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Letter

Pitfalls and limitations of a single-centre, retrospectively derived prognostic score for Phase I oncology trial participants – Reply to Fussenich et al.: A new, simple and objective prognostic score for Phase I cancer patients

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To the editors:

We read with interest the derivation of a new prognostic scoring system by Fussenich et al.[1] which adds to efforts by several groups aiming to provide objective risk stratification and optimise patient selection for Phase I trials.[2–6] As the series in the Nijmegen model comprised only 122 subjects treated at one site, and as Fussenich et al. acknowledged in their conclusion, larger studies are required in order to put their conclusions into context. For this reason, we have studied the utility of the Nijmegen score using data collected from the European Drug Development Network (EDDN[1]).[7]

In the original EDDN data collection, which was completed in September 2009 before the Fussenich et al. report was published, serum sodium, one of the prognostic variables in the Nijmegen score, was available in 330 patients from four different European countries (with 20–30% of patients each): France, Spain, The Netherlands and United Kingdom. There were no significant differences in baseline characteristics and outcomes between this subgroup and the rest of the patients in the EDDN. In the EDDN series, sodium (as continuous or <135 mmol/L) and haemoglobin (as continuous or <lower limit of normal [LLN] according to sex) were not significant factors associated with overall survival (OS) or 90-day mortality ($p > 0.05$). Of note, haemoglobin (only as continuous, but not as <LLN cut-off) was an independent factor associated with progression free survival (PFS, $p < 0.029$).

We have examined the agreement between the Nijmegen score and the prospectively[2,3] and multi-institutionally

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validated[7] Royal Marsden Hospital (RMH) score. The agreement between both scores was poor with a Kappa index (K) of 0.26, indicating that the scores classify patients very differently. Although there was a significant difference in overall survival (OS) in the EDDN series between the Nijmegen score low and high risk groups (median OS 44 versus 32 weeks; $p = 0.002$), the difference was small with a hazard ratio of just 1.34 (CI-95% 1.17–1.52). In fact, the detected difference was mainly between scores 0 and 1/2/3, as there was an absence of a clear separation of OS curves between scores 1, 2 and 3 (Fig. 1A). In addition to OS, the Nijmegen study considered other end-points, including PFS, to support the recommendation of this new score. In our series, the Nijmegen score 0 clearly differed from scores 1, 2 and 3 in terms of PFS (Fig. 1C, $p = 0.004$). However, using both OS and PFS as end-points, the RMH score provided a better discrimination of survival groups (Fig. 1B and D). The authors claimed that the RMH score did not add to the Nijmegen model. We hasten to point out that the presence of a common variable (i.e. LDH > ULN) can easily lead to false-negative conclusions and argue that the comparisons of multivariate prognostic models such as these ought to be made using specific parameters, especially when common variables exist. Nonetheless, similarly to Fussenich et al., we investigated whether the Nijmegen score provided additional value to the RMH score predicting OS or PFS by carrying out a Cox regression with two covariates (with each score as a predictor); the Nijmegen score did not add significant value to the model based on the RMH score only ($p = 0.356$ and $p = 0.304$, respectively).

Instead of OS and PFS, we and others have used the 90-day mortality rate as an end-point to assess the validity of these prognostic scores[7–10] as this is a more relevant end-point to use in studies that seek to examine factors directly related to patient attrition than OS and/or PFS. Fussenich et al. had a very

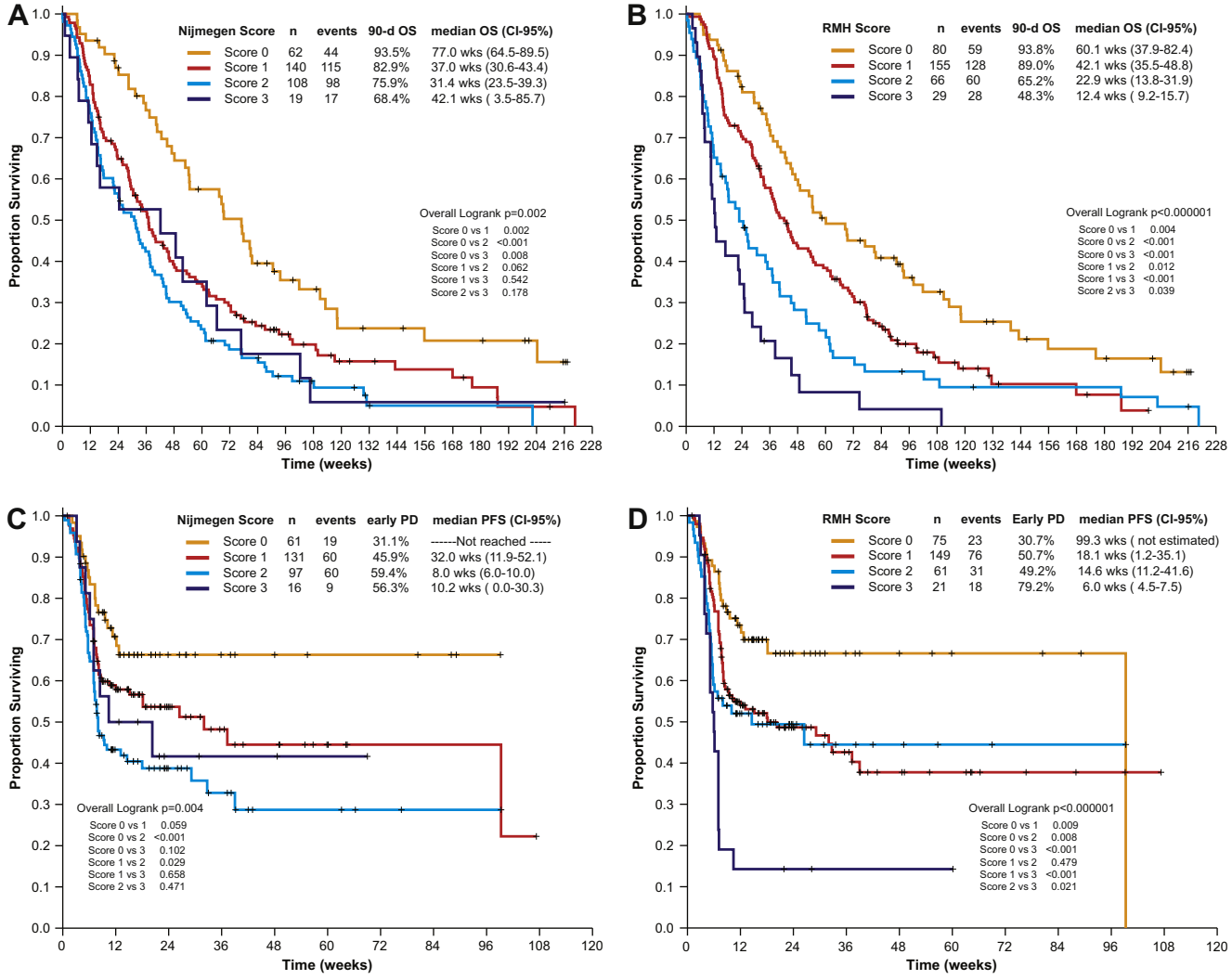

Fig. 1 – Kaplan–Meier curves: (A) Overall Survival (OS) and (C) Progression Free Survival (PFS) according to the Nijmegen score; (B) OS and (D) PFS according to the RMH score. The Nijmegen prognostic score range from 0 to 3 and includes the following risk factors: lactate dehydrogenase (LDH) > upper normal limit (UNL), +1; haemoglobin < lower normal limit (LNL) adjusted by sex, +1; and sodium < 135 mmol/L, +1. The RMH prognostic score also range from 0 to 3 and includes the following risk factors: LDH > UNL, +1; albumin < 35 g/L, +1; and >2 metastatic sites, +1. Early PD: progression rate at the first radiologic re-evaluation on trial.

limited number of events for the latter end-point (n = 13, 11%) and thus their multivariate analysis for this end-point could be over-fitted and may explain in part why they did not identify other prognostic factors validated in the literature.[8] We evaluated the performance of Nijmegen score in predicting 90-day mortality using a receiver operating characteristic (ROC) curve and comparing its areas under the curve (AUC) with that of the RMH score.[7,9] This analysis showed that the Nijmegen score has a significantly inferior performance in predicting 90-day mortality than the RMH score in the EDDN series (AUC 59% versus 76% respectively, p = 0.00003).

The authors also pointed out the addition of the Penel scoring system[10] significantly improved the Nijmegen system. This is questionable as the lymphocyte count was used in the Penel et al. series but the white cell count was used instead in the Nijmegen model; indeed, lymphocyte and white cell counts as well as other factors (including PS) had significantly different prognostic value in the EDDN series, but the addition of extra variables to the RMH score increased the complexity of the score without improving significantly the ability to discriminate patients who die within 90-days of Phase I inclusion.[7–9]

We examined the reproducibility of the Nijmegen score between screening and day 1 on trial using a second series of patients from the RMH previously reported elsewhere[9] and not included in the previous analysis. The K index for the Nijmegen score was just 0.65 whilst for the RMH score was 0.88. This could, at least in part, be explained by a high variability of two variables in the Nijmegen score, namely sodium and haemoglobin. The coefficients of correlation (r^2) of these two parameters, measured at screening and day 1 on study, were poor at 0.24 and 0.23, respectively.

In conclusion, the model proposed by the Nijmegen group had the best fit with their institutional data but it was not validated in the broader EDDN series. The low reproducibility of the model when measured at different time points prior to treatment exposure point to the limited utility of the proposed model. Furthermore, these results point to the importance of ascertaining the validity of clinical models derived from external data prior to implementation in daily practice.

Conflict of interest statement

The authors have no conflicts of interest.

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