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Baseline total lung capacity and all-cause mortality in restrictive pulmonary disorders: a meta-analysis

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Abstract

Rationale Forced vital capacity (FVC) has been utilized as a surrogate for vital capacity (VC) in monitoring the progression of restrictive pulmonary disorders, particularly in clinical trials of idiopathic pulmonary fibrosis (IPF). A dose-response relationship between decreased FVC and mortality in IPF has also been established. Since 2005, total lung capacity (TLC) has been routinely required to differentiate and diagnose restrictive pulmonary disorders. However, the relationship between changes in TLC change and the risk of mortality remains unclear.

Objectives To investigate and quantify the relationship between changes in TLC and the risk of mortality in patients with restrictive pulmonary disorders.

Methods This study employed a systematic review and meta-analysis following the PRISMA 2020 guidelines.

Results A total of 26 studies were included in the meta-analysis, comprising a combined sample of 16,579 subjects, which included 7,961 females, 4,460 subjects in the relative low TLC group, and 12,119 subjects in the high TLC group. A reduced TLC was associated with an increased risk of all-cause mortality, as indicated by both unadjusted and adjusted hazard ratios. The unadjusted hazard ratio (95% CI) was 1.76 (1.32, 2.35), while the adjusted hazard ratio (95% CI) was 1.70 (1.31, 2.20). The risk ratio (RR) estimated from the studies that reported both the number of participants and deaths was RR (95% CI) = 2.01 (1.56, 2.60). The included studies demonstrated significant heterogeneity.

Conclusion A low TLC at baseline, in comparison to individuals with relatively higher TLC, may increase the risk of all-cause mortality by at least 42–70% in cases of restrictive pulmonary disorders, although this conclusion is primarily based on observational studies, which carry low to moderate certainty.

Keywords Total lung capacity, Mortality, Hazard ratio, Restrictive pulmonary disorder

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Introduction

Pulmonary function tests (PFTs) are commonly employed to diagnose pulmonary diseases with ventilation impairment. Total lung capacity (TLC), the amount of air contained in the lungs after a deep inspiration, is a crucial parameter in PFTs. TLC was recommended in the diagnosis of restrictive pulmonary disorders [1], and TLC predicted value has also been proposed to stratify the severity of restrictive pulmonary disorders or other disease [2–5]. Restrictive ventilatory disorder is a common symptom of interstitial lung diseases (ILD), including idiopathic pulmonary fibrosis (IPF), a progressive and fibrotic form of ILD characterized by self-sustaining fibrosis and declining lung function [6, 7]. In addition to pulmonary deficits, non-pulmonary deficits can also lead to restrictive ventilatory disorders [8]. An individual with a restrictive ventilatory defect exhibits a low TLC, a low functional residual capacity (FRC), and a low residual volume (RV). The forced vital capacity (FVC, the maximum amount of air exhaled after a maximal inspiration) may be significantly reduced, but the forced expiratory volume in one second divided by the forced vital capacity (FEV1/FVC) is often normal or even above normal. Such characteristics differ ILD/IPF from obstructive ventilatory disorders, such as COPD (characterized by increased resistance to airflow due to partial or complete obstruction at any level from the trachea to the terminal bronchioles [8, 9]), which demonstrated a decreased FEV1/FVC ratio. Although obstructive syndromes constitute the majority (80%) of pulmonary syndromes, restrictive pulmonary syndromes still affect millions of people worldwide [10, 11]. This underscores the importance of accurately diagnosing these restrictive pulmonary diseases. However, there is currently a lack of consensus regarding the diagnostic criteria and grading evaluations for pulmonary function, highlighting the need for further standardization and enhancement in the diagnosis of pulmonary function.

Theoretically, TLC is the sum of RV and vital capacity (VC). However, in clinical practice, FVC, FEV1, and forced expiratory volume in 6 s (FEV6) are regarded as valid predictors of TLC [12], and FVC was used as a surrogate for TLC. This an alternative to circumvent the technical challenges associated with determining TLC [13]. Although the use of FVC to monitor the progression of IPF/ILD has provided significant convenience in clinical practice, FVC is not TLC. Accumulated evidence suggests that this approximation can be misleading, as changes in FVC may not closely correlate with TLC in certain situations [14–17]. The FVC of IPF patients enrolled in clinical trials with nintedanib/pirfenidone is typically less than 80%, often around 65%, prior to treatment. Consequently, the stabilization of FVC decline is significant and thus has been established as the primary endpoint for assessing drug efficacy in these studies. However, for most patients in the early stages of ILD, non-IPF fibrosing ILD (F-ILD), for instance, the FVC is generally above 80%. Currently, there is no widely accepted clinical standard to guide the evaluation of disease improvement and progression for these patients, nor is there a framework to direct treatment aimed at enhancing ILD outcomes. It is clinically essential to manage the early fibrotic progression of ILD to prevent its advancement to IPF and to enhance the treatment of pulmonary fibrotic diseases. In our clinical studies of novel drugs for the treatment of ILD (CTR20222921), we observed that many patients eligible for the clinical trials exhibited TLC levels below 80%, while the FVC was within the normal range (greater than 80%). This suggests a potential connection between improvements in TLC and benefits for patients in F-ILD.

Although early studies have established an association between decreased FVC and an increased risk of mortality in both the general population and elderly individuals [13, 18, 19], the association between TLC reduction and clinical outcomes or prognosis has been less studied. Hence, we designed this study to investigate and quantify the relationship between changes in TLC and the risk of mortality in patients with restrictive pulmonary disorders. In this study, baseline TLC was utilized to stratify patients, and all-cause mortality was observed. The risk of mortality was indicated using the hazard ratio from Cox proportional hazards regression analysis. A relatively lower TLC at baseline (less favorable in disease) compared to those with a relatively higher TLC (as a reference) may increase all-cause mortality by at least 42–70%. A reduction in TLC is a potential indicator of mortality in restrictive pulmonary disorders.

Methods

Protocol and guidance

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement in the systematic review process [20].

Eligibility criteria

The inclusion criteria: the published studies in English with TLC stratified comparison for all-cause mortality were eligible. The study could be prospective or retrospective, could be observational or clinical trial (some fatal diseases). The TLC should be measured either at baseline or enrollment, diagnosis, or any specified lead time period that explicitly described in original article (notice the time lapsed). Also included was the single-arm observational study with baseline TLC quantify and all-cause mortality indicated as hazard ratio (HR) in Cox proportional hazard regression. It was presumed that the

HR estimated from single-arm study would use the cases alive as control inevitably.

The exclusion criteria: the study population aged less than 18 years, or case series, or unpublished data were excluded.

The data would be synthesized in total and grouped by participants of disease (obstructive or restrictive pulmonary disorders), which the TLC would play different prognostic roles in disease course.

Information sources

We searched the database of PubMed, Embase and Web of science and Cochrane library from the inception to Sept 30, 2023.

Search strategy

The search syntax in PubMed was containing both ("long volume" OR "total lung capacity") AND (survival OR long-term OR mortality) in context. The same search syntax was translated to apply in Embase and Web of science database researches. There were 161 studies titled with "total lung capacity" from 1954 to Sept 30, 2023 could be found, containing three reviews (no meta-analysis) in PubMed database. The search syntax in Cochrane library was containing both ("total lung capacity") AND ("survival") in the fields of title, abstract and keywords. All records from database search were imported into Zotero reference management software for further screening.

Data collection process

In order to extracted data from negative TLC stratified results, "pulmonary function [test]" or "Cox [proportional hazard] regression" or "hazard ratio [HR]" were also used in title and abstract screening. If any suspect relevant to study objectives, the full-text would be retrieved and the final decision was made based upon the full-text screening. The full-text screening mainly focused on the baseline characteristics and outcomes, namely, whether the TLC was quantified at the beginning of observation, and whether the HR had been reported based upon the TLC stratification. The screening and data extraction were conducted by two experienced researchers independently, CY and ZG, and consensus was reached by discussion on any disagreement. The data were extracted in a predefined Excel table in long format (with more space on right side column for notes for each datum). Two researchers worked independently and settle the disagreement with discussion. The wide format table obtained from transformation by copy-and-paste manually. No other automatic tool (inlcuding language tool) was used in study screening, selection and data extraction.

Data items and effect measures

The data extracted included the authors, publication year, country, study design, truncated inclusion and exclusion criteria, population, sample size, age, female subjects, TLC quantity (quantity in litre and % of predicted), quantification method and time point, primary endpoint, follow-up duration, number of death and incidence. Data from individual study were extracted and displayed in table.

TLC is usually obtained by the measurement of functional residual capacity (FRC) plus the inspiratory capacity (IC), the TLC is sum total of four volumes, $TLC = IC + FRC = IRV + VT + ERV + RV = VC + RV$ [21]. The residual volume (RV) is the gas volume left in the lung after no matter how hard a full and complete expiration was, therefore, can not be measured by spirometry alone [21]. TLC was usually measured by using body plethysmography (the most precise method), inert gas (helium) dilution or volumetric CT quantification. The TLC quantification methods were regarded as not interchangeable.

The outcome of this study was all-cause mortality observed following stratification. The effect measures were HR estimated in Cox proportional hazard regression, which integrated the time-to-event data and incidence ratio between two groups. Both the unadjusted HR in univariate regression and adjusted HR in multivariate regression were collect. The covariates used in adjustment of HR in original studies were not the same. An alternative outcome of risk ratio (RR) compared between two parallel groups within the same time period (not strictly implemented in this study) was also considered, as the number of participants and number of deaths would often be reported as well (estimate RR directly from these number). We aimed to learn the effects of decreased TLC on the long-term survival indicated as by HR. We then synthesized the effects of unadjusted HR (from univariate Cox regression), adjusted HR (from multivariate Cox regression) and RR (estimated from reported number of death and participants) by using data available.

For the restrictive ventilatory disorders the reduced TLC would be viewed as harmful. In effects synthesis, the less reduced TLC (we named as high TLC group in this study but varied in almost every individual study) was presumably set as reference level (control) and would exchange the order of baseline TLC and used the reciprocal of HR (and its 95% CI) accordingly, if the relative low TLC group had been used a reference level in original study. When TLC % of predicted used as a continuous variable in Cox regression analysis (the increase of TLC would predict increase HR), also the reciprocal of HR was used in effect synthesis. The median of TLC % of predicted was used if only the range of TLC at baseline was reported. The key information on PICOS (participant, intervention, control, outcome and study

design) was extracted. For the studies that used a TLC cutoff value to divide two groups we presumed an extra 3% deviation from the cutoff value for each group, thus 6% (minimal clinical significant difference) [22] between groups in exploring the relationship of TLC quantity at baseline and the all-cause mortality risk indicated as HR. The median years in followup were also extracted. Both median (IQR) and mean (SD) of TLC reported were used directly (mixed median with mean not used to quantify our effects measures). The HR was also estimated from study only provided with life table (survival number at regular time interval in followup). The relative low TLC group was defined as the quantified TLC lower than a threshold (defined by the original studies), or TLC quantity (percentage in predicted or absolute value) was relative lower in a two-arm comparison pair in the original studies; vice verse of the relative high TLC groups.

Risk of bias assessment

For individual observational study, the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of case-control and cohort studies. The Cochrane risk of bias tool was used in assessment of clinical trial. No automatic tool was used in risk of bias assessment, two researchers worked indenpendently and manually. Publication bias was assessed using the Egger's weighted linear regression test and Begg's rank correlation test when studies number ≥ 10.

Statistical analysis

Apart from the reciprocal of HR from high-to-low comparison and the extra deviation allowed in baseline TLC for each group, no missing data imputation method was used (except one study reported no change of HR in their univariate and multivariate analysis). The random effects with 95% confidence interval (CI) were estimated in study synthesis (for HR or RR), weighted by the generic inverse variance or sample size and presented in forest plot. If single control group was used in comparison with greater than one relative low TLC groups, the sample size of the control group was averaged in each comparison in this study. The I^2 statistics were calculated and large heterogeneity was considered if $I^2 > 50\%$. All statistical analysis were performed by using R software (version 4.0.1) and packages of meta (version 6.5-0) and metafor (version 4.4-0).

Additional analyses

Subgroup analysis for definitive restrictive pulmonary diseases diagnosed at baseline, those with ILA/IPF, TLC quantity cutoff at 80% of predicted, and chronic obstructive pulmonary disease (COPD) with or without emphysema and definitive restrictive ventilatory disorders were conducted. A linear regression between effects measure HR and TLC quantity in relative low TLC group (in % of predicted), or the averaged (or median of) age at baseline, or the median years of followup were explored, and meta-regression analysis also performed when data available.

Results

Study selection and characteristics

The initial database search yielded 3,780 records, from which data of interest were extracted from 27 studies. Ultimately, a total of 26 studies were included in the quantitative analysis, encompassing a combined sample of 16,579 subjects, including 7,961 females. There were 4,460 subjects in the relative low TLC group and 12,119 subjects in the high TLC group (Fig. 1). Among all subjects, the overall death rate was 35.6% (1,042/2,929) in the relative low TLC group (with death data available from 18 studies) and 16.4% (1,590/9,662) in the high TLC group (with death data available from 10 studies). The median follow-up time ranged from 0.25 to 14 years, with three-quarters of the studies reporting a median follow-up time of at least 2 years. Eight studies utilized cutoff values of TLC to stratify participants, with these values ranging from 65 to 128% of the predicted TLC, or from 3.0 to 7.6 L in absolute volume. One study on severe emphysema indicated that the TLC ranged from 95 to 139% of the predicted value, while in the high TLC group, it ranged from 140 to 203%. Eight studies reported only unadjusted HR, four studies reported only adjusted HR, and three studies provided only the number of deaths in each group (Supplementary sTable 1).

Risk of bias in studies

The analysis included 26 studies published between 1992 and 2023. Among these, three were prospective trial designs, while the remainder were retrospective studies. Specifically, the analysis comprised eight case-control studies, eleven single-arm studies, and four studies utilizing registry data. Sample sizes varied significantly, ranging from 39 to 3,594 subjects. The overall quality of these studies was heterogeneous, as indicated by the scores on the Newcastle-Ottawa Scale (NOS) and the Cochrane Risk of Bias Tool (Supplementary sTable 2, sFigure 1).

Synthesis of evidence

Reduced TLC exerts risk for death in restrictive disorders

Only participants ($n = 14{,}032$) without COPD or emphysema were included in the calculation of the pooled effects of reduced TLC on all-cause mortality, with 3,129 subjects in the lower TLC group. The synthesized unadjusted hazard ratio (HR) from univariate regression, weighted using generic inverse variance, was HR (95% confidence interval [CI]) = 1.76 (1.32, 2.35) ($p = 0.0001$) (Fig. 2). The synthesized adjusted HR, which accounts for various predictive variables across different studies, was

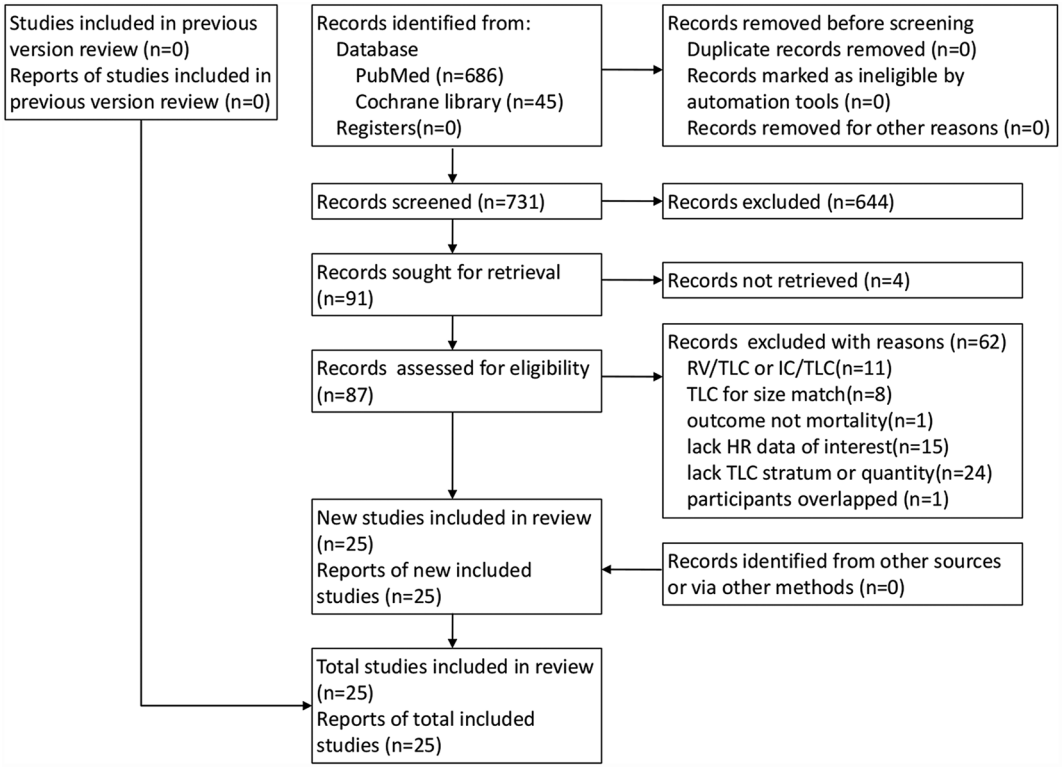

Fig. 1 PRISMA (2020) flowchat of article identification, screening, full-text accessing and data synthesis

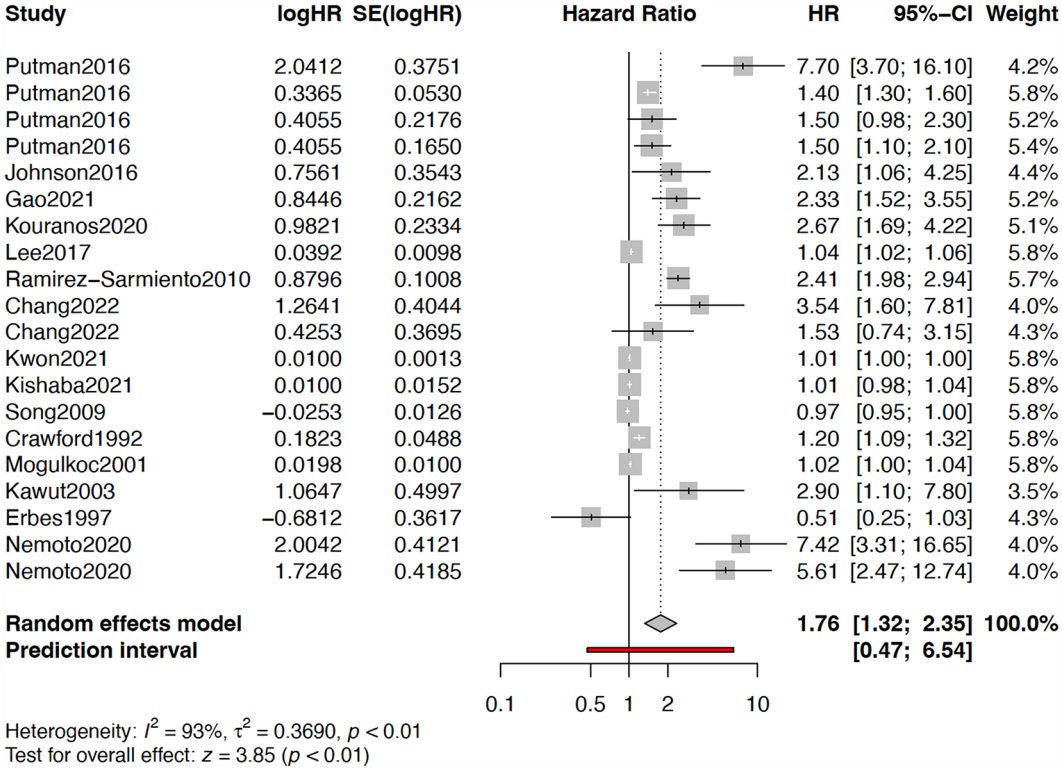

Fig. 2 Forest plot of pooled HR in univariate Cox proportional hazard analysis of relative lower TLC (relative higher TLC as reference). HR, hazard ratio; TLC, total lung capacity

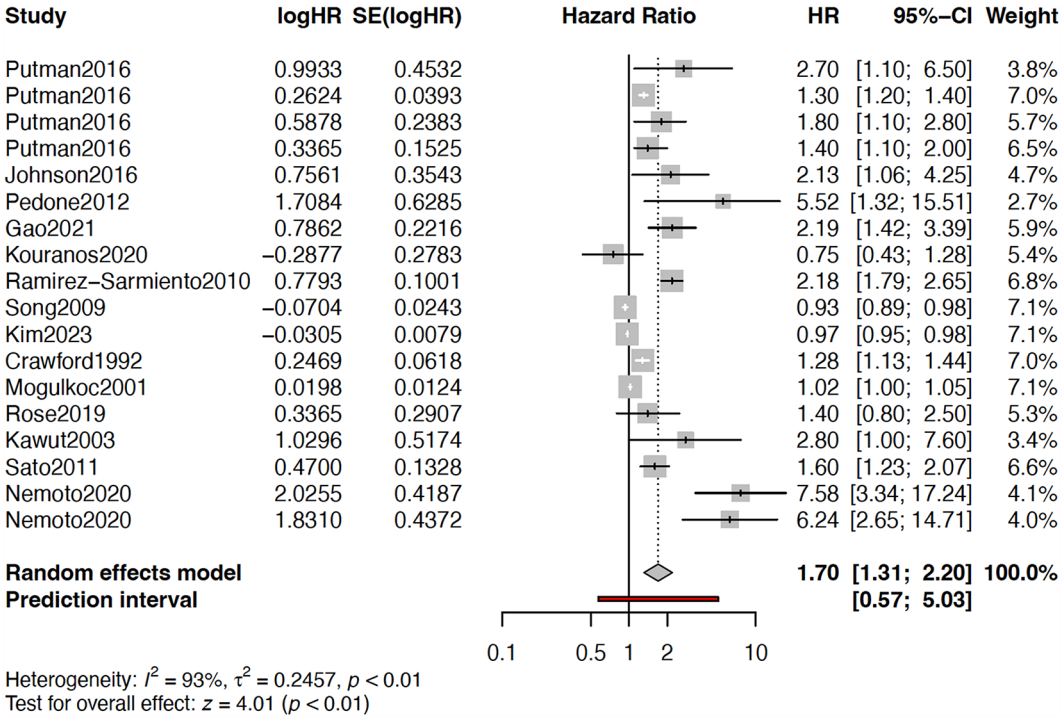

Fig. 3 Forest plot of pooled adjusted HR in multivariate Cox proportional hazard analysis of relative lower TLC (relative higher TLC as reference)

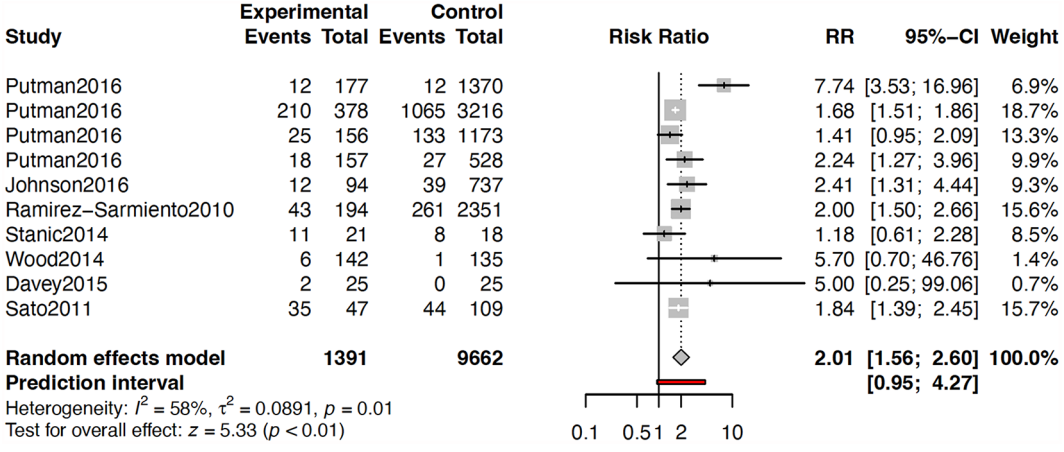

Fig. 4 Forest plot of pooled RR of relative lower TLC (reference: higher TLC) by using patient number and death reported. RR, risk ratio

aHR (95% CI) = 1.70 (1.31, 2.20) (p < 0.0001) (Fig. 3). For participants diagnosed with restrictive pulmonary disorders, the synthesized unadjusted HR and adjusted HR were HR (95% CI) = 1.46 (1.09, 1.94) (p = 0.0106) and aHR (95% CI) = 1.42 (1.14, 1.77) (p = 0.0015), respectively (Supplementary sFigs. 2 and 3).

If the number of participants in the patient group with reduced TLC was used as weights in the calculation of the pooled effects, the unadjusted (univariate) HR and adjusted HR were HR (95% CI) = 2.31 (1.75, 2.87) (p < 0.0001) and aHR (95% CI) = 1.86 (1.44, 2.29) (p < 0.0001), respectively (Supplementary sFigs. 4 and 5). Some studies reported both the number of participants and the number of deaths (events) during the observation period. The estimated risk ratio (an alternative to the hazard ratio within the same time window) derived from these absolute numbers of events and participants was RR (95% CI) = 2.01 (1.56, 2.60) (p < 0.0001) (Fig. 4). The pooled results indicate that reduced TLC increases the risk of all-cause mortality by at least 42–70%, whether for patients with restrictive disorders with or without reduced TLC from the beginning of the observation period or for those with TLC lower than that of the control group.

If we assume that TLC declines gradually with the progression of restrictive pulmonary disorders, the baseline

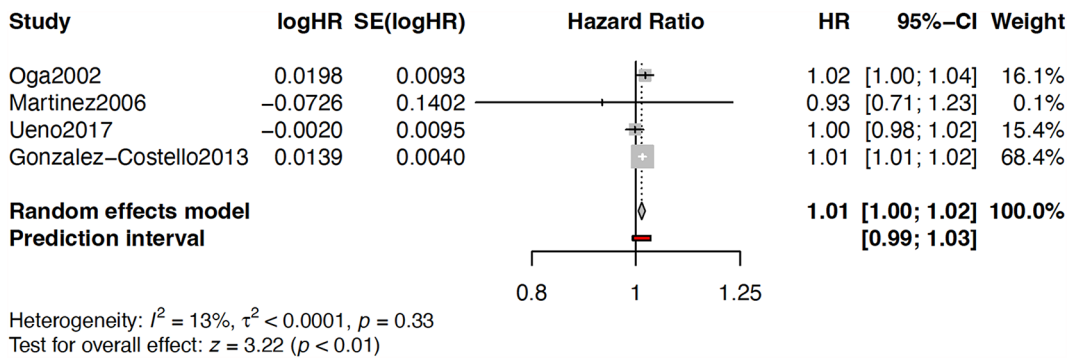

Fig. 5 Forest plot of pooled HR of COPD with median TLC > 100% of predicted (3/4 are single arm studies)

TLC measurement could serve as a predictor for prognosis (specifically, all-cause mortality in this study). We then investigated the association between the initial TLC values in the relative low TLC group and the risk of survival (unadjusted HR) using meta-regression (k = 14). After excluding cases of COPD and emphysema, the regression formula was HR = 1.413 – 0.014 * TLC % of predicted at baseline (p = 0.1715). The adjusted HR for the same relationship (k = 11) was aHR = 0.1014 + 0.0031 * TLC % of predicted (p = 0.7197). The relationship between the TLC values in the lower TLC group at baseline does not appear to predict survival risk effectively based on the currently available data (Supplementary sFigure 6 A, 6B). Nevertheless, considering that reduced TLC could significantly increase the risk of all-cause mortality, these results suggest an association between TLC and survival risk.

Elevated TLC is mildly harmful for COPD

TLC or FVC could indicate hyperinflation in advanced COPD with emphysema, as evidenced by an elevated RV/TLC ratio. Lung hyperinflation is considered detrimental because it not only increases the energy expenditure of expiratory muscles but also impairs the hydrodynamic efficiency of blood flow within the thoracic cavity [23]. An increased TLC, particularly when it exceeds 120% of the predicted value, poses a risk for patients with advanced COPD [23]. The pooled HR for elevated TLC, with medians all exceeding 100% of the predicted value, was found to be mildly harmful in COPD patients, with an HR of 1.01 (95% CI 1.00-1.02, p = 0.0013) (Fig. 5). Further research is necessary to elucidate the relationship between TLC reduction and obstructive ventilatory disorders or COPD based on more comprehensive investigations. Based on the limited analysis available, we can still conclude that elevated TLC is mildly harmful for individuals with COPD.

The participant age at baseline did not predict HR well

The relationship between the average age of participants at baseline and the risk of survival was examined. Using the average age of participants in the lower TLC group at baseline (k = 23), the meta-regression formula for the unadjusted HR was HR = 0.0368 + 0.0066 * aveAge (p = 0.588). The corresponding relationship for the adjusted hazard ratio (aHR) with k = 19 was aHR = -0.0448 + 0.0087 * aveAge (p = 0.394). The data suggest that the average age in the lower TLC group at baseline does not effectively predict the risk of survival based on the currently available information. (Supplementary sFigure 7 A, 7B).

The followup years is sufficient in included studies

The follow-up years may reflect the median time required to obtain a sufficient number of events in a prospective study. Conversely, an extended follow-up period would not alter the risk of survival, or it may indicate that the follow-up time was inadequate. The meta-regression analysis revealed a relationship between follow-up years and the unadjusted HR expressed as HR = 0.3602 + 0.0212 * median follow-up years (p = 0.139; k = 24). A similar relationship was found for the adjusted hazard ratio, represented as aHR = 0.4316 + 0.0117 * median follow-up years (p = 0.1146; k = 20). These results suggest that, for most of the included studies, the follow-up time was adequate (Supplementary sFigure 8 A,8B).

Publication bias

The Egger's test for the unadjusted HR of restrictive pulmonary disorders indicated significant publication bias (p = 0.0002), which was consistent for the adjusted HR (p = 0.0002), as demonstrated by Begg's test and the funnel plot (Supplementary sFigure 9 A, 9B). Next, we conducted an influence analysis for the unadjusted HR using the leave-one-out method. After omitting any single study, the lower and upper limits of the 95% confidence interval (CI) were 1.62 and 1.84, respectively. Heterogeneity remained high, with all I^2 values exceeding 90% (Supplementary material, Influence analysis). Similar results were observed in the influence analysis for the adjusted HR, although the lower and upper limits of the 95% CI were 1.54 and 1.77, respectively. To estimate the

number of missing studies that should be included, we employed the trim-and-fill method. It was estimated that eight studies may have been omitted for the unadjusted HR and seven studies for the adjusted HR (Supplementary material, Trim-and-fill for potential missing publication). After accounting for the estimated missing studies, the synthesized effects for the unadjusted and adjusted HR (95% CI) were 1.05 (0.71, 1.54) ($p = 0.805$) and 1.05 (0.72, 1.52) ($p = 0.803$), respectively.

Discussion

FVC determined by pulmonary function tests has long been utilized as a surrogate measure to quantify lung volume in place of TLC. This technically simple surrogate may raise concerns, and TLC is often necessary for the differential diagnosis of restrictive and mixed ventilatory disorders [8, 9]. However, the quantitative implications of TLC reduction have been largely unexplored. In this study, we conducted a systematic review and meta-analysis to assess and quantify the relationship between changes in TLC and the risk of mortality in patients with restrictive pulmonary disorders. Our findings indicate that a low TLC at baseline, compared to individuals with relatively higher TLC, may increase the risk of all-cause mortality in those with restrictive pulmonary disorders. These results suggest that TLC could serve as a potential indicator of mortality risk in patients with restrictive pulmonary disorders.

This systematic review and meta-analysis included 26 studies involving 16,579 subjects. We extracted the TLC quantity at baseline and its corresponding all-cause mortality observed during follow-up. The pooled unadjusted HR for reduced TLC, which may include some confounding effects, was HR (95% CI) = 1.76 (1.32, 2.35), while the pooled adjusted hazard ratio (aHR) was aHR (95% CI) = 1.70 (1.31, 2.20). A small effect shrinkage was observed in the pooled unadjusted HR (95% CI) = 1.46 (1.09, 1.94) and adjusted aHR (95% CI) = 1.42 (1.14, 1.77) for diagnosed restrictive pulmonary disorders. The synthesized risk ratio, calculated using the reported number of participants and deaths, was RR (95% CI) = 2.01 (1.56, 2.60). When TLC was greater than 100% of the predicted value, even relatively lower levels in patients with COPD or emphysema might represent a marginal risk factor, with HR (95% CI) = 1.01 (1.00, 1.02). However, the quantitative relationship between baseline TLC and COPD requires further investigation, as the sample size in this study was insufficient. The reported risk of all-cause mortality did not demonstrate a trend with baseline TLC quantity or participant age in the lower TLC group (with the high TLC group set as the reference). Considering the risk of bias in individual studies (primarily assessed using the Newcastle-Ottawa Scale score) and the results of the publication bias analysis, the included studies exhibited significant heterogeneity and a notable bias due to missing publications. To our knowledge, this is the first meta-analysis examining the impact of baseline TLC on all-cause mortality in patients with restrictive pulmonary diseases.

The participants in the included studies exhibited restrictive pulmonary abnormalities and disorders, such as interstitial lung abnormalities (ILA), ILD, and usual interstitial pneumonia (UIP), as well as COPD with or without emphysema (LVRS), pulmonary hypertension, and lung cancer. In this study, the lower TLC group displayed a range of pattern abnormalities on imaging (before the onset of clinical symptoms like ILA) and varying degrees of restrictive pulmonary disorders, with TLC values ranging from less than 65% to more than 100% of the predicted values. This broad spectrum of TLC measurements may reflect a continuous progression of restrictive disorders. Nine studies quantified TLC using body plethysmography, three studies employed helium dilution, while the remaining studies estimated TLC from CT imaging or formulas. A time lag between TLC quantification and the initiation of follow-up was reported in several studies. Unfortunately, twelve studies did not provide sufficient information. Only a limited number of studies reported respiratory system-specific mortality, and only a few included lung transplantation data in the context of all-cause mortality among COPD or emphysema patients.

The seemingly inconsistent results of pooled HR (or aHR) and the findings from meta-regression regarding the relationship between HR (or aHR) and baseline TLC quantity in the relative low TLC group may be explained by several factors. Firstly, the snapshot of TLC at baseline may not accurately predict long-term outcomes, such as all-cause mortality. The rate of TLC decline, as FVC decline observed in patients with IPF [24, 25], is likely more relevant to disease prognosis [26]. Continuous monitoring of TLC decline in future studies is necessary to elucidate the underlying dose-response relationship. Secondly, the baseline TLC in both the low and high groups, as determined by studies employing an arbitrary TLC cutoff value, was differentiated by a minimal margin of 6%. Eleven studies reported a standard deviation of TLC greater than 10% at baseline. The influence of baseline TLC on HR or aHR was likely observed in the meta-regression analysis. Furthermore, both the mean and median levels of baseline TLC were directly incorporated into the regression analysis. Thirdly, the TLC values even measured by using plethysmograghs (with great precision) might introduce variations when an international harmonization and quality control system had not been established yet [27, 28]. Nevertheless, the conclusion that low baseline TLC, with a median ranging from 62 to 117% of the predicted value in the relative low TLC

group, is associated with an increased risk of all-cause mortality remains valid. Additionally, due to insufficient data, it is unclear whether baseline TLC can be used to predict HR for patients with F-ILD. This uncertainty is significant, as FVC is not an effective diagnostic tool for F-ILD patients. Therefore, further analysis is necessary to evaluate the efficacy of baseline TLC in predicting HR for F-ILD patients, utilizing a larger pool of clinical data.

We also observed that some emerging studies utilized the decline of TLC during the observation period as a predictive factor [29–32]. Other studies employed the RV/TLC ratio or the inspiratory capacity (IC)/TLC ratio as predictive variables [33–40]; however, these studies were not included in our analysis. These investigations generally indicated a trend by using TLC or its component capacities/volumes as prognostic factors. In fact, the relationship between the decline in FVC and the risk of mortality was established only after a sufficient number of IPF patients had been treated in clinical trials [26, 41]. The components of TLC, which include IC and functional residual capacity (FRC) [ERV + RV], were studied prior to the mid-1980s, primarily focusing on technical specifications and clinical applications [42–46]. Another limitation in the clinical application of TLC is the availability and technical demands of body plethysmography. Recent efforts have provided reference equations for static TLC for populations of European ancestry; however, the data obtained from body plethysmography and gas dilution techniques are not directly interchangeable [47].

Limitations and strengths

We failed to include additional registered records in our article search; however, the likelihood of altering the synthesized HR (or aHR) in a different direction due to the missing studies is very low. Currently, there are not enough studies to conduct a high-quality meta-analysis based on well-designed randomized controlled trials or cohort studies. The same applies to the quantification method of TLC and the sequential measurement of TLC in relation to the progression of restrictive pulmonary disorders. The determination of TLC and the diagnosis of restrictive pulmonary disorders may vary, even when following the recommended guidelines. This variation could have a minor influence on our study, as we only extracted the quantity of TLC as a percentage of the predicted value or in absolute volume (liters) at baseline, and the availability of baseline TLC was essential for this study. The TLC quantity in liters could not be converted into a percentage of the predicted value, as this process involves equations that may introduce additional uncertainty. In exploring the relationship between HR and baseline TLC quantity, the average age of participants, and the years in follow-up, both the median and mean are used directly; therefore, bias in the estimation of effects will inevitably be introduced. The data available and the study design were the most significant limitations of this study. However, this study revealed the association of TLC and the risk of survival especially in restrictive pulmonary disorders. The TLC plays an essential role in diagnosis of restrictive pulmonary disorders in current standards. This study added the value that TLC may influence the prognosis of restrictive pulmonary disorders in the long run. Considering the emerging evidence of TLC-related predictive variables such as the inspiratory capacity to TLC (IC/TLC) ratio or the residual volume to TLC (RV/TLC) ratio, the clinical implementation of TLC and its derived indices in respiratory system diseases will become increasingly common. Nevertheless, this study helped to enhance our understanding of the role of TLC changes during the progression of restrictive pulmonary disorders.

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

F. L.: Formal analysis, Investigation; Y.C.: Formal analysis, Writing-original draft; G. Z.: Investigation, Writing-original draft; M.L.: Formal analysis; H.Z.: Conceptualization, Writing-review & editing; H.D.: Conceptualization, Writing-review & editing. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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