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ORIGINAL RESEARCH

The effects of beta-blocker use on cancer prognosis: a meta-analysis based on 319,006 patients

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Background: Beta-blockers are antihypertensive drugs and have shown potential in cancer prognosis. However, this benefit has not been well defined due to inconsistent results from the published studies.

Methods: To investigate the association between administration of beta-blocker and cancer prognosis, we performed a meta-analysis. A literature search of PubMed, Embase, Cochrane Library, and Web of Science was conducted to identify all relevant studies published up to September 1, 2017. Thirty-six studies involving 319,006 patients were included. Hazard ratios were pooled using a random-effects model. Subgroup analyses were conducted by stratifying ethnicity, duration of drug use, cancer stage, sample size, beta-blocker type, chronological order of drug use, and different types of cancers.

Results: Overall, there was no evidence to suggest an association between beta-blocker use and overall survival (HR=0.94, 95% CI: 0.87–1.03), all-cause mortality (HR=0.99, 95% CI: 0.94–1.05), disease-free survival (HR=0.59, 95% CI: 0.30–1.17), progression-free survival (HR=0.90, 95% CI: 0.79–1.02), and recurrence-free survival (HR=0.99, 95% CI: 0.76–1.28), as well. In contrast, beta-blocker use was significantly associated with better cancer-specific survival (CSS) (HR=0.78, 95% CI: 0.65–0.95). Subgroup analysis generally supported main results. But there is still heterogeneity among cancer types that beta-blocker use is associated with improved survival among patients with ovarian cancer, pancreatic cancer, and melanoma.

Conclusion: The present meta-analysis generally demonstrates no association between beta-blocker use and cancer prognosis except for CSS in all population groups examined. High-quality studies should be conducted to confirm this conclusion in future.

Keywords: cancer, prognosis, beta-blocker, meta-analysis

Introduction

Cancer is the main disease that endangers human life worldwide. The incidence of cancer remains grim that 1.7 million new cancer cases and 0.6 million cancer deaths are projected to occur in USA in 2017.[1] Since cancer often leads to poor survival and a marked decline in quality of life, effective and safe therapies for prolonging cancer survival are urgently needed.

Beta-blockers have been considered as a safe cardiovascular treatment for decades.[2] At present, the beta-adrenergic receptor downstream signaling pathway is certified as an important regulator of progression and metastasis of some important tumors,[3] making beta-blockers a new alternative for cancer adjuvant chemotherapy.[4] So far, a growing number of studies have supported the use of beta-blockers in prolonging survival of cancer patients,[8–30] but several studies have put forward controversial conclusions.[31–43]

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The purpose of this study was to use meta-analysis to quantitatively and comprehensively summarize the evidence for the relationship between beta-blocker exposure and survival outcomes of various cancers.

Materials and methods

Search strategy

Under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we conducted this meta-analysis. To identify the studies of interest, we systematically searched PubMed (Supplementary material online file), Embase, Cochrane Library, and Web of Science for research reports published up to September 1, 2017. Search terms included: {Adrenergic beta-Antagonist(s), beta-blocker(s), atenolol, bisoprolol, carvedilol, metoprolol, propranolol, sotalol, timolol, arotinolol, betaxolol, bevantolol, carteolol or celiprolol} combined with {cancer(s), carcinoma(s), malignancy(ies), neoplasm(s) or tumour(s)} and {prognosis, survival or mortality}. We scanned the titles and abstracts of the studies identified in the initial search, excluding those apparently unrelated. The full text of the remaining articles was read to determine the studies that can be included. In addition, we have further studied the reference lists of articles for additional studies.

Inclusion and exclusion criteria

Our inclusion criteria were: 1) case–control or cohort studies or randomized controlled trials (RCTs); 2) patients with cancer; 3) reported at least 20 patients; 4) evaluated the therapeutic value of beta-blockers in cancer prognosis; 5) compared beta-blocker users with non-users in patients; 6) reported survival outcomes like overall survival (OS), all-cause mortality, cancer-specific survival (CSS), disease-free survival (DFS), progression-free survival (PFS), and recurrence-free survival (RFS); 7) reported HR with 95% CI for survival of comparison between exposure group and control group or HR could be obtained from other sufficient information.

Articles were excluded from the analyses for any of the following reasons: 1) reviews, commentaries, experimental laboratory articles, animal studies, or letters; 2) repeated publications; 3) impossible to calculate HR with 95% CI for survival from the paper.

Data extraction

The following information was extracted from each study: 1) publication data: first author's name, publication year, and geographical location of the study; 2) study design; 3) number and characteristics of participants; 4) types of beta-blockers used; 5) HR estimates with their 95% CIs and control for multiple factors by matching or adjustments. If the HR and 95% CI could not be obtained directly, they were estimated from Kaplan–Meier curves.[5]

Quality assessment

Quality of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS). Studies of medium quality scored 6–7 points. This assessment was completed by two investigators (ZN and XQ) independently, and any disagreements were solved by a revaluation of the original article with a third author (XH).

Statistical analysis

For the meta-analysis, we calculated pooled HRs with 95% CI for all the studies. We used the Cochran's Q-test to examine whether the results of the studies were homogeneous. The P-value <0.10 for Q-test indicated heterogeneity. Quantity of I^2 was also calculated to describe the percentage variation across studies due to heterogeneity. We regarded an I^2 value $>50\%$ as indicative of significant heterogeneity. A fixed-effects model (inverse variance method) was used to calculate pooled results when no heterogeneity existed among the included studies; otherwise, a random-effects model (DerSimonian and Laird method) was used with the weights inversely proportional to the variance of hazard ratio of each trial.[6,7] To identify potential sources of between-study heterogeneity, subgroup analyses were conducted by stratifying ethnicity, duration of drug use, cancer stage, sample size, beta-blocker type, chronological order of drug use, and different types of cancers. We conducted sensitivity analysis to determine the relative effect of a particular study on the meta-analysis model. To assess the influence of potential causes, meta-regression models were fitted separately for each cause except for beta-blocker therapy. The Begg's adjusted rank correlation test and the Egger's regression asymmetry tests were used to evaluate the effects of publication bias. All analyses were conducted using Stata 12.0 software (Markummitchell, Torrance, CA, USA), and we read Kaplan–Meier curves with Engauge Digitizer version 9.8.

Results

Study search and characteristics

The flow of literature selection applying the systematic search and selection strategies to identify qualified reports

is shown in Figure 1. Six hundred and thirty studies were initially identified by the search. Of these, we retrieved 49 potential studies by filtering the titles and abstracts. Due to insufficient information (12 studies) or including the same patients (one study), 13 studies were excluded after further comprehensive review. Two studies were conducted in the same institute, but as the sample patients were at different stages and were treated differently, we considered them to be different cohorts.[8,9] Finally, a total of 36 studies were included in the pooled analyses.

Table 1 showed the characteristics of the 36 studies. The articles were published from 2011 to 2017, which included 319,006 patients. Of them, 35 studies utilized cohort design[8–10,12–43] and one study used case–control design.[11] Besides, there were 22 hospital-based studies[9–11,14–16,18,19,21,23,24,26–31,33–35,40,41] and 14 population-based studies.[8,12,13,17,20,22,25,32,36–39,42,43] Overall, all the 36 studies reported the prognostic value of beta-blockers in the survival of cancer patients.

Quality assessment

While there was small variation in the methodological quality of the included studies, all 36 included studies were judged as moderate to relative high quality according to the NOS assessment tool, with scores of 6 (11 studies), 7 (20 studies), and 8 (five studies, Table S1).

Beta-blockers and survival of cancer

Meta-analysis of overall survival

As displayed in Figure 2A, the forest plot showed that beta-blocker use was not associated with OS. The pooled HR was 0.94 (95% CI: 0.87–1.03, P=0.172) from 22 observational studies. Considering the high heterogeneity (I^2=83.3%, P<0.001), we used random-effects model to pool the studies.

Meta-analysis of all-cause mortality

Twelve studies focused on beta-blocker use and all-cause mortality. A random-effects model was used and

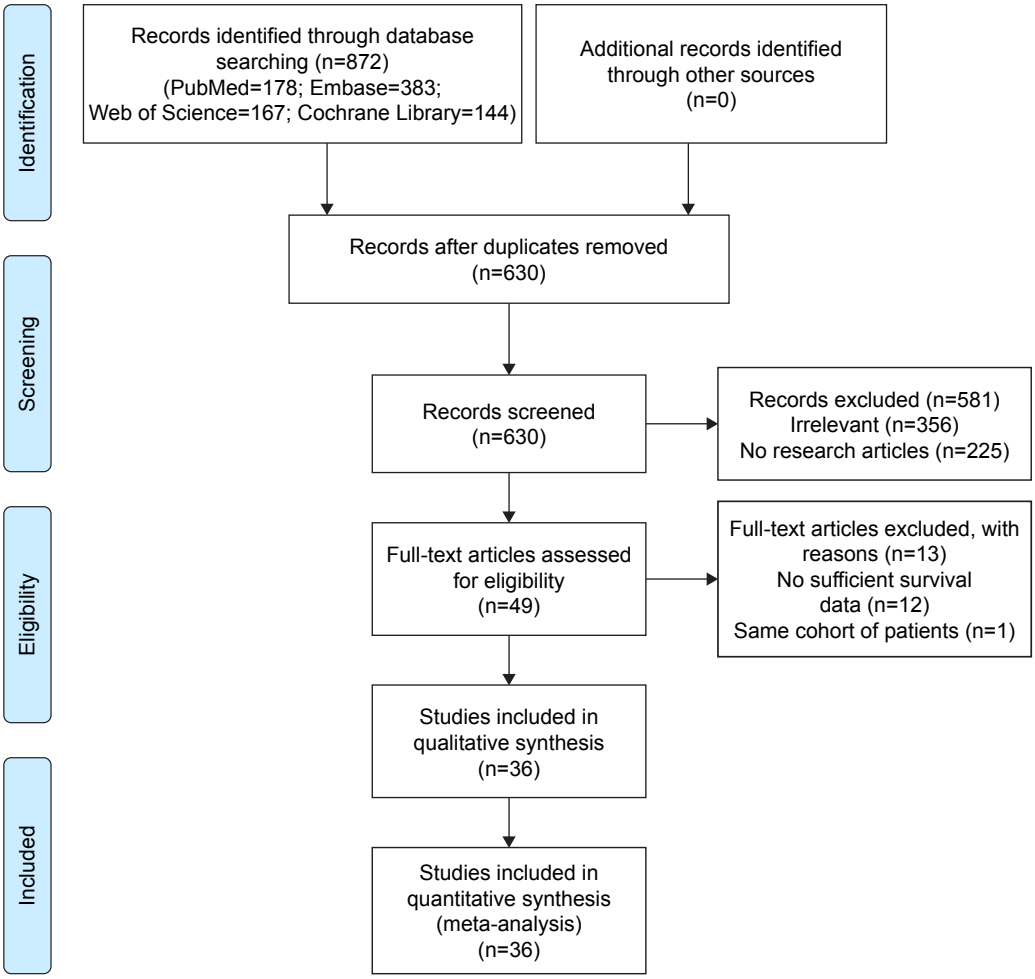

Figure 1 PRISMA flowchart of article selection for this meta-analysis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Characteristics of studies included for meta-analysis

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
8	Grytli et al (2013)	Norway	2004–2009	655	72	PB cohort	Prostate cancer	I/II 60.1%, III/IV 39.9%	NR	Mixed: beta selective (80.2%); non-selective (19.8%)
9	Grytli et al (2014)	Norway	2000–2011	3,561	76.3	HB cohort	Prostate cancer	≤T2A 14.9%; T2b–T2c 18.5%; ≥T3a 66.6%	NR	Mixed: beta 1 selective (77.9%); non-selective (3.0%); alpha and beta mixed (4.5%)
10	Al-Niaimi et al (2016)	USA	2000–2010	185	66.2 63.8	HB cohort	Ovarian cancer	I/II 26%, III/IV 74%	Yes	NR
11	Aydiner et al (2013)	Turkey	2003–2011	107	61 (42–81)	HB case–control	Non-small-cell lung cancer	NR	Mixed	Mixed
12	Barron et al (2011)	Ireland/USA	2001–2006	4,808	69.1 71	PB cohort	Breast cancer	I/II 75.6%, III/IV 24.4%	NR	Beta non-selective
12	Barron et al (2011)	Ireland/USA	2001–2006	5,263	69.1 71	PB cohort	Breast cancer	I/II 75.6%, III/IV 24.4%	NR	Beta selective
12	Barron et al (2011)	Ireland/USA	2001–2006	5,801	69.1 71	PB cohort	Breast cancer	I/II 75.6%, III/IV 24.4%	NR	Mixed: beta selective (88%); non-selective (12%)
13	Beg et al (2017)	USA	2006–2009	13,702	76	PB cohort	Pancreatic adenocarcinoma	I/II 38.1%, III/IV 61.9%	Mixed 69.3%	NR
14	Bir et al (2015)	USA	2001–2013	225	57.34± 10.98	HB cohort	Metastatic brain tumors	NR	Yes	Beta 1 selective
15	De Giorgi et al (2013)	Italy	1993–2009	741	64 53	HB cohort	Thick melanoma	NR	Mixed	Mixed: beta 1 selective (73%); non-selective (27%)
16	Diaz et al (2012)	USA	1996–2006	248	67	HB cohort	Ovarian cancer	III/IV 100%	Yes	Mixed: beta 1 selective (75%); non-selective (13%); mixed alpha and beta adrenergic antagonist (13%)

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
80	575	Pre-diagnostic beta-blocker use	122	ADT or not	0.88	0.56–1.38	OS	Yes	Age at diagnosis, metastasis at diagnosis, and level of education	8
					0.79	0.68–0.91	CSS			
1,115	2,446	Pre-diagnostic beta-blocker use	39	RT or radical prostatectomy	0.96	0.87–1.05	OS	Yes	Age, prostate-specific antigen level, Gleason score, clinical T stage, presence and type of metastases, performance status, and androgen deprivation, therapy initiated within 6 months after diagnosis	7
					0.97	0.72–1.31	CSS			
70	115	Post-diagnostic beta-blocker use (time-dependent)	91	CT	0.68	0.46–0.99	OS	Yes	Age, stage, grade, cytoreduction status, BMI, and presence or absence of diabetes	7
35	72	Post-diagnostic beta-blocker use (time-fixed)	17.8 (1–102)	CT	0.69	0.36–1.34	OS	Yes	Age, sex, performance status, histologic subtype, smoking status, presence of comorbidities (COPD, IHD, HT, and DM)	7
70	4,738	Pre-diagnostic beta-blocker use	42 43.2 32.4 36	CT or not	0.19	0.06–0.60	OS	Yes	Age, stage, grade, and comorbidity	7
525	4,738	Pre-diagnostic beta-blocker use	42 43.2 32.4 36	CT or not	1.08	0.84–1.40	OS	Yes	Age, stage, grade, and comorbidity	7
595	4,738	Pre-diagnostic beta-blocker use	42 43.2 32.4 36	CT or not	1.08	0.84–1.39	CSS	Yes	Age, stage, grade, and comorbidity	7
5,209	8,493	NR	NR	NR	0.9	0.85–0.95	OS	Yes	Age, sex, race, stage at diagnosis, site of cancer, and Charlson comorbidity index	8
40	185	NR	10.57	GKRS	1.08	0.65–1.79	OS	Yes	MBT kind, metastasis, tumor recurrence, tumor response, GKRS, prognostic factor	7
79	662	Post-diagnostic beta-blocker use (time-dependent)	50.4	NR	0.03	0.01–0.17	DFS	Yes	Age, Breslow thickness, and ulceration	7
					0.04	0.00–0.38	OS			
23	225	NR	NR	CT	0.56	0.43–1.26	OS	Yes	Age, stage, grade, and cytoreduction status	6

(*Continued*)

Table 1 (*Continued*)

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
17	Ganz et al (2011)	USA	1997–2002	1,779	NR	PB cohort	Breast cancer	I/II 96.9%, III/IV 3.1%	NR	Mixed: beta selective (86%); non-selective (14%)
18	Giampieri et al (2015)	Italy	2010–2013	235	NR	HB cohort	Colorectal cancer	NR	NR	NR
19	Hwa et al (2017)	USA	1995–2010	1,971	64	HB cohort	Myeloma	I/II 75%, III/IV 25%	Mixed	Mixed
20	Jansen et al (2014)	Germany	2003–2007	1,975	68	PB cohort	Colorectal cancer	I/II 55% III/IV 45%	Mixed 97.3%	Mixed: beta selective (86%); non-selective (14%)
21	Kim et al (2017)	Korea	2001–2012	1,274	61 (20–87)	HB cohort	Head and neck squamous cell carcinoma (HNSCC)	I/II 41.4% III/IV 58.6%	Mixed 69.2%	Mixed: beta 1 selective (84%); non-selective (16%)

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
204	1,372	NR	98.4	CT, RT, both or none	1.04	0.72–1.51	OS	Yes	Age at diagnosis, race, stage of disease, pre-diagnosis BMI, adjuvant treatment, hormone receptor status, tamoxifen use, and self-reported hypertension and diabetes	8
					0.86	0.57–1.32	RFS			
					0.76	0.44–1.33	CSS			
29	206	Pre-diagnostic beta-blocker use	NR	CT or with bevacizumab	1.51	0.88–2.31	OS	Yes	Age, sex, and site of metastases, previous adjuvant chemotherapy, and ECOG performance status	7
					1.19	0.81–1.72	PFS			
549	1,733	Post-diagnostic beta-blocker use (time-fixed)	74.3	CT	0.67	0.55–0.81	OS	Yes	Demographics, disease characteristics, diagnosis year, and various chemotherapies	7
					0.53	0.42–0.67	CSS			
509	1,311	Pre-diagnostic beta-blocker use	60	CT or RT	0.99	0.79–1.22	OS	Yes	Age at diagnosis, sex, Union for International Cancer Control (UICC) stage (I–IV), surgery, chemotherapy, radiotherapy, body mass index, hypertension, CVD (including heart failure, myocardial infarction, stroke, and cardiac circulatory disorder), diabetes, regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, regular use of statins, use of hormone replacement therapy (HRT), lifetime pack-years of active smoking, physical activity (quartiles of lifetime metabolic equivalents [METs] in hours per week), and participation in health check-up	8
					0.93	0.71–1.21	CSS			
114	1,160	Post-diagnostic beta-blocker use (time-fixed)	98	Primary curative surgery, RT, CRT with or without IC, or a combination of these treatments	1.33	0.93–1.91	DFS	Yes	Age, sex, BMI, CCI, smoking, alcohol, tumor site, tumor classification T3–4, nodal classification N1–3, overall TNM stage III–IV, primary treatment, second primary cancer, hypertension	6

(*Continued*)

Table 1 (*Continued*)

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
22	Lemeshow et al (2011)	Denmark	Since 1943	4,179	66	PB cohort	Melanoma	I/II 63.8%, III/IV 36.2%	Mixed	Mixed
23	Melhem-Bertrandt et al (2011)	USA	1995–2007	1,413	57 49	HB cohort	Breast cancer	I/II 55.6%, III/IV 44.4%	Yes	Mixed: beta selective (89%); non-selective (11%)
24	Springate et al (2015)	NR	1997–2006	11,302	NR	HB cohort	Mixed cancer	NR	NR	Mixed
24	Springate et al (2015)	NR	1997–2006	6,274	NR	HB cohort	Mixed cancer	NR	NR	Mixed
25	Udumyan et al (2017)	Swedish	2006–2009	2,394	70.9 67.1	PB cohort	Pancreatic adenocarcinoma	I/II 21%, III/IV 79%	NR	Mixed: beta 1 selective (89%); non-selective (11%)
26	Wang et al (2013)	USA	1998–2010	722	65 (34–95)	HB cohort	Non-small-cell lung cancer	I/II 6.2%, III 93.8%	Mixed	Mixed: beta selective (86%); non-selective (14%)
27	Watkins et al (2015)	USA	2000–2010	1,425	61.6 68	HB cohort	Ovarian cancer	I/II 10%, III/IV 90%	Yes	Mixed: beta selective (72.1%); non-selective (27.9%)

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
					1.49	0.99–2.22	CSS			
					1.54	1.17–2.05	OS			
372	3,807	Pre-diagnostic beta-blocker use	58.8	NR	0.81	0.67–0.97	OS	Yes	Age and comorbidity index score	7
					0.87	0.64–1.2	CSS			
102	1,311	Post-diagnostic beta-blocker use (time-fixed)	58.8	Anthracylines and taxane-based neoadjuvant CT	0.3	0.10–0.87	RFS	Yes	Age, race, stage, grade, receptor status, lymphovascular invasion, body mass index, diabetes, hypertension, and angiotensin-converting enzyme inhibitor use	7
					0.76	0.44–1.33	CSS			
					0.35	0.12–1.00	OS			
4,030	7,272	Pre-diagnostic beta-blocker use	29 30	NR	1.03	0.93–1.14	OS	No	No	7
1,406	4,868	Pre-diagnostic beta-blocker use	29 30	NR	1.18	1.04–1.33	OS	No	No	7
522	1,872	Pre-diagnostic beta-blocker use	5	NR	0.79	0.70–0.90	OS	Yes	Sociodemographic factors, tumor characteristics, comorbidity score, and other medications	8
					0.77	0.69–0.87	CSS			
155	567	Post-diagnostic beta-blocker use (time-fixed)	44 (1–155)	Definitive RT	0.91	0.64–1.31	PFS	Yes	Age, Karnofsky performance score, clinical stage, tumor histology, use of concurrent chemotherapy, radiation dose, GTV, hypertension, chronic obstructive pulmonary disease, and aspirin consumption	7
					0.67	0.50–0.91	DMFS			
					0.74	0.58–0.95	DFS			
					0.78	0.63–0.97	OS			
269	1,156	Post-diagnostic beta-blocker use (time-fixed)	NR	CT	0.26	0.19–0.37	OS	No	No	6
					0.24	0.17–0.34	CSS			

(*Continued*)

Table 1 (*Continued*)

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
28	Yusuf et al (2012)	USA	2000–2006	456	67	HB cohort	Mixed cancer	NR	NR	NR
29	Botteri et al (2013)	Italy	1997–2006	800	62 59	HB cohort	Breast cancer	I/II 86%, III/IV 14%	Yes	Mixed: beta 1 selective (84.1%); non-selective (4%); alpha and beta mixed (11.9%)
30	Spera et al (2017)	Canada	NR	1,144	60 53	HB cohort	Breast cancer	NR	Yes	Mixed
31	Johannesdottir et al (2013)	Denmark	1999–2010	6,253	65	HB cohort	Ovarian cancer	NR	Mixed	NR
31	Johannesdottir et al (2013)	Denmark	1999–2010	6,539	65	HB cohort	Ovarian cancer	NR	Mixed	NR
32	Assayag et al (2014)	Canada/UK	1998–2012	6,270	72.3	PB cohort	Prostate cancer	NR	Yes	Mixed: beta selective (59.4%); non-selective (40.6%)
33	Cata et al (2014)	USA	NR	391	NR	HB cohort	Non-small-cell lung cancer	I/II 75.2%, III 24.8%	Yes	Beta 1 selective
33	Cata et al (2014)	USA	NR	286	NR	HB cohort	Non-small-cell lung cancer	I/II 75.2%, III 24.8%	Yes	Beta non-selective
34	Heitz et al (2013)	Germany/ Canada	NR	381	60	HB cohort	Ovarian cancer	I/II 6.5%, III/IV 93.5%	Yes	Mixed: beta selective (84%); non-selective (16%)

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
211	245	NR	1.2	Chest RT or CT	0.64	0.51–0.81	OS	Yes	Age, cancer status, cancer type, previous chemotherapy, chest radiotherapy, hyperlipidemia	6
74	726	Pre-diagnostic beta-blocker use	72 67.2	Adjuvant CT and RT	0.42	0.18–0.97	CSS	Yes	Age, tumor stage, and treatment, peritumoral vascular invasion and use of other antihypertensive drugs, antithrombotics, and statins	7
153	991	Pre/post-diagnostic beta-blocker use (time-dependent)	25.1	CT	0.81	0.66–0.99	PFS	Yes	Treatment arm (RAM vs PBO), HHRR status, geographic region, THE	7
					1.05	0.85–1.29	OS			
87	6,166	Pre-diagnostic beta-blocker use	30.6	HRT	1.18	0.90–1.55	OS	Yes	Age, comorbidity level, prior use of diuretics, year of diagnosis, aspirin, and statins	7
373	6,166	Pre-diagnostic beta-blocker use	30.6	HRT	1.17	1.02–1.34	OS	Yes	Age, comorbidity level, prior use of diuretics, year of diagnosis, aspirin, and statins	7
673	1,088	Post-diagnostic beta-blocker use (time-dependent)	45.6	Prostatectomy, RT, ADT, and CT	0.97	0.8–1.16	OS	No	No	7
					0.97	0.72–1.31	CSS			
149	242	NR	NR	NR	1.304	0.973–1.747	RFS	Yes	Age, stage of disease, BMI, ASA physical status, smoking status, CAD, postoperative radiation treatment, type of surgery, and perioperative blood transfusions	7
					1.335	0.966–1.846	OS			
44	242	NR	NR	NR	0.989	0.639–1.532	RFS	Yes	Age, stage of disease, BMI, ASA physical status, smoking status, CAD, postoperative radiation treatment, type of surgery, and perioperative blood transfusions	7
					1.108	0.678–1.812	OS			
38	343	Post-diagnostic beta-blocker use (time-fixed)	17	CT	0.92	0.65–1.31	PFS	Yes	Age, stage, grade, and cytoreduction status	7
					0.74	0.49–1.11	OS			

(*Continued*)

Table 1 (*Continued*)

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
35	Heitz et al (2017)	Germany	1999–2014	801	58 (19–90)	HB cohort	Ovarian cancer	I/II 43.3%, III/IV 56.7%	Yes	Beta 1 selective
36	Holmes et al (2013)	Canada	2004–2008	2,433	68.3	PB cohort	Breast cancer	NR	NR	Mixed
36	Holmes et al (2013)	Canada	2004–2008	2,016	68.3	PB cohort	Colorectal cancer	NR	NR	Mixed
36	Holmes et al (2013)	Canada	2004–2008	2,125	68.3	PB cohort	Lung cancer	NR	NR	Mixed
36	Holmes et al (2013)	Canada	2004–2008	1,868	68.3	PB cohort	Prostate cancer	NR	NR	Mixed
37	Jansen et al (2017)	The Netherlands	1998–2011	2,530	73 68	PB cohort	Colorectal cancer	I/II 55.7%, III/IV 44.3%	Mixed 89.8%	Mixed: beta selective (55%); non-selective (45%)
37	Jansen (2017)	The Netherlands	1998–2011	1,374	73 68	PB cohort	Colorectal cancer	I/II 55.7%, III/IV 44.3%	Mixed 89.8%	Mixed: beta selective (66%); non-selective (34%)

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
141	660	NR	40	CT	0.94	0.69–1.29	OS	Yes	Age, ECOG, ASA, Charlton comorbidity score (metric), tumor residuals, histology, body mass index, and FIGO stage	7
					0.95	0.72–1.27	PFS			
123	2,310	Pre-diagnostic beta-blocker use	NR	NR	1.1	0.92–1.32	OS	No	No	6
152	1,864	Pre-diagnostic beta-blocker use	NR	NR	1.05	0.93–1.18	OS	No	No	6
196	1,929	Pre-diagnostic beta-blocker use	NR	NR	1.01	0.93–1.11	OS	No	No	6
163	1,705	Pre-diagnostic beta-blocker use	NR	NR	1.18	0.99–1.40	OS	No	No	6
1456	1,074	Pre-diagnostic beta-blocker use	79.2	NR	1.07	0.96–1.19	OS	Yes	Age at diagnosis, sex, year of diagnosis, socioeconomic status based on the place of residence, Union for International Cancer Control (UICC) stage (I, II, III, IV), cancer site (colon, rectum/rectosigmoid), surgery, chemotherapy, radiotherapy, cancer, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, time-dependent use of NSAIDs, statins and diabetes medication after diagnosis and number of distinct ATC classes prescribed during 4 months prior to diagnosis (0, 1–3, 4–5, 6+ distinct ATC classes [first letter of the ATC] dispensed during 4 months prior to diagnosis)	7
919	455	Post-diagnostic beta blocker use (time-dependent)	79.2	NR	1.1	0.98–1.23	OS	Yes	Age at diagnosis, sex, year of diagnosis, socio-economic status based on the place of residence, Union Internationale Contre le Cancer (UICC) stage (I, II, III, IV), cancer site (colon, rectum/rectosigmoid), surgery, chemotherapy, radiotherapy, previous cancer, cardiovascular disease, cerebrovascular	7

(*Continued*)

Table 1 (*Continued*)

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
38	Livingstone et al (2013)	Germany/ The Netherlands		709	67 59	PB cohort	Melanoma	NR	Mixed	Mixed: beta 1 selective (84%); non-selective (16%)
39	Musselman et al (2014)	Canada	2002–2010	66,889	NR	PB cohort	Breast cancer	NR	Yes	NR
39	Musselman et al (2014)	Canada	2002–2010	66,890	NR	PB cohort	Lung cancer	NR	Yes	NR
39	Musselman et al (2014)	Canada	2002–2010	66,891	NR	PB cohort	Colorectal cancer	NR	Yes	NR
40	Parker et al (2017)	USA	2000–2010	913	65 67	HB cohort	Renal cell carcinoma	I/II 51.6%, III/IV 48.4%	Yes	Mixed: beta 1 selective (90%); non-selective (4%); alpha and beta mixed (6%)
41	Sakellakis et al (2014)	Greece	1983–2013	610	63 55	HB cohort	Breast cancer	I/II 73.6%, III/IV 26.4%	Yes	Mixed
42	Shah et al (2011)	UK	1997–2009	3,462	HR	PB cohort	Mixed cancer	NR	NR	Mixed: beta selective (83%); non-selective (17%)

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
									disease, diabetes, hypertension, time-dependent use of NSAIDs, statins and diabetes medication after diagnosis and number of distinct ATC classes prescribed during four months prior to diagnosis (0, 1–3, 4–5, 6+ distinct ATC classes [first letter of the ATC] dispensed during four months prior to diagnosis)	
120	589	Post-diagnostic beta-blocker use (time-dependent)	39	NR	0.82	0.55–1.24	OS	No	No	6
4,372	7,013	NR	57.6 6 30.5, 43.1 6 28.7, and 53.4 6 31.0	NR	0.99	0.87–1.13	OS	No	No	6
1,901	2,314	NR	57.6 6 30.5, 43.1 6 28.7, and 53.4 6 31.0	NR	1.06	0.91–1.24	OS	No	No	6
22,170	30,118	NR	57.6 6 30.5, 43.1 6 28.7, and 53.4 6 31.0	NR	1.06	0.99–1.02	OS	No	No	6
104	809	Pre-diagnostic beta-blocker use	98.4	NR	0.83	0.59–1.16	OS	Yes	Age at surgery, sex, constitutional symptoms, smoking history, eGFR category, ECOG performance status, Charlson score, type of surgery, tumor size, 2010 pT classification, grade, coagulative tumor necrosis	7
					0.78	0.43–1.41	CSS			
47	430	Post-diagnostic beta-blocker use (time-dependent)	24 48	CT	0.849	0.537–1.343	DFS	No	No	6
1,406	2,056	Pre-diagnostic beta-blocker use	NR	NR	1.18	1.04–1.33	OS	No	No	6

(*Continued*)

Table 1 (*Continued*)

Reference	Study	Country	Duration	Sample size	Median age (years)	Study design	Cancer type	Stage	Surgery	Beta-blocker type
43	Weberpals et al (2017)	Holland	1998–2011	2,221	70.4	PB cohort	Lung cancer	I/II 24.1%, III/IV 75.9%	Mixed 17.4%	Mixed: beta selective (88%); non-selective (12%)
43	Weberpals et al (2017)	Holland	1998–2011	2,221	70.4	PB cohort	Lung cancer	I/II 24.1%, III/IV 75.10%	Mixed 17.5%	Mixed: beta selective (88%); non-selective (13%)

Abbreviations: NR, not reported; PB, population-based; HB, hospital-based; RT, radiation therapy; CT, chemotherapy; ADT, androgen deprivation therapy; CRT, concurrent chemoradiotherapy; IC, induction chemotherapy; GKRS, gamma knife radiosurgery; HRT, hormone replacement therapy; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; NOS, Newcastle–Ottawa Quality Assessment Scale; BMI, body mass index; IHD, ischemic heart disease; HT, hypertension; MBT, Metastatic brain tumors; ECOG, electrocorticogram; CVD, cardiovascular disease; GTN,GTV, gross tumor volume; RAM, Ramucirumab; PBO, Placebo; HHRR, hormonal receptor; THE, treatment emergent hypertension; ASA, American Standards Association; CAD, coronary artery disease; DM, diabetes mellitus; FIGO, International Federation of Gynecology and Obstetrics; eGFR, epidermal growth factor receptor; ATC, Anatomical Therapeutic Chemical; CCI, Charlson comorbidity index; DMFS, distant metastasis-free survivall; pT, primary tumour.

the combined HR of 0.99 (95% CI: 0.94–1.05, P=0.807, Figure 2B) showed that beta-blocker use was also not correlated with all-cause mortality.

Meta-analysis of cancer-specific survival

Thirteen studies presented the data concerning the association between beta-blocker use and CSS (Figure 2C). We calculated that beta-blocker use was significantly correlated with long CSS, with a pooled HR of 0.78 (95% CI: 0.65–0.95, P=0.012) by using a random-effects model.

Meta-analysis of disease-free survival

Four studies reported the data on beta-blocker use and DFS outcome. The pooled HR was 0.59 (95% CI: 0.30–1.17, P=0.134, Figure 2D) with significant heterogeneity between studies (I^2=89.5%, P<0.001), which demonstrated that beta-blocker use was also prominently not related to DFS.

Meta-analysis of progression-free survival

The data on beta-blocker use and PFS outcome was presented in six studies. Meta-analysis adopting the fixed-effects model revealed that beta-blocker use was not associated with PFS (HR=0.90, 95% CI: 0.79–1.02, P=0.087, Figure 2E) and exhibited no heterogeneity (I^2=0.00%, P=0.603).

Meta-analysis of recurrence-free survival

Four studies provided sufficient data on beta-blocker use and RFS outcome. The pooled HR was 0.99 (95% CI: 0.76–1.28, P=0.944, Figure 2F) by a random-effects model. Beta-blocker use was also significantly not related to RFS.

Subgroup analysis

To deeply explore the relationship between beta-blocker use and OS, we performed subgroup analysis based on ethnicity, duration of drug use, cancer stage, sample size, beta-blocker type, chronological order of drug use, and different types of cancers. The median values of original data from included studies in "duration of drug use" and "sample size" were chosen as cut-off values to divide our subgroups. The results are summarized in Table 2, with the corresponding forest plots presented in Figure S1.

The subgroups of sample size and ethnicity demonstrated no significant effect of beta-blocker use on OS. Similarly, beta-blocker showed no obvious impact on OS for patients with duration of drug use more than 2 years (HR=1.03, 95% CI: 0.93–1.14, P=0.617) or patients with duration of drug use less than 2 years (HR=1.01, 95% CI: 0.91–1.11, P=0.897). Additionally, the subgroup analysis indicated that the administration of beta-blockers had no relationship with longer OS when the meta-analysis was restricted to patients with cancer in I/II stage (HR=0.97, 95% CI: 0.89–1.06, P=0.507) or cancer in III/IV stage (HR=1.04, 95% CI: 0.94–1.14, P=0.468). In addition, the studies using selective beta-blocker (HR=0.93, 95% CI: 0.83–1.05, P=0.243) and non-selective beta-blocker (HR=1.04, 95% CI: 0.89–1.22, P=0.596) were found to have no effect on OS. However, beta-blocker showed a more positive effect on OS for patients with time-fixed post-diagnostic beta-blocker use (HR=0.65, 95% CI: 0.43–0.99, P=0.046) than pre-diagnostic beta-blocker use (HR=1.03, 95% CI: 0.95–1.11, P=0.493) and time-dependent post-diagnostic beta-blocker use (HR=0.87, 95% CI: 0.59–1.30, P=0.508).

No. of patients		Exposure category	Follow-up time (months)	Treatment	HR	95% CI	Survival outcome	Multivariable analysis	Adjusted for	Study quality (NOS score)
Exposure	Control									
1,107	1,114	Pre-diagnostic beta-blocker use	78	NR	1	0.92–1.08	OS	Yes	Comorbidities, time-varying treatment, and distinct numbers of medications used	7
1,224	997	Post-diagnostic beta-blocker use (time-dependent)	78	NR	1.03	0.94–1.11	OS	Yes	Comorbidities, time-varying treatment, and distinct numbers of medications used	7

Analysis according to cancer type showed predominantly longer OS in ovarian cancer (HR=0.59, 95% CI: 0.36–0.96, *P*=0.034), pancreatic cancer (HR=0.85, 95% CI: 0.75–0.97, *P*=0.014), and melanoma (HR=0.81, 95% CI: 0.67–0.97, *P*=0.026), but no effects on lung cancer (HR=1, 95% CI: 0.96–1.05, *P*=0.818), breast cancer (HR=0.97, 95% CI: 0.78–1.21, *P*=0.783), colorectal cancer (HR=1.16; 95% CI: 0.84–1.61, *P*=0.353), and mixed cancer (HR=1.00; 95% CI: 0.83–1.21, *P*=0.974). Owing to the small numbers of studies and lack of information, subgroup analyses were not performed on other survival outcomes.

Sensitivity analysis

Sensitivity analysis was conducted on different survival outcomes. The meta-analyses of beta-blockers and survival were performed by removing a single study in turn. After removing the study results, the comprehensive estimation direction and amplitude of OS, all-cause mortality, CSS, DFS, PFS, and RFS were not significantly changed, indicating that the reliability of the meta-analysis was good and the results were not affected by any research (Figure 3). In addition, sensitivity analyses were also conducted in those studies whose HR and 95% CI values were presented in original articles (not calculated from the Kaplan–Meier plots) (Figure S2) and whose NOS score was ≥7 (Figure S3). These factors did not affect the main results.

Publication bias

The funnel plot revealed no evidence of publication bias in the meta-analysis of beta-blocker use and OS (Figure 4A, Egger's test: *P*-value =0.358; Begg's test: *P*-value =0.115). There was no potential publication bias on beta-blocker use and all-cause mortality as well (Figure 4B, Egger's test: *P*-value =0.261; Begg's test: *P*-value =0.260). Besides, there was also no potential publication bias on beta-blocker use, CSS, DFS, PFS, and RFS of cancer patients (Figure 4C–F).

Meta-regression

The meta-regression analysis was performed to investigate the effects of various cohort study characteristics on the study estimates of the HRs. We grouped the studies according to specific characteristics, the size of sample, the sex of patients, the cancer sites, study duration, and study quality. There was no inverse association between sample size (*P*=0.892), sex of the patients (*P*=0.135), cancer sites (*P*=0.364), study duration (*P*=0.076), and study quality (*P*=0.571). Because of the lack of information, meta-regression was not performed on other survival outcomes.

Discussion

This meta-analysis summarizes 36 currently published studies examining the association between beta-blocker use and prognosis of cancer across a wide range of geographic regions and cancer types. Overall, the administration of beta-blocker was not associated with OS, all-cause mortality, DFS, PFS and RFS of cancer patients. However, beta-blocker use was significantly correlated with long CSS (HR=0.78, 95% CI: 0.65–0.95). Since the patients included in the clinical trials differed in stages, therapies, and so on, the heterogeneity was inescapable. Then we conducted subgroup analysis.

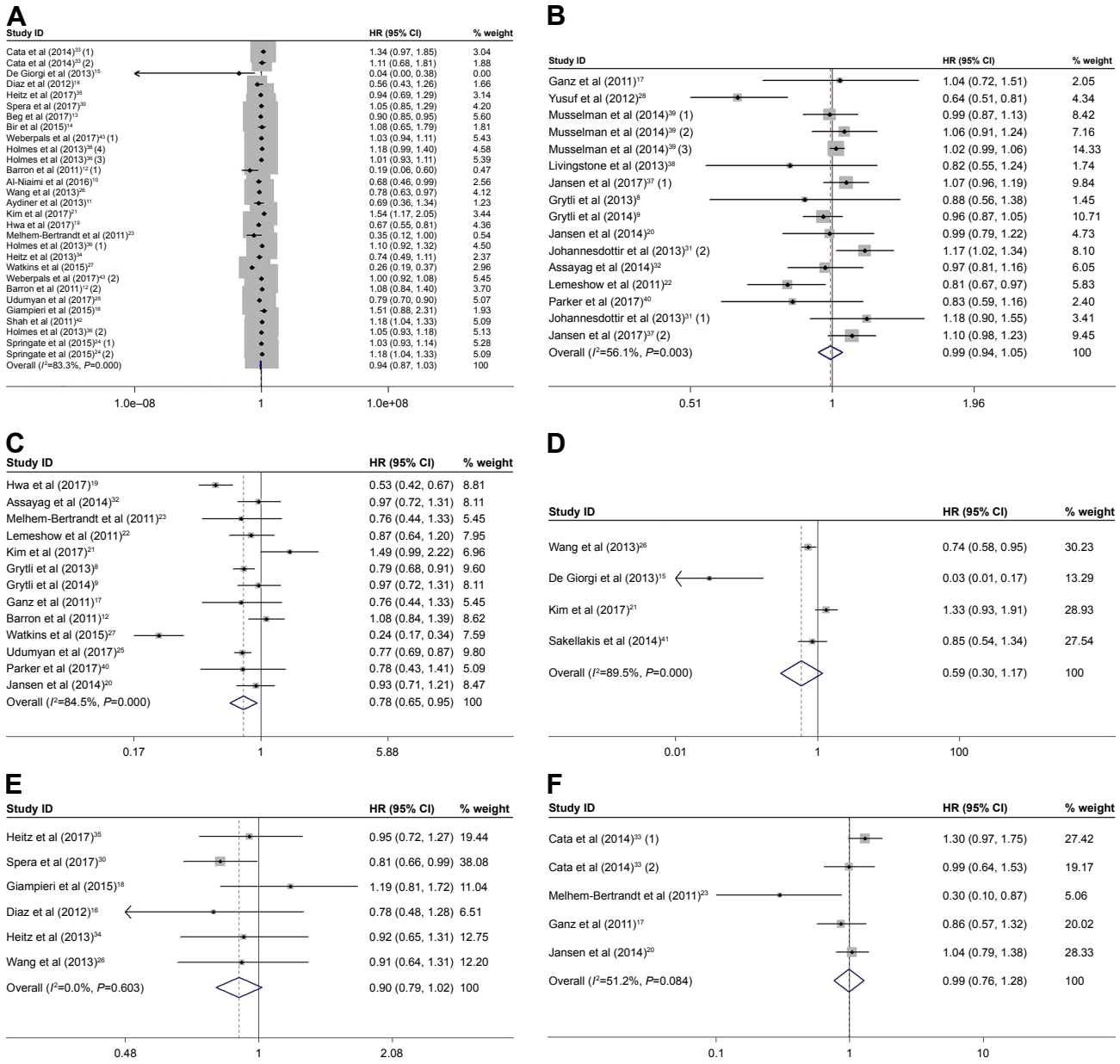

Figure 2 Forest plots showing the effects of beta-blocker use on OS (**A**), all-cause mortality (**B**), CSS (**C**), DFS (**D**), PFS (**E**), and RFS (**F**).
Notes: Weights are from random-effects analysis. The numbers in parentheses indicate the different included studies in the same year.
Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival.

Among the cancer types, positive associations between beta-blocker use and cancer prognosis were observed in breast cancer, pancreatic cancer, and melanoma, but could not be detected in lung cancer, ovarian cancer, colorectal cancer, and mixed cancer. Interestingly, beta-blocker use is associated with improved survival only among patients with ovarian cancer, pancreatic cancer, and melanoma. However, the results should be interpreted carefully because the number of studies on these three cancers was small. In addition, the results showed that beta-blockers prolonged OS for patients with time-fixed post-diagnostic beta-blocker use. Generally, the subgroups of cancer stage, beta-blocker type, cumulative beta-blocker use, sample size, and ethnicity demonstrated no significant effect of beta-blocker on longer OS. Hence, we did not find a beneficial effect of beta-blocker use on cancer survival.

To our knowledge, this meta-analysis is the fourth one to be conducted on beta-blocker use and prognosis in various cancers. Indeed, this analysis objectively confirmed the latest development in this topic. All the previous three articles drew a conclusion that beta-blocker use could prolong the survival of cancer patients,[44–46] but our current analysis showed an opposite conclusion that there is generally no relationship between beta-blocker use and cancer prognosis.

Table 2 Summary of the subgroup analysis results of beta-blocker use and OS

Variables	Number of studies	Number of patients	Model	Outcome (OS)		Heterogeneity	
				HR (95% CI)	*P*-value	I^2 (%)	*P*-value
Ethnicity							
Non-Europeans	16	30,607	R	0.90 (0.78–1.02)	0.106	87.2	<0.001
Europeans	8	12,182	R	1.00 (0.89–1.12)	0.958	72.2	0.001
Duration of drug use							
>2 years	6	8,899	F	1.03 (0.93–1.14)	0.617	0.0	0.576
<2 years	6	10,812	R	1.01 (0.91–1.11)	0.897	54.7	0.051
Cancer stage							
I/II	11	2,870	F	0.97 (0.89–1.06)	0.507	15.6	0.295
III/IV	13	4,835	R	1.04 (0.94–1.14)	0.468	59.1	0.003
Sample size							
>1,500	15	65,834	R	1.01 (0.94–1.08)	0.783	76.7	<0.001
<1,500	18	11,839	R	0.81 (0.66–1.00)	0.053	83.5	<0.001
Beta-blocker type							
Non-selective	12	17,714	R	1.04 (0.89–1.22)	0.596	75.7	<0.001
Selective	10	17,714	R	0.93 (0.83–1.05)	0.243	83.5	<0.001
Chronological order of drug use							
Pre-diagnostic beta-blocker use	13	55,710	R	1.03 (0.95–1.11)	0.493	74.7	<0.001
Post-diagnostic beta-blocker use (time-fixed)	7	6,372	R	0.65 (0.43–0.99)	0.046	91.0	<0.001
Post-diagnostic beta blocker use (time-dependent)	2	2,406	R	0.87 (0.59–1.30)	0.508	76.8	0.038
Cancer type							
Lung cancer	7	10,189	F	1.01 (0.96–1.05)	0.818	40.1	0.124
Melanoma	2	4,910	F	0.81 (0.67–0.97)	0.026	0.0	0.892
Mixed cancer	4	21,494	R	1.00 (0.83–1.21)	0.974	87.7	<0.001
Colorectal cancer	2	4,202	R	1.16 (0.84–1.61)	0.353	51.3	0.152
Ovarian cancer	5	3,140	R	0.59 (0.36–0.96)	0.034	88.0	<0.001
Breast cancer	6	16,637	R	0.97 (0.78–1.21)	0.783	61.20	0.024
Pancreatic cancer	2	16,096	R	0.85 (0.75–0.97)	0.014	71.10	0.063

Abbreviations: F, fixed-effects model; R, random-effects model; OS, overall survival.

We then hypothesize some possible reasons for this conclusion. Preclinical studies have suggested that β-blockers play an anti-cancer role in multiple kinds of cancers by targeting at β-adrenergic signaling pathway.[47,48] β-blockers can inhibit multiple processes of tumor progression and metastasis, including the inhibition of tumor cell proliferation, migration, invasion, as well as resistance to tumor angiogenesis and metastasis.[3] Although the basic research may be effective, it is not recommended for speculating on the clinical survival of cancer patients due to the current evidence of evidence-based medicine. Beta-blocker is not a necessary medication for general adjuvant chemotherapy in cancer patients.[49]

Since cardiovascular diseases are common in the population, cancer patients frequently receive cardiovascular medications, including beta-blockers,[2] but beta-blockers might not be recommended for chemotherapy in the absence of other indications. Further studies should be done to investigate the relationship between cancer survival and beta-blocker use in cancer patients without cardiovascular disease. Additionally, different effects in different cancers might have contributed to the lack of a discernible relationship between beta-blockers and OS of various cancers in the current studies. To find out the actual concrete relationship between the two, further analysis can be confined to beta-blocker use and one specific cancer based on a large enough population. Besides, beta-blockers themselves might have some undefined side effects on other organ systems, which might lead to cancer progression.[50]

However, there are still several limitations in this study. First, the studies included in this analysis were all cohort studies or case–control studies, as there were no RCTs yet investigating this topic. Second, while sensitivity analysis supported the stability of our results and a relatively large number of studies were included, we should still carefully interpret the results. The heterogeneity found in the study may be attributed to the multivariable influence factors in some studies. Third, the power of Begg's and Egger's tests to detect bias will be low with small number of studies, and when the between-study heterogeneity is large, none of the bias detection tests work well. Fourth, the dose–response analyses were not carried out due to a limited amount of literature.

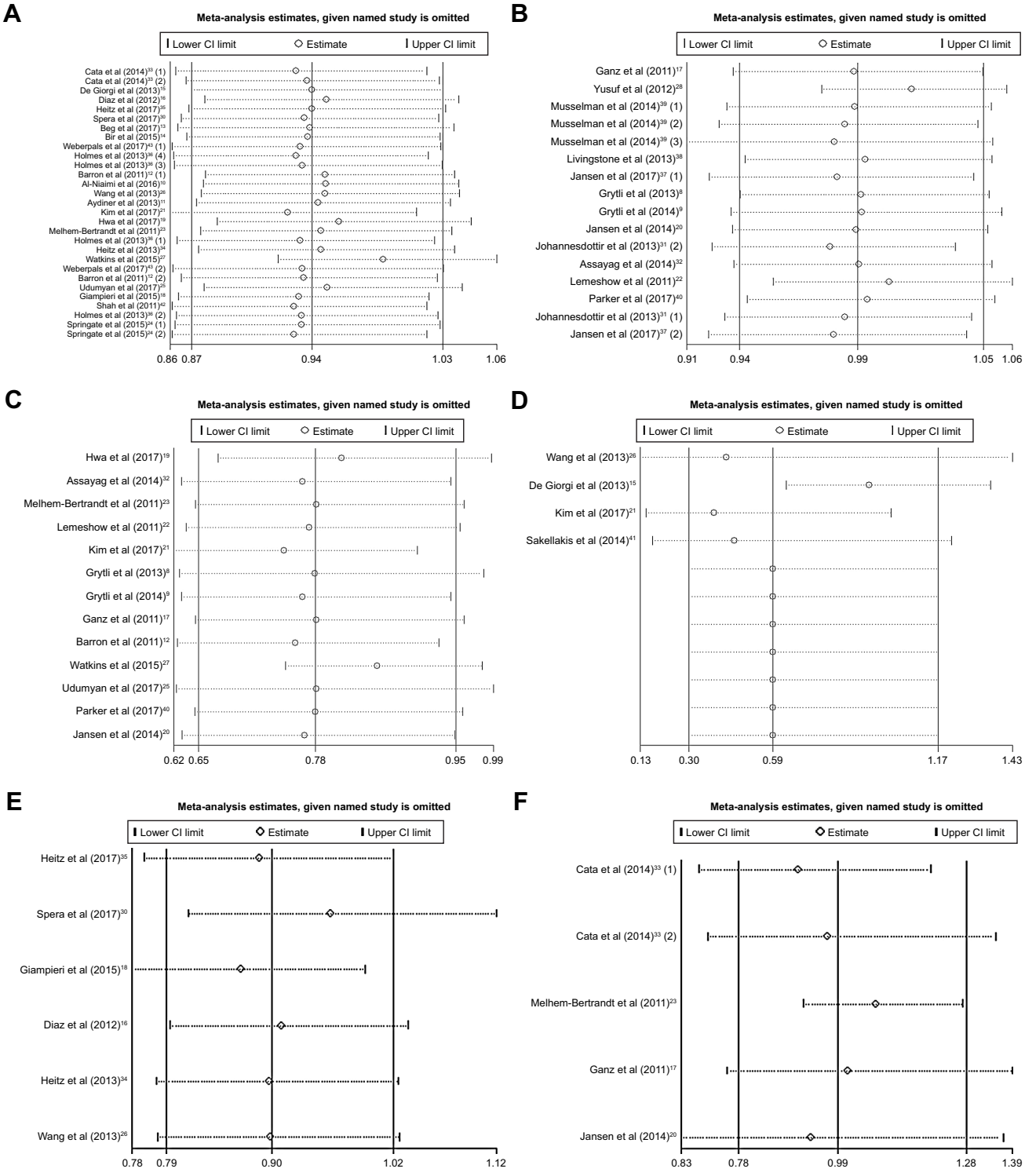

Figure 3 Sensitivity analysis of beta-blocker use on OS (**A**), all-cause mortality (**B**), CSS (**C**), DFS (**D**), PFS (**E**), and RFS (**F**).
Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival.

Despite the limitations, there are several strengths in our study compared with previous meta-analyses. First, our current analysis showed a completely different main conclusion from the previous meta-analyses that there was no relationship between beta-blocker use and cancer prognosis. Second, we separated all-cause mortality from OS to make the analysis more precise. Third, we included 36 studies involving 319,006 patients, which was a larger number of patients than previous meta-analyses. Fourth, we discussed almost all variables that could describe the outcome of

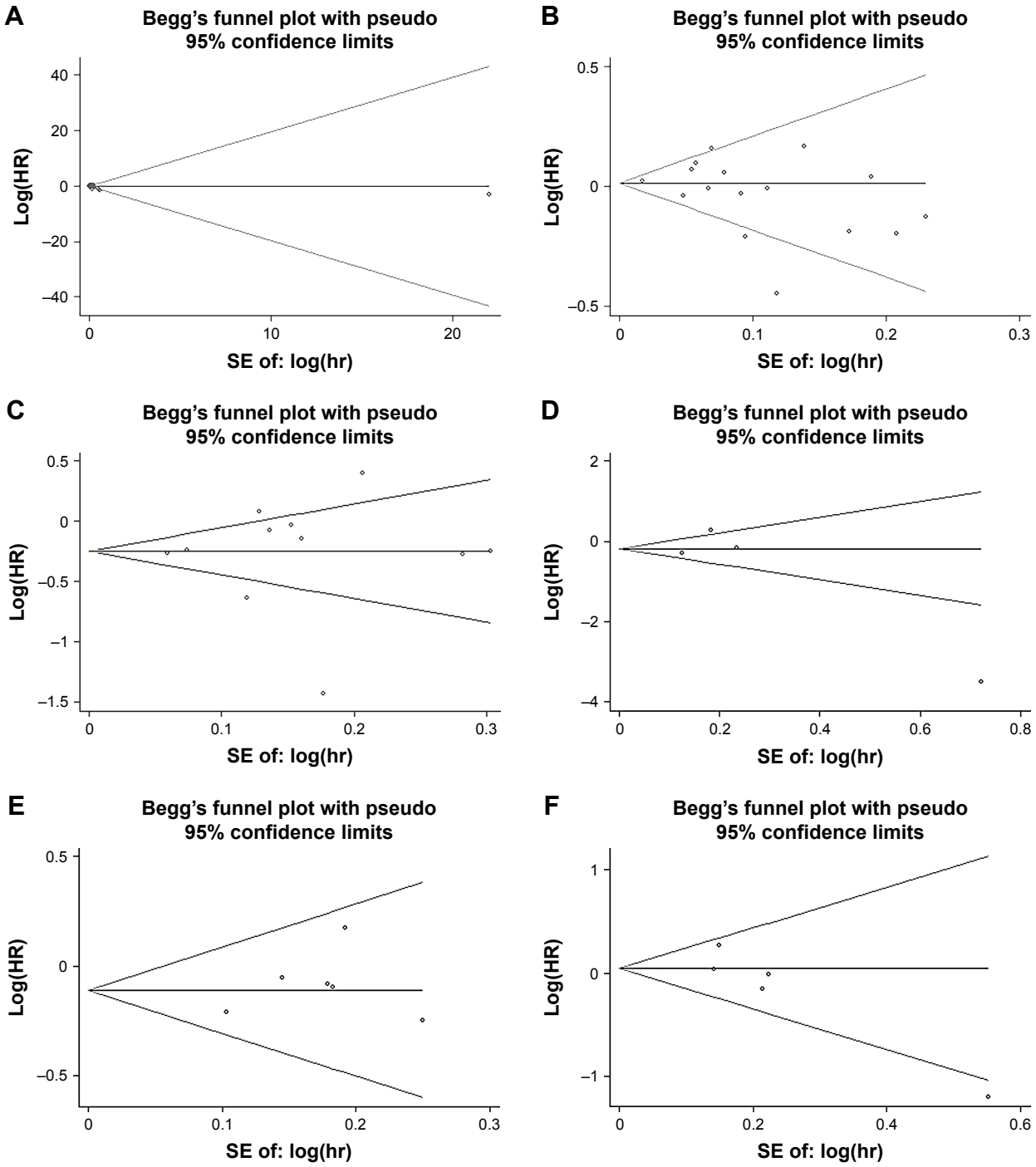

Figure 4 Funnel plot of Begg's test of beta blocker use on OS (**A**), all-cause mortality (**B**), CSS (**C**), DFS (**D**), PFS (**E**), and RFS (**F**).
Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; SE, standard error.

survival, including OS, all-cause mortality, CSS, DFS, PFS, and RFS.

Conclusion

The beta-blocker administration is not associated with cancer prognosis except for the positive effect on long CSS. Moreover, there are apparent protective effects of beta-blocker use in ovarian cancer, pancreatic cancer, and melanoma. We need more high-quality studies, such as RCTs, to confirm this conclusion in the future.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Quality assessment of the included studies

Subjects	Items	Standards	Reference no.					
			8	9	10	11	12	13
			Score					
			Grytli et al (2013)	Grytli et al (2014)	Al-Niaimi et al (2016)	Aydiner et al (2013)	Barron et al (2011)	Beg et al (2017)
Selection	1. Is the case definition adequate?	1. Yes, with independent validation* 2. Yes, eg, record linkage or based on self-reports 3. No description	1	1	1	1	1	1
	2. Representativeness of the cases	1. Consecutive or obviously representative series of cases* 2. Potential for selection biases or not stated	1	1	1	1	1	1
	3. Selection of controls	1. Community controls* 2. Hospital controls 3. No description	1	0	0	0	1	1
	4. Definition of controls	1. No history of disease (end point)* 2. No description of source	0	0	0	0	0	0
Comparability	Comparability of cases and controls on the basis of the design or analysis	1. Study controls for the most important factor*	1	1	1	1	1	1
		2. Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor*)	1	1	1	1	1	1
Exposure	1. Ascertainment of exposure	1. Secure record (eg, surgical records)* 2. Structured interview where blind to case/control status* 3. Interview not blinded to case/control status 4. Written self-report or medical record only 5. No description	1	1	1	1	1	1
	2. Same method of ascertainment for cases and controls	1. Yes* 2. No	1	1	1	1	1	1
	3. Nonresponse rate	1. Same rate for both groups* 2. Nonrespondents described 3. Rate different and no designation	1	1	1	1	1	1
			8	7	7	7	8	8

14	15	16	17	18	19	20	21	22	23	24	25
Bir et al (2015)	De Giorgi et al (2013)	Diaz et al (2012)	Ganz et al (2011)	Giampieri et al (2015)	Hwa et al (2017)	Jansen et al (2014)	Kim et al (2017)	Lemeshow et al (2011)	Melhem-Bertrandt et al (2011)	Springate et al (2015)	Udumyan et al (2017)
1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1
0	1	0	1	0	0	1	0	1	0	1 0	1
0	0	0	0	0	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	1	1	1	1
1	0	1	1	1	1	1	1	1	1	0	1
1	1	1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1	1	1
1	1	0	0	1	1	1	0	0	1	1	1
7	7	6	7	7	7	8	6	7	7	7	8

(*Continued*)

Table S1 (*Continued*)

Subjects	Items	Standards	Reference no.					
			26	27	28	29	30	31
			Score					
			Wang et al (2013)	Watkins et al (2015)	Yusuf et al (2012)	Botteri et al (2013)	Spera et al (2017)	Johannesdottir et al (2013)
Selection	1. Is the case definition adequate?	1. Yes, with independent validation*	1	1	1	1	1	1
		2. Yes, eg, record linkage or based on self-reports						
		3. No description						
	2. Representativeness of the cases	1. Consecutive or obviously representative series of cases*	1	1	1	1	1	1
		2. Potential for selection biases or not stated						
	3. Selection of controls	1. Community controls*						
		2. Hospital controls	0	0	0	0	0	0
		3. No description						
	4. Definition of controls	1. No history of disease (end point)*						
		2. No description of source	0	0	0	0	0	0
Comparability	Comparability of cases and controls on the basis of the design or analysis	1. Study controls for the most important factor*	1	1	1	1	1	1
		2. Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor*)	1	0	1	1	1	1
Exposure	1. Ascertainment of exposure	1. Secure record (eg, surgical records)*	1	1	1	1	1	1
		2. Structured interview where blind to case/control status*						
		3. Interview not blinded to case/control status						
		4. Written self-report or medical record only						
		5. No description						
	2. Same method of ascertainment for cases and controls	1. Yes*	1	1	1	1	1	1
		2. No						
	3. Nonresponse rate	1. Same rate for both groups*	1	1		1	1	
		2. Nonrespondents described			0			0
		3. Rate different and no designation						
			7	6	6	7	7	6

Note: *Indicates 1 score.

32	33	34	35	36	37	38	39	40	41	42	43
Assayag et al (2014)	Cata et al (2014)	Heitz et al (2013)	Heitz et al (2017)	Holmes et al (2013)	Jansen et al (2017)	Livingstone et al (2013)	Musselman et al (2014)	Parker et al (2017)	Sakellakis et al (2014)	Shah et al (2011)	Weberpals et al (2017)
I	I	I	I	I	I	I	I	I	I	I	I
I	I	I	I	I	I	I	I	I	I	I	I
I	0	0	0	I	I	I	I	0	0	I	I
0	0	0	0	0	0	0	0	0	0	0	0
I	I	I	I	I	I	I	I	I	I	I	I
0	I	I	I	0	I	0	0	I	0	0	I
I	I	I	I	I	I	I	I	I	I		I
										0	
I	I	I	I	I	I	I	I	I	I	I	I
I	I	I	I	0	0	0	0	I	I	I	0
7	7	7	7	6	7	6	6	7	6	6	7

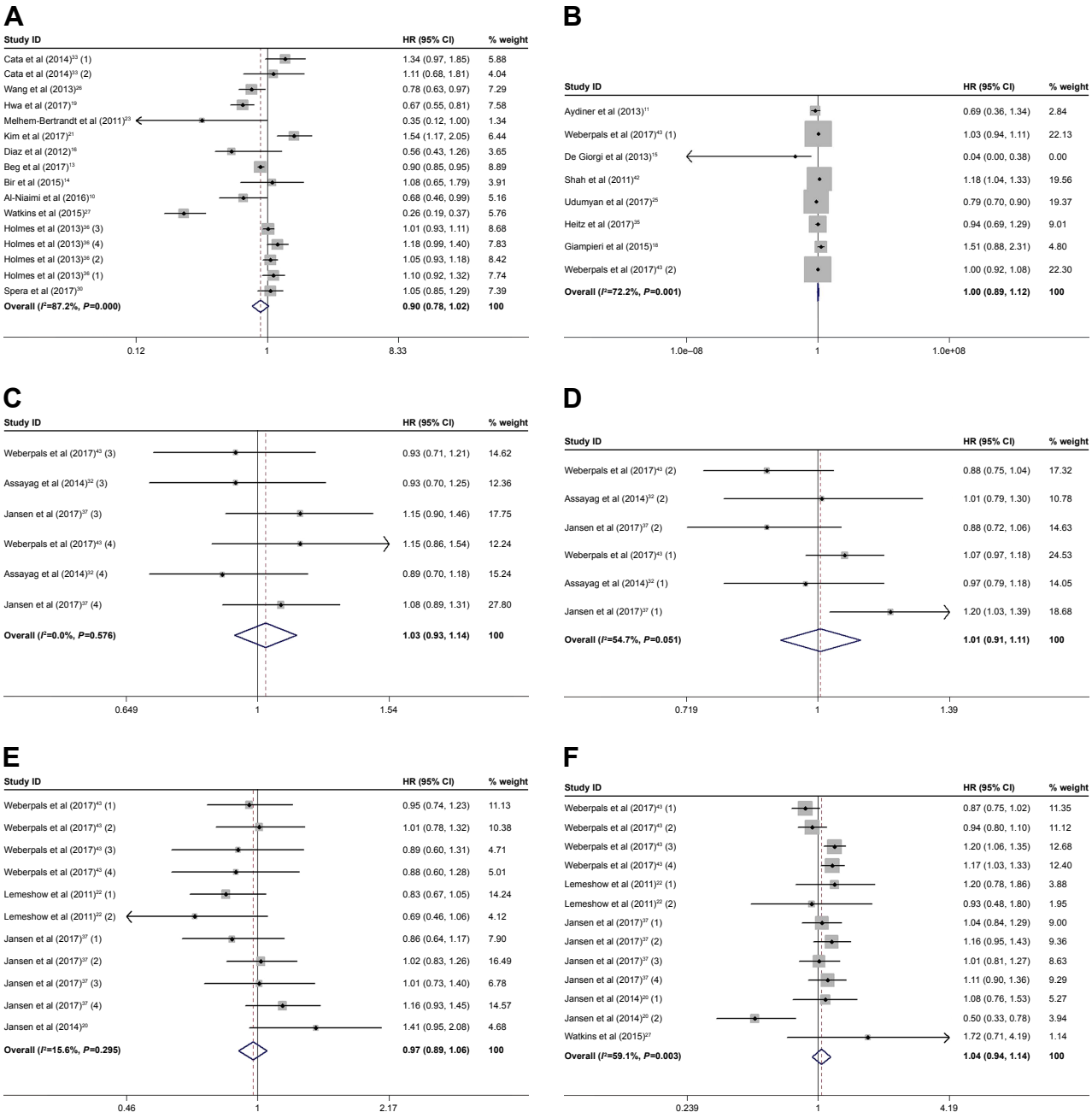
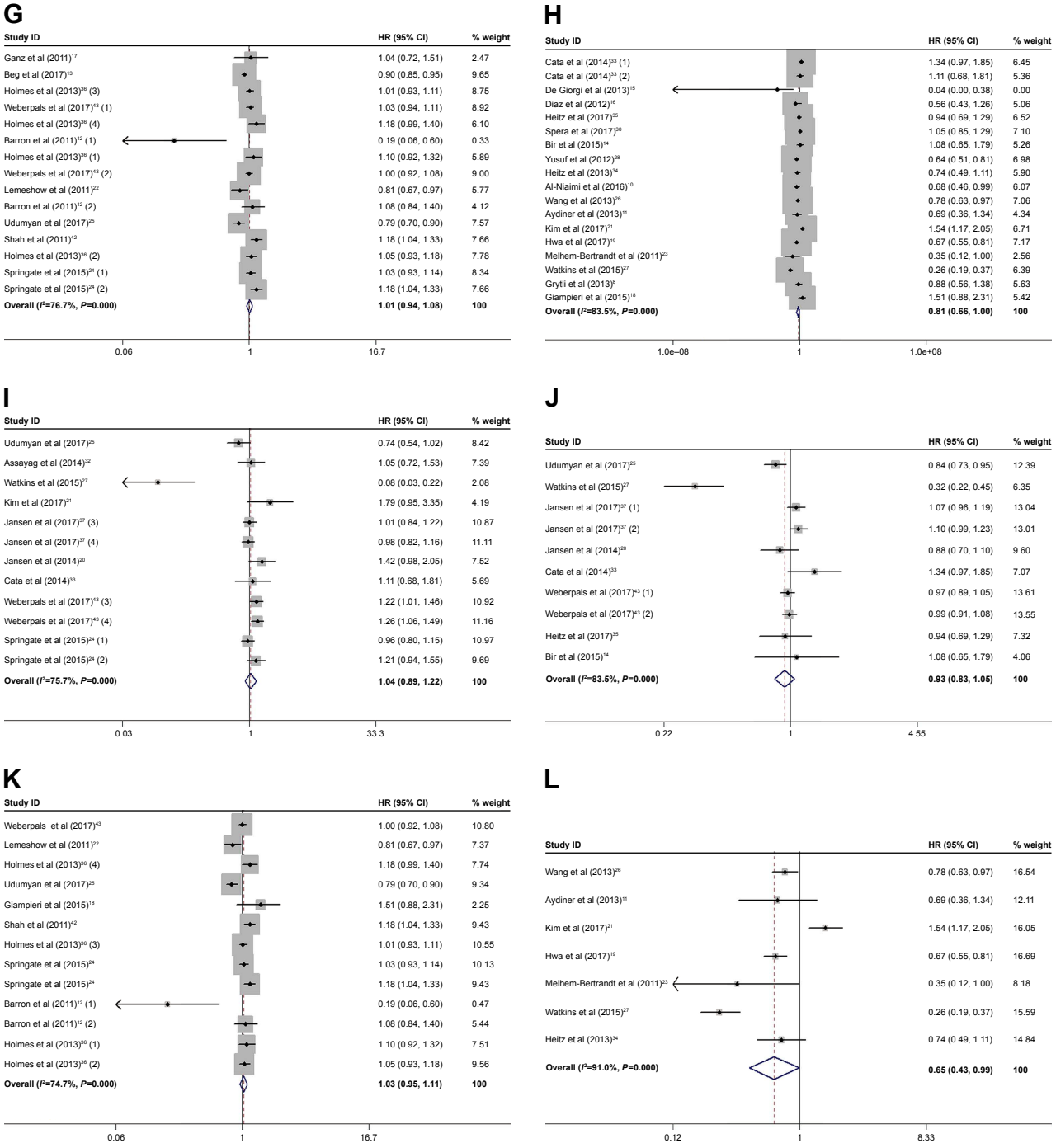


Figure S1 (*Continued*)



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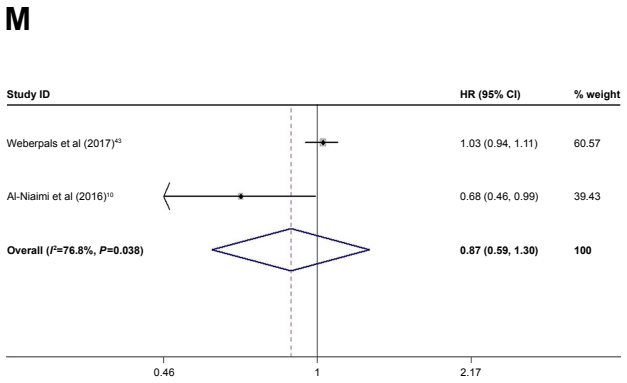

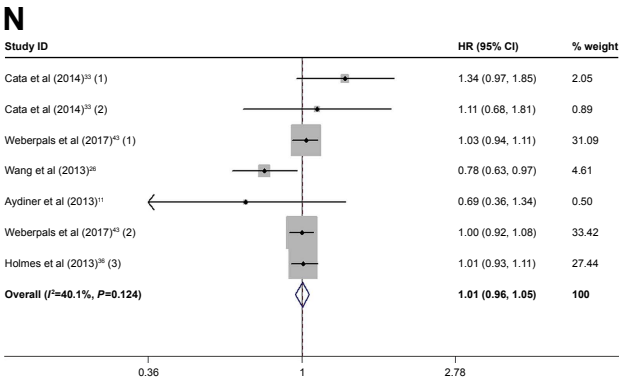

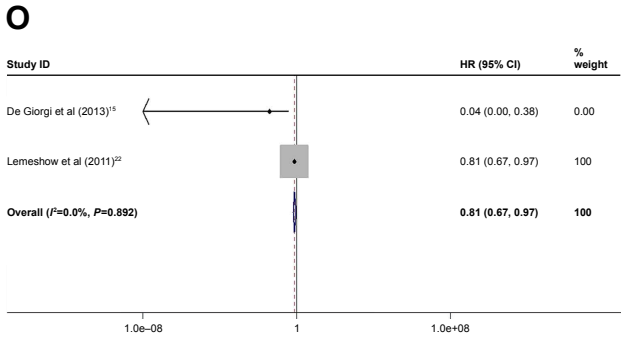

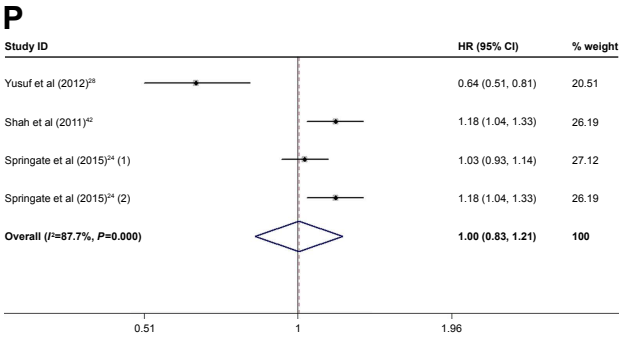

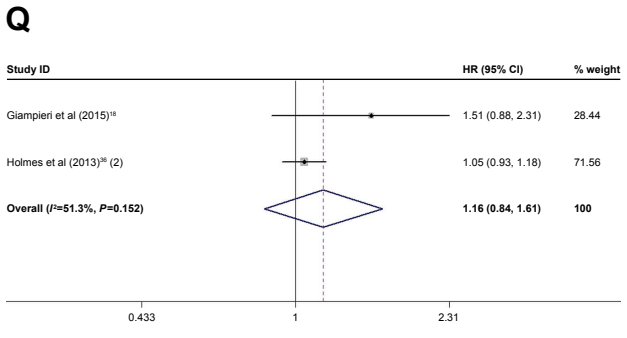

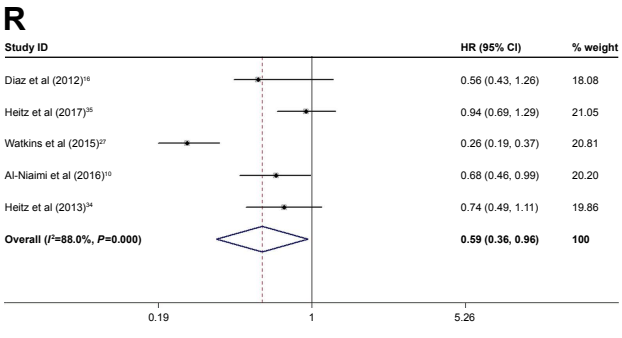

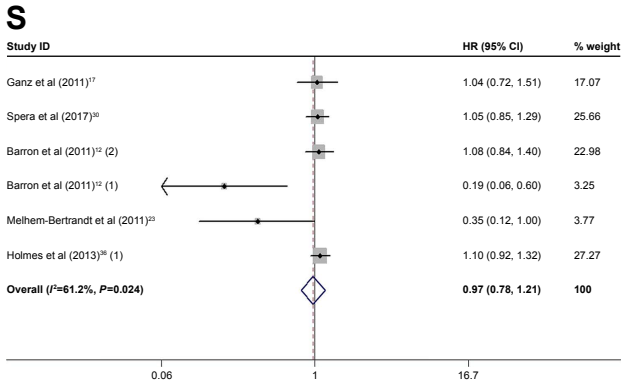

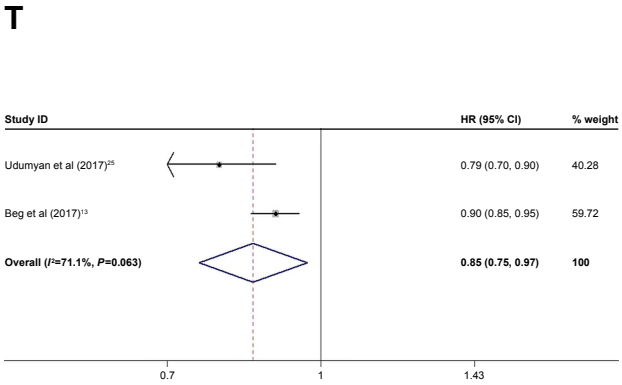

Figure S1 Subgroup analysis on beta-blocker use and OS in patients with non-Europeans (**A**), Europeans (**B**); duration of drug use >2 years (**C**), duration of drug use <2 years (**D**); Stage I/II (**E**), Stage III/IV (**F**); sample size >80 (**G**), sample size <80 (**H**); non-selective beta-blocker (**I**), selective blocker-type (**J**); pre-diagnostic beta-blocker use (**K**), post-diagnostic beta-blocker use (time-fixed) (**L**), post-diagnostic beta-blocker use (time-dependent) (**M**); lung cancer (**N**), melanoma (**O**), mixed cancer (**P**), colorectal cancer (**Q**), ovarian cancer (**R**), breast cancer (**S**), and pancreatic cancer (**T**).

Note: Weights are from random-effects analysis. The numbers in parentheses indicate the different included studies in the same year.

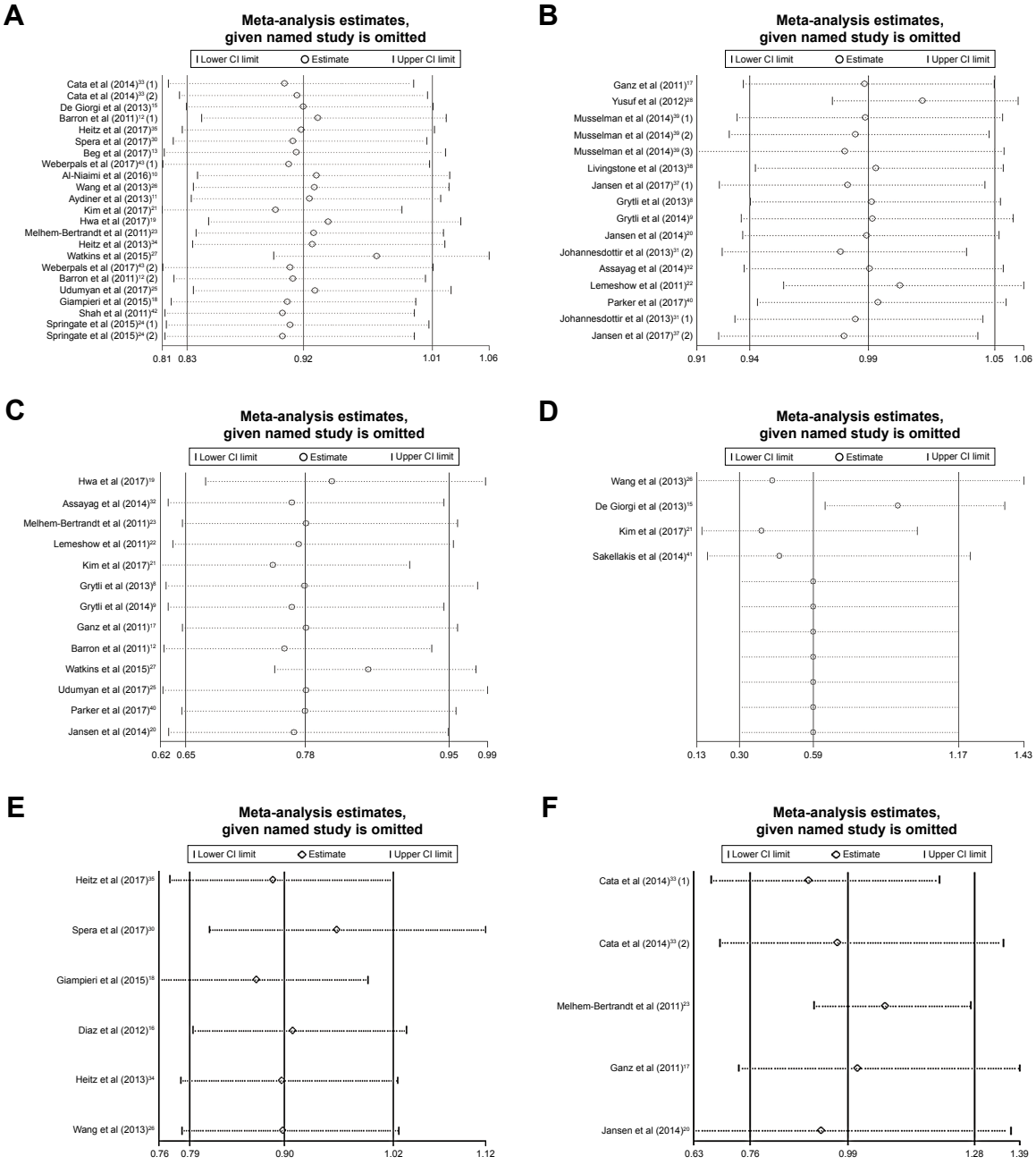

Figure S2 Sensitivity analysis of beta-blocker use on OS (**A**), all-cause mortality (**B**), CSS (**C**), DFS (**D**), PFS (**E**), and RFS (**F**) in studies except the studies obtaining estimates from KM plots.

Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; KM, kaplan-meier.

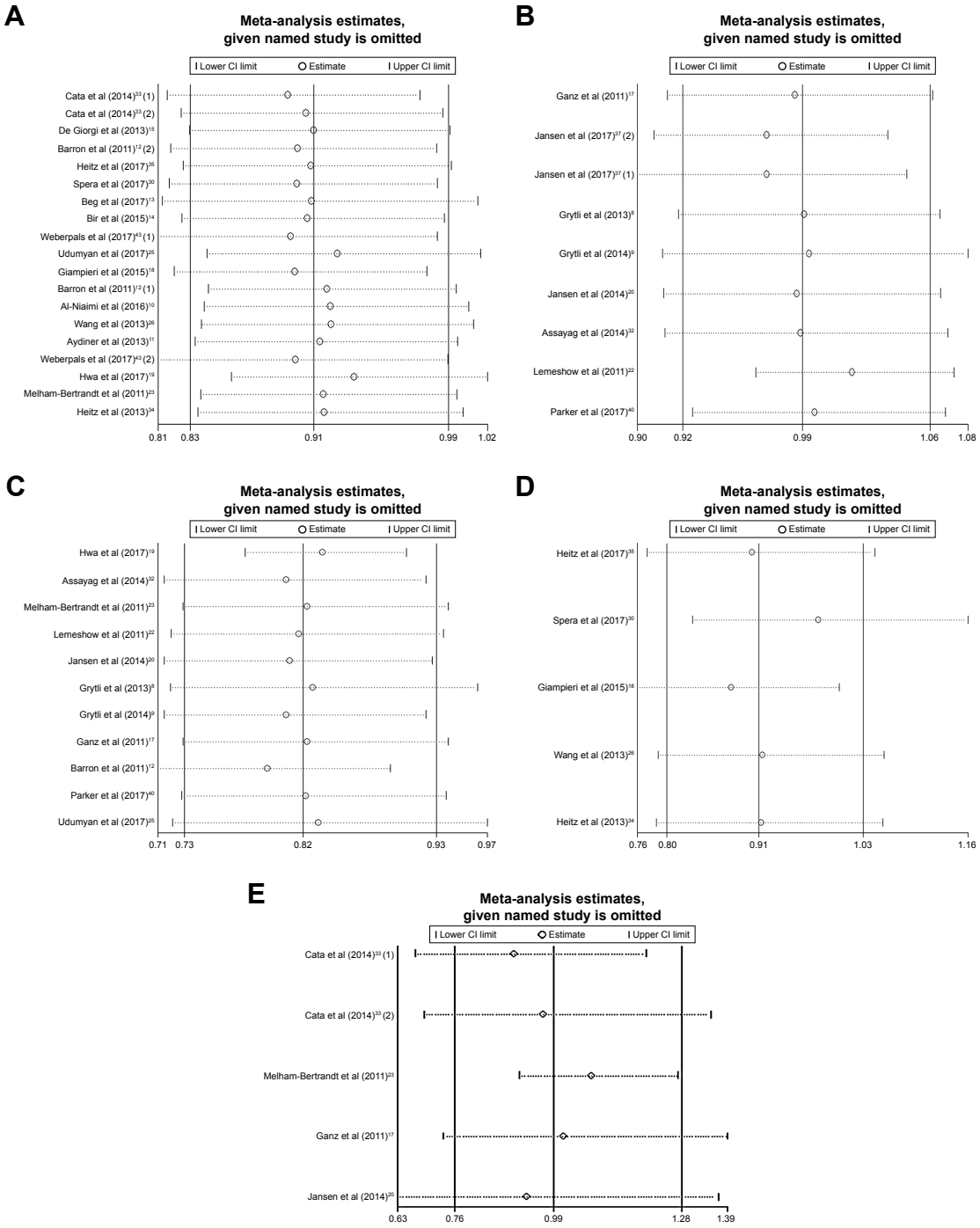

Figure S3 Sensitivity analysis of beta-blocker use on OS (**A**), all-cause mortality (**B**), CSS (**C**), PFS (**D**), and RFS (**E**) in high-quality studies (NOS score ≥7).
Abbreviations: OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; RFS, recurrence-free survival; NOS, Newcastle–Ottawa Quality Assessment Scale.