Am J Transl Res 2022;14(7):4657-4665
www.ajtr.org /ISSN:1943-8141/AJTR0140868

Original Article

Diagnostic value of cardiac magnetic resonance imaging for myocardial fibrosis in patients with heart failure and its predictive value for prognosis

Guangyao Lin, Bei Dong, Yuzhou Li, Wenqi Huang

Medical Imaging Center, The First People's Hospital of Shangqiu City, No. 292, Kai Xuan Nan Road, Shangqiu 476100, Henan, China

Received November 30, 2021; Accepted February 28, 2022; Epub July 15, 2022; Published July 30, 2022

Abstract: Objective: To determine the diagnostic value of cardiac magnetic resonance imaging (CMRI) for myocardial fibrosis (MF) in patients with heart failure (HF) and its predictive value for prognosis. Methods: A total of 180 patients with heart failure who were hospitalized in the Cardiology Department of The First People's Hospital of Shangqiu City from September 2019 to May 2021 were selected and assigned to Group B (n=80) given levosimendan and Group A (n=100) given levosimendan combined with ivabradine hydrochloride. The cardiac function indicators (left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and left ventricular end-systolic diameter (LVESD) were measured by nuclear magnetic resonance (MRI). Myocardial fibrosis (MF)-related indicators (pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP), N-terminal propeptide of procollagen type III (PIIINP), connective tissue growth factor (CTGF), and hyaluronic acid (HA), inflammatory factors (Hs-CRP and IL-8) were measured using ELISA. Quality of life (QoL) and physical recovery (6-min walking test (6MWT), Fugl-Meyer Assessment (FMA), and Barthel index) of the two groups were compared. The late gadolinium enhancement (LGE) was used to analyze the occurrence of MF in patients. The patients were further divided into the LGE (+) group (cases) and LGE (-) group (cases). The changes of cardiac function indicators before treatment were analyzed, and their predictive value was analyzed. Results: Compared with Group B, Group A showed a lower incidence of complications, and presented a higher LVEF level and lower levels of LVESV, LVESD, ICTP, PIIINP, CTGF, HA, LN, and inflammatory factors. The area under the curves of LVESV, LVESD, and LVEF in predicting MF were all >0.7. Conclusion: Levosimendan combined with ivabradine hydrochloride can effectively alleviate MF in patients with MF, and CMRI has a good predictive value for MF in such patients, which is worthy of clinical promotion.

Keywords: Cardiac magnetic resonance imaging, heart failure, myocardial fibrosis, FMA, Barthel index

Introduction

Heart failure (HF) is a heterogeneous syndrome featured by dyspnea and fatigue. It occurs when abnormal cardiac structure and function, usually myocardial fibrosis (MF), gives rise to insufficient cardiac output or increased ventricular filling pressure [1, 2], Ischemic heart disease, diabetes mellitus, obesity, hypertension, and smoking are all likely to trigger HF [3]. HF shows an annually growing incidence and thus gives rise to an increasing mortality. It increases medical care cost and shortens patients' life span while compromising their quality of life (QoL) [4, 5]. Over the past few years, there is an increase in clinical trials associated with HF. These studies have substantially lowered the morbidity and mortality of patients, but patients still need repeated visits to hospitals due to various adverse clinical processes [6, 7]. For patients, early detection of symptoms of HF ensures a safe outcome. This study probed into the role of various imaging techniques in the therapy of patients with MF and their diagnostic value.

Imaging technology such as computed tomography (CT) and intracavitary elastic ultrasound are extensively adopted in diseases including cancers and tumors [8-10]. Various kinds of ultrasonic imaging have been verified to be able to image blood vessels in many clinical studies of cardiovascular and cerebrovascular diseases. However, the harmful radiation of these

technologies and their poor imaging degree and slightly insufficient spatial resolution are a nucnace [11]. Another imaging diagnosis method, magnetic resonance imaging (MRI), can provide a favorable resolution [12]. For all kinds of gynecological tumors, MRI combined with other methods usually provides a stronger sensitivity and specificity [13]. However, the related research on the role of MRI in HF and its diagnostic and prognostic value is rare. This study intended to determine the role and diagnostic value of cardiac MRI (CMRI) based on indicators including MF-related factors.

Methods

General data

A retrospective study was conducted on 180 patients with MF who were hospitalized in the cardiology department of The First People's Hospital of Shangqiu City from September 2019 to May 2021, and they were assigned to Group A (n=100) and Group B (n=80). The two groups were similar in clinical data, so they were comparable. Inclusion criteria: Patients who received therapy in our hospital for the first time because of HF. Patients who were mentally normal and able to express their feelings correctly; patients whou could cooperate effectively when undergoing the testing. Exclusion criteria: Patients with systolic HF triggered by alcohol, drugs, fast or slow arrhythmia, atrioventricular block, myocardial ischemia, or nutritional and metabolic factors, patients with other types of cardiomyopathy such as hypertrophic cardiomyopathy, patients with congenital heart disease, valvular disease or a history of surgical heart surgery.

This study was conducted with approval (no. 2018-24) of the ethics committee of The First People's Hospital of Shangqiu City and informed consent forms were signed by all patients and their families after understanding this study.

Therapy

Both groups were given routine treatments such as oxygen inhalation, cardiotonic, diuresis and vasodilation. Additionally, patients in Group B were treated with levosimendan injection (Qilu Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number: H20100043), with intravenous drip of 12 μg/kg in the first 10 minutes, then pumping by micropump for 1 hour at 0.1 μg/(kg min) and finally pumping for 24 hours at 0.2 μg/(kg min). Seven days later, the patients were treated again two more times. Patients in Group A were orally given ivabradine hydrochloride tablets (Chongqing Decheng Yongdao Pharmaceutical Co., Ltd., SFDA number: H20213822), 5 mg/time, twice a day, for 14 days.

Cardiac magnetic resonance imaging (CMRI)

Patients in both groups were examined by CMRI. The specific detection was as follows: A MR7503.0T scanner made by GE Company in the United States was used for scanning, and two doctors from the Radiology Department and Cardiology Department, respectively, were arranged to complete image analysis and post-processing and routinely collect cardiac function indicators of patients such as left ventricular end diastolic diameter (LVDd). Intravenous gadolinium contrast agent was adopted for judgment of the delayed enhancement of left ventricle to understand cardiac fibrosis. The late gadolinium enhancement (LGE) imaging was used to determine the presence of MF. The 180 patients were divided into the LGE (+) group and LGE (-) group.

ELISA

ELISA was adopted for quantifying pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP, ml062889), N-terminal propeptide of procollagen type III (PIIINP, ml063225), connective tissue growth factor (CTGF, ml025961-2), and hyaluronic acid (HA, ml057972), laminin (LN, ml028571), high sensitivity C-reactive protein (hs-CRP, QK1707), interleukin-8 (IL-8, ml028580). Hs-CRP kits were purchased from American R&D company, and other kits from Shanghai ELISA.

Outcome measures

Primary outcome measures

Cardiac function-related indicators: The cardiac function of all patients was detected at admission and after treatment. The related indicators included left ventricular end-systolic volume (LVESV), LVEF and left ventricular end-systolic diameter (LVESD).

MF-related indicators: MF-related indicators of the two groups were determined at admis-

Table 1. General data of the two groups

Item	Group A (n=100)	Group B (n=80)	t/X^2	*P*-value
Sex			0.29	0.593
Male	49 (49.00)	36 (45.00)		
Female	51 (51.00)	44 (55.00)		
Age (Y)	49.31±6.23	50.26±5.93	1.04	0.301
BMI	26.43±1.89	26.57±1.76	0.51	0.611
Working condition			0.29	0.59
Laid off/Retired	76 (76.00)	58 (72.50)		
Be on the job	24 (24.00)	22 (27.50)		
Hypertension			0.50	0.48
Yes	81 (81.00)	68 (85.00)		
No	19 (19.00)	12 (15.00)		
Diabetes mellitus			0.09	0.762
Yes	73 (73.00)	60 (75.00)		
No	27 (40.00)	20 (25.00)		
Smoking history			0.22	0.639
Yes	54 (54.00)	46 (57.50)		
No	46 (46.00)	34 (42.50)		
Drinking history			0.78	0.781
Yes	63 (63.00)	52 (65.00)		
No	37 (37.00)	28 (35.00)		
Dietary habit			0.48	0.488
Light	77 (77.00)	65 (81.25)		
Irritating	23 (23.00)	15 (19.75)		

sion and after 14 days of therapy, and compared.

Serum inflammatory factors: Before the commencement of the study and 30 days after the start of the study, 5 ml of fasting cubital venous blood was drawn from the patient in the morning, placed in a test tube without anticoagulant, and naturally agglutinated at room temperature for 20-30 minutes, 1500xg at 4y agglutinate 5 ml then the serum was separated, and placed at 20acefor testing; ELISA was used to detect the levels of various inflammatory factors, including hs-CRP and IL-8.

Physical recovery and QoL: The 6-min walking test (6WMT), Fugl-Meyer Assessment of motor function (FMA) score, and Barthel Index were adopted to evaluate the physical recovery of patients in the two groups before therapy and after 30 days of therapy [14, 15].

After 6 months of therapy, the QoL scale was adopted for evaluation of patients' QoL [16], and the results were compared.

The changes of cardiac function indicators of patients in the LGE (+) group (cases) and LGE (-) group (cases) before treatment were compared, and their predictive value was analyzed.

Secondary outcome measures

Complications: The incidence of complications after treatment, such as arrhythmia, respiratory infection, dislocation of left ventricular lead and shock, were recorded and compared between the two groups.

The clinical data of the two groups were compared.

Statistical analysis

In this study, data were analyzed statistically using SPSS 22.0 (EASYBIO Company, China). Inter-group comparison of counting data was carried out using the chi-squared test, and inter-group comparison of measurement data (mean ± SD) was conducted via the independent-samples T test. The receiver operating curve (ROC) was adopted to analyze the indicators of cardiac function in predicting fibrosis in patients. GraphPad Prism 8 was adopted for visualization of data into figures. $P<0.05$ indicates a significant difference.

Results

General data

No significant difference was observed between the two groups with regards to general data including gender and age (P>0.05, **Table 1**).

The improvement of cardiac function-related indicators in Group A was better than that in Group B

After therapy, the two groups showed significant decreases in LVESV and LVESD and a significant increase in LVEF (all P<0.05), with greatly lower levels of LVESV and LVESD in Group A than those in Group B and a greatly higher LVEF level in Group A than that in the Group B (all P<0.05, **Figure 1**).

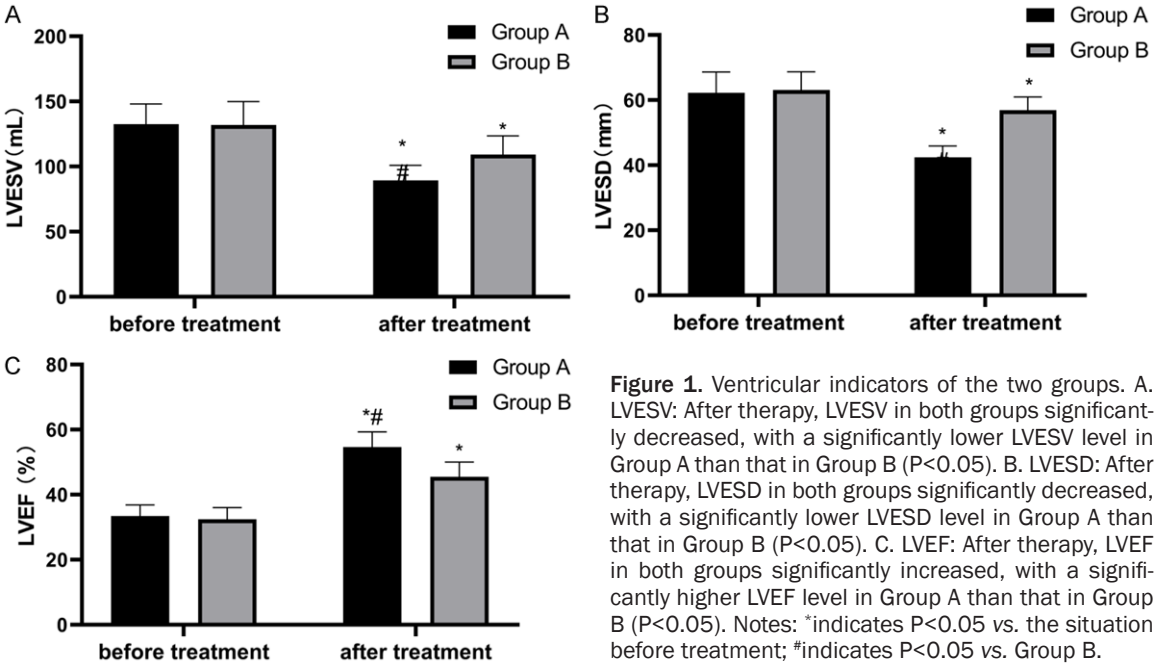

Figure 1. Ventricular indicators of the two groups. A. LVESV: After therapy, LVESV in both groups significantly decreased, with a significantly lower LVESV level in Group A than that in Group B (P<0.05). B. LVESD: After therapy, LVESD in both groups significantly decreased, with a significantly lower LVESD level in Group A than that in Group B (P<0.05). C. LVEF: After therapy, LVEF in both groups significantly increased, with a significantly higher LVEF level in Group A than that in Group B (P<0.05). Notes: *indicates P<0.05 *vs.* the situation before treatment; #indicates P<0.05 *vs.* Group B.

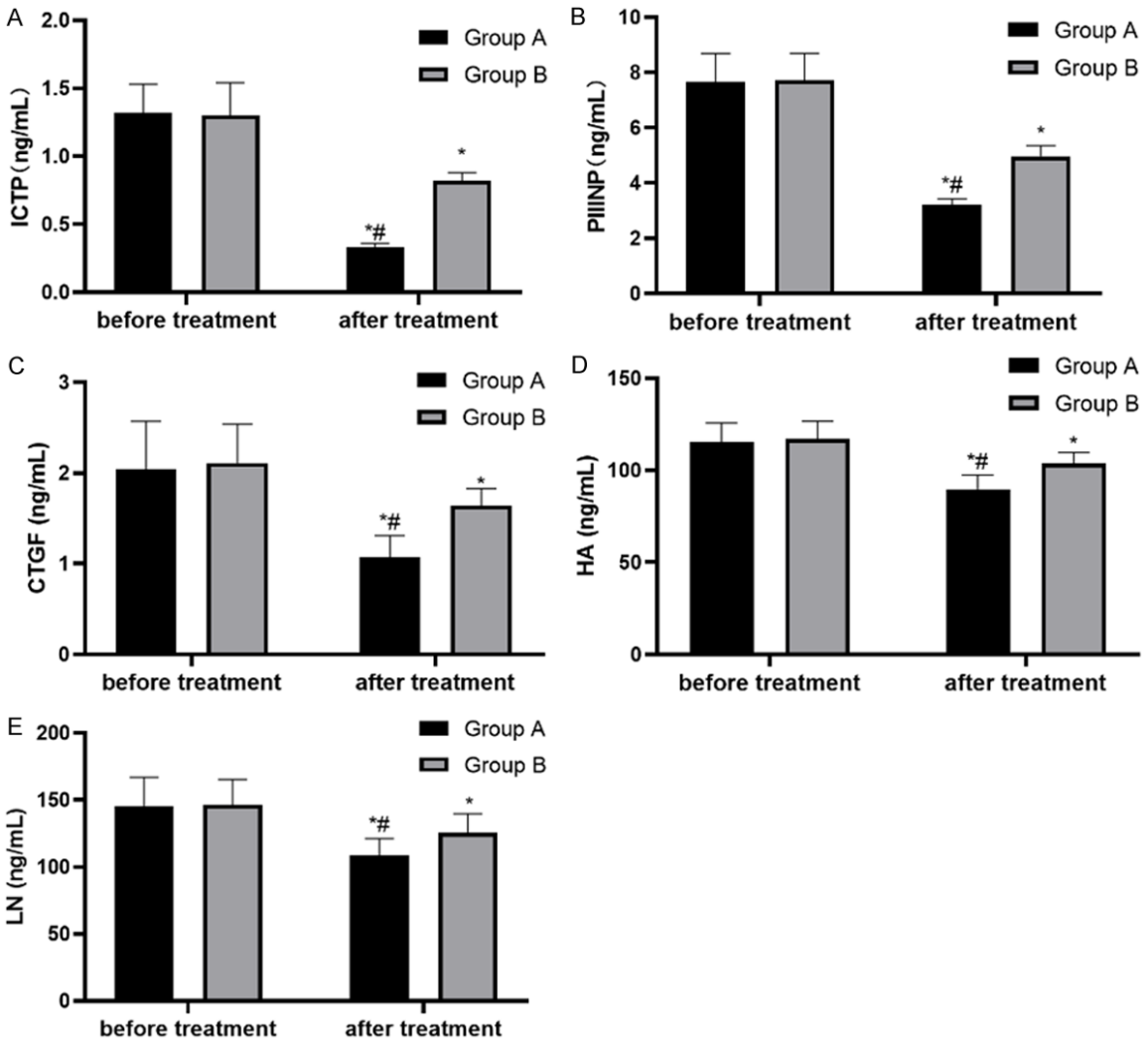

Figure 2. MF-associated indicators of the two groups. A. ICTP: After therapy, ICTP in both groups dropped significantly, with a lower ICTP level in Group A than that in Group B (P<0.05). B. PIIINP: After therapy, PIIINP in both groups dropped significantly, with a lower PIIINP level in Group A than that in Group B (P<0.05). C. CTGF: After therapy, CTGF in both groups dropped significantly, with a lower CTGF level in Group A than that in Group B (P<0.05). D. HA: After therapy, HA in both groups dropped significantly, with a lower HA level in Group A than that in Group B (P<0.05). E. LN: After therapy, LN in both groups dropped significantly, with a lower LN level in Group A than that in Group B (P<0.05). Notes: *indicates P<0.05 *vs.* the situation before treatment; #indicates P<0.05 *vs.* Group B.

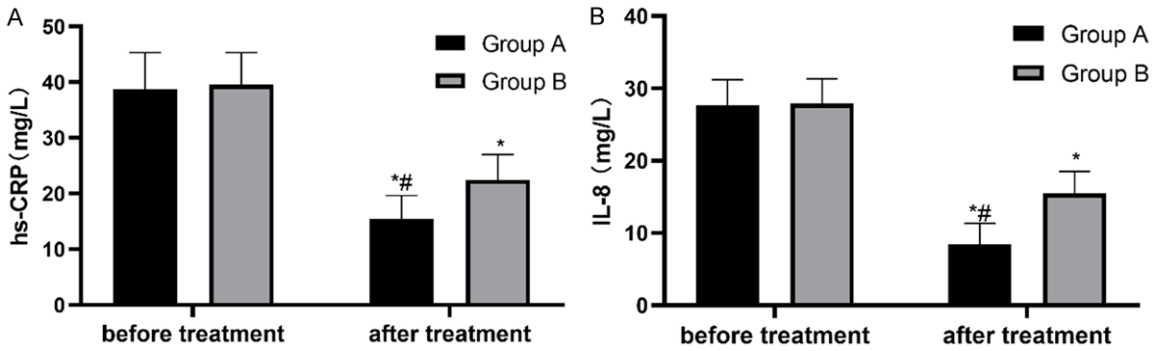

Figure 3. Serum inflammatory factors in the two groups. A. hs-CRP: After therapy, hs-CRP in both groups significantly dropped, with a lower hs-CRP level in Group A than that in Group B (P<0.05). B. IL-8: After therapy, IL-8 in both groups dropped significantly, with a lower IL-8 level in Group A than that in Group B (P<0.05) Notes: *indicates P<0.05 *vs.* the situation before treatment; #indicates P<0.05 *vs.* Group B.

The improvement of MF-related indicators in Group A was better than that in Group B

After therapy, ICTP, PIIINP, CTGF, HA and LN in both groups significantly dropped, with lower levels in Group A than those in Group B (all P<0.05, **Figure 2**).

The decrease in serum inflammatory factor levels in Group A was higher than that in Group B

According to comparison of serum inflammatory factors between the two groups, after therapy, hs-CRP and IL-8 in both groups dropped significantly, with lower levels in Group A than those in Group B (both P<0.05, **Figure 3**).

The physical recovery and improvement of QoL in Group A were better than those in Group B

According to comparison of physical recovery and QoL between the two groups, after 6 months of therapy, the total QoL score in both groups increased, with a higher total QoL score in Group A than that in Group B, and after 30 days of therapy, 6WMT, FMA, and Barthel index of both groups also significantly increased, with higher levels of 6WMT results, FMA score, and Barthel index in Group A than those in Group B (all P<0.05, **Figure 4**).

The incidence of MF in Group A was notably lower than that in Group B

Myocardial fibrosis in the two groups was statistically analyzed. The results showed a notably lower incidence of MF in Group A than Group B (P<0.05, **Table 2**).

The predictive value of cardiac function indicators for fibrosis in patients

According to the LGE imaging technology, patients with MF were divided into two groups, LGE (-) group (n=107) and LGE (+) group. The changes of cardiac function indicators were compared between the two groups before treatment. According to the results, the LGE + group showed notably higher LVES and LVESD levels and lower LVEF level than the LGE (-) group (**Figure 5**). Then we analyzed the value of LVESV, LVESD, and LVEF in predicting MF in patients through ROC curves. ROC curve analysis showed that the areas of under the curves of LVESV, LVESD, and LVEF for predicting MF were all larger than >0.7, but the area under the joint detection curve was 0.781 (**Figure 6**).

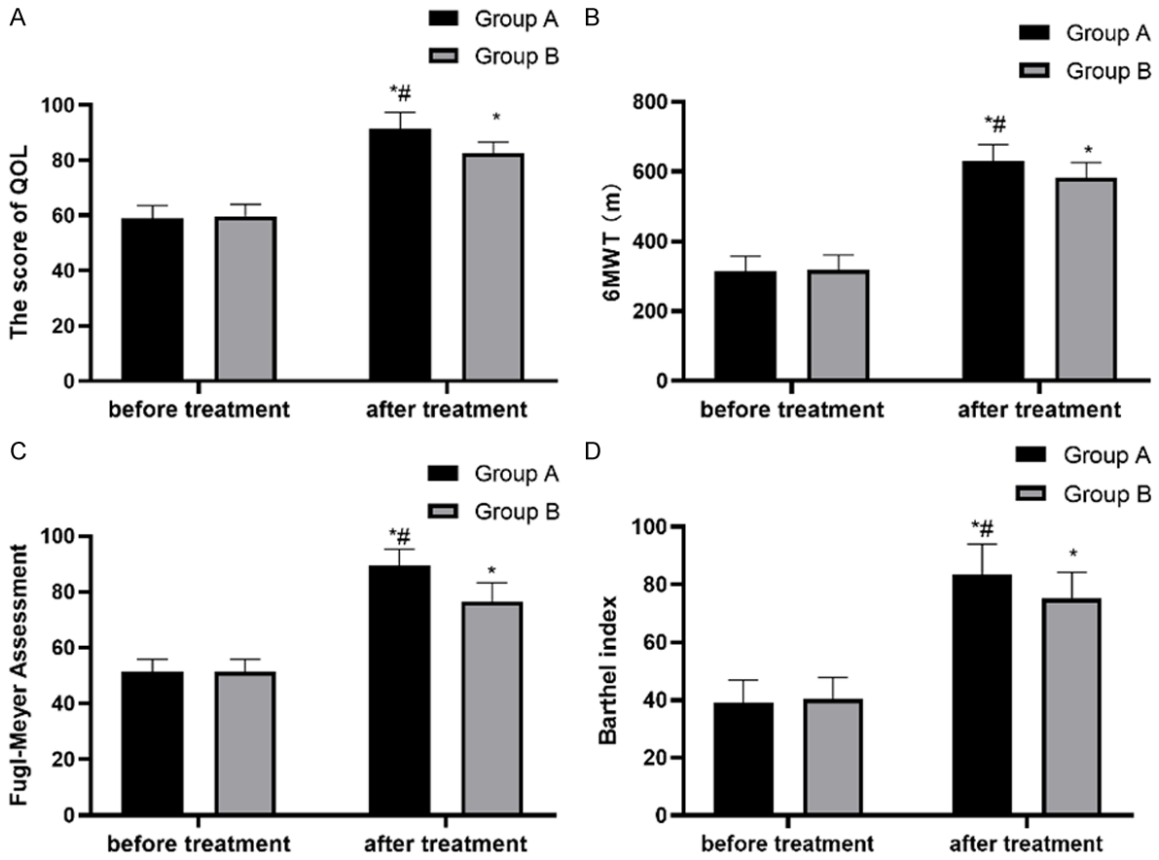

Figure 4. Physical recovery and QoL of the two groups. A. QoL: After 6 months of therapy, the total QoL score in both group increased, with a higher total QoL score in Group A than that in Group B ($P<0.05$). B. 6WMT: After 30 days of therapy, 6WMT results of both groups were improved, with better 6WMT results in Group A than those in Group B ($P<0.05$). C. FMA: After 30 days of therapy, FMA scores of both groups were improved, with better FMA scores in Group A than those in Group B. D. Barthel index: After 30 days of therapy, Barthel indicators of both groups were improved, with better Barthel index in Group A than that in Group B. Notes: *indicates $P<0.05$ *vs.* the situation before treatment; #indicates $P<0.05$ *vs.* Group B.

Table 2. Occurrence of MF

Group	LGE (-)	LGE (+)
Group A (n=100)	52	48
Group B (n=80)	55	25
χ^2	5.172	
P-value	0.023	

The incidence of complications in Group A was notably lower than that in Group B

Investigation of the incidence of complications in the two groups revealed a significantly lower incidence of complications in Group A than that in Group B ($P<0.05$, **Table 3**).

Discussion

HF is a severe complication, which can be triggered by diseases including type 2 diabetes mellitus [17, 18]. Despite a great process in the treatment of HF based on clinical research [19], not all patients have not obtained ideal therapy due to their significant differences in clinical features, biomarkers, genetic variation, and protein expression [20]. For patients with cardiovascular or cerebrovascular diseases, imaging detection before treatment is of crucial importance [21]. Here, we discussed the value of CMRI in detecting MF in patients with HF and the prognostic factors related to HF based on the results of this study.

Levosimendan is a new calcium sensitizer, which can enhance the myocardial contractility of patients with MF, but the curative effect is not good when being used alone [22]. Ivabradine hydrochloride can selectively act on patients' sinoatrial node, and thus reduce patients' heart rate without affecting their

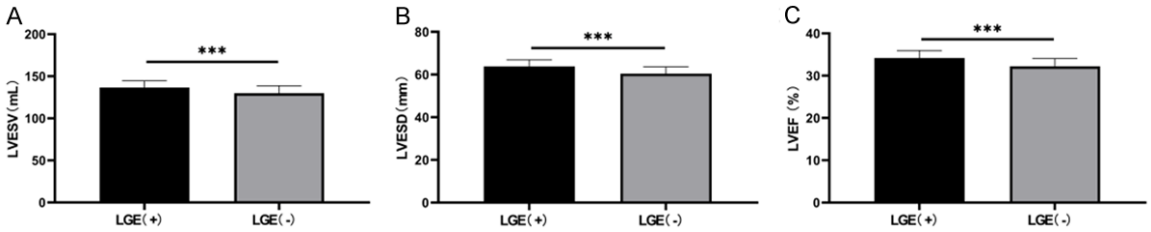

Figure 5. Cardiac function indicators in patients with MF. A. LVESV in patients with MF. B. LVESD in patients with MF. C. LVEF in patients with MF. ***P<0.001.

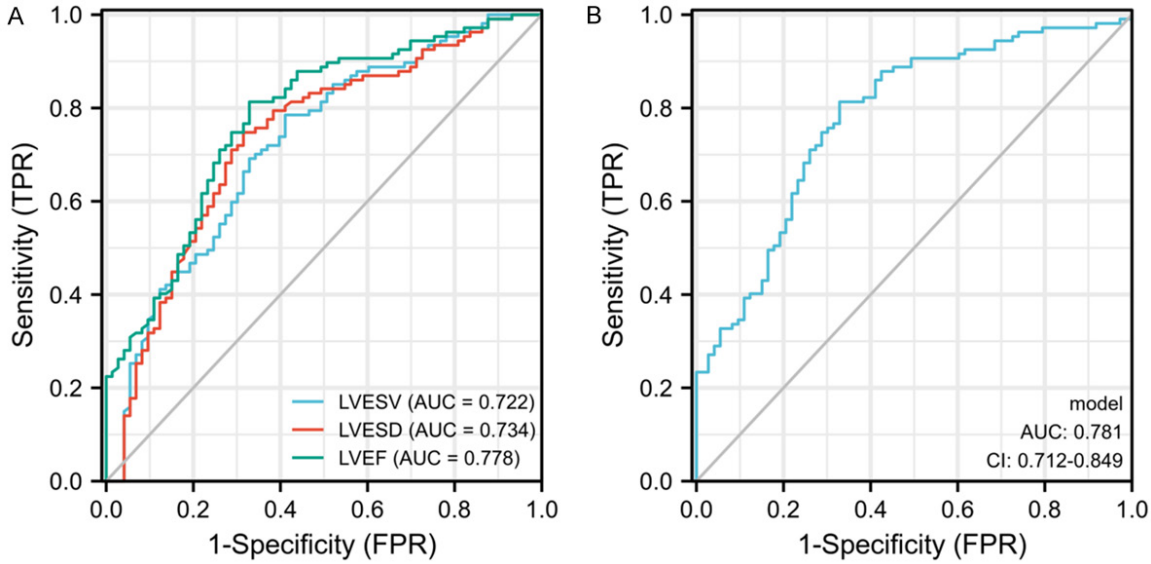

Figure 6. ROC curves of cardiac function indicators in predicting MF in patients. A. ROC curve of independent indicators in predicting MF in patients. B. ROC curve of joint indicator in predicting MF in patients.

Table 3. Comparison of the incidence of complications between the two groups

Item	Group A (n=100)	Group B (n=80)	X^2	*P*-value
Arrhythmia	0 (1.00)	3 (3.75)	-	-
Respiratory tract infection	2 (0.00)	3 (3.75)	-	-
Left ventricular lead dislocation	0 (0.00)	3 (3.75)		
Shock	1 (2.00)	7 (8.75)	-	-
Incidence of complications (%)	3 (3.00)	16 (20.00)	13.60	<0.001

myocardial contraction and intracardiac conduction system, which is effective in treating patients with chronic MF [23]. In this study, we found that the heart function and inflammatory response of patients with MF were significantly improved after levofloxacin combined with ivabradine hydrochloride. This is because irvabradine hydrochloride can selectively block the F channel of P cells in the sinoatrial node, slow down its automatic depolarization and regulate heart rate, but does not affect the myocardial contractility and blood pressure of patients [24]. At the same time, it can also improve the left ventricular remodeling, improve the cardiac function, prolong the left ventricular diastolic filling time and increase the coronary blood flow [25].

For patients with HF, MF is a crucial factor that triggers the deterioration of the disease. MF can trigger impairment of the patients' heart function and then the abnormal internal structure of the heart, and finally give rise to the impairment of ventricular diastolic or systolic function, further worsening the disease [26]. In this study, Group A showed notably lower MF-related indicators and a lower incidence of MF than Group B, indicating better relieved MF

and better ventricular function recovery in Group A than in Group B. The inflammatory process mediated by inflammatory factors has a great relationship with patients' MF. The increase of inflammatory factors and the further aggravation of inflammatory reaction will easily induce myocardial remodeling, leading to the further deterioration of patients' MF. In our analysis, we also found that the levels of serum inflammatory factors decreased notably after treatment, indicating that levosimendan combined with Irvabradine hydrochloride can significantly improve cardiac function in patients with chronic MF, reduce the inflammatory response and lower the incidence of MF in such patients.

In this study, we also analyzed the changes of cardiac function in patients with MF before treatment. Through the analysis of cardiac function indicators, it was found that before treatment, the LGE (+) group showed notably higher LVESV and LVESD and lower LVEF than the LGE (-) group. The results show that LVESV, LVESD and LVEF can be used as predictors of MF. In order to further verify their value, we draw corresponding ROC curves. The results showed that the area under the curves of LVESV, LVESD and LVEF in predicting MF was more than 0.7. This suggests that LVESV, LVESD and LVEF can be used as potential indicators for predicting MF. However, in this analysis, we also found that the area under the joint detection curve of the three indicators was not notably different from that of individual detection, which implies that joint detection will not increase the predictive value.

This study still has some limitations. As a retrospective study, we did not follow the patients for a period of time. In addition, as a retrospective study, the results of sample analysis may be biased. Therefore, we hope to carry out prospective studies in the future to improve our conclusions.

To sum up, levosimendan combined with irvabradine hydrochloride can effectively improve MF in patients with HF, and CMRI has a good predictive value for MF in patients with HF, which is worth popularizing in clinic.

Disclosure of conflict of interest

None.

Address correspondence to: Guangyao Lin, Medical Imaging Center, The First People's Hospital of Shangqiu City, No. 292, Kai Xuan Nan Road, Shangqiu 476100, Henan, China. Tel: +86-182-72685568; E-mail: linguangyao@126.com

References

[1] Groenewegen A, Rutten FH, Mosterd A and Hoes AW. Epidemiology of heart failure. Eur J Heart Fail 2020; 22: 1342-1356.

[2] Martin N, Manoharan K, Thomas J, Davies C and Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev 2018; 6: CD012721.

[3] Warden BA, Steiner J, Camacho A, Nguyen K, Purnell JQ, Barton Duell P, Craigan C, Osborn D and Fazio S. Optimizing sodium-glucose cotransporter 2 inhibitor use in patients with heart failure with reduced ejection fraction: a collaborative clinical practice statement. Am J Prev Cardiol 2021; 6: 100183.

[4] Li Y, Wang Y, Zou M, Chen C, Chen Y, Xue R, Dong Y and Liu C. AMPK blunts chronic heart failure by inhibiting autophagy. Biosci Rep 2018; 38: BSR20170982.

[5] AlHabeeb W, Al-Ayoubi F, AlGhalayini K, Al Ghofaili F, Al Hebaishi Y, Al-Jazairi A, Al-Mallah MH, AlMasood A, Al Qaseer M, Al-Saif S, Chaudhary A, Elasfar A, Tash A, Arafa M and Hassan W. Saudi Heart Association (SHA) guidelines for the management of heart failure. J Saudi Heart Assoc 2019; 31: 204-253.

[6] Kim MS, Lee JH, Kim EJ, Park DG, Park SJ, Park JJ, Shin MS, Yoo BS, Youn JC, Lee SE, Ihm SH, Jang SY, Jo SH, Cho JY, Cho HJ, Choi S, Choi JO, Han SW, Hwang KK, Jeon ES, Cho MC, Chae SC and Choi DJ. Korean guidelines for diagnosis and management of chronic heart failure. Korean Circ J 2017; 47: 555-643.

[7] Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M, Mohamed MO, Ahmed FZ, Deanfield J, de Belder M, Gale CP and Mamas MA. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. Eur Heart J Qual Care Clin Outcomes 2021; 7: 378-387.

[8] Wang L, Li Q, Wang XM, Hao GY, Jie B, Hu S and Hu CH. Enhanced radiation damage caused by iodinated contrast agents during CT examination. Eur J Radiol 2017; 92: 72-77.

[9] Raaschou H, Pilegaard M, Klausen L and Danielsen AK. Oncology patients' experience of a routine surveillance CT examination: relationships and communication. Radiography (Lond) 2019; 25: 308-313.

[10] Alcazar JL, Pineda L, Caparros M, Utrilla-Layna J, Juez L, Minguez JA and Jurado M. Transvaginal/transrectal ultrasound for preoperative identification of high-risk cases in well- or moderately differentiated endometrioid carcinoma. Ultrasound Obstet Gynecol 2016; 47: 374-379.
[11] Yu J, Lavery L and Kim K. Super-resolution ultrasound imaging method for microvasculature in vivo with a high temporal accuracy. Sci Rep 2018; 8: 13918.
[12] Marion-Audibert AM, Vullierme MP, Ronot M, Mabrut JY, Sauvanet A, Zins M, Cuilleron M, Sa-Cunha A, Levy P and Rode A. Routine MRI with DWI sequences to detect liver metastases in patients with potentially resectable pancreatic ductal carcinoma and normal liver CT: a prospective multicenter study. AJR Am J Roentgenol 2018; 211: W217-W225.
[13] Alcazar JL, Gaston B, Navarro B, Salas R, Aranda J and Guerriero S. Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: a systematic review and meta-analysis. J Gynecol Oncol 2017; 28: e86.
[14] Kim WS, Cho S, Baek D, Bang H and Paik NJ. Upper extremity functional evaluation by Fugl-Meyer assessment scoring using depth-sensing camera in hemiplegic stroke patients. PLoS One 2016; 11: e0158640.
[15] Silveira LTYD, Silva JMD, Soler JMP, Sun CYL, Tanaka C and Fu C. Assessing functional status after intensive care unit stay: the Barthel Index and the Katz Index. Int J Qual Health Care 2018; 30: 265-270.
[16] Shu Q, Wu L, Zhang R, Zhang Q, Huang J and Meng Y. Age-dependent changes in cardiac performance, motor function, QoL, and mental status in metoprolol-treated chronic heart failure patients. Sci Rep 2019; 9: 453.
[17] Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M, Mohamed MO, Ahmed FZ, Deanfield J, de Belder M, Gale CP, Mamas MA. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. Eur Heart J Qual Care Clin Outcomes 2021; 7: 378-387.
[18] Kenny HC and Abel ED. Heart failure in type 2 diabetes mellitus. Circ Res 2019; 124: 121-141.
[19] Askoxylakis V, Thieke C, Pleger S, Most P, Tanner J, Lindel K, Katus HA, Debus J and Bischof M. Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. BMC Cancer 2010; 10: 105.
[20] Cao TH, Jones DJL, Voors AA, Quinn PA, Sandhu JK, Chan DCS, Parry HM, Mohan M, Mordi IR, Sama IE, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Metra M, Ponikowski P, Samani NJ, Van Veldhuisen DJ, Zannad F, Lang CC and Ng LL. Plasma proteomic approach in patients with heart failure: insights into pathogenesis of disease progression and potential novel treatment targets. Eur J Heart Fail 2020; 22: 70-80.
[21] Zhou D, Li J, Liu D, Ji LY, Wang NQ, Deng J, Wang JC, Ye M and Zhao XH. Irregular surface of carotid atherosclerotic plaque is associated with ischemic stroke: a magnetic resonance imaging study. J Geriatr Cardiol 2019; 16: 872-879.
[22] Cholley B, Levy B, Fellahi JL, Longrois D, Amour J, Ouattara A and Mebazaa A. Levosimendan in the light of the results of the recent randomized controlled trials: an expert opinion paper. Crit Care 2019; 23: 385.
[23] Naguib MJ, Elsayed I and Teaima MH. Simultaneous optimization of oral and transdermal nanovesicles for bioavailability enhancement of ivabradine hydrochloride. Int J Nanomedicine 2021; 16: 2917-2931.
[24] Ma D, Xu T, Cai G, Wu X, Lei Z, Liu X, Li J and Yang N. Effects of ivabradine hydrochloride combined with trimetazidine on myocardial fibrosis in rats with chronic heart failure. Exp Ther Med 2019; 18: 1639-1644.
[25] Hu DY, Huang DJ, Yuan ZY, Zhao RP, Yan XW and Wang MH; Chinese Investigators of SHIFT Study. Efficacy and safety analysis of ivabradine hydrochloride treatment of Chinese patients with chronic heart failure: subgroup analysis of Chinese patients in the SHIFT study. Zhonghua Xin Xue Guan Bing Za Zhi 2017; 45: 190-197.
[26] Edelmann F, Knosalla C, Mörike K, Muth C, Prien P and Störk S. Chronic heart failure. Dtsch Arztebl Int 2018; 115: 124-130.