

Small-airway function and reduced diffusing capacity in hospitalised adults with preserved baseline spirometry: a retrospective cross-sectional study

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Abstract

Background Reduced diffusing capacity for carbon monoxide (DLCO) can coexist with preserved spirometry, but the relevance of routine small-airway flow indices in this setting is uncertain. We examined the association between maximal mid-expiratory flow (MMEF) and reduced DLCO, and the incremental discrimination provided by MMEF.

Methods We performed a single-centre retrospective cross-sectional study of 1338 hospitalised adults with preserved baseline spirometry and classifiable DLCO. Reduced DLCO was defined as DLCO < 80% predicted with forced expiratory volume in 1 second and forced vital capacity $\geq$ 80% predicted and a ratio $\geq$ 0.70. Logistic regression, natural cubic splines, sensitivity analyses and discrimination analyses were used.

Results Reduced DLCO was present in 824 participants (61.6%). Each 10-percentage-point decrease in MMEF was associated with higher adjusted odds of reduced DLCO (odds ratio 1.11, 95% confidence interval 1.06–1.16). The association persisted after haemoglobin correction (1.13, 1.08–1.18) and in participants with clearly normal baseline spirometry (1.11, 1.05–1.18). Adding MMEF to the clinical model increased the area under the receiver operating characteristic curve from 0.741 to 0.748.

Conclusions Lower MMEF was associated with reduced DLCO but added little discrimination beyond clinical variables. In patients with preserved baseline spirometry, low MMEF may prompt gas-transfer assessment when clinically appropriate but cannot replace DLCO measurement.

Clinical trial number: not applicable.

Introduction

The diffusing capacity of the lung for carbon monoxide (DLCO) measures alveolar-to-blood gas transfer. It is influenced by alveolar volume, haemoglobin, the pulmonary vascular bed, parenchymal disease and test quality. ERS/ATS standards therefore emphasise standardised measurement, appropriate reference equations and clinical context rather than interpretation of a threshold in isolation.[1, 2]

A reduced DLCO may occur despite preserved spirometry because of early emphysema, pulmonary vascular disease, mild interstitial change, anaemia or overlapping conditions.[3–5] Here, ‘isolated’ describes only this physiological discordance—low DLCO with preserved spirometric indices—and does not indicate absence of cardiopulmonary comorbidity. Whether routine spirometric indices can identify patients who particularly warrant DLCO measurement remains uncertain.

Maximal mid-expiratory flow (MMEF) and flows at different lung volumes are used as indices of small-airway function. They may reveal flow limitation before FEV1 becomes abnormal, but depend on effort, FVC, expiratory time and reference equations.[6, 7] Small-airway dysfunction and low DLCO may coexist through ventilation heterogeneity, gas trapping or early parenchymal injury. We examined whether MMEF was associated with isolated low DLCO after accounting for other flow indices, haemoglobin and major cardiopulmonary comorbidities, and whether it added information to a clinical model.

Zhou et al. recently reported an association between impaired DLCO and small-airway dysfunction, assessed using MMEF, FEF50, FEF75, impulse oscillometry and CT measures, in a broader cross-sectional population.[8] Their study did not restrict the analysis to preserved spirometry and did not evaluate whether spirometric flow indices provided incremental discrimination beyond routinely available clinical information. We therefore focused on the narrower

clinical problem of spirometry–gas-transfer discordance and used spline, mutually adjusted and AUC/NRI analyses to distinguish association from clinically meaningful incremental information.

Methods

Study design and data source

This single-centre retrospective cross-sectional study followed STROBE guidance.[9] We included eligible patients tested during admission to Xindu District People's Hospital of Chengdu from January to December 2025. No formal sample-size calculation was performed; the sample comprised all eligible patients in the prespecified period. The ethics committee approved retrospective use of routinely collected data (CXRY-IRB-AF-SW.08-02.1). Patients had provided general written consent for hospital care; separate study-specific consent was not obtained.

Pulmonary function measurements

Pulmonary function testing was performed by trained technicians using a MasterScreen system (Jaeger, Germany), in accordance with the 2025 Chinese recommendations for adult pulmonary function testing.[10] Bronchodilator testing was performed selectively when clinically indicated, rather than by a universal study protocol. In the classifiable primary cohort, 33 of 1338 participants (2.5%) underwent testing after salbutamol 200 µg; for the remaining 1305 (97.5%), the recorded spirometric values were single baseline (pre-bronchodilator) measurements. Recorded indices included FEV₁, FVC, FEV₁/FVC, MMEF, MEF25 and MEF50. In the MasterScreen nomenclature, MMEF corresponds to FEF25–75; MEF50 and MEF25 represent maximal expiratory flow at 50% and 25% of FVC remaining, respectively, corresponding to FEF50 and FEF75 when expressed according to expired volume. Inspiratory capacity/total lung capacity, residual volume % predicted, alveolar volume, KCO and single-breath DLCO were obtained during the same session.

Spirometric manoeuvres were assessed according to the 2019 ATS/ERS standardisation criteria and the 2025 Chinese recommendations.[11, 10] At least three acceptable forced expiratory manoeuvres were attempted. Repeatability was satisfactory when the differences between the two largest FVC values and between the two largest FEV₁ values were both ≤ 150 mL. GLI 2012 North-East Asian equations were used for FEV₁, FVC, FEV₁/FVC and MMEF.[12] For MEF50 and MEF25, the percentage-predicted values generated by the MasterScreen system under the centre's Chinese adult reference configuration were retained.

DLCO was measured using the single-breath technique according to the 2017 ERS/ATS technical standards.[1] An acceptable manoeuvre required an inspired volume of at least 90% of the largest vital capacity obtained during the same testing session, inhalation of at least 85% of the test-gas volume within 4 s, a stable breath-hold of 10 ± 2 s without leakage or a Valsalva or Müller manoeuvre, and completion of sample collection within 4 s of the start of exhalation.

At least two acceptable DLCO manoeuvres were obtained, with repeatability defined as a difference of < 2 mL·min⁻¹·mmHg⁻¹ (0.67 mmol·min⁻¹·kPa⁻¹); the mean of the two highest acceptable, repeatable measurements was reported, consistent with the 2025 Chinese recommendations.[10] Reference values for DLCO, alveolar volume and KCO (DLCO/alveolar volume) were derived from the GLI 2017 equations, as implemented in the MasterScreen system.[13] The instrument-reported DLCO values were not corrected for haemoglobin. Haemoglobin was included as a prespecified covariate in the primary analysis except when it was itself the exposure; a post hoc haemoglobin-corrected outcome was examined in sensitivity analysis.

Participants and outcome definition

Of 2455 patients with pulmonary-function data, 2134 had DLCO; 796 with abnormal spirometry were excluded. Among 321 without DLCO, 67 had preserved spirometry but an unclassifiable outcome. The cohort comprised 1338 patients: 514 with normal DLCO and 824 with isolated low DLCO. The primary outcome was DLCO < 80% predicted with preserved baseline/actual spirometric indices; <60% defined moderate-to-severe impairment in sensitivity analysis. Eligibility required age ≥ 18 years, testing during admission and data sufficient to classify spirometry, outcome and prespecified covariates. We retained the first complete, classifiable assessment. Preserved spirometry was defined as baseline/actual FEV₁ and FVC $\geq 80\%$ predicted and FEV₁/FVC ≥ 0.70 . This operational definition describes the available real-world measurements and is not intended to establish post-bronchodilator diagnostic status. Throughout, 'isolated' refers to preserved spirometric indices, not to absence of relevant comorbidity.

Exposures and covariates

The primary exposure was MMEF % predicted. Comparators were MEF25, MEF50, haemoglobin, alveolar volume and KCO. Small-airway dysfunction required at least two of MMEF, MEF50 and MEF25 to be < 65% predicted.[10] Prespecified covariates were age, sex, BMI, haemoglobin, smoking, emphysema, interstitial lung disease, chronic heart failure, pulmonary hypertension, pulmonary embolism, pneumonia and malignancy. Haemoglobin was omitted when examined as the exposure.

Statistical analysis

Continuous variables are reported as mean (standard deviation), median (interquartile range) or n (%), as appropriate. Groups were compared using t, Wilcoxon rank-sum, χ^2 or Fisher's exact tests. All tests were two-sided with $p < 0.05$. Analyses were performed using R version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Multivariable logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). We modelled dose-response relationships with natural cubic splines using four degrees of freedom and the median of each marker as the reference. Nonlinearity was assessed with a likelihood ratio test comparing the linear and spline models. In analyses stratified at 65 years of age, markers were standardised to one standard deviation; between-group differences were assessed by including an age-group interaction term.

Mutually adjusted models included MMEF and one comparator in the same model and estimated standardised effects within each age group. Incremental value was assessed using the area under the receiver operating characteristic curve (AUC), change in AUC, continuous net reclassification improvement (NRI) and mean calibration ratio. The 95% CI for continuous NRI was estimated from 100 bootstrap samples. To estimate the added information from haemoglobin itself, haemoglobin was excluded from its base model; its base AUC is therefore not directly comparable with those for the other markers. Internal validation used 1000 bootstrap resamples. We report apparent and optimism-corrected AUCs, calibration intercepts and calibration slopes, together with the number of invalid or non-convergent resamples. We prespecified that convergence failures would be reported rather than discarded without qualification, because resampled logistic models can be unstable when correlated predictors and sparse covariate-by-outcome cells produce quasi-separation.[22]

Sequential models were unadjusted; adjusted for age, sex and BMI; additionally adjusted for haemoglobin and smoking; and fully adjusted for prespecified comorbidities. Sensitivity analyses excluded emphysema, interstitial

lung disease or anaemia, used DLCO < 60%, used binary small-airway dysfunction, and repeated the primary MMEF analysis among participants with clearly normal baseline spirometry ($FEV_1 \geq 90\%$ predicted, $FVC \geq 90\%$ predicted and $FEV_1/FVC \geq 0.80$). Patients outside this subgroup, with at least one value in the boundary range of FEV_1 or FVC 80–<90% predicted or FEV_1/FVC 0.70–<0.80, were described separately. We also recalculated DLCO % predicted after multiplying predicted DLCO by $1.7 \times Hb / (10.22 + Hb)$ in males and $1.7 \times Hb / (9.38 + Hb)$ in females (Hb in $g \cdot dL^{-1}$), following 2017 ERS/ATS Cotes equations.[1] The corrected outcome used the < 80% threshold; haemoglobin was omitted to avoid mathematical double adjustment. Primary analyses used complete cases.

Bias and missing data

We selected covariates a priori on clinical grounds rather than according to univariable statistical significance. The adjustment set included age, sex, BMI, haemoglobin, smoking status and cardiopulmonary comorbidities with a plausible influence on DLCO. Emphysema, interstitial lung disease, pulmonary hypertension and other comorbidities were identified from the medical history recorded at admission.

In the primary cohort, missing values were present for haemoglobin and anaemia status (44, 3.29%), albumin (17, 1.27%), MEF25 and binary small-airway dysfunction (six each, 0.45%), smoking status (four, 0.30%) and MMEF (three, 0.22%); all other Table 1 variables were complete. A haemoglobin-corrected DLCO outcome could be calculated for 1294 patients before marker- and covariate-specific complete-case restrictions. Primary regressions used complete cases; sensitivity analyses imputed covariates alone and then both markers and covariates. Among patients with preserved spirometry, 67 (4.8%) lacked DLCO and could not be assigned an outcome. Because DLCO defined the outcome, it was not imputed.

Discrimination and reclassification used the same sample. Only 649–650 of 1000 internal-validation bootstrap resamples produced convergent models and valid predictions. This failure frequency has no established acceptable benchmark; it may reflect the combined effects of correlated flow indices and sparse cells for less common comorbidities in resampled data, including quasi-separation. Optimism-corrected results were therefore considered exploratory.[22]

Results

Study population

Of 2455 patients with pulmonary-function data, 2134 had DLCO. Excluding 796 with abnormal spirometry left 1338 with preserved spirometry and a classifiable outcome: 824 with isolated low DLCO and 514 with normal DLCO (Fig. 1). Another 67 had preserved spirometry but lacked DLCO. Isolated low DLCO accounted for 61.6% of the classifiable primary cohort; the 824 cases represented 33.6% of the source population.

Baseline characteristics

Participants had a mean age of 64.2 years, and 48.7% were male. Those with isolated low DLCO were older and had lower mean BMI, haemoglobin, albumin, FEV_1 , FVC and FEV_1/FVC % predicted than those with normal DLCO. MMEF, MEF25, MEF50, alveolar volume and KCO were also lower. Small-airway dysfunction, anaemia, emphysema, chronic heart failure and pulmonary hypertension were more common in the isolated-low-DLCO group; smoking-status distribution was similar (Table 1).

Table 1
Baseline characteristics of the primary analysis cohort

Characteristic	Overall (N = 1338)	Normal DLCO (n = 514)	Isolated low DLCO (n = 824)	p-value
Age, mean (SD), years	64.2 (13.5)	60.4 (12.7)	66.6 (13.4)	< .001
BMI, mean (SD), kg·m ⁻²	24.0 (3.4)	24.8 (3.4)	23.5 (3.3)	< .001
Haemoglobin, mean (SD), g·L ⁻¹	130.2 (17.3)	136.5 (14.8)	126.3 (17.7)	< .001
Albumin, mean (SD), g·L ⁻¹	41.4 (3.7)	42.2 (3.5)	40.8 (3.7)	< .001
FEV1, mean (SD), % predicted	104.0 (16.4)	106.9 (16.4)	102.3 (16.2)	< .001
FVC, mean (SD), % predicted	104.1 (14.4)	107.0 (14.6)	102.4 (14.0)	< .001
FEV1/FVC, mean (SD), % predicted	95.3 (9.1)	96.3 (8.5)	94.7 (9.4)	.001
MMEF, median (IQR), % predicted	69.1 (51.5–90.7)	75.5 (56.6–98.3)	66.4 (47.9–85.3)	< .001
MEF50, median (IQR), % predicted	75.2 (56.9–98.1)	82.9 (61.8–104.8)	71.5 (53.6–92.3)	< .001
MEF25, median (IQR), % predicted	65.7 (48.6–89.7)	69.0 (51.2–92.7)	63.1 (46.7–87.6)	.004
Alveolar volume, mean (SD), % predicted	91.0 (12.3)	96.4 (11.2)	87.7 (11.8)	< .001
KCO (DLCO/VA), median (IQR)	1.2 (1.1–1.4)	1.4 (1.3–1.6)	1.1 (0.9–1.3)	< .001
Length of stay, median (IQR), days	7.8 (5.9–10.6)	7.7 (5.9–10.0)	7.9 (6.0–10.9)	.077
Hospital costs, median (IQR), CNY	7593.4 (4940.1–15417.7)	7127.9 (4462.2–16052.9)	7777.4 (5150.4–14775.2)	.090
Male	651 (48.7)	265 (51.6)	386 (46.8)	.105
Smoking status: never	1018 (76.3)	400 (78.4)	618 (75.0)	.292
Smoking status: former	111 (8.3)	36 (7.1)	75 (9.1)	
Smoking status: current	205 (15.4)	74 (14.5)	131 (15.9)	
Small-airway dysfunction	558 (41.9)	183 (35.6)	375 (45.8)	< .001
Anaemia	405 (31.3)	81 (16.4)	324 (40.4)	< .001
Emphysema	124 (9.3)	28 (5.4)	96 (11.7)	< .001
Interstitial lung disease	33 (2.5)	7 (1.4)	26 (3.2)	.061
Chronic heart failure	48 (3.6)	9 (1.8)	39 (4.7)	.007
Pulmonary hypertension	35 (2.6)	6 (1.2)	29 (3.5)	.014
Pulmonary embolism	3 (0.2)	2 (0.4)	1 (0.1)	.562
Pneumonia	708 (52.9)	260 (50.6)	448 (54.4)	.196

Characteristic	Overall (N = 1338)	Normal DLCO (n = 514)	Isolated low DLCO (n = 824)	p-value
Malignancy	243 (18.2)	89 (17.3)	154 (18.7)	.575
ICU admission	29 (2.2)	10 (1.9)	19 (2.3)	.805

Data are mean (standard deviation), median (interquartile range) or n (%). Percentages use the non-missing observations for each variable as the denominator. p-values were obtained using the t-test, Wilcoxon rank-sum test, chi-squared test or Fisher's exact test, as appropriate.

Dose–response relationships for continuous markers

Lower MMEF, MEF25, MEF50, haemoglobin, alveolar volume and KCO were each associated with isolated low DLCO. We found no clear departure from linearity for MMEF, MEF25, MEF50, haemoglobin or alveolar volume (p for nonlinearity = 0.084, 0.212, 0.190, 0.094 and 0.088, respectively). The association with KCO was nonlinear (p = 0.004) (Fig. 2). Estimates at the extremes of each distribution were imprecise, as indicated by wider confidence intervals.

Age-stratified analyses

The adjusted OR per one-standard-deviation increase in MMEF was 0.69 (95% CI 0.57–0.84) among patients aged < 65 years and 0.77 (95% CI 0.64–0.92) among those aged ≥ 65 years (p for interaction = 0.330). Associations for MEF50, haemoglobin and alveolar volume pointed in the same direction in both groups, without clear evidence of interaction. MEF25 was more strongly associated with the outcome in the younger group, whereas KCO showed a stronger association in the older group (p for interaction = 0.043 and 0.006, respectively; Fig. 3 and supplementary table S1). Given the number of markers tested, these interactions should be considered exploratory.

Mutually adjusted analyses

When MMEF and either MEF25 or MEF50 were entered together, estimates for both flow indices were attenuated, with statistical significance depending on age group and comparator. With MEF25 in the model, the OR for MMEF was 0.73 (95% CI 0.50–1.07) in the younger group and 0.64 (95% CI 0.47–0.89) in the older group. With MEF50 in the model, the corresponding ORs were 0.67 (95% CI 0.37–1.19) and 0.87 (95% CI 0.53–1.45). Associations with haemoglobin, alveolar volume and KCO generally persisted, whereas the MMEF association weakened in some models (Fig. 4 and supplementary table S2). This instability is compatible with the substantial collinearity among small-airway flow indices and offers no consistent evidence that one measure is independently superior. Analyses using MEF25 or MEF50 as the reference marker are provided in supplementary tables S3 and S4.

Incremental model performance

In the complete-case sample, adding MMEF increased the AUC from 0.741 to 0.748, a change of 0.008, and produced a continuous NRI of 0.26 (95% CI 0.13–0.34). The AUC changes for MEF25 and MEF50 were 0.003 and 0.007, respectively. The corresponding changes for haemoglobin, alveolar volume and KCO were 0.040, 0.075 and 0.151 (Table 2). Because KCO is calculated from DLCO, its higher AUC and reclassification performance largely reflect mathematical coupling with the outcome and should not be interpreted as independent predictive ability.

Table 2
Incremental discrimination of physiological markers beyond the clinical model

Added marker	N	Base-model AUC	AUC after adding marker	Change in AUC	Continuous NRI (95% CI)	Event component (95% CI)	Non-event component (95% CI)	Mean calibration ratio
MMEF, % predicted	1287	0.741	0.748	+ 0.008	0.26 (0.13–0.34)	0.25 (0.20–0.30)	0.01 (–0.07–0.07)	1.000
MEF25, % predicted	1284	0.740	0.744	+ 0.003	0.23 (0.11–0.34)	0.34 (0.26–0.40)	-0.11 (–0.19––0.03)	1.000
MEF50, % predicted	1290	0.742	0.749	+ 0.007	0.24 (0.12–0.38)	0.22 (0.15–0.29)	0.02 (–0.05–0.11)	1.000
Haemoglobin, g·L ⁻¹	1290	0.702	0.742	+ 0.040	0.34 (0.23–0.49)	0.12 (0.05–0.19)	0.21 (0.16–0.31)	1.000
Alveolar volume, % predicted	1290	0.742	0.817	+ 0.075	0.68 (0.59–0.83)	0.41 (0.35–0.48)	0.28 (0.22–0.37)	1.000
KCO (DLCO/VA)	1290	0.742	0.893	+ 0.151	1.09 (1.01–1.20)	0.57 (0.51–0.62)	0.52 (0.45–0.60)	1.000

Confidence intervals for continuous NRI were estimated from 100 bootstrap samples. Changes in AUC were calculated from unrounded estimates. Haemoglobin was omitted from the base model in the haemoglobin row; all other base models contained the prespecified clinical covariates. Because KCO is calculated from DLCO, its apparent discrimination cannot be considered independent of DLCO.

Sequential models and sensitivity analyses

The MMEF OR per 10-percentage-point decrease was 1.12 (95% CI 1.07–1.16) unadjusted and 1.11 (1.06–1.16) fully adjusted. After haemoglobin correction, 701 of 1287 complete cases had the corrected outcome and the MMEF OR was 1.13 (1.08–1.18). Corrected-outcome ORs were 1.05 for MEF25, 1.14 for MEF50, 2.29 for alveolar volume and 2.21 for KCO; the haemoglobin OR attenuated from 1.46 to 1.00 (0.93–1.08; $p = 0.965$). Excluding emphysema, interstitial lung disease or anaemia yielded MMEF ORs of 1.12, 1.12 and 1.10. The OR was 1.16 (1.09–1.25) for $\text{DLCO} < 60\%$ and 1.29 (1.00–1.68; $p = 0.050$) for binary small-airway dysfunction. Among the 938 participants with clearly normal baseline spirometry, the fully adjusted analysis included 905 complete cases and gave an MMEF OR of 1.11 (1.05–1.18) per 10-percentage-point decrease. Of the 1305 participants without bronchodilator testing, 927 (71.0%) met these clearly normal baseline criteria, whereas only 11 of 33 (33.3%) selectively tested participants did so ($p < 0.0001$). The remaining 400 of 1338 participants (29.9%) had at least one boundary-range spirometric value and were retained in the primary real-world cohort but not in this restrictive sensitivity analysis.

In analyses of missing data, the ORs for MMEF were 1.11 in complete cases, 1.10 after covariate imputation and 1.10 after imputation of both markers and covariates; conclusions for the other markers were materially unchanged (supplementary table S7). The apparent and optimism-corrected AUCs for the clinical base model were 0.742 and 0.732. After MMEF was added, they were 0.748 and 0.738, with a calibration intercept of 0.003 and slope of 0.937

(supplementary table S8). Only 649–650 of 1000 bootstrap samples were valid for each model, however, so the corrected estimates should be interpreted as exploratory rather than as stable prediction-performance estimates.

Discussion

In 1338 hospitalised patients with preserved spirometry, lower MMEF was associated with isolated low DLCO after adjustment for demographic factors, haemoglobin, smoking and cardiopulmonary comorbidities. Estimates were similar after haemoglobin correction, exclusions and missing-data analyses. MMEF did not consistently outperform MEF25 or MEF50, and increased AUC by only 0.008. Thus, a low MMEF may raise suspicion of impaired gas transfer but is inadequate as a stand-alone screen.

Isolated low DLCO is a physiological pattern, not a disease entity or evidence that comorbid disease is absent. It is common in people with HIV and moderate-to-severe impairment has been associated with mortality.[14] In symptomatic veterans with preserved spirometry, baseline DLCO identified those who later deteriorated functionally.[15] Spirometry–gas-transfer discordance also occurs after pneumonia and in long COVID.[16, 17] Across these settings, preserved spirometry does not ensure preserved gas exchange.

Several mechanisms could account for the association between MMEF and DLCO. Narrowing or closure of small airways produces uneven ventilation and may reduce the contribution of poorly ventilated alveolar units during a single-breath DLCO manoeuvre. Early emphysema or peribronchiolar injury may simultaneously impair expiratory flow and reduce alveolar–capillary surface area. In an 8-year population study, Maio et al. found that nitrogen-washout measures of ventilation heterogeneity were associated with subsequent declines in DLCO and KCO.[18] Our cross-sectional data are compatible with these observations, but cannot show whether small-airway dysfunction precedes impaired gas transfer or whether both reflect the same underlying lung injury.

This direction of association is consistent with Zhou et al., who found that impaired DLCO and small-airway dysfunction coexisted in a broader cross-sectional population.[8] Our findings add a more restricted clinical perspective: in patients whose baseline spirometric indices were preserved, MMEF retained an adjusted association with low DLCO, including in the clearly normal baseline sensitivity analysis, but its incremental discrimination was minimal. Thus, the data support association rather than a clinically actionable prediction role for MMEF.

MMEF remains a difficult measurement to interpret in isolation. It varies with FVC, expiratory duration and effort, and shows greater within-person and between-person variability than FEV1. Percentage-predicted cut-offs may also misclassify individuals according to age, sex or body size.[7] We therefore do not interpret a low MMEF as diagnostic of small-airway disease. In otherwise preserved spirometry, it is better regarded as a prompt to review manoeuvre quality and, when clinically appropriate, to measure gas transfer.[19]

The results for alveolar volume and KCO require a different interpretation from those for candidate spirometric markers. DLCO is determined partly by the alveolar volume participating in the manoeuvre and by carbon monoxide transfer efficiency per unit lung volume; KCO is not simply DLCO corrected for volume.[20] Because KCO is calculated as DLCO divided by alveolar volume and our outcome was defined by a DLCO threshold, its high AUC is partly built into the mathematics. It should not be taken as evidence of independent predictive ability. MMEF is not part of the outcome definition, so its added performance—although small—is the more relevant result to test in an independent cohort.

The 0.008 AUC increase indicates little added discrimination. Continuous NRI was 0.26, but depends on prevalence, the base model and overfitting; improvement arose mainly in events, with little non-event gain.[21] Bootstrap

correction yielded AUC 0.738 and calibration slope 0.937, while about 35% of resamples failed. There is no accepted literature-based failure-rate threshold that would make this frequency routine or reassuring. In logistic bootstrap samples, correlated predictors and sparse covariate-by-outcome cells can lead to quasi-separation and non-convergence.[22] The model therefore cannot support individual risk estimates or testing decisions. External validation, preferably with a penalised modelling strategy if convergence remains problematic, and decision-curve analysis are needed.[23, 22]

MMEF showed no clear interaction with age group. Interaction p-values were 0.043 for MEF25 and 0.006 for KCO, but these findings arose from several marker comparisons using a dichotomised age variable without adjustment for multiplicity. They should be treated as hypothesis-generating, not as support for age-specific cut-offs. Future work should model age continuously and prespecify nonlinear interaction analyses.

Limitations should be interpreted first in light of bronchodilator testing. Only 33 of 1338 participants (2.5%) underwent selective bronchodilator testing, and preserved spirometry was therefore classified from baseline/actual measurements for most participants. This is an inherent feature of retrospective real-world hospital data, not evidence of a uniformly standardised post-bronchodilator protocol. Selective testing appeared to target patients nearer the fixed spirometric thresholds: among those without testing, 71.0% had all three baseline indices clearly normal, compared with 33.3% of tested participants. The consistent MMEF association in the clearly normal baseline sensitivity analysis reduces, but cannot eliminate, concern about spirometric misclassification. Cross-sectional data cannot establish temporality, and residual confounding and selection bias are possible. Test-level quality grades and tracings were unavailable. Instrument-reported DLCO was not haemoglobin corrected; the post hoc analysis used recorded haemoglobin. Fixed percentage-predicted thresholds and $FEV_1/FVC \geq 0.70$, rather than GLI lower limits of normal, may cause age-related misclassification. GLI 2017 DLCO equations were derived predominantly from Caucasian populations, with uncertain applicability in Chinese populations.[13, 10] Comorbidity coding, cumulative smoking and computed-tomography findings could not be fully verified. Collinearity destabilised mutually adjusted coefficients, and bootstrap failures plus absent external validation may leave performance overestimated.

The findings are most applicable when symptoms or clinical history already justify concern despite preserved spirometry. In that setting, a low MMEF could strengthen the case for DLCO measurement, interpreted alongside haemoglobin, thoracic imaging and cardiopulmonary findings. A prospective study should determine whether this targeted approach improves diagnostic yield or resource use without missing clinically important gas-transfer impairment.

Conclusion

Among patients with preserved spirometry, lower MMEF was associated with isolated low DLCO but added little discrimination beyond clinical variables. It may prompt gas-transfer assessment but should not guide diagnosis or individual risk prediction. Longitudinal study and external validation are required.

Abbreviations

ATS

American Thoracic Society

AUC

area under the receiver operating characteristic curve

BMI
body mass index
CI
confidence interval
DLCO
diffusing capacity for carbon monoxide
ERS
European Respiratory Society
FEV₁
forced expiratory volume in 1 second
FVC
forced vital capacity
GLI
Global Lung Function Initiative
KCO
carbon monoxide transfer coefficient
MMEF
maximal mid-expiratory flow
NRI
net reclassification improvement
OR
odds ratio
VA
alveolar volume.

Declarations

Ethics approval and consent to participate The Ethics Committee of Xindu District People's Hospital of Chengdu approved the study protocol and the retrospective use of routinely collected clinical data (CXRY-IRB-AF-SW.08-02.1). Patients had provided general written consent for hospital care at admission; no separate study-specific informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Patient and public involvement Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this retrospective study using routinely collected data.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because they contain potentially identifiable clinical information, but are available from the corresponding author on reasonable request and subject to ethics approval and institutional policy.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LL conceived and designed the study, acquired, analysed and interpreted the data, and drafted the manuscript. LH conceived and designed the study, acquired, analysed and interpreted the data, and drafted the manuscript. XZ contributed to data extraction. XG contributed to study conception. All authors critically revised the manuscript, read and approved the final manuscript. LL is the guarantor and takes responsibility for the integrity and accuracy of the data.

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Figures

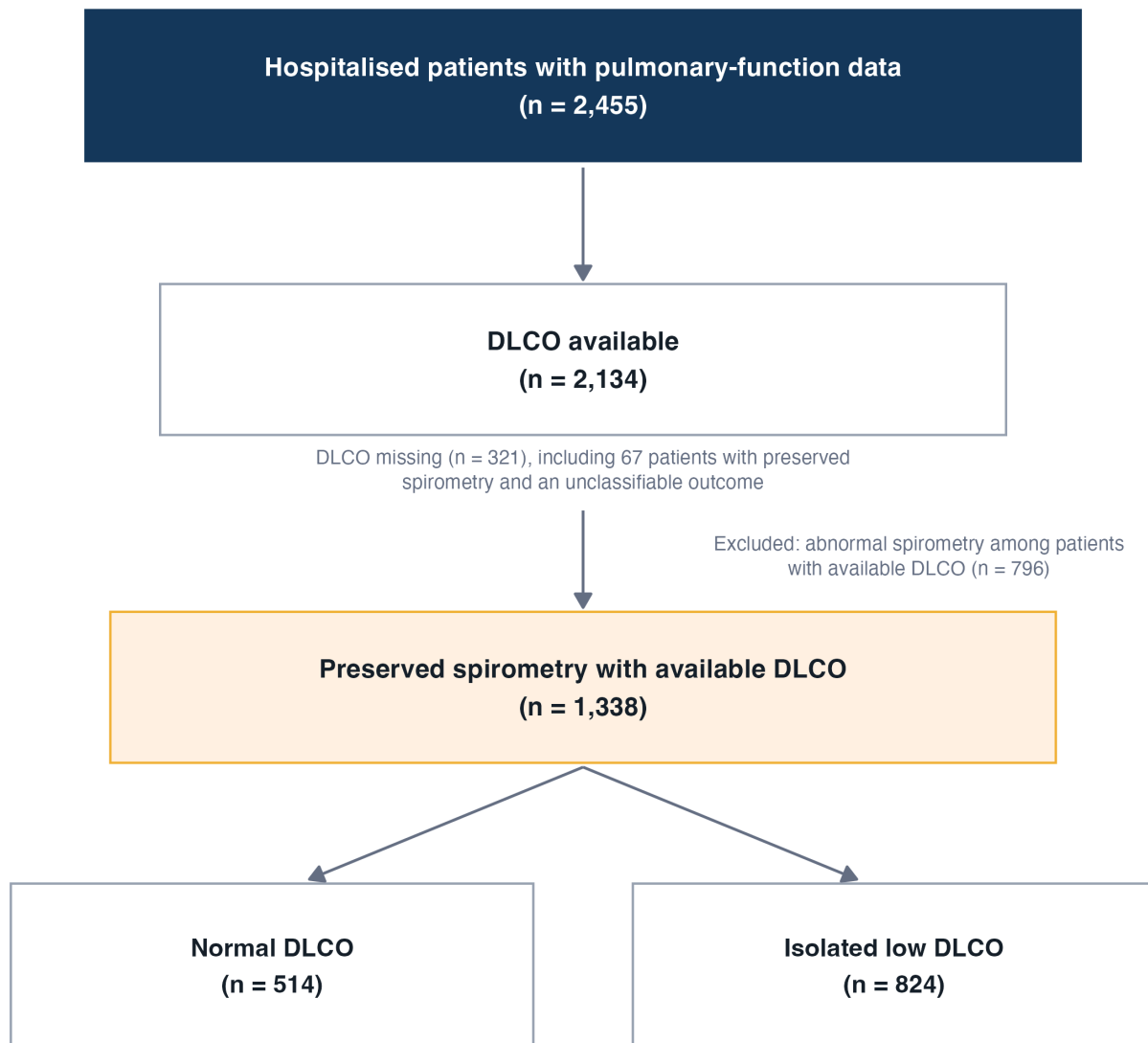


Figure 1

Participant flow diagram

Of 2455 patients with pulmonary-function data, 321 lacked DLCO measurements; 67 of these had preserved spirometry but an unclassifiable outcome. Among 2134 patients with DLCO, 796 with abnormal spirometry were excluded, leaving the primary cohort of 1338 patients.

Adjusted association of physiologic markers with iso-DLCO

Odds ratios are relative to the median marker value

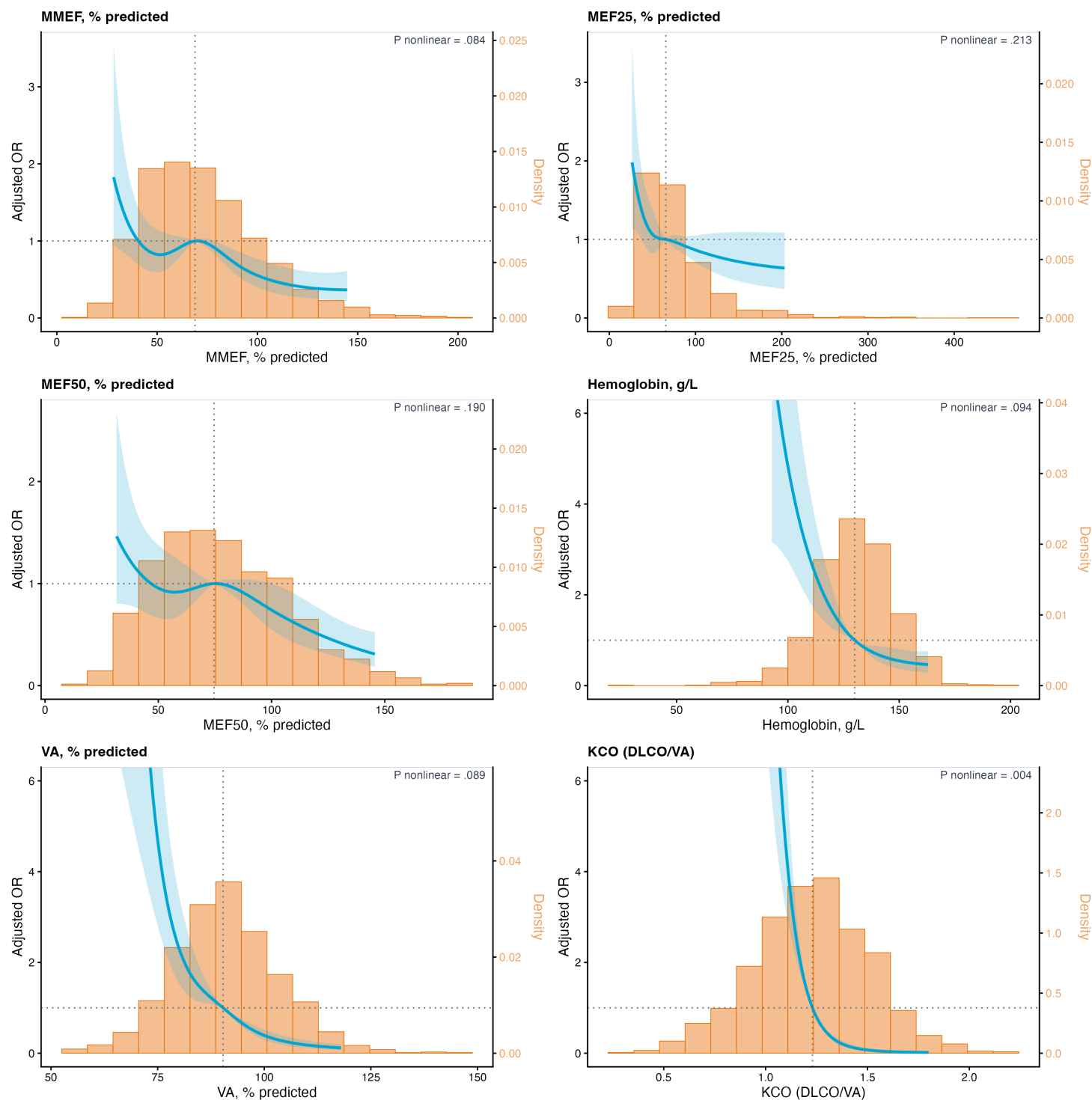


Figure 2

Adjusted dose–response relationships between continuous physiological markers and isolated low DLCO

Blue curves show adjusted ORs relative to the median of each marker; shaded areas show 95% CIs and orange histograms show the sample distributions. Models used natural cubic splines with four degrees of freedom and adjusted for prespecified clinical covariates. Confidence intervals widen at the extremes.

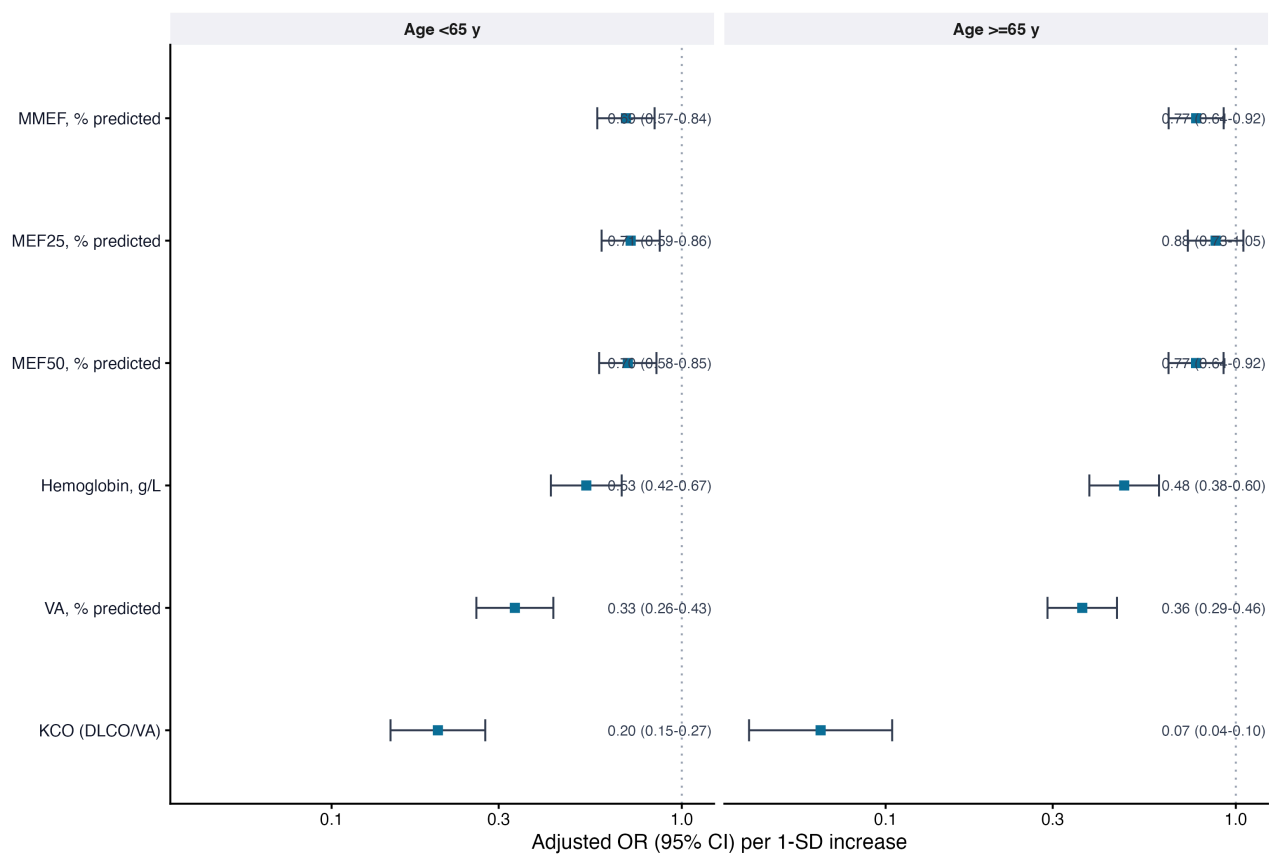


Figure 3

Standardised marker associations stratified by age

ORs are shown per one-standard-deviation increase in each marker. Interaction p-values were 0.043 for MEF25 and 0.006 for KCO; all other interaction p-values exceeded 0.05.

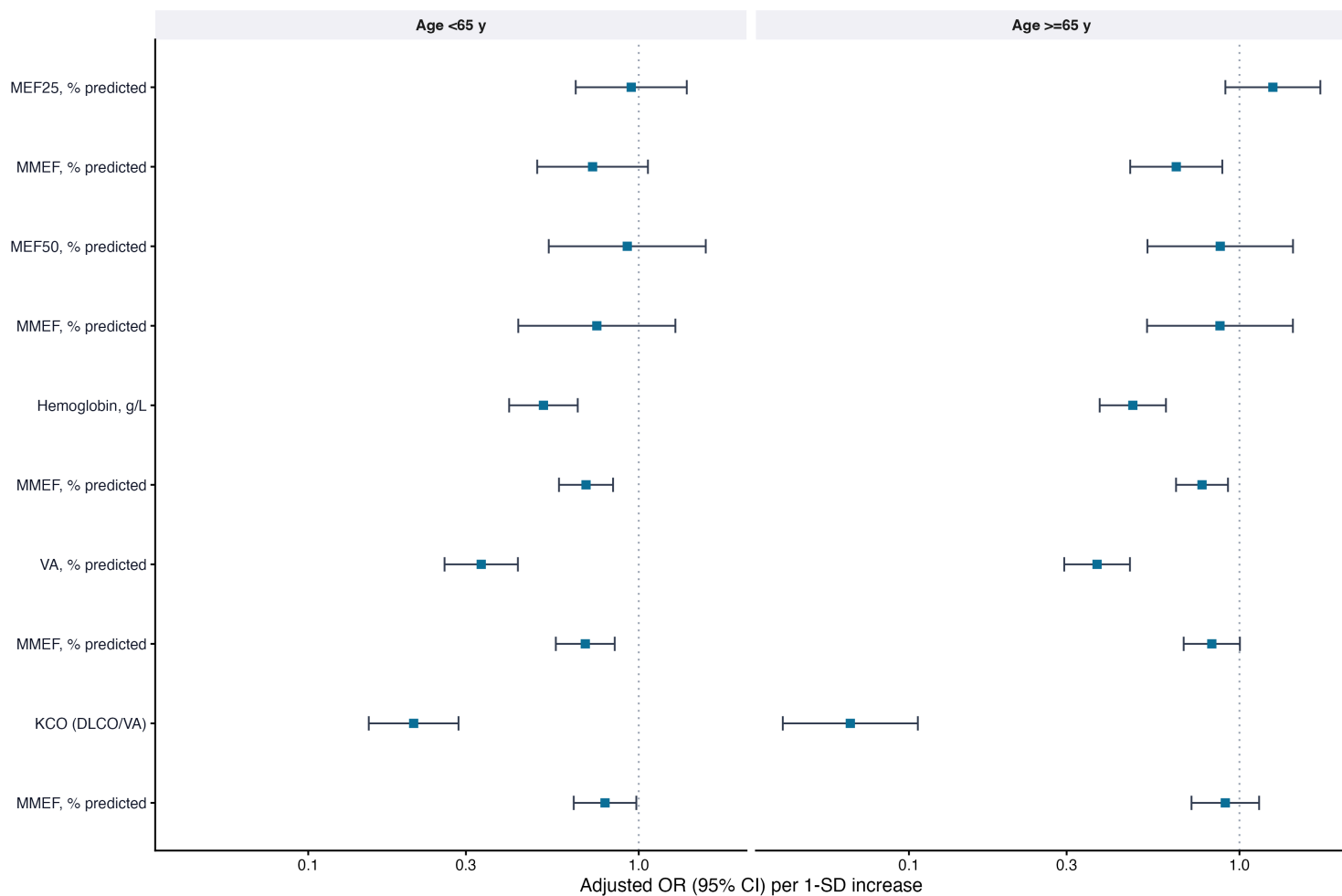


Figure 4

Mutually adjusted models using MMEF as the reference marker

Each model included MMEF and one comparator, with adjustment for the remaining prespecified covariates. Models A–E compared MMEF with MEF25, MEF50, haemoglobin, alveolar volume and KCO, respectively.

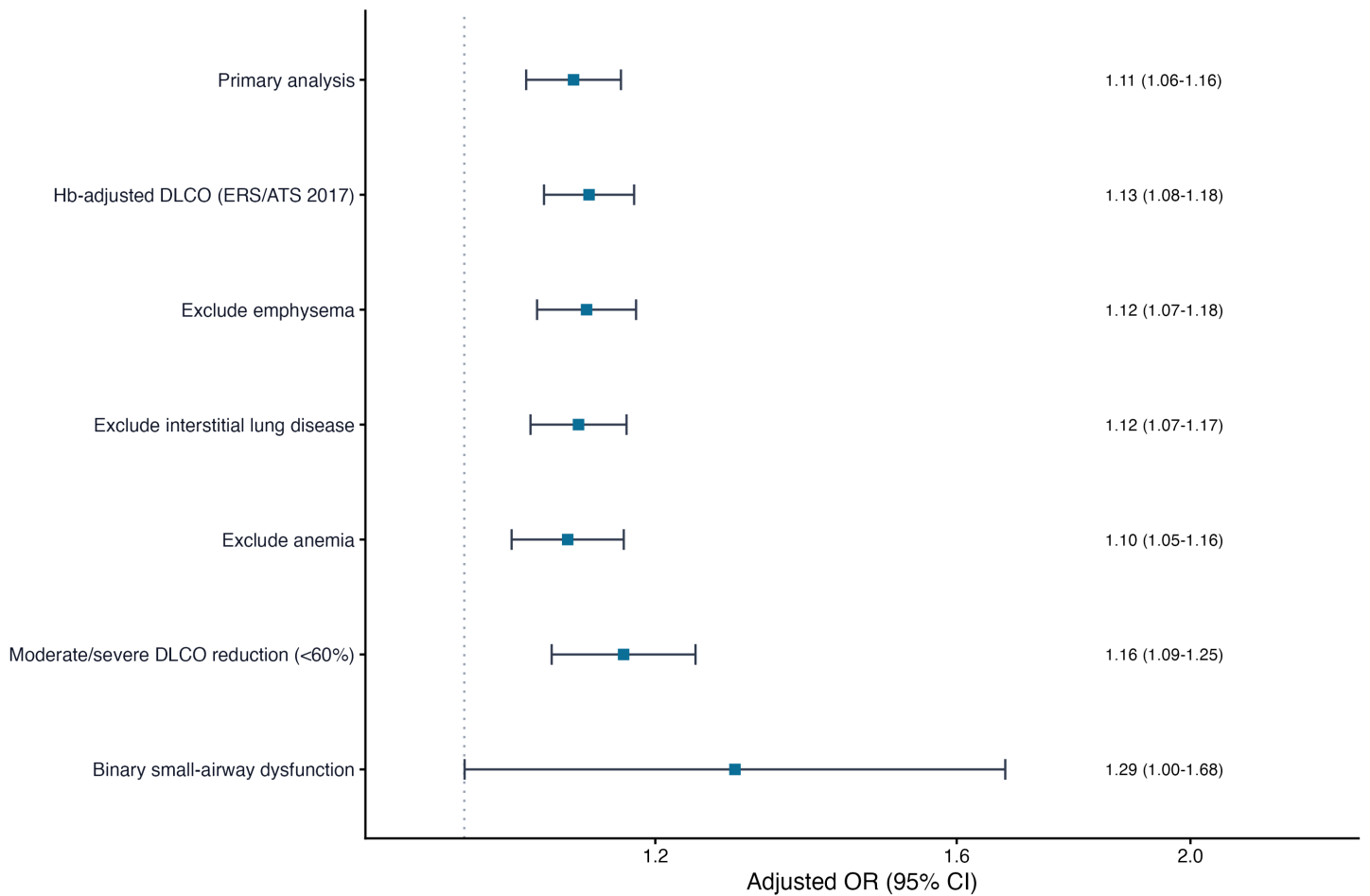


Figure 5

Primary and sensitivity analyses for MMEF

Effects for continuous MMEF are reported per 10-percentage-point decrease; binary small-airway dysfunction compares its presence with its absence. For the ERS/ATS haemoglobin-corrected analysis, predicted DLCO was adjusted with the sex-specific Cotes equations, DLCO % predicted and the <80% outcome were recalculated, and haemoglobin was omitted from the covariate set.