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# Impact of renal dysfunction on the Seattle Heart Failure Model

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**KEYWORDS:**
chronic kidney disease;
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risk prediction

**BACKGROUND:** Renal dysfunction (RD) is a strong predictor of mortality in patients with heart failure (HF). However, its impact on the discrimination of the Seattle Heart Failure Model (SHFM) is poorly understood.

**METHODS:** Serum creatinine (SCr) and creatinine clearance (CrCl) were reviewed for patients from four of the six cohorts originally used to derive and validate the SHFM. Patients were followed for death. The independent prediction of adding SCr or CrCl to the SHFM was assessed using multivariable Cox proportional hazards and the incremental value for prediction by changes in the ROC curves for 1- and 2-year event prediction.

**RESULTS:** Among 7,146 patients (mean age 63 ± 11 years), 1,511 deaths occurred during a mean follow-up of 2.04 years. SCr and CrCl had a modest positive correlation with SHFM ($r = 0.30$, $p = 0.002$). In combination with SHFM, SCr (hazard ratio [HR] per mg/dl 1.25, 95% CI 1.13 to 1.38, $p < 0.0001$) and CrCl (HR per 10 ml/min 0.95, 95% CI 0.93 to 0.97, $p < 0.0001$) were both multivariable predictors of events. When stratified by absolute risk based on the SHFM, SCr or CrCl provided more additional information in lower risk patients and less or no additional information in higher risk patients. The addition of SCr and the SHFM*SCr, or CrCl and the SHFM*CrCl interaction to the SHFM was associated with almost no change in the 1- and 2-year area under ROC curves for the SHFM score.

**CONCLUSIONS:** Compared with the SHFM alone, RD is independently predictive of mortality only in lower risk patients. Overall discrimination is only minimally improved with addition of SCr or CrCl to the SHFM.

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The prevalence of heart failure (HF) continues to steadily rise.[1] Further improvement in outcomes among patients with HF may involve providing existing treatments at a time when the risk-to-benefit ratio is favorable for treatment. These risks may be assessed by standard trial inclusion and exclusion criteria and augmented by multivariable risk models. Given the high mortality associated with HF, timely prognostication in these patients is important, allowing for maximized therapeutic efficacy. The Seattle Heart Failure Model (SHFM) is a well-validated method that uses commonly assessed clinical variables known to predict survival in ambulatory and hospitalized HF patients.[2,3]

Although underlying renal dysfunction (RD) is commonly present in patients with advanced HF[4] and is a known strong predictor of mortality,[5–8] it is not included in the

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SHFM as it was not a multivariate predictor in the derivation cohort. Among the existing models used for risk prediction in HF, RD has been inconsistently shown to predict outcomes.[9,10] Currently, only one study has assessed the impact of RD on the SHFM wherein most parameters of RD, except blood urea nitrogen (BUN), did not add to mortality risk above that conferred by the SHFM score.[11] Also, addition of renal function to the SHFM in earlier studies has not been shown to significantly improve its overall discrimination.[11,12] However, the populations previously studied were relatively small and consisted of predominantly high-risk patients with advanced heart disease.

In this study we hypothesized that incorporating a measure of renal function into the SHFM would improve its prognostic accuracy and allow better risk stratification among patients with systolic HF. As such, we aimed to assess the impact of RD on the discrimination of the model and its differential effect on mortality in low- and high-risk patients.

## Methods

### Study population and data collection

The SHFM score (Figure 1) was originally derived from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1)[13] cohort and was subsequently validated in five additional cohorts of patients with predominantly systolic HF. These included the Evaluation of Losartan in the Elderly (ELITE2),[14] Valsartan Heart Failure Trial (Val-HeFT),[15] Randomized Enbrel North American Strategy to Study Antagonism of Cytokines (RENAISSANCE),[16] Italian Heart Failure Registry (IN-CHF)[17] and University of Washington (UW)[18] cohorts. We retrospectively reviewed the data from four (PRAISE1, IN-CHF, UW and Val-HeFT) of these cohorts. Primary data from the RENAISSANCE and the ELITE2 studies were not available. Participant inclusion and exclusion criteria for patients in each cohort and the derivation and validation of the SHFM score have been described previously.[2]

### Estimation of renal function

We used serum creatinine (SCr) and serum creatinine clearance (CrCl), as calculated by the Cockcroft–Gault equation,[19] as measures of underlying RD. Chronic kidney disease (CKD) stages were classified based on National Kidney Foundation practice guidelines.[20] As there were very few patients with stage V CKD, they were included with the CKD stage IV patients for the analyses.

### Events and definitions

The primary event was all-cause mortality. In the PRAISE1, IN-CHF and Val-HeFT cohorts, a centralized adjudication committee classified events.[13–15] In the UW cohort, events were classified by one of the study cardiologists (W.C.L.) using review of medical records. The SHFM score was rounded to the nearest integer from 0 to 3. A SHFM score of 1.5 (annual mortality ~16.5%) was used as a cut-off value to distinguish low- and high-risk patients.

### Statistical analysis

Continuous and categorical variables are summarized as mean ± SD and frequency (%), respectively. The Kruskal–Wallis test was used to analyze differences across CKD stages. The independence of characteristics associated with events and the independent prediction of adding SCr or CrCl to the SHFM was assessed using multivariable Cox proportional hazards. Given that the SFHM score had a significant interaction with SCr and CrCl, an interaction term (SHFM*SCr and SHFM*CrCl) between them was created and added to the analysis. The incremental value of adding renal function to the SHFM was assessed by changes in the receiver operating characteristic (ROC) curves for 1- and 2- year event prediction. Kaplan–Meier (KM) survival curves were plotted to assess the differential effect of varying CKD stages among low- and high-risk patients. All analyses used $p$-values (2-sided), with $p \leq 0.05$ considered significant. Data were analyzed with SPSS version 19.0 (IBM, Armonk, NY) and STATA version 11.2 (StataCorp, College Station, TX).

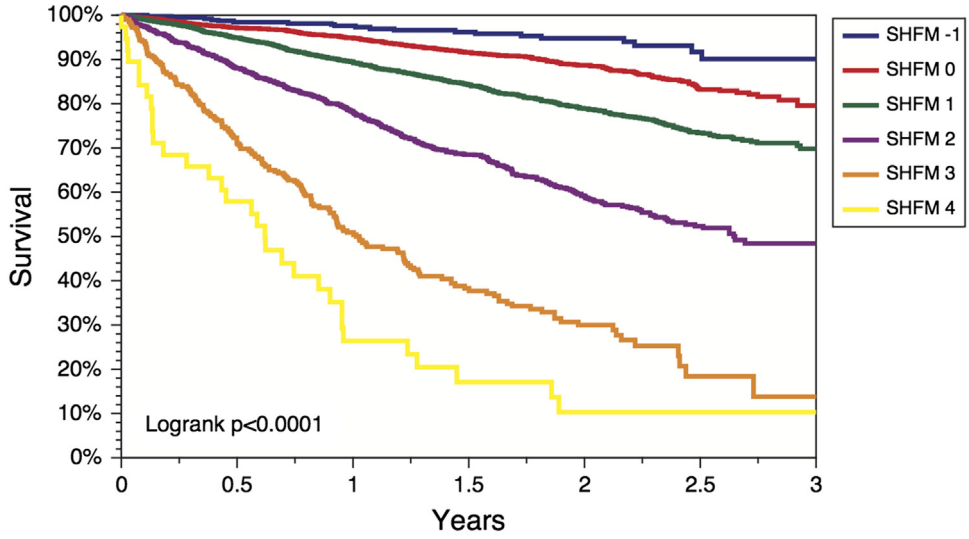


**Figure 1** The Seattle Heart Failure Model Score.