

Heart failure classification in clinical practice: time to redefine?

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Heart failure (HF) represents one of the major disease burdens worldwide now. Congestive HF-related medicare expenditures remain high, constituting a global challenge. After manifestation, patients with HF face significantly increased risk of recurrent hospitalizations, morbidity, and mortality despite modern therapy strategies.^[1]

Numerous definitions of HF have been proposed previously. Currently, the HF definition defined in the 2016 Guideline of the European Society of Cardiology is widely accepted, which is based on left ventricular functional assessment and symptoms. Patients are divided according to left ventricular ejection fraction (LVEF) to HF with reduced ejection fraction (HFrEF): HF with LVEF $\leq 40\%$; HF with mid-range ejection fraction (HFmrEF): HF with LVEF 41% to 49%; HF with preserved ejection fraction (HFpEF): HF with LVEF $\geq 50\%$.^[2] The New York Heart Association (NYHA) class defines severity of HF symptoms during exercise or at rest. Both classifications have therapeutic and prognostic impact.^[3] A new position paper proposed an “universal definition and classification of HF,”^[4] which viewed HF as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. HF is also staged as: at-risk for HF (Stage A), pre-HF (Stage B), symptomatic HF (Stage C), and advanced HF (Stage D). Finally, HF patients are divided into the following groups according to LVEF: HFrEF: symptomatic HF with LVEF $\leq 40\%$; HFmrEF: symptomatic HF with LVEF 41% to 49%; HFpEF: symptomatic HF with LVEF $\geq 50\%$; and symptomatic HF with a baseline LVEF $\leq 40\%$, a ≥ 10 -point increase from baseline LVEF, and a second measurement of LVEF $> 40\%$.

Until now, only HFrEF patients have benefited from therapy recommended in the guidelines based on random-

ised controlled trials. Newly finished randomized controlled clinical trials showed some promising results for HFpEF. In HF patients with preserved LVEF ($\geq 45\%$), sacubitril/valsartan did not significantly improve the outcome of total HF hospitalizations and cardiovascular death in the PARAGONHF trial. But in the pre-specified subgroup analysis, there are evidences of benefit in women and patients with LVEF $\leq 57\%$.^[5] It was reported that sodium-glucose cotransporter 2 inhibitor empagliflozin met its primary endpoint and demonstrated significant risk reduction with empagliflozin for the composite of cardiovascular death or hospitalization for HF in adults with HFpEF. The EMPEROR-Preserved phase III trial (NCT03057951) and the detailed results will be presented at ESC congress 2021.^[6] Thus, new therapy options might be available in the near future for HFpEF patients.

One of the main reasons for the neutral results of randomized controlled clinical trials might be the multiple etiologies of HFpEF. Furthermore, neurohormonal activation, which is a unique feature in HF patients with reduced left ventricular systolic function, is not that prevalent among HFpEF as compared to HFrEF patients. Thus, it is not surprising that the neurohormonal inhibition-oriented medication, which is effective for treating HFrEF, may fail in HFpEF patients.

To overcome this unsatisfactory situation, an alternative etiology-oriented classification might be discussed in HFpEF patients. Indeed, just recently, a new coding system has been proposed based on the etiology of HFpEF.^[7] Briefly, this etiology-oriented classification divides HFpEF patients as: HFpEF-1 (vascular-related HFpEF), HFpEF-2 (cardiomyopathy-related HFpEF), HFpEF-3 (right heart and pulmonary-related HFpEF), HFpEF-4 (valvular- and rhythm-related HFpEF), and HFpEF-5 (extracardiac disease-related HFpEF). The

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DOI:
10.1097/CM9.0000000000001823

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Chinese Medical Journal 2022;135(9)

Received: 16-03-2021; Online: 20-01-2022 Edited by: Ningning Wang and Yuanyuan Ji

hypothesis for this classification is that HFpEF patients may particularly benefit from a therapy guided by the diagnosis and treatment of the underlying disease. Thus, clinical studies will be needed on HFpEF patients classified according to their underlying disease.

Etiology certainly is just one aspect in the management of HF. Duration of the disease and severity of symptoms have previously proven important for treatment success. In line with Ge proposal,^[7] one might therefore envision to extend a similar etiology-oriented HF definition to the whole HF spectrum, combining LVEF, etiology, and symptom aspects in one faceted classification system. In our proposed Etiology-Systolic function-NYHA classification Heart Failure (ESN-HF) coding system, the first parameter of definition might be used to define the etiologies of the HF patients, followed by LVEF, amended by symptoms. The new classification proposal might result as follows: I–V represents the etiology, A–D represents EF (pEF, mrEF, rEF, and impEF), and 1 to 4 represents the NYHA classification. HFpEF, HFmrEF, and HFrEF are defined according to the current guidelines.^[2,4] HF with baseline LVEF (HFimpEF) is defined as follows to cover the whole spectrum of improved LVEF during the disease course in HF patients with a LVEF <50% at baseline: symptomatic HFimpEF <50% and a ≥10-point increase from baseline LVEF.

In summary, HF is an extremely complex systemic syndrome, which is not yet well reflected in the definitions used in clinical practice today. Distribution of a superordinate multifaceted classification system to widespread clinical use could greatly improve the accurateness of the diagnosis, thus simplifying patient risk stratification at the same time, which might substantially improve an etiology-and stage-oriented therapeutic decision making based on this simplified and comprehensive diagnosis system. Future studies are encouraged to validate if this approach could be useful or not as a general concept in improving the medicare of HF patients.

Conflicts of interest

None.

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How to cite this article: Hu K, Ertl G, Frantz S, Nordbeck P. Heart failure classification in clinical practice: time to redefine?. *Chin Med J* 2022;135:1039–1040. doi: 10.1097/CM9.0000000000001823