Robust validation of the UKALL high hyperdiploid risk profile using individual patient data, from children and adults, collected by the HARMONY Alliance

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INTRODUCTION

Definition of a core outcome set (COS), which represents an agreed set of outcomes for each hematological malignancy (HM) may improve the interpretation and comparability of clinical trials, especially if a respective COS addresses the needs of all stakeholders including patients, clinicians, industry, as well as regulators/HTA bodies. In accordance, HARMONY (the Healthcare Alliance for Resourceful Medicine Offensive against Neoplasms in Hematology) and the follow up project HARMONY PLUS have made it its task to develop COS for HMs.

AIM

The HARMONY Alliance (www.harmony-alliance.eu) is a European big data platform which has collected data on >150,000 patients with various haematological malignancies; including >10,000 patients with ALL.

a. Determine if the UKALL-HeH risk profile can be validated in a large independent cohort comprising data from multiple clinical trials and from both childhood and adults patients;
b. Assess the added benefit of validating a risk profile using data from the HARMONY platform compared with a single a country-specific cohort.

METHOD

Only cases with karyotype written according to ISCN were eligible for this study. A search of the cohort revealed 1169 karyotypes with a modal number of 51-67 chromosomes. Karyotypes with t(9;22)(q34;q11) or chromosome patterns indicative of masked haploidy or low hypodiploidy were excluded. Using a custom built R function, we sorted karyotypes according to trisomic status of chromosomes 5, 17, 18 and 20 (Figure 1). Karyotypes not definitively assigned to a risk group due to being incomplete or the presence of marker chromosomes were assigned to provisional groups but later combined with the definitive cases because their relapse rate was equivalent.

RESULTS

A total of 835 (74%) karyotypes had a UKALL HeH GR profile whilst 285 (26%) had a PR profile. The proportion of patients with a PR profile was significantly higher among those aged over 25 years compared to those under 25 (63% v 25%, p<0.001). Overall, patients with a PR profile had a significantly higher relapse rate at 5 years compared with those with a GR profile 6% (4-7) v 19% (14-23), log rank p<0.001. The hazard ratio from a univariate Cox model was 3.52 (SE 0.20 p<0.001). This effect was independent of MRD – hazard ratio for relapse from multivariate model was 3.30 (SE 0.26 p<0.001).

This effect was independent of MRD – hazard ratio for relapse from multivariate model was 3.30 (SE 0.26 p<0.001). The prognostic impact of the UKALL HeH profile was similar across all age groups examined including adults aged over 25 years but was greater among patients that were MRD negative (<0.01%) at the end of induction compared with MRD positive (≥0.01%) cases (Figure 2).

Compared to using the UKALL2003 cohort alone for validation, HARMONY provided a validation cohort that was 60% larger with a broader age range: 1-24 vs. 1-70 years. In addition, the Cox model estimates were more accurate with smaller standard errors. The standard error for the hazard ratio for risk of relapse reduced from 1.11 to 0.20. Moreover, validation on cohorts of patients treated on protocols from other study groups provides additional evidence for the robustness of the risk profile.

Figure 1

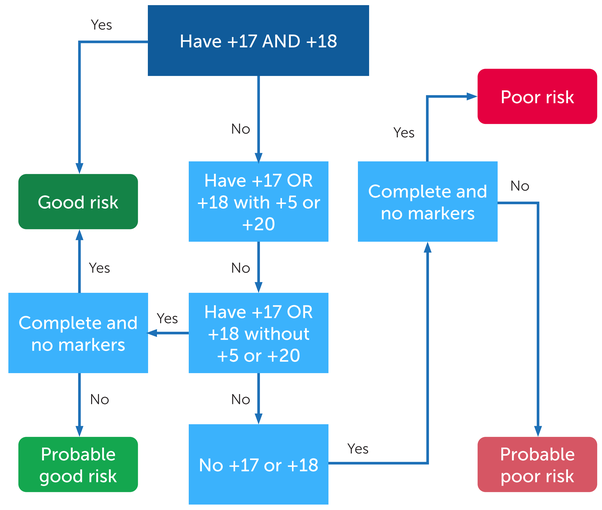
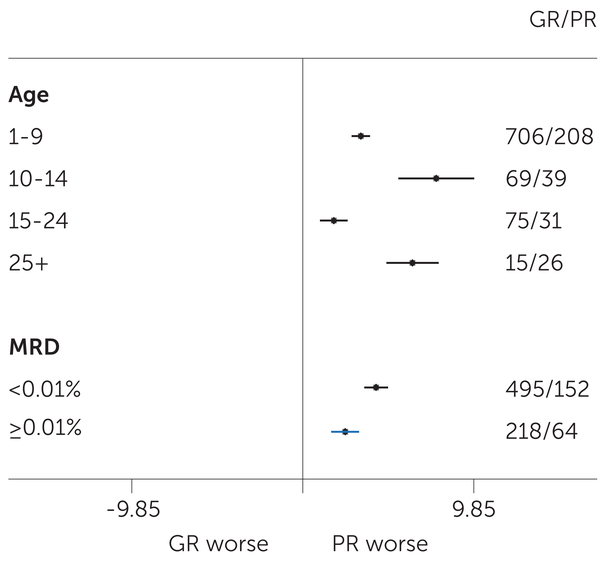


Figure 2



CONCLUSIONS

We have validated the UKALL HeH risk profile on a larger and more heterogeneous cohort of patients. We confirm that the profile defines both a low risk subgroup of HeH paediatric patients that could be considered for treatment reduction, as well as a subgroup of HeH that has a risk of relapse similar to patients with intermediate risk genetics. In addition, we have demonstrated how the HARMONY data platform, which provides access to a standardised disease-specific dataset, can rapidly facilitate biomarker research. In future studies, HARMONY can act as a valuable resource for discovery and validation of biomarkers for risk stratification of haematological malignancies.

REFERENCES

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The HARMONY Alliance is a Public-Private Partnership for Big Data in Hematology including over 100 organizations such as European medical associations, hospitals, research institutes, patient organizations, pharmaceutical and IT companies.

Funded by IMI (per 2020: Innovative Health Initiative, IHI) of the European Commission: HARMONY (January 2017-June 2023) and HARMONY PLUS (October 2020-September 2023). Using Big Data analytics to accelerate the development of more effective treatments for blood cancer patients. Data are stored in the HARMONY Big Data Platform, which has already identified over 150,000 anonymized patient records, making it one of the largest databases of its kind. Leading research teams are currently using this wealth of information to answer critical questions about hematologic malignancies that cannot be addressed with other methods.

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