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Association Between Antibiotic and Outcomes of Chemoimmunotherapy for Extensive-Stage Small Cell Lung Cancer: A Multicenter Retrospective Study of 132 Patients

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ABSTRACT

Introduction: To evaluate the impact of antibiotic (ATB) exposure on the outcome of chemoimmunotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC).

Methods: In this multicenter retrospective study, 132 patients with ES-SCLC who received chemoimmunotherapy were included from three hospitals in China. Patients receiving ATB within 30 days prior to initiating ICI therapy (p-ATB) and those receiving concurrent ICI therapy until cessation (c-ATB)were compared to those who did not (n-ATB). Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and immune-related adverse events (irAEs) were assessed. To avoid immortal time bias, c-ATB was analyzed as a time-dependent covariate in the Cox proportional hazards model.

Results: Among the 132 patients, 25 were included in the p-ATB group and 26 in the c-ATB group, while 81 patients were categorized in the n-ATB group. Multivariate analysis revealed no significant differences in PFS (aHR = 1.028, 95% CI: 0.666–1.589, $p = 0.900$) and OS (aHR = 0.957, 95% CI: 0.549–1.668, $p = 0.877$) between the p-ATB and n-ATB groups. Similarly, p-ATB had no significant impact on ORR ($p = 0.510$) or irAEs ($p = 0.516$). The use of c-ATB had no significant effect on either PFS (aHR: 1.165, 95% CI: 0.907–1.497; $p = 0.232$) or OS (aHR: 1.221, 95% CI: 0.918–1.624; $p = 0.171$) by multivariate analysis.

Conclusions: p-ATB has no significant impact on PFS, OS, ORR, or the incidence of irAEs in ES-SCLC patients receiving chemoimmunotherapy. Similarly, c-ATB does not seem to affect PFS or OS.

1 | Introduction

In recent years, the development of immune checkpoint inhibitors (ICIs), including programed death ligand 1 (PD-L1) inhibitors and programed death receptor 1 (PD-1) inhibitors, has significantly prolonged the survival of patients with extensive-stage small cell lung cancer (ES-SCLC). Clinical trials, such as IMpower133 and CASPIAN, have shown that atezolizumab/durvalumab with standard chemotherapy provides a significant survival advantage over chemotherapy alone for patients with ES-SCLC [1–3]. The recent ETER701 study further demonstrated that the median overall survival (mOS) of patients with ES-SCLC treated with first-line PD-L1 inhibitors in combination with anlotinib and chemotherapy reached an unprecedented 19.3 months [4]. These findings suggest that ES-SCLC treatment efficacy can be improved by enhancing the antitumor immune response.

However, the outcome of ICIs in malignant tumors may be influenced by various factors, including the use of concomitant medications [5–7]. Numerous studies have demonstrated that antibiotics may diminish the therapeutic efficacy of immunotherapy for non-small cell lung cancer (NSCLC) [8–12], yet their impact on the efficacy of immunotherapy combined with chemotherapy (chemoimmunotherapy) for NSCLC is not significant [13]. Furthermore, multiple studies have shown that antibiotics may negatively affect the efficacy of immunotherapy for various types of tumors, including melanoma, renal cell carcinoma, gynecological malignancies, and gastrointestinal tumors [14–19]. Nonetheless, the use of antibiotics remains widespread among lung cancer patients [20]. Lung cancer was associated with an increased likelihood of recent antibiotic prescriptions [21]. Gonugunta found that exposure to antibiotics is more common in lung cancer patients than in melanoma patients [22]. It remains an open question whether antibiotics might influence the outcomes of chemoimmunotherapy in patients with ES-SCLC. To date, there have been no data to confirm this hypothesis.

We conducted a multicenter, retrospective cohort study to evaluate the impact of antibiotic exposure within 30 days prior to or during ICIs on the efficacy and adverse reactions in patients with ES-SCLC who received chemoimmunotherapy.

2 | Methods

2.1 | Study Cohort and Patients

We retrospectively collected data from patients with ES-SCLC who received chemoimmunotherapy at three hospitals (Qilu Hospital of Shandong University, Qilu Hospital of Shandong University Dezhou Hospital, Weihai Municipal Hospital) in China from January 2018 to October 2023. The inclusion criteria were as follows: histologically or cytologically confirmed SCLC; staged ES-SCLC; at least one measurable lesion according to the RECIST 1.1 criteria at the start of chemoimmunotherapy; and having undergone at least two cycles of chemoimmunotherapy treatment with at least one efficacy assessment. Exclusion criteria included insufficient treatment duration of less than two cycles of chemoimmunotherapy, prior treatment with PD-1/PD-L1 inhibitors, and a history or concurrent presence of other malignancies.

Clinical information, including age, sex, smoking history, comorbidities, ECOG performance status score, PD-1/PD-L1 inhibitor use, treatment regimen, receipt of thoracic radiation therapy, and dates of progression, death, or last follow-up, was collected via electronic medical records or telephone follow-up. Information on antibiotic exposure, including name, specific class, indication, dose, route of administration, application time, and duration was collected.

2.2 | Ethical Approval of the Study Protocol

This study was performed in accordance with the provisions of the Declaration of Helsinki and was approved by the ethics committee of Qilu Hospital of Shandong University Dezhou Hospital (Approval No. 2024046).

2.3 | Patient Grouping

Patients were categorized into those with antibiotic exposure (ATB group) and those without (n-ATB group). Two ATB exposure windows were analyzed: ATB therapy within 30 days prior to initiating ICI therapy, termed p-ATB, and concurrent ICI therapy until cessation, termed c-ABT, respectively. We chose a 30-day window as the p-ATB period because it was the most common window in prior retrospective studies [13, 18, 19, 23, 24].

Follow-up for all patients was conducted until death or data cutoff (February 28, 2024). Disease efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or the immune-related RECIST (irRECIST) criteria. Outcome measures included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and incidence of immune-related adverse events (irAEs). PFS was defined as the time from the start of chemoimmunotherapy to disease progression or death from any cause (whichever occurred first). OS was defined as the time from the start of chemoimmunotherapy to death from any cause. The ORR was defined as the proportion of patients achieving a complete response (CR) or a partial response (PR).

2.4 | Statistical Analysis

Categorical variables were expressed as percentages and compared using chi-square tests and Fisher's exact tests. Survival curves were estimated using the Kaplan–Meier method and compared using log-rank tests. Univariate and multivariate analysis for PFS and OS were performed using the Cox proportional hazards model, calculating hazard ratio (HR) with 95% confidence interval (CI). To avoid introducing immortal time bias between the initiation of ICIs and the use of antibiotics in the c-ATB group [25–27], we incorporated c-ATB as a time-dependent covariate in the Cox proportional hazards model for univariate and multivariate analysis of PFS and OS. Variables with a p value <0.1 in the univariate analysis, along with the antibiotic variable, were included in the multivariate analysis. A two-sided p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 27.0 (IBM Corporation, Armonk, NY).

3 | Results

3.1 | Cohort Baseline Characteristics

A total of 132 patients were included in this study after applying the inclusion and exclusion criteria (Figure 1). Patients received 4–6 cycles of chemoimmunotherapy, followed by maintenance monotherapy with ICI until disease progression, intolerable adverse reactions, or other reasons for discontinuation. The combination chemotherapy was based on platinum with a two-drug regimen, including etoposide/irinotecan plus carboplatin/cisplatin. Monotherapy included etoposide, irinotecan, paclitaxel, nab-paclitaxel, and gemcitabine.

Among these patients, 51 (38.6%) were included in the ATB group, comprising 25 in the p-ATB subgroup and 26 in the c-ATB subgroup, while 81 patients (61.4%) were categorized in the

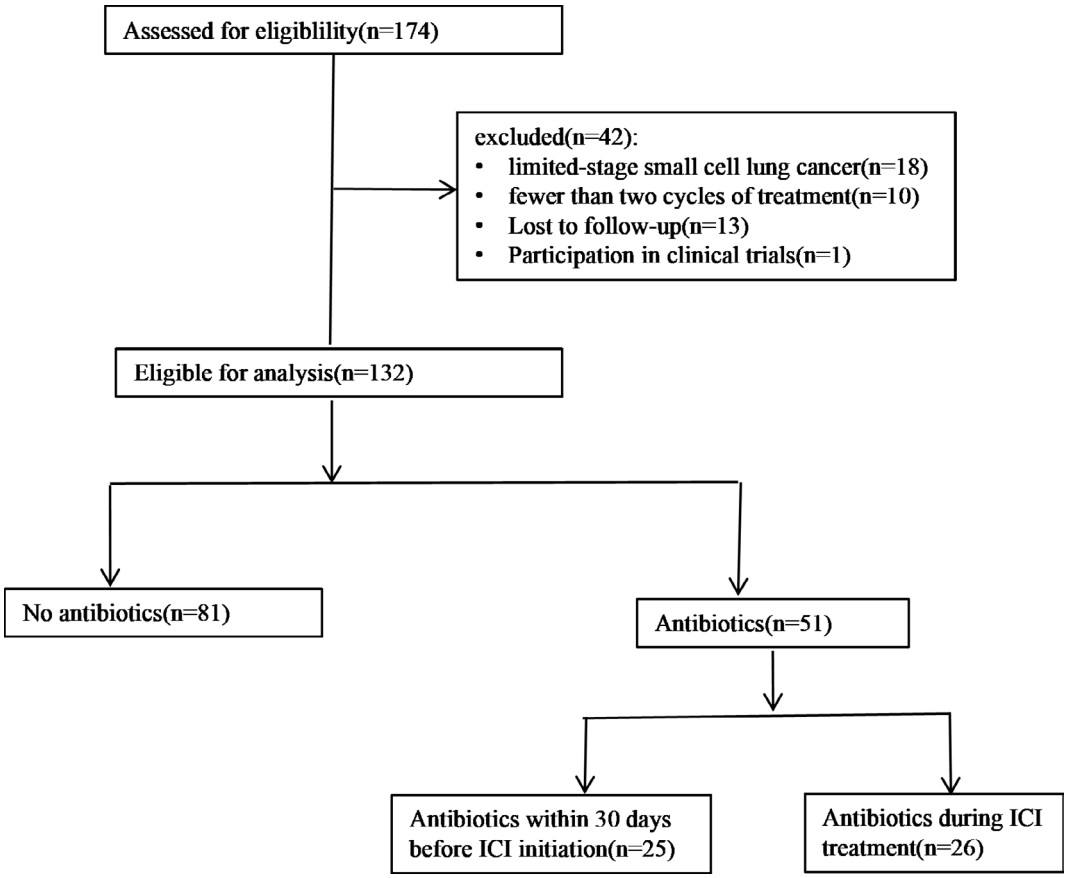

FIGURE 1 | Schematic presentation of the patient selection flow. 174 patients were identified at three hospitals. 132 patients were eligible for analysis.

n-ATB group. Most patients (72.7%) were male, 75 (56.8%) were current or former smokers, 33 (25.0%) had brain metastases, and 35 (26.5%) had liver metastases. Ninety-two patients (69.7%) received chemoimmunotherapy as first-line treatment. The majority of the patients ($n = 117$, 88.6%) received combination chemotherapy. A total of 31 patients (23.5%) received concurrent or sequential thoracic radiotherapy. Most clinical variables were well balanced between the p-ATB group and the n-ATB group, except for the chemotherapy regimen ($p = 0.020$). All other clinical characteristics between the c-ATB group and the n-ATB group were well balanced, except for PD-L1/PD-1 inhibitor use ($p = 0.048$). The clinical characteristics of all included patients are summarized in Table 1.

Table 2 provides a detailed list of ATB types and indications for ATB administration. The most frequently used antibiotics were β-lactams (18, 35.3%), followed by β-lactams in combination with quinolones (14, 27.4%) and then quinolones alone (13, 25.5%). Additionally, the combination of β-lactams and aminoglycosides was noted in one case, while the specific types of antibiotics used in five cases remained unspecified. The most common indication for ATB treatment was pulmonary infection, which occurred in 29 (56.8%) of the patients in the ATB group. Febrile neutropenia was observed in 12 cases (23.5%). Other infections included enterocolitis in two cases, concomitant pulmonary and urinary tract infections in one case, upper respiratory tract infection in one case, otitis in one patient, and undetermined conditions in five patients.

3.2 | Impact of ATB on the Efficacy of Chemoimmunotherapy

The median follow-up period was 22.6 months (95% CI: 18.961–26.246). The median PFS (mPFS) for the entire cohort was 6.3 months (95% CI: 5.650–6.966; 110 events); the median OS (mOS) was 14.6 months (95% CI: 12.026–17.214; 84 events), and the ORR was 56.1%.

The mPFS in the ATB group was 6.3 months (95% CI: 4.914–7.702), compared to 6.5 months (95% CI: 5.762–7.314) in the n-ATB group (log-rank: $p = 0.618$, Figure 2A). The mOS for the ATB group was 12.4 months (95% CI: 10.650–14.188), while for the n-ATB group, it was 15.9 months (95% CI: 14.079–17.790) (log-rank: $p = 0.195$, Figure 2B). Furthermore, the ORR showed no significant disparity between the ATB (52.9%) and n-ATB (58.0%) groups ($p = 0.567$).

3.3 | Impact of p-ATB on the Efficacy of Chemoimmunotherapy

No statistical difference in mPFS was observed (5.7 months versus 6.5 months, log-rank: $p = 0.387$, Figure 2C) between the p-ATB and n-ATB groups, nor in mOS (12.8 months versus 15.9 months, log-rank: $p = 0.546$, Figure 2D). The ORR was also similar between these two groups (48.0% vs. 58.0%, $p = 0.378$).

TABLE 1 | Baseline characteristics of patients.

	Total (%)	n-ATB (%)	p-ATB (%)		c-ATB (%)	
Patient characteristics	**132**	**81**	**25**	P_p	**26**	P_c
Age in years						
≤65 yr	71 (53.8%)	42 (51.9%)	13 (52.0%)	0.990	16 (61.5%)	0.388
>65 yr	61 (46.2%)	39 (48.1%)	12 (48.0%)		10 (38.5%)	
Sex						
Male	96 (72.7%)	59 (72.8%)	17 (68.0%)	0.639	20 (76.9%)	0.680
Female	36 (27.3%)	22 (27.2%)	8 (32.0%)		6 (23.1%)	
Smoking status						
Never	57 (43.2%)	36 (44.4%)	11 (44.0%)	0.969	10 (38.5%)	0.592
Former/current	75 (56.8%)	45 (55.6%)	14 (56.0%)		16 (61.5%)	
ECOG PS						
0–1	109 (82.6%)	66 (81.5%)	22 (88.0%)	0.554	21 (80.8%)	1.000
≥2	23 (17.4%)	15 (18.5%)	3 (12.0%)		5 (19.2%)	
Brain metastases						
No	99 (75.0%)	59 (72.8%)	20 (80.0%)	0.603	20 (76.9%)	0.680
Yes	33 (25.0%)	22 (27.2%)	5 (20.0%)		6 (23.1%)	
Liver metastases						
No	97 (73.5%)	59 (72.8%)	21 (84.0%)	0.301	17 (65.4%)	0.466
Yes	35 (26.5%)	22 (27.2%)	4 (16.0%)		9 (34.6%)	
Treatment line						
1st	92 (69.7%)	58 (71.6%)	17 (68.0%)	0.729	17 (65.4%)	0.547
≥2nd	40 (30.3%)	23 (28.4%)	8 (25.8%)		9 (34.6%)	
ICI type						
PD-L1 inhibitors	76 (57.6%)	52 (64.2%)	13 (52.0%)	0.274	11 (42.3%)	0.048
PD-1 inhibitors	56 (42.4%)	29 (35.8%)	12 (48.0%)		15 (57.7%)	
Chemotherapy regimen						
Combination	117 (88.6%)	76 (93.8%)	19 (76.0%)	0.020	22 (84.6%)	0.216
Monotherapy	15 (11.4%)	5 (6.2%)	6 (24.0%)		4 (15.4%)	
Chest radiotherapy						
No	101 (76.5%)	62 (76.5%)	22 (88.0%)	0.270	17 (65.4%)	0.260
Yes	31 (23.5%)	19 (23.5%)	3 (12.0%)		9 (34.6%)	

Abbreviations: ATB, antibiotic; c-ATB, antibiotic treatment concurrent immune checkpoint inhibitor therapy; ECOG, Eastern Cooperative Oncology Group; n-ATB, without antibiotic exposure; p-ATB, antibiotic treatment within 30 days prior to initiating immune checkpoint inhibitor therapy; P_c value, c-ATB versus n-ATB. P_p value, p-ATB versus n-ATB; PS, performance status.

The univariate and multivariate analyses of p-ATB on PFS and OS are presented in Table 3.

Univariate analysis revealed that ECOG PS, liver metastasis, treatment line, and chemotherapy regimen were significantly associated with PFS ($p < 0.05$), whereas sex, smoking status, liver metastasis, treatment regimen, and thoracic radiotherapy were significantly associated with OS ($p < 0.05$). These significant variables, along with the antibiotic variable, were further included in the multivariate analysis for both PFS and OS. After adjusting for these confounding factors, p-ATB treatment still showed no significant correlation with PFS (adjusted hazard ratio [aHR]: 1.194, 95% CI: 0.714–2.000; $p = 0.499$) and OS (aHR: 1.062, 95% CI: 0.600–1.880; $p = 0.837$).

TABLE 2 | Detailed ATB types and indications for ATB administration.

ATB information	ATB *n* (%)	p-ATB *n*	c-ATB *n*
ATB types			
β-lactams	18 (35.3)	11	7
β-lactams combined with quinolones	14 (27.4)	9	5
Quinolones	13 (25.5)	2	11
β-lactams combined with aminoglycosides	1 (2.0)	—	1
Unspecified	5 (9.8)	3	2
Indications			
Pulmonary infections	29 (56.8)	18	11
Febrile neutropenias	12 (23.5)	—	12
Enterocolitis	2 (3.9)	1	1
Pulmonary and urinary tract infections	1 (2.0)	—	1
Upper respiratory tract infection	1 (2.0)	1	—
Otitis	1 (2.0)	—	1
Unclear source	5 (9.8)	5	—

Abbreviations: ATB, antibiotic; c-ATB, antibiotic treatment concurrent immune checkpoint inhibitor therapy; p-ATB, antibiotic treatment within 30 days prior to initiating immune checkpoint inhibitor therapy.

3.4 | Impact of the Duration of p-ATB on the Efficacy of Chemoimmunotherapy

To address whether the results were confounded by the duration, we further evaluated the impact of p-ATB according to different durations (1–7 days vs. > 7 days). Among patients exposed to p-ATB, 10 cases (40.0%) and 15 cases (60.0%) received p-ATB for 1–7 days and > 7 days, respectively. The mPFS for 1–7 days and > 7 days was 5.7 months and 5.3 months, respectively (log-rank: $p = 0.604$, Figure 2E), and the mOS was 11.0 months and 14.6 months, respectively (log-rank: $p = 0.961$, Figure 2F). Similarly, there was no statistically significant difference in the ORR between 1–7 days (50.0%) and > 7 days (46.7%) exposure groups ($p = 0.870$).

3.5 | Impact of p-ATB on the Incidence of irAEs

A total of six patients in the p-ATB group and 16 in the n-ATB group developed any-grade irAEs, with no statistical difference in the incidence of irAEs between the groups ($p = 0.647$).

As shown in Table 4, most of the patients experienced irAEs in grades 1 or 2 (20 cases), and none discontinued therapy because of irAEs. Grade 3 irAEs were recorded in two patients, and no grade 4 or higher irAEs were observed.

3.6 | Impact of c-ATB on the Efficacy of Chemoimmunotherapy

Compared to the n-ATB group, the c-ATB group exhibited an mPFS of 7.8 months (log-rank: $p = 0.988$) and an mOS of 12.3 months (log-rank: $p = 0.132$) (Figure 2G,H). Similarly, the ORR showed no statistically significant difference between the c-ATB group (57.7%) and the n-ATB group (58.0%) ($p = 0.976$).

We considered c-ATB to be a time-dependent covariate in a Cox analysis. In the univariate analysis, c-ATB treatment was not associated with PFS (HR: 1.223, 95% CI: 0.951–1.574; $p = 0.117$) or OS (HR: 1.308, 95% CI: 0.997–1.714; $p = 0.052$). After multivariate analysis, c-ATB still had no significant impact on PFS (aHR: 1.250, 95% CI: 0.968–1.614; $p = 0.088$) or OS (aHR: 1.311, 95% CI: 0.988–1.740; $p = 0.061$) (Table 5).

4 | Discussion

To our knowledge, we are the first group to analyze the impact of antibiotics, including the timing within 30 days prior to ICIs or during ICIs, on the efficacy and safety of patients with ES-SCLC receiving chemoimmunotherapy. Our findings provide clinicians with additional insights into the use of antibiotics for ES-SCLC patients receiving ICIs.

In recent years, chemoimmunotherapy has become the standard first-line treatment for ES-SCLC. However, only a minor fraction of patients experience long-term benefits from chemoimmunotherapy. No predictive biomarkers have been approved for the efficacy of ICIs in ES-SCLC [28]. Recent studies have highlighted the correlation between the complexity of gut microbiota, the presence of certain microbial strains, metabolic products, and the efficacy and adverse effects of ICIs [29–31]. Qiu explained the probable mechanisms via which the gut microbiome modulates the efficacy of ICIs, potentially through the impact of microbial entities or their metabolites as signaling molecules on the host immune response and the tumor microenvironment (TME) [29].

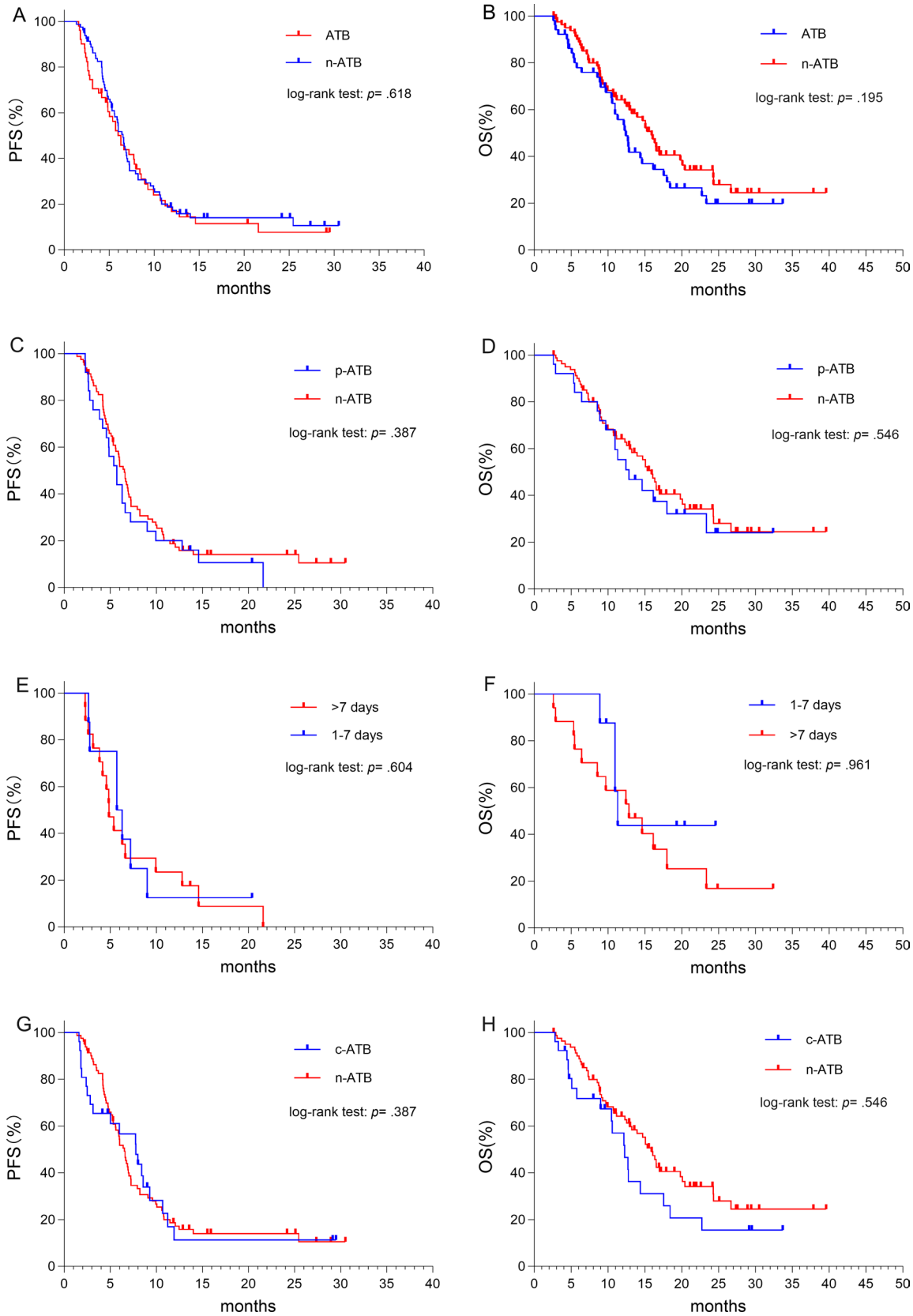

FIGURE 2 | Kaplan–Meier curves showing impact of antibiotic exposure on PFS and OS. (A) PFS according to any antibiotic exposure. (B) OS according to any antibiotic exposure. (C) PFS according to p-ATB. (D) OS according to p-ATB. (E) PFS according to the duration of p-ATB. (F) OS according to the duration of p-ATB. (G) PFS according to c-ATB. (H) OS according to c-ATB. PFS, progression-free survival; OS, overall survival; p-ATB, antibiotic exposure within 30 days prior to initiating immune checkpoint inhibitor therapy; c-ATB, antibiotic exposure concurrent immune checkpoint inhibitor therapy. ICI, immune checkpoint inhibitor.

TABLE 3 | Univariate and Multivariate Analyses of Clinical Parameters on PFS and OS (p-ATB).

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***
ATB								
n-ATB	1.0		1.0		1.0		1.0	
p-ATB	1.233 (0.766–1.983)	0.388	1.194 (0.714–2.000)	0.499	1.185 (0.682–2.059)	0.547	1.062 (0.600–1.880)	0.837
Sex								
Male	1.0				1.0		1.0	
Female	0.981 (0.618–1.558)	0.935	—		0.520 (0.290–0.932)	0.028	0.679 (0.311–1.484)	0.332
Age								
≤ 65 yr	1.0				1.0		—	
> 65 yr	1.243 (0.818–1.889)	0.308	—		1.288 (0.794–2.090)	0.305	—	
Smoking status								
Never	1.0				1.0		1.0	
Former/current	1.064 (0.702–1.612)	0.771	—		1.669 (1.014–2.748)	0.044	1.483 (0.769–2.858)	0.239
ECOG PS								
0–1	1.0		1.0		1.0		—	
≥ 2	1.679 (1.285–2.194)	< 0.001	1.582 (1.203–2.080)	0.001	1.264 (0.939–1.701)	0.123	—	
Brian metastases								
No	1.0		—		1.0		—	
Yes	1.334 (0.844–2.110)	0.217	—		1.382 (0.817–2.338)	0.228	—	
Liver metastases								
No	1.0		1.0		1.0		1.0	
Yes	2.084 (1.291–3.365)	0.003	1.504 (0.911–2.485)	0.111	2.497 (1.467–4.251)	< 0.001	2.244 (1.289–3.906)	0.004
Treatment line								
1st	1.0		1.0		1.0	< 0.001	1.0	
≥ 2nd	2.946 (1.853–4.683)	< 0.001	2.422 (1.430–4.100)	< 0.001	2.926 (1.784–4.799)		2.934 (1.743–4.939)	< 0.001
ICI type								
PD-L1 inhibitors	1.0		—		1.0		—	
PD-1 inhibitors	1.310 (0.861–1.991)	0.207	—		1.041 (0.634–1.707)	0.874	—	
Chemotherapy regimen								
Combination	1.0		1.0		1.0		—	
Monotherapy	2.261 (1.188–4.305)	0.013	1.119 (0.523–2.394)	0.772	1.324 (0.602–2.909)	0.485	—	

(Continues)

TABLE 3 | (Continued)

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***
Chest radiotherapy								
No	1.0		—		1.0		1.0	
Yes	0.656 (0.394–1.092)	0.105	—		0.422 (0.208–0.855)	0.017	0.550 (0.265–1.138)	0.107

Abbreviations: aHR, adjusted hazard ratio; ATB, antibiotic; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; p-ATB, antibiotic treatment within 30 days prior to initiating immune checkpoint inhibitor therapy; PFS, progression-free survival; PS, performance status.

TABLE 4 | The incidence of irAEs.

	n-ATB	p-ATB	*p*
Any irAEs	19.8% (16)	24.0% (6)	0.647
Grade1-2 irAEs	18.5% (15)	20.0% (5)	0.657
Grade3-4 irAEs	1.2% (1)	4.0% (1)	

Abbreviations: irAEs, immune-related adverse events; n-ATB, without antibiotic exposure; p-ATB, antibiotic treatment within 30 days prior to initiating immune checkpoint inhibitor therapy.

The utilization of antibiotics has been shown to elicit significant alterations in gut microbiota structure, species composition, and metabolic capacity, consequently affecting the efficacy of ICIs in cancer patients [8, 9, 32, 33]. Routy et al. reported that the use of antibiotics in patients diagnosed with lung, renal, and urothelial cancers who are receiving PD-1 inhibitors correlates with diminished PFS [8]. Subsequently, numerous studies have reported the adverse effects of antibiotics on the efficacy of ICIs in NSCLC [9–12]. Contrary to these studies, we found no statistically significant differences in PFS, OS, or ORR between ATB (either p-ATB or c-ATB) and n-ATB with ES-SCLC patients receiving chemoimmunotherapy. This finding is similar to the report by Cortellini, which indicated that the use of pATB or cATB had no significant impact on the clinical efficacy of first-line chemoimmunotherapy in patients with NSCLC [13].

The results we have observed may be attributed to the characteristics of the immunosuppressive TME in SCLC and the synergistic interaction between chemotherapy and immunotherapy. Most SCLC are characterized by significantly reduced levels of tumor-infiltrating lymphocytes (TILs), tumor cell CD8/CD3 ratios, and the expression of major histocompatibility complex (MHC) class I and II antigens, constituting a highly immunosuppressive TME [34]. These characteristics may affect the regulatory capacity of the gut microbiome on the TME, and limit efficacy of immunotherapy in SCLC [35]. The impact of antibiotics on the TME of SCLC, mediated by the gut microbiota, may also be limited. Another reason is the synergistic enhancement effect of chemotherapy on immunotherapy [13], which operates through various mechanisms, such as induced immunogenic cell death, increased antigenicity of cancer cells, depletion of immunosuppressive cells, and modulation of gene expression [36].

Previous research has established that antibiotics can influence not only the efficacy of ICIs but also the risk of immune-related adverse events (irAEs) [37]. Therefore, we explored the correlation between p-ATB and the incidence of irAEs. We found that patients in the p-ATB and n-ATB groups had a similar risk of experiencing irAEs. Meanwhile, no statistical difference in the grades of irAEs between the two groups was observed.

Previous studies have also highlighted that the effect seems to depend on the time window of antibiotic exposure [12, 14, 38, 39]. Lurienne's meta-analysis suggested that antibiotic exposure shortly before or after ICI initiation seems to be particularly harmful, whereas antibiotic use later during the disease course does not seem to alter survival [12]. Pinato et al. found that pATB (within 30 days before ICI) therapy, but not cATB therapy, was associated with poorer treatment response and OS in cancer patients treated with ICIs [38]. Khan et al. demonstrated that the use of antibiotics significantly negatively impacted the efficacy of immunotherapy in patients with advanced or metastatic malignancy. The maximal negative effect occurred when antibiotics were used in the first 6 weeks after initiating ICI [39]. This is one of the reasons we have analyzed p-ATB and c-ATB separately. Additionally, immortal time bias is also a factor we have taken into consideration. The study began follow-up from the start of the ICIs, while patients in the c-ATB group had not received antibiotic therapy within the standard timeframe. The immortal time bias between the start of follow-up and exposure to antibiotics must be accounted for to prevent overestimating the incidence of outcomes in the n-ATB group and underestimating it in the c-ATB group, or a combination of both [25–27]. We considered c-ATB to be a time-dependent covariate in Cox analysis. This statistical approach is also one of the strengths of our study.

This study does have some limitations. First, the retrospective study design may not provide comprehensive data, therefore failing to accurately reflect the actual use of antibiotics. The incidence of irAEs in our research is lower compared to that observed in the IMpower133 and CASPIAN trials [1, 3]. This may be due to the potential incompleteness in electronic medical record documentation. More data from prospective studies and long-term investigations in larger patient cohorts are undoubtedly needed. Second, there were a multitude of confounding factors, with patients exhibiting heterogeneity in PD-L1/PD-1 inhibitors and chemotherapy regimens, which might confound our analysis. We evaluated the impact of p-ATB or c-ATB by multivariable analysis to adjust for multiple prognostic factors. Furthermore, the species composition and metabolic capabilities of the gut microbiome vary among patients with different cancer

TABLE 5 | Univariate and multivariate analyses of clinical parameters on PFS and OS (c-ATB).

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***
ATB								
n-ATB	1.0		1.0		1.0		1.0	
c-ATB	1.223 (0.951–1.574)	0.117	1.250 (0.968–1.614)	0.088	1.308 (0.997–1.714)	0.052	1.311 (0.988–1.740)	0.061
Sex								
Male	1.0				1.0		1.0	
Female	0.939 (0.582–1.514)	0.795	—		0.446 (0.245–0.810)	0.008	0.570 (0.252–1.291)	0.178
Age								
≤65 yr	1.0				1.0		—	
>65 yr	1.246 (0.814–1.906)	0.312	—		1.321 (0.815–2.142)	0.258	—	
Smoking status								
Never	1.0				1.0		1.0	
Former/ current	1.142 (0.746–1.747)	0.541	—		2.008 (1.216–3.316)	0.006	1.628 (0.858–3.089)	0.136
ECOG PS								
0–1	1.0		1.0		1.0			
≥2	1.646 (1.266–2.139)	<0.001	1.562 (1.169–2.088)	0.003	1.402 (1.056–1.861)	0.019	1.358 (0.960–1.921)	0.084
Brian metastases								
No	1.0		—		1.0		—	
Yes	1.192 (0.752–1.887)	0.455	—		0.982 (0.576–1.672)	0.945	—	
Liver metastases								
No	1.0		1.0		1.0		1.0	
Yes	2.531 (1.592–4.023)	<0.001	1.660 (0.998–2.763)	0.051	2.598 (1.559–4.331)	<0.001	1.792 (1.009–3.180)	0.046
Treatment line								
1st	1.0		1.0		1.0	<0.001	1.0	
≥2nd	3.303 (2.093–5.213)	<0.001	2.819 (1.739–4.570)	<0.001	4.101 (2.488–6.758)		3.696 (2.124–6.430)	<0.001
ICI								
PD-L1 inhibitors	1.0		—		1.0		—	
PD-1 inhibitors	1.287 (0.839–1.973)	0.248	—		1.192 (0.734–1.935)	0.478	—	
Chemotherapy regimen								
Combination	1.0		1.0		1.0		1.0	
Monotherapy	2.802 (1.386–5.664)	0.004	1.860 (0.887–3.898)	0.100	2.802 (1.263–6.214)	0.011	1.575 (0.657–3.775)	0.309

(Continues)

TABLE 5 | (Continued)

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**HR (95% CI)**	***p***	**aHR (95% CI)**	***p***
Chest radiotherapy								
No	1.0		—		1.0		1.0	
Yes	0.676 (0.416–1.100)	0.115	—		0.453 (0.246–0.833)	0.011	0.779 (0.399–1.522)	0.465

Abbreviations: aHR, adjusted hazard ratio; ATB, antibiotic; c-ATB, antibiotic treatment concurrent immune checkpoint inhibitor therapy; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; PS, performance status.

types [40], which may also influence the efficacy of immunotherapy. Future research should validate these findings within a broader patient population and consider additional variables, such as specific types and patterns of antibiotics.

In conclusion, our study provided insights suggesting that the use of antibiotics had no significant impact on patients with ES-SCLC receiving chemoimmunotherapy. Additionally, p-ATB and c-ATB exposure were found to affect neither PFS nor OS. Moreover, p-ATB did not exert a significant impact on the ORR or the incidence of irAEs. Consequently, the initiation of chemoimmunotherapy should not be deferred in ES-SCLC patients who have recently received antibiotics. Furthermore, antibiotic treatment should be administered as needed, whether prior to or during chemoimmunotherapy.

Author Contributions

Conception and design: Zhongfei Yang, Fang Deng, Jing Xu and Yu Li. Data collection: Fang Deng, Hong Ye, Ping Zhang and Meiling Sun. Supervision and guidance: Zhongfei Yang, Yu Li and Jing Xu. Data analysis: Fang Deng, Hong Ye, Ping Zhang and Meiling Sun. Writing – original draft: Fang Deng, Hong Ye. Writing – review and editing, Zhongfei Yang, Yu Li and Jing Xu.

All authors participated in the research process and helped shape the research, analysis, and manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions, but are available from the corresponding author upon reasonable request.

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