Original Article

# Antibiotic exposure windows and the efficacy of immune checkpoint blockers in patients with cancer: a meta-analysis

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**Background:** Immune checkpoint blockers (ICBs) improve the survival of patients with cancer, but primary or acquired drug resistance is inevitable. Intestinal microorganisms play an important role in immunotherapy and antitumor response, and antibiotic use can cause changes in intestinal microbial abundance and diversity. At present, the effects of antibiotic exposure on the anticancer activity of immunotherapy remain controversial.

**Methods:** We performed a meta-analysis of relevant studies retrieved from electronic databases to assess the effects of the time window of antibiotic exposure on the efficacy of immune checkpoint inhibitors (ICIs). In accordance with the definition of antibiotic use in different articles, the time window of antibiotic exposure was divided into three groups, namely, Groups 1 (antibiotic use within 2 months before or after ICI), 2 (antibiotic use before ICI), and 3 (antibiotic use anytime during ICI).

**Results:** After retrieval from the PubMed and the Embase databases, 39 cohorts were included. In group 1, progression-free survival [PFS; hazard ratio (HR) =1.81, 95% confidence interval (CI): 1.40–2.34] and overall survival (OS; HR =1.81, 95% CI: 1.43–2.28) were prolonged in patients without antibiotic use. In group 2, the subgroup analysis showed that antibiotic use had no effect on PFS (HR =0.90, 95% CI: 0.65–1.26) and OS (HR =1.53, 95% CI: 0.89–2.62) when the exposure window defined as 0–3 months. In Group 3, pooled results indicated that PFS (HR =0.78, 95% CI: 0.65–0.93) was prolonged in patients with antibiotic during immunotherapy, and no difference was observed in the OS data (HR =0.98, 95% CI: 0.78–1.24) between the patients with antibiotic and without antibiotic.

**Conclusions:** Antibiotic use in shortly time (within before or after 2 months) around the initiation of immunotherapy was remarkably related to the efficacy of ICIs. A different scenario could be observed that during the long-term treatment of ICIs, the effect of antibiotic exposure seems to be eliminated.

**Keywords:** Antibiotics; gut microbiome; immune checkpoint inhibitors (ICIs); survival; meta-analysis

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## Introduction

Immune checkpoint inhibitors (ICIs), including anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and anti-programmed cell death protein-(L)-1 [anti-PD-(L)1] monoclonal antibodies (mAbs), reactivate the antitumor activity of $CD8^+$ T cells by blocking T cell signals and are extensively approved in multiple cancers (1). In recent years, ICIs have dramatically revolutionized the management of multiple types of cancer. Patients with cancer have achieved overall response rates of 13.3–87%, 18–23%, and 11.9–19% by anti-PD-1, anti-PD-L1, and anti-CTLA-4 mAbs, respectively (2). However, some patients with advanced cancer have poor response to ICIs. In this regard, we seek to find the factors that influence the efficacy of ICIs for improved clinical drug use.

The gut microbiome has been demonstrated to affect cancer therapy especially the efficacy of checkpoint inhibitors in patients with advanced cancer (3). Routy *et al.* have found that the composition of the gut microbiome is different between the responders and the non-responders to ICIs and that fecal microbiota transplantation from responders can improve the efficacy of cancer immunotherapy in non-responders (4). Several retrospective studies have found that the poor efficacy of immunotherapy is associated with antibiotic (ATB) exposure, whereas Hogue *et al.* (5) have observed the opposite outcome. Also, some studies deny the association. Notably, these studies have not reached a consistent definition on the ATB use especially the time window of ATBs. Thus, we performed a meta-analysis to determine whether the use of ATBs before, during, or after immunotherapy affect the efficacy of ICIs in patients with cancer. This study aimed to explore many predictors for patient with ICIs. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2076).

## Methods

### *Literature search*

We conducted a systematic review in the PubMed and the Embase databases by using the terms "(immune checkpoint inhibitor [Title/Abstract]) OR immune checkpoint inhibitors [Title/Abstract]) OR immune checkpoint blockade [Title/Abstract]) OR ICI [Title/Abstract]) OR ICIs [Title/Abstract]) OR ICB [Title/Abstract]) OR immunotherapy [Title/Abstract]) OR immunotherapies [Title/Abstract]" and references from relevant articles in the latest 5 years up to Nov. 7, 2020. The included articles were subjected to a dual review, and the references of the included studies were manually reviewed for any additional publication. We searched the PROSPERO database without restricted and no articles were found. Our registration number was CRD42020155823. As we performed a meta-analysis about researches of published studies, no need application for ethics approval.

### *Quality assessment and data extraction*

The data from each study that met the inclusion criteria were independently extracted by two authors (Litang Huang and Xi Chen). Any problem with data extraction was resolved by discussion. The retrieved and the extracted data included the author's name, year of publication, country, study design, cancer types, number of samples (number of patients exposed to ATBs), type of ICIs, ATB window, and outcomes [progression-free survival (PFS)/overall survival (OS), associated hazard ratio (HR), and 95% confidence interval (CI)]. If data were available in both sources, the source with more complete data were prioritized.

### *Grouping*

Here, we divided the included studies into three groups in accordance with the time windows of exposure. Group 1 was administered with ATBs within 2 months before or after immunotherapy. Group 2 was injected with ATBs before immunotherapy. Group 3 was exposed to ATBs at any time during the immunotherapy (*Figure 1*).

### *Statistical analysis*

The survival outcomes, including OS and PFS, were obtained. The effect of the time window of ATB exposure on the survival of patients with immunotherapy was determined using HRs and 95% CIs. Furthermore, the association between ATB exposure window and ICI efficacy was included. A meta-analysis was performed to compute the weighted average of PFS or OS reported for patients with and without exposure to ATB. The $I^2$ statistic and the P value were used to examine heterogeneity across articles for each outcome. A P value ≤0.05 was defined as significant heterogeneity. We conducted the subgroup analysis to examine studies in accordance with the type of group (ATB exposure window). The publication bias was assessed using the Begg's test and funnel plots, and significant publication

 

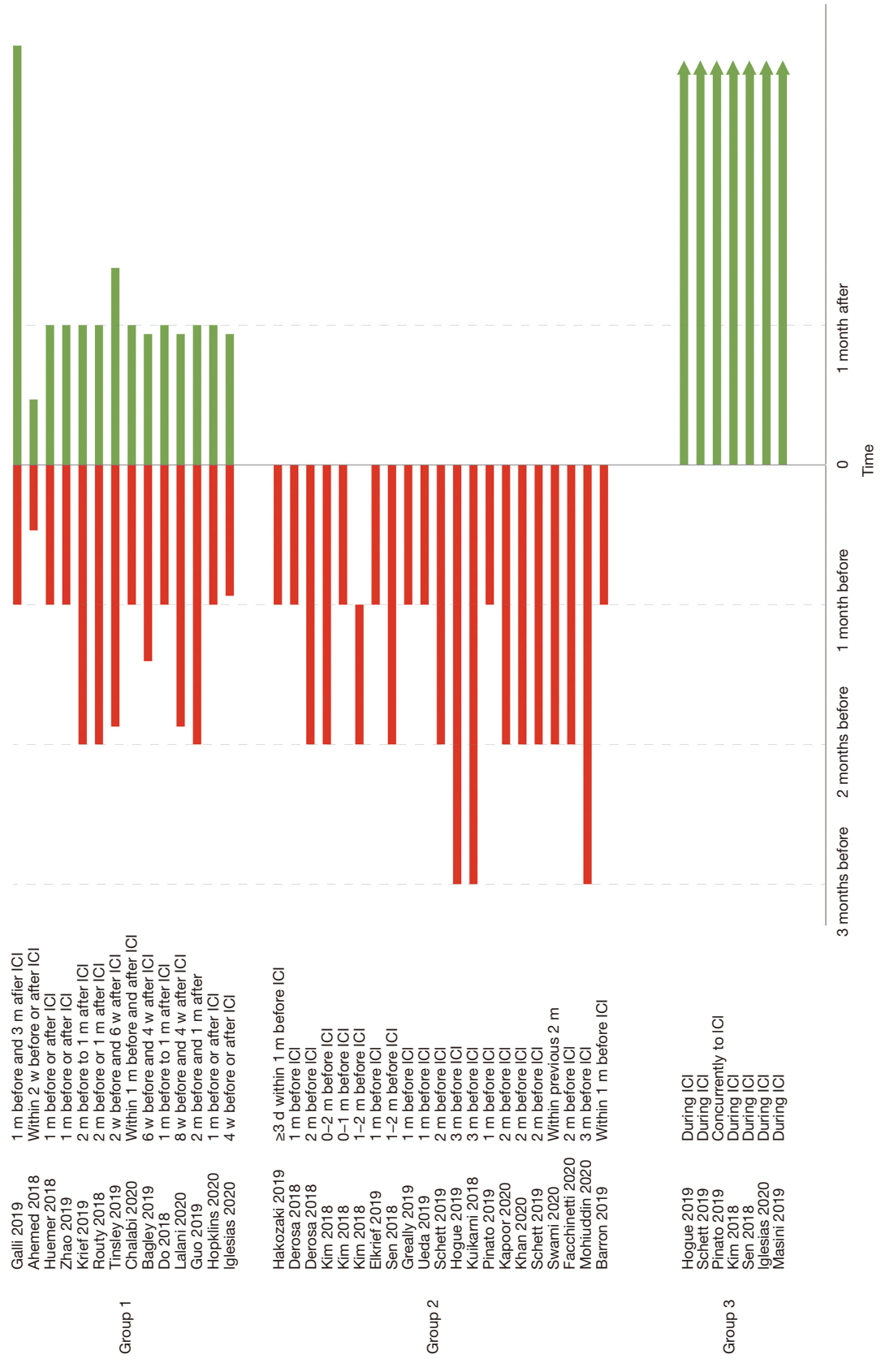


**Figure 1** Antibiotic exposure windows. ICI, immune checkpoint inhibitor.

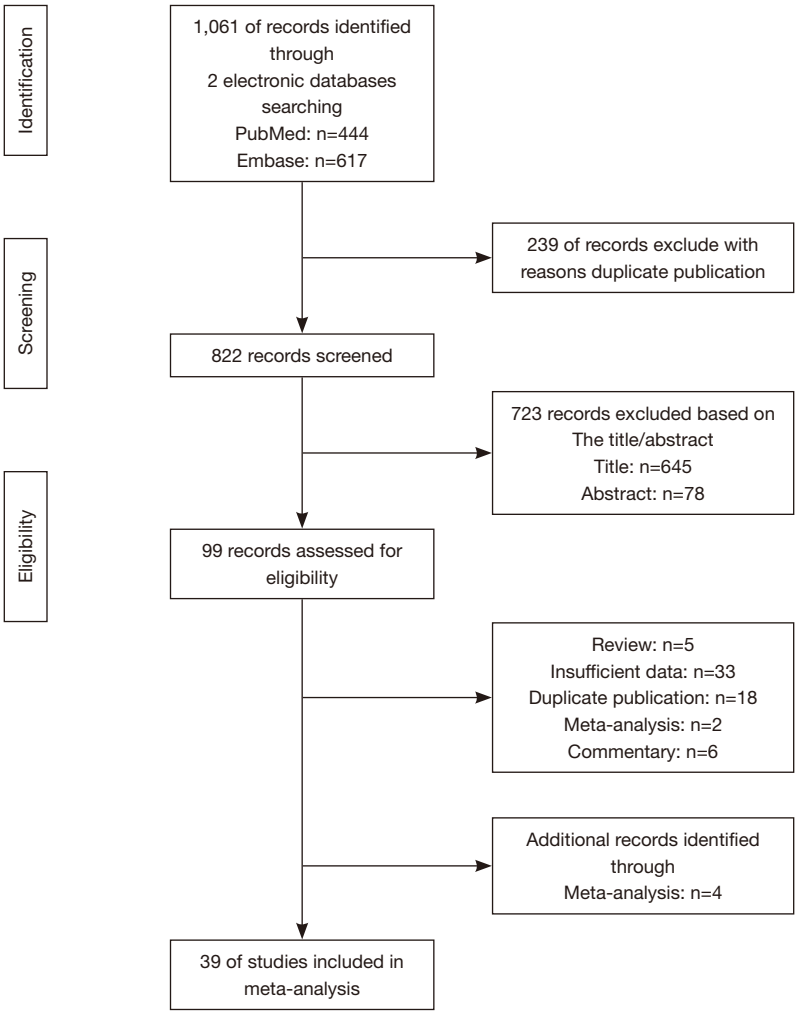


**Figure 2** Literature search and study selection.

bias was defined as P<0.05. All statistical analyses were conducted using the STATA version 15.

## Results

A total of 1,061 relevant reports from the PubMed and the Embase databases were retrieved, and three more studies were identified. A total of 239 studies were removed after duplicate checking, and 723 studies were removed after reviewing the title or the abstract. After screening and eligibility assessment, 99 studies remained for full-text screening. Sixty-four reports, including 5 reviews, 6 commentaries, 2 meta-analysis, 33 incomplete studies (lacking HR for PFS or OS), and 18 duplications, were subsequently excluded. Three records were identified through meta-analysis. Finally, 39 studies were included in our quantitative analysis (*Figure 2*). Twenty-eight studies were complete cohort studies, whereas the rest was shown only as abstract.

### *Characteristics*

*Table 1* shows the population distribution and the characteristics of the included studies. A total of 7,853 patients from 39 studies met our inclusion criteria. A total of 2,400 (30.6%) patients were exposed to ATBs. The included studies were published between 2017 and 2020, and most studies were conducted in 2019 (48%). Almost two-fifth (37%) of the studies were from the United States. Of the 39 included studies, 2 and 35 were prospective and

**Table 1** Baseline characteristics

| Publication | Country | Study design | Cancer type | Sample (ATB+/ATB–) | Immunotherapy | ATB window | Outcome |
|---|---|---|---|---|---|---|---|
| Kaderbhai (6) 2017 | France | Retrospective | NSCLC | 74 [15/59] | Anti-PD-1 | 3 months before or during ICI | PFS(–) |
| Thompson (7) 2017 | US | Retrospective | NSCLC | 74 [18/56] | Anti-PD-1 | Within 6 weeks of ICI | PFS ↓/OS ↓ |
| Ahmed (8) 2018 | US | Retrospective | Advanced cancer | 60 [17/43] | Anti-PD-(L)1 | Within 2 weeks before or after ICI | PFS ↓/OS ↓ |
| Chalabi (9) 2020 | Switzerland | Retrospective | NSCLC | 757 [169/588] | Atezolizumab | Within 1 month before and after ICI | OS ↓ |
| Derosa (10) 2018 | US | Retrospective | RCC | 121 [16/105] | Anti-PD-(L)1 or anti-CTLA-4 | 1 or 2 months before ICI | PFS↓/OS ↓ |
| | | | NSCLC | 239 [48/191] | | | PFS↓/OS ↓ |
| Huemer (11) 2018 | Austria | Retrospective | NSCLC | 142 [80/62] | Anti-PD-(L)1 | 1 month before or after ICI | PFS(–)/OS(–) |
| Kulkarni (12) 2018 | US | Retrospective | NSCLC | 111 [44/67] | Nivolumab or Pembrolizumab | 3 months before ICI | PFS(–)/OS(–) |
| Kulkarni (13) 2019 | US | NR | NSCLC | 148 [87/61] | ICI | <1 month or during ICI | PFS ↑/OS ↑ |
| | | | RCC | 55 [40/15] | | | PFS ↓/OS(–) |
| Sen (14) 2018 | US | Retrospective | RCC/NSCLC ex. | 177 [57/120] | Anti-PD-1 or anti-CTLA-4 | During ICI | PFS(–)/OS(–) |
| | | | | | | Within 1 month of ICI | PFS(–)/OS ↓ |
| | | | | | | 1–2 months before ICI | PFS(–)/OS(–) |
| Bagley (15) 2019 | US | Retrospective | NSCLC/melanoma | NR | ICI | 6 weeks before and 4 weeks after ICI | OS(–) |
| Barrón (16) 2019 | US | NR | NSCLC | 140 [18/122] | Anti-PD-L1 | Within 1 month before ICI | PFS(–)/OS ↓ |
| Elkrief (17) 2019 | Canada | Retrospective | Melanoma | 74 [10/64] | Anti-PD-1 or anti-CTLA-4 | 1 month before ICI | PFS ↓/OS(–) |
| Galli (18) 2019 | Italy | Retrospective | NSCLC | 157 [46/111] | Anti-PD-(L)1 or anti-CTLA-4 | 1 month before and 3 months after ICI | PFS(–)/OS(–) |
| Greally (19) 2019 | US | Retrospective | Esophagogastric | 162 [62/100] | Anti-PD-(L)1 or anti-CTLA-4 | During or within 2 months before ICI | PFS(–)/OS(–) |
| | | | | | | 1 month before ICI | PFS(–)/OS ↓ |
| Hakozaki (20) 2019 | Japan | Retrospective | NSCLC | 90 [13/77] | Nivolumab | ≥3 days within 1m before ICI | PFS ↓/OS(–) |
| Hogue (5) 2019 | US | Retrospective | NSCLC | 166 [NR] | Nivolumab or pembrolizumab | 3 months before ICI | PFS(–)/OS(–) |
| | | | | | | During ICI | PFS↑ |

**Table 1** (*continued*)

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| Publication | Country | Study design | Cancer type | Sample (ATB+/ATB–) | Immunotherapy | ATB window | Outcome |
|---|---|---|---|---|---|---|---|
| Kim (21) 2018 | Korea | Retrospective | NSCLC/others | 234 [108/126] | Anti-PD-(L)1 or anti-CTLA-4 | During ICI | PFS(–) |
| | | | | | | 0–2 months before ICI | PFS ↓/OS ↓ |
| | | | | | | 0–1 month before ICI | PFS ↓/OS ↓ |
| | | | | | | 1–2 months before ICI | PFS ↓/OS(–) |
| Lalani (22) 2020 | US | Retrospective | mRCC | 146 [31/115] | Anti-PD-(L)1 | 8 weeks before and 4 weeks after ICI | PFS ↓/OS(–) |
| Ouaknine Krief (23) 2019 | France | Retrospective | NSCLC | 72 [30/42] | Anti-PD-1 | 2 months before to 1 month after ICI | PFS(–)/OS ↓ |
| Pinato (24) 2019 | UK | Prospective | NSCLC/Melanoma/ other | 196 [29/167] | Anti-PD-(L)1 | 1 month before ICI | OS ↓ |
| | | | | | | Concurrently to ICI therapy | OS(–) |
| Schett (25) 2019 | Switzerland | Retrospective | NSCLC | 218 [33/185] | Anti-PD-(L)1 | 2 months before ICI | PFS ↓/OS ↓ |
| | | | | | | During ICI | PFS(–) |
| Tinsley (26) 2020 | UK | Retrospective | NSCLC/Melanoma/ mRCC | 291 [92/199] | ICI | 2 weeks before and 6 weeks after ICI | PFS ↓/OS ↓ |
| Ueda (27) 2019 | Japan | Retrospective | RCC | 31 [5/26] | Anti-PD-(L)1 or anti-CTLA-4 | 1 month before ICI | PFS ↓ |
| Zhao (28) 2019 | China | Retrospective | NSCLC | 109 [20/89] | Anti-PD-1 | 1 month before or after ICI | PFS ↓/OS ↓ |
| Routy (4) 2018 | France | Retrospective | NSCLC/UC | 249 [69/180] | Nivolumab or durvalumab | 2 months before or 1 month after ICI | PFS ↓/OS ↓ |
| Agarwal (29) 2019 | US | Retrospective | UC | 101 [26/75] | Anti-PD-(L)1 | 1 month before to during ICI | OS ↓ |
| Do (30) 2018 | US | Retrospective | Lung cancer | 109 [87/22] | Anti-PD-1 | 1 month before to 1 month after ICI | OS ↓ |
| Masini (31) 2019 | Italy | Retrospective | Advanced cancer | 169 [NR] | Nivolumab Pembrolizumab Ipilimumab | During ICI | OS(–) |
| Rounis (32) 2019 | Greece | Prospective | NSCLC | 44 [NR] | ICI | 1 month before or during ICI | PFS ↓/OS ↓ |
| Guo (33) 2019 | China | Retrospective | Esophagogastric | 49 [21/18] | ICI | 2 months before and 1 month after | PFS ↓/OS ↓ |
| Forde (34) 2020 | Ireland | Retrospective | NSCLC | 86 [34/52] | ICI | NR | PFS(–)/OS(–) |
| Hopkins (35) 2020 | Australia | Retrospective | UC | 896 [235/661] | Atezolizumab | 1 month before or after ICI | PFS↓/OS ↓ |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Publication | Country | Study design | Cancer type | Sample (ATB+/ATB–) | Immunotherapy | ATB window | Outcome |
|---|---|---|---|---|---|---|---|
| Iglesias-Santamaría (36) 2020 | Spain | Retrospective | Advanced cancer | 102 [60/42] | ICI | 4 weeks before or after ICI | PFS(–)/OS(–) |
| | | | | [33/42] | | During ICI | PFS(–)/OS(–) |
| Kapoor (37) 2020 | India | Retrospective | Advanced cancer | 155 [70/85] | ICI | 2 weeks before ICI | PFS(–)/OS(–) |
| Khan (38) 2020 | NR | Retrospective | UC | 146 [31/115] | ICI | 2 months before ICI | PFS(–)/OS(–) |
| | | | | [44/46] | | 2 months after ICI | PFS(–)/OS(–) |
| Mohiuddin (39) 2020 | NR | Retrospective | Melanoma | 568 [114/454] | ICI | 3 months before ICI | OS ↓ |
| Swami (40) 2020 | US | Retrospective | Melanoma | 166 [30/136] | ICI | Within previous 2 months | PFS↓/OS(–) |
| Abu-Sbeih (41) 2019 | US | Retrospective | Advanced cancer | 826 [569/257] | ICI | After ICI | OS ↓ |
| | | | | | | Before ICI | |
| | | | | | | Before and after ICI | |
| Facchinetti (42) 2020 | Italy | Retrospective | SCLC | 143 [36/107] | Pembrolizumab | 2 months before ICI | PFS(–)/OS(–) |

ATB, antibiotic; NSCLC, non-small cell lung cancer; anti-PD-(L)1, anti-programmed cell death protein-(L)-1; PFS, progression-free survival; OS, overall survival; RCC, renal cell carcinoma; ICI, immune checkpoint inhibitor; anti-CTLA-4, anti-cytotoxic T-lymphocyte-associated protein 4; NR, not reported; US, United States; UC, urothelium carcinoma; UK, United Kingdom.

retrospective studies, and two studies did not mention the type of study. The patients were diagnosed with lung cancer (49%), renal cell carcinoma (about 6%), melanoma (about 13%) and other advanced cancers, including esophageal cancer and urothelium carcinoma. The ICIs included anti-PD-(L)1 and anti-CTLA-4. The ATB window had different definitions in the studies (*Table 1*).

### *Outcome data*

#### Survival of group 1

Group 1 included 3,237 patients from 14 studies. These patients mostly had non-small cell lung and urethral cancers. Pooled results showed that the ATB exposure were negatively associated with the PFS (HR =1.81, 95% CI: 1.40–2.34, $I^2$=55.0%) and the OS (HR =1.81, 95% CI: 1.43–2.28, $I^2$=61.5%) of patients who underwent immunotherapy (*Figure 3*). The PFS and the OS were analyzed using the random-effects models due to significant heterogeneity.

#### Survival of group 2

Group 2 was divided into three subgroups on the basis of the duration of the ATB exposure before immunotherapy. Subgroups 1, 2, and 3 were exposed to ATB before immunotherapy within 1, 2, and 3 months, respectively. The pooled results of subgroups 1 and 2 showed that ATB was a risk factor of poor OS (subgroup 1: HR =2.25, 95% CI: 1.42–3.55; subgroup 2: HR =1.57, 95% CI: 1.16–2.11) and PFS (HR =1.70, 95% CI: 1.35–2.14; subgroup 2: HR =1.45, 95% CI: 1.04–2.02). However, the results of subgroup 3 showed that the ATB use was not related to the OS (HR =1.53, 95% CI: 0.89–2.62) and the PFS (HR =0.90, 95% CI: 0.65–1.26) of patients with cancer who received immunotherapy. In subgroup 3, two cohorts for OS data and two cohorts for PFS data were available (*Figure 4*).

#### Survival of group 3

Four cohorts were included for analysis. Pooled results showed that ATB use could prolong the PFS (HR =0.78,

 

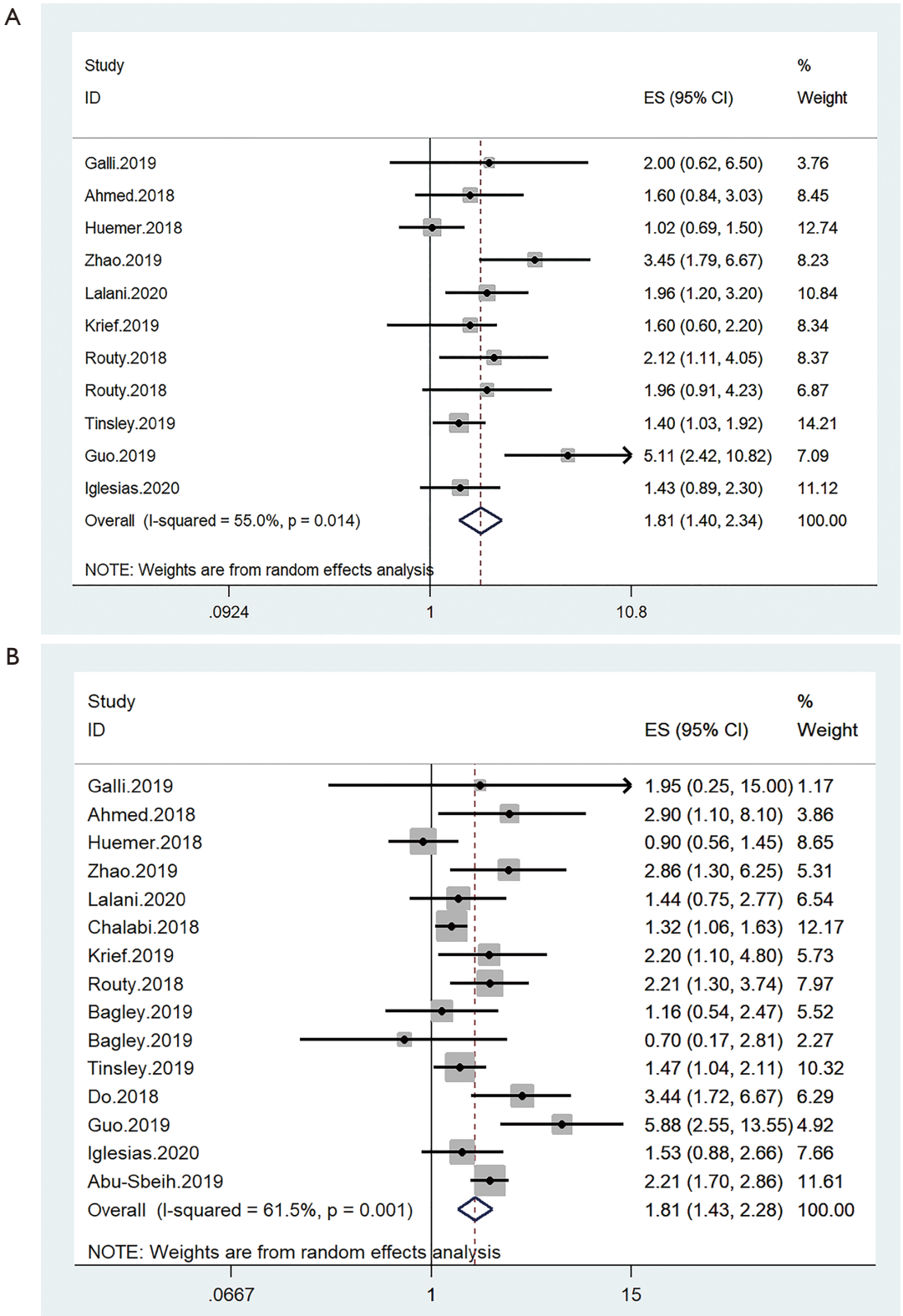


**Figure 3** The associations between antibiotic exposure and PFS (A) and OS (B) in group 1. ES, effect size; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

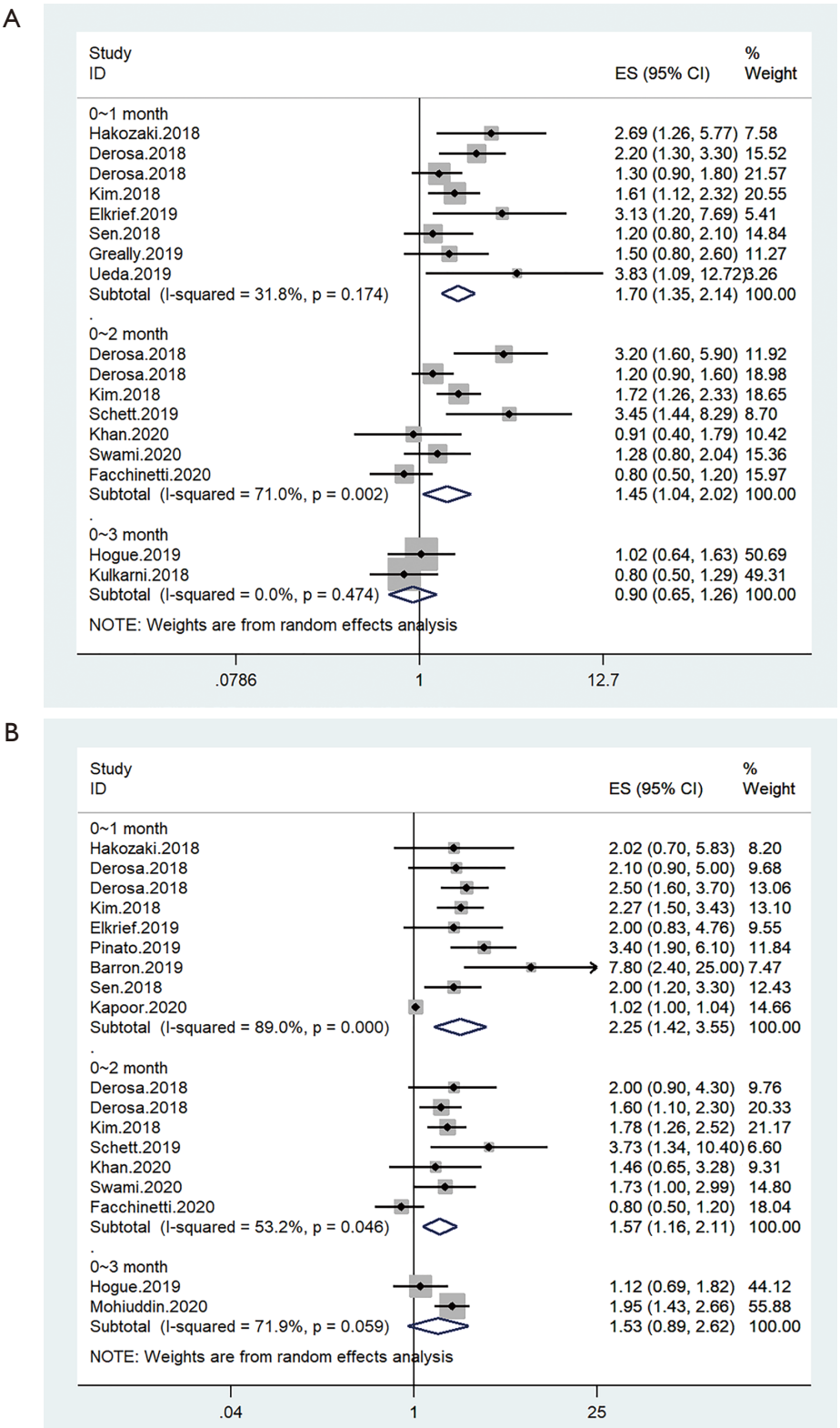


**Figure 4** The associations between antibiotic exposure and PFS (A) and OS (B) in group 2. ES, effect size; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

 

95% CI: 0.65–0.93) during immunotherapy. By contrast, the ATB use during immunotherapy was not related to the OS (HR =0.98, 95% CI: 0.78–1.24) of patients with cancer (*Figure 5*).

### *Publication bias analysis*

The Begger's funnel plot was used to assess the publication bias in this meta-analysis. Results indicated no publication bias in any study, as evidenced by the symmetrical funnel plots (Figures S1–S3).

## Discussion

Our meta-analysis has reported the relationship between the ATB exposure window and the efficacy of ICIs in patients with cancer. However, in the published meta-analysis, different results on the effect of ATBs on ICIs are observed. Huang *et al.* believe that ATB use was associated with poor survival in patients with immunotherapy (43). However, Wilson *et al.* have found that when a very broad definition of antibiotic exposure is adopted (antibiotic exposure anytime within the window 60 days before anytime after initiation of immunotherapy), the negative effect of antibiotic to PFS and OS was eliminated (44). Based on the work of Wilson *et al.*, we have re-divided the included cohorts into three groups in accordance with the different definitions of the ATB exposure window to avoid the overlapping definitions of ATB time in different studies as much as possible. We have investigated the effects of ATB exposure on the antitumor efficacy and the survival of ICIs during immunotherapy. Group 1 (ATB use within 2 months before or after ICI) indicates that ATB use is a prognostic factor in immunotherapy. In group 2 (ATB use before ICI), the subgroup analysis shows that ATB use has no effect on immunotherapy when the exposure window is defined as 0–3 months. Although the ATB exposure window of the patients included cannot be completely distinguished, the cohorts have no detailed data about the patients exposed. The prolonged time between the exposure of ATB and the start of ICI may lead to the disappearance of adverse prognosis caused by ATB. Many studies suggest that ATBs may cause the poor efficacy of immunotherapy by affecting the abundance or imbalance of intestinal flora, and the gut flora may return to baseline after 42 days (44). In group 3, pooled results show that ATB exposure is positively correlated with the PFS but not with the OS, Tinsley *et al.* noted that retrospective studies which failed to show any association between antibiotic therapy and ICI efficacy (26). Facchinetti *et al.* found that Eastern Cooperative Oncology Group performance status (ECOG PS) 2 was the only factor independently impacting on both PFS and OS (42), even though Hopkins *et al.* found the negative impact of antibiotic exposure, but the authors themselves are cautious in their interpretation of results, with a special situation was detected that ECOG PS was generally low in the cohort (35). Our results suggested that during the treatment of ICI, if ATB are required, perhaps, it may not cause the negative impact of efficacy of ICI. As we all known, patients with infection may cause bad PS, the findings about negative impact of antibiotic use which may be confounded by overall health status of patients that necessitates antibiotic use.

The limitations of our study are the same as those of several other published meta-analyses. The included studies are retrospective studies. Although we classify ATB exposure windows as best as we can, an overlap remains. In addition, the lack of baseline characteristics of the included patients, such as the type of ATB, specific infection site, duration of ATB use, and PS of patients, has prevented further subgroup analysis.

Several studies classify the patients who received ICIs into responders and non-responders in accordance with the best clinical response as assessed by the RECIST1.1 (4,45). The baseline gut microbiome diversity and the relative abundance of the two groups are different, as shown by the higher relative abundance of the Akkermansia of the responder. The fecal microbiota of the two groups of patients are transplanted to specific pathogen-free mice. The mice transplanted with the microbiota of non-responders had inferior response to ICI. Patients with high gut microbiome diversity and high relative abundance of some symbiotic bacteria are likely to benefit from ICIs. Studies have shown that the use of ATBs can affect the intestinal microbial diversity, thereby affecting the efficacy of ICIs. Different types of ATBs have different effects on the gut microbiome function. Mohiuddin *et al.* have found that the response of patients to ICIs is affected by the type of ATBs they use. Penicillin has the most serious adverse effects followed by cephalosporins and quinolones. However, vancomycin has no effect on the survival of patients (39). This article includes retrospective studies and cannot obtain the specific baseline characteristics of the included patients. Among all patients receiving immunotherapy, most patients using ATBs have respiratory or urinary tract infections. The immune characteristics,

 

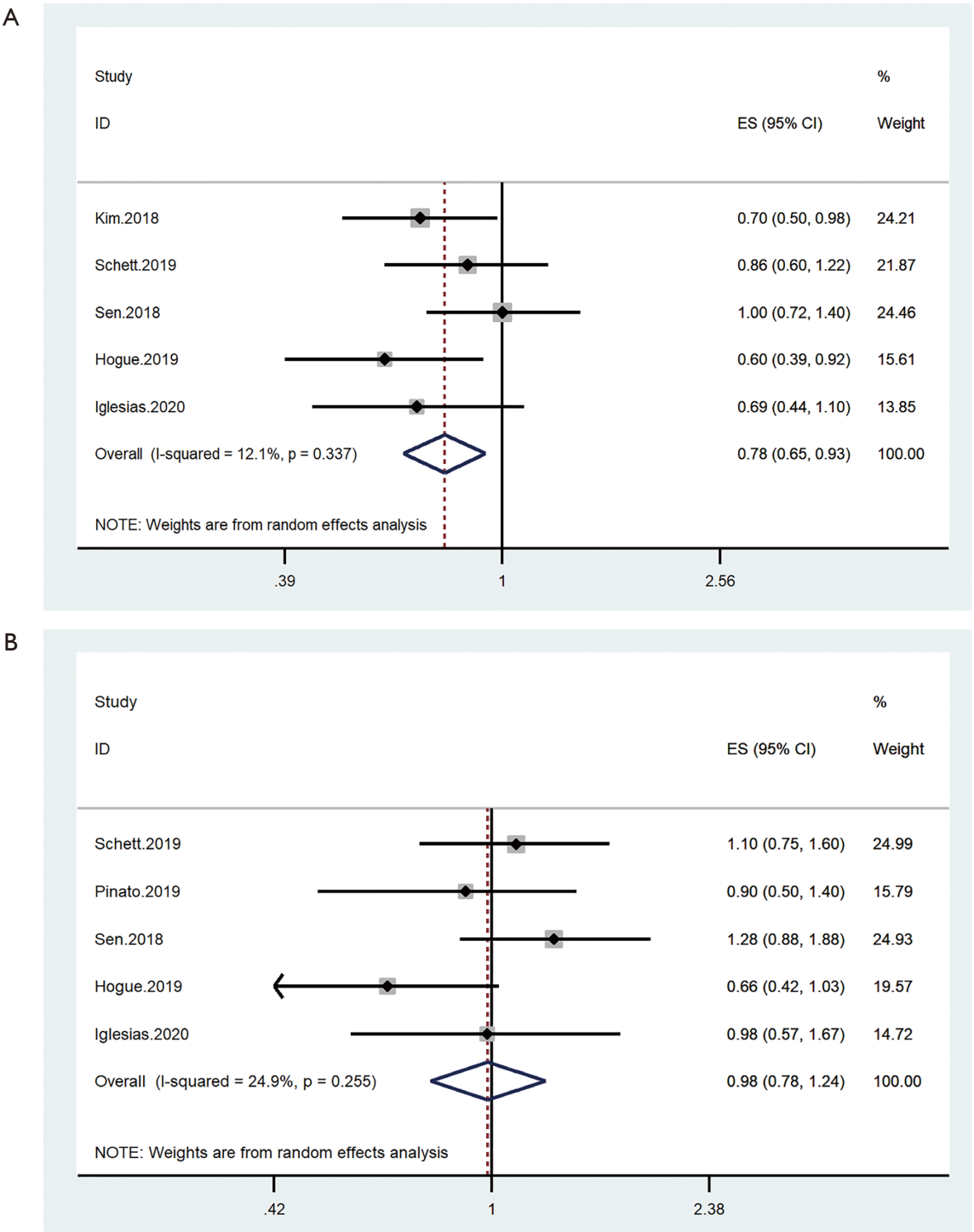


**Figure 5** The associations between antibiotic exposure and PFS (A) and OS (B) in group 3. ES, effect size; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

baseline intestinal microbial, and ECOG status of patients with ATB exposure are different from those without ATB exposure. In some cases, such as patients with bacteremia, the use of ATBs is inevitable. ATBs improve the response of such patients to immunosuppressants by inhibiting pathogenic bacteria, and this finding may partly explain the high PFS of patients taking ATBs in group 3 (ATB use at any time during the ICIs). Therefore, we need to understand the baseline characteristics of patients using ATBs and the dynamic changes in their intestinal microbes after using different ATBs. Summarizing from the current research data, high-dose broad-spectrum ATBs (such as cephalosporins, β-lactams, and quinolones) may affect the intestinal flora, impair the efficacy of immunotherapy, and shorten the survival time of patients (reviewed and non-prospective data). The timing of ATBs is important. Before immunotherapy, if infections are present, the corresponding anti-infective treatment based on bacteriological evidence is recommended to be provided to avoid the prophylactic and the long-term use of ATBs.

## Conclusions

This meta-analysis included 30 cohorts. Results showed that the survival of patients with cancer who underwent immunotherapy was associated with ATB exposure and that the timing of ATB use was an important factor. Different ATB exposure windows had different effects on the survival of patients with cancer. In the future, advanced prospective studies are needed to guide immunotherapy accurately and improve the patients' survival.

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## Footnote

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*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.



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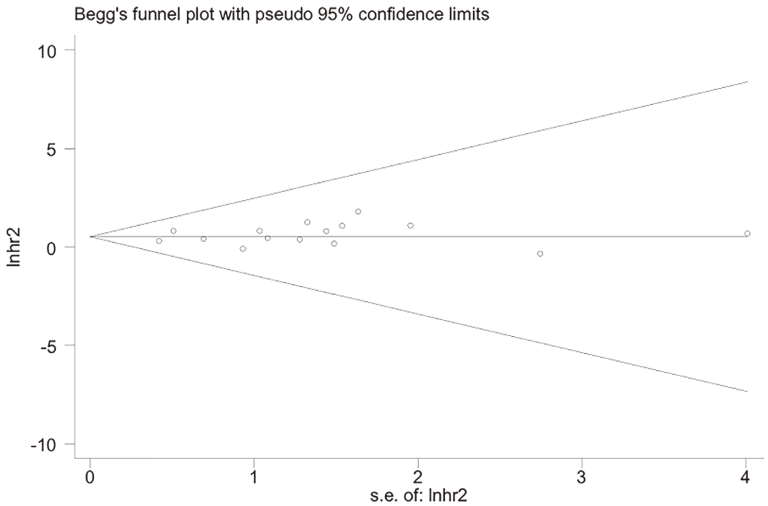


**Figure S1** Funnel plot of overall survival in group 1.

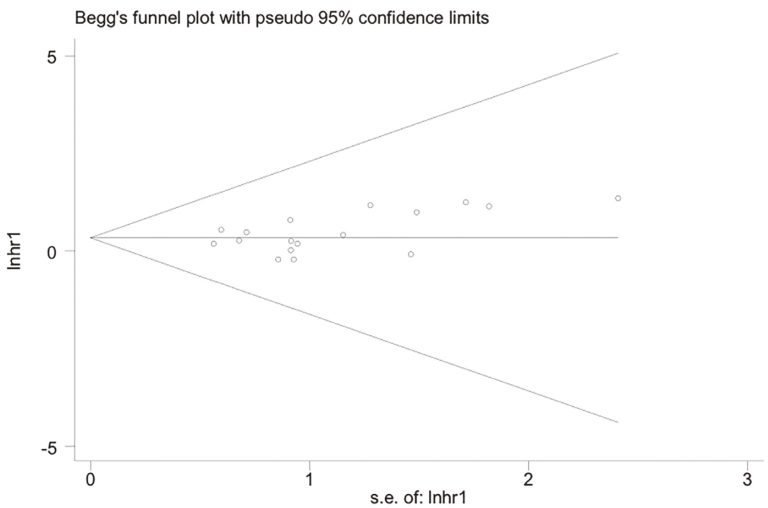


**Figure S2** Funnel plot of progression-free survival in group 2.


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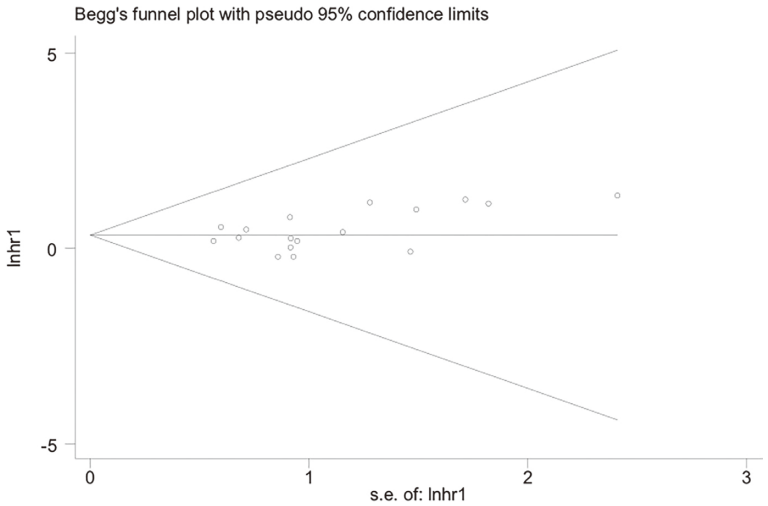


**Figure S3** Funnel plot of overall survival in group 2.


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