Systematic Review and Meta-Analysis

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The prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy

A systematic review and meta-analysis

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Abstract

Background: It is well known that liposome-based delivery of cytotoxic chemotherapeutics has been proposed as a putative strategy to enhance drug tolerability and efficacy compared to the conventional chemotherapy. However, its potential effect on improving prognosis remains largely unknown. The current meta-analysis is to explore the prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy.

Methods: A detailed review of English and Chinese literature was conducted up to March 21, 2020. We evaluate its possible correlations using hazard ratios (HRs) with 95% confidence intervals (CIs). The pooled data were calculated by STATA software and Review Manager 5.3 software.

Results: Consequently, 26 studies including 7943 patients were satisfied in current analysis. There were no significant differences between liposomal and conventional chemotherapy in OS (HR = 0.98, 95%CI: 0.93–1.04, $P = .544$) and PFS (HR = 1.00, 95%CI: 0.92–1.10, $P = .945$). Likewise, subgroup-analysis regarding country, cancer type, and sample sizes also showed the similar results of the 2 paired groups.

Conclusion: Taken together, our finding has demonstrated that there was no association of undergoing liposomal doxorubicin-based chemotherapy with cancer prognosis. However, detailed and further studies are needed to confirm our conclusion.

Abbreviations: CI = confidence interval, HR = hazard ratio, OC = ovarian cancer, OS = overall survival, PFS = progression-free survival, PLD = pegylated liposomal doxorubicin.

Keywords: chemotherapy, doxorubicin, liposome, meta-analysis, nanomedicine, prognosis

1. Introduction

Generally, patients with malignant diseases often have worse psychological and physical health. An estimation of 2020 cancer statistics revealed about 1,806,590 new cancer cases diagnosed and 606,520 new deaths assigned to cancer in US.[1] Although enormous progress against cancer have been made in the past decade, chemotherapy is of great importance for majority of the patients especially for the late-stage patients. However, most patients undergoing conventional chemotherapy suffer from serious side effects due to nonselective toxicity of drugs to normal cells.[2] There is an urgent need and tremendous value to develop novel chemotherapeutic drug carriers.

Advanced researches indicate that nano-sized carriers have presented an important therapeutic agents in both diagnosis and therapy of cancer because they have longer plasma half-life and may enhance chemotherapeutic drugs delivery while limiting nontumorous tissue distribution.[3] Consequently, it possesses increase anticancer efficacy and lower toxicity to normal tissue.[4] Liposomes are the most clinically established nanometer material that are used to deliver cytotoxic and antifungal drugs, genes, as well as vaccines.[5] The outstanding profile consist in its biocompatibility, biodegradability, reduced toxicity, capacity for size, and surface manipulations. Pegylated liposomal doxorubicin (PLD; Doxil/Caelyx) is unique formulation of doxorubicin, which have been used for various malignancies. It is a cytotoxic anthracycline antibiotic extracted from *Streptomyces peucetius* var. *caesius*.[6–7] PLD is the first FDA-approved anticancer nano-drug and has demonstrated tremendous benefits. PLD represents an improved formulation of conventional doxorubicin, with reduced cardiotoxicity and an improved pharmacokinetic profile.[8] As shown by evidence from clinical trials, intravenous PLD is a useful option in the treatment of malignancies. The possible mechanism of its antitumor has not been explained clearly. It may interfere with the DNA, RNA, and protein synthesis by blocking topoisomerase I and intercalate

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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between adjacent base pairs of the double helix structure of DNA.[9,10] Survival is highly dependent on and inversely correlated with the stage of disease at the initiation of treatment. Despite the well-established role of liposomal doxorubicin-based chemotherapy in prognosis for tumor patients, these conclusions were controversial and inconsistent. Meta-analysis is a statistical software that incorporates all available data to derive a pooled and authentic result.[11] Herein, we try to perform a meta-analysis to explore whether patients treated with PLD chemotherapy is associated with cancer prognosis.

2. Methods

2.1. Literature search strategy

A detailed review of literature was conducted from PubMed, Embase, Cochrane Library, CBM, and CNKI, using the terms ("liposom* and doxorubicin OR DOX-SL OR Lipodox OR Doxil OR Caelyx OR Lipo-Dox OR DaunoXome") and ("cancer OR tumor OR tumour OR neoplasm OR neoplasma OR neoplasia OR carcinoma"). The literature search was last updated on March 21, 2020. We also searched the reference of the relevant review articles to seek for the potentially included studies. The PRISMA statement for reporting systematic reviews and meta-analyses was cited in this meta-analysis.[12] In addition, the ethical approval was not applied in current study because there was no patient's privacy or clinical samples.

2.2. Inclusion and exclusion criteria

In order to derive a pooled and relatively authentic result, studies should meet the following criteria before being included: the included studies focused on the associations; and the studies provided available data. As per the exclusion criteria: no survival analysis data; studies involved cell lines and animals; similar or duplicate study; and other type articles including reviews, case reports, and letters.

2.3. Data extraction and quality assessment

We extracted the data including the first author, publication year, country, no of patients, age, cancer type, treatment arms, phase, follow-up time, survival outcomes, and hazard ratio (HR) (95% confidence interval [CI]) from included study. The data were independently extracted by 2 authors. Disagreements were resolved by discussion or reviewed by a third author.

Among these data, country came from USA, UK, Greece, and others; Sample size was separated into ≥100 and <100; Cancer type included soft tissue sarcoma, multiple myeloma, acute myelogenous leukaemia, nonsmall cell lung cancer, oesophago-gastric cancer, acute lymphoblastic leukemia, metastatic breast cancer, ovarian cancer (OC). Survival outcomes contained overall survival (OS) and progression-free survival (PFS).

2.4. Statistical analysis

We explored the prognosis of cancer patients undergoing liposomal doxorubicin-based chemotherapy by using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA 12.0 software (Stata Corpotation, College Station, TX). HR (95% CI) was obtained for assessing the prognosis of cancer patients. Meanwhile, the Q statistics and I^2 test were applied to calculate the heterogeneity of eligible study. $P < .05$ and/or $I^2 >$ 50% were considered as statistically heterogeneous, and random effects (DerSimonian and Laird method) model was used to pool the results.[13,14] Otherwise, fixed effects (Mantel–Haenszel method) model was applied.[15]

One-way sensitivity analyses removed each single included studies at a time were performed to assess the pooled results' stability. Moreover, the publication bias was assessed using Begg test. $P < .05$ indicated that there was a bias.[16] Additionally, different subgroups consisted of country, cancer type, and sample size were analysed in current meta-analysis.

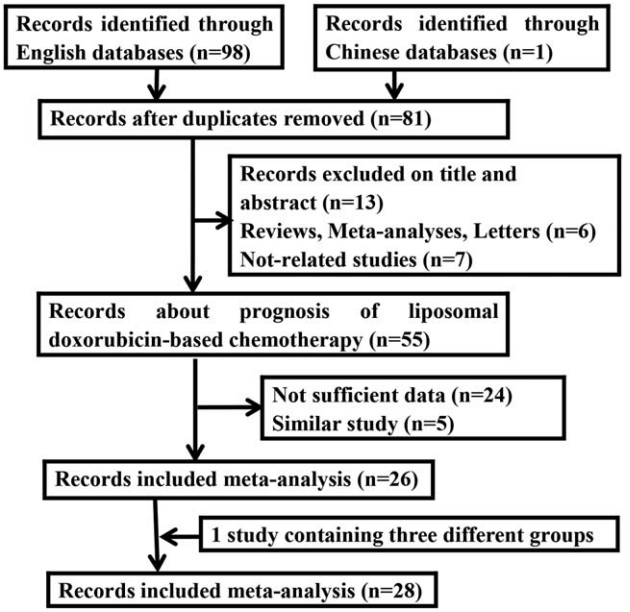

Figure 1. Flow diagram of the study selection process in the meta-analysis.

3. Results

3.1. Study characteristics

Consequently, 26 studies with a total of 7943 participants were selected in our meta-analysis (Fig. 1).[17–42] The main study characteristics are provided in Table 1. Among them, Kaye et al[31] phase II, open-label, randomized, multicenter study was performed to explore 3 different chemotherapy in OC. Therefore, we took it as 3 different studies independently. Twenty-eight studies were finally included in this analysis (Table 1).

Among these studies, only 1 study was conducted in China and the rest of studies came from English. The participants of each included studies ranged from 60 to 973. The cancer types contained 9 metastatic breast cancer, 10 OC, 3 nonsmall cell lung cancer, 2 multiple myeloma, 1 acute lymphoblastic leukemia, 1 acute myelogenous leukaemia, 1 oesophago-gastric cancer, and 1 soft tissue sarcoma. Meanwhile, 26 and 27 out of 28 studies reported OS and PFS, respectively. The detailed information is presented in Table 2. However, the treatment arms differed greatly in these eligible studies.

3.2. Meta-analysis of overall survival

As a result, 26 studies were analysed the prognosis of cancer patients undergoing liposomal doxorubicin chemotherapy. We

Table 1

Characteristics of included clinical studies.

First authors	Year	Country	No. of patients	Age, median (range)	Cancer types	Treatment arms	Phase	Follow-up	Outcomes
Judson I[17]	2001	USA	50/45	52 (19–80)/52 (27–77)	STS	PLD 50 mg/m^2 every 28 d; doxorubicin 75 mg/m^2 every 21 d	Phase II	NA	OS/PFS
Dimopoulos MA[18]	2003	Greece	132/127	65 (37–88)/66 (37–88)	MM	PLD 40 mg/m^2 every 28 days; doxorubicin 9 mg/m^2 every 28 days	Phase III	40 mo	OS/PFS
O'Brien ME[19]	2004	UK	254/255	59 (28–82)/58 (25–82)	MBC	PLD 50 mg/m^2 every 28 d; doxorubicin 60 mg/m^2 every 21 d	Phase III	NA	OS/PFS
Rifkin RM[20]	2006	USA	97/95	60 (37–84)/60 (44–81)	MM	PLD 40 mg/m^2 every 28 d; doxorubicin 9 mg/m^2 every 28 d	Phase III	21 mo	OS/PFS
Hunault-Berger M[21]	2011	France	31/29	68 (55–77)/66 (60–80)	ALL	PLD 40 mg/m^2 days 1 to 4; doxorubicin 12 mg/m^2/day days 1 to 4	Phase II	48 mo	OS/PFS
Batist G[22]	2001	Canada	142/155	55 (30–80)/54 (22–88)	MBC	Liposomal doxorubicin 60 mg/m^2 every 21 d; doxorubicin 60 mg/m^2 every 21 d	Phase III	20 mo	OS/PFS
Harris L[23]	2002	USA	108/116	58 (26–85)/58 (29–82)	MBC	Liposomal doxorubicin 75 mg/m^2 every 21 d; doxorubicin 75 mg/m^2 every 21 d	Phase III	4 mo	OS/PFS
Latagliata R[24]	2008	Rome	148/153	68.2 (61–74.8)/68 (61–74.8)	AML	Daunoxome 80 mg/m^2 days 1 to 3; daunorubicin 45 mg/m^2 days 1 to 3	Phase III	26.6 mo	OS/PFS
Mylonakis N[25]	2010	Greece	47/41	64 (49–83)/66 (52–77)	NSCLC	Liposomal cisplatin 120 mg/m^2 every 21 d; cisplatin 100 mg/m^2 every 21 d	Phase II	53 mo	OS/PFS
Stathopoulos GP[26]	2010	Greece	114/115	65 (37–80)/66 (41–85)	NSCLC	Liposomal cisplatin 200 mg/m^2 every 14 d; csplatin 75 mg/m^2 every 14 d	Phase II	15 mo	OS/PFS
Yang X[27]	2012	China	50/50	55.2 (34–76)/53.2 (25–73)	NSCLC	Liposomal paclitaxel 150 mg/m^2 every 21 d; paclitaxel 150 mg/m^2 every 21 d	NA	20 mo	OS/PFS
Roy AC[28]	2013	UK	44/44	56 (38–81)/62 (33–79)	OG cancer	Liposomal irinotecan 120 mg/m^2 every 21 d; irinotecan 300 mg/m^2 every 21 d	Phase II	NA	OS/PFS
Pignata S[29]	2011	Italy	410/410	57 (25–77)/57 (21–77)	OC	Carboplatin and PLD 30 mg/m^2 every 3 wk; carboplatin and paclitaxel 175 mg/m^2 every 3 wk	Phase III	20 mo	OS/PFS
Bafaloukos D[30]	2010	Greece	93/96	62 (38–89)/63 (37–81)	OC	Carboplatin and PLD 45 mg/m^2 every 3 wk; carboplatin and paclitaxel 175 mg/m^2 every 3 wk	Phase II	43.6 mo	PFS
Kaye SB-1[31]	2012	UK	33/32	53.0 (43–81)/58.5 (45–77)	OC	PLD 50 mg/m^2 every 28 d; olaparib 200 mg every 28 d;	Phase II	NA	OS/PFS
Kaye SB-2[31]	2012	UK	33/32	53.0 (43–81)/53.5 (35–76)	OC	PLD 50 mg/m^2 every 28 d; olaparib 400 mg every 28 d;	Phase II	NA	OS/PFS
Kaye SB-3[31]	2012	UK	33/64	53.0 (43–81)/NA	OC	PLD 50 mg/m^2 every 28 d; olaparib 400 + 200 mg every 28 d;	Phase II	NA	PFS

(*continued*)

Table 1

(continued).

First authors	Year	Country	No. of patients	Age, median (range)	Cancer types	Treatment arms	Phase	Follow-up	Outcomes
Alberts DS[32]	2008	USA	31/30	66.9 (43–87)/62.5 (31–80)	OC	Carboplatin and PLD 30 mg/m^2 every 4 wk; carboplatin every 4 wk	Phase III	22.4 mo	OS/PFS
Pujade-Lauraine E[33]	2010	France	466/507	60.5 (24–82)/61 (27–82)	OC	Carboplatin and PLD 30 mg/m^2 every 4 wk; carboplatin and paclitaxel 175 mg/m^2 every 3 wk	Phase III	22 mo	OS/PFS
Mutch DG[34]	2007	USA	96/99	62 (28–83)/59 (38–85)	OC	PLD 50 mg/m^2 every 28 d; gemcitabine 1000 mg/m^2 every 21 d	Phase III	29.2 mo	OS
Gordon AN[35]	2001	USA	239/235	60 (27–87)/60 (25–85)	OC	PLD 50 mg/m^2 every 28 d; topotecan 1.5 mg/m^2 every 21 d	Phase III	NA	OS/PFS
Colombo N[36]	2012	Italy	417/412	59 (23–84)/59 (25–87)	OC	PLD 50 mg/m^2 every 4 wk; patupilone 10 mg/m^2 every 3 wk	Phase III	27 mo	OS/PFS
Sparano JA[37]	2009	USA	378/373	52.5 (26–80)/51.8 (30–87)	MBC	PLD 30 mg/m^2 and docetaxel 60 mg/m^2 every 21 d; docetaxel 75 mg/m^2 every 21d	Phase III	NA	OS/PFS
Chan S[38]	2004	UK	80/80	54 (19–78)/54 (26–82)	MBC	Myocet 75 mg/m^2 and cyclophosphamide 600 mg/m^2; epirubicin 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 wk	Phase III	21 mo	OS/PFS
Keller AM[39]	2004	USA	150/151	56 (33–87)/56 (30–83)	MBC	PLD 50 mg/m^2 every 28 d; vinorelbine or mitomycin C and vinblastine every 6 to 8 wk	Phase III	NA	OS/PFS
Baselga J[40]	2014	USA	181/182	52 (22–79)/53 (30–76)	MBC	NPLD 50 mg/m^2 every 3 wk and trastuzumab and paclitaxel; trastuzumab and paclitaxel every 3 wk	Phase III	44 mo	OS/PFS
Smorenburg CH[41]	2014	Netherlands	40/38	NA	MBC	PLD 45 mg/m^2 every 4 wk; capecitabine 1000 mg/m^2 every 3 wk	Phase III	39 mo	OS/PFS
Harbeck N[42]	2017	Germany	105/105	62 (36–82)/63 (22–85)	MBC	PLD 50 mg/m^2 every 28 d; capecitabine 1250 mg/m^2 twice daily for 14 d every 21 d	Phase III	NA	OS/PFS

ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukaemia, MBC = metastatic breast cancer, MM = multiple myeloma, NA = not available, NPLD = nonpegylated liposomal doxorubicin, NSCLC = nonsmall cell lung cancer, OC = ovarian cancer, OG = oesophago-gastric, OS = overall survival, PFS = Progression-free survival, PLD = pegylated liposomal doxorubicin, STS = soft tissue sarcoma.

Table 2

The survival data of the selected studies.

First authors	Year	Country	No. of patients	Cancer types	Outcome	HR (95%CI)
Judson I	2001	USA	50/45	STS	OS	0.64 (0.38–1.10)
Judson I	2001	USA	50/45	STS	PFS	1.09 (0.75–1.58)
Dimopoulos MA	2003	Greece	132/127	MM	OS	1.36 (0.85–2.17)
Dimopoulos MA	2003	Greece	132/127	MM	PFS	1.15 (0.80–1.64)
O'Brien ME	2004	UK	254/255	MBC	OS	0.94 (0.74–1.19)
O'Brien ME	2004	UK	254/255	MBC	PFS	1.00 (0.82–1.22)
Rifkin RM	2006	USA	97/95	MM	OS	0.69 (0.31–1.52)
Rifkin RM	2006	USA	97/95	MM	PFS	1.15 (0.67–1.98)
Hunault-Berger M	2011	France	31/29	ALL	OS	0.97 (0.54–1.77)
Hunault-Berger M	2011	France	31/29	ALL	PFS	1.16 (0.67–2.03)
Batist G	2001	Canada	142/155	MBC	OS	1.04 (0.77–1.41)
Batist G	2001	Canada	142/155	MBC	PFS	1.03 (0.80–1.33)
Harris L	2002	USA	108/116	MBC	OS	0.76 (0.56–1.04)
Harris L	2002	USA	108/116	MBC	PFS	0.92 (0.66–1.26)
Latagliata R	2008	Rome	148/153	AML	OS	0.95 (0.72–1.26)
Latagliata R	2008	Rome	148/153	AML	PFS	1.10 (0.80–1.50)
Mylonakis N	2010	Greece	47/41	NSCLC	OS	0.92 (0.54–1.56)
Mylonakis N	2010	Greece	47/41	NSCLC	PFS	0.91 (0.59–1.42)
Stathopoulos GP	2010	Greece	114/115	NSCLC	OS	1.21 (0.87–1.68)
Stathopoulos GP	2010	Greece	114/115	NSCLC	PFS	0.86 (0.64–1.16)
Yang X	2012	China	50/50	NSCLC	OS	1.27 (0.81–1.97)
Yang X	2012	China	50/50	NSCLC	PFS	0.76 (0.53–1.09)
Roy AC	2013	UK	44/44	OG cancer	OS	1.32 (0.79–2.21)
Roy AC	2013	UK	44/44	OG cancer	PFS	1.06 (0.71–1.57)
Pignata S	2011	Italy	410/410	OC	OS	0.82 (0.72–1.12)
Pignata S	2011	Italy	410/410	OC	PFS	0.95 (0.81–1.13)
Bafaloukos D	2010	Greece	93/96	OC	PFS	1.15 (0.78–1.66)
Kaye SB-1	2012	UK	33/32	OC	OS	0.66 (0.27–1.55)
Kaye SB-1	2012	UK	33/32	OC	PFS	0.91 (0.48–1.74)
Kaye SB-2	2012	UK	33/32	OC	OS	1.01 (0.44–2.27)
Kaye SB-2	2012	UK	33/32	OC	PFS	0.86 (0.45–1.62)
Kaye SB-3	2012	UK	33/64	OC	PFS	0.88 (0.51–1.56)
Alberts DS	2008	USA	31/30	OC	OS	0.46 (0.22–0.95)
Alberts DS	2008	USA	31/30	OC	PFS	0.54 (0.32–0.93)
Pujade-Lauraine E	2010	France	466/507	OC	OS	0.99 (0.85–1.16)
Pujade-Lauraine E	2010	France	466/507	OC	PFS	0.82 (0.72–0.94)
Mutch DG	2007	USA	96/99	OC	OS	1.02 (0.71–1.42)
Gordon AN	2001	USA	239/235	OC	OS	0.82 (0.68–1.00)
Gordon AN	2001	USA	239/235	OC	PFS	0.79 (0.67–0.94)
Colombo N	2012	Italy	417/412	OC	OS	1.07 (0.91–1.26)
Colombo N	2012	Italy	417/412	OC	PFS	0.95 (0.8–1.12)
Sparano JA	2009	USA	378/373	MBC	OS	0.98 (0.82–1.17)
Sparano JA	2009	USA	378/373	MBC	PFS	1.52 (1.29–1.79)
Chan S	2004	UK	80/80	MBC	OS	1.15 (0.77–1.72)
Chan S	2004	UK	80/80	MBC	PFS	1.52 (1.06–2.19)
Keller AM	2004	USA	150/151	MBC	OS	1.05 (0.82–1.33)
Keller AM	2004	USA	150/151	MBC	PFS	1.26 (0.98–1.62)
Baselga J	2014	USA	181/182	MBC	OS	1.27 (0.98–1.65)
Baselga J	2014	USA	181/182	MBC	PFS	1.19 (0.92–1.53)
Smorenburg CH	2014	Netherlands	40/38	MBC	OS	0.87 (0.53–1.43)
Smorenburg CH	2014	Netherlands	40/38	MBC	PFS	0.68 (0.42–1.09)
Harbeck N	2017	Germany	105/105	MBC	OS	1.12 (0.79–1.58)
Harbeck N	2017	Germany	105/105	MBC	PFS	1.08 (0.76–1.54)

ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukaemia, CI = confidence interval, HR = hazard ratio, MBC = metastatic breast cancer, MM = multiple myeloma, NA = not available, NSCLC = nonsmall cell lung cancer, OG = oesophago-gastric, OC = ovarian cancer, OS = overall survival, PFS = progression-free survival, STS = soft tissue sarcoma.

found that no significant difference was explored in OS (HR = 0.98, 95%CI: 0.93–1.04, $P = .544$) (Fig. 2). Likewise, subgroup analysis demonstrated no significant differences regarding country, cancer type, and sample sizes (Table 3).

3.3. Meta-analysis of progression-free survival

There were 27 studies involved with PFS. Ultimately, we found that no association of patients after liposomal chemotherapy in tumors was detected with PFS (HR = 1.00, 95%CI: 0.92–1.10,

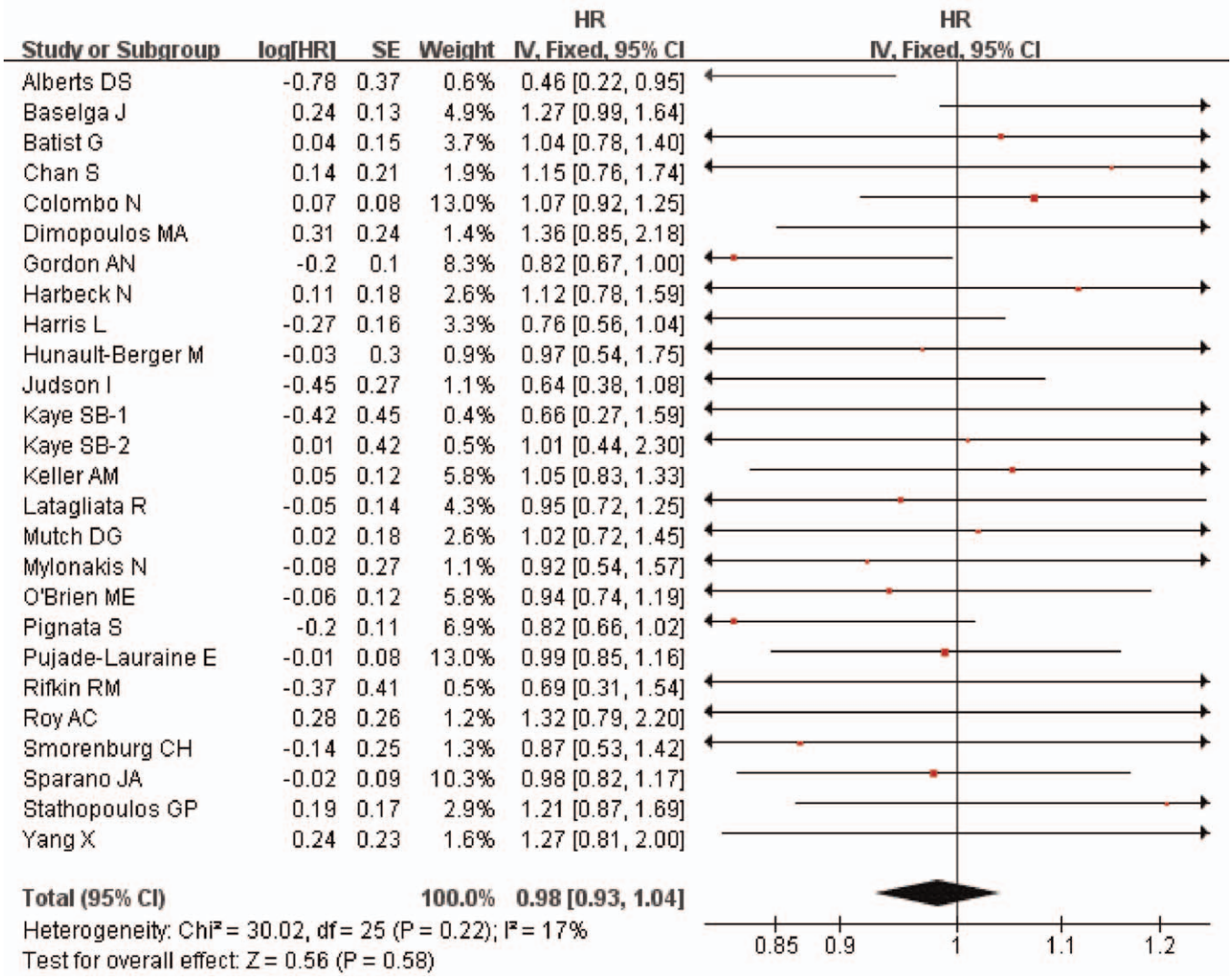

Figure 2. Forest plot of the association between liposomal doxorubicin-based chemotherapy in various tumors and OS. CI = confidence interval, HR = hazard ratio, OS = overall survival.

P = .945) (Fig. 3). A similar results were explored in subgroup analysis of sample sizes rather than country and cancer type. The details were shown in Table 4.

3.4. Sensitivity analysis and publication bias evaluation

Sensitivity analysis demonstrated that our conclusions were relatively stable in OS (Fig. 4) and PFS (Fig. 5). Furthermore, Begg

Table 3

Stratified analysis of liposomal doxorubicin-based chemotherapy and overall survival.

Categories	Subgroups	No.	Case/control	HR (95%CI)	*P*-value	I^2	P^h
All		26	3843/3911	0.98 (0.93–1.04)	.544	15.6%	.239
Country	USA	9	1330/1326	0.91 (0.79–1.06)	.217	51.0%	.038
	UK	5	331/363	1.01 (0.84–1.21)	.918	0.0%	.609
	Greece	3	293/283	1.18 (0.93–1.50)	.178	0.0%	.543
	Others	9	1889/1939	1.00 (0.92–1.08)	.915	0.0%	.670
Cancer types	MBC	9	1438/1455	1.01 (0.92–1.11)	.799	0.0%	.443
	OC	8	1692/1757	0.94 (0.86–1.02)	.132	35.1%	.148
	NSCLC	3	211/206	1.16 (0.92–1.47)	.215	0.0%	.620
	Others	6	502/493	0.98 (0.82–1.18)	.867	22.2%	.267
Sample sizes	≥100	18	3567/3620	0.99 (0.94–1.05)	.819	17.0%	.250
	<100	8	276/291	0.86 (0.69–1.06)	.152	5.2%	.390

CI = confidence interval, HR = hazard ratio, MBC = metastatic breast cancer, NSCLC = nonsmall cell lung cancer, OC = ovarian cancer, P^h = *P*-value of heterogeneity test, UK = The United Kingdom.

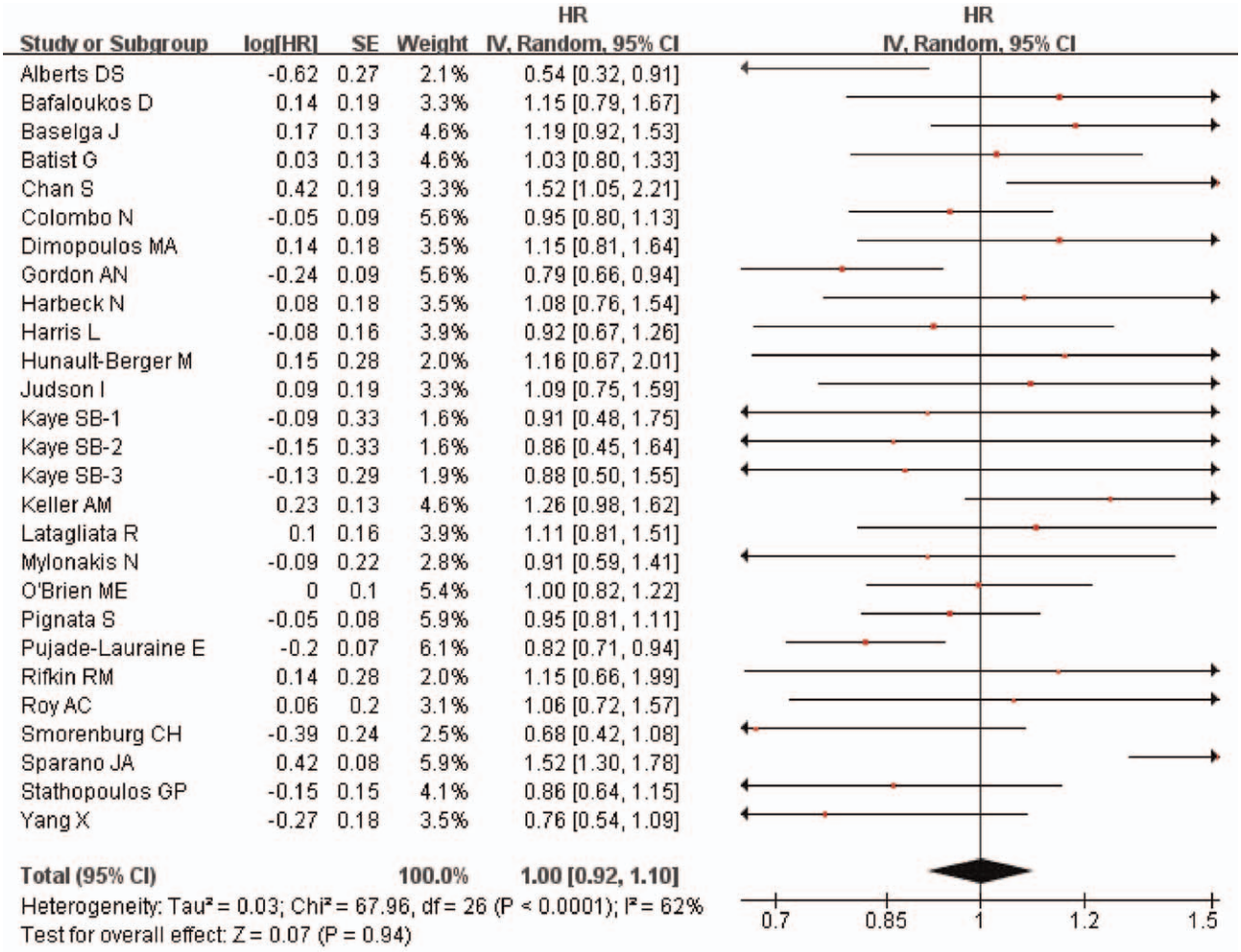

Figure 3. Forest plot of the association between liposomal doxorubicin-based chemotherapy in various tumors and PFS. CI = confidence interval, HR = hazard ratio, PFS = progression-free survival.

funnel plot observed no publication bias in this analysis of OS ($P = .508$) (Fig. 6A) and PFS ($P = .983$) (Fig. 6B, respectively).

4. Discussion

Although cancer is not completely curable by current therapies, it deserves effective treatment. Patients receiving proper chemotherapy would help to relieve the symptom, improve the quality of life, and prolong survival. However, conventional chemotherapy cannot satisfy people's demands. After persistent efforts over the recent years, many anticancer nanoplatforms have been explored and investigated in preclinical and clinical trials. Yet, only the minority has satisfied efficacy criteria for regulatory approval, and many liposomal platforms were applied.[43]

Table 4

Stratified analysis of liposomal doxorubicin-based chemotherapy and progression-free survival.

Categories	Subgroups	No.	Case/control	HR (95%CI)	*P*-value	I2	*Ph*
All		27	3840/3908	1.00 (0.92–1.10)	.945	60.7%	.000
Country	USA	8	1234/1227	1.04 (0.83–1.31)	.720	82.1%	.000
	UK	6	411/443	1.06 (0.91–1.22)	.468	3.3%	.396
	Greece	4	386/379	1.00 (0.83–1.19)	.964	0.0%	.518
	Others	9	1809/1859	0.91 (0.85–0.98)	.017	12.9%	.327
Cancer types	MBC	9	1438/1455	1.14 (0.98–1.32)	.101	64.8%	.004
	OC	9	1689/1754	0.87 (0.81–0.94)	.000	14.1%	.316
	NSCLC	3	211/206	0.84 (0.68–1.03)	.086	0.0%	.800
	Others	6	502/493	1.11 (0.94–1.31)	.204	0.0%	1.000
Sample sizes	≥100	18	3564/3617	1.03 (0.93–1.15)	.526	70.3%	.000
	<100	9	276/291	0.90 (0.77–1.06)	.217	0.0%	.499

CI = confidence interval, HR = hazard ratio, MBC = metastatic breast cancer, NSCLC = nonsmall cell lung cancer, OC = ovarian cancer, P^h = *P*-value of heterogeneity test, UK = The United Kingdom.

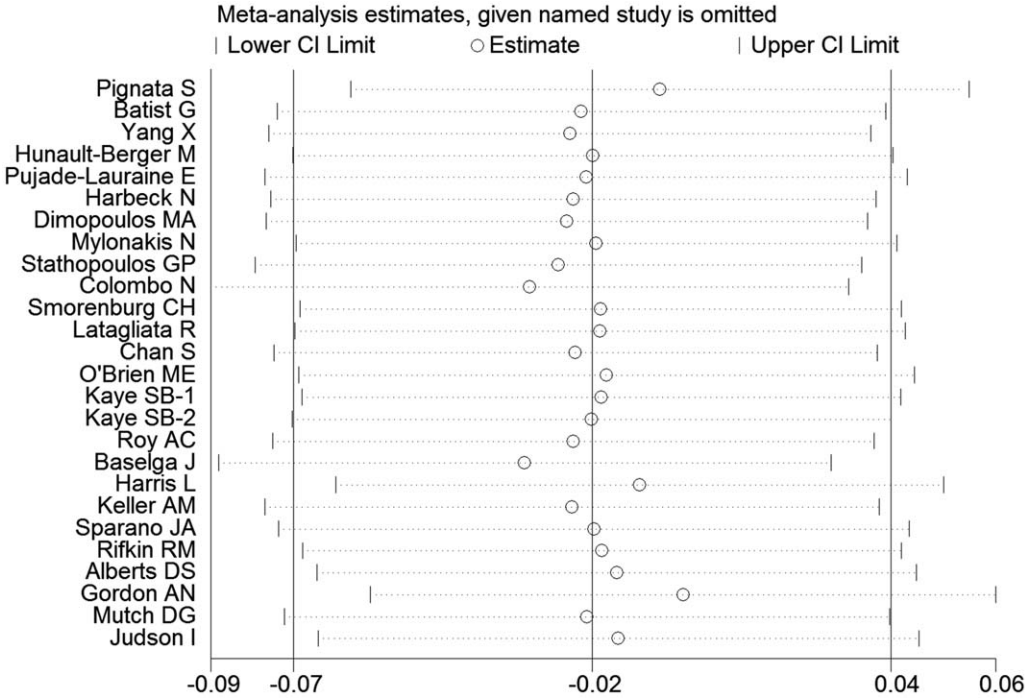

Figure 4. One-way sensitivity analysis of liposomal doxorubicin-based chemotherapy in various tumors with OS. CI = confidence interval, OS = overall survival.

Doxorubicin is generally regarded as the most effective anticancer drugs, but its clinical practice has limitation because of a cumulative dose-dependent cardiotoxicity that could result in some potentially fatal toxicity of nontarget normal tissues. Liposomes are proven candidates for delivery of a wide range of therapeutics, since their payload can be encapsulated in their internal aqueous compartment or embedded within the phospholipid bilayer.[44] Clinicians have used liposomes, self-assem-

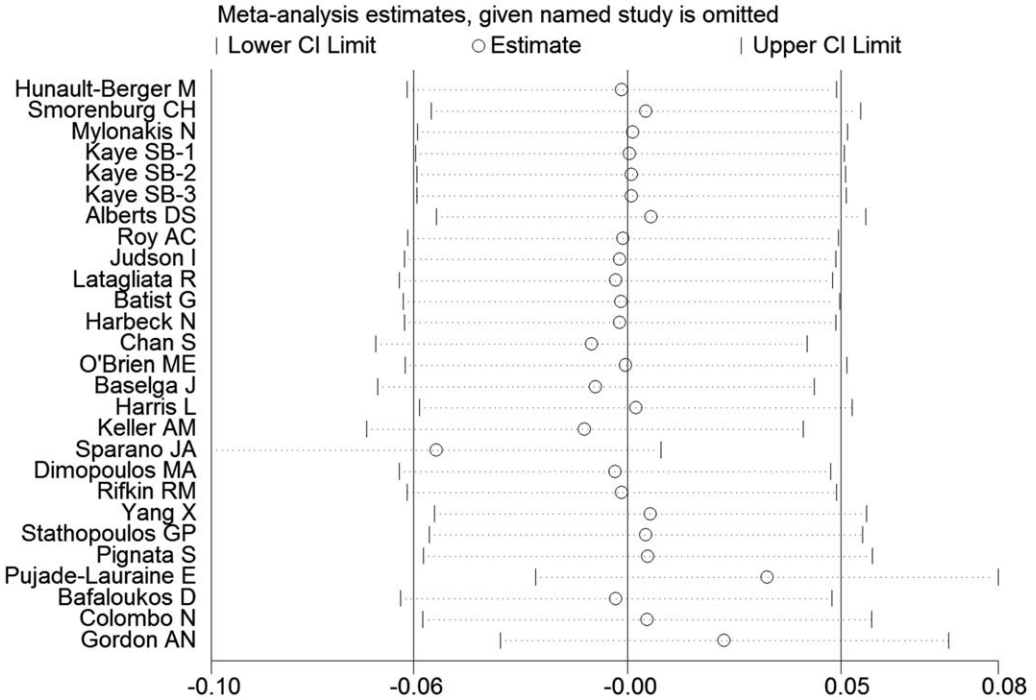

Figure 5. One-way sensitivity analysis of liposomal doxorubicin-based chemotherapy in various tumors with PFS. CI = confidence interval, PFS = progression-free survival.

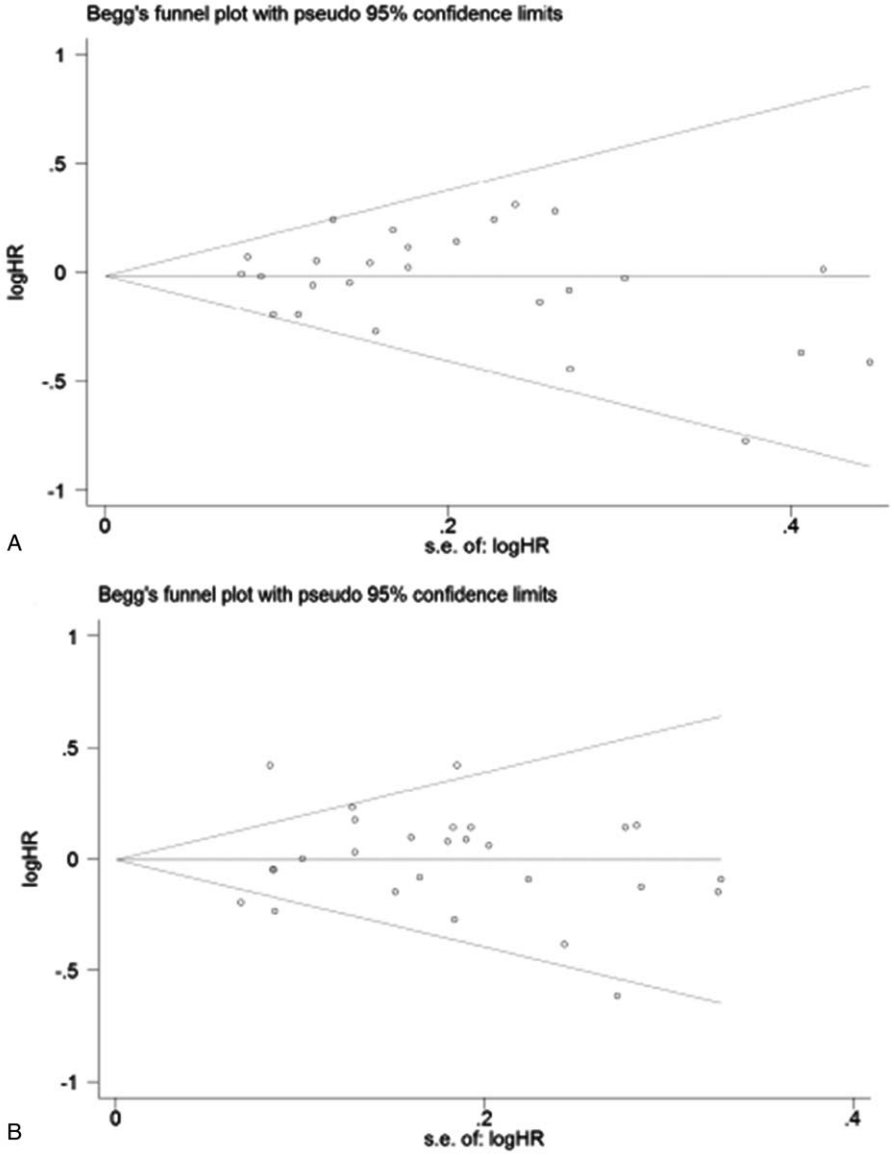

Figure 6. Begg funnel plot for publication bias test. (A) OS of liposomal doxorubicin-based chemotherapy in various tumors; (B) PFS of liposomal doxorubicin-based chemotherapy in various tumors. HR = hazard ratio, OS = overall survival, PFS = progression-free survival.

bled lipid vesicles, as nanoscale systems to deliver encapsulated anthracycline molecules for cancer treatment. Stealth liposomes can passively accumulate in solid tumors due to their inherently leaky vasculature and defective lymphatic drainage. PLD is an active and unique formulation of doxorubicin, which has been proven to be a better therapeutic choice for cancer patients. In this formulation, doxorubicin-encapsulated liposomes are sterically stabilized by grafting polyethylene glycol onto the liposomal surface (Stealth Liposome).[45] Its liposomal encapsulation reduces plasma free anticancer drug level and drug delivery to normal tissues, possibly decreasing immunosuppression and cardiotoxicity of doxorubicin.[46] It confers different pharmacokinetic characteristics that results in a circulation half-life compared with conventional free doxorubicin, which has a half-life of less than 10 minutes.[47] Then prolonged circulation in cancer tissues permits higher uptake of PLD. The selective accumulation of PLD in cancer tissue led to about 10-fold higher intracellular anticancer drug concentrations than adjacent normal tissues.[48] Consequently, patients who have received PLD reduced risk of nausea or vomiting, myelosuppression, alopecia, and cardiotoxicity.[49,50] In addition, acquisition of drug resistance of tumor cells in patients is a major challenge in previously treated patients, which could be explained by the barrier of the chemotherapy drug transport across the cell membrane. PLD directly fused with the tumor cell membrane rather than transporting across the cell membrane. Accordingly, PLD was gradually considered the most appropriate chemotherapeutic agents for the cancer patients, especially for resistant tumors.[51]

Chemotherapy is as effective or better in the treatment of recurrent and progressive cancer therapy compared to other therapies. The advantages of PLD often include longer circulation

and enhanced drug delivery to tumor tissue, however, these factors did not lead to improve prognosis in patients. Maybe it is closely linked with the dose and cycle dependent pharmacokinetic changes.[52] Another explanation for the lack of a prognostic advantage for the liposomal formulation could be the tumor immunologic milieu, which may be infiltrated with immunosuppressive leukocytes.[53] In previous study, the author pays more attention to tolerability and conclude that the choice of regimen could be based on individual patient preference on the basis of side effects.[54] To date, many clinical trials have confirmed the efficacy and cardiac safety of liposomal doxorubicin in various settings: a monotherapy or in combination with other drugs, a first-line therapy (compared with conventional doxorubicin),[55] a second-line therapy or later in patients with anthracycline- and taxanepretreated disease,[56] a maintenance therapy for patients with responding or stable disease after first-line chemotherapy.[57] However, there is no consensus for the superiority of PLD chemotherapy compared with conventional chemotherapy. The results reported in clinical trial, in some cases, failed to provide a formal proof that PLD is the best option for clinical practice.[58]

In general, PLD has substantial clinical activity of durable clinical responses in 26% of patients.[59] Recent researches have shown that PLD may prolong both PFS and OS when compared with conventional chemotherapy. Because of these relatively small sample size trials, the results cannot be considered definitive. This meta-analysis was performed to explore the prognosis of cancer patients after liposomal doxorubicin-based chemotherapy in various tumors. As results, PLD has not shown significant superiority to other approved conventional chemotherapy drugs in prognosis. No association was detected between liposomal vs conventional formulations in OS and PFS. Subgroup analysis also showed that there was no statistical difference rather than subgroups of country and cancer type in PFS. However, these results remains to be further evaluated in advanced research. The previously reported studies would suggest that we need to take dose ranges and cycle dependent pharmacokinetic changes into consideration.[60] Maybe larger single doses may be more efficacious than smaller split doses.[61] Thus, detailed studies are required to confirm our conclusions.

Our study has several limitations. First, merely published studies were included for eligible literatures. Then there were inconsistent chemotherapy regimen and dose of eligible studies, and may be influenced our conclusions. Meanwhile, the extreme heterogeneity suggested that potentially possible factors should be taken into consideration.

In conclusion, no association was explored among cancer patients after liposomal doxorubicin-based chemotherapy in prognosis in our study. However, detailed and further studies are needed to confirm our conclusion.

Author contributions

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Software: Kaiping Zhang, Xiang Fang.
Visualization: Xiang Fang.
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Writing – review & editing: Kaiping Zhang, Yin Zhang, Min Chao.

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