Original Article

Antibiotic treatment and survival in non-small cell lung cancer patients receiving immunotherapy: a systematic review and meta-analysis

Arwa Abdelhamid[1], Stephanie Tuminello[2], Tara Ivic-Pavlicic[1], Raja Flores[3], Emanuela Taioli[1,3,4]

[1]Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Department of Population Health, NYU Grossman School of Medicine, New York, NY, USA; [3]Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Contributions: (I) Conception and design: E Taioli, R Flores, S Tuminello; (II) Administrative support: E Taioli, R Flores; (III) Provision of study materials or patients: E Taioli, A Abdelhamid, T Ivic-Pavlicic; (IV) Collection and assembly of data: E Taioli, A Abdelhamid; (V) Data analysis and interpretation: E Taioli, A Abdelhamid; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Emanuela Taioli, MD, PhD. Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1133, New York, NY 10029, USA; Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. Email: Emanuela.taioli@mountsinai.org.

Background: In patients with non-small cell lung cancer (NSCLC), immune checkpoint inhibitors (ICIs) are an effective mode of treatment. Despite their efficacy, responses to ICIs have been shown to differ based on several factors; for example, antibiotic use prior to and/or during immunotherapy has been associated with lower survival in NSCLC patients. The objective of this study is to provide an updated review of the literature and to fill in important knowledge gaps by accounting for potential confounding in the relationship between ICIs and survival.

Methods: We performed a systematic review and meta-analysis on peer-reviewed studies that examined the effects of antibiotic use on overall survival (OS) and progression-free survival (PFS) in NSCLC patients treated with ICIs. We searched MEDLINE for studies published up to June 30th, 2023 that included NSCLC patients treated with anti-programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) agents, who received antibiotics before and/or during immunotherapy, and included a control group who did not receive antibiotics and had available data on the associations between antibiotics and OS and PFS. We calculated aggregated crude OS and PFS for all studies, and only for studies that reported multivariable hazard ratios (HRs). Risk of bias was assessed using a funnel plot. All results were synthesized and displayed using the metaphor statistical package in R, version 4.2.1.

Results: Nineteen studies, conducted between 2017 and 2022, met the inclusion criteria, and included 2,932 patients with advanced and/or metastatic NSCLC. Compared to those who did not receive antibiotics, immunotherapy patients who did had a significantly reduced PFS (HR: 1.22, 95% CI: 1.03–1.44) and OS (HR: 1.56, 95% CI: 1.23–1.99). Adjusted HRs were even more pronounced (OS HR_{adj}: 1.67, 95% CI: 1.23–2.27, PFS HR_{adj}: 1.64, 95% CI: 1.16–2.32).

Conclusions: NSCLC patients treated with antibiotics have significantly lowered survival compared with patients not treated with antibiotics. These results support the hypothesis that antibiotic use in conjunction with ICI among NSCLC patients lowers survival. Limitations of this analysis include the use of studies available only on a single database, limiting the literature search to NSCLC patients, which may impact the generalizability of results to other cancer patient populations, and the inability to account for and adjust the estimates for the same variables (e.g., age, sex) across all studies. Nevertheless, our findings underscore the importance of taking antibiotic use into consideration when using ICIs to treat NSCLC and suggest that confounders should be taken into account when designing future similar studies.

Keywords: Non-small cell lung cancer (NSCLC); antibiotics; immunotherapy

© Translational Lung Cancer Research. All rights reserved.

Submitted Sep 21, 2023. Accepted for publication Dec 15, 2023. Published online Dec 22, 2023.
doi: 10.21037/tlcr-23-597
View this article at: https://dx.doi.org/10.21037/tlcr-23-597

Introduction

Background

Lung cancer, diagnosed in around 230,000 Americans each year, is the leading cause of cancer death in males and the second leading cause in females (1). In non-small cell lung cancer (NSCLC), which includes adenocarcinoma, large cell carcinoma, and squamous cell carcinoma, immune checkpoint inhibitors (ICIs) offer a promising alternative to traditional chemotherapy. ICIs, which can target programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), used alone or in combination, have been shown to improve survival in cases of advanced NSCLC when compared with chemotherapy alone (2,3).

Despite their general efficacy, the success of ICI treatment is variable and highly dependent on the individual, with research suggesting that the composition of the gut microbiome is an important contributor to response to treatment. Antibiotics reduce the diversity of gut microbiota and alter the abundance of specific microbial species, among other effects. They are frequently prescribed in NSCLC patients to reduce infection risk from various avenues, including immunosuppression resulting from treatment, lung obstruction, and indwelling catheters (4). Because the gut microbiome and immune system are intricately linked, it is likely that antibiotics' modification of the gut microbiota affects the body's innate immune system, and eventually ICI efficacy (5-7). A study by Liu and colleagues showed that lung cancer patients exhibit decreased intestinal microbial diversity even before antibiotic treatments are introduced, thus suggesting that lung cancer patients may be particularly vulnerable to the interaction between antibiotics and ICI (8). Studies on a variety of cancers have suggested a lower overall survival (OS) and progression-free survival (PFS) in patients treated with ICIs that have also been treated with antibiotics (9-12).

While an exact mechanism by which antibiotics modify the efficacy of ICI has not yet been identified, several meta-analyses have been conducted to explore the relationship between ICIs and antibiotics and the overall effect on clinical outcomes. Taken together, the results of published studies and meta-analyses point at antibiotics affecting ICI efficacy and clinical outcomes, but likely with differences and to varying degrees in different patients.

Highlight box

Key findings

- In non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs), prior or ongoing antibiotic use significantly reduced overall and progression-free survival when compared with NSCLC patients treated with ICIs who do not receive antibiotics.

What is known and what is new?

- Previous meta-analyses found significantly lower survival in NSCLC patients treated with ICIs and antibiotics.
- This meta-analysis incorporates more recent research on population-representative NSCLC patients and accounts for confounders in its examination of the effects of antibiotics on the survival of NSCLC patients.

What is the implication, and what should change now?

- The results indicate that further research is required to elucidate the mechanisms by which antibiotics negatively affect survival in NSCLC patients treated with ICIs and urge healthcare practitioners to consider patients' antibiotic history when creating NSCLC treatment plans.

Rationale and knowledge gap

The published meta-analyses on NSCLC (Lurienne, Elkrief, Wilson, Jiang, and Crespin) have several shortcomings (13-17): the inclusion of unpublished work in the format of abstracts and posters, which could be responsible for the observed heterogeneity, the lack of a more comprehensive, standardized quality evaluation of the individual studies, and the outdated MEDLINE searches, even for the only meta-analysis published in 2023 (17). The current lack of meta-analysis of the adjusted survival estimates, to account for possible confounding, likewise remains an important limitation of the existing literature.

Objective

Here, we present an updated, comprehensive meta-analysis

© Translational Lung Cancer Research. All rights reserved.

of peer-reviewed publications on NSCLC patients treated with antibiotics and ICI, stratified by studies with univariate *vs.* multivariate survival estimates. Findings of this systematic review and meta-analysis will fill in important research gaps regarding this emerging but highly clinically important topic. We present this article in accordance with the PRISMA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-597/rc).

Methods

A systematic literature search was performed using MEDLINE (through PubMed) in order to retrieve all relevant studies published until June 30th, 2023 which reported data on the associations between antibiotic use and lung cancer outcomes after treatment with anti-PD-(L)1-based treatments. In order to include the largest possible patient population, no filters for language or year of publication were applied. Keywords used were "immunotherapy" or "immune checkpoint inhibitor" or "PD-L1" or "PDL1" AND "antibiotics" AND "lung cancer". In addition to the literature search, five previous meta-analyses (Crespin 2023, Jiang 2022, Lurienne 2020, Elkrief 2019, Wilson 2020) were manually reviewed to ensure that all published articles were included.

Study selection

Studies were included if they fulfilled the following criteria: (I) study included patients diagnosed with NSCLC and treated with anti-PD-(L)1 agents, either as monotherapy or in combination with other anticancer treatments; (II) patients received antibiotics before and/or during immunotherapy, regardless of antibiotics class, route of administration and duration of use; (III) inclusion of a control group who did not receive antibiotics within the defined timeframes; and (IV) availability of data on the associations between antibiotics and OS, PFS in the format of hazard ratios (HRs), or as patients at risk in a survival curve, so that HRs could be estimated (18). If studies were reporting on overlapping patient populations, the most recent study, or the study where OS and PFS were reported were selected for inclusion in the meta-analysis.

The PubMed literature search initially included 345 published texts and abstracts; one record was initially excluded for out-of-range publication date, as it was published after June 30th, 2023, and 314 were excluded based on irrelevant title or abstract. Of the 30 remaining records, six were excluded because they were not conducted on NSCLC patients or because they did not include treatment with PD-L1 or PD-1, two were excluded because they did not include a control group without antibiotics, and three were excluded because they did not report the HR for OS or for PFS, and did not provide the survival curves with persons-at-risk for HR calculation. Ultimately, nineteen published articles from peer-reviewed journals were included in the meta-analysis (see *Figure 1*). The literature screening was independently conducted by two reviewers (E.T., A.A.) who consulted with a third author to resolve any discrepancy.

Data extraction

The following data were independently collected by the two reviewers on a spreadsheet from each of the included studies: first author's name, publication year, country where the study was conducted, time frame of treatment, number of patients included, lung cancer stage, immunotherapy type, treatment scheme and line of treatment, antibiotics regimen, OS and progression free survival expressed as HRs and their 95% confidence intervals (CIs), variables used for adjustment, and adjusted results. When HR was not available, it was calculated from the survival curve using the person-at-risk reported in the figure (18). Additionally, multivariable HR estimates were used when univariate estimates were not reported or could not be calculated.

Quality assessment was completed by two reviewers (A.A., T.I.P.) using the 2018 Mixed Methods Appraisal Tool (MMAT) (19).

Statistical analysis

We summarized the HRs and their 95% CIs to assess the association between OS and PFS and use of antibiotics. A random effects model was used to pool HR estimates. Meta-analyses were stratified by univariate *vs.* multivariate survival estimates. Q and I^2 statistics were used to test heterogeneity across studies (20,21). For all tests, two-sided P values less than 0.05 were considered statistically significant. All analyses were performed using the metaphor statistical package in R, version 4.2.1 (22). Risk of publication bias was assessed using a funnel plot.

Results

There were nineteen studies, conducted between 2017 and

© Translational Lung Cancer Research. All rights reserved.

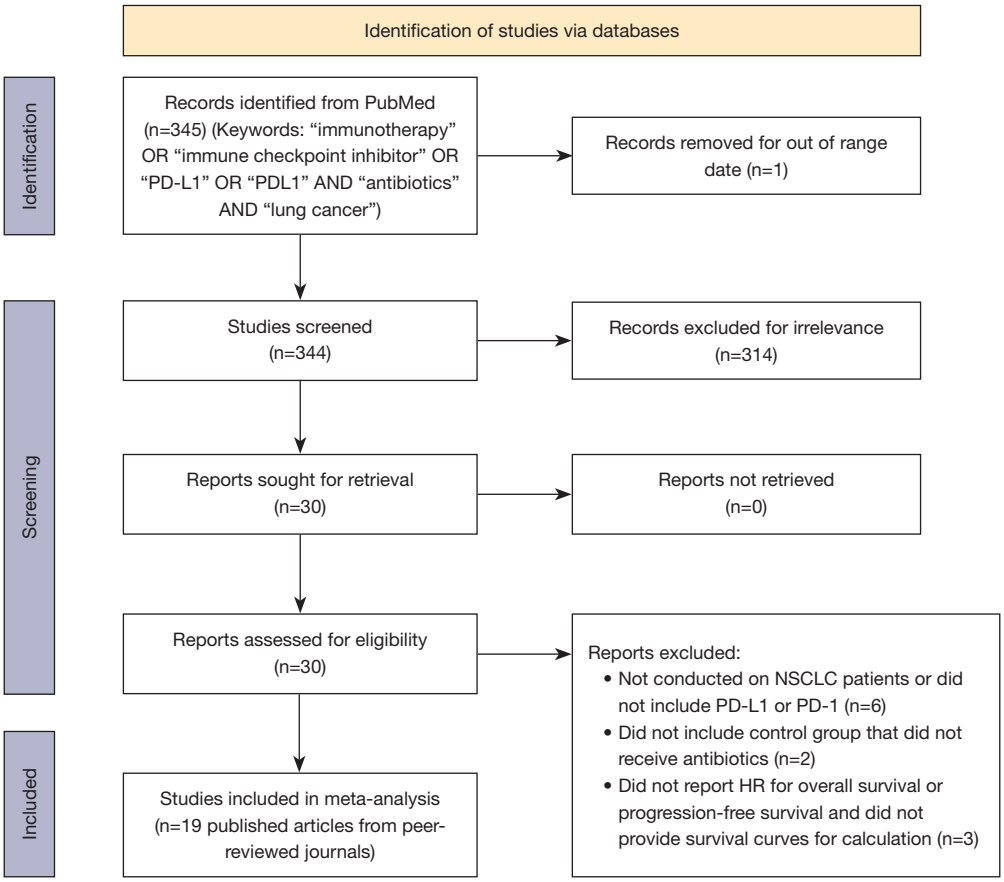

Figure 1 Meta-analysis study identification. PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; HR, hazard ratio.

2022, that met all the inclusion criteria, with 2,932 patients with advanced and/or metastatic NSCLC. As the nineteen papers received a MMAT score of 4–5, indicating that 80–100% of the quality standards were met, all identified studies were included (Table S1). Patients were treated with immunotherapy according to various lines of treatment, from 1st to all lines. The type of immunotherapy varied, or was not specified (*Table 1*). The antibiotic regimens also varied, but antibiotics were generally administered within two months before or after the start of immunotherapy. Two studies: Routy, 2018 and Derosa, 2018 reported on the same patient population (24,25). However, the population in the Derosa paper was the confirmation cohort used by Routy and colleagues (n=239), who had a separate discovery cohort (n=140). Therefore, only the discovery cohort (univariate analysis) from the Routy study was included in this meta-analysis, while the Derosa paper was included in its entirety. Additionally, no OS data was available in the Kaderbhai study, thus only PFS was used in this analysis (23).

Of the nineteen studies, eight showed worse OS and PFS in those NSCLC patients on ICI who were treated with antibiotics (*Table 1*) while four only showed worse OS, one only showed worse PFS, and six did not show a statistically significant difference in survival (23-41). Six of the eight studies showing worse OS and PFS at univariate analyses confirmed the results at multivariate analysis (23,27-29,32,34). Additionally, five studies confirmed worse OS only at multivariate analysis, one study confirmed worse PFS only, and one study did not include any multivariate analyses (24,31,33,36,37,39,41). Both univariate OS (pooled HR: 1.56, 95% CI: 1.23–1.99, *Figure 2*) and PFS (pooled HR: 1.22, 95% CI: 1.03–1.44, *Figure 3*) were significantly lower in patients receiving antibiotic treatment in conjunction with ICI when pooled estimates were calculated. The heterogeneity was low for OS (I^2=27.30%) and PFS (I^2=0.00%), and the Cochran's Q statistic test for

© Translational Lung Cancer Research. All rights reserved.

Table 1 Description of the studies included in the systematic review

Author, year	Country	NSCLC stage	N	Line of treatment	Antibiotics regimen in relation to ICI	Results	Time frame	Adjusted results	Adjustment variables	Immunotherapy
Kaderbhai, 2017, (23)	France	Locally advanced	74	≥2	1 to 3 months before	No differences in PFS	2015–2017	Confirmed	Age, gender, International mRCC Database Consortium risk groups, tumor burden, PPI	Nivolumab
Routy, 2018, (24)	France	Advanced	140	>1	2 months before, 1 after	Lower OS and PFS	N/A	Confirmed	Gender, age, smoking status, line of therapy	PD1-PD-L1 inhib
Derosa, 2018, (25)	France/ Canada	Advanced	239	All lines	1 month before	Lower OS and PFS	Up to 3/2017	Only OS is reduced	Age, sex, histology, number of prior lines, ECOG, clinical trial, hospitalization, treatment	PD1-PD-L1 inhib alone or with anti-CTLA-4
Huemer, 2018, 2019, (26)	Austria	Advanced	96	>1	1 month before, 1 after	No difference in OS	2015–2017	Confirmed	line of therapy, N/L, neutrophil count, lymphocyte count, ECOG PS, histology, age, sex	Immuno checkpoint blockade
Ouaknine, 2019, (27)	France	Advanced	72	N/A	2 to 1 months before	Lower OS and PFS	2014–2017	Confirmed		nivolumab
Galli, 2019, (28)	Italy	Metastatic	157	All lines	1 month before to 3 months after; early period, and days AB/Days Immuno	No differences in OS and PFS for early period; decreased OS and PFS for the ratio	2013–2018	Confirmed	Baseline performance status, immunotherapy line	Immuno checkpoint blockade
Zhao, 2019, (29)	China	Advanced	109	All lines, immunotherapy alone or in combination with chemotherapy	1 month before or after	Lower OS and PFS	2016–2018	Confirmed	Smoking, ECOG PS, histology, treatment line, on trial	Anti PD-L1
Hakozaki, 2019, (30)	Japan	IV	90	Any line	Treated ≥3 d within 1 mo	Lower OS and PFS	2016–2017	NS	ECOG PS, driver mutations, PPI, H2-blockers	Nivolumab
Pinato, 2020, (31)	UK	Metastatic	119	1st line	within 1 mo	Lower OS in previous AB use	2015–2018	Confirmed	Response to immunotherapy	PD1-PD-L1 inhib
Tinsley, 2020, (32)	UK	Advanced	64	All lines	2 wks before, 6 wks after	Lower OS and PFS	2015–2017	Confirmed	Comorbidity, ECOG performance status, on trial, number of metastatic sites	Immuno checkpoint blockade
Schett, 2020, (33)	Switzerland	locally advanced, inoperable or metastatic, EGFR wild, ALK-neg	218	Any line	Within 2 months	Lower OS	2013–2017	Confirmed	Age, gender, stage, histology, CNS metastases, smoking status, PD-L1 status, ECOG PS, ICI type, radiotherapy	Anti-PD-L1
Hamada, 2021, (34)	Japan	Advanced (all stages)	69	All lines	within 21 days	Lower OS and PFS	2016–2019	Confirmed	PPI, probiotics, ECOG PS, gender, EGFR	Anti PD-L1

Table 1 (*continued*)

© Translational Lung Cancer Research. All rights reserved.

Table 1 (*continued*)

Author, year	Country	NSCLC stage	N	Line of treatment	Antibiotics regimen in relation to ICI	Results	Time frame	Adjusted results	Adjustment variables	Immunotherapy
Cortellini, 2021, (35)	Italy, Netherlands, Switzerland	IV	302	Chemo-I 1st line	>30 d before, current	ns lower OS, PFS	2014–2020	Confirmed	Corticosteroids, PPI, statins, age, gender, ECOG PS, smoking status; central nervous system, bone, liver metastases	Immuno checkpoint blockade
Ochi, 2021, (36)	Japan	NR	531	Any line	2 months before, 1 after	Lower OS, not PFS	2015–2018	Multivariate on patients with PD-L1 expression (n=265), confirmed	Performance status, PD-L1, driver mutation status	Anti-PD-1 or anti-PD-L1 antibody
Castello, 2021, (37)	Italy	Advanced	50	Any line	1 month before and after	Lower PFS, not OS	2015–2019	PFS confirmed, no data for OS	ECOG, change in maximum SUV	Nivolumab, pembrolizumab, atezolizumab
Rounis, 2021, (38)	Greece	Non-oncogenic driven metastatic	66	Second line	30 days before or within 12 weeks after	No difference in PFS or OS	2017–2019	Confirmed; AB >14 days significantly reduces OS and PFS	Steroid, prolonged AB administration, BMI; liver, bone metastases	PD1-PD-L1 inhib
Geum, 2021, (39)	South Korea	Advanced	140		Not specified	Lower OS, not PFS	2015–2020	Only for AB class, confirmed for piperacillin/tazobactam	Antibiotic class	Nivolumab
Nyein, 2022, (40)	United States	III, IV	256	ICI + chemo, >1	2 months before, 1 after	ns lower OS and PFS	2011–2017	Confirmed	PPI, prior chemotherapy, age, ECOG, targeted therapy	Immuno checkpoint blockade
Barbosa, 2022, (41)	Spain	III, IV	140	Any line	2 months before and after	No difference in PFS or OS	2016–2021	Not performed		Atezolizumab, nivolumab, pembrolizumab

Nivolumab: PD-1 inhibitor; pembrolizumab: PD-1 inhibitor; atezolizumab: PD-L1 inhibitor. NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; PFS, progression-free survival; mRCC, metastatic renal cell carcinoma; PPI, proton pump inhibitor; OS, overall survival; N/A, not applicable; AB, antibiotics; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; inhib, inhibitor; Immuno, immunotherapy; ECOG PS, ECOG performance status; d, day; mo, month; wks, weeks; ns, not significant; CNS, central nervous system; EGFR, epidermal growth factor receptor; ALK-neg, anaplastic lymphoma kinase-negative; SUV, standardized uptake value.

© Translational Lung Cancer Research. All rights reserved.

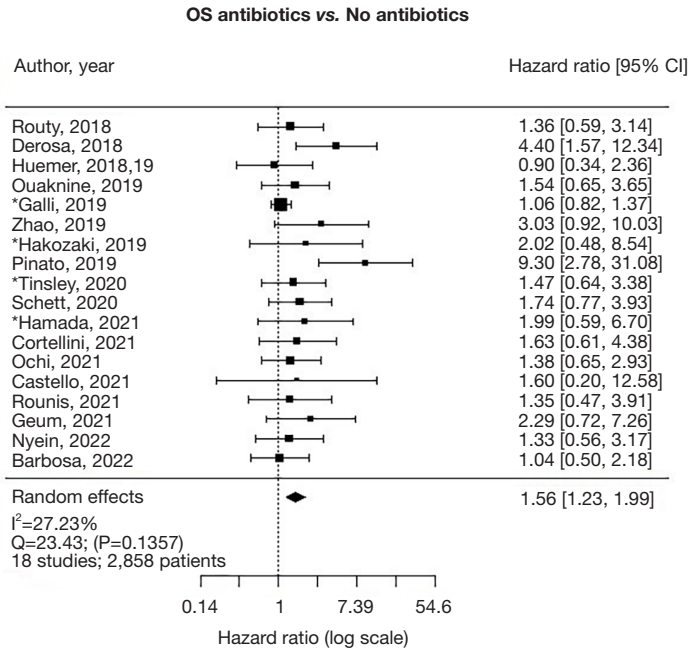

Figure 2 Meta-analysis of OS. *, multivariable HR estimate used. Studies are in temporal order of publication; a larger black box is indicative of a larger sample size. OS, overall survival; 95% CI, 95% confidence interval; HR, hazard ratio.

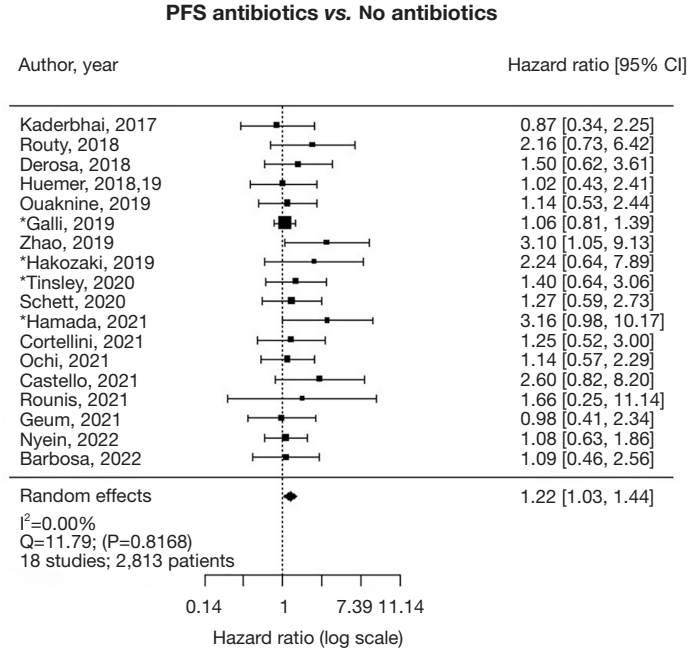

Figure 3 Meta-analysis of PFS. *, multivariable HR estimate used. Studies are in temporal order of publication; a larger black box is indicative of a larger sample size. PFS, progression-free survival; 95% CI, 95% confidence interval; HR, hazard ratio.

© Translational Lung Cancer Research. All rights reserved.

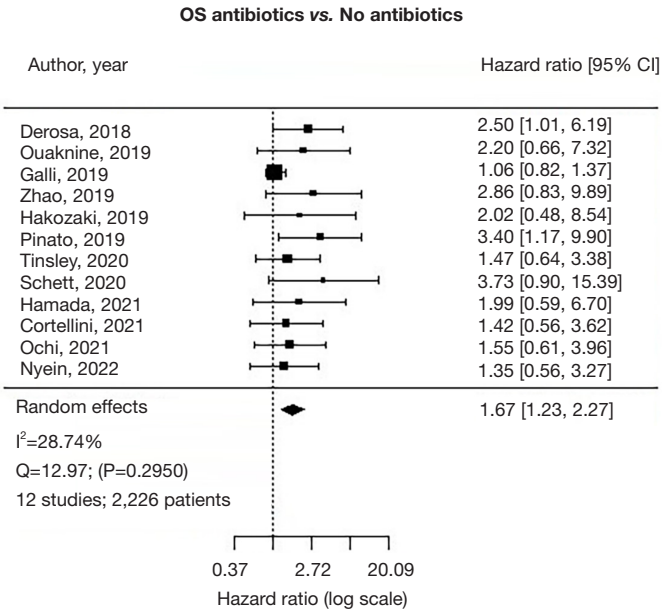

Figure 4 Meta-analysis of multivariable OS. Studies are in temporal order of publication; a larger black box is indicative of a larger sample size. OS, overall survival; 95% CI, 95% confidence interval.

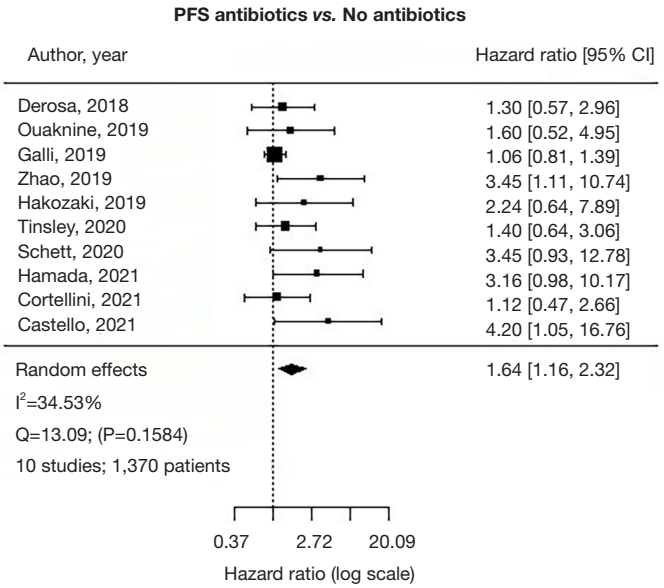

Figure 5 Meta-analysis of multivariable PFS. Studies are in temporal order of publication; a larger black box is indicative of a larger sample size. PFS, progression-free survival; 95% CI, 95% confidence interval.

heterogeneity was not statistically significant in both cases.

We next calculated pooled adjusted HRs for OS and PFS for the subset of studies reporting multivariate HR estimates (n=12 for OS, n=10 for PFS). When the adjusted survival estimates were considered, OS (pooled HR_{adj}: 1.67, 95% CI: 1.23–2.27, *Figure 4*) and PFS (pooled HR_{adj}: 1.64, 95% CI: 1.16–2.32, *Figure 5*) remained significantly lower in patients receiving antibiotic treatment.

© Translational Lung Cancer Research. All rights reserved.

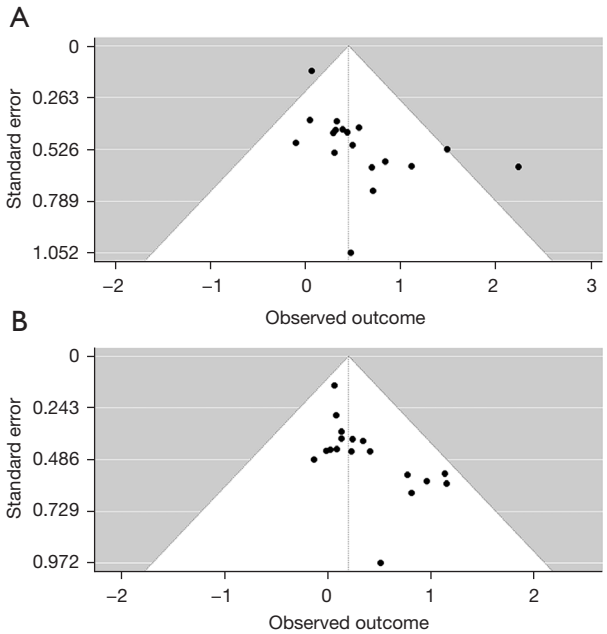

Figure 6 Funnel plots assessing publication bias using overall survival (A) and progression-free survival (B).

Discussion

This meta-analysis of published, peer-reviewed studies on NSCLC patients treated with ICI, who received antibiotics before or after the start of ICI, indicates that those patients treated with antibiotics have significantly lower OS and PFS compared with patients not treated with antibiotics. The results show a low degree of heterogeneity, and it appears that there is no publication bias from the funnel plots (*Figure 6*); these observations strengthen and confirm the overall hypothesis of lower survival associated with antibiotic use in conjunction with ICI among NSCLC patients. Indeed, while many of the individual studies included in the analysis did not report statistically significant effects, probably because of small sample size and low power, the pooled HRs point to a clinically significant limitation in the effectiveness of ICIs in improving survival if antibiotic treatments are present. Moreover, these results are in keeping with the previous meta-analyses on this topic. Lurienne and colleagues' meta-analysis in 2020 on 23 studies and 5,560 NSCLC patients drawn from publications, posters, and abstracts showed that antibiotic use was associated with lower OS (HR: 1.47, 95% CI: 1.12–1.9) as well as PFS (HR: 1.69, 95% CI: 1.25–2.29) in patients treated with ICIs, and that this effect was stronger when antibiotic use took place within 60 days of receiving ICI therapy (13). Elkrief *et al.*'s meta-analysis in 2019 was conducted on nine published studies of 1,057 NSCLC patients and three studies of other cancers (14). This study found a significant negative association between antibiotic use and survival in NSCLC patients treated with ICIs, though this effect was not quantified with a point estimate and CIs. In 2020, Wilson and colleagues looked at 2,889 patients with various solid malignancy types from eighteen papers and abstracts and found both lower OS (HR: 1.92, 95% CI: 1.37–2.68) and PFS (HR: 3.43, 95% CI: 2.29–5.14) with antibiotics in cancer patients treated with ICI (15). The meta-analysis by Jiang *et al.* in 2022 included four NSCLC studies and 974 patients, and also confirmed worse OS (point estimates not reported) and worse PFS (HR: 1.47, 95% CI: 1.11–1.95) in patients treated with antibiotics, particularly if treatment took place ~40 days before initiation of ICI treatment (16). In 2023, Crespin and colleagues obtained similar results from 47 studies on NSCLC, including posters and abstracts, and a total of 8,421 patients; OS (HR: 1.6, 95% CI: 1.4–1.83) and PFS (HR: 1.47, 95% CI: 1.27–1.7) were also lower in patients receiving antibiotic treatment (17). Of these five meta-analyses, three (Lurienne, Wilson, and Crespin) reported significant heterogeneity between studies despite the overall HRs being statistically significant. Our observed effect size (OS HR: 1.56, 95% CI: 1.23–1.99; PFS HR: 1.22, 95% CI: 1.03–1.44) was similar to what has been reported in the other meta-analyses (OS HR: 1.66; PFS HR: 1.57).

The present meta-analysis, however, has several unique strengths in comparison to previously conducted meta-analyses. First, we included only peer-reviewed studies. This criterion ensured that the analyzed studies exhibit high-quality methodology and well-reported results, reducing heterogeneity between studies. In addition, we applied the MMAT scoring system to ensure the quality of the included studies; compared to the Newcastle-Ottawa Quality Assessment Scale, used by Lurienne [2020], Jiang [2022], and Crespin [2023], the MMAT covers additional criteria and subjects studies to more rigorous scrutiny (13,16,17). Additionally, we considered the effect of confounders on the reported effect sizes by calculating separate pooled HRs for multivariable analyses. This independent multivariable analysis is unique to this meta-analysis and demonstrated that the negative effect of antibiotics on survival of NSCLC patients treated with ICIs is greater when accounting for confounders. Finally, most of the studies included here (fifteen out of nineteen) were observational studies, and only four studies re-analyzed data from randomized clinical

© Translational Lung Cancer Research. All rights reserved.

trials (Derosa 2018, Zhao 2019, Tinsley 2020, Castello 2021) (24,29,32,37). We also had the opportunity to include the most recent observational studies (as of June 2023). Therefore, the present meta-analysis includes patients who are more representative of the general population of real-world NSCLC cases, rather than selected patients involved in randomized clinical trials, thus strengthening the external validity of the results we report here.

This meta-analysis has some limitations. We included studies available only on a single database. Additionally, limiting the literature search to NSCLC patients may impact the applicability of results to other cancer patient populations, as lung cancer may affect the gut microbiome uniquely, independent of antibiotic use. The generalizability of the results to other lung cancer types, including small cell lung cancer, warrants further studies. Finally, as included studies collected different information and adjusted for different variables, this meta-analysis could not account and adjust the estimates for the same variables [e.g., age, sex, Eastern Cooperative Oncology Group (ECOG) performance status] across all studies. One surprising aspect is that none of the studies collected and/or analyzed information on race, despite the fact that the interaction between ICI and antibiotics could differ according to race. Although all the included studies contained a sizable number of female patients, none of the studies reported data separately by sex, even though the efficacy of immunotherapy has been reported to differ with sex (42-44). It is important to note that though most of the included studies adjusted for performance status or comorbidities and most still found antibiotics to be an independent predictor of OS and PFS even after adjusting for these factors, it is still difficult to determine whether baseline health status differences have fully been accounted for in these patient populations. It is documented that patients who develop an infection following immunotherapy treatment may present with distinct clinical characteristics that predict their infection risk, indicating that there may be key baseline differences in patients who are treated with antibiotics versus those who are not (45). Furthermore, evidence suggests that even among those who are treated with antibiotics, OS is better among those with multidisciplinary management of their infections, compared to those without (46).

Among the other understudied clinical factors that deserve future research are the fact that patients may experience delays in their cancer treatment due to infection, which may contribute to poorer survival, the lack of information on the outcome of the infection following the antibiotic treatment, the type of changes in microbiota associated with survival, the lack of information on cancer-specific survival (47). All of these are important considerations for future research studies. As immunotherapy becomes more widely practiced as a treatment for NSCLC and study numbers increase, a larger, future meta-analysis can attempt to take these and other important clinical factors into account.

Conclusions

Given the relative novelty of ICI treatment in cancer and the complexity of the gut microbiome, much remains unknown about their interaction in the bodies of cancer patients. Thus, while our results support an association between antibiotic use and decreased immunotherapy efficacy among NSCLC patients, the exact biological mechanisms will need to be elucidated in the future. Individual-level immunotherapy sensitivity is driven by a combination of both host and tumor-related factors, including the tumor immune microenvironment, systemic immunity, and the gut microbiome. Some have hypothesized that metabolites of gut microbiota impact antitumor immunity and, consequently, immunotherapy response. However, specifics of these mechanisms and networks remain unclear (48). As the results of newer research studies become available, the observed decrease in survival in patients treated with antibiotics may be explained by a well-understood mechanism.

According to the National Cancer Institute, current guidelines for health professionals do not consider antibiotic use when suggesting treatment of NSCLC with ICIs (49). As the findings of this and other meta-analyses point to significantly lower survival when NSCLC patients receive antibiotics just prior to or concurrently with immunotherapy, the guidelines may need to be updated to include possible restrictions in the use of antibiotics together with ICIs.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-597/rc

© Translational Lung Cancer Research. All rights reserved.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-597/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-597/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Clark SB, Alsubait S. Non-Small Cell Lung Cancer. In: Statpearls. StatPearls Publishing; 2022. Accessed 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK562307/
2. Wolf A, Stratmann JA, Shaid S, et al. Evolution of treatment patterns and survival outcomes in patients with advanced non-small cell lung cancer treated at Frankfurt University Hospital in 2012-2018. BMC Pulm Med 2023;23:16.
3. Overview of immune checkpoint inhibitors in NSCLC. Targeted Oncology. November 8, 2022. Accessed July 24, 2023. Available online: https://www.targetedonc.com/view/overview-of-immune-checkpoint-inhibitors-in-nsclc
4. Gonugunta AS, Von Itzstein MS, Hsiehchen D, et al. Antibiotic Prescriptions in Lung Cancer and Melanoma Populations: Differences With Potential Clinical Implications in the Immunotherapy Era. Clin Lung Cancer 2023;24:11-7.
5. Li X, Zhang S, Guo G, et al. Gut microbiome in modulating immune checkpoint inhibitors. EBioMedicine 2022;82:104163.
6. Wiertsema SP, van Bergenhenegouwen J, Garssen J, et al. The Interplay between the Gut Microbiome and the Immune System in the Context of Infectious Diseases throughout Life and the Role of Nutrition in Optimizing Treatment Strategies. Nutrients 2021;13:886.
7. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res 2020;30:492-506.
8. Liu X, Cheng Y, Zang D, et al. The Role of Gut Microbiota in Lung Cancer: From Carcinogenesis to Immunotherapy. Front Oncol 2021;11:720842.
9. Kim H, Lee JE, Hong SH, et al. The effect of antibiotics on the clinical outcomes of patients with solid cancers undergoing immune checkpoint inhibitor treatment: a retrospective study. BMC Cancer 2019;19:1100.
10. Wu Q, Liu J, Wu S, et al. The impact of antibiotics on efficacy of immune checkpoint inhibitors in malignancies: A study based on 44 cohorts. Int Immunopharmacol 2021;92:107303.
11. Yu J, Yin Y, Yu Y, et al. Effect of concomitant antibiotics use on patient outcomes and adverse effects in patients treated with ICIs. Immunopharmacol Immunotoxicol 2023;45:386-94.
12. Tsikala-Vafea M, Belani N, Vieira K, et al. Use of antibiotics is associated with worse clinical outcomes in patients with cancer treated with immune checkpoint inhibitors: A systematic review and meta-analysis. Int J Infect Dis 2021;106:142-54.
13. Lurienne L, Cervesi J, Duhalde L, et al. NSCLC Immunotherapy Efficacy and Antibiotic Use: A Systematic Review and Meta-Analysis. J Thorac Oncol 2020;15:1147-59.
14. Elkrief A, Derosa L, Kroemer G, et al. The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: a new independent prognostic factor? Ann Oncol 2019;30:1572-9.
15. Wilson BE, Routy B, Nagrial A, et al. The effect of antibiotics on clinical outcomes in immune-checkpoint blockade: a systematic review and meta-analysis of observational studies. Cancer Immunol Immunother 2020;69:343-54.
16. Jiang S, Geng S, Chen Q, et al. Effects of Concomitant Antibiotics Use on Immune Checkpoint Inhibitor Efficacy in Cancer Patients. Front Oncol 2022;12:823705.
17. Crespin A, Le Bescop C, de Gunzburg J, et al. A systematic review and meta-analysis evaluating the impact of antibiotic use on the clinical outcomes of cancer patients treated with immune checkpoint inhibitors. Front Oncol 2023;13:1075593.
18. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods

© Translational Lung Cancer Research. All rights reserved.

for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
19. Hong QN, Pluye P, Fàbregues S, et al. Mixed Methods Appraisal Tool (MMAT), version 2018. Registration of Copyright (#1148552), Canadian Intellectual Property Office, Industry Canada; 2018.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
21. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
22. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software 2010;36:1-48.
23. Kaderbhai C, Richard C, Fumet JD, et al. Antibiotic Use Does Not Appear to Influence Response to Nivolumab. Anticancer Res 2017;37:3195-200.
24. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359:91-7.
25. Derosa L, Hellmann MD, Spaziano M, et al. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol 2018;29:1437-44.
26. Huemer F, Lang D, Westphal T, et al. Baseline Absolute Lymphocyte Count and ECOG Performance Score Are Associated with Survival in Advanced Non-Small Cell Lung Cancer Undergoing PD-1/PD-L1 Blockade. J Clin Med 2019;8:1014.
27. Ouaknine Krief J, Helly de Tauriers P, Dumenil C, et al. Role of antibiotic use, plasma citrulline and blood microbiome in advanced non-small cell lung cancer patients treated with nivolumab. J Immunother Cancer 2019;7:176.
28. Galli G, Triulzi T, Proto C, et al. Association between antibiotic-immunotherapy exposure ratio and outcome in metastatic non small cell lung cancer. Lung Cancer 2019;132:72-8.
29. Zhao S, Gao G, Li W, et al. Antibiotics are associated with attenuated efficacy of anti-PD-1/PD-L1 therapies in Chinese patients with advanced non-small cell lung cancer. Lung Cancer 2019;130:10-7.
30. Hakozaki T, Okuma Y, Omori M, et al. Impact of prior antibiotic use on the efficacy of nivolumab for non-small cell lung cancer. Oncol Lett 2019;17:2946-52.
31. Pinato DJ, Howlett S, Ottaviani D, et al. Association of Prior Antibiotic Treatment With Survival and Response to Immune Checkpoint Inhibitor Therapy in Patients With Cancer. JAMA Oncol 2019;5:1774-8. Erratum in: JAMA Oncol 2020;6:302.
32. Tinsley N, Zhou C, Tan G, et al. Cumulative Antibiotic Use Significantly Decreases Efficacy of Checkpoint Inhibitors in Patients with Advanced Cancer. Oncologist 2020;25:55-63.
33. Schett A, Rothschild SI, Curioni-Fontecedro A, et al. Predictive impact of antibiotics in patients with advanced non small-cell lung cancer receiving immune checkpoint inhibitors : Antibiotics immune checkpoint inhibitors in advanced NSCLC. Cancer Chemother Pharmacol 2020;85:121-31.
34. Hamada K, Yoshimura K, Hirasawa Y, et al. Antibiotic Usage Reduced Overall Survival by over 70% in Non-small Cell Lung Cancer Patients on Anti-PD-1 Immunotherapy. Anticancer Res 2021;41:4985-93.
35. Cortellini A, Ricciuti B, Facchinetti F, et al. Antibiotic-exposed patients with non-small-cell lung cancer preserve efficacy outcomes following first-line chemo-immunotherapy. Ann Oncol 2021;32:1391-9.
36. Ochi N, Ichihara E, Takigawa N, et al. The effects of antibiotics on the efficacy of immune checkpoint inhibitors in patients with non-small-cell lung cancer differ based on PD-L1 expression. Eur J Cancer 2021;149:73-81.
37. Castello A, Rossi S, Toschi L, et al. Impact of Antibiotic Therapy and Metabolic Parameters in Non-Small Cell Lung Cancer Patients Receiving Checkpoint Inhibitors. J Clin Med 2021;10:1251.
38. Rounis K, Makrakis D, Papadaki C, et al. Prediction of outcome in patients with non-small cell lung cancer treated with second line PD-1/PDL-1 inhibitors based on clinical parameters: Results from a prospective, single institution study. PLoS One 2021;16:e0252537.
39. Geum MJ, Kim C, Kang JE, et al. Broad-Spectrum Antibiotic Regimen Affects Survival in Patients Receiving Nivolumab for Non-Small Cell Lung Cancer. Pharmaceuticals (Basel) 2021;14:445.
40. Nyein AF, Bari S, Hogue S, et al. Effect of prior antibiotic or chemotherapy treatment on immunotherapy response in non-small cell lung cancer. BMC Cancer 2022;22:101.
41. Martinez-Mugica Barbosa C, Cercós Lletí AC, Pampín Sánchez R, et al. Impact of the use of antibiotics on the clinical response to immune checkpoint inhibitors in patients with non-small cell lung cancer. Rev Esp Quimioter 2022;35:551-8.
42. Tuminello S, Veluswamy R, Alpert N, et al. MA07.10 The influence of sex on immunotherapy efficacy in non-small cell lung cancer. J Thorac Oncol 2019;14. doi: 10.1016/

© Translational Lung Cancer Research. All rights reserved.

j.jtho.2019.08.554.
43. Liang J, Hong J, Tang X, et al. Sex difference in response to non-small cell lung cancer immunotherapy: an updated meta-analysis. Ann Med 2022;54:2606-16.
44. Wang C, Qiao W, Jiang Y, et al. Effect of sex on the efficacy of patients receiving immune checkpoint inhibitors in advanced non-small cell lung cancer. Cancer Med 2019;8:4023-31.
45. Bavaro DF, Diella L, Pizzutilo P, et al. Incidence and predictors of infections in patients with advanced non-small cell lung cancer treated with checkpoint inhibitor immunotherapies: A monocentric retrospective cohort study. Scand J Immunol 2023;98:e13303.
46. Bavaro DF, Pizzutilo P, Catino A, et al. Incidence of Infections and Predictors of Mortality During Checkpoint Inhibitor Immunotherapy in Patients With Advanced Lung Cancer: A Retrospective Cohort Study. Open Forum Infect Dis 2021;8:ofab187.
47. Burns EA, Gee K, Kieser RB, et al. Impact of Infections in Patients Receiving Pembrolizumab-Based Therapies for Non-Small Cell Lung Cancer. Cancers (Basel) 2022;15:81.
48. Yang X, Guo Y, Chen C, et al. Interaction between intestinal microbiota and tumour immunity in the tumour microenvironment. Immunology 2021;164:476-93.
49. Non-small cell lung cancer treatment (PDQ®). National Cancer Institute. February 17, 2023. Accessed August 22, 2023. Available online: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_484931

Cite this article as: Abdelhamid A, Tuminello S, Ivic-Pavlicic T, Flores R, Taioli E. Antibiotic treatment and survival in non-small cell lung cancer patients receiving immunotherapy: a systematic review and meta-analysis. Transl Lung Cancer Res 2023;12(12):2427-2439. doi: 10.21037/tlcr-23-597

© Translational Lung Cancer Research. All rights reserved.

Supplementary

Table S1 MMAT scores

Paper	Are there clear research questions?	Does the collected data allow us to address the research question?	Are the participants representative of the target population?	Are measurements appropriate regarding both outcome and intervention/ exposure?	Are there complete outcome data?	Are cofounders accounted for in design and analysis?	During the study period, is the intervention administered/did exposure occur as intended?	Overall
Kaderbhai, 2017, (23)	Yes	Yes	1	1	0.75	1	1	4.75
Routy, 2018, (24)	Yes	Yes	1	1	1	1	1	5
Derosa, 2018, (25)	Yes	Yes	1	1	1	1	1	5
Huemer, 2019, (26)	Yes	Yes	1	1	1	0.5	1	4.5
Ouaknine, 2019, (27)	Yes	Yes	1	0.5	1	0.75	1	4.25
Galli, 2019, (28)	Yes	Yes	1	0.5	0.75	1	1	4.25
Zhao, 2019, (29)	Yes	Yes	1	1	1	1	1	5
Hakozaki, 2019, (30)	Yes	Yes	1	1	0.75	1	1	4.75
Pinato, 2019, (31)	Yes	Yes	1	1	1	1	1	5
Tinsley, 2020, (32)	Yes	Yes	0.75	0.5	0.75	1	1	4
Schett, 2020, (33)	Yes	Yes	1	1	1	1	1	5
Hamada, 2021, (34)	Yes	Yes	1	1	0.75	1	1	4.75
Cortellini, 2021, (35)	Yes	Yes	1	1	1	1	1	5
Ochi, 2021, (36)	Yes	Yes	1	0.5	1	1	1	4.5
Castello, 2021, (37)	Yes	Yes	0.75	1	1	1	1	4.75
Rounis, 2021, (38)	Yes	Yes	1	1	1	1	1	5
Geum, 2021, (39)	Yes	Yes	1	1	1	1	1	5
Nyein, 2022, (40)	Yes	Yes	1	1	1	1	1	5
Barbosa, 2022, (41)	Yes	Yes	1	1	0.5	1	1	4.5

© Translational Lung Cancer Research. All rights reserved.
https://dx.doi.org/10.21037/tlcr-23-597