Clinical Index to Predict Survival in Ambulatory Patients Referred for Heart Transplantation

Lars Lund

A. Purpose

The Heart Failure Survival Score (HFSS) is currently used to predict prognosis in patients with severe CHF. The HFSS survival score was developed before the widespread use of B-blockers. The purpose of this study is to validate the HFSS in patients on B-blockers.

B. Background

Cardiac transplantation (orthotopic heart transplantation, OHT) improves morbidity and mortality in patients with end-stage congestive heart failure (CHF) who remain symptomatic despite optimal medical therapy. In 1992, one-year survival post OHT was 85% and peri-operative mortality was only 10% (1). In large trials of ACE inhibitors, the one-year mortality in the placebo arms were 5%, 15%, and 64% for NYHA class I, II-III, and IV respectively (2-4). The addition of ACE inhibitors, B-blocker, and in some cases, spironolactone, has brought down one-year mortality to less than 10% for class II-IV (3, 5-8). Despite these improvements in medical therapy, OHT compares favorably in terms of both mortality and morbidity. Patients in decompensated CHF requiring in-hospital inotropic support constitute the traditional candidates for OHT; they often do not survive until transplant and are considered the highest priority. However, patients with stable class III CHF also stand to benefit from OHT, which has expanded the pool of suitable recipients. It is estimated that there are 4,000 patients suitable for transplant each year but only 2,000 donor hearts available.(9). At the same time, many patients on transplant lists survive for long periods of time. In several studies, 20-30% were "de-listed" because of clinical improvement and they fared equally well to transplanted patients in terms of morbidity and mortality at two years of follow-up (10, 11).

Because of these considerations, accurate risk stratification of potential OHT candidates would facilitate more efficient use of scarce donor hearts. Univariate predictors of survival, such as NYHA class, left ventricular ejection fraction (LVEF), and peak oxygen consumption (VO2 max), have been used as prognostic markers, but as single variables they poorly predict outcome in individual patients. VO2 max is the best objective predictor; we have previously shown that patients with a VO2 max <14 mL/kg/min are at low risk for cardiac mortality and can have transplant safely deferred (12). We have previously developed multivariate risk stratification model (the HFSS) utilizing weighted inputs of the following parameters: etiology (ischemic or not), resting heart rate, LVEF, mean blood pressure, intra-ventricular conduction delay, VO2 max, and serum sodium. A combination of these variables performed better than any single variable and allowed accurate stratification into three risk groups with one-year event free survival of 88-93%, 60-72%, and 35-43% respectively (13). We also found that an invasive right heart catheterization with measurement of pulmonary capillary wedge pressure did not add to the model's accuracy. Therefore, our model was useful as a simple, non-invasive, yet accurate means of selecting patients for OHT. Others have also developed algorhitms for transplant selection (14, 15), but despite our and others data, the selection process for OHT remains subjective and certainly imperfect.

Adding to the difficulty of prognosis is the rapid development of medical treatment. In our model, ACE inhibitor use was 90% but the benefit of B-blockers still not conclusively shown, and their use was only 10%. We have since conducted serial risk stratification in an independent cohort in which 23% were on B-blockers (Aaronson, submitted). Today, the benefits of B-blockers have been firmly established (5-7) and their use is widespread; in our transplant referral cohort (mainly class III and IV), approximately 50% are on B-blockers (Mancini, unpublished). Although several variables in our

multivariate model are likely to be favorably affected by B-blockers (resting HR, LVEF, and VO2 max) and thus reflect their beneficial effect, it is possible that our current model, based on 10% B-blocker use, is no longer valid. Therefore, we propose to re-evaluate the HFSS. Specifically we will validate the current HFSS in patients on B-blockers. This will indicate whether the current HFSS is still useful, or whether an updated model should be derived and validated in order to facilitate more appropriate prognosis in CHF and selection for OHT.

C. Patient Population

Patients referred to CPMC for OHT evaluation or severe CHF between July 1995 and April 2001, with LVEF<40 and age 18-70. Patients must have performed an exercise test without angina or claudication. Patients must have been ambulatory and on B-blocker therapy and not on inotropic support at the time of referral.

D. Protocol

Retrospective longditudinal cohort. Determine outcome (presence or absence of death or UNOS1 transplant) ar one year of follow-up. UNOS 2 transplant recipients will censored.

E. Statisitcal Analysis

Data will be collected for the 7 HFSS parameters, an HFSS will be calculated, the proportion that reaches outcome at one year will be determined, and survival will be compare to 1-year survival scores from the previous HFSS. Kaplan-Meier survival curves will be plotted for each of the three HFSS risk strata. Risk starta will be compared using log rank tets, and Cox proportional hazards models will be evaluated, with the HFSS being the independent variable and event-free survival the dependent variable.

F. Sample size

The exisiting cohort consists of approximately 550 patients. The following table lists anticipated values for each parameter, with standard deviations, the resultant HFSS, and the n required for power of 80% and p=0.05, as well as the difference that can be detected given a total sample size of 550.

at 1 year	coefficient	Expired or UNOSI	alive	n needed	effect detectable
number (%)		165 (30)	385(70)	Expired/UNOSI vs alive	Given=550
EF$	-0.0464	20.±5	22±5	72 vs 164	1.3
resting HR$	0.0216	75±10	73±10	263 vs 650	2.6
mean BP$	-0.0255	78±15	82±15	159 vs 366	3.9
VO2 max$	-0.0546	12±5	15±5	32 vs 74	1.3
serum Na$	-0.0470	136±5 % yes	138±5 % yes	72 vs 164	1.3
ischemic #	0.6083	49	46	3169 vs 7289	<36, >62
IVCD#	0.6931	45	40	1131 vs 2601	<32, >58
HFSS$		7.67±0.5	8.28±0.5	9 vs 19	0.13

$ from un-paired t-test; n different in each group. (www.biomath.info)
 # from chi-square test: n different in each group. (www.biomath.info)
data estimated from Circ 97, 95:2660

G. Risks and Precautions

All tests and procedures have been performed. They were performed only if clinically indicated; i.e. not for the sake of this study. Right heart catheterization, coronary angiography or exercise testing entailed the risk of bleeding, arrhytmia, syncope, myocardial infarction or death. However, all were performed under the supervision of trained medical personnel who were equipped to deal with any emergencies. Phlebotomy may have been associated with pain.

H. Study Limitations

The study is limited by the fact that only a validation will be performed. If the HFSS proves to be invalid in patients on B-blockers, a derivation and if possible validation of an new HFSS should be performed. It is also limited by the fact that the effectiveness of current medical therapy prevents many outcomes and thus a large sample size is required.

I. Confidentiality

All information associated with the patient will be confidential.

J. Compensation

Patients will not be compensated for their participation.

K. Location

All testing was be performed at CPMC.

L. Radiation

Chest roentgenogram, right heart catheterization, and coronary angiography involved exposure to small amounts of radiation.

M. References

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8. RALES. NEJM 99, 341:709
9. JACC 93, 22:21
10. Am Heart J 96, 132:1189
11. Am Heart J 00, 140:857
12. Circ 91, 83:778
13. Circ 97, 95:2660
14. EPICAL. Am Heart J 00, 139:895
15. JACC 37:1049