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Early View

Original article

The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicenter observational study

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Title Page

Title: The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicenter observational study

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Take home message: This is the first-ever validated clinical prediction model and point-score index for all-cause mortality in IPF that includes comorbidity variables. Their inclusion significantly improved prediction of survival beyond demographic and physiologic parameters.

Abstract

Background: The Gender-Age-Physiology (GAP) model was developed to predict the risk of death. Comorbidities are common in Idiopathic pulmonary fibrosis (IPF) and may impact on survival. We evaluated the ability of comorbidities to improve prediction of survival in IPF patients beyond the variables included in the GAP model.

Methods: We developed a prediction model named TORVAN using data from two independent cohorts. Continuous and point score prediction-models were developed with estimation of full and sparse versions of both. Models discrimination was assessed by the c-index and calibrated by comparing predicted and observed cumulative mortality at 1-5 years.

Results: Discrimination was similar for the sparse continuous model in the derivation and validation cohorts (c-index 71.0 vs. 70.0), and significantly improved upon performance of the GAP model in the validation cohort (increase in c-index of 3.8, p=0.001). In contrast, the sparse point-score model did not perform as well in the validation cohort (c-index 72.5 in the derivation cohort vs 68.1 in the validation cohort), but still significantly improved upon the performance of the GAP model (c-index increased of 2.5, p=0.037).

Conclusions: The inclusion of comorbidities in TORVAN models significantly improved the discriminative performance in prediction of risk of death comparing to GAP.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare lung disease of unknown etiology, characterized by irreversible, progressive fibrosis of the lungs that leads to an increasing worsening of lung function [1,2]. Prognosis of IPF is very poor with a median survival estimated at 3-5 years, which is worse than many types of cancer [3–5]. However, there is substantial heterogeneity in risk of death among individual patients with survival times ranging from less than 1 year to greater than 10 years [6–8]. Accurate prediction of survival in IPF is important both for patient counseling and for informing management decisions.

Several studies have reported predictors of survival in IPF, either alone or in combinations, the latter usually through the use of multivariable risk prediction models [9–13]. The Gender-Age-Physiology (GAP) model is the most widely validated multivariable prediction model for mortality in IPF, which includes variables for age, sex, forced vital capacity % predicted (FVC % predicted) and diffusing capacity % predicted (DLCO % predicted) [14]. While this model has demonstrated consistent prediction across multiple cohorts, its discriminative performance is modest. Because the GAP model is intended to predict all-cause mortality in IPF, it lacks accounting for other mortality reasons than respiratory. This is important as only 60–70% of patients with IPF die from causes directly related to IPF [7], and the remaining causes of death may be due to other comorbid diseases present in this older population. It was also reported that comorbid diseases and IPF and other progressive ILDs interact to increase the risk of both IPF and non-IPF mortality [15,16]. Comorbidities are common in IPF, and several have been shown to be associated with survival in IPF; the most notable examples include lung cancer, pulmonary hypertension, and cardiovascular diseases [17–25]. However, the ability of these comorbidities to improve survival prediction in IPF, beyond basic demographics and measures of disease severity (i.e. pulmonary function) has not been systematically evaluated.

In this study (the TORVAN study), we evaluated the ability of comorbidities to improve prediction of overall survival in patients with IPF beyond those variables included in the GAP model. To do

this, we derived and validated multivariable prediction models that considered comorbidities, in addition to the GAP variables, in two large, multinational, independent cohorts of IPF. We then evaluated their predictive performance, including discrimination and calibration, in comparison to the GAP models in order to assess the contribution of comorbidities to survival prediction in IPF.

Methods

Study patients

The study population consisted of 931 consecutive patients with IPF evaluated at four international academic ILD centers. Data were retrospectively extracted from clinical medical records. All patients were required to have received a diagnosis of IPF according to established criteria [1,26]. Patients were then divided into a derivation and a validation cohort. The derivation cohort included a total of 476 patients diagnosed at the Regional Referral Centre for Interstitial and Rare Lung Diseases of the University of Catania, Catania, Italy (n=126); the Department of Respiratory Medicine of the Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands (n=91) and the Centre for Interstitial and Rare Lung Diseases, Thoraxklinik, University of Heidelberg, Heidelberg, Germany (n=259) between January 2004 and December 2016. The validation cohort included 461 patients diagnosed at the University of California, San Francisco, United States between January 2007 and March 2017. Some patients in the derivation cohort were previously included by Kreuter et al. in their study on the establishment of a comorbidome in IPF [15], while some others (228 patients) in the validation cohort were already used in the derivation of the GAP model [14]. This excluded the possibility of a self-validating of the study.

Pulmonary function tests

Pulmonary function tests (PFTs) were performed according to ATS/ERS criteria [27]. Only patients with PFTs within 3 months of the time of diagnosis were included in the analysis. As in the GAP

model, FVC% and DLCO% were considered as potential predictors of prognosis and if patients were found to be unable to perform DLCO, this was considered as a further indicator of worse prognosis.

Comorbidities

In the derivation cohorts, comorbidities and related treatments were routinely collected at baseline visits through direct questioning to the patient (including standardized questionnaires) and a systematic analysis of related medical reports and exams. Comorbidities collected in the derivation cohort included systemic hypertension, coronary artery disease, cerebrovascular diseases, atrial arrhythmias, valvular heart diseases defined as mitral, tricuspid or aortic stenosis or regurgitation assessed through echocardiography, venous thromboembolism, peripheral vascular disease, emphysema defined as areas of decreased attenuation in comparison with contiguous normal lung assessed through CT scan [28], diabetes mellitus, gastroesophageal reflux (GERD) assessed through direct questioning about symptoms and use of Proton-Pump Inhibitors/Histamine 2 blocker drugs and/or through evaluation with 24-h pH monitoring and endoscopy, pulmonary hypertension defined as mean pulmonary artery pressure of ≥25 mmHg on right heart catheterization or estimated systolic pulmonary artery pressure of ≥ 40 mmHg according to Galiè et al criteria [29], sleep apnea assessed through polysomnography, major depressive disorder assessed through medical reports and related drugs, dyslipidemia, hypo/hyperthyroidism, lung cancer, kidney, and liver failure. These comorbidities represented the candidate comorbidity variables for the derivation model. In the validation cohort, only comorbidities selected as important for survival prediction in the derivation cohort were collected through a combination of retrospective review of the medical record and from an intake ILD questionnaire that specifically asks patients about a history of GERD, diabetes, pulmonary hypertension, and OSA. Only comorbidities present at the time of diagnosis were considered for the analysis.

Outcome

The primary outcome was survival, which was defined as the time from initial diagnosis to death, with right-censoring at the time of lung transplantation or at the end of the observation period for those individuals who were alive and transplant-free at the end of the observation period.

Statistical analysis

The distributions of baseline continuous variables were reported as mean and standard deviation and compared between cohorts using the Student's T-test. For baseline binary variables, the number and percentage of the cohort were reported and compared between cohorts using the Chi square test. Multivariable Cox proportional hazards models for transplant-free survival were estimated in the derivation cohort using the least absolute shrinkage and selection operator (LASSO) [30]. We decided to choose LASSO analysis because is able to improve the prediction accuracy and interpretability of regression models. LASSO forces the sum of the absolute value of the regression coefficients to be less than a fixed value and forces certain coefficients to be set to zero. This leads to alter the model fitting process to select only a subset of the provided covariates for use in the final model rather than using all of them. Moreover, since our analysis directly compares TORVAN to GAP, this results much easier using the same statistical test. Age, sex, baseline FVC, and baseline DLCO as well as all comorbidity variables were considered as potential predictors. The LASSO Cox model was first estimated using continuous variables (e.g. age, FVC, DLCO) as observed; in addition, we categorized the continuous variables, re-estimated the model, and re-scaled the resulting coefficients, generating point scores. Full and parsimonious (sparse) versions of both models were estimated, respectively minimizing cross-validated prediction error and obeying a more parsimonious criterion accounting for simulation variability in the cross-validation. In a final step, model results were used to estimate probability of transplant-free survival 1-5 years after diagnosis for patients in both the derivation and validation cohorts.

Model discrimination was evaluated using the C-index, with 95% confidence intervals estimated using bias-corrected bootstrap resampling with 500 repetitions. The LASSO models were compared

in terms of the C-index to the Gender-Age-Physiology model, re-estimated using the derivation cohort, using bootstrapping to evaluate differences. In addition, model calibration was evaluated by comparing model-based and non-parametric Kaplan-Meier transplant-free survival estimates at years 1–5, by quartile of model-estimated risk for the continuous models and approximate quartiles of point scores for the point-score models. We also formally compared the Kaplan-Meier survival rates across quartiles using the log-rank test. LASSO was implemented using the *glmnet* package version 1.0 in R version 3.4.3 (www.R-project.org). All other analyses were performed using STATA version 15.0 (StataCorp, College Station, Texas).

Results

Cohort characteristics

Characteristics of both cohorts are reported in table 1. Compared to the validation cohort, patients in the derivation cohort were, on average, younger and had higher baseline FVC % predicted, but had similar DLCO % predicted. Fewer patients had GERD, while more patients had lung cancer, pulmonary hypertension, cerebrovascular disease, diabetes, and systemic hypertension. The proportion of patients with atrial arrhythmias, valvular heart disease, and depression were similar between the two cohorts. Median follow-up time was comparable between the cohorts (2.9 vs. 2.5 years, p=0.95). A higher proportion of patients died in the derivation cohort (57% vs. 41%) while fewer patients underwent lung transplantation (1.26% vs. 13%). Overall median transplant-free survival was shorter in the derivation cohort compared to the validation cohort (3.7 vs. 4.6 years, log-rank p=0.001).

Table 1. Comparison of baseline characteristics and outcomes between cohorts

	Derivation Cohort (476 pts)	**Validation Cohort (461 pts)**	**P value**
Age in years, mean +/- SD	68.08±8.41	70.20±8.63	0.0002
Sex, number male (%)	366 (76.73)	344 (74.46)	0.41
FVC % predicted, mean +/- SD	75.24±19.85	70.04±17.67	<0.001
DLCO % predicted, mean +/- SD	47.58±18.30	47.70±17.85	0.91
Atrial Arrhythmias, n (%)	33 (6.92)	27 (5.84)	0.51
GERD, n (%)	117 (24.53)	150 (32.47)	0.007
Lung Cancer, n (%)	60 (12.58)	9 (1.95)	<0.001

Pulmonary Hypertension, n (%)	128 (26.83)	53 (11.47)	0.001
Valvular Heart disease, n (%)	30 (6.29)	24 (5.19)	0.47
Cerebrovascular disease, n (%)	68 (14.26)	25 (5.41)	<0.001
Diabetes mellitus, n (%)	114 (23.90)	73 (15.80)	0.002
Systemic Hypertension, n (%)	227 (47.59)	172 (37.23)	0.001
Depression, n (%)	32 (6.71)	40 (8.68)	0.25
Transplanted, n (%)	6 (1.26)	60 (12.99)	<0.001
Deceased, n (%)	272 (57.02)	190 (41.13)	<0.001
Median Follow-up time (years)	2.9	2.4	0.95
Median Transplant-free survival (years)	3.7	4.6	0.001

Footnotes

Abbreviation: SD =standard deviation; GERD = gastroesophageal reflux

Model derivation and variable selection

Variables selected, and their effect sizes, for each version of the model (full vs sparse and continuous vs point-score) are shown in table 2. All models selected age, FVC, DLCO, GERD (the presence of which was protective), pulmonary hypertension, lung cancer, valvular heart disease, and atrial arrhythmias as important for survival prediction. The full models also selected for diabetes, cerebrovascular disease, arterial hypertension, and major depressive disorder. None of the models selected for sex. Comorbidities not selected for in any of the models included coronary artery disease, venous thromboembolism, peripheral vascular disease, emphysema, sleep apnea, dyslipidemia, hypo/hyperthyroidism, kidney failure, and liver failure.

Table 2. Models estimated by least absolute and shrinkage selection (LASSO) in the derivation cohort

Variables	Model			
	Sparse, Continuous Coefficient (HR)	**Sparse, Point-score** Coefficient (Points)*	**Full, Continuous** Coefficient (HR)	**Full, Point-score** Coefficient (Points)*
Age (per year increase)	0.0234 (1.02)	n/a	0.0296 (1.03)	n/a
>55	n/a	0.4715 (6)	n/a	0.7305 (6)
>70	n/a	0.2112 (3)	n/a	0.2813 (2)
FVC % predicted (per 1% increase)	-0.0069 (0.99)	n/a	-0.0097 (0.99)	n/a
<=80	n/a	0.0573 (1)	n/a	0.134 (1)
<=60	n/a	0.4225 (5)	n/a	0.5719 (5)
DLCO % predicted (per 1% decrease)	0.0061 (1.01)	n/a	0.0151 (1.02)	n/a
<=60	n/a	0.5240 (6)	n/a	0.6724 (6)
<=30	n/a	0.1642 (2)	n/a	0.1003 (1)
Unable to Perform	0.4814 (1.62)	0.0402 (1)	1.1797 (3.25)	0.1003 (2)
Diabetes mellitus	NS	0.0501 (1)	0.1909 (1.21)	0.2026 (2)
Cerebrovascular disease	NS	NS	0.0315 (1.03)	NS
Systemic Hypertension	NS	NS	0.0757 (1.08)	0.0469 (1)
GERD	-0.761 (0.93)	Absence 0.0834 (1)	-0.1938 (0.82)	Absence 0.2211 (2)
Pulmonary Hypertension	0.1126 (1.12)	0.1253 (2)	0.216 (1.24)	0.2436 (2)
Major Depressive disorder	NS	0.0570 (1)	0.2339 (1.26)	0.3181 (3)
Lung Cancer	0.5281 (1.70)	0.5289 (6)	0.8425 (2.32)	0.7608 (6)
Valvular heart disease	0.165 (1.18)	0.3794 (5)	0.5619 (1.75)	0.686 (6)
Atrial Arrhythmias	0.3284 (1.39)	0.4784 (6)	0.6028 (1.83)	0.6636 (6)

Footnotes:
*Points are additive within categories.
Comorbidity variables not selected by any model included coronary artery disease, venous thromboembolism, peripheral vascular disease, emphysema, sleep apnea, dyslipidemia, hypo/hyperthyroidism, kidney failure and liver failure.
Abbreviations: HR=Hazard Ratio; NS = not selected; n/a =not applicable.

Model performance and external validation

Model discrimination in the derivation and validation cohorts compared to the GAP model is shown in table 3. Discrimination was similar for the sparse continuous model in the derivation and validation cohorts (C-index 71.0 [95% CI 67.8–74.2] vs. 70.0 [65.6–74.3], respectively), and significantly improved upon performance of the GAP model in the validation cohort (increase in C-index of 3.8, p=0.001). In contrast, the sparse point-score model did not perform as well in the validation cohort (C-index 72.5 [69.5–75.6] in the derivation cohort compared to 68.1 [65.1–72.1] in the validation cohort), but still significantly improved upon the performance of the GAP model (increase in C-index of 2.5, p=0.037). The full versions of the continuous and point-score models demonstrated similar discrimination as the sparse versions, without appreciable improvement in discrimination despite inclusion of more variables. Table 4 shows how calculate TORVAN index and stage.

Model calibration in years 1–5 for both cohorts is shown in figure 1 for the sparse models and Supplemental figure 1 for the full models. In general, all models tended to over-estimate risk of death at each time-point in the validation cohort. Kaplan-Meier survival plots, by quartile of risk, for both cohorts, is shown in figure 2 for the sparse models and Supplemental figure 2 for the full models. Survival by these groupings was significantly different for all models in both cohorts (log-rank p-value < 0.001 for all comparisons).

Table 3. Model discrimination in the derivation and validation cohorts and compared to the Gender-Age-Physiology Model

	Model						
	GAP	*Sparse*			*Full*		
Cohort	C-index (95% CI)	C-index (95% CI)	Difference compared to GAP	p-value for difference	C-index (95% CI)	Difference compared to GAP	p-value for difference
Continuous Models							
Derivation	68.8 (65.3–72.2)	71.0 (67.8–74.2)	2.3	0.055	71.3 (68.1–74.6)	2.6	0.032
Validation	66.1 (61.8–70.5)	70.0 (65.6–74.3)	3.8	0.001	70.3 (66.1–74.5)	4.2	0.003
Point-Score Models							
Derivation	69.4 (66.1–72.7)	72.6 (69.5–75.6)	2.8	0.005	71.9 (68.9–75)	2.5	0.040
Validation	65.5 (61.3–70)	68.1 (64.1–72.1)	2.5	0.037	68.2 (64–72.3)	2.6	0.079

Table 4. The TORVAN index calculation and staging system.

Predictors	Points (sparse model)		Points (full model)	
Age, y				
≤55	0		0	
56-70	6		6	
>70	9		8	
FVC % predicted				
>80	0		0	
61-80	1		1	
≤60	6		6	
DLCO % predicted				
>60	0		0	
31-60	6		6	
≤30	8		7	
Unable to perform	9		9	
Diabetes mellitus	1		2	
Systemic Hypertension	/		1	
GERD	1 (Absence)		2 (Absence)	
Pulmonary Hypertension	2		2	
Major Depressive disorder	1		3	
Lung Cancer	6		6	
Valvular heart disease	5		6	
Atrial Arrhythmias	6		6	
Points (both for sparse and full models)	<14	14-16	17-22	≥23
TORVAN Stage	**I**	**II**	**III**	**IV**

Footnotes:
Points are assigned to each variable in order to obtain a final score. Based on that, patients can be grouped into four different staging categories.

Discussion

In this study, we developed and validated the first-ever clinical prediction model and point-score index (called the TORVAN model and index) for all-cause mortality in IPF that includes comorbidity variables. In addition to the model's potential clinical value, we made other important observations in developing the models. These include: (1) inclusion of comorbidities improves prediction of survival beyond basic demographic and physiologic information (i.e., the GAP model), (2) relatively few comorbidities demonstrated significant improvement in survival prediction when considered along with basic demographic and physiologic information and these tended to be comorbidities expected to influence short-term mortality, and (3) patient sex becomes a less important prognostic indicator when considered in the context of comorbidities.

We found that the most important comorbidities for survival prediction in IPF are GERD, PH, lung cancer, valvular heart disease, and atrial arrhythmias. These variables were selected in all modeling analyses, and the inclusion of more comorbidities in models (by relaxing the LASSO selection criterion) did not appreciably improve prediction. Most of the selected comorbidity variables have previously been associated with survival in IPF [17–25]. It is notable that selected variables, with the exception of GERD, tended to be less common but highly morbid, whereas more common comorbidities such as systemic hypertension and coronary artery disease were not selected. We speculate that this may be because these comorbidities would be expected to influence longer-term mortality (relative to PH and lung cancer) and IPF itself has high short-term mortality. Somewhat unexpected was the consistent, protective association of GERD in all of our modeling analyses. The reason for this association is unclear, but is consistent with findings of previous studies [15–31]. Potential explanations include: (1) patients with GERD may have received an earlier diagnosis of IPF because of symptoms related to reflux, (2) a GERD-driven endotype of IPF may exist that has better prognosis relative to non-GERD-driven endotypes, and/or (3) the association could indirectly reflect benefits of anti-acid therapies in IPF. We also explored the possibility that the selection of atrial arrhythmia could have represented a surrogate measure of anti-coagulant use [32]. However,

since only a small and not significant number of patients were treated with vitamin k antagonists, we concluded that in our study the impact of atrial arrhythmias is due to the comorbidity itself and not related to its therapy. Finally, in contrast to the GAP model, sex was not selected as an important predictor of survival in the context of comorbidities. We speculate that this may be because male sex serves as a marker of greater comorbidity burden, rather than a biologic marker of disease behavior, and thus becomes less important of a predictor when comorbidities are considered.

All models (sparse vs full, continuous vs point-score) demonstrated acceptable, but modest discriminative performance with very little difference in the C-index across models and the derivation and validation cohorts. Importantly, the comorbidity models significantly improved upon discriminative performance compared to basic demographic and physiologic variables included in the widely-validated GAP prediction models. Because the comorbidity variables included in our models are routinely collected in the course of patient evaluations, their use in the clinical setting should be straight-forward, adding relatively little complexity compared to the GAP model. Calibration (the comparison of model-predicted and observed mortality risk) was generally good in both cohorts, but the TORVAN models tended to over-estimate risk in the validation cohort because of overall reduced mortality risk in this cohort compared to the derivation cohort, which was mostly explained by the higher rate of lung transplantation in the validation cohort. We believe that the use of the TORVAN model may provide to clinicians a way to discuss the prognosis of patients and also a means by which to identify patients at greater risk of mortality to focus on for an early referral to lung transplant or for future clinical trials dedicated to these subsets and also to discuss end-of life care and palliative support [33, 34].

There are several strengths of our study. First, our study design has several features that increase generalizability of our prediction model. These include the use of large, multicenter and multinational cohorts of well-characterized patients with IPF, collection of data from the real-world

clinical setting, and the use of independent model derivation and validation cohorts. Second, our analytic strategy, which utilized the LASSO procedure, is also expected to improve generalizability by limiting overfitting of the model and overly optimistic (inflated) predictor effects. Third, we evaluated model performance by assessing both model discrimination and calibration—the two essential features of model fit. Finally, we compared the ability the TORVAN models to improve upon the discriminative performance of a widely validated base model, the GAP model.

There are also important limitations of our study to consider. Perhaps the most important limitation is the retrospective design, which could affect the quality and accuracy of our comorbidity data. This is because comorbidities were collected from retrospective review of medical records and patient intake questionnaires and were not prospectively and systematically evaluated at the onset of the study. This could cause both under-reporting (especially in the case of pulmonary hypertension, where echocardiography was not routinely performed in all patients) and over-reporting of certain comorbidities (e.g. GERD, where confirmatory tests performed on all patients). However, both forms of misclassification would be expected to reduce overall model performance. We are missing the effects of IPF therapies (i.e. antifibrotics as pro and immunomodulators as negative effect on survival) and potential influences of comorbidities related treatments on survival. We were also not able to evaluate the cause of death in most cases, and therefore we were only able to develop models predictive of all-cause mortality. This is unfortunate because we may expect to find different sets of predictors, and predictor effects, for IPF versus non-IPF related causes of death. Differentiating the probabilities of death from IPF versus non-IPF causes of death could be useful clinically by informing certain aspects of management such as treatment of comorbidities, anticipated benefit from anti-fibrotic therapy, and appropriateness for lung transplantation. However, it must be said that the separation between IPF and non-IPF related causes of mortality might be somewhat artificial and, in a "intention to prognosticate" approach, all-cause mortality is the only end-point that captures the true prognostic significance of a comorbidity.

In conclusion, the TORVAN prediction index demonstrates that inclusion of comorbidities improves the prediction of survival beyond basic clinical and physiologic parameters in IPF, with similar predictive performance in two independent, multinational cohorts. Risk stratification by this index may inform both clinical practice and the design of new clinical trials.

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FIGURE CAPTIONS

Figure 1. Calibration plots for the (A) continuous sparse model in the derivation and the (B) validation cohorts, and the (C) point-score sparse model in the derivation and (D) validation cohort.

Figure 2. Kaplan-Meier plots of transplant-free survival by (A) quartile of model-predicted risk for the continuous sparse model in the derivation and (B) validation cohorts, and by (C) point-score grouping for the point-score sparse model in the derivation and (D) validation cohort.

Figure 3. Comorbidome of IPF

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S.E. Torrisi and C. Vancheri conceived and designed the study. S.E. Torrisi collected the data. B. Ley and E. Vittinghoff did the statistical analysis. All authors contributed to data interpretation. S.E. Torrisi and B. Ley wrote the original draft of the paper and all authors reviewed and edited drafts and approved the final version for submission.

Conflict of interest: STE has received speaker fees from Roche and Boehringer Ingelheim, outside the submitted work. BL has received a speaker's fee from Genentech, outside the submitted work. MK has received grants and personal fees from Boehringer Ingelheim and Roche/InterMune, outside the submitted work. MW has received grants and other funding from Boehringer Ingelheim and Intermune/F Hoffman La-Roche and other funding from Galapagos, outside the submitted work. HRC reports personal fees from Bayer, Boehringer Ingelheim, Global Blood Therapeutics, Genoa, ImmuneWorks, Navitor, Parexel, PharmAkea, Prometic, Toray, and Veracyte, outside of the submitted work. CV has received grants and speaker's fees from Boehringer Ingelheim and Intermune/F Hoffman La-Roche, outside the submitted work. All other authors declare no competing interests.

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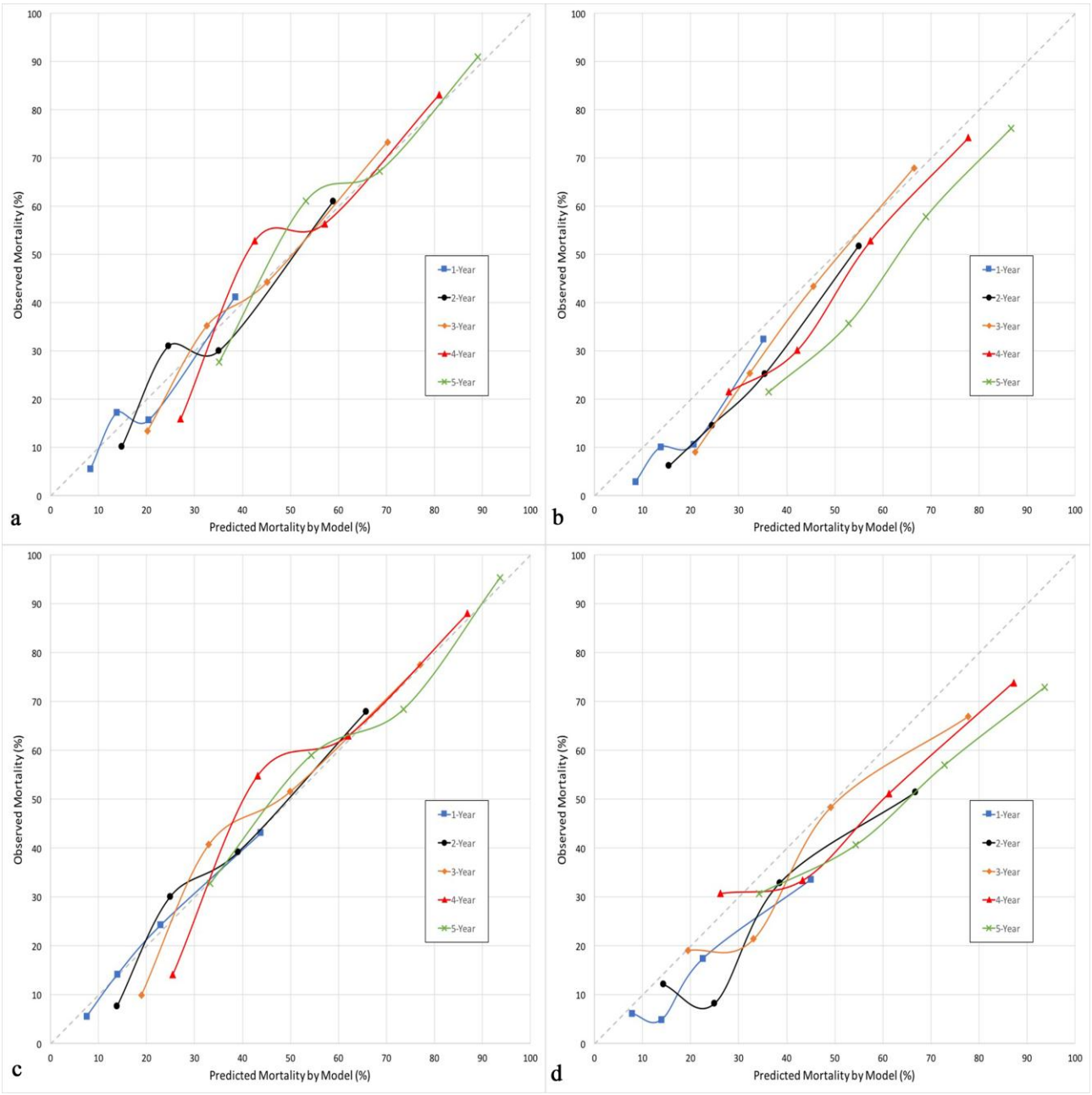
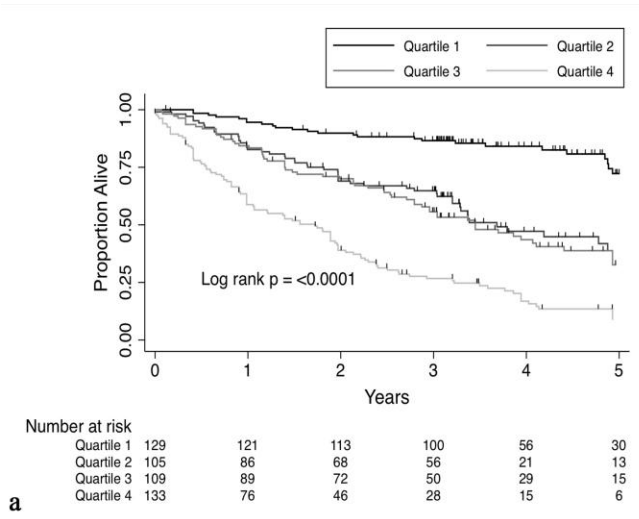
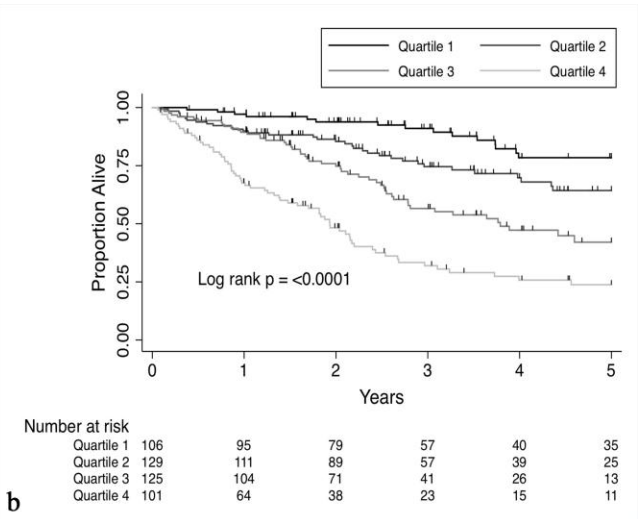

a
b
c
d
Observed Mortality (%)
Predicted Mortality by Model (%)
1-Year
2-Year
3-Year
4-Year
5-Year



Number at risk

Quartile 1	129	121	113	100	56	30
Quartile 2	105	86	68	56	21	13
Quartile 3	109	89	72	50	29	15
Quartile 4	133	76	46	28	15	6

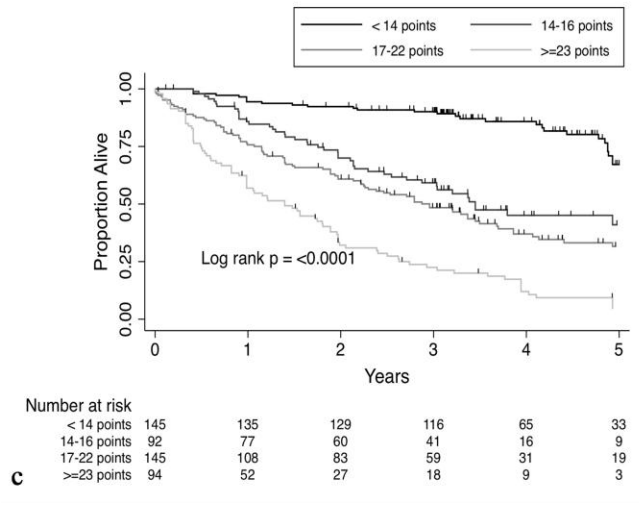
a



Number at risk

Quartile 1	106	95	79	57	40	35
Quartile 2	129	111	89	57	39	25
Quartile 3	125	104	71	41	26	13
Quartile 4	101	64	38	23	15	11

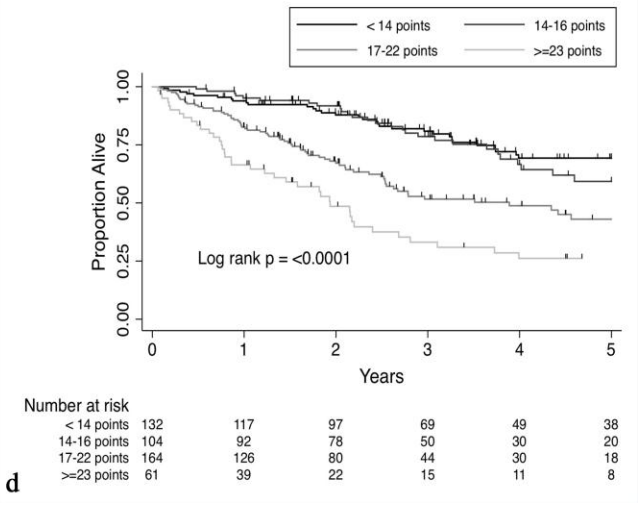
b



Number at risk

< 14 points	145	135	129	116	65	33
14-16 points	92	77	60	41	16	9
17-22 points	145	108	83	59	31	19
>=23 points	94	52	27	18	9	3

c



Number at risk

< 14 points	132	117	97	69	49	38
14-16 points	104	92	78	50	30	20
17-22 points	164	126	80	44	30	18
>=23 points	61	39	22	15	11	8

d

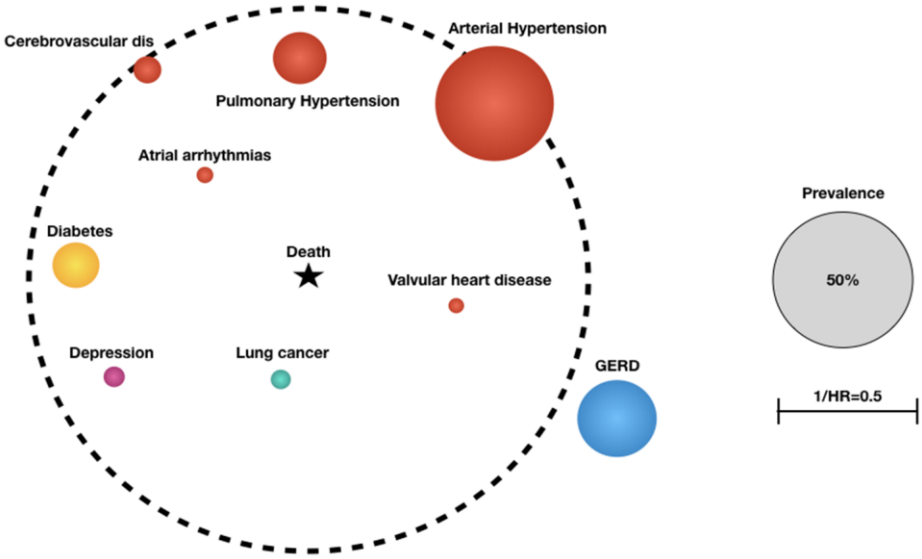
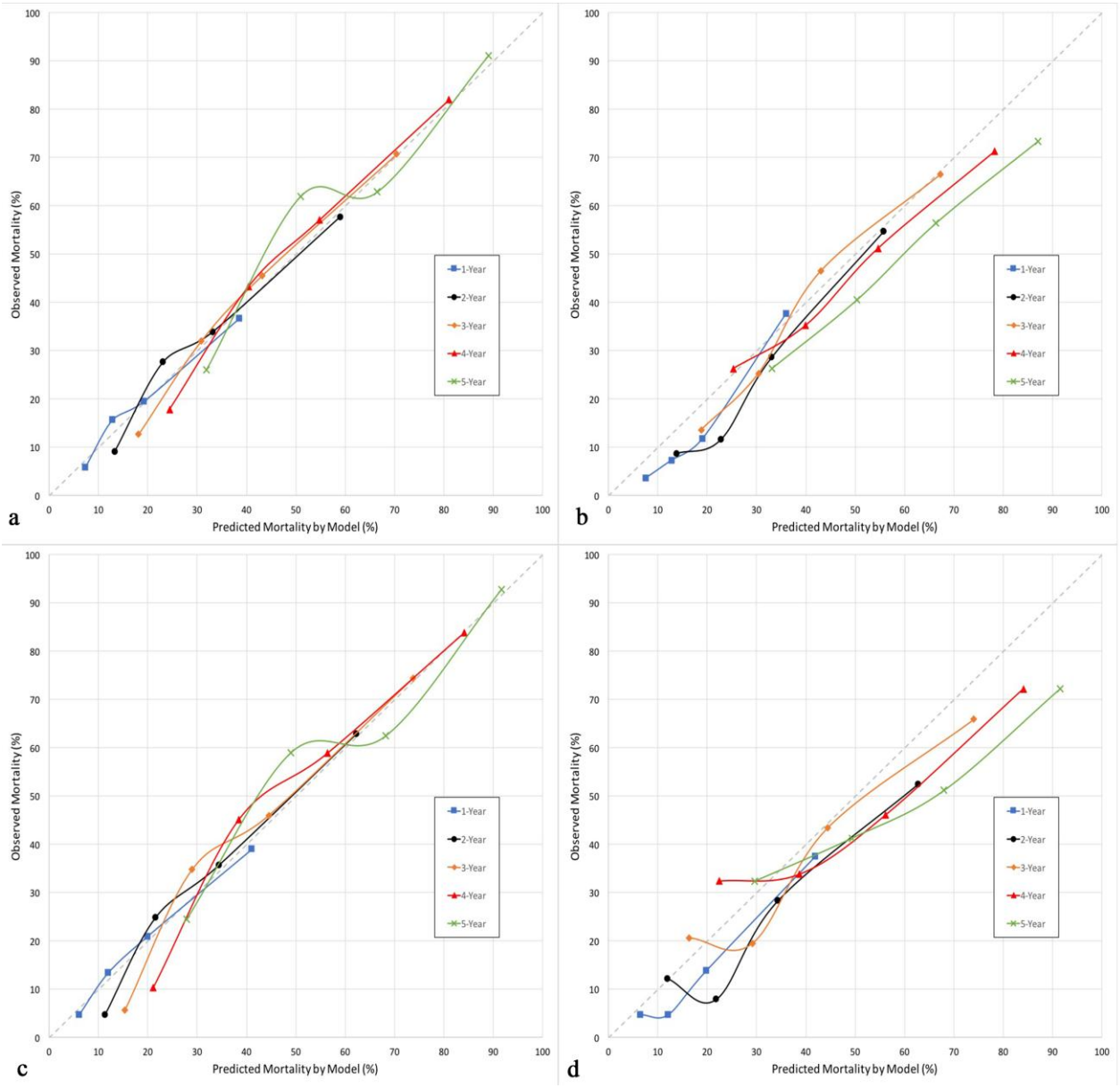
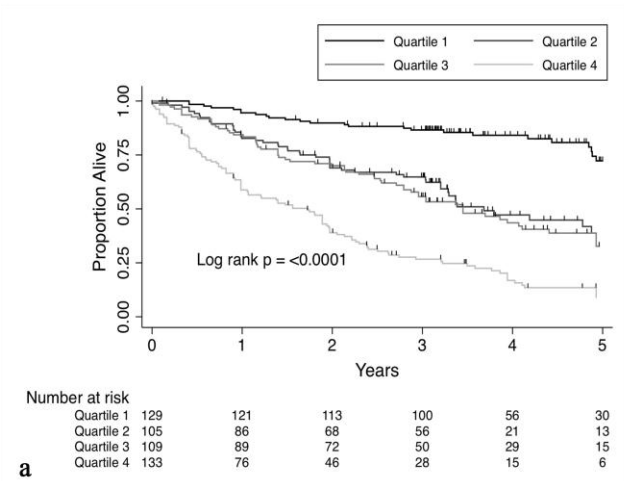

Cerebrovascular dis
Arterial Hypertension
Pulmonary Hypertension
Atrial arrhythmias
Diabetes
Death
Valvular heart disease
Depression
Lung cancer
GERD
Prevalence
50%
1/HR=0.5

FIGURE LEGENDS

Figure 1. Calibration plots for the (A) continuous full model in the derivation and the (B) validation cohorts, and the (C) point-score full model in the derivation and (D) validation cohort.

Figure 2. Kaplan-Meier plots of transplant-free survival by (A) quartile of model-predicted risk for the continuous full model in the derivation and (B) validation cohorts, and by (C) point-score grouping for the point-score full model in the derivation and (D) validation cohort.

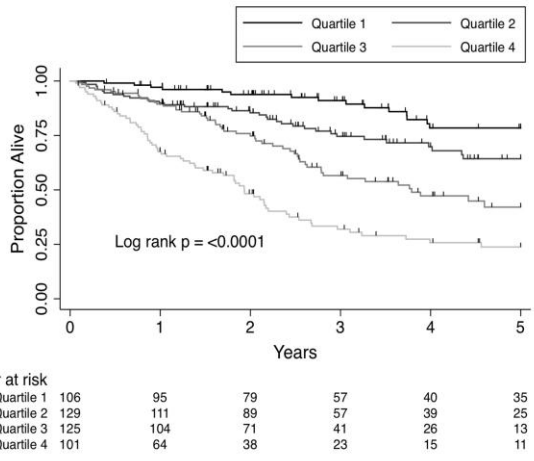

a
b
c
d
Observed Mortality (%)
Predicted Mortality by Model (%)
1-Year
2-Year
3-Year
4-Year
5-Year



Number at risk

Quartile 1	129	121	113	100	56	30
Quartile 2	105	86	68	56	21	13
Quartile 3	109	89	72	50	29	15
Quartile 4	133	76	46	28	15	6

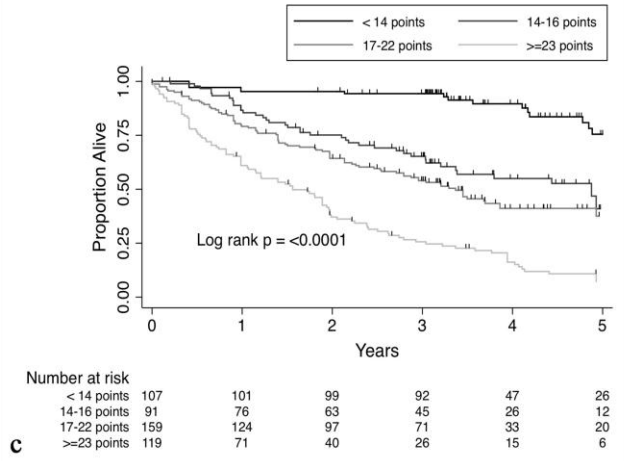
a



Number at risk

Quartile 1	106	95	79	57	40	35
Quartile 2	129	111	89	57	39	25
Quartile 3	125	104	71	41	26	13
Quartile 4	101	64	38	23	15	11

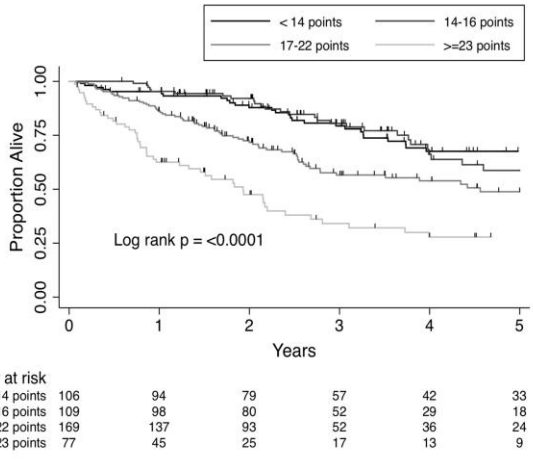
b



Number at risk

< 14 points	107	101	99	92	47	26
14-16 points	91	76	63	45	26	12
17-22 points	159	124	97	71	33	20
>=23 points	119	71	40	26	15	6

c



Number at risk

< 14 points	106	94	79	57	42	33
14-16 points	109	98	80	52	29	18
17-22 points	169	137	93	52	36	24
>=23 points	77	45	25	17	13	9

d