Reviewer's report

Title: Validation of a registry-derived risk algorithm based on treatment protocol as a proxy for disease risk in childhood acute lymphoblastic leukemia

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Reviewer: Karen Rabin

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Gupta et al have compared a risk algorithm based on two characteristics readily available in a pediatric cancer registry (age and protocol name) to a biologically based risk classification in 579 patients with pediatric ALL. They report that the registry-based algorithm showed good agreement (kappa=0.85) with the biologically based algorithm.

Discretionary Revisions

1. The findings presented here are sound for the specific scenario analyzed, although their generalizability is unclear, since treatment protocol is not always a surrogate marker for risk group as it was here, either in pediatric ALL or in other malignancies.

2. Treatment stratum is often a better indicator of risk status than treatment protocol, since patients of varying risk groups are often treated on different strata within a single protocol. It would be informative if the authors could comment on whether or not treatment stratum is generally available in the registry. If so, inclusion of this information in the registry-based algorithm would be optimal. If not, the utility of a registry-based algorithm based only on protocol name would be limited whenever a treatment protocol contained strata for multiple risk groups.

3. It is not uncommon for risk group to be reassigned based on information obtained at a late time point (over 4 weeks following start of treatment), eg based on end-induction MRD (in ALL and AML), or surgical outcome (in many solid tumors). This did not cause problems in the current study because nearly half the patients were treated on older protocols that did not use MRD for risk assignment, and the remainder were treated on protocols that used a higher MRD cutoff of 0.1% than is presently used, which resulted in relatively few patients being reassigned from SR to HR based on MRD positivity. However, in the present era, a substantial number of SR patients are reassigned to HR based on MRD exceeding the 0.01% cutoff, so agreement between post-induction risk status and initial treatment protocol assignment would be poorer. Therefore for ALL patients treated on modern regimens, a use of registry-based algorithm would more accurately reflect risk status if it were based on the post-induction treatment protocol assignment rather than the protocol assigned during the first four weeks of therapy.
Minor Essential Revisions

1. Third paragraph of discussion - new cytogenetic abnormalities – should add reference(s) re another recently identified lesion, iAMP21, in addition to ref 21.

2. Table 1 – hypodiploidy – legend says >45 instead of <45 chromosomes

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.