to the metalloproteinase family and are involved in regulating the degradation and remodeling of the ECM. Finally, ADAMTS14, ADAM19, ADAM8 were screened by two GSE datasets of HF. Adamts14 KO mice exhibited reduced obesity and weight gain under obese conditions, along with an improved metabolic rate and overall health status during the same period [21]. The expression of ADAM19 has been linked to tumor immune cell infiltration, and increased expression of ADAM19 has been associated with a favorable prognosis of osteosarcoma [22]. However, the relationship between ADAMTS14 and ADAM19 and cardiovascular disease has not yet been elucidated. Some studies have pointed out that ADAM8 plays an important role in cardiovascular disease [10]. In this study, we aim to further explore the role of ADAM8 in HF caused by various cardiovascular diseases.

Table 4
Logistic regression of ADAM8 in predicting the occurrence of MACE. Body Mass Index (BMI), Creatinine (Cr), Hemoglobin (Hb), Triglyceride (TG), Low Density Lipoprotein Cholesterol (LDL-C), *p < 0.05, **p < 0.01, ***p < 0.001.

Variables	Enter			Forward/Backward		
	Exp(B)	p value	95 % CI	Exp(B)	p value	95 % CI
High ADAM8 expression	2.160	0.021*	1.123–4.158	2.243	0.012*	1.198–4.199
Sex	0.597	0.186	0.278–1.283			
Age	0.988	0.464	0.957–1.020			
Smoking history	1.385	0.385	0.664–2.888			
Diabetes history	0.762	0.434	0.387–1.504			
Hypertension history	2.999	0.004**	1.430–6.291	2.603	0.007**	1.293–5.238
BMI	0.881	0.010*	0.799–0.970	0.874	0.004**	0.797–0.958
Cr	1.000	0.916	0.993–1.006			
Hb	0.991	0.314	0.974–1.008			
NT-proBNP	1.000	0.004**	1.000–1.000	1.000	0.005**	1.000–1.000
TG	0.743	0.206	0.469–1.178			
LDL-C	1.206	0.341	0.820–1.773			

Table 5
Cox regression of ADAM8 in predicting the occurrence of MACE. Body Mass Index (BMI), Creatinine (Cr), Hemoglobin (Hb), Triglyceride (TG), Low Density Lipoprotein Cholesterol (LDL-C), *p < 0.05, **p < 0.01, ***p < 0.001.

Variables	Enter			Forward/Backward		
	Exp(B)	p value	95 % CI	Exp(B)	p value	95 % CI
High ADAM8 expression	1.735	0.052	0.996–3.024	1.883	0.020*	1.107–3.203
Sex	0.624	0.161	0.323–1.207			
Age	0.991	0.498	0.966–1.017			
Smoking history	1.236	0.500	0.668–2.288			
Diabetes history	0.767	0.347	0.441–1.333			
Hypertension history	2.461	0.006**	1.291–4.692	2.185	0.013*	1.176–4.061
BMI	0.911	0.016*	0.844–0.983	0.896	0.003**	0.834–0.963
Creatinine	0.999	0.642	0.995–1.003			
Hb	0.995	0.479	0.981–1.009			
NT-proBNP	1.000	0.002**	1.000–1.000	1.000	0.002**	1.000–1.000
TG	0.736	0.175	0.472–1.146			
LDL-C	1.170	0.326	0.855–1.602			

We first demonstrated that ADAM8 was elevated in HFmEF and HFrEF. Although the increase in ADAM8 expression in HFpEF was not significant, expanding the sample size may reveal a significant difference. Many studies have reported the roles of the ADAM family in HF. ADAMTS4 expression and cleavage activity were markedly increased in failing human hearts [23,24]. Levels of ADAM15 and ADAM17 levels were markedly decreased in HF patients [25,26]. ADAM17 was increased in diabetic cardiomyopathy (DCM), and cardiomyocyte-specific knockout of ADAM17 alleviated cardiac fibrosis and cardiomyocyte apoptosis, and improved cardiac function in DCM mice [27]. ADAM23 expression is decreased in failing human hearts [7]. ADAMTSL4 were significantly increased in HF patients with pulmonary hypertension [28]. ADAM10 expression was elevated in patients with ischemic cardiomyopathy [29]. However, there is few related articles have been published about ADAM8 and HF. To further analyze the role of ADAM8, enrolled patients were divided by the median of ADAM8. The prevalence of HF was found to be significantly higher in individuals with high ADAM8 levels compared to those with low ADAM8 levels. This difference was particularly notable for HF with HFrEF and HFmEF. Elevated levels of ADAM8 may be a risk factor for HF, especially in cases of HFrEF and HFmEF. The high ADAM8 group had a higher prevalence of major adverse cardiovascular events (MACE) compared to the low ADAM8 group. Regression analysis further demonstrated that high ADAM8 levels were a predictor of long-term prognosis in HF. Thus, these results all demonstrated the essential role of ADAM8 in HF.

In our study, ADAM8 was compared with traditional indicators for HF diagnosis, such as NT-proBNP, ALB, CK, and LDH, which are closely related to HF. Lower levels of ALB have been shown to predict the occurrence of HF in adults aged ≥65 years without cardiovascular diseases [30]. Hypoalbuminemia is also very common in HF patients, usually leading to a higher mortality rate. LDH has a significant impact on the 30-day unplanned readmission of elderly patients with HF [31]. In the heart, the CK system is a major component of the metabolic mechanism because it plays a role in energy transfer between mitochondria and the cytoplasm. We found that high ADAM8 showed a better ability than ALB and CK, but lower than LDH in diagnosing HF. ADAM8 also had higher predicting MACE performance compared to ALB, CK, and LDH.

Limitations

There are also some limitations to this study. Firstly, we only measured ADAM8 levels at baseline and did not assess changes during follow-up. Secondly, the sample size of our study was relatively small, and long-term follow-up exceeding one year was not conducted.

Notably, the difference in MACE between the high ADAM8 group and the low ADAM8 group continued to increase during a follow up after 60 days. Third, whether ADAM8 was released by cardiomyocytes in HF, or by other inflammatory cells, could not be determined. The strength of our study lies in the utilization of bioinformatics methods to identify and validate ADAM8 expression in plasma using clinical patient blood samples, which holds significance for the diagnosis and prognosis of HF.

In conclusion, this study was the first to demonstrated the predicting role of ADAM8 in adverse prognosis in HF, which may provide measuring methods guiding the treatment of HF.

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Ethics statement

This study has been approved by IEC for Clinical Research of Zhongda Hospital. Affiliated to Southeast University (2021ZDSYLL167-P01).

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Zhenjun Ji: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jiaqi Guo:** Writing – review & editing, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yang Xu:** Writing – review & editing, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **Wenjie Zuo:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Rui Zhang:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Abdlay Carvalho:** Writing – review & editing, Visualization, Supervision, Investigation. **Xiaoguo Zhang:** Writing – review & editing, Visualization, Resources, Project administration. **Zaixiao Tao:** Writing – review & editing, Resources, Project administration, Investigation. **Xinxin Li:** Writing – review & editing, Supervision, Project administration, Investigation. **Yuyu Yao:** Writing – review & editing, Supervision, Conceptualization. **Genshan Ma:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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