



# The effect of concomitant use of statins, NSAIDs, low-dose aspirin, metformin and beta-blockers on outcomes in patients receiving immune checkpoint inhibitors: a systematic review and meta-analysis

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## ABSTRACT

Immunotherapy shows promising therapeutic efficacy against various types of cancer, but most fail to respond. Preclinical studies have suggested that concomitant medications, such as statins, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, metformin and beta-blockers, might affect clinical outcomes if used with immune checkpoint inhibitors (ICIs), but their clinical roles are conflicting. This meta-analysis investigates the effect of these concomitant medications on outcomes in patients treated with ICIs. A search was conducted for all reports published until 31 March 2021 in PubMed, Web of Science, Cochrane Library, EMBASE and conference proceedings. Studies were included if they investigated the association between the concomitant use of these medications and progression-free survival (PFS) or overall survival (OS) during ICI treatment. A total of 3331 patients from 13 eligible studies were included. Among them, five articles on statins, six studies evaluating NSAIDs, five studies employing low-dose aspirin, eight studies on metformin and four articles on beta-blockers were included. The concomitant use of statins during ICI treatment was correlated with improved OS and PFS. Low-dose aspirin was associated with better PFS instead of OS. No significant association was demonstrated between the concurrent use of NSAIDs, beta-blockers and metformin and OS or PFS. The concomitant use of statins and low-dose aspirin during ICI treatment showed a positive impact on treatment outcomes. The concurrent use of NSAIDs, beta-blockers and metformin is not significantly associated with clinical benefits. The effect of these medications in different cancer patients treated with ICI is needed to be further validated.

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## Introduction

Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte-associated-4 (CTLA-4) and programmed cell death protein-1 (PD-1) or its ligand (PD-L1) have revolutionized the treatment landscape of multiple solid tumors, such as melanoma, non-small-cell lung cancer (NSCLC) and elicited durable survival benefits.<sup>1</sup> Nevertheless, a significant portion of patients do not benefit from ICIs creating an unmet need to identify determinants that impact the efficacy of ICIs and to develop combined treatment modalities to improve the clinical outcome of ICIs.<sup>2</sup>

Drug–drug interactions affect the efficacy and safety profile of medications. The expanded indications of ICIs pose new challenges in clinical practice due to interactions with medications used concomitantly. Several studies and meta-analyses on the use of simultaneous medications, including corticosteroids, proton pump inhibitors (PPIs) and antibiotics, have demonstrated that the concomitant use of these drugs influences survival outcomes in patients treated with ICIs compared with those who treated with ICIs alone.<sup>3–6</sup> Cortellini et al. further demonstrated that negative impact of antibiotics on ICIs monotherapy but not chemotherapy might be as a result of their underlying immune-modulatory effect, while the effects of corticosteroids and PPIs on clinical outcomes might be driven by adverse disease features.<sup>7</sup>

Recently, great interest has been garnered in the anticancer properties of commonly prescribed drugs, such as statins, non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin that is different from non-aspirin NSAIDs in terms of indications and adverse effects, metformin and beta-blockers. Several studies have demonstrated the direct or indirect anticancer roles of these drugs in preclinical models. These medications have also been postulated to have positive roles in the reduced incidence and mortality of various cancer types (e.g., hepatocellular carcinoma, NSCLC, melanoma) in clinical settings.<sup>8–13</sup>

More recently, researchers have revealed that these medications exert immunomodulatory effects on components of the tumor microenvironment and can enhance the efficacy of ICIs in preclinical studies. However, the impact of these medications is conflicting in patients administered ICIs. We thus undertook a meta-analysis to examine the effect of concomitant use of these drugs on outcomes and their potential combined treatment in patients treated with ICIs.

## Materials and methods

### Search strategies

An electronic search was performed using PubMed, EMBASE, Cochrane Library, Web of Science database and the abstracts

from conference proceedings from the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) of were also screened to identify more potentially relevant studies up to March 31, 2021. Studies were identified with MESH terms and free text including “immune check point inhibitor\*”, “neoplasm”, “statin\*”, “anti-inflammatory agents, Non-Steroidal”, “aspirin”, “metformin”, “adrenergic beta-antagonists” as well as specific drug names (details are seen in Supplement Table 1).

### Study selection criteria

The inclusion criteria for the study were as follows: (1) Studies focusing on patients with solid tumors or hematological malignancy treated with ICIs; (2) Studies involved the association between concurrent use of metformin, statin, NSAIDs, low-dose aspirin (considered for cardiovascular prevention), beta blocker and ICIs efficacy in patients with cancer reporting overall survival (OS) or progression-free survival (PFS); (3) Sufficient data were provided to calculate the hazard ratio (HR) and 95% confidence interval (CI). Studies with insufficient information to evaluate HRs and 95% CIs, and in languages other than English are excluded.

### Data extraction and quality assessment

Two investigators selected the studies that fulfilled our inclusion criteria and extracted the relevant information independently. Disagreements were resolved by discussion with an independent expert. The following information was extracted: first author’s name, publication year, country, sample size, concomitant medications received, study design, type of cancer, ICIs agent, ICIs line of treatments, concomitant medications median PFS and OS, HRs for OS and PFS and 95% CIs between uses and non-users. The Quality Assessment of Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of studies. This scale consists of three parameters: selection, comparability and outcome assessment. NOS scores  $\geq 6$  are considered high-quality studies.

### Statistical analysis

HRs with their 95% CIs from included studies were used to calculate pooled HR. Heterogeneity of pooled results was assessed by using Higgins  $I^2$  statistics.  $I^2 > 50\%$  was defined as significant heterogeneity. A fixed effect model or random effect model was employed according to the heterogeneity of the studies. The data were synthesized using a fixed effect model with  $I^2 < 50\%$ . Otherwise, a random effect model was utilized. The sources of heterogeneity were evaluated by sensitivity and subgroup analysis. Sensitivity analysis was used to appraise the stability of the outcome. Funnel plots and Egger’s test were constructed to evaluate publication bias. All statistical tests were two-sided, and statistical significance was defined as  $P < .05$ . The pooled data were analyzed with STATA 16.0.

## Results

### Selection and characteristics of studies

A flowchart showing our literature selection is shown as Figure 1. Initially, 2517 relevant records were retrieved from selected databases. A total of 2184 records were retained after duplicate removal. Of these, 2152 were excluded by screening the title and abstract, thereby leaving 32 potentially relevant full-text articles. Eventually, we selected 13 studies<sup>14–26</sup> that evaluated the impact of related concomitant medications on the survival of patients with cancer treated with ICIs. All eligible studies were retrospective and involved 3331 patients, who were included in our meta-analysis. All studies were graded as “moderate” or “high” quality according to NOS criteria and qualified for a meta-analysis.

Among them, five articles<sup>16–19,24</sup> evaluating statins, six studies<sup>18,19,21,24–26</sup> employing NSAIDs, five studies<sup>16,18,19,22,25</sup> evaluating low-dose aspirin, eight studies<sup>14–16,18–20,24,25</sup> based on metformin and four articles<sup>18,19,23,25</sup> on beta-blockers were included in the quantitative synthesis. The most common types of cancer investigated were NSCLC and melanoma. The characteristics of patients in the studies at baseline are summarized in Table 1.

### Statins

Five studies reported the influence of concurrent use of statins on OS and PFS in cancer patients administered ICIs. The study by Cantini and colleagues in 2021<sup>17</sup> included two cohorts in which patients were diagnosed with NSCLC or malignant pleural mesothelioma (MPM) and showed the HR and 95% CI, respectively, so we termed them “Cantini 2021 cohort 1” and “Cantini 2021 cohort 2”. Overall, the concomitant use of statins was significantly associated with improved OS and PFS in patients receiving ICIs (statin users *versus* non-statin users: OS: HR = 0.76, 95% CI = 0.63–0.92,  $P = .005$ ; PFS: HR = 0.86, 95% CI = 0.75–0.99,  $P = .036$ ) (Figure 2a, b). Subgroup analyses stratified by ICIs showed that concomitant use of statins was significantly associated with favorable OS and PFS in patients receiving PD-1/PD-L1 inhibitors alone, whereas other ICIs regimens showed no significant difference. The results for subgroups based on cancer types showed that the concomitant use of statins was related to better OS and PFS in MPM patients. Interestingly, the concomitant use of statins was linked to improved PFS but not OS in NSCLC patients. No association between the concomitant use of statins and outcomes in patients with other types of cancer was shown in our meta-analysis. Moreover, we performed stratified analysis by analysis model, which showed that the concomitant use of statins led to better OS and PFS for patients in the multivariate analysis, but not in the univariate analysis (Table 2).

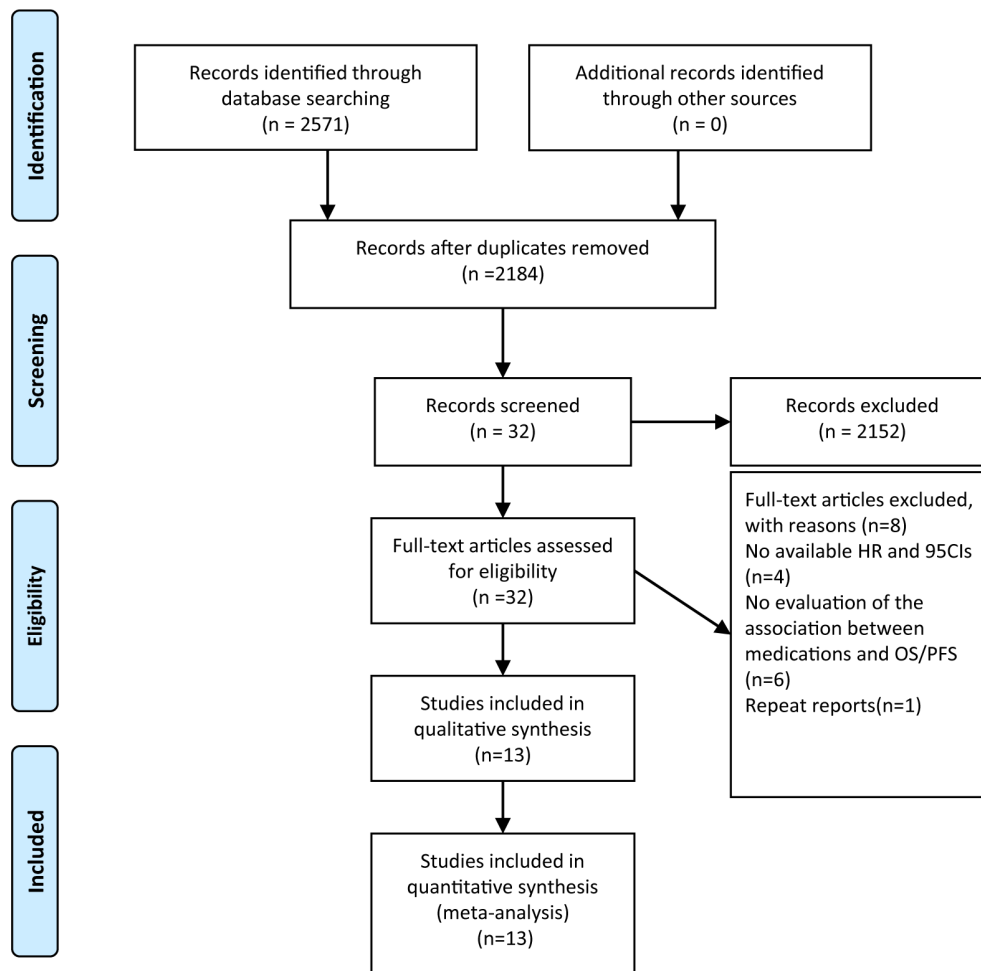
A funnel plot of the included studies showed no obvious asymmetry for HR of OS and PFS (Supplementary Figure S1, S2), suggesting that no publication bias existed. Egger’s test further confirmed these results (OS:  $P = .416$ ; PFS:  $P = .153$ , respectively). Sensitivity analyses for OS demonstrated that the pooled HRs and 95% CIs were not changed significantly, but PFS was influenced significantly if the studies by Cortellini et al. 2020,<sup>18</sup> Cantini et al. 2021 cohort 1, cohort 2<sup>17</sup> or

Table 1. The main characteristics of studies included in this meta-analysis.

ID	Country	Cancer type	ICIs treatment	ICIs line of treatments	Concomitant medications	Sample size (Y/N)	Outcome	Median PFS (Users vs non-users) (Month)	Median OS (Users vs non-users) (Month)	Analysis model	NOS
Afzal2019	US	NSCLC	Pembrolizumab Nivolumab Atezolizumab	First-line Second-line Third-line	Metformin	21/29	PFS/OS 4 vs 3	11.5 vs 7.6	11.5 vs 7.6	Univariate	6
Afzal2018	US	Melanoma	Pembrolizumab Nivolumab Ipilimumab + Nivolumab Ipilimumab	First-line	Metformin	33/22	PFS/OS 19.8 vs 5	46.7 vs 28	46.7 vs 28	Univariate	6
Buti2021	Italy	NSCLC Melanoma RCC Others	PD-1 inhibitors PD-L1 inhibitors CTLA-4 inhibitors	First-line Second-line Third-line	Statin Low-dose aspirin Metformin	56/161 43/174 17/200	PFS/OS 3.6 vs 3.6 3.2 vs 3.6 3.8 vs 3.6	12.4 vs 8.4 8.9 vs 8 12.6 vs 8.7	12.4 vs 8.4 8.9 vs 8 12.6 vs 8.7	Univariate	6
Cortellini2020	Italy	NSCLC Melanoma RCC Others	Pembrolizumab Nivolumab Atezolizumab Others	First Non- first	Statin NSAIDs Low-dose aspirin Metformin Beta blockers	192/820 59/953 189/ 823 114/ 868 114/ 898	PFS/OS NA	NA	NA	Multivariate	7
Cantini 2021	Italy	NSCLC MPM	Nivolumab Pembrolizumab	Second-line Third-line	Statin	67/186	PFS/OS 7.8 vs 3.6 6.7 vs 2.3	13.1 vs 10.1 NR vs 6	13.1 vs 10.1 NR vs 6	Multivariate	6
Falling2016	US	Melanoma	Ipilimumab	First-line	Statin NSAIDs Low-dose aspirin Metformin	40/119 31/128 38/121 12/147	PFS/OS NA	NA	NA	Multivariate	6
Kanai2021	Japan	NSCLC	Atezolizumab Nivolumab	Second-line Third-line	NSAIDs	65/133	PFS/OS 3.45 vs 3.94	7.85 vs 15.11	7.85 vs 15.11	Univariate	5
Gaucher2021	France	Lung Melanoma Renal and urothelial Head and neck Others	Pembrolizumab Nivolumab Ipilimumab Nivolumab + Ipilimumab	First-line Second-line Third-line	Metformin	17/355	OS NA	NR vs 15.62	NR vs 15.62	Multivariate	6
Michael 2020	US	NSCLC	Nivolumab Pembrolizumab Atezolizumab	Second-line Third-line	Beta-blockers	28/81	PFS/OS 10.3 vs 5	21.5 vs 13.3	21.5 vs 13.3	Univariate	5
Nichetti 2020	Italy	NSCLC	PD-1 inhibitors PD-L1 inhibitors CTLA-4 inhibitors	First-line Second-line Third-line	Low-dose aspirin	61/156	PFS 6.59 vs 3.18	NA	NA	Univariate	5
Svaton2020	Czech	NSCLC	Nivolumab	First-line Second-line Third-line or higher	Statin NSAIDs Metformin	31/193 45/178 18/206	PFS/OS 7.2 vs 5.4 6.9 vs 5.3 3.3 vs 6	16.8 vs 12.9 16.8 vs 12.8 10.6 vs 13.1	16.8 vs 12.9 16.8 vs 12.8 10.6 vs 13.1	Multivariate	6
Wang D.Y 2020	Mixed	Melanoma	Nivolumab Pembrolizumab	First-line	NSAIDs Low-dose aspirin Metformin Beta-blocker	122/208 47/283 34/296 65/265	PFS/OS 8.5 vs 5.2 NA 11.1 vs 5.6 11.2 vs 5.5	25.7 vs 27.3 NA 27.6 vs 26.0 27.8 vs 25.8	25.7 vs 27.3 NA 27.6 vs 26.0 27.8 vs 25.8	Multivariate/ Univariate	5
Wang S.J 2020*	US	Melanoma NSCLC	PD-1 inhibitors PD-L1 inhibitors CTLA-4 inhibitors	NA	NSAIDs	32/58 20/17	OS NA	25.44 vs 22.08 37.68 vs 14.28	25.44 vs 22.08 37.68 vs 14.28	Multivariate	6

\*Wang S.J 2020 study included 2 cohorts which are melanoma patients and NSCLC patients, respectively.

**Abbreviations:** OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer; NSAIDs, non-steroidal anti-inflammatory drugs; MPM, malignant pleural mesothelioma; RCC, renal cell carcinoma; NA, not available; NR, not reached.



**Figure 1.** Flow chart of literature search and study selection. A total of 2571 articles were initially retrieved. After carefully reviewed 13 studies reporting the impact of related concomitant medications on the survival of patients with cancer treated with ICI were included in the analysis.

Svaton et al. 2020<sup>24</sup> were excluded, suggesting that pooled results were unstable (Supplementary Figure S3, S4).

### NSAIDs

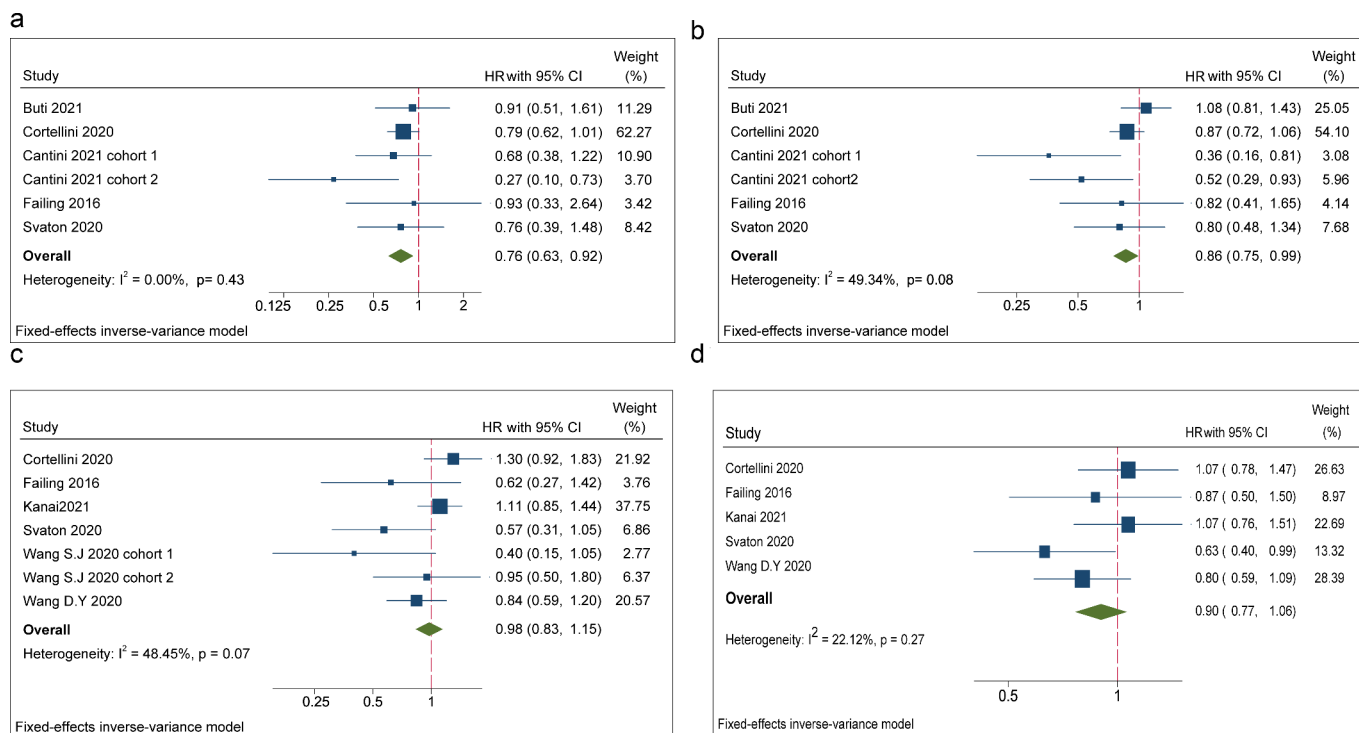
Six studies and five studies exhibited the effect of NSAIDs on OS and PFS in patients treated with ICIs, respectively. The study by Wang et al. 2020<sup>26</sup> included two cohorts in which patients had melanoma or NSCLC and the HR and 95% CI were reported, respectively, so we termed them “Wang et al. 2020 cohort 1” and “Wang et al. 2020 cohort 2”. Pooled data of HRs showed that the concurrent use of NSAIDs was not significantly related to OS or PFS in patients receiving ICIs (NSAIDs users *versus* non-NSAIDs users: OS: HR = 0.98, 95% CI = 0.83–1.15,  $P = .769$ ; PFS: HR = 0.90, 95% CI = 0.77–1.06,  $P = .213$ ) (Figure 2c, d). In subgroup analyses of ICI agents, cancer type and analytical model, no significant association between the concomitant use of NSAIDs and OS and PFS, respectively, was observed (Table 2).

A funnel plot demonstrated slight asymmetry for HR of OS but not for PFS (Supplementary Figure S5, S6). Egger’s test was done to further confirm these results (OS:  $P = .037$ ; PFS:  $P = .504$ ), and indicated a low risk of a potential publication bias in OS but not PFS. Sensitivity analyses of OS and PFS

showed that the pooled HRs and their 95% CIs were not changed significantly if a single study was removed, suggesting that pooled results were robust and stable (Supplementary Figure S7, S8).

### Low-dose aspirin

Low-dose aspirin revealed its combined effect on OS and PFS in four studies and five studies, respectively. Pooled data of HRs showed that the concurrent use of low-dose aspirin was not significantly relevant to OS, whereas PFS was improved significantly in patients receiving ICIs concomitantly (low-dose aspirin users *versus* non-aspirin users: OS: HR = 0.93, 95% CI = 0.76–1.15,  $P = .514$ ; PFS: HR = 0.84, 95% CI = 0.72–0.98,  $P = .024$ ) (Figure 3a, b). Then, in subgroup analyses according to ICI agents, cancer type and analytical model, a significant association between the concomitant use of aspirin and OS was not observed. However, the concomitant use of aspirin and ICIs was found to be associated with better PFS in patients treated with PD-1/PD-L1 inhibitors, NSCLC patients and in a multivariate subgroup (PD-1/PD-L1: HR = 0.80, 95% CI = 0.65–0.99,  $P = .043$ ; NSCLC patients: HR = 0.67, 95% CI = 0.48–0.94,  $P = .02$ ; multivariate subgroup: HR = 0.82, 95% CI = 0.67–1.00,  $P = .048$ , respectively) (Table 2).



**Figure 2.** Forest plots of the hazard ratios and 95% CIs for overall survival (a) and progression-free survival (b) in patients with the concomitant use of statins compared patients without use of these drugs. Forest plots of the hazard ratios and 95% CIs for overall survival (c) and progression-free survival (d) in patients with the concomitant use of NSAIDs compared patients without use of these drugs. **Abbreviation:** NSAIDs, non-steroidal anti-inflammatory drugs; HR, hazard ratio; CI, confidence interval.

A funnel plot of all eligible studies (Supplementary Figure S9, S10) and Egger's test demonstrated no evidence of a publication bias (Egger's test OS:  $P = .664$ ; PFS:  $P = .239$ , respectively). Sensitivity analyses revealed that no individual study could substantially affect the pooled HRs of OS, whereas the pooled HRs of PFS were influenced significantly by removal of the studies by Cortellini et al. 2020<sup>18</sup> or Nichetti et al. 2020,<sup>22</sup> thereby suggesting that pooled results were not robust or stable (Supplementary Figure S11, S12).

### Metformin

Eight studies and seven studies reported the impact of metformin on OS and PFS, respectively. Overall, the concomitant use of metformin was not significantly associated with OS in patients receiving ICIs (metformin users *versus* non-metformin users: HR = 1.07, 95% CI = 0.89–1.30,  $P = .46$ ). Likewise, there was no significant association between the concomitant use of metformin and PFS for patients undergoing ICI therapy (metformin users *versus* non-metformin users: HR = 1.08, 95% CI = 0.92–1.27,  $P = .51$ ) (Figure 3c, d). In subgroup analyses stratified by ICI agents, cancer type and analytical model, the concomitant use of metformin showed no significant association with OS or PFS, respectively (Table 2).

A funnel plot of all eligible studies (Supplementary Figure S13, S14) and Egger's test demonstrated no evidence of a publication bias (Egger's test OS:  $P = .227$ ; PFS:  $P = .765$ , respectively). Sensitivity analyses for OS and PFS showed that the combined HRs and their 95% CIs were not altered significantly if a study was excluded, which suggested that no single

study had a significant impact on the pooled results (Supplementary Figure S15, S16).

### Beta-blockers

Four studies reported the impact of beta-blockers on OS and PFS in patients treated with ICIs. Our meta-analysis demonstrated that the concomitant use of beta-blockers was not significantly related to OS and PFS in patients receiving ICIs (beta-blocker users *versus* non-beta-blocker users: OS: HR = 0.87, 95% CI = 0.71–1.08,  $P = .207$ ; PFS: HR = 0.91, 95% CI = 0.66–1.22,  $P = .486$ ) (Figure 4a, b). In subgroup analyses stratified by cancer type showed that the concomitant use of beta-blockers and ICIs had a trend toward improved PFS in NSCLC patients ( $P = .052$ ), but a significant association in patients with melanoma or other cancer types was not observed. Furthermore, no statistical association between the concomitant use of beta-blockers and improved OS and PFS was found in subgroup analyses based on ICIs regimen and analysis models (Table 2).

A funnel plot of included studies demonstrated no obvious asymmetry for HRs of OS and PFS (Supplementary Figure S17, S18). Egger's test further validated these results (OS:  $P = .851$ ; PFS:  $P = .982$ , respectively). Sensitivity analyses for OS and PFS revealed that the pooled HRs and their 95% CIs were not changed significantly if a single study was omitted, thereby suggesting that these results were robust and stable (Supplementary Figure S19, S20).

Table 2. Results of subgroup analysis.

Analysis	N	OS			N	PFS		
		Association HR (95% CI)	P	Heterogeneity $I^2$		Association HR (95% CI)	P	Heterogeneity $I^2$
<b>Statin</b>								
Total	6 <sup>a</sup>	0.76(0.63–0.92)	<b>0.005</b>	48.4%	6 <sup>a</sup>	0.86(0.75–0.99)	<b>0.036</b>	22.1%
Agent								
PD-1/PD-L1	4	0.74 (0.60–0.91)	<b>0.004</b>	29.6%	4	0.79(0.67–0.94)	<b>0.008</b>	54.1%
CTLA-4	1	0.93(0.33–2.64)	0.891	0%	1	0.82(0.41–1.65)	0.578	0%
Mixed	1	0.91(0.51–1.61)	0.747	0%	1	1.08(0.81–1.43)	0.596	0%
Cancer type								
NSCLC	2	0.71(0.46–1.11)	0.131	0%	2	0.64(0.41–0.98)	<b>0.041</b>	62.4%
Melanoma	1	0.93(0.33–2.64)	0.891	0%	2	0.82(0.62–1.07)	0.578	0%
MPM	1	0.27(0.1–0.73)	<b>0.010</b>	0%	1	0.52(0.29–0.93)	<b>0.028</b>	0%
Multiple	2	0.81(0.65–1.01)	<b>0.062</b>	0%	1	0.93(0.79–1.09)	0.385	34.2%
Analysis model								
Multivariate	5	0.74(0.61–0.91)	<b>0.004</b>	10.0%	5	0.80(0.75–0.99)	<b>0.006</b>	38.9%
Univariate	1	0.91(0.51–1.61)	0.747	0%	1	1.08(0.81–1.43)	0.596	0%
<b>NSAIDs</b>								
Total	7 <sup>b</sup>	0.98(0.83–1.15)	0.769	48.4%	5	0.90(0.77–1.06)	0.213	22.1%
Agent								
PD-1/PD-L1	5	1.03 (0.86–1.22)	0.769	56.5%	4	0.90(0.76–1.07)	0.250	41.4%
CTLA-4	1	0.62(0.27–1.42)	0.259	0%	1	0.87(0.50–1.50)	0.617	-
Mixed	2	0.73(0.43–1.25)	0.249	53.2%	-	-	-	-
Cancer type								
NSCLC	4	0.95(0.76–1.18)	0.645	64.3%	2	0.88(0.67–1.16)	0.356	70.4%
Melanoma	2	0.80(0.58–1.11)	0.184	12.2%	2	0.82(0.62–1.07)	0.137	0%
Multiple	1	1.30(0.92–1.83)	0.135	56.1%	1	1.07(0.78–1.47)	0.676	0%
Analysis model								
Multivariate	6	0.90(0.74–1.11)	0.327	50.8%	4	0.86(0.71–1.03)	0.104	22.9%
Univariate	1	1.11(0.85–1.44)	0.435	0%	1	1.07(0.76–1.51)	0.699	0%
<b>Low-dose aspirin</b>								
Total	4	0.93(0.76–1.15)	0.514	9.2%	5	0.84(0.72–0.98)	<b>0.024</b>	38.3%
Agent								
PD-1/PD-L1	2	0.86(0.68–1.08)	0.192	0%	2	0.80(0.65–0.99)	<b>0.043</b>	34.6%
CTLA-4	1	1.56(0.79–13.10)	0.202	0%	1	0.93(0.55–1.57)	0.786	-
Mixed	1	1.10(0.62–1.95)	0.744	0%	2	0.87(0.69–1.10)	0.2436	38.3%
Cancer type								
NSCLC	0	-	-	-	1	0.67(0.48–0.94)	<b>0.020</b>	0%
Melanoma	2	1.55(0.81–2.94)	0.184	0%	2	1.01(0.61–1.66)	0.968	0%
Multiple	2	0.88(0.71–1.10)	0.256	0%	2	0.88(0.73–1.05)	0.144	66.9%
Analysis model								
Multivariate	3	0.91(0.73–1.14)	0.41	32.1%	3	0.82(0.67–1.00)	<b>0.048</b>	0%
Univariate	1	1.10(0.62–1.95)	0.744	0%	2	0.87(0.69–1.10)	0.246	38.3%
<b>Metformin</b>								
Total	8	1.07(0.89–1.30)	0.462	40.3%	7 <sup>c</sup>	1.08(0.92–1.27)	0.346	29.2%
Agent								
PD-1/PD-L1	5	1.12 (0.91–1.38)	0.204	53.6%	5	1.02(0.85–1.23)	0.799	29.6%
CTLA-4	1	1.37(0.48–3.90)	0.555	0%	1	1.83(0.87–3.85)	0.238	-
Mixed	2	0.85(0.52–1.37)	0.266	62.6%	1	1.33(0.83–2.14)	0.112	-
Cancer type								
NSCLC	2	1.22(0.73–2.04)	0.438	64.3%	2	1.09(0.71–1.69)	0.691	16.3%
Melanoma	3	0.82(0.54–1.24)	0.347	12.2%	3	0.89(0.64–1.24)	0.501	60.9%
Multiple	3	1.13(0.90–1.43)	0.284	56.1%	2	1.17(0.95–1.44)	0.149	0%
Analysis model								
Multivariate	6	1.21(0.96–1.53)	0.103	52.5%	3	1.68(0.71–1.19)	0.084	0%
Univariate	4	0.85(0.62–1.17)	0.322	0%	4	1.20(0.98–1.48)	0.516	29.4%
<b>Beta-blockers</b>								
Total	4	0.87(0.71–1.08)	0.588	53.6%	4	0.91(0.66–1.26)	0.207	0%
Agent								
PD-1/PD-L1	3	0.86 (0.69–1.06)	0.159	0%	3	0.88(0.73–1.06)	0.183	32.8%
CTLA-4	1	1.37(0.48–3.90)	0.555	0%	1	1.83(0.87–3.85)	0.112	0%
Cancer type								
NSCLC	1	0.66(0.38–1.16)	0.148	0%	1	0.48(0.23–1.01)	0.052	0%
Melanoma	2	0.94 (0.65–1.36)	0.739	0%	2	0.97 (0.72–1.32)	0.685	69.7%
Multiple	1	0.90(0.68–1.20)	0.467	0%	1	0.95(0.74–1.21)	0.679	0%
Analysis model								
Multivariate	2	0.93(0.70–1.22)	0.585	0%	3	0.94(0.53–1.68)	0.839	68.0%
Univariate	2	0.81(0.71–1.08)	0.192	0%	1	0.86(0.62–1.20)	0.371	0%

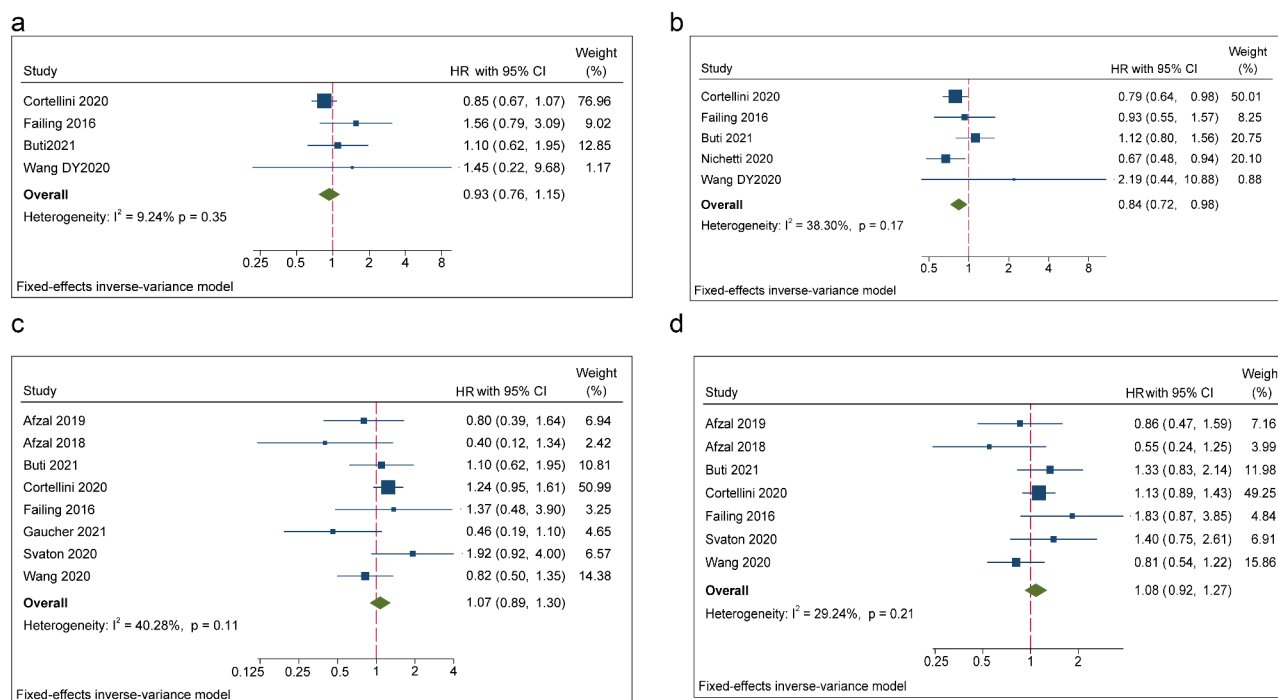
Abbreviations: OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer; NSAIDs, non-steroidal anti-inflammatory drugs; MPM, malignant pleural mesothelioma.

#### Annotation

a. The study by Cantini et al. included two cohorts and showed the HR and 95% CI respectively, and the total number refers to cohorts rather than studies.

b. The study by Wang et al. 2020 included two cohorts and the HR and 95% CI were reported, respectively, and the total number refers to cohorts rather than studies.

c. The study by Gaucher et al. only reported the HR and 95%CI for OS, and the total number for PFS is 7.



**Figure 3.** Forest plots of the hazard ratios and 95% CIs for overall survival (a) and progression-free survival (b) in patients with the concomitant use of aspirin compared patients without use of these drugs. Forest plots of the hazard ratios and 95% CIs for overall survival (c) and progression-free survival (d) in patients with the concomitant use of metformin compared patients without use of these drugs. **Abbreviation:** HR, hazard ratio; CI, confidence interval.

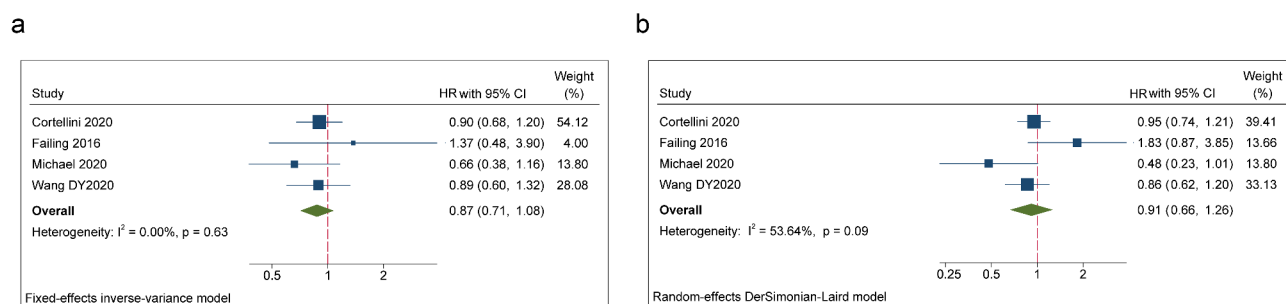
## Discussion

Recently, the anticancer effects of commonly used drugs, including statins, NSAIDs, low-dose aspirin, beta-blockers and metformin, have attracted considerable attention. Numerous studies have demonstrated that these medications can directly or indirectly inhibit the proliferation and genesis of tumors *in vitro* and *in vivo* and decrease the incidence and mortality rate of various cancers compared with patients who do not use such medications.<sup>6,8,9,11,13</sup>

This is the first meta-analysis to assess the impact of the concomitant use of statins, NSAIDs, low-dose aspirin, beta-blockers and metformin on the survival of patients with various types of cancer treated with ICIs. We revealed that the concomitant use of statins during ICI treatment was correlated with improved OS and PFS of patients. Moreover, the concurrent use of low-dose aspirin was associated with better PFS instead of OS in patients treated with ICIs. In addition, we found no significant association between the concurrent use of

NSAIDs, beta-blockers and metformin and OS or PFS for patients receiving ICI treatment.

We demonstrated that the concurrent use of statins was correlated with improved OS and PFS in cancer patients receiving ICIs, particularly in the anti-PD-1/PD-L1 subgroup, NSCLC patients and multivariate subgroup. Sensitivity analysis showed robustness of pooled results of PFS was poor, primarily due to limited studies and heterogeneity of populations. Studies have been inconsistent with regard to the association between statin use and improved outcomes, so study of the concomitant use of statins in different cancer types and types of ICIs is needed to provide further evidence. The potential reason why subgroup analysis differed by analytical model (univariate vs multivariate) is partly due to limited studies in univariate analysis and the fact if variables have no statistical association in the univariate analysis, they will not be included in the multivariate analysis. Although no statistical association in univariate analysis, statin users have better median PFS and OS than non-statin users.<sup>17,24,27</sup> Statins, inhibitors of



**Figure 4.** Forest plots of the hazard ratios and 95% CIs for overall survival (a) and progression-free survival (b) in patients with the concomitant use of beta-blockers compared patients without use of these drugs. **Abbreviation:** HR, hazard ratio; CI, confidence interval.

3-hydroxy-3-methylglutaryl coenzyme A reductase, are commonly used cholesterol-lowering medications with an excellent safety profile.<sup>28</sup> Cholesterol metabolism has an important role in tumor growth and regulation of the immunological landscape.<sup>29</sup> Preclinical studies have shown that statin arrest cells in G1 or S phases by affecting cell-cycle regulatory proteins, which results in the apoptosis of cancer cells and inhibition of intracellular signaling pathways in cancer cells. Furthermore, studies have reported that statins (particularly lipophilic statins) downregulate expression of PD-1 and CTLA-4 in T cells,<sup>30</sup> reduce T-cell exhaustion in patients infected with human immunodeficiency virus-1,<sup>31</sup> increase antigen occupation in dendritic cells and synergize with PD-1 inhibitors in murine models.<sup>32</sup> Those features explain the biological rationale of our meta-analysis. Notably, intensity of statins, the duration of concurrent therapy using statins and immunotherapy, and lipophilicity of statins probably affect immune response. Cantini et al.<sup>17</sup> reported that statin intensity might be essential in the response to ICIs, particularly high-intensity statins boosting the activity of PD-1 inhibitors. If statins work as immune adjuvants, temporary accumulation of statins in combination with antigens is probably not sufficient to induce an adaptive immune response. Long-term duration of concurrent therapy using statins and immunotherapy is probably indispensable to enhance immune responses.<sup>33</sup> The lipophilicity of statins has been shown to have an effect on response in one preclinical study,<sup>32</sup> whereas only one study in our meta-analysis analyzed this association.

Overall, our study confirmed that the concurrent use of NSAIDs was not associated significantly with improved OS or PFS in cancer patients receiving ICIs. However, the concomitant use of low-dose aspirin was related to significantly improved PFS rather than OS, especially in patients receiving PD-1/PD-L1 blockade, in patients with NSCLC, and HR from multivariate subgroup. Preclinical studies and clinical studies have demonstrated that cyclo-oxygenase-2 (COX2), whose overexpression has been observed to be associated with poor prognoses in multiple cancer types, promotes immune evasion and, by increasing the production of prostaglandin E2 (PGE2), it weakens the ability and reduces the number of immune cells in the tumor microenvironment.<sup>34</sup> Moreover, studies have reported that NSAIDs and aspirin can enhance the efficacy of PD-1/PD-L1 blockade by inhibiting COX-2 activity in animal models.<sup>35–37</sup> The potential explanation of different results between aspirin and NSAIDs is that aspirin non-selectively and irreversibly blocks expression of COX-1 and COX-2, whereas other NSAIDs reversibly inhibit COX enzymes or selectively block COX-2. Zelenay et al. reported that melanoma mice administrated with celecoxib, a COX-2-specific inhibitor, significantly regressed combined with anti-PD-1 treatment, but the combined efficacy is inferior to combined aspirin and PD-1 inhibitors, possibly owing to suboptimal COX-2 inhibition and/or an underlying contribution of COX-1-derived PGE2.<sup>35</sup> The different results for the concomitant use of aspirin between OS and PFS may be explained (at least in part) by the fact that OS, unlike PFS, may not reflect the positive effect of combined treatment because of the influence of post-treatment and poor systemic conditions in NSAIDs users and low-dose

aspirin users. For low-dose aspirin, the different results based on analytical model are partly due to similar reasons to statins. However, in contrast to statins, improved median PFS was not consistent for low-dose aspirin users in two studies, which might be explained by patient heterogeneity.<sup>16,22</sup>

We found no significant association between the concomitant use of metformin and OS or PFS in patients undergoing ICI treatment. Metformin is the most widely used agent for type-2 diabetes mellitus. It has received considerable publicity over its potential anticancer function. Metformin appears to arrest the cell cycle and cell proliferation by regulating adenosine monophosphate-activated protein kinase (AMPK)/liver kinase B1, thereby suppressing cancer cells and inducing apoptosis.<sup>38</sup> Metformin also: (i) activates the immune response by targeting cancer cells; (ii) inhibiting expression of CD39/73 on MDSCs to prevent the development of immune tolerance of cancer cells by targeting CD8+ tumor-infiltrating leukocytes; (iii) enhancing the antitumor activity of PD-1 blockers by regulating the oxygen tension in the tumor microenvironment in murine models.<sup>13,39</sup> However, all eligible studies in a clinical setting reported no significant association between the use of metformin and improved outcomes. Notably, Afzal et al.<sup>14,15</sup> reported that the objective response rate (melanoma: 68.2% vs. 54.5%,  $P = .31$ ; NSCLC: 41.1% vs. 30.7%,  $P = .4$ ), disease control rate (77.3% vs. 60.6%,  $P = .19$ ; NSCLC: 70.5 vs. 61.6%,  $P = .5$ ), median PFS (46.7 vs. 28 months,  $P = .15$ ; 4.0 vs. 3.0 months,  $P = .6$ ) and median OS (melanoma: 46.7 vs. 28 months,  $P = .12$ ; NSCLC: 11.5 vs. 7.6 months  $P = .5$ ) was higher in melanoma patients and NSCLC patients receiving concurrent use of metformin and ICI treatment, but did not reach significance.<sup>14,15</sup> A phase-II trial (NCT03800602) of nivolumab and metformin in patients with treatment-refractory microsatellite-stable (MSS) metastatic colorectal cancer (mCRC) was reported in the 2021 Gastrointestinal Cancers Symposium.<sup>40</sup> Briefly, stage-IV metastatic treatment-refractory MSS mCRC patients were administered nivolumab (480 mg, i.v.) every 4 weeks and metformin (1000 mg, p.o., b.d.) in 28-d cycles following a 14-d metformin-only lead-in phase. Eighteen patients could tolerate this regimen and two patients achieved stable disease, but an objective response rate was not seen, so the study did not proceed. Hence, recent studies have, like our meta-analysis, shown that metformin may be unable to potentiate PD-1/PD-L1 inhibitors in the clinical setting.

Our meta-analysis revealed no significant association between the concomitant use of beta-blockers and OS or PFS in patients given ICIs. Increasing evidence suggests that beta-adrenergic signaling has been shown to influence the genesis and progression of multiple tumors and to intertwine with immune cells (e.g., CD8 + T cells, regulatory T cells, myeloid-derived suppressor cells).<sup>41,42</sup> Nevertheless, all eligible studies reported no significant association between the concomitant use of beta-blockers and OS and PFS in the multivariate analysis. Cortellini et al.<sup>18</sup> reported that beta-blockers are significantly associated with a favorable objective response rate in the multivariate analysis. Michael et al.<sup>23</sup> showed that NSCLC patients were associated with improved PFS in the univariate analysis, but



the effect was offset by other factors in the multivariate analysis, thereby indicating that beta-blockers may have no impact on clinical outcomes in patients receiving ICIs.

Most of the studies included in our meta-analysis failed to report the doses and duration of medications used concomitantly. Preclinical studies demonstrated that the anticancer effect of these drugs was dependent on the dose and time.<sup>19</sup> Interestingly, Afzal et al.<sup>14,15</sup> reported that the overall duration of metformin therapy and metformin dose had no impact on OS and PFS in the multivariate analysis, whereas the duration of concurrent therapy using metformin and ICIs had a significant impact on OS and PFS in NSCLC patients in univariate and multivariate analyses. Those results are partly contrary to data from preclinical studies and this phenomenon warrants further investigation. It seems that, to be more efficacious, medications should be employed long term and at high doses, but there is no consensus concerning optimal doses and treatment duration in patients without indications for these drugs. Although exact time frame of these baseline medications, which are generally indefinite prescriptions, might be unretrievable in prospective clinical trials, collection of the duration and dose of concurrent medications and ICIs might be feasible, which have been reported by Afzal et al.<sup>14</sup> Basic-science studies and phase-I/II trials are also needed to explore these issues.

Of note, these medications are often taken by patients with high body mass index (BMI) or metabolic syndrome, who have been confirmed to be better outcomes when treated with ICIs instead of chemotherapy.<sup>43</sup> Cortellini et al.<sup>18</sup> reported that the significant association between statins, low-dose aspirin,  $\beta$ -blockers and higher baseline BMI in a large cohort. Interestingly, multivariate analysis revealed that BMI was not significantly associated with improved ORR, PFS and OS, while statins, low-dose aspirin and  $\beta$ -blockers were independently related to an increased ORR and low-dose aspirin were significantly associated with PFS. These results might be due to the distinct study population compared to previous studies. An alternative explanation might be that BMI was a confounder, and the positive roles of these baseline medications were revealed when BMI was adjusted in multivariate analysis. It is these baseline medications taken by obese patients that exert immune-modulatory effect, which enhanced efficacy of ICIs and improved clinical outcomes in high BMI patients. Since most studies<sup>43,46,47,48,49</sup> 44,45 that reported better clinical outcomes in high BMI patients fail to consider the roles of these concurrent medications, those complex interaction between high BMI and the immune-modulating effect of these drugs on survival of patients receiving ICIs deserves to be further elucidated.

Our meta-analysis had fifth main limitations. First, all of the eligible studies were retrospective, whose results have an inevitable bias in terms of selection and reporting. Second, although we have performed subgroup based on types of cancers and treatment modality (including ICI alone or in combination), different lines of treatment might have affected the stability and reliability of our results. Third, the small number of studies and small sample size did not permit comprehensive subgroup analyses according to confounders, which may have influenced our results. Fourth, poor systemic status may have been present in patients using these medications concomitantly. Fifth,

patients in eligible studies often assume several concomitant medications to treat comorbidities or cancer-related symptoms, and the effect of concomitant use of these drugs on patients receiving ICIs has not been evaluated, which might affect our results. Drug-based prognostic score, which includes the comorbidities and the possible concomitant baseline medications for patients, is likely to become promising tools in clinical practice.<sup>16</sup>

## Conclusions

The concomitant use of statins during ICI treatment was correlated with improved OS and PFS. The concurrent use of low-dose aspirin was associated with better PFS in patients treated with ICIs. The ICI regimen, cancer type and analytical model may have affected these outcomes. We found no significant association between the concurrent use of NSAIDs, beta-blockers and metformin and clinical outcomes. These findings need to be confirmed with larger and perspective studies.

## Availability of data and material

The data used in the present study are available from the corresponding author on reasonable request.

## Authors' contributions

Conception/design: Yongchao Zhang and Wei Li. Collection and/or assembly of data: Hualei Chen, Shanshan Chen and Zhen li. Wei Li Data analysis and interpretation: Yongchao Zhang, Jinglong Chen and Wei Li. Manuscript writing: Yongchao Zhang and Wei Li. Final approval of manuscript: Yongchao Zhang, Hualei Chen, Shanshan Chen, Zhen li, Jinglong Chen, Wei Li

## Ethics approval and consent to participate

Not applicable.

## Abbreviations

ICIs, Immune checkpoint inhibitors; CTLA-4, cytotoxic T-lymphocyte-associated-4; PD-1/PD-L1, programmed cell death protein-1/programmed cell death protein-1 ligand; NSCLC, non-small cell lung cancer; NSAIDs, non-steroidal anti-inflammatory drugs; MPM, malignant pleural mesothelioma; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; COX2: cyclo-oxygenase-2; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; ASCO, Society of Clinical Oncology; ESMO, European Society for Medical Oncology; MSS, microsatellite-stable; mCRC, metastatic colorectal cancer

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## Disclosure statement

Authors have no conflict of interest.

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