PAH biomarker study

Figures and Tables

Innsbruck PAH registry

2021-10-07

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Figures

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

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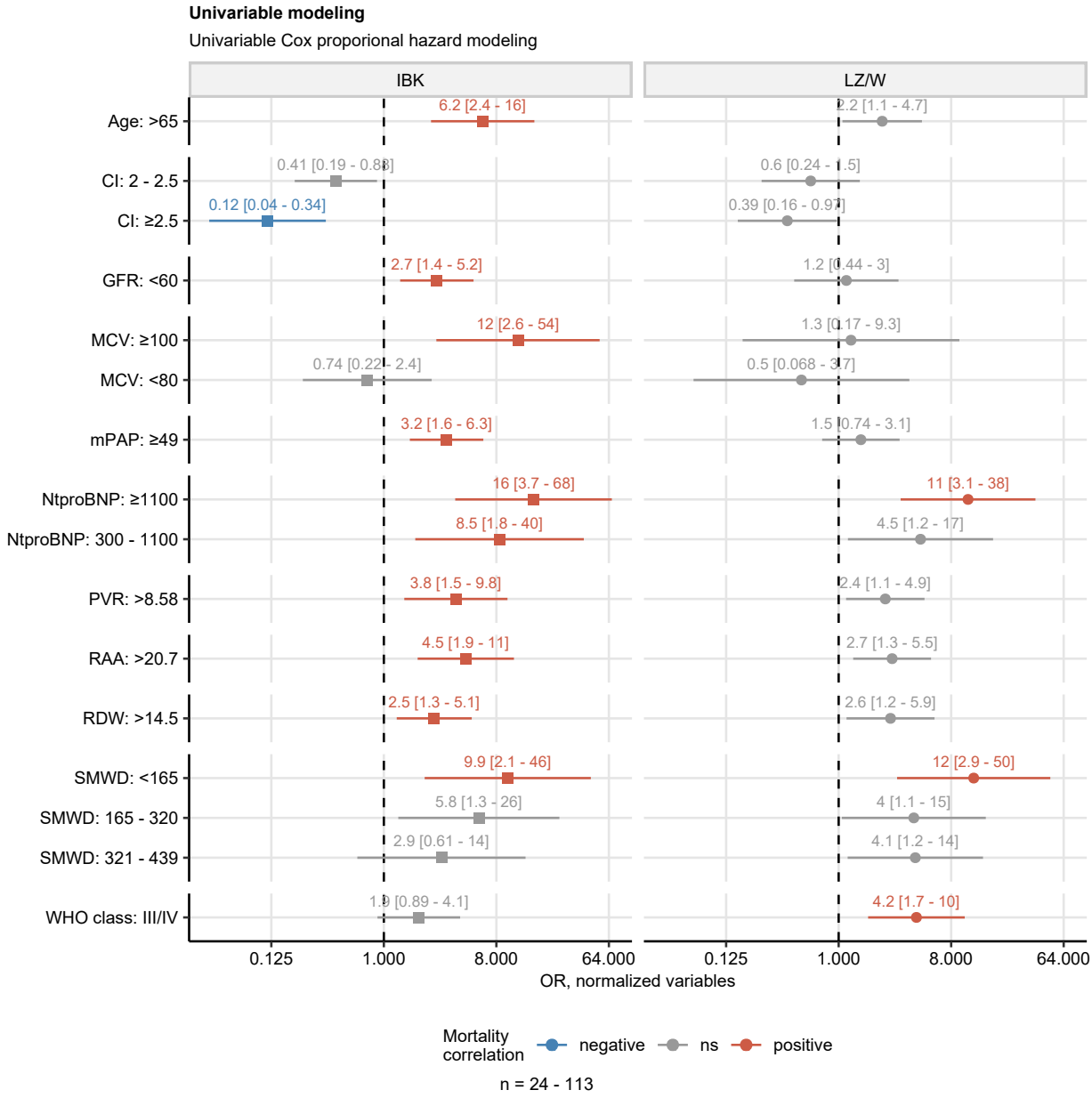

Figure 2: Factors associated with overall survvial identified by univariable Cox modeling.

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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) 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 inn the plot. Range of N number of complete observation is shown under the plot.

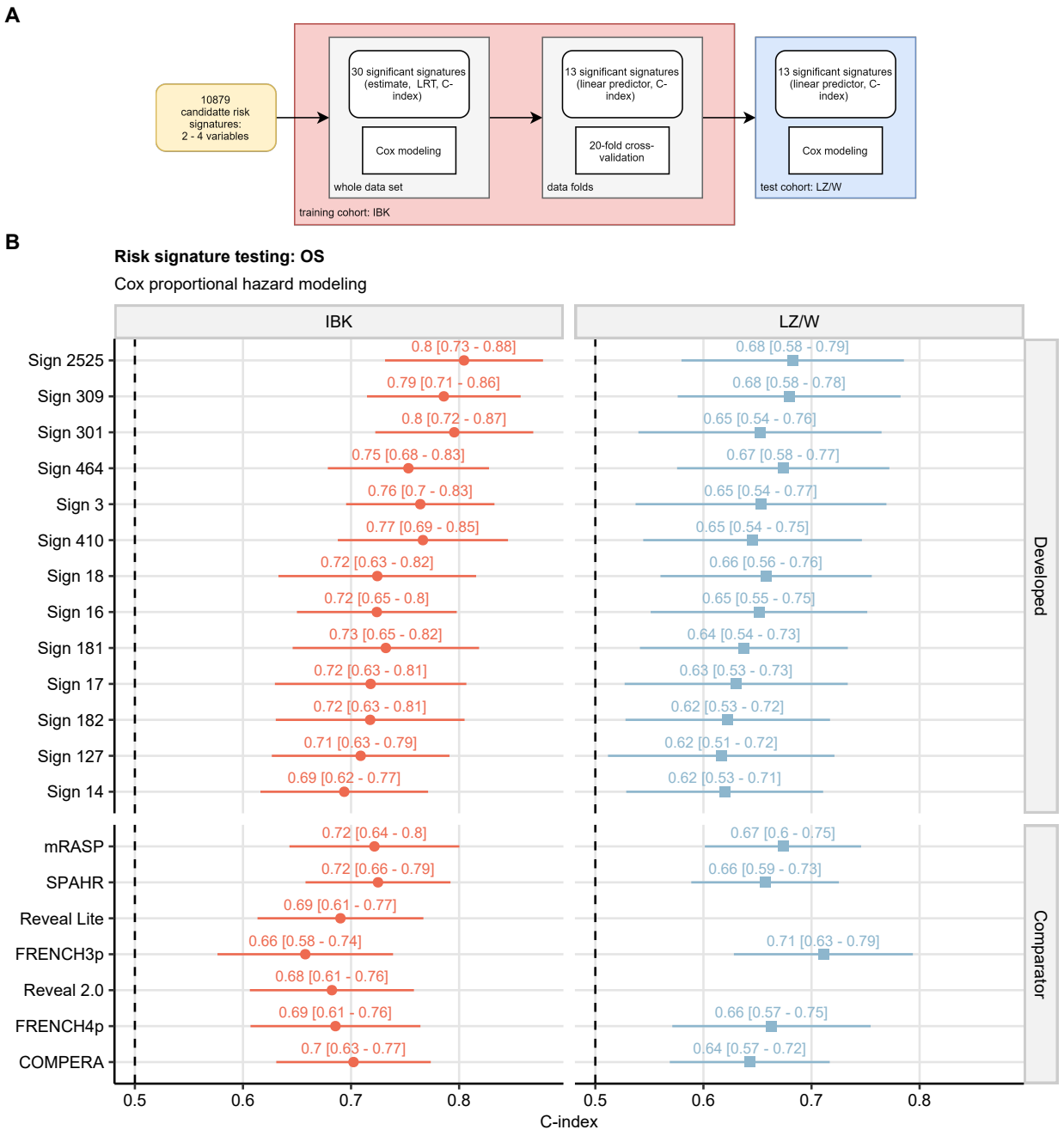

Figure 3: Prediction of overall PH survival by candidate multivariable risk signatures and established risk assessment tools.

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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 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. Significance of model estimates was determined by Wald test, model relevance was assessed by 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 13 developed significant signatures and the established PH risk assessment tools in the training and test cohorts.

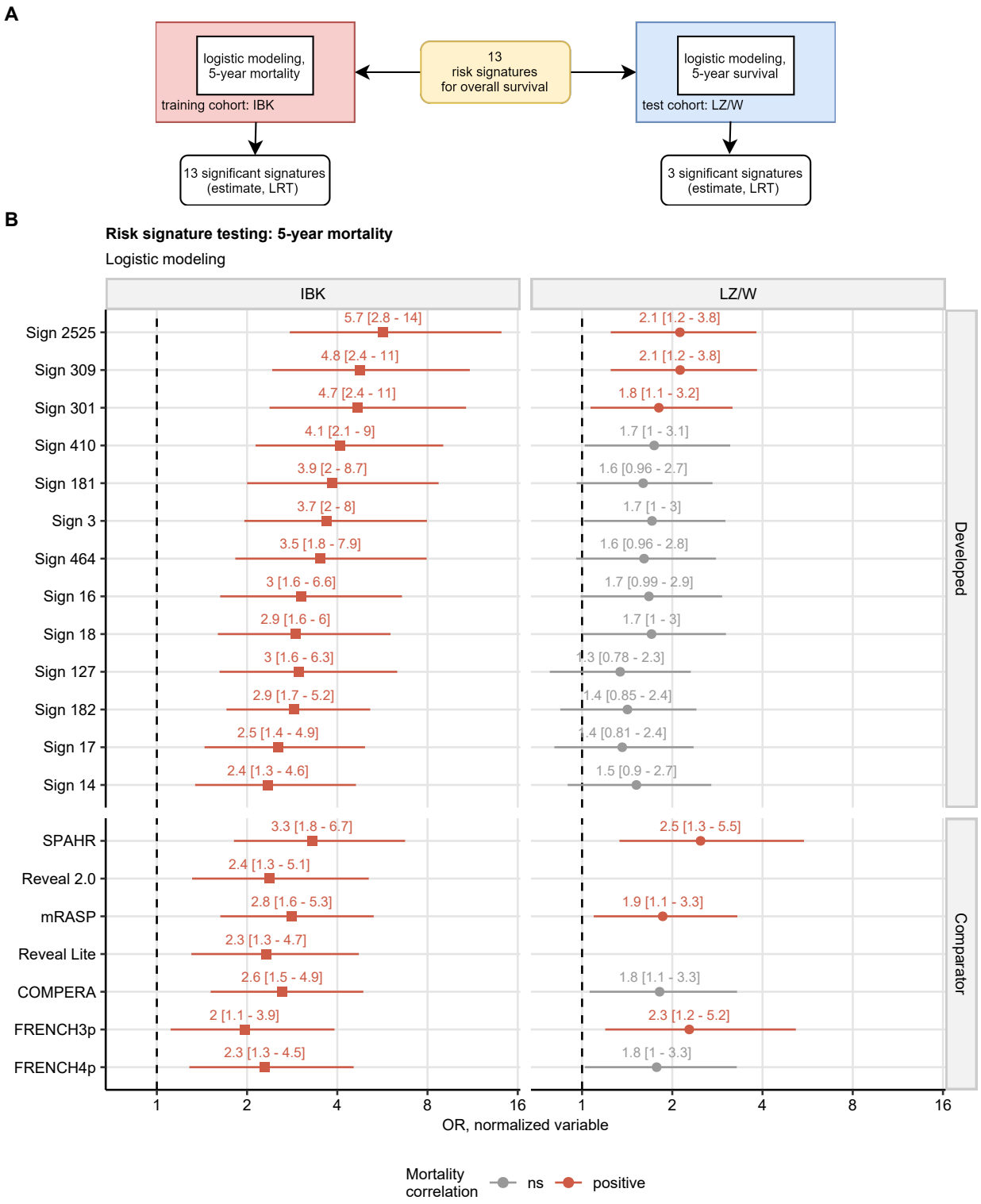

Figure 4: Correlation of the developed candidate risk signatures with 5-year mortality.

Figure 4. Correlation of the developed candidate risk signatures with 5-year mortality. Correlation of linear predictor scores (**Supplementary Table S5**) of the 23 developed risk signatures

significantly associated with overall survival (**Figure 3**) with 5-year mortality in the Innsbruck training (IBK) and Linz/Vinna (LZ/W) cohort 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 or Cox models of the 13 tested signatures and the established PH risk assessment tools in the training and test cohorts.

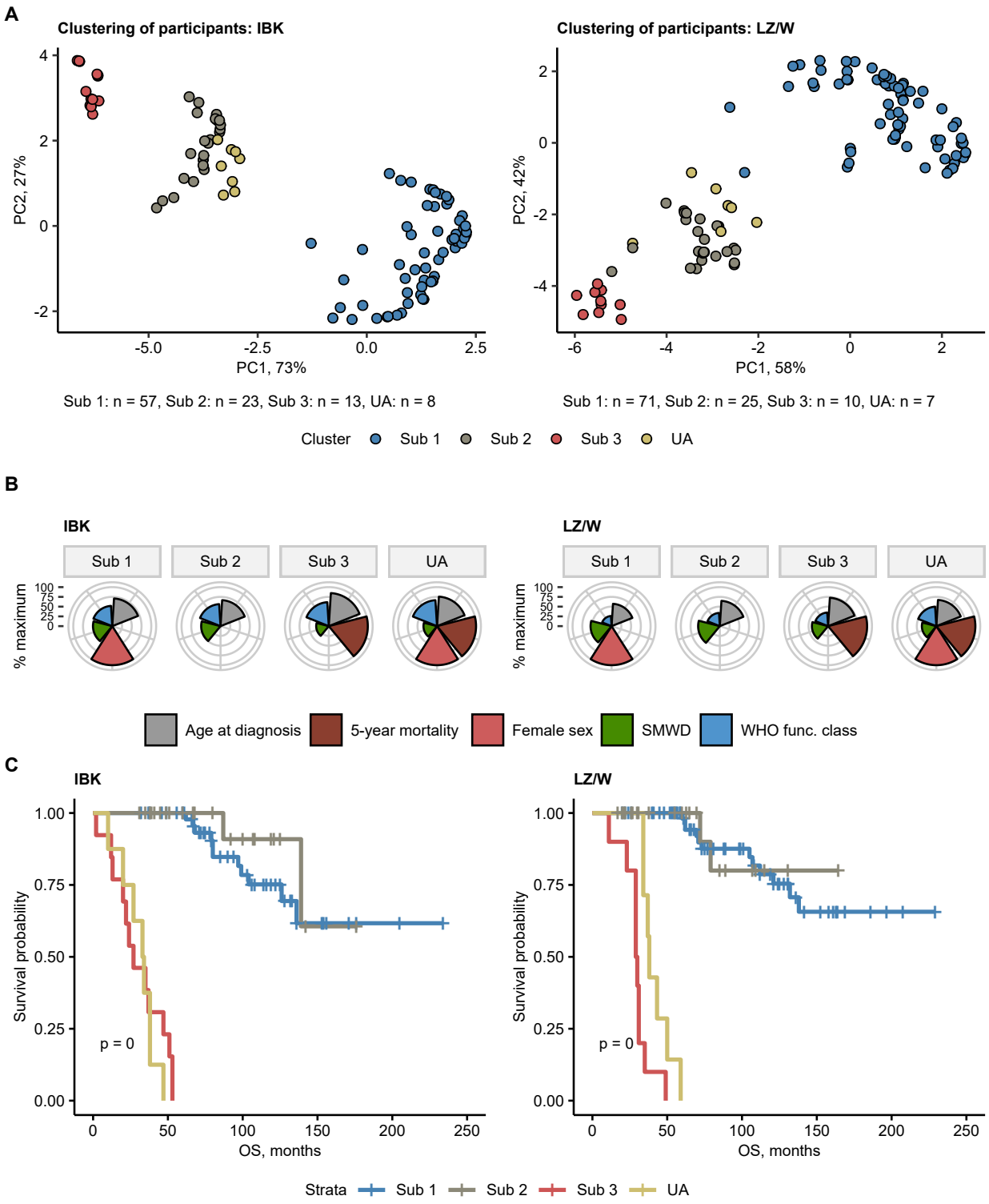

Figure 5: Distinct risk phenotypes of PH defined by acute mortality, motility, daily functioning and age and sex.

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PH patients in the Innsbruck (IBK) and Linz/Vienna cohort (LZ/W) were subjected to association analysis in respect to age at diagnosis, sex (0: male), six-minute walking distance (SMWD), WHO functional classification and 5-year mortality (0: survivor) using DBSCAN algorithm. Three subsets were identified (Subset 1 - 3, UA: unassigned).

(A) Subset assignment displayed in a score plot of results of two-dimensional PCA (principal component analysis) in respect to the clustering variables. PC: principal component, percents of variation associated with the given PC is presented in the axes. Cluster n numbers are presented below the plots.

(B) Comparison of minimum/maximum normalized levels of the clustering variables between the subsets.

(C) Survival differences between the subsets investigated by Kaplan-Meier analysis and log-rank test. OS: overall survival. Test p values are shown in the plots.

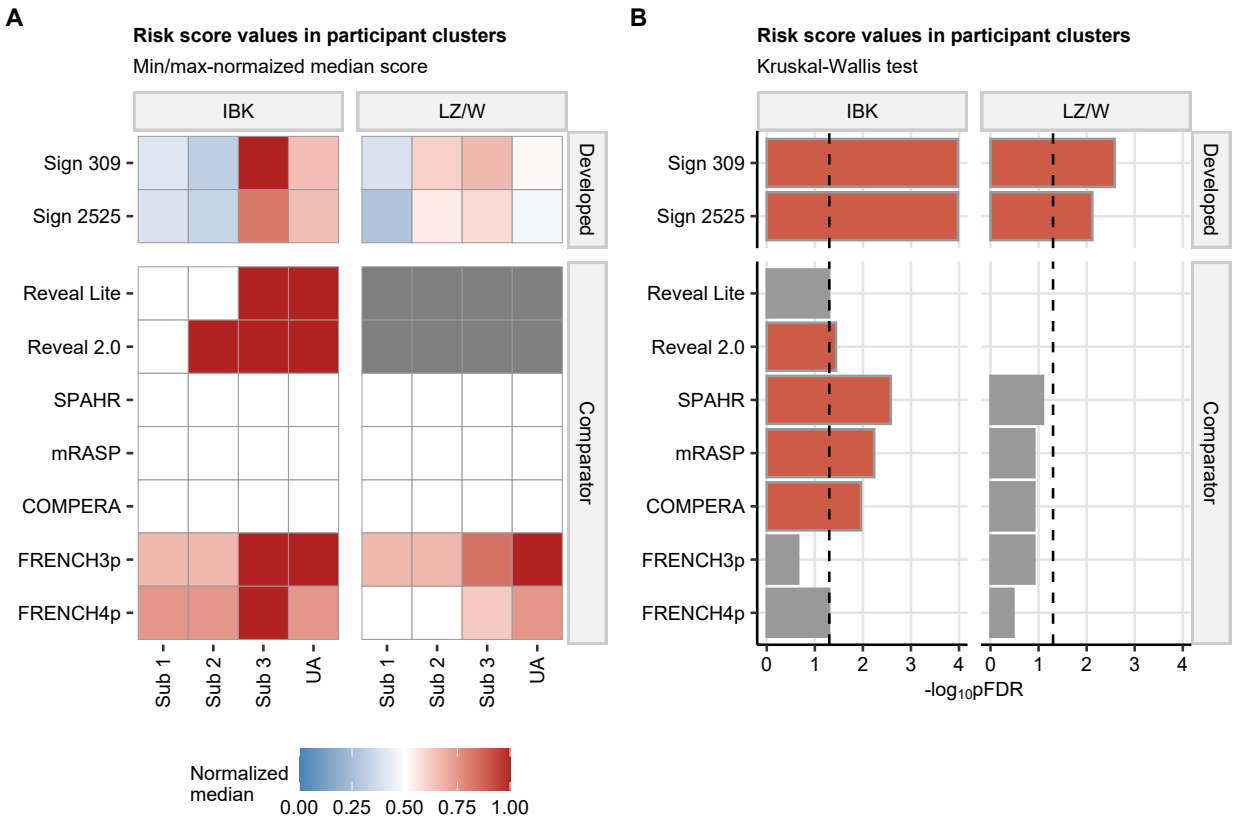

Figure 6: Newly developed risk signatures differentiate between age, sex, motility, daily functioning and mortality-defined risk phenotypes.

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Linear predictor score values (**Supplementary Table S5**) for the best performing risk signatures 309 (age, cardiac index and sex) and 2525 (age, cardiac index, mPAP and sex) and the established PH risk assessment tools were compared between the PH risk subsets defined in **Figure 5** with Kruskal-Wallis test. P values were corrected for multiple comparisons with Benjamini-Hochberg method.

(A) Normalized score medians in the risk subsets presented as a heat map.

(B) Kruskal-Wallis test p values. Orange: significant comparisons.