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

Figures and Tables

Innsbruck PAH registry

2022-03-08

Tables

Table 1: Characteristic of the study cohorts.

Variable	IBK	LZ/W	Significance	Effect size
N participants	100	83		
Age, y	Mean = 62 (SD: 15) Median = 66 [IQR: 53 - 71] Range: 4 - 84	Mean = 64 (SD: 15) Median = 70 [IQR: 54 - 74] Range: 23 - 82	ns (p = 0.32)[1]	r = 0.094[1]
SMWD, m	Mean = 310 (SD: 130) Median = 320 [IQR: 200 - 400] Range: 50 - 610	Mean = 340 (SD: 150) Median = 350 [IQR: 270 - 440] Range: 50 - 620	ns (p = 0.11)[1]	r = 0.15[1]
mPAP, mmHg	Mean = 42 (SD: 16) Median = 40 [IQR: 30 - 50] Range: 26 - 120	Mean = 40 (SD: 11) Median = 39 [IQR: 31 - 49] Range: 18 - 67	ns (p = 0.91)[1]	r = 0.024[1]
Sex	female: 64% (64) male: 36% (36)	female: 66% (55) male: 34% (28)	ns (p = 0.94)[3]	V = 0.024[4]
PVR, Wood	Mean = 13 (SD: 8.9) Median = 10 [IQR: 6.7 - 17] Range: 3.3 - 43	Mean = 6.2 (SD: 3.8) Median = 5 [IQR: 3.5 - 7.8] Range: 1.4 - 20	p < 0.001[1]	r = 0.54[1]
PCWP, mmHg	Mean = 14 (SD: 5.6) Median = 13 [IQR: 10 - 16] Range: 4 - 32	Mean = 11 (SD: 5.2) Median = 11 [IQR: 8 - 14] Range: 1 - 27	p = 0.0051[1]	r = 0.25[1]
Anemia	19% (19)	17% (14)	ns (p = 0.94)[3]	V = 0.028[4]
log RDW, %	Mean = 2.7 (SD: 0.12) Median = 2.7 [IQR: 2.6 - 2.8] Range: 2.5 - 3.1	Mean = 2.7 (SD: 0.11) Median = 2.7 [IQR: 2.7 - 2.8] Range: 2.5 - 3.1	p = 0.012[1]	r = 0.22[1]
Renal insufficiency	35% (35)	18% (15)	p = 0.047[3]	V = 0.19[4]
log FT, ng/ml	Mean = 4.1 (SD: 0.99) Median = 4.1 [IQR: 3.5 - 4.7] Range: 1.1 - 6.5	Mean = 4.2 (SD: 1) Median = 4.4 [IQR: 3.4 - 4.9] Range: 1.9 - 7.1	ns (p = 0.58)[1]	r = 0.056[1]
log TF-Sat, %	Mean = 2.9 (SD: 0.61) Median = 3 [IQR: 2.6 - 3.3] Range: 0.69 - 4.3	Mean = 3 (SD: 0.6) Median = 3 [IQR: 2.5 - 3.4] Range: 0.69 - 4.5	ns (p = 0.5)[1]	r = 0.066[1]

Variable	IBK	LZ/W	Significance	Effect size
MCV, fl	Mean = 88 (SD: 6) Median = 88 [IQR: 85 - 91] Range: 58 - 100	Mean = 89 (SD: 6.1) Median = 89 [IQR: 86 - 93] Range: 76 - 110	ns (p = 0.3)[1]	r = 0.1[1]
log NT-pro-BNP, pg/ml	Mean = 6.4 (SD: 1.7) Median = 6.6 [IQR: 5.1 - 7.7] Range: 3.4 - 11	Mean = 6.5 (SD: 1.4) Median = 6.6 [IQR: 5.3 - 7.4] Range: 3.2 - 10	ns (p = 0.95)[1]	r = 0.0079[1]
Percardial effusion	16% (16)	3.6% (3)	p = 0.04[3]	V = 0.2[4]
RAA, cm2	Mean = 22 (SD: 4.9) Median = 22 [IQR: 17 - 24] Range: 13 - 34	Mean = 20 (SD: 4.1) Median = 18 [IQR: 17 - 23] Range: 13 - 30	p = 0.012[1]	r = 0.22[1]
CI	Mean = 2.4 (SD: 0.53) Median = 2.4 [IQR: 1.9 - 2.8] Range: 1.6 - 4.2	Mean = 2.6 (SD: 0.52) Median = 2.6 [IQR: 2.2 - 3] Range: 1.4 - 3.8	p = 0.033[1]	r = 0.19[1]
mRAP, mmHg	Mean = 10 (SD: 4.7) Median = 10 [IQR: 6 - 13] Range: 2 - 26	Mean = 6.2 (SD: 4.3) Median = 6 [IQR: 3 - 9] Range: 0 - 20	p < 0.001[1]	r = 0.43[1]
WHO class	I/II: 39% (39) III/IV: 61% (61)	I/II: 53% (44) III/IV: 47% (39)	ns (p = 0.17)[3]	V = 0.14[4]
SO2, %	≥95: 47% (47) <95: 53% (53)	≥95: 48% (40) <95: 52% (43)	ns (p = 0.99)[1]	V = 0.012[1]
3-year mortality	13% (13)	11% (9)	ns (p = 0.94)[3]	V = 0.033[4]
5-year mortality	21% (21)	13% (11)	ns (p = 0.35)[3]	V = 0.1[4]
Overall mortality	33% (33)	24% (20)	ns (p = 0.35)[1]	V = 0.098[1]
OS, months	Mean = 80 (SD: 46) Median = 70 [IQR: 46 - 110] Range: 2 - 230	Mean = 71 (SD: 42) Median = 63 [IQR: 32 - 110] Range: 11 - 170	ns (p = 0.3)[1]	r = 0.099[1]
mRASP	Mean = 0.84 (SD: 0.68) Median = 1 [IQR: 0 - 1] Range: 0 - 2	Mean = 0.7 (SD: 0.62) Median = 1 [IQR: 0 - 1] Range: 0 - 2	ns (p = 0.3)[1]	r = 0.1[1]
COMPERA	Mean = 1.9 (SD: 0.6) Median = 2 [IQR: 2 - 2] Range: 1 - 3	Mean = 1.6 (SD: 0.53) Median = 2 [IQR: 1 - 2] Range: 1 - 3	p = 0.0091[1]	r = 0.23[1]

Variable	IBK	LZ/W	Significance	Effect size
SPAHR	Mean = 1.9 (SD: 0.58) Median = 2 [IQR: 2 - 2] Range: 1 - 3	Mean = 1.7 (SD: 0.5) Median = 2 [IQR: 1 - 2] Range: 1 - 3	ns (p = 0.065)[1]	r = 0.17[1]
FPHR 3p	Mean = 2.1 (SD: 0.97) Median = 2 [IQR: 1 - 3] Range: 0 - 3	Mean = 1.9 (SD: 1) Median = 2 [IQR: 1 - 3] Range: 0 - 3	ns (p = 0.3)	r = 0.099
FPHR 4p	Mean = 2.8 (SD: 1.1) Median = 3 [IQR: 2 - 4] Range: 0 - 4	Mean = 1.9 (SD: 1.2) Median = 2 [IQR: 1 - 3] Range: 0 - 4	p < 0.001	r = 0.33

[1]Mann-Whitney U test.1

[1]Wilcoxon r effect size statistic.2

[3]χ^2 test.

[4]Cramer V effect size statistic.

Figures

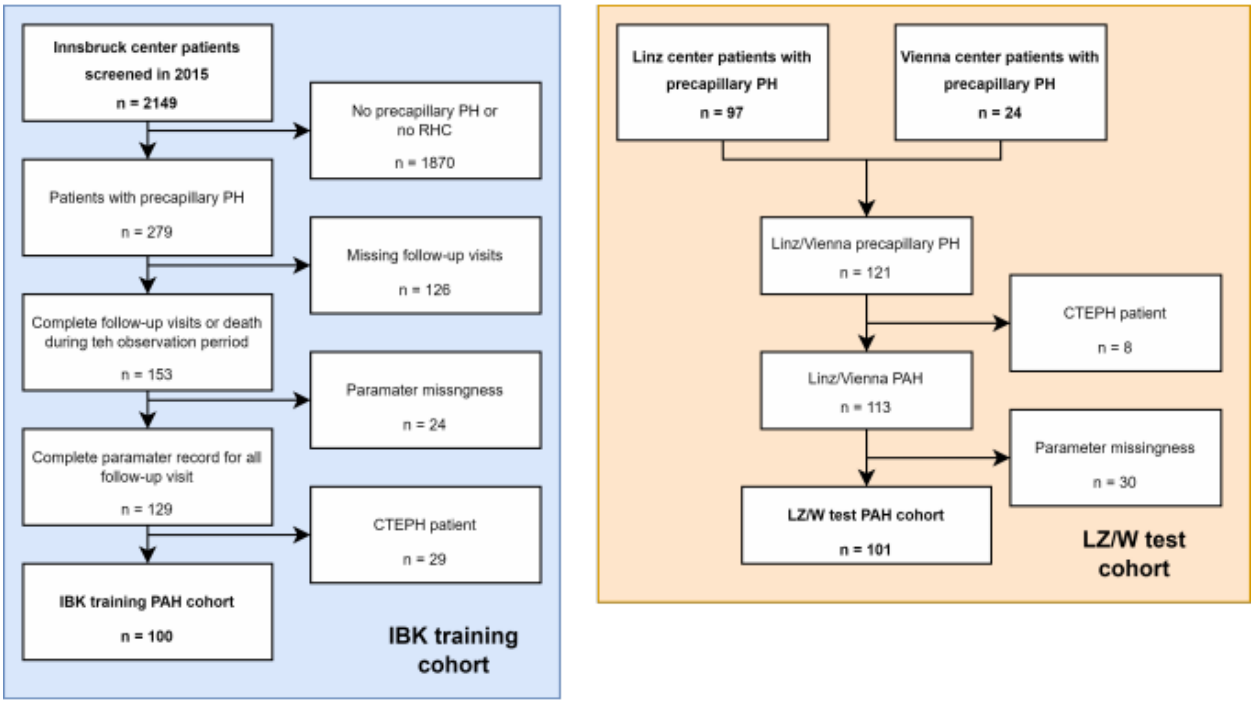

Figure 1. CONSORT flow diagram of the study analysis inclusion process.

PH: pulmonary hypertension; RHC: right heart catheterization; CTEPH: chronic thromboembolic pulmonary hypertension.

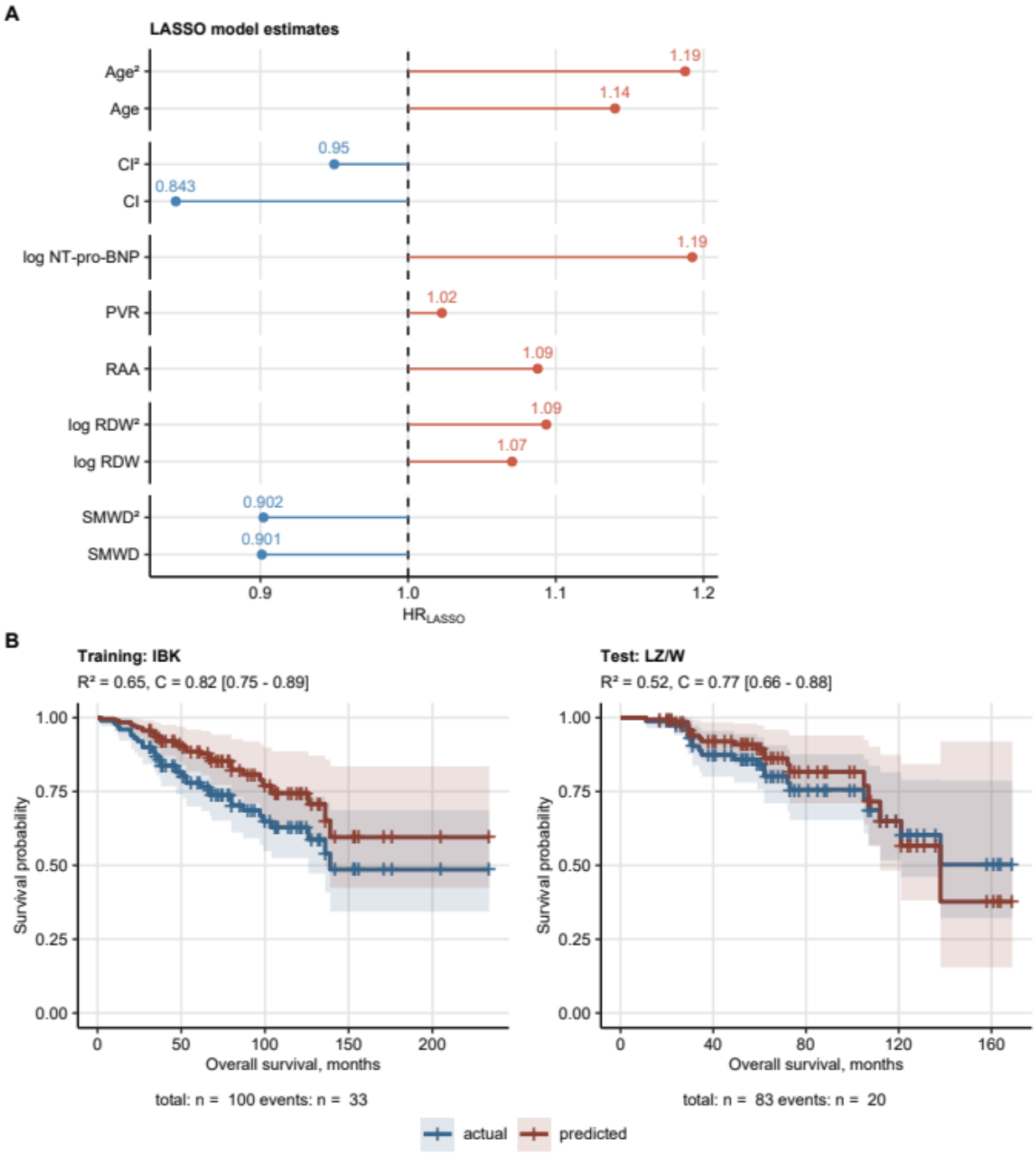

Figure 2. Multi-parameter survival modeling.

The elastic net multi-parameter Cox regression model with the set of 19 (**Supplementary Table S1**) independent variables and overall survival as a response was developed in the training Innsbruck cohort. Numeric independent variables were median centered and their

first and second order terms included in the model. Numbers of complete observations and mortality is indicated in **B**.

(A) Non-zero model coefficients represented as hazard ratios (HR). Plot points are labeled with the HR values.

(B) Association of the elastic net model linear predictor score with overall survival in the training IBK and test Linz/Vienna (LZ/W) cohort. Actual and modeled survival are presented in Kaplan-Meier plots. R^2 and concordance index (C) with 95% confidence intervals are shown in the plot captions.

CI: cardiac index; NT-pro-BNP: N terminal pro brain natriuretic peptide; RDW: red blood cell distribution width; PVR: pulmonary vascular resistance; RAA: right atrial area; SMWD: six minute walking distance.

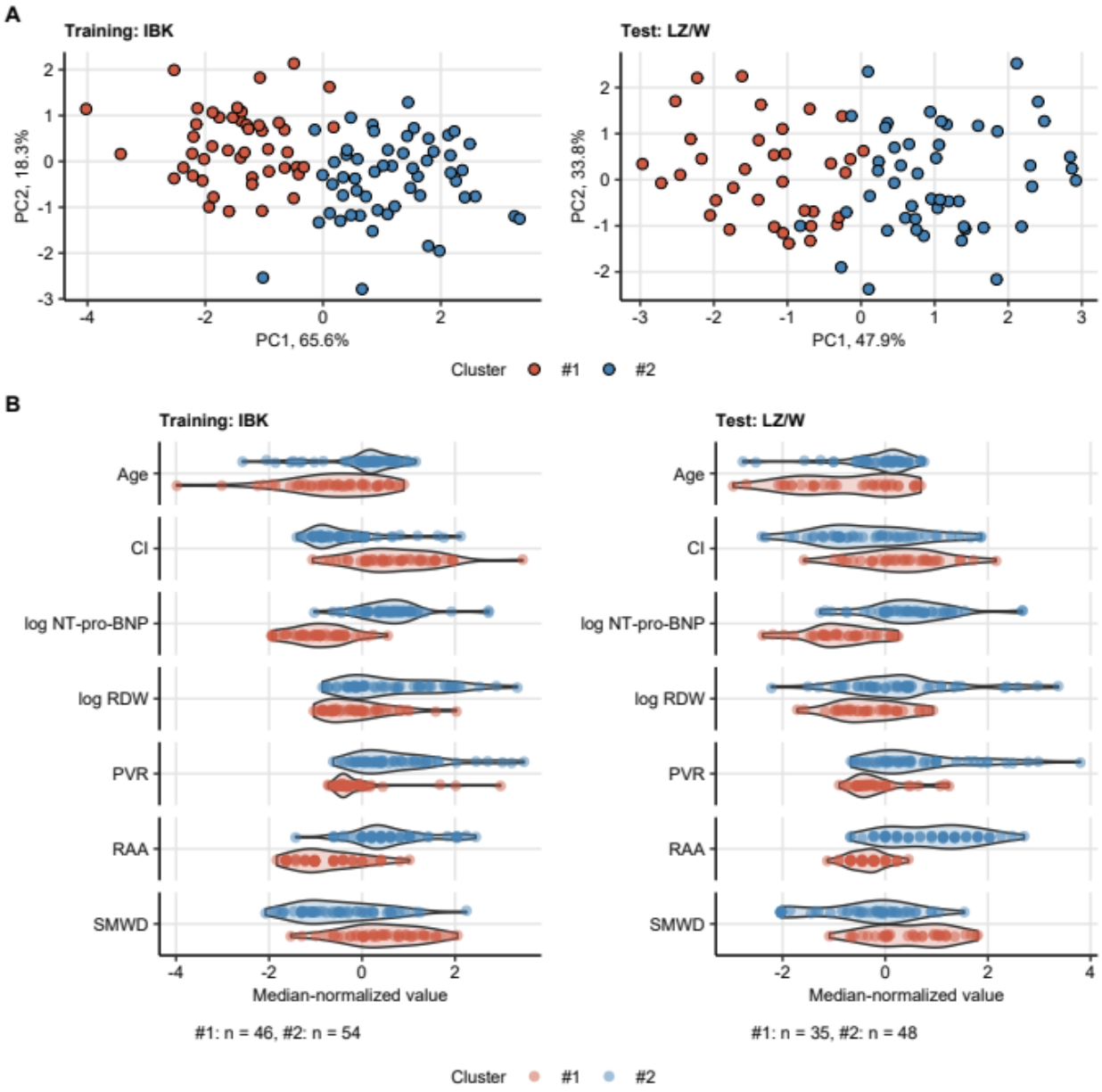

Figure 3. Clustering of the study participants.

Clustering of the training Innsbruck (IBK) cohort participants in respect to the survival-associated factors identified by elastic-net modeling (**Figure 2**) was investigated by PAM (partition around medoids) algorithm and cosine distance measure. Numeric clustering features were median centered prior to the clustering. Cluster assignment in the training Linz/Vienna cohort (LZ/W) was done with the k-nearest neighbor classification technique. Numbers of individuals assigned to the clusters are presented in **B**.

(A) Cluster assignment overlaid on the 3-dimensional principal analysis (PCA) score plots. The first two principal components (PC) are presented, percentages of variance associated with the components are indicated in the plot axes.

(B) Differences in the clustering features between the participant clusters presented in violin plots. Points represent single observations.

CI: cardiac index; NT-pro-BNP: N terminal pro brain natriuretic peptide; RDW: red blood cell distribution width; PVR: pulmonary vascular resistance; RAA: right atrial area; SMWD: six minute walking distance.

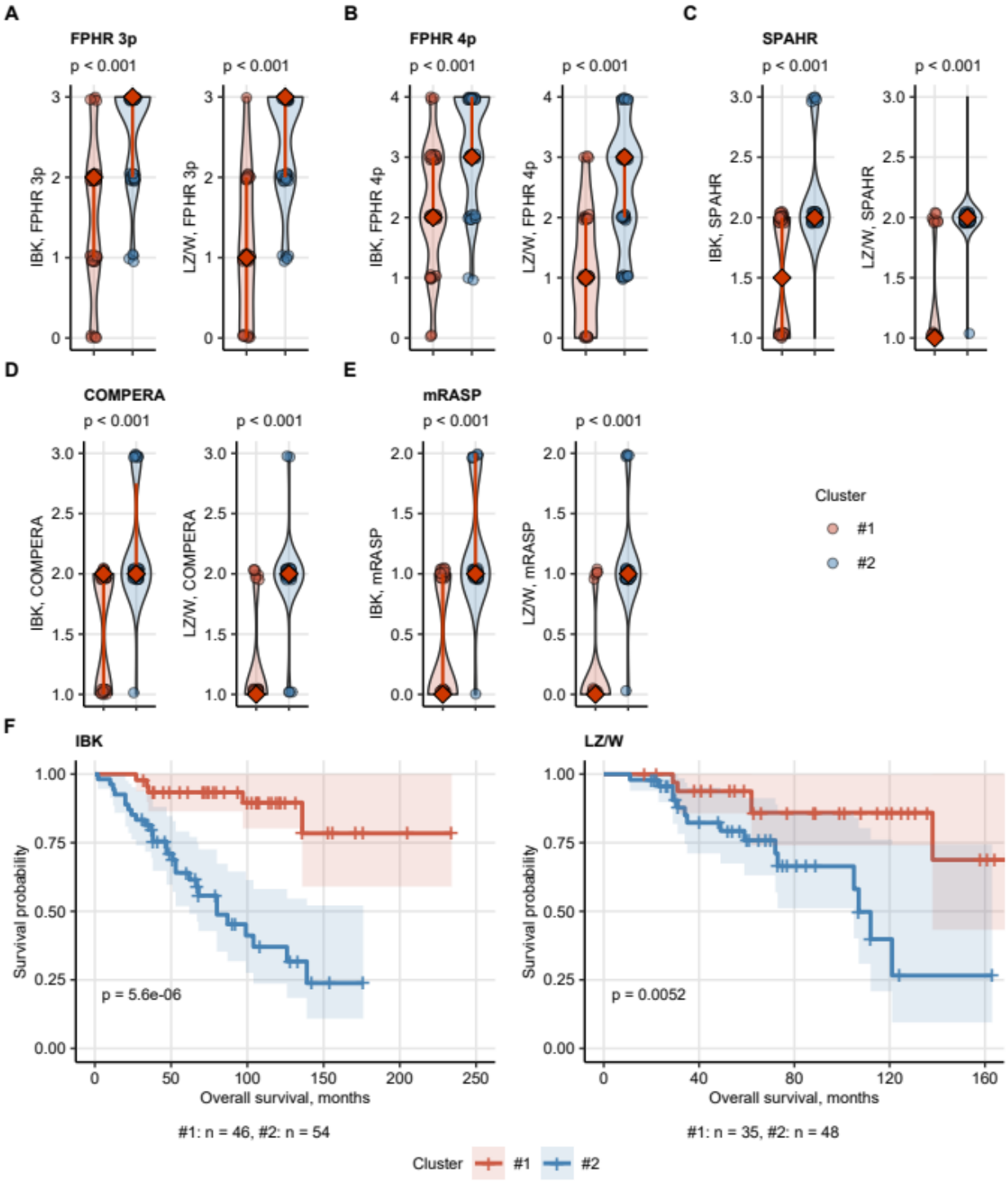

Figure 4. Risk assessment and survival differences in the participant clusters.

Risk assessment scoring and overall survival was compared between the study participant clusters (**Figure 3**, **Supplementary Figure S3**) with Mann-Whitney and Mentel-Hensezl

test, respectively. P values were adjusted for multiple testing with Benjamini-Hochberg method. Numbers of individuals assigned to the clusters are presented in **F**.

(A - E) Risk assessment score values presented in violin plots. Points represent single observations, diamonds with whiskers indicate medians with interquartile ranges. P values are presented in plot captions.

(F) Differences in overall survival in the participant clusters visualized in Kaplan-Meier plots. P values are indicated in the plots.

FPHR: French pulmonary hypertension register; SPAHR: Swedish pulmonary arterial hypertension register; COMPERA: comparative, prospective registry of newly initiated therapies for pulmonary hypertension; mRASP: modified risk assessment score of PAH.

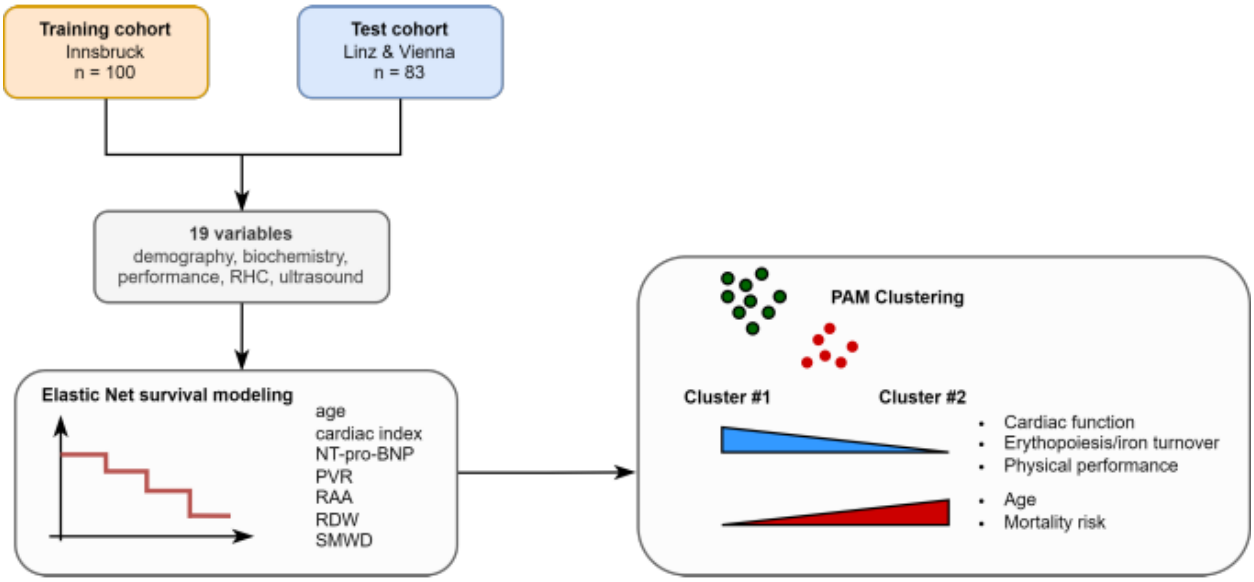

Figure 5. Summary of the analysis results.

RHC: right heart catheterization; CI: cardiac index; NT-pro-BNP: N terminal pro brain natriuretic peptide; RDW: red blood cell distribution width; PVR: pulmonary vascular resistance; RAA: right atrial area; SMWD: six minute walking distance.