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The Model for End-Stage Liver Disease (MELD) can predict outcomes in ambulatory patients with advanced heart failure who have been referred for cardiac transplantation evaluation

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Abstract

Risk stratification in heart failure (HF) patients is an important element for management. There are several risk stratification models that can be used to predict the prognosis of patients with HF, such as Aaronson's scale, CVM-HF (CardioVascular Medicine Heart Failure), the Seattle Heart Failure Model (SHFM) and the Munich score. These models fail to adequately address the impact of multiorgan dysfunction on prognosis.

The classical Model for End-Stage Liver Disease (MELD) score consists of: total bilirubin, INR (international normalized ratio) and creatinine level. There are some modifications of the MELD scale: MELD-XI, which excludes the INR score; the mod-MELD score, in which INR is replaced with albumin levels; and MELD-Na, which consists of the bilirubin and creatinine levels, INR ratio and the sodium level. Therefore, the MELD score systems are markers of multisystem dysfunction (renal, cardiac, hepatic). It is important that they are composed of routinely collected laboratory measures which are easy to use.

Key words: chronic heart failure, prognosis, MELD scale.

Streszczenie

W etiologicznie i funkcjonalnie niejednorodnej grupie chorych z niewydolnością serca istotnym elementem postępowania jest stratyfikacja ryzyka. Istnieją liczne modele prognostyczne stosowane do oceny ryzyka u chorych z niewydolnością serca, takie jak: skala Aaronsona, skala CVM-HF (*CardioVascular Medicine Heart Failure*), skala Seattle (*The Seattle Heart Failure Model*) i skala Monachium. Wymienione skale nie biorą jednak pod uwagę markerów dysfunkcji wielonarządowej mających istotne znaczenie rokownicze w tej grupie chorych. W skład klasycznej skali MELD (*Model for End-stage Liver Disease*) wchodzi natomiast stężenie bilirubiny, wskaźnik INR oraz stężenie kreatyniny. Istnieje kilka modyfikacji skali MELD: skala MELD XI, z której wyeliminowano wskaźnik INR, skala mod-MELD, w której wskaźnik INR został zastąpiony przez stężenie albumin, oraz skala MELD-Na, obejmująca stężenie kreatyniny, bilirubiny, sodu i wartość wskaźnika INR. Skale MELD są więc markerami dysfunkcji wielonarządowej (nerkowej, sercowej, wątrobowej). Ich zaletą jest to, że w ich skład wchodzą rutynowo oceniane parametry laboratoryjne.

Słowa kluczowe: przewlekła niewydolność serca, rokowanie, skala MELD.

Introduction

Risk stratification in an etiologically and functionally inhomogeneous group of heart failure (HF) patients is an important element for management from both a medical and an economic point of view. Accurate identification of patients who are most likely to benefit from heart transplantation is imperative due to an organ shortage and perioperative complications [1, 2].

There are several risk stratification models that can be used to predict the prognosis of patients with HF. The first is Aaronson's scale, which consists of such clinical data as resting heart rate, left ventricular ejection fraction, mean blood pressure, interventricular conduction defects, serum sodium, mean wedge pressure, ischemic etiology of cardiomyopathy and assessment of peak oxygen consumption [3]. The necessity for the assessment of peak oxygen con-

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sumption limits the possibility of using this model widely. In addition, changes in the medical treatment of HF since 1995 (especially the widespread use of β blockers) and the predictive value of hemodynamic changes over time are not adequately taken into account in Aronson's stratification model [1, 4].

The next prognostic scale is the CVM-HF, which was created by Senni *et al*. in 2006 and includes: medications (β blockers, ACEI), NYHA class III/IV, left ventricular ejection fraction < 20%, severe valvular heart disease, atrial fibrillation and coexisting diseases (anemia, arterial hypertension, chronic obstructive pulmonary disease, complicated diabetes mellitus, moderate to severe kidney dysfunction, metastatic cancer) [5]. This model was derived and validated in a single center with stable HF patients who were mostly undergoing optimal pharmacological treatment. The limitations of this model are that patients with preserved and impaired systolic function were included in the study group and the study group was relatively small.

The Seattle Heart Failure Model (SHFM) was constructed in 2006 by Levy *et al*. It was developed in the PRAISE-1 database and validated among patients participating in observational studies, clinical trials and registries (ELITE-2, Val-HeFT, University of Washington cohort, RENAISSANCE and Italian Heart Failure Registry). An SHFM score is calculated based on 24 variables, including clinical characteristics (gender, age, NYHA class, weight, ischemic etiology, systolic blood pressure, left ventricular ejection fraction), laboratory data (serum cholesterol, sodium and uric acid level, lymphocyte percentage, hemoglobin), medications and device therapy (implantable cardioverter-defibrillator, cardiac resynchronization therapy) [6]. This model consists of a large number of parameters, such as commonly obtained baseline clinical data, medications and devices, which do not reflect the multiorgan dysfunction that is the essence of advanced heart failure.

The next risk stratification scale, which was created in 2008, is the Munich score [7]. This model contains five parameters: etiology of HF, systolic blood pressure, left ventricular end diastolic diameter, maximum workload and the change in the fractional shortening of the left ventricle over 12 months. This scale offers an efficient and non-invasive tool for pre-transplant risk stratification. Univariate and multivariate analyses in this model show no statistical significance of elements of Aronson's scale such as heart rate at rest, serum sodium, intraventricular conduction defect or peak oxygen consumption. Its main limitation is that the data came from a single center and this scale predicts a combined end point (death and heart transplantation).

The changes in medical treatment and device therapy of HF over time are not adequately taken into account in the above-mentioned stratification models. In addition, although a number of risk stratification scales have been established to assess risk in heart failure patients who are referred for heart transplantation evaluation, these models fail to adequately address the impact of liver dysfunction.

Abnormal liver function tests that reflect liver dysfunction are important indices of heart failure severity and higher risk of death [8]. The pathophysiology of liver failure in heart failure has been attributed to venous congestion and reduced cardiac output that leads to hepatic congestion and hepatic low perfusion [9]. Low perfusion is less important than congestion because oxygen consumption can be increased when hepatic blood flow is decreased [10, 11]. Moreover, compared to other organs, the liver's dual blood supply (from the portal system and hepatic artery) makes it relatively resistant to hepatocyte necrosis from haemodynamic instability [9, 12].

For these reasons chronic cardiac hepatopathy shows no significant deviations from physiologic levels of transaminases. A critical elevation of transaminases is observed only in cases of marked hypotension [10, 13]. Multiple studies have shown a decrease in serum total protein, albumin, coagulation factors and lipid levels and as a result cachexia and bleeding [13].

Most frequently, we can observe a mild increase in the serum bilirubin level (in 30-70% of patients) and an increased level of other cholestatic indices such as alkaline phosphatase or γ-glutamyltranspeptidase (in 20% of patients) [9, 14, 15]. Several studies performed on heart failure patients have shown that serum bilirubin level correlates with hemodynamic parameters such as right atrial pressure, severity of tricuspid regurgitation, wedge pressure, left ventricular ejection fraction and the cardiac index [8, 10, 16].

Two non-cardiac biomarkers which reflect the severity of the effect of hepatic dysfunction on metabolism (total bilirubin) and synthesis (INR – international normalized ratio) are elements of the classical Model for End-Stage Liver Disease (MELD) score. The third component of the MELD score system is the creatinine level. Therefore, the MELD score system is a marker of multisystem dysfunction (renal, cardiac, hepatic) and coagulopathy. It is composed of three routinely collected laboratory measures which are easy to use.

The MELD was initially developed to assess mortality in subjects with cirrhosis who had undergone transjugular intrahepatic portosystemic shunt procedures [17, 18]. In addition, it was validated as a predictor of survival in patients with end-stage liver disease. Moreover, the clinical utility of MELD was used to select patients who might profit from liver transplantation and to predict operative morbidity and mortality in cirrhotics undergoing cardiac and non-cardiac procedures [19, 20, 21]. Northup *et al*. and Ailavadi *et al*. observed dependence between the MELD score and postoperative mortality in the group of non-cardiac cirrhotic patients undergoing non-transplant procedures [22, 23]. MELD is currently applied to determine the prognosis of patients with chronic heart failure who are referred for mechanical circulatory support or heart transplantation [24, 25].

Matthews *et al*. analyzed patients from the INTERMACS (Interagency Registry of Mechanically Assisted Circulatory Support) registry and the UMHS (University of Michigan Health System) mechanical circulatory support database

[24]. These authors demonstrated that preoperative MELD scores can identify left ventricular assist device candidates who are at high risk for perioperative bleeding and mortality. This analysis showed an increased frequency of postoperative device infections and renal failure in patients who required many perioperative transfusions. The association between the MELD score and renal failure is due to the fact that creatinine is a part of the MELD model. The association between the MELD score and infection may be related to bacterial exposures during prolonged intensive care unit and total hospital stays. In addition, Matthews *et al*. have demonstrated an increased frequency of right ventricular failure in patients with higher MELD scores. The reason cited for this was that blood transfusions can increase the right ventricular preload and provoke the release of cytokines which then cause respiratory insufficiency and pulmonary hypertension. Many transfusions also increase risk of allosensitization, which is associated with a worse outcome in patients after heart transplantation [26].

Chokshi *et al*. [25] retrospectively analyzed patients before and after heart transplantation and assessed the serum levels of hepatic function tests and MELD scores. The percentage of patients with a pathologic serum level of hepatic function markers decreased significantly after heart transplantation. Elevated MELD scores also improved after heart transplantation. The authors confirmed that liver dysfunction was associated with higher rates of postoperative complications and an impaired prognosis in patients undergoing orthotopic heart transplantation. They concluded that higher MELD scores can identify patients who are at a higher risk for complications and reduced survival after heart transplantation.

The MELD score may not be a valid prognostic index in patients who are undergoing warfarin therapy because warfarin affects the international normalized ratio (INR). There are some alternative MELD scales without INR.

An alternative MELD scale that omits INR, which can be used for patients undergoing anticoagulant therapy, was created by Heuman *et al.* [27]. The authors confirmed that a modified MELD score, MELD-XI (MELD excluding INR score), which is calculated based on two parameters, bilirubin and creatinine, was a predictor of pretransplant mortality in cirrhotic patients. Comparable MELD and MELD-IX scores were associated with a comparable prognosis.

Assenza *et al*. adopted the MELD-IX score to determine disease severity and to predict mortality in patients who were undergoing Fontan surgery [28]. They concluded that patients with a higher MELD-XI score have higher risk of death and cardiac transplantation.

Tsuda *et al*. excluded the INR variable from the MELD score and created a simplified model which only used total bilirubin and creatinine [29]. The authors assessed the ability of this scale to predict mortality for patients who were undergoing tricuspid valve surgery. This analysis demonstrated that the simplified MELD score was an independent risk factor for hospital mortality and morbidity.

Choshi *et al*. [25] used a modified MELD score that replaced INR with albumin levels to substitute for the impaired production of coagulation factors of prothrombin complex with albumin. The substitution of INR with albumin was based on the fact that both are indicators of secretory liver function. The modified MELD score correlates with the standard score and is better than the standard score due to the lack of an interaction with oral anticoagulants. Elevated modified MELD scores before heart transplantation were associated with worse morbidity and mortality after the operation.

Kim *et al*. evaluated the MELD score and its modifications in predicting survival and endpoint (death, heart transplantation, ventricular assist device implantation) in a group of end-stage heart failure patients who were undergoing a cardiac transplantation evaluation [30]. They compared the prognostic value of MELD, MELD-XI and MELD-Na in patients who were either on or off anticoagulant treatment. MELD-Na consisted of the bilirubin and creatinine levels, INR ratio and the sodium level, which is an important marker of mortality. The authors found that MELD was a good predictor of a worse outcome and that the presence of serum sodium in the MELD scale resulted in an improved prognostic strength. This relationship was evident in patients without oral coagulation. For patients being treated with anticoagulation, MELD-XI was a prognostic factor of the necessity of heart transplantation. MELD-XI had a worse prognostic strength in patients being treated with oral anticoagulation compared with patients who were not receiving anticoagulation therapy. The reason for this could be the fact that patients receiving anticoagulation have multiple comorbidities which are risk factors of poorer outcome.

In conclusion, the Aaronson and Seattle scales that were previously used widely demonstrated a high prognostic value in ambulatory patients with stable heart failure. The predictive value of Aaronson's scale is less reliable today than it used to be due to the changes in the guidelines on the management of heart failure. The MELD scale and its modifications are better in terms of a prognostic index in patients with advanced heart failure than previous models because they take into account multiorgan failure, which is the essence of this pathological state. They show an increased risk of death due to heart failure decompensation. A good option is to use the MELD-XI scale combined with other prognostic models for patients who need oral anticoagulation.

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