

Time from presentation to pre-diagnostic chest X-ray in symptomatic lung cancer patients: a cohort study using electronic patient records

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Abstract

Background

National guidelines in England recommend prompt chest X-ray (within 14-days) in patients presenting in General Practice with unexplained symptoms of possible lung cancer, including persistent cough, shortness of breath or weight loss.

Aim

To examine time to chest X-ray in symptomatic patients in English General Practice prior to lung cancer diagnosis and explore variation by demographics.

Design and Setting

Retrospective cohort study using routinely collected General Practice, cancer registry and imaging data from England.

Method

Patients with lung cancer who presented symptomatically in General Practice in the year pre-diagnosis and had a pre-diagnostic chest X-ray were included. Time from presentation to chest X-ray (presentation-test interval) was determined and intervals classified based on national guideline recommendations as concordant (≤ 14 days) or non-concordant (> 14 days). Variation in intervals was examined by age, sex, smoking status and deprivation.

Results

In a cohort of 2102 lung cancer patients, the median presentation-test interval was 49 days (interquartile range, IQR:5-172). 727 (35%) patients had presentation-test intervals of ≤ 14 days (median:1 day; IQR:0-6) and 1375 (65%) had presentation-test intervals of > 14 days (median:128 days; IQR:52-231). Intervals were longer among smokers than non-smokers (equivalent to 63% longer; $p < 0.001$), older patients (equivalent to 7% longer for every 10-years; $p = 0.013$) and females (equivalent to 12% longer than males; $p = 0.016$).

Conclusion

In symptomatic primary care patients who underwent chest X-ray before lung cancer diagnosis, only 35% were tested within the timeframe recommended by national guidelines. Smokers, older patients and females experienced longer intervals. These findings could help guide initiatives aimed at improving timely lung cancer diagnosis.

Keywords

Lung cancer; chest X-ray; early diagnosis, diagnostic intervals, cancer guidelines

How this fits in

England's national cancer referral guidelines recommend that patients attending General Practice with unexplained symptoms possibly caused by lung cancer, such as persistent cough, shortness of breath and weight loss, have a chest X-ray promptly (within 14-days) to aid timely diagnosis. Only 35% of lung cancer patients in this study had a chest X-ray within the recommended 14-days and time between attending General Practice with symptoms and having an X-ray was longer among smokers, women and older patients. This research highlights a potential source of delayed lung cancer diagnosis and could inform initiatives aiming to achieve earlier diagnosis and improve outcomes.

INTRODUCTION

In the United Kingdom (UK), 47,000 patients are diagnosed with lung cancer each year, and the disease is the leading cause of cancer mortality accounting for 21% of all UK cancer-related deaths.^{1,2} Although lung cancer survival rates in the UK have improved over the last decade, they remain less favourable than in other Northern and Western European countries, partly due to the more advanced stage at diagnosis in UK patients.^{3,4} Missed diagnostic opportunities, which can result from interactions between patient, healthcare practitioner and health-system factors, may contribute to late stage diagnosis and poor cancer outcomes.^{5,6}

Achieving more timely cancer diagnosis is a key strategy of England's National Health Service (NHS).⁷ This strategy is supported by the National Institute for Health and Care Excellence (NICE) cancer guidelines which provide evidence-based recommendations to general practitioners (GPs) in England, Wales and Northern Ireland on the investigation and referral of patients with symptoms of possible cancer.^{8,9} However, few studies have assessed how frequently these guidelines are followed. With limited evidence on guideline concordance, assessing the impact of recommendations is challenging.

Previous studies have investigated timeliness of diagnostic activities for lung cancer which occur after referral from primary care, such as waiting times for specialist appointments.¹⁰⁻¹³ However, little is known about potential missed diagnostic opportunities in primary care when patients first present with symptoms. An improved understanding of how patients with cancer-associated features are managed in primary care before referral to specialist care could help identify missed diagnostic opportunities and guide interventions aimed at improving the timeliness of cancer diagnosis and treatment.⁵

Chest X-ray was recommended as the first-line investigation in patients presenting with features of possible lung cancer in the 2005 NICE guidelines and the revised 2015 guidelines.^{8,9} They recommended that chest X-ray is performed within 14 days of symptomatic presentation.^{8,9} This study aimed to examine the time to chest X-ray in symptomatic patients presenting in English General Practice prior to lung cancer diagnosis, and to determine what proportion of patients had a chest X-ray within the recommended 14-day timeframe. In addition, we sought to explore how time to chest X-ray varied with age, sex, smoking and deprivation level.

METHOD

Study design and population

This retrospective cohort study utilised routinely collected datasets from NHS patients in England. This included primary care data (The Clinical Practice Research Datalink, CPRD), cancer registry data (The National Cancer Registration and Analysis Service, NCRAS) and imaging data (Hospital Episode Statistics Diagnostic Imaging Dataset, HES DID). CPRD consists of anonymised, coded data collected from GP records, including information on demographics, symptoms, and diagnoses. CPRD contains data on some 11 million patients and is broadly representative of the UK population.¹⁴ NCRAS data contains information on patients diagnosed with cancer including diagnosis date, tumour type, and stage. HES DID data contains imaging information, including test type and imaging dates for patients undergoing imaging in NHS hospitals.^{15,16} Datasets for this study were linked at patient level by NHS digital.¹⁶

Patient sample

This research forms part of a broader study (protocol number 17_107R). The cohort for the broader study includes patients with a code for any of 11 common cancers recorded in CPRD between 1 April 2012 and 31 December 2015. From this baseline cohort, patients were included if they had a code for lung cancer in NCRAS. Date of diagnosis was taken as the first record of lung cancer in NCRAS rather than CPRD because NCRAS uses a hierarchical approach for determining diagnosis dates.¹⁷

Patients were included if they:

- Had a new record of primary lung cancer
- Presented with symptoms and/or signs of possible lung cancer in the year before diagnosis (**Box 1**)
- Had a pre-diagnostic chest X-ray after first symptomatic presentation

First presentation

Symptomatic presentations were identified from CPRD data using a predeveloped list of codes for the lung cancer symptoms and signs from the 2005 NICE guidelines.¹⁸⁻²⁰ This includes haemoptysis, dyspnoea, weight loss, hoarseness and cough (**Box 1**).⁸ As in similar studies, first presentation was taken as the first recorded symptom or sign of possible lung cancer in the year pre-diagnosis.^{18,19} Patients without a recorded symptomatic presentation in the year pre-diagnosis were excluded. We also excluded smokers/ex-smokers aged ≥ 40 years with haemoptysis and patients with superior vena caval obstruction and stridor, as NICE guidelines recommend direct specialist referral rather than chest X-ray for these patients (**Box 1**).⁸ The number of recorded symptoms and signs on the date of first presentation was documented as 1 or >1 for analysis.

Chest X-ray

Patients with a pre-diagnostic chest X-ray recorded in HES DID after first presentation were included. Time from first symptomatic presentation to chest X-ray, the 'presentation-test' interval was calculated for each patient (**Figure 1**). As NICE 2005 guidelines recommended a chest X-ray within 14 days of presentation, we considered presentation-test intervals of ≤ 14 days as guideline concordant.⁸

Demographics

Patients were categorized as 'smoker', 'ex-smoker' or 'non-smoker' using their most recent smoking code before chest X-ray (**Supplementary Text Box 1**). As NICE guidelines made recommendations for investigation and referral based on smoking status, patients without smoking data were excluded.⁸ Only the year of birth for each patient was available. We assigned the 1st of July as the birthday for all patients. The index of multiple deprivation was documented in quintiles, 1 being the least and 5 the most deprived.

Statistical analysis

We investigated the association between presentation-test interval duration (number of days as an integer), and sex, age, smoking and deprivation. Age and sex were evaluated because of their association with timeliness in cancer diagnosis in previous studies.^{10,19} Deprivation was included because lung cancer mortality rates are highest amongst deprived groups.^{21,22} Smoking was included because of its strong link to respiratory comorbidity and its importance in lung cancer etiology.^{23,24} We accounted for number of clinical features at first presentation as multiple features are more predictive of lung cancer than single features.²⁵

Unadjusted analyses were performed to explore the isolated effect of each variable and adjusted multivariable regression to explore combined effects. Regression model diagnostics were examined, and assumptions were satisfied (i.e. negative binomial dispersion parameter alpha was significant, residual plot was satisfactory). Incidence rate ratios (IRR) were calculated to determine relative effects of variables on presentation-test interval duration using negative binomial regression. Variables with an IRR >1 were interpreted as being associated with more days between presentation and chest X-ray which is equivalent to longer intervals (E.g. IRR of 1.5 = 50% more days which is equivalent to a 50% longer interval). A Cox proportional-hazards model was fitted as a sensitivity analysis and gave very similar conclusions.

All data management and analyses were conducted using Stata version 15.1.

RESULTS

Patient cohort and demographics

3645 patients had a new lung cancer diagnosis during the study period, of whom 2553 (70%) presented with features of possible lung cancer in the year pre-diagnosis. 2201 patients (86%), had a pre-diagnostic chest X-ray after presentation. A further 99 patients were excluded: 85 (4%) qualified for direct specialist referral, 2 had missing deprivation data and 12 had missing smoking data (<1%) (**Figure 2**). The final cohort (n=2102) had a median age of 72 years. 1148 patients (55%) were male. The majority were ex-smokers (56%) or smokers (37%). Demographics are summarized in **Table 1**.

Stage and histology

Most patients had a histological (n=1479, 70%) or cytological (n=217, 10%) diagnosis. 1472 (70%) had non-small-cell lung cancer, 249 (12%) had small-cell lung cancer and 381 (18%) were unspecified. Stage was documented for 1959 patients (93%); most had stage III (25%) or stage IV (52%) lung cancer.

Time to chest X-ray and guideline concordance

The overall median presentation-test interval was 49 days (interquartile range, IQR:5-172). 727 patients (35%) had a presentation-test interval ≤ 14 days, i.e. guideline concordant (median:1 day; IQR:0-6). The remaining 1375 patients (65%) had a presentation-test interval of >14 days, i.e. guideline non-concordant (median:128 days; IQR:52-231).

Demographic variation in intervals

Median presentation-test intervals are displayed by demographics in **Table 2**. Multivariable regression showed longer presentation-test intervals amongst smokers than non-smokers (IRR=1.63; equivalent to 63% longer; $p<0.001$), older patients (IRR=1.07 for every 10-years age; equivalent to 7% longer; $p=0.013$) and females (IRR=1.12; equivalent to 12% longer than males; $p=0.016$). Deprivation was weakly associated with presentation-test intervals, showing longer intervals with greater deprivation. Presentation-test intervals were longer amongst patients with >1 symptom on presentation, although this association was weak (IRR=1.2; equivalent to 20% longer; $p=0.052$).

DISCUSSION

Summary

In this study, only 35% of patients with lung cancer had a pre-diagnostic chest X-ray within the NICE-recommended 14-day timeframe following symptomatic presentation to primary care. Time between symptomatic presentation and chest X-ray was longer amongst females, smokers and older patients, reflecting a lower rate of guideline concordance in these groups. These findings highlight a potential missed opportunity for timely lung cancer diagnosis in England and could be used to guide interventions aimed at improving outcomes, particularly targeting sociodemographic disparities in healthcare access and quality.

Strengths and limitations

This study's strengths include the large sample size, high proportion of complete data, the retrospective cohort design and originality. The reliance on Codes to identify presentations in CPRD is a limitation because information about duration was unavailable. The 2005 NICE guidelines recommend chest X-ray if patients had 'persistent' features (i.e. ≥ 3 weeks).⁸ We assumed that symptoms and signs recorded within CPRD had been present for this time period, however, some patients may have been symptomatic for <3 weeks which could contribute to an underestimation of guideline concordance.

Some patients had no pre-diagnostic chest X-ray in HES DID; we were unable to identify whether this resulted from no pre-diagnostic X-ray or no recorded data. The cohort was restricted to patients diagnosed with lung cancer; patients without lung cancer who had symptomatic presentations warranting a chest X-ray were not evaluated. Therefore, we were unable to assess overall concordance with guideline-recommended X-ray timeframes, only concordance in those subsequently diagnosed with lung cancer. Nevertheless, the group evaluated is the most likely to benefit from timely investigation and diagnosis.

We did not investigate the effect of comorbid diseases on presentation-test intervals, but did investigate the effect of smoking, which is strongly related to key comorbidities including

Chronic Obstructive Pulmonary Disease (COPD). Previous studies found that comorbidities are associated with longer secondary care intervals in lung cancer and longer diagnostic intervals in other cancer types.^{13,26,27} Further research investigating the relationship between comorbidities and presentation-test intervals in lung cancer is needed.

Comparison with existing literature

A previous study reported no significant change in lung cancer diagnostic intervals after the introduction of the 2005 NICE guidelines, which may in part be explained by the low concordance with guideline recommendations on chest X-ray investigations observed in our study.¹⁸ Nicholson *et al.* found that GPs in the UK only followed national guidelines when investigating possible lung cancer 47% of the time, lower than non-UK jurisdictions (58%).²⁸ In contrast, Baughan *et al.* found a high rate (91%) of compliance with national referral guidelines for any cancer.¹² The validity of these studies is limited by recall bias and missing information, as both analysed self-evaluated accounts of compliance.

The low guideline concordance identified in our study is likely to be due to interacting patient, clinician and health system factors. Health systems can contribute to delays if demand for services exceeds available resources (e.g. imaging equipment, professionals to perform tests).^{5,29} Difficulty accessing X-rays from primary care could also extend intervals. In one study, 33% of GPs reported waiting a week or more to obtain a chest X-ray.³⁰ While such system delays may lengthen presentation-test intervals, they are likely to affect all groups and therefore do not necessarily explain differences in interval length between demographic subgroups e.g. men and women. Lung cancer poses a real diagnostic challenge in General Practice as patients usually present with 'low-risk but not no-risk' clinical features, most frequently cough or dyspnoea, which are common in non-malignant conditions.³¹ This is demonstrated in our study as only 85 of 2201 patients (4%) presented with high-risk presentations warranting specialist referral and were therefore excluded. Diagnostic difficulty can lead to multiple pre-diagnostic consultations and potential diagnostic delay, particularly amongst individuals with comorbidities.^{25,32} Comorbid disease, most evidently COPD, may also mask symptoms of lung cancer and lengthen intervals.^{6,33-35}

Associations between timely lung cancer diagnosis in the UK and sociodemographic factors have been evaluated in previous studies.^{10,19,36} As in our study, age inequalities in cancer services have been previously reported, with evidence of longer intervals and lower proportions of urgent referrals amongst older patients.^{10,12,19,37} Authors have suggested that this may reflect a tendency towards therapeutic nihilism or discrimination against older patients, whose care is often determined by age rather than need, despite cancer being more common in this population.^{12,19,36} Furthermore, age-related comorbidities may contribute to delays and accessibility issues.^{19,38} Din *et al.* noted longer lung cancer diagnostic intervals amongst females, as observed in our study.¹⁹ GP behaviour may be influenced by gender, with symptoms treated as more serious in males prompting more rapid investigation.^{5,19} GPs may consider the higher incidence of lung cancer in males (particularly historically) when considering whether to request investigations.¹ The longer time to chest X-ray experienced by smokers could result from their increased risk of respiratory comorbidity (a potential confounding factor).²³ In addition, stigmatisation of smoking may influence patients' decisions to return for chest X-ray after being informed of suspected lung cancer.³⁹ Our finding that greater deprivation is only weakly associated with longer test-diagnostic intervals

is in keeping with a recent systematic review conducted by Forrest *et al.*³⁶ Although other evidence shows that higher deprivation is associated with increased lung cancer incidence and mortality, its relationship to risk and outcomes is complex.^{21,22} It is thought that social class contributes to the differences in smoking that drives health inequalities between the least and most deprived groups, particularly impacting the prevalence of lung cancer.⁴⁰ Accounting for smoking, a potential mediating factor, in our analysis could partly explain why we found a weak association between deprivation and interval duration.

Implications for future research and practice

It is thought that concordance with NICE and other evidence-based guidelines will improve timely cancer diagnosis, although the supporting evidence for lung cancer is lacking.^{7,18,41-44} Longer time intervals allow tumour growth and disease progression and thus could contribute to poorer lung cancer survival.^{2,45-47} This suggests that the two thirds (65%) of lung cancer patients who did not receive guideline concordant care in this study may have experienced a missed diagnostic opportunity, and may experience poorer outcomes, including reduced survival, as a result. However, further research exploring the effect of longer presentation-test intervals on stage and survival would be needed to confirm this. As discussed, the poor overall concordance with recommended intervals for chest X-ray are unlikely to be due to a single cause but rather a range of factors. Given the importance of early lung cancer diagnosis, further research is needed to identify causes for low guideline concordance and to address them. Our findings support theories that older patients, women and smokers are more likely to experience delayed diagnosis and missed diagnostic opportunities.^{19,25,32,35} These findings could inform future guidelines, education programs, and early diagnostic initiatives. Further research aimed at understanding the mechanisms by which presentation-test intervals are prolonged in the groups of patients identified in this study, could help direct strategies aimed at reducing diagnostic delay in lung cancer.

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Competing interests

The authors declare no competing interests.

Ethical approval

This study gained appropriate regulatory approval as part of the International Scientific Advisory Committee application for a broader study (protocol number 17_107R).

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Box 1: NICE Guidelines for Referral of Suspected Cancer. Section 1.3: Lung Cancer (2005)

1.3. Lung Cancer

Specific recommendations

1.3.2. An urgent referral for a chest X-ray should be made when a patient presents with:

- haemoptysis, or
- any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs: chest and/or shoulder pain, dyspnoea, weight loss, chest signs, hoarseness, finger clubbing, cervical and/or supraclavicular lymphadenopathy, cough with or without any of the above, features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).

1.3.3. An urgent referral should be made for either of the following:

- persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older
- a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation).

1.3.4. Immediate referral should be considered for the following:

- signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)
- stridor.

Referral timelines

The referral timelines used in this guideline are as follows:

- **immediate:** an acute admission or referral occurring within a few hours, or even more quickly if necessary
- **urgent:** the patient is seen within the national target for urgent referrals (currently 2 weeks)

Figure 1: Illustration of evaluated time intervals from presentation to diagnosis

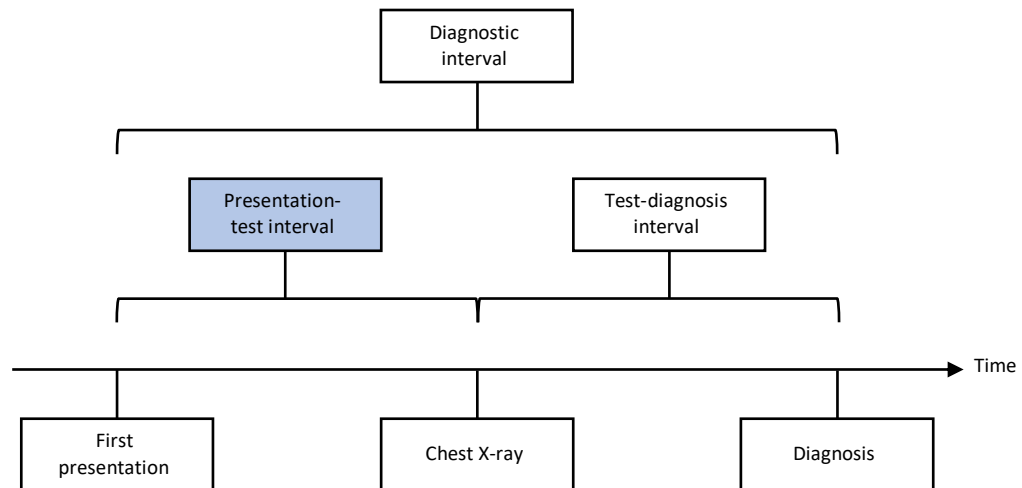


Figure 2: Application of study inclusion criteria

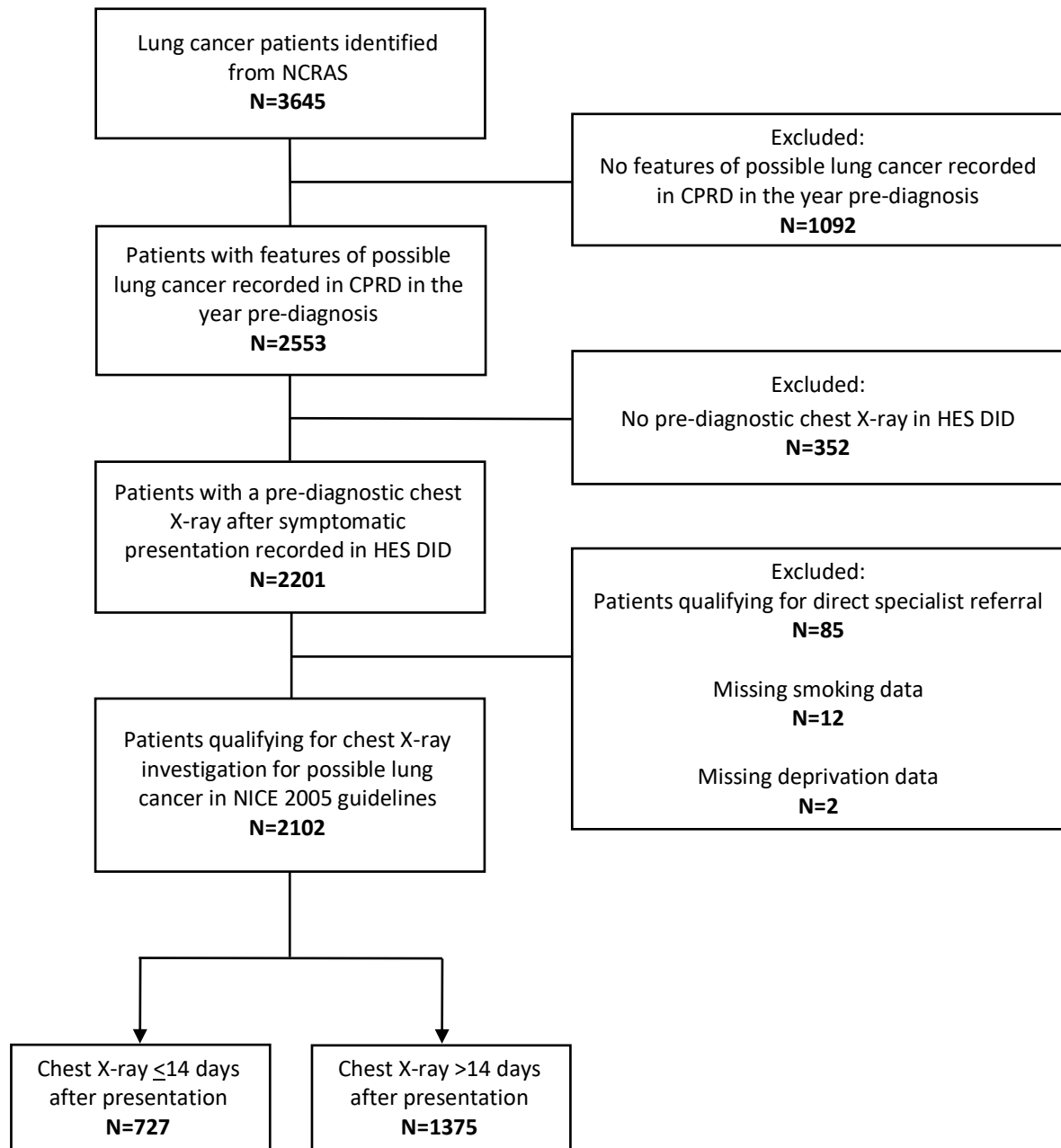


Table 1: Proportion of NICE guideline concordant pre-diagnostic chest X-rays (≤ 14 days after presentation) among symptomatic lung cancer patients by sociodemographic factors

	Patients in cohort, <i>n</i> (%)		
	chest X-ray ≤ 14 days (guideline concordant)	chest X-ray > 14 days (guideline non-concordant)	Total
All	727 (34.6)	1375 (65.4)	2102 (100)
Sex			
Male	426 (37.1)	722 (62.9)	1148 (100)
Female	301 (31.6)	653 (68.4)	954 (100)
Age categories			
<40	1 (33.3)	2 (66.7)	3 (100)
40-49	25 (48.1)	27 (51.9)	52 (100)
50-59	85 (35.3)	156 (64.7)	241 (100)
60-69	214 (37.2)	362 (62.8)	576 (100)
70-79	240 (31.7)	517 (68.3)	757 (100)
80-89	142 (33.7)	279 (66.3)	421 (100)
90+	20 (38.5)	32 (61.5)	52 (100)
Deprivation			
Least deprived	133 (36.2)	234 (63.8)	367 (100)
Quintile 2	147 (39.7)	223 (60.3)	370 (100)
Quintile 3	141 (33.5)	280 (66.5)	421 (100)
Quintile 4	152 (34.7)	286 (65.3)	438 (100)
Most deprived	154 (30.4)	352 (69.6)	506 (100)
Smoking status			
Non-smoker	71 (47.7)	78 (52.3)	149 (100)
Ex-smoker	396 (33.9)	772 (66.1)	1168 (100)
Smoker	260 (33.1)	525 (66.9)	785 (100)
Number of features on 1st presentation			
1	692 (35.0)	1285 (65.0)	1977 (100)
>1	35 (28.0)	90 (72.0)	125 (100)

Table 2: Association between demographics and presentation-test intervals using negative binominal regression¹

	Patients in cohort	Presentation-test interval (days)		
	n (%)	Median (IQR ²)	IRR ³ (adjusted ⁴)	95% CI ⁵ (p-value)
Total	2102 (100)	49 (5-172)	-	-
Constant	-	-	35.77	23.09-55.40(<0.001)
Sex				-
Male	1148 (54.6)	41 (4-162)	Reference	-
Female	954 (45.4)	63 (7-182)	1.12	1.02-1.24 (0.016)
Age				
For every 10-years age	-	-	1.07	1.01-1.12 (0.013)
Deprivation				
Least deprived	367 (17.5)	43 (4-162)	Reference	-
Quintile 2	370 (17.6)	37 (3-147)	0.86	0.73-1.02 (0.081)
Quintile 3	421 (20.0)	46 (6-173)	1.01	0.86-1.18 (0.927)
Quintile 4	438 (20.8)	49 (6-184)	1.03	0.88-1.21 (0.704)
Most deprived	506 (24.1)	73 (9-184)	1.08	0.93-1.25 (0.326)
Smoking status				
Non-smoker	149 (7.1)	18 (1-85)	Reference	Reference
Ex-smoker	1168 (55.6)	52 (6-173)	1.58	1.26-1.99 (<0.001)
Smoker	785 (37.3)	55 (6-181)	1.63	1.29-2.05 (<0.001)
Number of features on 1st presentation				
1	1977 (94.1)	48 (5-170)	Reference	Reference
>1	125 (5.9)	91 (10-190)	1.20	1.00-1.43 (0.052)
ln(alpha)	-	-	0.82	0.77-0.88

¹ Likelihood ratio (LR) test of alpha=0, chi-sq=240,000, p<0.001

² IQR = interquartile range

³ IRR = incidence rate ratio

⁴ Variables included in the adjusted analysis include sex, age in years, level of deprivation, smoking status and number of features at 1st presentation

⁵ CI = confidence interval

SUPPLEMENTARY TEXT BOX 1: DETERMINING SMOKING STATUS

Patient smoking data is recorded within CPRD ('Additional' file) as a categorical variable:

- 0 = "data not entered"
- 1 = "Yes"
- 2 = "No"
- 3 = "Ex"

We used this information to determine patient smoking status, with "Yes" indicating a current smoker, "No" a non-smoker and "Ex" an ex-smoker. While further information on smoking is available within CPRD ('Additional' file) for some patients, e.g. number of cigarettes per day or ounces of tobacco, we did not make use of it in this study.

Different smoking statuses can be recorded for a given patient at different points in time. Using the 'event date' we identified the most recent smoking status for each patient, recorded on or prior to the date of chest X-ray. This status was accepted as the patient smoking status. An exception was made where the most recent code indicated that the patient was a non-smoker, but the patient had past codes indicating a history of smoking e.g. previous codes for smoking. In such cases we classified the patient as an ex-smoker.