Validation of the Manchester Score from a modern perspective

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Introduction

- Less than 25% of patients with small cell lung cancer (SCLC) survive beyond one-year post diagnosis and only 5% beyond five years.
- Many patients with SCLC are frail, comorbid, elderly or have poor performance status and thus are often underrepresented in clinical trials.
- Underrepresentation introduces uncertainty to decision-making for the best treatments for these patients.
- Prognostic models combine a range of data to estimate patients' likely survival.
- The Manchester prognostic score is a widely known decision-support tool for SCLC, described by Cerny et al. (1987).
- Derived from a Cox model based on six routinely measured pre-treatment factors.
- A critical step in the clinical deployment of models is robust and continuous validation.
- Here, we revisited the original model and tested its utility in the modern treatment era for an unselected cohort of patients with routinely collected data.

The Manchester Score

Prognostic factor	Manchester Score threshold	Cox linear predictor coefficient
Stage	Extensive disease	+ 0.63 (if extensive)
KPS	< 60	- 0.02 * KPS
LDH	> 450 U/l	+ 1.17 * log10(LDH)
Alkaline Phosphatase	> 165 mmol/L	+ 0.69 * log10(Alk.Phos.)
Sodium	< 132 mmol/L	-8.43 * log10(Sodium)
Bicarbonate	< 24 mmol/L	-0.047 * Bicarbonate

Table 1. showing the thresholds for use of the Manchester score nomogram and the equation to calculate the original Cox score.

Prognostic group	Manchester Score	Cox linear predictor group
Good	0, 1	< -16.5
Intermediate	2, 3	-16.0 to -16.5
Bad	4, 5, 6	> -16.0

Table 2. showing the thresholds for separating the scores into good, intermediate and bad prognostic groups.

Conclusion

- The Manchester Score discriminates between survival risk groups despite changes in patient survival since 1987 (likely due to improvements in treatment)
- The prognostic factors remain predictive and routinely measured.
- Updates to the model allow survival predictions to be made for individual patients, allowing for clinical use as a decision aid.
- Performance decreases at later time points.
- Inclusion of more routinely measured prognostic factors and treatment variables would improve accuracy and model relevance in a clinical setting.

Future work

Next steps will be to incorporate treatment factors into the model through the application of causal techniques.

Results and Discussion

- Kaplan-Meier plots show good discrimination between risk groups.
- The "good" prognostic group had 2-6 months higher median survival than the original 1987 cohorts.
- Both scores exhibited acceptable concordance (0.68 and 0.70).
- Full recalibration revealed that alkaline phosphatase levels are no longer significantly related to survival.
- LDH, stage and performance status do remain significant.
- Observed to expected ratio of survival probability at six months, one and two years were 1.001, 0.971 and 0.795, respectively.
- This means the model performs poorly at later time points despite being calibrated in the same dataset used to develop the baseline hazard.

Method

- Consecutive (2013-2022 inclusive), single-centre, retrospective data from 1783 routinely treated SCLC patients was used to evaluate the model's performance.
- Multiple imputation was used to fill in missing data, avoiding bias from complete case analysis or mean substitution.
- All outputs were calculated on 30 imputed datasets and combined using Rubin's rules.
- Both the categorical Manchester score and its underlying Cox linear predictor were calculated for each patient.

External validation

- Kaplan-Meier curves were plotted stratified according to the same score thresholds used in the original publication and compared to the survival curves seen in 1987.
- Harrel's C-index was calculated for both scores.
- The Cox proportional Hazard model was fully recalibrated.

Survival estimation and internal validation

- A baseline hazard for the Cox linear predictor was estimated using the modern data at six months, one year, and two years post-diagnosis.
- Resulting survival estimates were calibrated with optimism adjustment from bootstrapping.

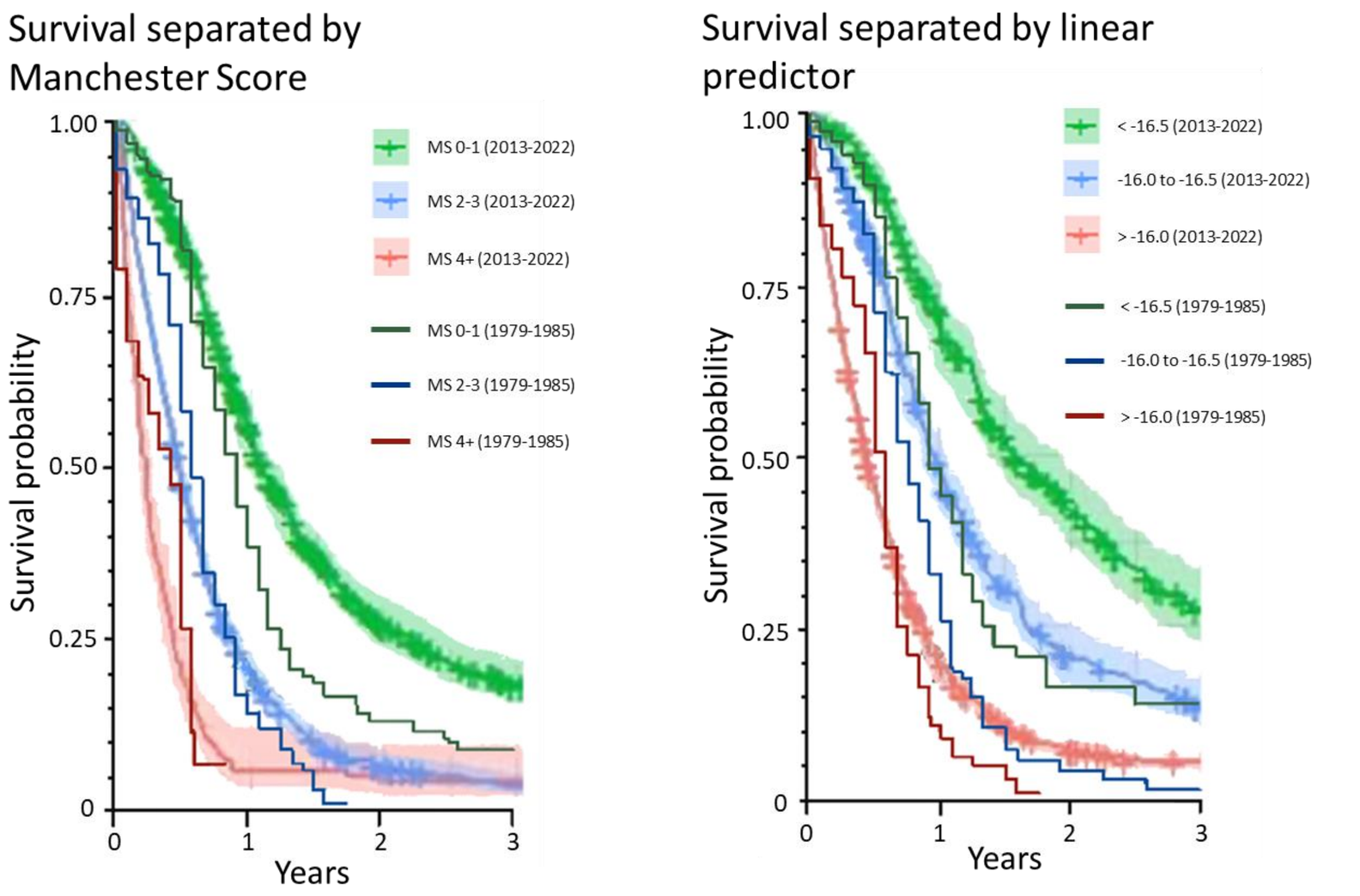

Figure 1. shows the Kaplan-Meier survival curves for the pooled Manchester Score and Cox linear predictor groups overlayed with the equivalent graphs from Cerny et al. (1987).

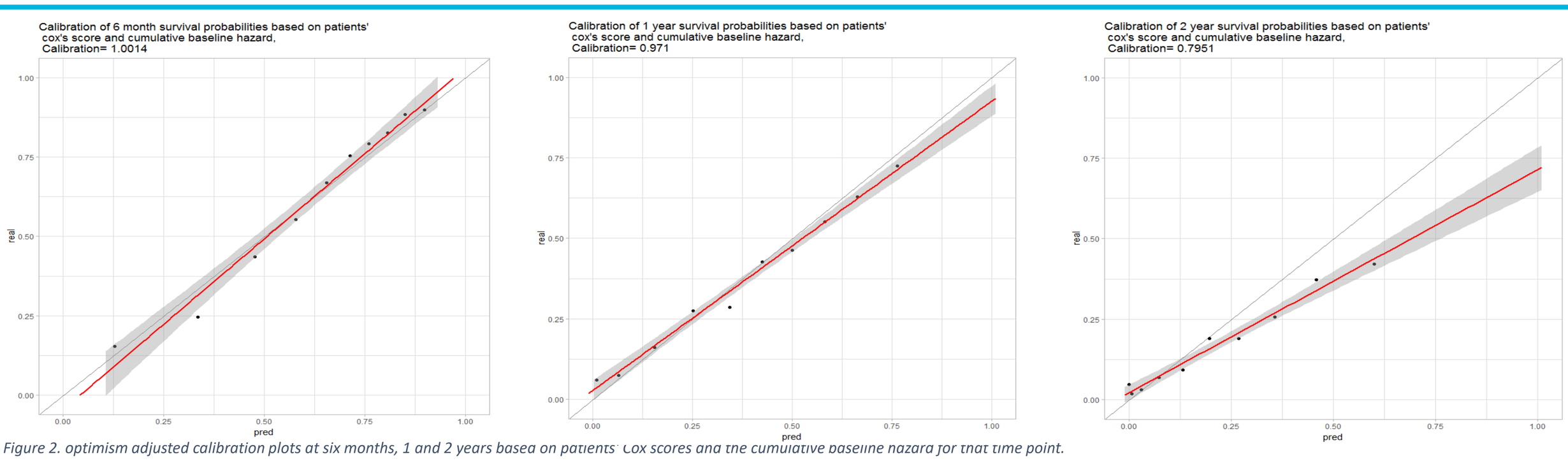

Figure 2. optimism adjusted calibration plots at six months, 1 and 2 years based on patients' Cox scores and the cumulative baseline hazard for that time point.

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