Comprehensive multivariate risk modeling improves mortality risk prediction in pulmonary arterial hypertension

Figures and Tables

Innsbruck PAH registry

2021-11-24

Contents

Figures

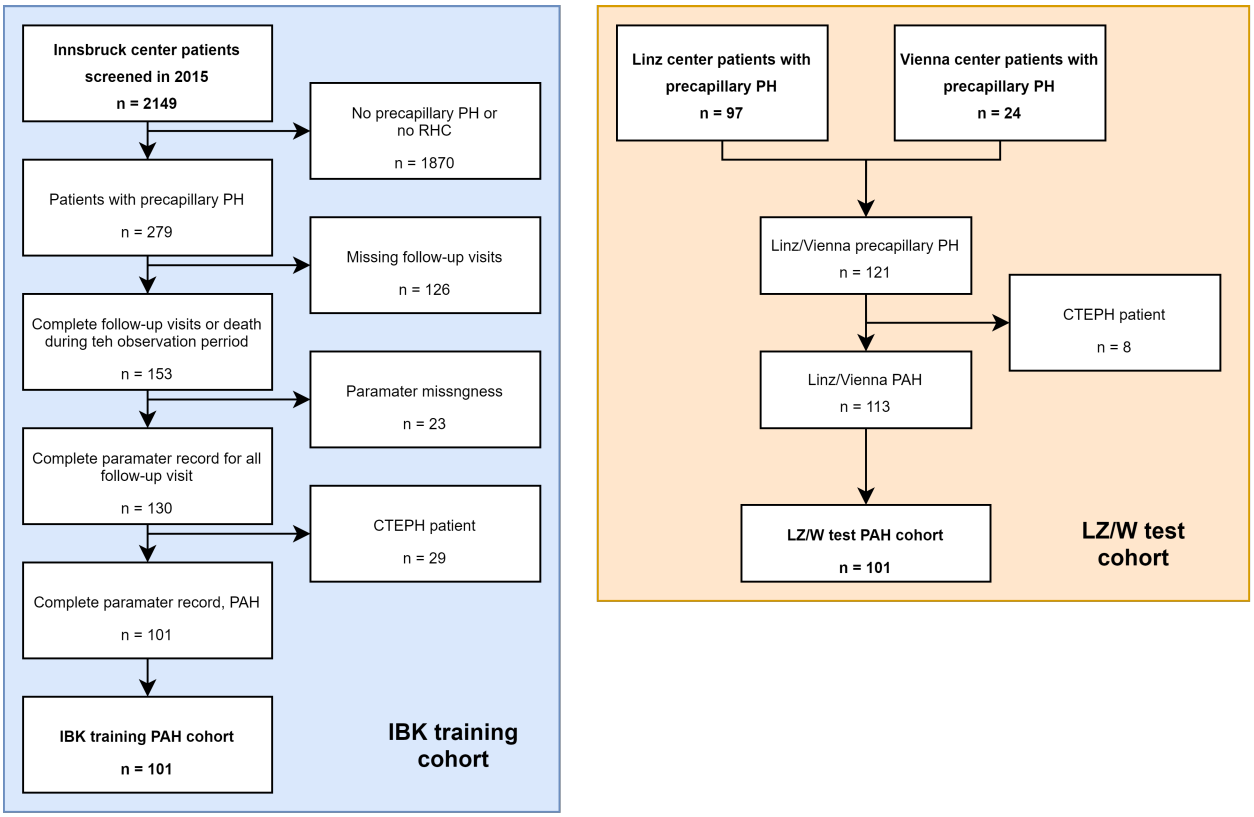

Figure 1: CONSORT flow diagram of the study ana analysis inclusion process.

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PH: pulmonary hypertension, PHC: right heart catheterization, CTEPH: chronic thromboembolic pulmonary hypertension.

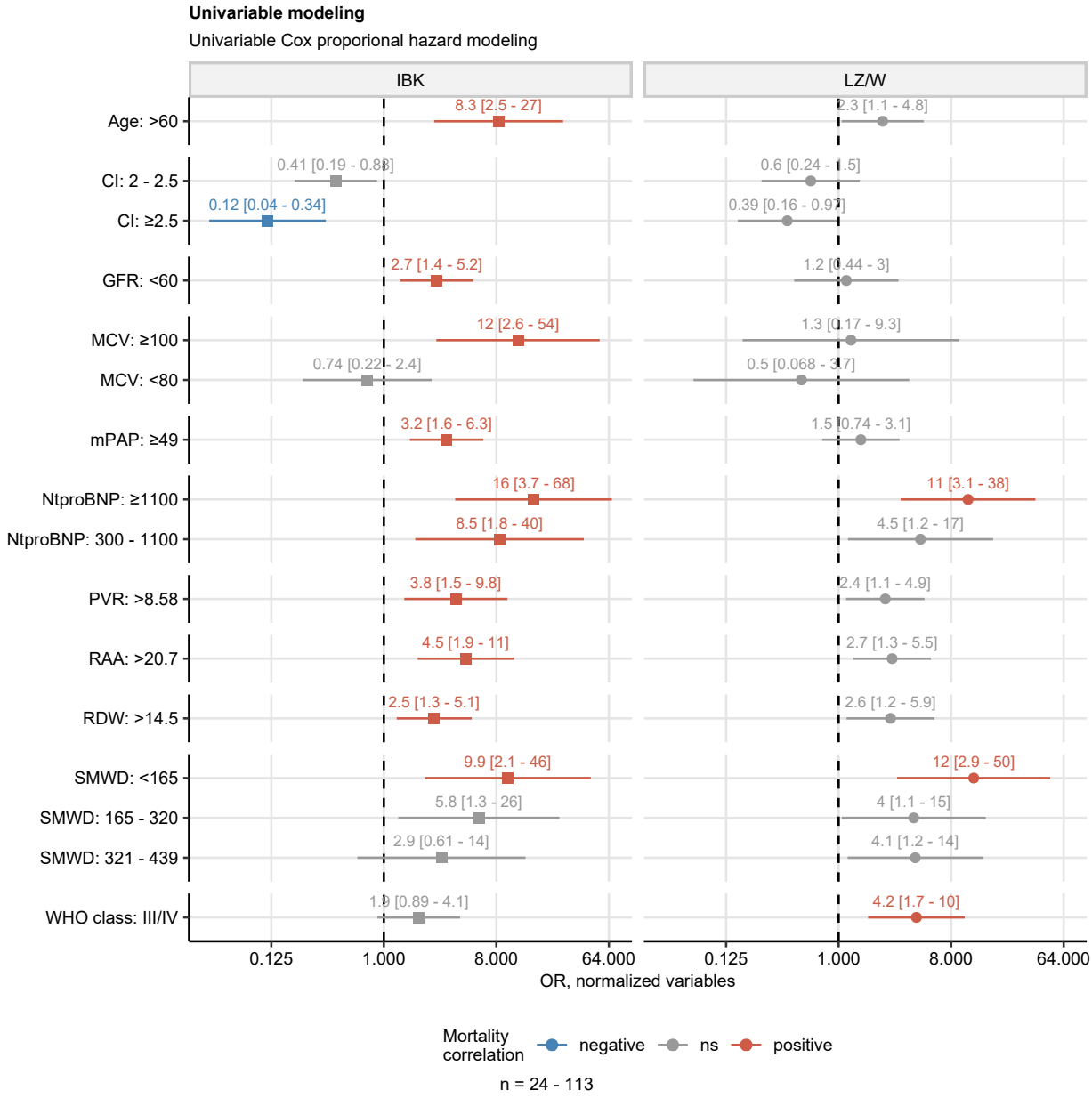

Figure 2: Factors associated with overall survival identified by univariable Cox modeling.

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Correlations of 23 candidate variables (**Supplementary Table S1**) with overall survival was investigated with a series of Cox proportional hazard models in the Innsbruck (IBK) and Linz/Vienna (LZ/W) PAH collective (**Supplementary Table S2**). Hazard ratio (HR) significance was assessed with Wald test and corrected for multiple comparisons with Benjamini-Hochberg method. HR with 95% confidence intervals for the factors correlating significantly with survival in at least one cohort are presented in the plot. The range of N number of the complete observations is shown under the plot.

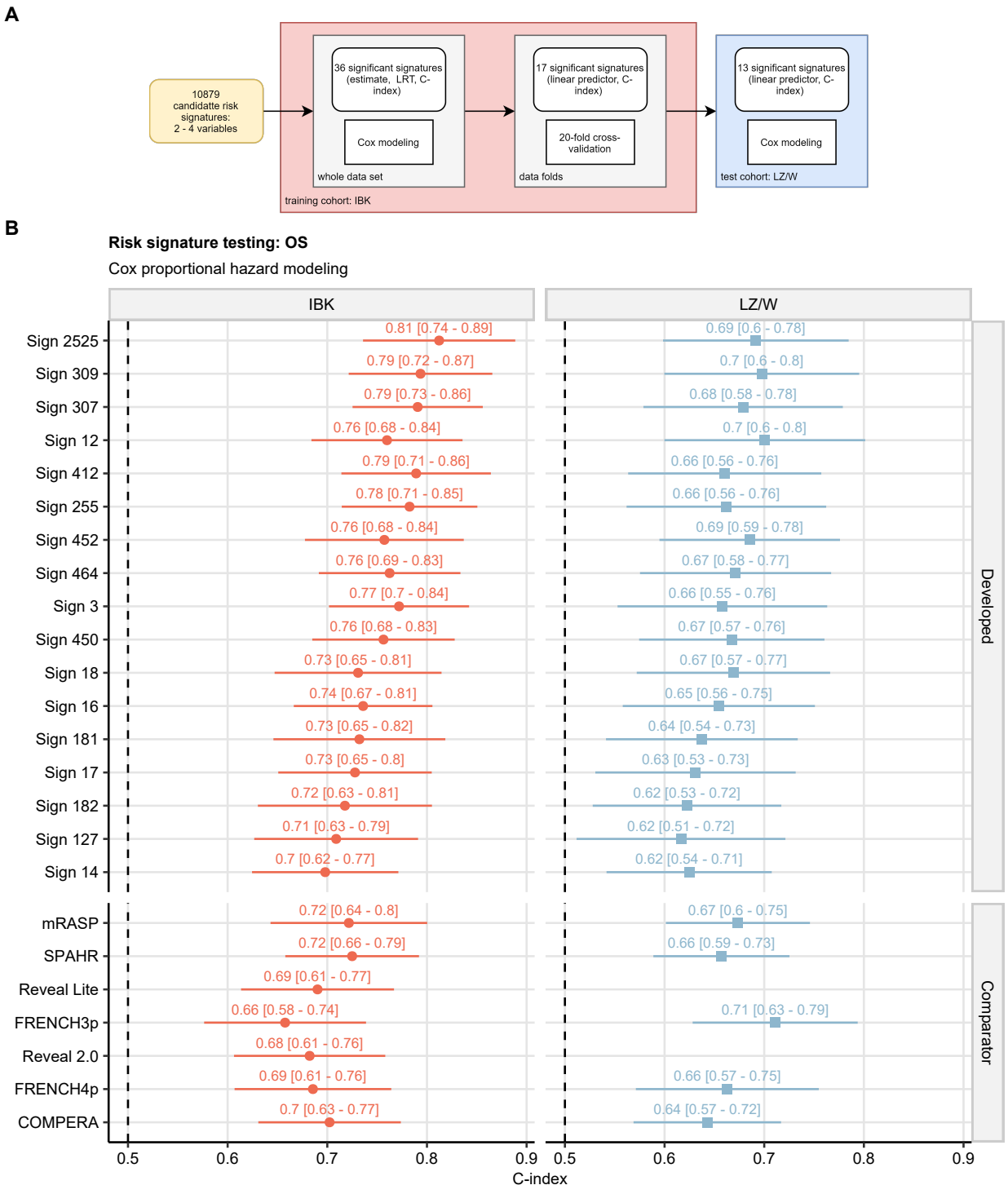

Figure 3: Prediction of overall PH survival by candidate multivariable risk signatures and established risk assessment tools.

Figure 3. Prediction of overall PAH survival by candidate multivariable risk signatures and established risk assessment tools.

Correlation of the candidate 2 - 4 parameter risk signatures (all possible combinations of 23 variables, **Supplementary Table S1**) with overall survival (OS) in the Innsbruck PAH training cohort (IBK) was

investigated by Cox proportional hazard modeling and verified by 20-fold cross-validation. The association of the linear predictor scores for the significant risk signatures was subsequently tested in the Linz/Vienna (LZ/W) cohort by Cox proportional hazard modeling. The significance of model estimates was determined by Wald test, model relevance was assessed by the likelihood ratio test (LRT) and concordance index (C-index). P values were corrected for multiple comparisons with Benjamini-Hochberg method.

(A) Scheme of selection of the developed significant risk signatures.

(B) C-index values with 95% confidence intervals for Cox models of the 17 newly developed significant signatures and the established PH risk assessment tools in the training and test cohorts.

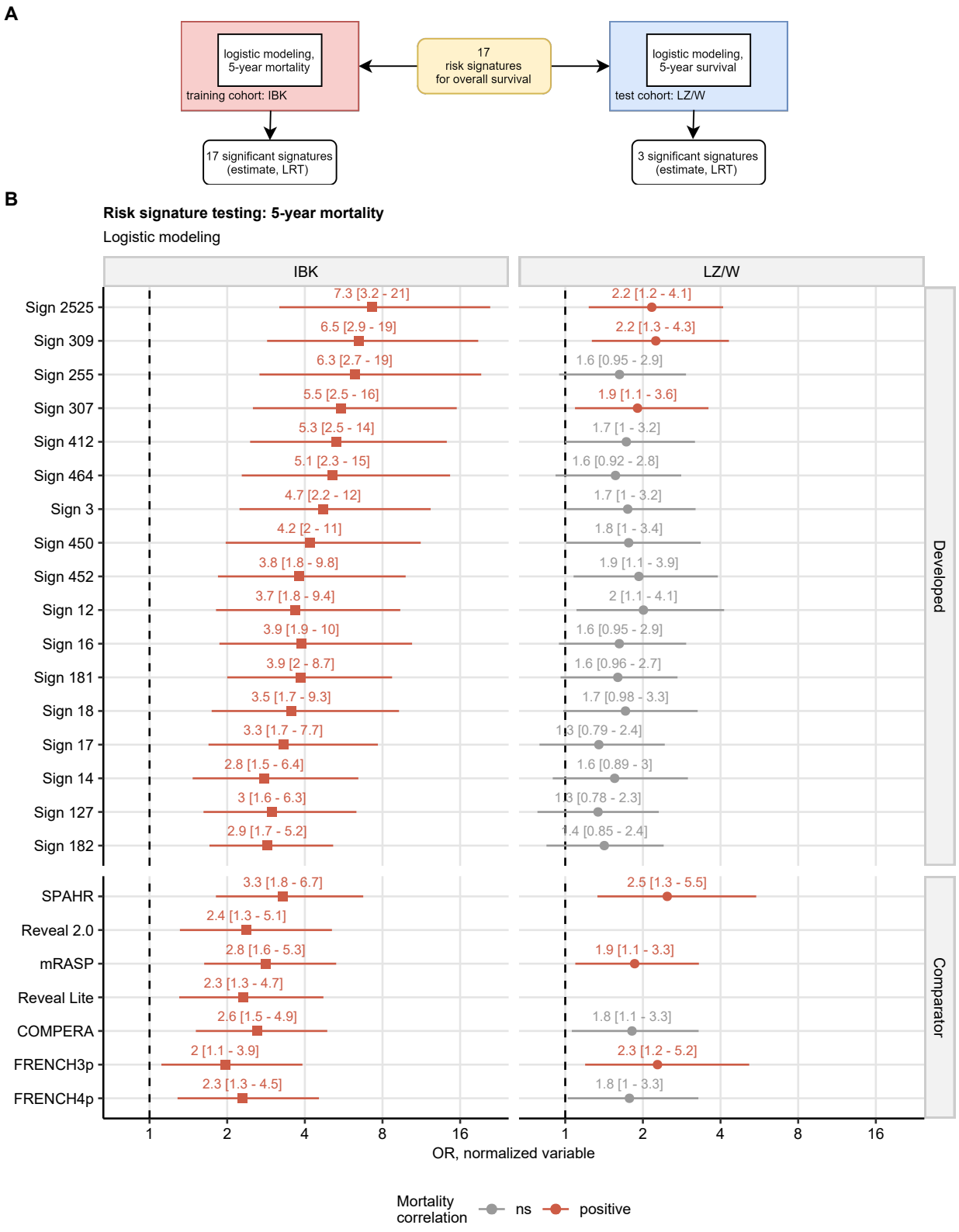

Figure 4: Correlation of the newly developed risk signatures with 5-year mortality.

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The correlation of normalized linear predictor scores (**Supplementary Table S4**) of the 17 developed risk signatures significantly associated with overall survival (**Figure 3**) with 5-year mortality in the Innsbruck training (IBK) and Linz/Vienna (LZ/W) validation PAH cohorts was investigated by logistic regression. Odds ratio (OR) significance was determined by Wald test and corrected for multiple comparisons with Benjamini-Hochberg method.

(A) Scheme of signature testing.

(B) OR values with 95% confidence intervals for the 17 tested signatures and the established PH risk assessment tools in the training and test cohorts.

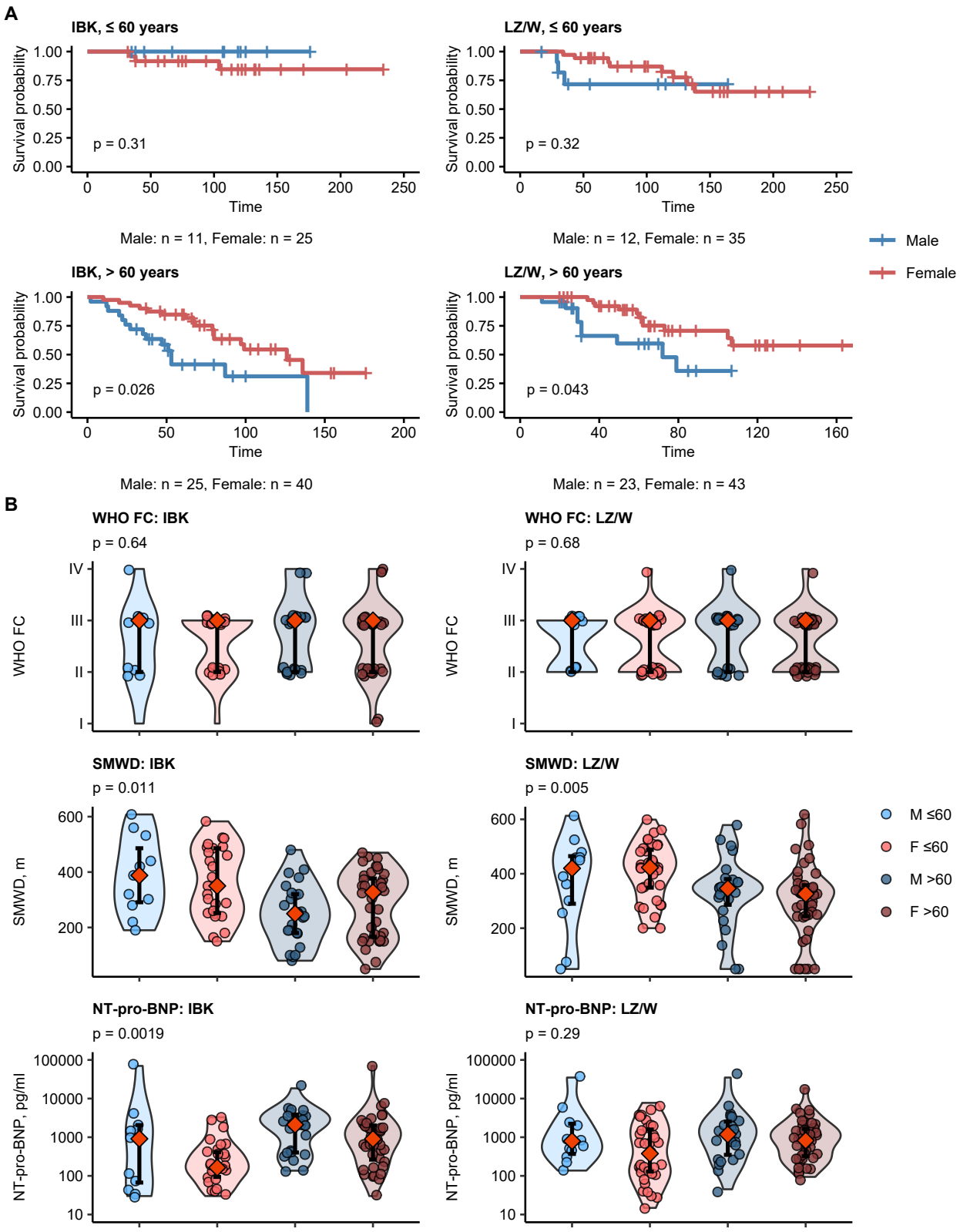

Figure 5: The interplay of gender and age affects PAH survival independently of functional classification, six-minute walking distance and NT-pro-BNP levels.

Figure 5. The interplay of gender and age affects PAH survival independently of functional classification, six-minute walking distance and NT-pro-BNP levels.

(A) Differences in PAH survival between the participants stratified by age class and sex (IBK: Innsbruck, LZ/W: Linz/Vienna cohort) were assessed by Kaplan-Meier analysis and Mentel-Henszel test. P values corrected for multiple comparisons with Benjamini-Hochberg method are shown in the plots. The numbers of males and females in the age strata are indicated below the plots.

(B) Differences in WHO functional classification (WHO FC), six-minute walking distance (SMWD) and circulating NT-pro-BNP levels at PH diagnosis in the participants stratified by age class and sex were assessed by Kruskal-Wallis test. P values corrected for multiple comparisons with Benjamini-Hochberg method are shown in the plot captions.

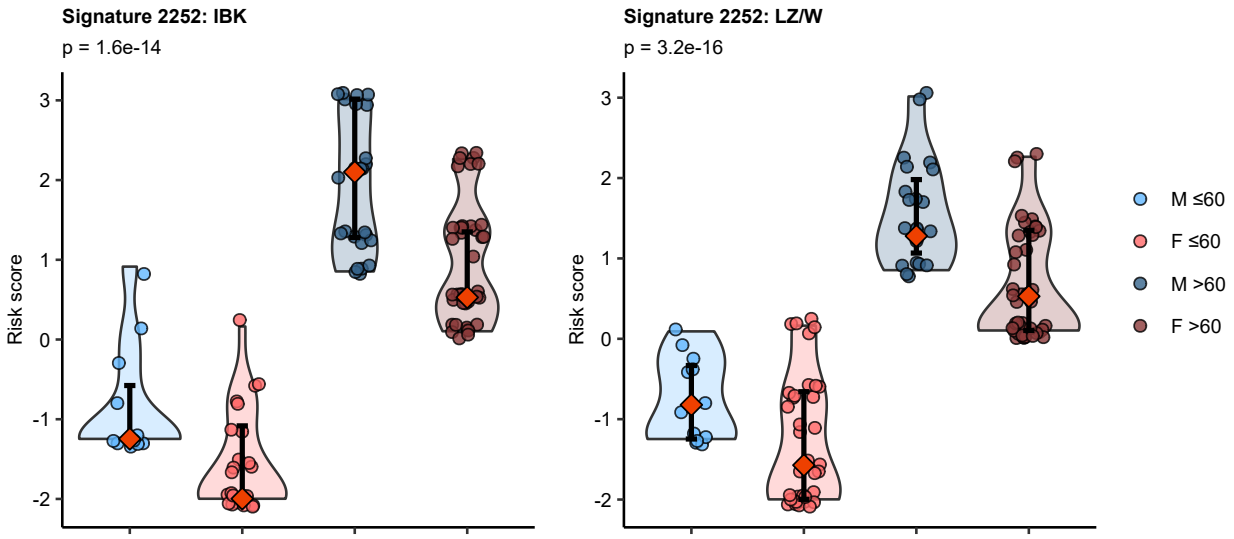

Figure 6: Values of the best performing machine-learning risk signature score in gender and age strata.

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The risk signatures predicting overall survival in PH were developed as presented in **Figure 3**. The differences in the signature 2525 linear predictor scores (**Supplementary Table S4**) between the participants stratified by age class and sex (IBK: Innsbruck, LZ/W: Linz/Vienna cohort) were assessed by Kruskal-Wallis test. P values corrected for multiple comparisons with Benjamini-Hochberg method are shown in the plot captions. IBK $\leq$ 60: male n = 11, female n = 25, IBK >60: male n = 25, female n = 40, LZ/W $\leq$ 60: male n = 12, female n = 35, LZ/W >60: male n = 23, female n = 43.