*Full research paper*

European Journal of Preventive Cardiology

ESC European Society of Cardiology

# Role of gender, age and BMI in prognosis of heart failure

European Journal of Preventive Cardiology
2020, Vol. 27(2S) 46–51

DOI: 10.1177/2047487320961980
journals.sagepub.com/home/cpr


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**Abstract**

The prognostic stratification of heart failure remains an urgent need for correct clinical management of the affected patients. In fact, due to the high mortality and morbidity rates, heart failure constantly requires an updated and careful management of all aspects that characterise the disease. In addition to the well-known clinical, laboratory and instrumental characteristics that affect the prognosis of heart failure, gender, age and body mass index have a different impact and deserve specific insights and clarifications. At this scope, the metabolic exercise cardiac kidney index score research group has produced several works in the past, trying to identify the role of these specific factors on the prognosis of heart failure. In particular, the different performances in the cardiopulmonary exercise test of specific categories of heart failure patients, such as women, elderly and obese or overweight individuals, have requested dedicated evaluations of metabolic exercise cardiac kidney index score power.

**Keywords**

Gender, age, BMI, chronic heart failure, metabolic exercise cardiac kidney index (MECKI) score

Received 21 July 2020; accepted 2 September 2020

## Peculiarities of heart failure in women

Cardiovascular disease (CVD) is the leading cause of mortality[1] and morbidity in Europe and worldwide. Every year, almost 50% of deaths in Europe are caused by CVD, 42% in men and 51% among women.[1] The misleading idea that women are protected lifelong against CVD is the cause of this disparity. Among CVDs, chronic heart failure (CHF) is one of the most significant causes of hospitalisation[2] and mortality in women.[3] CHF in women has peculiar characteristics in the clinical presentation, response to treatment (pharmacological and electrical devices) and use of evidence-based recommendations, which create disparities between men and women.[4]

The risk stratification and prognostic evaluation of CHF in women is a challenge for clinicians. The actual prognostic scores are, in fact, lacking a specific sex-oriented assessment. The need for a more suitable prognostic instrument arises from the evidence that as women have specific cardiovascular risk factors[5] and peculiar CVDs, the prognostic instruments must take into account the possible different impact of the single item on women's prognosis.

Frequently, women have typical heart failure with preserved ejection fraction (HFpEF);[3,6] in fact, women have less ischaemic myocardial disease (more frequent in men and related to a reduced ejection fraction) and later in life symptom onset. In women, arterial

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hypertension and diabetes are the most important cardiovascular risk factors associated with HFpEF, which affects small myocardial vessels and causes diastolic heart failure (HF).

Moreover, the impact of CHF on quality of life is more impairing and stronger in women than in man, probably due not only to the presence of CHF itself, but also to a higher degree of comorbidity related to older age.[7]

In addition, women are at risk of specific CHF causes such as peripartum heart disease (gestation diabetes and hypertension, preterm delivery) and, in the case of breast cancer, chemotherapy and radiotherapy-induced cardiomyopathy, associated with the use of anthracyclines and human epidermal growth factor receptor 2 (HER2) monoclonal inhibitors and X-ray locoregional treatment.[4,5]

Moreover, in randomised clinical trials women are often underrepresented,[4] so clinicians frequently administer therapies the efficacy of which are not proved in real-life female patients, who are often older, with HFpEF, with different HF aetiology, with different pharmacokinetics, a better response to resynchronisation therapy,[8] a higher incidence of complications after implantable cardioverter defibrillator (ICD) implantation[9] and less orthotopic heart transplantation access.[10] In addition, age at menopause should be considered an important piece of information to acquire, in order to understand better the correct timing of changes in the cardiovascular system due to the progressive reduction in oestrogens[11] that are able to lead to microvessel damage and, ages later, to HFpEF.

Prognostic stratification plays a dramatic role in the clinical management and in the indication for orthotopic heart transplantation. In clinical practice the most used prognostic scores are the Seattle heart failure model (SHFM),[12] the heart failure survival score (HFSS),[13] the meta-analysis global group in chronic heart failure (MAGGIC)[14] and the metabolic exercise cardiac kidney index (MECKI) score.[15]

The HFSS and MECKI score include some cardiopulmonary exercise testing (CPET) parameters, in order better to analyse the patient's functional status. Oxygen consumption ($VO_2$) and the ventilation/carbon dioxide production ($VE/VCO_2$) slope are important predictors of HF prognosis.[16]

Some parameters used in these prognostic scores have important differences in women. For example, the ejection fraction is an important item in all these scores, but it could be a bias because women often have HFpEF, so with a better ejection fraction than men but a worse functional impairment and more severe symptoms. Moreover, the HFSS and MECKI score use peak oxygen uptake (MECKI score peak $VO_2$% predicted) from CPET (Table 1).

Women have better survival and prognosis, despite a comparatively lower peak $VO_2$; this raises doubt about the accuracy of risk assessment by CPET in women. Accordingly, Corrà et al. checked whether the predictive role of well-known CPET risk indexes; that is, peak $VO_2$ and ventilatory response ($VE/VCO_2$ slope), are sex independent and if sex-related characteristics that impact outcome in HF should be considered as associations that may confound the effect of sex on survival.[17] The low peak $VO_2$ and female association with a better outcome in HF might be counterfeit; the female prognostic advantage is lost when sex-specific differences are correctly taken into account with propensity score matching. So, with propensity score matching, female sex was not prognostically informative, but the $VE/VCO_2$ slope was, suggesting that for an effective and efficient HF model, adjustment must be made for sex-related characteristics.[17]

In addition, the MECKI score research group[18] has recently produced a specific paper in which the authors tried to ameliorate the predictive role of the $VE/VCO_2$ slope for gender and even the age of patients. In fact, they have produced $VE/VCO_2$ slope prediction equations based on a large population of healthy subjects, then applying formulas to the MECKI score database. As result, the authors observed that $VE/VCO_2$, as a percentage of predicted value, resulted in stronger prognostic prediction in HF patients, but with a power similar to that observed using absolute $VE/VCO_2$ values. However, in patients with severe HF (with low peak $VO_2$), data reported as percentages of predicted value have a stronger prognostic capacity.

Accurate diagnosis, appropriate risk management and monitoring are key in the prevention and treatment of CVD; however, the assessment tools used must also be useful or at least assessed for utility in both sexes. In other words, going forward, we need to evaluate sex-specific reference intervals or cut-offs for laboratory tests used to assess CVD to help close the diagnostic gap between men and women.

## Impact of ageing on CHF prognosis and risk stratification

The aetiology of the decompensation does not present substantial differences between young and elderly patients; in the latter group, however, the disease is often multifactorial and frequently presents comorbidities that could alter, and also confuse, the clinical picture and the evaluation of the patient.

The CHF in this group of patients represents the convergence of multiple factors: (a) age-induced

**Table 1.** Main characteristics of MECKI score registry population according to the enrolment steps.

| | *n* | Age (years) | | Men (*n*) | % | $VO_2$/kg (ml/min/kg) | Events (*n*) | % | Cardiovascular deaths (*n*) | % | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2019** | 7004 | 61 | ±13 | 5740 | 82 | 14.8±4.8 | 1899 | 27 | 1419 | 20 | 1421 (627–2713) |
| **2012** | 2716 | 60 | ±13 | 2285 | 84 | 14.4±4.4 | 598 | 22 | 618 | 23 | 1040 (513–1811) |

MECKI: metabolic exercise cardiac kidney index; $VO_2$: oxygen consumption.

changes in the cardiovascular system; (b) lifelong lifestyle habits; (c) the increased survival of people with conditions such as diabetes and high blood pressure, which predispose to decompensation; (d) the increase in the prevalence of the same heart diseases such as, for example, ischaemic heart disease, valve disease, hypertensive heart disease; (e) comorbidities (atrial fibrillation, renal dysfunction, chronic obstructive pulmonary disease, peripheral vascular disease and orthopaedic disorders).[19]

Therefore, the prognostic stratification of these patients can represent a challenge and the models available are not always of any benefit to the clinician to support the decision.

Anyway, the MECKI score was increased in older patients, but its prognostic value was maintained independently of patient age, with a similar predictive power across age groups. Indeed, this aspect could be due to the presence of the modification of diet in renal disease (MDRD) equation in the calculation of the patient's renal function, which is correct for the patient's age and sex; so the MECKI score can be applied to a broad range of patients with chronic HF.[19]

During CPET, reduced stroke volume and chronotropic incompetence led to suboptimal exercise performance in elderly patients, with a peak $VO_2$ less than 14 mL/min/kg. In this population, characterised by more events, the use of the $VE/VCO_2$ slope as a percentage of predicted value significantly increased its prognostic power, and it allowed the correct reclassification of 6.6% of cases, as recently described by the MECKI score research group.[18] Thus, it is very desirable that the $VE/VCO_2$ slope should be reported as a percentage of predicted value at least in this category of HF patients.

The MECKI score increased according to age and also maintained its prognostic value in older patients.[19]

The greater deconditioning, typical of older patients, is the possible cause of these data.

## Role of body mass index in prognosis of HF

The relationship between obesity and CVDs, among which is HF, is widely recognised.[20]

Overweight and obesity are diagnosed by a body mass index (BMI) of 25 kg/m$^2$ or higher and a BMI of 30 kg/m$^2$ or higher, respectively. However, BMI should be considered as a size of heaviness rather than of body composition, so that an increased BMI is not necessarily equivalent to an increased fat mass as happens for athletes. This can explain why the lack of accuracy of the BMI in predicting prognosis has been observed in some extreme conditions of chronic diseases, as in sarcopenic obesity, a combined increase of fat mass and muscle loss related to poor outcomes, and in obesity with a preserved muscle mass, which on the contrary exhibits a better prognosis.

Consequently, BMI is an inaccurate measure of the extent of obesity as it provides no information on fat distribution, which is noteworthy information in cardiovascular risk.

In order to overcome this inaccuracy of the BMI, some authors proposed the use of the body surface area (BSA) as a better index of metabolic mass unbiased by pathological adipose mass in CHF. BSA was assessed in the HF long-term registry of the Heart Failure Association of the European Society of Cardiology.[21] In CHF patients of both genders total and cardiovascular mortality, but not HF hospitalisations were inversely correlated with BSA levels.

The close correlation between HF and obesity observed in the Framingham Heart Study was characterised by an increased risk of disease in men and women by 5% and 7%, respectively, for a continuous increase in BMI by 1 kg/m$^2$.[22]

The span of morbid obesity is also closely related to the prevalence of HF so that after 20 years it accounts for 70% and after 30 years for 90% of the patients. The prevalence of obesity is different in the various forms of HF: it is present in 85% of patients affected by HFpEF, but in less than 50% of those with heart failure with reduced ejection fraction (HFrEF).[23]

Hormones and proinflammatory cytokines with well-known cardiodepressant properties (interleukin (IL) 1b, tumour necrosis factor $\alpha$, and IL-18) produced by the adipose tissue have been supposed to play a role in the relationship between HFpEF and obesity.[24]

Conversely, the relationship between HFrEF and obesity is unclear due to the influence of numerous confounding factors.

Obesity may lead to HF fundamentally through haemodynamic changes linked to the activation of the renin–angiotensin–aldosterone system, increased activity of both the sympathetic nervous system and the mineralocorticoid receptor expression, production of inflammatory cytokines and acute-phase proteins.[24]

However, if there is no doubt about a cause–effect link between obesity and the development of HF, on the other hand in the case of an already developed HF, indeed excess weight and obesity are strangely associated with a favourable prognosis so that the findings of numerous meta-analyses have shown evidence of the phenomenon of the obesity paradox.[25]

So as to say that obesity could have a protective effect on HF patients. However, the obesity paradox was not confirmed in HF patients with a relatively preserved functional capacity, defined by a peak $VO_2$ of 14 ml/kg/min or higher.[26]

A more prominent role of functional capacity, rather than BMI, in defining HF prognosis emerged in some studies so that patients with an impaired but relatively higher peak $VO_2$ and a higher degree of lean mass showed a better clinical trajectory, regardless of BMI.[26]

The survival paradox of BMI also vanishes in diabetes patients with HF, nevertheless both obesity and diabetes are prevalent in patients with HF.[27]

The obesity paradox is not alone in the HF field. The spectrum of 'reverse epidemiology' is unlimited in HF: higher levels of blood pressure and cholesterol are also related to a better prognosis.

In addition, obesity together with low haemoglobin are potent contributors to impaired peak exercise oxygen uptake during CPET, as previously demonstrated,[28] suggesting the importance of considering these features together when interpreting peak exercise oxygen uptake and underlying exercise limitations.

A comprehensive methodological approach in the intriguing scientific debate about the equivocal role of BMI in the prognosis of HF has recently been pursued through the elaborated analysis of the large database from the MECKI score research group.[29]

The entire study population (4623 patients) was divided into four groups according to BMI: less than 25, 25–30, over 30 to 35 or less and greater than 35 kg/m$^2$, but the 220 patients of the last group were excluded from the data analysis, reducing the study cohort to 4623 cases. These groups presented with different clinical characteristics; in particular, the highest BMI group patients were younger, with a greater use of beta-blockers, higher value of LVEF, peak $VO_2$, VE/$VCO_2$ slope, renal function and haemoglobin level.

The study population was also divided into three subgroups according to predicted peak $VO_2$ (<50, 50–80 and >80%).

Total and cardiovascular mortality (urgent cardiac transplant included) occurred in 28.6% and 17.4%, respectively, of the entire study population.

Seemingly, the obesity paradox was confirmed as the highest mortality rate occurred not only in the lowest BMI group (<25 kg/m$^2$; $P<0.001$) but also separately in the minority group of underweight patients (BMI <18.5). However, the novel solution of the obesity paradox raised from the two multivariable Cox proportional hazard models applied for assessing the independent prognostic magnitude of BMI: the first one adjusted for class of $VO_2$ as a percentage of predicted value, and the second one for peak $VO_2$ as an absolute value, age, gender and LVEF. At univariable analysis, both BMI and peak $VO_2$ (both as absolute values and predicted values) were associated with prognosis. But Cox analysis showed that BMI class adjusted for peak $VO_2$% of the predicted value or by age, gender, LVEF and absolute peak $VO_2$ missed its prognostic capacity in terms of total or cardiovascular death.

A second analysis took into consideration the patients of the three BMI groups matched according to age, gender, LVEF and peak $VO_2$ (absolute value or percentage of the predicted value); no significant difference in prognosis was observed for both total and cardiovascular death in the 628 triplets of matched subjects.

The study of the MECKI score research group downsizes the veracity of the obesity paradox, explaining it as a result of a series of confounding factors including the underlying bias for which the most obese subjects are excluded from performing functional tests.[29]

In conclusion, the findings of the MECKI score database analysis strengthen the superior prognostic power of enhanced functional capacity and the relevance of physical conditioning on BMI.

## Conclusions

The lesson learnt from the MECKI score database analysis is clear: women, elderly and obese patients constitute heterogeneous categories, deserving a specific approach and evaluation. Nevertheless, the MECKI score maintains its prognostic power even in these subgroups of patients, working on the percentage of predicted CPET values (peak $VO_2$, VE/$VCO_2$ slope).

In fact, analysis conducted on these specific categories has highlighted how they can benefit from a dedicated assessment for a correct stratification of the death risk or urgent transplant request.

Even with 'worse' CPET performances, women have a better survival. The elderly, due to the frequent state of deconditioning and muscle hypotrophy, cannot

frequently reach thresholds. The reduced lean mass in the elderly, however, is an additional frailty element, which therefore negatively impacts the prognosis.

Moreover, the MECKI score has been demonstrated to be capable of overcoming the 'obesity paradox', confirming its superior prognostic power.

In conclusion, the MECKI score confirms its power and suitability even in these specific subgroups.

## Author contribution

SS, FM, ES, GM, MB, UC and MFP contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work and they drafted the manuscript. All authors critically revised the manuscript and gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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