Comorbidity Index Predicts Severity of Acute Gvhd in Transplant Patients

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Blood cancers are aggressive and life-threatening diseases. Curative treatments such as hematopoietic cell transplantation (HCT) are used to reconstitute the blood system after wiping out both the leukemia and normal blood cells. Graft-versus-host disease (GVHD) is a frequent complication in HCT patients impacting morbidity and mortality. In acute GVHD, the donor immune cells attack and destroy the cells of the transplant recipient in various organs, including the gut, skin and liver. Older patients or those with additional medical problems have worse outcomes due to suboptimal treatment of their blood cancers, as doctors are less likely to recommend HCT in these patients. Age is often used as an arbitrary determinant of risk; however, additional organ dysfunctions, or "comorbidities", in patients are probably more relevant for assessing risk. In a recent study published in *Blood*, Drs. Mohamed Sorror and Ted Gooley, along with additional colleagues in the Clinical Research Division, and collaborators from City of Hope, Oregon Health & Science University, University of Utah, and Colorado Blood Cancer Institute, evaluate a newly developed index that assigns scores based on the number and/or severity of organ comorbidities.
The researchers demonstrate this index score could provide patients and physicians before transplantation with accurate estimates of the likelihood of developing acute GVHD and if it happens, the likelihood that a patient would not survive that complication.

In 2005, Dr. Sorror and colleagues at the Fred Hutchinson Cancer Research Center developed the HCT comorbidity index (HCT-CI) and demonstrated it could predict whether a patient would survive a transplant (Sorror ML *et al*., 2005). HCT-CI is calculated from a weighted score of 17 components of the patient's medical history, including dysfunctions of organs like liver, lung, heart, or kidney in addition to diseases like diabetes, peptic ulcer, obesity, infection, and psychiatric disturbances. The reason why these pre-transplant comorbidities were associated with post-transplant mortality was postulated to be due to initiating or aggravating treatment-related complications in patients.

In the current study, the researchers investigated whether the HCT-CI could predict acute GVHD, a common post-transplant complication influencing patient survival. Their study included pre-transplant medical histories and post-transplant outcomes for 2985 patients provided by five medical institutions. The authors found that HCT-CI scores stratified patients into three risk groups for the

development of severe acute GVHD, and this magnitude of prediction was consistent regardless of variables such as conditioning intensity, donor, or graft used for transplantation. Higher HCT-CI scores predicted increased risk of grade III-IV acute GVHD ($p<0.0001$), with probabilities estimated at 13%, 18%, and 24% for HCI-CI risk groups of low (score 0), intermediate (scores 1-4), and high (scores ≥5), respectively. Importantly, the impact of HCI-CI scores on risk of acute GVHD did not vary with different age groups.

The researchers also found that once patients are diagnosed with acute GVHD, the same HCT-CI scores could then be used to predict mortality rates. HCT-CI scores were associated with mortality after diagnosis of both grade II acute GVHD (HR=1.24, $p<0.0001$) and grade III-IV acute GVHD (HR=1.9, $p<0.0001$). In addition, the prognostic impact of comorbidities on mortality was additive to that of development of acute GVHD. For example, patients with HCT-CI scores at or above 3 who also developed grade II-IV acute GVHD had a 2.63 fold higher risk of mortality (95% CI of 2.25-3.08, $p<0.0001$) than those with HCT-CI scores of 0-2 without acute GVHD.

According to Dr. Sorror, "The results of these studies will significantly advance our knowledge about how to tailor treatments so that we recommend intensive treatments to those who can tolerate them, but suggest less intensive treatments to those whom we will only harm. It will also provide a better understanding of how successful the different transplant strategies are in curing blood cancers with an acceptable quality of life." The HCI-CI score along with other risk factors can help predict and treat patients with higher risks for severe acute GVHD or mortality before clinical onset of GVHD to potentially reduce patient side effects and deaths. The researchers hypothesize that chronic tissue injury and inflammation associated with the comorbidities could contribute to the development and severity of acute GVHD, and future research on the biological associations could identify new targets for therapeutic intervention to reduce post-transplant mortality.

Sorror ML, Martin PJ, Storb R, Bhatia S, Maziarz RT, Pulsipher MA, Maris MB, Davis C, Deeg HJ, Lee SJ, Maloney DG, Sandmaier BM, Appelbaum FR, Gooley T. 2014. Pre-transplant comorbidities predict severity of acute graft-versus-host disease and subsequent mortality. *Blood* Epub ahead of print, doi 10.1182/blood-2014-01-550566.

See also: Sorror ML, Maris M, Storb RF, Baron F, Sandmaier BM, Maloney DG, Barry SE. 2005. Hematopoietic cell transplantation (HCT) - specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 106: 2912-2919

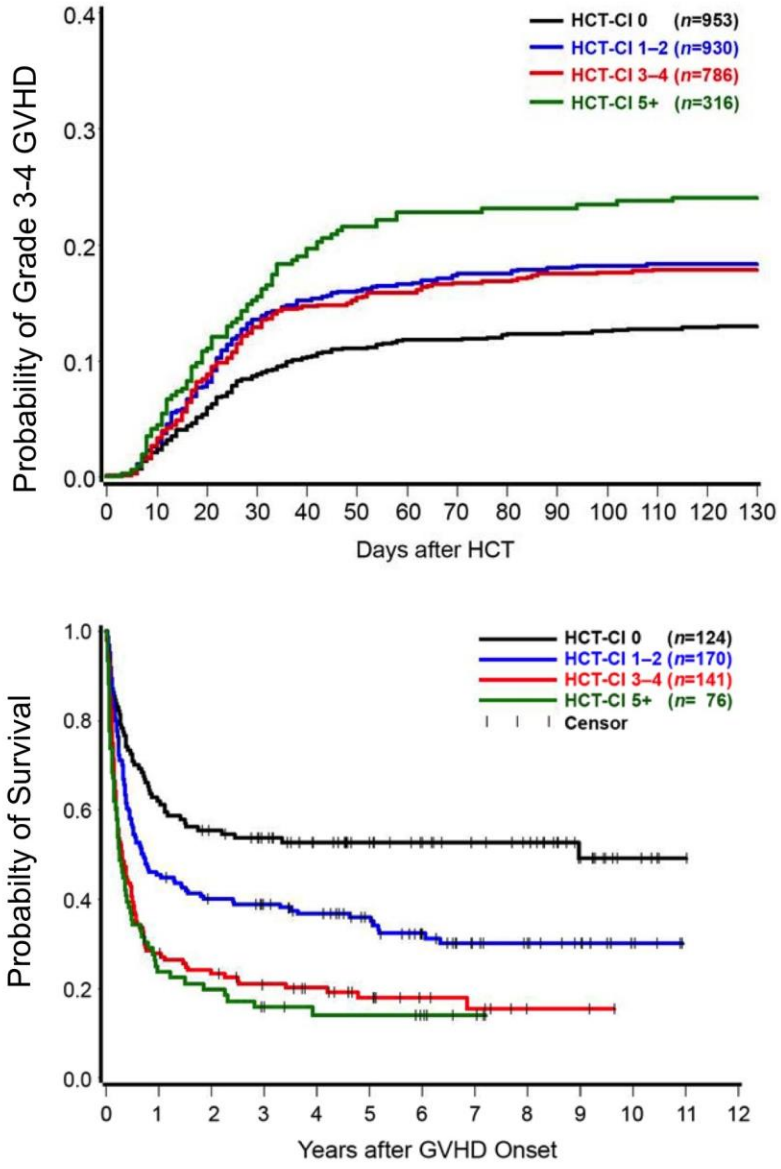

Image adapted from Sorror et al., 2014

The hematopoietic cell transplant comorbidity index (HCT-CI) predicts development of acute graft-versus-host disease (GVHD) and mortality in transplant patients. Transplant patients with increased HCT-CI scores had increased probability of developing grade III-IV acute GVHD (top). HCT-CI scores of 0, 1-2, 3-4, and 5 had decreasing 3-year rates of survival of 54%, 39%, 21%, and 16%, respectively, after diagnosis with grade III-IV acute GVHD as estimated with the Kaplan Meier method (bottom).