A Systematic Review and Meta-Analysis of Inclusion Criteria for Lung Cancer Screening in European Randomized-Controlled Trials

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ABSTRACT

Background: According to current medical knowledge, lung cancer represents one of the most common cancers worldwide in which prognosis is often compromised by late diagnosis of the condition. Despite significant improvements in the treatment being made over the past 50 years, the prognosis remains poor due to diagnostic delays. Early detection of disease became the utmost priority, leading to the development of several screening programs. Differently from the United States, European countries do not have established yet the inclusion criteria for lung cancer screening. In the last 10 years, different European countries made combined efforts in conducting randomized-controlled trials (RCTs) to establish uniform inclusion criteria for lung cancer screening that can detect lung cancer at the earliest stage possible. Data from these population-based studies demonstrated that computed tomography (CT) via volumetric analysis can detect lung cancer nodules at smaller sizes than chest X-ray since this method measures the volume of each nodule. This enables early detection of lung cancer and treatment, thus reducing mortality. Interestingly, the inclusion criteria used for qualifying individuals for lung cancer screening varied greatly across different European RCTs and so was their efficiency in early lung cancer detection. This study aims to evaluate how the inclusion criteria used in the European RCTs that have assessed CT screening using volumetric analysis have performed the task of identifying the optimal target group to screen.

Methods: In the study, five trials were included that employed CT scanning via volumetric analysis and were carried out in Europe from 2003-2020. The trials were selected by searching MEDLINE and EMBASE databases and were compared for three inclusion criteria: 1) upper and lower age limit, 2) the number of cigarettes smoked per day, and 3) the smoking duration. Each criterion was scored based on both the Liverpool Lung Project (LLP) prediction criteria and a Microsoft (MS) Excel scoring method. The trials were ranked according to the score value. The best-ranked trial had the highest score. The difference between trials' total scores and cumulative lung cancer detection rates was tested by the Chi-squared statistical test.

Results: Based on both the LLP proposed screening criteria and an MS Excel score method, the selected trials were ranked according to their cumulative scores. The scores for the lower and upper age limits showed that the NELSON trial had the best score. The age limit was from 50 to 75 years. The MILD trial scored highest with regards to the minimum number of cigarettes per day and smoking duration; it included a minimum of 19 cigarettes per day, 29 pack years, and a maximum of 10 years of smoking cessation. The best-ranked trial was MILD with a total score of 11. The second best-ranked trial was NELSON (10) followed by DLCST (7), LUSI (7), and UKLS (5). The comparison between total scores and cumulative lung cancer detection rates did not demonstrate a statistical significance between trials ($p=7.5882$) and confirmed that the MILD trial had the best scores by both parameters.

Conclusion: In conclusion, this review revealed that CT lung cancer screening in Europe should be recommended for individuals older than 50 years who have smoked a minimum of 19 cigarettes per day, have 29 years of smoking exposure, or ceased smoking 10 years ago or less, as they represent the highest risk groups for developing lung cancer. Moreover, this analysis demonstrated the importance of lung cancer screening criteria re-validation in future studies that will include more European RCTs and inclusion criteria that are not analyzed in this paper.

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1. Introduction

In the current literature, the data about lung cancer prevalence and incidence in Europe are mostly reported from population-based studies in the United Kingdom (UK). According to these data, after breast and prostate cancer, lung cancer is the third most common cancer in the UK with an incidence of 72 persons per 100,000, accounting for 13% of all cancer cases. Recent studies showed that the risk of developing lung cancer increases with age, with the highest rates being found in those aged 75 and over. Besides age, other risk factors include smoking, a family history of lung cancer, and exposure to second-hand smoke, asbestos, radon, and aromatic hydrocarbons (Dubey, Gupta, and Jain 2016). Smoking is the most important factor and is associated with 86% of all lung cancer cases worldwide (Snowsill et al. 2018; UK 2017) Despite lung cancer mortality rates decreasing by more than 28% over the last five decades, lung cancer remains the leading cause of cancer deaths in the UK, accounting for an estimated 21% of all cancer deaths. Late presentation of lung cancer remains a contributing factor to these figures, with 75% of all lung cancer diagnoses being made at late stages (III and IV) in the UK when the cancer is spread to both lungs, into the area around the lungs, or to distant organs. Recent data showed that the one-year overall survival decreases as the stage of cancer progress from 88% in stage I to 19% in stage IV (Snowsill et al. 2018).

Since lung cancer fulfilled the Wilson-Jungner criteria for validation of a screening program many countries in Europe have developed trials for different screening programs to detect dysplasia before a lung nodule becomes a carcinoma or allow pre-symptomatic diagnosis. The latest data showed that the lung cancer 10-year survival rate has improved from 3.1% to 4.9% in the UK between 1971 and 2001. The National Health Service (NHS) reported that the estimated cost of lung cancer treatment was £9071 per patient per year in 2012, with a total cost to the UK economy of £2.4 billion, more than that of any other cancer (Snowsill et al. 2018).

Many randomized control trials (RCTs) have been conducted to examine whether low-dose computed tomography (LDCT) could be used to diagnose asymptomatic patients with early stages of lung cancer. Based on these results, the European Union's (EU) position on lung cancer screening has recommended volumetric analysis of lung nodule size over measuring the diameter of the nodule as it is more sensitive in detecting nodule growth (Oudkerk et al. 2017). Computed tomography (CT)

allows for cancerous, non-calcified nodules to be volumetrically analyzed with precision (Snowsill et al. 2018).

Data from all European trials were combined to accurately assess whether CT lung cancer screening was effective (Gill, Jaklitsch, and Jacobson 2013; McCartney 2017). This prompted the EU position statement on lung cancer screening in December 2017 which outlines how the pooling of data is not recommended when trials contain different populations of varying risks (Oudkerk et al. 2017). This review aims to evaluate the effectiveness of the inclusion criteria in the five European trials carried out from 2003-2020 which used CT scanning via volumetric analysis in the early detection of lung cancer (Becker et al. 2020; Criner et al. 2022; de Koning et al. 2020; Seigneurin et al. 2014; Wille et al. 2016).

2. Methods

2.1. Systematic Review

MEDLINE and EMBASE Ovid databases were used for the selection of publications that were relevant to this study's research objectives. These databases were selected because they are the largest in the medical field and contain some peer-reviewed journals. The search was filtered according to the following medical subject heading (MeSH) parameters: "Randomized Control Trial", "RCT", "lung cancer", "lung neoplasm", "Europ*", "2003-2020", "Computed Tomography", "CT", "screening" "volumetric analysis" and "detection". After applying all filters, the search yielded 60 valid publications that best fit the search criteria and were available in a free-for-all-to-view full-text format. The search was extended to the other sources and through citation searching, we found 15 more publications.

None of those publications were relevant to this review. Upon review of the 60 publications, 45 duplicates were removed. Thus, a total of 15 publications were screened and assessed for eligibility for further analysis. The meta-analysis was narrowed to five publications that qualified for quantitative synthesis since 10 articles were excluded due to insufficient scientific relevance to this review.

2.2. Selection Criteria

To identify the study inclusion criteria and formulate a valid research question we have used the PICO (Population/ Intervention/ Comparison/ Outcome) model as an evidence-based tool for primary concept identification.

Only trials which used CT scanning via volumetric analysis and were carried out in Europe from 2003-2020 were included in this meta-analysis. Based on those criteria five RCTs (by Nederland's Leuvens Longkanker Screenings Onderzoek-NELSON, Danish Lung Cancer Screening Trial -DLCST, Lung Cancer Screening Intervention -LUSI, UK Lung Cancer Screening -UKLS and Multicentric Italian Lung Detection-MILD) were identified as having volumetrically analyzed CT screening for lung cancer. RCTs with volumetrically analyzed CT screening demonstrated a high level of detection rates (3.40-3.65%) in individuals with early stages of lung cancer (Becker et al. 2020; Criner et al. 2022; de Koning et al. 2020; Seigneurin et al. 2014; Wille et al. 2016).

Furthermore, these European RCTs covered a large enough population (around 30 000 people) to study successful lung cancer detection whilst maintaining a

demographic and environmental similarity to the rest of Europe. RCTs that started on or after the year 2003 were chosen as this was when NELSON, the first major European study testing CT screening for lung cancer, had started and demonstrated CT scanning via volumetric analysis to be a more powerful method than chest X-ray in detecting small lung nodules. The search ends in January 2020 with the finalization of the NELSON trial. A similar methodology used across each study facilitates a direct comparison.

The phases of the literature search are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 diagram (Page et al. 2021).

To improve the transparency of the search, the PRISMA diagram only includes journal article citations as full references for publications that were assessed for study eligibility. In addition to the previously cited inclusion and exclusion criteria, the search was limited to articles published in English (Figure 1).

3. Results

In this review, the inclusion criteria from five European RCTs using the volumetric CT scans in early-stage lung cancer detection were collected and analyzed. The inclusion criterion received weighted scores based on both the Liverpool Lung Project (LLP) risk prediction model and the Microsoft (MS) Excel scoring method, with the highest scoring trial being the most effective. The distribution of each trial score for three inclusion criteria is presented in table 1.

The NELSON trial ranked highest for age, using lower and upper age limits, with the age range from 50-75 years proving most appropriate for selecting high-risk individuals for lung cancer screening. The MILD trial had the best scores for two inclusion criteria: 1) a minimum number of cigarettes per day (19 vs. 10) and 2) a smoking duration (29 vs. 25-26 years) when compared to other trials.

Interestingly, there was no difference in the maximum number of years to stop smoking between trials as they equally accounted for 10 years. The overall score ranked MILD and NELSON trials as the best performing trials with a total score of 11 and 10 respectively.

The UKLS trial had the lowest total score (5) as it included only one of the three scored criteria. To determine whether a relationship existed between detection rates and total scores, the Chi-squared statistical test was used (p=7.5882) which demonstrated no statistical difference ($p > 0.05$; degrees of freedom (DF) = 4) between trials. The total scores and cumulative detection rates of trials are presented in table 2.

Table 1: Distribution of scores for age, number of cigarettes per day and smoking duration in randomized clinical trials

Trial	Citation	Score fo Age	Score for Number of cigarettes per day	Score for Smoking duration
NELSON	De Koning et al., 2020	5	2	3
DLCST	Saghir et al., 2014	3	2	2
MILD	Wille et al., 2016	1	5	5
LUSI	Becker et al., 2020	2	2	3
UKLS	Seigneurin et al., 2014	3	1	1

Table 2: Total score calculation and cumulative detection rate for each European trial

Trial	Citation	Total score	Cumulative detection rate in percent
NELSON	De Koning et al., 2020	10	2.60
DLCST	Saghir et al., 2014	7	3.40
MILD	Wille et al., 2016	11	2.40
LUSI	Becker et al., 2020	7	3.65
UKLS	Seigneurin et al., 2014	5	2.10

When trials were ranked by both parameters (total score and cumulative detection rate), the comparative analysis showed a discrepancy between ranks for detection rate and total score of each trial. Using the Chi-squared test, the calculated p-value showed that the difference between each trial total score and the cumulative detection rate was not statistically significant (p=0.13155; DF = 4). However, there is a trend that MILD and NELSON trials should be considered the best-ranked trials. The data is presented in table 3.

Table 3: Ranks of each European trial

Trial	Citation	Total score rank	Detection rate rank
NELSON	De Koning et al. 2020	2	3
DLCST	Saghir et al., 2014	3	2
MILD	Wille et al., 2016	1	4
LUSI	Becker et al., 2020	3	1
UKLS	Seigneurin et al., 2014	5	5

FIGURE LEGENDS

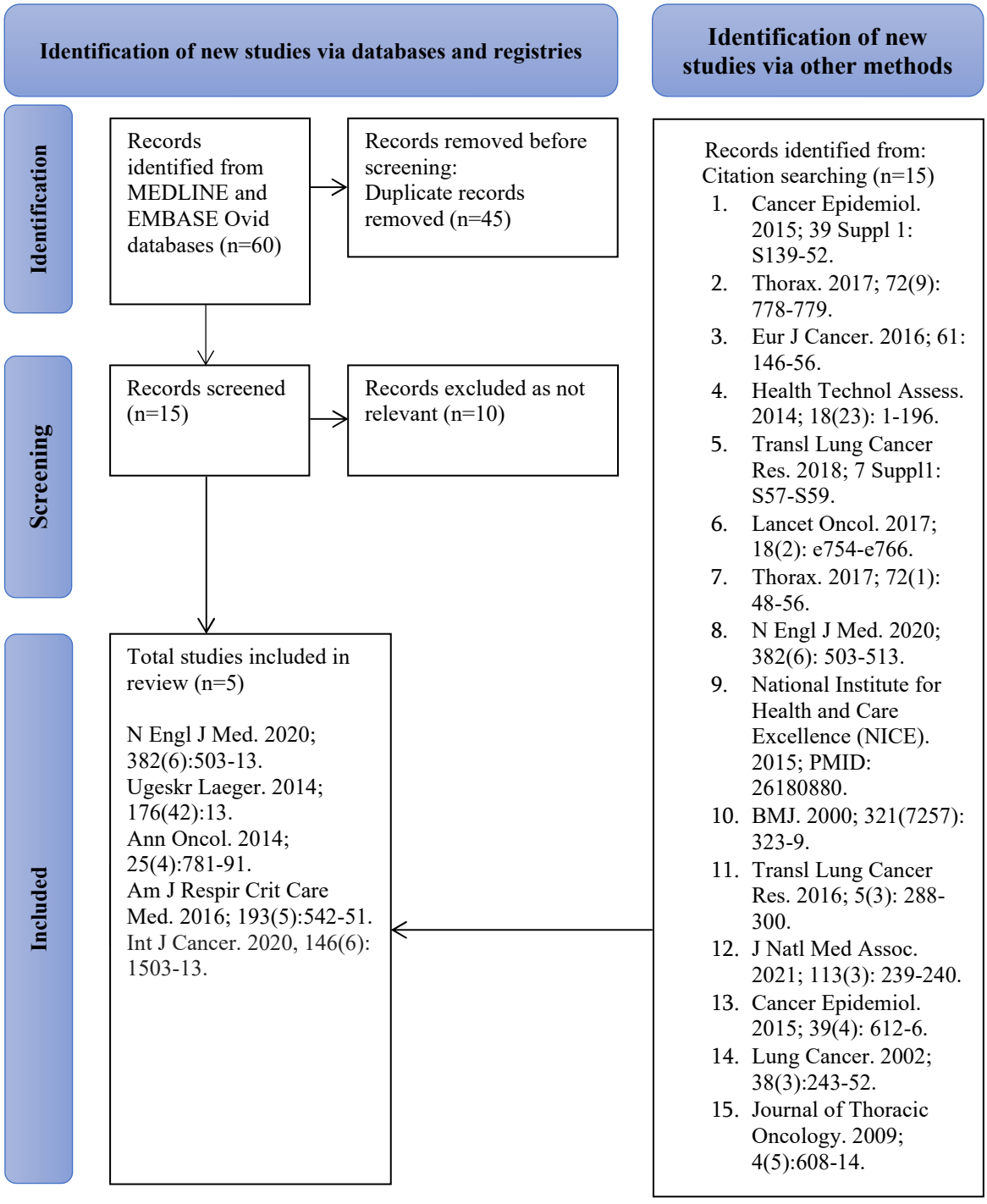

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

The comparison has shown that the 50-75- year age range, a minimum of 19 cigarettes per day, and a smoking duration longer than 29 years were the best criteria in selecting high-risk individuals for lung cancer screening.

4. Discussion

Several RCTs have been conducted to assess whether LDCT may be used in screening programs for detection of lung cancer at early stages. Given the one-year net survival is four times higher (88% vs. 19%) than in late stages; early detection is of great importance (Snowsill et al. 2018). The first major trial concerned with CT screening for lung cancer was launched in the United States (US) in 2002.

This clinical trial named the National Lung Cancer Screening Trial (NLST) screened 53,454 participants aged 55 to 74 who were either currently smokers or used to smoke for 15 years at least 30 pack-years. The control group were screened annually using chest x-ray whilst CT scan was used to screen the intervention group. At the end of the trial, the intervention group showed a relative reduction in lung cancer mortality by 20% after seven years of follow up when compared to the control group (Gp et al. 2013; Team 2011). Many European countries created their own screening trials by replicating the NLST. The largest of the European trials was the Nederland's Leuvens Longkanker Screenings Onderzoek (NeLSOn) trial, conducted in the Netherlands and Belgium, with a population of 15,882 participants. Other trials testing lung cancer CT screening were the Danish Lung Cancer Screening Trial (DLCST), Multicentric Italian Lung Detection (MILD), Lung Cancer Screening Intervention (LUSI) and UK Lung Cancer Screening (UKLS) trial. These trials had a population ranging from 4052 to 4104. Mortality reduction varied from 39% in the MILD trial to no mortality reduction in the DLCST (Criner et al. 2022; Seigneurin et al. 2014; Wille et al. 2016). The UK National Screening Committee (UKNSC) used the Wilson-Jungner criteria as guidelines to select health conditions for screening at an early stage when an acceptable treatment exists. Currently, no screening strategy for lung cancer fulfils the Wilson-Jungner criteria due to poor specificity as highlighted by over-diagnosis reported in lung cancer CT screening trials (Team 2011). Such over-diagnosis of lung cancer becomes a greater problem when asymptomatic patients are recruited into screening. The NLST estimated that 18.5% of all lung cancers detected were considered over-diagnosis and it showed a false positive rate of 96.4% (Patz et al. 2014; Team 2011).

Therefore, the UKNSC has not recommended a specific strategy for lung cancer screening. Despite this, as of January 20, 2020 the NELSON study reported recent improvements in nodule volume measurement which improved testing efficiency. Following this, the final report of the NELSON trial revealed a low rate of false positive results, 20% in first screening and only 1.9-6.7% in subsequent screening. Using volumetric analysis, the NELSON study showed that, at most, 10% of the screened cases were over-diagnosed. The ten years of follow up has shown that the percentage of over-diagnosis cases compared to the percentage of individuals who developed lung cancer was significantly less so it confirmed that CT scan via volumetric analysis can be a better method for detection of lung cancer at an early stage (Criner et al. 2022; de Koning et al. 2020; Seigneurin et al. 2014). According to these results, the NELSON trial confirmed the efficacy of LDCT screening. It additionally sets to ensure that policy makers in the Europe define the optimal target population and a strategy for screening that would be both cost effective and acceptable in reduction mortality rate from lung cancer (Duffy and Field 2020).

This review has shown that European RCTs differ among the inclusion criteria used in selection individuals for lung cancer screening. To compare the efficacy of each trial in early detection of lung cancer screening we scored five trials in MS Excel for three important inclusion criteria that were recommended for lung cancer screening with LDCT: 1) age range, 2) number of cigarettes smoked per day and 3) number of years smoking in current or ex-smokers. Each inclusion criterion was weighted to define the score for each trial. Trials were then ranked according to this value. Specific weights for different criteria were determined by the LLP risk prediction model criteria which display the individual risk of developing lung cancer that increase by age, cumulative effect of smoking exposure and smoking duration. The decision for using the LLP risk prediction model was in accordance with the current EU position statement, recommending LLP as an appropriate prediction model for selecting individuals for lung cancer screening (Oudkerk et al. 2017).

4.1. Age - Inclusion Criteria

Results from the study that included smoking history as a contributing factor in the development of lung cancer recommended choosing ex-smokers/smokers who had at least a 30-year smoking history in lung cancer screening program (Wille et al. 2016). The rationale for this recommendation was that the average age when people start smoking was 25 years so the optimal age to begin lung screening should be at an age below 55 years. Even though all trials demonstrated good performance in lung cancer screening, there were differences in the scores for lower and upper age limits between them. The lowest age limit of 49 years was found in the MILD trial, whilst the highest age limit of 75 years was found in the NELSON trial. The MILD trial included individuals from the age of 49 and had the lowest performance score (Becker et al. 2020; de Koning et al. 2020). In fact, the DLCST study concluded that extending the age group to 50 was not recommended as it did not show a change in mortality (Becker et al. 2020). The NELSON publication does not state the rationale behind choosing lower age limit of 50 (de Koning et al. 2020). The upper age limit

varied throughout all trials as well. The MILD study did not have an upper age limit. The LUSI trial had a maximum age of 69, whilst DLCST and NELSON had age limits of 70 and 75 respectively (Becker et al. 2020; de Koning et al. 2020). The NELSON study chose to extend the upper age limit to eliminate the difference of 15 years in life expectancy between women and men (Wille et al. 2016). As previously mentioned, the one-year net survival rates for stage I and stage IV cancers are 88% and 19%, respectively (Snowsill et al. 2018). A possible bias in this measurement is lead time bias, referring to a possibility that actual survival time might not have changed despite appearing as though it has due to differences in the time measurements were taken. For the patient, it has the effect of appearing as though survival time is either longer or shorter as time is measured from the time of diagnosis. In CT screening studies, lead time was defined as 10 years after the diagnosis of lung cancer therefore the target population must have a life expectancy of at least 10 years to see a real effect on mortality (Ge et al. 2018). Since the life expectancy of men in Western Europe aged 70 was between eight to 10 years, the DLCST chose 70 to be the upper age limit however; this can exclude women who have a higher life expectancy of 85. Using life expectancy as a means of determining the upper age cut-off takes into account the increased likelihood that the target population die from co-morbid disease (Wille et al. 2016). Patients also need to be young enough to undergo thoracic surgery where parts or whole lung with local lymph nodes can be removed. It is recommended for the lung cancer at stage I-II when it is non-spread distantly (Van Iersel et al. 2007). Based on scoring calculation it was found that the NELSON trial had the best performance when scoring for the lower and upper age limits. In contrast to others RCTs, this trial extended the upper age limit to 75 years accounting both criteria: five years difference in life expectancy between men and women and higher lung cancer prevalence after the age of 70 (Horeweg et al. 2013).

4.2. Smoking History - Inclusion Criteria

The DLCST and MILD study used a 20-pack year history as exclusion criteria, whereas the NELSON and LUSI study used a minimum of 15 cigarettes per day over 25 years (equivalent to 18.75 pack years) or a minimum of 10 cigarettes per day over 30 years (equivalent to 15 pack years) as exclusion criteria (Horeweg et al. 2013). Pack years are calculated by multiplying the number of cigarette packs smoked per day by the duration of smoking in years. Therefore, the duration of smoking and number of cigarettes consumed per day are equally weighted. This being said, Haldorsen and Grimsrud have measured that lung cancer incidence increases by a power of 4.5 for each year of smoking, and only by a power of 1.5 for each pack smoked per day (Haldorsen and Grimsrud 1999). As a result, the NELSON and LUSI trial used the individual components of a pack year. The number of packs smoked per day and total duration of smoking are contributing factors but each of them has a separate impact on lung cancer predisposition (Gp et al. 2013; Horeweg et al. 2013). In the MILD study the individuals that smoked for less than 29 years were included in the trial although this made up only a small proportion of the study population (8.3%). This review accounted for an additional criterion, the number of cigarettes per day and increased the minimum number of cigarettes per day to 19. In doing so, the study increased the proportion of eligible individuals based on their higher risk of lung cancer development by 23% (Gp et al. 2013). Since both recommended models (LLP and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening model) measure pack years and duration of smoking separately, there is no valid model to score compound risk of both factors. Therefore, the UKLS used the LLP model which accounts smoking duration as a risk factor. Contribution of smoking history to individual risk is sometimes underestimated because smoking behaviour was mostly recorded via participant self-reporting with little or no confirmation of true smoking status, such as the measurement of exhaled carbon monoxide, a method used only in the DLCST (Ashraf et al. 2009).

All studies looked at current and former smokers but definitions of what constituted a former smoker varied slightly among them. Despite this, all studies agreed with defining smoking cessation as not smoking for at least 10 years. It is unclear why the 10-year limit was set (Støvring et al. 2004). The NELSON trial was the first trial that recommended using a target population of ex-smokers who had quit no more than five years ago as opposed to 10 years used in other trials (Wille et al. 2016). The DLCST added that the participant must have ceased smoked before the age of 50. The paper did not explain why this additional age limit was added however, it should be noted that there is evidence that smoking cessation after the age of 50 still carries significant risk reduction in lung cancer (Cassidy et al. 2008).

The trials compared in this review also differed with regards to the inclusion of the number of cigarettes per day as one of the significant risk factors for developing lung cancer. From the cohort analysed in this study, UKLS was the only trial which failed to provide information about the number of cigarettes per day in their selection criteria. Instead, the individuals were selected based on predictions of 5% lung cancer risk calculated using the LLP model. Most trials only included participants who have smoked at least 10 cigarettes per day, with MILD as the only trial that increased the minimum number to 19 cigarettes per day (Becker et al. 2020). Scoring studies for the number of cigarettes per day demonstrated that the MILD trial had the best performance, with an inclusion criterion of almost double the number of cigarettes per day than that of other compared trials (19 vs. 10). The importance of this criterion is highlighted by the LLP study which showed that the individual risk for lung cancer correlates directly with the number of cigarettes smoked per day (Cassidy et al. 2008).

The trials were additionally analysed regarding smoking duration and the number of years of smoking cessation as the other significant risk factors for lung cancer. The MILD trial demonstrated the highest performance score, selecting participants using two criteria: 1) current smoker and having smoked a minimum 29 years or 2) ex-smoker and quitted smoking for a maximum of 10 years. The other trials included smoking duration as a minimum of 25-26 years. The MILD trial had the highest score because it included individuals with the longest smoking history, and this was the largest weighted selection criterion as demonstrated by the LLP model (Cassidy et al. 2008).

When all trials were compared by their total scores and ranked accordingly, the best performing trial over three inclusion criteria was MILD (11) followed by NELSON (10), DLCST (7) and LUSI (7). The UKLS trial had the lowest total score (5) as its selection criteria were based on the LLP prediction model of 5% lung cancer risk rather than defining the value of each inclusion criterion (Cassidy et al. 2008). To further this analysis, the total score of each trial were compared to the cumulative lung cancer detection rates for LDCT screening. The selection of cumulative lung cancer detection rates as a comparator to trials scores was based on its significance as the best indicator of trial performance in early detection of lung cancer (Van Iersel et al. 2007). To test the difference between trials regarding detection rates and total scores, the Chi-squared statistical test ($p=7.5882$) was used, and it demonstrated no statistical difference ($p > 0.05$) between trials. However, when ranked trials were compared by both detection rate and total scores, the comparative analysis showed that there was a discrepancy between trials despite the Chi-squared test demonstrating no statistical significance ($p=0.13155$). Since the total scores for MILD (1st rank) and NELSON (2nd rank) trials are consistent with their hazard ratio data, these trials have been shown to have high performance scores in both parameters (Becker et al. 2020). It is recommended that these trials include criteria for age, number of cigarettes smoked per day and smoking duration as the best criteria for selection of individuals for LDCT screening. Therefore, the recommended inclusion criteria are as follow: 1) Age range from 50-75 years, 2) A minimum of 19 cigarettes smoked per day, 3) A smoking history of 29 years smoking and 4) Maximum 10 years of smoking cessation.

4.3. Strengths and Weaknesses

The significance of the findings in this review is limited because it encounters many caveats. The studies included in this review were searched through two databases and only papers with free access are selected. The data were derived from population based RCTs conducted in Europe. Selection of trials based on two criteria: 1) European RCTs conducted in the period from 2003 to 2020 and 2) RCTs that used LDCT with volumetric analysis, may lead to selection bias as they may exclude other trials with better screening performance but used different inclusion criteria and/or screening methods. The small sample size additionally lacked sufficient power to attain a statistically significant difference between the trials. Only three risk factors were compared although results showed that the trials performed better if they included greater numbers of selection criteria for screening. The ranking of trials based on a small number of factors is prone to bias, as the LLP model employs more risk factors than were included in this analysis. The variation of inclusion criteria across the group of RCTs additionally biased the calculation of their scores. This bias was higher if there was a missing value for a specific inclusion criterion assessed within this study and the trial received the lowest score. Nevertheless, this review showed the importance of using a scoring system as an objective measure to compare the inclusion criteria of different RCT protocols. To validate the ranking of each trial, the total scores were compared to the trials' cumulative lung cancer detection rates that are known to be strong indicators of screening performance. The use of the LLP model as the best prediction model in selecting individuals for lung cancer screening, as per the EU for ranking inclusion criteria of RCTs, provided a credible basis for the analysis in this study.

5. Conclusions

This review has shown that the upper age limit, number of cigarettes and smoking duration represent the strongest inclusion criteria in the selection of individuals for lung cancer screening. The screening performance and lung cancer detection rate were better when the trials increased the upper age limit to 75 years as the highest incidence of lung cancer is in people aged 75 and over. However, the analysis of both criteria number of cigarettes per day and smoking duration permits better discrimination between current and ex-smokers.

The importance of this is clear, as according to previously published data, smoking cessation history of less than 10 years does not diminish lung cancer risk and continues to be the same as at the time when the individual smoked. Based on these results, the lung cancer screening program should be recommended for the individuals aged 50-75 years, current smokers with a smoking history of at least 19 cigarettes per day for at least 29 years or ex-smokers with a maximum of 10 smoke free years.

Since this study used for the first time MS Excel scoring method as a validation method to compare inclusion criteria between RCTs that were different it may contribute with adding new information to the available literature on lung cancer screening. In addition, the inclusion criteria derived from this analysis may serve as new recommendations for lung cancer screening in Europe, upon validation of those results in future systematic reviews that will compare the performance of a larger sample of European RCTs and involve analysis of a wider range of inclusion criteria.

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