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Performance of Risk-Stratification Scores for Patients With Pulmonary Arterial Hypertension in a Multi-Ethnic Asian Population

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ABSTRACT

Guidelines recommend risk stratification of pulmonary arterial hypertension (PAH) patients to guide management. There are currently several risk stratification scores available, which have largely been validated in various pulmonary hypertension registries in the West but not in Asia. We aim to study the performance of these different risk scores in PAH patients from a multi-ethnic Asian population. A retrospective review of all PAH patients from Jan 2014 to Jun 2021 from a tertiary cardiac center was performed. Mortality outcomes were obtained from national registries. Using the 2022 ESC/ERS, REVEAL Lite 2.0 and COMPERA 2.0 risk scores, patients were classified into different risk strata at baseline and at follow-up and changes in any risk strata recorded. The prognosis of patients based on these factors was compared. A total of 153 patients (mean age: 57 ± 17 years; 117 women; 94 Chinese, 33 Malay, 19 Indian) were included. All three scores showed significant difference in mortality outcomes between the different risk strata both at baseline and at follow-up ($p < 0.05$), with the highest risk group showing the highest mortality. Patients who worsened to or remained at intermediate/high-risk generally had a worse prognosis than those who remained stable at or improved to low-risk strata. The 2022 ESC/ERS and COMPERA 2.0 risk scores had C-statistics of 0.73 (0.58–0.88) and 0.80 (0.72–0.88), respectively, for predicting 1-year mortality. Serial risk stratification is a useful tool in prognosticating Asian PAH patients and may play an important role in guiding therapeutic management.

Pulmonary arterial hypertension (PAH) is a disease with historically poor prognosis [1]. In the contemporary era, advancements in PAH-specific drugs and combination therapy have significantly improved short to medium-term mortality [2–4]. The concept of risk stratification has been well established in guidelines as an important tool in guiding the management of these patients [5]. As one of the first risk scores, the 2015 European Society for Cardiology/European Respiratory

Abbreviations: 6MWD, 6-min walk distance; APAH-CHD, associated pulmonary arterial hypertension-congenital heart disease; APAH-CTD, associated pulmonary arterial hypertension-connective tissue disease; AUC, area under curve; ERS, European Respiratory Society; ESC, European Society of Cardiology; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; ROC, receiver operating curve.

Haowen Jiang and Ju Le Tan are co-first authors.

Society (ESC/ERS) pulmonary hypertension (PH) guidelines originally adopted a multiparametric approach using a three-strata model to classify patients at low, intermediate, or high risk of death [6]. Since then, several modified risk scores have been developed and validated, mostly in western PH registries [7–9]. These include the Swedish Pulmonary Arterial Hypertension Registry (SPAHR) [9], the French PH Registry (FPHR) [8], and the Comparative, Prospective Registry of Newly Initiated Therapies for PH (COMPERA) [7, 10]. Other risk stratification scores have also been developed on non-European cohorts, including the initial United States (US) Registry to Evaluate Early And Long-term PAH disease management (REVEAL) risk scores, followed by the more contemporary revised REVEAL 2.0 and REVEAL Lite 2.0 [11–13]. Each of these have also been externally validated in other western cohorts [14–16]. These studies were also notable for their use of risk stratification not only at baseline, but also at follow-up (i.e., serial risk assessment). Risk strata at follow-up and change in risk strata from baseline were consistently demonstrated to be significant predictors of mortality vis-à-vis baseline values alone [8, 9, 14, 17], reflecting the prognostic importance of response to therapy. More recently, the 2022 ESC/ERS guidelines published a revised risk stratification score [17]. Besides incorporating newer parameters for a more comprehensive risk assessment at baseline, the 2022 ESC/ERS guidelines also advocates for a simpler, 4-strata model for risk stratification at follow-up identical to that of the COMPERA 2.0 score [17]. Despite the laudable progress in the literature, these studies are mostly based on Western patients with limited contemporary Asian data [18]. We aim to evaluate and validate the accuracy of baseline and follow-up risk stratification using 3 commonly used risk scores (2022 ESC/ERS guidelines, the 4-strata COMPERA 2.0 and the REVEAL Lite 2.0 scores) in a multi-ethnic Asian cohort.

1 | Methods

1.1 | Study Design and Patient Population

This is a retrospective study involving consecutive patients diagnosed with PAH at a single tertiary pulmonary hypertension center from Jan 2014 to Jun 2021.

The diagnosis of PAH was established by the pulmonary hypertension team based on clinical, echocardiographic and in majority of cases (125/153) right heart catheterization (RHC) data. When RHC was performed, PAH was defined as a mean pulmonary arterial pressure (mPAP) of ≥ 20 mmHg and pulmonary vascular resistance of ≥ 2WU, with exclusion of other causes of pre-capillary PH as per the 2022 ESC/ERS guidelines. When RHC was not performed, patients were included with an estimated echocardiographic systolic pulmonary artery pressure of > 50 mmHg on echocardiogram with exclusion of other causes of pulmonary hypertension and diagnosed as PAH by the pulmonary hypertension team. Other inclusion criteria included availability of at least 2 out of 3 of the following variables (WHO functional class, 6-min walk distance [6MWD], or N-terminal pro b-type natriuretic peptide [NT-proBNP]) at initial consult for the 2022 ESR/ERS and COMPERA 2.0 risk scores, with at least one follow-up at 3–12 months after initial consult. For the REVEAL Lite 2.0 risk score, due to differences in methodology of calculation of risk scores (variables are summed up), all key variables (WHO functional class, 6MWD and NT-proBNP) were required to be present for calculation. Thus for analysis of the REVEAL Lite 2.0 risk score, a smaller subset of patients which had the complete set of key variables was utilized. All patients were followed up until June 2022. Demographics, clinical, biochemical, imaging, hemodynamic, treatment and functional parameters were collected from the medical records at baseline and at follow-up. Ethics approval was obtained from the institution's Institutional Review Board.

1.2 | Risk Stratification

Patients were risk stratified into low-, intermediate- (intermediate-low, intermediate-high for COMPERA 2.0), and high-risk groups based on the 2022 ESC/ERS guidelines, COMPERA 2.0, and REVEAL Lite 2.0 scores. For the 2022 ESC/ERS and COMPERA 2.0 scores, a “score-and-average” method was used. Parameters classified as low-, intermediate- and high-risk were assigned a score of 1, 2, and 3, respectively, with the 2022 ESC/ERS guidelines, and parameters classified as low-, intermediate-low-, intermediate-high-, and high-risk were assigned a score of 1, 2, 3, or 4, respectively, with the COMPERA 2.0 score. The mean score of available parameters for each patient were computed and rounded to the nearest integer. For the REVEAL Lite 2.0 score, each variable was assigned a weight and summed up to determine the final risk strata. Stratification was performed for baseline parameters, as well as follow-up parameters. For the 2022 ESC/ERS guidelines, some modifications were made in the computing of the score as data was collected before publication of the 2022 guidelines, and hence some variables were not collected to sufficient detail to differentiate between a score of 2 and 3. The changes are: Any progression of symptoms and clinical manifestation, syncope, or pericardial effusion on echocardiography was allocated a score of 3 if present and 1 if absent. As recommended in the 2022 ESR/ERS guidelines, the comprehensive 3-strata model was used at baseline, and the simplified 4-strata model (which is identical to the COMPERA 2.0 score) was used for follow-up risk stratification. Missing variables were handled as defined by the original validation cohorts, respectively. For the ESC/ERS and COMPERA 2.0 scores based on a score and average method, missing variables were excluded from the analysis [10, 17]; for REVEAL Lite 2.0, all the key variables of WHO functional class, 6MWD and NT-proBNP were required and a score of 0 was taken for any missing non-key variables (heart rate, systolic blood pressure [SBP], eGFR) [13]. See Supporting Information S1: Tables S1–3 in for summary of the different risk scores.

1.3 | Outcomes

The primary outcome studied was all-cause mortality and secondary outcome was change in risk strata. Mortality outcomes were obtained from national registries with all patients followed up till 30 Jun 2022 or till date of death, whichever was earlier.

1.4 | Statistical Analysis

Statistical analysis was performed using R version 4.2.1. Continuous variables were presented as means ± standard error and categorical variables as frequencies and percentages. Cox-adjusted survival curves were plotted with adjusted p-values shown. The discriminant ability of the various risk scores were assessed by Harrell's C-index and receiver operating characteristics (ROC) area under the curve (AUC). For determination of significant predictors of mortality, multiple imputation using a random forest model was performed for missing values with the MICE package in R. These imputed values were not used in the derivation of risk scores. Uni- and multi-variate Cox-proportional hazards analysis, adjusting for age, gender and PAH subtype, were then performed to determine significant predictors of mortality at both baseline and at follow-up. A p-value of < 0.05 was taken to be significant. The change in risk strata from first visit to follow-up was visualized using Sankey diagrams. A separate sensitivity analysis was performed in patients with RHC-diagnosed PAH to analyse the discriminant ability of the risks scores at baseline and follow-up.

2 | Results

2.1 | Patient Characteristics

In total, 153 PAH patients were included in the study (Supporting Information S1: Figure S1). The average age was 57 ± 17 years old and the cohort predominantly female (80.4%). In terms of ethnicity, 94 patients (61.4%) were Chinese, 33 patients (21.6%) patients were Malay, 19 patients (12.4%) were Indian, and 7 patients (4.6%) were other ethnicities. 68 patients (44.4%) had idiopathic PAH, 47 patients (30.7%) had PAH associated with connective tissue disease, 32 patients (20.9%) had PAH associated with congenital heart disease and 6 patients (3.9%) had PAH related to other etiologies. 80.4% of patients were WHO FC I/II, and mean 6MWD was 318 ± 118 m (see Table 1). Median time from initial visit to first follow up was 5.1 (IQR: 4.2–7.0) months, and median follow-up for the whole study was 39.7 (IQR: 22.6–65.7) months. A total of 153 (100%), 66 (43.2%), and 150 (98.0%) patients had WHO functional class, 6MWD, and NT-proBNP collected, respectively, at baseline. For the REVEAL Lite 2.0 risk scores, 65, 62, and 52 patients with complete set of key variables were included at initial consult, follow-up, and change in risk strata, respectively.

2.2 | Baseline Risk Strata

With the 2022 ESC/ERS guidelines, 56 patients (36.6%) were low-risk, 93 patients (60.8%) were intermediate-risk, and 4 patients (2.6%) were high-risk at baseline. With the COMPERA 2.0 score, 34 patients (22.2%) were low-risk, 49 patients (32.0%) were intermediate-low-risk, 52 patients (34.0%) were intermediate-high-risk, and 18 patients (11.8%) were high-risk at baseline. With the REVEAL Lite 2.0 score, 28 patients (43.1%) were low-risk, 21 patients (32.3%) were intermediate-risk, and 16 patients (29.6%) were high-risk at baseline. See Supporting

TABLE 1 | Overview of baseline characteristics.

Subjects, *n*	153
Age, years	57 ± 17
Female gender, %	117 (80.4)
Race, Chinese/Malay/Indian/Others	94/33/19/7
BMI, kg m^{-2}	24.3 ± 6.6
PAH subsets	
IPAH, %	68 (44.4)
APAH-CTD, %	47 (30.7)
Systemic sclerosis, %	23 (48.9)
Mixed connective tissue disorder, %	13 (27.7)
Sjogren syndrome, %	4 (8.5)
Systemic lupus erythematosus, %	4 (8.5)
Rheumatoid arthritis, %	3 (6.4)
APAH-CHD, %	32 (20.9)
APAH-others, %	6 (3.9)
Co-morbidities	
Hypertension, %	62 (40.5)
Diabetes, %	43 (28.1)
Hyperlipidemia, %	56 (36.6)
Ischemic heart disease, %	27 (17.6)
Atrial fibrillation, %	27 (17.6)
Chronic kidney disease, %	
Previous stroke, %	3 (2.0)
Thyroid disease, %	10 (6.5)
WHO FC Class, I/II/III/IV	23/100/27/3
6MWD, m	318 ± 118
NT-proBNP, ng L^{-1}	3435 ± 8490
Echocardiography	
Right atrial area (cm^2)	19.8 ± 7.2
Pericardial effusion, %	39 (25.5)
Hemodynamics	
mRAP, mmHg	10.3 ± 8.3
mPAP, mmHg	45.1 ± 11.8
PVR, WU	9.4 ± 5.3
Cardiac index, L/min/m^2	2.72 ± 0.95
SvO_2, %	62 ± 11
Supportive therapy	
Warfarin	20 (13.1)
Diuretics	46 (30.1)
Supplemental oxygen	19 (12.4)
Calcium channel blockers	10 (6.5)
PAH-targeted treatment	
PDE5 inhibitor, %	102 (66.7)
Endothelin receptor antagonist, %	30 (19.6)

(Continues)

TABLE 1 | (Continued)

Prostacyclin, %	5 (3.3)
Monotherapy, %	81 (52.9)
Dual therapy, %	23 (15.0)
Triple therapy, %	4 (2.6)
No therapy, %	46 (30.1)

Information S1: Table S4 for breakdown of patient characteristics by baseline strata.

One-year mortality was 1.8%, 6.5%, 75% for low-, intermediate-, high-risk risk strata with the 2022 ESC/ERS guidelines; 0%, 0%, 13%, 17% for low-, intermediate low-, intermediate high-, high risk strata with the COMPERA 2.0 score; and 0% for all low-, intermediate-, high-risk strata with the REVEAL Lite 2.0 score. Three- and 5-year mortality with each score can be seen in Table 2. All scores had significant differences in mortality between risk strata at baseline, with the highest risk strata having the highest mortality risk ($p < 0.05$ for all scores) (Figure 1). On multivariate analysis, with the 2022 ESC/ERS guidelines, intermediate- (adj HR: 2.78, CI: 1.25–6.2, $p = 0.012$) and high-risk patients (adj HR: 35.53, CI: 7.59–166.2, $p < 0.001$) had a significantly higher risk of mortality compared to low-risk patients. With the COMPERA 2.0 score, intermediate-high- (adj HR: 3.20, CI: 1.02–10.1, $p = 0.046$) and high-risk patients (adj HR: 4.30, CI: 1.13–16.3, $p = 0.032$) had a significantly higher risk of mortality compared to low-risk patients. With the REVEAL Lite 2.0 score, intermediate- (adj HR: 6.4, CI: 1.23–33.3, $p = 0.027$) and high-risk patients (adj HR: 7.6, CI: 1.29–45.1, $p = 0.025$) had a significantly higher risk of mortality compared to low-risk patients (Figure 2).

2.3 | Follow-Up Risk Strata

With the 2022 ESC/ERS guidelines and COMPERA 2.0 score, 46 patients (30.1%) were low-risk, 48 patients (31.3%) were intermediate-low risk, 41 patients (26.8%) were intermediate-high risk, and 18 patients (11.8%) high-risk at follow-up. With the REVEAL Lite 2.0 score, 33 patients (53.2%) were low-risk, 13 patients (21.0%) were intermediate-risk, and 16 patients (25.8%) were high-risk at follow-up.

One-year mortality was 4.5%, 2.4%, 17%, 33% for low-, intermediate low-, intermediate high-, high risk strata at follow-up with the 2022 ESC/ERS guidelines and COMPERA 2.0 score; and 0%, 9.1%, 0% for low-, intermediate-, high-risk strata at follow-up with the REVEAL Lite 2.0 score. Three- and 5-year mortality with each score can be seen in Table 2. All scores had significant differences in mortality between risk strata at follow-up, with the highest risk strata having the highest mortality risk ($p < 0.05$ for all scores) (Supporting Information S1: Figure S2). On multivariate analysis, with the 2022 ESC/ERS and COMPERA 2.0 score, intermediate-high- (adj HR: 3.06, CI: 1.03–9.0, $p = 0.043$) and high-risk patients (adj HR: 11.31, CI: 3.82–33.4, $p < 0.001$) had a significantly higher risk of mortality compared to low-risk patients. With the REVEAL Lite 2.0 score, intermediate- (adj HR: 7.5, CI: 1.18–47.6, $p = 0.033$) and high-risk patients (adj HR: 6.0, CI: 1.04–34.8, $p = 0.045$) had a significantly higher risk of mortality compared to low-risk patients (Supporting Information S1: Figure S3).

TABLE 2 | 1/3/5-year mortality rates stratified by risk score and risk strata.

Risk score	1-year mortality	3-year mortality	5-year mortality
Initial strata			
2022 ESC/ERS			
Low risk	1.8%	8.1%	11%
Intermediate risk	6.5%	20%	39%
High risk	75%	75%	—
COMPERA 2.0			
Low risk	0%	6.6%	6.6%
Intermediate-low risk	0%	10%	21%
Intermediate-high risk	13%	24%	41%
High risk	17%	33%	60%
REVEAL Lite 2.0			
Low risk	0%	5.0%	5.0%
Intermediate risk	0%	12%	22%
High risk	0%	14%	33%
Follow-up strata			
2022 ESC/ERS and COMPERA 2.0			
Low risk	4.5%	4.5%	8.3%
Intermediate-low risk	2.4%	12%	38%
Intermediate-high risk	17%	36%	40%
High risk	33%	58%	78%
REVEAL Lite 2.0			
Low risk	0%	0%	5.3%
Intermediate risk	9.1%	32%	55%
High risk	0%	33%	55%

2.4 | Changes in Risk Strata

At follow-up, 57 (37.3%), 78 (51.0%), and 21 (40.4%) patients experienced a change in risk status with the 2022 ESC/ERS, COMPERA 2.0, and REVEAL Lite 2.0 scores, respectively (Figure 3). With the 2022 ESC/ERS guidelines, 31 patients (20.3%) remained stable at low risk, 15 patients (9.8%) improved to low risk, 68 patients (44,4%) remained stable at intermediate/high risk or improved only to intermediate risk, and 39 patients (25.5%) worsened to intermediate/high risk. With the COMPERA 2.0 score, 28 patients (18.3%) remained stable at low risk, 18 patients (11.8%) improved to low risk, 78 patients (51.0%)

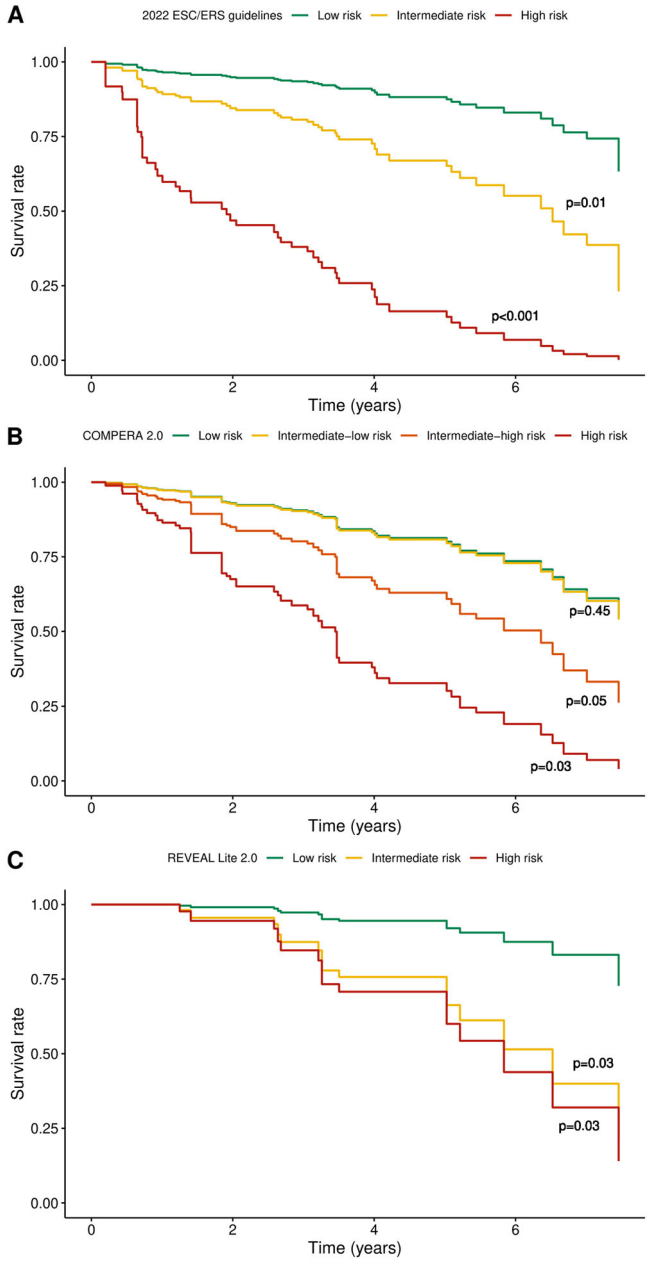

FIGURE 1 | Cox survival curves* by baseline risk strata using (A) 2022 ESC/ERS guidelines, (B) COMPERA 2.0 score, and (C) REVEAL Lite 2.0 score. *Adjusted for age, gender, and pulmonary arterial hypertension subtype.

remained stable at intermediate/high risk or improved only to intermediate risk, and 29 patients (19.0%) worsened to intermediate/high risk. With the REVEAL Lite 2.0 score, 25 patients (48.1%) remained stable at low risk, 7 patients (13.4%) improved to low risk, 9 patients (17.3%) remained stable at intermediate/high risk or improved only to intermediate risk, and 11 patients (21.2%) worsened to intermediate/high risk.

On multivariate analysis, there was no significant difference in mortality between patients who improved to low risk compared to patients who remained at low/intermediate-low risk for all 3 scores (adj HR: 1.78, CI: 0.29–11.1, $p = 0.536$ for 2022 ESC/ERS; adj HR: 0.60, CI: 0.097–3.7, $p = 0.581$ for COMPERA 2.0; adj HR: 9.72, CI: 0.80–117.5, $p = 0.074$ for REVEAL Lite 2.0). There was a significant increase in mortality in patients who had worsened to intermediate/high risk strata for the 2022 ESC/ERS and COMPERA 2.0 scores ($p < 0.05$), but not the REVEAL Lite 2.0 score ($p = 0.061$) (Figure 4). With the 2022 ESC/ERS guidelines, patients who were stable at intermediate-high/high-risk (adj HR: 3.99, CI: 1.13–14.1, $p = 0.031$) and patients who worsened to intermediate-high/high risk (adj HR: 4.42, CI: 1.28–15.3, $p = 0.019$) had a significantly higher risk of mortality compared to patients who remained stable at low- or intermediate-low-risk. With the COMPERA 2.0 score, patients who remained at intermediate-high/high risk had a higher risk of mortality compared to those who remained stable at low-/intermediate-low risk on univariate analysis but this effect was attenuated after adjustment for confounders (adj HR: 2.01, CI: 0.57–7.1, $p = 0.276$). Patients who worsened to intermediate-high/high risk (adj HR: 4.44, CI: 1.24–15.9, $p = 0.022$) had a significantly higher risk of mortality compared to patients who remained stable at low/intermediate-low risk at follow-up. With the REVEAL Lite 2.0 score, patients who were stable at intermediate/high-risk had a significantly higher risk of mortality (adj HR: 23.06, CI: 2.06–258.6, $p = 0.011$) compared to patients stable at low risk (Figure 5).

2.5 | Predictors of Mortality: Baseline and Follow-Up Parameters

At baseline, significant predictors of mortality on multivariate analysis included age > 65 (adj HR: 2.34, CI: 1.22–4.48, $p = 0.010$), NYHA class III/IV (adj HR: 2.09, CI: 107–4.08, $p = 0.030$) and NT-proBNP > 1100 ng/L (adj HR: 3.44, CI: 1.36–8.68, $p = 0.009$) (Supporting Information S1: Table 5). At follow-up the only significant multivariate predictor of mortality was NT-proBNP levels > 1100 ng/L (adj HR: 4.74, CI: 1.84–12.16, $p = 0.001$) (Supporting Information S1: Table 6). The number of variables affected by multiple imputation is shown in Supporting Information S1: Table 7.

2.6 | Comparison Between Risk Scores at Baseline and Follow-Up

The C-statistic for predicting 1-year mortality at baseline was 0.73 (95% CI: 0.58–0.88) and 0.80 (95% CI: 0.72–0.88) for the 2022 ESC/ERS and COMPERA 2.0 scores, respectively (Figure 6A). The C-statistic was unable to be assessed for the REVEAL Lite 2.0 score at 1 year as there were no mortalities. With regards to 3- and 5-year mortality, the C-statistic was 0.66/0.67, 0.69/0.70 and 0.64/0.69, respectively, for the 2022 ESC/ERS, COMPERA 2.0, and REVEAL Lite 2.0 scores, respectively (Supporting Information S1: Figures S4–5). The C-statistic for predicting 1-year mortality at follow-up was 0.63 (95% CI: 0.52–0.74) and 0.54 (95% CI: 0.36–0.72) for the 2022 ESC/ERS/COMPERA 2.0 and REVEAL Lite 2.0 scores, respectively (Figure 6B).

Sensitivity analysis on patients with RHC-diagnosed PAH revealed a C-statistic for predicting 1-year mortality at baseline of 0.69 (95% CI: 0.51–0.87) and 0.81 (95% CI: 0.72–0.90) for the 2022 ESC/ERS and COMPERA 2.0 scores, respectively (Supporting Information S1: Figure S6). The C-statistic for predicting 1-year mortality at follow-up was 0.73 (95% CI:

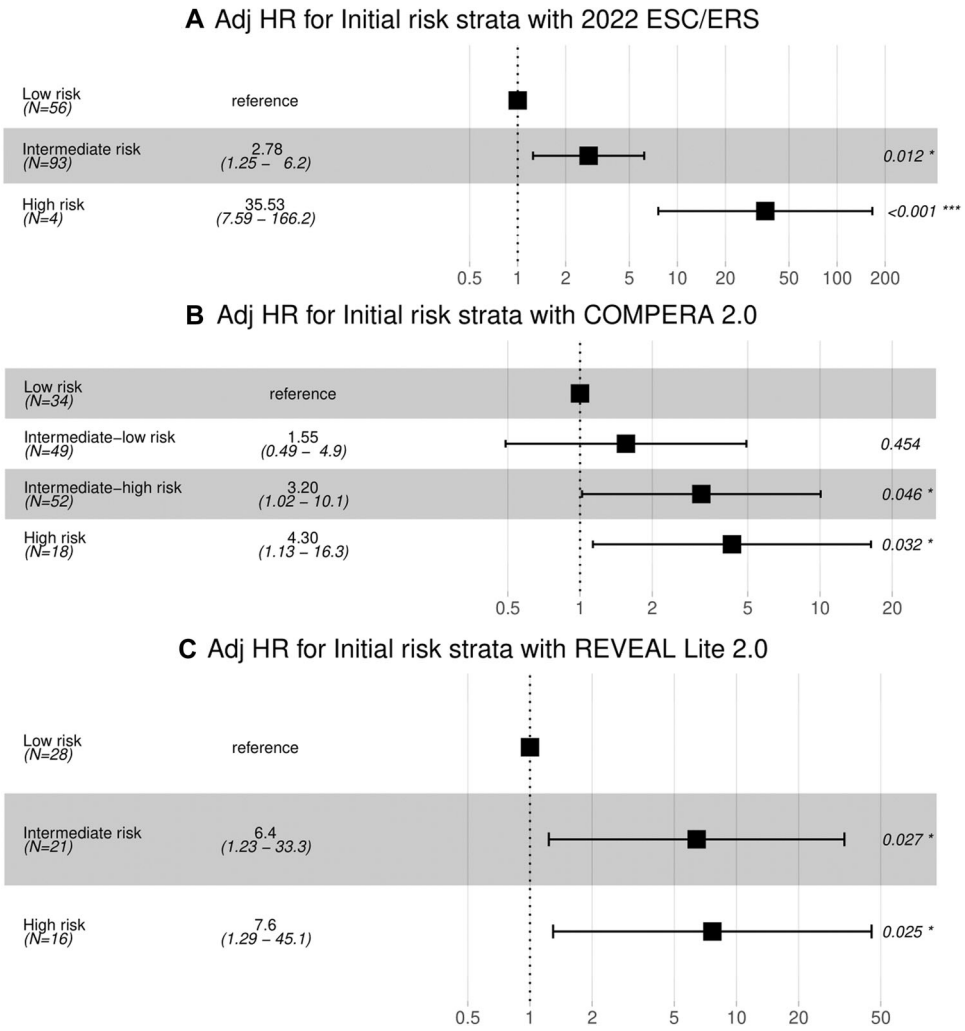

FIGURE 2 | Adjusted hazards ratios* at baseline for each risk strata using (A) 2022 ESC/ERS guidelines, (B) COMPERA 2.0 score, and (C) REVEAL Lite 2.0 score. *Adjusted for age, gender, and pulmonary arterial hypertension subtype.

0.58–0.88) and 0.54 (95% CI: 0.34–0.74) for the 2022 ESC/ERS/COMPERA 2.0 and REVEAL Lite 2.0 scores, respectively, (Supporting Information S1: Figure S7).

3 | Discussion

The salient findings of the study are that in this multi-ethnic Asian cohort: (1) The 2022 ESC/ERS risk score and COMPERA 2.0 risk score performed well at baseline in predicting 1-year mortality. Limited events in the smaller patient subset for REVEAL 2.0 precluded meaningful conclusions to be drawn; (2) Remaining at or progression to intermediate/high risk strata generally predicted increased mortality, while improving to low-risk achieved similar prognosis as those initially at low-risk. (3) Majority of patients were not at low-risk on follow-up. The above findings are on a background of a limited sample size and retrospective study design which may limit applicability of the findings. Nonetheless, we provide evidence for the utility of serial risk stratification in a Southeast Asian population.

Data on Asian PH patients are relatively scarce and are based on national registries and small cohort studies [19–25]. One of the larger registries is the PRO-KERALA registry from India which enrolled 424 PAH patients from 50 centers [19]. Compared to western cohorts, Asian PAH registries had a greater proportion of PAH associated with connective tissue disease (APAH-CTD) and congenital heart disease (APAH-CHD) relative to idiopathic PAH (IPAH), with a similar mean age of diagnosis of PAH and female preponderance [18]. A similar epidemiology is seen in our registry, where patients with APAH-CTD and APAH-CHD consist of 30.7% and 20.9% of our cohort, respectively, with 44.4% of patients diagnosed with IPAH. Compared to other Asian registries which enrolled patients between 2003 and 2015, our cohort enrolled patients between 2014 and 2021 and thus better reflecting more contemporary practices and outcomes [26]. Of note, the uptake of RHC is poor in parts of Asia due to costs and other concerns. Despite RHC remaining an important tool in the diagnosis and phenotyping of PAH, it is invasive and costly and not all patients have the means or are keen to undergo RHC. In other Asian registries, PAH is often diagnosed based on clinical and echocardiographic evidence with or without RHC [19, 22]. In our local population, a minority of patients (16%) diagnosed with PAH did not receive RHC. This group of patients may still benefit from risk stratification.

There are few studies evaluating the latest 2022 ESC/ERS guidelines while the 2015 ESC/ERS guidelines have been

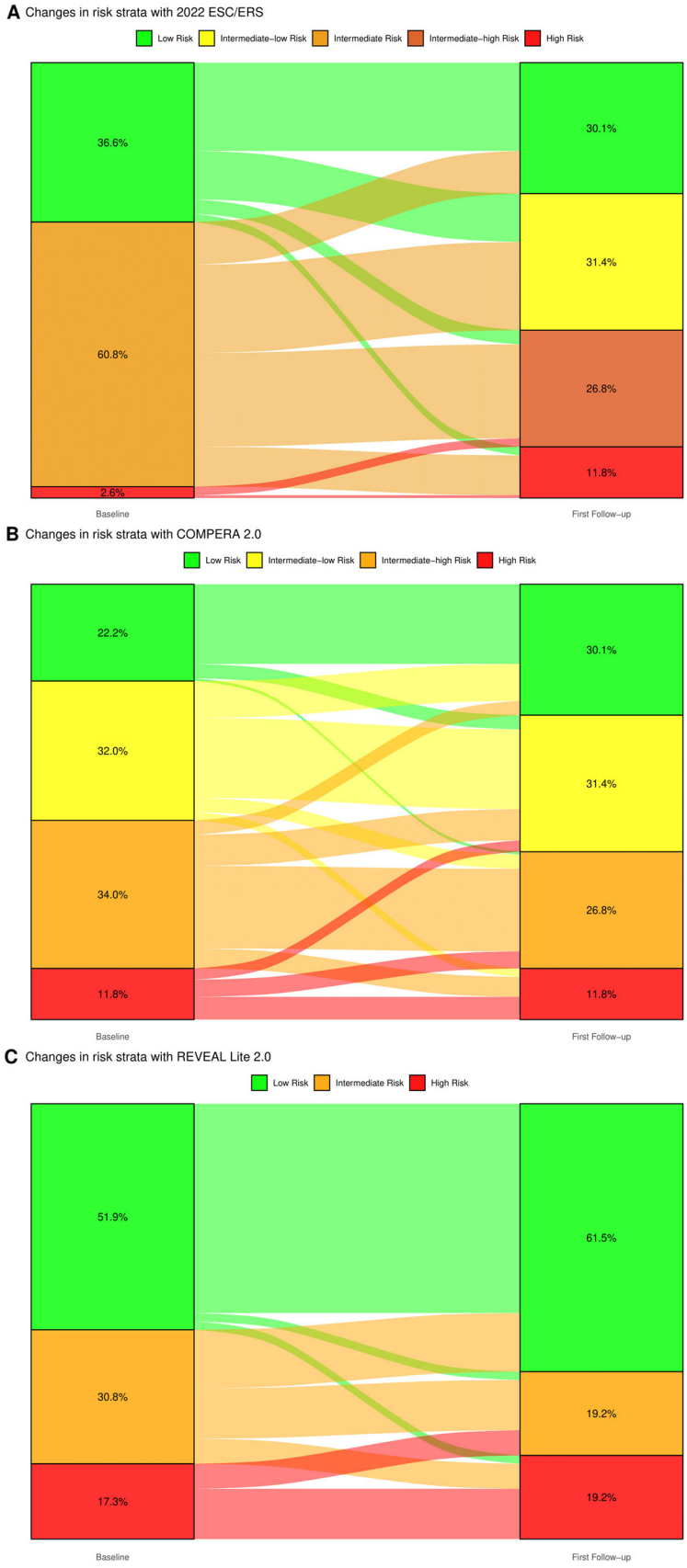

FIGURE 3 | Sankey diagrams showing changes in risk strata using (A) 2022 ESC/ERS guidelines, (B) COMPERA 2.0 score, and (C) REVEAL Lite 2.0 score.

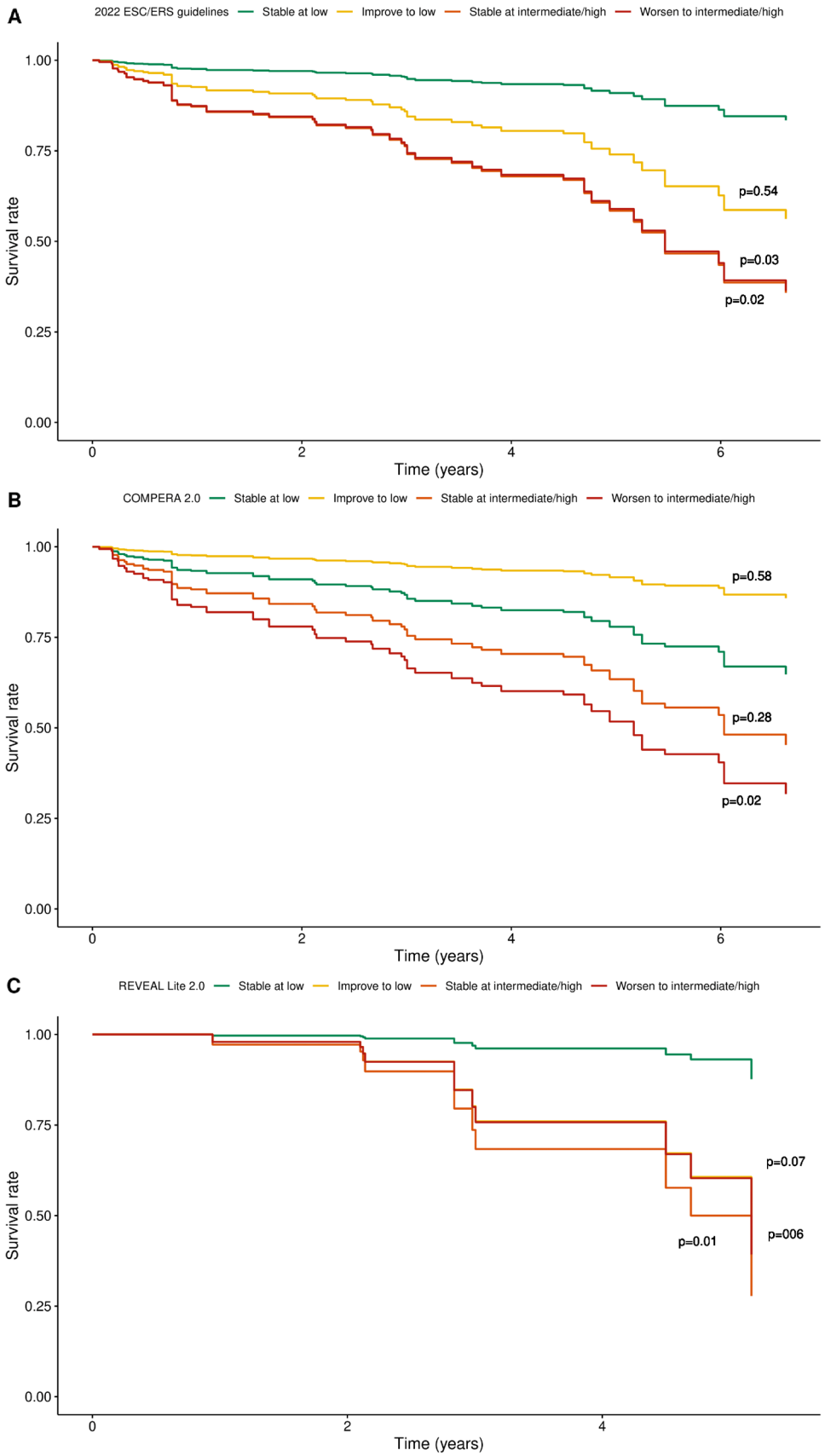

FIGURE 4 | Cox survival curves* by changes in risk strata using (A) 2022 ESC/ERS guidelines, (B) COMPERA 2.0 score, and (C) REVEAL Lite 2.0 score. *Adjusted for age, gender, and pulmonary arterial hypertension subtype.

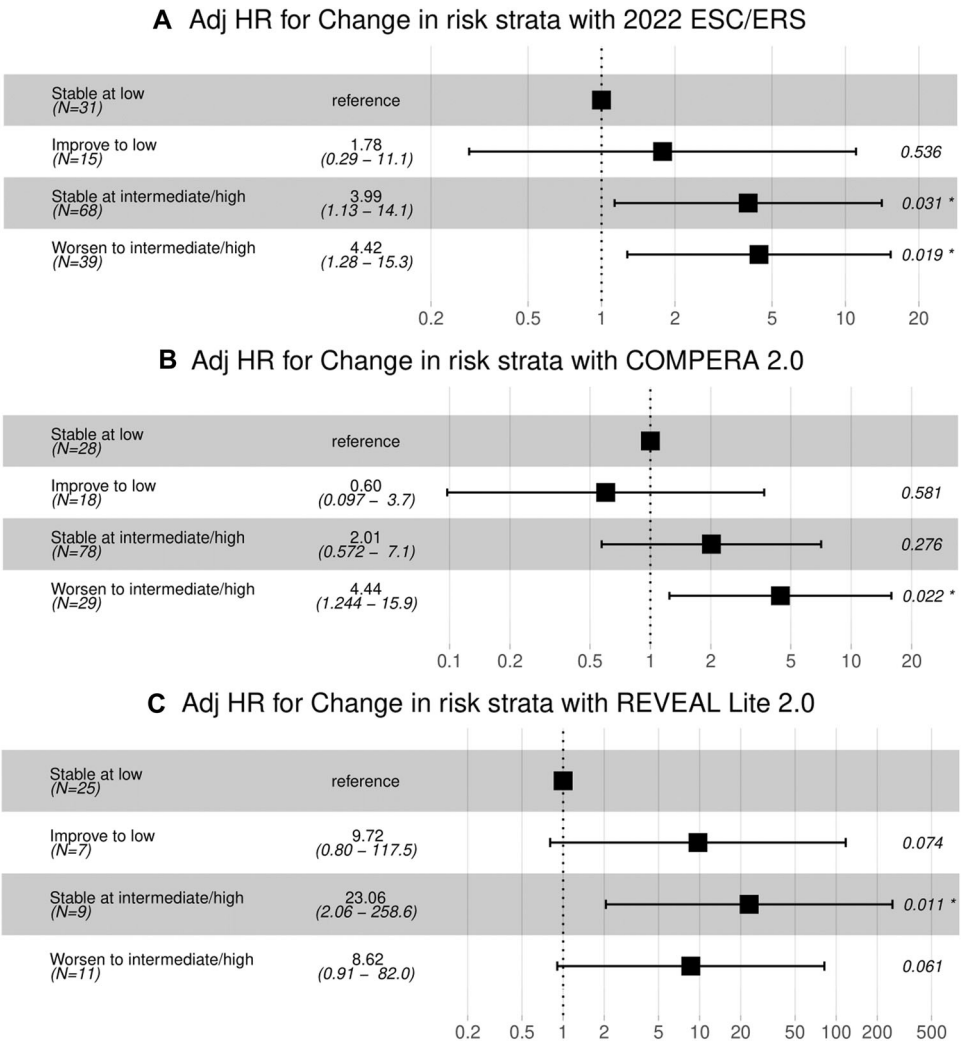

FIGURE 5 | Adjusted hazards ratios* for changes in risk strata using (A) 2022 ESC/ERS guidelines, (B) COMPERA 2.0 score, and (C) REVEAL Lite 2.0 score. *Adjusted for age, gender, and pulmonary arterial hypertension subtype.

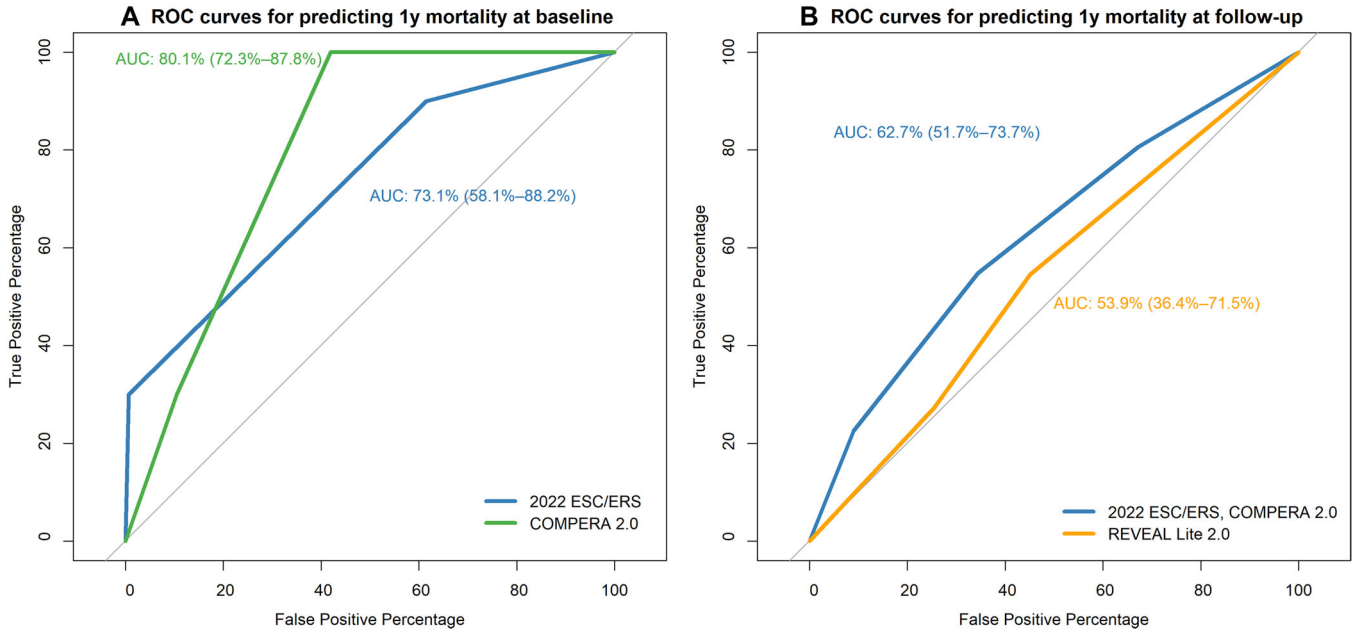

FIGURE 6 | Receiver Operating Curve for 1-year mortality at (A) baseline and (B) follow-up.

well-validated in large western cohorts [7–9, 14]. This latest version has refined some of the variables as well as redefined the intermediate and high-risk group to better reflect prognosis [6, 17]. Based on the estimated 1-year mortality rates (< 5% for low risk, 5%–20% for intermediate risk, > 20% for high risk) for the 2022 guidelines [17], this approximates relatively well in our local population with a 1-year mortality of 5.5%, 11%, and 75% for low-, intermediate- and high-risk populations, respectively, at baseline and a C-statistic of 0.73 (95% CI: 0.58–0.88). The unusually high mortality rate in the high-risk cohort is likely due to a small population of high-risk individuals ($n = 4$). As described in other cohorts, the main limitation of the ESC/ERS guidelines is that 60%–70% of patients will be classified as intermediate risk [7, 9, 14, 16], with our local population having 60.8% of patients classified as intermediate risk and only 2.6% of patients classified as high-risk. However, it should be noted that this low proportion of high-risk patients is on a background of several limitations—including the relatively small overall sample size compared to European cohorts and missing variables which may affect the accuracy of prognostication.

Several registries have shown that simplified versions of the ESC/ERS guideline provided reliable prognostication as well, in particular focusing on a combination of WHO functional class, 6MWD and BNP/NT-proBNP which have the strongest prognostic significance [7, 9, 13]. The REVEAL Lite 2.0 score, in comparison to the original REVEAL 2.0 score, is an abridged version incorporating only heart rate, SBP, and eGFR in addition to the previously mentioned factors, allowing for a far simpler score with relatively good discrimination power (C-index 0.70 for REVEAL Lite 2.0 vs. 0.73 for REVEAL 2.0) [13]. Due to the method of calculation of the REVEAL Lite 2.0, missing data tended to have a greater effect on risk stratification as compared to the other 2 risk scores included. As such, the decision was made to only include patients with a complete set of key variables. This limited the number of available patients for analysis for the REVEAL Lite 2.0 score in our local population. Nonetheless, the existing analysis suggests that higher risk strata with the REVEAL Lite 2.0 is associated with worse prognosis. In addition, the 3- and 5-year C-index is comparable to the 2022 ESC/ERS risk score in our local population (3-year: 0.64 vs. 0.66; 5-year: 0.69 vs. 0.67). Nonetheless, these findings are limited by the small sample size and will require further validated in future prospective cohort studies.

The COMPERA 2.0 score was developed to better risk stratify the intermediate risk group of patients into intermediate-low and intermediate-high strata providing based on more granularity within the cut-off levels of 6MWD, WHO FC and BNP/NT-proBNP and thus providing more discrimination on mortality outcomes [10]. This has also been externally validated in the FPHR cohort, whereby it performed better than the 3-stratum approach [27]. However, this has not been validated in an Asian cohort. In our local cohort, the COMPERA 2.0 score had a C-statistic of 0.80 for predicting 1-year mortality. The simplicity of the COMPERA 2.0 score also makes it practical to use in clinical settings, where limitations in data availability as well as time constraints favors risk scores with fever variables [10, 13]. Despite the good-to-excellent C-statistics of the risk scores at baseline, these scores are unable to capture all clinical information of a patient and thus should serve as a guide to prognosis whilst simultaneously considering other factors including PAH subtype and other cardiovascular comorbidities which may negatively impact prognosis, especially when there are missing variables [28, 29].

Changes in risk strata from baseline to follow-up has been demonstrated to be a significant predictor of mortality compared to baseline strata alone [30]. Several registries have also demonstrated serial risk stratification to be useful to prognosticate and guide treatment [10, 27]. These findings were similar in our cohort. PAH patients who improved to low-risk strata at follow-up had similar risks to those stable at low risk. Conversely, those who remained at or progressed to intermediate/high risk had worse outcomes. This suggests that optimizing treatment to improve risk strata in PAH patients may result in a prognostic benefit and efforts should be focused as such. Of note, a majority of our patients were not at low risk at follow-up. This is similar to that of other cohorts in Europe where few patients achieved the treatment goal of a low-risk profile during follow-up, regardless of the score used [7, 10, 27]. In the COMPERA cohort, less than 20% of patients achieved low-risk status at follow-up, and among high- or intermediate-high-risk patients at baseline only 7.5% of patients achieved low-risk status at follow-up [10]. Similarly in the French pulmonary hypertension registry, only 24% of patients were low-risk at first follow-up [27]. This could be partially explained by treatment limitations. Despite guidelines recommending starting all high-risk patients with triple combination therapy [17], in the COMPERA registry combination therapy was only used in 17% of high-risk patients, with only 7% of patients on intravenous or subcutaneous prostacyclin analogues at follow-up [7]. In our cohort, about half of the patients were on monotherapy at baseline. There are several possible reasons. In older patients with multiple cardiovascular comorbidities, physicians may prefer monotherapies as patients may not be able to tolerate combination therapy [7]. This is especially relevant in the present cohort with a mean age of diagnosis of 57 ± 17 years. The presence of concomitant post-capillary PH in some patients may also caution physicians against starting combination therapy at baseline [31]. Other important reasons include cost and accessibility concerns. In the local context, the high costs of PAH specific therapy maybe a barrier to combination therapy [32]. Additionally, this includes an older cohort from 2014 whereby risk stratification and early initiation of combination treatment was less in vogue compared to contemporary trends. Further work needs to be done to help more patients achieve low-risk status at follow-up.

4 | Limitations

To our knowledge, this is the largest study validating the three scores in an Asian PAH cohort. In addition, this is the first Asian study evaluating serial risk assessment with the newly refined 2022 ESC/ERS guidelines. This study also focused on a more contemporary group of patients from 2014 onwards where PAH-specific drugs are more likely to be used. Nonetheless, there are some limitations. As a retrospective study with its attendant drawbacks, our study was limited by missing data and follow-ups, which curtailed the number of included patients and analysis. This was especially with regards to the REVEAL

Lite 2.0 score, where large numbers of missing 6MWD data resulted in a much smaller patient cohort for analysis and thus impacting potential generalizability. The lower discrimination powers of the risk scores at follow-up in our local cohort may be in part related to a higher proportion of missing variables highlighting the importance of having a complete set of data and potentially limiting clinical applicability of the scores at follow-up. The smaller number of patients also limited our ability to further stratify the risk of patients moving between risk strata (e.g., from low to intermediate-low risk) which is an important consideration in management. Additionally, this is a single-center study with a predominantly Chinese and Malay population and thus the results may not be generalizable to other Asian populations. The decision to include patients with missing RHC data in the primary analysis, whilst better reflective of real-world practice, may carry some potential risk of inclusion of patients who may be misdiagnosed as PAH, especially in our cohort of older adults at higher risk of Group 2 PH. Lastly, the reasons for the discrepancy in classification of high-risk strata between risk scores are not clear and may be related to the limited sample size of the present study and missing data. Nevertheless, these initial results form the foundation for future studies in larger Asian cohorts.

5 | Conclusion

The current risk scores show promise in prognosticating PAH patients at both baseline and follow-up in a multi-ethnic Asian population, with changes in risk strata having a significant impact on mortality. However, validation in a larger, multicenter cohorts are needed to confirm the above findings. Initiatives to optimize the treatment of PAH patients and improve their risk strata should be emphasized.

Author Contributions

Haowen Jiang: writing–original draft, data curation, formal analysis. Ju Le Tan: writing–review and editing, conceptualization. Wen Ruan: writing–review and editing. Jin Shing Hon: writing–review and editing. Aidila Ismail: writing–review and editing. Chee Lan Lim: writing–review and editing. Michelle Koh: writing–review and editing. Duu Wen Sewa: writing–review and editing. Ghee Chee Phua: writing–review and editing. Ying Zi Oh: writing–review and editing. Sue-Ann Ng: writing–review and editing. Cassandra Hong: writing–review and editing. Andrea Low: writing–review and editing. Soo Teik Lim: writing–review and editing. Jonathan Yap: writing–review and editing, conceptualization, supervision.

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Ethics Statement

This human study was approved by SingHealth Centralized Institutional Review Board (CIRB)—approval: 2017/2388.

Consent

The authors have nothing to report.

Conflicts of Interest

JY received speaker's honorarium from Abbott, Biosensors, Biotronik, Boston Scientific, Edwards, GE healthcare, J&J, Kaneka, Medtronic and Terumo. AL received consultancy fees and is on the advisory boards of Janssen and Boehringer-Ingelheim, and is on the steering committee and received research grants from Boehringer-Ingelheim. All other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. R. L. Benza, D. P. Miller, R. J. Barst, D. B. Badesch, A. E. Frost, and M. D. McGoon, "An Evaluation of Long-Term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry," *Chest* 142 (2012): 448–456.

2. N. Galiè, B. H. Brundage, H. A. Ghofrani, et al., "Tadalafil Therapy for Pulmonary Arterial Hypertension," *Circulation* 119 (2009): 2894–2903.

3. N. Galiè, H. A. Ghofrani, A. Torbicki, et al., "Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension," *New England Journal of Medicine* 353 (2005): 2148–2157.

4. O. Sitbon, C. Sattler, L. Bertoletti, et al., "Initial Dual Oral Combination Therapy in Pulmonary Arterial Hypertension," *European Respiratory Journal* 47 (2016): 1727–1736.

5. A. Raina and M. Humbert, "Risk Assessment in Pulmonary Arterial Hypertension," *European Respiratory Review* 25 (2016): 390–398.

6. N. Galiè, M. Humbert, J.-L. Vachiery, et al., "2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)," *European Heart Journal* 37 (2016): 67–119.

7. M. M. Hoeper, T. Kramer, Z. Pan, et al., "Mortality in Pulmonary Arterial Hypertension: Prediction by the 2015 European Pulmonary Hypertension Guidelines Risk Stratification Model," *European Respiratory Journal* 50 (2017): 1700740.

8. A. Boucly, J. Weatherald, L. Savale, et al., "Risk Assessment, Prognosis and Guideline Implementation in Pulmonary Arterial Hypertension," *European Respiratory Journal* 50 (2017): 1700889.

9. D. Kylhammar, B. Kjellström, C. Hjalmarsson, et al., "A Comprehensive Risk Stratification at Early Follow-Up Determines Prognosis in Pulmonary Arterial Hypertension," *European Heart Journal* 39 (2018): 4175–4181.

10. M. M. Hoeper, C. Pausch, K. M. Olsson, et al., "COMPERA 2.0: A Refined Four-Stratum Risk Assessment Model for Pulmonary Arterial Hypertension," *European Respiratory Journal* 60 (2022): 2102311.

11. J. J. Anderson, E. M. Lau, M. Lavender, et al., "Retrospective Validation of the REVEAL 2.0 Risk Score With the Australian and New Zealand Pulmonary Hypertension Registry Cohort," *Chest* 157 (2020): 162–172.

12. R. L. Benza, M. Gomberg-Maitland, D. P. Miller, et al., "The REVEAL Registry Risk Score Calculator in Patients Newly Diagnosed With Pulmonary Arterial Hypertension," *Chest* 141 (2012): 354–362.

13. R. L. Benza, M. K. Kanwar, A. Raina, et al., "Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension," *Chest* 159 (2021): 337–346.

14. C. Hjalmarsson, G. Rådegran, D. Kylhammar, et al., "Impact of Age and Comorbidity on Risk Stratification in Idiopathic Pulmonary Arterial Hypertension," *European Respiratory Journal* 51 (2018): 1702310.

15. Y. T. Yaylalı, I. Başarıcı, B. Kılıçkıran Avcı, et al., "Risk Assessment and Survival of Patients With Pulmonary Hypertension: Multicenter Experience in Turkey," *Anatolian Journal of Cardiology* 21 (2019): 322–330.

16. M. Humbert, H. W. Farber, H.-A. Ghofrani, et al., "Risk Assessment in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension," *European Respiratory Journal* 53 (2019): 1802004.

17. M. Humbert, G. Kovacs, M. M. Hoeper, et al., "2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension," *European Respiratory Journal* 61 (2023): 2200879.

18. J. J. Anderson and E. M. Lau, "Pulmonary Hypertension Definition, Classification, and Epidemiology in Asia," *JACC: Asia* 2 (2022): 538–546.

19. S. Harikrishnan, G. Sanjay, M. Ashishkumar, et al., "Pulmonary Hypertension Registry of Kerala, India (PRO-KERALA) - Clinical Characteristics and Practice Patterns," *International Journal of Cardiology* 265 (2018): 212–217.

20. R. Zhang, L.-Z. Dai, W.-P. Xie, et al., "Survival of Chinese Patients With Pulmonary Arterial Hypertension in the Modern Treatment Era," *Chest* 140 (2011): 301–309.

21. A. Y. Jang, B.-G. Kim, S. Kwon, et al., "Prevalence and Clinical Features of Bone Morphogenetic Protein Receptor Type 2 Mutation in Korean Idiopathic Pulmonary Arterial Hypertension Patients: The Pilgrim Explorative Cohort," *PLoS One* 15 (2020): e0238698.

22. Y. Lim, T.-T. Low, S.-P. Chan, et al., "Pulmonary Arterial Hypertension in a Multi-Ethnic Asian Population: Characteristics, Survival and Mortality Predictors From a 14-year Follow-Up Study," *Respirology* 24 (2019): 162–170.

23. A. Y. Jang and W.-J. Chung, "Current Status of Pulmonary Arterial Hypertension in Korea," *The Korean Journal of Internal Medicine* 34 (2019): 696–707.

24. Y. Tamura, H. Kumamaru, T. Satoh, et al., "Effectiveness and Outcome of Pulmonary Arterial Hypertension-Specific Therapy in Japanese Patients With Pulmonary Arterial Hypertension," *Circulation Journal: Official Journal of the Japanese Circulation Society* 82 (2017): 275–282.

25. Z.-C. Jing, X.-Q. Xu, Z.-Y. Han, et al., "Registry and Survival Study in Chinese Patients With Idiopathic and Familial Pulmonary Arterial Hypertension," *Chest* 132 (2007): 373–379.

26. H. Deshwal, T. Weinstein, and R. Sulica, "Advances in the Management of Pulmonary Arterial Hypertension," *Journal of Investigative Medicine* 69 (2021): 1270–1280.

27. A. Boucly, J. Weatherald, L. Savale, et al., "External Validation of a Refined Four-Stratum Risk Assessment Score From the French Pulmonary Hypertension Registry," *European Respiratory Journal* 59 (2022): 2102419.

28. V. Mercurio, G. Peloquin, K. I. Bourji, et al., "Pulmonary Arterial Hypertension and Atrial Arrhythmias: Incidence, Risk Factors, and Clinical Impact," *Pulmonary Circulation* 8 (2018): 2045894018769874.

29. C. Pausch, D. Pittrow, M. M. Hoeper, and D. Huscher, "Performance of the ESC/ERS 4-strata Risk Stratification Model for Pulmonary Arterial Hypertension With Missing Variables," *European Respiratory Journal* 62 (2023): 2301023.

30. N. Nickel, H. Golpon, M. Greer, et al., "The Prognostic Impact of Follow-Up Assessments in Patients With Idiopathic Pulmonary Arterial Hypertension," *European Respiratory Journal* 39 (2012): 589–596.

31. J.-L. Vachiéry, M. Delcroix, H. Al-Hiti, et al., "Macitentan in Pulmonary Hypertension Due to Left Ventricular Dysfunction," *European Respiratory Journal* 51 (2018): 1701886.

32. Y. Lim, M. Siti, T. Low, I. Kuntjoro, J. Yip, and E. Tay, "Help-Seeking Patterns and Funding Strategies in Patients With Pulmonary Arterial Hypertension on Phosphodiesterase-5 Inhibitors: An Orphan Disease With Effective but Costly Treatment," *Singapore Medical Journal* 62 (2021): 199–203.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.