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Frailty, comorbidity and survival comparisons between populations eligible for screening according to risk factor versus risk score criteria: results from the Yorkshire Lung Screening Trial

Anas Almatrafi ,[1,2] Rhian Gabe,[3] Rebecca J Beeken,[2,4] Richard D Neal,[2,5] Andrew Clegg,[6] Kate E Best,[6] Samuel Relton,[2] Martel Brown,[7] Hui Zhen Tam ,[3] Daniel Vulkan,[3] Neil Hancock,[2] Philip A Crosbie ,[8] Matthew E J Callister [2,9]

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For numbered affiliations see end of article.

Correspondence to
Dr Anas Almatrafi;
A.A.Almatrafi@leeds.ac.uk

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ABSTRACT

Background Lung cancer screening is effective for people at higher risk of the disease, but there is no international consensus on eligibility criteria. Some programmes use risk factors; others use multivariable risk scores, which might target an older, more comorbid population and thus limit life years gained. In this study, we compare frailty, comorbidities and overall survival between different eligible populations.

Methods Participants aged 55–74 years undergoing lung cancer risk assessment in the Yorkshire Lung Screening Trial were analysed, comparing those who met the US Preventive Services Task Force 2021 lung cancer screening criteria ($USPSTF_{2021}$) criteria against established risk-based criteria currently used in screening protocols (Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model ($PLCO_{m2012}$) ≥1.51%, used internationally, and the Liverpool Lung Project risk model (version 2) (LLP_{v2}) ≥2.5%, used in the UK), examining the number of individuals with frailty and comorbidities selected by each approach. In addition, risk score thresholds were set to select equivalent numbers of people screened compared with $USPSTF_{2021}$. Data recorded in primary care prior to randomisation were retrospectively extracted to allow calculation of the electronic Frailty Index (eFI) and an overall comorbidity count. Frailty, comorbidity counts and 3-year overall survival were compared between these various populations.

Results Of 11 994 individuals aged 55–74 undergoing risk assessment, 3502 were eligible by $USPSTF_{2021}$, 3139 by $PLCO_{m2012}$ ≥1.51% and 3957 by LLP_{v2} ≥2.5%. The proportion of individuals with moderate/severe frailty was lower for the $USPSTF_{2021}$ population (10.6%) compared with $PLCO_{m2012}$ ≥1.51% (13.1%, adjusted p=0.0777) and LLP_{v2} ≥2.5% (13.4%, adjusted p=0.0272). The $USPSTF_{2021}$ identified significantly fewer individuals with multiple comorbidities (30.8%) than the $PLCO_{m2012}$ (36.1%, adjusted p=0.0033) and the LLP_{v2} (37.3%, adjusted p=0.0001).

When compared in equivalent populations, both $PLCO_{m2012}$ with a threshold of 1.32%, and LLP_{v2} with a threshold of 2.92%, had a higher proportion of people both with moderate/severe frailty (12.6%, adjusted p=0.221 and 14.0%, adjusted p=0.0067 respectively) and multiple comorbidities (35.1%, adjusted p=0.0211 and 38.5%, adjusted p<0.0001 respectively) than $USPSTF_{2021}$.

There were no apparent differences in 3-year overall survival between the eligible populations overlapping 95% CIs across risk groups.

Conclusion These data suggest that currently used risk models identify populations with a small increase in

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The risk-factor selection strategy for lung cancer screening is thought to select healthier individuals with fewer comorbidities compared with risk-score strategies. However, the magnitude of the difference in frailty and comorbidities between populations selected using these strategies has not been adequately quantified before.

WHAT THIS STUDY ADDS

⇒ The study examined frailty, comorbidities and survival of populations eligible for lung cancer screening by three different eligibility criteria using data from the Yorkshire Lung Screening Trial. The study shows that the currently used lung cancer screening risk models in the UK ($PLCO_{m2012}$ (Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model) and LLP_{v2} (the Liverpool Lung Project risk model (version 2)) identify populations with slightly more frailty and comorbidities than the $USPSTF_{2021}$ (the US Preventive Services Task Force 2021 lung cancer screening criteria) risk-factor criteria. However, there are no apparent differences in 3-year survival between populations identified by the risk models versus the risk-factor strategies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study findings suggest that the differences between risk-factor and risk-score strategies may be less substantial in terms of frailty than previously believed. Further evidence is needed to understand the long-term survival differences between populations identified by these eligibility strategies.

moderate/severe frailty and multimorbidity compared to the $USPSTF_{2021}$ criteria, but there is no evidence to suggest that this results in differences in 3-year overall survival.

INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality worldwide for both men and women.[1] Treatment advances have improved the 5-year survival rates over the last two decades, but these remain poor compared with other cancer types.[2] This poor survival is mainly associated with delayed detection, as early-stage lung cancers have mild or no apparent symptoms. Large randomised controlled trials (RCTs) have demonstrated that lung cancer screening (LCS) using low-dose CT (LDCT) can reduce lung cancer mortality by at least 20% in high-risk individuals.[3–5] Identifying optimal criteria to select these high-risk individuals for screening is a challenging task, but it is crucial for maximising LCS benefits while reducing potential harms and costs.

The original randomised trials demonstrating screening efficacy used risk factors to determine eligibility for screening (eg, pack years smoked, time since quit smoking), and these informed the US Preventive Services Task Force (USPSTF)[6] with $USPSTF_{2021}$ criteria being aged 50–80 years, ≥20 pack-years smoking exposure and smoking quit time of within 15 years for those who have stopped smoking.[7] Multivariable risk models have been suggested as an alternative way to define eligibility with evidence of increased cancer detection within the eligible population.[8] Two examples of risk prediction models are the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial model ($PLCO_{m2012}$)[9] and the Liverpool Lung Project model (LLP_{v2}),[10] which predict the likelihood of developing lung cancer within the next 6 or 5 years, respectively. Lung cancer screening implementation programmes in Canada are currently using the $PLCO_{m2012}$ model,[11 12] and the England-wide National Health Service Lung Cancer Screening Programme (NHS LCSP, previously known as the Targeted Lung Health Check programme) uses both the $PLCO_{m2012}$ and LLP_{v2} risk models concurrently with risk thresholds of ≥1.51% and ≥2.5%, respectively, to select candidates for LCS.[13]

Previous studies have assessed various lung cancer screening selection strategies, comparing risk prediction models, such as the $PLCO_{m2012}$ and LLP_{v2} models, against the $USPSTF_{2021}$ risk criteria. These analyses evaluated different factors, including the size of eligible population, lung cancer detection rates, averted deaths and potential racial or sex disparities.[8 9 14–21] One concern about using risk models is that they may identify an older, more comorbid population for screening, and thus limit the life-years gained by the programme due to competing causes of death. Therefore, frailty, comorbidity and overall survival are key considerations in determining the optimal population for lung cancer screening programmes.

The Yorkshire Lung Screening Trial (YLST)[22] offered community-based LDCT screening for high-risk people who have ever smoked and who met one of three eligibility criteria: the $USPSTF_{2013}$ (age 55–80 years, ≥30 pack-years, smoked within 15 years), the $PLCO_{m2012}$ 6-year risk of ≥1.51% or the LLP_{v2} 5-year risk of ≥5%. In this study, we compared frailty, comorbidity and 3-year overall survival rates among individuals who would have been eligible for LCS based on the updated version of USPSTF criteria ($USPSTF_{2021}$) and the risk criteria currently used in the NHS LCSP ($PLCO_{m2012}$ ≥1.51% and LLP_{v2} ≥2.5%).

METHODS

This comparative study used data prospectively collected from the intervention arm of the YLST, alongside retrospectively collected data on frailty and comorbidities from primary care. The YLST design and results of invitation response, screening eligibility and uptake of community-based LDCT screening have been previously described.[22 23] Briefly, the YLST is a RCT assessing invitations to community-based lung health checks (which involve LDCT screening) for individuals aged 55–80 years with a smoking history documented in their general practitioner (GP) records. For this study, frailty and comorbidity data were retrospectively extracted from 54 participating practices that use The Phoenix Partnership SystmOne electronic patient record. This represents 64% (54/84) of the practices participating in the YLST, with 12 practices not responding to requests for data and 18 practices using a different software system (EMIS) from which we were unable to access data.

Frailty was investigated using the electronic Frailty Index (eFI),[24 25] which contains 36 equally weighted deficits identified from a set of Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) codes. The eFI score can be categorised into a four-level variable (fit, mild, moderate, severe) according to predefined cut-offs (0–0.12, >0.12–0.24, >0.24–0.36, >0.36, respectively).

Comorbidities were investigated using comorbidity count (0, 1, 2, 3 and ≥4) summed from 12 selected comorbidities derived from the extracted SNOMED codes and based on inclusion in the Charlson Comorbidity Index,[26] namely cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), diabetes, heart failure, inflammatory arthritis, ischaemic heart disease (IHD), liver problems, mono/hemiparesis, peripheral vascular disease (PVD), peptic ulcer disease and stroke.

Comorbidity and frailty data were extracted between August 2022 and February 2023, and analyses were performed using SNOMED CT codes that had been in the GP record before the YLST randomisation date. Socio-demographic variables were collected at baseline, with ethnicity and smoking status being self-reported by all participants.[22]

Screening eligibility

Individuals were included in this study if they had primary care records indicating a smoking history, were aged 55–80, were randomised to the intervention arm of YLST, responded to and took part in the baseline lung cancer risk assessment invitation[22] and would have been identified as having a high risk of lung cancer determined by either the $USPSTF_{2021}$ criteria (≥20 pack-year smoking history and ≤15 quit-years), a $PLCO_{m2012}$ risk threshold of ≥1.51% at 6 years or an LLP_{v2} risk threshold of ≥2.5% at 5 years. The original YLST design used the $USPSTF_{2013}$ age criteria of 55–80 years and did not invite individuals 50–55 years who are additionally included in $USPSTF_{2021}$.

In this study, we present data for people aged 55–74 years, matching the current NHS protocol for lung cancer screening.[13] Additional results for those aged 55–80 years are provided as supplementary data (online supplemental tables S1–S4 and figure S1).

Statistical analysis

Descriptive statistics, including counts (n), proportions, means, SD, medians and IQRs, as appropriate, were calculated for socio-demographic characteristics, frailty and comorbidity measures for each of the five eligibility criteria ($USPSTF_{2021}$, $PLCO_{m2012}$

score ≥1.51% and LLP_{v2} risk score ≥2.5%, plus the 'equivalent populations' as defined below).

The proportions of people with moderate/severe frailty, and those with ≥2 comorbidities (multiple comorbidities) were determined for each of the eligibility criteria, and 95% Wald CIs were calculated for each proportion. In order to allow for the three populations overlapping (since some individuals would have been eligible under more than one of the criteria), the CIs were then adjusted using a Bonferroni correction (for three hypotheses/ three comparisons).

Comparisons of the criteria were carried out by, for each pair, determining the level of significance at which the upper bound of a CI for the criterion with the smaller proportion would be identical to the lower bound for the criterion with the higher proportion. As above, a Bonferroni correction was applied to the corresponding p value.

In addition, we determined the risk score thresholds for $PLCO_{m2012}$ and LLP_{v2} that would result in each case in approximately the same number of individuals being deemed eligible as were selected according to the $USPSTF_{2021}$ criterion. This is similar to methods used by Tammemägi *et al*.[8] The analysis above was repeated in order to compare $USPSTF_{2021}$ with these two new groups (hereafter referred to as 'equivalent populations').

We derived 3-year overall survival (and 95% CIs) from the date of randomisation until the date of death due to any cause with a censoring date of 26 January 2024, for each risk-eligible group of interest and stratified by frailty and comorbidity categories. The date of death was obtained from PPM+ (patient pathway manager), the electronic health record of Leeds Teaching Hospitals linked to the central NHS records (Spine Portal). The proportions of people with moderate/severe frailty and with ≥2 comorbidities were plotted separately against the number of people eligible by different risk scores (for $PLCO_{m2012}$ and LLP_{v2}) or risk factor ($USPSTF_{2021}$). The eFI calculation and all analyses were conducted using Stata V.18.0 (StataCorp, College Station, Texas, USA).

RESULTS

Of the 11 994 YLST participants aged 55–74 who underwent lung cancer risk assessment, 3502 individuals met the $USPSTF_{2021}$ criteria, 3139 met the $PLCO_{m2012}$ ≥1.51% threshold and 3957 met the LLP_{v2} ≥2.5% risk threshold. The risk score thresholds that identified a similar number of individuals as the $USPSTF_{2021}$ criteria were 1.32% for $PLCO_{m2012}$ (n=3488) and 2.92% for LLP_{v2} (n=3498). As noted above, these groups are referred to as 'equivalent populations' for comparative purposes.

Demographic characteristics, frailty and comorbidity are summarised by criterion in table 1 showing a younger and more evenly distributed age profile for $USPSTF_{2021}$ than either of the risk score criteria. A higher proportion of females was eligible under the $USPSTF_{2021}$ and $PLCO_{m2012}$ criteria (around 51%) compared with LLP_{v2} (around 43%).

Deprivation, as measured by the Index of Multiple Deprivation (IMD) (the UK government's official measure of relative deprivation in England, ranking small areas by combining indicators across seven domains), was broadly similar between the criteria, with LLP showing a slightly less deprived profile. Under each of the criteria, the overwhelming majority of those eligible (95–97%) self-reported white ethnicity.

Self-reported people who have quit smoking were most prevalent among those eligible under LLP_{v2} (63–65%) compared with $USPSTF_{2021}$ and $PLCO_{m2012}$ (57–59%); this group also tended to have lower pack-years and a longer quit time.

Table 2 sets out the proportion of those eligible under each of the criteria who had moderate or severe frailty, together with 95% CIs, both unadjusted and adjusted to allow for multiple comparisons as described above. The proportion for USPSTF (10.6%, adjusted 95% CI 9.4% to 11.9%) was smaller than for either of the risk scores as used in the NHS LCSP (PLCO 13.1%, adjusted 95% CI 11.7% to 14.6%; LLP 13.4%, adjusted 95% CI 12.1% to 14.7%). The difference between USPSTF and LLP was significant (adjusted p=0.0272), but that between USPSTF and PLCO was not (adjusted p=0.0777). There was no significant difference between PLCO and LLP.

Using equivalent populations (thresholds of 1.32% and 2.92% for $PLCO_{m2012}$ and LLP_{v2}, respectively), the proportions were 12.6% (95% CI 11.2% to 13.9%) for $PLCO_{m2012}$ and 14.0% (95% CI 12.6% to 15.4%) for LLP_{v2}. In this scenario, the difference between USPSTF and LLP continues to be significant (adjusted p=0.0067), and that between USPSTF and PLCO continues not to be significant (adjusted p=0.2210), and similarly for the comparison between PLCO and LLP.

Considering comorbidity (table 3), again the USPSTF eligible population had a lower proportion of individuals with multiple comorbidities (30.8%, adjusted 95% CI 28.9% to 32.6%) than $PLCO_{m2012}$ ≥1.51% (36.1%, 95% CI 34.1% to 38.2%) and LLP_{v2} ≥2.5% (37.3%, 95% CI 35.4% to 39.1%). The differences were significant for both comparisons of USPSTF with the risk scores (PLCO, adjusted p=0.0033; LLP, adjusted p=0.0001). Again, when compared in equivalent populations, the proportions with multiple comorbidities were higher for the risk scores (PLCO 35.1%, adjusted 95% CI 33.1% to 37.0%; LLP 38.5%, adjusted 95% CI 36.6% to 40.5%) than for USPSTF, and the differences were significant (PLCO, adjusted p=0.0211; LLP, adjusted p<0.0001). There were no significant differences between PLCO and LLP.

Adjusted p values were lower for all comparisons when analyses included individuals up to 80 years old and are presented in supplementary data (online supplemental tables S2a, 2b). Differences between $USPSF_{2021}$ and each of the risk scores were significant in all cases, and the difference between the two risk scores was also significant (40.6% for PLCO compared with 45.0% for LLP) when comparing comorbidities in equivalent populations.

The mean follow-up time was 49.9 months (SD±9.9) for the whole analytical sample in this study (55–74 years population), with at least 3 years of follow-up time from the latest date of randomisation. Online supplemental table S3a shows the 3-year survival (3YS) for each risk criterion overall and stratified by frailty and comorbidity levels in individuals aged 55–74 years who were eligible for LCS according to different risk strategies studied. While 3YS was very similar for the risk groups at 96% (with narrow CIs), survival did vary when stratified by frailty and comorbidity. With respect to frailty categories, survival was higher in those deemed fit (97.8% to 98.2%) versus those with severe frailty (81.3% to 83.7%). Similarly, survival was higher in those with no comorbidities (98.0% to 98.5%) compared with those with ≥4 comorbidities (86.3% to 87.8%). Overall, there were no apparent differences (overlapping 95% CIs across all comparisons) between the LCS eligibility strategies ($USPSTF_{2021}$, $PLCO_{m2012}$ and LLP_{v2}) in terms of 3YS (online supplemental table S3a).

Figure 1 illustrates how frailty and comorbidity vary with lung cancer risk threshold. Both risk scores show a progressive reduction in the proportion of patients with moderate/severe frailty or multiple comorbidities as the lung cancer risk threshold falls and the size of the eligible population rises. The proportion of 12 individual comorbidities according to different $PLCO_{m2012}$

Table 1 Baseline factors by criterion among screen-eligible participants aged 55–74 years

	$USPSTF_{2021}$	$PLCO_{m2012}$ ≥1.51%	LLP_{v2} ≥2.5%	$PLCO_{m2012}$ ≥1.32%*	LLP_{v2} ≥2.92%*
Eligible participants	n=3502	n=3139	n=3957	n=3488	n=3498
Age in years: mean (SD)	63.7 (5.5)	66.1 (5.3)	67.1 (5.0)	65.9 (5.3)	67.2 (4.9)
Age group					
<60	1019 (29.1%)	480 (15.3%)	390 (9.9%)	572 (16.4%)	323 (9.2%)
60–64	915 (26.1%)	701 (22.3%)	825 (20.8%)	789 (22.6%)	638 (18.2%)
65–69	916 (26.2%)	979 (31.2%)	1257 (31.8%)	1058 (30.3%)	1202 (34.4%)
70–74	652 (18.6%)	979 (31.2%)	1485 (37.5%)	1069 (30.6%)	1335 (38.2%)
Gender					
Female	1805 (51.5%)	1606 (51.2%)	1688 (42.7%)	1772 (50.8%)	1505 (43.0%)
Male	1697 (48.5%)	1533 (48.8%)	2269 (57.3%)	1716 (49.2%)	1993 (57.0%)
IMD rank: median, (IQR)	10 103 (3174–20 503)	10 120 (3208–21 113)	11 974 (3790–21 681)	10 125 (3208–21 210)	11 974 (3758–21 819)
IMD quintile					
1 (most deprived)	1213 (34.7%)	1088 (34.7%)	1237 (31.3%)	1196 (34.3%)	1107 (31.7%)
2	778 (22.1%)	689 (22.0%)	850 (21.5%)	766 (22.0%)	742 (21.2%)
3	544 (15.6%)	476 (15.2%)	618 (15.6%)	526 (15.1%)	547 (15.6%)
4	647 (18.6%)	600 (19.0%)	840 (21.2%)	672 (19.3%)	745 (21.3%)
5 (least deprived)	318 (9.0%)	285 (9.1%)	411 (10.4%)	327 (9.4%)	356 (10.2%)
Missing	2 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Ethnicity (self-reported)					
White	3338 (95.3%)	3038 (96.8%)	3789 (95.8%)	3364 (96.4%)	3356 (95.9%)
Black	29 (0.8%)	26 (0.8%)	38 (1.0%)	33 (0.9%)	31 (0.9%)
Hispanic	4 (0.1%)	–	2 (0.1%)	–	2 (0.1%)
Asian	63 (1.8%)	28 (0.9%)	67 (1.7%)	33 (0.9%)	60 (1.7%)
Other	48 (1.4%)	31 (1.0%)	37 (0.9%)	38 (1.1%)	29 (0.8%)
Prefer not to say	20 (0.6%)	16 (0.5%)	24 (0.6%)	20 (0.6%)	20 (0.6%)
Smoking status (self-reported)					
Previously smoked	2011 (57.4%)	1778 (56.6%)	2552 (64.5%)	2045 (58.6%)	2215 (63.3%)
Currently smoking	1491 (42.6%)	1361 (43.4%)	1405 (35.5%)	1443 (41.4%)	1283 (36.7%)
Pack-years	36 (28.2–45.0)	38.0 (30.5–48.0)	31.5 (19.5–43.2)	37.5 (29.2–46.8)	32.5 (20.5–44.0)
Quit time (previously smoked): median, (IQR)	7 (4–11)	10 (4–16)	13 (5–26)	10 (5–17)	12 (5–25)
eFI score: mean (SD)	0.12 (0.09)	0.13 (0.09)	0.13 (0.09)	0.13 (0.09)	0.13 (0.09)
eFI category (eFI range)					
Fit (0–0.12)	2187 (62.1%)	1762 (56.1%)	2211 (55.9%)	1999 (57.3%)	1920 (54.9%)
Mild (>0.12–0.24)	952 (27.2%)	965 (30.7%)	1216 (30.7%)	1051 (30.1%)	1088 (31.1%)
Moderate (>0.24–0.36)	319 (9.2%)	350 (11.2%)	447 (11.3%)	370 (10.6%)	412 (11.8%)
Severe (>0.36)	53 (1.5%)	62 (2.0%)	83 (2.1%)	68 (1.9%)	78 (2.2%)
Comorbidity count					
0	1376 (39.3%)	1009 (32.1%)	1250 (31.6%)	1168 (33.5%)	1059 (30.3%)
1	1048 (29.9%)	996 (31.7%)	1233 (31.2%)	1097 (31.5%)	1091 (31.2%)
2	545 (15.6%)	549 (17.5%)	719 (18.2%)	597 (17.1%)	654 (18.7%)
3	284 (8.1%)	311 (9.9%)	396 (10.0%)	335 (9.6%)	364 (10.4%)
≥4	249 (7.1%)	274 (8.8%)	359 (9.1%)	291 (8.3%)	330 (9.4%)

*$USPSTF_{2021}$ equivalent population.
eFI, electronic Frailty Index; IMD, Index of Multiple Deprivation; LLP_{v2}, the Liverpool Lung Project risk model (version 2); $PLCO_{m2012}$, Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model; $USPSTF_{2021}$, the US Preventive Services Task Force 2021 lung cancer screening criteria.

and LLP_{v2} risk scores and the $USPSTF_{2021}$ risk criteria is shown in figure 2 (and online supplemental table S4). COPD was the most prevalent comorbidity, occurring in 24% of the $USPSTF_{2021}$ group, 27.3% of the $PLCO_{m2012}$≥1.32% group, and 28.1% of the LLP_{v2}≥2.92% group; COPD prevalence increased with lung cancer risk. Other comorbidities, including CKD, IHD, cancer, PVD and stroke, showed similar increases in burden among the highest-risk groups compared with the lowest-risk (figure 2).

Table 2 Frailty in those aged 55–74 years eligible for lung cancer screening by $USPSTF_{2021}$, $PLCO_{m2012}$ or LLP_{v2}

	$USPSTF_{2021}$	$PLCO_{m2012}$ ≥1.51%	LLP_{v2} ≥2.5%	$PLCO_{m2012}$ ≥1.32%*	LLP_{v2} ≥2.92%*
Eligible participants	3502	3139	3957	3488	3498
Frailty					
Moderate/severe	372 (10.62%)	412 (13.13%)	530 (13.39%)	438 (12.56%)	490 (14.01%)
95% CI (unadjusted)	9.60% to 11.64%	11.94% to 14.31%	12.33% to 14.46%	11.46% to 13.66%	12.86% to 15.16%
95% CI (adjusted)	9.38% to 11.87%	11.68% to 14.57%	12.10% to 14.69%	11.21% to 13.90%	12.60% to 15.41%
Comparison of criteria		**P value (unadjusted)**		**P value (adjusted)†**	
$USPSTF_{2021}$ vs $PLCO_{m2012}$ ≥1.51%		0.0259		0.0777	
$USPSTF_{2021}$ vs LLP_{v2} ≥2.5%		0.0091		**0.0272**	
$PLCO_{m2012}$ ≥1.51% vs LLP_{v2} ≥2.5%		0.8143		1.0000	
$USPSTF_{2021}$ vs $PLCO_{m2012}$ ≥1.32%		0.0737		0.2210	
$USPSTF_{2021}$ vs LLP_{v2} ≥2.92%		0.0022		**0.0067**	
$PLCO_{m2012}$ ≥1.32% vs LLP_{v2} ≥2.92%		0.2063		0.6190	

Bold indicates significance at P<0.05.
*$USPSTF_{2021}$ equivalent population.
†P values based on pairwise comparisons using adjusted Wald CIs with Bonferroni correction (see Methods).
LLP_{v2}, the Liverpool Lung Project risk model (version 2); $PLCO_{m2012}$, Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model; $USPSTF_{2021}$, the US Preventive Services Task Force 2021 lung cancer screening criteria.

DISCUSSION

This study, to our knowledge, is the first to report frailty using a validated index in individuals undergoing lung cancer risk assessment for screening. Within this YLST cohort, we observed that the $USPSTF_{2021}$ criteria identified fewer LCS candidates with severe or moderate frailty (10.6%) than the risk score thresholds currently used by the NHS LCSP (13.1% for $PLCO_{m2012}$ ≥1.51% and 13.4% for LLP_{v2} ≥2.5%). A similar pattern was observed for those with ≥2 comorbidities.

This study demonstrates that both frailty and comorbidity increase with lung cancer risk as measured by the risk scores. Given that these scores are primarily driven by age and smoking history, this finding is to be expected and has been shown (with regard to comorbidity) in one previous study.[19] A notable difference observed between eligibility methods was the age distribution of the selected populations, with a larger proportion of younger individuals identified under the $USPSTF_{2021}$ criteria compared with the risk score-based approaches. This difference reflects the nature of $USPSTF_{2021}$ criteria, which define eligibility using two key variables (age and smoking history) with fixed thresholds, in contrast to risk prediction models that incorporate a wider range of factors. As a result, younger individuals are less likely to meet eligibility thresholds under risk models unless they have a stronger combination of additional risk factors. This discrepancy does not affect the validity of our comparisons but rather highlights an inherent difference in how these approaches define high-risk populations. Our findings emphasise how eligibility criteria shape the demographic and clinical characteristics

Table 3 Multiple comorbidities in those aged 55–74 years eligible for lung cancer screening by $USPSTF_{2021}$, $PLCO_{m2012}$ or LLP_{v2}

	$USPSTF_{2021}$	$PLCO_{m2012}$ ≥1.51%	LLP_{v2} ≥2.5%	$PLCO_{m2012}$ ≥1.32%*	LLP_{v2} ≥2.92%*
Eligible participants	3502	3139	3957	3488	3498
Comorbidities					
Two or more	1078 (30.78%)	1134 (36.13%)	1474 (37.25%)	1223 (35.06%)	1348 (38.54%)
95% CI (unadjusted)	29.25% to 32.31%	34.45% to 37.81%	35.74% to 38.76%	33.48% to 36.65%	36.92% to 40.15%
95% CI (adjusted)	28.91% to 32.65%	34.07% to 38.18%	35.41% to 39.09%	33.13% to 37.00%	36.57% to 40.51%
Comparison of criteria		**P value (unadjusted)**		**P value (adjusted)†**	
$USPSTF_{2021}$ vs $PLCO_{m2012}$ ≥1.51%		0.0011		**0.0033**	
$USPSTF_{2021}$ vs LLP_{v2} ≥2.5%		<0.0001		**0.0001**	
$PLCO_{m2012}$ ≥1.51% vs LLP_{v2} ≥2.5%		0.4893		1.0000	
$USPSTF_{2021}$ vs $PLCO_{m2012}$ ≥1.32%		0.0070		**0.0211**	
$USPSTF_{2021}$ vs LLP_{v2} ≥2.92%		<0.0001		**<0.0001**	
$PLCO_{m2012}$ ≥1.32% vs LLP_{v2} ≥2.92%				0.0996	

Bold indicates significance at P<0.05.
*$USPSTF_{2021}$ equivalent population.
†P values based on pairwise comparisons using adjusted Wald CIs with Bonferroni correction (see Methods).
LLP_{v2}, the Liverpool Lung Project risk model (version 2); $PLCO_{m2012}$, Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model; $USPSTF_{2021}$, the US Preventive Services Task Force 2021 lung cancer screening criteria.

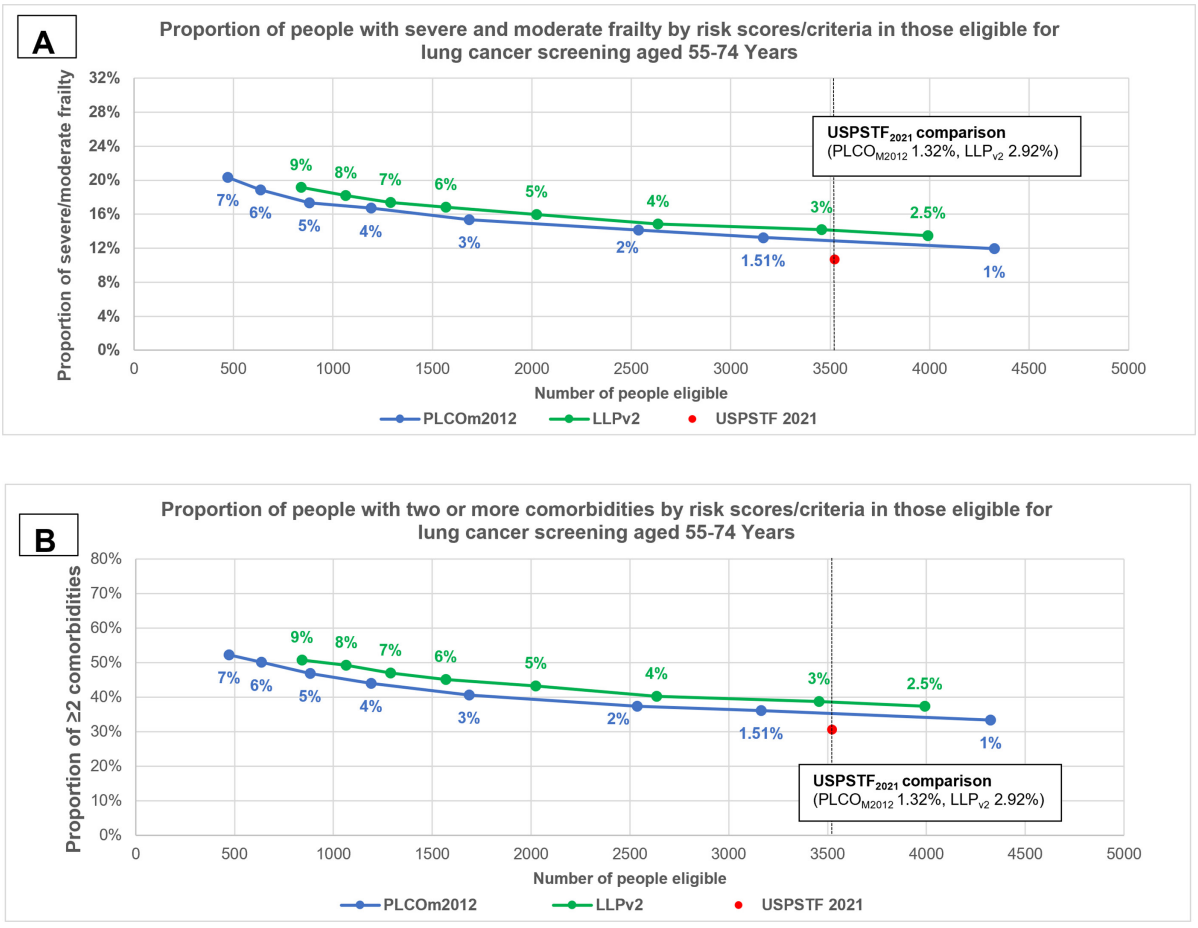

Figure 1 The proportion (%) of (A) severe/moderate frailty and (B) ≥2 comorbidities in those eligible for lung cancer screening by different risk scores ($PLCO_{m2012}$ and LLP_{v2}) versus risk criteria ($USPSTF_{2021}$) in individuals aged 55–74 years. The dotted line shows the comparison between the criteria when used in an equivalent population to $USPSTF_{2021}$. LLP_{v2}, the Liverpool Lung Project risk model (version 2); $PLCO_{m2012}$, Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model; $USPSTF_{2021}$, the US Preventive Services Task Force 2021 lung cancer screening criteria.

of the screened population, which is an important consideration for screening programme design and evaluation. The finding that the risk scores generally select more comorbid individuals than the USPSTF criteria matches results from other studies.[8 15 27 28] Furthermore, our study shows that both risk thresholds used in the current NHS LCSP identify a greater proportion of people with moderate/severe frailty compared with $USPSTF_{2021}$. However, this difference was only significant for LLP_{v2}, and this remained the case when used in equivalent populations. While the USPSTF criteria are widely adopted and validated in US cohorts, their applicability to other populations may be influenced by socioeconomic and healthcare disparities inherent to the US system, such as differential access to screening due to insurance coverage.[29] This could lead to under-representation of older, frailer or socioeconomically disadvantaged individuals in US screening populations. However, risk factor criteria remain a pragmatic benchmark for international comparisons due to their evidence-based linkage to mortality reduction in trials like the National Lung Screening Trial (NLST)[3] and the Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON).[5] In this study, their use as a comparator allows direct assessment of how risk-score-based eligibility alters the screened population's frailty and comorbidity profiles. Importantly, our analysis focuses on relative differences between eligibility methods rather than absolute generalisability of USPSTF itself.

Preliminary analysis of all-cause mortality revealed similar 3YS rates across all eligibility criteria, ranging from 95.3% to 96.6%, with overlapping CIs. These survival rates align with what has been reported among LCS-eligible individuals in the USA[30] and Poland.[31] While these findings suggest comparable short-term outcomes, the limited follow-up duration may not capture emerging differences in survival related to varying levels of frailty and comorbidity among the screened populations. Longer-term studies are necessary to determine whether the selection criteria, particularly those incorporating comprehensive risk assessments, influence survival outcomes over extended periods.

There are two broad considerations in selecting eligibility criteria for screening. The first is the efficiency of the criteria—specifically the cancer yield in the eligible population identified for screening. Lung cancer screening saves lives by detecting early-stage lung cancers, so the more cancers detected, potentially the more lung cancer deaths are prevented and thus lives saved. The second consideration is the clinical characteristics of the population identified for screening—specifically related to the life-years that might be gained by preventing lung cancer deaths in people within the eligible population. Individuals who are younger, fitter and less comorbid will be expected to live longer following successful treatment of their screen-detected cancers, and thus contribute to more life-years gained by the screening programme overall.

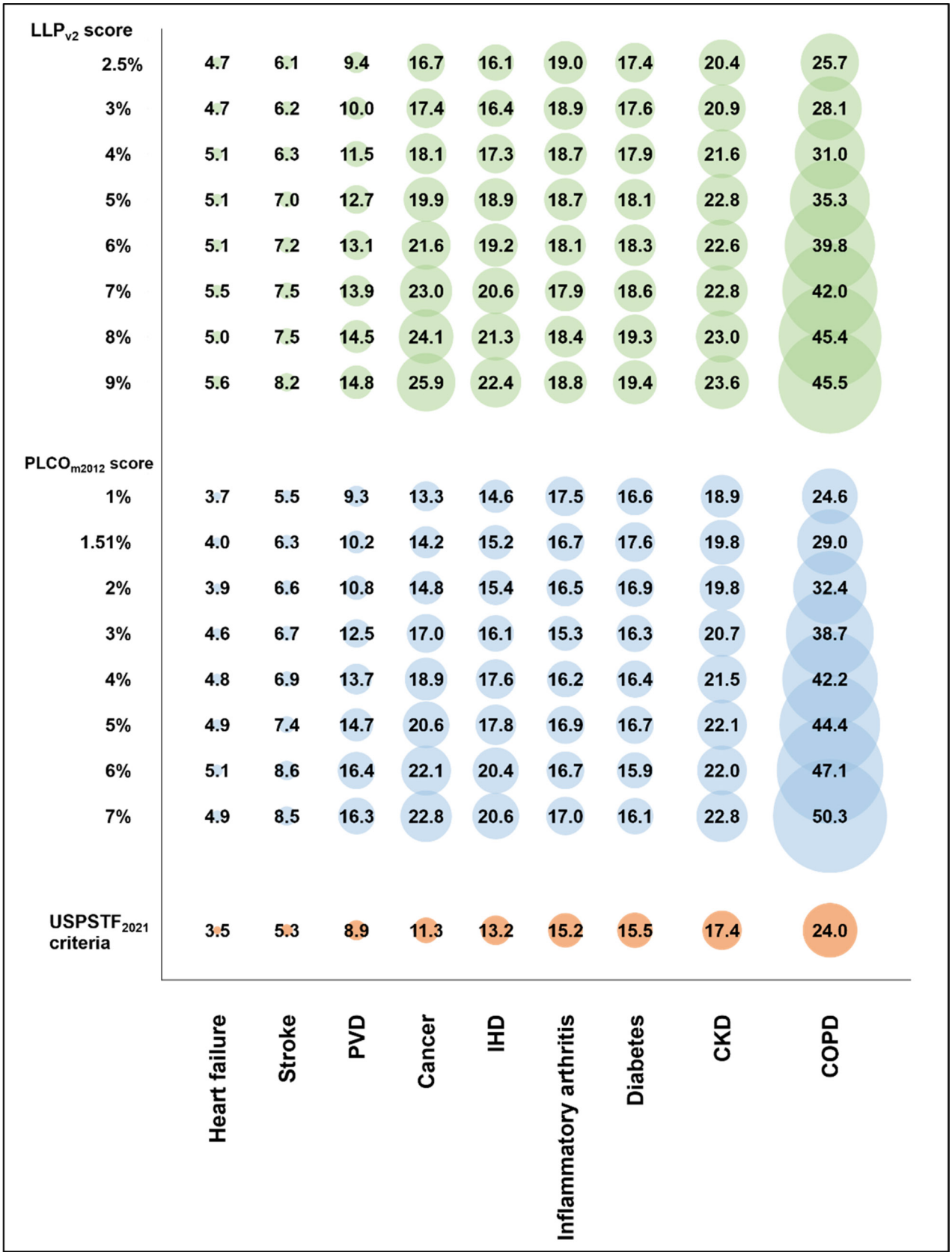

Figure 2 Proportion (%) of individual comorbidities by different lung cancer risk scores (LLP$_{v2}$ and PLCO$_{m2012}$) and LCS eligibility criteria (USPSTF$_{2021}$) in individuals aged 55–74 years. Data for liver problems, mono/hemiparesis and peptic ulcer disease were not visualised in this figure as their proportions were <2%. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; LCS, lung cancer screening; LLP$_{v2}$, the Liverpool Lung Project risk model (version 2); PLCO$_{m2012}$, Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial risk model; PVD, peripheral vascular disease; USPSTF$_{2021}$, the US Preventive Services Task Force 2021 lung cancer screening criteria.

The evidence to date has suggested that, when comparing risk factor versus risk score-based eligibility criteria, these considerations have opposite effects—that is, the risk score-based criteria identify a population with a higher cancer incidence but who are older and more comorbid, thus with potentially shorter life expectancy. The data presented here therefore help inform discussions about the potential trade-off between these competing effects. Overall, the risk score criteria do appear to select older, more comorbid and frailer participants, but the differences in these parameters between equivalent populations identified for screening are relatively small and, in this preliminary analysis, do not appear to translate into measurable differences in life expectancy. However, further research with longer follow-up is needed to confirm this finding.

Strengths and limitations

Strengths of this study include the prospective calculation of lung cancer risk using data collected directly from individuals during telephone triage consultations. Another strength is that using eFI as an established frailty assessment tool and collecting comorbidities from participants' primary care records allowed us to quantify frailty and comorbidities comprehensively and reliably. Limitations include the fact that our study only recruited people aged 55 and above (and so was unable to fully evaluate the $USPSTF_{2021}$ criteria, which includes people between the ages of 50 and 80). Also, it is important to note that the eFI has been primarily validated for individuals aged 65 and over; as such, findings related to frailty in individuals aged under 65 should be interpreted with caution. In addition, we only have complete follow-up data for 3 years to date. It is possible, therefore, that clinically important differences in survival become apparent with longer follow-up. Finally, these results are from a single centre, so these analyses need to be reproduced elsewhere to determine generalisability.

CONCLUSION

In conclusion, $PLCO_{m2012}$ and LLP_{v2} risk-based models selected slightly higher proportions of eligible individuals with frailty and comorbidities than the $USPSTF_{2021}$ risk criteria. Despite these differences, individuals selected by all examined LCS strategies had similar 3YS rates. Future research is required to confirm these findings in multi-centre studies and examine differences in long-term survival.

Author affiliations
[1]Department of Epidemiology and Medical Statistics, College of Public Health and Health Informatics, Umm Al-Qura University, Makkah, Saudi Arabia
[2]University of Leeds Leeds Institute of Health Sciences, Leeds, UK
[3]Centre for Evaluation and Methods, Wolfson Institute of Population Health, Queen Mary University of London, London, UK
[4]Department of Behavioural Science and Health, University College London, London, UK
[5]University of Exeter, Exeter, UK
[6]Academic Unit of Ageing and Stroke Research, University of Leeds, Leeds, UK
[7]Leeds Office of Data Analytics, Leeds Health and Care Partnership, NHS West Yorkshire Integrated Care Board, Leeds, UK
[8]Division of Immunology, Immunity to Infection & Respiratory Medicine, The University of Manchester Faculty of Biology Medicine and Health, Manchester, UK
[9]Department of Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, UK

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Contributors AA, RG, RJB, RDN, AC, KEB, SR, MB, HZT, DV, NH, PAC, MEJC. All authors contributed to the manuscript. AA is the guarantor. MEJC, RG, RJB and RDN assisted in designing the study, revised the manuscript content and provided mentorship. AA, RG and DV developed the statistical methods, with DV providing the major contribution. AA led the manuscript writing, analysis, drafting and interpretation of results. Primary data were collected and verified by AA with assistance from MB and NH. Secondary data originally collected by the YLST were provided by RG, NH and HZT. AC and KEB provided the original list of SNOMED CT codes for the eFI calculation. SR revised all STATA code relevant to the eFI computation. PAC reviewed and revised the manuscript.

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Patient consent for publication Not applicable.

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Data availability statement Data are available upon reasonable request. Researchers wishing to use the data will need to complete a request for data sharing form describing a methodologically sound proposal. The form will need to include the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent, etc. A data sharing agreement from the sponsor may be required.

ORCID iDs
Anas Almatrafi https://orcid.org/0000-0002-7893-0123
Hui Zhen Tam https://orcid.org/0000-0002-8542-1749
Philip A Crosbie https://orcid.org/0000-0001-8941-4813
Matthew E J Callister https://orcid.org/0000-0001-8157-0803

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