Prognostic significance of serum dynamin-related protein 1 in patients with heart failure: Findings from a prospective observational study

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Abstract. Mitochondrial dysfunction plays a critical role in the development and exacerbation of heart failure (HF). Dynamin-related protein 1 (Drp1), a key regulator of mitochondrial fission, influences cardiac energy metabolism. The present study investigated the relationship between serum Drp1 levels and the prognosis of patients with HF across a broad spectrum. Serum Drp1 concentrations were measured using ELISA. The primary outcome was the risk of composite major adverse cardiac events (MACEs), which included instances of cardiac death and HF-related readmissions. To assess the prognostic significance of serum Drp1, a receiver operating characteristic curve was constructed to predict MACE-free survival. Additionally, an optimal threshold value for Drp1 was determined and was used to stratify patients into different risk categories. A total of 256 HF patients were finally included and categorized into two groups based on their serum Drp1 levels, labeled as the low (Drp1 ≤2.66 ng/ml, n=101) and high group (Drp1 >2.66 ng/ml, n=155). Patients with low serum Drp1 concentrations showed impaired heart structure and function, as assessed by echocardiography. The 6-month follow-up results indicated that patients with reduced Drp1 concentrations faced a substantially increased risk of MACEs (21.1% vs. 2.8%; P<0.001). The present study revealed that diminished serum Drp1 concentrations could potentially act as a predictive marker for the prognosis of HF in a broad patient population.

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Introduction

Heart failure (HF), a critical endpoint of cardiac dysfunction due to significant structural abnormalities, stands as a primary contributor to cardiac mortality and recurrent hospital admissions worldwide, imposing substantial healthcare and socioeconomic costs (1,2). Over the past years, HF classification has evolved into four stages (A-D), highlighting the progression of the disease and the varying phenotypes discernible via echocardiography (3). Unlike HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) exhibits normal systolic function but impaired ventricular filling and relaxation (4). This distinction underscores the need for tailored treatment approaches for the diverse HF categories. Despite significant advancements in medical treatments and cardiac support devices reducing the incidence of hospitalization and improving survival rates for HFrEF, the overall outlook for heart failure patients remains suboptimal (5). There is also a pressing need to refine the selection process for various treatments, including standard medications and newer oral agents such as sodium-glucose cotransporter 2 inhibitors (SGLT2is) and vericiguat, to suit individual patient groups (6,7). A deeper comprehension of the underlying mechanisms of HF is crucial for the creation of more effective therapeutic strategies.

Mitochondria are the powerhouse of the cell and their well-being is crucial for maintaining normal cellular metabolism and shielding cells from oxidative damage caused by reactive oxygen species (ROS) (8). Dynamin-related protein 1 (Drp1) is present in the cytoplasm and initiates mitochondrial division, effectively isolating impaired mitochondrial parts within a depolarized offspring organelle marked for mitophagy, which is pivotal in managing mitochondrial integrity (9). The heart is the most metabolically active organ in the body, and some previous studies have demonstrated that impaired mitochondrial energetics could greatly contribute toward the

onset and progression of maladaptive cardiac hypertrophy and HF (10,11). Our previous research also suggested that regulating Drp1 expression might normalize mitochondrial fission and enhanced cardiac metabolism, which in turn could decrease apoptosis in cardiomyocytes within the infarcted myocardium, thereby improving heart function (12). However, there is a notable scarcity of studies investigating the relationship between serum Drp1 levels and HF prognosis. As a result, the present study was initiated to uncover independent risk predictors for patients with HF.

Materials and methods

Study design and patient selection. The present study was an observational, single-center, prospective analysis aimed of investigating the association between serum Drp1 concentrations and the clinical outcomes in a broad spectrum of HF patients. Between 1 June, 2021 and 31 March, 2022, patients hospitalized at Zhongda Hospital (Nanjing, China) were consecutively assessed for eligibility. A comprehensive cohort of HF patients (aged 18-85 years) were included, encompassing those with major risk factors such as ischemic heart disease (IHD), hypertension, cardiomyopathy, diabetes mellitus (DM) and obesity, as well as individuals who had received a definitive HF diagnosis confirmed by at least two experienced cardiologists. Patient characteristics are given in Table I. The exclusion criteria were: i) Primary diagnosis of macrovascular conditions such as aortic dissection or arteritis, congenital heart defects, pulmonary diseases, peripheral vascular disorders, pericardial diseases, myocarditis, cardiophobia, costochondritis and shock; endocrine disorders including thyroid diseases; malignancies, or severe infections; ii) presence of significant hepatic impairment (aspartate aminotransferase levels >140 U/l, alanine aminotransferase levels >140 U/l) or renal impairment (estimated glomerular filtration rate <30 ml/min/1.73 m^2); and iii) non-compliance with, or refusal to participate in, the present study. For the classification and progression of HF, the diagnostic criteria adhered to the current guidelines (3,5). Additionally, HF was categorized into HFrEF (EF <50%) and HFpEF (EF ≥50%) based on echocardiographic results. The ethics committee of Zhongda Hospital (Nanjing, China) approved the present study protocol (approval no. 2020ZDSYLL306-P01).

Biochemical analyses, procedure and medications. On the next morning following admission, fasting blood samples were collected from patients. (3-5 ml) and temporarily maintained at 4˚C, before being processed within 2 h. After centrifugating at 1,500 x g for 30 min at 4˚C, the serum was collected for further measurements of Drp1 concentrations using an ELISA kit (cat. no. EH14381) following manufacturer's instructions (Wuhan Fine Biotech Co., Ltd.). All ELISA data were analyzed according to the standard curve and each sample was measured twice to acquire a mean value. In addition, three experienced primary interventionists were in charge of all the potential interventional procedures according to the current standards and the common perioperative antithrombotic therapies were applied following the current guidelines (13). Routine therapies, including β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aldosterone antagonists, or sacubitril valsartan sodium were applied as appropriate, while possible use of sodium-glucose co-transporter 2 inhibitions or ivabradine were also recommended as adjunctive therapies for secondary prevention if necessary (14).

Study endpoints and relevant definitions. Patients were evaluated at 1 and 6 months after discharge, mainly through telephone call or clinical office visits. An independent cardiologist blinded to the present study assessed and recorded the relevant clinical events. The primary outcome was the risk of composite major adverse cardiac events (MACEs), incuding cardiac mortality and rehospitalization for HF. Cardiac mortality was defined as mortality without a clear non-cardiac cause as confirmed in clinic or autopsy. Rehospitalization for HF was defined following the criteria described in Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial (15).

Statistical analysis. Statistical analyses were performed using SPSS software (version 23.0; IBM Corp.). The present study summarized baseline characteristics and clinical outcomes using frequencies with percentages or means with standard deviation as appropriate. Continuous variables were first assessed for normality using the Shapiro-Wilk test. For data following a normal distribution, comparisons between two groups were conducted with the Student's t-test. For non-normally distributed data, the Mann-Whitney U test was applied instead. Categorical variables were compared using the chi-square test or Fisher's exact test, depending on the expected frequencies. To evaluate the predictive value of serum Drp1 levels for the absence of MACEs, a receiver operating characteristic (ROC) curve was constructed and the optimal threshold determined using the Youden index. This threshold was then used to categorize the subjects. In addition, binary logistic regression was performed to control for confounding factors and pinpoint independent predictors of the primary endpoint. Time-to-event data were illustrated using Kaplan-Meier curves, with group differences assessed through the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient selection and baseline characteristics. A total of 256 patients from Zhongda Hospital (Nanjing, China) were finally enrolled in the present study (Fig. 1). A 6-month follow-up was accomplished in most of the enrolled patients and contact was lost in only 6.25% of participants. The serum Drp1 concentrations were measured in all participants (5.2±4.5 ng/ml). Upon analyzing the ROC curve for serum Drp1 levels in assessing the absence of MACE risk, a threshold of 2.66 ng/ml was established as the optimal cutoff point (Youden index=0.529). This value forecasts the likelihood of evading MACEs with a sensitivity of 65.9% and a specificity of 87% [area under the curve: 0.752; 95% confidence interval (CI): 0.679-0.824, $P<0.001$; Fig. 2]. Subsequently, the participants of the present study were categorized into two cohorts: Low Drp1 group (Drp1 ≤2.66 ng/ml; n=101) and high Drp1 group (Drp1 >2.66 ng/ml; n=155). An overview of the baseline traits

Table I. Baseline characteristics between the low and high Drp1 groups.

A, Demographics				
Variables	Total	Drp1 ≤2.66 ng/ml (n=101)	Drp1 >2.66 ng/ml (n=155)	P-value
Age, years	68.7±10.8	68.6±12.3	68.8±9.7	0.87
Sex (male), n (%)	152 (59.4)	67 (66.3)	85 (54.8)	0.07
BMI, kg/m^2	25.5±4.3	25.5±4.8	25.5±3.9	0.916
Heart rate, bpm	80.3±17.8	83.9±16.2	81.3±18.8	0.247
SBP, mmHg	131.8±21.9	129.7±22.5	133.2±21.5	0.219
DBP, mmHg	77.5±13.7	77.0±14.4	77.8±13.2	0.627
B, Risk factors				
Smoking, n (%)	64 (25.0)	30 (29.7)	34 (21.9)	0.185
Coronary artery diseases, n (%)	162 (63.3)	81 (80.2)	81 (52.3)	<0.001
Prior MI, n (%)	91 (35.5)	68 (67.3)	23 (14.8)	<0.001
Hypertension, n (%)	181 (70.7)	75 (74.3)	106 (68.4)	0.329
Diabetes, n (%)	85 (33.2)	39 (38.6)	46 (29.6)	0.174
Stroke, n (%)	81 (31.6)	39 (38.6)	42 (27.1)	0.056
Hypercholesterolemia, n (%)	24 (9.4)	8 (7.9)	16 (10.3)	0.662
C, Laboratory results				
NT-proBNP, pg/ml[a]	1015.0 (22.0, 35000.0)	1970.0 (77.0, 35000)	182.5 (22.0, 20400.0)	<0.001
WBC, x10^9/l	6.9±3.1	7.1±2.3	6.8±3.6	0.495
Hb, g/l	132.1±19.5	130.5±20.8	133.2±18.6	0.27
Plt, x10^9/l	202.2±74.6	189.7±68.2	210.4±77.7	0.03
FPG, mmol/l	6.7±2.8	6.9±3.0	6.5±2.5	0.223
HbA1C, %	6.6±1.6	6.8±1.6	6.5±1.5	0.151
ALT, U/l	24.7±22.0	27.1±28.6	23.1±16.4	0.209
eGFR, ml/(min*1.73 m^2)	79.4±21.1	75.5±22.7	81.9±19.6	0.018
Urea nitrogen, mmol/l	7.0±3.4	7.9±4.5	6.4±2.3	0.002
Total-cholesterol, mmol/l	3.9±1.2	3.7±1.0	4.1±1.3	0.004
Triglycerides, mmol/l	1.3±0.9	1.3±1.0	1.4±0.9	0.652
LDL-C, mmol/l	2.2±0.8	2.1±0.7	2.3±0.9	0.02
HDL-C, mmol/l	1.2±0.3	1.1±0.3	1.2±0.3	0.004
D, NYHA classification				
I, n (%)	81 (31.6)	1 (1.0)	80 (51.6)	<0.001
II, n (%)	136 (53.1)	77 (76.2)	59 (38.1)	<0.001
III, n (%)	33 (12.9)	19 (18.8)	14 (9.0)	0.034
IV, n (%)	6 (2.3)	4 (4.0)	2 (1.3)	0.216
E, Clinical presentation[b]				
HFrEF, n (%)	86 (50.3)	65 (64.4)	21 (13.5)	<0.001
HFpEF, n (%)	85 (49.7)	35 (34.7)	50 (32.3)	0.786
DAPA, n (%)	56 (21.9)	23 (22.8)	33 (21.3)	0.877

Values are mean ± SD; [a]data are presemted as the median with minimum and maximum; [b]analysis of the HF patients with stage B-D (n=171). ALT, alanine aminotransferase; BMI, body mass index; bpm, beats per minute; DAPA, Dapagliflozin; DBP, diastolic blood pressure; Drp1, Dynamin-related protein 1; eGFR, estimated glomerular filtration rate; EF, left ventricular ejection fraction; FPG, fasting plasma glucose; Hb, hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; n, number; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Plt, platelet; SBP, systolic blood pressure; WBC, white blood cells.

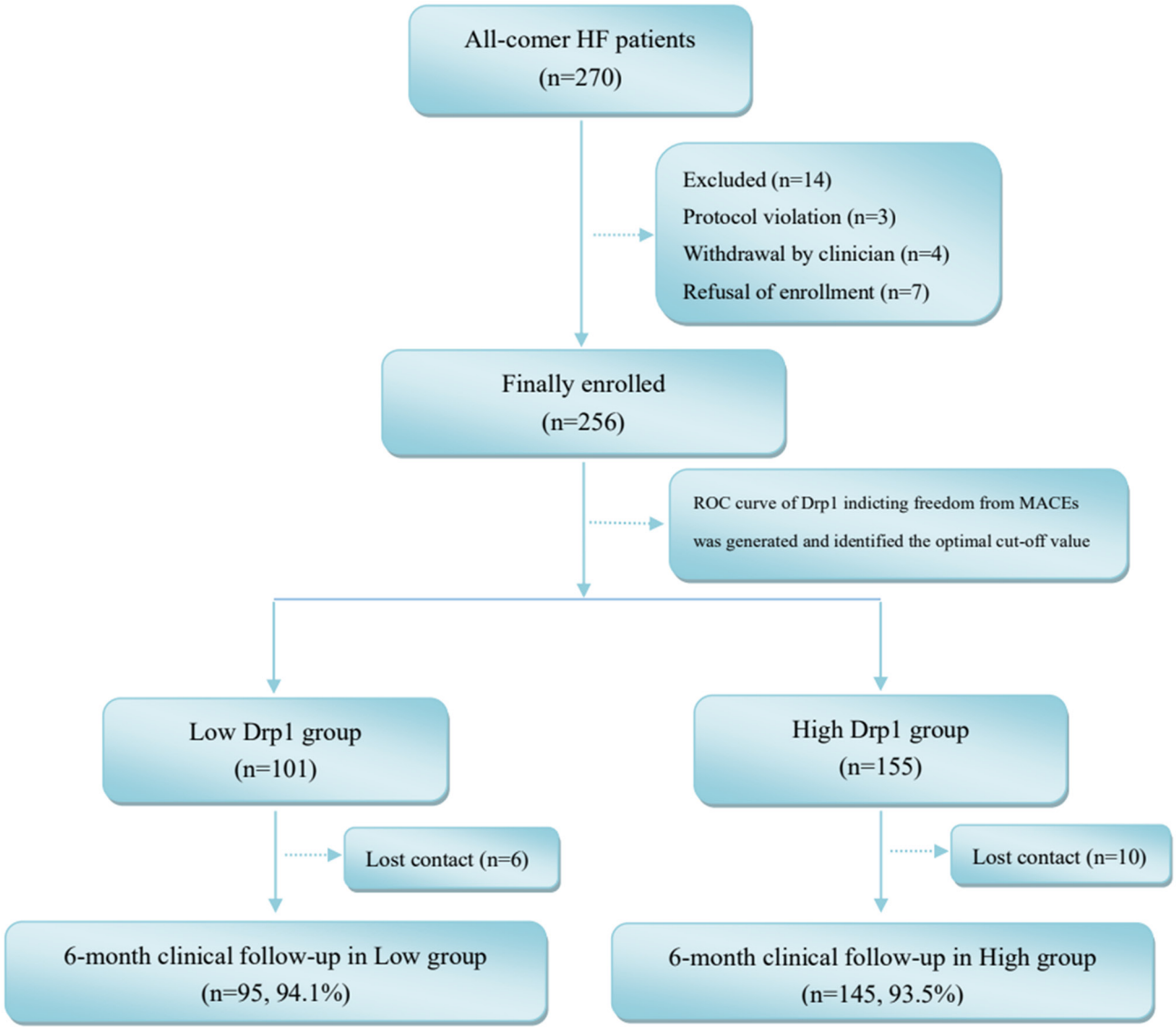

Figure 1. A flow chart of the selection of patients enrolled in the present study. HF, heart failure; ROC, receiver operating characteristic; Drp1, dynamin-related protein 1; MACEs, major adverse cardiac events.

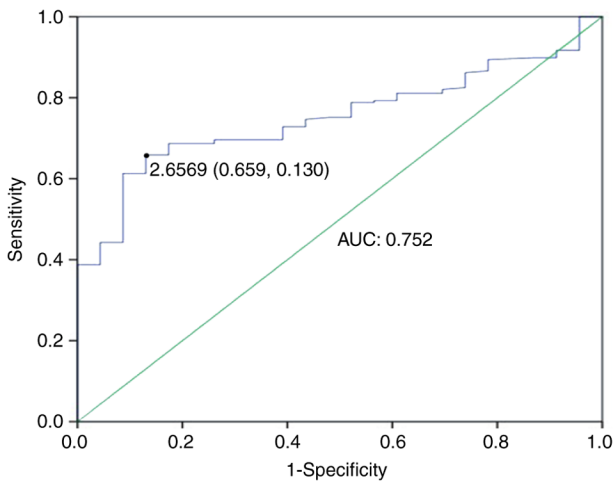

Figure 2. ROC curve of Drp1 level for predicting the freedom from the risk of MACEs after 6-month follow-up. The AUC was 0.752 and the optimal cut-off value was 2.66 ng/ml (sensitivity 65.9%; specificity 87%). ROC, receiver operating characteristic; Drp1, dynamin-related protein 1; MACEs, major adverse cardiac events; AUC, area under the curve.

of these individuals revealed comparable demographics across both groups, with the exception of higher incidences of coronary artery disease (80.2% vs. 52.3%, P<0.001) and previous myocardial infarction (MI; 67.3% vs. 14.8%; P<0.001) in the high Drp1 group (Table I).

Association between the serum Drp1 level and cardiac function and clinical outcomes. Fig. 3 illustrates that the serum Drp1 levels were significantly reduced in the low Drp1 group, with a mean concentration of 1.8 ng/ml, in contrast to 7.4 ng/ml in the high Drp1 group (P<0.001; Fig. 3A). By contrast, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were substantially elevated in the low Drp1 group, with a median of 1,970.0 pg/ml compared with 182.5 pg/ml in the high Drp1 group (P<0.001; Fig. 3B). Additionally, patients with diminished serum Drp1 concentrations were associated with a more severe New York Heart Association (NYHA) functional classification, averaging 2.3, as opposed to 1.6 for those with elevated concentrations (P<0.001; Fig. 3C).

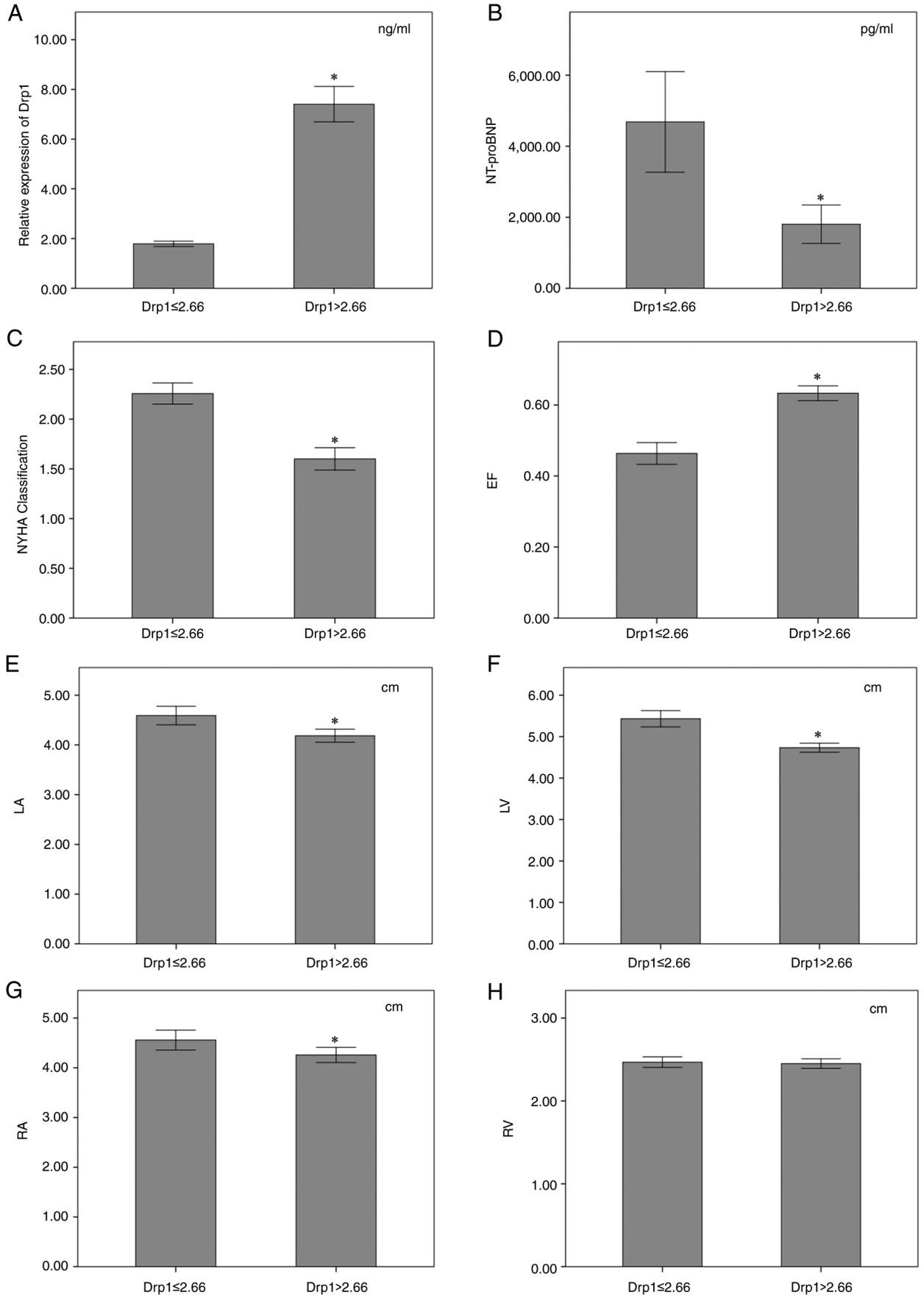

Figure 3. Characteristics of clinical manifestation, cardiac structure and function in the low Drp1 group (Drp1 ≤2.66 ng/ml) and the high Drp1 group (Drp1 >2.66 ng/ml). Comparisons of (A) serum Drp1 level, (B) NT-proBNP level, (C) NYHA classification, (D) left ventricular EF, (E) internal diameter of LA, (F) internal diameter of LV, (G) internal diameter of RA and (H) internal diameter of RV in low Drp1 group vs. the high Drp1 group. Error bars indicate ± SD. *P<0.05. Drp1, dynamin-related protein 1; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; EF, ejection fraction; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table II. Clinical follow-up in the low and high Drp1 groups.

	1-month, n (%)			6-month, n (%)		
Parameter	Drp1 ≤2.66 (n=101)	Drp1 >2.66 (n=155)	P-value	Drp1 ≤2.66 (n=101)	Drp1 >2.66 (n=155)	P-value
MACEs	11 (10.9)	2 (1.3)	0.001	20 (19.8)	4 (1.8)	<0.001
Rehospitalization for HF	11 (10.9)	1 (0.6)	<0.001	20 (19.8)	3 (1.9)	<0.001
Cardiac mortality	1 (1.0)	1 (0.6)	1.000	4 (4.0)	1 (0.6)	0.082
All-cause mortality	1 (1.0)	1 (0.6)	1.000	4 (4.0)	2 (1.3)	0.217

Drp1, Dynamin-related protein 1; HF, heart failure; MACEs, major adverse cardiac events; n, number.

As shown in Fig. 3, the serum Drp1 concentrations were markedly decreased in the low Drp1 group (1.8±0.5 vs. 7.4±4.5 ng/ml, P<0.001; Fig. 3A) while the NT-proBNP levels were much higher (1970.0 pg/ml vs. 182.5 pg/ml, P<0.001; Fig. 3B). Patients with low serum Drp1 concentrations showed higher grade of NYHA functional classification than those with high concentrations (2.3±0.5 vs. 1.6±0.7, P<0.001; Fig. 3C). Simultaneously, the echocardiography data revealed a clear association between low serum Drp1 levels and compromised heart structure and function. This was especially evident in the reduced ejection fraction (EF), which was significantly lower in the group with diminished Drp1 (46.3±15.5% vs. 63.3±13.0%; P<0.001; Fig. 3D). Additionally, there was an increase in the internal diameter measurements of the left atrium (LA; 4.6±0.9 cm vs. 4.2±0.8 cm; P<0.001; Fig. 3E), left ventricle (LV; 5.4±1.0 cm vs. 4.7±0.7 cm; P<0.001; Fig. 3F), and right atrium (RA; 4.6±1.0 vs. 4.3±1.0 cm; P=0.018; Fig. 3G), indicating significant dilatation of heat. By contrast, the right ventricular internal diameter (RV) showed no significant difference between groups (2.5±0.3 cm vs. 2.5±0.4 cm; P=0.703; Fig. 3H), suggesting that specific areas of the heart were more affected by Drp1 levels.

The clinical outcomes are listed in Table II. After 6-month follow-up, a significant association was observed between low serum Drp1 levels and an elevated risk of MACEs, with incidences of 21.1% in the low Drp1 group compared with 2.8% in the counterpart group (P<0.001; Fig. 4A). This association appears to be primarily driven by increased rates of rehospitalization in the low Drp1 group (21.1% vs. 2.1%; P<0.001; Fig. 4B). Although not statistically conclusive, patients with higher Drp1 concentrations exhibited a notable decrease in cardiac death risk (4.2% for the low Drp1 group vs. 0.7% for the high Drp1 group; P=0.082). However, the comparison of all-cause mortality between the two groups did not yield statistically significant results (4.2% vs. 1.4%; P=0.217).

For further confirmation of the associations, logistic regression analysis was performed to identify the potential independent risk predictors of MACEs in these patients (Fig. 4C). Low serum Drp1 concentration [odds ratio (OR): 4.800, 95% CI: 1.161-19.839; P=0.03)], NT-proBNP levels (OR: 1.000, 95% CI: 1.000-1.000; P=0.001) and left ventricular ejection fraction (OR: 0.002, 95% CI: 0.000-0.228; P=0.01) were identified as the independent factors for predicting the occurrence of MACEs after regressing in a multivariate model. These three predictors were also confirmed to be associated with an increased risk of rehospitalization for HF after adjusting for confounding factors, including IHD, prior MI, estimated glomerular filtration rate, internal diameter of right atrium and lipoprotein (Fig. 4D).

Discussion

The present study unveiled a novel link between serum Drp1 levels and the outcomes of patients with HF across the board. The pivotal discovery revealed that lower serum Drp1 concentrations were associated with significant cardiac structural abnormalities and impaired heart function. This association significantly heighted the risk of MACEs, positioning serum Drp1 as a standalone predictor of risk.

HF is typically a consequence of abnormalities in cardiac structure and function. Despite advancements in medical treatment and rehabilitation efforts, HF remains linked to a significant rate of readmissions and cardiac incidents globally. This persistent challenge may be attributed to the predominant clinical focus on symptom alleviation rather than addressing underlying causes (16,17). Notably, a number of standard medical treatments, which have been rigorously evaluated in large clinical trials, have yielded underwhelming results in terms of efficacy. For instance, the use of ß-blockers in the OPTIMIZE-HF study (18), spironolactone in the TOPCAT trial (19) and Ibersartan in the I-Preserve study (20), all reported outcomes that fell short of expectations. Therefore, it should be crucial to tailor medical interventions to the specific progressive stages and phenotypes of HF to avoid varying clinical outcomes (21). Moreover, while novel oral medications such as SGLT2 inhibitors and vericiguat have demonstrated significant advantages for HF patients (7,22,23), their application in clinical practice continues to be a subject of discussion. As a result, there has been a surge in research efforts aimed at deciphering the intricate mechanisms driving HF progression, with the goal of creating more targeted and effective treatments.

A recent study by Zhuang *et al* (24). showed a direct association between the inhibition of mitochondrial bioenergetics and the advancement of cardiac hypertrophy and HF. Drp1, a member of the dynamin family of GTPases, exhibits several splice variants and is predominantly expressed in vital tissues such as the heart, skeletal muscle, brain and

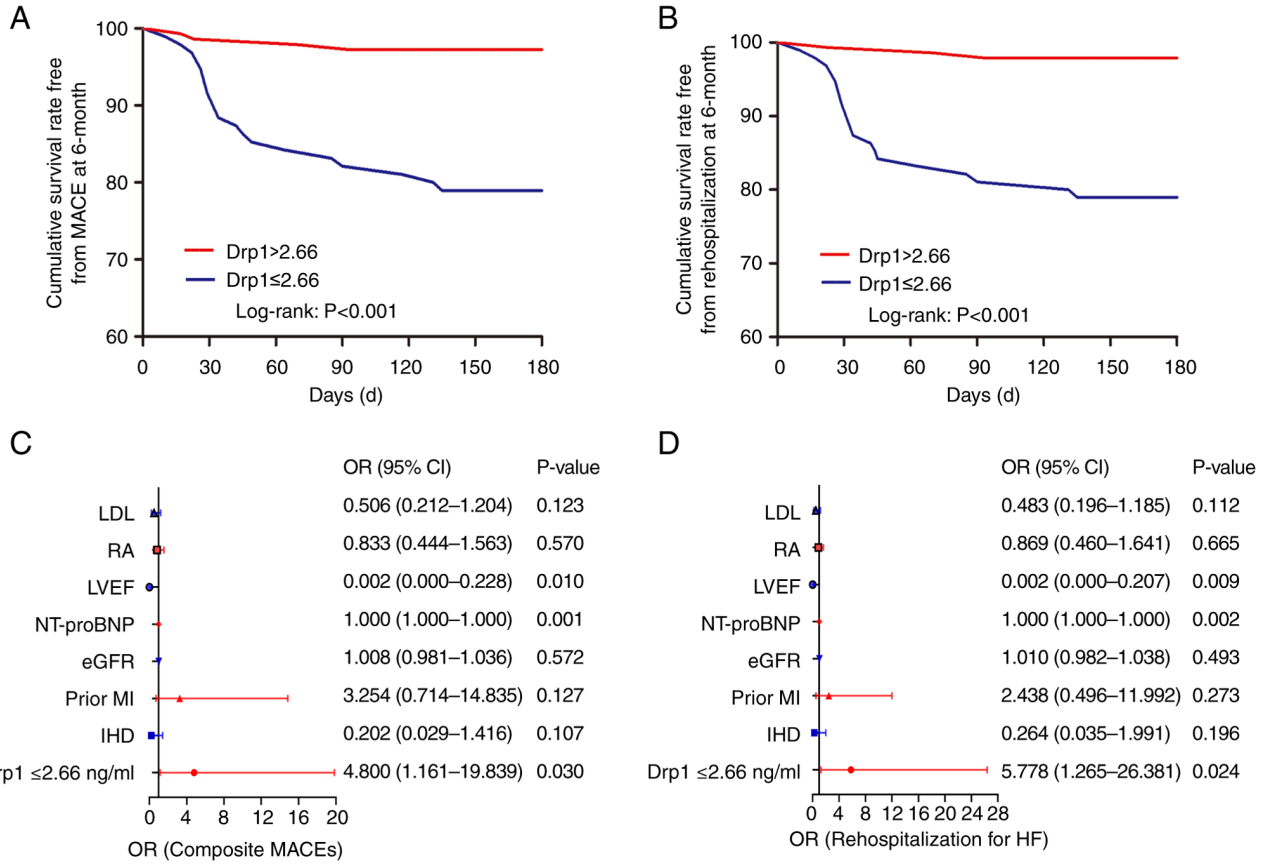

Figure 4. Survival curves and forest plots. (A) Kaplan-Meier curves for MACEs and (B) rehospitalization for HF in the low Drp1 group (Drp1 ≤2.66 ng/ml, red line) vs. the high Drp1 group (Drp1 >2.66 ng/ml; blue line) at 6-month follow-up. Forest plots revealing the association between Drp1 at the threshold of >2.66 ng/ml and (C) a composited MACE and (D) rehospitalization for HF. MACEs, major adverse cardiac events; HF, heart failure; OR, odds ratio; LDL, lipoprotein; RA, right atrium; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; IHD, ischemic heart disease.

kidneys (25,26). It is recognized for its pivotal role in regulating mitochondrial fission, a process integral to maintaining mitochondrial integrity (9). This regulation is critically important as it substantially influences cardiac metabolism and the mechanisms of programmed cell death (27). The key pathophysiological factors contributing to HF progression include both the reduction in contractile units and the diminished mitochondrial bioenergetics within surviving cardiomyocytes after myocardial injuries (28,29). Building on our previous research, restoring balance to mitochondrial fission by regulating Drp1 expression in the affected myocardial tissue could enhance cardiac metabolism and then mitigate apoptosis in MI (12). The current study indicated an association between lower serum levels of Drp1 and more pronounced cardiac structural anomalies, alongside deteriorated cardiac function. The findings correspond with earlier fundamental research that demonstrated the conditional suppression of Drp1 in mice leads to gradual LV enlargement followed by a notable decrease in EF (8). However, it is important to note that a majority of subjects in the Low Drp1 group (67.3%) had a history of MI, predisposing them to a high likelihood of developing HFrEF as a consequence of severe ROS-induced cellular damage. This might mainly account for the significantly decreased serum Drp1 concentrations and the deteriorated cardiac function observed in these participants. Moreover, low serum Drp1 concentrations were observed to have a positive association with a heightened risk of MACEs, predominantly due to a surge in the rate of rehospitalization. Indeed, epidemiological studies have previously reported comparable rates of mortality and morbidity in cases of HFpEF compared with HFrEF (30). Notably, despite a substantially higher prevalence of HFrEF in the group with low Drp1 levels (64.4% vs. 13.5%; P<0.001), only the rehospitalization rates increased correspondingly, whereas mortality rates remained unchanged.

By contrast, Chen *et al* (31) indicated that Drp1 could act as a regulator of hyperlipidemia, inflammation and myocardial injuries in rats with hyperlipidemia-MI by affecting mitochondrial dysfunction and NLRP3 expression. The low Drp1 group exhibited substantially reduced serum levels of total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C). These markers, integral to lipid metabolism, have a strong association with the fibrous cap thickness in lipid-rich plaques. Thinner caps can precipitate sudden cardiac events through the rupture of coronary atherosclerotic plaques (32). This association could further explain the lack of a significant difference in cardiac mortality rates between the two study groups. To the best of the authors' knowledge, sudden mortality is frequently a consequence of cardiovascular diseases, particularly due to mechanical complications or severe arrhythmias following a MI (33). Additionally, research had shown that Drp1-dependent mitochondrial autophagy is initially triggered but subsequently

suppressed in mouse hearts under pressure overload, a process that is critical in the progression of mitochondrial dysfunction and HF (34). Thus, in light of the logistic regression analysis in the present study, lower serum levels of Drp1 might serve as an independent prognostic indicator for MACEs in patients with HF.

There are several limitations in the design and conduct of the current study. Initially, despite incorporating data from 256 patients, the research was characterized by its single-center, prospective, observational nature, coupled with a relatively limited sample size. To enhance the robustness of the findings, future research would benefit from a larger-scale, multi-center, randomized trial with greater statistical power. Furthermore, the potential influence of oral medications on Drp1 expression cannot be entirely ruled out. This is particularly relevant concerning the use of Dapagliflozin (DAPA), which has been shown to modulate Drp1 expression in infarcted heart tissue (12). Despite no substantial disparity in the baseline utilization of DAPA between the low and high Drp1 groups, the origin of plasma Drp1 is yet to be determined, underscoring the need for further research. Additionally, a longer follow-up period is recommended to reinforce the established association. Finally, while white blood cell counts did not differ significantly between the groups, the absence of data on hypersensitive C-reactive protein and procalcitonin hinders a comprehensive assessment of these inflammatory markers and the prevention of measurement bias.

The findings of the present study revealed that individuals exhibiting diminished levels of serum Drp1 were more likely to experience pronounced cardiac structural irregularities and impaired heart functionality. Furthermore, a low serum Drp1 concentration was validated as an autonomous prognostic indicator, heightening the likelihood of MACE and recurrent hospital admissions in patients with HF irrespective of the underlying cause. Consequently, serum Drp1 could potentially act as a predictive biomarker for the clinical outcome of such all-comer HF cases and may also represent an innovative therapeutic avenue within the disease's pathological trajectory.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

GSM conceived the project and designed the present study. ZGF and YX assessed the patients for eligibility in terms of inclusion and exclusion criteria. ZGF, YX and MYJ performed the ELISA. SHH evaluated and recorded all clinical events. ZGF and CC performed the statistical analyses. MYJ, CC and YX constructed the figures. All authors analyzed and discussed the data. ZGF wrote the manuscript, and revision was by CC, GSM and SHH. All authors contributed to drafting the manuscript. GSM and SHH confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of Zhongda Hospital (Nanjing, China) approved the present study protocol (approval no. 2020ZDSYLL306-P01). Informed consent was obtained from all participants in the present study.

Patient consent for publication

All patients provided written informed consent for the publication of any data and/or accompanying images.

Competing interests

The authors declare that they have no competing interests.

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