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Corticosteroid administration for cancer-related indications is an unfavorable prognostic factor in solid cancer patients receiving immune checkpoint inhibitor treatment

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ABSTRACT

Objective: Immunotherapies targeting immune checkpoints have achieved encouraging survival benefits in patients with various solid cancers. Corticosteroids are frequently administrated for cancer/non-cancer related indications and immune-related adverse events (irAEs). This study aimed to clarify the prognostic significance of corticosteroid administration in solid cancer patients receiving immune checkpoint inhibitor (ICI) treatment.

Method: First, a meta-analysis was performed using the literatures searched from PubMed, Cochrane Library, Web of Science, Embase, and Clinicaltrials.gov before January 2021. The Hazard ratios (HRs) coupled with 95% confidence intervals (CIs) were used to evaluate the correlation of corticosteroid administration with overall survival (OS) and progression-free survival (PFS). Then, a retrospective analysis enrolling 118 ICI-treated cancer patients was performed for validation, among which 26 patients received corticosteroids for cancer-related indications.

Result: In the meta-analysis, corticosteroid administration for cancer-related indications was significantly correlated with worse PFS (HR = 1.735(1.381–2.180)) and OS (HR = 1.936(1.587–2.361)) of the ICI-treated patients. However, corticosteroid administration for non-cancer-related indications and irAEs was unrelated with PFS (non-cancer-related indications: HR = 0.830(0.645–1.067); irAEs: HR = 1.302(0.628–2.696)) and OS (non-cancer-related indications: HR = 0.786(0.512–1.206); irAEs: HR = 1.107(0.832–1.474)) of the ICI-treated patients. The following retrospective analysis identified corticosteroid administration for cancer-related indications was an independent unfavorable predictor for PFS (P = 0.006) and OS (P = 0.044) of the ICI-treated patients. The subgroup analysis based on non-small cell lung cancer (NSCLC) demonstrated the similar results (P = 0.002 for PFS and P = 0.047 for OS).

Conclusion: Our study demonstrated corticosteroid administration for cancer-related indications is an unfavorable prognostic factor in solid cancer patients receiving ICI treatment. Therefore, careful selection of corticosteroid-treated patients for ICI therapy is quite necessary in individualized clinical management.

1. Introduction

The past few years have witnessed the great success of immune checkpoint inhibitors (ICIs) in improving the clinical outcome of patients with various malignancies [1]. Currently, three categories of ICIs are mainly used in clinical practice, including anti-Programmed cell death 1(PD-1), Programmed cell death-Ligand 1(PD-L1) and Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody [2]. Despite of encouraging results from clinical trials, a considerable proportion of patients fail to obtain clinical benefits from these drugs. For instance, only 20–40% of cancer patients are estimated to benefit from anti-PD-1/PD-L1 antibody [3]. Recent clinical investigations have discovered

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numerous factors affecting ICI efficacy such as tumor mutational burden, circulating tumor DNA, immune-related adverse events and antibiotic administration [4–7]. However, that is far from sufficiency and more efforts are needed to identify and validate reliable predictors for ICI efficacy, which will undoubtedly benefit the tailored decision making for cancer patients.

In the clinical management of cancer patients, corticosteroids are frequently used in alleviating cancer related symptoms such as fatigue, pain and dyspnea [8,9]. In addition, corticosteroid administration are recommended to ameliorate chemotherapy-induced nausea and vomiting [10]. On the same line, corticosteroid administration combined with abiraterone acetate had been found to lead significant improvement in the clinical outcome of chemotherapy-naive prostate cancer patients [11]. Despite of its crucial role in cancer treatment, emerging studies have proposed controversial viewpoints regarding corticosteroid administration in cancer patients treated with ICI therapy. For instance, a recent study has demonstrated that corticosteroid administration for cancer-related indications is a risk factor of disease progression and death in patients treated with PD-1/PD-L1 inhibitors, while another study has found no significant correlation between that and overall survival (OS) in pembrolizumab monotherapy treated non-small cell lung cancer (NSCLC) patients with brain metastases [12,13]. With regard to ICI related adverse events, Martin et al have found corticosteroid administration was correlated with worse progression-free survival (PFS) in nivolumab-treated NSCLC patients, while Shafqat et al have reported an opposite result in PD-1/PD-L1 inhibitor-treated patients with various cancer types [14,15]. Therefore, much more efforts are still needed to further clarify the prognostic significance of corticosteroid administration in cancer patients receiving ICI therapy.

For achieving this goal, in this study, a meta-analysis enrolling 32 clinical studies was firstly performed to investigate the actual impact of corticosteroid administration on cancer patients receiving ICI therapy. Then, an independent cohort enrolling 118 ICI-treated cancer patients was utilized to validate the results of the meta-analysis. This study will not only contribute to the individualized corticosteroid management during ICI therapy, but further highlight the nonnegligible impact of concomitant medications on the efficacy of ICI drugs.

2. Materials and methods

2.1. Search strategy for meta-analysis

As shown in Fig. 1A, the systematic literature search was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The relevant literatures that focus on the prognostic significance of corticosteroid administration in solid cancer patients receiving ICI treatment, were searched online using PubMed, Cochrane Library, Web of Science, Embase, and Clinicaltrials.gov (up to January 1th, 2021). The key words for search strategy include "steroids", "corticosteroids", "immune checkpoint inhibitor (ICI)", "Programmed cell death (Ligand) 1 (PD-1(PD-L1))", "cytotoxic T lymphocyte antigen 4 (CTLA-4)", "cancer", "tumor", "malignancy", "neoplasm" and "prognosis". The references of original articles and reviews were carefully screened for identifying additional eligible studies that may be missed in the initial search phase.

2.2. Inclusion and exclusion criteria for meta-analysis

The inclusion criteria for meta-analysis are as follows: (1) clinical studies focusing on the prognostic significance of corticosteroid administration in ICI-treated solid cancer patients; (2) therapeutical strategies including anti-PD-(L)1/CTLA-4 alone or combined with other anti-cancer approaches; (3) available Hazard ratios (HRs) for OS/PFS with 95% confidence intervals (CIs). The exclusion criteria for meta-analysis are as follows: (1) irrelevant topics or reviews; (2) lack of control group; (3) animal experiments; (4) insufficient prognostic information; (5) repetitive publication or data.

2.3. Data extraction and quality assessment for meta-analysis

The article information such as author, publication year, country, cancer type, sample size, median age, therapeutic strategy, corticosteroid type, reasons for corticosteroid administration and prognostic information were extracted and details were shown in Table 1 and Table 2. For prognostic information, the results of multivariate analysis were preferentially extracted. In case that HRs or 95 %CIs are unavailable, the data were calculated using the method described in previous studies [16,17]. The paper quality was assessed using the Nottingham-Ottawa-Scale (NOS) and Cochrane Risk of Bias tool [18,19]. A NOS score no less

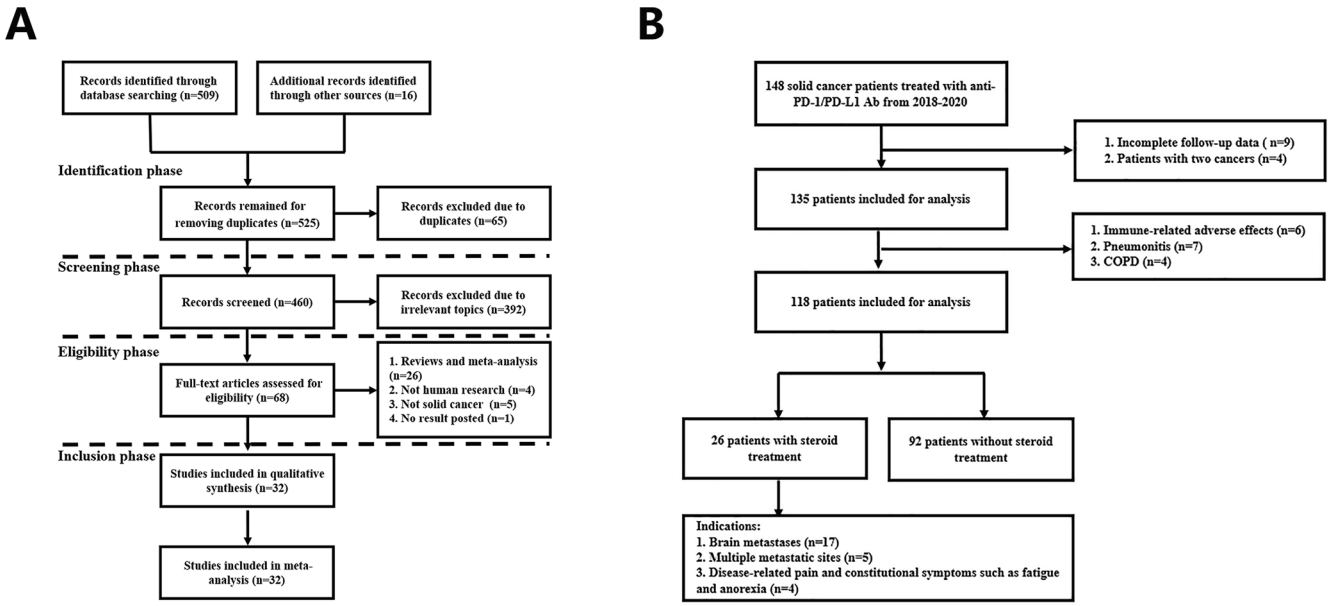

Fig. 1. Flowcharts of the literature search (A) and independent retrospective study (B).

Table 1
General information of the included studies in meta-analysis.

Author year	Region	Cancer type	Sample size	Age	Immunotherapy	Corticosteroid exposure	Corticosteroid Type	Reason for corticosteroid use
Adachi 2020	Japan	NSCLC	296	70	PD-1	Within	NA	Cancer/non-cancer indications etc.
Buti 2020	Italy	Mix	217	69	ICI	Prior	prednisone	Cancer/non-cancer indications etc.
Cortellini-1 2020	Italy (Multicenter)	Mix	1012	68.5	PD-1/PD- L1	Prior	prednisone	Non-cancer indications
Cortellini-2 2020								Cancer indications
De Giglio-1 2020	France	NSCLC	413	63	ICI + Other	Within	prednisone	Non-cancer indications
De Giglio-2 2020								Cancer indications
Drakaki-NSCLC 2020	America (Multicenter)	NSCLC	862	69	PD-1/PD- L1	Prior, Within	Dexamethasone prednisone	Cancer/non-cancer indications etc.
Drakaki-Mel 2020		Mel	742	69				
Drakaki-UC 2020		UC	609	74				
Gauci 2020	France	Mel	339	52	ICI	NA	NA	irAEs
Martin 2020	Argentina (Multicenter)	NSCLC	109	65	PD-1	Within	NA	irAEs
Metro 2020	Europe (Multicenter)	NSCLC	282	69	Pembrolizumab	Prior	prednisone	Cancer/non-cancer indications etc.
Metro-BM 2020	Europe (Multicenter)	NSCLC		65	Pembrolizumab	Prior	prednisone	BM
Mountzios 2020	Europe (Multicenter)	NSCLC	265	66.7	Pembrolizumab	Prior, Within	Dexamethasone prednisone	Cancer/non-cancer indications etc.
Vitale 2020	Italy (Multicenter)	RCC	167	66.8	Nivolumab	Within	NA	irAEs
Pinato-1 2020	Global	HCC	304	NA	ICI + Other	Prior ,Within	prednisone	Non-cancer indications
Pinato-2 2020	(Multicenter)			NA	ICI + Other		prednisone	Cancer indications
Riudavets-1 2020	Spain (Multicenter))	NSCLC	267	66.4	ICI + Other	Prior, Within	Dexamethasone prednisone	irAEs
Riudavets-2 2020		NSCLC		66.1	ICI + Other	Prior, Within		Cancer indications
Spakowicz 2020	America	Mix	690	62.27	ICI	Within	Dexamethasone prednisone	Cancer/non-cancer indications etc.
Svaton 2020	Czech	NSCLC	224	67	Nivolumab	Prior, Within	prednisone	Cancer/non-cancer indications etc.
Thompson 2020	America	Mix	90	61	ICI	Within	NA	irAEs
Tozuka 2020	Japan	NSCLC	197	66.5	PD-1/PD- L1	Within	prednisone	BM
Tamiya 2019	Japan (Multicenter)	NSCLC	213	71	Pembrolizumab	Within	prednisone	Cancer/non-cancer indications etc.
Sukari 2019	America	Mix	168	63	PD-1	Within	NA	irAEs
Ricciuti-1 2019	America	NSCLC	650	70	ICI	Within	prednisone	Non-cancer indications
Ricciuti-2 2019				65	ICI	Within	prednisone	Cancer indications
Hendriks 2019	Europe (Multicenter)	NSCLC	1025	64.3	ICI	Within	prednisolone	Cancer indications
Fucà 2019	France	NSCLC	151	NA	ICI	Within	prednisolone	Cancer/non-cancer indications etc.
Arbour 2018	Global (Multicenter))	NSCLC	640	63.5	PD-1/PD- L1	Within	prednisone	Cancer indications
Dumenil 2018	France (Multicenter)	NSCLC	67	68.5	Nivolumab	Within	NA	Cancer indications
Shafqat 2018	America	Mix	157	65	PD-1/PD- L1	Within	prednisone	irAEs
Scott 2018	America	NSCLC	210	67.5	Nivolumab	Within	prednisone	Cancer/non-cancer indications etc.
Faje 2018	America	Mel	64	65.6	CTLA-4	Within	prednisone	irAEs
Taniguchi 2017	Japan (Multicenter)	NSCLC	201	68	Nivolumab	Within	prednisolone	Cancer/non-cancer indications etc.
Zaragoza 2016	France (Multicenter)	Mel	58	54.7	CTLA-4	Prior	NA	Cancer indications
Chasset 2015	France	Mel	45	59	CTLA-4	Within	Prednisone Methylprednisolone	Cancer indications
Johnson 2015	America	Mel	33	60	CTLA-4	Within	Hydrocortisone	irAEs
Horvat 2015	America	Mel	298	65	CTLA-4	Within	NA	irAEs
Weber 2009	NA (Multicenter)	Mel	115	58	CTLA-4	Within	Budesonide	irAEs

Abbreviations: NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; UC, urothelial carcinoma; Mel, melanoma; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor, CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4, PD-1, programmed cell death protein-1; PD-L1, programmed cell Death-Ligand 1; IrAEs, immune-related adverse events; NA, not available.

Table 2
Prognostic information and quality assessment of included studies.

Author, year	Method	Outcome	PFS Hazard ratios (95 %CI)	OS Hazard ratios (95 %CI)	Analysis	NOS score/Risk of Bias
Adachi 2020	RE	PFS/OS	2.57 (1.65–4.01)	2.00 (1.26–3.17)	M	7
Buti 2020	RE	PFS/OS	2.09 (1.58–2.77)	2.30 (1.60–3.30)	U	6
Cortellini-1 2020	RE	PFS/OS	0.96 (0.68–1.36)	0.85 (0.54–1.31)	M	8
Cortellini-2 2020	RE	PFS/OS	1.72 (1.43–2.07)	2.16 (1.76–2.65)	M	8
De Giglio-1 2020	RE	PFS/OS	1.00 (0.51–1.98)	1.49 (0.50–4.46)	M	7
De Giglio-2 2020	RE	PFS/OS	2.64 (1.24–5.61)	4.53 (1.84–11.12)	M	7
Drakaki-NSCLC 2020	RE	OS	NA	1.34 (1.12–1.61)	M	8
Drakaki-Mel 2020	RE	OS	NA	1.24 (0.97–1.57)	M	8
Drakaki-UC 2020	RE	OS	NA	1.44 (1.12–1.87)	M	8
Gauci 2020	RE	OS	NA	1.69 (0.58–4.94)	NA	6
Martin 2020	RE	PFS	2.06 (1.22–3.48)	NA	M	8
Metro 2020	RE	OS	NA	2.65 (1.64–4.26)	M	8
Metro-BM 2020	RE	OS	NA	0.78 (0.16–3.67)	M	8
Mountzios 2020	RE	OS	1.864 (1.179–2.949)	2.292 (1.441–3.644)	M	8
Vitale 2020	RE	PFS/OS	0.66 (0.36–1.22)	0.58 (0.26–1.29)	M	8
Pinato-1 2020	RE	PFS/OS	0.6 (0.3–1.0)	0.4 (0.2–0.9)	M	8
Pinato-2 2020	RE	PFS/OS	4.4 (1.7–11.1)	2.1 (0.9–5.3)	M	8
Riudavets-1 2020	RE	PFS/OS	NA	1.81 (0.57–5.74)	NA	6
Riudavets-2 2020	RE	PFS/OS	NA	2.28 (1.63–3.20)	NA	6
Spakowicz 2020	RE	OS	NA	1.21 (1.08–1.30)	NA	5
Svaton 2020	RE	PFS/OS	1.07 (0.58–1.99)	1.36 (0.63–2.91)	M	7
Thompson 2020	RE	PFS/OS	2.54 (1.11–5.80)	1.62 (0.56–4.70)	M	7
Tozuka 2020	RE	PFS/OS	4.06 (1.61–10.23)	2.96 (1.06–8.25)	M	7
Tamiya 2019	RE	PFS	2.94 (1.45–5.95)	NA	M	8
Sukari 2019	RE	OS	NA	0.81 (0.51–1.30)	M	7
Ricciuti-1 2019	RE	PFS/OS	0.62 (0.33–1.17)	0.91 (0.47–1.79)	M	7
Ricciuti-2 2019	RE	PFS/OS	1.40 (0.98–2.00)	1.60 (1.07–2.39)	M	7
Hendriks 2019	RE	PFS/OS	1.31 (1.07–1.62)	1.46 (1.16–1.84)	M	8
Fucà 2019	RE	PFS/OS	0.86 (0.61–1.21)	1.18 (0.79–1.75)	M	6
Arbour 2018	RE	PFS/OS	1.31 (1.03–1.67)	1.66 (1.28–2.16)	M	8
Dumenil 2018	RE	PFS/OS	3.27 (1.39–7.69)	1.31 (0.51–3.38)	M	8
Shafqat 2018	RE	PFS	0.383 (0.160–0.918)	NA	M	7
Scott 2018	RE	OS	NA	2.3 (1.27–4.16)	M	7
Faje 2018	RE	PFS/OS	2.78 (1.30–7.14)	4.17 (1.61–14.29)	M	7
Taniguchi 2017	RE	PFS	2.37 (1.44–3.74)	NA	M	8
Zaragoza 2016	RE	OS	NA	1.28 (0.54–3.06)	M	8
Chasset 2015	RE	OS	NA	5.82 (2.45–13.8)	U	6
Johnson 2015	RE	OS	NA	1.12 (0.19–6.93)	NA	6
Horvat 2015	RE	OS	NA	1.02 (0.74–1.41)	NA	6
Weber 2009	Randomized	OS	NA	1.06 (0.66–1.70)	NA	Low risk

Abbreviations: RE, retrospective; PFS, progression-free survival; OS, overall survival; NA, not available; U, univariate; M, multivariate.

than six indicates a high-quality study.

2.4. Patient data for clinical validation

A retrospective cohort was utilized for validating the results of the meta-analysis and the study design was shown in Fig. 1B. A total of 148 patients with advanced solid cancers were initially enrolled in the department of oncology, Affiliated Hospital of Yangzhou University, from 2018 to 2020. All the patients were treated with PD-(L)1 inhibitors. After excluding patients with incomplete follow-up data (n = 9), multiple primary tumors (n = 4), corticosteroids administration for immune-related adverse effects (n = 6), pneumonitis (n = 7) and COPD (n = 4), a total of 118 patients were finally included for retrospective analysis. The clinical information of the patients were provided in Table 5. The corticosteroids were administrated within 60 days before or after ICI initiation. For prognostic evaluation, OS and PFS were used where OS was defined as the interval from ICI initiation to death caused by any reasons and PFS was defined as the interval from ICI initiation to disease progression. This study was approved by the ethics committees of Affiliated Hospital of Yangzhou University. Written informed consents were obtained from patients for using their clinical information in scientific investigations.

2.5. Statistical analysis

The meta-analysis was performed using Stata SE14.0 software. Cochran Q test and Higgins inconsistency index (I^2) were used for heterogeneity evaluation. $P < 0.05$ and $I^2 > 50\%$ indicate existing heterogeneity and a random effect model was selected for data analysis, while $P > 0.05$ and $I^2 < 50\%$ indicate no significant heterogeneity and a fixed-effect model was selected accordingly. The stability of results was assessed using sensitivity analysis and publication bias was assessed using Begg's and Egger's test. For clinical validation, all the statistical analysis were performed using SPSS 21.0 statistical software. The correlations of corticosteroid administration with clinical features were assessed using chi-squared test. The survival curves were constructed using Kaplan-Meier model and intergroup difference was analyzed using log-rank test. Independent prognostic factors were identified using univariate and multivariate analysis based on Cox proportional hazards regression model. A P value less than 0.05 indicates statistically significant.

3. Results

3.1. Characteristics and quality evaluation of included studies in the meta-analysis

As shown in Fig. 1A, a total of 525 candidate literatures were firstly obtained from web databases and other sources. Then, 65 and 392 literatures were excluded due to repetition and irrelevant topics respectively. In the eligibility phase, additional 36 literatures were excluded due to reviews/meta-analysis (n = 26), nonclinical researches (n = 4),

nonsolid cancer (n = 5) and unavailable results (n = 1). Finally, a total of 32 literatures were included in our meta-analysis and related details were provided in Table 1 [12–15,20–47]. Majority of the included studies were published between January 2018 and December 2020, and are mainly related with NSCLC and melanoma. Most patients received corticosteroids after ICI initiation and prednisone was the most frequently used drug type. The main reasons for corticosteroid administration included cancer/non-cancer indications, brain metastases and immunotherapy related adverse events.

The prognostic information and quality evaluation of included studies were provided in Table 2. Only one study was a randomized controlled trial while the others were retrospective investigations. The HRs (95 %CI) of PFS/OS were calculated by univariate or multivariate analysis in 26 studies. Using NOS scores, only one study was found to have a NOS score of five. In addition, Cochrane Risk of Bias tool revealed low risk for the randomized controlled study.

3.2. Prognostic significance of corticosteroid administration in the meta-analysis

As shown in Fig. 2A and B, as a whole, corticosteroid administration was significantly correlated with worse PFS (HR = 1.51(1.25–1.82), random-effect model) and OS (HR = 1.51(1.33–1.73), random-effect model). In the subgroup analysis based on therapeutic purposes, no significant correlations were found between corticosteroid administration for non-cancer-related indications and PFS/OS (PFS: HR = 0.830 (0.645–1.067); OS: HR = 0.786(0.512–1.206)). However, for cancer-related indications, the negative correlation of corticosteroid administration with PFS and OS was significant (PFS: HR = 1.735(1.381–2.180); OS: HR = 1.936(1.587–2.361)). With regard to immune-related adverse events (irAEs), no significant correlation was observed between corticosteroid administration and PFS/OS (PFS: HR = 1.302(0.628–2.696); OS: HR = 1.107(0.832–1.474)).

As shown in Fig. 3A and B, the sensitive analysis demonstrated both the pooled HRs of PFS and OS were unable to be significantly affected by any single study, supporting the reliability of our results. For evaluating the potential publication bias, the Begg's (Fig. 3C and D) and Egger's test were performed. As a result, both the tests suggested there was no publication bias affecting the significant correlation of corticosteroid administration with PFS (Begg's test: P = 0.298; Egger's test: P = 0.706) or OS (Begg's test: P = 0.806; Egger's test: P = 0.176).

3.3. Subgroup analysis based on clinical features

For further investigating the prognostic significance of corticosteroid administration in patients receiving ICIs, subgroup analysis was performed based on various clinical features including cancer type, sample size, age, therapeutic strategies and timeframes of corticosteroid administration (Tables 3 and 4). For cancer type, this correlation with PFS was only significant in NSCLC (HR = 1.607(1.291–2.000)), while that with OS was significant in NSCLC (HR = 1.703(1.467–1.978)) and melanoma (HR = 1.518(1.064–2.164)). For sample size, corticosteroid administration was significantly correlated with worse PFS (HR = 1.521 (1.254–1.845)) and OS (HR = 1.555(1.350–1.790)) in studies with sample size more than 200. For patient age, this correlation with PFS ((>65: HR = 1.707(1.315–2.215), ≤65: HR = 1.395(1.094–1.780)) or OS (>65: HR = 1.672(1.394–2.006), ≤65: HR = 1.401(1.166–1.683)) was both significant in patients older and younger than 65 years. For therapeutic strategy, the unfavourable impact of corticosteroid administration on PFS could be observed in patients receiving PD-1/PD-L1 (HR = 1.600(1.240–2.064)) and CTLA-4 (HR = 2.780 (1.300–7.140)) inhibitors, while that on OS was observed in patients receiving PD-1/PD-L1 inhibitors (HR = 1.509(1.256–1.813)) and ICIs (HR = 1.423 (1.178–1.718)). Finally, for the timeframes, corticosteroid administration both prior to and within ICI therapy was significantly correlated with worse PFS (prior to: HR = 1.538(1.052–2.250); within: HR = 1.539 (1.209–1.960)) and OS (prior to: HR = 1.707(1.175–2.481); within: HR = 1.454(1.224–1.728)).

3.4. Independent clinical validation for the meta-analysis

For validating the results of the meta-analysis, an independent cohort enrolling 118 ICI-treated cancer patients was utilized, among which 26 patients received corticosteroids for cancer-related indications

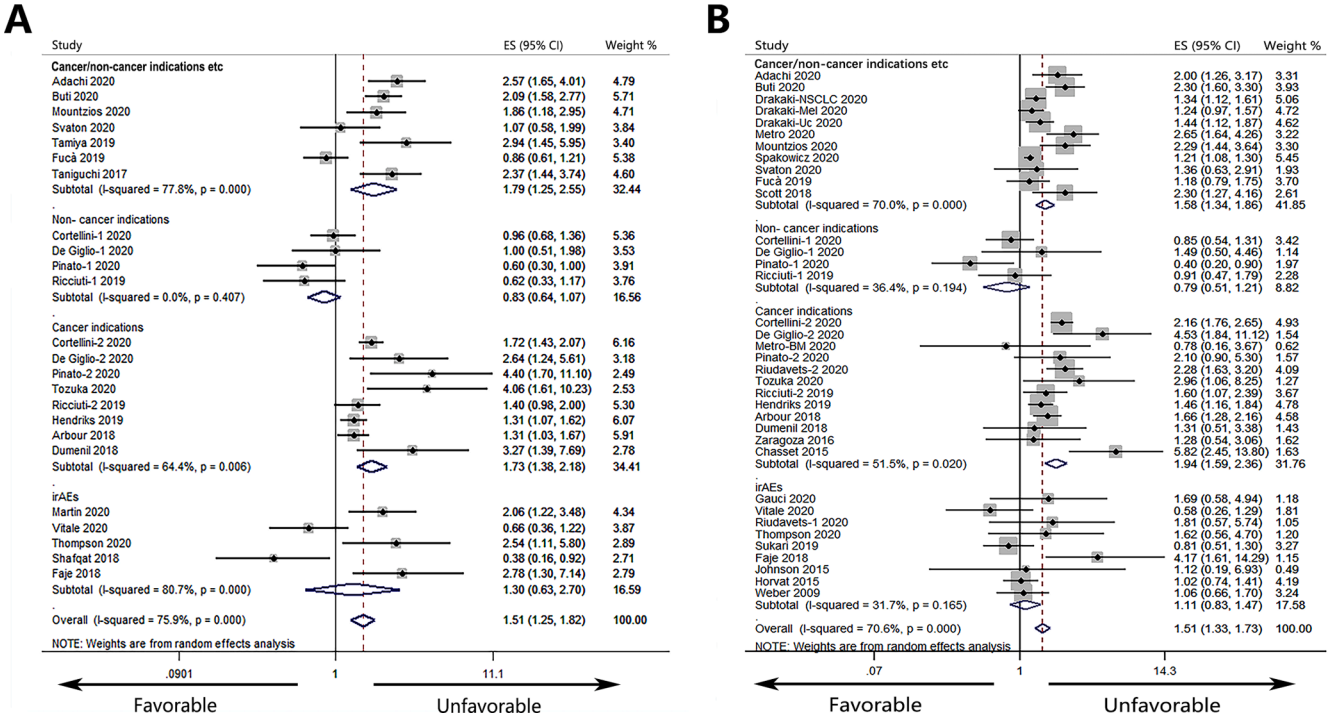

Fig. 2. Forest plots of HRs for the correlations of corticosteroid administration with progression-free survival (A) and overall survival (B).

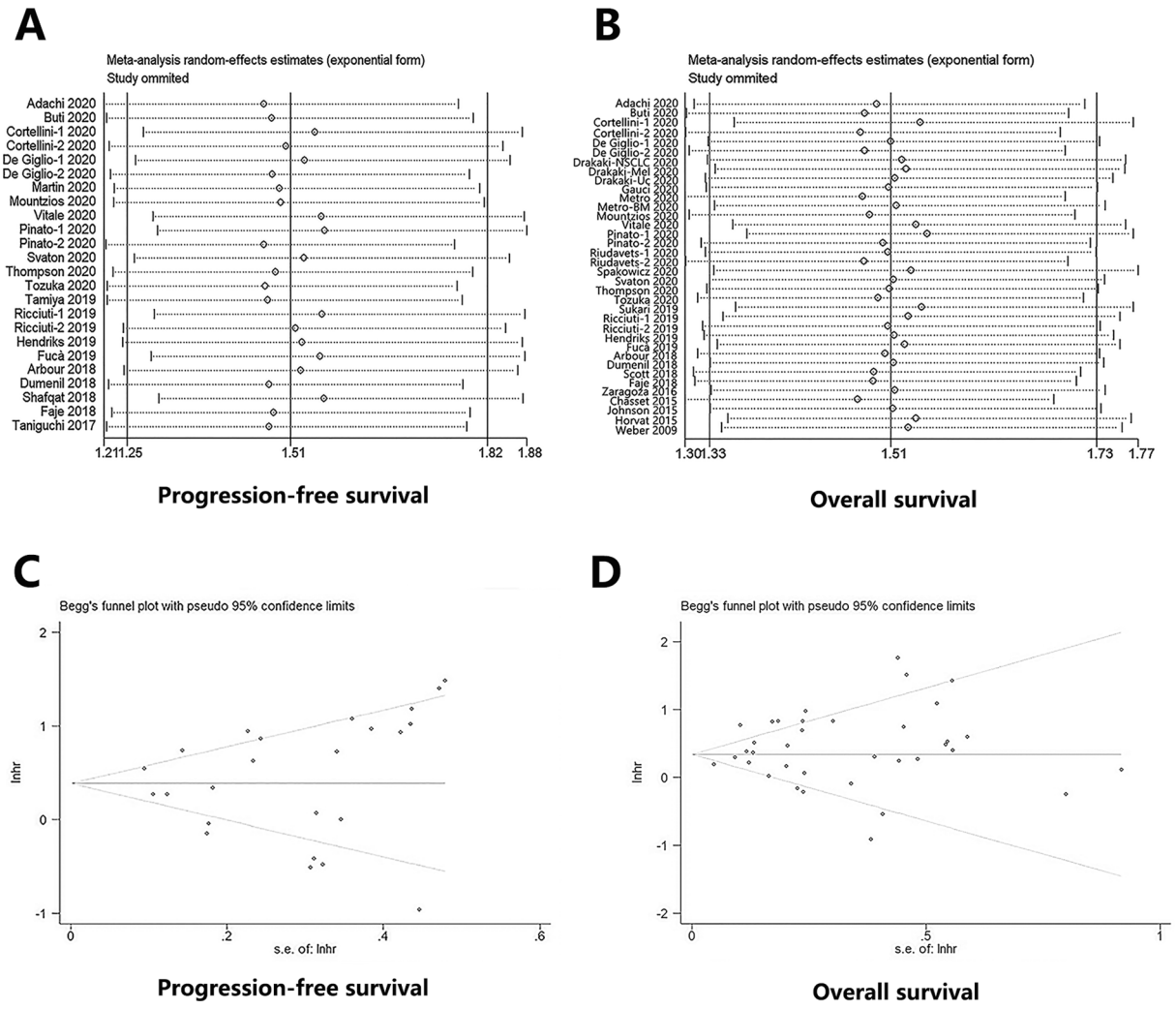

Fig. 3. Sensitivity analysis and publication bias. (A) Sensitivity analysis of the studies assessing progression-free survival (PFS). (B) Sensitivity analysis of the studies assessing overall survival (OS). (C) Begg's funnel plots for evaluating publication bias of PFS. (D) Begg's funnel plots for evaluating publication bias of OS.

Table 3
Subgroup analysis for the association of corticosteroid administration with progression-free survival.

Subgroup	Hazard ratios (95% CI)	P value	Heterogeneity		Publication bias	
			P value	I^2	Begg's test	Egg's test
Cancer type						
NSCLC	1.607 (1.291–2.000)	<0.001	<0.001	70.5%	0.102	0.103
Mix	1.376 (0.910–2.081)	0.130	<0.001	83.3%	0.142	0.448
Other	1.403 (0.553–3.561)	0.476	<0.001	84.6%	0.042	<0.001
Sample Size						
≥200	1.521 (1.254–1.845)	<0.001	<0.001	73.4%	0.653	0.898
<200	1.540 (0.901–2.632)	0.115	<0.001	80.9%	0.048	0.146
Age						
>65	1.707 (1.315–2.215)	<0.001	<0.001	75.1%	0.464	0.880
≤65	1.395 (1.094–1.780)	0.007	0.020	58.1%	0.621	0.813
Therapeutic strategy						
PD-1/PD- L1	1.600 (1.240–2.064)	<0.001	<0.001	75.6%	0.542	0.834
ICI	1.304 (0.939–1.812)	0.113	<0.001	79.3%	0.851	0.785
ICI+Other	1.551 (0.655–3.676)	0.319	<0.001	82.1%	0.042	0.047
CTLA-4	2.780 (1.300–7.140)	0.019	/	/		
Corticosteroid time						
Prior	1.538 (1.052–2.250)	0.026	0.002	83.7%	0.602	0.645
Prior, Within	1.437 (0.706–2.925)	0.317	<0.001	74.8%	0.249	0.764
Within	1.539 (1.209–1.960)	<0.001	<0.001	75.1%	0.497	0.284

Abbreviations: NSCLC, non-small cell lung carcinoma; ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4; PD-1, programmed cell death protein-1; PD-L1, programmed cell Death-Ligand 1.

Table 4
Subgroup analysis for the association of corticosteroid administration with overall survival.

Subgroup	Hazard ratios (95% CI)	P value	Heterogeneity		Publication bias	
			P value	I^2	Begg's test	Egg's test
Cancer type						
NSCLC	1.703 (1.467–1.978)	<0.001	0.025	43.8%	0.677	0.217
Mix	1.384 (0.976–1.963)	0.068	<0.001	88.3%	0.851	0.738
Mel	1.518 (1.064–2.164)	0.021	0.008	63.4%	0.216	0.162
Other	0.933 (0.460–1.889)	0.847	0.002	79.7%	1.000	0.420
Sample Size						
≥200	1.555 (1.350–1.790)	<0.001	<0.001	73.5%	1.000	0.153
<200	1.444 (0.991–2.105)	0.056	0.002	63.2%	0.073	0.145
Age						
>65	1.672 (1.394–2.006)	<0.001	<0.001	69.2%	0.970	0.691
≤65	1.401 (1.166–1.683)	<0.001	0.002	59.0%	0.882	0.214
Therapeutic strategy						
PD-1/PD- L1	1.509 (1.256–1.813)	<0.001	<0.001	69.7%	1.000	0.761
ICI	1.423 (1.178–1.718)	<0.001	0.030	54.9%	1.000	0.259
ICI+Other	1.682 (0.872–3.245)	0.121	0.001	76.7%	0.851	0.665
CTLA-4	1.726 (0.979–3.042)	0.059	0.002	73.4%	0.348	0.185
Corticosteroid time						
Prior	1.707 (1.175–2.481)	0.005	0.002	73.8%	0.188	0.344
Prior, Within	1.469 (1.159–1.862)	0.001	0.002	68.1%	0.330	0.097
Within	1.454 (1.224–1.728)	<0.001	<0.001	63.9%	0.532	0.860

Abbreviations: Mel, melanoma; NSCLC, non-small cell lung carcinoma; ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4; PD-1, programmed cell death protein-1; PD-L1, programmed cell Death-Ligand 1.

Table 5
The basic clinical features of the validation cohort.

Characteristic	Subgroup	Number	No-corticosteroid	Corticosteroid	P value
Gender					0.429
	Male	60	45	15	
	Female	58	47	11	
Age					0.175
	≤65	50	42	8	
	>65	68	50	18	
Cancer type					0.590
	NSCLC	65	49	16	
	Esophageal	21	16	5	
	Others	32	27	5	
ECOG					0.258
	0–1	103	82	21	
	≥2	15	10	5	
Brain metastases					0.048
	No	61	52	9	
	Yes	57	40	17	
Therapy type					0.452
	Monotherapy	79	60	19	
	Combination	39	32	7	

Abbreviations: NSCLC, non-small cell lung carcinoma; ECOG, Eastern Cooperative Oncology Group.

(Fig. 1B). The basic clinical features of the cohort were provided in Table 5. There were no significant differences between corticosteroid group and non-corticosteroid group in gender (P = 0.429), age (P = 0.175), cancer type (P = 0.590), ECOG scores (P = 0.258) and ICI therapy (P = 0.452). Using Kaplan-Meier model (Fig. 4A and B), corticosteroid administration was found to be significantly associated with worse OS (P = 0.02) and PFS (P = 0.002). In the univariate analysis (Fig. 4C and D), both brain metastases and corticosteroid administration were significantly correlated with OS (P = 0.001 and P = 0.027), while age and corticosteroid administration were with PFS (P = 0.028 and P = 0.003). In the multivariate analysis (Fig. 4E and F), both brain metastases and corticosteroid administration were identified as independent prognostic factors for OS (P < 0.001 and P = 0.044), while only corticosteroid administration was for PFS (P = 0.006).

Since 55% (65/118) of the enrolled patients were diagnosed as NSCLC, we next made efforts to investigate the prognostic significance of corticosteroid administration in ICI-treated NSCLC patients. As shown in Fig. 5A and B, patients receiving corticosteroids had a significantly worse OS and PFS than those did not (P = 0.015 and P = 0.0003). In the univariate analysis (Fig. 5C and D), brain metastases and corticosteroid administration were significantly correlated with OS (P = 0.013 and P = 0.019, Fig. 5C), while only corticosteroid administration was with PFS (P = 0.001, Fig. 5D). In the multivariate analysis (Fig. 5E and F), brain metastases and corticosteroid administration were identified as independent prognostic factors for OS (P = 0.008 and P = 0.047), while only corticosteroid administration was for PFS (P = 0.002).

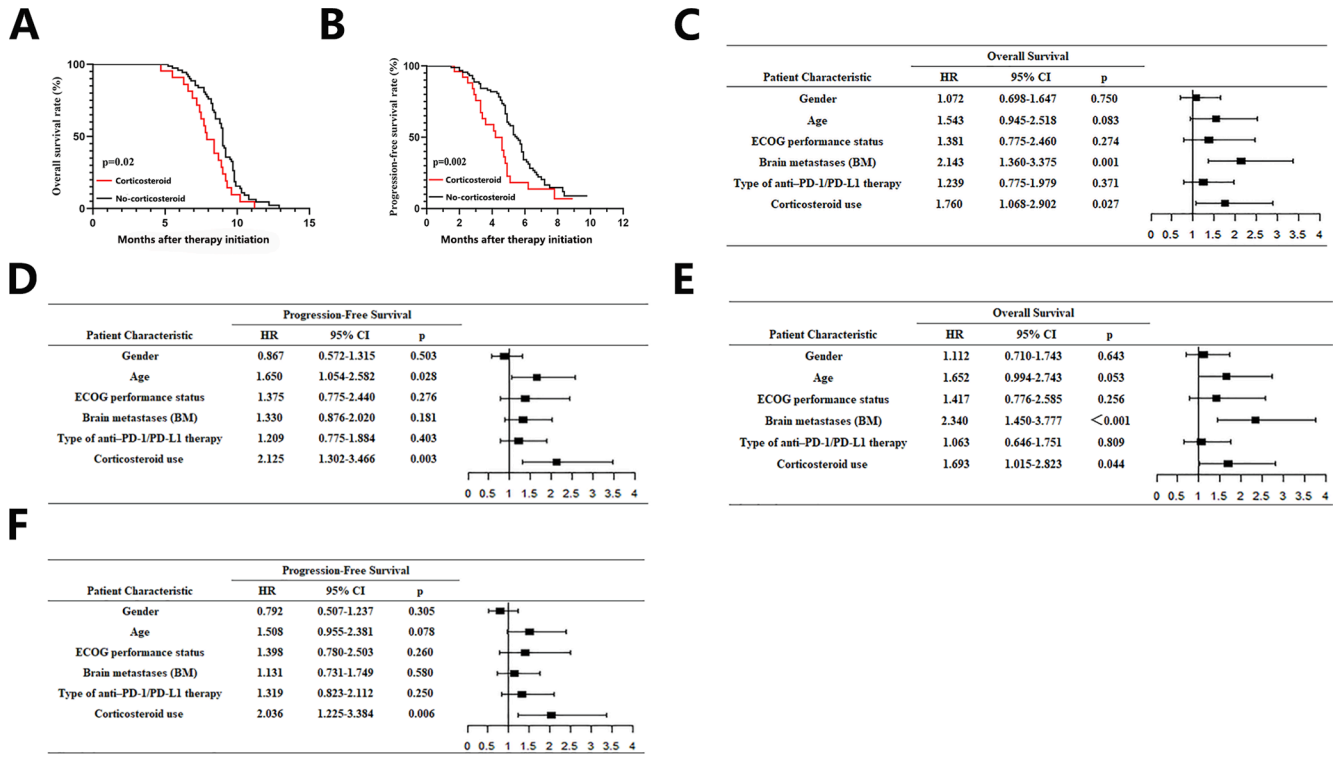

Fig. 4. Clinical validation for the whole clinical cohort. (A-B) Kaplan-Meier curves for the association of corticosteroid administration with overall survival (OS) (A) and progression-free survival (PFS) (B). (C-D) Univariate analysis to identify significant prognostic factors for OS (C) and PFS (D). (E-F) Multivariate analysis to identify independent prognostic factors for OS (E) and PFS (F).

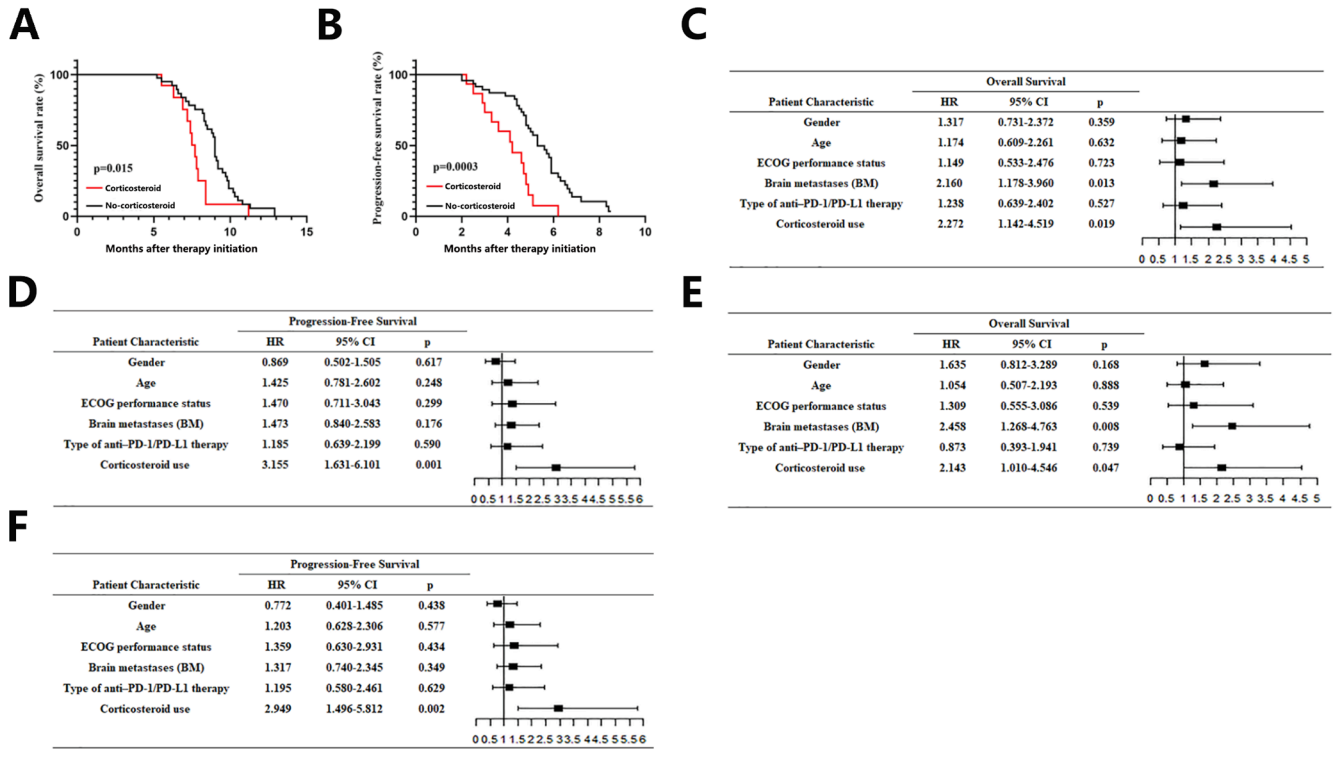

Fig. 5. Subgroup analysis for NSCLC patients. (A-B) Kaplan-Meier curves for the association of corticosteroid administration with overall survival (OS) (A) and progression-free survival (PFS) (B) in NSCLC patients. (C-D) Univariate analysis to identify significant prognostic factors for OS (C) and PFS (D) in NSCLC patients. (E-F) Multivariate analysis to identify independent prognostic factors for OS (E) and PFS (F) in NSCLC patients.

4. Discussion

The cancer immunotherapies targeting PD-1/PD-L1 or CTLA-4 have dramatically revolutionized the current anti-cancer approaches and achieved durable clinical benefits in various human malignancies. However, numerous inherent and extrinsic factors are found to limit their actual efficacy. For instance, impaired T cell activation was correlated with the acquired resistance to PD-1/PD-L1 inhibitors in patients with NSCLC [48]. In addition, accumulating evidences have suggested gut microbiota modulates the efficacy of ICIs, and our previous work has indicated antibiotic administration that diminished gut microbiota was an unfavourable prognostic factor for patients receiving ICI therapy [7,49]. In this study, we made an effort to clarify the prognostic significance of corticosteroid administration in ICI-treated cancer patients, although we have noted a similar study by Petrelli et al was published last year [50]. Compared with that study, we concluded several novel points as follows: (1) Our study included much more studies (n = 32 for 11,180 patients vs. n = 16 for 4045 patients), especially collecting more literatures published in 2020 (n = 16); (2) Our study additionally analyzed the prognostic significance of corticosteroid administration for various purposes including cancer/non-cancer indications and irAEs, therefore benefiting more precise administration of corticosteroids in clinical practice; (3) An independent retrospective cohort was utilized for validation, directly strengthening our meta-analysis. Therefore, our present study may provide some novel insights into the role of corticosteroid administration during ICI therapy and contribute to the individualized decision-making by clinicians.

In this study, as a whole, we firstly found that corticosteroid administration was significantly correlated with worse PFS and OS in cancer patients receiving ICI therapy. The following analysis of sensitivity and publication bias further confirmed the reliability of the results, implying that corticosteroids may be cautiously considered during or before ICI therapy. For further clarifying the correlation between corticosteroid administration and ICI efficacy, subgroup analysis was performed based on therapeutic purposes. First, we found the correlation of corticosteroid administration with PFS/OS was not statistically significant in patients receiving corticosteroid for non-cancer indications such as COPD and inflammation, which is consistent with all the four included studies [12,27,31,38]. In addition, a recent evidence-based investigation has advocated that the detrimental prognostic impact of corticosteroids for non-palliative intents is negligible in ICI-treated patients, firmly supporting our finding [51]. Second, although a similar result was observed in patients receiving corticosteroids for irAEs, significant differences were existing among the included studies. For instance, corticosteroid administration for ipilimumab-induced hypophysitis was correlated with reduced PFS in patients with melanoma, while it was opposite for another retrospective analysis enrolling 157 patients with various cancers [15,42]. A recent mechanism investigation revealed prednisone treatment was unable to affect expressions of ICI inhibitory receptors, T cell proliferation and PD-1/PDL-1 interaction [52]. This study also provides a case report of a patient with metastatic melanoma who received steroid treatment for ICI-induced irAEs and had a favorable anti-cancer immune response, partly suggesting corticosteroids for irAEs may not diminish the clinical efficacy of ICI drugs. On the other hand, considering inherent immune heterogeneity among various cancers, more clinical validations regarding other cancers in addition to melanoma are urgently needed. Finally, we observed corticosteroid administration for cancer-related indications was significantly correlated with worse PFS and OS, which was in accordance with the results of most included studies. To our knowledge, several following potential mechanisms may be concluded for explaining this finding. First, corticosteroid administration may inhibit the proliferation of CD8-positive T cells to induce the resistance to PD-1/PD-L1 inhibitors [45]. Using mice bearing colon adenocarcinoma MC38 flank tumors, researchers also found dexamethasone treatment diminished the efficacy of anti-PD-1 therapy through altering peripheral CD8/Treg ratio [53]. Second, dexamethasone treatment was proved to upregulate PD-1 expression, impair T cell function and induce T cell apoptosis [54]. Third, in clinical practice, corticosteroid administration for cancer indications may exert its adverse prognostic impact through its association with several poor prognostic features such as rapid disease progression and serious cancer-related symptoms rather than directly diminishing the ICI efficacy [27]. Taken together, we concluded that corticosteroid administration for cancer indications instead of non-cancer indications and irAEs was an unfavourable prognostic predictor in solid cancer patients receiving ICI treatment.

Next, we also performed subgroup analysis based on various clinical features. First, in cancer types, it was worth noting that corticosteroid administration was significantly correlated with worse PFS and OS in patients with NSCLC. A recent study has demonstrated corticosteroid administration for palliative treatment instead of irAEs was an independent factor for predicting poor OS in patients with advanced NSCLC [55]. Since corticosteroids were very frequently administrated for various indications in NSCLC patients, therefore selecting candidates for ICI therapy should be particularly careful in these patients. Then, we found the negative correlation of corticosteroid administration with PFS and OS was only significant in studies with sample sizes more than 200, suggesting the crucial role of sample size in determining the prognostic factors in ICI-treated patients. With regard to patient age, corticosteroid administration was significantly associated with worse outcome in patients both older and younger than 65 years, indicating that its unfavorable prognostic impact should be considered across the age range. In terms of therapeutic strategy, corticosteroid administration was significantly correlated with worse PFS and OS in patients receiving anti-PD1/PD-L1 treatment, suggesting that its potential detrimental impact on the efficacy of these drugs. Finally, since we noted that the timeframes of corticosteroid administration varied among some studies, therefore we performed subgroup analysis based on defined time frames [13,20,32,33]. We found its negative correlation with PFS and OS was significant in patients receiving corticosteroids both prior to and within ICI therapy, indicating that timeframes may be unrelated with its prognostic impact.

For validating the results of our meta-analysis, we additionally performed an independent retrospective analysis enrolling 118 ICI-treated cancer patients. As a result, we found corticosteroid administration for cancer-related indications was a significantly independent factor for predicting poor PFS and OS. In the subgroup analysis based on NSCLC, we observed the similar results, which was in accordance with our meta-analysis as well as several previous reports [21,26,31]. These findings confirmed the negative impact of corticosteroid administration for cancer-related indications on the efficacy of ICI therapy.

Despite of our novel findings, several inherent limitations of our present study should be mentioned. First, our meta-analysis was solely based on the results of published studies, some of which failed to provide important information such as the types of ICI inhibitors, the timeframes and doses of corticosteroid administration. This limitation potentially impacts the results of our subgroup analysis and is hoped to be improved by including more high-quality studies based on continuing comprehensive literature review. Second, we included literatures published in English and therefore inevitably ignored eligible ones published in other languages, which can be improved by well-organized multinational cooperation in future. Third, although we utilized an independent cohort for validation, the prognostic significance of corticosteroid administration for non-cancer indications or irAEs has not been well-validated due to limited sample size. The impact of corticosteroid doses on ICI efficacy has also not been investigated. Furthermore, our meta-analysis and retrospective study mainly focused on NSCLC and the correlation of corticosteroid administration with ICI efficacy in other cancers are poorly known. These issues are expected to be addressed by multicenter studies based on sufficient clinical resources. Finally, the underlying mechanisms for the detrimental impact of corticosteroid administration on ICI therapy are still poorly investigated. In future,

multi-omics detection of clinical samples and well-designed animal experiments will be useful in related mechanism investigations.

In summary, our study demonstrated that corticosteroid administration for cancer-related indications was significantly correlated with worse PFS and OS of solid cancer patients receiving ICI treatment, which was subsequently confirmed by our independent clinical validation. However, no significant correlation of corticosteroid administration for non-cancer-related indications or irAEs with patient prognosis was observed. Therefore, careful selection of corticosteroid-treated patients for ICI therapy is quite necessary in individualized clinical management. Considering study limitations, more clinical validations are still needed and mechanism investigations may provide novel antagonistic strategies for the corticosteroid-induced failure of ICI therapy.

CRediT authorship contribution statement

Ying Wang: Conceptualization, Writing–original draft. **Mengxue Yang:** Data curation, Formal analysis. **Mingyang Tao:** Project administration, Writing–review & editing. **Peipei Liu:** Resources, Software. **Cheng Kong:** Supervision, Validation. **Hao Li:** Validation, Visualization. **Yingmei Chen:** Conceptualization, Methodology. **Xudong Yin:** Project administration. **Xuebing Yan:** Investigation, Funding acquisition, Writing–review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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