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Anti-hypertensives associated with survival in cancer patients receiving immunotherapy: new evidence from a real-world cohort study and meta-analysis

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Abstract

Background: The efficacy of immune checkpoint inhibitors (ICIs) in cancer patients taking anti-hypertensive drugs is still not well established.

Objective: To elucidate the effect of anti-hypertensive drugs on the clinical outcome of cancer patients receiving immunotherapy.

Design: A retrospective cohort study and meta-analysis.

Method: We conducted a real-world retrospective study of cancer patients treated with immunotherapy at two tertiary centers between January 2019 and June 2023, with primary outcomes being overall survival (OS) and progression-free survival (PFS). In addition, we performed a meta-analysis to synthesize currently relevant clinical studies.

Results: A retrospective clinical study of 336 patients from 2 centers suggested that the use of anti-hypertensive drugs was related to a preferable OS (hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.33–0.90) compared to non-users. For PFS, no significant correlation was detected (HR = 0.71, 95% CI: 0.49–1.03). Further analysis revealed that renin–angiotensin system inhibitor (RASi) and calcium channel blocker (CCB) have a synergistic effect with ICIs. In addition, subgroup analysis found that the benefits of RASi or CCB in combination with ICIs are greater in women or patients ⩾65 years of age. There was better disease control in lung cancer patients using RASi, and a significantly longer OS was observed in patients with gastrointestinal tumors taking CCB. Meta-analysis suggested that anti-hypertensive drugs were associated with improved OS, but only the combination of RASi and immunotherapy showed a synergistic effect. No significant correlation with OS was found for other anti-hypertensive drugs, and there was no overall positive effect on PFS.

Conclusion: Our study found that use of anti-hypertensive drugs, particularly RASi or CCB, was associated with improved OS in patients undergoing immunotherapy. The synergistic effects of RASi or CCB with ICIs were more pronounced in females or elderly. RASi or CCB exhibited different benefits in various types of tumors. These findings provide valuable insights for treating cancer patients with hypertension.

Keywords: anti-hypertensive drugs, calcium channel blocker, cancer survival, immune checkpoint inhibitors, renin–angiotensin system inhibitor

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Introduction

Significant advancements have been achieved in the field of cancer therapeutics through the application of immunotherapy. In contrast to conventional therapies, immune checkpoint inhibitors (ICIs) function by activating the host's immune system to effectively eliminate tumor cells.[1] ICIs have been utilized in the treatment of various solid cancers, including but not limited to non-small-cell lung cancer (NSCLC),[2] melanoma,[3] breast cancer,[4] and renal cell carcinoma.[5] However, the efficacy of ICIs is restricted to a limited proportion of patients, with only approximately 20%–40% of cancer patients responding to ICIs.[6] As a result, it is essential to investigate the factors influencing the effectiveness of ICIs and to devise strategies to enhance the response to immunotherapy.

Currently, concomitant medication is recognized as a factor that can impact the effectiveness of immunotherapy. Studies have shown that certain medications, such as proton pump inhibitors (PPIs) and antibiotics, can have a detrimental effect on the outcomes of immunotherapy.[7] Anti-hypertensive drugs are a common concomitant medication among cancer patients receiving ICIs.[8] Therefore, there is a growing interest in the impact of anti-hypertensive drugs on immunotherapy. Preliminary preclinical studies have suggested that anti-hypertensive drugs, such as renin–angiotensin system inhibitor (RASi)[9] and beta-blocker,[10] may have beneficial effects on immunotherapy. However, previous clinical studies have investigated the association between anti-hypertensive medications and immunotherapy, which remains contentious. Some retrospective clinical studies have suggested that the use of RASi[11] or beta-blocker[12] may improve clinical outcomes in cancer patients receiving ICIs, while other studies have not found similar findings.[13] The influence of calcium channel blockers (CCBs) and diuretics on patient prognosis lacks robust support in the literature, with a lack of evidence-based medical evidence from clinical studies. To further elucidate the relationship between anti-hypertensive drugs and immunotherapy, we conducted a real-world retrospective study across two tertiary hospitals and performed a meta-analysis to synthesize the existing clinical evidence.

Materials and methods

Clinical cohort

Patients. We conducted a retrospective clinical study in two centers: The 960th Hospital of the People's Liberation Army (PLA) and the Affiliated Cancer Hospital of Shandong First Medical University. Cancer patients included in the study were those who received ICIs either as monotherapy or in combination with chemotherapy at the two medical centers between January 2019 and June 2023. Exclusion criteria were defined as follows: (1) receiving ⩽2 cycles of treatment; (2) primary multiple tumors; (3) receiving radiotherapy or surgery; (4) participation in clinical trials; and (5) incomplete baseline or follow-up information. Basic patient characteristics including gender, age, tumor type, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, smoking history, use of anti-hypertensive drugs, underlying disease, concomitant medications, and ICIs were recorded. The study was approved by the hospital's ethical committees (Approval No. 2023-061). A waiver of informed consent was granted due to the retrospective nature of the study.

Outcomes. Patients underwent tumor marker detection at each treatment cycle and an imaging examination every 2–3 cycles to evaluate the response of the cancer therapies. The primary outcomes were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the start of ICI treatment to death from any cause, while PFS was defined as the time from the initiation of ICI treatment to the first occurrence of disease progression or death. Subsequently, patients were followed up either during outpatient visits or by telephone.

Statistical analysis. To describe patient characteristics, categorical variables were expressed as the number of cases and percentage and analyzed using the Chi-squared test or Fisher's exact test (where appropriate); continuous variables were expressed as means and compared using *t*-tests. To ensure similarity in baseline characteristics between groups, the propensity score matching (PSM) method was used to match patients taking anti-hypertensive drugs and non-users. Matching with a ratio of 1:1 was conducted (caliper value is

0.02). Propensity scores were calculated based on age, smoking history, coronary heart disease (CHD), and diabetes mellitus (DM). We compared OS and PFS between anti-hypertensive drug users and non-users using Kaplan–Meier analysis and Cox proportional hazard model analysis. The analysis was performed using Free Statistics software, version 1.8, and SPSS 26.0 software (IBM Corporation, Armonk, NY, USA). Statistical significance was defined at $p < 0.05$.

Meta-analysis

Literature search. The analysis is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplemental Table S1). We systematically searched the following online databases for relevant literature: Web of Science, PubMed, Cochrane Library, and Embase from inception until July 2024. We chose "anti-hypertensive drug," "immune checkpoint inhibitor," "cancer," and "tumor" as MeSH terms and keywords (Supplemental Table S2). To ensure the inclusion of all eligible studies, we also carefully reviewed the references and proceedings.

Literature selection and data collection. Meta-analysis incorporated studies that met the specified criteria: (1) adult individuals diagnosed with cancer who have received at least one ICI treatment; (2) using any anti-hypertensive drugs for non-oncological reasons at the initiation of ICI treatment; and (3) randomized controlled trials or observational studies. The following were the exclusion criteria: (1) patients receiving radiotherapy, surgery, or other invasive treatment; (2) reviews, case reports, or meta-analysis; (3) non-clinical studies; (4) no relevant clinical outcome data were reported; and (5) duplicate publication of the same study. The primary outcome was the hazard ratio (HR) for OS or PFS with 95% confidence intervals (CI), gained either directly from the article or estimated from the Kaplan–Meier survival curve. Two researchers independently extracted basic information from the included studies: author, country, publication year, age, tumor, sample size, ICIs, type of anti-hypertensive medications, and outcomes, and compiled this information into a comprehensive table. Two researchers conducted an in-depth examination of the studies and obtained relevant information, and any disagreements were resolved by discussion.

Statistical and bias analysis. The Newcastle–Ottawa Scale (NOS) was employed to assess the quality of included studies. Meta-analysis was conducted utilizing R 4.3.2 software (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance set at $p < 0.05$. Cochran Q and I^2 tests were used to detect the heterogeneity between different studies. When heterogeneity was moderate or high (>50%), the random effect model was applied. In other cases, the fixed-effects model was utilized. The stability of outcomes was evaluated through the sensitivity analysis, and the bias of publication was tested using Egger's and Begg's test and funnel plots.

Results

Clinical cohort

Patient characteristics. We collected a cohort of 336 cancer patients receiving ICIs from the 960th Hospital of PLA and the Affiliated Cancer Hospital of Shandong First Medical University. The study population was divided into two groups based on their utilization of anti-hypertensive medications. The cohort included 151 patients on anti-hypertensive therapy and 185 patients without such treatment. Among the patients taking anti-hypertensive drugs, 101 were administered RASi, 75 were on CCB, 19 were given beta-blockers, and 16 were taking diuretics. The baseline clinical characteristics are detailed in Table 1. The mean age of the total cohort was 63.3 years. Notably, the subgroup receiving anti-hypertensive drugs had a higher average age (65.0 years) compared to the non-users (61.9 years), which was a statistically significant difference. The majority of the cohort was male (74.1%), with the most prevalent tumor types being gastrointestinal (GI) tumors (56.5%) and lung cancer (36.9%). Patients concurrently on anti-hypertensive drugs exhibited a higher prevalence of comorbidities, including CHD and DM. A total of 87.8% of patients were treated with a combination of immunotherapy and chemotherapy, with platinum-based chemotherapy being the most common. First-line immunotherapy was administered to 73.5% of the patients, and the most frequently used immunotherapy drugs were sintilimab and camrelizumab. Other than age, smoking history, comorbidities, and anti-hypertensive medications, no significant differences were observed in other variables between the two groups.

Table 1. Clinical characteristics of the patients in the cohort.

Variables	Total ($n=336$)	No anti-hypertensive drugs ($n=185$)	Anti-hypertensive drugs ($n=151$)	*p* Value
Gender, *n* (%)				0.14
Female	87 (25.9%)	42 (22.7%)	45 (29.8%)	
Male	249 (74.1%)	143 (77.3%)	106 (70.2%)	
Age	63.3 (29–85)	61.9 (29–85)	65.0 (48–85)	0.003
Cancer, *n* (%)				0.611
Lung cancer	124 (36.9%)	64 (34.4%)	60 (40%)	
Gastrointestinal cancer	190 (56.5%)	108 (58.4%)	82 (54.3%)	
Other cancer	22 (6.5%)	13 (7%)	9 (6%)	
ECOG-PS, *n* (%)				0.515
0–1	315 (93.8%)	172 (93%)	143 (94.7%)	
2–3	21 (6.2%)	13 (7%)	8 (5.3%)	
Smoking, *n* (%)				0.038
Never	186 (55.4%)	93 (50.3%)	93 (61.6%)	
Current or former	150 (44.6%)	92 (49.7%)	58 (38.4%)	
Metastatic site, *n* (%)				0.95
<2	213 (63.4%)	117 (63.2%)	96 (63.6%)	
$\geqslant 2$	123 (36.6%)	68 (36.8%)	55 (36.4%)	
Coronary heart disease, *n* (%)				<0.001
Yes	33 (9.8%)	7 (3.8%)	26 (17.2%)	
No	303 (90.2%)	178 (96.2%)	125 (82.8%)	
Diabetes mellitus, *n* (%)				<0.001
Yes	68 (20.2%)	24 (13%)	44 (29.1%)	
No	268 (79.8%)	161 (87%)	107 (70.9%)	
Renin–angiotensin system inhibitors, *n* (%)				<0.001
Yes	101 (30.1%)	0 (0%)	101 (66.9%)	
No	235 (69.9%)	185 (100%)	50 (33.1%)	
Calcium channel blocker, *n* (%)				<0.001
Yes	75 (22.3%)	0 (0%)	75 (49.7%)	
No	261 (77.7%)	185 (100%)	76 (50.3%)	

(Continued)

Table 1. (Continued)

Variables	Total (*n* = 336)	No anti-hypertensive drugs (*n* = 185)	Anti-hypertensive drugs (*n* = 151)	*p* Value
Beta-blocker, *n* (%)				<0.001
Yes	19 (5.7%)	0 (0%)	19 (12.6%)	
No	317 (94.3%)	185 (100%)	132 (87.4%)	
Diuretic, *n* (%)				<0.001
Yes	16 (4.8%)	0 (0%)	16 (10.6%)	
No	320 (95.2%)	185 (100%)	135 (89.4%)	
Antibiotic, *n* (%)				0.873
Yes	14 (4.2%)	8 (4.3%)	4 (4%)	
No	322 (95.8%)	177 (95.7%)	145 (96%)	
Glucocorticoid, *n* (%)				0.669
Yes	59 (17.6%)	31 (16.8%)	82 (18.5%)	
No	277 (82.4%)	154 (83.2%)	123 (81.5%)	
Proton pump inhibitor, *n* (%)				0.692
Yes	174 (51.8%)	94 (50.8%)	80 (53%)	
No	162 (48.2%)	91 (49.2%)	71 (47%)	
ICIs, *n* (%)				0.245
PD-1 inhibitors, *n* (%)				
Sintilimab	158 (47.0%)	91 (49.2%)	67 (44.4%)	
Camrelizumab	78 (23.2%)	38 (20.5%)	40 (26.5%)	
Tirellizumab	64 (19.0%)	35 (18.9%)	29 (19.2%)	
Toripalimab	22 (6.5%)	16 (8.6%)	6 (4%)	
Pembrolizumab	6 (1.8%)	2 (1.1%)	4 (2.6%)	
Nivolumab	2 (0.6%)	1 (0.5%)	1 (0.7%)	
Penpulimab	1 (0.3%)	0 (0%)	1 (0.7%)	
PD-L1 inhibitors, *n* (%)				
Atezolizumab	2 (0.6%)	2 (1.1%)	0 (0%)	
Envafolimab	2 (0.6%)	0 (0%)	2 (1.3%)	
Durvalumab	1 (0.3%)	0 (0%)	1 (0.7%)	

(Continued)

Table 1. (Continued)

Variables	Total ($n=336$)	No anti-hypertensive drugs ($n=185$)	Anti-hypertensive drugs ($n=151$)	p Value
Chemotherapy, *n* (%)				0.887
Yes	295 (87.8%)	162 (87.6%)	133 (88.1%)	
No	41 (12.2%)	23 (12.4%)	18 (11.9%)	
Treatment line, *n* (%)				0.232
First line	247 (73.5%)	135 (73%)	112 (74.2%)	
Second line	63 (18.8%)	39 (21.1%)	24 (15.9%)	
Third line and above	26 (7.7%)	11 (5.9%)	15 (9.9%)	

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Table 2. Baseline characteristics of patients before and after propensity score-matched analysis.

Variables	Before matched ($n=336$)			After matched ($n=238$)		
	No anti-hypertensive drug ($n=185$)	Anti-hypertensive drug ($n=151$)	p Value	No anti-hypertensive drug ($n=119$)	Anti-hypertensive drug ($n=119$)	p Value
Age	61.9 (29–85)	65.0 (48–85)	0.003	62.9 (48–80)	64.2 (35–85)	0.235
Smoking, *n* (%)	92 (49.7)	58 (38.4)	0.038	45 (37.85)	48 (40.3)	0.690
CHD, *n* (%)	7 (3.8)	26 (17.2)	<0.001	7 (5.9)	6 (5)	0.775
DM, *n* (%)	24 (13)	44 (29.1)	<0.001	23 (19.3)	23 (19.3)	1

CHD, coronary heart disease; DM, diabetes mellitus.

After PSM, a total of 119 cases and their corresponding 119 controls were included in the survival analysis, totaling 238 participants. Baseline demographic and clinical characteristics before and after matching are presented in Table 2. After matching, there was no significant difference between groups for each matching variable ($p>0.05$). Furthermore, 93 pairs of patients who received RASi were successfully matched with non-users of RASi (Supplemental Table S4). Similarly, 71 pairs of patients treated with CCB were successfully matched with those not undergoing CCB treatment (Supplemental Table S5).

Effect of anti-hypertensive drugs on immunotherapy. The follow-up observation of the survival of patients in the clinical retrospective cohort revealed that those taking anti-hypertensive drugs had a longer median OS compared to non-users (18.9 vs 35.4 months, $p=0.009$, Figure 1(a)). The survival curve showed that patients taking anti-hypertensive drugs also had a tendency toward extending the median PFS (11.8 vs 20.5 months, $p=0.128$, Figure 1(b)), although not statistically significant. Analysis of different types of anti-hypertensive drugs showed that RASi patients had a significant benefit on OS (15.8 vs not reached, $p<0.001$, Figure 1(c)) and PFS (11.2 vs 20.5 months, $p=0.006$, Figure 1(d)). An extended median OS was also observed in those taking CCB (15.8 vs 35.4 months, $p<0.001$, Figure 1(e)). But no similar benefit was observed in the median PFS (11.8 vs 21.3 months, $p=0.055$, Figure 1(f)). To further determine the factors influencing the efficacy of immunotherapy, we

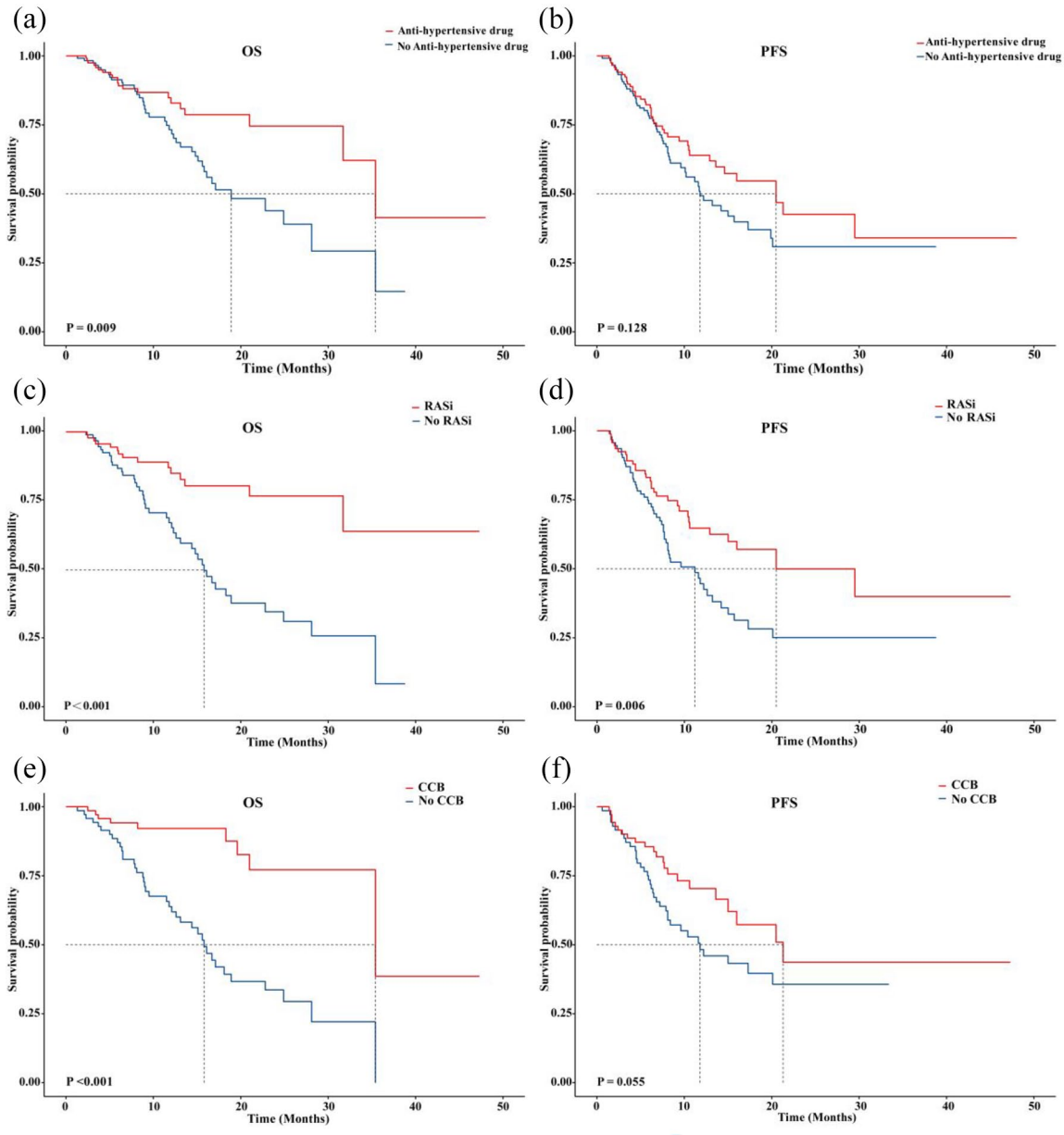

Figure 1. The relationship between anti-hypertensive drugs and immunotherapy. (a and b) Kaplan–Meier curves for the association of anti-hypertensive drug use with OS and PFS. (c and d) OS and PFS in RASi versus non-RASi patients. (e and f) OS and PFS in CCB versus non-CCB patients (after matched).
CCB, calcium channel blocker; OS, overall survival; PFS, progression-free survival; RASi, renin–angiotensin system inhibitor.

conducted univariate and multivariate analyses. In the univariate analysis, anti-hypertensive drugs decreased mortality risk by 45%, suggesting a significant association between anti-hypertensive drug use and OS (HR = 0.55, 95% CI: 0.35–0.89). The use of RASi and CCB was also associated with an extended OS (RASi: HR = 0.58, 95% CI: 0.34–0.99; CCB: HR: 0.43, 95% CI: 0.22–0.84). After adjusting for gender, age, tumor type, ECOG-PS, metastatic site, treatment line, and chemotherapy, a multivariate analysis revealed that the use of anti-hypertensive drugs conferred a stable benefit on OS of patients receiving immunotherapy (Table 3). For controlling disease

Table 3. Univariate and multivariate analyses to determine the factors affecting OS.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Gender	0.67 (0.42–1.08)	0.104		
Age	1.06 (0.67–1.66)	0.811		
ECOG-PS	2.26 (1.19–4.29)	**0.013**	1.98 (1.01–3.91)	**0.048**
Smoking	1.09 (0.69–1.7)	0.72		
Metastatic site	0.59 (0.36–0.97)	**0.037**	0.65 (0.39–1.09)	0.104
Coronary heart disease	0.9 (0.43–1.88)	0.785		
Diabetes	0.97 (0.55–1.71)	0.926		
Anti-hypertensive drug	0.55 (0.35–0.89)	**0.015**	0.55 (0.33–0.90)	**0.019**
RASi	0.58 (0.34–0.99)	**0.044**	0.57 (0.39–0.98)	**0.042**
CCB	0.43 (0.22–0.84)	**0.014**	0.43 (0.21–0.87)	**0.019**
Beta-blocker	0.56 (0.18–1.79)	0.329		
Diuretic	1.94 (0.78–4.83)	0.154		
Chemotherapy	0.31 (0.19–0.51)	<**0.001**	0.41 (0.24–0.72)	<**0.001**
Treatment line	1.91 (1.21–3.00)	**0.005**	1.45 (0.86–2.43)	0.163
Antibiotic	0.85 (0.31–2.35)	0.759		
Proton pump inhibitor	0.5 (0.31–0.80)	**0.004**	0.53 (0.32–0.87)	**0.013**
Glucocorticoid	0.55 (0.26–1.14)	0.11		

Significant *p* values ($p<0.05$) are indicated in **bold**.
CCB, calcium channel blocker; 95% CI, 95% confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; OS, overall survival; RASi, renin–angiotensin system inhibitor.

progression, it was found that anti-hypertensive drugs reduced disease progression by 30% (HR = 0.70, 95% CI: 0.49–0.99). No significant effect on PFS was observed among patients treated with RASi (HR = 0.67, 95% CI: 0.45–1.00) and CCB (HR = 0.71, 95% CI: 0.46–1.11). In multivariate analysis, it was found that only the use of RASi could delay disease progression, and CCB had no significant effect on PFS (Table 4). We did not observe an effect on survival with either beta-blockers (OS: HR = 0.56, 95% CI: 0.18–1.79; PFS: HR = 0.98, 95% CI: 0.46–2.10) or diuretics (OS: HR = 1.94, 95% CI: 0.78–4.83; PFS: HR = 1.10, 95% CI: 0.48–2.49). In addition, it was found that ECOG-PS, treatment line, and combination chemotherapy were factors affecting the prognosis of tumor patients.

Subgroup analysis of the influence of RASi or CCB on immunotherapy. To further explore the potential benefits of RASi or CCB use in different patients, subgroup analysis was conducted and stratified by gender, age, and tumor type. Regarding RASi (Figure 2), the female patients using RASi exhibited a significant prolongation of OS (HR = 0.22, 95% CI: 0.07–0.72) and PFS (HR = 0.37, 95% CI: 0.16–0.84) compared to non-users. However, for male patients, the use

Table 4. Univariate and multivariate analyses to determine the factors affecting PFS.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Gender	0.73 (0.51–1.06)	0.095		
Age	0.92 (0.65–1.30)	0.638		
ECOG-PS	1.76 (0.99–3.13)	0.053		
Smoking	0.72 (0.51–1.02)	0.067		
Metastatic site	1.28 (0.91–1.80)	0.162		
Coronary heart disease	0.57 (0.29–1.13)	0.108		
Diabetes	1.05 (0.68–1.61)	0.824		
Anti-hypertensive drug	0.70 (0.49–0.99)	**0.046**	0.71 (0.49–1.03)	0.069
RASi	0.67 (0.45–1.00)	**0.048**	0.65 (0.43–0.97)	**0.035**
CCB	0.71 (0.46–1.11)	0.130	0.73 (0.46–1.16)	0.188
Beta-blocker	0.98 (0.46–2.10)	0.958		
Diuretic	1.10 (0.48–2.49)	0.826		
Chemotherapy	0.67 (0.42–1.08)	0.099		
Treatment line	1.64 (1.16–2.34)	**0.006**	1.53 (1.04–2.33)	**0.029**
Antibiotic	1.08 (0.47–2.45)	0.859		
Proton pump inhibitor	1.07 (0.76–1.51)	0.681		
Glucocorticoid	1.04 (0.68–1.59)	0.868		

Significant *p* values ($p<0.05$) are indicated in **bold**.
CCB, calcium channel blocker; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; PFS, progression-free survival; RASi, renin–angiotensin system inhibitor.

of RASi was not associated with improved OS and PFS (OS: HR = 0.81, 95% CI: 0.42–1.57; PFS: HR = 0.70, 95% CI: 0.43–1.15). When stratified by age, RASi use did not show an association with patient prognosis in patients <65 years of age (OS: HR = 0.66, 95% CI: 0.31–1.39; PFS: HR = 0.73, 95% CI: 0.43–1.25), but patients ⩾65 years of age, the use of RASi was linked to a positive OS (HR = 0.23, 95% CI: 0.08–0.62) and PFS (HR = 0.47, 95% CI: 0.24–0.91) compared to non-users. In terms of tumor type, no association between RASi use and OS was found in lung cancer and GI tumors (lung cancer: HR = 0.39, 95% CI: 0.11–1.40; GI cancer: HR = 0.55, 95% CI: 0.25–1.22). However, the use of RASi demonstrated better disease control in lung cancer patients compared to non-users (HR = 0.37, 95% CI: 0.17–0.79), as evidenced by longer PFS, although similar results were not found in GI cancer (HR = 0.79, 95% CI: 0.45–1.38).

An association between CCB use and OS was observed in women and elders compared to men or patients <65 years of age. In lung cancer patients, no benefit of CCB use in OS and PFS was found. However, we observed a longer OS in GI cancer patients using CCB compared to

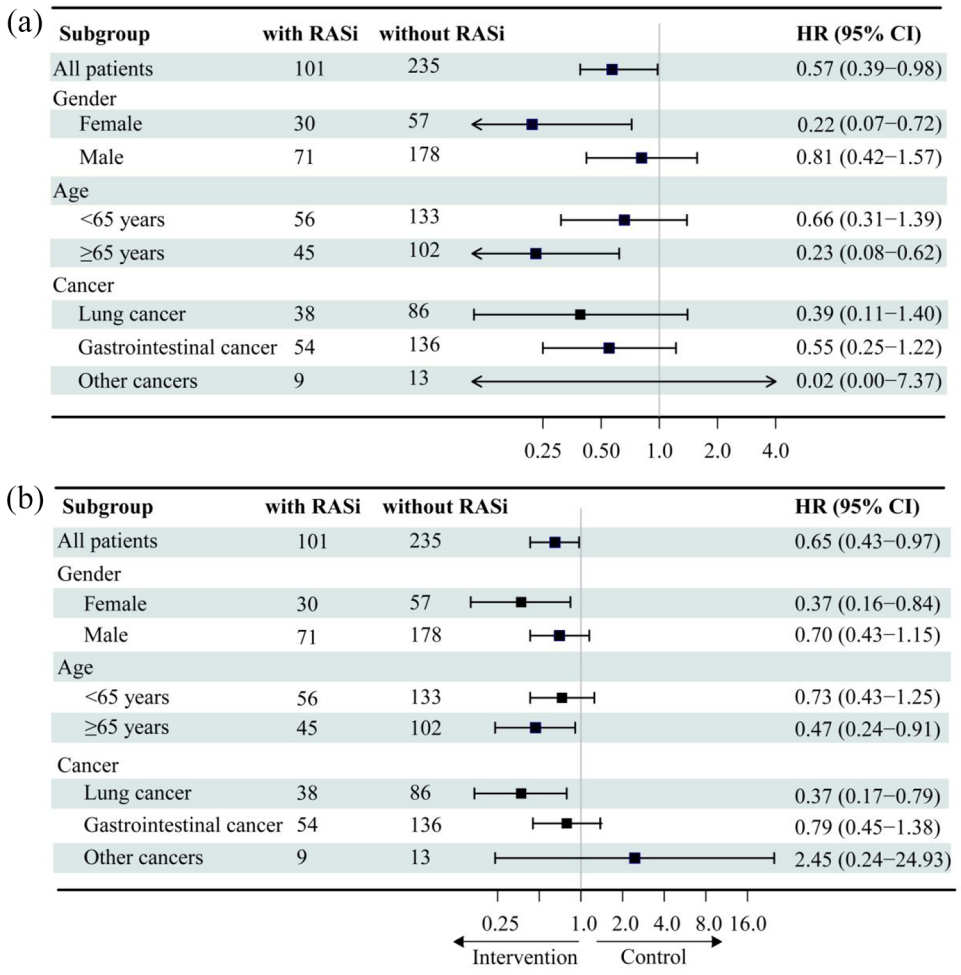

Figure 2. Subgroup analysis of the effect of RASi use on OS (a) and PFS (b) in patients receiving ICIs.
Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; ICIs, immune checkpoint inhibitors; OS, overall survival; PFS, progression-free; RASi, renin–angiotensin system inhibitor.

non-users (HR = 0.24, 95% CI: 0.07–0.87), the similar results were not found in PFS (Figure 3).

Meta-analysis

Study characteristics. The meta-analysis included a total of 17 studies, enrolling 13,707 patients. A flowchart illustrating the screening process for literature is presented in Figure 4. Anti-hypertensive drugs, commonly used in hypertensive patients, include RASi, CCB, beta-blockers, and diuretics. However, the effect of diuretics in patients receiving immunotherapy has only been shown in a single study. The most prevalent cancers among the included studies were lung cancer and melanoma. Patients were from various regions, primarily the United States, Europe, and Asia. The studies were published from 2016 to 2024. The median patient age ranged from 57.6 to 73.7 years. The analysis included only retrospectively conducted studies. The general characteristics of the included studies are shown in Table 5. The NOS was used to assess the quality of the 17 studies, all of which were of moderate or high quality (Supplemental Table S3).

Effect of anti-hypertensive drugs. Seventeen studies examined the impact of anti-hypertensive medications on OS among patients treated with ICIs. In comparison to patients not receiving

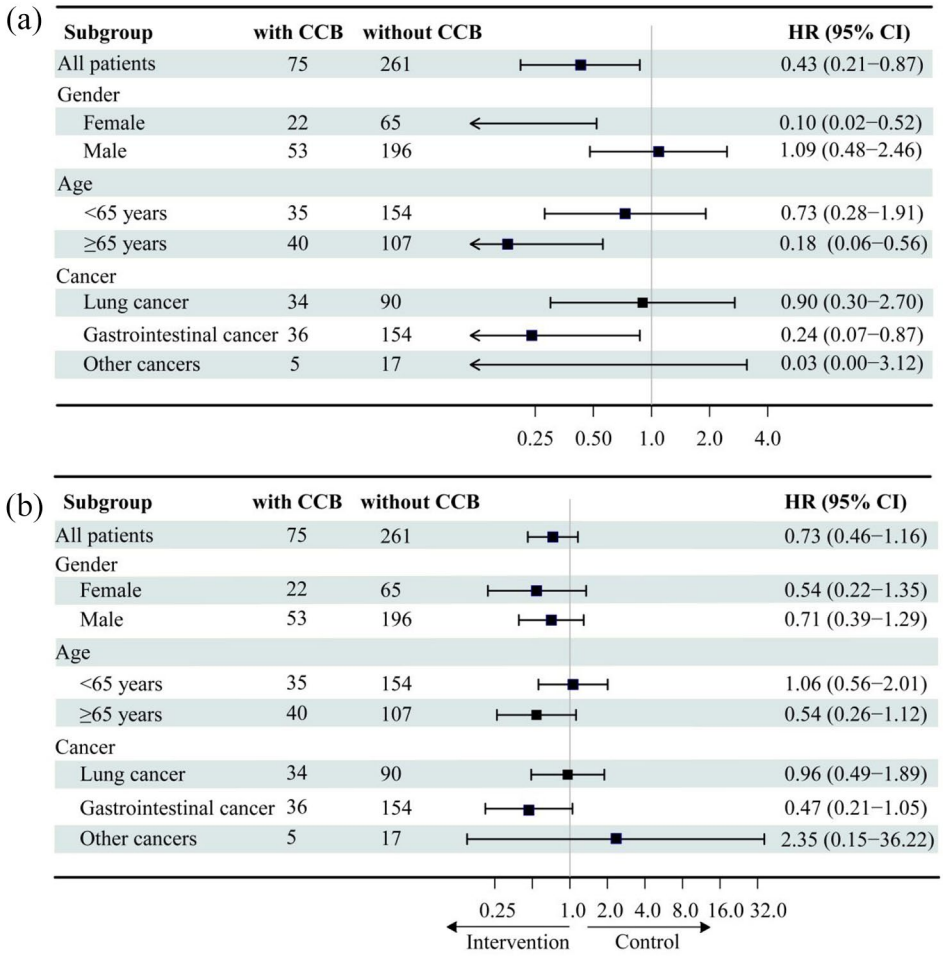

Figure 3. Subgroup analysis of the effect of CCB use on OS (a) and PFS (b) in patients receiving ICIs.
CCB, calcium channel blocker; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; ICIs, immune checkpoint inhibitors; OS, overall survival; PFS, progression-free survival.

anti-hypertensive medication, those who were administered anti-hypertensive drugs had an extended OS (HR = 0.94, 95% CI: 0.89–0.99, $p = 0.0134$, Figure 5). Heterogeneity in studies was low ($I^2 = 45\%$, $p = 0.01$); thus, a fixed-effects model was used to combine effect sizes. However, in a pooled meta-analysis of 12 studies on PFS, no significant association was observed between the use of anti-hypertensive medication and PFS (HR = 0.97, 95% CI: 0.85–1.09, $p = 0.567$, Figure 6) and a random-effects model was used to analyze PFS due to the high heterogeneity observed among the studies ($I^2 = 59\%$, $p < 0.01$).

To investigate the impact of different types of anti-hypertensive drugs on immunotherapy and potential factors affecting heterogeneity, we conducted subgroup analyses stratified by type of anti-hypertensive drugs and tumor type. For the effect of different anti-hypertensive drugs on OS (Figure 7) or PFS (Figure 8), the use of RASi was found to be associated with longer OS (HR = 0.89, 95% CI: 0.84–0.94, $p < 0.01$). However, no improvement was observed for PFS (HR = 0.91, 95% CI: 0.70–1.20, $p = 0.421$). When taking CCB to treat hypertension, the use of CCB was not associated with OS (HR = 1.04, 95% CI:

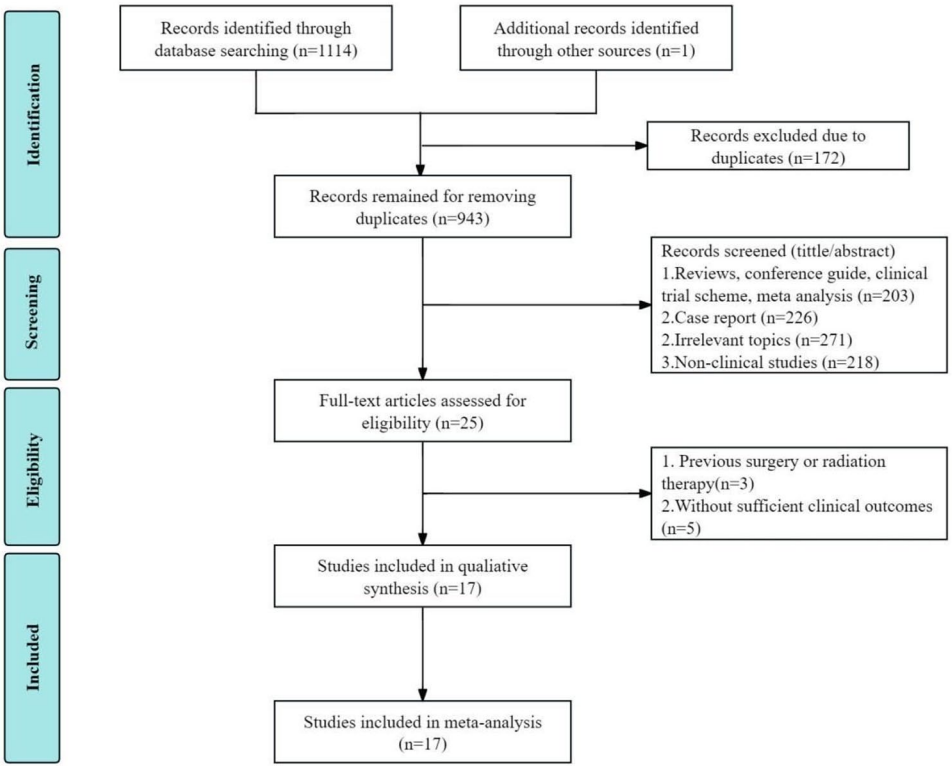

Figure 4. PRISMA flow chart.
Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

0.92–1.18, $p=0.492$) or PFS (HR = 1.03, 95% CI: 0.92–1.16, $p=0.670$). The same results were observed in patients receiving beta-blockers (OS: HR = 1.02, 95% CI: 0.93–1.11, $p=0.706$; PFS: HR = 0.96, 95% CI: 0.83–1.12, $p=0.642$). For tumor type (Figures 9 and 10), no significant correlation was observed between the use of anti-hypertensive drugs and PFS (HR = 0.98, 95% CI: 0.75–1.29) or OS (HR = 1.04, 95% CI: 0.92–1.27) in lung cancer treated with ICIs. Similarly, anti-hypertensive drugs did not show a significant association with the prognosis of melanoma patients undergoing immunotherapy (OS: HR = 0.90, 95% CI: 0.65–1.23, $p=0.503$; PFS: HR = 0.88, 95% CI: 0.67–1.15, $p=0.580$). However, in the case of urothelial cancer, anti-hypertensives were associated with a favorable OS (HR = 0.44, 95% CI: 0.28–0.70, $p=0.001$).

Stability of result. The results indicated the absence of publication bias in HR analysis of PFS (Begg's test: $p=0.2629$, Egger's test: $p=0.4669$, Supplemental Figure 1) and OS (Begg's test: $p=0.3587$, Egger's test: $p=0.7729$, Supplemental Figure 2). The sensitivity analysis results indicated that the HR for OS and PFS was not significantly impacted by any individual study (Supplemental Figures 3 and 4). Collectively, these findings demonstrate the stability of the study outcomes, which appear to be unaffected by potential publication bias.

Discussion

Based on a retrospective cohort study and meta-analysis, we performed a comprehensive and systematic investigation of the impact of anti-hypertensive drugs on immunotherapy and had two key findings. First, we found that anti-hypertensive treatment can work synergistically to improve the antitumor efficacy of ICIs, significantly extending patients' OS and PFS. Notably, RASi or CCB demonstrated a stronger synergistic effect. Second, we identified for the first time that the synergistic benefits of RASi or CCB on ICIs were concentrated in females or patients ⩾65 years of age. It is worth noting that RASi or CCB exhibited different benefits in various types of tumors. In lung cancer patients, RASi showed a tendency to be associated with better clinical outcomes,

Table 5. Baseline characteristics of studies included ($n = 17$).

First author	Age	Region	Cancer	Sample size	ICIs	Anti-hypertensive drugs	Outcomes	HR (95% CI) for PFS	HR (95% CI) for OS	Analysis	NOS score
Buti (2021)[14]	69	Italy	Multiple	217	ICIs	ACEI	OS	NA	0.69 (0.48–1.01)	Univariate analysis	7
Cortellini (2021)[15]	70.1	Europe	NSCLC	950	PD-1	Beta-blocker	OS/PFS	1.03 (0.86–1.22)	1.03 (0.85–1.25)	Univariate analysis	7
Cortellini (2020)[13]	68.5	Europe	Multiple	1012	PD-1/L1	RASi	OS/PFS	0.94 (0.79–1.12)	0.91 (0.74–1.11)	Multivariate analysis	7
						CCB		1.07 (0.86–1.34)	1.19 (0.92–1.54)		
						Beta-blocker		0.95 (0.75–1.22)	0.90 (0.68–1.20)		
Drobni (2022)[16]	NA	America	Multiple	5910	ICIs	RASi	OS	NA	0.90 (0.84–0.98)	Multivariate analysis	7
			Melanoma						1.02 (0.81–1.27)		
Failing (2016)[17]	57.6	America	Melanoma	159	CTLA-4	RASi	OS/PFS	0.67 (0.33–1.36)	0.41 (0.10–1.71)	Univariate analysis	6
						CCB		2.77 (0.86–8.95)	2.15 (0.51–9.02)		
						Beta-blocker		0.82 (0.41–1.66)	0.93 (0.33–2.65)		
Jain (2021)[18]	67.8	America	mUC	178	PD-1/L1	RASi	OS	NA	0.52 (0.29–0.93)	Multivariate analysis	7
	73			101					0.57 (0.17–1.96)		
Kichenadasse (2021)[19]	65	Multiple	Multiple	2539	PD-L1	All	OS/PFS	1.06 (0.96–1.17)	1.01 (0.89–1.13)	Multivariate analysis	8
						RASi		0.95 (0.84–1.08)	0.92 (0.79–1.07)		
						CCB		1.04 (0.88–1.21)	1.03 (0.88–1.21)		
						Beta-blocker		1.01 (0.90–1.13)	1.05 (0.91–1.21)		
						Diuretic		1.15 (0.92–1.19)	1.15 (0.95–1.4)		
Leshem (2023)[20]	69	Asia	NSCLC	200	PD-1	Beta-blocker	OS/PFS	1.92 (1.32–2.79)	1.80 (1.18–2.75)	Multivariate analysis	8
Medjebar (2020)[21]	65.5	France	NSCLC	178	PD-1/L1	ACEI	OS/PFS	1.79 (1.13–2.83)	1.61 (0.96–2.69)	Univariate analysis	8

(Continued)

Table 5. (Continued)

First author	Age	Region	Cancer	Sample size	ICIs	Anti-hypertensive drugs	Outcomes	HR (95% CI) for PFS	HR (95% CI) for OS	Analysis	NOS score
						ARB		0.84 (0.53–1.33)	1.00 (0.60–1.65)		
						Beta-blocker		1.17 (0.80–1.73)	1.27 (0.83–1.95)		
Mellgard (2022)[22]	65.2	America	Multiple	339	ICIs	Beta-blocker	OS	NA	0.77 (0.54–1.08)	Multivariate analysis	8
			HCC						1.03 (0.48–2.24)		
			Melanoma						0.89 (0.41–1.96)		
			NSCLC						0.82 (0.40–1.65)		
			UC						0.24 (0.09–0.62)		
Nuzzo (2022)[23]	63	America	mRCC	166	ICIs	RASi	OS	NA	0.59 (0.37–0.95)	Multivariate analysis	7
Oh (2021)[12]	73.7	America	NSCLC	109	PD-1/L1	Beta-blocker	OS/PFS	0.58 (0.36–0.93)	0.66 (0.38–1.17)	Univariate analysis	7
Silva (2021)[24]	64	Europe	mRCC	698	PD-1	Beta-blocker		0.99 (0.82–1.20)	1.07 (0.83–1.37)	Univariate analysis	6
Tozuka (2021)[11]	69	Japan	NSCLC	256	PD-1/L1	RASi	OS/PFS	0.59 (0.4–0.88)	0.71 (0.45–1.11)	Univariate analysis	8
	67					CCB		0.88 (0.65–1.21)	0.88 (0.65–1.21)		
Wang (2020)[25]	60	Multiple	Melanoma	330	PD-1	Beta-blocker	OS/PFS	0.86 (0.62–1.20)	0.89 (0.60–1.32)	Univariate analysis	8
Yan (2022)[26]	NA	China	Multiple	194	ICIs	Beta-blocker	OS/PFS	0.69 (0.47–1.03)	0.69 (0.47–1.03)	Multivariate analysis	6
Duarte Mendes (2024)[27]	65.8	Portugal	NSCLC	171	ICIs	Beta-blocker	PFS	0.78 (0.50–1.20)	NA	Multivariate analysis	7

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; CTLA-4, cytotoxic T lymphocyte antigen 4; HCC, hepatocellular carcinoma; HR, hazard ratio; ICIs, immune checkpoint inhibitors; MRCC, metastatic renal cell cancer; mUC, metastatic urothelial carcinoma; NA, not available; NOS, Newcastle–Ottawa Quality Assessment Scale; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed cell death 1; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival; RASi, renin–angiotensin system inhibitor.

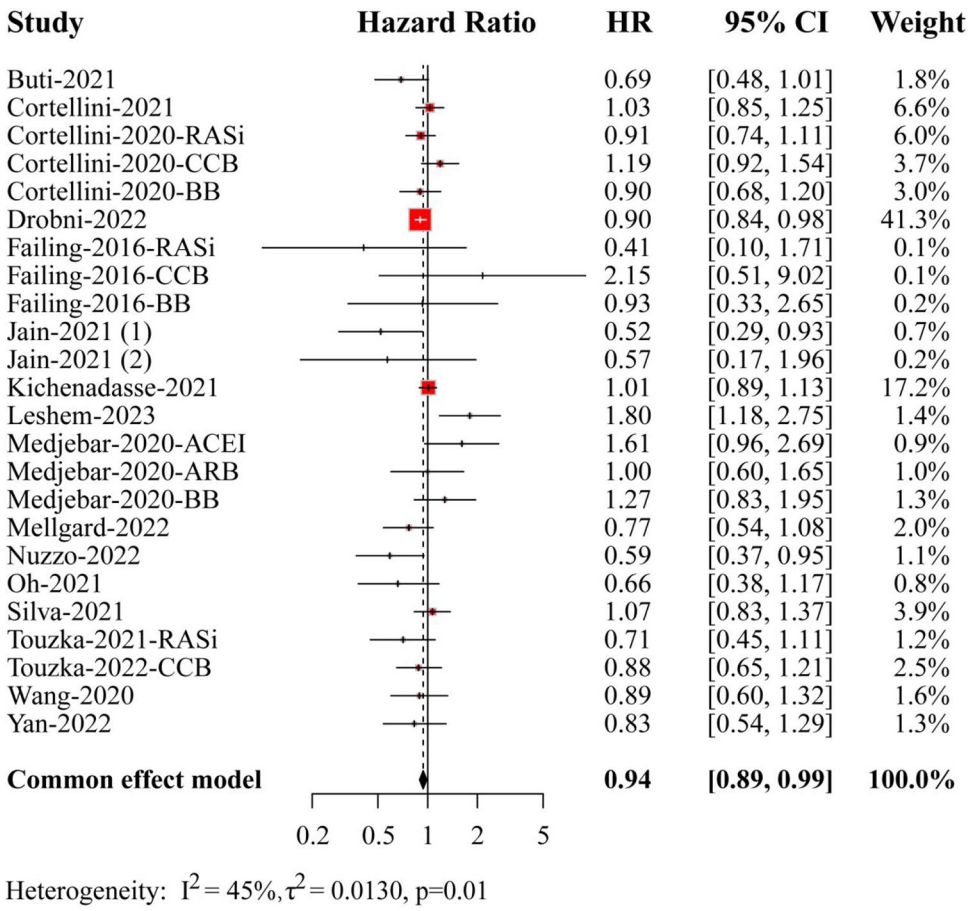

Figure 5. Forest plots of the hazard ratio of OS in patients receiving immunotherapy combined with anti-hypertensive drugs.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; OS, overall survival; RASi, renin–angiotensin system inhibitor.

while the benefit of CCB was more pronounced in patients with GI tumors.

For RASi, Drobni et al.[16] enrolled 5910 cancer patients who were taking anti-hypertensive drugs and receiving immunotherapy. A total of 57.9% of the patients were on RASi. They found that RASi was related to better prognosis (HR = 0.92, 95% CI: 0.85–0.99), which aligns with our findings. The results remained stable even after adjusting for baseline characteristics, tumor type, ECOG PS, tumor metastasis, treatment line, and combination chemotherapy. Although some previous studies have reported negative results, our meta-analysis of pooled studies still supports the synergistic effect of RASi on immunotherapy.

For CCB, we found that using CCB significantly improved OS in patients undergoing immunotherapy, but previous studies have not found similar results. The proportion of CCB use ranged from 8% to 23% in the four available studies, with two focusing on NSCLC[11] and melanoma,[17] and the others examining multiple cancer types.[13,19] In our study, the percentage of CCB users was 22.3%, with a majority having GI tumors (48%). The discrepancy with previous studies might be attributed to sample size limitations and tumor heterogeneity, yet our findings offer valuable insights. Future studies with larger sample sizes are necessary to address the research gap in this field. However, the number of beta-blocker or diuretic users was minimal in our study. Only one study mentioned that the use of diuretics did not affect patient survival.[19] Therefore, further large-scale studies are required to determine the effect of beta-blockers or diuretics on the efficacy of immunotherapy.

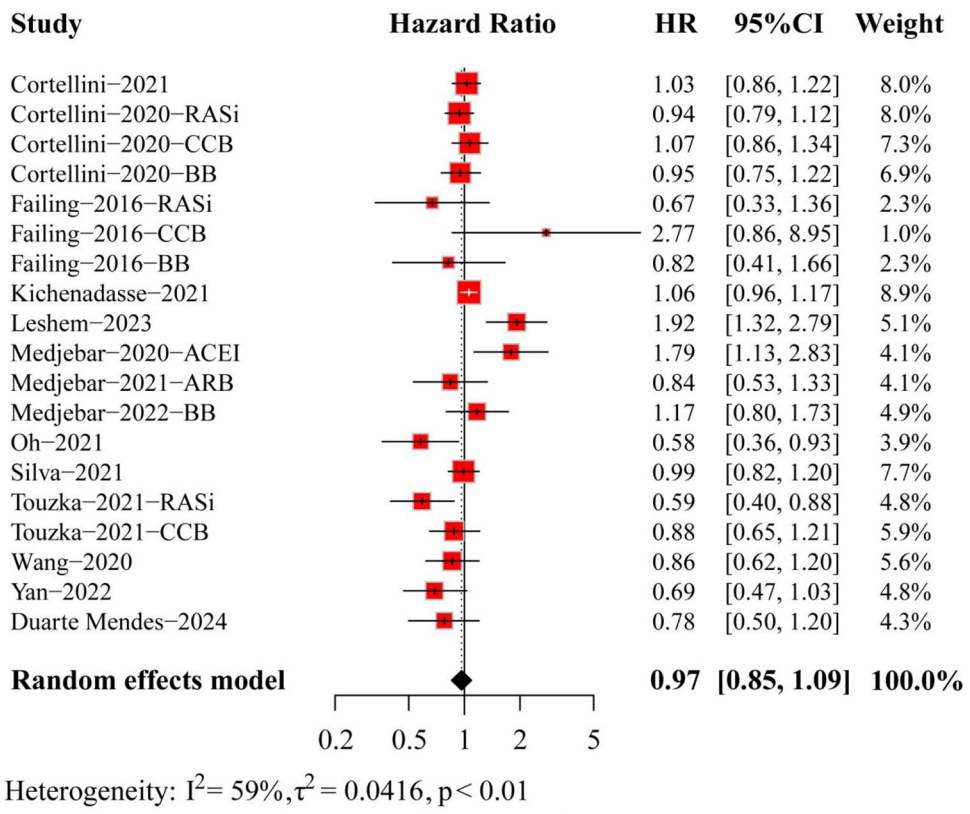

Figure 6. Forest plots of the hazard ratio of PFS in patients receiving immunotherapy combined with anti-hypertensive drugs.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RASi, renin–angiotensin system inhibitor.

Based on real-world data, the present study is the first attempt to explore the patient populations potentially benefiting from the synergistic effects of RASi or CCB with ICIs. A subgroup analysis was performed, taking into account variables such as gender, age, and tumor type. Surprisingly, our findings revealed notable disparities in the efficacy of RASi or CCB among patients with different tumor types. In lung cancer patients, RASi showed potential in controlling disease progression. In preclinical studies, RAS may facilitate the development of a tumor immunosuppressive microenvironment by upregulating the expression of PD-L1[28] or influencing myeloid cells and fibroblasts.[29] Consequently, RASi has the potential to enhance the efficacy of immunotherapy by mitigating immunosuppression. This may explain why RASi can enhance the efficacy of ICIs and lead to a significant extension of PFS in lung cancer patients.[11] However, our meta-analysis did not reveal a significant association between the use of anti-hypertensive drugs and prognosis in lung cancer patients. This discrepancy may be attributed to the limited sample size of our clinical cohort. Therefore, we believe that larger-scale studies are needed to draw more comprehensive and precise conclusions. CCB has been found to improve the prognosis for patients with GI tumors, as demonstrated by significantly longer OS. In colorectal cancer mice, CCB effectively reduced the expression of programmed cell death ligand 1 (PD-L1) in tumor cells and programmed cell death 1 (PD-1) in T lymphocytes.[30] This indicates a potential to boost the antitumor effects when combining CCB with ICIs. However, more research is needed to validate these findings. Currently, there is a lack of studies specifically investigating the prognostic effects of CCB among patients receiving immunotherapy for GI tumors, and there is insufficient data for meta-analysis. The present study aptly fills the gap. In the future, we will continue to investigate the potential effects of anti-hypertensive drugs on the prognosis of GI cancer patients. In addition, we discovered that RASi or CCB exhibit stronger synergistic effects

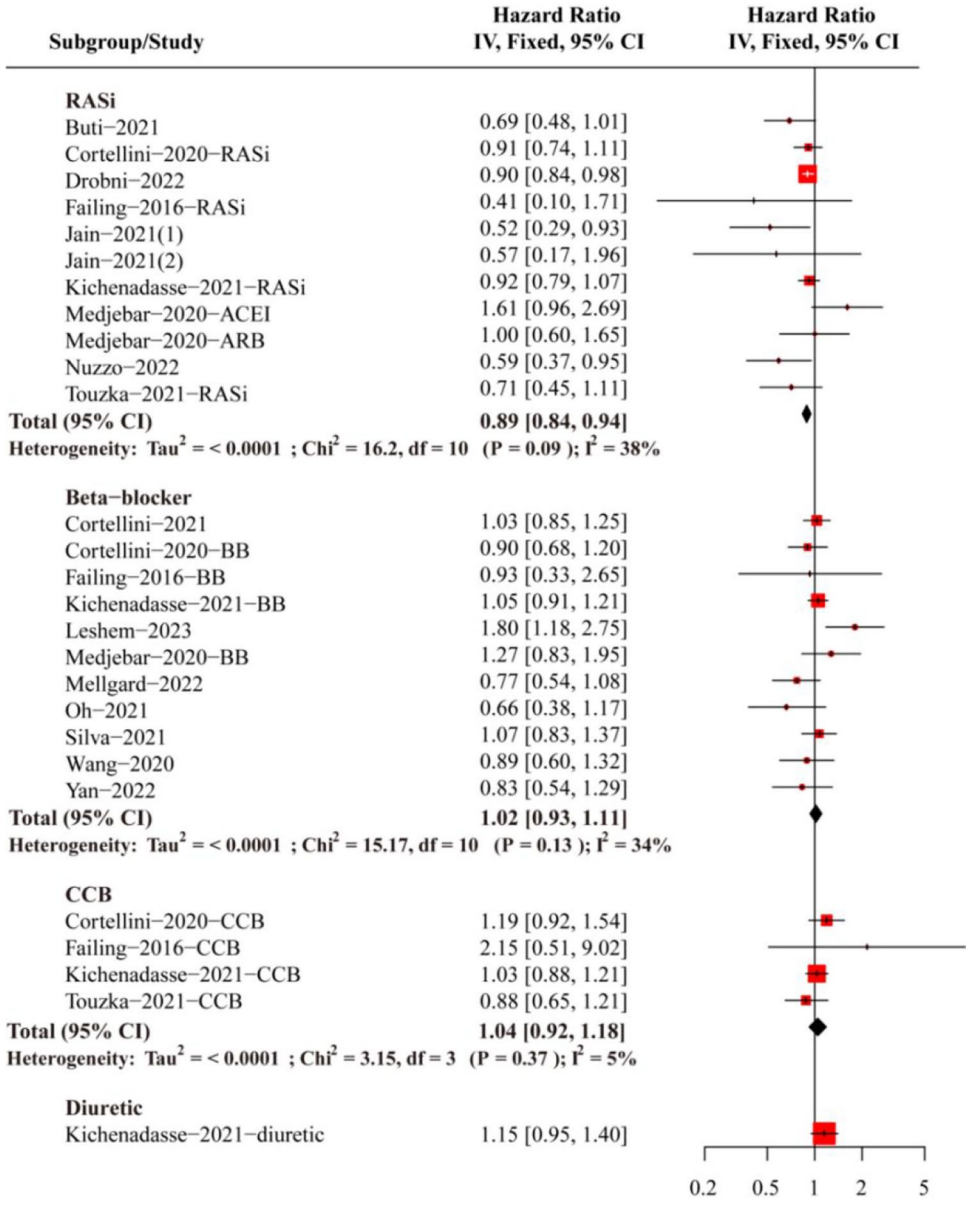

Figure 7. Forest plots of HR of OS in patients receiving ICIs combined with different anti-hypertensive drugs.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; ICIs, immune checkpoint inhibitors; OS, overall survival; RASi, renin–angiotensin system inhibitor.

in women or patients ⩾65 years of age. However, there is limited research on how gender or age influences the relationship between anti-hypertensive drugs and immunotherapy. Future prospective studies are necessary to strengthen the validity of our results. These findings highlight the potential for personalized treatment strategies that combine RASi or CCB with ICIs and emphasize the need for further research to optimize treatment approaches for various patient subgroups.

In clinical practice, patients are often treated with multiple drugs. To eliminate the influence of other concomitant medications, we specifically analyzed the impact of drugs known to influence immunotherapy, such as antibiotics,[31] glucocorticoids,[32] and PPI.[33] However, we did not obtain any significant effect of antibiotics and glucocorticoids on patients' prognosis, which may be attributed to the limited sample size and the brief duration of their use. Our results showed that using PPI was associated with improved clinical

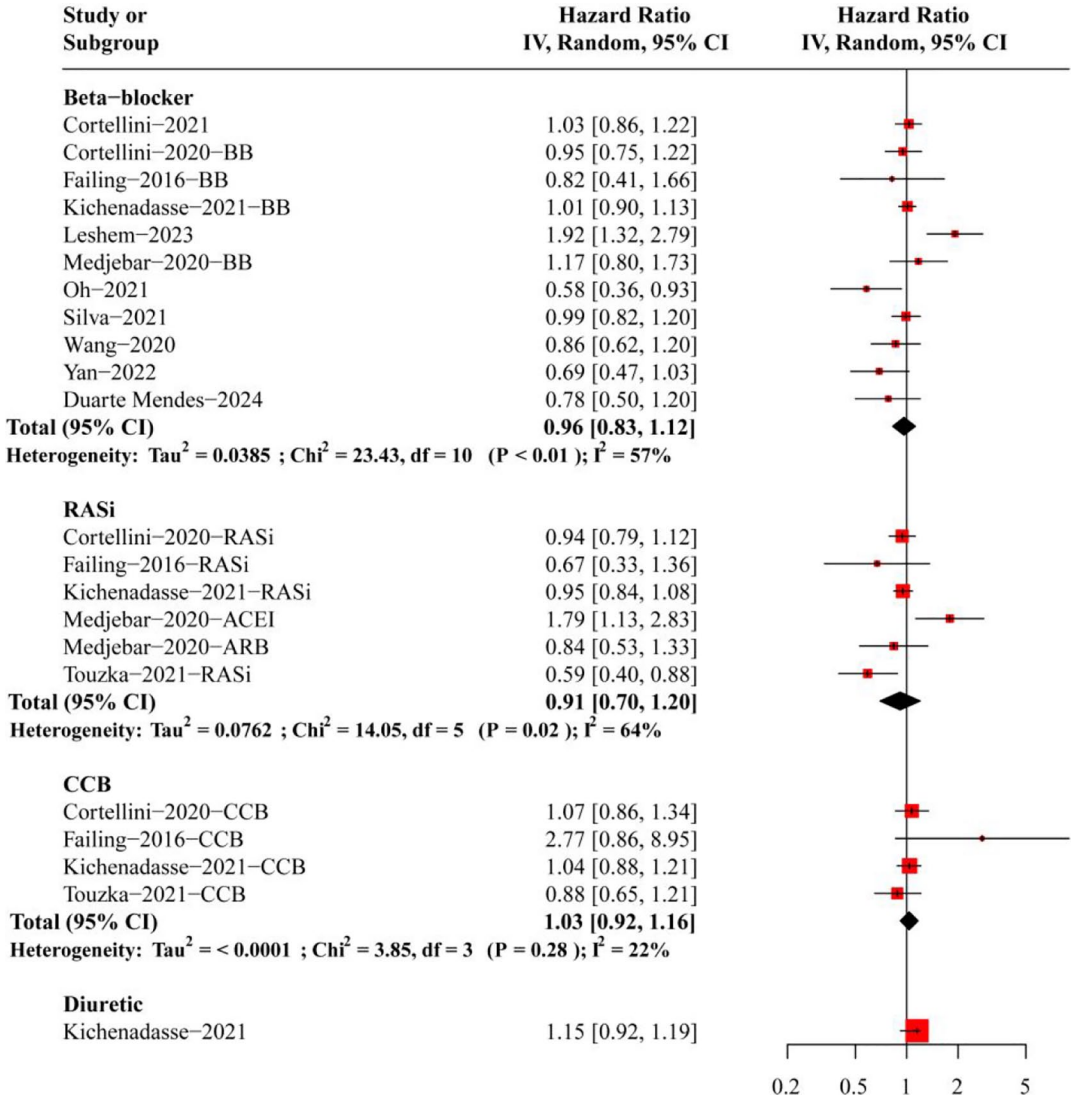

Figure 8. Forest plots of the HR of PFS in patients receiving ICIs combined with different anti-hypertensive drugs.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; ICIs, immune checkpoint inhibitors; PFS, progression-free survival; RASi, renin–angiotensin system inhibitor.

outcomes. Previous research has discovered a connection between PPI and ICI monotherapy. A recent study suggested that patients taking PPI in combination with chemotherapy and ICIs experienced more favorable outcomes compared to those undergoing immune monotherapy.[34] However, only 25% of the patients receiving ICIs and chemotherapy in the cohort of this study were on PPI. Our clinical cohort demonstrated that 87.8% of patients received chemotherapy in combination with immunotherapy, with over half of these patients concurrently taking PPI, which may have contributed to the positive results observed in our study. Upon conducting multivariate analysis while controlling for PPI use, we found that the association between anti-hypertensive medications and ICIs remained stable. However, the conflicting results need to be verified through further experiments.

Despite the medical importance of anti-hypertensive drugs in cancer remaining inconclusive, the outcomes from cellular and animal experiments are encouraging. The Ang II/Angiotensin 1 signaling axis plays a crucial role in regulating the cellular matrix, which, in turn, affects tumor

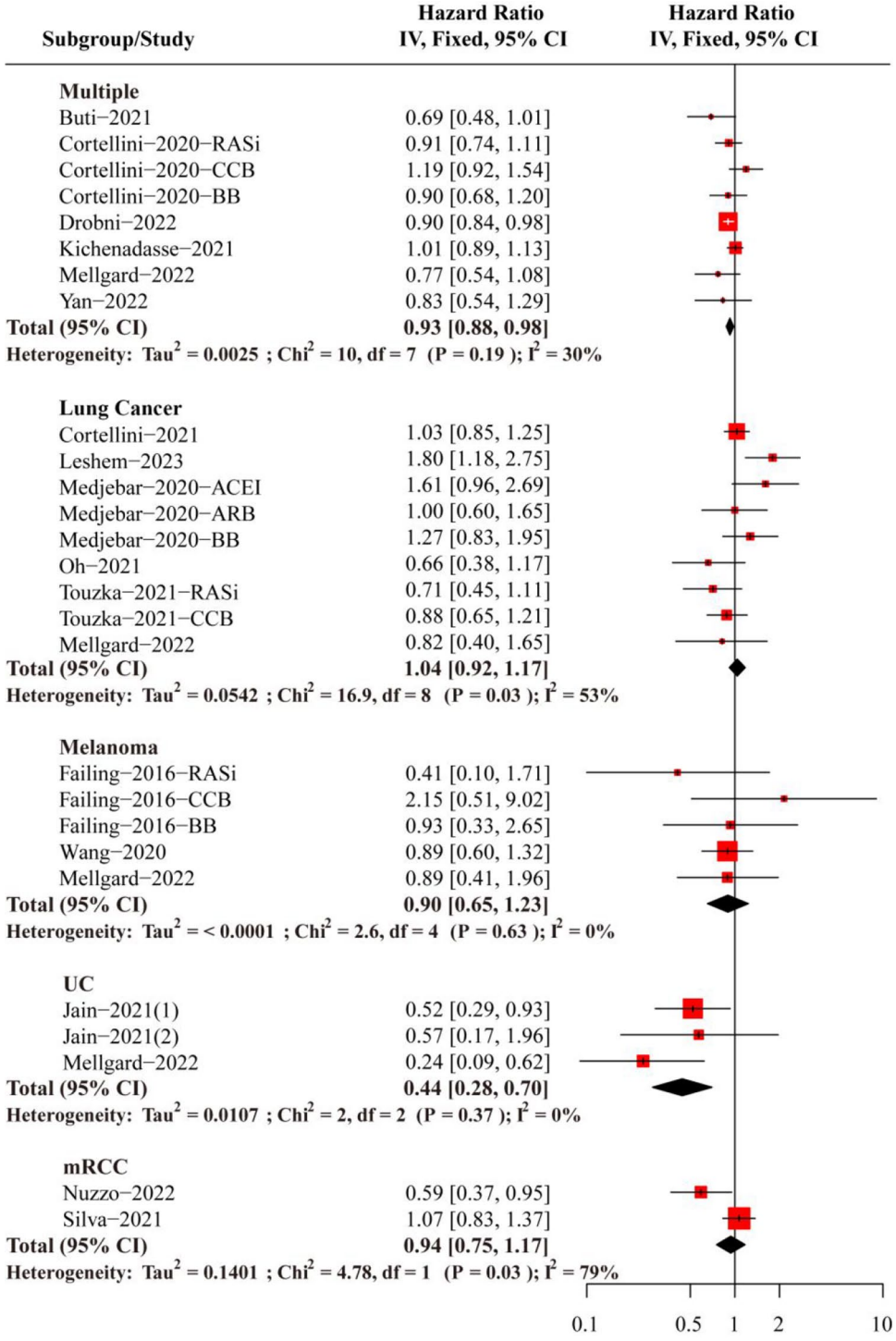

Figure 9. Forest plots of the HR of OS with regard to cancer.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; mRCC, metastatic renal cell cancer; NSCLC, non-small-cell lung cancer; OS, overall survival; RASi, renin–angiotensin system inhibitor; UC, urothelium cancer.

perfusion and promotes an immunosuppressive microenvironment.[9,35] So, the use of RASi may represent a viable strategy for adjunctive antitumor therapy. Recently, clinical trials are underway that investigate the combination of losartan with nivolumab for the treatment of

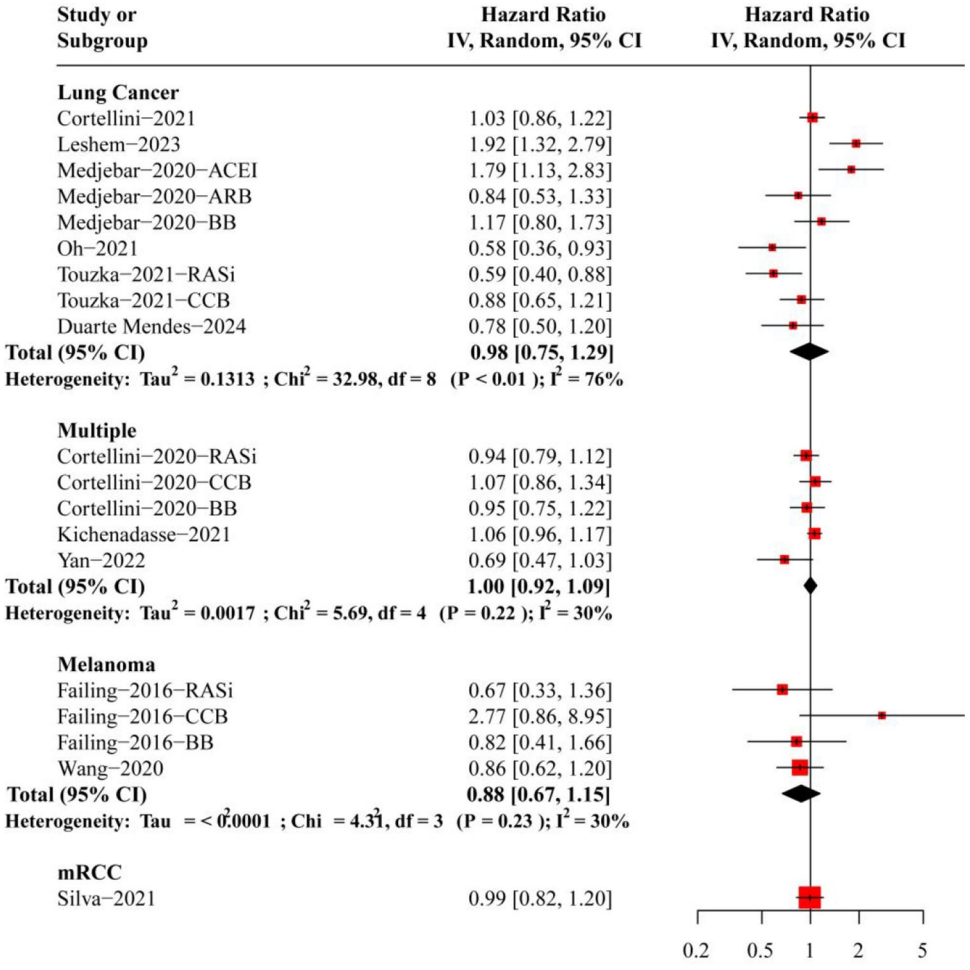

Figure 10. Forest plots of the HR of PFS with regard to cancer.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; mRCC, metastatic renal cell cancer; PFS, progression-free survival; RASi, renin–angiotensin system inhibitor.

pancreatic cancer. Furthermore, the combination of verapamil with a PD-1 inhibitor has been associated with improved survival rate in a mice model of cervical cancer.[36] This indicated that CCB may offer a promising therapeutic option for cervical cancer patients with hypertension. In addition, the inhibition of beta-adrenergic signaling has the potential to enhance antitumor immune responses.[37] Kokolus et al.[10] demonstrated that the combination of propranolol and PD-1 significantly slowed tumor growth in melanoma mice. Further clinical studies are needed to validate the above findings.

Our study is limited by several factors. First, the inclusion of a small clinical cohort restricts the ability to evaluate the relationship between beta-blockers or diuretics and the efficacy of immunotherapy, as well as the impact of anti-hypertensive drugs on prevalent tumors or various ICIs. Prospective validation in a larger group is necessary to enhance confidence in the conclusions. Second, a chemotherapy control group should be established to determine the relationship between immunotherapy and anti-hypertensive drugs, but the limited number of patients receiving ICIs as monotherapy, mainly elderly patients, and confounding baseline characteristics in the preliminary patient analysis hindered a controlled study. Future clinical studies should aim to rectify these issues and establish a control group. Third, our analysis did not include data regarding the dose–response relationships of the anti-hypertensive drugs, due to being underpowered to analyze the dose on the outcome (data not presented). Prospective studies are required to further explore this relationship. Lastly, the 17 studies included in the meta-analysis were retrospective and

exhibited inadequate control of variables due to reporting and selection biases, resulting in a lack of comparability at baseline. Although we performed meta-regression to address heterogeneity among studies, no factors explaining the observed heterogeneity were identified. In summary, additional randomized clinical trials are necessary to validate the relationship between hypertensive medications and immunotherapy.

Conclusion

Overall, based on clinical trials and meta-analysis, we found that taking anti-hypertensive drugs was associated with a favorable OS in cancer patients receiving ICIs, with RASi or CCB demonstrating superior synergy effects. However, due to the inherent limitations of current research, a significant number of prospective and fundamental studies are required to elucidate the effects of RASi or CCB on immunotherapy. The objective of our study was to provide more precise clinical guidance aimed at enhancing cancer patient outcomes in clinical practice.

Declarations

Ethics approval and consent to participate

This study was approved by the People's Liberation Army 960th Hospital Research Ethics Committee (Approval No. 2023-061). A waiver of informed consent was granted due to the retrospective nature of the study.

Consent for publication

Not applicable.

Author contributions

Ping Ma: Conceptualization; Data curation; Formal analysis; Methodology; Software; Writing – original draft; Writing – review & editing.

Zhihuan Zhang: Conceptualization; Data curation; Formal analysis; Methodology; Writing – review & editing.

Mengying Qian: Conceptualization; Data curation; Formal analysis; Methodology; Writing – review & editing.

Hao Jiang: Data curation; Investigation; Methodology; Software; Writing – review & editing.

Yu Zhao: Data curation; Software; Writing – review & editing.

Qing Shan: Data curation; Software; Writing – review & editing.

Xia Liu: Investigation; Methodology; Project administration; Validation; Writing – review & editing.

Tianming Yao: Investigation; Methodology; Project administration; Validation; Writing – review & editing.

Jinmin Guo: Investigation; Methodology; Project administration; Resources; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request (gjm90h@126.com).

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Supplemental material

Supplemental material for this article is available online.

References

1. Shiravand Y, Khodadadi F, Kashani SMA, et al. Immune checkpoint inhibitors in cancer therapy. *Curr Oncol* 2022; 29: 3044–3060.
2. Tang S, Qin C, Hu H, et al. Immune checkpoint inhibitors in non-small cell lung cancer: progress, challenges, and prospects. *Cells* 2022; 11: 320.
3. Luke JJ, Ascierto PA, Carlino MS, et al. KEYNOTE-716: phase III study of adjuvant pembrolizumab versus placebo in resected

high-risk stage II melanoma. *Future Oncol* 2020; 16: 4429–4438.

4. Kwapisz D. Pembrolizumab and atezolizumab in triple-negative breast cancer. *Cancer Immunol Immunother* 2021; 70: 607–617.
5. Grimm MO, Leucht K, Grünwald V, et al. New first line treatment options of clear cell renal cell cancer patients with PD-1 or PD-L1 immune-checkpoint inhibitor-based combination therapies. *J Clin Med* 2020; 9: 565.
6. Hargadon KM, Johnson CE and Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. *Int Immunopharmacol* 2018; 62: 29–39.
7. Giordan Q, Salleron J, Vallance C, et al. Impact of antibiotics and proton pump inhibitors on efficacy and tolerance of anti-PD-1 immune checkpoint inhibitors. *Front Immunol* 2021; 12: 716317.
8. van Dorst DCH, Dobbin SJH, Neves KB, et al. Hypertension and prohypertensive antineoplastic therapies in cancer patients. *Circ Res* 2021; 128: 1040–1061.
9. Pinter M and Jain RK. Targeting the renin–angiotensin system to improve cancer treatment: implications for immunotherapy. *Science Transl Med* 2017; 9: eaan5616.
10. Kokolus KM, Zhang Y, Sivik JM, et al. Beta blocker use correlates with better overall survival in metastatic melanoma patients and improves the efficacy of immunotherapies in mice. *Oncoimmunology* 2018; 7: e1405205.
11. Tozuka T, Yanagitani N, Yoshida H, et al. Impact of renin–angiotensin system inhibitors on the efficacy of anti-PD-1/PD-L1 antibodies in NSCLC patients. *Anticancer Res* 2021; 41: 2093–2100.
12. Oh MS, Guzner A, Wainwright DA, et al. The impact of beta blockers on survival outcomes in patients with non-small-cell lung cancer treated with immune checkpoint inhibitors. *Clin Lung Cancer* 2021; 22: e57–e62.
13. Cortellini A, Tucci M, Adamo V, et al. Integrated analysis of concomitant medications and oncological outcomes from PD-1/PD-L1 checkpoint inhibitors in clinical practice. *J Immunother Cancer* 2020; 8: e001361.
14. Buti S, Bersanelli M, Perrone F, et al. Effect of concomitant medications with immune-modulatory properties on the outcomes of patients with advanced cancer treated with immune checkpoint inhibitors: development and validation of a novel prognostic index. *Eur J Cancer* 2021; 142: 18–28.
15. Cortellini A, Di Maio M, Nigro O, et al. Differential influence of antibiotic therapy and other medications on oncological outcomes of patients with non-small cell lung cancer treated with first-line pembrolizumab versus cytotoxic chemotherapy. *J Immunother Cancer* 2021; 9: e002421.
16. Drobni ZD, Michielin O, Quinaglia T, et al. Renin–angiotensin–aldosterone system inhibitors and survival in patients with hypertension treated with immune checkpoint inhibitors. *Eur J Cancer* 2022; 163: 108–118.
17. Failing JJ, Finnes HD, Kottschade LA, et al. Effects of commonly used chronic medications on the outcomes of ipilimumab therapy in patients with metastatic melanoma. *Melanoma Res* 2016; 26: 609–615.
18. Jain RK, Skelton Iv WP, Pond GR, et al. Angiotensin blockade modulates the activity of PD1/L1 inhibitors in metastatic urothelial carcinoma. *Clin Genitourin Cancer* 2021; 19: 540–546.
19. Kichenadasse G, Miners JO, Mangoni AA, et al. Effect of concomitant use of antihypertensives and immune check point inhibitors on cancer outcomes. *Journal of Hypertens* 2021; 39: 1274–1281.
20. Leshem Y, Etan T, Dolev Y, et al. The prognostic value of beta-1 blockers in patients with non-small-cell lung carcinoma treated with pembrolizumab. *Int J Cardiol* 2024; 397: 131642.
21. Medjebar S, Truntzer C, Perrichet A, et al. Angiotensin-converting enzyme (ACE) inhibitor prescription affects non-small-cell lung cancer (NSCLC) patients response to PD-1/PD-L1 immune checkpoint blockers. *Oncoimmunology* 2020; 9: 1836766.
22. Mellgard G, Patel VG, Zhong X, et al. Effect of concurrent beta-blocker use in patients receiving immune checkpoint inhibitors for advanced solid tumors. *J Cancer Res Clin Oncol* 2022; 149: 2833–2841.
23. Nuzzo PV, Adib E, Weise N, et al. Impact of renin–angiotensin system inhibitors on outcomes in patients with metastatic renal cell carcinoma treated with immune-checkpoint inhibitors. *Clin Genitourin Cancer* 2022; 20: 301–306.
24. Silva CAC, Derosa L, Dalban C, et al. Impact of β-blockers (BB) on outcomes of metastatic renal cell carcinoma (mRCC) patients treated with nivolumab (N). *Ann Oncol* 2021; 32: S710–S710.

25. Wang DY, McQuade JL, Rai RR, et al. The impact of nonsteroidal anti-inflammatory drugs, beta blockers, and metformin on the efficacy of anti-PD-1 therapy in advanced melanoma. *Oncologist* 2020; 25: e602–e605.

26. Yan XB, Liu PP, Li DL, et al. Novel evidence for the prognostic impact of β-blockers in solid cancer patients receiving immune checkpoint inhibitors. *Int Immunopharmacol* 2022; 113: 109383.

27. Duarte Mendes A, Freitas AR, Vicente R, et al. Beta-adrenergic blockade in advanced non-small cell lung cancer patients receiving immunotherapy: a multicentric study. *Cureus* 2024; 16: e52194.

28. Yang K, Zhou J, Chen Y, et al. Angiotensin II contributes to intratumoral immunosuppression via induction of PD-L1 expression in non-small cell lung carcinoma. *Int Immunopharmacol* 2020; 84: 106507.

29. Nakamura K, Yaguchi T, Ohmura G, et al. Involvement of local renin–angiotensin system in immunosuppression of tumor microenvironment. *Cancer Sci* 2018; 109: 54–64.

30. Wu L, Lin W, Liao Q, et al. Calcium channel blocker Nifedipine suppresses colorectal cancer progression and immune escape by preventing NFAT2 nuclear translocation. *Cell Rep* 2020; 33: 108327.

31. Eng L, Sutradhar R, Niu Y, et al. Impact of antibiotic exposure before immune checkpoint inhibitor treatment on overall survival in older adults with cancer: a population-based study. *J Clin Oncol* 2023; 41: 3122–3134.

32. Bruera S and Suarez-Almazor ME. The effects of glucocorticoids and immunosuppressants on cancer outcomes in checkpoint inhibitor therapy. *Front Oncol* 2022; 12: 928390.

33. Qin BD, Jiao XD, Zhou XC, et al. Effects of concomitant proton pump inhibitor use on immune checkpoint inhibitor efficacy among patients with advanced cancer. *Oncoimmunology* 2021; 10: 1929727.

34. Kawachi H, Yamada T, Tamiya M, et al. Concomitant proton pump inhibitor use with pembrolizumab monotherapy vs immune checkpoint inhibitor plus chemotherapy in patients with non-small cell lung cancer. *JAMA Netw Open* 2023; 6: e2322915.

35. Heffelfinger SC. The renin angiotensin system in the regulation of angiogenesis. *Curr Pharm Des* 2007; 13: 1215–1229.

36. Liao YQ, Fang BB, Wu QX, et al. Verapamil modulates NFAT2 to inhibit tumor growth and potentiates PD1ab immune checkpoint inhibitor therapy in cervical cancer treatment. *J Recept Signal Transduct Res* 2023; 43: 93–101.

37. Massalee R and Cao X. Repurposing beta-blockers for combinatory cancer treatment: effects on conventional and immune therapies. *Front Pharmacol* 2023; 14: 1325050.