Soluble transferrin receptor as a marker of tissue iron deficiency: impact on clinical outcomes in patients with heart failure without systemic iron deficiency or anaemia

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Background: Soluble receptor of transferrin (sTfR) is a marker of tissue iron status and may help to inform on subtle iron depletion and increased iron demand of functional proteins at tissular level even in the absence of overt systemic iron deficiency or anaemia. Raised sTfR levels have been associated with increased risk of all-cause mortality in general population and in patients with heart failure (HF). However, the prognostic significance of raised sTfR levels in non-anaemic HF patients with otherwise normal systemic iron status has not been evaluated.

Purpose: The aim of our study was to describe the association between sTfR as a marker of increased iron demand and tissue iron deficiency on outcomes in non-anaemic patients with HF and normal systemic iron status.

Methods: We conducted an observational, prospective, cohort study of 1120 consecutive patients with chronic HF (DAMOCLES study). For the current sub-study, we selected all patients form the DAMOCLES cohort that had a complete iron status evaluation including sTfR, normal haemoglobin levels and normal systemic iron status. Tissue ID was defined as levels of sTfR>75th percentile (1.63mg/L). The primary and secondary endpoints were all-cause mortality and HF hospitalization respectively. Multivariate Cox proportional hazards models were constructed to explore the associations between tissue ID and the studied outcomes. In addition, the multivariate parametric and non-parametric associations between sTfR and the estimated risk of the occurrence of the primary and secondary endpoints were explored using General Additive Models (GAM). All models were adjusted by age, sex, and prognostic factors such as LVEF, NYHA, NT-proBNP levels and iron status parameters among other well-known determinants of HF severity.

Results: The final study cohort consisted in 215 patients from the DAMOCLES study. Mean age was 70±12 years, mean LVEF was 43±15% and 62 (29%) were women. Mean sTfR values were 1.42±0.66 mg/L. Tissue ID was present in 54 patients (25%). Hospital readmission occurred in 55 patients (25.6%) and death occurred in 60 (27.9%).

In multivariate Cox proportional hazards models (table 1) higher levels of sTfR and Tissue ID were significantly associated with the risk all-cause death. This association was not observed for HF readmission. As shown in figure 1 panel A, adjusted GAM showed there was a significant linear association between higher levels of sTfR and the mortality risk. Moreover, the adjusted cumulative risk of all-cause death (Figure 1 panel B) confirmed higher risk of death among patients with tissue ID compared to patients’ levels of sTfR≤ the 75th percentile with early divergence of the curves during follow-up.

Conclusions: In a cohort of HF patients without iron deficiency or anaemia, higher levels of sTfR indicating tissue ID were associated with increased risk of mortality. This association was linear and was not observed for HF readmission.

### Table 1. Multivariate (adjusted) Cox proportional hazards analyses exploring the effect on outcomes of sTfR and tissue ID in the cohort of non-anaemic patients with HF and normal systemic iron parameters (Backward Stepwise Method).

<table>
<thead>
<tr>
<th>ALL-CAUSE DEATH</th>
<th>Measures of Tissue ID</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTfR, 1mg/L</td>
<td>sTfR&lt;75th percentile (1.63mg/L)</td>
<td>1.455</td>
<td>1.121 - 1.887</td>
<td>0.005</td>
</tr>
<tr>
<td>HEART FAILURE HOSPITALIZATION</td>
<td>Measures of Tissue ID</td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>sTfR, 1mg/L</td>
<td>sTfR&lt;75th percentile (1.63mg/L)</td>
<td>1.174</td>
<td>0.829 - 1.663</td>
<td>0.366</td>
</tr>
</tbody>
</table>
Figure 1. Adjusted GAM models (panel A) and adjusted Cox Hazards models (panel B) evaluating the association between sTfR (panel A) and Tissue ID (panel B) with all-cause death.

PANEL A
Smooth cubic spline curves from multivariate Generalized Additive Models of the risk of all-cause death across sTfR values

PANEL B
Event-free cumulative survival (all-cause death)

Tissue ID (sTfR>1.63 mg/L)

- no
- yes

adjusted p-value = 0.023

Time to first event (years)