



## Predicting Postoperative Lung Function Following Lung Cancer Resection: A Systematic Review and Meta-analysis

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### ABSTRACT

**Background:** Lung resection remains the gold standard treatment for early stage lung cancer; prediction of postoperative lung function is a key selection criterion for surgery with the aim of determining risk of postoperative dyspnoea. We aimed to identify the different prediction techniques used, and compare their accuracy.

**Methods:** A systematic review and meta-analysis sought to synthesise studies conducted that assess prediction of postoperative lung function up to 18/02/2018 (n = 135). PROBAST was used to assess risk of bias in studies, 17 studies were judged to be at low risk of bias.

**Findings:** Meta-analysis revealed CT volume and density measurement to be the most accurate (mean difference 71 ml) and precise (standard deviation 207 ml) of the reported techniques used for predicting FEV<sub>1</sub>; evidence for predicting gas transfer was lacking.

**Interpretation:** The evidence suggests using CT volume and density is the preferred technique in the prediction of postoperative FEV<sub>1</sub>. Further studies are required to ensure that the methods and thresholds we propose are linked to patient reported outcomes.

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### Research in Context

#### Evidence Before This Review

Multiple methods of predicting postoperative lung function had been reported in patients undergoing surgery for lung cancer but the methods had not been objectively compared in a meta-analysis. Decisions about whether patients were suitable for curative lung cancer resection were being influenced by these predictions.

### Added Value of This Review

A systematic review of available literature was performed and meta-analysis of predicting FEV<sub>1</sub>, but not gas transfer factor, was possible. This provides an objective comparison of different prediction methods.

#### Implications of all the Available Evidence

Using a more accurate and precise method to predict postoperative FEV<sub>1</sub> may enable more accurate personalised decisions about lung cancer resection; CT volume and density measures appear outperform segment counting. Further evidence is required to compare the available methods to predict postoperative gas transfer factor.

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## 1. Introduction

Surgical resection with curative intent is the standard of care for stage I and II Non-small Cell Lung Cancer (NSCLC) but such invasive treatment requires careful preoperative assessment, including assessment of forced expiratory volume in 1 s (FEV<sub>1</sub>) and transfer factor (TLCO) [1]. The predicted postoperative values of FEV<sub>1</sub> and TLCO are used to stratify risk of mortality and postoperative dyspnoea, a predicted value of between 30% and 60% expected being the cut off for requesting further investigation [1–3].

Different techniques to predict postoperative lung function have been reported but there has not been a quantitative review of their accuracy and precision. Predictions are used to inform important treatment decisions such as whether to proceed with surgical resection or recommend other treatment modalities (such as radiotherapy or chemotherapy). Predictions are a factor in counselling patients about their operative risk and a national audit reported that patient preference is a significant reason that patients with resectable tumours do not undergo resection [4]. In addition, prediction resulting in high-risk assessment may delay treatment to allow time for further investigations, such as cardiopulmonary exercise testing. Thus, there is a need for formal comparison of prediction methods.

## 2. Methods

This is a systematic review and meta-analysis of the techniques to predict postoperative lung function in patients undergoing lung cancer resection in line with the standards set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5]. This review was registered on the International Prospective Register of Systematic Reviews (PROSPERO), record number [CRD42017058955].

### 2.1. Inclusion and Exclusion Criteria

The population for inclusion was adults with suspected or confirmed primary lung cancer. The intervention was lung resection with curative intent (pneumonectomy, lobectomy, segmentectomy, or wedge resection) with lung function measured before and after surgery; a technique of predicting postoperative lung function must have been applied and the results reported (outcome). Surgery for known benign conditions, palliation, diagnosis only, emergencies, and bronchoscopy only were excluded. Studies reporting combined results of surgery for both benign and malignant pathology were eligible provided the majority of the study population had primary lung cancer. Comparison between the predicted postoperative lung function and the actual measured postoperative lung function must have been performed; comparison of the accuracy and precision of the techniques was planned for meta-analysis. All retrospective and prospective studies were eligible, case reports and case series (n < 8) were excluded.

### 2.2. Search Strategy and Study Selection

The following electronic bibliographic databases were searched: EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Cochrane Database of Systematic Reviews (CDSR). The search strategy combined terms relating to lung surgery, terms relating measuring lung function, terms relating to the postoperative period and terms relating to prediction or correlation between measures (see Appendix 1 for details of search terms). No language, date or other restrictions were applied. The searches included all eligible studies from inception to 18/01/2018. We also considered additional sources of

studies such as reference lists of included papers and contact with experts in the field.

Titles and abstracts of studies retrieved were screened independently by two reviewers to identify studies that potentially met the inclusion criteria. The full texts of potentially eligible studies were independently assessed for eligibility by two reviewers. Any disagreement about eligibility was resolved through consensus (with a third reviewer where necessary). Studies assessed as low risk of bias were included in the meta-analysis.

### 2.3. Data Management

A pre-piloted electronic form (Microsoft Excel 2010) was used to record extracted data from eligible studies and record risk of bias assessment. Extracted information included: study population and participant demographics; prediction technique; funding; study methodology; recruitment and study completion rates; type of surgery performed; lung function at baseline and post-operatively; postoperative time lung function was assessed. One reviewer extracted data independently (NO) and a second reviewer (JHS, RM, AT) checked the data, discrepancies were resolved through consensus (with a third author where necessary). Missing data from studies eligible for meta-analysis was requested from study authors via electronic mail.

### 2.4. Bias Assessment

There are few bias tools specific to prediction studies. A preliminary version of the Prediction study Risk Of Bias Assessment Tool (PROBAST) was sought from the authors of the tool and used to assess full papers that met eligibility criteria [6].

### 2.5. Evidence Synthesis

The principal summary measures were the mean difference between measured and predicted postoperative lung function (accuracy) and the standard deviation of the mean difference (precision). Meta-analysis of mean difference was performed using the generic inverse variance method in Revman Version 5.3 [7]. Multilevel meta-analysis of Variance Ratio, as described in detail by Senior et al., was used to analyse the Standard Deviation in RStudio Version 1.1.463 [8,9]. Where necessary, patient level data was extracted from article scatter plots using online software WebPlot-Digitizer Version 4.1 [10]. Meta-analysis was performed on absolute values; the corresponding authors of papers that provided percentage values only were contacted to provide additional data but no response was received to these enquiries. I<sup>2</sup> or Cochran's Q was calculated as a measure of consistency across studies as provided by software packages. Analysis of funnel plots was planned to assess risk of publication bias.

### 2.6. Role of the Funding Source

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## 3. Results

### 3.1. Included Studies

We found 135 full papers that met criteria for inclusion (Fig. 1). The most common reason for exclusion was that the article did not measure postoperative lung function or did not perform prediction of postoperative lung function.

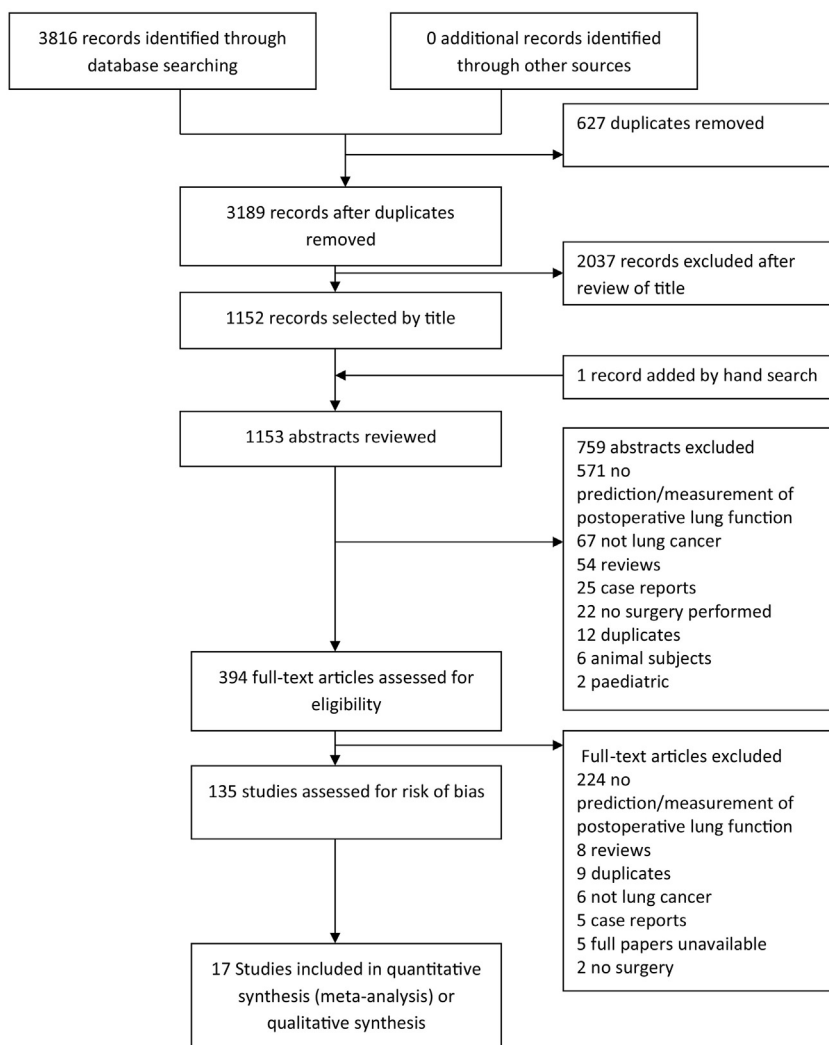


Fig. 1. Study screening and selection flow diagram.

Articles reported 16 different types of prediction tests, in order of frequency they reported:

1. Perfusion scintigraphy
2. Segment counting – 19 segments, Juhl and Frost formula [11]
3. Ventilation scintigraphy
4. Single Photon Emission Computed Tomography (SPECT)
5. Computed Tomography volume and density (CT-VD)
6. Vibration Response Imaging (VRI)
7. Ventilation/perfusion scintigraphy
8. Subsegment counting – 42 subsegments, Nakahara formula [12]
9. Computed Tomography (CT) volume
10. Co-registered SPECT-CT
11. Perfusion Magnetic Resonance Imaging (MRI)
12. Perfusion CT
13. Newly derived regression equation
14. Ventilation CT
15. CT volumetry and partial densitometry
16. Lateral position test

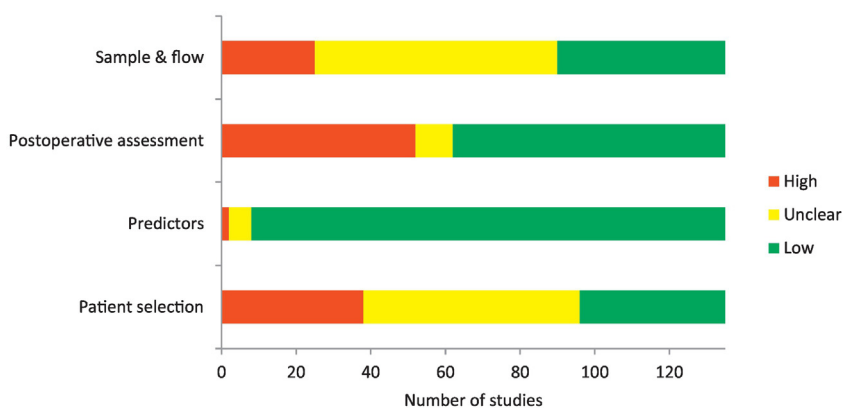


Fig. 2. Risk of bias assessment for all eligible studies.

The tests broadly involve estimation of how much lung tissue is to be removed with or without estimation of the functionality of the lung. CT volume tests used the volume of the lobe to be resected as measured on CT relative to the total lung volumes as the proportion of function expected to be lost [13]. CT-VD tests take into account the density of lung tissue in Hounsfield units, a measure of emphysematous destruction, in addition to lung volumes to define functional lung tissue [13–17]. CT density masks to define functional lung tissue varied between –1024 and –910 for the lower limit –650 and –500 for the upper limit [13–16]. CT volumetry and partial densitometry used the volume of lung tissue but only defined a lower limit of Hounsfield units below which the tissue was considered emphysematous; an upper limit was not defined [18].

### 3.2. Risk of Bias and Applicability

The risk of bias assessments for all studies are presented in Appendix 2 and Fig. 2. The method of patient selection was often unclear or appeared to be based upon convenience; exclusion of patients based upon postoperative factors was also frequently described [19–28]. The timings of postoperative lung function measurement were judged as a source of potential bias if they were performed within 3 months of surgery, before measurements plateau, or when measurements varied vastly in their timing such as a range between 24 days and 5 years [22,28–32]. Follow up rates were low in many studies and few studies fully described patients who were lost to follow up [16,21,23,33–37]. Study outcomes and predictors were generally applicable to the review question.

**Table 1**  
Study characteristics of the 17 with low risk of bias overall.

Author, year Country, language	Population	Procedures	Prediction technique	Time to postoperative lung function	Sample analysed (total)	Outcomes	Analysis
Fourdrain et al., 2017 [11] France, English	N = 23 82.6% male Mean age 61	Lobectomy & Pneumonectomy	Segment counting Subsegment counting Perfusion scintigraphy Ventilation scintigraphy CT partial density & volume	3 months	23 (37)	FEV1	Mean difference Correlation
Yabuuchi, 2016[12] Japan, English	N = 49 53.1% male Mean age 67	Lobectomy	Subsegment counting CT volumetry CT volume & density	6–7 months	49 (49)	FEV1 Change only	Mean difference Correlation
Ohno, 2015[13] Japan, English	N = 60 65.0% male Mean age 68	Segmentectomy, lobectomy & bilobectomy	Segment counting Perfusion scintigraphy CT volume & density MRI perfusion	6 months	60 (60)	FEV1 % only	Mean difference Correlation
Chae, 2013[14] Korea, English	N = 51 74.5% male Mean age 64	Lobectomy & pneumonectomy	Perfusion scintigraphy CT perfusion	6 months	51 (67)	FEV1	Mean difference Correlation
Yanagita, 2013[15] Japan, English	N = 30 63.3% male Mean age 70	Lobectomy & pneumonectomy	SPECT CT ventilation	6 months	30 (34)	FEV1	Mean difference Correlation
Yamashita, 2010[16] Canada, English	N = 14 60.0% male Mean age 65	Lobectomy & pneumonectomy	Perfusion scintigraphy CT perfusion	3 months	14 (25)	FEV1	Mean difference Correlation
Yoshimoto, 2009[17] Japan, English	N = 37 59.4% male Mean age 65	Lobectomy	Segment counting CT volume & density SPECT–CT	3 months	37 (37)	FEV1	Mean difference Correlation
Ohno, 2007[18] Japan, English	N = 60 50.0% male Mean age 70	Lobectomy & pneumonectomy	Perfusion scintigraphy Ventilation scintigraphy SPECT SPECT–CT	6 months	60 (60)	FEV1 % only	Mean difference Correlation
Sudoh, 2006[19] Japan, English	N = 22 86.4% male Mean age 71	Lobectomy & segmentectomy	Subsegment counting SPECT–CT	3–4 months	22 (22)	FEV1	Correlation
Wang, 2006[20] Canada, English	N = 28 61.0% male Mean age 65	Segmentectomy, lobectomy & pneumonectomy	Segment counting	12 months	28 (57)	DLCO % only	Mean difference
Wu, 2002[21] Taiwan, English	N = 34 79.5% male Mean age 67	Lobectomy & pneumonectomy	Perfusion scintigraphy CT volume & density	3 months	34(52)	FEV1	Mean difference Correlation
Beccaria, 2001[22] Italy, English	N = 62 82.3% male Mean age 62	Lobectomy & pneumonectomy	Segment counting	6 months	62 (93)	FEV1	Correlation
Larsen, 1997[23] Denmark, English	N = 23 65.2% male Mean age 67	Lobectomy & pneumonectomy	Perfusion scintigraphy	6 months	23 (41)	FEV1	Mean difference
Bolliger, 1995[24] Switzerland, English	N = 22 68.0% male Mean age 63	Wedge resection, segmentectomy, lobectomy & pneumonectomy	Perfusion scintigraphy	6 months	22 (25)	FEV1 & DLCO	Correlation
Wu, 1994[25] China, English	N = 38 86.8% male Mean age 68	Lobectomy & pneumonectomy	CT volume & density	3 months	38 (38)	FEV1	Mean difference Correlation
Egeblad, 1986[26] Denmark, English	N = 30 70.8% male Mean age 61	Lobectomy & pneumonectomy	Segment counting	6 months	30 (30)	FEV1	Correlation
Taube, 1980[27] Germany, German	N = 27 100% male Mean age 53	Pneumonectomy	Perfusion scintigraphy	6 months	27 (29)	FEV1	Correlation

**Table 2**  
Meta-analysis results of prediction of postoperative FEV<sub>1</sub>: Mean difference.

Prediction technique	Studies	Mean difference (measured – predicted FEV <sub>1</sub> )	95% Confidence interval	I <sup>2</sup>
CT – volume & density	3 (n = 109)	71 ml	38 to 103	0%
Perfusion scintigraphy	7 (n = 194)	101 ml	– 11 to 214	88%
SPECT-CT	2 (n = 59)	107 ml	– 10 to 225	66%
CT – perfusion	2 (n = 65)	143 ml	59 to 228	0%
Segment counting	4 (n = 145)	192 ml	88 to 295	74%
Subsegment counting	3 (n = 82)	233 ml	135 to 332	65%
SPECT	1 (n = 30)	10 ml	– 114 to 134	Single study
CT – ventilation	1 (n = 30)	70 ml	– 24 to 164	Single study
CT – volumetry	1 (n = 30)	90 ml	– 21 to 201	Single study
CT – volume & partial density	1 (n = 23)	266 ml	172 to 360	Single study
Ventilation scintigraphy	1 (n = 23)	312 ml	188 to 435	Single study

A total of 17 of the 135 full papers had sufficiently low risk of bias to warrant inclusion for meta-analysis. The characteristics of studies that were judged as low risk of bias are presented in Table 1. In some cases the analysis reported in the article was not adequate but sufficient patient level data or summary data was reported to allow the reviewers to perform agreement analysis independently and hence include the data in meta-analysis [38–40]. There were too few studies reporting each method ( $n < 10$ ) to perform a valid funnel plot analysis of publication bias.

### 3.3. Quantitative Synthesis: Meta-analysis of Mean Difference

It was only possible to perform meta-analysis for studies predicting FEV<sub>1</sub>; their results are presented in Table 2, corresponding Forest plots are displayed in Appendix 3. CT-VD was shown to be the most accurate technique (mean difference 71 ml, 95% Confidence Interval 38–103). The minimum clinically important difference in FEV<sub>1</sub> after surgery is not known but this has been established as 100 ml in the context of Chronic Obstructive Pulmonary Disease (COPD); as such a difference in FEV<sub>1</sub> in the measured versus the predicted should not be noticeable clinically if it is less than 100 ml [41]. SPECT, CT ventilation and CT volumetry may fulfil these criteria but there was only one study that reported each of these techniques. Heterogeneity was low for CT-VD and CT perfusion, moderate for SPECT-CT, segment counting and subsegment counting but high for perfusion scintigraphy.

### 3.4. Quantitative Synthesis: Meta-analysis of Standard Deviation

Meta-analysis of precision was only possible for four prediction techniques because of missing data on variability of the mean difference in full papers. CT-VD was found to be the most precise FEV<sub>1</sub> prediction method (SD 207 ml, Table 3), Cochran's Q did not provide evidence of heterogeneity in any of the techniques. A perfect test that predicted FEV<sub>1</sub> within 100 ml of the measured postoperative value (as is accepted in spirometry repeatability standards) would have a standard deviation of 16.7 ml, as such all methods of prediction showed low precision.

**Table 3**  
Meta-analysis results of prediction of postoperative FEV<sub>1</sub>: Standard deviation.

Prediction technique	Studies	Standard deviation	Cochran's Q test of heterogeneity (p value)
CT – volume & density	2 (n = 75)	207 ml	1.569 (0.2103)
Subsegment counting	2 (n = 60)	274 ml	0.047 (0.8279)
Perfusion scintigraphy	5 (n = 109)	285 ml	3.690 (0.4495)
Segment counting	4 (n = 145)	331 ml	3.361 (0.3392)
CT – volume & partial density	1 (n = 23)	229 ml	Single study
SPECT-CT	1 (n = 37)	249 ml	Single study
Ventilation scintigraphy	1 (n = 23)	303 ml	Single study
CT – perfusion	1 (n = 14)	329 ml	Single study

This meta-analysis produces a combined standard deviation of the mean difference based on the standard deviations quoted in included studies. It should be noted this is mathematically distinct from the standard error of the mean for the reported meta-analysis mean difference. Null hypothesis for Cochran's Q test is homogeneity.

### 3.5. Qualitative Synthesis

Three studies of FEV<sub>1</sub> prediction could not be meta-analysed but did describe comparisons of the accuracy different prediction techniques (Appendix 4). Yabuuchi et al. reported change in FEV<sub>1</sub> rather than absolute values, they found CT-VD to outperform subsegment counting and CT volumetry [13]. Ohno et al. 2015 reported FEV<sub>1</sub> percent of expected values rather than absolute values; they reported CT-VD and perfusion MRI (with and without contrast) to be comparable to each other but superior to both segment counting and perfusion scintigraphy [14]. Ohno et al. 2007 also reported FEV<sub>1</sub> percent of expected values; they compared ventilation scintigraphy, perfusion scintigraphy, SPECT, and SPECT-CT. They found the latter two methods to be better than the former two methods [42].

Only two studies with low risk of bias and 23 of all eligible studies predicted TLCO. One of these papers reported segment counting and the other perfusion scintigraphy meaning quantitative synthesis was not possible [43,44]. The mean difference was 2 percentage points (standard error 1.5) for segment counting and mean difference 11 percentage points (standard error 1.7) for perfusion scintigraphy.

## 4. Discussion

Our meta-analysis has shown that prediction of FEV<sub>1</sub> after lung resection is most accurate and precise when using combined CT volume and density measures; however the precision of all methods to predict postoperative FEV<sub>1</sub> is low. The common practise of using segment counting to guide treatment decisions and patient counselling may warrant changing in light of this finding. Prediction of TLCO has a limited evidence base but seems to be more accurate using segment counting than perfusion scintigraphy. These findings are of particular relevance to the future guidelines regarding assessment of fitness for lung cancer resection; the most recent British guidelines having been archived in 2017 [1].

#### 4.1. Current Risk Assessment for Surgery

Patients undergo CT scanning at least twice prior to resection in the form of the initial diagnostic CT and subsequent staging Positron Emission Tomography (PET) CT; utilising existing imaging without further appointments and concomitant delays makes CT an appealing technique for predicting postoperative lung function. Additionally, CT densitometry has been shown to be superior to spirometry in predicting pulmonary complications, including prolonged air leak, after pulmonary resection and identification of patients at increased risk of these complications could facilitate targeted interventions or adjustments to surgical technique as preventative measures [45,46]. A combined CT based risk assessment of predicting postoperative pulmonary function and the risk of postoperative pulmonary complications would be an attractive and relevant tool for clinicians.

#### 4.2. Barriers to Clinical Implementation

Calculations of CT density and volume have been possible since 1994 but have not become routine clinical measures and the availability of analysis software to clinicians is an important problem [17]. Six different software programs were specified in papers eligible for this review including AZE VirtualPlace, Pulmo-CMS, Ziosoft M900 QUADRA, GE Healthcare Thoracic VCAR, Fujifilm Healthcare SYNAPSE VINCENT, and 'standard software' within a Somatom HiQ unit; this indicates a competitive market for image analysis. Developers of software may charge for novel types of image analysis and healthcare institutions are subsequently faced with additional expense that has no proof of clinical efficacy, additionally the number of patients requiring specific analysis may not justify subscription to software services even if benefit has been demonstrated. This can lead to new techniques not being utilised, these techniques then fail to be clinically validated, and patients cannot benefit from technological advancements.

#### 4.3. Strengths and Limitations

This is the first systematic review and meta-analysis to consider how best to predict postoperative lung function as part of perioperative risk assessment. A key strength is that the results should be internationally applicable due to the wide range of countries articles originated from (34 from Japan, 28 from other countries outside Western Europe/North America). The clinical scenarios are broad meaning variation in operative procedure, time to follow up lung function, and precise details of prediction technique (including human error) could all contribute to heterogeneity. However, heterogeneity was only high for perfusion scintigraphy predicting FEV<sub>1</sub>. We were limited by insufficient information about study methodology being reported to enable risk of bias assessment resulting in bias being considered 'unclear' in many cases. Many papers did not report the primary outcome or sufficient data to enable independent calculation of this; as such the information from many additional patients could not be included. Five studies could not be retrieved in full but this is a small proportion of the total studies considered for full paper assessment (2.3%). Finally, reviews are generally subject to limitations of reporting bias, it was not possible to assess this using funnel plots due to the low number of full papers included.

#### 4.4. Future research Recommendations

Future research in this field might focus on direct comparison of different prediction techniques to predict TLCO. Further validation of the utility of postoperative FEV<sub>1</sub> and TLCO prediction might

include assessments of how these relate to patient reported outcome measures (PROMs) such as quality of life, dyspnoea, ability to live independently and performance of preoperative activities. Postoperative quality of life has been shown to be equivalent in patients with impaired preoperative lung function compared to those without impairment, making the integration of PROMs an important complementary part of risk assessment when counselling patients about treatment options [47]. Prediction of postoperative lung function could potentially be combined with prediction of postoperative complications to give a global respiratory risk score. Finally the optimal CT protocol for prediction could be determined by direct comparison utilising different CT settings and different software to define functional lung tissue within the same patient group. The interaction between medical imaging companies and healthcare providers is likely to be critical in the implementation of research findings.

#### 4.5. Conclusions

In conclusion, using CT volume and density is the most accurate and precise way to predict postoperative FEV<sub>1</sub>. There is limited evidence about predicting postoperative TLCO but segment counting appears to outperform perfusion scintigraphy.

#### Author Contributions

NKO, BN, and AMT conceived and designed the work. NKO, JH-S, RM, and AMT extracted and checked data. NKO and PN analysed data. NKO, BN, PN, and AMT interpreted data. NKO drafted the manuscript; JH-S, RM, PN, BN, and AMT revised it critically for content. All authors approved the final manuscript version for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### Declaration of Competing Interest

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eclinm.2019.08.015>.

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