The Efficacy and Safety of Beta-blockers and Immune Checkpoint Inhibitors in Patients with Cancer: A Systematic Review and Meta-Analysis

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Supplementary Table 1. Search strategy for a systematic review.

Immune checkpoint inhibitors	#1	(Atezolizumab) OR (MPDL3280A) OR (RG7446) OR (Tecentriq) OR (Avelumab) OR (MSB0010718C) OR (Bavencio) OR (Cemiplimab) OR (REGN2810) OR (Libtayo) OR (Durvalumab) OR (MEDI4736) OR (Imfinzi) OR (Ipilimumab) OR (BMS-734016) OR (MDX-010) OR (MDX-101) OR (Yervoy) OR (Nivolumab) OR (ONO-4538) OR (BMS-936558) OR (MDX1106) OR (Opdivo) OR (Pembrolizumab) OR (MK-3475) OR (lambrolizumab) OR (Keytruda) OR (Tremelimumab) OR (CP-675,206) OR (Ticilimumab) OR (Relatlimab) OR (BMS-986016) OR (Dostarlimab) OR (TSR-042) OR (Jemperli) OR (Spartalizumab) OR (PDR001) OR (Penpulimab) OR (AK105) OR (Camrelizumab) OR (SHR-1210) OR (Tislelizumab) OR (BGB-A317) OR (Toripalimab) OR (JS001) OR (Tuoyi) OR (Sintilimab) OR (IBI308) OR (Sugemalimab) OR (CS1001) OR (Adebrelimab) OR (SHR-1316) OR (WBP-285) OR (CD223) OR (immune checkpoint inhibitor) OR (immune checkpoint inhibitors) OR (immune checkpoint blockade) OR (immune checkpoint blockades) OR (PD-1 antibody) OR (PD-1 inhibitor) OR (PD-1 blockade) OR (PD-L1 antibody) OR (PD-L1 inhibitor) OR (PD-L1 blockade) OR (CTLA-4 inhibitor) OR (CTLA-4 blockade) OR (CTLA-4 antibody) OR (CTLA4 inhibitor) OR (CTLA4 blockade) OR (CTLA4 antibody) OR (LAG-3 inhibitor) OR (LAG-3 blockade) OR (LAG-3 antibody) OR (LAG3 inhibitor) OR (LAG3 blockade) OR (LAG3 antibody)
Beta-blockers	#2	(beta blocker) OR (beta-blocker) OR (β-blocker) OR (β blocker) OR (Acebutolol) OR (Atenolol) OR (Betaxolol) OR (Bisoprolol) OR (Carteolol) OR (Carvedilol) OR (Celiprolol) OR (Esmolol) OR (Labetalol) OR (Metoprolol) OR (Nadolol) OR (Nebivolol) OR (Oxprenolol) OR (Penbutolol) OR (Pindolol) OR (Propranolol) OR (Sotalol) OR (Timolol)
Solid cancers	#3	(Solid tumor) OR (Cancer) OR (Neoplasm) OR (Malignancy)
Search strategy	#4	#1 AND #2 AND #3

A systematic search was performed using PubMed/MEDLINE and Embase up to July 27, 2024, with the following search terms.

Supplementary Table 2. Inclusion and exclusion criteria of a systematic review.

Inclusion criteria:	1. Clinical trials, case-control, or cohort studies evaluating the efficacy and/or safety of patients with any type of solid tumors receiving at least one type of immune checkpoint inhibitor (ICI). 2. Studies with a design defined above that evaluated the efficacy and/or safety of the concurrent use of beta-blockers (BBs) and ICIs. 3. Single cohort studies or single-arm clinical trials evaluating the efficacy and/or safety of BBs combined with ICIs. 4. The most recent or informative article was used for multiple articles on the same studies. 5. Supplementary issues and conference abstracts were also assessed and included.
Exclusion criteria:	1. Systematic reviews or meta-analyses. 2. Case reports. 3. Case series with fewer than five patients. 4. Studies published in languages other than English.

Supplementary Table 3. Studies excluded after full-text review and reasons for exclusion.

	Reason for exclusion	References
1	Review article	[1]
2	Clinical study plan	[2]
3	Insufficient outcomes reported	[3]
4	Insufficient outcomes reported	[4]
5	Insufficient outcomes reported	[5]
6	Insufficient outcomes reported	[6]
7	Insufficient outcomes reported	[7]
8	Insufficient outcomes reported	[8]
9	Wrong Intervention	[9]
10	Wrong Intervention	[10]
11	Wrong Intervention	[11]
12	Wrong Intervention	[12]

Supplementary Table 4. Quality assessment of included studies according to the NOS.

Study	Selection				Comparability	Outcome			Total score
	1	2	3	4	1	1	2	3	
Alves Costa Silva 2021	1	1	1	1	1	1	1	0	7
Cortellini 2021	1	1	1	1	2	1	1	0	8
Duarte Mendes 2024	1	1	1	1	1	1	1	0	7
Gandhi 2021	1	1	1	1	0[a]	1	1	0	6
Hong 2020	1	1	1	1	1	1	1	0	7
Leshem 2024	1	1	0	1	2	1	1	0	7
Mellgard 2023	1	1	1	1	1	1	1	1	8
Oh 2021	1	1	1	1	1	1	1	0	7
Oren 2020-1	1	1	1	1	2	1	1	0	8
Oren 2020-2	1	1	1	1	1	1	1	1	8
Wu 2023	1	1	1	0	2	1	1	0	8
Yan 2022	1	1	1	1	2	1	1	1	9

Abbreviations: NOS, Newcastle–Ottawa Quality Assessment Scale.
Footnote: [a]The study by Gandhi et al. is a phase 1 single-arm study, so its comparability cannot be assessed.

This scoring of NOS was conducted by K.T. based on three domains: selection, comparability, and outcome. In selection, points were awarded for 1) the representativeness of the exposed cohort, 2) the selection of the non-exposed cohort, 3) the method of exposure ascertainment, and 4) confirmation that the outcome of interest was not present at the start. In comparability, points were awarded for 1) controlling key confounding factors and additional variables. For outcome, points were given based on 1) the method of outcome assessment, 2) the sufficiency of follow-up duration, and 3) the adequacy of follow-up.

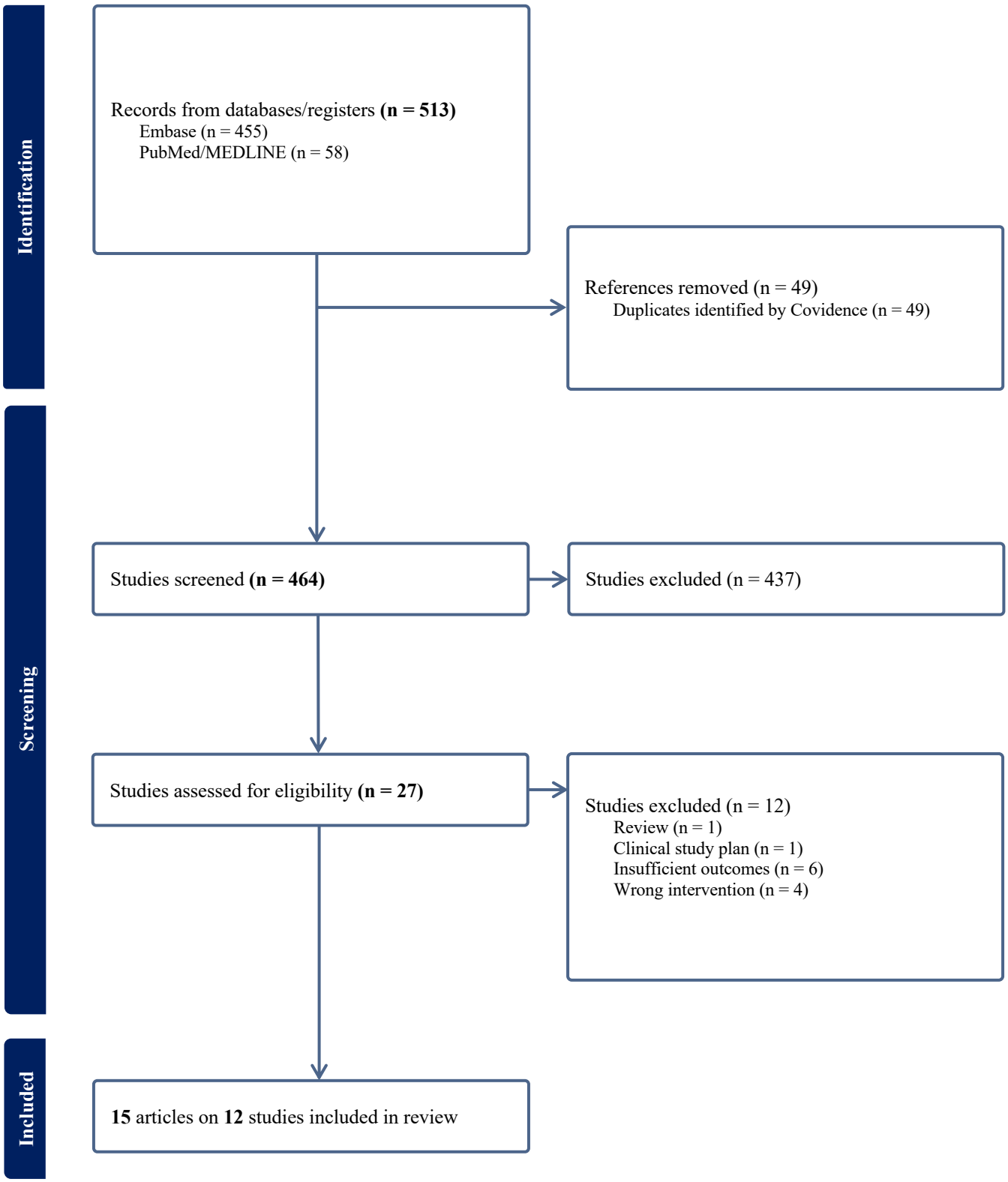
Supplementary Table 5. Summary of Findings and Certainty of Evidence (GRADE)

Outcome	No. of studies	Study design	Overall certainty (GRADE[a])	Effect (pooled)	Key reasons for rating
OS	9 studies	Observational	Low	HR 1.02 (95% CI 0.84–1.23); I^2 = 69%	(a) Risk of bias (retrospective), (b) Variability in effect estimates (high heterogeneity), and (c) No clear imprecision upgrade (CI crosses the line of no effect)
PFS	7 studies	Observational	Low	HR 0.98 (95% CI 0.80–1.20); I^2 = 71%	(a) Risk of bias (retrospective), (b) Variability in effect estimates, and (c) No clear imprecision upgrade
AEs	6 studies	Observational and one prospective phase 1 trial	Very low to Low	No consistent effect	(a) Risk of bias and confounding (BB users often have CV comorbidities), (b) Differences in outcomes measured and reported across studies, and (c) Potential reporting bias.

Abbreviations: AEs, adverse events; BB, beta-blocker; CI, confidence interval; CV, cardiovascular; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HR, hazard ratio; ICIs, immune checkpoint inhibitors; OS, overall survival; PFS, progression-free survival.

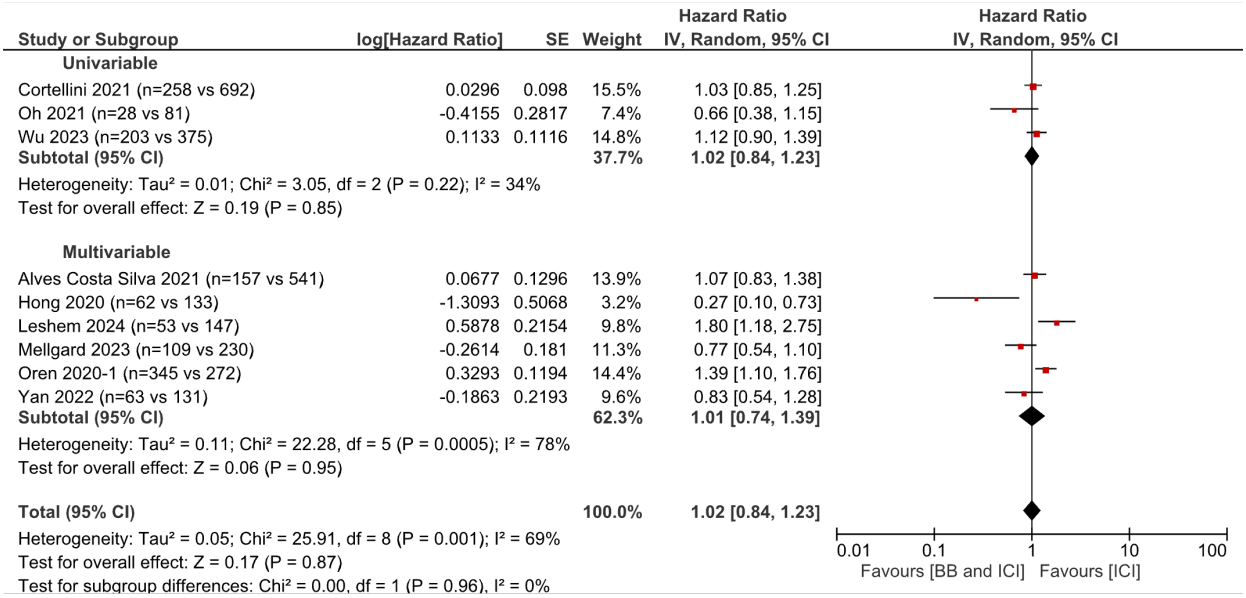
[a] Certainty ratings: High, Moderate, Low, Very low.

Supplementary Fig.1. Systematic review flowchart.



Supplementary Fig.2. Forest plots of HRs for (a) OS and (b) PFS with subgroup analyses based on analysis types, prioritizing multivariable analyses.

a



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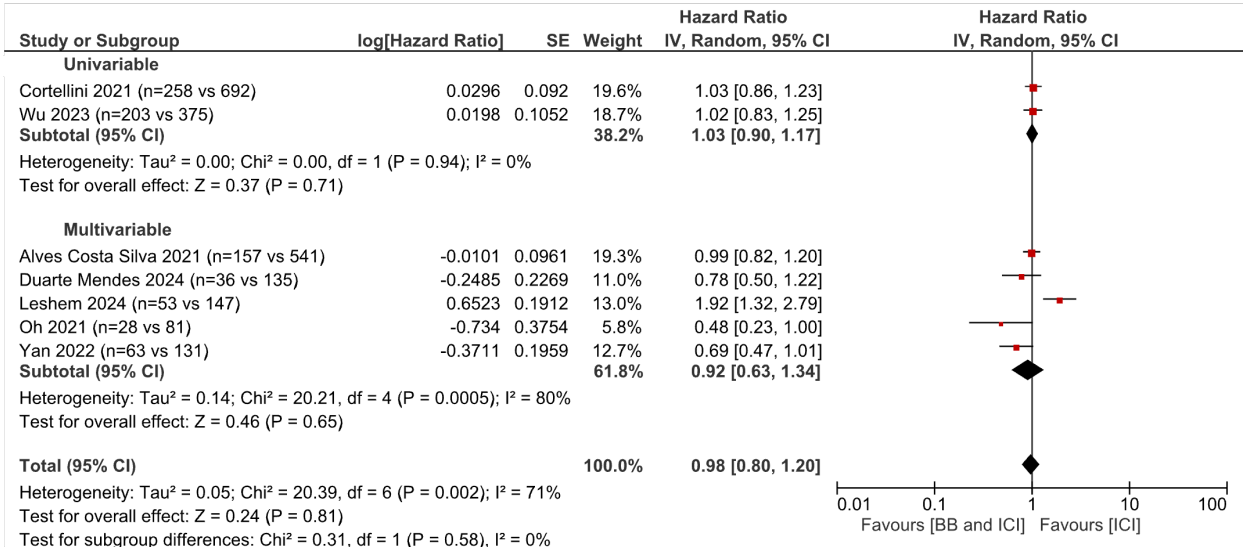
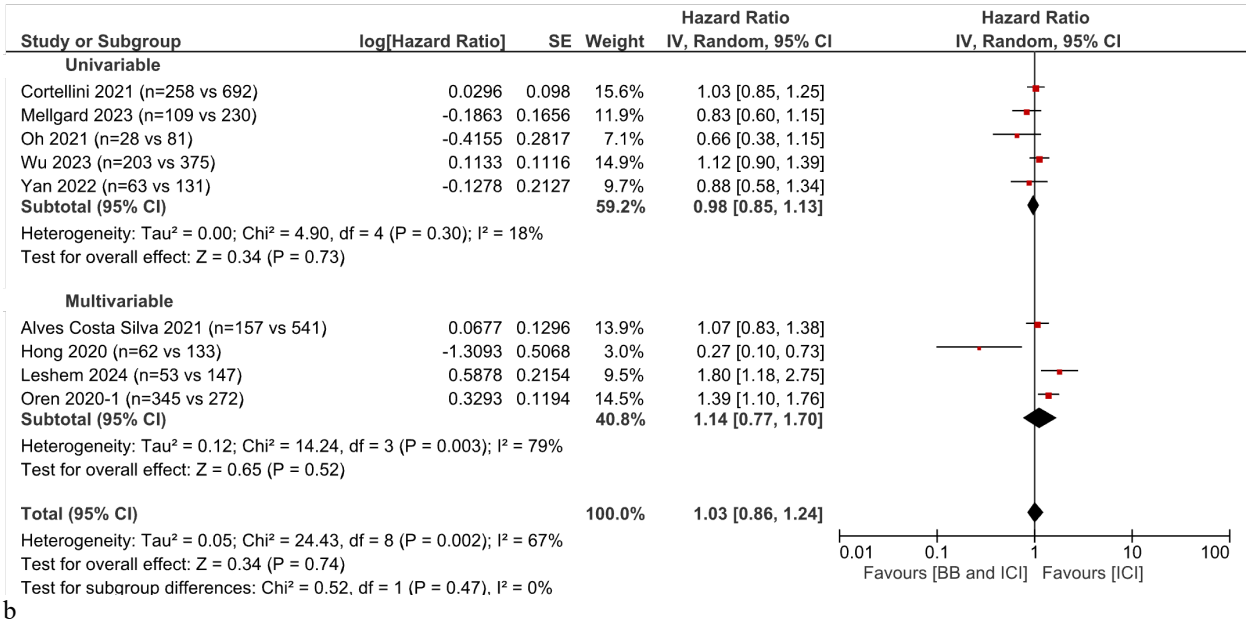


Abbreviations: BB, beta-blocker; CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; IV, inverse variance; OS, overall survival; PFS, progression-free survival; SE, standard error; Z, z-statistic.

Supplementary Fig.3. Forest plots of HRs for (a) OS and (b) PFS with subgroup analyses based on analysis types, prioritizing univariable analyses.

a



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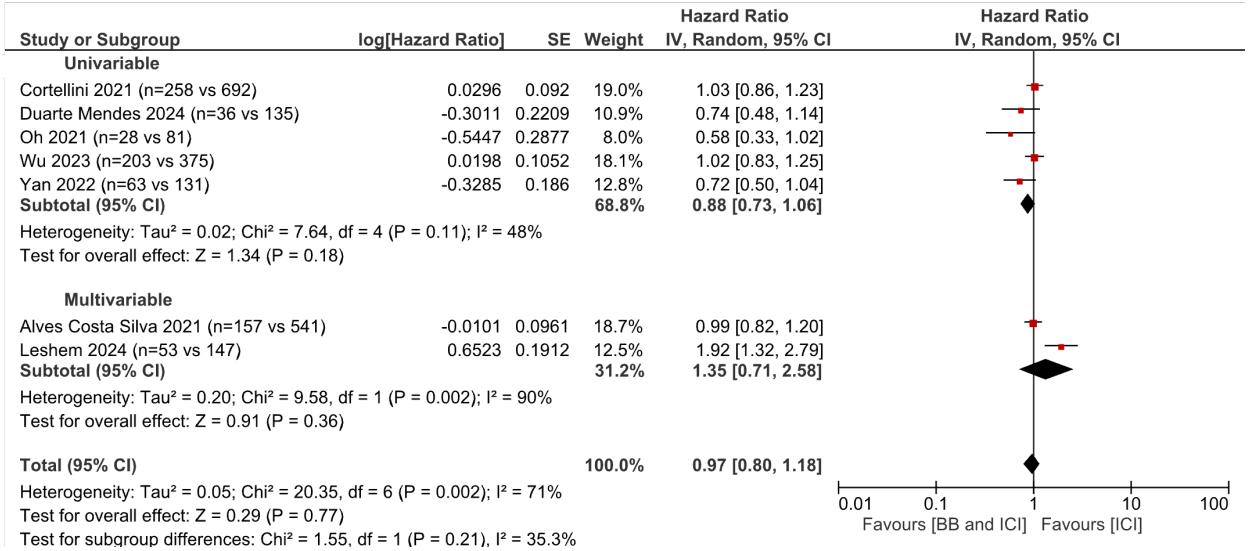
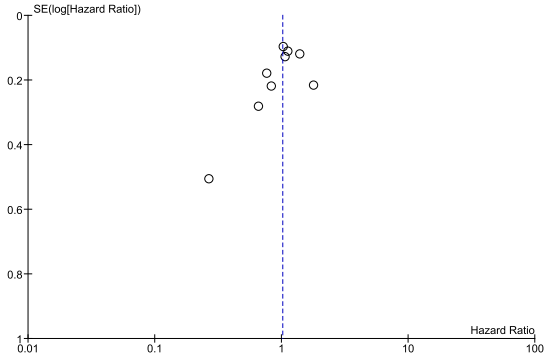


Abbreviations: BB, beta-blocker; CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; IV, inverse variance; OS, overall survival; PFS, progression-free survival; SE, standard error; Z, z-statistic.

Supplementary Fig.4. Funnel plots of studies evaluating HRs for OS: (a) Analysis including all studies, (b) Subgroup analysis based on cancer types, (c) Subgroup analysis based on BB types.

a



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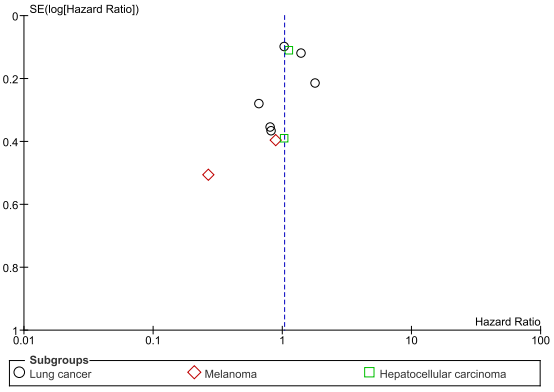

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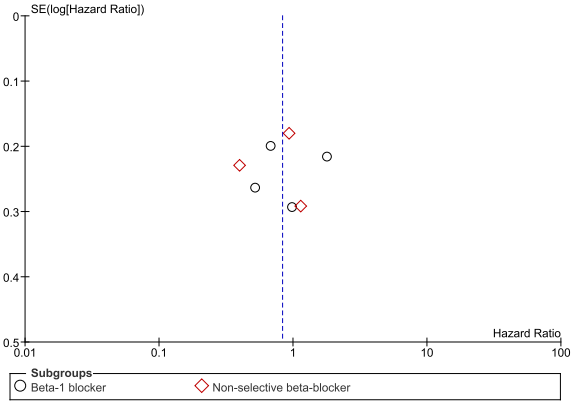
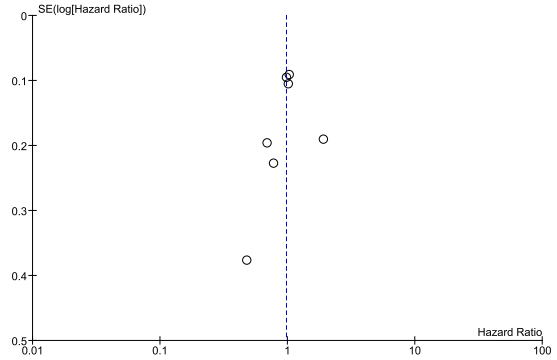


Abbreviations: BB, beta-blocker; HR, hazard ratio; OS, overall survival; SE, standard error.

Supplementary Fig.5. Funnel plots of studies evaluating the HR for PFS: (a) Analysis including all studies, (b) Subgroup analysis based on cancer types, (c) Subgroup analysis based on BB types.

a



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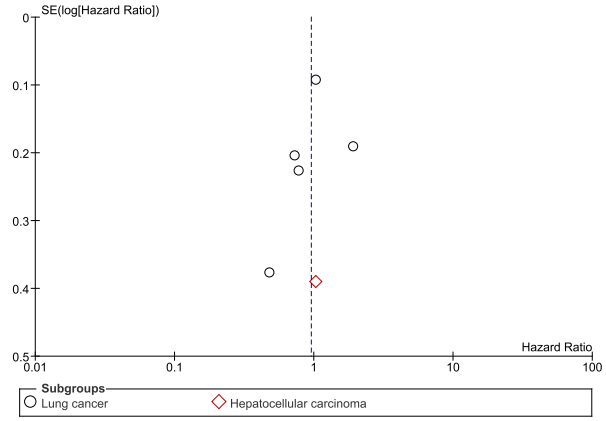

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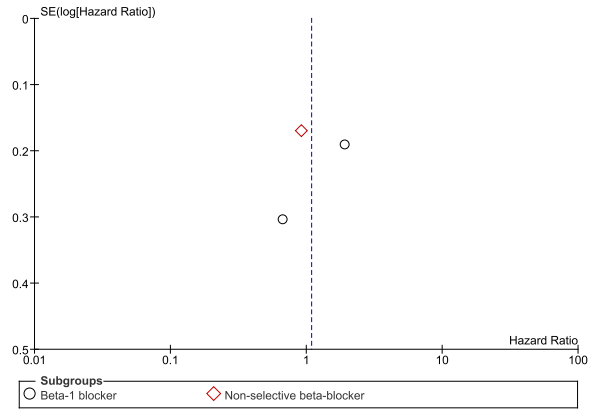

Abbreviations: BB, beta-blocker; HR, hazard ratio; PFS, progression-free survival; SE, standard error.

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