Superiority of the heart failure survival score to peak exercise oxygen consumption in the prediction of outcomes in an independent population referred for heart transplant evaluation

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Heart failure survival score; Heart transplantation; Risk stratification.

Background. **The heart failure survival score (HFSS), a multivariable predictive index that has been shown to predict death or inotrope-dependent transplant in ambulatory patients referred for transplant evaluation has not been independently validated. We sought to independently assess the prognostic ability of the HFSS in a group of patients undergoing transplant evaluation in Italy, and to compare its prognostic value to that of peak exercise oxygen consumption (VO_2), the standard tool for risk stratification in most transplant centers.**

Methods. **Data for the seven variables that constitute the HFSS, including peak VO_2, were collected for 107 ambulatory patients referred to the heart transplant center of the University of Turin. Patients were followed prospectively for 997 ± 32 days, with outcome events defined as death prior to transplant or inotrope-dependent transplant.**

Results. **The discriminative abilities of peak VO_2 and the HFSS and their respective risk strata were compared. At univariate Cox regression models, peak VO_2 did not successfully predict outcomes, neither when evaluated continuously ($p = 0.25$) nor when dichotomized at 14 ml/kg/min ($p = 0.18$). Both the HFSS ($p = 0.011$) and the HFSS strata ($p = 0.008$) successfully predicted outcome events.**

Conclusions. **The HFSS was more accurate than peak VO_2 for the prediction of event-free survival, both when evaluated continuously and as risk strata. The HFSS is a valid and widely applicable tool for the identification of patients who, in the absence of contraindications, would benefit from transplantation.**

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The number of patients who could benefit from cardiac transplantation far outstrips the available donor pool. It is therefore essential that only those patients most likely to benefit from transplantation be placed on the waiting list. Peak exercise oxygen consumption (VO_2) is widely considered the best indicator of whether heart failure is severe enough to warrant placing a patient on the heart transplantation waiting list, and is recommended for this use in several guidelines and statements[1-8]. On the basis of Mancini's landmark study, a peak VO_2 < 14 ml/kg/min is most commonly used[9], but several other cut-off values have been proposed[10-14]. The ease of use renders a threshold value for a single test an attractive criterion, but this approach has important limitations. First, dichotomizing continuous data tends to oversimplify a complex issue. Patients with a value just below or just above the predefined cut-off have a similar expected survival even if they are artificially placed in different risk categories. We and others have shown that the relationship between peak VO_2 and survival in heart failure is continuous within the range of values commonly observed in patients evaluated for transplant candidacy[15-17]. Second, in adopting a single parameter, many other prognostic factors are ignored despite the incremental information that they may provide.

Multivariate statistical models may provide a more effective means of assessing individual mortality risks in the absence of transplantation. The heart failure survival score (HFSS) was specifically developed for this purpose[18]. It incorporates seven non-invasively derived measurements, which with appropriate weighting, are combined into the overall risk score. The HFSS was shown to segregate into three HFSS strata (low-, medium- and high-risk); both the HFSS and the strata have been shown to predict death or urgent transplant in ambulatory patients referred for transplant evaluation[18]. We have recommended that patients in the medium- or high-risk strata be listed for heart transplantation (in the absence of significant contraindications), whereas patients in the low-risk stratum may be placed on the waiting list at a later date.

This clinical index was derived and then validated on data from two separate heart transplant centers (the Hospital of the University of Pennsylvania and the Columbia-Presbyterian Medical Center, respectively). However, the investigators at both centers were the same, so the validation was not truly independent. Furthermore, both study centers are located in the urban northeastern United States; this homogeneity may have falsely enhanced the HFSS performance.

Therefore, the aims of the present study were to evaluate the predictive value of the HFSS and to compare these predictions to those of peak VO_2 in a fully independent sample of patients being evaluated for transplant at the University of Turin.

Methods

Patients. Among all patients referred since 1 year to the University of Turin for cardiac transplant evaluation, we retrospectively evaluated the data of patients for whom the seven variables needed to calculate the HFSS had been obtained. During the study period, it was standard practice at the University of Turin to exclude patients with the most severe functional limitations as evaluated at cardiopulmonary exercise testing; accordingly, the data of these patients were not available for analysis. The study population therefore consisted of 107 ambulatory patients (86 males, 21 females) with chronic heart failure followed prospectively for at least 1 year. Follow-up information was obtained at clinic visits or by telephone interview and was complete for all patients, with mean ± SEM follow-up of 997 ± 32 days.

Cardiopulmonary exercise testing. Peak VO_2 was determined during maximal treadmill exercise using a modified Bruce protocol and a metabolic cart. The anaerobic threshold was defined using the V-slope method[19].

Calculation of the heart failure survival score. The HFSS is a clinical index derived from a Cox proportional-hazards regression model that was developed and subsequently validated in ambulatory patients with advanced heart failure. Details of the model derivation and the determination of the threshold values for the HFSS strata have been published[18]. Of 80 original candidate variables considered for the model, a seven variable model was selected that reflects different aspects of the pathophysiology of heart failure: resting heart rate, mean blood pressure, left ventricular ejection fraction, serum sodium, and peak VO_2 during treadmill exercise as continuous variables, and intraventricular conduction delay (defined as a QRS complex ≥ 120 ms) and coronary artery disease as the heart failure etiology as dichotomous measures (i.e., present or absent).

For each patient, the HFSS was calculated as the absolute value of the sum of the products of the seven prognostic variables and their computed coefficients (i.e., $| \beta_1 x_1 + \beta_2 x_2 + ... + \beta_n x_n |$, where x_1, x_2, ... x_n are the values for the explanatory variables (for dichotomous variables, 0 = no and 1 = yes), and β_1, β_2, ... β_n are the coefficients [i.e., weights] assigned to each variable) (Table I). Finally, the HFSS strata were grouped into the low-, medium- and high-risk strata using the HFSS ranges previously defined (Table II)[18]. The calculation of the HFSS and the assignment to strata were performed by one of the investigators (KDA) who was unaware of the patients' outcome event status.

Statistical analysis. Outcome events were defined as death prior to transplant, or inotrope-dependent transplant; no patient received a left ventricular assist device prior to transplant. Follow-up was censored for all other (i.e., non-urgent) transplants, or for those alive (without transplant) at the end of the follow-up period. The event-free survival for peak VO_2 stratum (defined as ≤ 14 ml/kg/min or as > 14 ml/kg/min) was calculated using the Kaplan-Meier method, and was compared between strata using the log-rank test. Similar calculations were made for the HFSS strata.

The discriminative values of peak VO_2 and the HFSS were quantified by calculating both the area under a receiver operating characteristic curve (AUC) for the de-

Table I. Heart failure survival score model coefficients.

Variable	Coefficient
Resting heart rate (b/min)	0.0216
Mean blood pressure (mmHg)	-0.0255
Left ventricular ejection fraction (%)	-0.0464
Serum sodium (mmol/l)	-0.0470
Peak VO_2 (ml/kg/min)	-0.0546
Intraventricular conduction delay	0.6083
Ischemic cardiomyopathy	0.6931

VO_2 = oxygen consumption.

Table II. Heart failure survival score (HFSS) strata according to the score and the relative odds of an outcome event at 1 year in the original derivation sample.

HFSS	HFSS strata	Relative odds of event at 1 year
≥ 8.10	Low-risk	0.23
7.20-8.09	Medium-risk	1.19
≤ 7.19	High-risk	5.00

velopment of an outcome event at 1 year (excluding patients with censored follow-up at < 1 year), and the censored c-index for the development of an outcome event at any time during follow-up[20,21]. The c-index is an estimate of the probability that, of two randomly selected patients, the patient with the higher peak VO_2 or HFSS will live longer free of an outcome event than the patient with the lower peak VO_2 or HFSS[20]. The censored c-index differs from the 1-year AUC in that it continues to differentiate between outcome events occurring after 1 year of follow-up, and is able to consider censored events that occur at < 1 year of follow-up. Calculations of the AUCs and the censored c-indices were made separately for peak VO_2 and HFSS considered as continuous measures and for the peak VO_2 and HFSS strata.

Univariate Cox proportional-hazards modeling was performed to test the significance of peak VO_2 and the HFSS as predictors of survival; multivariate modeling was then performed to test whether each was independently predictive in the context of the other. The same methods were used with the peak VO_2 and HFSS strata to test their predictive values.

Results

Patient characteristics. The descriptive characteristics for the 107 study patients are presented in table III where the results of the seven variables included in the HFSS are reported. Peak VO_2 was 16.0 ± 4.7 ml/kg/min. Peak VO_2 was ≤ 14 ml/kg/min in 51 patients (48%) and > 14 ml/kg/min in 56 patients (52%). The anaerobic threshold was achieved in 67% of patients with a peak VO_2 < 14 ml/kg/min vs 91% of patients with a peak VO_2 ≥ 14 ml/kg/min ($p = 0.004$). A separate analysis was performed for the 34 patients with both peak VO_2 < 14 ml/kg/min and achieved anaerobic threshold. The HFSS was 9.03 ± 0.67, with 87 patients (81%) during the study period classified in the HFSS low-risk stratum, 17 (16%) in the medium-risk stratum, and 3 (3%) in the high-risk stratum (Table III).

Table III. Heart failure survival score (HFSS) model characteristics of the patient population and HFSS strata.

Continuous variable	
Heart rate (b/min)	80 ± 14
Mean blood pressure (mmHg)	99 ± 14
Left ventricular ejection fraction (%)	26 ± 9
Serum sodium (mg/dl)	140 ± 4
Peak VO_2 (ml/kg/min)	16.0 ± 4.7
Dichotomous variables	
Intraventricular conduction delay	35 (33%)
Ischemic cardiomyopathy	39 (36%)
HFSS	9.03 ± 0.97 (range 6.42-11.43)
HFSS strata	
Low-risk stratum	87 (81%)
Medium-risk stratum	17 (16%)
High-risk stratum	3 (3%)

VO_2 = oxygen consumption.

Table IV displays the relationship between the HFSS and peak VO_2 strata. In this sample, all but 2 of the 56 patients with a peak VO_2 > 14 ml/kg/min were classified as low-risk using the HFSS. However, of the 51 patients who were classified as high-risk using the peak VO_2 criterion (≤ 14 ml/kg/min), 33 (65%) were classified as low-risk using the HFSS and 19 (56%) of these with either ≤ 14 ml/kg/min and achieved anaerobic threshold.

Table IV. Relationship between the heart failure survival score (HFSS) strata and peak exercise oxygen consumption (VO_2) strata.

Peak VO_2 strata	HFSS strata		
	Low-risk	Medium-risk	High-risk
> 14 ml/kg/min	54	1	1
≤ 14 ml/kg/min	33	16	2
≤ 14 ml/kg/min and anaerobic threshold	19	13	2

Outcomes. At 1 year, 3 (2.8%) deaths and 4 (3.7%) inotrope-dependent heart transplantations occurred. During this first year of observation, 23 patients (21.5%) were electively transplanted, leaving 77 patients (72.0%) alive without transplantation. Throughout the entire follow-up period we observed 23 events: 19 (17.8%) deaths and 4 (3.7%) inotrope-dependent transplants. Twenty-six patients (24.3%) were "electively" transplanted, and 58 (54.2%) were still alive without heart transplantation.

Predictive value of peak exercise oxygen consumption. The Kaplan-Meier event-free survival curves for the peak VO_2 strata are shown in figure 1; these did not differ significantly ($p = 0.173$), due to the relatively low event rate in patients with a peak VO_2 < 14 ml/kg/min. The event-free survival curve for patients with either ≤ 14 ml/kg/min and achieved anaerobic threshold was very similar to that of the group of patients with a peak VO_2 ≤ 14 ml/kg/min. The AUC for the 1-year event-free survival and the censored c-index were respectively 0.76 ± 0.08 and 0.62 for peak VO_2, and 0.67 ± 0.09 and 0.68 for the peak VO_2 strata. Peak VO_2 was not a significant predictor of survival at univariate Cox regression models, both when evaluated continuously ($p = 0.25$) and as strata ($p = 0.18$).

Predictive value of the heart failure survival score. As shown in figure 2, the actuarial event-free survival at 1-year was 96 ± 2% in the low-risk stratum and 64 ± 15% for patients in the medium-risk stratum, with an

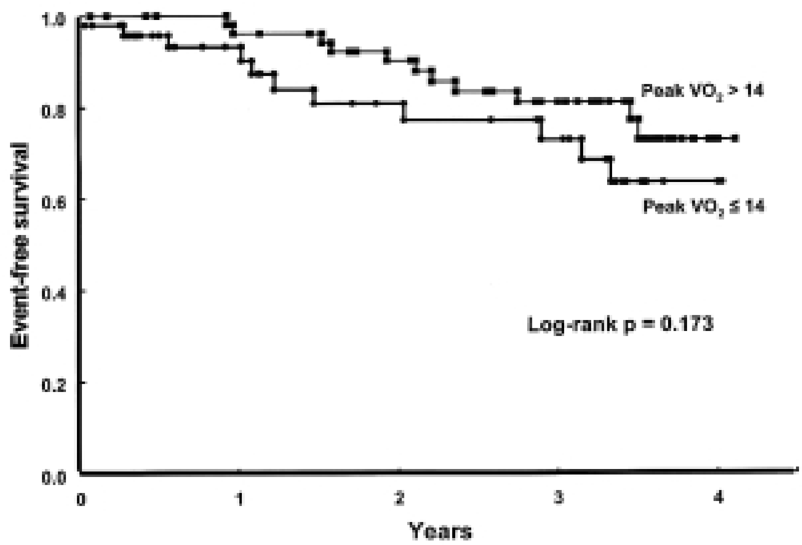

Figure 1. *Kaplan-Meier actuarial event-free survival curves for patients with a peak exercise oxygen consumption (VO_2) > 14 ml/kg/min and a peak $VO_2 \leq 14$ ml/kg/min.*

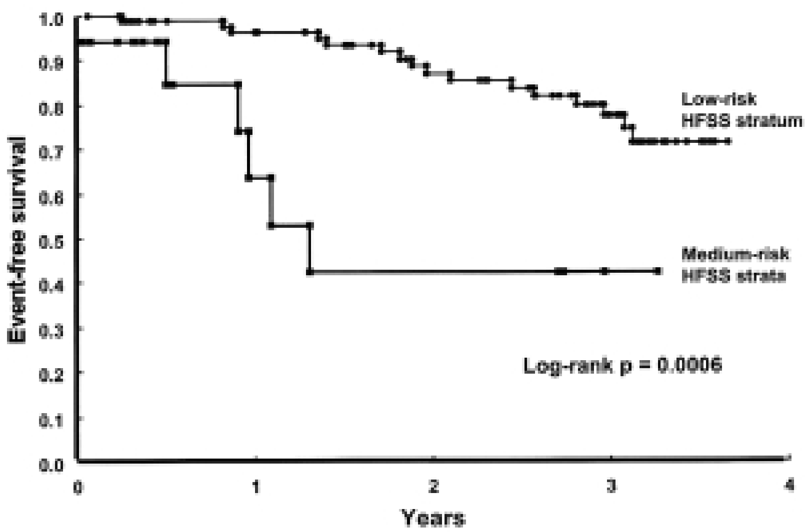

Figure 2. *Kaplan-Meier actuarial event-free survival for patients with a low- and medium-risk stratum. HFSS = heart failure survival score.*

event-free survival over the entire course of follow-up markedly better in the low-risk stratum (log-rank p = 0.0006). When the 3 patients in the high-risk stratum were added to those in the medium-risk stratum, the 1-year event-free survival for the combined group was 68 ± 14% (log-rank p = 0.005 compared to the low-risk group).

The HFSS was equally effective in identifying patients with a low-risk of experiencing an outcome event despite a "high-risk" peak $VO_2 \leq 14$ ml/kg/min (Fig. 3). Among these 51 patients, the 1-year event-free survival was 97 ± 3% for the 33 subjects classified as low-risk by the HFSS vs 67 ± 14% for the 18 patients classified as medium- or high-risk (log-rank p = 0.037). In the subgroup of the 34 patients with either ≤ 14 ml/kg/min and achieved anaerobic threshold, the 1-year event-free survival was 94 ± 6% for the 19 classified as low-risk vs 62 ± 18% for the 15 patients classified as medium- or high-risk (log-rank p = 0.028).

In table V, the survival rates for each of the HFSS strata of the Turin model derivation and model validation cohorts are shown. The survival rates for the low- and medium-risk strata of the Turin cohort were quite similar to those of the model derivation and validation cohorts (log-rank, all p = NS).

The AUC for the 1-year event-free survival and the censored c-index were respectively 0.91 ± 0.04 and 0.70 for the HFSS, and 0.74 ± 0.08 and 0.83 for the HFSS strata. Both the HFSS (p = 0.011) and HFSS strata (p = 0.008) were significant predictors of survival when entered as the independent variable in separate univariate Cox regression models. Even when the peak

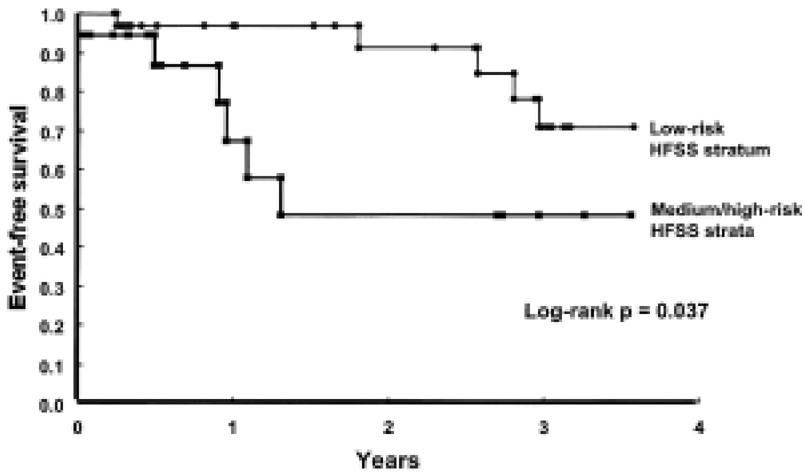

Figure 3. *Kaplan-Meier actuarial event-free survival for patients with a low- and medium-risk stratum among the subgroup of 51 patients with a peak exercise oxygen consumption ≤ 14 ml/kg/min. HFSS = heart failure survival score.*

Table V. Comparison of the 1-year outcomes between the study sample (Turin) and the original model derivation (Hospital of the University of Pennsylvania) and validation (Columbia-Presbyterian Medical Center) samples.

Samples	Low-risk	Medium-risk	High-risk
Turin	96 ± 2%	63 ± 15%	No data (n=3)
Hospital of the University of Pennsylvania	93 ± 2%	72 ± 5%	43 ± 7%
Columbia-Presbyterian Medical Center	88 ± 4%	60 ± 6%	35 ± 10%

VO_2 was "forced" into the regression model, the HFSS remained a significant predictor of survival (p = 0.026); the same held true for the peak VO_2 and HFSS strata (p = 0.044).

Discussion

The main findings of this study are the independent validation of both the HFSS and its strata as accurate methods for the prediction of event-free survival in ambulatory patients with advanced heart failure and the superiority of these measures to peak VO_2 or its strata, especially among patients with a peak $VO_2 \le 14$ ml/kg/min who do not achieve maximal exercise.

The HFSS and HFSS strata were strong predictors of event-free survival in this independent sample of ambulatory patients with chronic advanced heart failure from Turin. Predictive models often perform less well when applied by different investigators in new clinical settings. Since the same investigators cared for the patients in both the original model derivation (Hospital of the University of Pennsylvania) and validation (Columbia-Presbyterian Medical Center) samples, there was a possibility that aspects of this care could have uniquely affected patient outcomes. There was also concern that the similarity of the original model development and validation sites in Philadelphia and New York could have falsely enhanced the HFSS performance. Given the need to censor non-urgent transplants in the survival analysis, the similar waiting list dynamics at these sites could have biased the results of the original validation. Yet, with new investigators collecting the relevant data and caring for the patients in a country with quite different waiting list dynamics (e.g., very few inotrope-dependent transplants in Turin), the HFSS and its strata predicted outcomes quite well.

A major strength of the HFSS in this study was its ability to identify patients with a peak $VO_2 \le 14$ ml/kg/min who remained nevertheless at low risk for death or inotrope-dependent transplant over the next few years. This group, which constituted 65% of the "high-risk" peak VO_2 group (33 of 51 individuals) had the same excellent event-free survival as did the HFSS low-risk stratum patients with a peak $VO_2 > 14$ ml/kg/min. Thus, a listing strategy based on the HFSS strata would have led us to place only one third as many patients on the transplant waiting list as would have occurred if a peak VO_2 threshold of 14 ml/kg/min were used.

Since the work of Mancini et al.[8,9], peak VO_2 has assumed a central role in the decision-making process for heart transplantation listing. In this study, peak VO_2 was not a statistically significant predictor of survival, both when evaluated continuously and when stratified at a threshold value of 14 ml/kg/min. The poor performance of peak VO_2 may have been due to that one third of patients in the low peak VO_2 group did not achieve the anaerobic threshold. Failure to perform truly maximal cardiopulmonary exercise will systematically underestimate peak VO_2, thereby overestimating the risk; submaximal ventilatory parameters may be helpful in these situations[22-24]. Adjusting peak VO_2 for age, gender and weight may improve its predictive ability, particularly for women and those who are significantly younger or older than the usual patients evaluated for a heart transplant[25,26]. The relatively high range of peak VO_2 values in this sample and the moderate sample size may have also limited the predictive value of this parameter in this study.

The ability of the HFSS to outperform peak VO_2, one of its component measures, should not be surprising. The HFSS provides a more comprehensive assessment of heart failure severity. Its seven variables bring together multiple aspects of the pathophysiology of heart failure: myocardial ischemia (ischemic cardiomyopathy), systolic dysfunction (left ventricular ejection fraction), activation of the renin-angiotensin-aldosterone system (serum sodium), activation of the sympathetic nervous system (resting heart rate), myocardial injury/fibrosis (intraventricular conduction delay), and more integrative measures (peak VO_2 and mean blood pressure). Measurement error and day-to-day variability may have a large adverse impact on performance if a single parameter is chosen for prognostication. The danger of over-reliance on a single measure of disease severity is highlighted by this study, in which submaximal exercise by some of the study subjects probably contributed to the limited predictive ability of peak VO_2. Although a component of the HFSS, peak VO_2 is only the sixth (of seven) most important contributors to the model[18]. By incorporating multiple weakly correlated variables, the HFSS is more robust than any of its single component clinical parameters when prospectively applied for risk stratification.

Study limitations. Our study does have important limitations. First, the study sample is small and the most severely ill patients were excluded. Only 3 patients were classified at high-risk according to the HFSS strata. Therefore, validation of the HFSS for the most severely ill patients who would be in the high-risk stratum could not be performed with this sample. However, the critical issue in evaluating the HFSS is its ability to distinguish between the low- and medium-risk groups, since our recommendation has been to transplant the latter group and to defer listing (with appropriate close follow-up and serial re-evaluations) in the former. The lack of high-risk patients in this sample provided a more difficult, but nevertheless successful test for the model.

Second, data collection was performed retrospectively. However, the outcomes were independently defined before determining the HFSS and were hence not influenced by the *post-hoc* knowledge of the estimated risk.

In conclusion, the HFSS and the HFSS strata have been independently validated as an effective tool to discriminate between patients at low- and medium-risk for death or urgent transplantation. The HFSS was more accurate than peak VO_2 in predicting the event-free survival at 1 year and throughout the follow-up period, both when evaluated continuously and as risk strata. The HFSS is a valid and widely applicable method for the estimation of the event-free survival in patients with advanced heart failure referred for transplant. The event-free survival for patients in the high- and medium-risk strata is poor, and, in the absence of contraindications, these patients should be listed for transplant. Transplant listing may be safely deferred for low-risk stratum patients.

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