Best survival model for resected HCC
A systematic review and meta-analysis

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INTRODUCTION

- Many prognostic models for hepatocellular carcinoma (HCC) have been developed

- Novel biomarkers are increasingly discovered, but added value is not always clear

- Once models are developed, generalizability is the main concern

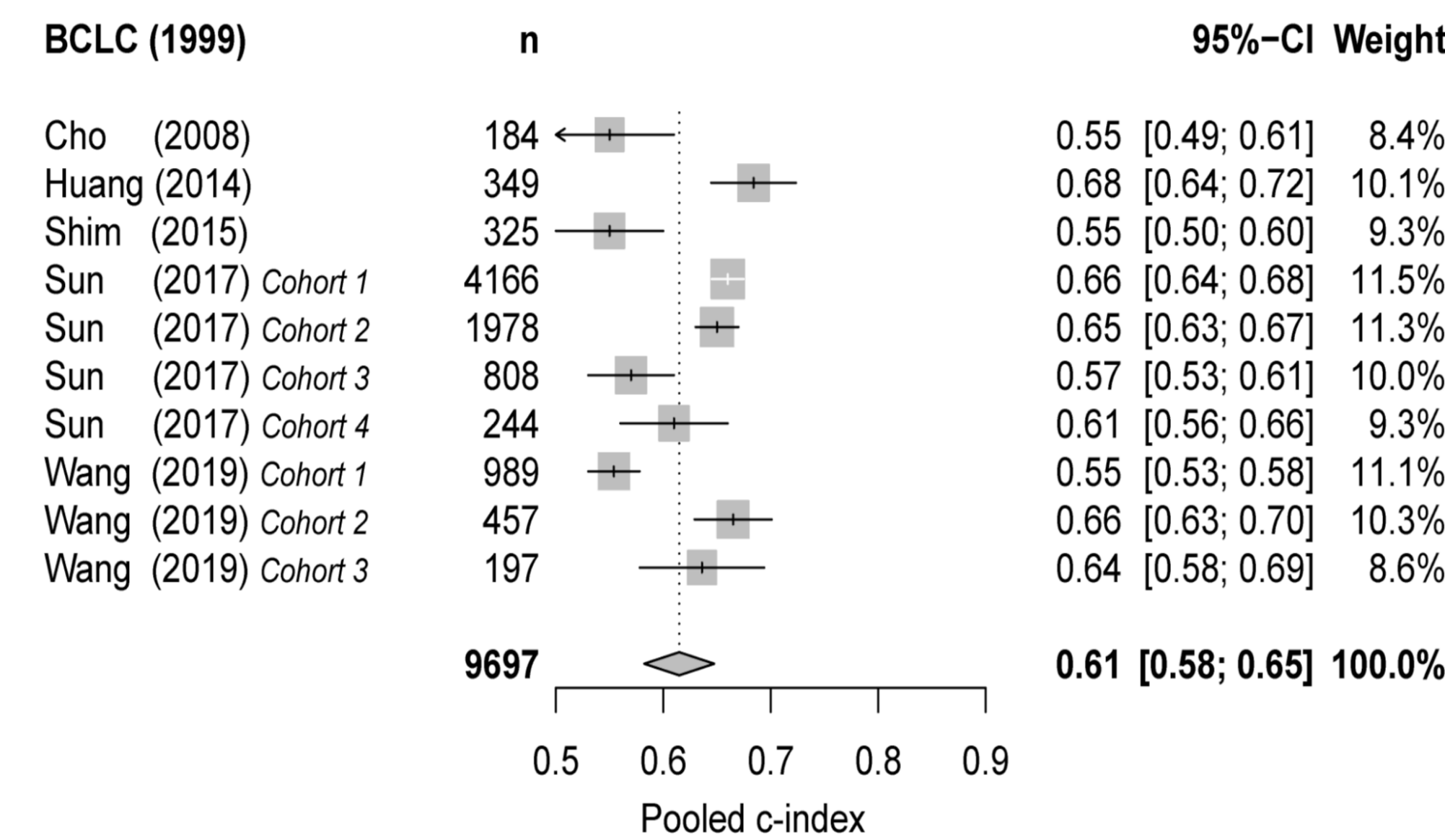- Previous reviews were descriptive and did not assess performance at external validation[1-4]

AIM

1. To assess performance of prognostic models for HCC at external validation

2. To determine trends in the selection of prognostic factors
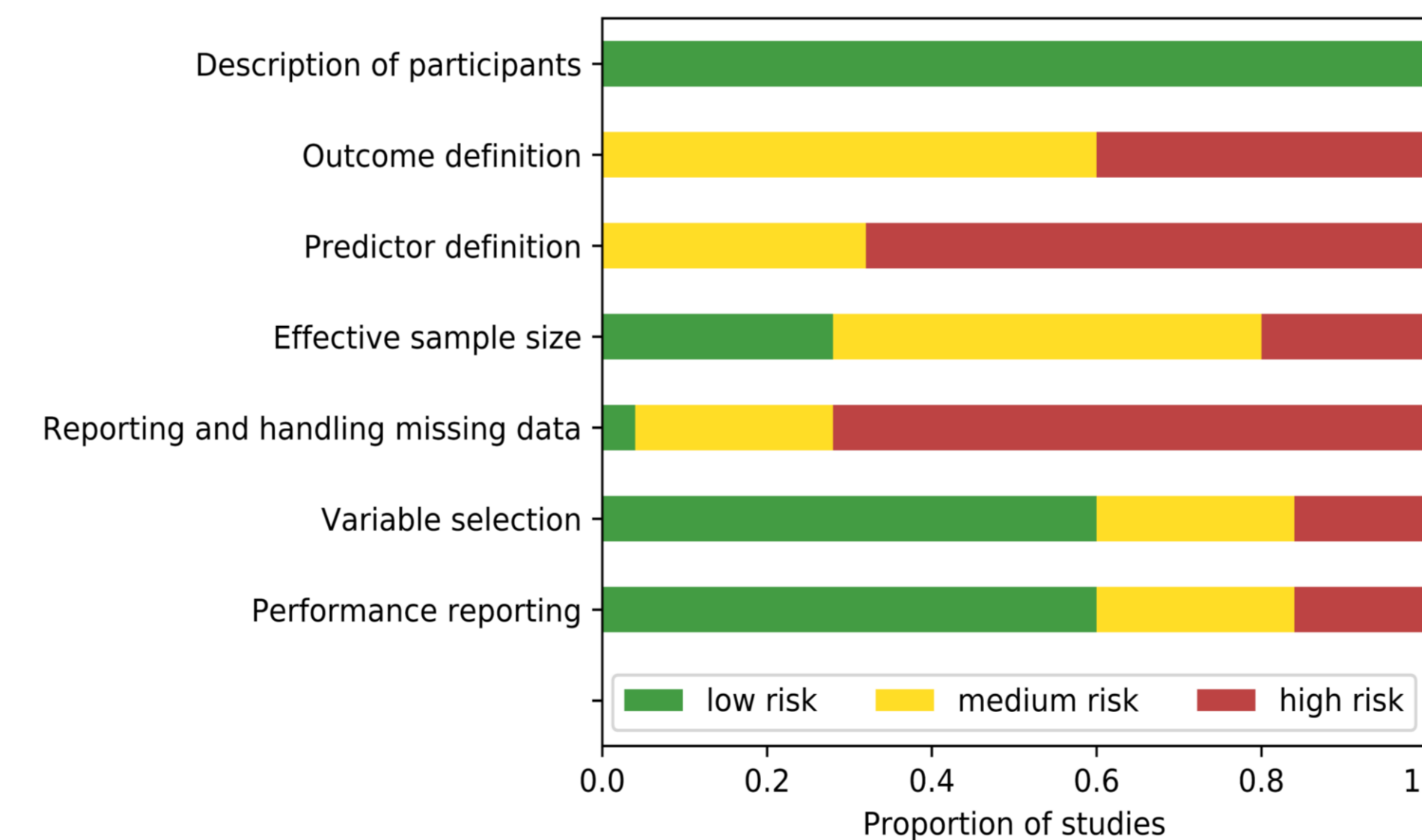
RESULTS

- 24 of the 38 validated models predicted OS

- Models improved over time

- 6 out of 25 models predicting OS had good performance at external validation (C-index > 0.7)
  - Li-post (0.77)
  - Yang-post (0.76)
  - Li-OS (0.74)
  - Yang-pre (0.74)
  - Wang-nomogram (0.71)
  - Shanghai-score (0.70)

- All established models for predicting OS had a C-index below 0.7

- On average models had 7 prognostic factors
  - Always included: tumour size, tumour number, and vascular invasion
  - Alpha-fetoprotein increasingly included
  - Ascites and encephalopathy increasingly dropped

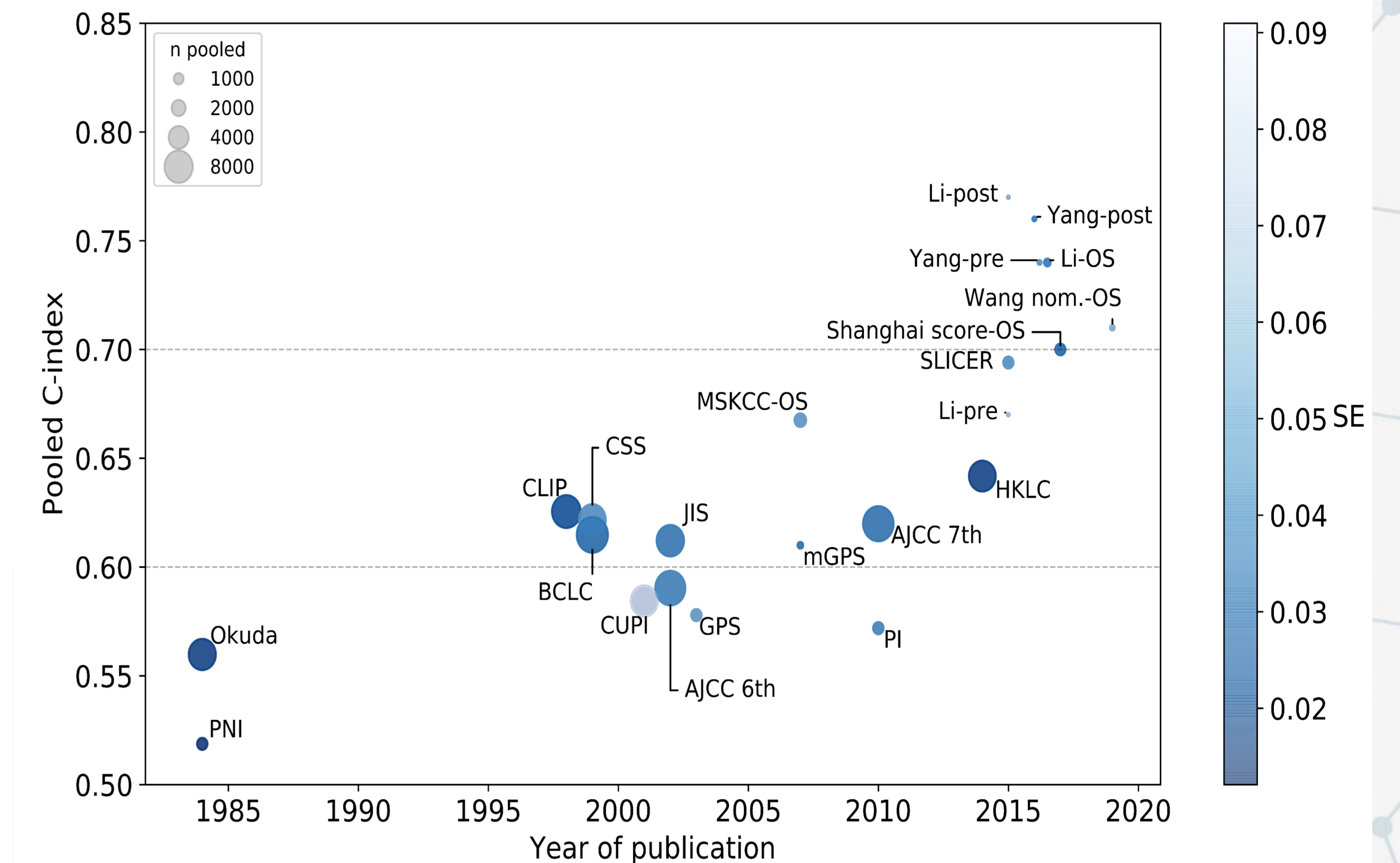- Overall performance and quality of the development studies remained low

Forrest plot of studies externally validating the BCLC

BCLC (1999)	n		95%-CI	Weight
Cho (2008)	184		0.55 [0.49; 0.61]	8.4%
Huang (2014)	349		0.68 [0.64; 0.72]	10.1%
Shim (2015)	325		0.55 [0.50; 0.60]	9.3%
Sun (2017) Cohort 1	4166		0.66 [0.64; 0.68]	11.5%
Sun (2017) Cohort 2	1978		0.65 [0.63; 0.67]	11.3%
Sun (2017) Cohort 3	808		0.57 [0.53; 0.61]	10.0%
Sun (2017) Cohort 4	244		0.61 [0.56; 0.66]	9.3%
Wang (2019) Cohort 1	989		0.55 [0.53; 0.58]	11.1%
Wang (2019) Cohort 2	457		0.66 [0.63; 0.70]	10.3%
Wang (2019) Cohort 3	197		0.64 [0.58; 0.69]	8.6%
	9697		**0.61 [0.58; 0.65]**	**100.0%**

Pooled c-index

Risk of Bias (derivation studies)

low risk · medium risk · high risk

Proportion of studies

Performance OS models at external validation

Each point represents the pooled c-index of a model. The size corresponds to the total number of patients in which the model is validated. The color represents standard error (SE) of the estimate; the darker the color the more precise the estimate. Lastly, the horizontal dashed lines represent the performance thresholds.

METHOD

Systematic review following PRISMA

Inclusion criteria
- Models predicting overall survival (OS) or disease free survival (DFS)
- Externally validated in patients with resected HCC
- Report performance in terms of C-index or AUC-ROC

Exclusion criteria
- Prognostic factors not readily available in clinical practice (e.g. RNA/DNA or liquid biopsies)
- Resection for recurrence of malignancies

Validation studies
- Extraction of publication and cohort characteristics
- Primary outcome measure: C-index
- Meta-analysis of c-indices using inverse variance weighting
- Graphing the pooled c-indices in a scatterplot

Derivation studies
Derivation studies were identified though the reference list of the validation studies. We extracted:
- Type of information included in the final model
- Publication and cohort characteristics
- Variable definitions
- Statistical techniques
- Performed: Risk of bias assessment (CHARMS/TRIPOD)

CONCLUSIONS

- We presented the performance at external validation of all externally validated prognostic models for HCC

- We provide a benchmark for future models incorporating novel biomarkers

- Six validated prognostic models demonstrated a good performance for predicting OS after resection of HCC

- These most promising models need additional validation in western cohorts

- Performance gains are likely if the risk of bias in derivation studies is reduced

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