COMPERA 2.0 risk stratification in medically managed chronic thromboembolic pulmonary hypertension

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To the Editor:

The COMPERA 2.0 model has been validated as a novel risk stratification system in pulmonary arterial hypertension (PAH), yet awaits validation in other causes of pulmonary hypertension [1, 2]. This study aimed to validate this model in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were either inoperable or had residual CTEPH following intervention.

A retrospective analysis was undertaken of all records of patients who were diagnosed with CTEPH at the Scottish Pulmonary Vascular Unit between 1 January 2010 and 31 December 2020. Patients were included if they met the following criteria: 1) age ⩾18 years; 2) diagnosis of CTEPH according to standard diagnostic criteria [3, 4] and based on multidisciplinary consensus; 3) incident diagnosis of treatment-naïve CTEPH, and did not have pulmonary endarterectomy (PEA) or balloon angioplasty (BPA) during follow-up; or 4) had residual pulmonary hypertension after PEA or BPA, included at the point of right heart catheterisation confirming residual pulmonary hypertension (mean pulmonary artery pressure ⩾25 mmHg). Patients were excluded if they were missing any of: baseline World Health Organization functional class (WHO FC), 6-min walk distance (6MWD) or N-terminal prohormone brain natriuretic peptide (NT-proBNP). Diagnostic admission, including right heart catheterisation, served as the baseline visit. Risk according to the three-stratum method and four-stratum method was performed as described by Hoeper *et al.* [1]. Repeat risk stratification was performed at first follow-up.

The primary outcome was all-cause mortality with survival time calculated from the date of diagnosis until death, truncated at 5 years. Survival analysis was performed with Kaplan–Meier analysis with the log-rank test. Cox proportional hazard ratios (HRs) were calculated in reference to the high risk category and Harrell's C-statistic was used to compare Cox models for mortality. Significance was set at the $p<0.05$ level. GraphPad Prism (v9.3.0, San Diego, CA, USA) was used for analysis. Approval was obtained from London-Riverside Research Ethics Committee (21/PR/1607).

218 patients were diagnosed with CTEPH in the study period. 20 patients were excluded due to missing baseline data and 70 patients had no residual pulmonary hypertension following PEA. 128 patients were therefore included in the baseline cohort, of whom 52 (40.6%) were surgically inoperable, 26 (20.3%) were medically inoperable, 23 (17.9%) declined PEA, 19 (14.8%) had residual pulmonary hypertension following PEA or BPA and seven (5.4%) died whilst PEA was being considered. At baseline, 53.9% were male, 18% were WHO FC II, 77.3% FC III and 4% FC IV. The mean age was 69.4 years, mean NT-proBNP was 2244 $pg \cdot mL^{-1}$ and mean 6MWD was 262 m.

At baseline, using the four-stratum model, eight (6.3%) patients were low risk, 32 (25%) patients were intermediate-low risk, 63 (49.2%) patients were intermediate-high risk and 25 (19.5%) patients were high risk. Using the three-stratum model, 10 (7.8%) patients were low risk, 93 (72.7%) patients were intermediate risk and 25 (19.5%) were high risk. The four-stratum model calculated survival at 1, 3 and 5 years respectively as 100%, 100% and 100% for low risk; 93%, 79.4% and 57% for intermediate-low risk; 91.5%, 68.4% and 42.8% for intermediate-high risk; and 83.3%, 46.2% and 22.9% for high risk ($p<0.0001$ for between group comparison) (figure 1a). Survival calculated by the three-stratum model was 100%, 100% and 100% for low risk; 86.9%, 68.8% and 48.3% for intermediate risk; and 80%, 48.5% and

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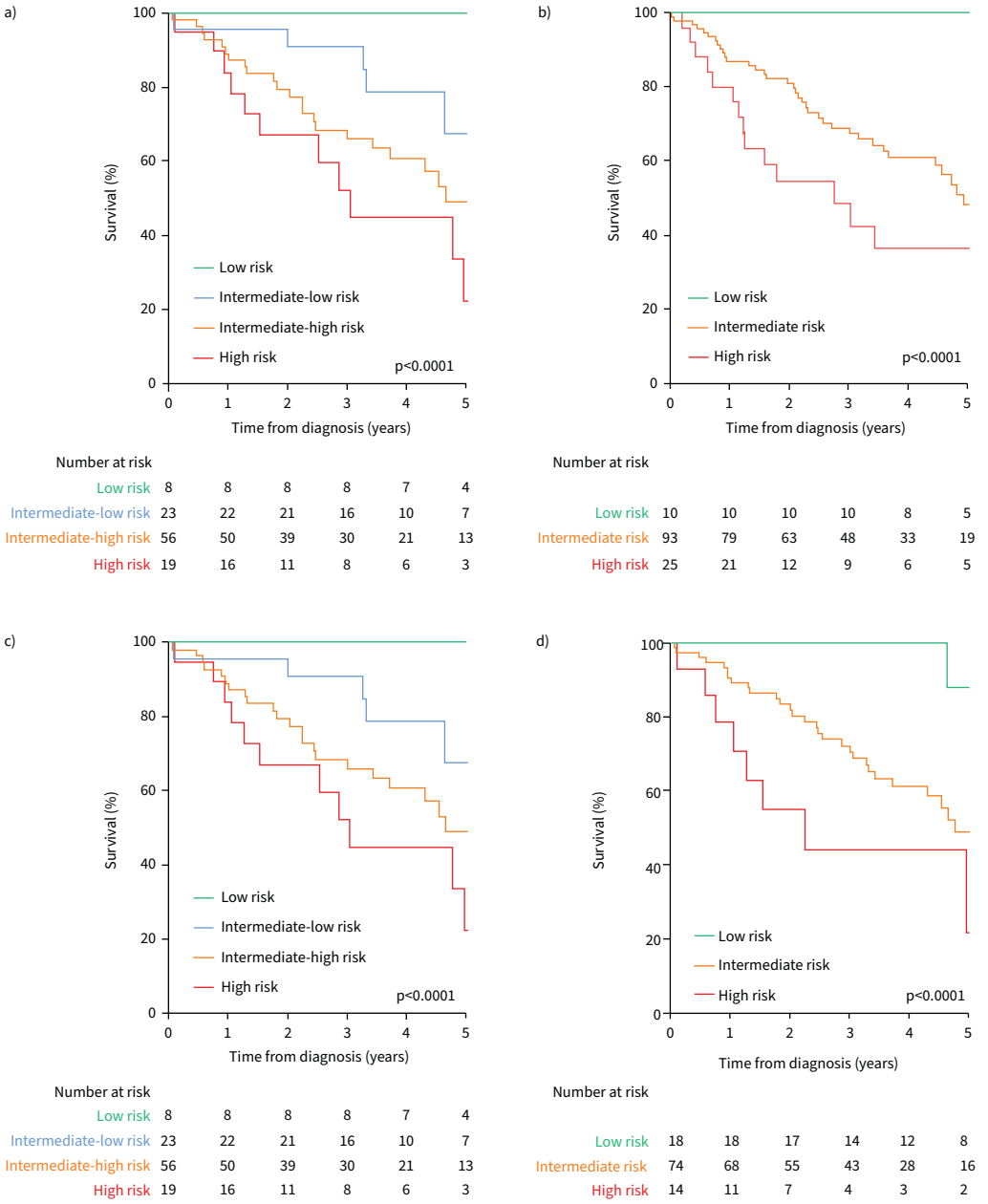

FIGURE 1 5-year survival for medically managed chronic thromboembolic pulmonary hypertension, as calculated by the a) four-stratum model from baseline, b) three-stratum model from baseline, c) four-stratum model from follow-up and d) three-stratum model from follow-up.

36.3% for high risk (p<0.0001) (figure 1b). There was a reduced risk of death for patients in the intermediate groups compared to high-risk groups for either method (four-stratum HR 0.47 for intermediate-high, and 0.32 for intermediate-low, *versus* three-stratum 0.44 for intermediate risk) with no difference in discrimination between methods (Harrell's C-statistic 0.62 for both methods).

The median time to first follow-up was 3.6 months and information for risk variables at this time was available in 106 (83%) of cases. 80% of patients were on monotherapy, 5% dual and 15% were untreated. Overall, 35 (33%) patients changed risk group between diagnosis and first follow-up when the four-stratum model was used, as opposed to 25 (23.6%) for the three-stratum model. Within the intermediate risk groups, 31.6% of patients moved out of an intermediate risk group with the four-stratum model, as opposed to 10.4% with the three-stratum model. At follow-up, using the four-stratum model 1-, 3- and

5-year survival was calculated at 100%, 100% and 100% for low risk; 95.6%, 90.8% and 67.4% for intermediate-low risk; 88.9%, 68.2% and 49% for intermediate-high risk; and 83.7%, 52.2% and 22.3% for high risk ($p<0.0001$) (figure 1c). Using the three-stratum model, this was 100%, 100% and 87.5% for low risk; 90.5%, 72.2% and 48.9% for intermediate risk; and 78.7%, 44% and 22.3% for high risk ($p<0.0001$) (figure 1d). Both models predicted reduced mortality when compared to high-risk groups (four-stratum HR 0.48 for intermediate-high, and 0.21 for intermediate-low, *versus* three-stratum 0.38 for intermediate, and 0.07 for low risk) yet the four-stratum model had greater discrimination (Harrell's C-statistic 0.70 *versus* 0.65 for three-stratum).

The main findings are: 1) the four-stratum model identified four distinct prognostic groups with different survival profiles; 2) more patients moved risk group using the four-stratum method, both overall and within the intermediate risk groups; and 3) the four-stratum method had improved discrimination of overall mortality at follow-up. In CTEPH, the four-stratum model allows for greater delineation of prognosis over the three-stratum model, as it defines one additional risk group with distinct survival estimates. It conforms to the established model of estimating 1-year mortality at <5% for low risk and >10% for high risk. It is strengthened by simplicity, relying on three non-invasive variables, and therefore can be calculated at both baseline and follow-up without haemodynamic measurements. This study is limited by the relatively low study numbers. The relatively small proportion of patients who moved between risk groups may be as a result of the high proportion of untreated patients, a consequence of including patients between 2010–2015, when PAH-specific therapy use in CTEPH was often delayed whilst an opinion on surgical intervention was sought. We conclude that the COMPERA 2.0 model is applicable for risk stratification in medically managed CTEPH and offers greater clinical discrimination.

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