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Understanding risk of poor outcomes in adults hospitalised with respiratory syncytial virus infection: evidence from a multicentre UK cohort

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ABSTRACT

Background Respiratory syncytial virus (RSV) causes substantial winter pressure on adult services. In the UK, RSV vaccination currently targets adults aged ≥75 years and care home residents; it remains uncertain whether this age criterion alone meaningfully discriminates risk of poor outcome among adults hospitalised with RSV.

Methods We pooled three UK hospital cohorts (one prospective, two retrospective) of adults admitted with acute respiratory infection (ARI) and PCR-confirmed RSV. The primary outcome was intensive care unit/high dependency unit (ICU/HDU) admission or all-cause mortality within 60 days. Prespecified predictors (age, sex and comorbidities) entered a least absolute shrinkage and selection operator (LASSO) penalised logistic regression; selected variables were refitted using standard logistic regression. Discrimination, calibration and decision-analytic performance were assessed using 1000-bootstrap internal validation and decision-curve analysis.

Results Among 334 adults, 37 (11.1%) experienced the primary outcome. An age-only rule mirroring current UK vaccine age-eligibility (≥75 years) demonstrated only modest discrimination (optimism-adjusted area under the receiver operating characteristic curve (AUC) 0.58, 95% CI 0.48 to 0.65) and a compressed distribution of predicted risks. A four-predictor model—including age, COPD, active/previous cancer and dementia—achieved higher discrimination AUC (0.77 (0.69 to 0.85)), a wider spread of predicted risks and the greatest net benefit across clinically plausible escalation thresholds (5–20%).

Conclusions In adults hospitalised with RSV-associated ARI, simple age-based heuristics—including the UK ≥75-year threshold—showed only modest ability to discriminate risk of ICU/HDU admission/60-day mortality once hospitalised. Comorbidity-inclusive approaches may provide more informative hospital-level risk stratification and warrant evaluation in future RSV vaccine-effectiveness and outcome studies. Any application requires external validation, more systematic RSV testing and comparison with physiology-based scores in larger, vaccinated cohorts.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ UK respiratory syncytial virus (RSV) vaccination policy prioritises age (≥75 years) and care home residence; it is unclear whether age alone meaningfully discriminates risk among adults once hospitalised with RSV.

WHAT THIS STUDY ADDS

⇒ Current UK age-based vaccine eligibility (≥75 years) and other age-only rules showed only modest discrimination for poor outcome once hospitalised, whereas a simple four-factor model—age plus chronic obstructive pulmonary disease, cancer and dementia—demonstrated higher internally validated performance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings support consideration of comorbidity-stratified analyses in future RSV prevention and vaccine-effectiveness studies, rather than reliance on age thresholds alone.

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of acute respiratory infection (ARI) and winter healthcare pressure in older adults,[1] with an estimated 470 000 hospital admissions and 33 000 in-hospital deaths annually among adults aged ≥60 years in high-income countries.[2] Under-diagnosis—particularly in older adults—likely means that the true burden is greater than currently recognised.[2–7]

Both age and comorbidity contribute substantially to the risk of severe RSV outcomes. In US

population-based surveillance, RSV hospitalisation incidence rose from 7.7 to 11.9 per 100 000 at ages 18–49 years to 136.9–255.6 per 100 000 among those aged ≥65 years.[8] Chronic conditions such as chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease (CKD), diabetes and malignancy confer additional independent risk. In some cohorts, younger adults with these comorbidities experience post-hospitalisation mortality comparable to—or exceeding—that of older adults without comorbidity.[9] There are no specific treatments, making accurate early risk stratification central to clinical decision-making and service planning.

Prefusion F-protein vaccines (Arexvy, Abrysvo, mRESVIA) have transformed prevention strategies. Vaccination policies vary internationally. In the USA, the Centers for Disease Control and Prevention recommends vaccination for all adults ≥75 years and for those aged 50–74 years with high-risk comorbidities.[10] Across Europe, authorities generally recommend vaccination for adults ≥60 years and/or those with chronic conditions.[4] However, pivotal trials primarily evaluated prevention of RSV lower respiratory tract disease, used heterogeneous case definitions and under-represented hospitalised adults and outcomes such as intensive care unit (ICU) admission or death.[4 11–14] Real-world evidence is encouraging: a large US test-negative study reported 87–89% vaccine effectiveness against RSV-related hospitalisation or emergency visits in adults ≥60 years.[15]

In the UK, initial vaccine eligibility was restricted to ages 75–79 years on cost-effectiveness grounds.[16] Mid-season evaluation demonstrated ≈30% reductions in RSV hospitalisation in this age group—consistent with implied vaccine effectiveness of ~70% at observed uptake.[17] End-of-season sentinel data similarly suggested high effectiveness (~82% against RSV hospitalisation).[18] Current UK policy now includes all adults ≥75 years and care-home residents, with modelling indicating that targeting ≥80 years may be even more cost-effective.[19] Younger adults with comorbidities are not currently included in UK adult RSV vaccination eligibility criteria.

Whether age-based vaccine eligibility criteria alone meaningfully discriminate risk among adults already hospitalised with RSV-associated ARI remains uncertain.[20–22] We therefore undertook an exploratory analysis of a multicentre UK cohort of adults hospitalised with PCR-confirmed RSV to: (1) identify demographic and clinical predictors of poor outcome—defined as ICU/high dependency unit (HDU) admission or all-cause mortality within 60 days and (2) compare age-based and comorbidity-based risk models for discrimination and clinical utility. Rather than proposing a new eligibility policy, this analysis examines whether simple age-band heuristics meaningfully discriminate risk once adults are hospitalised with RSV.

METHODS

Study design and data sources

We undertook a pooled individual participant analysis of adults admitted to UK hospitals with ARI and PCR-confirmed RSV. ARI was defined as an acute upper or lower respiratory illness (eg, rhinitis, pneumonia) or an acute exacerbation of chronic respiratory disease (eg, COPD, asthma), diagnosed by the treating clinician based on respiratory symptoms.

Three cohorts contributed data: (1) UNIVERSAL[23] (prospective, 10 National Health Service (NHS) hospitals, August 2022–November 2024); (2) Royal Devon & Exeter (retrospective, PCR testing, January 2023–January 2024) and (3) Manchester (retrospective, microbiology databases, November–December 2023). Cohorts were non-overlapping.

Due to varying recruitment periods and testing strategies, the pooled cohort should be interpreted as a convenience sample of RSV-tested adults, not a nationally representative population. Additional methodological details are provided in the online supplemental Methods.

Eligibility criteria

Inclusion: age ≥18 years, hospital admission for ARI, RSV detected by PCR within 36 hours. Exclusion: viral co-infection, non-ARI primary admission reason, emergency department (ED) or ambulatory care only, prior RSV vaccination.

Predictors

We recorded age, sex and prespecified comorbidities: COPD, asthma, interstitial lung disease, bronchiectasis, heart failure, CKD, chronic liver disease, diabetes (type 1 or 2), active/previous cancer, rheumatological disease, dementia and HIV. These were defined using clinician-documented diagnoses at or before admission. Transplant status and treatment-related immunosuppression were not included as candidate predictors because these exposures were incompletely and inconsistently recorded across contributing cohorts and could not be harmonised reliably.

To examine pragmatic, policy-aligned risk strategies, three binary indicators were defined: age ≥75 years (UK vaccine eligibility), age ≥60 years (international threshold) and ≥1 core comorbidity (COPD, heart failure, diabetes, cancer, CKD) based on prior evidence.[9]

Outcome

The primary outcome was a composite of ICU/HDU admission or all-cause mortality within 60 days of hospital admission. ICU/HDU admission captures acute physiological deterioration requiring escalation of care, while 60-day mortality represents severe outcomes among patients potentially excluded from critical care due to frailty or comorbidity. 60-day mortality was ascertained from hospital electronic records and administrative systems.

Missing data and sample size

Predictor data were complete. Six participants (1.8%) lacked primary outcome data, leaving 334 for analysis. Sample size adequacy was assessed using pmsampsize,[24] assuming an anticipated C-statistic of 0.80, outcome prevalence of 0.11 and a target shrinkage factor ≥0.90. This required a minimum of 280 participants with ≥32 outcome events, which was met by the final cohort (n=334; 37 events), though precision for individual coefficients was limited.

Statistical analysis

This analysis was conducted as a prediction model development study rather than a hypothesis-testing exercise. Reporting follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement.[25] Interpretation was directed primarily towards bootstrap-validated model-level performance (discrimination, calibration and clinical utility), with coefficient estimates reported descriptively rather than interpreted as confirmatory evidence of association.

Univariable p values were not used for predictor screening. Four logistic models were evaluated: (a) age≥75 years; (b) age≥60 years; (c)≥1 core comorbidity and (d) a multivariable model derived by penalised selection.

Model D predictors were selected using least absolute shrinkage and selection operator (LASSO) penalised logistic

regression, with the penalty parameter (λ_min) selected via 10-fold cross-validation. Selected predictors were refitted using standard logistic regression to obtain ORs and predicted probabilities. Penalised estimates were not used for interpretation or clinical utility.

Firth's penalised logistic regression was used solely as a sensitivity analysis to assess robustness to small cell counts and potential separation and was not used for variable selection or prediction.

To characterise uncertainty arising from data-driven selection, three complementary analyses were undertaken: (1) bootstrap stability selection (B=1000) to quantify selection frequencies at λ_min; (2) selective-inference estimation using fixedLassoInf, presented descriptively and not used for predictor inclusion or prediction and (3) a pipeline bootstrap sensitivity analysis (B=1000) repeating selection and refitting within resamples to quantify optimism attributable to the full modelling process. These robustness analyses were undertaken to characterise stability and uncertainty in model development and were not used to guide predictor inclusion or redefine the primary model.

Prespecified sensitivity analyses examined alternative representations of age (age ≥60 years, age ≥75 years and exclusion of age) to reflect vaccine-policy-relevant formulations rather than define additional primary models.

Given the modest event count, penalisation and bootstrap internal validation were used to limit and quantify overfitting, prioritising parsimony, conservative validation and transparent uncertainty quantification over model expansion or formal causal inference.

Model performance

Discrimination was assessed using the area under the receiver operating characteristic curve (AUC). Calibration was assessed using the calibration slope, calibration-in-the-large (CITL), loess-smoothed plots and decile-based observed versus predicted risks. Overall predictive accuracy was summarised using the Brier score.

Internal validation used 1000 bootstrap resamples, with optimism subtracted from apparent performance metrics. Predicted risks were recalibrated using the optimism-adjusted slope and intercept as: $p^* = \text{expit}(\text{CITL} + \text{slope} \times \text{logit}(p))$. These recalibrated predictions were used for calibration plots and all downstream clinical-utility analyses.

Clinical utility

Decision-curve analysis was performed using optimism-adjusted, recalibrated predictions. Net benefit was evaluated across threshold probabilities from 1–20%, reflecting plausible escalation ranges in hospitalised adults.[26] The 'treat-all' curve was included solely as a formal decision-analytic comparator.

Software

Analyses were performed in R V.4.5.0.

RESULTS

Cohort description

Across the three contributing cohorts, 340 adults with PCR-confirmed RSV infection met eligibility criteria and were admitted to participating UK hospitals. Six participants (1.8%) lacked complete primary-outcome data and were excluded, leaving 334 adults for analysis (figure 1).

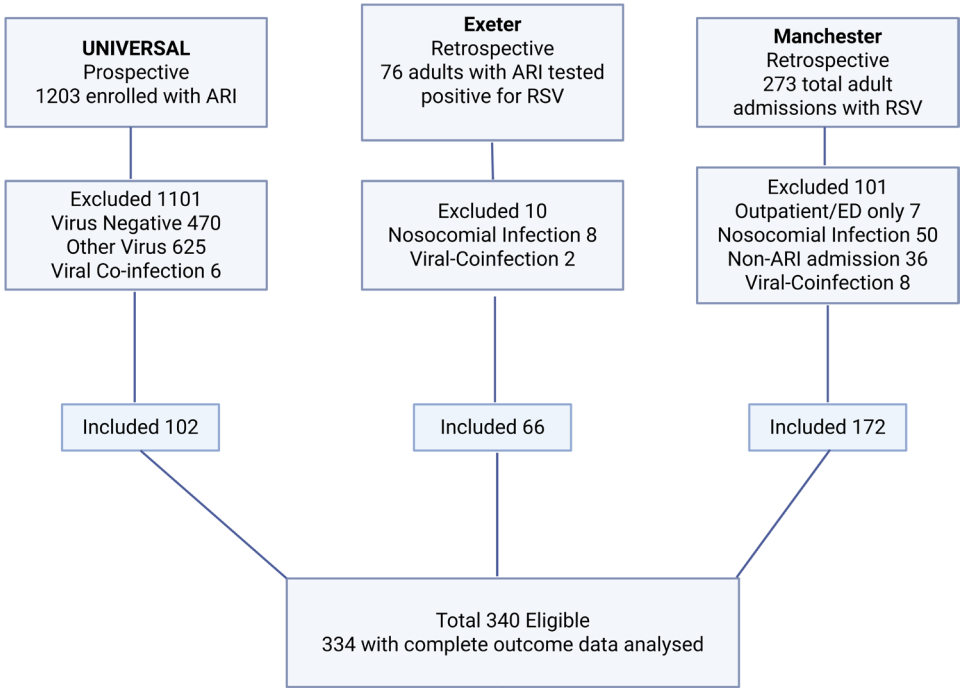

Figure 1 Flow of participants into the analytic cohort.Participants were drawn from three non-overlapping cohorts: a prospective UNIVERSAL cohort recruiting across 10 UK hospitals (University Hospital Southampton; Addenbrooke's Hospital, Cambridge; Castle Hill Hospital, Hull; Derriford Hospital, Plymouth; Glenfield Hospital, Leicester; St Mary's Hospital, London; Ninewells Hospital, Dundee; Princess Royal Hospital, Haywards Heath; Royal Sussex County Hospital, Brighton; and Royal Devon and Exeter Hospital, Exeter), and retrospective cohorts from Royal Devon and Exeter Hospital and Manchester University NHS Foundation Trust. Recruitment under the UNIVERSAL protocol at Exeter occurred in November–December 2022, preceding retrospective case ascertainment (January 2023–January 2024). Of 340 eligible adults with PCR-confirmed respiratory syncytial virus (RSV) infection, 334 had complete primary-outcome data and were included in the primary analysis.

Table 1 Baseline demographics, comorbidities and outcomes for eligible adults hospitalised with RSV (n=340); primary analyses used complete primary-outcome data (n=334)

Characteristic	Value	Missing N	Missing %
Age (years)	69.5 (59.0, 78.0)	0	0.0%
Age ≥60 years	247 (73%)	0	0.0%
Age ≥75 years	117 (34%)	0	0.0%
Male sex	134 (39%)	0	0.0%
COPD	107 (31%)	0	0.0%
Asthma	121 (36%)	0	0.0%
Interstitial lung disease	15 (4.4%)	0	0.0%
Bronchiectasis	22 (6.5%)	0	0.0%
Heart failure	42 (12%)	0	0.0%
CKD	66 (19%)	0	0.0%
Chronic liver disease	16 (4.7%)	0	0.0%
Diabetes mellitus	70 (21%)	0	0.0%
Active/previous cancer	40 (12%)	0	0.0%
Rheumatological disease	41 (12%)	0	0.0%
Dementia	19 (5.6%)	0	0.0%
HIV	5 (1.5%)	0	0.0%
≥1 Core comorbidity	209 (61%)	0	0.0%
ICU/HDU admission	12 (3.6%)	3	0.9%
60-day mortality	29 (8.7%)	6	1.8%
Primary outcome	37 (11%)	6	1.8%

Baseline characteristics are reported for all eligible participants (n=340); model development and performance analyses used those with complete primary outcome data (n=334). Categorical variables are shown as n (%); continuous variables as median (IQR). Missing n (%) refers to the number and proportion of records with missing data for each variable. The primary composite outcome was ICU/HDU admission or all-cause mortality within 60 days of the index hospital admission. Core comorbidity denotes the presence of at least one of COPD, heart failure, diabetes mellitus, active/previous cancer or CKD.
Percentages are calculated using non-missing denominators.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HDU, high dependency unit; HDU, high dependency unit; ICU, intensive care unit; RSV, respiratory syncytial virus.

The median age was 69.5 years (IQR 59.0–78.0); 73% were aged ≥60 years and 34% were aged ≥75 years. At least one core comorbidity (COPD, heart failure, diabetes mellitus, active or previous cancer or CKD) was present in 61% of participants. The most prevalent conditions were asthma (36%), COPD (32%), diabetes mellitus (21%) and CKD (19%) (table 1).

The composite primary outcome of ICU/HDU admission or all-cause mortality within 60 days occurred in 11.1% of participants (37/334). Of the 37 participants who experienced the primary outcome, 18 (48.6%) were aged ≥75 years and therefore age-eligible under current UK RSV vaccination policy. Baseline characteristics stratified by contributing cohort are shown in online supplemental table S1, and the distribution of the composite outcome across key demographic and clinical covariates is summarised in online supplemental table S2.

Penalised variable selection

Penalised variable selection was performed using LASSO logistic regression including continuous age, sex and all prespecified comorbidities. At the cross-validated optimal penalty (λ_min), four predictors retained non-zero coefficients: age, COPD, active/previous cancer and dementia (online supplemental figures S1–S3).

Bootstrap stability selection supported this pattern. COPD and dementia were selected in >94% of bootstrap resamples, cancer in 79.5% and age in 60.8%, whereas all remaining candidate predictors were selected in fewer than half of resamples (online supplemental table S3).

Selective-inference-adjusted estimates were derived on the penalised scale to illustrate additional post-selection uncertainty following LASSO selection. These estimates are presented descriptively in the online supplemental Material and were not used for predictor inclusion, prediction, performance evaluation or clinical interpretation (online supplemental table S4).

In a pipeline bootstrap sensitivity analysis repeating tuning, selection and refitting within each resample, optimism-adjusted discrimination and calibration were attenuated, as expected. Relative performance of the LASSO-derived modelling approach compared with the prespecified age-only comparator models was preserved on average, supporting the same overall interpretation (online supplemental tables S5 and S6).

Correlations between age and comorbidities were modest (all $|r| \leq 0.29$), and variance inflation factors for the refitted model ranged from 1.02 to 1.15, indicating no evidence of concerning multicollinearity (online supplemental figure S3 and table S7).

Predictor estimates

In age-based comparator models, age ≥75 years was associated with approximately doubled odds of the composite outcome (OR 2.01, 95% CI 1.01 to 4.03), while the broader age ≥60 years threshold yielded a larger but imprecise estimate (OR 4.93, 95% CI 1.71 to 20.83). The presence of ≥1 core comorbidity was also associated with higher odds (OR 3.07, 95% CI 1.38 to 7.81).

In the LASSO-selected multivariable model (model D), including age (continuous), COPD, active/previous cancer and dementia, refitting with standard logistic regression yielded ORs of 1.02 per year increase in age (95% CI 0.99 to 1.05), 4.46 for COPD (95% CI 2.09 to 9.95), 2.90 for active/previous cancer (95% CI 1.09 to 7.27) and 8.35 for dementia (95% CI 2.58 to 27.80) (figure 2; table 2).

Firth's penalised logistic regression, used as a sensitivity analysis to assess robustness to small cell counts and potential separation, produced very similar point estimates, showing comparable effect sizes despite the modest number of events (online supplemental table S8).

Individual coefficient estimates are presented descriptively, with inference directed primarily towards internally validated model-level performance rather than individual predictor effects.

Model performance

After bootstrap internal validation (1000 resamples), discrimination of the three simple comparator models remained modest, with optimism-adjusted AUCs of 0.58 (95% CI 0.48 to 0.65) for age ≥75 years, 0.61 (95% CI 0.56 to 0.67) for age ≥60 years and 0.61 (95% CI 0.55 to 0.69) for the core-comorbidity model (table 3 and figure 3; online supplemental figure S4 shows apparent ROC curves; online supplemental table S9 shows apparent performance). For model A, predicted probabilities were highly compressed and calibration slope estimates were consequently unstable with wide uncertainty; calibration assessment for this rule-based model should therefore be interpreted cautiously. Predicted risks from these models occupied

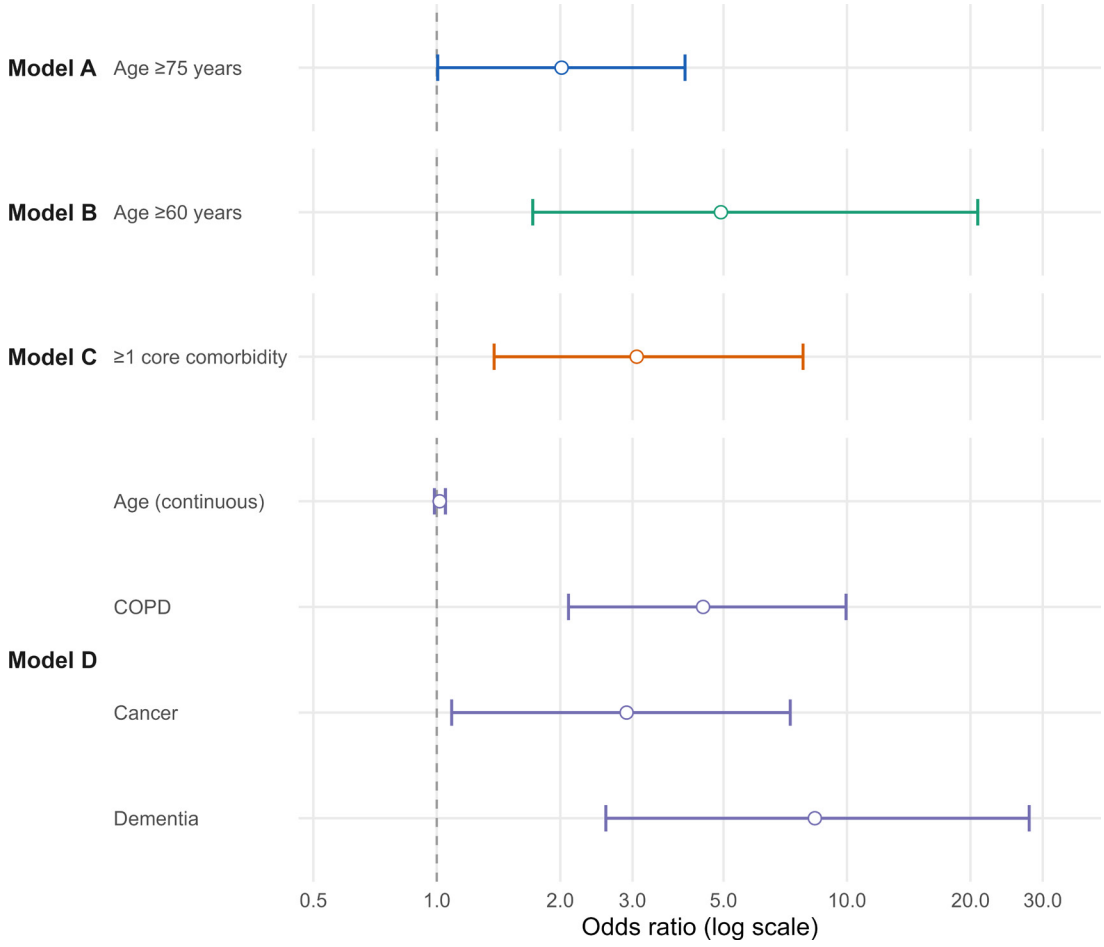

Figure 2 Descriptive adjusted ORs for predictors of ICU/HDU admission or 60-day all-cause mortality across four standard logistic regression models. Forest plot showing descriptive adjusted ORs and 95% CIs for predictors included in models A–D, each fitted using standard logistic regression (generalised linear model (glm) framework). Model A (age ≥75 years) and model B (age ≥60 years) represent age-based rules reflecting current or proposed RSV vaccine eligibility thresholds. Model C reflects a pragmatic clinical rule based on the presence of ≥1 core comorbidity (COPD, heart failure, diabetes mellitus, active/previous cancer or chronic kidney disease). Model D, a LASSO derived multivariable model, included age (continuous), COPD, active/previous cancer and dementia. ORs are presented descriptively, and interpretation is directed towards internally validated model-level performance rather than individual predictor effects. Circles denote point estimates and horizontal bars indicate 95% CIs; the dashed vertical line marks OR=1. COPD, chronic obstructive pulmonary disease; HDU, high dependency unit; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator; RSV, respiratory syncytial virus.

Table 2 Descriptive predictor estimates for ICU/HDU admission or 60-day all-cause mortality from four standard logistic regression models (models A–D): age-based rules, core-comorbidity model and LASSO derived multivariable model

Model	Predictor	OR	95% CI	P value
Model A	Age ≥75 years	2.01	1.01 to 4.03	0.046
Model B	Age ≥60 years	4.93	1.71 to 20.83	0.010
Model C	≥1 core comorbidity	3.07	1.38 to 7.81	0.010
Model D	Age (continuous)	1.02	0.99 to 1.05	0.301
(LASSO-derived)	COPD	4.46	2.09 to 9.95	<0.001
	Active/previous cancer	2.90	1.09 to 7.27	0.026
	Dementia	8.35	2.58 to 27.80	<0.001

All predictor estimates are reported descriptively; interpretation is directed primarily towards internally validated model-level performance. All estimates are ORs with 95% CIs obtained from ordinary unpenalised logistic regression (glm framework). Core comorbidity denotes the presence of at least one of COPD, heart failure, diabetes mellitus, active/previous cancer or chronic kidney disease.
COPD, chronic obstructive pulmonary disease.glm, generalised linear model; LASSO, least absolute shrinkage and selection operator.

a relatively narrow range (approximately 5–15%), limiting risk separation.

By contrast, the optimism-adjusted AUC for the LASSO-derived model was 0.77 (95% CI 0.69 to 0.85). Calibration appeared more favourable for the LASSO-derived model, with an optimism-adjusted calibration slope of 0.91 (95% CI 0.62 to 1.27) and CITL close to zero, alongside a broader distribution of predicted risks extending to approximately 40%. Brier scores were similar across models but lowest for the LASSO-derived specification (0.09, 95% CI 0.07 to 0.12). Apparent and optimism-adjusted calibration plots are shown in online supplemental figures S5 and S6.

In the pipeline bootstrap sensitivity analysis, repeating tuning, selection and refitting within each resample, performance estimates were more conservative (optimism-adjusted AUC 0.72 (0.63–0.80); slope 0.59 (0.08–1.10)), as expected. However, the relative ordering of performance compared with the prespecified age-only comparator models was preserved on average, supporting the same overall conclusion that the LASSO-derived model provides greater risk discrimination than age-only heuristics (online supplemental tables S5 and S6).

Table 3 Optimism-adjusted performance of candidate RSV risk prediction models following bootstrap internal validation

Model (definition)	AUC (95% CI)	Slope (95% CI)	CITL (95% CI)	Brier (95% CI)
A (age ≥75 years only)	0.58 (0.48 to 0.65)	−0.62 (-3.30 to 5.79)	0.02 (-0.30 to 0.39)	0.099 (0.074 to 0.126)
B (age ≥60 years only)	0.61 (0.56 to 0.67)	1.07 (0.03 to 2.40)	0.01 (-0.31 to 0.37)	0.097 (0.074 to 0.123)
C (core comorbidity only)	0.61 (0.55 to 0.69)	0.99 (0.50 to 2.95)	0.02 (-0.32 to 0.39)	0.098 (0.075 to 0.124)
D LASSO-derived: age (cont) COPD active/previous cancer dementia	0.77 (0.69 to 0.85)	0.91 (0.62 to 1.27)	0.02 (-0.38 to 0.42)	0.093 (0.070 to 0.116)

Optimism-adjusted discrimination, calibration and overall accuracy for models A–D following bootstrap internal validation (1000 resamples) of standard logistic regression (glm framework) fits in the combined cohort. For each model, the table reports the area under the receiver operating characteristic curve (AUC), calibration slope, calibration-in-the-large (CITL) and Brier score with percentile 95% CIs derived from bootstrap resampling. Model A: age ≥75 years only; model B: age ≥60 years only; model C: core-comorbidity model (≥1 of COPD, heart failure, diabetes mellitus, active or previous cancer or chronic kidney disease); model D: LASSO derived multivariable model including age (continuous), COPD, active or previous cancer and dementia.
CITL, calibration-in-the-large; COPD, chronic obstructive pulmonary disease; glm, generalised linear model; LASSO, least absolute shrinkage and selection operator.

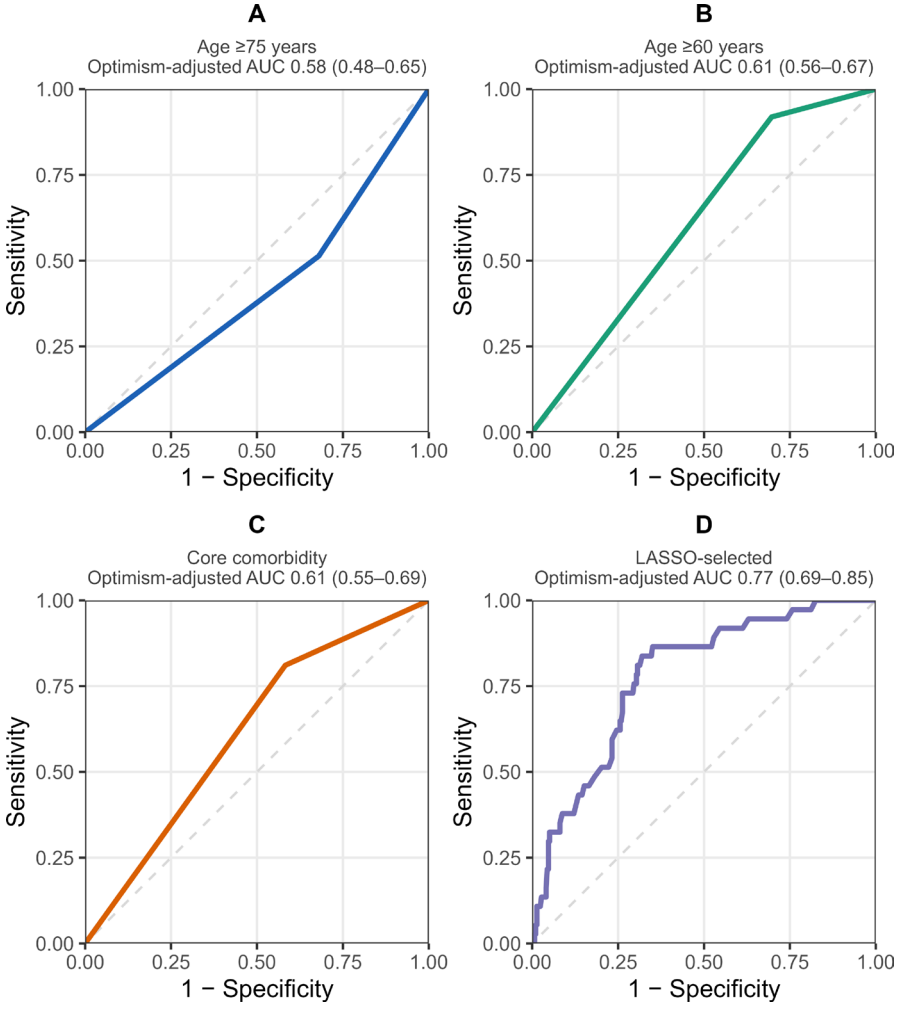

Figure 3 Receiver operating characteristic (ROC) curves for four logistic regression models (models A–D) predicting ICU/HDU admission or 60-day all-cause mortality in adults hospitalised with RSV. All models were fitted using ordinary unpenalised logistic regression, with optimism-adjusted performance obtained from 1000-sample bootstrap internal validation. Each panel displays sensitivity plotted against 1–specificity; the diagonal dashed line indicates no discrimination (area under the ROC curve (AUC) = 0.50). Age-based models (models A and B) and the core-comorbidity rule (model C) showed modest discrimination, whereas model D, the LASSO derived multivariable model incorporating age, COPD, active/previous cancer and dementia demonstrated higher discrimination. COPD, chronic obstructive pulmonary disease; HDU, high dependency unit; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator; RSV, respiratory syncytial virus.

Table 4 Decision-curve analysis for prediction of ICU/HDU admission or 60-day all-cause mortality Net benefit per 100 patients at prespecified risk thresholds using optimism-adjusted, recalibrated predictions

Model (definition)	Threshold (%)	Net benefit per 100
A (age ≥75 years only)	5%	6.4
	10%	1.2
	15%	−4.6
B (age ≥60 years only)	5%	6.9
	10%	3.3
	15%	0.0
C (core comorbidity only)	5%	6.4
	10%	3.2
	15%	−0.2
D (LASSO-derived) age, active/previous cancer, COPD, dementia	5%	7.3
	10%	6.0
	15%	4.1

Net benefit is reported per 100 patients and calculated using optimism-adjusted, recalibrated predicted probabilities following bootstrap internal validation (1000 resamples). Threshold probabilities of 5%, 10% and 15% were prespecified to reflect clinically plausible decision thresholds in hospitalised adults. Model A: age ≥75 years; model B: age ≥60 years; model C: presence of ≥1 core comorbidity (COPD, heart failure, diabetes mellitus, active or previous cancer, or chronic kidney disease); model D: LASSO derived multivariable model including age (continuous), COPD, active or previous cancer and dementia.
HDU, high-dependency unit.COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator.

Sensitivity analyses

Sensitivity analyses examining alternative age specifications around the LASSO-derived comorbidity triad are reported in online supplemental tables S10–S15. Models combining COPD, active/previous cancer and dementia with age ≥60 years or ≥75 years yielded optimism-adjusted AUCs of 0.77 (95% CI 0.70 to 0.85) and 0.76 (95% CI 0.68 to 0.83), respectively. A comorbidity-triad-only model excluding age showed similar discrimination (AUC 0.77, 95% CI 0.70 to 0.85).

Across all formulations, optimism-adjusted calibration slopes ranged from 0.87 to 0.92, with CITL close to zero. Together, these analyses indicate that model-level performance and qualitative conclusions were consistent across alternative age parameterisations and were not materially altered across these specifications.

Clinical utility

Decision-curve analysis based on optimism-adjusted, recalibrated predictions demonstrated limited net benefit for age-only rules and the core-comorbidity model across clinically plausible thresholds (5–20%), with attenuation as thresholds increased (table 4; figures 4 and 5).

By contrast, the LASSO-derived model showed higher net benefit across this range and remained above zero at thresholds where simpler comparator models approached the null decision line.

DISCUSSION

In this multicentre UK cohort of predominantly older, comorbid adults hospitalised with PCR-confirmed RSV ARI, simple age-based rules reflecting current or proposed RSV vaccination eligibility thresholds (≥75 years or ≥60 years) demonstrated only modest prognostic performance for ICU/HDU admission/60-day all-cause mortality. By contrast, a parsimonious four-predictor LASSO-derived model incorporating age, COPD, active/previous cancer and dementia showed higher discrimination, more coherent calibration and broader separation of predicted risk. Decision-curve analyses based on optimism-adjusted predictions suggested greater net benefit for this comorbidity-inclusive model across clinically plausible thresholds, although estimates were imprecise. Within this hospitalised cohort, incorporating selected comorbidities alongside age therefore appeared to provide more informative risk stratification than age-band thresholds alone; however, the model should be regarded as developmental rather than a definitive clinical tool.

Although age and, to a lesser extent, cancer were selected less consistently than COPD or dementia during penalised selection, sensitivity analyses re-parameterising age using policy-relevant thresholds or omitting age entirely yielded similar discrimination, calibration and decision-analytic performance. Together with bootstrap stability and pipeline resampling analyses, this suggests that the primary conclusions are driven by model-level performance rather than individual coefficient estimates and that risk stratification in this cohort appeared to be more strongly influenced by selected comorbidities than by age alone.

These findings should be interpreted alongside extensive epidemiological evidence that RSV hospitalisation in adults increases steeply with age at the population level.[1–3] Age is also an upstream determinant of frailty and of the prevalence and severity of chronic conditions such as COPD, CKD and dementia.[9] Consistent with this, older age was associated with higher odds of poor outcome in univariable analyses. A cautious interpretation is that, among adults already sick enough to require hospital admission with RSV-associated ARI, much of the apparent age-related risk of ICU/HDU admission or early mortality may be mediated through accumulated comorbidity and frailty rather than reflecting a large direct effect of chronological age itself.[8 9 27] Notably, fewer than half of those experiencing the composite primary outcome of ICU/HDU admission/60-day mortality met the current UK age-based vaccination threshold (≥75 years), indicating that severe outcomes in this cohort were common among comorbid adults below the UK vaccine-age cut-off.

It is important to distinguish the simple age thresholds evaluated here from multivariable prognostic scores more generally. Established tools for community-acquired pneumonia and COVID-19 incorporate age alongside physiological and biochemical parameters rather than using age in isolation (eg, confusion, urea, respiratory rate, blood pressure, age ≥65 years (CURB-65) and the Coronavirus Clinical Characterisation Consortium (4C) Mortality Score).[28 29] Our focus was deliberately narrow: to evaluate age-band thresholds that mirror current or proposed RSV vaccine eligibility criteria, because these heuristics are prominent in policy.[16–19] Within this specific question, selected comorbidity-inclusive models outperformed age-band thresholds in this cohort, but they are not intended to replace physiology-based prognostic assessment or clinical judgement.

The pattern of predictors identified here is consistent with prior adult RSV literature, in which severe outcomes cluster among older adults with substantial respiratory, cardiometabolic and neurological disease.[9] COPD, malignancy and dementia have been repeatedly associated with severe RSV outcomes in adults, supporting their prominence in the penalised model.[9] All

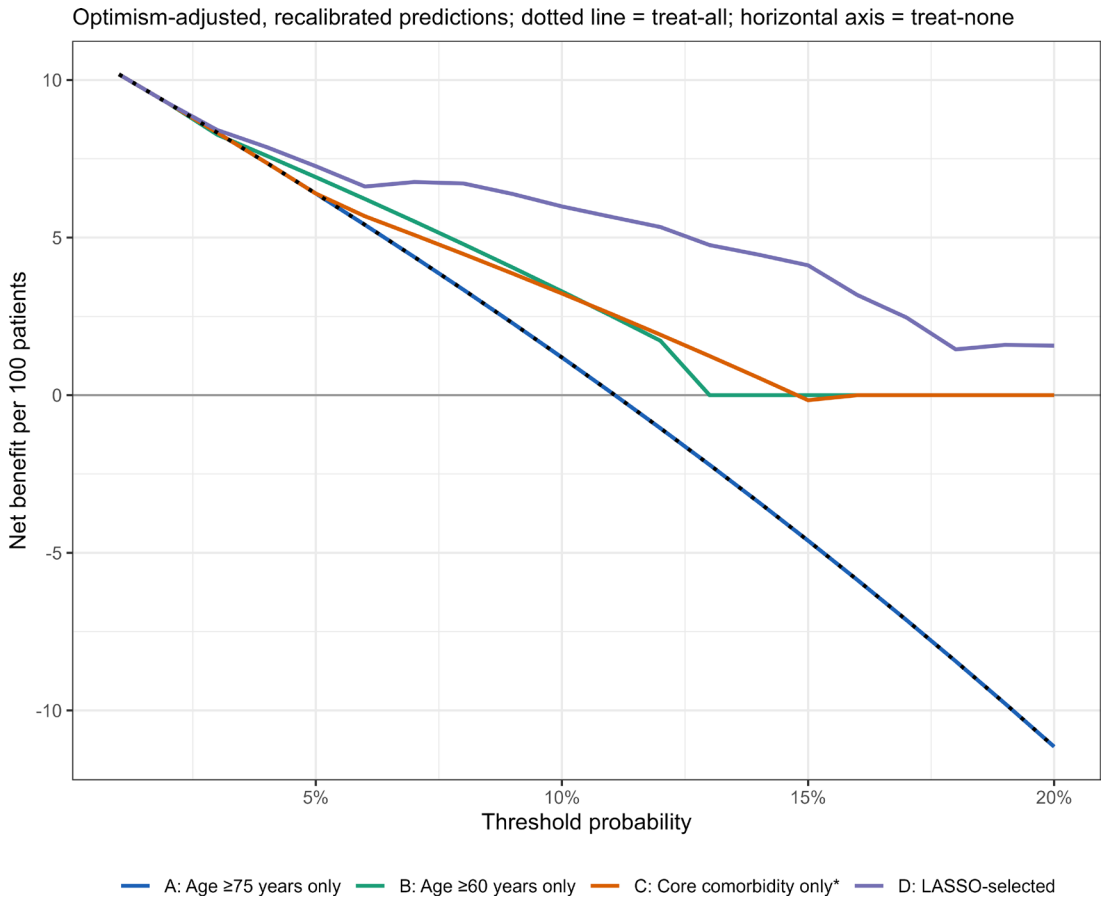

Figure 4 Decision-curve analysis for four logistic regression models (models A–D) predicting ICU/HDU admission or 60-day all-cause mortality in adults hospitalised with RSV, using optimism-adjusted, recalibrated predicted probabilities obtained from 1000-sample bootstrap internal validation. Coloured curves show the net benefit of each model across threshold probabilities from 1–20%, compared with strategies of treating all patients (dashed line) or treating none (horizontal line), included as formal decision-analytic comparators rather than literal escalation strategies. Net benefit reflects the balance between correctly identifying patients who experience poor outcomes (true positives) and the harms of unnecessary intervention (false positives) at a given threshold. Models A and B (age ≥75 years and age ≥60 years), and model C (≥1 core comorbidity), demonstrated limited net benefit across most thresholds, whereas model D, the LASSO selected model (age, COPD, active or previous cancer and dementia), showed greater net benefit across most clinically plausible thresholds. COPD, chronic obstructive pulmonary disease; HDU, high dependency unit; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator; RSV, respiratory syncytial virus.

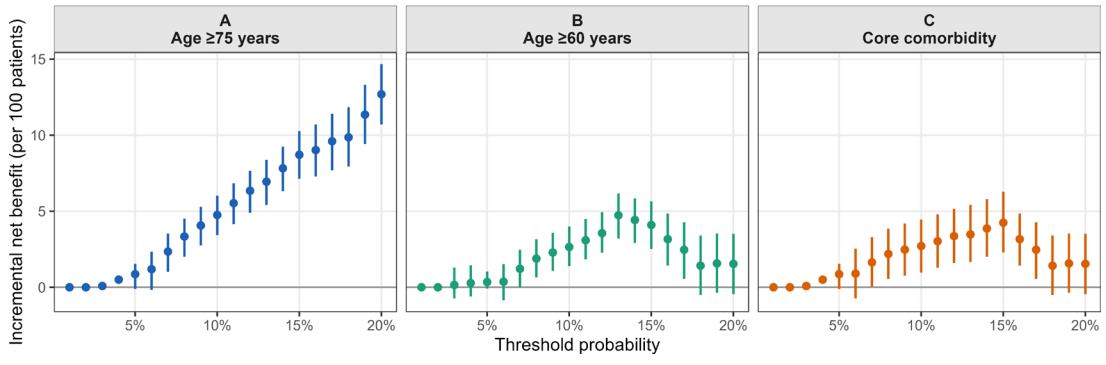

Figure 5 Incremental net benefit of the LASSO selected model for predicting ICU/HDU admission or 60-day mortality, incorporating age, COPD, active or previous cancer and dementia, compared with prespecified rule-based models: (A) age ≥75 years; (B) age ≥60 years and (C) ≥1 core comorbidity. Each panel displays the difference in net benefit between the LASSO-selected model and the comparator across threshold probabilities of 1–20%. Net benefit is expressed per 100 patients and estimated using optimism-adjusted, recalibrated predictions derived from 1000 bootstrap resamples. Error bars indicate percentile 95% CIs. Positive values indicate greater net benefit of the LASSO-selected model relative to the comparator. COPD, chronic obstructive pulmonary disease; HDU, high dependency unit; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator.

prespecified comorbidities were entered into penalised selection; asthma, bronchiectasis and interstitial lung disease were selected less frequently and did not materially improve model performance under strict constraints on model complexity. This should not be interpreted as clinical irrelevance of these conditions but rather reflects limited incremental prognostic information in a small dataset where parsimony was essential.

Several limitations warrant emphasis. RSV testing in adults is non-systematic and shaped by clinician preference and local pathways; consequently, this pooled dataset should be interpreted as a convenience sample of RSV-tested hospitalised adults rather than a nationally representative population, and ascertainment bias cannot be excluded.[5–7] In addition, our pooled cohorts were drawn largely from general hospital admission pathways; transplant recipients and other profoundly immunocompromised patients were under-represented and could not be characterised in sufficient detail to support modelling. Risk stratification in these populations should rely on dedicated tools (eg, Immunodeficiency Scoring Index for Respiratory Syncytial Virus (ISI-RSV)[30]), as such patients are typically managed through specialist pathways rather than general admission streams and warrant separate, population-enriched models. Furthermore, acute physiological measures, radiological findings and detailed treatment data were not consistently available across cohorts. Viral co-infections were excluded where identified, but ascertainment was limited by PCR panel coverage, and systematic data on bacterial pneumonia markers and oxygenation indices were unavailable. Data on nursing or residential home status were also unavailable across all cohorts. These factors may carry prognostic information orthogonal to comorbidity burden and should be evaluated in future studies incorporating richer acute-severity data.

Finally, the modest number of outcome events constrained model complexity and limited precision for individual coefficient estimates, with events-per-parameter acceptable but near the lower recommended threshold. To mitigate overfitting and characterise uncertainty, we adopted a parsimonious strategy incorporating penalised variable selection, bootstrap internal validation, pipeline resampling and post-hoc recalibration. Consistent with guidance for prediction-model development, interpretation was directed towards internally validated model-level performance—including discrimination, calibration and decision-analytic utility—rather than individual predictors. Because variable selection and estimation were performed within the same dataset, some selection-related optimism was unavoidable despite these safeguards. Accordingly, external validation and model updating are required before any consideration of clinical implementation.

From a hospital-level perspective, these findings suggest that simple age-based heuristics alone—prominent in current and potential future RSV vaccination policy—may be insufficient for identifying adults at highest risk of ICU/HDU admission or early death once hospitalised with RSV-associated ARI. In this context, incorporating routinely recorded comorbidity information alongside age provided more informative risk stratification than age thresholds alone.

At a policy level, this analysis does not directly inform optimal vaccine targeting or cost-effectiveness, which depend on population-level RSV incidence, vaccine effectiveness and economic evaluation. Rather, it offers a complementary view of post-admission risk among adults hospitalised with RSV. As adult RSV vaccination becomes more widespread, future analyses should examine model calibration and performance in vaccinated populations and prespecify effect modification by key comorbidities. More broadly, COPD, cancer and dementia represent plausible strata for RSV vaccine effectiveness, therapeutic and outcome studies, and may help refine understanding of vulnerability in adults hospitalised with RSV infection.

CONCLUSION

In adults admitted to hospital with RSV-associated ARI, simple age-based rules that mirror current or proposed vaccine eligibility thresholds (≥75 years or ≥60 years) provided limited prognostic discrimination and poor separation of risk for ICU/HDU admission or 60-day all-cause mortality. In contrast, a parsimonious comorbidity-inclusive model incorporating age alongside COPD, active/previous cancer and dementia demonstrated higher internal discrimination, calibration and decision-analytic performance within this cohort, indicating that routinely recorded comorbidities capture a substantial proportion of the hospital-level risk signal in this setting.

These findings should be interpreted as developmental and hypothesis-generating. External validation, recalibration and updating in larger, more representative cohorts—including vaccinated populations—are required before any consideration of clinical implementation, alongside direct comparison with physiology-based prognostic scores. Nevertheless, the results suggest that among hospitalised adults with RSV, comorbidity-informed approaches are likely to be more informative than age-based heuristics alone. COPD, cancer and dementia warrant a priori consideration in the design, analysis and stratification of future RSV vaccine-effectiveness, therapeutic and outcome studies, and may help refine understanding of vulnerability in adults hospitalised with RSV infection.

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