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EDITORIAL COMMENT

On the trail of the perfect prognosticator in advanced heart failure patients

À procura do melhor preditor de eventos em doentes com insuficiência cardíaca avançada

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> ''It appears to me a most excellent thing for the physician to cultivate Prognosis; for by foreseeing and foretelling, in the presence of the sick, the present, the past, and the future, and explaining the omissions which patients have been guilty of, he will be the more readily believed to be acquainted with the circumstances of the sick; so that men will have confidence to intrust themselves to such a physician.''
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> HIPPOCRATES, *The Book of Prognostics*

In Greek mythology, nothing could be done to alter one's fate, as the *Moirai* (the three Fates) made certain that the destiny assigned by them to every human being would take its course without obstruction. In our era, we dare to predict the course of diseases and the ability of our interventions to alter the fate of our patients.[1]

In chronic heart failure (HF), an insidious and progressive syndrome, patients are at high risk of death.[2] However, the availability of heart transplantation can dramatically change the prognosis of the most severe patients. These patients must be identified before a major event jeopardizes their eligibility for transplantation.[3] At present, prognostication and selection of patients for heart transplantation is a complex issue.[4] As the candidate list grows and guidelines expand candidacy, heart transplantation rates remain static.[5] This highlights the need for better candidate selection, dynamic delisting and waiting list trimming. Integration of multiple factors, including functional capacity variables, scores, and clinical assessments (e.g. frailty scores), may help to select vulnerable patients for transplantation.[6] The aging of the population and heterogeneity in clinical presentation underscore the need for a multiparametric clinical and epidemiological approach to these risk stratification systems.[7]

The statistical concepts supporting risk stratification scores are complex and can be prone to bias. The most commonly used parameter to assess the performance of a risk score is the concordance statistic (C-statistic). This reflects the probability of a patient in whom an event occurs (in this case, death or heart transplantation) having a worse score than a patient in whom the event does not occur or occurs at a later point of time.[8] A value of 1.0 reflects perfect concordance between the prediction and outcome, whereas a C-statistic of 0.5 indicates random concordance. Usually,

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scores display C-statistics of 0.6 to 0.9. HF risk stratification scores usually display values between 0.75 and 0.85, commonly classified as good concordance. Other indices can also be used in this context, like the net reclassification index (NRI), which measures how often addition of a new variable, such as VE/VCO_2 slope, results in a change in classification that can be used to assess the effect of changes of this magnitude on the C-statistic.[9] Importantly, without an assessment of the clinical impact of the change in classification, the NRI can be misleading, as it overemphasizes the importance of small increases in the C-statistic.

Several risk stratification scores have been developed to help physicians identify the high-risk vulnerable patients who would benefit from early heart transplantation listing. The most commonly used score is the Seattle Heart Failure Model (SHFM), which is based on 24 clinical variables.[10] Both the SHFM and the HF Survival Score (HFSS)[11] are recommended in the latest heart transplantation guidelines.[5] Some scores also include functional capacity variables, particularly from cardiopulmonary exercise testing (CPET); these include the HFSS, the HF-ACTION score[12] and the recently developed Metabolic Exercise Cardiac Kidney Indexes (MECKI) score.[13] The latter score, combining information on hemoglobin, sodium, kidney function, left ventricular ejection fraction and two CPET parameters – peak oxygen consumption (VO_2 max) in proportion to expected VO_2 and the VE/VCO_2 slope – have recently demonstrated superiority (C-statistic 0.781) over the commonly used SHFM (0.739) and HFSS (0.723).[6] These results were recently supported by a report by a Portuguese group that again demonstrated the superiority of the MECKI score, with C-statistics between 0.83 and 0.87 for endpoints including heart transplantation, values that indicate good agreement with predictions.[14] The good discriminative power of the MECKI score is evident and may be related to the inclusion of both VO_2 max and VE/VCO_2 in the score's composition.

Risk scores can also be subject to bias. Sources of potential biases include selection bias, as most scores are developed in homogeneous, highly selected randomized controlled trial cohorts exposed to standard of care interventions. Using real-world data, as Pereira-da-Silva et al.[15] have done in this issue of the *Journal*, may help to minimize this source of bias. The authors aimed to identify which prognostic factors can best discriminate HF patients who will progress to death or transplantation, focusing specifically on variables obtained from CPET testing. Enrolling 263 patients spanning a nine-year period, the authors developed a two-step model for assessing HF risk. In a highly specific first step, high-risk patients are identified by a VE/VCO_2 slope of $\geq$39, with a C-statistic of 0.79, without the contribution of any other variable. The VE/VCO_2 slope is a particularly interesting parameter, as it reflects ventilatory efficiency and is associated with pulmonary hypertension.[16] It also possesses prognostic value at submaximal levels of effort, increasing the usefulness of CPET in a population that is not accustomed to exercise or may be reluctant to provide maximal effort. In fact, VE/VCO_2 >35 is recommended as a listing criterion in the presence of submaximal CPET (respiratory exchange ratio <1.05).[5] In the second step, after excluding high-risk patients, low-risk patients were identified by a VE/VCO_2 slope <39, in association with serum sodium >136 mmol/l, serum creatinine <1.0 mg/dl or variation in end-tidal carbon dioxide partial pressure of >0.45 kPa. The presence of two or three factors had an additive effect for a better prognosis. These results are clinically significant, as most studies in this area have focused on identifying high-risk patients. Identification of a low-risk population may help advanced HF physicians to step down care in some selected patients, thereby optimizing resources and intensity of care.

Somewhat surprisingly, no additive value was found for very strong prognostic variables, such as creatinine, natriuretic peptides or echocardiographic variables. The lack of invasive hemodynamic data is a caveat, as all patients referred for transplantation should have an invasive assessment for candidacy. It would be interesting from a pathophysiological standpoint to have an invasive characterization of high-risk patients, particularly to help understand which hemodynamic profiles were present in patients with VE/VCO_2 slopes >39. Also, only patients able to perform CPET were enrolled. Finally, the score should be tested in a validation cohort, as models are intervention-dependent.

Despite these important insights from Pereira-da-Silva et al.'s study, several questions remain regarding advanced HF risk assessment. Are we ready to use other variables besides peak VO_2 for risk stratification? Is variability between serial VE/VCO_2 measurements a problem? Do these results correlate with invasive hemodynamics? Can we ignore other clinical variables that are included in other scores, such as the MECKI score? The guidelines recommend against relying solely on scores to select patients for heart transplantation.[4] Heart transplantation patient selection remains a complex decision that requires a team-based approach, extensive clinical experience, surgical input, social support and a multiparametric approach.

Conflicts of interest

The author has no conflicts of interest to declare.

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