



Hypertension Induced by Combination Therapy of Cancer: A Systematic Review and Meta-Analysis of Global Clinical Trials

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Guo X, Qian X, Jin Y, Kong X, Qi Z, Cai T, Zhang L, Wu C and Li W (2021) Hypertension Induced by Combination Therapy of Cancer: A Systematic Review and Meta-Analysis of Global Clinical Trials. Front. Pharmacol. 12:712995. doi: 10.3389/fphar.2021.712995 **Background:** Nowadays, due to the limitation of single therapy, combination therapy for cancer treatments has become important strategy. With the advancement of research on cardiotoxicities induced by anti-cancer treatment, among which cancer treatment-induced hypertension is the most frequent case. However, due to the small sample size and the absence of comparison (single-arm study alone), these studies have limitations to produce a feasible conclusion. Therefore, it is necessary to carry out a meta-analysis focusing on hypertension caused by cancer combination therapy.

Methods: We systematically searched PubMed, Embase, Cochrane Library, Web of Science, and CNKI, from database inception to November 31, 2020, with randomized controlled trials (RCTs) associated with hypertension induced by cancer combination drugs. The main endpoint of which was to assess the difference in the incidence of hypertension in cancer patients with monotherapy or combination therapy. We calculated the corresponding 95% confidence interval (95% CIs) according to the random effect model and evaluated the heterogeneity between different groups.

Results: According to the preset specific inclusion and exclusion criteria, a total of 23 eligible RCTs have been included in the present meta-analysis, including 6,241 patients (Among them, 2872 patients were the control group and 3369 patients were the experimental group). The results showed that cancer patients with combination therapy led to a higher risk of hypertension (All-grade: RR 2.85, 95% CI 2.52~3.22; 1~2 grade: RR 2.43, 95% CI 2.10~2.81; 3~4 grade: RR 4.37, 95% CI 3.33~5.72). Furthermore, compared with the control group who received or did not receive a placebo, there was a higher risk of grade 3-4 hypertension caused by cancer combination treatment.

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Conclusion: The present meta-analysis carries out a comprehensive analysis on the risk of patients suffering from hypertension in the process of multiple cancer combination therapies. Findings in our study support that the risk of hypertension may increase significantly in cancer patients with multiple cancer combination therapies. The outcomes of this meta-analysis may provide a reference value for clinical practice and may supply insights in reducing the incidence of hypertension caused by cancer combined treatment.

Keywords: hypertension, combination therapy, angiogenesis inhibitors, meta-analysis, randomized controlled trial

INTRODUCTION

Hypertension has been recognized as the most common comorbidity among various types of cancers, which directly affects the prognosis of cancer patients, and is one of the high-risk factors for cancer survivors suffering from the comorbidity of heart diseases (Jain and Townsend, 2007). In the early stage of diagnosis, there is generally a similar probability of developing hypertension. However, with different cancer treatment patterns, patients may experience significantly altered incidence of hypertension, especially those receiving chemotherapy, which can reach 38% (Piccirillo et al., 2004; Maitland et al., 2010). In addition, novel cancer therapies, such as targeted therapy, which is a type of cancer treatment that targets proteins controlling cancer cells' growth, division, and spreading, are also associated with the incidence of hypertension. Cardio-Oncology is an evolving discipline which aims to analyze the relationship between cancer treatment and cardiotoxicity (Lenneman et al., 2016; Barac, 2020). Cardiovascular toxicity in cancer treatment refers to the occurrence of cardiovascular disease during the disturbance or elimination of cancer cells in patients in vivo. Significantly, cardiovascular disease is the second leading cause of the morbidity and mortality of cancer survivors. According to previous studies, the probability of all-grade hypertension is between 15 and 67% during the treatment by using small molecule vascular endothelial growth factor tyrosinase inhibitors (e.g., sunitinib, sorafenib, pazopanib, etc.), and the rate would be higher with the use of inhibitors with higher efficiency (e.g., axitinib) (Brinda et al., 2016). The incidence of hypertension induced by tyrosinase inhibitors ranges from 5 to 80% in a dose-dependent manner (Agarwal et al., 2018). In addition, some patients may have a history of hypertension before the diagnosis of cancer. However, some patients develop hypertension due to anti-cancer treatment, and hypertension may be the direct result of cancer treatment under this circumstance.

The progress of cancer treatment has promoted the development of multiple new treatment strategies. Combination therapies means combining two or more therapies for cancer patients and the effectiveness may be excellent than single therapy. However, most programs will be accompanied by a series of cardiovascular adverse reactions, especially the existed high correlation of some new drugs with

hypertension. In addition, the use of some chemotherapy drugs can also induce hypertension.

Generally, angiogenesis is a necessary process of tumorigenesis, growth, and metastasis. Vascular endothelial growth factor (VEGF) is an angiogenic growth factor. Angiogenesis inhibitor is a classic drug highly associated with the occurrence of hypertension (Hamnvik et al., 2015), primarily including monoclonal antibodies and small-molecule drugs. It has been documented that the proposed highly specific drugs are important inhibitors of angiogenesis, which play a role by blocking the signaling pathways necessary for angiogenesis, such as blocking Vascular Endothelial Growth Factor Receptor (VEGFR), Epidermal Growth Factor Receptor (EGFR), basic Fibroblast Growth Factor (bFGF), Platelet-derived Growth Factor Receptor (PDGFR), etc. (Folkman, 2007). To be specific, VEGF is the main growth factor that controls angiogenesis. Epidermal growth factor (EGF) is responsible for differentiation and apoptosis. bFGF can regulate the proliferation and differentiation of specific types of cells and has an effective effect on angiogenesis. Platelet-derived growth factor (PDGF) involves significantly cell growth, cell division, and angiogenesis (Wilkins et al., 2014; Agarwal et al., 2018).

With the emergence of various novel approaches to cancer treatment, the survival of cancer patients is becoming higher, which, however, is accompanied by an increasingly more obvious change in cardiotoxicity. Given the differences in cancer tissue types, therapeutic drugs, and drug doses, a systematic review and meta-analysis were carried out on hypertension caused by cancer treatment (Said et al., 2017), which aimed to clarify the incidence and risk of hypertension in cancer patients treated with combination therapy. At present, there is incomplete knowledge of hypertension caused by cancer combination therapy. Besides, there is few systematic reviews or metaanalyses in this aspect based on the comprehensive analysis of previous literature. Accordingly, through comprehensive literature analysis, it is expected to analyze and elaborate the risk factors of hypertension caused by cancer combination therapy, to provide a certain reference value for clinical treatment.

METHODS

The present systematic review and meta-analysis were conducted following PRISMA guidelines (Moher et al., 2009). The protocol

has been registered in PROSPERO with the registration number CRD42021220923.

Data Sources and Searches

A comprehensive literature search was made in databases [PubMed, embase, Cochrane Library, Web of Science, and CNKI] since November 31, 2020, to identify all articles related to the subject. In addition to the above databases, the clinical trial registration website (https://clinicaltrials.gov/) was searched to obtain information about registered prospective trials.

The keywords used in PubMed were listed as follows:

- 1) randomized controlled trial [pt]
- 2) controlled clinical trial [pt]
- 3) randomized [tiab]
- 4) placebo [tiab]
- 5) clinical trials as topic [mesh: noexp]
- 6) randomly [tiab]
- 7) trial [ti]
- 8) (1) OR (2) OR (3) OR (4) OR (5) OR (6) OR (7)
- 9) animals [mh] NOT humans [mh]
- 10) (8) NOT (9)

The final selected literatures were checked and reviewed separately to include the latest and most complete clinical trial reports in the case of repeated publications. All the search results were incorporated into the management tool of Endnote.

Study Selection and Data Extraction

The major objective of our study was to determine the incidence of hypertension associated with combination therapy for cancer and to establish a relationship between combination therapy and the risk of hypertension. Therefore, eligible studies were those evaluating the combination of drugs with hypertension induced in cancer patients. Phase I trial was excluded considering the multi-dose level and limited sample size. In addition, phase II, III, and IV randomized controlled trials (RCTs) in combination therapy were enrolled in the analysis compared with those without combination therapy.

The eligible studies met the inclusion criteria:

- 1) Phase II, III, and IV trials involving cancer patients;
- 2) RCTs for cancer treatment;
- Intervention group: combination therapy (including targeted therapy and chemotherapy);
- 4) Control group: monotherapy or placebo treatment;
- 5) Studies with available data on hypertension events or incidence and sample size.

The exclusion criteria:

- 1) Review articles
- 2) Not randomized control trial
- 3) Reports from same study sample
- 4) Not report associate with hypertension
- 5) Not report associate with cancer combination therapy
- 6) No usable data

- 7) No comparable trial
- 8) Republished literature

Two investigators (G.X and Q.X) extracted data independently, and any disagreements between the two reviewers were resolved by consensus. Online studies before publication were also eligible, but not including reviews, Conference reviews, studies published only in abstract form, quality of life research, non-randomized trials, and studies that could not determine the toxicity of combination therapy. Data extraction covered author, year of publication, research institution, journal name, trial phase, cancer tissue type, combination therapy, number of patients, age of patients, administration schedule and drug dose, size of control group, number of patients with hypertension, with the data of hypertension at all grades extracted.

Data Synthesis and Analysis

Statistical analysis of this study was performed by using the Cochrane Review Manager (RevMan 5.3) software provided by the Cochrane Library Collaboration Network.

The proportion of patients with hypertension in each study was calculated by dividing the number of patients with hypertension caused by combination therapy extracted from eligible clinical trials by the total number of patients receiving combination therapy in each study. We refer to all levels of hypertension events as "All-grade," "1–2 grade" is combined the grade of 1 or 2 hypertension events, and "3–4 grade" which is the sum of the level of 3 or 4 hypertension events.

For each study enrolled in this analysis, the relative risk (RR) and 95% confidence interval (95% CI) of the incidence of events between the intervention group and the control group were calculated according to the number of reported events and sample size. The I2 index and Q-statistics were used to evaluate the heterogeneity among studies, among which the Q-test is widely used at present (Zintzaras and Ioannidis, 2005). p < 0.05 of the Q-test indicated the existence of heterogeneity (Zhang et al., 2019), and p < 0.05 meant the existence of statistical significance. If p > 0.05, the results of the independent studies might be homogeneous, suggesting the use of the fixed-effect model; On the contrary, the random-effect model should be used and/or consider the clinical suitability of combination therapy when there was heterogeneity with p < 0.05. I^2 can quantify the heterogeneity among studies, which is calculated generally based on χ^2 test. It describes the percentage of variation among studies in total variation, which may indicate a higher heterogeneity with the increase of the value of I^2 (Huedo-Medina et al., 2006). $I^2 > 25$, 50, and 75% suggest that there may be low, moderate, and high heterogeneity among studies. Besides, it is generally believed that there is substantial heterogeneity when $I^2 > 50\%$.

RESULTS

Search Results

A total of 3,915 articles were identified by literature search and reference list review. After screening and qualification evaluation,



23 clinical trials involving 6,241 patients were finally included after excluding review articles, case reports, and meta-analysis articles, with the flow chart of literature selection shown in **Figure 1**. Of the 23 studies, there were 12 phase II, 11 phase III, and 1 phase IV trials, with the year of publication ranging from 2005 to 2020 (**Table 1**) (Miller et al., 2005; Heymach et al., 2008; Goss et al., 2010; Mok et al., 2011; Rugo et al., 2011; Baselga et al., 2012; Kato et al., 2012; Johnston et al., 2013; Laurie et al., 2014; Liu et al., 2014; Mackey et al., 2015; Rini et al., 2016; Baselga et al., 2017; Kubota et al., 2017; Yan et al., 2017; Dummer et al.,

2018; Lu et al., 2018; Liu et al., 2019; Nakagawa et al., 2019; Cortot et al., 2020; Guo et al., 2020; Sinn et al., 2020; Tao et al., 2020). According to the published Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute (NCI), hypertension caused by anti-cancer treatment includes 5 grades of grade 1–5 (**Table 2**) (National Cancer Institute, 2017). Among them, grade 5 hypertension includes fatal elevated blood pressure. There were no patients with grade 5 hypertension in the included literatures. Consequently, only grade 1–4 hypertension was enrolled in the data extraction. After research, there is no

						phase	type	therapy	Patient number	Age (Range)	Hypertension Event	Hypertension Event	Regimen	Patient number	Age (Range)	Hypertension Event	Hypertension Event	Regimen	
											Grade 1-2	Grade 3-4				Grade 1-2	Grade 3-4		
Miller et al.(2005)	2005	United States	Indiana University	Journal of Clinical Oncology	=	Breast Cancer	Capecitabine + bevacizumab vs Capecitabine	232	29-78	ε. ε	41	Orally Capecitabre (2,500 mg/m ⁹ /d) twose daily for 14 days followed by a 7.days rest period, bevactumab (15 mg/mg) intravenously on day 1 of aach 3.weeks syde. Patients continued therapy for a maximum of 35 cycles	33 53	22-08	4	-	Crally Capecitable (2,500 mg/m ² /d) twice daily for 14 days followed by a 7-days rest period. Patients continued therapy for a maximum of 35 cycles	9
Heyr at al.	Heymach 24 et al.(2008)	5008	United States	Dana-Farber Cancer Institute	Journal of Clinical Oncology	=	Non-Small- Cell Lung Cancer	Vandetanib + Paciitaxel and Carboptin vs Placebo + Pacifiaxel and Carboptatin	<u>ດ</u>	36-79	4	4	Orally vandetanib (300 mg) + Paclitaxel (200 mg/m ²) and Carboptatin (area under the concentration- time curve at steady-state, 6 mg/m ² min) once every 3 weeks for a maximum of six cycles	25	42-83	N	0	Orally Placebo + Pacifizvel (200 mg/m²) and Carboplatin (area under the concentration-time curve at steady-state, 6 mg/mł mi) once every 3 weeks for a maximum of sk cycles	17
Goss et al.(2	0)	2010	Canada	The Ottawa Hospital Cancer Centre	Journal of Clinical Oncology	Ē	Non-Small- Cell Lung Canoer	Cediranib + Pacifiaxel and Carboplatin vs Placebo + Pacifiaxel and Carboplatin	126	36-77	0	0	Pacifitaxel 200 mg/m ² by intravenous 3-h intusion and carbopatin dosed to an area under the serum concentration-time curve of 6 every 3 weeks for 6 to 8 sycles, cedrarib 30 mg was administered orally once clairy concurrently with chemotherapy	125	8 5	ω	0	Pacitizael 200 mg/m ² by intravenous 3-h intusion and catopalatin dosed to an area under the serum concentration-tume curve of 6 every 3 weeks for 6 to 8 cycles, placebo was administered orally once daily concurrently with chemotherapy	8
Mok et alu	(2011)	2011	China	Prince of Wales Hospital	Asia- Pacific Journal of Clinical Oncology	=	Non-Small- Cell Lung Canoer	Bevacizumab + Cisplatin and Gemcitabine vs Placebo + Cisplatin and Gemcitabine	б 4	35-79	6	m	Bevacizumab 15 mg/kg plus Cisplatin was administered I.v. at 80 mg/ m [*] on day 1 and gemciabine was administered I.v. at 1.250 mg/m ² on days 1 and 8. Chemotherapy every 3 weeks for up to six cycles	ŝ	29-75	ى س	0	Placebo + Cisplatin was administered i.v. at 80 mg/ m²on day 1 and gemortabine was administered i.v. at 1,250 mg/m² on days 1 and 8. Chemotherapy every 3 weeks for up to six cycles	<u>م</u>
Rugo et al.(2	2011)	2011	United States	University of California	Journal of Clinical Oncology	=	Breast Cancer	Docetaxel + axitinib vs Docetaxel + Placebo	112	30-79	56	a	Docetaxel 80 mg/m ² once every 3 weeks plus axitinib 5 mg twice per day	20	34-71	0	0	Docetaxel 80 mg/m ² once every 3 weeks plus placebo twice per day	20
Base et al.	Baselga 24 et al.(2012)	2012 L	United States	Massachusetts General Hospital Cancer Center	Journal of Clinical Oncology	=	Breast Cancer	Capecitabine + Sorafenib vsCapecitabine + Placebo		55 (mean)	17	-	Capecitabine 1,000 mg/ m ² orally twice a day for days 114 of every 21- days cycle with soratemb 400 mg orally twice a day	1 4	54(mean)	6	N	Capecitabine 1,000 mg/ m ² orally twice a day for days 1-14 of every 21- days cycle with placebo orally twice a day	5

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TABLE 1 | Characteristics of the studies included in this meta-analysis.

Ref			8	8	3	24	55	28
tion	Regimen		Once-daily placebo combination with 14-days treatment cycles of mFOLFOX6 (oxalipatin 85 mg/m ² IV, day 1; leucoorin 200 mg/m ² IV, day 1; 5-y1 and then bolus, 45-y1 and then 2,400 mg/m ² continuous IV infusion over 46 h)	Once-daily placebo combination with 14-days treatment cycles of mFOLFOX6 (oxaliplatin 85 mg/m² IV, day 1; Heucoonin 200 mg/m² IV, day 1; 5-FU 400 mg/m² N, day 1; 5-FU 400 mg/m² N, bolus, day 1 and then 2,400 mg/m² continuous IV infusion over 46 h)	Daily lapatinib 1,500 mg	Pacifizxel (200 mg/m ²) and carboptetin (area under the concentration time curve 6) intravously every 3 weeks. Daily oral placebo was commenced day 1 of cycle 1 and continued as monotherapy after completion of 4–6 cycles of chemotherapy	Olaparib capsules 400 mg twice daily	Docetaxel 75 mg/m ² plus placebo once every 3 weeks
n informat	ension nt	Grade 3-4	÷	÷	0	m	0	~
Control arm information	Hypertension Event	Grade 1-2	4	1	m	Ŧ	0	37
•	Age (Range)		8- 8- 8-	8- 8- 8:	29-80	36-77	42-86	29-81
	Patient number		30 20	Ω Ω	72	2	46	385
nation	Regimen		Once-daily cedirarib 20 mg contbination with 14-days treatment cycles of mPOLFOX6 (oxalipatin 65 mg/m ² N, day 1; leucovorin 200 mg/m ² N day 1; 5F U 400 mg/m ² N bolus, 45 m 1 and then 2400 mg/m ² continuous N initision over 46 h)	Once-deliy cedirarib 30 mg combination with 14-days teatment cycles of mFOLFOX6 (exaliplatin 86 mg/m ² N, day 1; heucovinn 200 mg/m ² N, day 1; 5-FU 400 mg/m ² N bolus, day 1 and then 2,400 mg/m ² continuous N infusion over 46 h)	Daily lapatinib 1,500 mg plus pazopanib 800 mg	Pacitasel (200 mg/m ²) and carbopidin (area under the concentration time curve 6) intra-enously every 3 weeks, and and cedirarib 20 mg was commenced day 1 of cycle 1 and continued as monthreapy after completion of 4-6 cycles of chemotherapy	Cediranib 30 mg daliy and olaparib capsules 200 mg twice daliy	Docetaxel 75 mg/m ² plus ramucirumab 10 mg/kg once every 3 weeks
arm inforı	ension	Grade 3-4	4	Q	N	ά	8	51
Intervention arm information	Hypertension Event	Grade 1-2	43	42	12	é	17	152
Ш	Age (Range)		33-79	40-82	3-82	23-85	32-82	24-82
	Patient number		ß	ß	ŵ	15.3	44	759
Combination	therapy		Cediranib + mFOLFOX6 vs Plazebo + mFOLFOX6	Cedranb + mFOLFOX6 vs Placebo + mFOLFOX6	Lapatinib + pazopanib vs Lapatinib	Cedirantb + Pacifizxel and Carboplatin vs Pacifizxel and Carboplatin	Cediranib + Olaparib vs Olaparib	Ramucirumab + Docetaxel vs Placebo +
Cancer	type		Colorectal Cancer	Colorrectal	Breast Cancer	Non-Small- Cal Lung Cancer	Ovarian Cancer	Breast Cancer
Study	phase		=	=	=	E	=	=
Journal			Annals of Oncology	Annals of Oncology	Breast Cancer Research and Treatment	European Journal of Cancer	Lancet Oncol	Journal of Clinical Oncology
Institution			National Hospital Organization Cosika National Hospital	National Hospital Organization Osaka National Hospital	Institute of Cancer Research	University of Ottawa	Dana-Farber Cancer Institute	Cross Cancer Institute
Country			Japan	Japan	United Kingdom	Canada	United States	Canada
Year			2012	2012	2013	2014	2014	2015
Author			kato et al.(2012)	Kato et al.(2012)	Johnston et al.(2013)	et al.(2014)	Liu et al.(2014)	Mackey et al.(2015)
Entry			~	00	o	þ	÷	5

	Author Year	r country	ry insutution		Journal	phase	type	Combination therapy	Patient number	n Age (Range)	Incervention arm information Hypertension Event	ion arm intorr ertension Event	Regimen	Patient number	Age (Range)	Hyperi Ev	Control arm Information Hypertension Event	Regimen	не
											Grade 1-2	Grade 3-4				Grade 1-2	Grade 3-4		
Rini et al.(2016)	20 16 1 0j	6 United States	Cleveland Clinic Taussig Cancer Institute		Oncology Oncology	=	Renal Cell Carcinoma	IMA901 + sundinib vs Suntinib	204	9 9	5	24	Suntimite (50 mg) was given orally once daily with each cycle dafined as 4 weeks on treatment followed by 2 weeks off treatment, plus up to ten intradement, plus up to ten intradement, plus up to ten orallocyte maccophage colony-stimulating factor (75 ug) and granulocyte maccophage colony-stimulating factor (75 ug) and granulocyte maccophage colony-stimulating factor (75 ug) and granulocyte maccophage (300 mg/m ³) a days before the first vaccination	35	5 6 6	24	~	Suntitrib (50 mg) was given orally once daily, with each cycle defined as a weeks on treatment followed by 2 weeks off treatment	27
Baselga et al.(2017)	2017	7 United States	Memorial Sloan Kettering Cancer Center		Clin Breast Cancer	=	Breast Cancer	Sorafenib + Capecitabine vs Placebo + Capecitabine	266	53 (Median)	32	8	Capecitabine (1,000 mg/ m ² bid on days 1–14 of each 21-days cycle) plus sorafenib (600 mg/day)	271	55 (Median)	σ	Q	Capecitabine (1,000 mg/ m ² bid on days 1–14 of each 21-days cycle) plus placebo	28
Kubota et al.(2017)	2017 117)	7 Japan	Graduate School of Medicine	00	Journal of Clinical Oncology	=	Non-Small- Cell Lung Cancer	Motesanib + Paclitaxel and Carboptatin vs Placebo + Paclitaxel and Carboptatin	197	59-70	ი 4	8	Once daily oral motesantb 125 mg and received pacificatel 200 mg/m ² IV and carboptatin area under the concentration-time curve 6 mg/m/min IV on day 1 of each 3-weeks cycle for up to six cycles	204	09 85	55	4	Once dally oral placebo and received pacificatel 200 mg/m ² IV and carbobith area under the concentration-time curve 6 mg/mirimi IV onday 1 of each 3-weeks cycle for up to six cycles	5
Yan et al.(2017)	2017	China	Baoji Central Hospital		Cancer Research and Clinic	2	Gastric Canoar	Apapatirib + Oxaliptin and Tiggio vs Oxaliptin and Tiggio	۵ ۲	34-75	<u> </u>	0	Apatinib 850 mg/d, 0.5 h after meal begin oral administration, from the first day of chemotherapy and each 4-weeks cycle. Oxaliptin (130 mg/m ² bid or 1 day of each 27-days cycle IV. Tiggio depends on the body surface area (c1 2.6m ² - 1.50m ² take 40 mg, 1.55m ² - 1.60m ² take 50 mg, > 1.50m ² take 60 mg, twice a day)	75	34-75	0	0	Oxaliptith (130 mg/m² bid on 1 day of each 21-days cycle) IV. Tiggio depends on the body surface area (<1.25m² take 40 mg.1.25m² -1.50m² take 60 mg. twice a day) 60 mg. twice a day)	30
Dummer et al.(2018)	r 2018 18)	8 Switzerland	and University Hospital Zürich Skin Cancer Center		Lancet Oncol	=	Melanoma	Encoratenib + binimetinib vs Encoratenib	192	20-89	9	5	Encoratenib 450 mg once daily orally plus binimetinib 45 mg twice daily orally	194	23-88	a	Q	Encoratenib 300 mg once daily orally	31
Lu et al.(2018)	2018)	8 China	Jiao Tong University		Journal of Clinical Oncology	=	Non-Small- Cell Lung Cancer	Fruquintinib + Best supportive care vs Placebo + Best supportive care	6	54 (Median)	σ	ى س	Oral fruquintinb (5 mg once daly) was given in 4- weeks cycles of 3 weeks of treatment followed by 1 week off, and combination with best supportive care	õ	55 (Median)	0	-	Oral placebo was given in 4-weeks sycles of 3 weeks of treatment followed by 1 week off, and combination with best supportive care	32

Author Year Country Institution Journal S	Country Institution Journal	Institution Journal	Journal		s	tudy	Cancer	Combination		Ξ	Intervention arm information	rm inform	ation			Control arm information	n informa	ation	Ref
phase type therapy Tatient number	type therapy	type therapy	type therapy	type therapy	type therapy	therapy		Patie	je je	Age (Range)	Hypertension Event	nsion It	Regimen	Patient number	Age (Range)	Hypertension Event	nsion nt	Regimen	
											Grade 1-2	Grade 3-4				Grade 1-2	Grade 3-4		
Liu 2019 Uniled Dana-Farber Annals of II Ovarian Cediranb + ⁴ et al.(2019) States Cancer Institute Oncology Cancer Olaparib vs Olaparib	United Dana-Farber Annals of II Ovarian Cediranib + States Cancer Institute Oncology Cancer Olsparib vs Olsparib	Dana-Farber Annals of II Ovarian Cadiranb + Cancer Institute Oncology Cancer Olsparib vs Olsparib	Annais of II Ovarian Cediranib + Oncology Cancer Olaparib vs Olaparib	II Ovarian Ceciranib + Cancer Olaparib vs Olaparib	Ovarian Cediranib + Cancer Olaparib vs Olaparib	Cediranib + Olaparib vs Olaparib	+ ø	*	44		16	18	Cediranib 30 mg daily and olaparib capsules 200 mg twice daily	46		0	0	Olaparib capsules 400 mg twice daily	33
Nakagawa 2019 Japan Kindai University The Lancet III Non-Small- Ramucirumab + 2: Faculty of Oncology Call Lung erformb vs Medicine Cancer Placebo + erformb	Japan Kindai University The Lancet III Non-Small- Ramucirumab + Faculty of Oncology Call Lung enfotinb vs Medicine Cancer Placebo + enfotinb	Kindai University The Lancet II Non-Small- Ramucirumab + Faculty of Oncology Call Lung enformb vs Medicine Cancer Placebo + enformb	versity The Lancet III Non-Small-Ramucirumab + Oncology Call Lung enformb vs Cancer Placebo + enformb	et II Non-Small- Flamucirumab + Call Lung enformb vs Cancer Placebo + enformb	Non-Small- Ramucirumab + Call Lung entotinb vs Cancer Placebo + entotinb	ial- Ramucirumab + g entotinib vs Placebo + entotinib	ab +	~	224	57-71	8	52	Oral erlotinib (150 mg/day) plus intravenous ramucirumab (10 mg/kg) once every 2 weeks	225	56-70	15	5	Oral ertotinib (150 mg/day) plus placebo once every 2 weeks	34
Control 2020 France Thoracic European III Non-Small- Pacifiaxel + 111 et al.(2020) Oncology Journal of Call Lung bevacizumab vs 1 Docetaxel Department Cancer Cancer Cancer Cancer Cancer 1 1	France Thoracic European II Non-Small- Pacifiaxei + Oncology Journal of Cali Lung bevacizumab vs Department Cancer Cancer	Thoracic European II Non-Small- Paolitaxel + Oncobegy Journal of Call Lung bevacizumab vs Department Cancer Cancer	European III Non-Small- Pacifaxei + Journal of Cell Lung bevacizumab vs tt Cancer Cancer	n II Non-Small- Pacifaxei + of Cell Lung bevacizumab vs Cancer	Non-Small- Pacritaxei + Cell Lung bevacizumab vs Canosr	- Paciftaxel + bevacizumab vs		÷		18-81	4	ω	90 mg/m2of pacitraxel (D1, D8, D15) plus 10 mg/kg of bevacizumab (D1,D15) every 28 days	55	35–78	0	0	Docetaxel (75 mg/m2) every 21 days	35
Guo 2020 China Shandong Medicine II Cervical Aparimb + 30 et al.(2020) Provincial (Baltimore) Cancer Pacifaxel and Cartoplatin vs Africated to Shandong Cartoplatin vs Pacifaxel and Cartoplatin vs Pacifaxel and University	China Shandong Medicine II Cervical Apatimb + Provincial (Baltimore) I Cancer Pacificarel and Hespital Cancer Pacificarel and Afflated to Shandong Carboplatin vs Shandong Carboplatin vs University	Shandong Medicine II Cervical Apatimb + Provincial (Baltimore) Cancer Pacificarel and Hespital Cancer Pacificarel and Alfalact to Pacificarel and Shandong Carboplatin vs University Carboplatin	Medicine II Canvical Apatimb + (Baltimore) Cancer Pacifizvel and Carboptin vs Pacifizvel and Carboptin	II Cervical Apatimb + Cancer Pacifitaxel and Carboptitin vs Pacifitaxel and Carboptitin	Cervical Apatinib + Cancer Pacitaxel and Carbopttin vs Pacitaxel and Carbopttin	Apatinb + Pacifaxel and Carbopttin vs Pacifaxel and Carbopttin		Э́е		28-62	0	N	500 mg apatinib mesylate orally in between chemothreapy cycles, 135-175 mg/m² pacitaxel 135-175 mg/m² pacitaxel (altuda in 500 ml of 0.9% saline and inflused intravenously over 3 h) on day 1 and carboplatin AUC 5 (altuda in 500 ml of 0.9% saline solution and inflused intravenously over 30 mil) on day 2 every 3 weeks, for 6 cycles	50	89- 26	Ν	0	135–175 mg/m ² pacitaxel (diluted in 500 ml of 0.9% saitre and intread intravenously over 3 h) on day 1 and carboptian ALO 5 (diluted in 500 ml or 0.9% saitre solution and intrased intravenously over 30 mh) on day 2 every 3 weeks, for 6 cycles	8
Sim 2020 Germany Department of European II Panorealic Soratenb + 57 Medical Journal of Cancer Gernctabrie Vs Oncology and Cancer Vs Hematology Gernctabrie Gernctabrie	Germany Department of European II Pancreatic Sonafenb + Medical Journal of Cancer Gernctabine Oncology and Cancer Vs Hematology Elecebo + Gernctabine	Department of European II Pancreatic Sonafenib + Medical Journal of Cancer Gemcitable Oncology and Cancer Vs Henatology Pacebo + Gemcitable	nt of European II Pancreatic Sorafenib + Journal of Cancer Gemctablie and Cancer vs gy Gemctablie	n II Pancreatic Sonafenb + of Cancer Gemctabrie V Piacebo + Gemctabrie	Pancreatic Sorafenib + Cancer Gemcitabine vs Placebo + Gemcitabine	tic Sorafanib + Gemcitabine vs Gemcitabine		57		38-78		ო	The average weekly dose of gemotabline was 630 mg/m², the average day dose of soratenib in the GemSoratenib arm was 650 mg (planned 800 mg daly)	9	43-80		-	The average weeky dose of gencitabine was 690 mg/m² and placebo	37
Tapo 2020 China Medicine School Dose- III Cervical Pacifiaxei + 127 et al.(2020) China Medicine School Dose- III Cervical Pacifiaxei + 127 Electronic Beschona de Cancer Carboplatin + Electronic Pacifiaxei + Pacifiaxei + Technology Carboplatin	China Medicine School Dose- III Cervical Pacifaxei + of University of Response Cancer Carbopatin + Electronic Science and Pacifaxei + Technology Carbopatin	Medicine School Dose- III Cervical Pacifaxei + of University of Response Cancer Carbopatin + Electronic bevacizumab vs Science and Pacifaxei + Technology Carbopatin	ool Dose- III Cervical Pacifiaxel + of Response Cancer Carboptitin + berezizumab vs Pacifiaxel + Carboptitin	III Cervical Pacifiaxel + Cancer Carboplatin + bevezizumab vs Pacifiaxel + Carboplatin	Canvical Pacifiaxei + Cancer Carbopatin + bevacizumab vs Pacifiaxei + Carbopatin	Pacifiaxel + Carboptatin + bevacizumab vs Pacifiaxel + Carboptatin	\$ + Q	121		30-70	5	÷	Intravenous 175 mg/m ² pactitaxel, intravenous 6 mg/mL/min area under the curve carboplatin, and intravenous 15 mg/m ² bevacizumab (Floche, Holding AO) every 3 weeks	161	30-70	£	a	Intravenous 175 mg/m ² pecifizeval (Taxot: Bristol- Myers Squibb) and Intravenous 6 mg/m/L/min area under the curve carbotatin (Paraplatin; Bristol-Myers Squibb) every 3 weeks	ŝ

TABLE 1 | (Continued) Characteristics of the studies included in this meta-analysis.

TABLE 2 | Characterized of hypertension in CTCAE.

		Hypertension		
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adult: Systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg	Adult: Systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by > 20 mm Hg (diastolic) or to >140/ 90 mm Hg; monotherapy indicated initiated	Adult: Systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Adult and Pediatric: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Pediatric: Systolic/diastolic BP > 90th percentile but< 95th percentile	Pediatric and adolescent: Recurrent or persistent (≥24 h) BP > ULN; monotherapy indicated; systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile	Pediatric and adolescent: Systolic and/ or diastolic >5 mmHg above the 99th percentile		
Adolescent: $BP \ge 120/80$ even if < 95th percentile	Adolescent: Systolic between 130 and 139 or diastolic between 80 and 89 even if < 95th percentile			

Author (Year)	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts	Score
Baselga et al. (2012)	2	2	2	1	7
Baselga et al. (2017)	1	1	2	1	5
Cortot et al. (2020)	2	1	1	1	5
Dummer et al. (2018)	2	2	2	1	7
Goss et al. (2010)	2	2	0	1	5
Guo et al. (2020)	1	1	0	1	3
Heymach et al. (2008)	1	1	2	1	5
Johnston et al. (2013)	0	2	1	1	4
Kato et al. (2012)	2	2	2	1	7
Kato et al. (2012)	2	2	2	1	7
Kubota et al. (2017)	2	2	2	1	7
Laurie et al. (2014)	1	2	0	1	4
Liu et al. (2014)	2	2	2	1	7
Liu et al. (2019)	2	2	2	1	7
Lu et al. (2018)	2	2	2	1	7
Mackey et al. (2015)	2	2	2	1	7
Miller et al. (2005)	2	2	2	1	7
Mok et al. (2011)	1	1	2	1	5
Nakagawa et al. (2019)	2	2	2	1	7
Rini et al. (2016)	2	2	2	1	7
Rugo et al. (2011)	2	2	2	1	7
Sinn et al. (2020)	2	2	2	1	7
Tao et al. (2020)	2	2	2	1	7
Yan et al. (2017)	1	1	1	1	4

discovery showing that the patients enrolled in the reviewed RCTs were taking anti-hypertensive drugs.

In this study, cancer types were Breast Cancer (n = 6), Cervical Cancer (n = 2), Colorectal Cancer (n = 1), Gastric Cancer (n = 1), Melanoma (n = 1), Non-Small-Cell Lung Cancer (n = 8), Ovarian Cancer (n = 2), Pancreatic Cancer (n = 1), and Renal Cell Carcinoma (n = 1). As for cancer combination therapy regimens, there was the combination of 2 drugs (n = 14), 3 drugs (n = 8), and >3 drugs (n = 1). Among the 23 therapeutic regimens, there were targeted therapy combined with chemotherapy (n = 17), two targeted therapies combined with

chemotherapy (n = 5), and targeted therapy combined with other treatments (n = 1). In the control group, 10 studies adopted monotherapy, and 13 studies used placebo combined with monotherapy.

In all eligible studies, the average age of patients ranged from 18 to 89 years old. Among the eligible research articles, papers published in the United States accounted for the majority, with 8 articles, followed by China with 5 articles, Canada with 3 articles, Japan with 3 articles, Britain with 1 article, France with 1 article, Germany with 1 article and Switzerland with 1 article. Meanwhile, 8 articles were published in "Journal of Clinical

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RI SI Y2 TC HI TC HI TC BB BB CD GG HI	ugo et al 2011 met et 2/2020 ao et al 2/2020 ao et al 2/2020 otal (95% CI) stal events eterogeneity: Chi ² = 49 est for overall effect: Z = tudy or Subgroup aselga et al 2/012 aselga et al 2/012 aselga et al 2/012	26 0 21 17 671 40, df = 22 (F 12.03 (P < 0 Intervention	112 57 127 75 3369 = 0.000	0 0 11 0 205	56 65 161 75 2872	0.3% 4.4% 0.3%	26.73 [1.66, 430.79] Not estimable 2.42 [1.21, 4.83] 35.00 [2.14, 571.60]	
SI Ta Ya Ta Ha Ha Ta Ha Ta Ha Ta Ha SI Bi Bi Bi Bi Gi Ha	nn et al. 2020 an et al. 2017 otal (95% CI) tal events eterogeneity: Chi ² = 49 ast for overall effect. Z = <u>tudy or Subgroup</u> aseiga et al. 2012 aseiga et al. 2012 aseiga et al. 2012	0 21 17 671 .40, df = 22 (F 12.03 (P < 0 Intervention	57 127 75 3369 = 0.000	0 11 0 205	65 161 75 2872	4.4% 0.3%	Not estimable 2.42 [1.21, 4.83] 35.00 [2.14, 571.60]	
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TO HI TO SI BI BI BI BI CO O GI HI	otal events eterogeneity: Chi [#] = 49. ast for overall effect: Z = <u>tudy or Subgroup</u> aselga et al.2012 aselga et al.2017 ortot et al.2020	40, df = 22 (F 12.03 (P < 0 Intervention	= 0.000			100.0%	2 43 [2 40 2 04]	
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Hi Te Bi Bi Bi C D G G H	eterogeneity: Chi¤= 49, ast for overall effect: Z = <u>tudy or Subgroup</u> aseiga et al.2012 aseiga et al.2017 ortot et al.2020	12.03 (P < 0		07); I ² = 5	596			
SI Bi Bi Ci Di Gi Gi Hi	tudy or <u>Subgroup</u> aselga et al.2012 aselga et al.2017 ortot et al.2020	Intervention	.00001)		0.00			0.01 0.1 1 10 100
Bi Bi Ci Di Gi Hi	tudy or Subgroup aselga et al.2012 aselga et al.2017 ortot et al.2020						F	avours experimental Favours control
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Bi Bi Ci Di Gi Hi	tudy or Subgroup aselga et al.2012 aselga et al.2017 ortot et al.2020						Di 1 5	
BECDGGH	aselga et al.2012 aselga et al.2017 ortot et al.2020	CYCIIIS 1		Control. Events	Arm Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV. Fixed, 95% CI
BCDGGH	aselga et al.2017 ortot et al.2020		115	Events 2	114	1.3%	0.50 [0.05, 5.39]	IV. FIACU, 35% CI
C D G G H	ortot et al.2020	36	266	6	271	10.1%	6.11 [2.62, 14.27]	
Gi Gi Hi		8	111	0	55	0.9%	8.50 [0.50, 144.62]	+
G H	oss et al.2010	12 19	192 126	6 2	194 125	7.9%	2.02 [0.77, 5.27] 9.42 [2.24, 39.61]	†• <u> </u>
н	uo et al.2010	19	30	0	125	3.5%	4.84 [0.24, 96.66]	
	eymach et al.2008	4	56	0	52	0.9%	8.37 [0.46, 151.74]	
	phnston et al.2013	2	36	0	72	0.8%	9.86 [0.49, 200.23]	
	ato et al.2012	4	58	1	58	1.6%	4.00 [0.46, 34.71]	
	ato et al.2012 ubota et al.2017	6 32	56 197	1	58 204	1.7%	6.21 [0.77, 49.99] 8.28 [2.98, 22.99]	
	aurie et al.2014	15	153	3	153	4.9%	5.00 [1.48, 16.92]	
Li	u et al.2014	18	44	Ū	46	0.9%	38.64 [2.40, 622.36]	
	u et al.2019	18	44	0	46	0.9%	38.64 [2.40, 622.36]	
	u et al.2018 ackev et al.2015	5 51	61 759	1	30 385	1.6%	2.46 [0.30, 20.12] 3.70 [1.69, 8.07]	
	iller et al.2005	41	232	1	230	1.9%	40.65 [5.64, 293.02]	
M	ok et al.2011	3	34	0	33	0.9%	6.80 [0.36, 126.76]	
	akagawa et al.2019	52	224	12	225	20.2%	4.35 [2.39, 7.93]	
	ini et al.2016	24	204	7	135	11.0%	2.27 [1.01, 5.12]	
	ugo et al.2011 inn et al.2020	5	57	0	56 65	0.9%	5.55 [0.31, 98.60] 3.42 [0.37, 31.98]	
	ao et al.2020	11	127	5	161	6.8%	2.79 [0.99, 7.82]	
	an et al.2017	0	75	0	75		Not estimable	
-	otal (95% CI)		3369		0070	100.00	107/000 5 703	▲
	otal events	372	2209	59	2012	100.0%	4.37 [3.33, 5.72]	· · ·
	eterogeneity: Chi ² = 23.		= 0.39)					0.01 0.1 1 10 100
	est for overall effect: Z =						F	0.01 0.1 1 10 100 avours experimental Favours control
	Chudu an Cubanau	Interventio		Contro		1 Mainte	Risk Ratio	Risk Ratio
	Study or Subgroup Baselga et al.2012	Events 18	<u>Tota</u> 115					
	Baselga et al.2012 Baselga et al.2017	68	266					
	Cortot et al.2020	22	111				22.50 [1.39, 364.1	4]
	Dummer et al.2018	28	192				2.57 [1.32, 5.0	021
	Goss et al.2010 Guo et al.2020	38 12	126					30
	Heymach et al.2008	12	56				5 5.60 [1.42, 23.0 5 8.36 [2.04, 34.2	27]
	Johnston et al.2013	14	36	3 3	7	2 1.1%	9.33 [2.87, 30.4	
	Kato et al.2012	47	58					
	Kato et al.2012 Kubota et al.2017	48	56 197					
	Kubota et al.2017 Laurie et al.2014	86	19/					
	Liu et al.2014	35	44				5 74.16 [4.69, 1173.0	11
	Liu et al.2019	34	44	4 C	1 4	6 0.2%	72.07 [4.55, 1140.6	32]
	Lu et al.2018 Maakeu et al.2015	14	61					32]
	Mackey et al.2015 Miller et al.2005	203 54	759					
	Mok et al.2005	19	34					
	Nakagawa et al.2019	100	224	27	22	5 10.3%	3.72 [2.54, 5.4	
	Rini et al.2016	51	204					
	Rugo et al.2011 Sinn et al.2020	31 3	112					
	Sinn et al.2020 Tao et al.2020	32	121					
	Yan et al.2017	32	75					
	Total (95% CI)		3369			2 100.09	2.85 [2.52, 3.2	2]
	Total events Heterogeneity: Chi ^a = 7	1043 0 94 df= 23	(P < 0 0	264				
	Test for overall effect: 2	2= 16.73 (P <	0.0000	1)	00.00			0.01 0.1 i 10 1
								Favours experimental Favours control
=10	GURE 2 (A)	Forest	Ploto	s for t	he ()veral	Compariso	n of Hypertension
a	used by can	cer con	nbina	ation	ther	apy. (B) Summar	y Relative Risks for

Oncology,", 4 in "The Lancet Oncology,", and 3 in "European Journal of Cancer."

Evaluation of Included Studies

The Modified Jadad Scores scale (Jadad et al., 1996) was used to evaluate the quality of the 23 eligible articles. Following the evaluation based on the Randomization, Concealment of Allocation, Double Blinding, Withdrawals, and Dropouts, etc., there were 15 articles in 7 points, 5 articles in 5 points, 3 articles in 4 points, and 1 article in 3 points, as shown in **Table 3**.

Relative Risk of Hypertension

A total of 3,369 patients received cancer combination therapy, as well as 2,872 patients received cancer single therapy and/or placebo, which was available for comparative analysis. The incidence of grade 1-2 hypertension events ranged from 0 to 75%, and cediranib combined with mFOLFOX6 for the treatment of Colorectal Cancer had the highest probability of inducing hypertension (Kato et al., 2012). However, no events were observed in grade 1-2 hypertension in one trial (Sinn et al., 2020). Using the random-effect model, the RR in all patients developing grade 1-2 hypertension was 2.43 [95% CI 2.10-2.81, p < 0.001, Figure 2A]. Furthermore, the probability of grade 3–4 hypertension in all patients ranged from 0 to 40.9%, among which cediranib combined with Olaparib in treating Ovarian Cancer showed the highest probability of developing hypertension events (Liu et al., 2014; Liu et al., 2019). However, no grade 3-4 hypertension events were observed in the use of Oxaliplatin combined with oxaliplatin and Tiggio in the treatment of Gastric Cancer (Yan et al., 2017). Based on the random-effect model, the RR in all patients developing grade 3-4 hypertension was 4.37 [95% CI 3.33–5.72, *p* < 0.001, Figure 2B]. In addition, the incidence of all-grade hypertension ranged from 5.26 to 85.71%, and the highest incidence of hypertension was observed in the use of cediranib combined with mFOLFOX6 for the treatment of Colorectal Cancer (Kato et al., 2012). In the random-effect model, the RR in all patients developing grade 3-4 hypertension was 2.85 [95% CI 2.52–3.22, *p* < 0.001, Figure 2C].

Overall Comparison of Hypertension

For all grades of hypertension, cancer patients receiving combination therapy had a relatively higher probability of developing hypertension (All-grade: RR 2.85, 95% CI 2.52–3.22; 1–2 grade: RR 2.43, 95% CI 2.10–2.81; 3–4 grade: RR 4.37, 95% CI 3.33–5.72) (**Figure 2**). In terms of all grades of hypertension caused by targeted drugs combined with chemotherapy, schemes with a relatively higher risk of developing hypertension included Paclitaxel combined with bevacizumab (RR 22.50, 95%CI 1.39–364.14) (Cortot et al., 2020), cediranib combined with Olaparib (RR 74.16, 95%CI 4.69–1,173.01; RR 72.07, 95%CI 4.55–1,140.62) (Liu et al., 2014; Liu et al., 2019), Docetaxel combined with axitinib (RR 31.78, 95%CI 1.98–509.95) (Johnston et al., 2013), as well as apapatinib combined with Oxaliplatin and Tiggio (RR 35.00, 95% CI 2.14–571.60) (Yan et al., 2017).

In six RCTs on the treatment of breast cancer, combination therapies included Capecitabine combined with bevacizumab (All-grade: RR 10.71, 95% CI 4.36–26.28; 1–2 grade: RR 3.22, 95% CI 1.07–9.73; 3–4 grade: RR 40.65, 95% CI 5.64–293.02) (Miller et al., 2005), Docetaxel combined with axitinib (All-grade: RR 31.78, 95% CI 1.98–509.95; 1–2 grade: RR 26.73, 95% CI 1.66–430.79; 3–4 grade: RR 5.55, 95% CI 0.31–98.60) (Rugo et al., 2011), Capecitabine combined with Sorafenib (All-grade: RR 1.49, 95% CI 0.75–2.94; 1–2 grade: RR 1.69, 95% CI 0.81–3.52;





3-4 grade: RR 0.50, 95% CI 0.05-5.39) (Baselga et al., 2012), lapatinib combined with pazopanib (All-grade: RR 9.33, 95% CI 2.87-30.41; 1-2 grade: RR 8.00, 95% CI 2.41-26.57; 3-4 grade: RR 9.86, 95% CI 0.49-200.23) (Johnston et al., 2013), ramucirumab combined with Docetaxel (All-grade: RR 2.34, 95% CI 1.73-3.17; 1-2 grade: RR 2.08, 95% CI 1.49-2.92; 3-4 grade: RR 3.70, 95% CI 1.69-8.07) (Mackey et al., 2015), Sorafenib combined with Capecitabine (All-grade: RR 4.62, 95% CI 2.71-7.87; 1-2 grade: RR 3.62, 95% CI 1.76-7.44; 3-4 grade: RR 6.11, 95% CI 2.62-14.27) (Baselga et al., 2017). According to the treatment of breast cancer, the RR of combination therapies induced hypertension is different, and the RR of Docetaxel combined with axitinib is higher than that of other treatments. In the combined treatment of breast cancer patients, Figure 3, it is not difficult to see that the RR of hypertension caused by ramucirumab combined with Docetaxel is small when the number of patients is gradually increasing, which indicates that ramucirumab combined with Docetaxel is the best

treatment for low risk of hypertension caused by breast cancer in 6 RCTs of this research.

In eight RCTs on the treatment of non-small cell lung cancer, combination therapies included vandetanib combined with Paclitaxel and Carboplatin (All-grade: RR 8.36, 95% CI 2.04-32.27; 1-2 grade: RR 6.50, 95% CI 1.55-27.24; 3-4 grade: RR 8.37, 95% CI 0.46–151.74) (Heymach et al., 2008), cediranib combined with Paclitaxel and Carboplatin (All-grade: RR 3.77, 95% CI 1.97-7.23; 1-2 grade: RR 2.36, 95% CI 1.07-5.18; 3-4 grade: RR 9.42, 95% CI 2.24-39.61) (Goss et al., 2010), bevacizumab combined with Cisplatin and Gemcitabine (Allgrade: RR 3.69, 95% CI 1.56-8.72; 1-2 grade: RR 3.11, 95% CI 1.28-7.51; 3-4 grade: RR 6.80, 95% CI 0.36-126.76) (Mok et al., 2011), cediranib combined with Paclitaxel and Carboplatin (Allgrade: RR 3.64, 95% CI 2.11-6.30; 1-2 grade: RR 3.27, 95% CI 1.73-6.19; 3-4 grade: RR 5.00, 95% CI 1.48-16.92) (Laurie et al., 2014), motesanib combined with Paclitaxel and Carboplatin (Allgrade: RR 3.07, 95% CI 2.12-4.46; 1-2 grade: RR 2.24, 95% CI



1.45–3.44; 3–4 grade: RR 8.28, 95% CI 2.98–22.99) (Kubota et al., 2017), fruquintinib combined with Best supportive care (All-grade: RR 6.89, 95% CI 0.95–49.92; 1–2 grade: RR 9.50, 95% CI 0.57–157.94; 3–4 grade: RR 2.46, 95% CI 0.30–20.12) (Lu et al., 2018), ramucirumab combined with erlotinib (All-grade: RR 3.72, 95% CI 2.54–5.45; 1–2 grade: RR 3.21, 95% CI 1.86–5.57; 3–4

grade: RR 4.35, 95% CI 2.39–7.93) (Nakagawa et al., 2019), Paclitaxel combined with bevacizumab (All-grade: RR 22.50, 95% CI 1.39–364.14; 1–2 grade: RR 14.50, 95% CI 0.88–238.66; 3–4 grade: RR 8.50, 95% CI 0.50–144.62) (Cortot et al., 2020). Depending on the above data, **Figure 4**, in 8 RCTs of non-small cell lung cancer, the highest RR of hypertension caused



TABLE 4 | Risk of bias of included randomized controlled trials.

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baselga et al. (2012)	Low	Low	Low	Unclear	Low	Low	Low
Baselga et al. (2017)	Unclear	Unclear	Low	Low	Low	Low	Low
Cortot et al. (2020)	Low	Unclear	Unclear	Low	Low	Low	Low
Dummer et al. (2018)	Low	Low	Low	Low	Low	Low	Low
Goss et al. (2010)	Low	Low	High	Low	Low	Low	Low
Guo et al. (2020)	Unclear	Unclear	High	Unclear	Low	Low	Low
Heymach et al. (2008)	Unclear	Unclear	Low	Low	Low	Low	Low
Johnston et al. (2013)	High	Low	Unclear	Low	Low	Low	Low
Kato et al. (2012)	Low	Low	Low	Low	Low	Low	Low
Kato et al. (2012)	Low	Low	Low	Low	Low	Low	Low
Kubota et al. (2017)	Low	Low	Low	Low	Low	Low	Low
Laurie et al. (2014)	Unclear	Low	High	Low	Low	Low	Low
Liu et al. (2014)	Low	Low	Low	Low	Low	Low	Low
Liu et al. (2019)	Low	Low	Low	Low	Low	Low	Low
Lu et al. (2018)	Low	Low	Low	Low	Low	Low	Low
Mackey et al. (2015)	Low	Low	Low	Low	Low	Low	Low
Miller et al. (2005)	Low	Low	Low	Low	Low	Low	Low
Mok et al. (2011)	Unclear	Unclear	Low	Low	Low	Low	Low
Nakagawa et al. (2019)	Low	Low	Low	Low	Low	Low	Low
Rini et al. (2016)	Low	Low	Low	Low	Low	Low	Low
Rugo et al. (2011)	Low	Low	Low	Low	Low	Low	Low
Sinn et al. (2020)	Low	Low	Low	Low	Low	Low	Low
Tao et al. (2020)	Low	Low	Low	Low	Low	Low	Low
Yan et al. (2017)	Unclear	Unclear	Unclear	Low	Low	Low	Low

by Paclitaxel combined with bevacizumab, With the increase of the number of patients, ramucirumab combined with erlotinib has a relatively small and better chance of inducing hypertension in the treatment of non-small cell lung cancer.

From an intuitive point of view, the incidence of hypertension caused by combination therapy of cancer is higher than that of single therapy, whether it is at all-grade, 1–2 grade or 3–4 grade

hypertension, the results shown in **Figure 5A–C**. As cancer combination therapy regimens, **Figure 6**, the result of analyze show that the RR of hypertension caused by two drugs combination therapy is higher than three drugs combination therapy, because there are very few plans of multi-drug (n > 3) combination therapy, it is not included as a comparison. For more details of the other schemes, please refer to **Table 1**.





Heterogeneity and Bias of Included Studies

As presented in **Figure 2**, there was moderate heterogeneity in grade 1–2 hypertension ($I^2 = 55\%$, p < 0.001), low heterogeneity in grade 3–4 hypertension ($I^2 = 5\%$, p = 0.39), and moderate heterogeneity in all grades of hypertension ($I^2 = 68\%$, p < 0.001) caused by cancer combination therapy, with the presence of statistical significance. Using the risk-of-bias assessment tool (Higgins et al., 2011), the results of the Cochrane risk-of-bias assessment of the enrolled 23 RCTs are shown in **Table 4** and **Figures 7–9** showed that the funnel plot indicated evidence of heterogeneities and publication bias in the studies included in the

meta-analysis with scatters beyond 95% CI and asymmetry display (p < 0.00001).

DISCUSSION

To our knowledge, the present meta-analysis for the first time evaluated the potential risk of hypertension in cancer patients treated with combination therapy. As a "silent killer,", hypertension has been reported to have a doubled prevalence in the past 40 years, with 7.6 million people dying of

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	
Baselga et al.2012	•	•	•	?	•	•	•	
Baselga et al.2017	?	?	•	•	•	•	•	
Cortot et al.2020	•	?	?	•	•	•	•	
Dummer et al.2018	•	•	•	•	•	•	•	
Goss et al.2010	•	•	•	•	•	•	•	
Guo et al.2020	?	?	•	?	•	•	•	
Heymach et al.2008	?	?	•	•	•	•	•	
Johnston et al.2013	•	•	?	•	•	?	•	
Kato et al.2012	•	•	•	•	•	•	•	
Kubota et al.2017	•	•	•	•	•	•	•	
Laurie et al.2014	?	•	•	•	•	•	•	
Liu et al.2014	•	•	•	•	•	•	•	
Liu et al.2019	•	•	•	•	•	•	•	
Lu et al.2018	•	•	•	•	•	•	•	
Mackey et al.2015	•	•	•	•	•	•	•	
Miller et al.2005	•	•	•	•	•	•	•	
Mok et al.2011	?	?	•	•	•	•	•	
Nakagawa et al.2019	•	•	•	•	•	•	•	
Rini et al.2016	•	•	•	•	•	•	•	
Rugo et al.2011	•	•	•	•	•	•	•	
Sinn et al.2020	•	•	•	•	•	•	•	
Tao et al.2020	•	•	•	•	•	•	•	
Yan et al.2017	?	?	?	•	•	•	•	
FIGURE 9 Risk of bias of in summary.	cludeo	d rand	omize	d con	trolled	trials		

hypertension annually in the world (Arima et al., 2011). Despite no significant direct influence, long-term hypertension may result in damage of the heart and blood vessels, and cerebral artery vasospasm as well.

In the field of Cardio-Oncology, cancer combination therapy may produce the effective outcome in killing cancer cells and controlling the deterioration of cancer. Nevertheless, there is an inevitable adverse effect of heart disease, especially the occurrence of hypertension. In this regard, there is an urgent need for medical staff to adjust the therapeutic schemes of patients, timely prevent and alleviate side effects during and after cancer treatment, to ensure the life safety of patients.

Current anti-hypertensive therapeutics included Selective $\alpha 1$ adrenoceptor antagonist, non-selective $\alpha 1$ and $\alpha 2$ -antagonists, β -adrenoceptor antagonists, angiotensin II receptor blockers, calcium channel blockers, ACE inhibitors, renin inhibitors, direct vasodilators, loop diuretics (Kumar et al., 2020). However, we should pay more attention to the related complications which they are accompanied, such as organ damage, hypotension and so on (Kumar et al., 2020).

In our meta-analysis, based on the collection of all relevant data from retrospective clinical trials, the final objects of study were a total of 23 clinical trials involving 6,241 patients. The combination therapy of cancer patients resulted in a higher risk of developing hypertension (All-grade: RR 2.85, 95% CI 2.52–3.22; 1–2 grade: RR 2.43, 95% CI 2.10–2.81; 3–4 grade: RR 4.37, 95% CI 3.33–5.72). According to the results, the risk of grade 3–4 hypertension induced by cancer combination therapy was higher than that of the control group with or without placebo therapy.

There may exist different mechanisms of increase in blood pressure under different anti-cancer therapeutic schemes. The mechanism of elevated blood pressure by using anti-cancer drugs may exhibit a direct association with its anti-cancer mechanism. The mechanism of hypertension induced by cancer combination therapy may be explained by the following reasons. To be specific, monoclonal antibodies (for example, bevacizumab) may reduce the number of capillaries in microcirculation, competitively inhibit the binding of EGFR with other ligands, and block the interaction between VEGF and endothelial cell surface receptors, resulting in inhibit the signal pathway of VEGF, reduce the activity of endothelial nitric oxide synthase and the production of NO and PGI₂ by vascular endothelial cells, decrease vascular permeability and vasodilation, increased peripheral vascular resistance and blood flow, and finally lead to hypertension (Chen et al., 2011; Mayer et al., 2011; Mourad and Levy, 2011; Campia et al., 2019). Besides, it has been reported that reducing the activity of eNOS will lead to expression of uncoupling protein of eNOS, produces a large amount of reactive oxygen species and then decrease the level of NO (Kumar et al., 2020). Meanwhile, NO is involved in maintaining the steady state of sodium ions and participating in tubuloglomerular feedback to regulate renal blood flow and glomerular filtration, which can increase systemic blood pressure (Lankhorst et al., 2017). Another possible mechanism of hypertension caused by inhibiting other VEGF pathways is that angiogenesis inhibitors may reduce the number of blood vessels and lead to hypertension owing to the thinning of peripheral microvessels



(Aparicio-Gallego et al., 2011). In addition, additional research also reveals that the increase in blood pressure may be related to the inhibition of VEGFR-2 (Kamba and McDonald, 2007). Also, Small molecular targeted drugs (such as sunitinib) can upregulate endothelin-1, increase salt sensitivity, and further increase in blood pressure owing to thrombotic glomerular injury (Kidoguchi et al., 2021). In addition, some novel targeted drugs (e.g., brutinib) may increase the risk of hypertension by inhibiting PI3K/Akt or reducing the level of NO (Dickerson et al., 2019). (Figure 10)

With respect to the above, there is necessary to adopt targeted treatment of hypertension. Before the treatment of cancer patients, it is recommended to adopt a comprehensive risk assessment, including blood pressure measurement and examination of known risk factors. For cancer patients with existed cardiovascular diseases, it is necessary to consider carefully whether to use anti-cancer drugs that may lead to cardiotoxicity or not. In the field of Cardio-Oncology, further consideration of the overall health status of patients is required for doctors to make a prudent decision in patients with a high risk of hypertension and those with hypertension prior to the use of anti-cancer drugs. Moreover, in case of poor control of cancer development by monotherapy, the better therapeutic outcome may be produced by combination therapy, However, it should be noted that combination therapy may also lead to a higher risk of hypertension.

So far, there is still no systematic analysis of hypertension caused by cancer combination therapy. Data in our study fully supports that cancer combination therapy has a high risk of inducing hypertension. Findings in this meta-analysis suggest that much attention shall be paid constantly to the adverse reactions of combined use of drugs, with in-time prevention required simultaneously. However, there are limitations in this study. For example, due to the absence of experimental data, relevant experiments are needed in the future to fully clarify the pathophysiological basis of hypertension caused by the combination of drugs and to increase the credibility of the results of our study.

CONCLUSION

The accuracy of meta-analysis research is high, but there is also a certain degree of publication bias, and risk of bias is low. It is worth mentioned that the reliability of meta-analysis results as well as the suitability in clinical practice might still requires critical thinking and objective judgments.

To sum up, the present meta-analysis carries out a comprehensive analysis on the risk of patients suffering from hypertension in the process of multiple cancer combination therapies. Findings in our study support that the risk of hypertension may increase significantly in cancer patients with multiple cancer combination therapies. The outcomes of this meta-analysis may provide a reference value for clinical practice and may supply insights in reducing the incidence of hypertension caused by cancer combined treatment.

AUTHOR CONTRIBUTIONS

XG, XQ, YJ, XK, ZQ, TC, LZ, CW, WL: Study concept and design; acquisition of data; statistical analysis; interpretation of data; drafting and critical review of the manuscript for important intellectual content; approval of the final version of the manuscript.

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