Review Article

Comparison of Prognosis for Lung Transplantation between Older and Younger Donors: A Systematic Review and Meta-Analysis Based on Cohort Studies

Yongkang Di,[1] Rongrong Fu,[2] Zhiyi Xiang,[2] Huiwen Sun,[2] Min Dai,[3] Qiufeng Zhang,[2] and Yuexiu Si[4]

Purpose: This meta-analysis aimed to compare the prognosis of lung transplantation recipients based on donor age.

Methods: A detailed search was performed in PubMed, Embase, Web of Science, and the Cochrane Library for cohort studies on lung transplantation. The prognosis of lung transplant recipients was investigated based on the donor age, with the primary outcomes being 1-year overall survival (OS), 3-year OS, 5-year OS, and 5-year chronic lung allograft dysfunction (CLAD)-free survival.

Results: This meta-analysis included 10 cohort studies. Among the short-term outcomes, the older donor group demonstrated no significant difference from the young donor group in primary graft dysfunction within 72 hours, use of extracorporeal membrane oxygenation, length of ventilator use, and intensive care unit hours. However, a longer hospital stay was associated with the older donor group. In terms of long-term outcomes, no difference was found between the two groups in 1-year OS, 3-year OS, and 5-year OS. Notably, patients with older donors exhibited a superior 5-year CLAD-free survival.

Conclusions: The results of this meta-analysis indicate that older donors are not inferior to younger donors in terms of long-term and short-term recipient outcomes. Lung transplantation using older donors is a potential therapeutic option after rigorous evaluation.

Keywords: lung transplantation, older donor, younger donor, prognosis; meta-analysis

[1]*Intensive Care Unit, Hospital of Zhejiang People's Armed Police, Hangzhou, Zhejiang, China*
[2]*The First Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China*
[3]*The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China*
[4]*Basic Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China*

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Corresponding author: Yuexiu Si. Basic Medical College, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Hangzhou, 310053 Zhejiang, China
Email: syx@zcmu.edu.cn

Abbreviations

CLAD	=	chronic lung allograft dysfunction
OS	=	overall survival
ISHLT	=	International Society for Heart and Lung Transplantation
PGD	=	primary graft dysfunction
LOS	=	hospital length of stay
NOS	=	Newcastle–Ottawa Scale
RR	=	relative risks
CI	=	confidence intervals
SMD	=	standardized mean difference
ICU	=	intensive care unit
ECMO	=	extracorporeal membrane oxygenation
h	=	hours

Introduction

Lung transplantation is an effective treatment to prolong the survival of patients with end-stage lung disease and can significantly improve the quality of life. While the number of lung transplants increases annually, the demand for lung transplants is also increasing.[1] Between 2006 and 2015, the number of lung transplants in the United States increased by 44.3%, while the number of patients on the waiting list increased by 42.4% during the same period.[2] In medical centers across the world, 17%–49% of patients die while on waiting lists due to a shortage of donor lungs.[3–5] Despite the urgent need for lung donors, donor lung utilization remains very poor, with only about 22% of lungs being used for transplantation.[6–8] The application of lung allocation scoring or ex vivo lung perfusion can increase the availability of donor organs and reduce patient waiting times.[9,10] Furthermore, lungs from older donors can be used, which expands the donor pool by expanding the organ selection criteria.

The registry report of the 2012 International Society for Heart and Lung Transplantation (ISHLT) noted a gradual increase in the median age of lung donors. In 2010, 10.9% of lung donors were 60 years of age or older.[11] According to the traditional criteria for an ideal lung donor, the donor should be younger than 55.[12] Christie et al. concluded that using organs from donors over the age of 45 years was associated with a significantly increased risk of primary graft dysfunction (PGD).[13] In 2014, Chaney et al. analyzed studies from the past decades and reported that the age criteria for lung donors should be between 18 and 65 years.[14] However, many studies have reported success with older donors, and some have even shown that donors over the age of 70 years are not inferior to younger donors.[15,16] Nevertheless, the use of older donors has been shown to decrease post-transplant survival.[17] Factors such as low lung elasticity, prolonged environmental exposure, and low recovery potential in older donors often raise concerns about the recipient's prognosis. A meta-analysis investigating the prognosis of lung transplantation recipients comparing older donors to younger donors is currently lacking. Therefore, this study examined the prognostic impact of the age of the lung transplant donor on lung transplant recipients based on published cohort studies.

Materials and Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement: an updated guideline for reporting systematic reviews,[18] registered in the "International Prospective Register of Systematic Reviews" (PROSPERO) in 2023 (CRD42023458423). The objective of this present study was to compare the prognosis of lung transplant recipients based on the age of the donors.

Literature search strategy

Two researchers performed systematic and detailed searches in PubMed, Web of Science, Embase, and Cochrane Library databases from the establishment of the databases to September 2023 using the search formula below: (Lung transplant OR pulmonary transplantation OR lung allotransplantation OR lung allograft) AND (donor OR tissue donor OR donator) AND (older OR aged OR elderly). In addition, the references of relevant articles were searched manually to avoid the omission of any articles.

Inclusion and exclusion criteria

According to the PICOS principles, the inclusion criteria of the article were as follows: (1) Participants: recipients who met the criteria for lung transplantation and had a successful transplant; (2) Intervention: the recipient used an elderly donor; (3) Comparison: the recipient used a younger donor; (4) Outcomes: overall survival (OS), the occurrence of PGD II or III, the occurrence of chronic lung allograft dysfunction (CLAD), hospital length of stay (LOS), etc.; (5) Studies: the included studies were cohort studies.

The exclusion criteria were as follows: (1) the full text of the article was not available; (2) the language of the article was not English; (3) relevant data were not available; and (4) for articles with overlapping study populations, the study that was the most recent or contained the largest number of people was included.

Data extraction

Based on the traditional criteria for an ideal donor, a lung donor over 55 years old was considered an older donor, and less than 55 years old was considered a younger donor.[12] However, recent studies suggested that the criteria for an ideal lung donor could be extended to 18–65 years.[14] Therefore, the age thresholds for older donors were not strictly defined in the inclusion criteria, and relevant studies were included as long as they were grouped based on age thresholds.

Data extraction was performed independently by two researchers using a pre-designed form. For studies that

met the inclusion criteria, the following relevant data were extracted. (1) Study characteristics: authors, year of publication, country, sample size, and duration of follow-up; (2) donor characteristics: gender, age, smoking history, and cause of death; (3) recipient characteristics: gender, age, and indication for lung transplantation; and (4) outcomes that used for comparison.

Quality assessment

The included articles' quality was assessed using the Newcastle–Ottawa Scale (NOS) (15). Cohort studies were evaluated by object selection, inter-group comparability, and outcome measurement. Articles with a score lower than 6 were considered of low quality. Two researchers conducted quality evaluations independently, and disparities were discussed and settled with a third researcher.

Statistical analysis

Data were statistically analyzed by Review Manager 5.3. Risk ratios (RR) and 95% confidence intervals (CIs) were used for dichotomous data, and standardized mean difference (SMD) and 95% CI were used to calculate continuous data. Owing to the potential heterogeneity of the included study populations, the random effects model was uniformly applied in statistical analyses to improve the credibility of the results. I^2 was used to determine heterogeneity, with $I^2 \geq 75\%$ indicating severe heterogeneity, ≥50% and <75% suggesting higher heterogeneity, ≥25% and <50% representing moderate heterogeneity, and <25% showing low heterogeneity. In this study, funnel plots were used to detect publication bias, and a two-sided $p < 0.05$ was deemed statistically significant.

Results

Study selection

A total of 7010 records were retrieved with the set search formula across the four databases, and no additional records were retrieved from other sources. A total of 4385 articles remained after excluding duplicate records. After reading the article titles and abstracts, 4367 articles were excluded. The full text of the remaining 18 articles was read, and 2 articles were excluded due to duplicate data sources, 4 articles were excluded owing to the absence of the outcomes of interest, 1 article was excluded as the methodology did not meet the inclusion criteria, and 1 article was excluded because the language was not English. Finally, a total of 10 cohort studies were included in this meta-analysis.[15–17,19–25] As displayed in **Fig. 1**, the flow chart shows the detailed screening process.

Study characteristics and quality assessment

Between 2005 and 2023, a total of 10 cohort studies investigated the prognosis of lung transplantation recipients, comparing older and younger donors. Three of these articles set up experimental and control groups with a threshold of 70 years of age; of the remaining articles, 2 had a threshold of 65 years of age, 1 had a threshold of 60 years of age, 3 had a threshold of 55 years of age, and 1 had a threshold of 50 years of age. A total of 13586 patients were included, of which 1401 patients were included in the experimental group (older donor group) and the remaining 12185 patients were included in the control group (younger donor group). The shortest median follow-up period was 1.9 years, and the longest median follow-up period was 8 years. For each included study, OS was provided, and the majority of studies provided LOS, intensive care unit (ICU) duration, ventilator use, and incidence of PGD II or III. The characteristics of the studies included in this meta-analysis are shown in **Table 1**, **Supplementary Table 1-1,** and **Supplementary Table 1-2**.

Supplementary Table 2 displays the quality ratings of the included studies using the NOS checklist. Three of the studies were given a score of 9, two were given a score of 7, and all of the remaining included studies were given a score of 8. None of the articles had a score lower than 6.

Short-term endpoints

Five studies reported the incidence of PGD II or III within 72 hours (h). The pooled results showed no difference in the incidence of PGD II or III within 72 h between the older donor group and the younger donor group in lung transplantation (RR = 1.08, p = 0.61) (**Fig. 2**). Four studies reported postoperative extracorporeal membrane oxygenation (ECMO) utilization, with the pooled results showing no significant difference between the two groups (RR = 1.12, p = 0.53) (**Fig. 3A**). In addition, seven studies included the length of postoperative ventilator use as an outcome, and the pooled results indicated no difference between the two groups (SMD = –0.03, p = 0.68) (**Fig. 3B**). Eight studies reported recipient ICU duration, and the pooled results showed no difference in ICU duration between the two groups (SMD = 0.03, p = 0.73) (**Fig. 4B**). In contrast, the

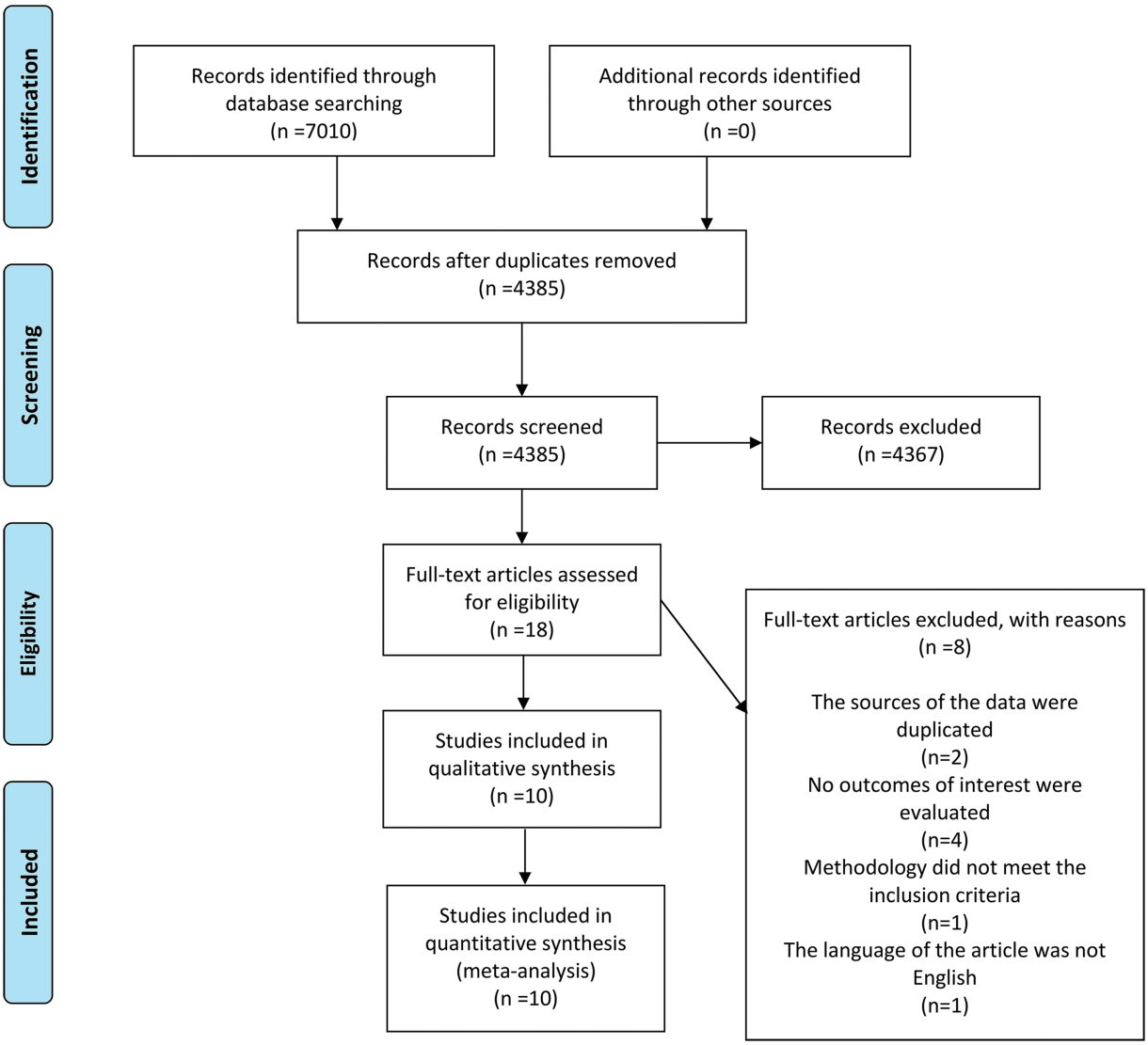

Fig. 1 Flow diagram of the selection process.

Table 1 Characteristics of all the studies included in the meta-analysis

Author	Year	Country	Experiment (year)	Control (year)	Number of patients		Median follow-up (years)	Outcomes
					Experiment	Control		
Hecker	2017	Germany	≥70	<70	16	80	NA	OS, LOS, ECMO/ventilation
Renard	2021	France	≥65	<65	44	197	1.9	OS, LOS, PGD, CLAD, ECMO/ventilation/ICU
Vanluyten	2023	Belgium	≥70	<70	69	69	NA	OS, LOS, PGD, CLAD, ventilation/ICU
Sommer	2023	Germany	≥70	<70	62	1106	8.9	OS, LOS, PGD, CLAD, ECMO/ventilation/ICU
Pizanis	2010	Germany	≥55	<55	19	167	2.5	OS, LOS, ventilation
Bittle	2013	America	≥55	<55	1018	9648	3	OS, LOS
López	2015	Spain	≥60	<60	53	177	NA	OS, LOS, PGD, ventilation/ICU
Fischer	2005	Germany	≥50	<50	49	244	NA	OS, ventilation/ICU
Glorion	2023	France	≥65	<65	30	326	8	OS, LOS, PGD, CLAD, ECMO/ICU
Dahlman	2006	Sweden	≥55	<55	41	171	NA	OS, ventilation/ICU

NA: not available; OS: overall survival; LOS: length of stay; PGD: primary graft dysfunction; CLAD: chronic lung allograft dysfunction; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit

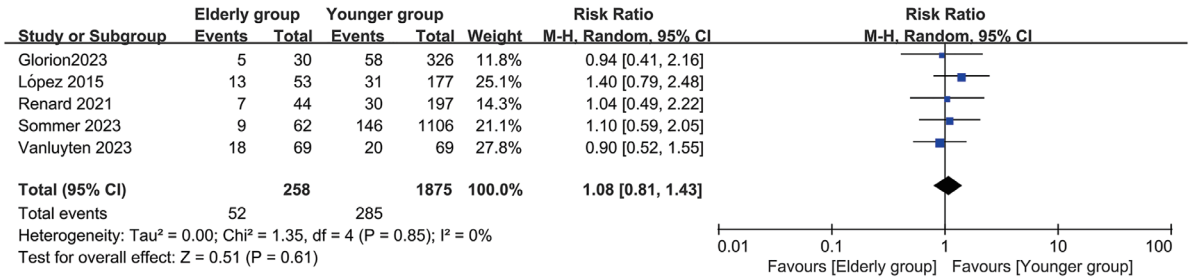

Fig. 2 Forest plot of meta-analysis comparing older and younger lung donors on the incidence of PGD II or III within 72 hours. PGD: primary graft dysfunction

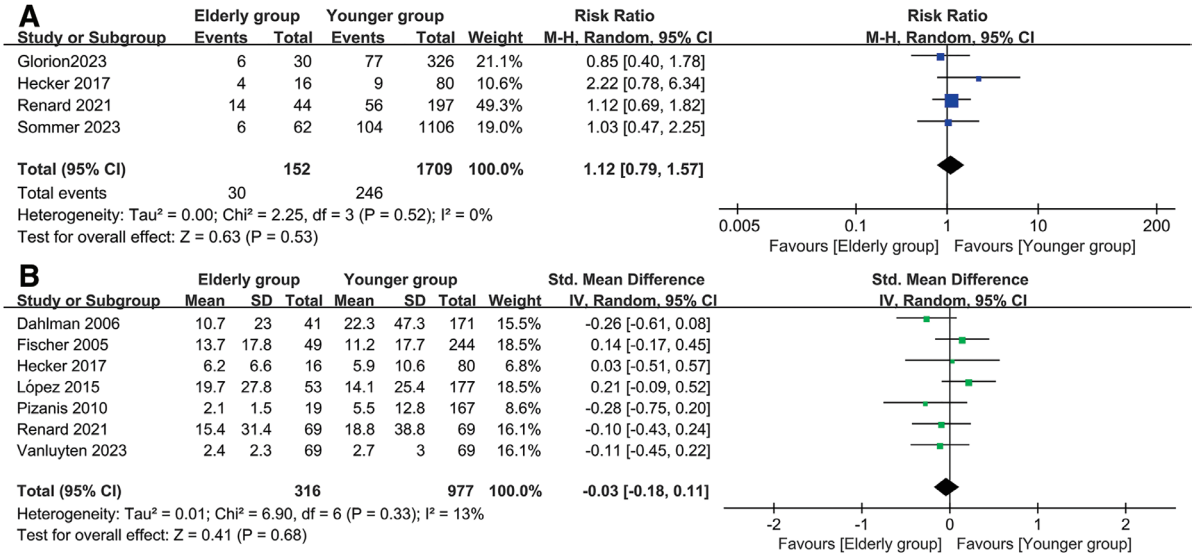

Fig. 3 Forest plot of meta-analysis comparing older and younger lung donors on (**A**) the ECMO utilization and (**B**) the ventilator use. ECMO: extracorporeal membrane oxygenation

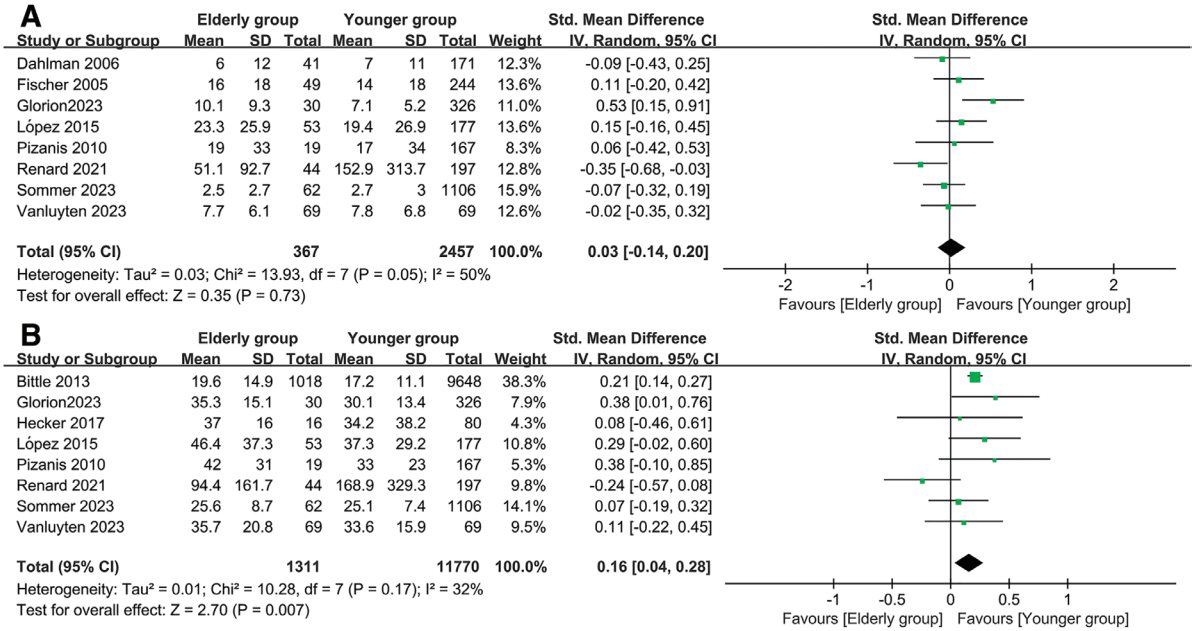

Fig. 4 Forest plot of meta-analysis comparing older and younger lung donors on (**A**) the length of time in the ICU and (**B**) the LOS. ICU: intensive care unit; LOS: length of hospital stay

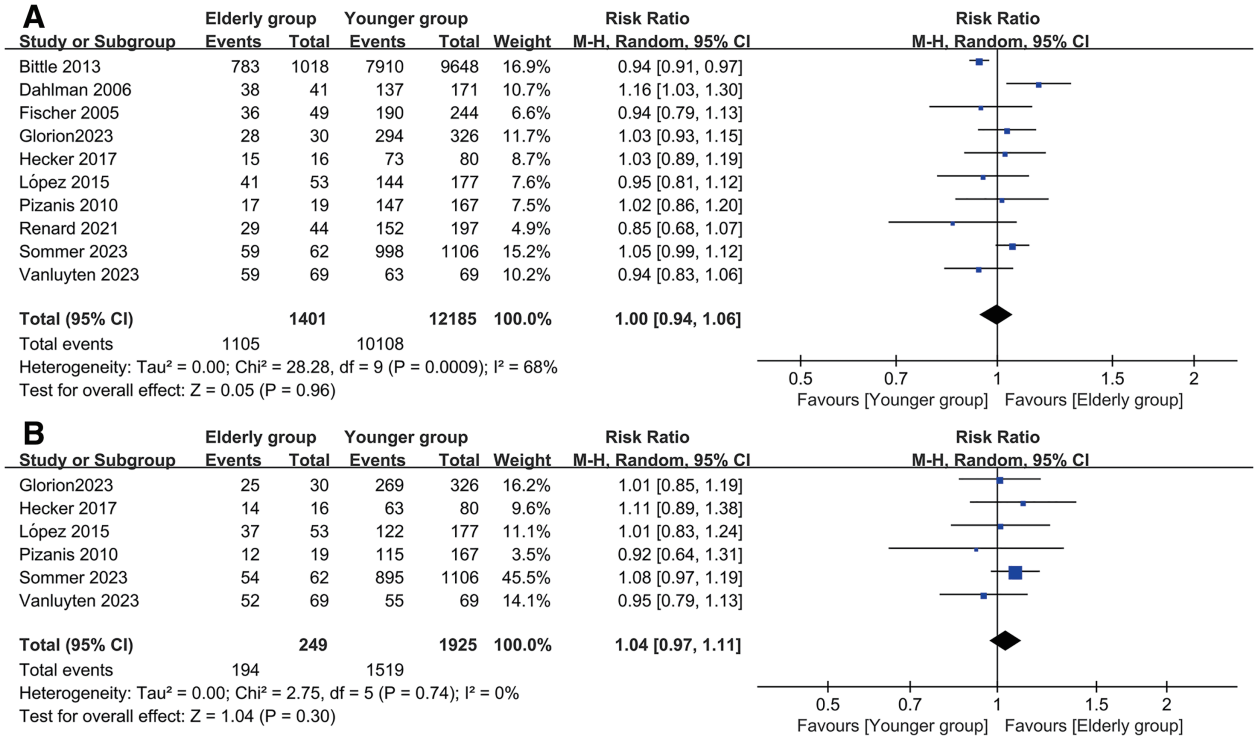

Fig. 5 Forest plot of meta-analysis comparing older and younger lung donors on (**A**) the 1-year OS and (**B**) the 3-year OS. OS: overall survival

pooled results of eight studies showed that the younger donor group had a significantly shorter LOS than the older donor group (SMD = 0.16, 95% CI = 0.04–0.28, p = 0.007) (**Fig. 4B**).

Long-term endpoints

Ten studies included 1-year OS, and the pooled results showed no difference in 1-year OS between the older donor group and the younger donor group following lung transplantation (RR = 1.00, p = 0.96) (**Fig. 5A**). Moreover, six studies evaluated the 3-year OS, with the pooled results demonstrating no significant difference between the two groups (RR = 1.04, p = 0.30) (**Fig. 5B**). A further eight studies provided 5-year OS and the pooled results showed no difference between the two groups (RR = 0.98, p = 0.37) (**Fig. 6A**). Remarkably, a total of four studies provided 5-year CLAD-free survival, and the pooled results showed a significantly higher 5-year CLAD-free survival in the older donor group compared to the younger donor group (RR = 1.12, 95% CI = 1.01–1.23, p = 0.03) (**Fig. 6B**).

Publication bias

Furthermore, publication bias was evaluated for the outcomes of 1-year OS, 3-year OS, 5-year OS, and 5-year CLAD-free survival. The funnel plots were approximately symmetrical, suggesting no significant publication bias, as detailed in **Supplementary Figure 1** and **Supplementary Figure 2**.

Discussion

The high mortality rate of patients on the lung transplantation waiting list may be attributed to the imbalance between the high number of patients waiting for lung transplantation and the low number of organ donors.[15] According to data published by the United Nations in 2019, the world's life expectancy per capita is increasing, and people over 65 years of age already make up 9.1% of the world's population.[26] With the aging population, the number of potential organ donors and recipients also increases.[27] Given the scarcity of donors and the aging population, the feasibility and safety of using elderly donor lungs should be explored. This meta-analysis investigated the outcomes of lung transplantation recipients, comparing older donors to younger donors. Overall, our findings demonstrated that older donors are not inferior to younger donors regarding short- and long-term outcomes, with a longer 5-year CLAD-free survival in the older donor group

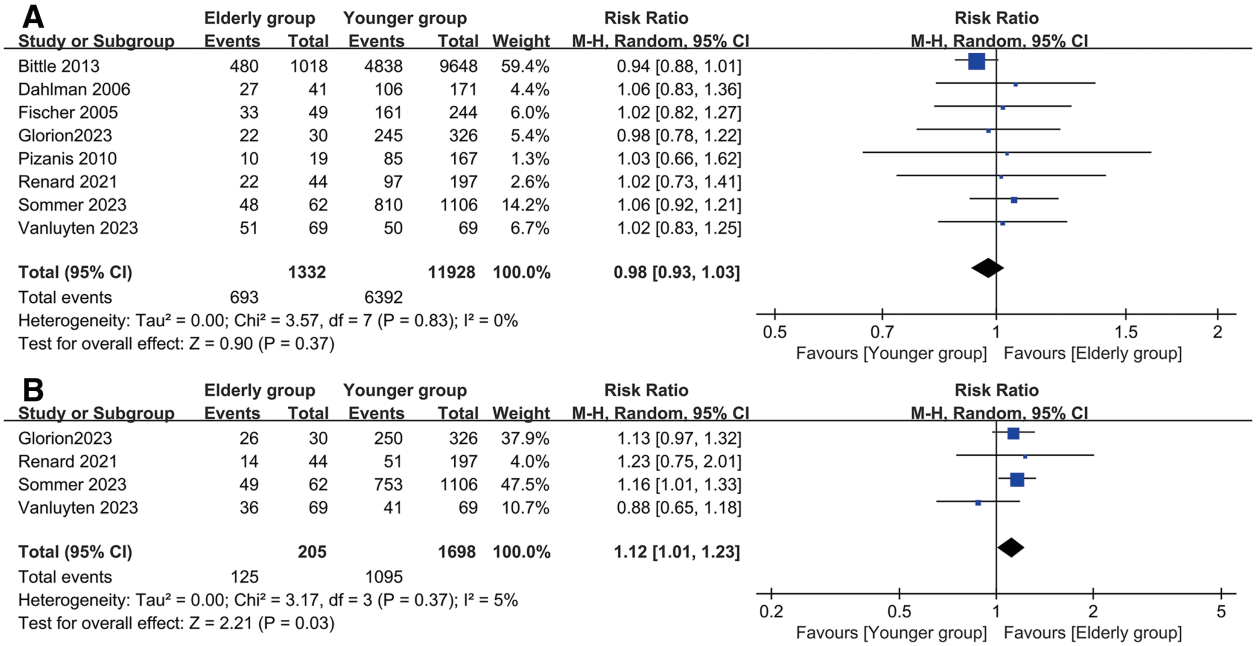

Fig. 6 Forest plot of meta-analysis comparing older and younger lung donors on (**A**) the 5-year OS and (**B**) the 5-year CLAD-free survival. OS: overall survival; CLAD: chronic lung allograft dysfunction

compared to the younger donor group. However, lung transplantation recipients from the older donor group also exhibited longer LOS than recipients from the younger donor group.

In terms of short-term results, no significant difference was observed in the incidence of PGD II or III within 72 h between recipients of the two donor groups. PGD is a severe acute lung injury characterized by a typical pathological pattern of diffuse alveolar injury reflecting the damage to the donor lung caused by the transplantation process (retrieval, preservation, implantation, and reperfusion) and by other factors (e.g., acid inhalation, pneumonia).[28] Christie et al. and Whitson et al. noted that donor age affects the incidence of PGD, with the former reporting a linear relationship between the odds of developing PGD and donor age starting at age 35 years.[13,29] In contrast, the research of Diamond et al. concluded that there was no association between donor age and PGD.[30] Some studies have alternatively concluded that it is not donor age alone that contributes to the development of PGD, but rather the interaction between recipient and donor factors (e.g., age and duration of ischemia),[31] which appears to be supported by the results of our present research. That is, the increase in the risk of PGD may be limited if the older donor fulfills other factors of organ adaptation, thereby reducing the risk factors.

Furthermore, poor lung elasticity and slow recovery of lung function in older donors were theorized to lead to increased ECMO utilization and prolonged ventilator duration. However, the results of this research revealed no significant difference in ECMO utilization and ventilator duration between patients with older and younger donors. On the one hand, this is probably due to the similar incidence of PGD II or III within 72 h between the two groups, as ECMO and ventilator utilization are important therapeutic tools for PGD. On the other hand, physicians tend to have stricter criteria for the selection of older donors.[32] Lungs with additional risk factors, such as a history of smoking, severe infiltrates, discolorations, or parenchymal changes, are usually not selected as donors, and surgeons favor lungs with a high PaO_2/FiO_2 ratio (preferentially >400 mmHg), no infiltrates on chest X-ray, and no signs of infection. As displayed in **Supplementary Table 2**, smoking prevalence was lower in older donors than in younger donors in most of the included studies. Owing to environmental exposures such as tobacco smoke and air pollution, the biological age of the lungs of older donors may be lower than the actual age of the donor. Selected older donor lungs may have a slight decrease in elasticity and function but only minimally affect postoperative recovery, so the ECMO and ventilator use showed no significant difference between older donors and younger donors.

Furthermore, the ICU duration was similar between recipients from the older donor group and those from the younger donor group. However, the LOS was significantly longer in recipients from the older donor group than in those from the younger donor group. In general, older lung donors are assigned to older lung transplantation patients, that is, the "old for old" policy, with almost 80% of lung donors older than 60 years being used in patients older than 50 years.[22] The occurrence of PGD or other serious complications may not show significant differences based on donor age, which may be reflected by the similar ICU duration. However, considering the relatively older age of the recipients and the correspondingly slower rate of postoperative recovery, a relative increase in LOS was observed. Another possible reason is that lungs from older donors require a longer break-in time.

In long-term outcomes, no significant difference was found between the two groups in terms of 1-year OS, 3-year OS, and 5-year OS. This may also be attributed to the selection process of older donors, as increasing donor age may be balanced by keeping most other risk factors low. Interestingly, recipients from the older donor group outperformed those from the younger donor group in terms of 5-year CLAD-free survival. Telomere shortening is a key mechanism in aging. Faust et al. found that short telomeres in donor peripheral blood cells were not associated with CLAD but that short telomeres in donor airway epithelial cells could directly contribute to the development of CLAD. Donors with short telomeres were hypothesized to possess more senescent cells and would pose an increased risk of developing airway centrality or pulmonary fibrosis, which are associated with CLAD.[33] Moreover, Greenland et al. reported that external factors (e.g., PGD) may damage the telomere and result in an increased risk of CLAD, the donor's own genetic risk of short telomeres.[34] As mentioned previously, age appears to play a limited role in increasing the risk of PGD in the absence of other risk factors. Hence, the risk of telomere abrasion in donor airway epithelial cells due to external factors is similar in older and younger donors. Nevertheless, older transplant recipients are generally considered to have a lower risk of acute and chronic rejection owing to decreased immune function.[35] The combination of these factors may account for the superior 5-year CLAD-free survival of recipients from the older donor group.

Overall, our findings emphasize the potential value of elderly donors in lung transplantation. For older donor lungs with better physiologic conditions, which have lower risk factors after rigorous evaluation and screening using pulmonary function tests and imaging examinations, such as some donor lungs with no history of smoking, no signs of infection, and no parenchymal changes, the selection of the donor for transplantation does not increase the rate of complications such as PGD in the recipients or decrease the rate of long-term survival even if the donor is older, and therefore age should not be a limiting factor when the donor lung meets certain physiologic parameters. Accordingly, some donor lungs with moderate to severe age-related obstructive lung disease would be excluded from the candidate list because of poor physiologic status and would not be considered for inclusion because of the increased donor age threshold. Our findings further support an individualized selection strategy based on donor physiological status. In addition, data on recipient gender, age, and indications for lung transplantation are provided in **Supplementary Tables 1–2**. The median age of recipients with known older donors in the included literature ranged from 30 to 61 years, whereas the median age of older donors ranged from 54 to 73 years. The most common indication for transplantation in recipients was emphysema or chronic obstructive pulmonary disease, followed by pulmonary fibrosis. Elderly donor lungs show potential for the treatment of end-stage respiratory disease, and their use is not limited to recipients of a specific age but has the potential to be equally applicable even to younger recipients.

The limitations of this research were primarily the retrospective nature of the included studies, which have potential unmeasured confounders due to the lack of prospective studies and randomized controlled trials; yet, conducting randomized studies in this field is difficult. Second, the small number of relevant studies included in the analysis did not allow for further subgroup analysis. The number of recipients from the older donor group was relatively small, and additional large-scale multicenter studies are required to confirm the results. Finally, a noteworthy limitation is the variation in age thresholds among the included studies. The inconsistent definition of age thresholds for older donors across studies leads to unavoidable heterogeneity between studies, and this heterogeneity may lead to the introduction of bias, affecting the interpretation and comparison of results. This is the first meta-analysis to compare the prognosis of lung transplantation recipients based on donor age.

Conclusion

Overall, our meta-analysis demonstrated that older donors were not inferior to younger donors both in short- and long-term outcomes. Although recipients from the older donor group had longer LOS, they also exhibited a better 5-year CLAD-free survival. Considering the shortage of lung donors, older donors may be considered after rigorous evaluation.

Acknowledgments

None.

Declarations

Ethics approval and consent to participate

Not applicable (this paper was written based on data from global databases).

Consent to publish

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article. The detailed data in this article can be obtained by contacting the corresponding author.

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Author contributions

YXS designed the research process. YKD, ZYX, and RRF searched the database for corresponding articles. RRF and QFZ extracted useful information from the articles above. HWS used statistical software for analysis. ZYX drafted the meta-analysis. YXS and MD polished this article. All authors had read and approved the manuscript and ensured that this was the case.

Disclosure statement

The authors declare that they have no conflict of interest.

Supplementary Materials

Supplementary Fig. 1. Funnel plot of analysis of a. 1-year OS; b. 3-year OS

Supplementary Fig. 2. Funnel plot of analysis of a. 5-year OS; b. 5-year CLAD-free survival

Supplementary Table 1-1. Characteristics of all donors included in the meta-analysis

Supplementary Table 1-2. Characteristics of all recipients included in the meta-analysis

Supplementary Table 2. Quality assessment of observational studies included

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