

Antibiotics Treatment and Immune-checkpoint Inhibitors Efficacy: A Systematic Review and Meta-analysis

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Research

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Abstract

Background: Immune-checkpoint inhibitors (ICIs) have been approved as 1st line therapy and benefit patients with advanced cancer. However, still many patients fail to achieve the significant efficacy, a predictor for precise patient selection is needed. The aim of our study is to determine whether the administration of antibiotics before or at the beginning of ICIs treatment is a prognostic factor of progression-free survival (PFS) and overall survival (OS) in patients with advanced cancer.

Methods: A systematic search in PubMed, Embase, Cochrane and Web of Science databases was conducted using the search terms antibiotic, PD-1, PD-L1, CTLA-4, combined with cancer, tumor, neoplasm, or carcinoma. Data extraction was performed independently. Hazard ratio (HR) for PFS and OS of antibiotics (+) group vs antibiotics (-) group were pooled according to random or fixed-effects models. HRs with 95% confidence intervals (CIs) for PFS and OS were pooled to obtain prognostic information and aggregate values.

Results: Nine studies including 1163 patients were included in this meta-analysis. By PFS analysis, antibiotics administration was associated with a significantly increased risk of disease progression (HR, 1.76; 95% CI, 1.37-2.26; $P < 0.01$). By OS analysis, antibiotics uptake also showed an HR in favor of death (HR, 1.7; 95% CI, 1.40-2.07; $P < 0.01$).

Conclusions: Based on the existing evidence, antibiotics administration is a prognostic factor for reduced PFS and OS in patients receiving ICIs treatment. The time interval between antibiotics administration and ICIs treatment should be considered.

Background

Cancer immunotherapy has become highly successful against an array of distinct hematological and solid metastatic malignancies. Administration of ICIs unleashes T lymphocyte-mediated immune responses by targeting the inhibitory signals, Programmed cell death (PD)-1, Programmed cell death ligand (PDL)-1 and Cytotoxic T-lymphocyte associated protein (CTLA)-4. However, despite these multiple ICIs were utilized in cancer treatment, overall survival in patients remains heterogeneous[1, 2]. Predictor is a good indicator of the efficacy of immunotherapy, but the current relevant researches are extremely limited, and results regarding the best-studied marker PD-L1 is not yet ideal[3]. Therefore, an improved understanding of factors associated with clinical outcomes of ICIs could optimize personalized treatment and provide new insights into resistance mechanisms.

The microbiota is an extremely important and complex ecosystem that continuously interacts with and regulates its host's immune system. Early in life, the developing gut microbiota helps train and shape the immature immune system, and improper immune responses or poor prognosis later in life are often associated with an altered gut microbiota. The balance of microbiome needed for immune homeostasis could be influenced by factors such host genetics, lifestyle and exposure to antibiotics treatment. Given the widespread use of antibiotics in clinical settings, attention has been recently drawn upon the association between antibiotics use and immunotherapy efficacy. Previous studies, predominantly in mice, consistently indicated that the dysbiosis of microbiota by antibiotics impacts individual's response to cyclophosphamide, platinum agents and immunotherapies, such as anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies[4–7], but substantive data in humans are scarce. Now that the results of several cohort trials with ICIs have become available, we performed a systematic review and meta-analysis to determine whether the effectiveness of ICIs was affected by antibiotics use or not in the duration of treatment.

Materials And Methods

- Literature Search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions. We systematically searched PubMed, Embase, the Cochrane Library, and Web of Science to identify studies published from inception to July 2019 that examined the association of antibiotics use with the prognosis of patients undergoing ICIs treatment for advanced cancer. The bibliographic search was performed by Yang Zhao and Yunlong Wang in July 2019. The following search terms were used: “cancer or tumor or neoplasm or carcinoma” and “antibiotic” and “PD-1 or PD-L1 or CTLA-4”. Outcomes of interest included PFS and OS.

- Study Selection and Data Extraction

Studies that fulfilled the following criteria were included: (1) antibiotics usage was reported among variables of survival analysis, (2) survival information (progression-free survival [PFS] or overall survival [OS]) was available, (3) articles were published in English. If studies with overlapping participants were encountered, the reports with the larger sample size were included in the present meta-analysis. Abstracts, reviews, letters to the editor, and investigations with designs other than a cohort study were excluded.

Two authors (Jie Hao and Yang Zhao) conducted the search and identification independently, and the selection of an article was reached by consensus with a third author (Jiangyi He). The following information was extracted from each report by the 2 authors independently: author, year of publication, country, tumor type, patient number, time of antibiotic treatment, median PFS and OS, and survival data (HRs, 95% CIs) of antibiotics (+) group vs antibiotics (-) group. If the necessary data were provided in a graph of the study, Engauge Digitizer version 4.1 (<http://digitizer.sourceforge.net/>) was employed to extract the corresponding data. Otherwise, the corresponding author of the published study was contacted to obtain the data required for the analysis.

Statistical Analysis

Data of HRs and the lower and upper limits of their 95% CIs were extracted to calculate log HRs and their corresponding SEs. The logarithmically transformed SIRs and their corresponding SEs were used to stabilize the variance and normalize the distribution. The Cochran Q test and the I^2 statistic were used to evaluate the heterogeneity among the included cohort studies, $P < 0.05$ or $I^2 > 50\%$ was defined as heterogeneity, and the random-effects model would be used. Potential publication bias was assessed by funnel plots with the Egger regression asymmetry test. Sensitivity analysis was performed to assess the influence of each individual dataset on overall results. RevMan, version 5.3 (Cochrane Collaboration) was used for the statistical analyses. $P < 0.05$ was considered significant.

Results

The literature searching process and study identification were summarized in Fig. 1. In brief, for the 1635 records that were initially identified from the database searching, and 16 were further screened for full-text review. For the 16 records, 2 reported the risk ratio, 3 did not included patient cohort, 2 were overlapped with the smaller sample size, and 9 were finally identified for systematic review and meta-analysis[8–16]. Overall, the total number of patients included was 1163 ranging from 42 to 239 per tumor type of study, and 999 (85.9%) were prescribed antibiotics mostly within 2 months before or 1 month after the first administration of PD-1/PD-L1/CTLA-4 mAb, which represented non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial carcinoma (UC), and melanoma (MELAN). Among patients with NSCLC, some participants were overlapped in 3 studies respectively[12, 17, 18], the larger sample size and the most informative one was selected[12]. The major characteristics were shown in Table 1.

Table 1
 Characteristics of the Included Studies Comparing Antibiotics (+) With Antibiotics (-).

Author, year	Country	Tumor type	Participants	ATB(+)/ATB(-) number	Use time of antibiotic	ATB(+)/ATB(-) median PFS	ATB(+)/ATB(-) median OS
Ahmed et al, 2018	America	Advanced cancer	60	17 vs 43	-0.5 ~ +0.5	NA	5.6 vs 20.8
Derosa et al, 2018	France	Non-small cell lung cancer	239	48 vs 191	-2 ~ 0	1.9 vs 3.8	7.9 vs 24.6
Derosa et al, 2018	France	Renal cell carcinoma	121	16 vs 105	-2 ~ 0	1.9 vs 7.4	17.3 vs 30.6
Routy et al, 2018	France	Urothelial carcinoma	42	12 vs 30	-2 ~ +1	1.8 vs 4.3	11.5 vs NA
Routy et al, 2018	France	Non-small cell lung cancer	140	37 vs 103	-2 ~ +1	3.5 vs 2.8	8.3 vs 15.3
Huemer et al, 2019	Austria	Non-small cell lung cancer	142	62 vs 80	-1 ~ +1	3.8 vs 4.0	14.6 vs 11.2
Kaderbhai et al, 2017	France	Non-small cell lung cancer	74	15 vs 59	-3~	NA	NA
Hakozaki et al, 2019	Japan	Non-small cell lung cancer	90	13 vs 77	-4 ~ 0	1.2 vs 4.4	8.8 vs NR
Elkrief et al, 2019	Canada	Melanoma	74	10 vs 64	-1 ~ 0	2.4 vs 7.3	10.7 vs 18.3
Zhao et al, 2019	China	Non-small cell lung cancer	109	20 vs 89	-1 ~ +1	3.7 vs 9.6	6.1 vs 21.9
Krief et al, 2019	France	Non-small cell lung cancer	72	30 vs 42	-2 ~ +1	2.8 vs 3.3	5.1 vs 13.4

Forest plot analyses of outcomes from traditional random or fixed effects meta-analyses comparing antibiotics (+) group with antibiotics (-) group ICI patients were shown in Fig. 2 and Fig. 3. For PFS analysis, 8 studies with at least 4 tumor types were included, a pooled HR of 1.76 (Random; 95% CI, 1.37–2.26; $P < 0.01$) from analysis suggested that patients under ICIs treatment with antibiotics administration had an inferior PFS compared with those without antibiotics use,

with moderate heterogeneity ($I^2 = 53\%$, $P_h = 0.02$). Subgroup analyses based on the type of tumors showed that the association between antibiotics use and PFS was moderately weakened in non-small cell lung cancer compared to the other cancers (HR 1.54, 95% CI 1.16–2.04, Fig. 4). Furthermore, based on the statistical methods, subgroup analyses resulted in significant heterogeneity between subgroups (subgroup difference $P \leq 0.01$, $I^2 = 89.2\%$) and non-significant differences in subgroups (Multivariate analysis: HR 2.52, 95% CI 1.84–3.46, $I^2 = 0\%$, $P_h = 0.42$; Non-multivariate analysis: HR 1.39, 95% CI 1.11–1.72, $I^2 = 22\%$, $P_h = 0.28$, respectively, Fig. 5). For OS analysis, the pooled HR also indicated the shorter survival time for ICIs patients with antibiotics treatment (Fixed; HR 1.70, 95% CI 1.40–2.07, $I^2 = 28\%$, $P = 0.17$, Fig. 3).

The publication bias of PFS and OS was determined (Fig. 6). The shape of funnel plots showed a slight asymmetry, and the power of the test was insufficient for the limited studies. We also conducted Begg's and Egger's test for the 2 effect sizes mentioned above, the results demonstrated that PFS may have potential bias ($P < 0.05$), and no obvious bias was indicated for OS ($P \geq 0.05$). Sensitivity analyses did not indicate alterations in the results due to the inclusion of any individual study (Fig. 7), that is, no single study affected the pooled HR.

Discussion

Advanced cancer treatment was dominated by chemotherapy and radiotherapy, the progress in target therapy and immunotherapy has greatly improved the outcome of cancer patients, especially the administration of ICIs benefits many of them[19]. However, part patients treated with ICIs still failed to achieve significant efficacy and prolonged PFS. Although there are reported that the expression level of PD-L1, tumor mutation burden, infiltrate lymphocytes could partly predict the efficacy of ICIs treatment[20–22], finding out more precise predictive factor is essential to improve the immunotherapy.

The microbiota is a relatively fragile but extremely important ecosystem influencing host immunity[23]. The microbiota loses homeostasis in a constitutive manner is closely related to tumor progression, raising the question of whether antibiotics changing the composition of microbiota affects immunologic processes, especially its immunotherapy. In recent years, there has been an upsurge of interest in gut microbiota due to its regulatory potential for the immunotherapy of cancers. It was first evaluated in murine models and preclinical studies showed the contribution of gut microbiome in the efficacy of ICIs. Civan et al. demonstrated that tumor progression of melanoma in mice harboring distinct Bifidobacterium was nearly abolished with anti-PD-L1 combination treatment. Augmented dendritic cell function leading to enhanced CD8 + T cells priming and accumulation in the tumor microenvironment mediated the effect[5]. Similarly, tumor growth of sarcomas in mice housed in specific pathogen-free condition was inhibited by anti-CTLA-4 in contrast to mice housed in germ-free condition, and the activation of splenic lymphocytes and tumor-infiltrating lymphocytes mediated by anti-CTLA-4 could be significantly decreased in germ-free and antibiotic-treated mice[6]. In addition, the higher alpha diversity and relative abundance of Ruminococcaceae bacteria in melanoma patients was confirmed to be associated with enhancing systemic and anti-tumor immunity[24]. The important role of microbiota in tumors makes them interesting forecast indicators for the immunotherapy.

Antibiotics are recognized to be able to shift the microbiota composition, decrease the microbiota diversity and impact on taxonomic richness, which returns to its baseline within 1–3 months or even longer after antibiotics discontinuation[25, 26]. Moreover, according to the statistics in 2010, the estimated global consumption of antibiotics was 70 billion individual doses, and the annual rates continue to grow steadily[27]. Given this widespread use of antibiotics, their potential effects on gut microbiota-associated immunotherapy and links with prognostic outcomes has substantial implications for public health. In the present study, our analyses of large and independent cohorts of patients with advanced cancer treated with contemporary ICIs showed that antibiotics administration was associated with both

reduced PFS and OS in patients receiving ICIs treatment. In addition, the data indicated that the difference between patients with and without antibiotics use in PFS was more significant than OS, although a moderate heterogeneity was presented in PFS ($I^2 = 53\%$; $P = 0.02$). Regarding the differences in inclusion criteria of various researches, such as tumor types, statistical methods, broader intervention time of antibiotic medication[11, 13], and polycentric source[12], the heterogeneity for PFS was reasonable.

Our study has some limitations that should be considered when interpreting the results. As inherent in other meta analyses of observational studies, we could not exclude the possibility that some residual factors may confound the association between antibiotics and immunotherapy efficacy, such as the categories, doses, and duration of antibiotics, because we did not have access to individual patient data of the included cohorts. Also, factors such as age at onset of treatment, or gender may potentially affect the association between antibiotics and immunotherapy efficacy, these factors were generally not reported in the original studies, so they could not be analyzed accordingly in the meta-analysis. In addition, we did not include studies in other databases, not written in English, or published as a conference abstract. However, including literature reports from PubMed, EMBASE, Web of Science, and the Cochrane Library published only in English should have covered the majority of the cases. Finally, the main tumor types were focused on lung and urinary system included in the meta-analysis, more types and larger sample size are needed to determine the association between antibiotics and immunotherapy efficacy.

Conclusions

The results of this meta-analysis demonstrated that antibiotics use during immunotherapy is a prognostic factor for an increasing risk of disease progression compared with the general population. Given the widespread use of antibiotics in clinical settings, harmful aspect may be noted especially for patients with immunotherapy. Reasonable time of maintaining antibiotic treatment efficacy while minimizing its impact on immunotherapy should be well considered.

Declarations

Ethics approval and consent to participate

Not applicable' for that section.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data, models, and code generated or used during the study appear in the submitted article.

Competing interests

The authors declare no conflict of interests.

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Author Contributions

Concept and Design, Hao Jie; Collection and assembly of data, Zhao Yang, Wang Yunlong and He Jiangyi; Data analysis and interpretation, Zhao Yang and Hao Jie; Manuscript writing, all authors; Final approval of manuscript, all authors.

List Of Abbreviations

Progression-free survival [PFS], Overall survival [OS], Immune-checkpoint inhibitors (ICIs), Programmed cell death [PD], Programmed cell death ligand [PDL], Cytotoxic T-lymphocyte associated protein [CTLA], Systematic Reviews and Meta-Analyses [PRISMA], Hazard ratio [HR], Confidence intervals [CIs], Standard Error [SE], Standardized incidence ratio [SIR].

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Figures

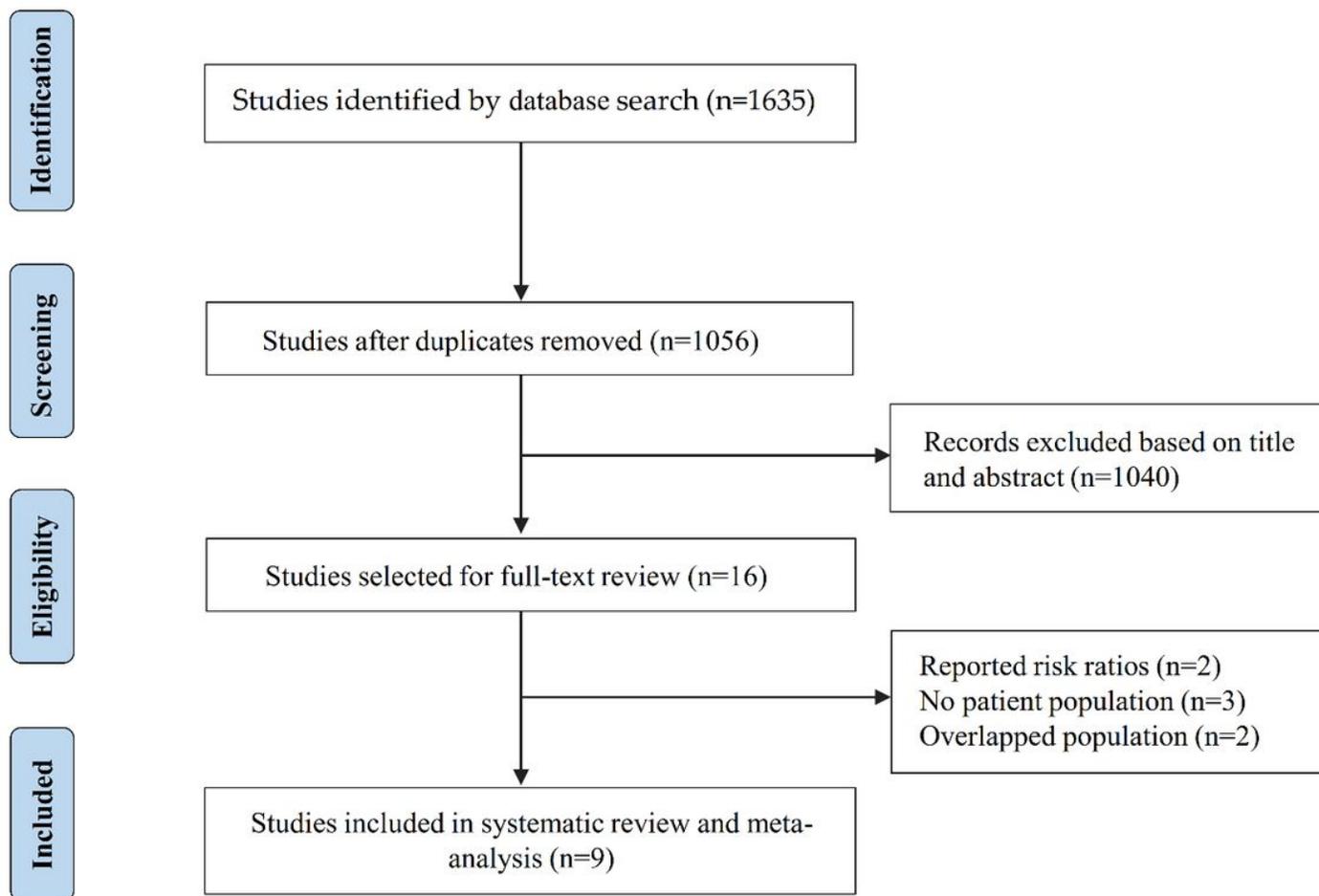


Figure 1

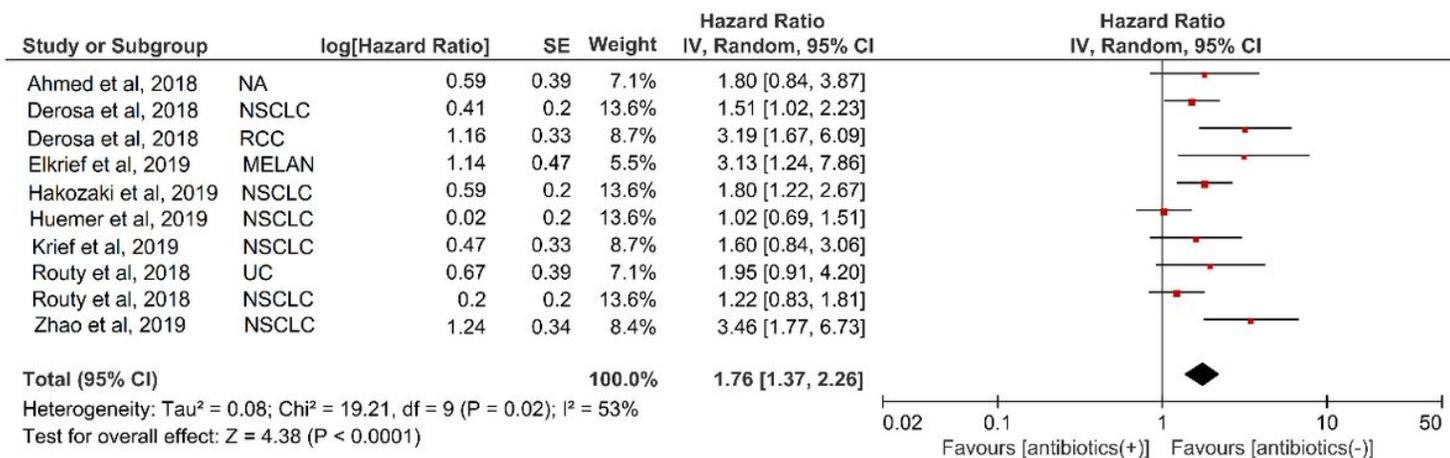


Figure 2

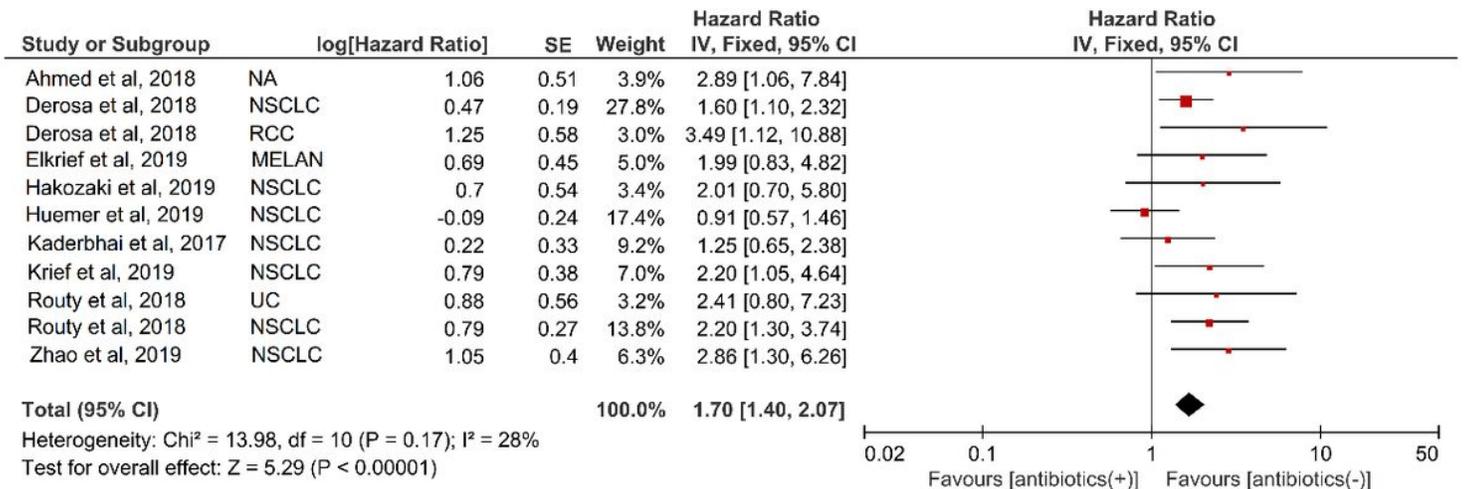


Figure 3

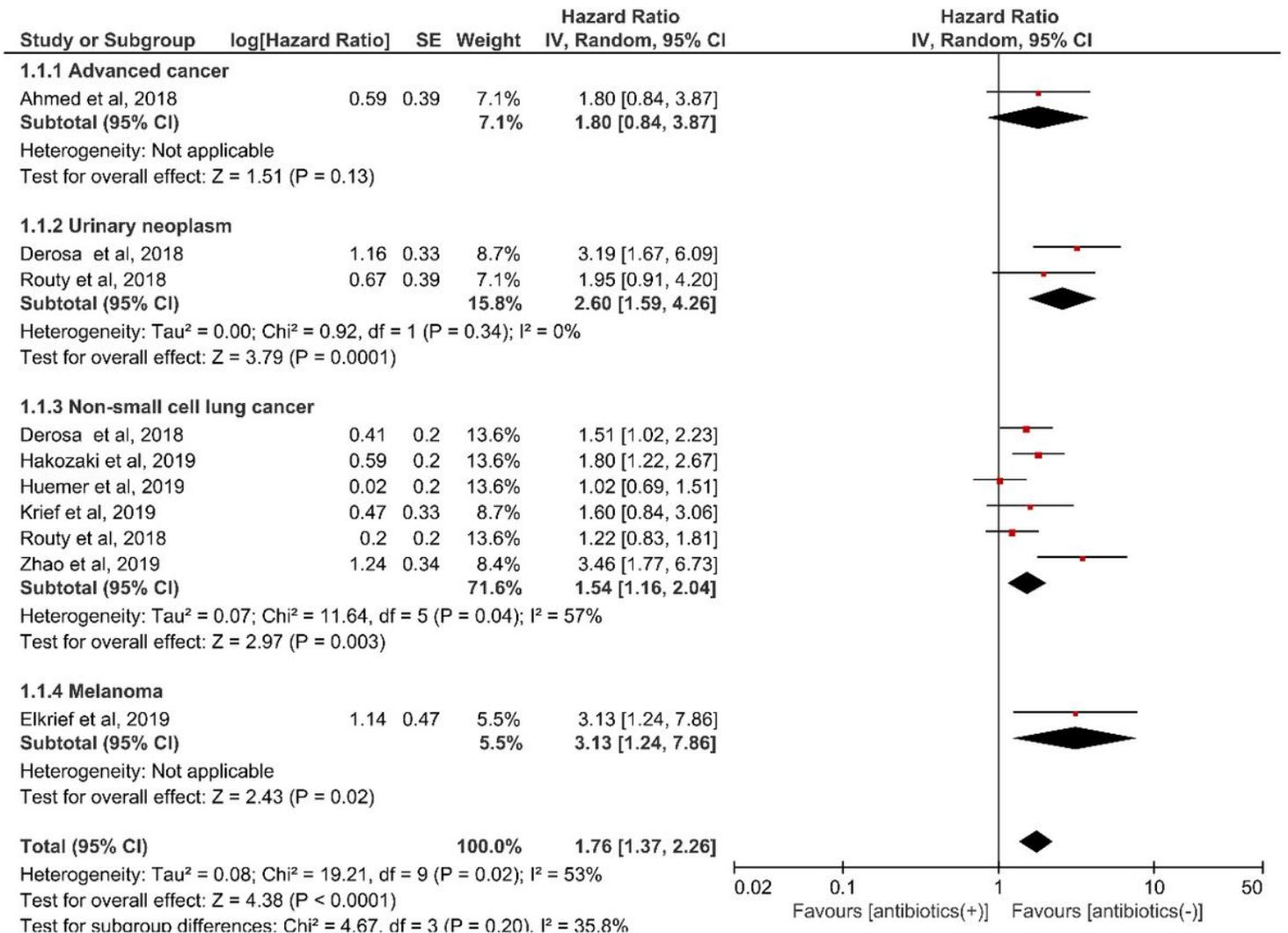


Figure 4

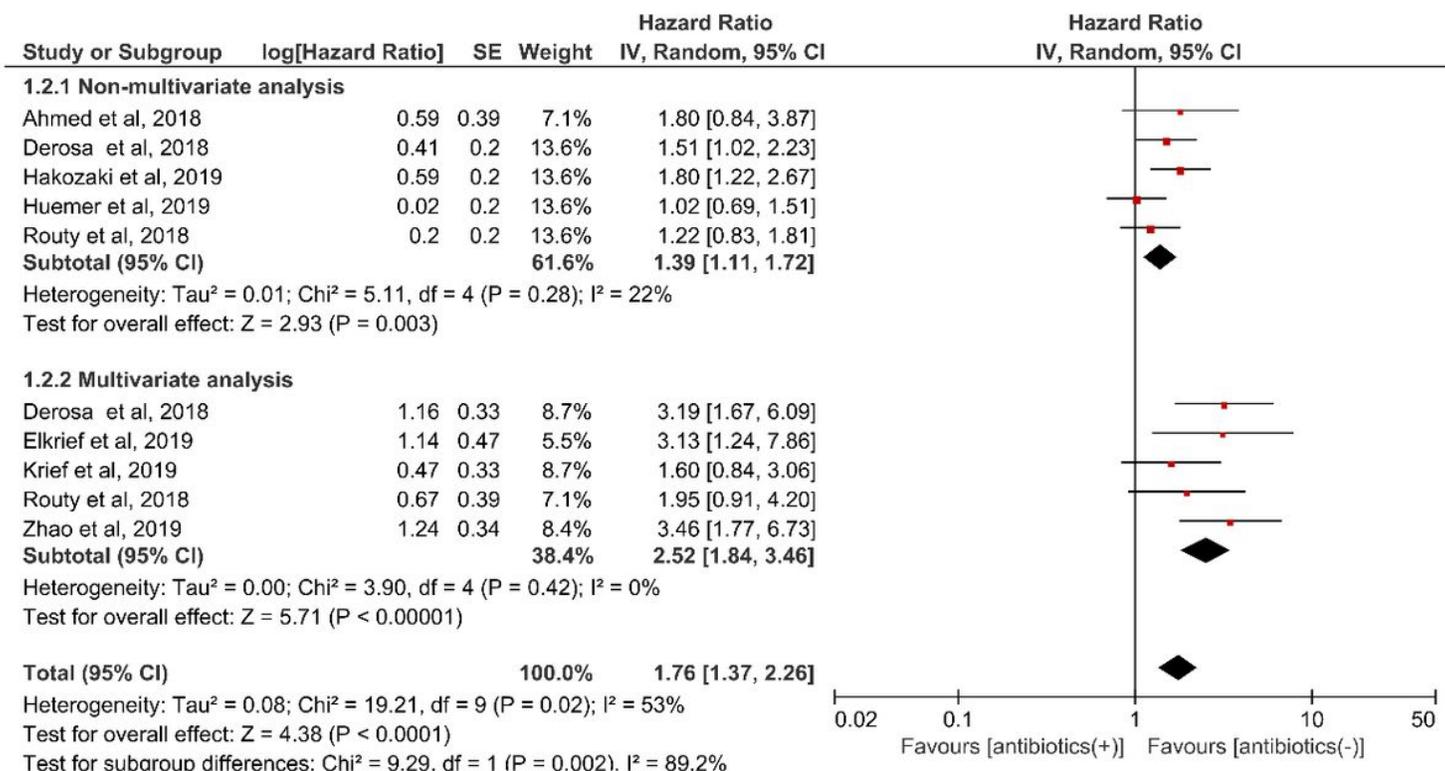


Figure 5

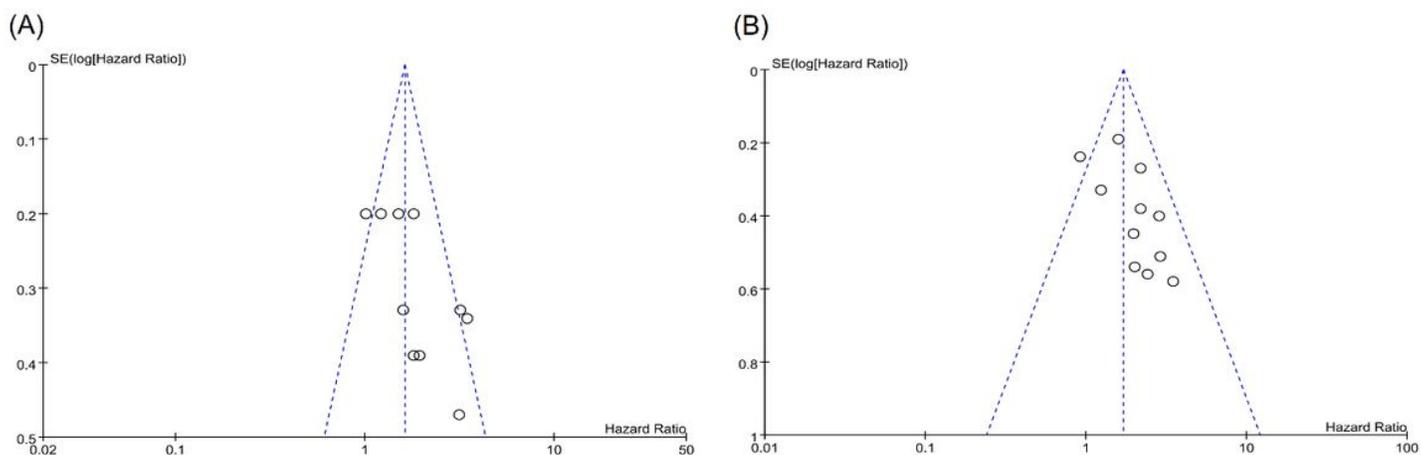


Figure 6

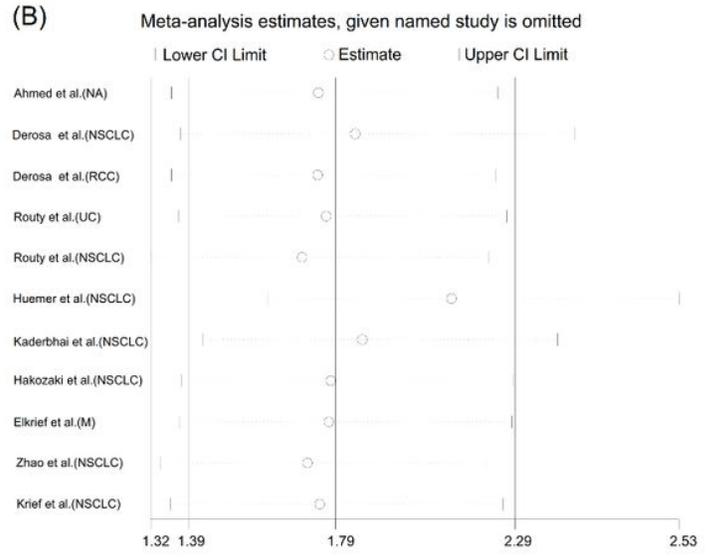
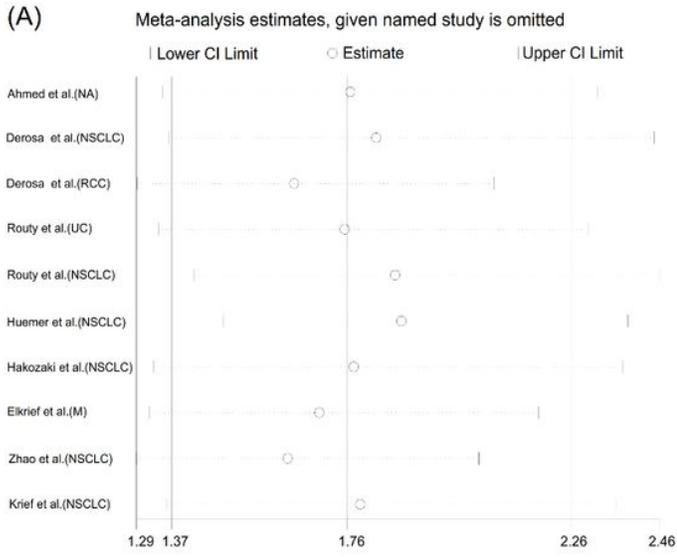


Figure 7