Role of low dose computed tomography on lung cancer detection and mortality - an updated systematic review and meta-analysis

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Abstract

Chest low dose computed tomography (LDCT) is reported to be a sensitive tool for detection of lung cancer at asymptomatic stage, thus reducing the mortality. The review assesses the effect of LDCT screening on all-cause mortality, lung cancer mortality and incidence rates. We conducted literature searches of PubMed, Scopus, and the Cochrane Library from inception through January 2020 to identify relevant studies assessing the diagnostic accuracy of LDCT for lung cancer. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting this meta-analysis and review. The inclusion criteria were i) randomized control trials, ii) comparing LDCT to any other form of screening or standard of care and, iii) primary outcome studied: all-cause mortality, lung cancer specific mortality, rate of early detection lung cancer. A total of 11 studies encompassing 97,248 patients were included. When compared with controls (no screening or chest X-ray), LDCT screening was associated with statistically significant reduction in lung cancer mortality [pooled risk rate (RR) 0.86; 95% CI 0.75-0.98]; low heterogeneity observed (I^2: 27.86). However, LDCT screening was not associated with statistically significant reduction in all-cause mortality (RR: 0.96; 95% CI: 0.92 - 1.01). Notably, the LDCT screening was associated with statistically significant increase in lung cancer detection (RR: 1.76; 95% CI: 1.14-2.72). LDCT screening has a potential to reduce mortality due to lung cancer among high-risk individuals. LDCT could be considered as a screening modality after careful assessment of other factors like prevalence of TB, proportion of high-risk population, cost, access and availability of LDCT.

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Introduction

Worldwide lung cancer is the most common form of cancer, as well as the leading cause of cancer-related mortality [1]. India, according to the GLOBOCAN 2020 report, had an estimated age-standardized incidence rate of lung cancer of 5.4 per 100,000 (72,510 cases per year). The estimated age-standardized lung cancer mortality rate in India was 2.8 per 100,000 (18,578 deaths per year), making it the fifth most common cause of cancer mortality in India [2]. Low dose computed tomography (LDCT) of thorax is reported to be a sensitive tool for screening of lung cancer. Lung cancer is asymptomatic in the early stages, hence usually missed in clinical practice. Diagnosing lung cancer when the disease is in its early stages, the 5-year survival rate is about 55% to 60%, compared with 4% for patients with advanced-stage disease [3]. Screening strategies are expected to detect disease at an early stage leading to reduction in disease-specific and all-cause mortality. The two major trials of this decade, the NELSON and NSLT, have shown prominent reduction in mortality with LDCT [4,5] while other studies have failed to demonstrate mortality reduction. In medical literature, systematic reviews of randomized controlled trials [RCTs] are the most authentic evidence to answer issues of multiple types of medical intervention.

The present study aims to systematically review the updated

evidence regarding the ability of LDCT to reduce lung cancer and all-cause mortality. This study also explores the utility of lung cancer screening in tuberculosis endemic countries.

Materials and Methods

Data sources

We conducted online literature searches of PubMed, Scopus, and the Cochrane Library from inception through January 2020 to identify relevant studies assessing the effect of low-dose CT on all-cause mortality and lung cancer mortality & incidence rates. Search terms included ("Tomography, X-Ray Computed"[mesh] OR "Tomography, Spiral Computed"[mesh] OR "CT"[tiab] OR "CAT"[tiab] OR "tomography"[tiab]) AND ("low-dose"[tiab] OR "low-dose"[text] OR "lower-dose"[tiab] OR "lower-dose"[text] OR "low radiation"[tiab] OR "low radiation"[text] OR "lower radiation"[tiab] OR "lower radiation"[text] OR "low kv"[tiab] OR "low kv"[text]) AND ("Lung Neoplasms"[Mesh]) AND ("Mass Screening"[Mesh] OR "Early Detection of Cancer"[Mesh]) were applied. In addition, reference lists of identified articles were manually examined to refine the potentially relevant studies. Two investigators () screened titles and abstracts for potential eligibility, and disagreements were resolved by discussion. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [PRISMA] guidelines [6] for reporting this meta-analysis and review (Figure 1).

Study selection

The studies that met the following criteria were included: i) Study design was randomized controlled trials, ii) study population being adult males and females with no history of lung cancer, iii) intervention or exposure group received LDCT for screening of lung cancer, iv) control group received any other form of screening or standard care, and v) outcomes studies were all-cause mortality, lung cancer mortality and incidence rates. Exclusion criteria were: i) modelling studies, and ii) studies not conducted in humans.

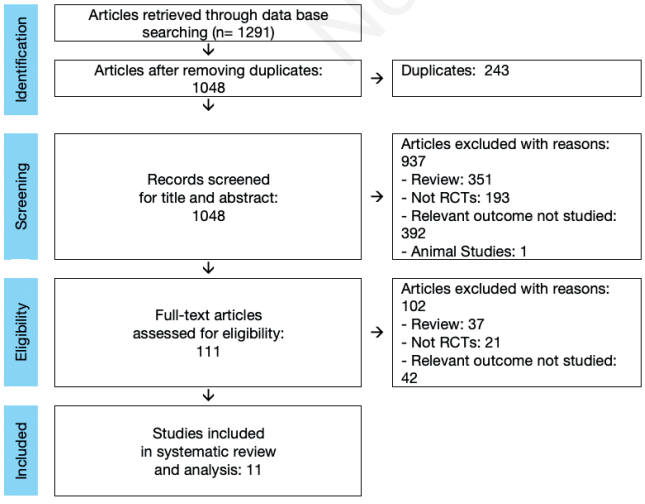

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Data extraction and summary measures

First of all, duplicate articles were identified and removed. An investigator screened the titles and abstracts of the non-duplicate articles to screen out the non-relevant articles. This was followed by full-text reading to identify the potential articles for inclusion on the basis of inclusion and exclusion criteria.

Two reviewers independently extracted the details in the pre-coded spreadsheet. Extracted details included details about study design, description of patient selection, number of patients enrolled, patient demographic characteristics, number of positives for lung cancer in both groups with screening with LDCT and no screening or any other means of screening respectively. Any conflict was resolved by the third reviewer.

Assessment of quality of study

Risk of bias of included studies was assessed using the Cochrane Collaboration's Risk of Bias assessment tool for randomized control trials [7]. All the included studies were assessed on following domains: i) random sequence generation, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data, vi) selective reporting, and vii) other bias. The included studies were labelled as "high risk", "low risk", or "unclear risk" on the basis of assessment by the reviewers.

Data synthesis and analysis

Summary estimates (relative risk) were provided for pooled all-cause and lung cancer mortality and number of lung cancer cases identified with 95% confidence intervals to assess precision of estimates. Heterogeneity of estimates was assessed using Cochrane Q and I^2 statistic. I^2 of more than 50% was considered to indicate presence of heterogeneity. Publication bias was assessed using funnel plots.

The article was written according to PRISMA guidelines (PRISMA checklist compliance sheet).

Results

Study selection

A total of 1,291 records were identified at initial database extraction, of which 243 duplicates were removed and 1,048 records were screened for title and abstract. Of those, 937 records were excluded for various reasons. A total of 111 full text articles were assessed for eligibility, of which 102 were excluded [reviews (n=37), non-randomized controlled trials (RCTs) (n=21), and relevant outcomes not studied (n=42)], and 11 studies were included in the systematic review and meta-analysis (Figure 1).

Characteristics of included studies

A total of 11 studies encompassing 97,248 patients were included in the review (Supplementary Table 1). Of these, two studies were from USA [5,8], seven studies were from Europe [4,9-14],one study was from UK [15], and only one study was conducted in countries of high endemicity for tuberculosis in China [16].The total number of included subjects for low-dose CT was 50,226. Studies have included asymptomatic people at high risk for lung cancer. Age range included varies from 45-75 years between studies and pack-years of smoking varies from 20 to 30 years. All the studies were randomized controlled trials comparing the role of LDCT *vs* either no screening or chest radiography in

high-risk individuals for lung cancer. The outcomes studied in the trials were incidence rate of lung cancers in all studies and eight studies have also studied the mortality (all-cause or lung cancer specific) benefits of the intervention done.

LDCT screening and lung cancer mortality

When compared with controls (no screening or CXR), LDCT screening was associated with a statistically significant reduction in lung cancer mortality (pooled RR 0.86; 95% CI 0.75-0.98) with low heterogeneity observed (I^2= 27.86) (Figure 2, Supplementary Table 2 a,b). As there was no symmetry in funnel plots for mortality due to lung cancer, it shows that there was a low risk of publication bias related to this outcome (Figure 3).

LDCT screening and all-cause mortality

As compared to controls (no screening or CXR), LDCT screening was not associated with all-causemortality. The pooled RR for all-cause mortality was 0.96 (95% CI: 0.92 -1.01) (Figure 4; Supplementary Table 3 a,b). The study had a low risk of publication bias related to this outcome due to no symmetry in funnel plots for all-cause mortality (Figure 5).

LDCT screening and lung cancer detection

When compared with controls (no screening or CXR), LDCT screening was associated with statistically significant increase in lung cancer detection. The pooled RR was 1.76 (95% CI: 1.14-2.72) (Figure 6; Supplementary Table 4 a,b). As there was no symmetry in funnel plots for lung cancer cases detected, it shows that there was a low risk of publication bias related to this outcome (Figure 7).

Discussion

The present meta-analysis includes results of 11 RCT's on LDCT screening till date including the latest NELSON trial results. The trials are predominantly distributed in European countries, with two trials in USA, and a single trial from Asia conducted in China. The latest meta-analysis on effects of LDCT on lung cancer screening was done by Huang et al in 2019. They had included 9 studies showing significant beneficial role of LDCT for decreasing lung cancer specific mortality but no benefit in all-cause mortality. There was significantly increased case detection in the screening group [17].

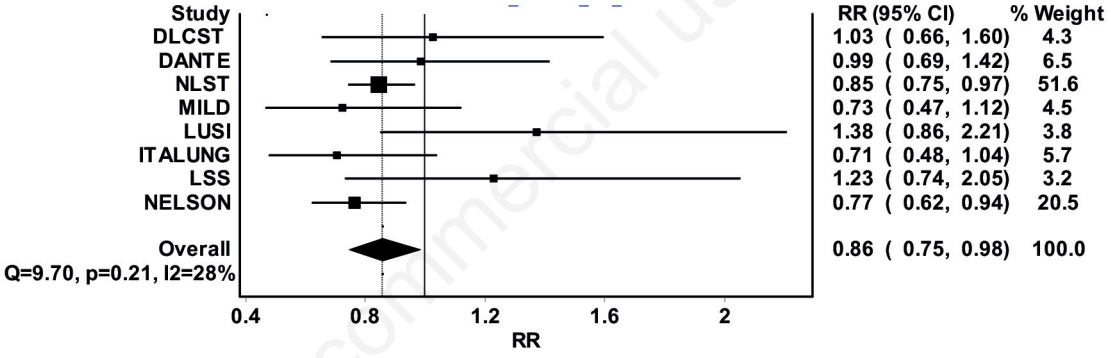

Figure 2. Forest plot for lung cancer specific mortality.

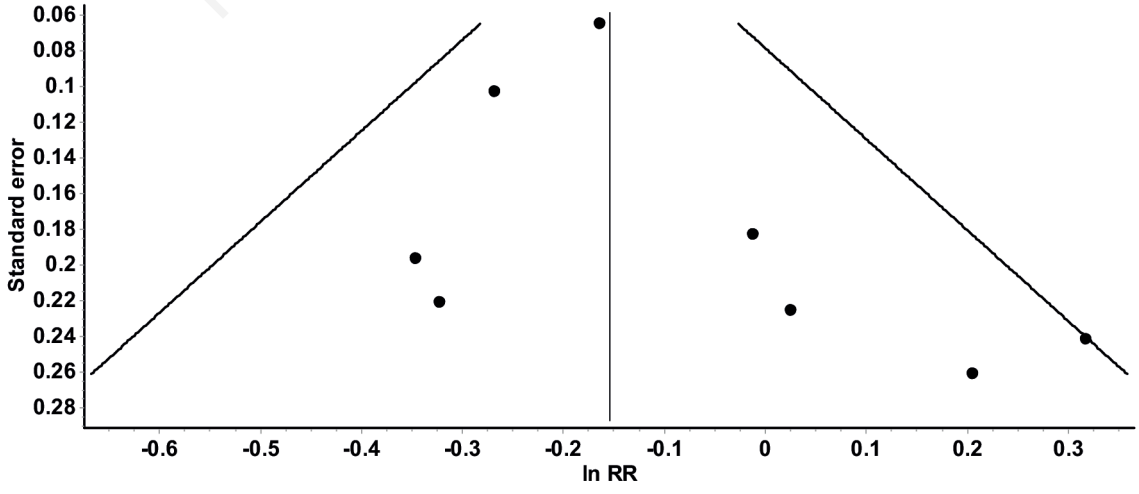

Figure 3. Funnel plot for lung cancer specific mortality.

The randomized trial, the DANTE trial, results were also not encouraging in terms of mortality benefit [14]. However, it was a single-center, study with a limited sample size compared to the power to detect high mortality benefit.

A major trial, the NLST, enrolled 53,454 patients with high-risk criteria defined as 55-74 years of age with ³30 pack-years of smoking, >50 years with 20 pack-years of smoking with one additional risk factor. This trial showed a 20% decrease in lung cancer-related mortality and 7% in overall mortality [5]. NCCN guidelines enrolled these findings, and LDCT recommended as routine screening for these patients [18].Various other trials like MILD and DANISH failed to report this benefit, but again these are single-center studies and probably not powered enough to detect a significant mortality benefit [12,13].The latest major trial, the NELSON trial, a 10 year follow up study, conducted in Belgium and Netherlands, gives a significant reduction in LC mortality with LDCT screening. Their high-risk population included people in the age group between 50-75 years with ³15 pack-years of smoking [4]. At 10 years of follow-up, the cumulative rate ratio for death from lung cancer at 10 years was 0.76 [95% confidence interval (CI), 0.61 to 0.94; p=0.01] in the screening group.

The results of the most extensive observational study, the International-ELCAP (Early Lung Cancer Action Program) study, showed a 88% 10-year survival rate after surgical resection in screen-detected stage I lung cancers [19].

We now have two significant trials in this area, the NSLT and the NELSON trial conducted in the US and Europe, respectively [4,5]. Both of them have shown a significant decrease in lung cancer mortality with LDCT in high-risk groups, with both also reporting a high rate of over-diagnosis and false positivity. The current meta-analysis shows that there is a significant difference in terms of lung cancer specific mortality when LDCT is used as a screening method in high-risk groups, though there is no significant difference in all-cause mortality.

Credibility of findings

A number of factors vouch for the credibility of the findings of our study. We explored multiple databases for retrieving relevant studies. Also, we assessed quality of all the included studies to gauge the risk of bias of studies. Lastly, we also tried to assess publication bias for all the outcomes included in our study.

Implications of the study

The harms of lung cancer screening include detection of non-cancerous nodules varied from 3% to 30% in RCTs, 20% in NELSON and 24% in NLST [4,5]. The NELSON and NLST trials had

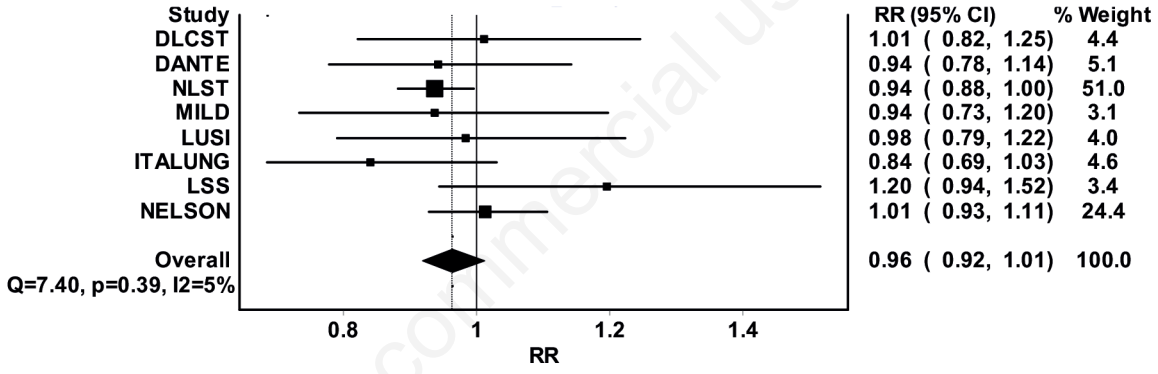

Figure 4. Forest plot for all-cause mortality.

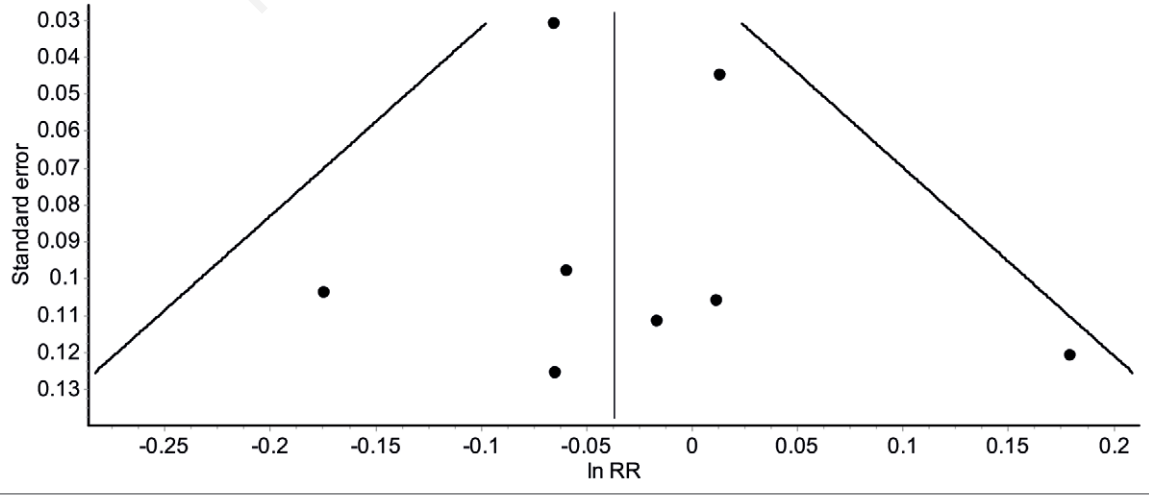

Figure 5. Funnel plot for all-cause mortality.

a different algorithm and protocol to study detected nodules. Though there is a tendency towards lower nodule detection rate in repeat screening, NLST did not observe this pattern. These nodules, in most cases, lead to further investigations like repeat imaging, including PET, the fewer number also subjected to invasive evaluation. The overdiagnosis is the presence of lesion found on screening known to be cancerous, however identifying it at an early stage is not going to affect the patient's life. The likely reasons may be either slow-growing nature of the lesion or patient may die earlier due to other cause. It makes the patient not only go through various further investigations but also causes a mental effect. NSLT study reports that the rate of overdiagnosis when compared with chest X-ray screening is not large [5]. Again, more follow-up will be needed to measure the extent of overdiagnosis by various trials.

LDCT uses a shallow dose of radiation, an estimated 1.5 mSv *vs* 8 mSv for C.T. People in the screening program underwent annual/biannual screening depending on the study design and more imaging for diagnostic purposes as well for suspicious lesions. Approximately 1 cancer death is attributed to radiation from imaging 2500 persons screened [20]. Therefore, we can see that the benefit of screening to prevent lung cancer deaths does outweigh the risk.

The guidelines for LDCT in tuberculosis endemic countries should be defined. This is mainly because many symptoms of TB like fever, cough, weight loss overlap with that of lung cancer and imaging findings in these two can be similar [22]. Many cases also have TB and lung cancer co-existing. The WHO Global report for tuberculosis lists 30 countries as highly endemic for tuberculosis. These countries contribute 86.9% incidence of tuberculosis burden. Of 30, only 3 countries China, Brazil, and the Russian Federation have reported LDCT studies for lung cancer screening. Similar clinical picture and imaging findings of TB and lung cancer warrants careful assessment of study findings before advocating the mass implementation of LDCT screening in TB endemic countries. Mass screening may inflate the proportion of overdiagnosis in these countries which in turn may contribute to screened individuals being subjected to unnecessary investigations and probably misdiagnosis as well.

Along with the TB burden in a country, there are other factors as well which needs to be examined before considering the mass

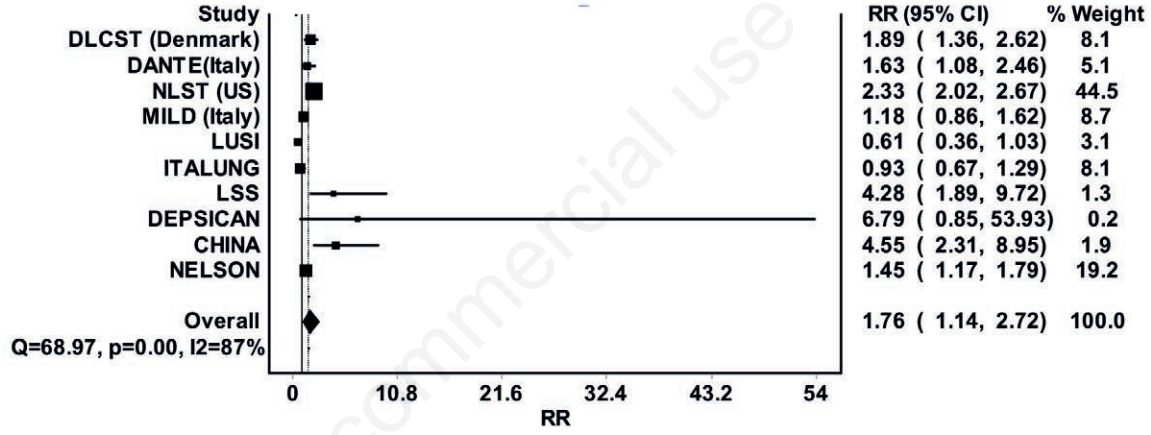

Figure 6. Forest plot for lung cancer detection.

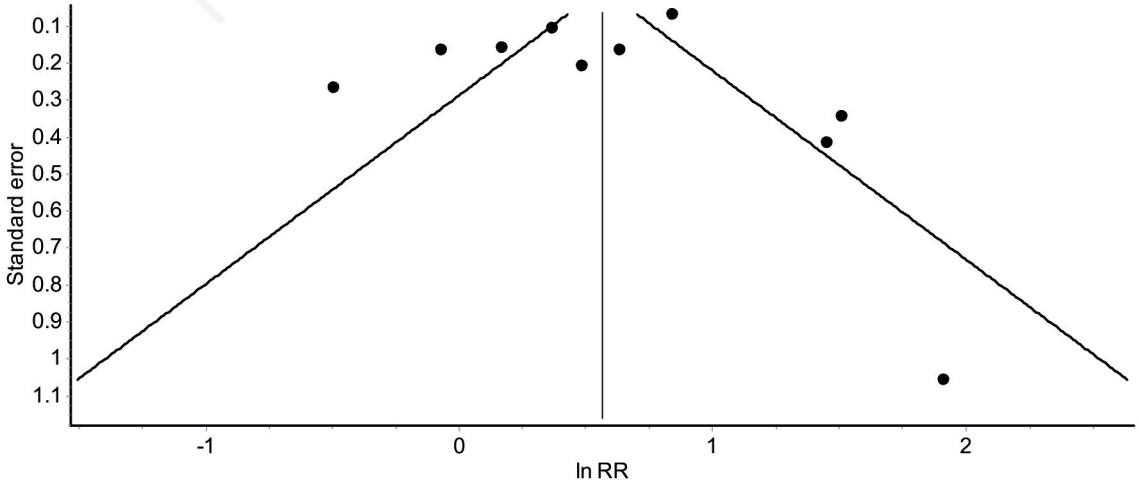

Figure 7. Funnel plot for lung cancer detection.

screening. The LDCT screening has proven efficacy only in high-risk population. As a result, the burden of risk factors of lung cancer in a developing country and their distribution across the country will also influence the mass screening strategy for such countries. Another factors that will play an important role in developing countries is that of access and availability of LDCT screening facilities. Likewise, the cost of screening using CT scanning needs to be examined before implementing screening program. All these factors warrant context-specific cost-effectiveness studies to assess the cost incurred and expected benefits of the screening program. The studies regarding the cost-effectiveness of LDCT as a screening program has not come to a definitive conclusion of its benefit. Most of them show variable results based on the prevalence of the condition, the population, and the cost of care in the area [21]. Area-specific studies can better derive such a conclusion. Such studies are specifically relevant in context of developing countries where the resources are already scarce. Careful assessment of these factors should precede before applying these findings to other settings.

Strengths and limitations

We used a standard comprehensive search strategy to ensure that all the relevant articles are included in our study. To the best of our knowledge, ours is the most updated systematic review to present evidence on this topic. Hence, we have been able to collate all the evidences available so far regarding this topic. Thirdly, we included and pooled results only from RCTs on this topic which are considered as highest level of medical evidence among individual studies.

There were few limitations as well in our study. We included studies only in English language. However, we believe that the majority of published literature is available in English language. We could not perform sub-group and sensitivity analyses in our review due to the small number of available studies. Similarly, we could also not perform meta-regression and therefore, could not examine the sources heterogeneity in the pooled estimates.

Conclusions and recommendations

LDCT screening has a potential to reduce mortality due to lung cancer among high-risk individuals. However, the all-cause mortality in this population was not affected.

LDCT could be considered as a screening modality for lung cancer after careful assessment of other factors like burden of TB, prevalence of risk-factors and proportion of high-risk population, and cost, access and availability of LDCT for population-level implementation of this facility. These context-specific factors should always be considered, and more so in case of developing countries.

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