

Online Resource 1

Article title: Short-time deep-inspiratory breath-hold perfusion SPECT/CT in pulmonary emphysema: perfusion defect extent, not CT-quantified emphysema extent, tracks major adverse events

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Abbreviations: as defined in the main text.

Supplementary methods

Meyer regional scores

Planar perfusion images were divided into 6 zones by visually trisecting each lung. Relative uptake in each zone was graded as 1.0 (normal relative to the best-preserved zone in the same patient), 0.75, 0.50, 0.25, or 0 (absent). The Meyer P-score (%) was calculated as the volume-weighted total deficiency:

$$\text{Meyer P-score} = (1 - \sum_i w_i \times u_i) \times 100$$

where u_i is the relative uptake in zone i and w_i its volume weight (right upper 0.18, right middle 0.12, right lower 0.25, left upper 0.13, left middle 0.12, left lower 0.20; $\sum w_i = 1.00$). Higher values indicate greater perfusion impairment. The weights are those that Meyer et al. derived for the pulmonary lobes (reference 28 of the main text), applied here to visually defined zones. Meyer et al. validated the method on perfusion images. The same method, applied to planar $^{81\text{m}}\text{Kr}$ gas ventilation scintigraphy, gave the Meyer V-score in the 46 patients with paired ventilation imaging.

Exclusions

The 9 patients excluded for pulmonary thromboembolism had received that diagnosis before the STDIBH SPECT/CT analyzed here, so the exclusion did not depend on the perfusion findings that define %PPD.

Definition of AECOPD

AECOPD followed the definition of exacerbation in the GOLD 2023 report (reference 1 of the main text).

Variables and scaling

The %PPD hazard ratio (HR) is reported per 10% increase in the main text, and per 1%, per SD (22.9%), and per IQR (37.2%) where stated. In the single-covariate models, age was scaled per 10 years, %FEV1.0 per 10%, BNP per 100 pg/mL, and %LAA per 10%. Other continuous covariates were entered per unit, and binary covariates as present versus absent. The clinical models entered BNP as log2 BNP. Each model used complete cases, and the number of patients and events is given with every estimate. Among the 74 patients, %VC (percent predicted vital capacity), %FEV1.0, and FEV1.0/FVC were each missing in 1 patient, %DLCO in 19, TRPG in 6, RVEF in 1, and LVEF in 3. The Meyer V-score was not available in the 28 patients without ventilation imaging. CPFE denotes emphysema with coexisting interstitial pneumonia, diagnosed by pulmonologists on clinical and CT findings, as defined in the main text.

Pulmonary function, BNP, and RVEF measurement

Spirometry was performed before bronchodilator inhalation, and %VC and %FEV1.0 were calculated from the Japanese Respiratory Society reference equations [S1]. %DLCO was calculated without hemoglobin correction from the Global Lung Function Initiative reference equations, which were derived in a Caucasian population [S2]. The equations for %VC and %FEV1.0 were derived in Japanese adults, but those for %DLCO were not. BNP was measured by chemiluminescent enzyme immunoassay in the hospital laboratory. RVEF was measured by two-dimensional transthoracic echocardiography.

Functional form

Two restricted cubic splines of %PPD were fitted, one with 3 knots at the 10th, 50th, and 90th percentiles (19.2%, 44.8%, and 80.8%) and one with 4 knots at the 5th, 35th, 65th, and 95th percentiles (13.7%, 34.4%, 55.3%, and 84.5%). Nonlinearity was tested by the likelihood ratio test of each spline against the linear term, and the forms were compared by partial AIC in the same patients (Table S3). The curves in Fig. 3 of the main text are shown relative to the median %PPD. Of the 74 patients, 8 had a %PPD below the lowest of the 3 knots and 8 above the highest. Beyond the outer knots, the spline is linear by construction, so the curve there is not interpreted.

Proportional hazards

For each covariate, the Schoenfeld residuals were tested against rank-transformed event time, and the resulting *P* values are listed in Tables S1 and S4. The test is a diagnostic check and does not prove proportionality.

Penalized estimation

Firth-penalized Cox regression used the Breslow approximation with profile penalized-likelihood confidence intervals. Ridge regression applied an L2 penalty of $\lambda = 0.01, 0.1, \text{ or } 1.0$ to the coefficients on the standardized covariate scale, and the resulting estimates are reported without inference (Table S1).

Internal validation and calibration

The primary model was refitted in 1000 bootstrap resamples (seed 20260933), with the model form held fixed. One resample did not converge and was excluded, leaving 999. The apparent concordance index of 0.702 was reduced by a mean optimism of 0.008 to a corrected value of 0.694. The corrected calibration slope was 0.921. The main text reports the corrected value of 0.692 from the original validation run, which used a different seed. Because the AIC selection that produced the model was not repeated within the resamples, the corrected concordance is an upper estimate. Calibration at 36 months compared the mean predicted MAE-free survival with the Kaplan-Meier estimate within tertiles of the linear predictor, without optimism correction. The model overestimated risk in the middle tertile and underestimated it in the highest tertile (Table S5).

Change in concordance

The concordance of each reference model was compared with that of the same model after %PPD was added. Intervals are percentile intervals of the refitted apparent difference across 1000 bootstrap resamples, and the optimism-corrected difference is given alongside. These intervals do not apply to the corrected difference (Table S6).

Time-dependent discrimination

Time-dependent AUCs followed the cumulative/dynamic definition, in which cases had MAE by the horizon and controls remained event-free beyond it. Observations were weighted by the inverse probability of remaining uncensored, estimated by the Kaplan-Meier method under an assumption of independent censoring. Intervals for each AUC and for the paired differences (%PPD minus each marker) are percentile intervals across 1000 bootstrap resamples. The comparison markers were %LAA, the Meyer P-score, and BNP, as in the main text, and the exploratory %PPD – %LAA mismatch, which contains %PPD itself and is shown for completeness. The 12 paired contrasts over 3 correlated horizons were not adjusted for multiplicity (Table S9).

Binary receiver operating characteristic analysis and Kaplan-Meier display

Binary AUCs used MAE at any time during follow-up as the outcome. Of the 20 patients without MAE, 11 were censored before 60 months, so the binary cutoffs and their operating characteristics are descriptive. AUC intervals are percentile intervals across the resamples of the original validation run (seed 20260624), and these reproduce the reported interval

for %PPD. Paired AUCs were compared by the DeLong method. For each marker, the Youden cutoff and the censoring-weighted Youden cutoff at 36 months are reported (Table S7). Kaplan-Meier curves split at the Youden cutoff are shown in Fig. S2, and the log-rank tests are descriptive. RMST differences to 60 months are reported with percentile bootstrap intervals computed with the cutoff held fixed.

Multiplicity

No adjustment was made for multiplicity in the main text, where *P* values and confidence intervals outside the primary analysis are interpreted descriptively. Benjamini-Hochberg *q* values are given by family: the clinical univariable screen (32 tests); the imaging markers in all 74 patients (3 tests) and in the 46 patients with ventilation imaging (2 tests); and the DeLong comparisons of %PPD with the other markers (4 tests).

Precision

With 54 events, a 2-sided test at $\alpha = 0.05$ had 80% power for an unadjusted HR of 1.4641 per SD of %PPD. After the variance was inflated to account for the correlation of %PPD with the other covariates, the corresponding HR was 1.4726 in the primary model (R^2 0.030) and 1.4916 in the clinical model (R^2 0.091). These values describe the precision the study could achieve.

Independent re-derivation

Every estimate reported here was re-derived in R 4.6.1 with survival 3.8.6 and coxphf 1.13.4, with an independent data-reading path and independently declared variable definitions. All 7198 comparisons agreed within a relative tolerance of 10^{-6} (10^{-4} for Firth profile limits). Numerical agreement is technical verification of the computation.

References cited only in Online Resource 1

S1. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig* 2014;52:242-50.

S2. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017;50:1700010.

Supplementary tables

Table S1 Multivariable Cox models of MAE

Model	Covariate	n/events	EPV	HR (95% CI)	<i>P</i>	Rank Schoenfeld <i>P</i>	VIF	Firth HR (profile 95% CI)	Ridge HR
Primary: %PPD + BNP + CPFE	%PPD (per 10%)	74/54	18.0	1.1641 (1.0437–1.2982)	0.006	0.550	1.030	1.1643 (1.0445–1.2984)	1.1619 / 1.1452 / 1.0719
	BNP (per 100 pg/mL)	74/54	18.0	1.0219 (1.0099–1.0340)	< 0.001	0.473	1.027	—	—
	CPFE	74/54	18.0	2.4153 (1.3418–4.3475)	0.003	0.963	1.004	—	—
Clinical: age, sex, %FEV1.0, CPFE	Age (per 10 years)	73/53	10.6	1.0572 (0.7858–1.4225)	0.713	0.757	1.166	—	—
	Male sex	73/53	10.6	1.4176 (0.6883–2.9195)	0.344	0.034	1.131	—	—
	%FEV1.0 (per 10%)	73/53	10.6	1.0295 (0.9379–1.1299)	0.541	0.797	1.279	—	—
	CPFE	73/53	10.6	2.0645 (1.0915–3.9048)	0.026	0.881	1.167	—	—
	%PPD (per 10%)	73/53	10.6	1.1651 (1.0392–1.3063)	0.009	0.677	1.100	1.1631 (1.0384–1.3041)	1.1630 / 1.1462 / 1.0717
Clinical + log2 BNP	Age (per 10 years)	73/53	8.8	1.0186 (0.7509–1.3816)	0.906	0.348	1.232	—	—
	Male sex	73/53	8.8	1.3388 (0.6301–2.8447)	0.448	0.084	1.182	—	—
	%FEV1.0 (per 10%)	73/53	8.8	1.0231 (0.9318–1.1233)	0.632	0.554	1.292	—	—
	CPFE	73/53	8.8	1.6806 (0.8730–3.2352)	0.120	0.847	1.208	—	—
	%PPD (per 10%)	73/53	8.8	1.1887 (1.0566–1.3372)	0.004	0.968	1.100	1.1858 (1.0557–1.3339)	1.1858 / 1.1634 / 1.0756
	log2 BNP (per doubling)	73/53	8.8	1.2005 (1.0619–1.3571)	0.004	0.445	1.142	—	—

Clinical, stratified by sex	Age (per 10 years)	73/53	13.2	1.0623 (0.7883–1.4315)	0.691	—	—	—
	%FEV1.0 (per 10%)	73/53	13.2	1.0260 (0.9338–1.1274)	0.593	—	—	—
	CPFE	73/53	13.2	1.9967 (1.0467–3.8088)	0.036	—	—	—
	%PPD (per 10%)	73/53	13.2	1.1767 (1.0459–1.3238)	0.007	—	—	—
Clinical + log2 BNP, stratified by sex	Age (per 10 years)	73/53	10.6	1.0247 (0.7537–1.3931)	0.876	—	—	—
	%FEV1.0 (per 10%)	73/53	10.6	1.0245 (0.9316–1.1266)	0.618	—	—	—
	CPFE	73/53	10.6	1.6816 (0.8687–3.2553)	0.123	—	—	—
	%PPD (per 10%)	73/53	10.6	1.1871 (1.0536–1.3376)	0.005	—	—	—
	log2 BNP (per doubling)	73/53	10.6	1.1541 (1.0171–1.3096)	0.026	—	—	—

A dash marks a value that does not apply. Ridge estimates are the %PPD HRs at $\lambda = 0.01 / 0.1 / 1.0$, reported without inference. Stratified models have no VIF, Firth, or ridge estimates. Partial AIC in the 73 patients with complete data was 358.32 for the primary model, 369.82 for the clinical model, 363.45 with log2 BNP added, 321.05 for the clinical model stratified by sex, and 318.10 for that model with log2 BNP. Stratified likelihoods are not comparable with unstratified ones. Apparent concordance: primary 0.702 (74 patients), clinical 0.699 and clinical + log2 BNP 0.715 (73 patients). CPFE, combined pulmonary fibrosis and emphysema; EPV, events per variable (per estimated coefficient); VIF, variance inflation factor

Table S2 Cox models of MAE with %PPD and one additional covariate

Model	n/events	%PPD HR (95% CI)	P	Covariate HR (95% CI)	Covariate P	Unadjusted %PPD HR, same patients
Unadjusted	74/54	1.1568 (1.0409–1.2855)	0.007	—	—	—
+ Age (per 10 years)	74/54	1.1599 (1.0425–1.2906)	0.006	1.0920 (0.8395–1.4204)	0.512	—
+ Male sex	74/54	1.1390 (1.0234–1.2676)	0.017	1.7020 (0.8461–3.4236)	0.136	—
+ %FEV1.0 (per 10%)	73/53	1.1952 (1.0673–1.3385)	0.002	1.0776 (0.9955–1.1665)	0.065	1.1577 (1.0395–1.2894)
+ FEV1.0/FVC	73/53	1.2672 (1.1186–1.4355)	< 0.001	1.0219 (1.0062–1.0379)	0.006	1.1577 (1.0395–1.2894)
+ %DLCO	55/40	1.1157 (0.9807–1.2694)	0.096	0.9818 (0.9662–0.9977)	0.025	1.1599 (1.0256–1.3117)
+ GOLD stage	74/54	1.2178 (1.0865–1.3650)	< 0.001	0.6884 (0.4929–0.9612)	0.028	—
+ Pack-years	74/54	1.1633 (1.0458–1.2941)	0.005	1.0069 (0.9999–1.0139)	0.054	—
+ BNP (per 100 pg/mL)	74/54	1.1602 (1.0417–1.2922)	0.007	1.0209 (1.0094–1.0326)	< 0.001	—
+ SaO ₂	74/54	1.1492 (1.0316–1.2801)	0.012	0.9852 (0.9614–1.0095)	0.230	—
+ TRPG	68/51	1.1365 (1.0090–1.2801)	0.035	1.0257 (1.0100–1.0416)	0.001	1.1546 (1.0299–1.2944)
+ TRPG > 31 mmHg	68/51	1.1413 (1.0163–1.2817)	0.026	1.7900 (1.0046–3.1892)	0.048	1.1546 (1.0299–1.2944)
+ RVEF	73/53	1.1371 (1.0190–1.2688)	0.022	0.9832 (0.9613–1.0057)	0.142	1.1573 (1.0407–1.2869)
+ Atrial fibrillation	74/54	1.1063 (0.9847–1.2428)	0.089	0.4862 (0.1926–1.2275)	0.127	—
+ CPFE	74/54	1.1589 (1.0420–1.2888)	0.007	2.3942 (1.3336–4.2981)	0.003	—
+ HOT use at baseline	74/54	1.1156 (0.9952–1.2506)	0.060	1.6891 (0.9383–3.0407)	0.081	—
+ %LAA (per 10%)	74/54	1.2346 (1.0751–1.4176)	0.003	0.8293 (0.6301–1.0915)	0.182	—

A dash marks a value that does not apply. %PPD HRs are per 10% increase. Covariates are scaled as shown in the model labels. Other continuous covariates are scaled per unit, and binary covariates compare presence with absence (male with female for sex). When a covariate was missing in some patients, the last column gives the unadjusted %PPD HR in the same patients. Baseline HOT use precludes the new-HOT component of MAE, so the HOT row is not an ordinary adjustment and is omitted from Fig. 2 of the main text. The covariate estimates for %FEV1.0, FEV1.0/FVC, GOLD stage, and %LAA ran counter to the expected direction. GOLD stage was assigned from pre-bronchodilator %FEV1.0 cut points regardless of FEV1.0/FVC, so the staging departs from the GOLD classification. The patient with a missing %FEV1.0 was recorded as stage 1. CI, confidence interval; HOT, home oxygen therapy; HR, hazard ratio; MAE, major adverse events

Table S3 Functional form of %PPD

Model	Form	Knots (%)	Nonlinearity P	Partial AIC	HR (95% CI)
Unadjusted	Spline, 3 knots	19.2, 44.8, 80.8	< 0.001	365.95	—
Unadjusted	Spline, 4 knots	13.7, 34.4, 55.3, 84.5	< 0.001	367.67	—
Unadjusted	Linear (per 1%)	—	—	378.80	1.0147 (1.0040–1.0254)

Unadjusted	log2 (per doubling)	—	—	374.96	1.7098 (1.2189–2.3985)
Adjusted for BNP and CPFE	Spline, 3 knots	19.2, 44.8, 80.8	< 0.001	354.12	—
Adjusted for BNP and CPFE	Spline, 4 knots	13.7, 34.4, 55.3, 84.5	0.002	355.92	—
Adjusted for BNP and CPFE	Linear (per 1%)	—	—	364.92	1.0153 (1.0043–1.0264)
Adjusted for BNP and CPFE	log2 (per doubling)	—	—	361.31	1.7221 (1.2171–2.4368)

A dash marks a value that does not apply. Knots are %PPD values in percent. Nonlinearity *P* is from the likelihood ratio test of the spline against the linear term. Partial AIC compares forms within the same adjustment set

Table S4 Sensitivity analyses

Analysis	n/events	EPV	HR (95% CI)	<i>P</i>	Rank Schoenfeld <i>P</i> for %PPD
5-component MAE, unadjusted	74/56	56.0	1.1211 (1.0110–1.2431)	0.030	0.802
5-component MAE, primary model	74/56	18.7	1.1186 (1.0055–1.2444)	0.039	0.952
Without CPFE, unadjusted	48/32	32.0	1.1369 (0.9928–1.3019)	0.064	0.090
Without CPFE, adjusted for BNP	48/32	16.0	1.1413 (0.9943–1.3100)	0.060	0.196
With CPFE, unadjusted	26/22	22.0	1.1994 (1.0056–1.4306)	0.043	0.467
%PPD × CPFE interaction	74/54	18.0	1.0480 (0.8435–1.3022)	0.672	—

A dash marks a value that does not apply. HRs are per 10% increase in %PPD. The interaction row is the ratio of the %PPD HRs with and without CPFE in a model containing %PPD, CPFE, and their product. That model shares one baseline hazard, so the ratio differs from that of the subgroup HRs above. The 5-component composite adds heart failure hospitalization to MAE. The CPFE subgroups are shown with the interaction test and do not indicate effect modification. CPFE, combined pulmonary fibrosis and emphysema

Table S5 Calibration of the primary model at 36 months

Risk tertile	n	Events	Predicted MAE-free survival	Observed MAE-free survival (95% CI)
Tertile 1	25	13	0.624	0.583 (0.350–0.758)
Tertile 2	24	16	0.418	0.580 (0.360–0.748)
Tertile 3	25	25	0.138	0.000

Tertiles are ordered from lowest (1) to highest (3) predicted risk. Events are MAE at any time during follow-up. The primary model with the Breslow baseline hazard gave the apparent predicted MAE-free survival, averaged within tertiles of the linear predictor and compared with the Kaplan-Meier estimate and its log-log 95% CI. All 25 patients in the highest tertile had MAE by 36 months, so the interval for that tertile is undefined. The optimism-corrected concordance index was 0.692 in the original validation run. In the run described in the Supplementary methods, it was 0.694, and the corrected calibration slope in that run was 0.921

Table S6 Change in concordance when %PPD was added to reference models

Reference model	n/events	C, reference	C, with %PPD	Apparent ΔC (95% CI)	Optimism-corrected ΔC
BNP	74/54	0.594	0.659	0.066 (–0.023 to 0.165)	0.064
CPFE	74/54	0.603	0.681	0.079 (0.023–0.158)	0.071
BNP + CPFE	74/54	0.656	0.702	0.045 (–0.013 to 0.124)	0.041
Clinical (age, sex, %FEV1.0, CPFE)	73/53	0.645	0.699	0.054 (–0.003 to 0.116)	0.054
%LAA	74/54	0.584	0.666	0.082 (–0.009 to 0.247)	0.087

Columns give the apparent concordance of each reference model before and after %PPD was added. The interval is the percentile interval of the refitted apparent difference across 1000 bootstrap resamples and is not an interval for the optimism-corrected difference. One resample of the BNP + CPFE comparison did not converge and was excluded. C, concordance index; CPFE, combined pulmonary fibrosis and emphysema

Table S7 Binary discrimination and descriptive survival by marker

Marker	AUC (95% CI)	Youden cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Weighted 36-month cutoff	Log-rank <i>P</i>	RMST difference, months (95% CI)	ΔAUC, %PPD minus marker (95% CI)	DeLong <i>P</i>	<i>q</i>
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%PPD	0.776 (0.639–0.898)	34.2%	81.5 (69.2–89.6)	75.0 (53.1–88.8)	38.5%	< 0.001	31.7 (21.9–40.6)	—	—	—
%LAA	0.662 (0.510–0.801)	4.0%	70.4 (57.2–80.9)	65.0 (43.3–81.9)	1.0%	0.072	13.5 (1.6–25.1)	0.113 (–0.013 to 0.240)	0.080	0.318
Meyer P-score	0.813 (0.694–0.928)	33.3%	87.0 (75.6–93.6)	80.0 (58.4–91.9)	34.5%	< 0.001	32.0 (22.3–41.1)	–0.037 (–0.102 to 0.028)	0.263	0.358
%PPD – %LAA	0.744 (0.606–0.873)	33.8%	72.2 (59.1–82.4)	75.0 (53.1–88.8)	33.8%	< 0.001	32.2 (22.5–40.2)	0.031 (–0.024 to 0.087)	0.269	0.358
BNP	0.703 (0.575–0.827)	164 pg/mL	66.7 (53.4–77.8)	70.0 (48.1–85.5)	138 pg/mL	0.005	13.4 (2.8–24.3)	0.073 (–0.130 to 0.276)	0.480	0.480

A dash marks a value that does not apply. The outcome is MAE at any time, with 54 events and 20 patients without MAE. Eleven of those 20 were censored before 60 months, so the cutoffs and their operating characteristics are descriptive. AUC intervals are percentile bootstrap intervals. Sensitivity and specificity are percentages at the Youden cutoff with Wilson 95% CIs. The weighted cutoff maximizes the censoring-weighted Youden index at 36 months. RMST difference is the restricted mean MAE-free survival to 60 months below the cutoff minus that at or above it. Δ AUC is the AUC of %PPD minus that of the marker, compared by the DeLong method, with Benjamini-Hochberg q across these 4 tests. AUC, area under the curve; RMST, restricted mean survival time

Table S8 Univariable Cox regression for MAE

Variable	Scale	n/events	HR (95% CI)	<i>P</i>	<i>q</i>	Firth HR (profile 95% CI)
Age	per year	74/54	1.0070 (0.9822–1.0323)	0.585	0.810	1.0065 (0.9824–1.0324)
Male sex	male vs female	74/54	1.9406 (0.9739–3.8669)	0.059	0.211	1.8675 (0.9889–3.8725)
BMI	per kg/m ²	74/54	0.9868 (0.9287–1.0485)	0.667	0.819	0.9885 (0.9281–1.0479)
Pack-years	per pack-year	74/54	1.0064 (0.9994–1.0134)	0.072	0.231	1.0065 (0.9994–1.0133)
%VC	per 1%	73/53	0.9986 (0.9858–1.0114)	0.826	0.869	0.9986 (0.9859–1.0115)
%FEV1.0	per 1%	73/53	1.0039 (0.9960–1.0118)	0.333	0.667	1.0039 (0.9961–1.0118)
FEV1.0/FVC	per 1%	73/53	1.0073 (0.9938–1.0209)	0.291	0.621	1.0070 (0.9939–1.0209)
%DLCO	per 1%	55/40	0.9786 (0.9633–0.9943)	0.007	0.060	0.9795 (0.9631–0.9940)
GOLD stage	per stage	74/54	0.8459 (0.6239–1.1470)	0.281	0.621	0.8560 (0.6229–1.1418)
BNP	per 100 pg/mL	74/54	1.0218 (1.0099–1.0339)	< 0.001	0.007	1.0225 (1.0099–1.0336)
SaO ₂	per 1%	74/54	0.9810 (0.9584–1.0040)	0.105	0.306	0.9794 (0.9591–1.0043)
TRPG	per mmHg	68/51	1.0275 (1.0121–1.0431)	< 0.001	0.007	1.0277 (1.0120–1.0430)
LVEF	per 1%	71/52	0.9951 (0.9714–1.0194)	0.691	0.819	0.9939 (0.9719–1.0196)
RVEF	per 1%	73/53	0.9769 (0.9550–0.9993)	0.044	0.175	0.9773 (0.9550–0.9993)
Heart rate	per beat/min	74/54	1.0090 (0.9959–1.0222)	0.180	0.444	1.0099 (0.9957–1.0218)
Creatinine	per mg/dL	74/54	1.0426 (0.8784–1.2376)	0.633	0.810	1.0667 (0.8806–1.2220)
eGFR	per mL/min/1.73 m ²	74/54	0.9974 (0.9885–1.0064)	0.575	0.810	0.9975 (0.9885–1.0064)
Coronary artery disease	present vs absent	74/54	1.2224 (0.5492–2.7207)	0.623	0.810	1.2932 (0.5478–2.6466)
Hypertension	present vs absent	74/54	1.0566 (0.6160–1.8123)	0.841	0.869	1.0614 (0.6169–1.8081)
Dyslipidemia	present vs absent	74/54	0.8478 (0.4605–1.5606)	0.596	0.810	0.8682 (0.4602–1.5472)
Diabetes mellitus	present vs absent	74/54	1.0333 (0.5510–1.9377)	0.919	0.919	1.0587 (0.5496–1.9154)
CKD	present vs absent	74/54	1.2276 (0.7050–2.1374)	0.469	0.810	1.2323 (0.7059–2.1315)
TRPG > 31 mmHg	present vs absent	68/51	1.9159 (1.0793–3.4013)	0.026	0.121	1.8936 (1.0832–3.3976)
Atrial fibrillation	present vs absent	74/54	0.3639 (0.1551–0.8539)	0.020	0.108	0.3903 (0.1551–0.8271)
CPFE	present vs absent	74/54	2.3739 (1.3272–4.2461)	0.004	0.038	2.3756 (1.3270–4.2280)
Calcium-channel blocker	present vs absent	74/54	1.1567 (0.6600–2.0273)	0.611	0.810	1.1702 (0.6595–2.0159)
ARB	present vs absent	74/54	1.1126 (0.6036–2.0507)	0.732	0.837	1.1380 (0.6025–2.0310)
ACE inhibitor	present vs absent	74/54	1.2386 (0.5815–2.6379)	0.579	0.810	1.3019 (0.5808–2.5823)
Spironolactone	present vs absent	74/54	1.6467 (0.8212–3.3022)	0.160	0.427	1.7071 (0.8192–3.2495)
Beta-blocker	present vs absent	74/54	1.0747 (0.5380–2.1471)	0.838	0.869	1.1135 (0.5361–2.1100)
Statin	present vs absent	74/54	1.2926 (0.7089–2.3569)	0.402	0.757	1.3174 (0.7073–2.3354)
HOT use at baseline	present vs absent	74/54	2.0676 (1.1936–3.5816)	0.010	0.061	2.0523 (1.1977–3.5797)

%PPD	per 1%	74/54	1.0147 (1.0040–1.0254)	0.007	—	1.0146 (1.0040–1.0254)
%LAA	per 1%	74/54	1.0080 (0.9884–1.0280)	0.425	0.425	1.0092 (0.9883–1.0274)
Meyer P-score	per 1%	74/54	1.0188 (1.0062–1.0315)	0.003	0.005	1.0188 (1.0063–1.0315)
Meyer V-score	per 1%	46/35	1.0257 (1.0030–1.0490)	0.026	0.026	1.0259 (1.0029–1.0487)
%PPD – %LAA	per 1%	74/54	1.0215 (1.0077–1.0355)	0.002	0.005	1.0216 (1.0077–1.0355)
Meyer P – V mismatch	per 1%	46/35	1.0283 (1.0078–1.0493)	0.007	0.013	1.0285 (1.0078–1.0493)

A dash marks a value that does not apply. Benjamini-Hochberg *q* values were computed within 3 families: the clinical screen (32 tests), the imaging markers in all 74 patients (3 tests), and those in the 46 patients with ventilation imaging (2 tests). %PPD, the exposure, is outside these families. GOLD stage was assigned from pre-bronchodilator %FEV1.0 cut points regardless of FEV1.0/FVC, so the staging departs from the GOLD classification. The patient with a missing %FEV1.0 was recorded as stage 1. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CPFE, combined pulmonary fibrosis and emphysema; %DLCO, percent predicted diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; %FEV1.0, percent predicted forced expiratory volume in 1 s; FEV1.0/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HOT, home oxygen therapy; %LAA, percentage of low-attenuation area; LVEF, left ventricular ejection fraction; %PPD, percent perfusion defect; RVEF, right ventricular ejection fraction; SaO₂, arterial oxygen saturation; TRPG, tricuspid regurgitation pressure gradient; %VC, percent predicted vital capacity

Table S9 Time-dependent AUCs for MAE

Horizon	Cases/controls	Estimate	%PPD	%LAA	Meyer P-score	%PPD – %LAA	BNP
12 months	28/43	AUC	0.705 (0.576–0.824)	0.655 (0.516–0.774)	0.705 (0.577–0.818)	0.716 (0.590–0.833)	0.616 (0.477–0.748)
		%PPD minus marker	—	0.050 (–0.069 to 0.164)	0.000 (–0.045 to 0.040)	–0.010 (–0.093 to 0.067)	0.090 (–0.107 to 0.282)
36 months	44/24	AUC	0.754 (0.600–0.888)	0.571 (0.414–0.719)	0.725 (0.582–0.864)	0.811 (0.680–0.922)	0.648 (0.502–0.799)
		%PPD minus marker	—	0.183 (0.069–0.303)	0.028 (–0.017 to 0.077)	–0.058 (–0.154 to 0.019)	0.106 (–0.134 to 0.338)
60 months	46/17	AUC	0.713 (0.511–0.887)	0.524 (0.350–0.712)	0.682 (0.486–0.860)	0.784 (0.627–0.922)	0.615 (0.439–0.789)
		%PPD minus marker	—	0.189 (0.044–0.338)	0.032 (–0.024 to 0.086)	–0.071 (–0.190 to 0.020)	0.098 (–0.226 to 0.394)

A dash marks a value that does not apply. AUCs are cumulative/dynamic, with inverse probability of censoring weighting. Cases had MAE by the horizon, and controls were event-free beyond it. Intervals are 95% percentile bootstrap intervals (1000 resamples). The 12 paired contrasts over 3 correlated horizons were not adjusted for multiplicity

Supplementary figures

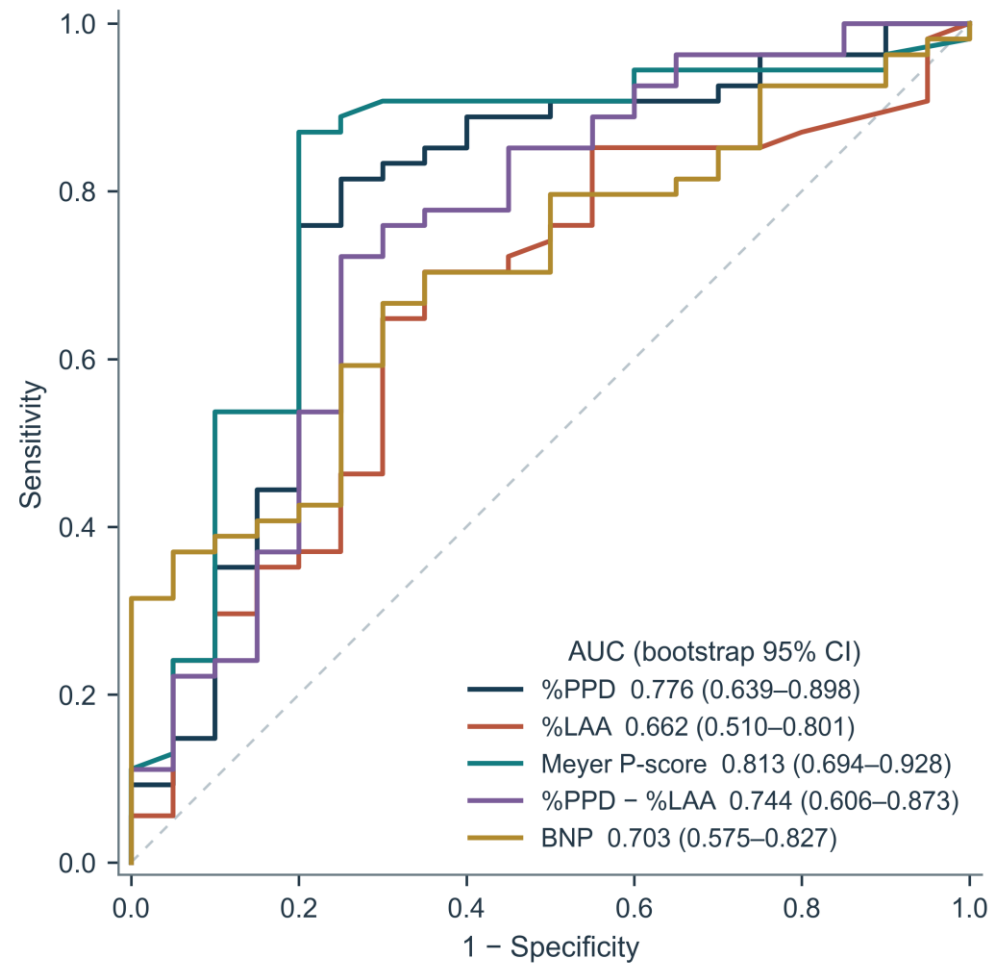


Fig. S1 Receiver operating characteristic curves of the 5 markers for MAE at any time during follow-up ($n = 74$). The key in the plot gives each AUC with its bootstrap 95% CI. The curves, and the cutoffs derived from them in Table S7, are descriptive

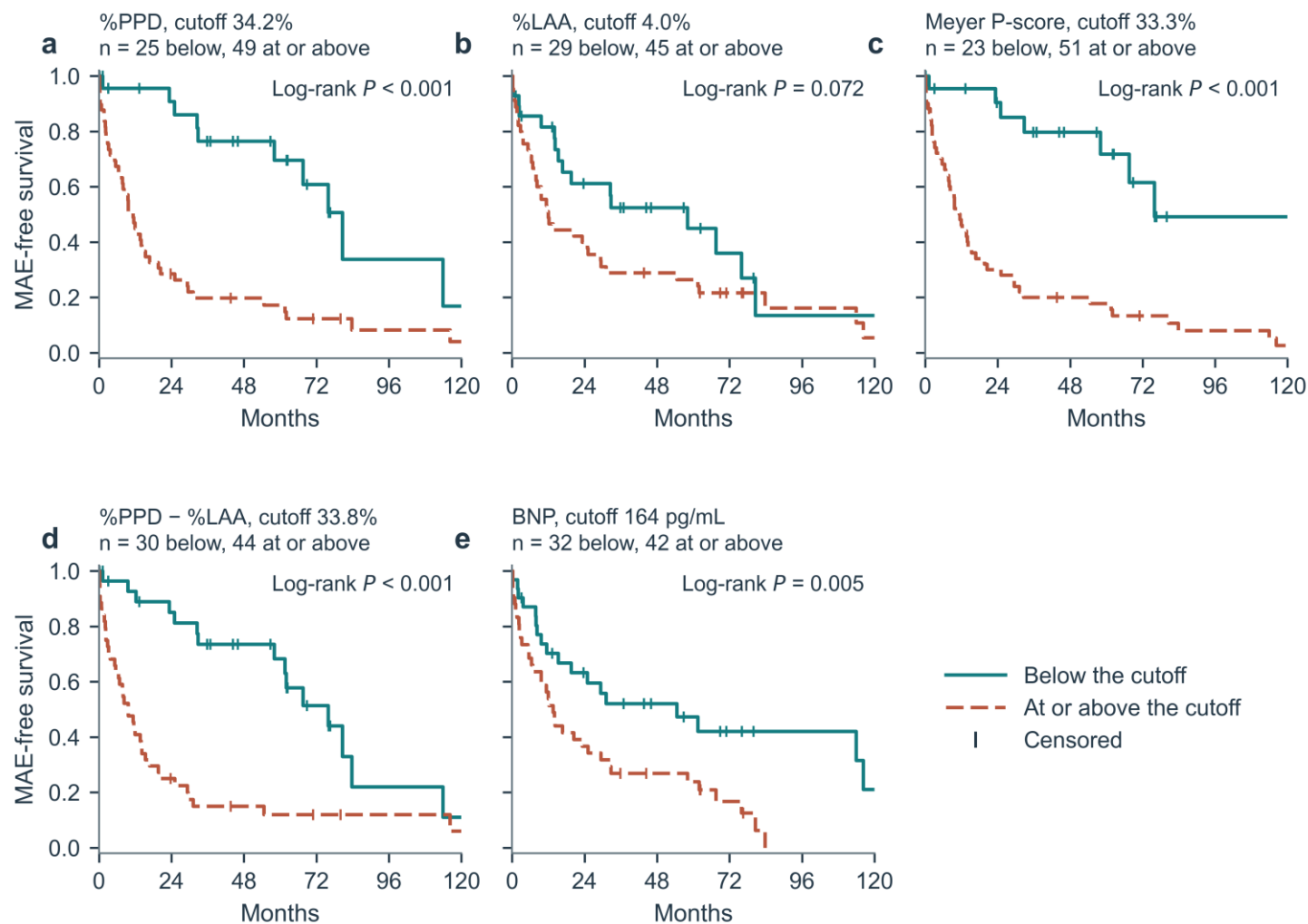


Fig. S2 Kaplan-Meier curves of MAE-free survival for the 5 markers, each split at its Youden cutoff for MAE (a, %PPD; b, %LAA; c, Meyer P-score; d, %PPD – %LAA; e, BNP). Solid lines show patients below the cutoff, dashed lines those at or above it, and tick marks show censored observations. Follow-up is displayed to 120 months. The cutoffs were derived in these data, and the log-rank tests are descriptive