HARMONY
Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Validation and Improvement Opportunities of the Revised International Staging System for Multiple Myeloma: An Analysis on Mature Data from European Clinical Trials Within the HARMONY Big Data Platform

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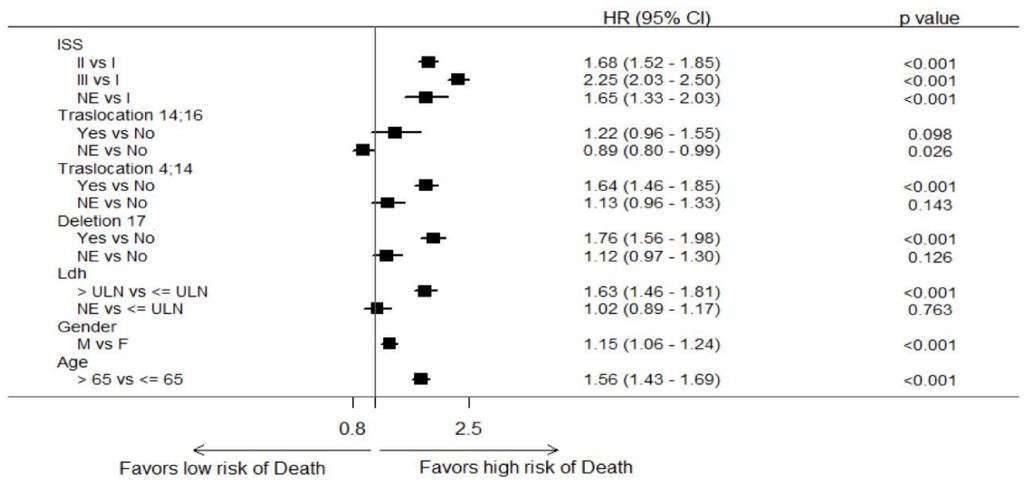
Abstract 1773

Background — The outcome of multiple myeloma (MM) patients is heterogeneous. In 2015, analyzing 4445 newly diagnosed MM (NDMM) patients enrolled into 11 clinical trials after a median follow-up of 46 months, a risk stratification algorithm named Revised-ISS (R-ISS) was developed combining International Staging System (ISS), chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization and serum lactate dehydrogenase (LDH) (Palumbo et al., *JCO* 2015). Here we report a mature follow-up of 5584 patients enrolled in 14 clinical trials (Table 1), providing an updated report on the R-ISS prognostic role and highlighting potential improvements.

Methods — Data from different European cooperative groups were collected through the European Myeloma Network (EMN) and registered in a big data platform developed by HARMONY, which is a European public-private partnership focusing on hematologic malignancies with unmet medical needs and providing a legal-ethical framework for international data sharing and analysis. The primary endpoint of this analysis was overall survival (OS) according to R-ISS. All NDMM patients received immunomodulatory agents (IMiDs) or proteasome inhibitors (PIs) as part of their upfront treatment.

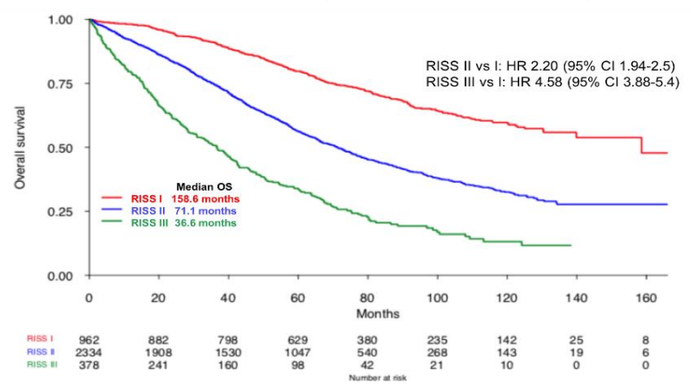
Results — 584 NDMM patients with a median age of 65 years were analyzed after a median follow-up of 74 months. 35% of evaluable patients had ISS I disease, 40% ISS II and 25% ISS III. LDH was ≤ the upper limit of normal (ULN) in 87% of evaluable patients, >ULN in 13%. To define high-risk CA, we performed a multivariate Cox model for OS individually evaluating del(17p), t(4;14) and t(14;16) positivity. Del(17p) (HR 1.76, p<0.001) and t(4;14) (HR 1.64, p<0.001) confirmed their role as independent risk factors, while t(14;16) (HR 1.22, p=0.10) did not (Figure 1).

Figure 1. R-ISS defining variables affecting OS in NDMM: are all variables the same?



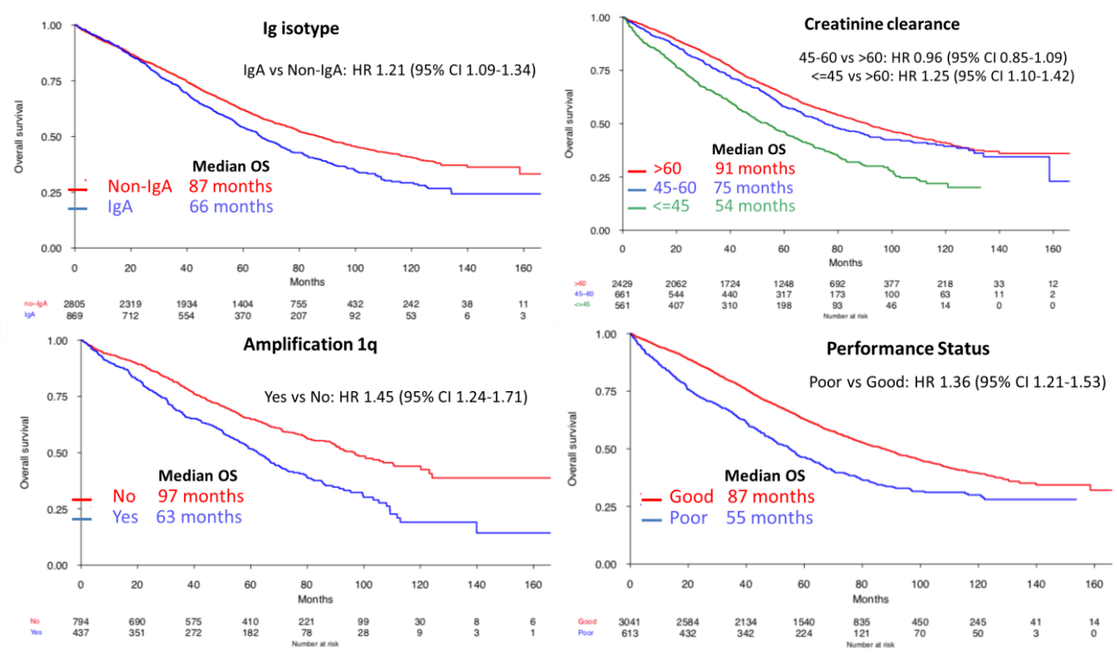
We therefore defined high-risk CA as del(17p) and/or t(4;14) positivity. High-risk CA were present in 23% of evaluable patients, while low-risk CA in 77%. Overall, 3674 patients (66%) had complete ISS, CA and LDH data and were thus eligible for R-ISS analysis. Baseline characteristics and OS of patients with complete vs incomplete data (median OS 80.6 vs 80.2 months, p=0.95) were similar, excluding a selection bias. R-ISS I was calculated as ISS I, no high-risk CA [del(17p) and/or t(4;14)] and normal LDH; R-ISS III was calculated as ISS III and high-risk CA or high LDH; R-ISS II included all the other possible combinations. 962 (26.2%) patients had R-ISS I disease, 2334 (63.5%) R-ISS II and 378 (10.3%) R-ISS III. Median OS was 158.6 months for R-ISS I, 71.1 months for R-ISS II and 36.6 months for R-ISS III patients (Figure 2). 5-year OS rates were 80%, 56% and 34%, while 10-year OS rates were 60%, 33% and 13% for R-ISS I, II and III respectively.

Figure 2. OS in NDMM patients stratified by R-ISS



In a multivariate Cox model, R-ISS II vs I (HR 2.20, 95% CI 1.94-2.5), R-ISS III vs I (HR 4.58, 95% CI 3.88-5.4), male sex (HR 1.20 vs female sex, 95% CI 1.09-1.31) and age >65 years (HR 1.62 vs ≤65 years, 95% CI 1.47-1.78) significantly increased the risk of death (p<0.001). The prognostic role of R-ISS was also confirmed in the 1244 patients that were not included in the original R-ISS report (R-ISS II vs I HR 2.38, R-ISS III vs I HR 4.40, p<0.001), validating it. The prognostic role of R-ISS was confirmed by subgroup analyses on: transplant-eligible patients [2161, 58.8%; both receiving (1611, 43.8%) or not receiving (550, 15.0%) transplant]; transplant-ineligible patients (1513, 41.2%); and patients receiving PIs (874, 23.8%), IMiDs (1669, 45.4%) or both (1131, 30.8%).
We next tested whether additional factors can impact OS in a multivariate Cox model including R-ISS, age and sex (Figure 3 A-D). NDMM patients with an IgA monoclonal component showed a worse OS compared to non-IgA patients (HR 1.21, p<0.001). A baseline creatinine clearance ≤45 ml/min independently predicted OS, as compared to a normal renal function (HR 1.25, p<0.001). The amp(1q) effect on OS was solid (HR 1.45, p<0.001), although data were only available in 1231 patients due to many missing values. Patients with a poor prognostic performance status (ECOG >1 or Karnofsky <80) were at higher risk of death as well (HR 1.36, p<0.001).

Figure 3. Additional factors not included in the R-ISS model impacting OS.



Conclusion — We confirmed the prognostic role of R-ISS within the largest cohort of NDMM patients analyzed so far. Moreover, we detected other independent OS predictors that can help us to further refine the current prognostic method. The addition of new datasets is planned; the improvement of the current R-ISS may foster a worldwide collaboration.

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