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REVIEW

Impact of Concomitant Statin Use on Survival Outcomes in Non-Small Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis

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Abstract

Background: Preclinical and observational evidence suggests that statins may enhance the efficacy of immune checkpoint inhibitors (ICIs) in cancer, including non-small cell lung cancer (NSCLC). However, existing meta-analyses have included mixed cancer types or lacked updated data. We conducted a comprehensive, NSCLC-specific meta-analysis to evaluate the association between statin use and clinical outcomes in ICI-treated patients. **Methods:** We systematically searched PubMed, Embase, and Cochrane Library for studies published up to May 2025 that assessed statin use in NSCLC patients receiving ICIs. Outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and immune-related adverse events (IRAEs). Random-effects models were used to pool hazard ratios (HRs) or odds ratios (ORs). Subgroup analyses were performed based on statistical adjustment (multivariate vs. univariate) and ICI type. **Results:** A total of 10 retrospective studies comprising 3,761 patients were included. Statin use was associated with improved OS (HR: 0.83, 95% CI: 0.71–0.98, P = 0.03, I^2 = 36%) and a non-significant trend toward better PFS (HR: 0.83, 95% CI: 0.68–1.02, P = 0.08, I^2 = 62%). Statin use significantly increased the ORR (OR: 2.91, 95% CI: 1.72–4.94, P < 0.0001), without a statistically significant rise in IRAEs (OR: 1.59, 95% CI: 0.76–3.34, P = 0.22). Subgroup analysis revealed that OS benefit was primarily driven by studies using multivariate adjustment (HR: 0.73, 95% CI: 0.61–0.87), with no significant effect observed in univariate studies. **Conclusions:** This NSCLC-focused meta-analysis suggests that statin use is associated with improved survival and response in patients treated with ICIs, without a clear increase in toxicity. These findings support further prospective studies to explore the immunomodulatory potential of statins in lung cancer.

Keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors- Survival- Meta-Analysis- Progression- Free Survival

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1. Introduction

Immune checkpoint inhibitors (ICIs) are a group of anticancer agents that have demonstrated substantial therapeutic efficacy in patients with various types of solid tumors, including those with non-small cell lung cancer (NSCLC) [1]. Antitumor therapies targeting the programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis have revolutionized the treatment of NSCLC by reducing the inhibitory effects of tumors on T lymphocytes, thereby enhancing T cell activation, proliferation, and differentiation, improving immune function, and increasing the abundance of proteins involved in the immune response [2, 3]. Recent systematic reviews have demonstrated the beneficial effects of immune checkpoint inhibitors on overall survival (OS) and progression-free survival (PFS) for both first and second-line treatment compared to

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chemotherapy in patients with stage IV NSCLC [4]. The efficacy of anti-PD-(L)1 ICIs in advanced NSCLC has been demonstrated in randomized controlled clinical trials in both second-line and first-line setting, and anti-PD-(L)1 ICIs are now considered the first-line systemic therapy for metastatic NSCLC without specific driver mutations [3]. However, previous studies have also shown that therapeutic responses to ICIs vary among cancer patients, with factors such as age, smoking history, metastatic site or status, and geographic region potentially influencing the efficacy of PD-1 inhibitors in the treatment of NSCLC [1]. Additionally, statins have been identified as potent inhibitors of YES-associated protein (YAP), a downstream transcriptional activator in the HIPPO pathway that regulates tumor immunity and PD-L1 expression, and has been shown to contribute to cancer progression and metastasis in NSCLC [1].

The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, commonly known as statins, are widely prescribed hypolipidemic medications for patients with atherosclerosis and cardiovascular diseases [1]. By inhibiting the key enzyme in the mevalonate pathway, statins reduce the isoprenylation of small GTPases, which affects immune processes such as T cell signaling, antigen presentation, and cytokine production, suggesting significant immunomodulatory effects [5]. Furthermore, preclinical studies have demonstrated that statins disrupt cell activity in the G1 or S phases by affecting cell cycle regulatory proteins, leading to apoptosis in cancer cells and inhibition of intracellular signaling pathways, thereby exerting anticancer efficacy through antiproliferative, anti-inflammatory, pro-apoptotic, and anti-invasive mechanisms [1]. Additionally, studies have reported that statins reduce the expression of PD-1 and CTLA-4 on T cells [6]. Previous meta-analyses of observational studies have shown that statin use can favorably impact the survival of lung cancer patients through their immunomodulatory activity, indicating improved OS and potential clinical synergy between statins and ICIs [2, 5]. The possible impact of statin uses on outcomes in patients NSCLC receiving ICIs has been examined in several previous meta-analyses, including Zhang et al.'s (2022) study [1]. Zhang's meta-analysis included a subgroup analysis comparing univariate and multivariate models and found a modest OS benefit linked to statin use. A smaller number of included studies and lack of outcome type stratification (e.g., ORR, and IRAEs). Furthermore, their study lacked larger, more recent cohorts like Serino et al. (2024) [7] and Marrone et al. (2024) [3], which significantly broadened the evidence. Our updated meta-analysis, however, shows that the observed survival benefit is primarily driven by studies using multivariate statistical adjustment. It disaggregates outcomes (OS, PFS, ORR, and IRAEs), including a larger and more recent set of studies, and conducts thorough subgroup analyses based on adjustment type. These methodological advancements highlight the necessity of prospective validation and assist in elucidating the strengths and limitations of the available evidence.

This meta-analysis aimed to evaluate the association between statin use and clinical outcomes in patients with NSCLC treated with ICIs. Our goal was to provide an updated, NSCLC-specific synthesis of the evidence to clarify the potential role of statins in immunotherapy-treated populations.

2. Material and Methods

2.1 Eligibility Criteria

The eligibility of studies for inclusion in this meta-analysis was determined using the PICOT framework [8]. Eligible studies enrolled adult patients (≥18 years) diagnosed with NSCLC of any histologic subtype such as adenocarcinoma or squamous cell carcinoma who were treated with ICIs, including PD-1, PD-L1, or CTLA-4 inhibitors, alone or in combination. The intervention of interest was the concomitant use of statins, regardless of type, dosage, duration, or timing relative to ICI initiation, as documented in medical or pharmacy records. The comparator group comprised NSCLC patients treated with ICIs who did not receive statins, confirmed by the absence of relevant prescriptions or medical documentation. The primary outcomes were OS and PFS, reported as HRs with corresponding 95% confidence intervals (CIs). OS was defined as the time from ICI initiation to death from any cause, while PFS was defined as the time from ICI initiation to disease progression, recurrence, or death. Only retrospective or prospective cohort studies published as full-length, peer-reviewed journal articles and conducted in human populations were considered eligible.

2.2 Exclusion Criteria

The following exclusion criteria were applied to ensure the methodological rigor and relevance of included studies. Case reports, editorials, narrative or systematic reviews, and conference abstracts were excluded. Preclinical or animal studies were not considered. Studies focusing on cancers other than NSCLC, or those that did not involve ICI therapy, were also excluded. Additionally, studies that did not report OS or PFS as outcomes, or lacked a comparison group of statin non-users, were omitted. Grey literature and unpublished data were excluded to maintain consistency with peer-reviewed methodological standards.

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. A comprehensive literature search was performed across PubMed, EMBASE, Cochrane Library, and Medical Subject Headings (MeSH) databases, covering studies published up to 2025. A systematic search was conducted across PubMed, EMBASE, the Cochrane Library, and MeSH to identify studies evaluating statin use in patients with non-small cell lung cancer (NSCLC) receiving immunotherapy. The search terms included variations of "non-small cell lung cancer" and "statins" combined with immunotherapy-related keywords. The search yielded 260 results in PubMed, 675 in EMBASE, 7 in the Cochrane Library, and 942 references through MeSH. After removal of

duplicates, two independent reviewers screened titles and abstracts for relevance, followed by full-text review to determine final inclusion based on predefined eligibility criteria. Any disagreements were resolved by consensus or by a third reviewer. The study selection process is detailed in the PRISMA flow diagram (Figure 1).

2.3 Endpoints and sub analysis

The primary endpoints were overall survival (OS) and progression-free survival (PFS), both reported as hazard ratios (HRs) with 95% confidence intervals (CIs). OS was defined as the time from initiation of immune checkpoint inhibitor (ICI) therapy to death from any cause, and PFS as the time from ICI initiation to disease progression, recurrence, or death. Secondary endpoints included objective response rate (ORR), where reported, and the incidence of immune-related adverse events (IRAEs), to evaluate both efficacy and safety outcomes. Subgroup analyses were performed based on the type of statistical model used univariate versus multivariate to assess whether the observed associations remained consistent after adjustment for confounding variables.

2.4 Quality assessment

The risk of bias in the included observational studies was assessed using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool, which evaluates seven domains: bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results [10]. Each study was independently reviewed by two investigators, and discrepancies were resolved by consensus. A traffic light plot was generated to visually summarize the risk of bias across domains, categorizing each as low, moderate, serious, or critical risk.

2.5 Statistical analysis

This systematic review and meta-analysis were performed in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [11]. We pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS) using a random-effects model to account for differences across studies. For binary outcomes, such as objective response rate (ORR) and immune-related adverse events (IRAEs), we calculated pooled odds ratios (ORs) with 95% CIs. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. We also performed subgroup analyses to explore differences between univariate and multivariate models. Publication bias was evaluated by visual inspection of funnel plots and, when applicable, using Egger's test. All statistical analyses were carried out using Review Manager (RevMan) version 4.3.

3. Results

3.1 Baseline characteristics

A total of 10 studies were included, encompassing 3,761 patients with NSCLC treated with ICIs. Table 1 summarizes the key baseline characteristics of the included studies. Most studies were retrospective in design and conducted between 2019 to 2025. The median patient age ranged from 66 to 71 years, and most study populations were male. Adenocarcinoma was the most common histologic subtype reported. The most frequently used ICIs were PD-1 or PD-L1 inhibitors, either as monotherapy or in combination. Statin exposure varied across studies in terms of type (lipophilic vs. hydrophilic), dose, and timing relative to ICI initiation. Follow-up duration, outcome

Table 1. Baseline Characteristics of Included Studies

Study	Country / Setting	Study Design	Sample Size	Statin Users (n, %)	ICI Type	Line of Therapy	Adjustment Method	Follow-up Duration
Takada et al. (2022) [12]	Japan	Retrospective cohort	90	45 (50%)	Niv or Pembrolumab	First or later	Propensity score	NR
Miura et al. (2021) [13]	Japan	Retrospective cohort	300	26 (8.7%)	Niv or Pembrolumab	Mixed	Multivariate Cox	11.5 months
Omori et al. (2019) [14]	Japan	Retrospective cohort	68	12 (17.6%)	Niv	Second or later	Univariate and Kaplan-Meier	10.5 months
Rossi et al. (2021) [15]	Italy	Retrospective cohort	122	NR	Niv or Pembrolumab or Atezolimab	First or second	Multivariate Cox	NR
Kostine et al. (2021) [16]	France	Retrospective cohort	150	NR	PD-1/PDL1 inhibitor	Unclear	Univariate	NR
Marrone et al. (2024) [3]	USA	Retrospective cohort	1401	NR	PD-1/PDL1 inhibitor	First or later	Stratified Cox + Propensity score	4.2 months
Svaton et al. (2020) [17]	Czech Republic	Retrospective cohort	224	31 (13.8%)	Niv	Second	Multivariate Cox	12 months
Cortellini et al. (2021) [18]	Italy	Retrospective cohort	1012	NR	PD-1/PDL1 inhibitor	First	Multivariate Cox	NR
Cantini et al. (2021) [19]	Italy	Retrospective cohort	179	NR	Niv or Pembrolumab	First or second	Multivariate Cox	NR
Serino (2024) [7]	Italy	Retrospective cohort	215	35 (16.3%)	PD-1/PDL1 inhibitor	First or later	Multivariate Cox	13.2 months

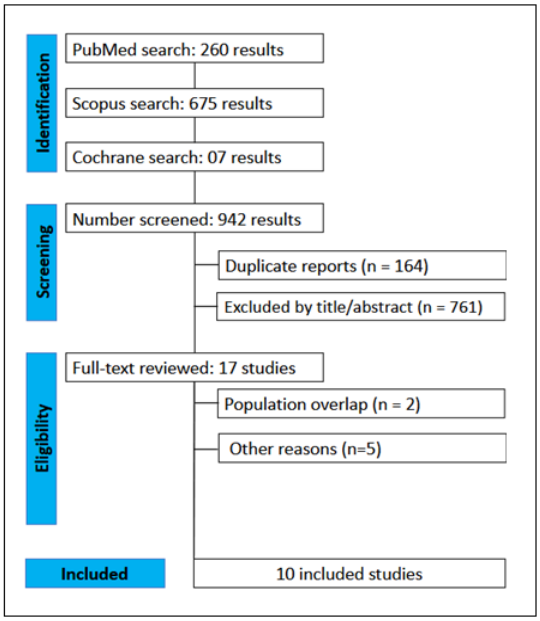

Figure 1. PRISMA Flow Diagram of Study Screening and Selection

definitions, and adjustment for confounders also differed among studies. Table 1 below summarizes the baseline characteristics of studies.

3.2 Statistical Analysis

We pooled HRs and 95% confidence intervals (CIs) for OS and PFS using a random-effects model to account for differences across studies. For binary outcomes, such as ORR and IRAEs, we calculated pooled odds ratios (ORs) with 95% CIs. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. We also performed subgroup analyses to explore differences between univariate and multivariate models. Publication bias was evaluated by visual inspection of funnel plots and, when applicable, using Egger's test. All statistical analyses were carried out using Review Manager (RevMan) version 4.3.

3.3 Pooled analysis of all studies

3.3.1 Overall survival (OS)

As shown in Figure 2, a meta-analysis of 9 observational studies [3,12-19] assessing the impact of statin use on OS in patients with NSCLC receiving ICIs demonstrated a statistically significant association. The pooled HR was 0.83 [95% CI: 0.71–0.98], indicating a 17% relative reduction in the risk of death among statin users (P = 0.03). Heterogeneity across studies was low to moderate (I^2 = 36%), suggesting a relatively consistent effect. These findings support a potential survival benefit of concomitant statin therapy in this population, warranting further prospective validation.

As shown in Figure 3, a subgroup meta-analysis based on the statistical adjustment method was conducted to explore the association between statin use and OS in NSCLC patients receiving ICIs. Among studies that used multivariate-adjusted models, the pooled HR was 0.73 [95% CI: 0.61–0.87], indicating a statistically significant survival benefit in statin users (P < 0.001, I^2 = 0%). In contrast, studies using univariate analysis showed no significant association (HR = 0.99 [0.84–1.15], P = 0.87, I^2 = 2%). A test for subgroup differences was statistically significant (P = 0.01), suggesting that the observed survival benefit is primarily driven by studies employing multivariate adjustment. These findings reinforce the importance of adequately controlling confounding variables when assessing the impact of statin use in this context.

3.3.2 Progressive free survival (PFS)

As shown in Figure 4, a random-effects meta-analysis of 9 studies [3, 12-19] evaluating the association between statin use and PFS in patients with NSCLC treated with ICIs yielded a pooled HR of 0.83 [95% CI: 0.68–1.02], favoring statin use but not reaching statistical significance (P = 0.08). Moderate heterogeneity was observed (I^2 = 62%, P = 0.007), suggesting variability in effect estimates across studies. While the point estimate indicates a potential reduction in the risk of disease progression among statin users, further prospective or stratified analyses are needed to confirm this association.

A subgroup meta-analysis of PFS stratified by statistical adjustment (multivariate vs. univariate analysis) included 9 studies, as seen in Figure 5. The pooled HR for studies using multivariate analysis was 0.78 [0.59–1.03], with moderate heterogeneity (I^2 = 61%) and a non-significant overall effect (P = 0.08). For studies reporting univariate analysis, the pooled HR was 0.93 [0.69–1.25] (P = 0.63, I^2 = 57%). The overall pooled HR was 0.83 [0.68–1.02], favoring statin use, but this did not reach

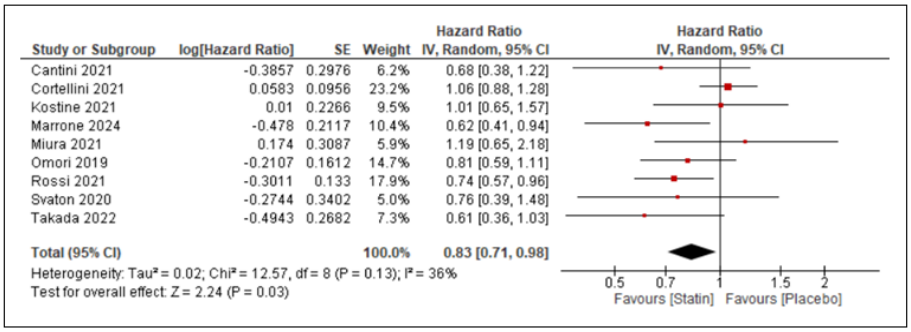

Figure 2. Forest Plot of the OS in Patients with NSCLC Treated with Statin Concomitant with ICI. SE = standard error; IV = inverse variance; CI = confidence interval.

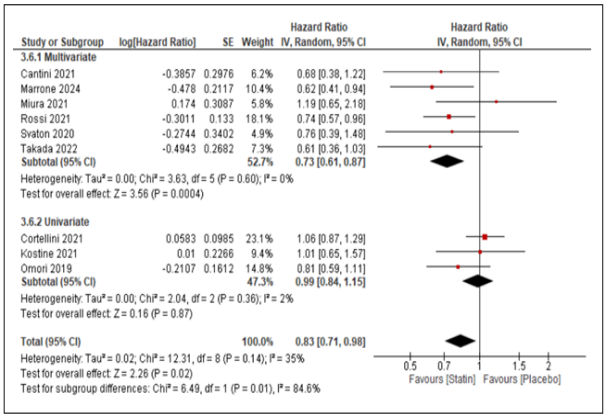

Figure 3. Forest Plot of Subgroup Analysis of Multivariate and Univariate Studies within Overall Survival. SE = standard error; IV = inverse variance; CI = confidence interval.

statistical significance (P = 0.08). No significant subgroup difference was found between univariate and multivariate models (P = 0.39). These findings suggest a possible but not definitive association between statin use and improved PFS in NSCLC patients treated with ICIs, especially in multivariate-adjusted studies.

3.3.3 Objective Rate Response (ORR)

A meta-analysis of three studies [14, 15, 19] reporting ORR in NSCLC patients treated with ICIs showed a significantly higher likelihood of response among statin users compared to non-users, as shown in Figure 6. The pooled OR was 2.91 [95% CI: 1.72–4.94], indicating nearly a threefold increase in response associated with statin use (P < 0.0001). Heterogeneity was low (I^2 = 12%), suggesting consistent effects across studies. These findings support the hypothesis that statins may enhance antitumor efficacy of ICIs in NSCLC, though confirmatory prospective studies are warranted.

3.3.4 Immune-related adverse events (IRAEs)

A meta-analysis of three studies [7, 12, 13] evaluating the association between statin use and IRAEs in NSCLC patients treated with ICIs found no statistically significant difference, as seen in Figure 7. The pooled OR was 1.59 [95% CI: 0.76–3.34], suggesting a non-significant trend toward increased IRAE risk in statin users (P = 0.22). Moderate heterogeneity was present (I^2 = 63%), largely influenced by between-study variability. Although Serino et al. (2024) reported a significant association individually, pooled data do not confirm a definitive signal, indicating the need for further large-scale prospective evaluation.

3.3.5 Publication bias (funnel plot, Egger's test)

As shown in Figure 8A, the funnel plot of included studies appears generally symmetrical, with studies scattered evenly around the pooled effect size (blue dashed line), although there is some dispersion among smaller studies (i.e., those with higher standard errors). No clear evidence of small-study effects or publication bias is apparent visually.

3.3.6 Funnel progression-free survival (PFS)

The funnel plot of PFS shows a reasonably symmetrical distribution of studies around the pooled HR, as seen in Figure 8B. While some asymmetry is present among smaller studies (with higher standard errors), there is no strong visual indication of publication bias. The distribution suggests that the observed effect is not driven solely by small, extreme-result studies.

3.4 Risk of Bias

Risk of bias was assessed using the ROBINS-I tool for all included observational studies, as shown in Figure 9. [20]. Among the 10 studies analyzed, the overall risk of bias ranged from low to serious. Most studies were judged to have moderate risk of bias due to confounding, given their retrospective nature and limitations in controlling for key prognostic factors. Selection bias was generally low to moderate, as patient inclusion was often consecutive or registry based. The classification of interventions (i.e., statin use) was consistently rated as low risk due to reliance on well-documented medication records. Deviations from intended interventions and selective reporting bias were uniformly low across all studies. Missing data presented moderate concerns in several studies due to incomplete baseline or toxicity information. Notably, Serino et al. (2024) [7] had a serious risk of bias in outcome measurement, as immune-related adverse events were retrospectively reported and potentially under-detected. Only Marrone et al. (2024) [3] was judged to have a uniformly low risk of bias across all domains. Overall, the evidence base is acceptable for synthesis, though caution is warranted in interpreting findings from studies with serious confounding or outcome measurement

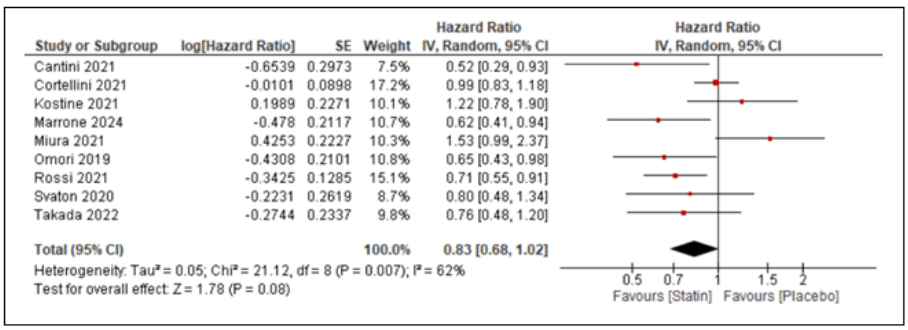

Figure 4. Forest Plot of Progressive-free Survival of Included Studies. SE = standard error; IV = inverse variance; CI = confidence interval.

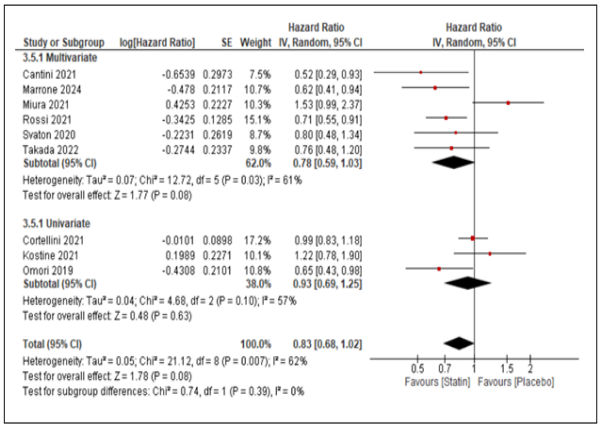

Figure 5. Forest Plot of Subgroup Analysis of Multivariate and Univariate Studies within Progressive-free Survival. SE = standard error; IV = inverse variance; CI = confidence interval.

limitations.

4. Discussion

Our meta-analysis demonstrates that concomitant statin use in patients with NSCLC treated with ICIs is associated with improved OS, with a pooled HR of 0.83 [95% CI: 0.71–0.98]. This finding was primarily driven by multivariate adjustment studies, in which the survival benefit was more pronounced (HR = 0.73 [0.61–0.87]). Although the pooled PFS and ORR analyses showed trends favoring statins, these did not consistently reach statistical significance. Importantly, statin use was not linked to a higher risk of IRAEs, which supports a favorable overall risk-benefit profile.

The potential clinical benefit of statins is supported by biological plausibility. In addition to lowering cholesterol, statins have immunomodulatory effects that may help strengthen the body's antitumor immune response. Statins have been shown to promote T-cell activation, reduce myeloid-derived suppressor cell function, and improve antigen presentation through inhibition of the mevalonate pathway [21, 22]. These mechanisms may synergize with ICIs to amplify immune-mediated tumor control, providing a rationale for the observed survival advantage in statin users.

Our findings align with and expand upon prior observational studies and meta-analyses. A 2022 meta-analysis by Zhang et al. [1] reported a pooled OS HR of 0.86 [0.74–1.01], though it included fewer multivariate-adjusted studies. By incorporating newer studies and stratifying by statistical methodology, our analysis provides a more refined estimate of the statin effect. It highlights the importance of appropriate confounder control in observational research. Only our meta-analysis found a statistically significant OS benefit when accounting for analytic rigor.

Clinically, these findings raise the question of whether statins should be routinely considered in ICI-treated NSCLC patients. While causality cannot be established from retrospective data, the strength and consistency of the association, coupled with the low cost and widespread availability of statins, suggests that prospective evaluation is warranted. In patients with concurrent cardiovascular risk factors, initiating or continuing statin therapy during ICI treatment may offer dual benefit without added toxicity.

This meta-analysis has several strengths. It is the most comprehensive synthesis to date, including 9 OS studies with robust subgroup analyses, risk of bias assessments, and evaluation of IRAEs. The inclusion of newly published studies, stratification by adjustment method, and low heterogeneity in the multivariate subgroup add to the reliability of the findings.

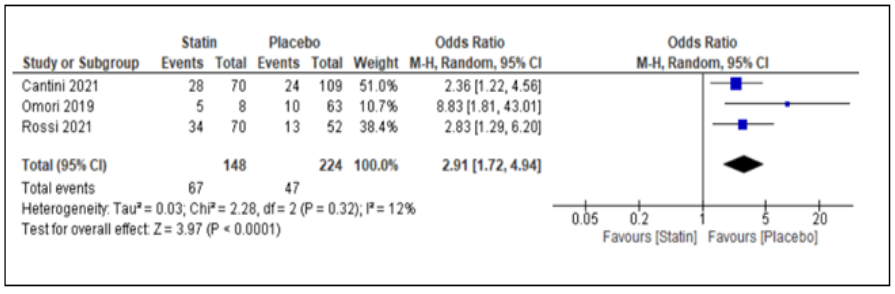

Figure 6. Forest Plot of Objective Rate Response of Included Studies. SE = standard error; CI = confidence interval. M-H: Mantel-Haenszel.

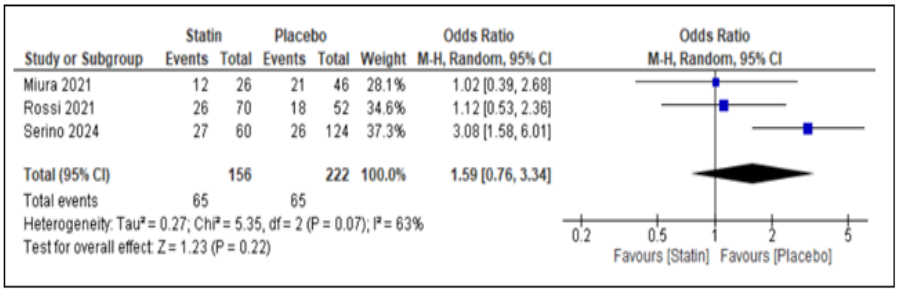

Figure 7. Forest Plot of Immune-related Adverse Events of Included Studies. SE = standard error; CI = confidence interval. M-H: Mantel-Haenszel.

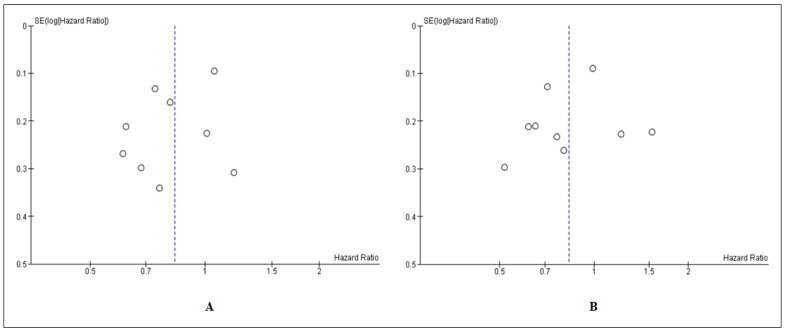

Figure 8. A; Funnel plot of overall survival of included studies. SE = standard error. B; Funnel plot of progression-free survival of included studies. SE = standard error.

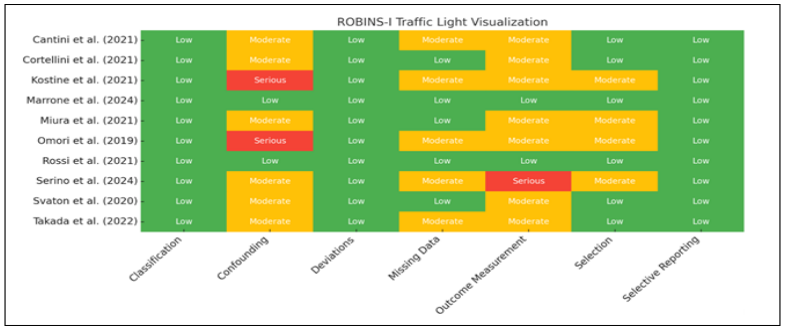

Figure 9. Risk of Bias Traffic Light Plot for Included Studies

However, several limitations should be acknowledged. All included studies were retrospective and observational, introducing the potential for residual confounding and selection bias. Variability in statin type, dose, and timing was not consistently reported, limiting mechanistic interpretation. Furthermore, publication bias cannot be completely ruled out, even though funnel plots revealed little asymmetry. Finally, the lack of randomized controlled trials prevents definitive causal inference.

In conclusion, according to this meta-analysis, statin use may be linked to better survival in patients with NSCLC receiving ICIs, without a discernible rise in immune-related adverse effects. These results add to the growing body of evidence suggesting that statins may help modulate the tumor immune environment and enhance the effectiveness of immunotherapy. While the findings are clinically encouraging, they should be interpreted with caution given the observational design of the included studies and the potential for confounding factors. To confirm these correlations and elucidate statins' function as supplementary agents in the immunotherapy landscape for NSCLC, well-designed prospective studies and randomized controlled trials are necessary.

Disclosures

All authors report no relantionships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of data presented and their discussed interpretation

Acknowledgments

Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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