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Comparison of contemporary risk scores in all groups of pulmonary hypertension - a PVRI GoDeep meta-registry analysis

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Comparison of contemporary risk scores in all groups of pulmonary hypertension - a PVRI GoDeep meta-registry analysis

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Keywords: pulmonary hypertension; risk stratification; multicentric; predictive power; PVRI GoDeep meta-registry

Abstract

Background. Pulmonary hypertension (PH) is a heterogeneous disease with poor prognosis. Accurate risk stratification is essential for guiding treatment decisions in pulmonary arterial hypertension (PAH). While various risk models were developed for PAH, their comparative prognostic potential requires further exploration. Additionally, the applicability of risk scores in PH groups beyond group 1 remains to be investigated.

Research Question. Are risk scores originally developed for PAH predictive in PH group 1–4?

Study Design and Methods. We conducted a comprehensive analysis of outcomes among incident PH patients enrolled in the multicenter worldwide PVRI-GoDeep meta-registry. Analyses were performed across PH groups 1-4 and further subgroups to evaluate the predictive value of PAH-risk scores, including REVEAL Lite 2, REVEAL 2.0, ESC/ERS 2022, COMPERA 3-strata and COMPERA 4-strata.

Results. 8565 patients were included in the study, of whom 3537 patients were assigned to group 1 PH while 1807, 1635, and 1586 patients were diagnosed with group 2, group 3, and group 4 PH. Pulmonary hemodynamics were impaired with median mPAP of 42 [33,52]mmHg and PVR of 7 [4,11]WU. All risk scores were prognostic in the entire PH population and in each of the PH groups 1–4. The REVEAL scores, when used as continuous prediction models, possessed the highest statistical prognostic power and granularity; the COMPERA 4-strata risk score provided sub-differentiation of the intermediate-risk group. Similar results were obtained when separately analyzing various subgroups (PH subgroups 1.1, 1.4.1, 1.4.4; 3.1, 3.2; group 2 with isolated post-capillary-PH versus combined pre-/post-capillary-PH; patients of all groups with concomitant cardiac comorbidities; severe [> 5 WU] versus non-severe PH).

Interpretation. This comprehensive study with real-world data from 15 PH-centers showed that PAH-designed risk scores possess predictive power in a large PH cohort, whether considered as common group or calculated separately for each PH group (1-4) and various subgroups.

299 words

Keywords: pulmonary hypertension; risk stratification; multicentric; predictive power; PVRI GoDeep meta-registry

Pulmonary hypertension (PH) is a multifaceted and heterogeneous disease with classification into five distinct groups, namely pulmonary arterial hypertension (Group 1, PAH), PH associated with left heart disease (Group 2, LHD-PH), PH associated with lung disease and/or hypoxia (Group 3, LD-PH), PH associated with pulmonary artery obstructions (Group 4, CTEPH), and PH with an unclear and/or multifactorial etiology (Group 5)[1]. It is noteworthy that the survival of all PH patients is substantially compromised when compared to individuals without PH[2-5]. Particularly in PAH, risk stratification plays a pivotal role as it guides essential treatment decisions, including the consideration of parenteral prostacyclin therapy for high-risk patients[1]. Among the critical determinants of symptoms and prognosis in PH patients, right ventricular (RV) function stands out[6]. It is well-known that RV function is compromised across all PH groups, making it pertinent to evaluate the applicability of risk stratification originally designed for PAH to PH groups 2 – 4, a subject that has only received limited attention in previous studies[7-11].

In Europe, a comprehensive risk score, initially introduced in the 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines on PH, was designed to assess risk in PAH patients and has recently been updated in the latest guidelines[1,12]. However, in the absence of specific recommendations for calculating overall risk, various methods have emerged, including calculating the mean with rounding to the nearest integer or simply tallying low risk parameters using a truncated version of the risk score[10,13-15]. In the United States, the REVEAL 2.0 risk score and the REVEAL Lite 2 risk score are preferred tools for assessing mortality risk in PAH patients[16]. Both risk assessment tools categorize patients into three risk groups: low-, intermediate- and high risk[1,12,16]. A key distinction between the REVEAL and ESC/ERS approaches lies in the inclusion of demographics, such as gender and age, as well as PAH subtype analysis in the REVEAL 2.0 score, but also in the possibility to use the REVEAL scores as a continuous (ordinal) scoring system[16-20].

In addition to the 3-strata risk models mentioned so far, 4-strata risk models have been developed to provide a more comprehensive characterization of patients during follow-up[1,14,15]. While the current ESC/ERS guidelines recommend using a 3-strata risk approach at the time of diagnosis and a 4-strata

risk approach during follow-up, the added benefits of using 4-strata risk scores during baseline evaluation remain uncertain[1]. Notable, the recommended 4-strata risk score does not encompass pulmonary hemodynamics, whereas the ESC/ERS 3-strata incorporates pulmonary hemodynamics as well as imaging and cardiopulmonary exercise testing. The extent to which including hemodynamic measurements adds prognostic value remains to be determined.

While certain parameters are common to all risk assessment scores, such as six-minute walking distance (6MWD) and world health organization (WHO) functional class, major components differ between the various scores (e-Table 1). Furthermore, there is no consensus on whether the PAH-designed risk scores can be usefully extended to PH groups 2 – 4. This study utilizes the large PVRI GoDeep meta-registry[21] to compare the predictive power of both 3-strata (including REVEAL scores, additionally allowing a continuous scoring approach) and 4-strata risk scores in a large multicentric cohort. Moreover, it aims to investigate whether these risk scores are equally applicable to patients assigned to groups 2 – 4 PH.

Study Design and Methods

Study population

All patients enrolled in the Pulmonary Vascular Research Institute (PVRI) GoDeep meta-registry with right heart catheter confirmed PH diagnosis made by the participating PH expert center based on the PH World Symposium definition of PH, age at diagnosis ≥ 18, and without any data discrepancies were included in this study[21]. The time range for baseline data was set at −3 to +3 months around the time of reported initial diagnosis. If multiple data points were available for the same variable, the data point closest to the diagnosis date was selected. The current analysis included all centers from which sufficiently granular data for comparative risk sore analysis could be entered into the study, namely the centers in Giessen (2198 patients), London (2143), Sheffield (2023), Baltimore (632), Kiev (380), Stanford (342), Johannesburg (220), Thessaloniki (156), Abu Dhabi (117), Rochester (109), Houston (87), Pittsburgh (76), Nashville (46), Pavia (28), and Athens (8). University of Giessen/University Hospital Ethics Committee and the responsible local ethic committees have approved the PVRI-GoDeep central data repository, listed under ClinTrials.gov (NCT05329714).

Risk assessment models

We included the REVEAL Lite 2 risk score, the REVEAL 2.0 risk score, the ESC/ERS 2022 risk score, and the COMPERA registry 3-/4-strata risk scores (e-Table 1).

REVEAL Lite 2 and REVEAL 2.0 risk scores:

As described by Benza and co-workers, the REVEAL 2.0 score was calculated using the following variables: WHO group 1 subgroup, demographics, estimated glomerular filtration rate (eGFR), WHO functional class, vital signs (systolic blood pressure (SBP) and heart rate (HR)), 6MWD, BNP, presence of pericardial effusion, lung function test (i.e. diffusion capacity (DLCO)) and right heart catheterization data (i.e., mean right artery pressure (mRAP) and pulmonary vascular resistance (PVR) at the time of diagnosis)[20]. The REVEAL scores were used as continuous scoring system, unless otherwise noted[20].

Missing values were substituted by a score of zero[20]. Similarly, REVEAL Lite 2.0 risk was calculated by incorporating BNP, 6MWD, WHO functional class, SBP, HR, and eGFR[20].

ESC/ERS 2022 risk score:

The Kylhammar approach was used with the new threshold/parameters mentioned in the 2022 ESC/ERS guidelines on PH including WHO functional class, 6MWD, BNP, right atrial (RA) area, tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (sPAP) ratio, presence of pericardial effusion, peak VO2, VE/VCO2 slope, RAP, CI, stroke volume index (SVI), and SvO_2[1,10].

COMPERA registry 3-strata and 4-strata risk score:

The COMPERA registry 3- and 4-strata approach was performed as described by Hoeper and colleagues using WHO functional class, 6MWD, and BNP[14]. In brief, each variable was rated as previously described using numbers between one and three or one and four, respectively. The mean was then determined and rounded to the nearest whole number.

The prognostic determinants included in each risk score are detailed in e-Table 1, with missing parameters in the GoDeep registry indicated in italics.

Data extraction and Statistical analyses

Data were analyzed with R version 4.3.0[23] using the package *survival* version 3.5-3[24]. The package *flextable* version 0.9.1 was used to create tables and the package *mice* version 3.15.0 was used for multiple imputations by multivariate imputation by chained equations[25,26].

On October 16th, 2023, the data were extracted from the database. Missing values of BNP were calculated from given NT-proBNP values using the following formular:

$$\log_e BNP = \frac{\log_e NTproBNP - 0.079}{1.348}.$$

Median and interquartile range were used to summarize variables in tables.

Missing data were imputed using *mice* version 3.15.0[26]. Reliability of imputation is shown in e-Figure 1. Patients were considered for imputation if they had at least two of the variables WHO functional

class, 6MWD, and BNP. Missing data were allowed up to 40%, and continuous variables were log-transformed before imputation. The following variables were imputed (percent of missing values in parentheses): WHO FC (4%), BSA (10%), BMI (13%), height (14%), 6MWT distance (18%), mPAP (18%), PVR (27%), sSAP (28%), PAWP (36%), BNP (36%), CO (38%), and CI (38%). Additionally, the information from following variables without missing values was used for imputation: PH Group, sex, age at diagnosis, diagnosis decade, and center.

Kaplan-Meier estimators with log-rank tests as well as univariate and multivariate Cox regression analyses were used to examine the prognostic relevance of parameters. In addition, predictive power was evaluated with Akaike Information Criteria (AIC) and C-statistic[27]. AIC values were compared to the respective AIC values of the ESC/ERS risk score and for the C-statistic bootstrapping was used to determine the statistical significance of the difference between the respective risk score and the ESC/ERS risk score.

Results

Baseline Characteristics

As of October 16th 2023, the PVRI GoDeep meta-registry comprised a total of 27070 patients, including 8565 incident and treatment-naïve patients, enrolled in 15 different PH centers, all of whom met the hitherto mentioned criteria for analysis (Figure 1). Among these patients, 3537(41%) patients were diagnosed with group 1 PH, while 1807 (21%), 1635 (19%), and 1586 (19%) patients were diagnosed with group 2, group 3, and group 4PH, respectively (Table 1a). 101 patients diagnosed with group 5 PH were excluded from subsequent analyses due to the low patient count and the inherent heterogeneity within this group. The median age of the study population was 65 [52, 74] years; 39% were male, and the pulmonary hemodynamics were severely impaired with median pulmonary arterial pressure of 42 [33, 52] mmHg and median pulmonary vascular resistance of 7 [4, 11] WU, as detailed in Table 1a. Overall, one-, three-, and five-year survival rates were 85%, 64%, and 51%, respectively. Table 2 presents the distribution of the included risk scores. Most patients were categorized as intermediate risk using the ESC/ERS 2022 risk score and the COMPERA registry 3-strata score (81% respectively), while the REVEAL 2.0 score showed a more balanced distribution (Table 2).

Prognostic Power of Risk Scores in Incident and Treatment-Naïve PH Patients

All risk scores predicted survival in patients with incident PH, as illustrated in Figure 2. The predictive power of all sores is presented in Table 3. Notably, the REVEAL scores significantly outperformed the ESC/ERS risk 2022 score and also compared favourably to the COMPERA registry 3-strata risk score. For patients with a REVEAL Lite 2.0 score ≤6, the 1-, 3-, and 5-year survival rates were 93%, 78%, and 66%, respectively, in the overall PH population including patients of all PH groups. In contrast, patients with higher scores showed significantly worse prognosis, as depicted in Figure 2A. Univariate Cox regression analysis further confirmed significantly increased hazard ratios for each point increase both for REVEAL 2.0 and REVEAL Lite 2, as compared to patients with a total score ≤6 points (Figure 3). The COMPERA registry 4-strata risk score successfully discriminated between intermediate-low and intermediate-high risk patients, also significantly outperforming the ESC/ERS risk 2022 score (Table 3).

When compared to the low-risk score group, 2-fold, 5-fold, and 11-fold increased hazard ratios were noted for the intermediate-low, intermediate-high, and high-risk score patients (Figure 3). Similarly, significantly increased hazard ratios were noted when comparing intermediate-high to intermediate-low patients.

Prognostic Power of Risk Scores in Incident Patients with PH Group 1 - 4

Next, we performed PH group-based analyses, with baseline characteristics shown in Table 1. All included risk scores predicted survival in PH groups 1 – 4 (Figure 5). Kaplan-Meier curves of all scores for all groups are shown in Figure 5. Corresponding to the overall PH group, the ESC/ERS 2022 risk score showed an uneven distribution with strong predominance of the intermediate risk score group in all four PH groups. The COMPERA 4-strata risk score was able to discriminate between intermediate-low and intermediate-high patients in all PH groups (Figure 4 and Figure 5). Again, the C-indices of the REVEAL scores, when used as a continuous scoring system, were the highest in each of the individually analyzed PH groups (Table 3).

Sensitivity Analysis using Non-Imputed Data

To enhance the robustness of our findings, we performed a sensitivity analysis employing the subset of incident and treatment-naïve patients without any data imputation (n = 3603; non-imputed study population). Only patients with complete 6MWD, BNP, and WHO FC data sets were included (e-Table 2a). Overall, one-, three-, and five-year survival rates were 88%, 70%, and 56%, respectively. Baseline characteristics and distributions of the risk scores within the non-imputed cohort are displayed in e-Table 2 and in e-Table 3, respectively. Significantly, outcomes gleaned from this analysis exhibited concurrence with those derived from the analyses incorporating imputation, as delineated in the supplementary materials (e-Figure 2, 3, 4 and 5, along with e-Table 4). The non-imputed dataset again underscores the strong discriminative potency of the continuous REVEAL scores and the efficacy of the 4-strata risk score to discriminate between intermediate-low and intermediate-high cohorts. This

179 further supports the reliability of the imputation procedure chosen for the current study, also obvious
180 from e-Figure 1.

181 ***Sensitivity Analysis addressing Specific Subgroups***

182 We conducted additional subgroup analyses to validate our findings across specific patient
183 populations. As depicted in e-Table 5, PAH-designed 3- and 4-strata risk scores were found to possess
184 predictive power also in each of these subgroups, with the particular strong discriminative potency of
185 the continuous REVEAL scores and the efficacy of the 4-strata risk score to discriminate between
186 intermediate-low and intermediate-high cohorts being again demonstrated. The following subgroups
187 were analyzed:

188 (i) Group 1.1: Idiopathic pulmonary arterial hypertension (IPAH)
189 (ii) Group 1.4.1: Connective tissue disease-associated PAH
190 (iii) Group 1.4.4: Congenital heart disease-associated PAH
191 (iv) Group 2 PH patients with isolated postcapillary PH (i.e., PVR ≤2 WU)
192 (v) Group 2 PH patients with combined pre- and postcapillary PH (i.e., PVR >2 WU)
193 (vi) Group 3.1: PH associated with obstructive lung disease
194 (vii) Group 3.2: PH associated with restrictive lung disease
195 (viii) PAH patients with cardiac comorbidities (defined as the presence of at least three of the
196 following comorbidities: arterial hypertension, obesity, diabetes, coronary heart disease, and atrial
197 fibrillation)

198 Corresponding results were obtained, when dichotomizing the entire PH population as well as each of
199 the PH groups in in severe versus non-severe PH (i.e., PVR ≥5 WU and PVR <5 WU; e-Table 5).

Discussion

This multicentric study comprehensively validates and compares five major existing approaches for risk stratification in PH. It used the largest, worldwide meta-registry published to date, the PVRI GoDeep meta-registry[21]. The major findings are: (i) commonly applied risk stratification schemes are prognostic in patients with PH irrespective of clinical subtype, (ii) the COMPERA 4-strata risk score provides sub-differentiation of the intermediate risk group, (iii) including further variables, both modifiable (e.g., hemodynamics or renal function) and non-modifiable (e.g., sex and age), adds to the prognostic power in incident and treatment-naïve PH patients compared to strata models mainly focusing on WHO-FC, BNP, and 6MWD, and (iv) the REVEAL scoring systems, when used as continuous prediction models, possess the highest statistical prognostic power and granularity.

In recent years, there has been a rapid increase in studies investigating risk stratification and proposing independent risk parameters for PH patients[8-11,13-15,27-29]. In parallel, several risk scores have been developed, validated, and established for PAH patients, including the ESC/ERS risk scores and the REVEAL scores[1,18,30]. The complexity of the risk scores varies from simple non-invasive approaches (e.g., the COMPERA registry 3-/4-strata scores) to more sophisticated invasive approaches (e.g., the REVEAL and ESC/ERS risk scores). Although some parameters are represented in most risk scores (such as 6MWD, WHO functional class, and BNP), age, gender, PAH subgroup and renal function are only represented in the REVEAL 2.0 score. Risk scores are typically applied on a country/region basis.

Determining the most accurate predictive tool is essential as treatment decisions rely on the estimated prognosis, in particular the 1-year prognosis in patients with P(A)H[1]. The current study extends this approach by exploring a putative predictive power of 3- and 4-strata risk scores for PH groups 2 – 4. This study is the first to assess the predictive power of the updated version of the ESC/ERS risk score. In particular, BNP thresholds were changed leading to more patients categorized as intermediate risk regarding laboratory biomarkers. In addition, imaging gained more importance. When comparing to major studies assessing the prognostic power of the 2015 ESC/ERS risk score, our study indicates that

the changes lead to substantially more patients being classified as intermediate risk. Though still separating patients according to risk, the usefulness of the 2022 ESC/ERS risk score is impaired due to the fact that over 80% of the patients are at intermediate risk.

Current practice, following European guidelines, favors 4-strata risk scores, at least during follow-up, as they provide clinical useful insights into the large population of patients at intermediate risk[1,14,15]. Indeed, in our patient population, COMPERA 4-strata risk score classified up to 40% of the intermediate risk patients as intermediate-low risk patients with 1-year mortality rates below 10%. However, 5-year survival rates are compromised compared with low-risk patients, underscoring the importance of frequent monitoring and treatment adjustments in this subset of patients and the importance of 'treating to goal' to achieve (and maintain) a low risk profile[1]; for example, switching from phosphodiesterase type 5 inhibitors to soluble guanylate cyclase stimulators (based on the REPLACE study) or addition of prostacyclin receptor agonists (based on the GRIPHON study)[31,32]. On the other hand, intermediate-high risk patients have a 1-year mortality rate of nearly 20% and may justify more intense early treatment.

REVEAL risk scores are – in comparison to the ESC/ERS risk assessment – continuous scoring systems. When applied as continuous prediction models, the REVEAL scoring systems showed the highest statistical prognostic power and granularity in the various presented analyses. Besides this superiority from a statistical point of view, the granularity of prognostic information may also be advantageous from a clinical standpoint, even in comparison to 4-strata risk scores. Impact of such more granular information on treatment and further clinical decision making will, however, to be delineated in further clinical trials.

The "real world data" collected from patients enrolled in the GoDeep meta-registry are comparable with previous findings. For instance, the initial COMPERA 2.0 risk paper indicated 79% and 50% 5-year survival rates for intermediate-low and intermediate-high risk PAH patients, which aligns with the survival rates observed in this study[14]. Concerning published data on the prognostic power of the REVEAL 2.0 risk score, 5-year survival rates of low-, intermediate-, and high risk patients where

comparable, albeit intermediate risk patients showed slightly higher mortality rates[20]. The C-index of the REVEAL 2.0 score was comparable to previously published studies (0.68 in this study vs 0.73 published previously)[20]. When comparing 5-year survival rates of CTEPH patients at low-, intermediate-, and high risk with previous studies, the ESC/ERS 2015 showed lower mortality rates for low and intermediate risk patients than in previous studies[7]. However, this finding demands more detailed analysis in future studies, as the treatment algorithm of CTEPH patients has considerably changed over the past years with the entrance of balloon angioplasty and combination therapies.

Our study shows that risk scores originally developed for PAH patients (at risk for right heart failure and PH-related death) can also be meaningfully used to risk stratify patients assigned to other PH groups. This contrasts with a previous study showing that the ESC/ERS risk score may not be predictive in patients with PH group 3[9]. However, this observation was limited by small sample size. The clinical relevance of risk scores in PH patients assigned to group 3 will increase if more PH-centered therapies, beyond inhaled Treprostinil, become available for this patient cohort[33]. It is important to highlight that we defined several clinically significant patient groups/phenotypes and conducted subgroup analyses within these categories (e.g., PAH patients with cardiac comorbidities). Across all tested subgroups, our findings consistently demonstrate that the COMPERA 4-strata risk score provides sub-differentiation of the intermediate risk group and that the REVEAL scoring systems, when used as continuous prediction models, possess the highest statistical prognostic power. Interestingly, when examining the hazard ratios directly, patients classified as high-risk according to the COMPERA 4-strata risk score demonstrated a HR of 11, whereas those classified as high-risk using the REVEAL 2.0 and REVEAL Lite 2 scores exhibited HRs of 6 and 10, respectively. Consistently, Kaplan-Meier analyses revealed that patients identified as high-risk by the COMPERA 4-strata risk score experienced significantly lower survival rates compared to those classified as high-risk by the other risk scores. Hence, the COMPERA 4-strata risk score might be particularly more effective in identifying extremely high-risk patients compared to the other risk scores.

Regarding PH-LHD (Group 2), this study is the first to show that PAH-designed risk scores possess predictive potency. In this meta-registry analysis, Group 2 patients also encompass well-controlled HFpEF-PH individuals with PAWP levels ≤15 mmHg. The classification of Group 2, even in cases of borderline PAWP, was determined by each center, considering further clinical characteristics such as volume challenge or exercise testing results. Notably, the REVEAL scores and the 4-strata risk scores had the highest prognostic power, not only in group 2 PH patients but also in group 1 PH patients with cardiac comorbidities. This is commensurate with the importance of right heart function as a predictor of mortality in PH. The use of risk stratification to better describe patients recruited to studies of potential treatments for group 2 PH, and indeed enrich these studies with high-risk patients, may enable the evaluation of new therapies in this patient group.

Our study emphasizes that WHO functional class, BNP levels, and 6MWD are not exclusive to PAH but also hold relevance in other diseases, such as left heart disease (group 2 PH) and lung diseases (group 3 PH). While they may provide useful information in the evaluation and monitoring of PAH patients, their interpretation should also consider the possibility of alternative underlying causes. For instance, the deterioration of left heart failure can affect these three parameters similarly to the worsening of right heart insufficiency in patients with group 2 PH or group 1 PH with cardiopulmonary comorbidities. A comprehensive evaluation of risk scores in groups 2 – 5 will thus consider both the underlying diseases and the severity of PH and right heart failure.

Moreover, our study stands out as one of the pioneering initiatives to encompass regions of the world that have often been overlooked in previous risk assessment studies. Locations such as Johannesburg and Abu Dhabi, which were traditionally underrepresented in research assessing risk in PH, are included in our study. Notably, these regions exhibit substantial differences when compared to their Western counterparts. In Europe and America, a significant proportion of PH cases are associated with either left heart disease or chronic lung disease[35]. However, in Africa, a distinct pattern emerges, where approximately 10% of patients are diagnosed with PH linked to conditions such as sickle cell anemia or rheumatic heart disease, respectively[35]. The inclusion of such diverse regions in the GoDeep meta-

registry, a global PH meta-registry, allows us to consider and account for these regional disparities in PH etiology and patient demographics[36]. This approach ensures a more comprehensive and representative assessment of risk factors, acknowledging the unique characteristics and challenges faced by patients across the world.

A limitation of this study is its retrospective study design. As is often the case when relying on routinely collected clinical data, some data are missing requiring imputation following statistical standard procedures. In mitigation, the analyses without any imputation yielded largely corresponding results. Prospective verification concerning the predictive power of the risk scores investigated in the individual PH groups is warranted. Based on the data available in the GoDeep meta-registry, only limited subgroup analyses could be undertaken, which did, however, again confirm the main findings in the overall PH population. As a further limitation, no information on interventions such as pulmonary endarterectomy or balloon pulmonary angioplasty in CTEPH patients were included in the analysis of group 4. Potential biases, such as selection bias, cannot be entirely ruled out.

Interpretation

This comprehensive study with real-world data from 15 PH centers substantially extends our understanding of the predictive power of PAH-designed risk scores, including their potential application in PH patients beyond the PAH group.

Take-home Points

Study Question: Do risk scores originally developed for pulmonary arterial hypertension (PAH; group 1 PH) have predictive power in patients with non-PAH pulmonary hypertension?

Results: 3- and 4-strata risk scores predicted survival in all PH groups 1 – 4 with the COMPERA 4-strata risk score effectively distinguishing high- and low-risk patients within the intermediate-risk group, while the Reveal scores, used as a continuous scoring system, have the highest statistical prognostic power and granularity in this global multicenter study including 8565 incident and treatment-naïve patients.

Interpretation: PAH-designed 3- or 4- or continuous data-risk scores possess predictive power in a large cohort of PH patients, whether considered as a common group or calculated separately for each PH group (1-4) as well as various subgroups.

Keywords: pulmonary hypertension; risk stratification; multicentric; predictive power; PVRI GoDeep meta-registry

References

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022.

2. Gall H, Felix JF, Schneck FK, et al. The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2017; **36**(9): 957–67.

3. Douschan P, Kovacs G, Avian A, et al. Mild Elevation of Pulmonary Arterial Pressure as a Predictor of Mortality. *American journal of respiratory and critical care medicine* 2018; **197**(4): 509–16.

4. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; **34**(4): 888-94.

5. Trammell AW, Shah AJ, Phillips LS, Michael Hart C. Mortality in US veterans with pulmonary hypertension: a retrospective analysis of survival by subtype and baseline factors. *Pulm Circ* 2019; **9**(1): 2045894019825763.

6. Naeije R, Richter MJ, Rubin LJ. The physiological basis of pulmonary arterial hypertension. *Eur Respir J* 2022; **59**(6).

7. Delcroix M, Staehler G, Gall H, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. *The European respiratory journal* 2018; **52**(5).

8. Yogeswaran A, Tello K, Faber M, et al. Risk assessment in severe pulmonary hypertension due to interstitial lung disease. *The Journal of Heart and Lung Transplantation* 2020.

9. Yogeswaran A, Kuhnert S, Gall H, et al. Relevance of Cor Pulmonale in COPD With and Without Pulmonary Hypertension: A Retrospective Cohort Study. *Front Cardiovasc Med* 2022; **9**: 826369.

10. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *European heart journal* 2017.

11. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *The European respiratory journal* 2017; **50**(2).

12. Galie N, Humbert M, Vachiery JL, 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). *Eur Heart J* 2016; **37**(1): 67-119.

13. Humbert M, Farber HW, Ghofrani HA, et al. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019; **53**(6).

14. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. *Eur Respir J* 2022; **60**(1).

15. Yogeswaran A, Richter MJ, Sommer N, et al. Advanced risk stratification of intermediate risk group in pulmonary arterial hypertension. *Pulmonary Circulation* 2020; **10**(4).

16. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* 2012; **141**(2): 354–62.

17. Benza RL, Farber HW, Frost A, et al. REVEAL risk score in patients with chronic thromboembolic pulmonary hypertension receiving riociguat. *J Heart Lung Transplant* 2018; **37**(7): 836-43.

18. Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. *Chest* 2019; **156**(2): 323-37.

19. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest* 2012; **142**(2): 448-56.

20. Benza RL, Kanwar MK, Raina A, 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* 2021; **159**(1): 337-46.

21. Majeed RW, Wilkins MR, Howard L, et al. Pulmonary Vascular Research Institute GoDeep: A meta-registry merging deep phenotyping datafrom international PH reference centers. *Pulm Circ* 2022; **12**(3): e12123.

23. RC T. R: A language and environment for statistical computing. R Foundation for Statistical Computing. . 2022.

24. Therneau MT, Grambach MP. Modeling Survival Data: Extending the Cox Model: Springer; 2000.

25. Gohel D, Skintzos P. flextable: Functions for Tabular Reporting. *R package version 085* 2023; **https://CRAN.R-project.org/package=flextable**.

26. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software* 2011; **45**(3): 1 - 67.

27. Yogeswaran A, Tello K, Lund J, et al. Risk assessment in pulmonary hypertension based on routinely measured laboratory parameters. *The Journal of Heart and Lung Transplantation* 2021.

28. Galie N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019; **53**(1).

29. Xanthouli P, Koegler M, Marra AM, et al. Risk stratification and prognostic factors in patients with pulmonary arterial hypertension and comorbidities a cross-sectional cohort study with survival follow-up. *Respiratory Research* 2020; **21**(1).

30. Galiè N, Humbert M, Vachiery J-L, 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* 2016; **37**(1): 67–119.

31. Hoeper MM, Al-Hiti H, Benza RL, et al. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med* 2021; **9**(6): 573-84.

32. Sitbon O, Channick R, Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2015; **373**(26): 2522-33.

33. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. *N Engl J Med* 2021; **384**(4): 325-34.

34. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019; **53**(1).

35. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med. 2016;4(4):306-322.

36. Majeed RW, Wilkins MR, Howard L, et al. Pulmonary Vascular Research Institute GoDeep: A meta-registry merging deep phenotyping datafrom international PH reference centers. Pulm Circ. 2022;12(3):e12123.

Table 1: Baseline characteristics of the study population.

PH patients' characteristics at baseline and stratified by PH group including imputed data. Median and interquartile range are given. Column "5*" in **a)** shows the values for PH patients in group 5 without imputation.

a) Baseline table stratified by PH group.
b) Comorbidities stratified by PH group.

PH = pulmonary hypertension; WHO FC = WHO functional class; 6MWd = six minute-walking distance; BNP = B-type natriuretic peptide; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; CI = Cardiac Index.

a)

PH Group	1	2	3	4	Overall	5*
N	3537	1807	1635	1586	8565	101
age at diagnosis (years)						
Median [Q1, Q3]	57 [43, 69]	73 [65, 78]	67 [58, 73]	66 [52, 74]	65 [52, 74]	67 [52, 73]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
sex						
male	1061 (30%)	659 (36.5%)	836 (51.1%)	811 (51.1%)	3367 (39.3%)	42 (41.6%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
WHO FC						
I	61 (1.72%)	41 (2.27%)	9 (0.55%)	27 (1.7%)	138 (1.61%)	5 (4.95%)
II	573 (16.2%)	296 (16.4%)	221 (13.5%)	226 (14.2%)	1316 (15.4%)	7 (16.8%)
III	2380 (67.3%)	1298 (71.8%)	1079 (66%)	1162 (73.3%)	5919 (69.1%)	71 (70.3%)
IV	523 (14.8%)	172 (9.52%)	326 (19.9%)	171 (10.8%)	1192 (13.9%)	8 (7.92%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6MWD (m)						
Median [Q1, Q3]	291 [195, 390]	257 [167, 350]	243 [174, 333]	291 [200, 384]	273 [188, 367]	244 [152, 341]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BNP (pg/ml)						
Median [Q1, Q3]	177 [63.9, 422]	199 [91.1, 432]	138 [48.5, 390]	171 [63.4, 426]	175 [65, 416]	193 [58, 447]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%
mPAP (mmHg)						
Median [Q1, Q3]	48 [38, 57]	37 [30, 45]	37 [29, 46]	44 [34, 52]	42 [33, 52]	43 [34.5, 50.5]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	34 (33.7%)
PAWP (mmHg)						
Median [Q1, Q3]	10 [7, 13]	17 [12, 22]	10 [7, 14]	10 [8, 14]	11 [8, 15]	11 [7, 14]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	57 (56.4%)
PVR (WU)						
Median [Q1, Q3]	9.25 [5.59, 13.9]	3.52 [2.27, 5.74]	5.6 [3.87, 9]	7.72 [4.64, 11.3]	6.7 [3.87, 11]	5.86 [4.32, 8.85]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	50 (49.5%)
CI (L/(min·m²))						
Median [Q1, Q3]	2.21 [1.77, 2.75]	2.54 [2.1, 2.97]	2.43 [2, 2.88]	2.25 [1.84, 2.72]	2.34 [1.89, 2.82]	2.73 [2.35, 3.1]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	58 (57.4%)

b)

PH Group	1	2	3	4	Overall
N	3537	1807	1635	1586	8565
Obesity	1212 (34.3%)	867 (48%)	576 (35.2%)	584 (36.8%)	3239 (37.8%)
Diabetes mellitus	329 (9.3%)	290 (16%)	220 (13.5%)	106 (6.68%)	945 (11%)
Coronary heart disease	201 (5.68%)	34 (1.88%)	49 (3%)	13 (0.82%)	297 (3.47%)
Arterial hypertension	617 (17.4%)	538 (29.8%)	413 (25.3%)	317 (20%)	1885 (22%)
Atrial Fibrillation	169 (4.78%)	490 (27.1%)	160 (9.79%)	130 (8.2%)	949 (11.1%)
Renal Comorbidities	157 (4.44%)	195 (10.8%)	163 (9.97%)	122 (7.69%)	637 (7.44%)
Cancer	118 (3.34%)	98 (5.42%)	141 (8.62%)	78 (4.92%)	435 (5.08%)
Sleep Apnea Syndrome	259 (7.32%)	179 (9.91%)	173 (10.6%)	90 (5.67%)	701 (8.18%)
Oxygen Treatment	904 (25.6%)	200 (11.1%)	752 (46%)	392 (24.7%)	2248 (26.2%)

Table 2: Risk score classification of the imputed study population stratified by PH group 1-4

NRisk scores classification at baseline and stratified by PH Group. Only patients with available 6MWD, BNP, and WHO FC were included.

PH = pulmonary hypertension; WHO FC = WHO functional class; 6MWd = six minute-walking distance; BNP = B-type natriuretic peptide; int. = intermediate; int.-high = intermediate-high; int.-low = intermediate-low.

PH Group	1	2	3	4	Overall
N	3537	1807	1635	1586	8565
REVEAL 2.0					
≤6	1866 (52.8%)	1144 (63.3%)	817 (50%)	963 (60.7%)	4790 (55.9%)
7	433 (12.2%)	236 (13.1%)	228 (13.9%)	207 (13.1%)	1104 (12.9%)
8	408 (11.5%)	167 (9.24%)	201 (12.3%)	148 (9.33%)	924 (10.8%)
9	338 (9.56%)	125 (6.92%)	155 (9.48%)	102 (6.43%)	720 (8.41%)
10	211 (5.97%)	77 (4.26%)	104 (6.36%)	89 (5.61%)	481 (5.62%)
11	137 (3.87%)	34 (1.88%)	75 (4.59%)	46 (2.9%)	292 (3.41%)
12	70 (1.98%)	16 (0.885%)	33 (2.02%)	18 (1.13%)	137 (1.6%)
≥13	74 (2.09%)	8 (0.443%)	22 (1.35%)	13 (0.82%)	117 (1.37%)
REVEAL Lite 2					
≤5	866 (24.5%)	348 (19.3%)	365 (22.3%)	404 (25.5%)	1983 (23.2%)
6	484 (13.7%)	229 (12.7%)	207 (12.7%)	197 (12.4%)	1117 (13%)
7	603 (17%)	370 (20.5%)	286 (17.5%)	315 (19.9%)	1574 (18.4%)
8	647 (18.3%)	395 (21.9%)	314 (19.2%)	294 (18.5%)	1650 (19.3%)
9	513 (14.5%)	304 (16.8%)	250 (15.3%)	213 (13.4%)	1280 (14.9%)
10	271 (7.66%)	127 (7.03%)	135 (8.26%)	119 (7.5%)	652 (7.61%)
11	118 (3.34%)	29 (1.6%)	63 (3.85%)	37 (2.33%)	247 (2.88%)
≥12	35 (0.99%)	5 (0.277%)	15 (0.917%)	7 (0.441%)	62 (0.724%)
ESC/ERS 2022					
low	220 (6.22%)	93 (5.15%)	102 (6.24%)	89 (5.61%)	504 (5.88%)
int.	2790 (78.9%)	1550 (85.8%)	1338 (81.8%)	1271 (80.1%)	6949 (81.1%)
high	527 (14.9%)	164 (9.08%)	195 (11.9%)	226 (14.2%)	1112 (13%)
COMPERA 3-strata					
low	439 (12.4%)	132 (7.3%)	121 (7.4%)	173 (10.9%)	865 (10.1%)
int.	2794 (79%)	1543 (85.4%)	1337 (81.8%)	1292 (81.5%)	6966 (81.3%)
high	304 (8.59%)	132 (7.3%)	177 (10.8%)	121 (7.63%)	734 (8.57%)
COMPERA 4-strata					
low	283 (8%)	87 (4.81%)	74 (4.53%)	114 (7.19%)	558 (6.51%)
int.-low	1163 (32.9%)	527 (29.2%)	499 (30.5%)	525 (33.1%)	2714 (31.7%)
int.-high	1830 (51.7%)	1082 (59.9%)	922 (56.4%)	841 (53%)	4675 (54.6%)
high	261 (7.38%)	111 (6.14%)	140 (8.56%)	106 (6.68%)	618 (7.22%)

Figure 1: Study flow chart.

Flow chart illustrating the sequential steps of the study design.

PH = pulmonary hypertension.

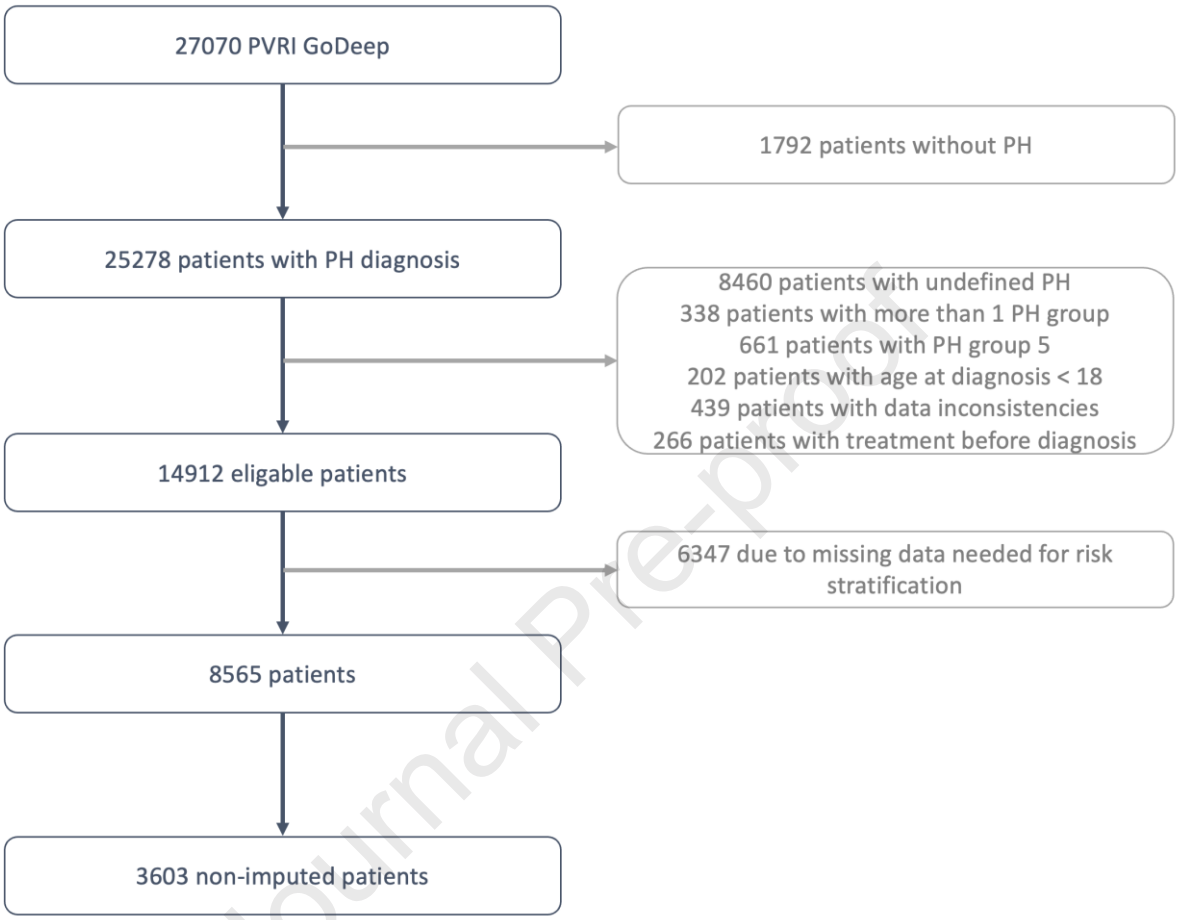


Figure 2: Kaplan-Meier curves of risk scores.

Survival of all PH patients stratified by risk score. Kaplan-Meier curves with 95 % confidence bands. PH = pulmonary hypertension; int. = intermediate.

a) Kaplan-Meier curve stratified by REVEAL 2.0 risk score.
b) Kaplan-Meier curve stratified by REVEAL Lite 2 risk score.
c) Kaplan-Meier curve stratified by ESC/ERS 2022 risk score.
d) Kaplan-Meier curve stratified by COMPERA 3-strata risk score.
e) Kaplan-Meier curve stratified by COMPERA 4-strata risk score.

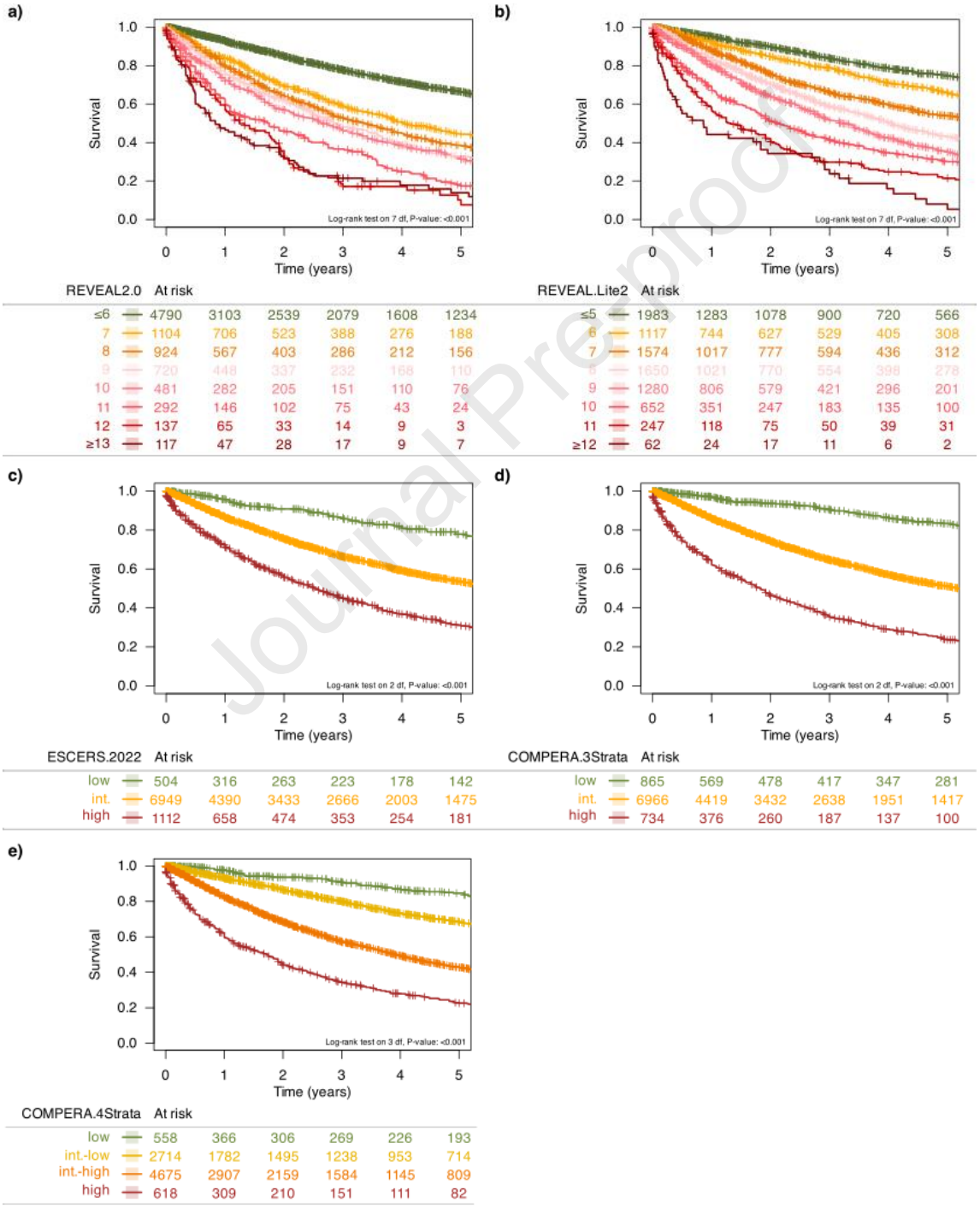


Table 3: Predictive power of the included risk scores.

C-Index and the difference of AIC estimates between the ESC/ERS 2022 score and the respective risk score of the Cox proportional hazards model based on the entire data set including imputed data are shown. Center and diagnosis decade are included as stratification variables, as is center as a cluster. Values are given for risk scores for overall PH and groups 1-4.

ΔAIC = difference of Akaike information criterion between the ESC/ERS 2022 score and the respective risk score; C-Index = concordance index; PH = pulmonary hypertension.
*p-values <0.001 in comparison to ESC/ERS 2022 score.

		Reveal 2.0	**Reveal Lite 2**	**ESC/ERS 2022**	**COMPERA 3-strata**	**COMPERA 4-strata**
PH overall	**Δ**AIC	558	491	0	182	417
	C-Index	0.65*	0.66*	0.57	0.58*	0.63*
Group 1	**Δ**AIC	294	261	0	64	191
	C-Index	0.68*	0.68*	0.58	0.59	0.65*
Group 2	**Δ**AIC	39	37	0	14	32
	C-Index	0.61*	0.61*	0.56	0.57	0.58
Group 3	**Δ**AIC	90	73	0	17	54
	C-Index	0.63*	0.63*	0.56	0.57	0.60*
Group 4	**Δ**AIC	60	38	0	16	38
	C-Index	0.66*	0.66*	0.58	0.59	0.63*

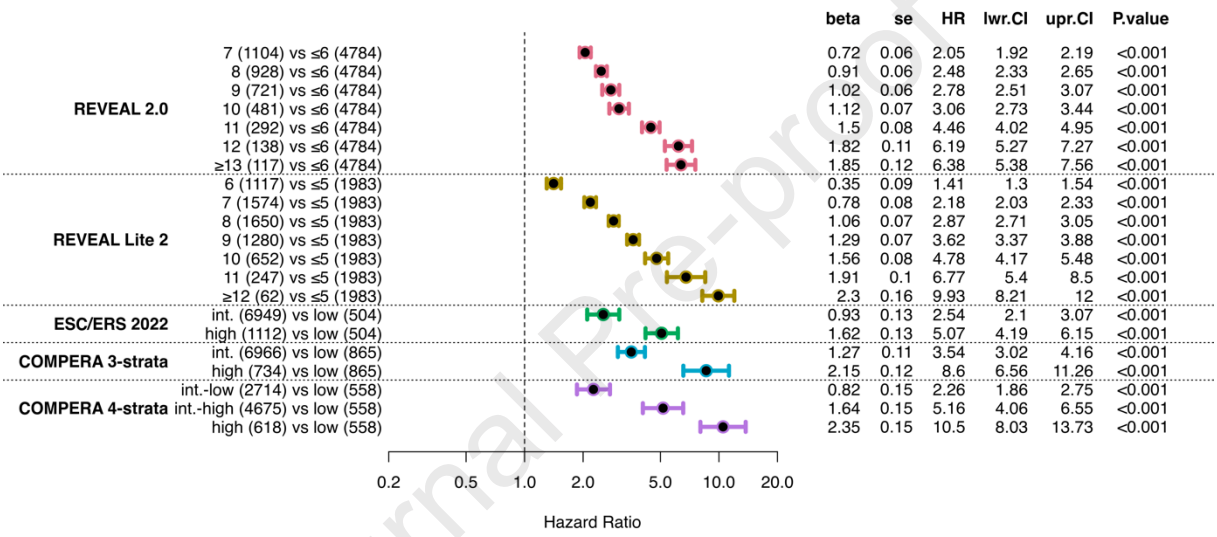
Figure 3: Forest Plots of the included risk scores.

a) Forest plot for the overall PH group, stratified by risk score.
b) Forest plot for PH group 1 stratified by risk score.
c) Forest plot for PH group 2 stratified by risk score.
d) Forest plot for PH group 3 stratified by risk score.
e) Forest plot for PH group 4 stratified by risk score.

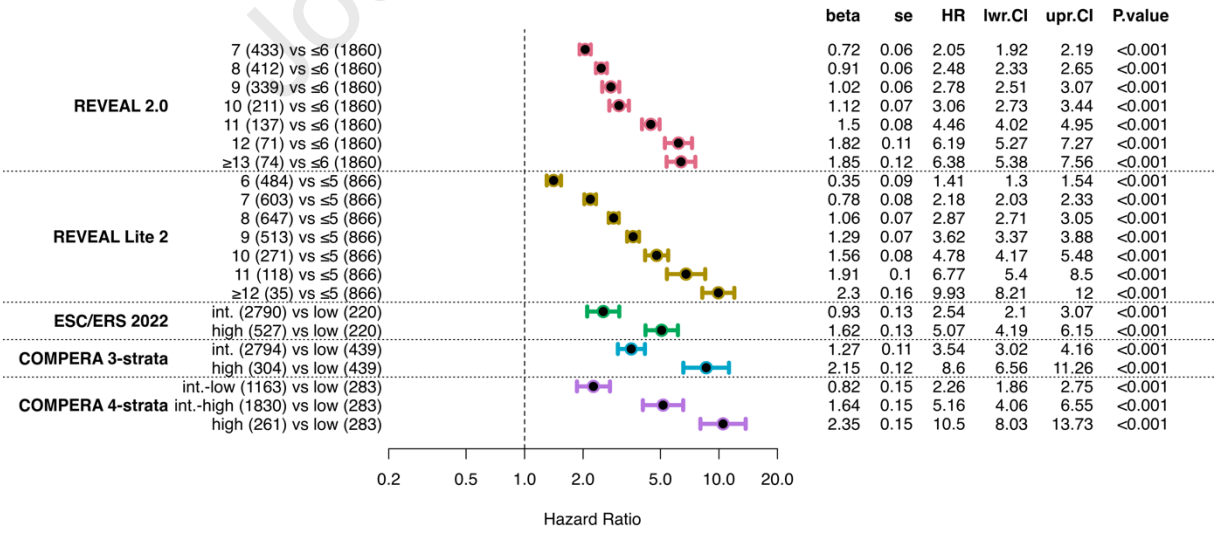
All in relation to the low-risk category of the respective risk score.

PH = pulmonary hypertension; HR = hazard ratio, lwr.CI = lower 95% confidence bound; upr.CI = upper 95% confidence bound; int.-high = intermediate-high; int.-low = intermediate-low.

a)



b



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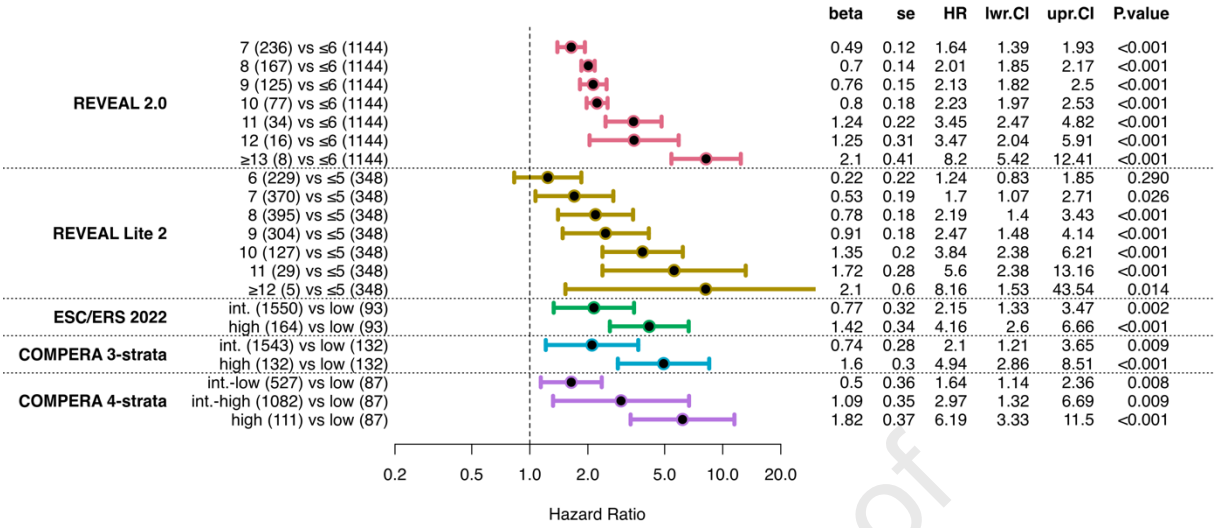

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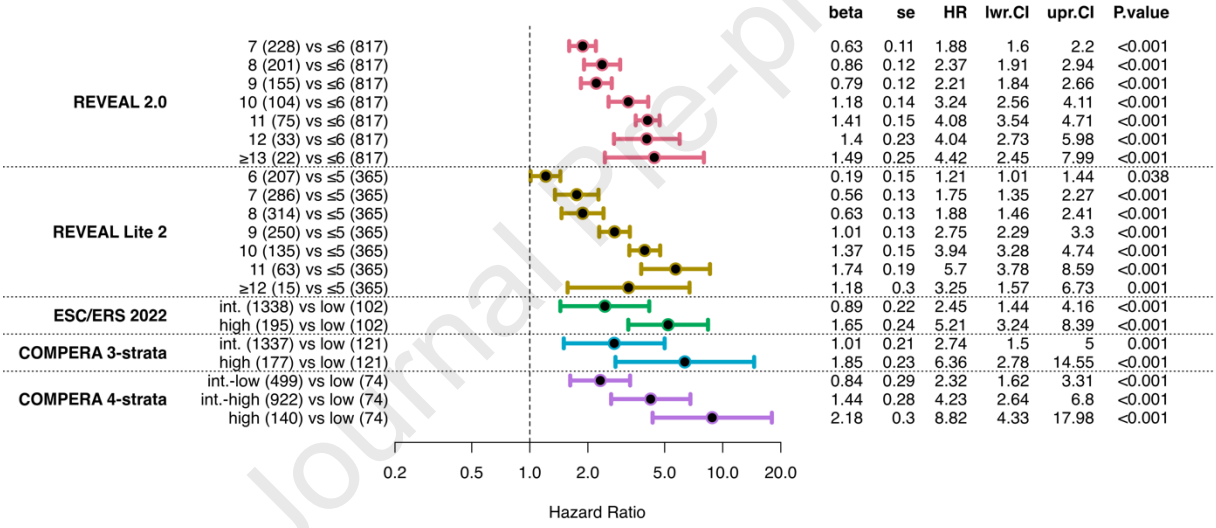


e)

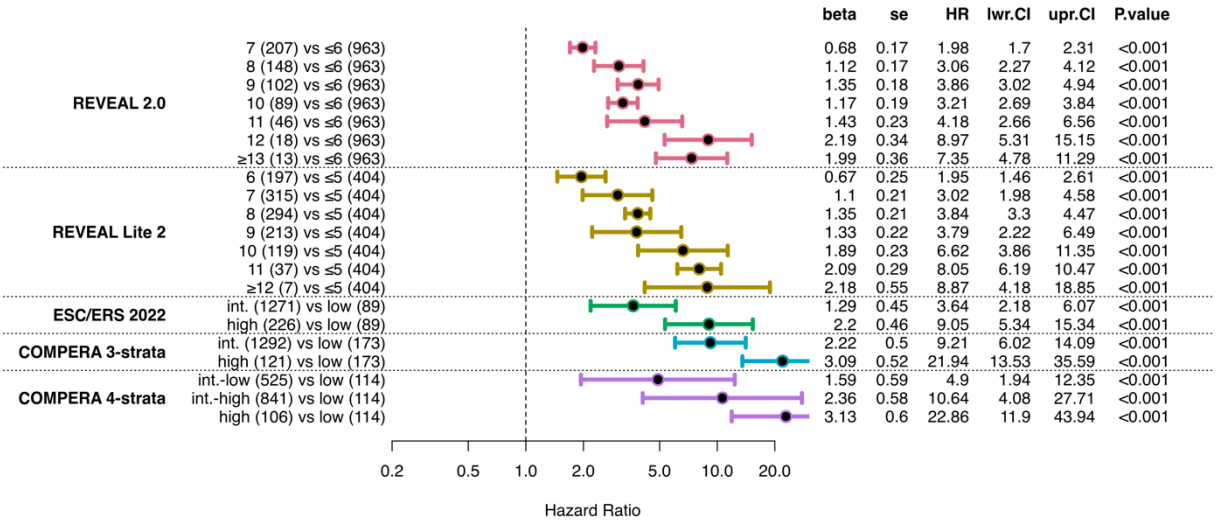


Figure 4: Forest plot of COMPERA 4-strata risk score in relation to the intermediate-low risk category of the respective risk score.

PH = pulmonary hypertension; HR = hazard ratio, lwr.CI = lower 95% confidence bound; upr.CI = upper 95% confidence bound; int.-high = intermediate high; int.-low = intermediate-low.

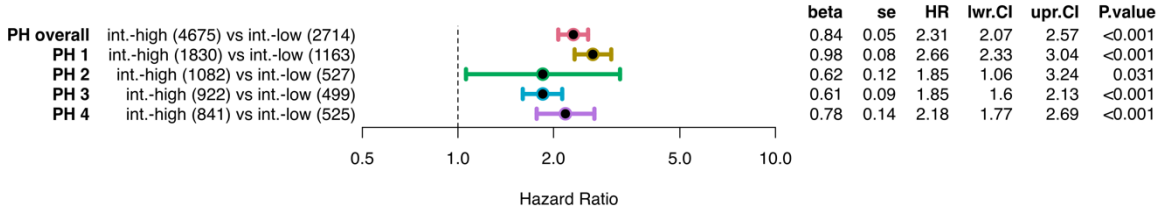
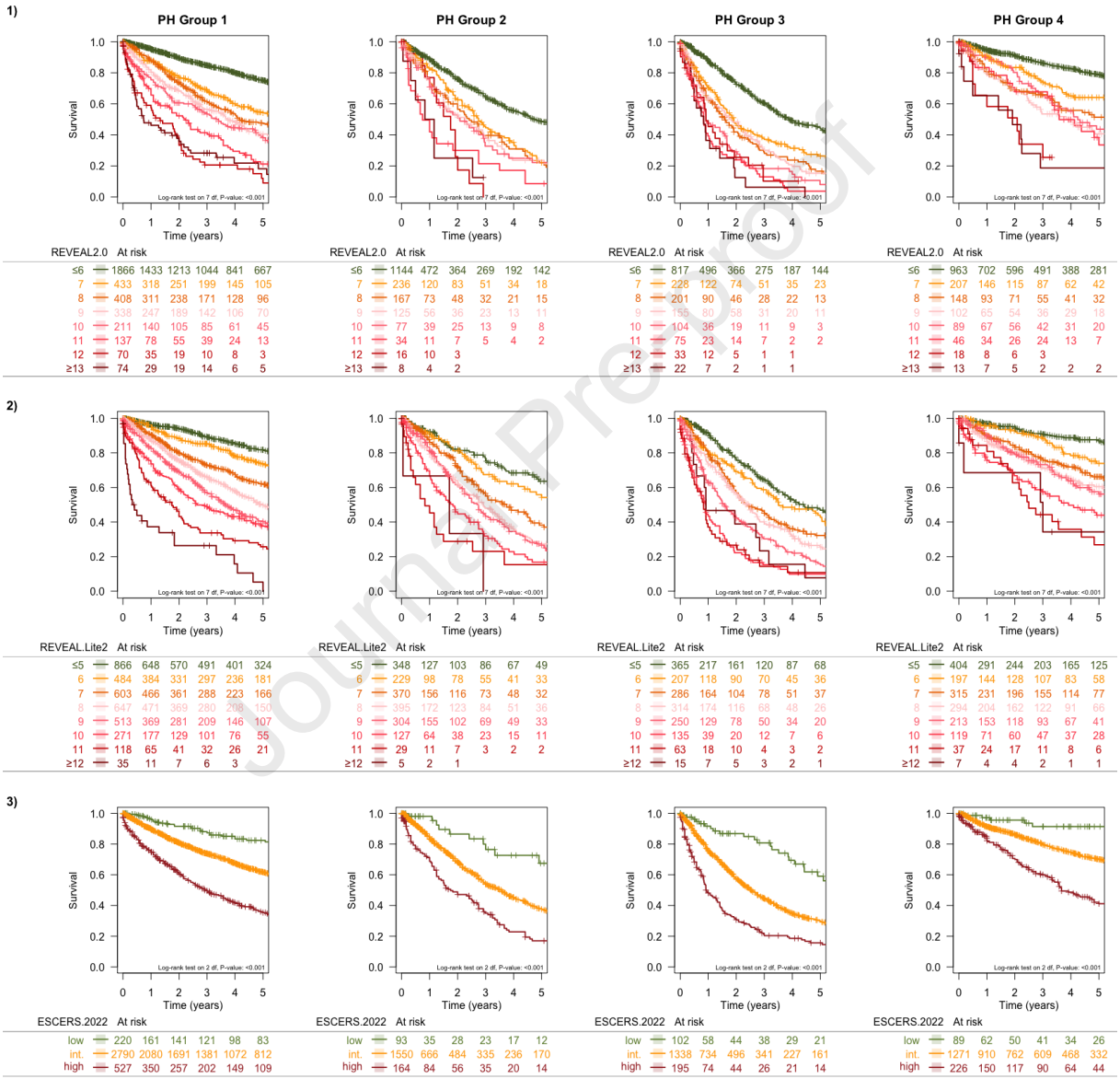
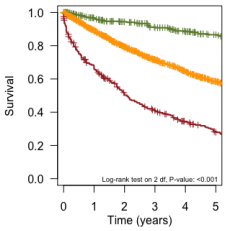


Figure 5: Kaplan-Meier curves of 3-strata and 4-strata risk scores for PH group 1 – 4.

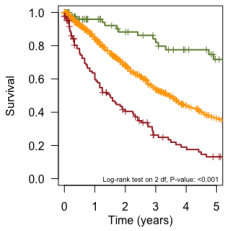
Survival rates for each PH group (1-4) stratified by REVEAL 2.0, REVEAL Lite 2, ESC/ERS 2022, COMPERA 3-strata and COMPERA 4-strata, respectively. Kaplan-Meier curves with 95 % confidence bands are shown for patients in each risk score group. Center and diagnosis decade are included as stratification variables, as is center included as cluster.
a) Survival rates for REVEAL 2.0.
b) Survival rates for REVEAL Lite 2.
c) Survival rates for ESC/ERS 2022.
d) Survival rates for COMPERA 3-strata.
e) Survival rates for COMPERA 4-strata.
PH = pulmonary hypertension; int. = intermediate; int.-high = intermediate-high; int.-low = intermediate-low.



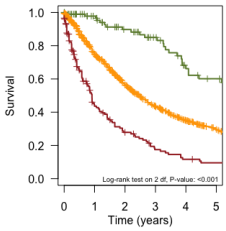
4)



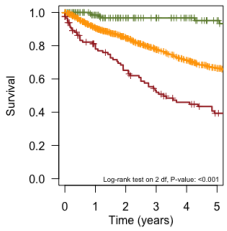
COMPERA.3Strata	At risk					
low	439	319	282	250	212	177
int.	2794	2087	1677	1350	1032	772
high	304	185	130	104	75	55



COMPERA.3Strata	At risk					
low	132	54	45	39	31	23
int.	1543	670	485	335	229	165
high	132	61	38	19	13	8

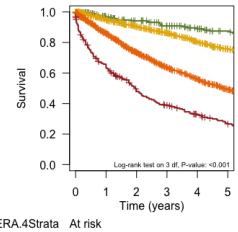


COMPERA.3Strata	At risk					
low	121	78	59	48	34	28
int.	1337	734	494	339	231	159
high	177	54	31	18	12	9

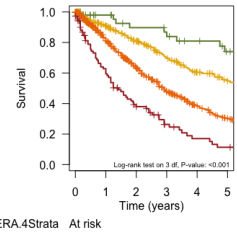


COMPERA.3Strata	At risk					
low	173	118	92	80	70	53
int.	1292	928	776	614	459	321
high	121	76	61	46	37	28

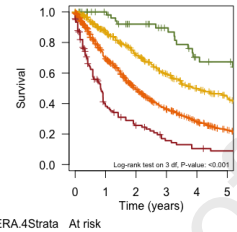
5)



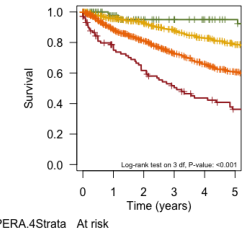
COMPERA.4Strata	At risk					
low	283	199	176	156	134	116
int.-low	1163	903	785	686	539	412
int.-high	1830	1334	1021	777	583	429
high	261	155	107	85	63	47



COMPERA.4Strata	At risk					
low	87	38	32	30	25	20
int.-low	527	201	158	117	85	62
int.-high	1082	494	348	231	154	108
high	111	52	30	15	9	6



COMPERA.4Strata	At risk					
low	74	51	40	33	23	21
int.-low	499	292	216	160	115	87
int.-high	922	485	306	200	131	82
high	140	38	22	12	8	6



COMPERA.4Strata	At risk					
low	114	78	58	50	44	36
int.-low	525	386	336	275	214	153
int.-high	841	594	484	376	277	190
high	106	64	51	39	31	23

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Athiththan Yogeswaran reports a relationship with MSD that includes: speaking and lecture fees. Henning Gall reports a relationship with Actelion, AstraZeneca, Bayer, BMS, , GossamerBio, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, United Therapeutics that includes: consulting or advisory and speaking and lecture fees. David G Kiely reports a relationship with Sheffield Biomedical Research Centre, Jansen Pharmaceuticals, Ferrer, Altavant, MSD, United therapeutics that includes: consulting or advisory. Hossein Ardeschir Ghofrani reports a relationship with Actelion, AstraZeneca, Bayer, GSK, Janssen-Cilag, Lilly, Novartis, OMT, Pfizer, United Therapeutics that includes: consulting or advisory and speaking and lecture fees. Khodr Tello reports a relationship with Bayer, AstraZeneca, Gossamer that includes: consulting or advisory and speaking and lecture fees. Luke Howard reports a relationship with Janssen, MSD, Gossamer, Altavant that includes: consulting or advisory and speaking and lecture fees. Manuel Richter reports a relationship with Janssen Pharmaceutica, Bayer Pharma AG, OMT that includes: consulting or advisory and speaking and lecture fees. Martin Wilkins reports a relationship with MorphogenIX, Janssen, Chiesi, Aerami, British Heart Foundation, NIHR, MSD, Benevolent AI, Tiakis Biotech that includes: consulting or advisory, funding grants, and speaking and lecture fees. Paul M. Hassoun reports a relationship with Merck & Co Inc that includes: consulting or advisory and speaking and lecture fees. Sandeep Sahay reports a relationship with Gossamer Bio, Merck, Keros, Janssen, United Therapeutics, Liquidia that includes: consulting or advisory and speaking and lecture fees. Stephen Chan reports a relationship with Janssen, Bayer, Pfizer, United Therapeutics, Acceleron Pharma that includes: consulting or advisory and speaking and lecture fees. Stylianos Orfanos reports a relationship with MSD, Janssen, Gallenica-Ferrer that includes: consulting or advisory and speaking and lecture fees. Werner Seeger reports a relationship with United Therapeutics, Tiakis Biotech AG, Liquidia, Pieris Pharmaceuticals, Abivax, Pfitzer, Medspray BV that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

e-Table 1: Comparison of risk scores.

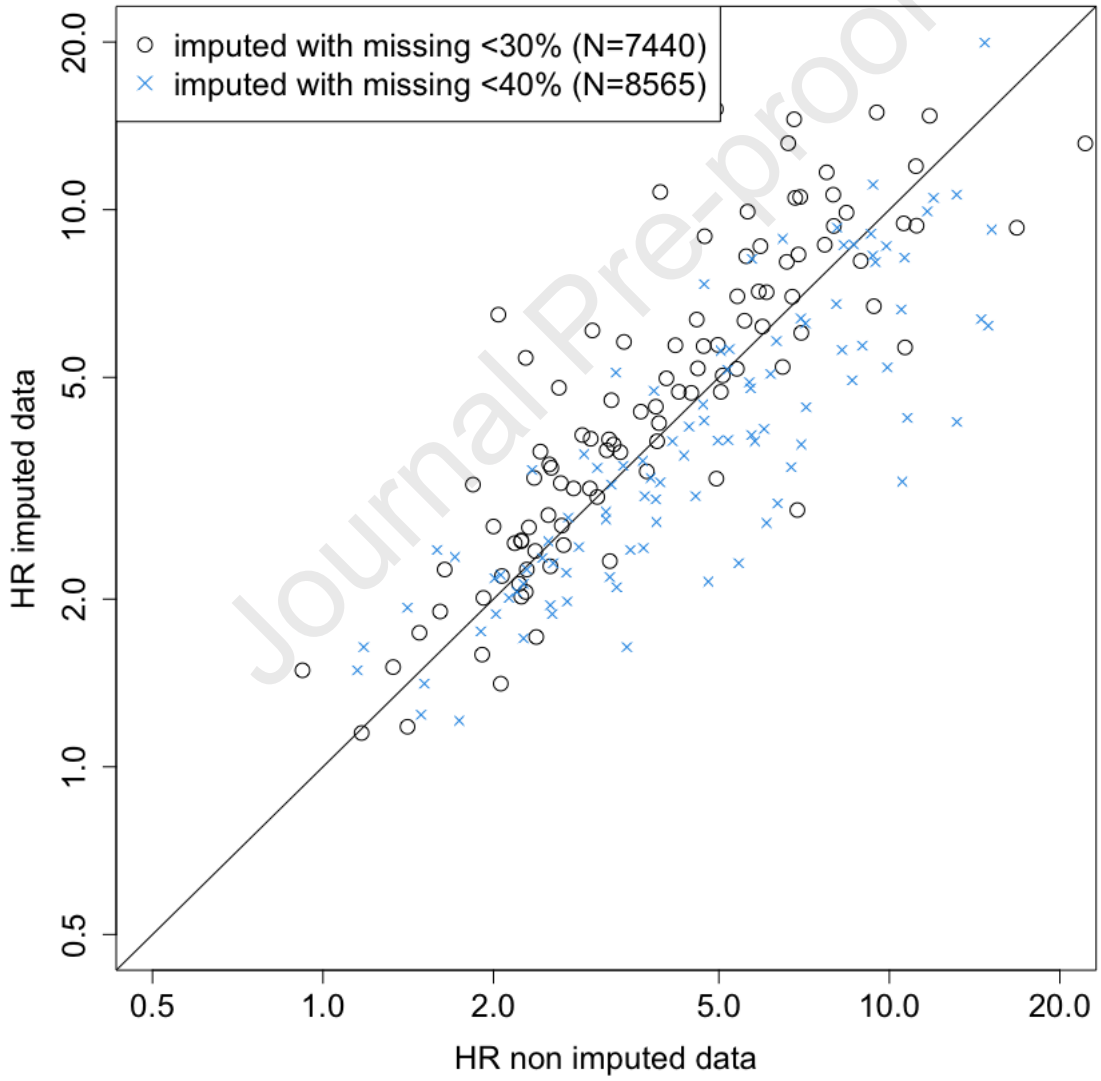
WHO FC = WHO functional class; 6MWd = six minute-walking distance; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; DLCO = diffusing capacity of the lung for carbon monoxide; RAP = right atrial pressure; PVR = pulmonary vascular resistance; VO2 peak = peak oxygen consumption; VE/VCO2 = minute ventilation/carbon dioxide production; RA area = right atrial area; SvO2 = mixed venous oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; sPAP = systolic pulmonary arterial pressure; SVI = stroke volume index; cMRI = cardiac magnetic resonance imaging; *italic = not included in calculation in this study*.

Parameter	**REVEAL 2.0**	**REVEAL Lite 2**	**ESC/ERS 2022**	**COMPERA 3-strata**	**COMPERA 4-strata**
WHO Group 1 Subgroup	X				
Demographics	X				
Renal function	X	X			
WHO FC	X	X	X	X	X
Vital Signs	X	X			
6MWd	X	X	X	X	X
BNP/NT-proBNP	X	X	X	X	X
Pericardial effusion	X		X		
DLCO	X				
RAP	X		X		
PVR	X				
VO2 peak			X		
VE/VCO2 slope			X		
RA area			X		
Cardiac index			X		
SvO_2			*X*		
TAPSE/sPAP ratio			*X*		
SVI			*X*		
Hospitalization within 6 months	*X*				
Clinical observations			*X*		
cMRI			*X*		

e-Figure 1: Imputation reliability.

The figure shows the hazard ratios obtained from the unimputed data set plotted against the hazard ratios from the imputed data set with a missingness of at most 30% and 40%. The following procedure was used for imputation: Patients were included if they had at least two of the parameters WHO functional class, 6MWD and BNP. Two different imputations were conducted: In the first imputation, missing data was allowed up to 30%. This resulted in 7440 patients and several parameters being imputed. In the second imputation, up to 40% missing data was allowed, and no additional patients were excluded. This imputation involved 8565 patients and multiple parameters. Continuous variables were log-transformed before imputation, and the analysis was conducted on both datasets. Hazard ratios from the imputed datasets were compared to those from the dataset without any imputation. The mean standard deviation for the imputation with a maximum of 30% missing data was 0.16 compared to the data without imputation, and 0.15 for the imputation with a maximum of 40%. Both imputations showed that hazard ratios were not overestimated, and the results were presented using the larger dataset in the main analysis.

HR = hazard ratio; 6MWd = six minute-walking distance; BNP = B-type natriuretic peptide.



e-Table 2: Baseline characteristics of the non-imputed study population stratified by PH group 1-4

PH patients' characteristics at baseline and stratified by PH Group. Only patients with available 6MWD, BNP, and WHO FC were included. Median and interquartile range are given.

a) Baseline Table stratified by PH group.
b) Comorbidities stratified by PH group.

PH = pulmonary hypertension; WHO FC = WHO functional class; 6MWd = six minute-walking distance; BNP = B-type natriuretic peptide; CI = cardiac index, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance.

a)

PH Group	1	2	3	4	Overall
N	1617	680	620	686	3603
age at diagnosis (years)					
Median [Q1, Q3]	54 [40, 65]	72 [65, 78]	67 [57, 74]	66 [52, 74]	63 [49, 73]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
sex					
male	464 (28.7%)	238 (35%)	310 (50%)	355 (51.7%)	1367 (37.9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
WHO FC					
I	28 (1.73%)	13 (1.91%)	5 (0.806%)	17 (2.48%)	63 (1.75%)
II	317 (19.6%)	104 (15.3%)	109 (17.6%)	109 (15.9%)	639 (17.7%)
III	1062 (65.7%)	514 (75.6%)	412 (66.5%)	497 (72.4%)	2485 (69%)
IV	210 (13%)	49 (7.21%)	94 (15.2%)	63 (9.18%)	416 (11.5%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6MWD (m)					
Median [Q1, Q3]	317 [195, 409]	248 [100, 354]	240 [144, 325]	300 [192, 388]	288 [168, 384]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BNP (pg/ml)					
Median [Q1, Q3]	163 [60, 371]	228 [112, 450]	111 [39, 348]	163 [57.9, 416]	167 [61.8, 395]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
mPAP (mmHg)					
Median [Q1, Q3]	49 [39, 58]	36 [29, 44]	36 [29, 44]	44 [34, 51]	43 [33, 53]
Missing	236 (14.6%)	226 (33.2%)	153 (24.7%)	80 (11.7%)	695 (19.3%)
PAWP (mmHg)					
Median [Q1, Q3]	9 [7, 12]	19 [15, 22]	9 [7, 12]	9 [7, 12]	10 [7, 13]
Missing	608 (37.6%)	429 (63.1%)	234 (37.7%)	366 (53.4%)	1637 (45.4%)
PVR (WU)					
Median [Q1, Q3]	9.88 [6, 14.7]	3.51 [2.29, 5.53]	5.55 [3.94, 8.4]	7.75 [4.71, 11.3]	7.25 [4.25, 11.8]
Missing	349 (21.6%)	278 (40.9%)	185 (29.8%)	132 (19.2%)	944 (26.2%)
CI (L/(min·m²))					
Median [Q1, Q3]	2.19 [1.77, 2.75]	2.42 [2.08, 2.84]	2.47 [2.1, 2.86]	2.25 [1.87, 2.64]	2.3 [1.86, 2.78]
Missing	649 (40.1%)	429 (63.1%)	243 (39.2%)	370 (53.9%)	1691 (46.9%)

b)

PH Group	1	2	3	4	Overall
N	1617	680	620	686	3603
Obesity	334 (20.7%)	184 (27.1%)	124 (20%)	140 (20.4%)	782 (21.7%)
Diabetes mellitus	172 (10.6%)	128 (18.8%)	106 (17.1%)	62 (9.04%)	468 (13%)
Coronary heart disease	119 (7.36%)	23 (3.38%)	16 (2.58%)	8 (1.17%)	166 (4.61%)
Arterial hypertension	360 (22.3%)	246 (36.2%)	198 (31.9%)	182 (26.5%)	986 (27.4%)
Arterial fibrillation	88 (5.44%)	226 (33.2%)	65 (10.5%)	75 (10.9%)	454 (12.6%)
Renal Comorbidities	83 (5.13%)	65 (9.56%)	63 (10.2%)	64 (9.33%)	275 (7.63%)
Cancer	64 (3.96%)	38 (5.59%)	52 (8.39%)	42 (6.12%)	196 (5.44%)
Sleep Apnea Syndrome	167 (10.3%)	89 (13.1%)	81 (13.1%)	64 (9.33%)	401 (11.1%)
Oxygen Treatment	371 (22.9%)	81 (11.9%)	303 (48.9%)	154 (22.4%)	909 (25.2%)

e-Table 3: Risk score classification of the non-imputed study population stratified by PH group 1-4

Risk scores classification at baseline and stratified by PH Group. Only patients with available 6MWD, BNP, and WHO FC were included.

PH = pulmonary hypertension; WHO FC = WHO functional class; 6MWd = six minute-walking distance; BNP = B-type natriuretic peptide; int. = intermediate; int.-high = intermediate-high; int.-low = intermediate-low.

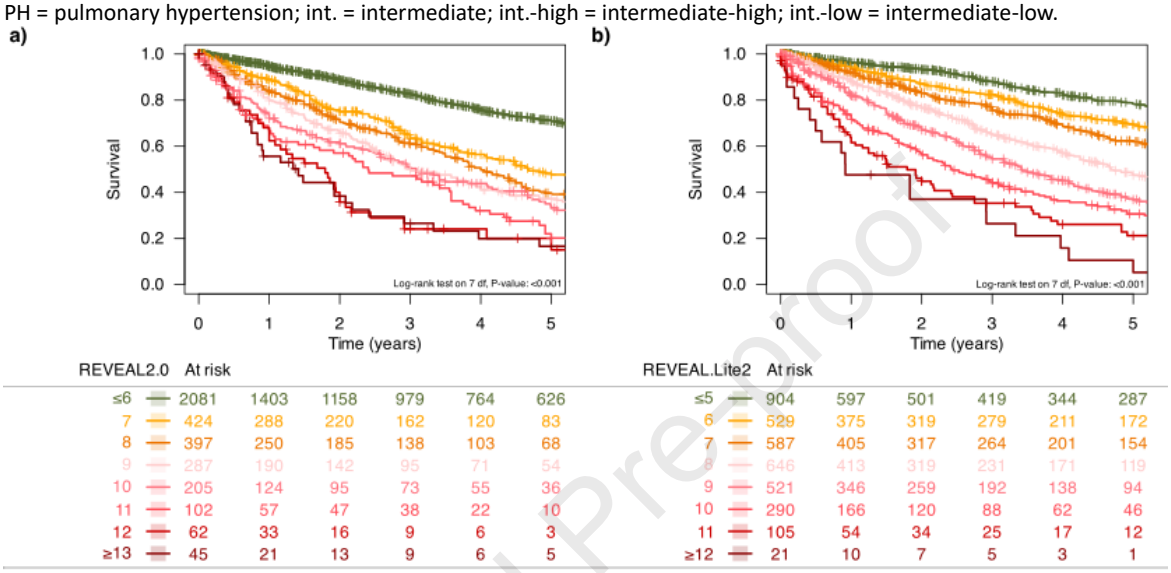
PH Group	1	2	3	4	Overall
N	1617	680	620	686	3603
REVEAL 2.0					
≤6	944 (58.4%)	387 (56.9%)	327 (52.7%)	423 (61.7%)	2081 (57.8%)
7	189 (11.7%)	79 (11.6%)	89 (14.4%)	67 (9.77%)	424 (11.8%)
8	152 (9.4%)	98 (14.4%)	74 (11.9%)	73 (10.6%)	397 (11%)
9	135 (8.35%)	52 (7.65%)	55 (8.87%)	45 (6.56%)	287 (7.97%)
10	84 (5.19%)	44 (6.47%)	37 (5.97%)	40 (5.83%)	205 (5.69%)
11	57 (3.53%)	8 (1.18%)	16 (2.58%)	21 (3.06%)	102 (2.83%)
12	30 (1.86%)	9 (1.32%)	12 (1.94%)	11 (1.6%)	62 (1.72%)
≥13	26 (1.61%)	3 (0.441%)	10 (1.61%)	6 (0.875%)	45 (1.25%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
REVEAL Lite 2					
≤5	451 (27.9%)	107 (15.7%)	159 (25.6%)	187 (27.3%)	904 (25.1%)
6	257 (15.9%)	95 (14%)	92 (14.8%)	85 (12.4%)	529 (14.7%)
7	256 (15.8%)	115 (16.9%)	96 (15.5%)	120 (17.5%)	587 (16.3%)
8	266 (16.5%)	146 (21.5%)	113 (18.2%)	121 (17.6%)	646 (17.9%)
9	190 (11.8%)	146 (21.5%)	89 (14.4%)	96 (14%)	521 (14.5%)
10	128 (7.92%)	60 (8.82%)	44 (7.1%)	58 (8.45%)	290 (8.05%)
11	57 (3.53%)	10 (1.47%)	21 (3.39%)	17 (2.48%)	105 (2.91%)
≥12	12 (0.742%)	1 (0.147%)	6 (0.968%)	2 (0.292%)	21 (0.583%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ESC/ERS 2022					
low	131 (8.1%)	31 (4.56%)	48 (7.74%)	42 (6.12%)	252 (6.99%)
int.	1219 (75.4%)	576 (84.7%)	500 (80.6%)	516 (75.2%)	2811 (78%)
high	267 (16.5%)	73 (10.7%)	72 (11.6%)	128 (18.7%)	540 (15%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
COMPERA 3-strata					
low	244 (15.1%)	55 (8.09%)	53 (8.55%)	92 (13.4%)	444 (12.3%)
int.	1234 (76.3%)	568 (83.5%)	500 (80.6%)	532 (77.6%)	2834 (78.7%)
high	139 (8.6%)	57 (8.38%)	67 (10.8%)	62 (9.04%)	325 (9.02%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
COMPERA 4-strata					
low	172 (10.6%)	38 (5.59%)	31 (5%)	63 (9.18%)	304 (8.44%)
int.-low	579 (35.8%)	174 (25.6%)	213 (34.4%)	225 (32.8%)	1191 (33.1%)
int.-high	742 (45.9%)	418 (61.5%)	322 (51.9%)	345 (50.3%)	1827 (50.7%)
high	124 (7.67%)	50 (7.35%)	54 (8.71%)	53 (7.73%)	281 (7.8%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

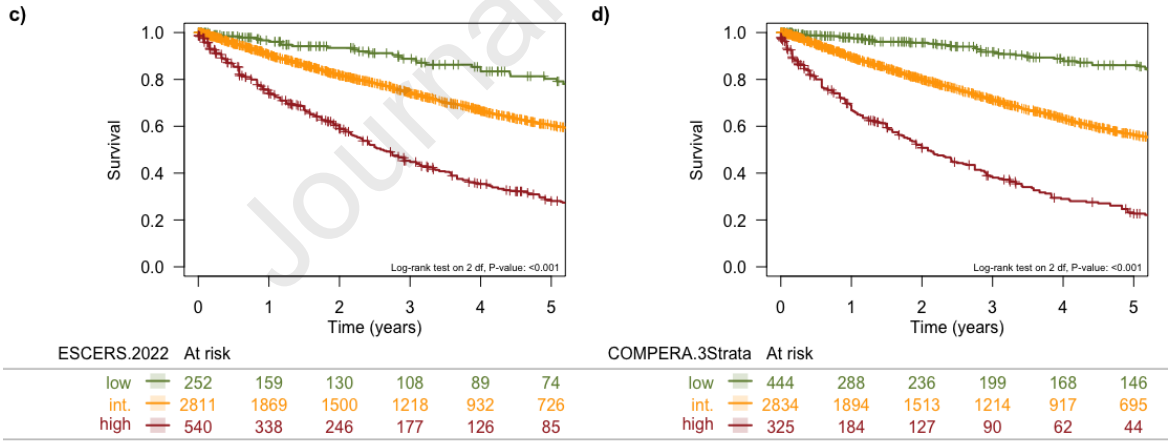
e-Figure 2: Kaplan-Meier curves of risk scores (non-imputed study population).

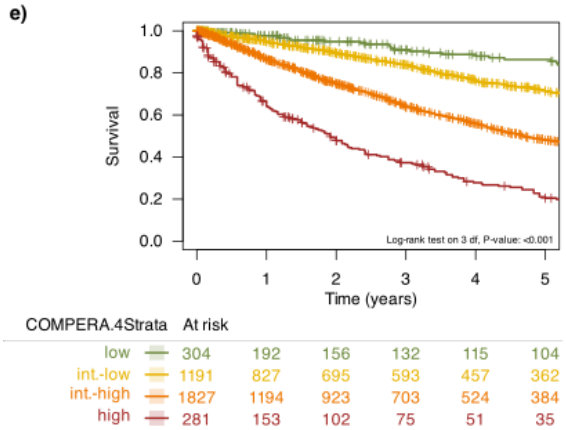
Survival of all PH patients stratified by risk score. Kaplan-Meier curves with 95 % confidence bands.

a) Kaplan-Meier curve stratified by REVEAL 2.0 risk score.
b) Kaplan-Meier curve stratified by REVEAL Lite 2 risk score.
c) Kaplan-Meier curve stratified by ESC/ERS 2022 risk score.
d) Kaplan-Meier curve stratified by COMPERA 3-strata risk score.
e) Kaplan-Meier curve stratified by COMPERA 4-strata risk score.

PH = pulmonary hypertension; int. = intermediate; int.-high = intermediate-high; int.-low = intermediate-low.







e-Table 4: Predictive power of all included risk scores, non-imputed study population.

C-Index and the difference of AIC estimates between the ESC/ERS 2022 score and the respective risk score of the Cox proportional hazards model based on non-imputed data are shown. Center and diagnosis decade are included as stratification variables, as is center included as cluster. Table with values for risk scores at baseline for overall PH and groups 1-4.

ΔAIC = difference of akaike information criterion between the ESC/ERS 2022 score and the respective risk score; C-Index = concordance index; PH = pulmonary hypertension.

*p-values <0.001 in comparison to ESC/ERS 2022 score.

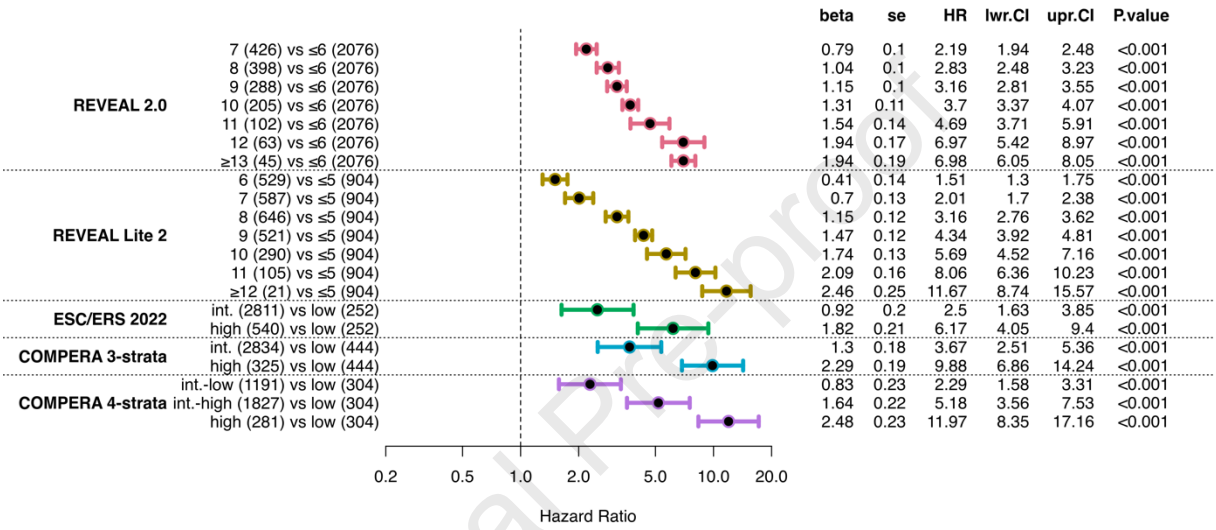
		Reveal 2.0	**Reveal Lite 2**	**ESC/ERS 2022**	**COMPERA 3-strata**	**COMPERA 4-strata**
PH overall	AIC	178	179	0	41	129
	C-Index	0.67*	0.67*	0.60	0.60	0.64*
Group 1	AIC	88	70	0	6	47
	C-Index	0.70*	0.69*	0.62	0.61	0.67*
Group 2	AIC	-2	-4	0	-7	-2
	C-Index	0.65	0.61	0.60	0.58	0.58
Group 3	AIC	9	22	0	0	14
	C-Index	0.67	0.67*	0.60	0.59	0.64
Group 4	AIC	29	13	0	0	3
	C-Index	0.73*	0.69*	0.62	0.61	0.64

e-Figure 3: Forest plots with Hazard Ratios (all in relation to the lowest risk category of the respective risk score), non-imputed study population.

a) Forest plot for the overall PH group stratified by risk score
b) Forest plot for PH group 1 stratified by risk score.
c) Forest plot for PH group 2 stratified by risk score.
d) Forest plot for PH group 3 stratified by risk score.
e) Forest plot for PH group 4 stratified by risk score.

PH = pulmonary hypertension; HR = hazard ratio; lwr.CI = lower 95% confidence bound; upr.CI = upper 95% confidence bound; int. = intermediate; int.-high = intermediate-high; int.-low = intermediate-low.

a)



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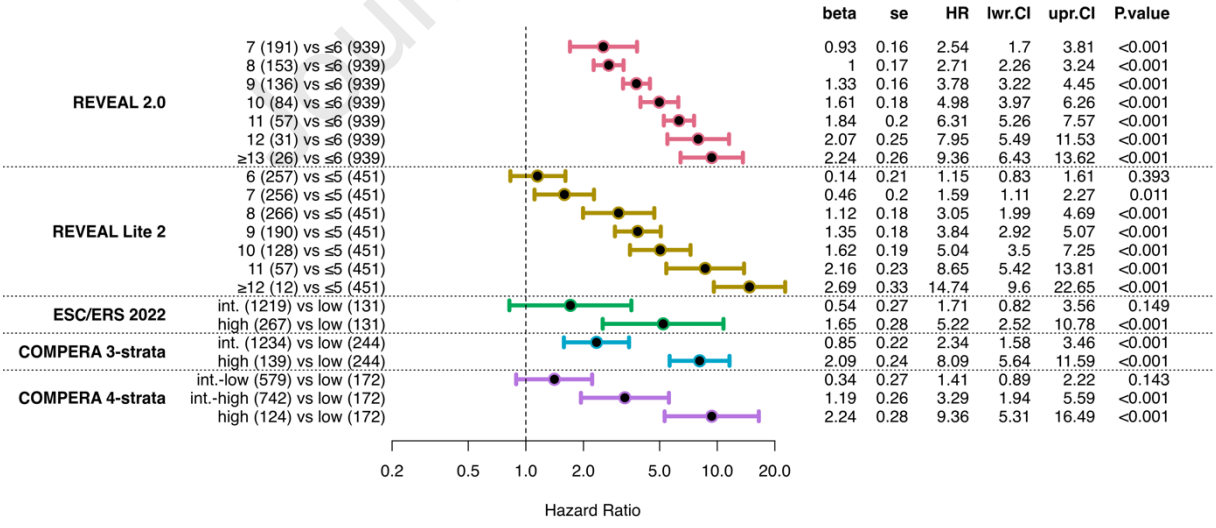

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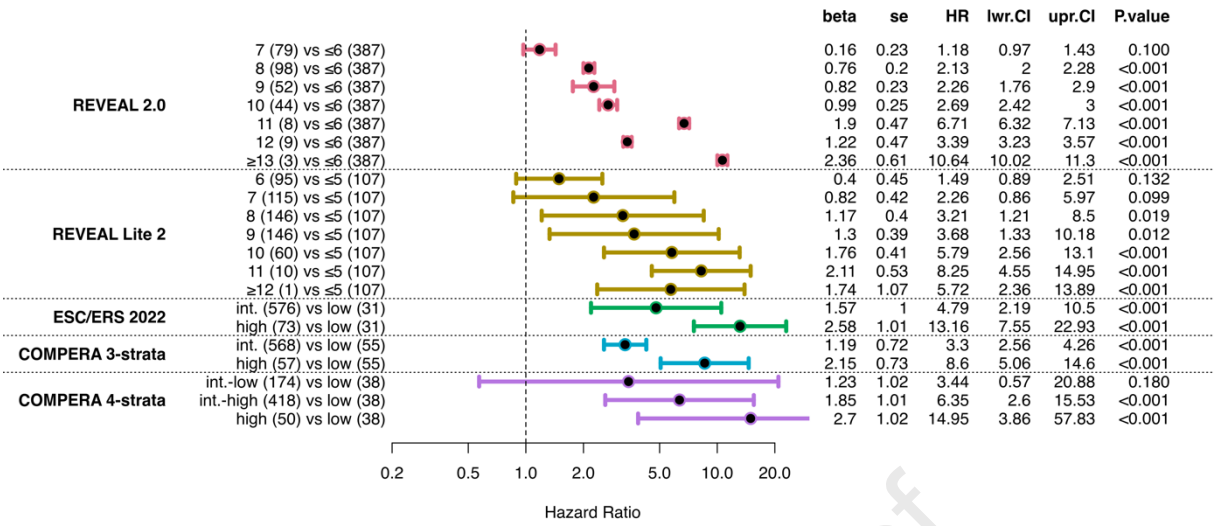
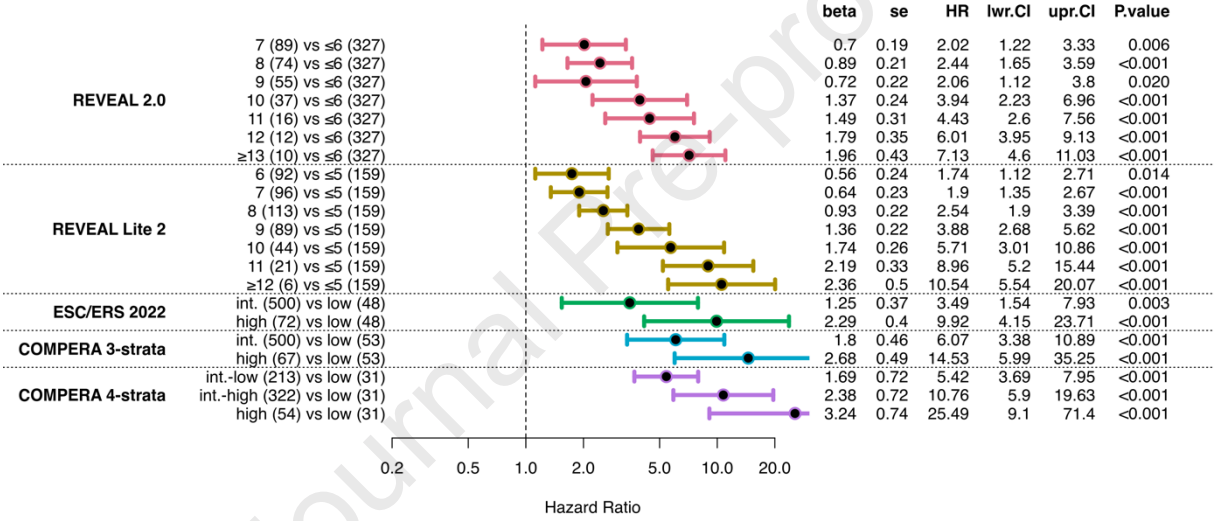
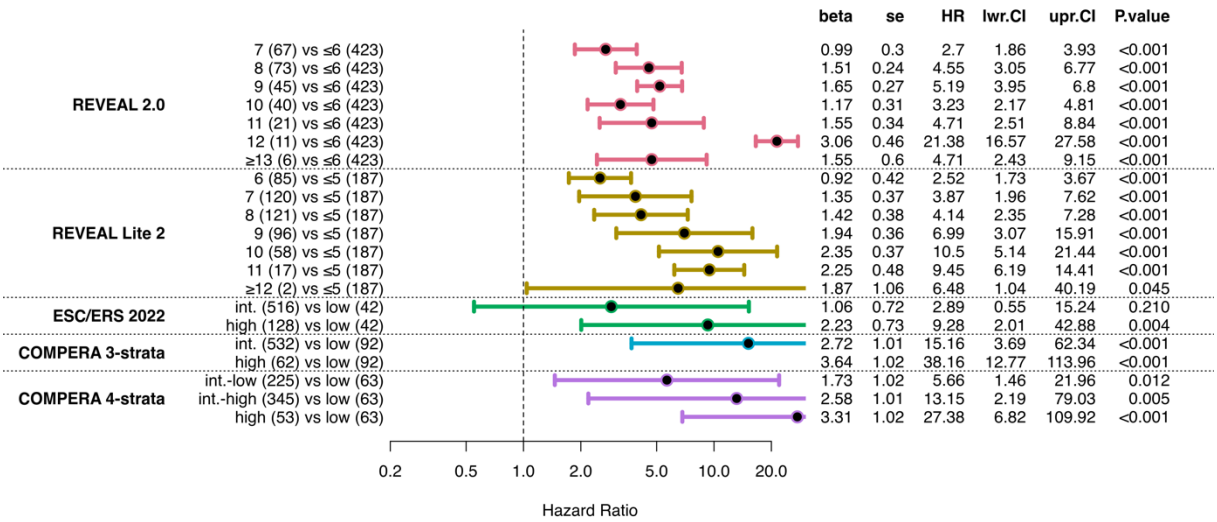


d)



e)

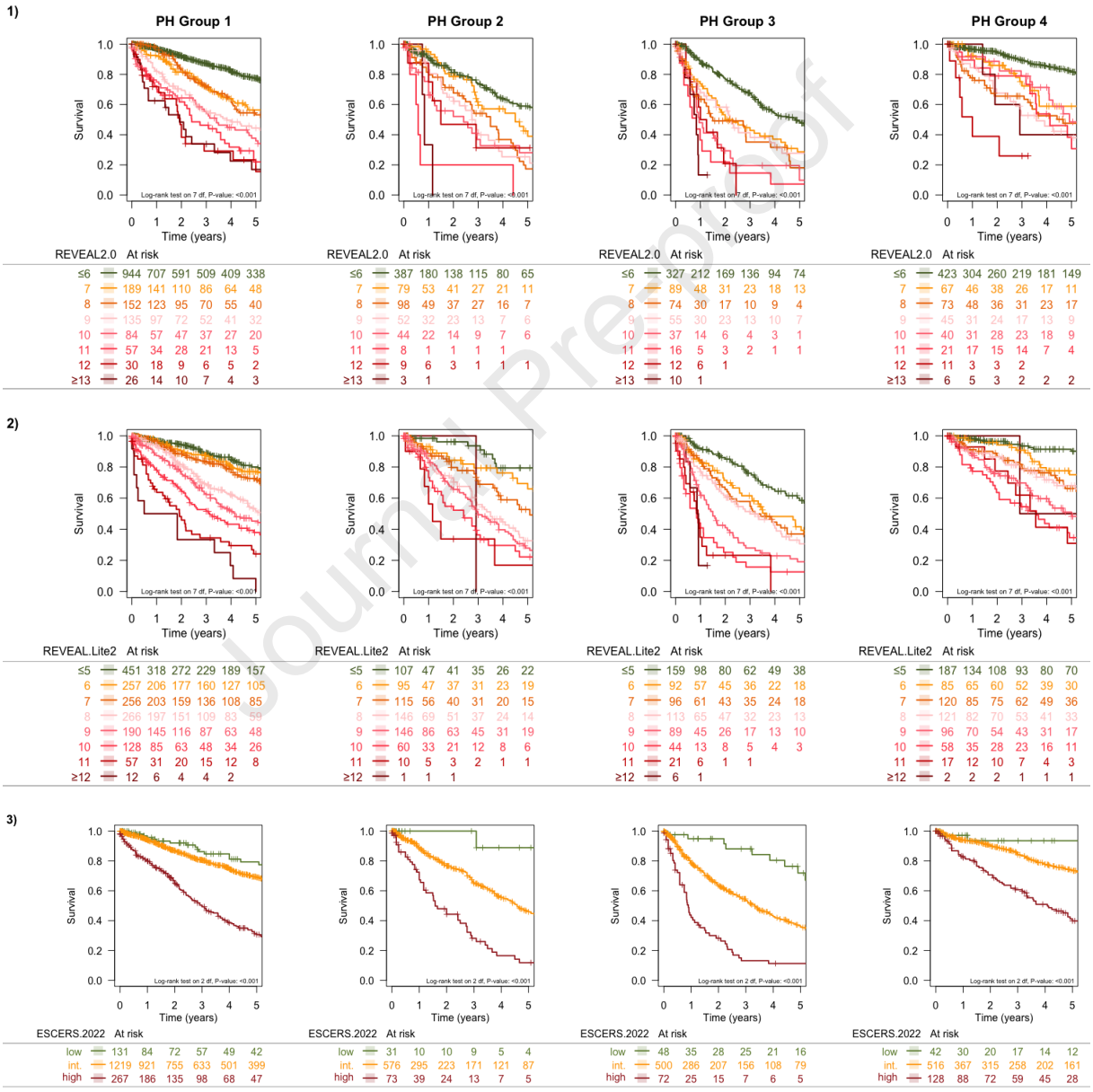


e-Figure 4: Kaplan-Meier curves of 3- and 4-strata risk scores for PH group 1 – 4, non-imputed study population.

Survival rates for each PH group 1 - 4 stratified by REVEAL 2.0, REVEAL Lite 2, ESC/ERS 2022, COMPERA 3-strata and COMPERA 4-strata, respectively. Kaplan-Meier curves with 95 % confidence bands are shown for patients in each risk score group.

a) Survival rates for REVEAL 2.0.
b) Survival rates for REVEAL Lite 2.
c) Survival rates for ESC/ERS 2022.
d) Survival rates for COMPERA 3-strata.
e) Survival rates for COMPERA 4-strata.

PH = pulmonary hypertension; int. = intermediate; int.-high = intermediate-high; int.-low = intermediate-low.



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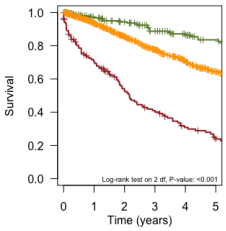
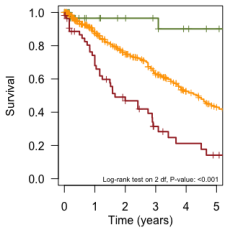
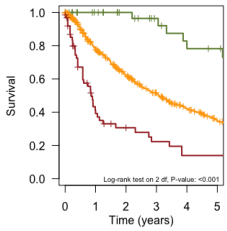


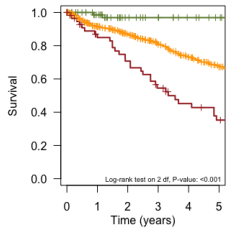
COMPERA.3Strata	At risk					
low	244	168	145	121	103	89
int.	1234	933	757	621	483	377
high	139	90	60	46	32	22



COMPERA.3Strata	At risk					
low	55	20	17	15	12	10
int.	568	291	219	168	115	83
high	57	33	21	10	6	3

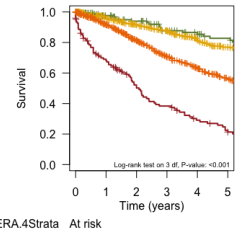


COMPERA.3Strata	At risk					
low	53	35	28	22	18	16
int.	500	292	211	158	112	79
high	67	19	11	8	5	5

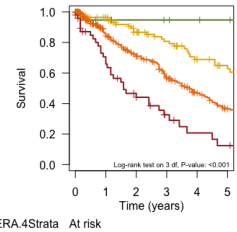


COMPERA.3Strata	At risk					
low	92	65	46	41	35	31
int.	532	378	326	267	207	156
high	62	42	35	26	19	14

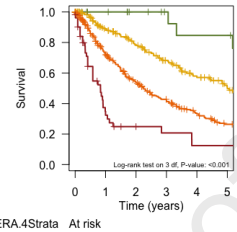
5)



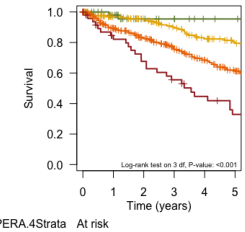
COMPERA.4Strata	At risk					
low	172	113	98	81	72	63
int.-low	579	441	375	332	257	206
int.-high	742	559	438	336	262	201
high	124	78	51	39	27	18



COMPERA.4Strata	At risk					
low	38	15	13	12	11	10
int.-low	174	87	65	53	37	29
int.-high	418	214	162	119	80	54
high	50	28	17	9	5	3



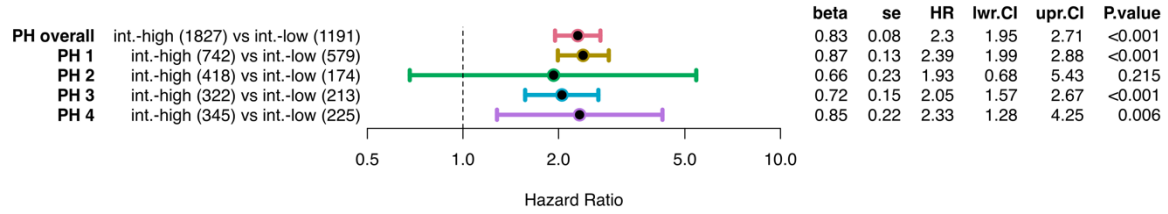
COMPERA.4Strata	At risk					
low	31	20	16	13	11	11
int.-low	213	136	109	85	63	46
int.-high	322	177	119	85	58	40
high	54	13	6	5	3	3



COMPERA.4Strata	At risk					
low	63	44	29	26	21	20
int.-low	225	163	146	123	100	81
int.-high	345	244	204	163	124	89
high	53	34	28	22	16	11

e-Figure 5: Forest plot of COMPERA 4-strata risk score with Hazard Ratios in relation to the intermediate-low risk category, non-imputed study population.

PH = pulmonary hypertension; HR = hazard ratio, lwr.CI = lower 95% confidence bound; upr.CI = upper 95% confidence bound; int.-high = intermediate-high; int.-low = intermediate-low.



e-Table 5: Predictive power for subgroups analyses of all included risk scores, imputed study population.

C-Index and the difference of AIC estimates between the ESC/ERS 2022 score and the respective risk score of the Cox proportional hazards model based on non-imputed data are shown. Center and diagnosis decade are included as stratification variables, as is center included as cluster. Table with values for risk scores at baseline for overall PH and groups 1-4 for patients with PVR ≥5 WU and PVR <5 WU and for

a) Patients with PVR <5 WU.
b) Patients PVR ≥5 WU
c) Further subgroup analyses:
(i) Group 1.1: Idiopathic pulmonary arterial hypertension (IPAH)
(ii) Group 1.4.1: Connective tissue disease-associated pulmonary arterial hypertension
(iii) Group 1.4.4: Congenital heart disease-associated pulmonary arterial hypertension
(iv) Group 2 PH patients with isolated postcapillary PH (i.e., PVR ≤2 WU)
(v) Group 2 PH patients with combined pre- and postcapillary PH (i.e., PVR >2 WU)
(vi) Group 3.1: PH associated with obstructive lung disease
(vii) Group 3.2: PH associated with restrictive lung disease
(viii) PAH patients with cardiac comorbidities (defined as the presence of at least three of the following comorbidities: arterial hypertension, obesity, diabetes, coronary heart disease, and atrial fibrillation)

ΔAIC = difference of akaike information criterion between the ESC/ERS 2022 score and the respective risk score; C-Index = concordance index; PH = pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; CTDPH = connective tissue disease-associated pulmonary hypertension; CHDPH = congenital heart disease-associated pulmonary hypertension; IpcPH = isolated post-capillary pulmonary hypertension; CpcPH = combined post- and pre-capillary pulmonary hypertension; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease.

*p-values <0.001 in comparison to ESC/ERS 2022 score.

a)

		Reveal 2.0	Reveal Lite 2	ESC/ERS 2022	COMPERA 3-strata	COMPERA 4-strata
PH overall	**Δ**AIC	136	99	0	44	71
	C-Index	0.66*	0.65*	0.57	0.59*	0.62*
Group 1	**Δ**AIC	72	64	0	17	35
	C-Index	0.71*	0.71*	0.60	0.62	0.66
Group 2	**Δ**AIC	-8	4	0	-7	-4
	C-Index	0.61	0.62*	0.57	0.56	0.58
Group 3	**Δ**AIC	22	4	0	3	5
	C-Index	0.66*	0.64*	0.56	0.58	0.61*
Group 4	**Δ**AIC	1	-9	0	5	3
	C-Index	0.65	0.61*	0.56	0.58	0.57

b)

		Reveal 2.0	Reveal Lite 2	ESC/ERS 2022	COMPERA 3-strata	COMPERA 4-strata
PH overall	**Δ**AIC	262	248	0	83	216
	C-Index	0.65*	0.65*	0.57	0.58	0.63*
Group 1	**Δ**AIC	134	138	0	18	101
	C-Index	0.68*	0.68*	0.58	0.59	0.65*
Group 2	**Δ**AIC	45	12	0	16	21
	C-Index	0.64	0.60	0.54	0.58	0.59
Group 3	**Δ**AIC	22	41	0	-2	16
	C-Index	0.62*	0.63*	0.57	0.55	0.59
Group 4	**Δ**AIC	16	17	0	13	16
	C-Index	0.65*	0.67*	0.59	0.59	0.63

c)

		Reveal 2.0	Reveal Lite 2	ESC/ERS 2022	COMPERA 3-strata	COMPERA 4-strata
IPAH	**Δ**AIC	117	98	0	40	84
	C-Index	0.68*	0.67*	0.57	0.60	0.65*
CTDPH	**Δ**AIC	54	40	0	-14	31
	C-Index	0.67*	0.67*	0.57	0.56	0.64*
CHDPH	**Δ**AIC	27	31	0	12	23
	C-Index	0.66	0.73*	0.54	0.60	0.67
IpcPH	**Δ**AIC	9	-1	0	5	4
	C-Index	0.62	0.55	0.55	0.58	0.55
CpcPH	**Δ**AIC	17	7	0	-6	5
	C-Index	0.62	0.59	0.55	0.53	0.57
PH-COPD	**Δ**AIC	32	21	0	10	29
	C-Index	0.60*	0.60*	0.54	0.55	0.59*
PH-ILD	**Δ**AIC	16	12	0	-1	3
	C-Index	0.63	0.63	0.58	0.56	0.60
PAH patients with cardiac comorbidities	**Δ**AIC	14	22	0	3	7
	C-Index	0.70*	0.70*	0.57	0.58	0.62