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Original Article

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The Prevalence of 5-Fluorouracil and Capecitabine Cardiotoxicity: A Systematic Review and Meta-Analysis

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Abstract

Background: The incidence of cardiotoxicity events in patients who use 5-fluorouracil (5-FU) and capecitabine monotherapy remains unclear since previous studies reported the prevalence in patients who used combination regimens. We aimed to systematically review and meta-analyze the incidence of cardiotoxicity in fluorouracil and capecitabine monotherapy users.

Methods: The study protocol was registered with PROSPERO (CRD42023441627). Systematic searches were conducted in five databases (CINAHL, OpenGrey, PubMed, ScienceDirect, and Scopus). The Cochrane Risk-of-Bias tool and the Risk Of Bias In Non-randomized Studies were used to evaluate the risk of bias. Pooled prevalence and 95% confidence interval (CI) were calculated using the DerSimonian-Laird random effect models. The funnel plot was used to assess the publication bias.

Results: Eighty studies were included. There were 24 randomized controlled trials (RCTs) with low to high risk of bias and 56 non-RCTs with critical risk of bias. The pooled prevalence of cardiotoxicity from 5-FU was 3.5% (95% CI: 2.7 - 4.2; $P < 0.001$; $I^2 = 73.86\%$). The pooled prevalence of cardiotoxicity in capecitabine users was 2.8% (95% CI: 1.6 - 4.0; $P < 0.001$; $I^2 = 72.62\%$).

Conclusions: The prevalence of cardiotoxicity from 5-FU and capecitabine was classified as common. Cardiotoxicity may have not been associated with the cumulative dose of 5-FU or capecitabine.

Keywords: 5-Fluorouracil; Capecitabine; Cardiotoxicity

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Introduction

5-Fluorouracil (5-FU) and its oral pro-drug, capecitabine, are anticancer drugs that exert their biological activity by inhibiting DNA synthesis [1]. They are widely used as monotherapy or in combination regimens for the treatment of solid malignancies including colorectal cancer and other types of cancer, e.g., head and neck cancer, esophageal cancer, stomach cancer, and bladder cancer [2]. In addition, they can be combined with radiation therapy or concurrent chemoradiation (CCRT) [3]. 5-FU and capecitabine are significantly crucial for the treatment of cancer that the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend 5-FU and capecitabine as the first-line treatment for metastatic colorectal cancer [4] and the World Health Organization (WHO) listed 5-FU and its oral pro-drug in the 21st list of the WHO Model List of Essential Medicine [5]. However, the use of 5-FU and its pro-drug can be limited by their toxicities.

The dose-limiting toxicities of 5-FU bolus injection are associated with hematological toxicities but 5-FU continuous infusion causes hand-foot syndrome, diarrhea, and mucositis [6, 7]. In addition, cardiac toxicities, which include chest pain, coronary vasospasm, and myocardial infarction, are common for fluorouracil. Other less common symptoms include congestive heart failure, arrhythmias, pericarditis, and sudden cardiac death [8, 9]. Although cardiotoxicity induced by 5-FU has long been discovered [10], and the prevalence is known to be the second most commonly reported after anthracyclines [11], the exact incidence of fluorouracil-induced cardiotoxicity is difficult to estimate. This is because most of the research reported the prevalence or incidence of cardiotoxicity from fluorouracil-containing regimens whose compositions are largely diverse. In addition, most studies fail to report the total number of patients who are treated with fluorouracil which complicates the estimation of such prevalence [12-15].

The Council for International Organizations of Medical Sciences [16] categorized the prevalence of adverse drug reactions (ADRs) into very common, common (or frequent), uncommon (or infrequent), rare, and very rare. The categorization of the risk of cardiotoxicities from 5-FU and capecitabine

assists the risk communication to the patients, which affects how patients perceive the risk and adhere to the anticancer treatment [17]. Since the incidence of adverse events is crucial for patient care, we aimed to systematically review and meta-analyze the incidence of cardiotoxicity during the use of fluorouracil.

Materials and Methods

Search strategy

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [18]. The study protocol was registered with PROSPERO (CRD42023441627). The Institutional Review Board (IRB) approval does not apply to this study. Systematic searches were conducted in five databases (CINAHL, OpenGrey, PubMed, ScienceDirect, and Scopus) without language and study design restrictions. The search was conducted from their inception to June 1, 2024. The following search concept was used: "5-fluorouracil" OR "capecitabine" AND "cardiotoxicity" (Supplementary Material 1, www.wjon.org).

Study eligibility criteria

The systematic review was conducted using the following eligibility criteria: 1) were clinical trials or observational studies; 2) explicitly reported details of 5-FU or capecitabine treatment regiments; 3) used 5-FU or capecitabine as monotherapy for any cancer treatment indication; and 4) explicitly reported the number of cardiotoxicity events. We excluded studies that did not have sufficient data on cardiotoxicity incidence.

Data extraction

Three authors independently screened retrieved articles' titles, abstracts, and full texts. Disagreements were resolved by consulting the senior author in the team. Also independently, three authors extracted the author's name, year of publication, region, study design, sample size, duration of the study, mean age, sex, characteristics of participants, comorbidity of participants, cancer type, treatment regimen, cumulative dose, and cardiotoxicity events. Data deemed important but unavailable in the publications were retrieved by contacting the corresponding authors. The articles were excluded if the corresponding authors did not respond in a reasonable time. The median age (with interquartile range) was converted to mean and standard deviation using a formula by Wan et al [19]. The cumulative dose was calculated from the total 5-FU or capecitabine dose received before cardiotoxicity occurred. ADRs were classified according to the Council for International Organizations of Medical Sciences [16] into five groups as follows: very common (frequency higher than 1/10), common (less than 1/10 to higher than 1/100), uncommon (less than 1/100 to higher than 1/1,000), rare (less than 1/1,000 to higher than 1/10,000), and very rare (less than 1/10,000).

Quality assessment

Three authors independently assessed the risk of bias in the included studies. The risk of bias in randomized controlled trials and non-randomized trials was evaluated using the Cochrane Risk-of-Bias tool 2.0 (RoB 2.0) [20], and the Risk Of Bias In Non-randomized Studies (ROBINs) [21], respectively.

Statistical analysis

The pooled prevalence of cardiotoxicity induced by 5-FU or capecitabine and 95% confidence interval (CI) were calculated using the DerSimonian-Laird random effect models [22] (OpenMetaAnalyst for Windows 8). Heterogeneity was assessed using Cochrane's Q statistic and I^2 values. The P-value of Cochrane's Q of less than 0.10 was considered significant. I^2 of greater than 75% indicated high heterogeneity while I^2 of less than 25% indicated high homogeneity [23]. The funnel plot was used to observe publication bias.

Subgroup analysis and meta-regression

The influence of baseline characteristics, which may have caused heterogeneity, was determined by meta-regression (OpenMetaAnalyst for Windows 8 [24]). The effect of the following variables was planned for the analysis *a priori*: age, sex, study site, total cumulative dose, and year of study.

Results

Study characteristics

From 34,705 articles from the systematic search, 80 studies were selected for meta-analysis [8, 15, 25-102]. Twenty-four were randomized studies and 56 were non-randomized studies. Details of the systematic search and screening are shown in the PRISMA diagram (Fig. 1). This systematic review included 18,524 participants, 5,836 of which were males. The average age of the participants was approximately 53.65 ± 7.32 years old. Most had gastrointestinal cancer such as colorectal cancer or gastric cancer. Almost all studies did not report patients' medications for other comorbidities. Baseline characteristics are shown in Table 1 and additional participant characteristics are in Supplementary Material 2 (www.wjon.org). Information on dosage regimens and cardiotoxicity outcomes in patients who received 5-FU or capecitabine monotherapy is shown in Supplementary Materials 3 and 4 (www.wjon.org).

Risk of bias assessment

We found two randomized studies with a high risk of bias [27,

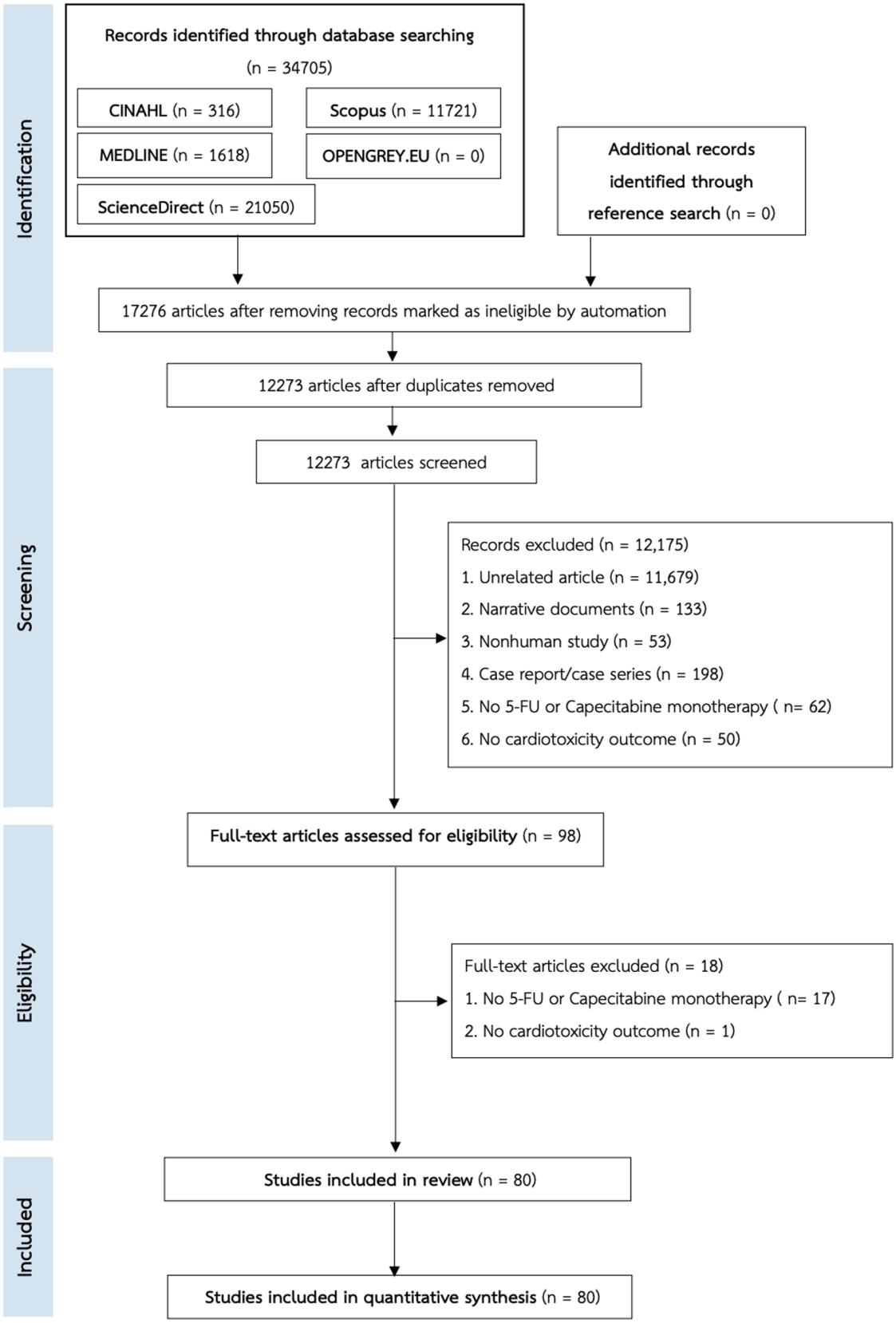

Figure 1. The PRISMA flow chart of the study selection.

Table 1. Characteristics of the Included Studies

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
1	Alberto et al, 1988 [27]	Switzerland	Randomized trial	52	27	25	-	10.1	61.5 ± 2.12	27, 51.92%	N/A	Colon or rectum cancer	None
2	Ansari et al, 2017 [28]	Australia and New Zealand	Randomized controlled trial	322	161	161	-	3	62.75 ± 10.05	235, 72.98%	N/A	Rectal cancer	N/A
3	Bajetta et al, 1993 [29]	Italy	Prospective randomized Trial	222	110	112	-	16.75	61.34 ± 9.18	123, 55.41%	N/A	Advanced colorectal cancer	None
4	Barutca et al, 2004 [30]	Turkey	Prospective study	28	28	-	-	15 days	67.51 ± 10.44	17, 61%	N/A	Colorectal cancer, gastrointestinal system cancers	N/A
5	Becouarn et al, 1995 [31]	France	Prospective study	86	86	-	-	52	61.81 ± 8.79	42, 48.84%	N/A	Advanced colorectal cancer	Palliative chemotherapy (8.14%)
6	Berenberg et al, 1995 [32]	United States	Phase II clinical study	76	76	-	-	5	N/A	N/A	N/A	Advanced gastric cancer	None
7	Bonnetain et al, 2005 [33]	France	Randomized phase II trial	134	45	89	-	6	63.26 ± 7.73	110, 82.09%	N/A	Metastatic gastric cancer	N/A
8	Breton et al, 2021 [34]	France	Pooled analysis	2,190	1,068	395	727	3.6	66.8 ± 2.33	654, 61.2%	N/A	Metastatic colorectal cancer	N/A
9	Brucher et al, 2004 [35]	Germany	Prospective study	76	76	-	-	64.8	54 ± 6.48	59, 77.6%	N/A	Esophageal squamous cell carcinoma	N/A
10	Cascinu et al, 2003 [36]	Italy	Randomized controlled trial	183	91	92	-	48	61.84 ± 8.58	100, 54.64%	N/A	Stage III colon cancer	N/A
11	Cashin et al, 2016 [37]	Sweden	Randomized controlled trial	48	24	24	-	78	60±10.61	24, 50%	N/A	Colorectal peritoneal metastases	N/A
12	Ceyhan et al, 2005 [38]	Turkey	Prospective study	37	37	-	-	N/A	60	26, 70.27%	N/A	Colorectal cancer, gastric cancer, breast cancer, metastatic lung carcinoid, nasopharyngeal carcinoma	N/A
13	Citron et al, 1992 [39]	United States	Prospective study	86	86	-	-	6	61.26 ± 9.41	65, 76%	N/A	Non-small cell lung cancer	N/A
14	Cunningham et al, 2009 [40]	United Kingdom	Randomized controlled trial	725	363	362	-	48	61.2 ± 8.89	126, 17.38%	N/A	Metastatic colorectal cancer	N/A
15	Daniele et al, 2003 [41]	Italy	Prospective study	34	34	-	-	3.9	76.33 ± 3.59	23, 67.65%	Cardiovascular (55.88%), respiratory (32.35%), gastrointestinal/ hepatobiliary (17.65%), genitourinary (17.65%), osteoarticular (14.71%), diabetes (17.65%), endocrinologic (5.88%)	Stage IV colorectal cancer	Previous adjuvant chemotherapy (11.76%)

Table 1. Characteristics of the Included Studies - *(continued)*

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
16	de Forni et al, 1992 [8]	France	Prospective study	367	65	302	-	N/A	55.25 ± 12.40	230, 62.67%	N/A	Head and neck cancer, breast cancer, colon/ rectum cancer, esophagus cancer, cervix cancer	N/A
17	Dencausse et al, 2002 [42]	Germany	Prospective randomized study	155	105	50	-	60	62.58 ± 10.03	108, 69.68%	N/A	Colon cancer	N/A
18	Dencausse et al, 2001 [43]	Germany	Prospective study	21	21	-	-	6.75	60.69 ± 3.27	14, 66.67%	N/A	Rectal cancer	N/A
19	Ducreux et al, 2002 [44]	France	Randomized trial	207	103	104	-	36	59.95 ± 9.05	134, 64.73%	N/A	Metastatic or locally advanced adenocarcinoma of the pancreas	None
20	Ducreux et al, 2004 [45]	France	Randomized controlled trial	63	15	17	31	N/A	55.63 ± 11.58	42, 66.67%	N/A	Advanced pancreatic carcinoma	N/A
21	Ducreux et al, 2005 [46]	Belgium	Randomized phase II trial	57	29	28	-	8	59.96	31, 54.39%	N/A	Locally advanced or metastatic biliary tract cancer	None
22	Dyhl-Polk et al, 2021 [47]	Denmark	Prospective study	108	108	-	-	N/A	65.15 ± 9.11	59, 54.6%	Ischemic heart disease (0.9%), previous stroke (7.4%), heart failure (0.9%), atrial fibrillation (4.6%), other heart disease (2.7%), hypertension (32.4%), hypercholesterolemia (67.6%), diabetes mellitus (5.6%)	Colorectal or anal cancer	N/A
23	Francini et al, 1994 [48]	Italy	Randomized controlled trial	239	118	121	-	54	56.76	126, 52.72%	N/A	Surgically resected colon cancer	N/A
24	Garufi et al, 1997 [49]	Italy	Phase I study	34	34	-	-	9	55.34 ± 12.19	19, 55.88%	N/A	Metastatic adenocarcinoma of the colon or rectum	Prior chemotherapy (13/34)
25	Gradishar et al, 1991 [50]	United States	Retrospective review	244	34	210	-	N/A	N/A	N/A	N/A	Gastric cancer, Head and neck cancer	N/A
26	Granito et al, 2015 [51]	Italy	Retrospective study	26	26	-	-	31	65.48 ± 7.07	23, 88.46%	Mild ascites (30.76%), absent ascites (69.23%)	Hepatocellular carcinoma	N/A

Table 1. Characteristics of the Included Studies - *(continued)*

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
27	Haas et al, 1995 [52]	USA	Phase II study	37	37	-	-	N/A	61.24 ± 9.19	24, 64.86%	One patient had a myocardial infarction four years before presenting colon cancer. He was maintained on stable doses of nitrates and a calcium channel blocker.	Metastatic adenocarcinoma of the colon or rectum	Adjuvant CMT 2, adjuvant CMT/RT 1, adjuvant immunotherapy/ CMT 2, advanced CMT 2, immunotherapy 3, immunotherapy/ RT 1, RT 5, none 22
28	Harbeck et al, 2017 [53]	Germany	Randomized controlled trial	210	105	105	-	N/A	61.82 ± 10.96	0	N/A	Metastatic breast cancer	Prior PLD (37%), capecitabine (36%)
29	Hartung et al, 1996 [54]	Germany	Retrospective study	92	55	37		13	Median 59.7	55, 59.78%	N/A	Colon cancer, rectal cancer	N/A
30	Hartung et al, 2001 [55]	Germany	Phase II clinical study	51	51	-	-	20.2	58.35 ± 11.77	38, 74.51%	N/A	Metastatic colorectal cancer	N/A
31	Highley et al, 2009 [56]	United Kingdom	Phase II study	46	46	-	-	6	68.09 ± 2.49	33, 71.74%	N/A	Transitional cell carcinoma of the urinary tract	None
32	Hoff et al, 2001 [57]	United States, Canada, Brazil, Mexico	Phase III randomized controlled study	605	303	302	-	13.3	63.05 ± 10.98	378, 62.48%	N/A	Advanced or metastatic colorectal cancer	Adjuvant 5-FU (36.3%)
33	Jack et al, 1995 [58]	Southeast Scotland	Randomized controlled trial	332	167	165	-	Median follow-up of 15 years	53.97 ± 8.34	0	N/A	Breast cancer	N/A
34	Jager et al, 1995 [59]	Germany	Prospective study	69	69	-	-	N/A	55.98 ± 8.67	50, 72.46%	N/A	Advanced colorectal and rectal carcinoma	N/A
35	Jegannathen et al, 2011 [60]	United Kingdom	Phase II clinical study	50	50	-	-	N/A	55.35 ± 8.47	40, 80%	N/A	Head and neck cancer	N/A
36	Jensen et al, 2006 [25]	Denmark	Prospective study	668	362	92	214	N/A	N/A	N/A	Hypercholesterolemia, diabetes, hypertension, cerebral ischemia	Colorectal cancer, gastric cancer	N/A
37	Kerr et al, 1995 [61]	United Kingdom	Phase I clinical trial	43	43	-	-	N/A	56 ± 9.38	28, 65.12%	N/A	Colorectal cancer	N/A
38	Khan et al, 2012 [62]	Pakistan	Retrospective study	301	18	283	-	N/A	47.13 ± 10.99	75, 24.92%	N/A	N/A	N/A
39	Kim et al, 2003 [63]	Korea	Prospective study	122	53	69	-	N/A	55.98 ± 11.16	70, 57.38%	N/A	Adenocarcinoma of the colon (colon cancer)	N/A

Table 1. Characteristics of the Included Studies - *(continued)*

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
40	Klausner et al, 1987 [64]	Israel	Prospective study	30	30	-	-	19	51.03 ± 11.03	20, 66.67%	N/A	Metastatic malignant melanoma	None
41	Kohne et al, 2005 [65]	Europe	Phase III prospective, multicenter, randomized, non-blinded	427	213	214	-	27.6	60.25 ± 9.24	268, 62.32%	N/A	Metastatic colorectal cancer	N/A
42	Kok et al, 1996 [66]	The Netherlands	Prospective study	29	29	-	-	24 weeks or until progression.	59.39 ± 8.14	25, 86.21%	N/A	Metastatic adenocarcinoma of the esophagus or esophagogastric junction area.	None
43	Kolaric et al, 1986 [67]	Slovenia	Controlled phase III clinical study	115	56	59	-	N/A	51.89 ± 8.34	71, 61.74%	N/A	Gastric cancer, rectosigmoid cancer	N/A
44	Kosmas et al, 2008 [68]	Greece	Prospective study	644	397	193	54	N/A	65.91 ± 2.26	N/A	Hyperlipidemia, obesity, chronic obstructive pulmonary disease	Colorectal cancer, head and neck cancer, breast cancer	N/A
45	Kuzel et al, 1993 [69]	USA	Phase II study	22	22	-	-	1	68.29 ± 6.55	22, 100%	N/A	Metastatic prostate carcinomas refractory to hormonal therapy	None
46	Kwakman et al, 2017 [70]	United Kingdom	Retrospective study	2,461 event	397	2,064	-	N/A	N/A	N/A	N/A	Colorectal cancer	N/A
47	Labianca et al, 1982 [26]	Italy	Retrospective study	1,083	480	603	-	N/A	N/A	N/A	Ischemic heart disease	Gastric cancer, breast cancer	N/A
48	Labianca et al, 1988 [71]	Italy	Randomized trial	54	28	26	-	22	55.48 ± 9.53	33, 61%	N/A	Advanced colorectal cancer	None
49	Leichman et al, 2005 [72]	United States	Retrospective study	690	340	350	-	13	60.78 ± 11.38	407, 57%	N/A	Metastatic or recurrent colorectal cancer	Previous adjuvant CMT or immunotherapy (or both) was allowed as long as ≥ 1 year had elapsed since discontinuation of therapy. No previous chemotherapy for advanced disease was permitted.

Table 1. Characteristics of the Included Studies - *(continued)*

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
50	Lestuzzi et al, 2014 [15]	Italy and Germany	Prospective study	231	49	182	-	9	57.5	148, 64.07%	Obesity (9.09%), diabetes mellitus (12.12%), hypertension (33.33%), dyslipidemia (23.81%), coronary artery disease (3.46%), active smoker (40.69%), former smoker (23.38%)	Colorectal cancer, breast cancer, head and neck cancer, gastric or bowel cancer	N/A
51	Mayer et al, 2021 [73]	Unites States	Phase III randomized controlled study	308	160	148	-	58	51.85 ± 9.00	0	N/A	Breast cancer	Prior neoadjuvant taxane 160/160, prior RT 122/160, prior neoadjuvant anthracycline 136/160
52	Meydan et al, 2005 [74]	Turkey	Prospective study	231	163	68	-	N/A	57 ± 18.47	138, 59.74%	Coronary artery disease, hypertension, diabetes mellitus	Colorectal cancer, gastric cancer, pancreas and gallbladder, breast cancer, neuroendocrine, head and neck cancer	N/A
53	Naredi et al, 2003 [75]	Sweden	Prospective randomized study	39	21	18	-	46	64.38 ± 8.74	27, 69.23%	N/A	Metastasis colorectal cancer	N/A
54	Ngan et al, 2001 [76]	Australia and New Zealand	Prospective study	82	82	-	-	12	58.74 ± 12.36	55, 67.07%	N/A	Localized adenocarcinoma of the rectum	N/A
55	Nobile et al, 1985 [77]	Italy	Phase II clinical study	38	38	-	-	N/A	60.59 ± 8.43	20, 52.63%	N/A	Advanced colorectal cancer	7/38 had failed prior 5-FU treatment.
56	Oman et al, 2005 [78]	Sweden	Phase I/II clinical trial	68	68	-	-	3.9	62.07 ± 11.23	29, 42.65 %	N/A	Non-resectable pancreas cancer	N/A
57	Poorter et al, 1995 [79]	The Netherlands	Prospective study	30	30	-	-	22	54.69 ± 10.54	12, 40%	N/A	Metastatic gastrointestinal cancer	N/A
58	Primrose et al, 2019 [80]	United Kingdom	Randomized controlled trial	447	223	224	-	N/A	62.92 ± 2.48	224, 50.11%	N/A	Biliary tract cancer	N/A
59	Regazzoni et al, 1996 [81]	Switzerland	Retrospective study	106	106	-	-	N/A	56 ± 10.32	N/A	N/A	Breast cancer	81% had previously received anthracyclines
60	Rosso et al, 1994 [82]	Italy	Prospective study	79	79	-	-	28.75	61.34 ± 7.46	50, 63.29%	N/A	Advanced colorectal carcinoma	N/A

Table 1. Characteristics of the Included Studies - *(continued)*

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
61	Schober et al, 1993 [83]	Germany	Prospective study	390	250	89	51	N/A	52 ± 13.85	260, 66.67%	Hypertension, diabetes, hyperlipidemia, history of coronary or peripheral artery disease	Gastric cancer, colorectal cancer	Pretreatment with etoposide, adriamycin, and cisplatin 1/390
62	Schuster et al, 1991 [84]	Germany	Randomized controlled trial	61	30	31	-	24	56.29 ± 9.29	39, 63.93%	N/A	Advanced colorectal carcinoma	None
63	Smorenburg et al, 2014 [85]	The Netherland	Randomized controlled trial	78	38	40	-	39	75.07 ± 4.36	0	N/A	Metastatic breast cancer	Previous adjuvant CMT with anthracyclines was allowed, considering a cumulative dose of < 240 mg/m^2 of doxorubicin or < 450 mg/m^2 of epirubicin and completion for at least 12 months
64	Stockler et al, 2011 [86]	Australia, New Zealand	Randomized controlled study	323	214	109	-	39.6	59.67	0	N/A	Advanced breast cancer	N/A
65	Terzoli et al, 2004 [87]	Italy	Prospective study	80	80	-	-	14	60.24 ± 9.34	46, 57.50%	N/A	Advanced colorectal cancer	Adjuvant CMT 13/80
66	Tsavaris et al, 1990 [88]	Greece	Prospective study	74	74	-	-	7.4	61	46, 62.16%	N/A	Advanced colorectal cancer	RT 16/74, 5-FU with or without mitomycin C 17/74
67	Tsavaris et al, 2005 [89]	Greece	Prospective study	522	333	189	-	N/A	62.04 ± 2.31	N/A	Hyperlipidemia, obesity, chronic obstructive pulmonary disease	Head and neck cancer, colorectal cancer	None
68	Tsuchida et al, 2005 [90]	Japan	Retrospective study	14	14	-	-	27	64.11 ± 9.08	12, 86%	N/A	Recurrence of esophageal squamous cell carcinoma	Cisplatin (50 - 80 mg/m^2) for 1 day and 5-FU (500 - 800 mg/m^2) for 5 days (eight patients)
69	Urba et al, 1992 [91]	United states	Prospective study	24	24	-	-	12.5	61.04 ± 9.25	20, 83%	One patient died of a myocardial infarction with the risk factors of mild hypertension and mild obesity.	Resectable adenocarcinoma of the esophagus	None

Table 1. Characteristics of the Included Studies - *(continued)*

No.	Author, year	Region	Study design	Sample size	No. of participants[a]			Study duration (months)	Age (years)	Male (N, %)	Comorbidity	Cancer type	Prior CMT
					Arm A	Arm B	Arm C						
70	Van Cutsem et al, 2001 [92]	Europe, Australia, New Zealand, Taiwan and Israel	Phase III randomized controlled study	602	301	301	-	N/A	63.60 ± 9.59	343, 56.98%	N/A	Colorectal cancer	Capecitabine 56/301, 5-FU 41/301
71	Van Erning et al, 2016 [93]	The Netherland	Retrospective study	357	164	193	-	N/A	74.53	109, 58.60%	None	Stage III colon cancer	N/A
72	Van Groeningen et al, 1989 [94]	The Netherlands	Prospective study	22	22	-	-	6	59.46 ± 12.57	8, 36.36%	N/A	Advanced colorectal cancer	Prior hepatic intra-arterial 3/22, IV 5-aza-2'-deoxycytidine 1/22, IV cisplatin and hepatic intra-arterial 5-FU 1/22
73	Wang et al, 1998 [95]	Taiwan	Prospective study	41	41	-	-	18.4	59.92 ± 7.62	33, 80.48%	N/A	Advanced colorectal cancer	N/A
74	Weh et al, 1994 [96]	Germany	Prospective study	57	57	-	-	41	56.27 ± 9.38	36, 63.16%	N/A	Metastatic colorectal carcinoma	N/A
75	Wenzel et al, 2002 [97]	Austria	Prospective study	26	26	N/A	-	25	58.9 ± 7.32	19, 73.08%	N/A	Metastatic renal cell carcinoma	N/A
76	Yang et al, 1999 [98]	Taiwan	Prospective study	36	36	-	-	9	57.68 ± 10.64	21, 58.33%	N/A	Colorectal cancer	5-FU/levamisole (4/36), 5-FU/LV (17/36)
77	Yang et al, 2001 [99]	Taiwan	Phase II clinical study	26	26	-	-	N/A	55.48 ± 12.62	18, 69.23%	N/A	Advanced colorectal cancer	None
78	Yang et al, 2002 [100]	Taiwan	Prospective study	51	26	25	-	N/A	59 ± 10.22	29, 56.9%	N/A	Metastatic colorectal cancer	Oral UFT 300 mg/m^2/day plus LV 90 mg/day
79	Ychou et al, 2003 [101]	France	Prospective study	53	53	-	-	38	65.05 ± 9.05	25, 47.17%	N/A	Metastatic colorectal cancer	Prior CMT 16/53, 30.19%
80	Yilmaz et al, 2007 [102]	Turkey	Prospective study	27	27	-	-	24 h	51.60 ± 12.77	15, 55.56%	Diabetes, hypertension	Colorectal cancer, gastric cancer, liver cancer, distal esophagus cancer	N/A

[a]Details of the dosage regimen for each arm are shown in Supplementary Materials 3 and 4 (www.wjon.org). 5-FU: 5-fluorouracil; CMT: chemotherapy; LV: leucovorin; N/A: not applicable; PLD: pegylated liposomal doxorubicin; RT: radiotherapy; UFT: uracil/ftorafur.

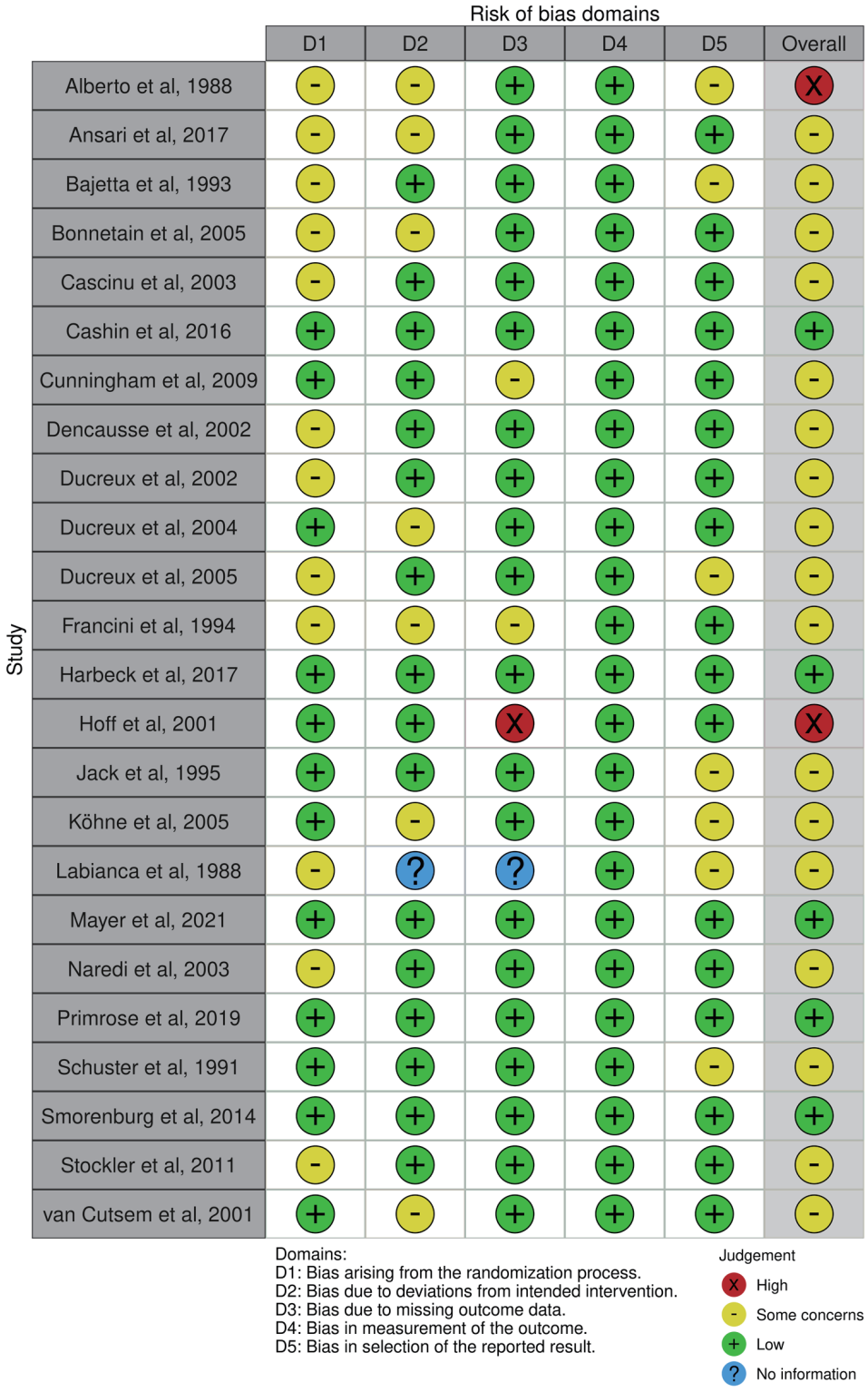

Figure 2. The evaluation of the risk of bias in randomized control trials using the Cochrane Risk-of-Bias tool 2.0 (RoB 2.0).

57] since more than 10% of data were missed and reasons for missing patients were not reported. The remaining had some concerns (N = 17) and a low risk of bias (N = 5) (Fig. 2). All non-randomized studies (N = 56) reported a crude prevalence of cardiotoxicity outcomes, so they were evaluated as having a critical risk of bias (Fig. 3).

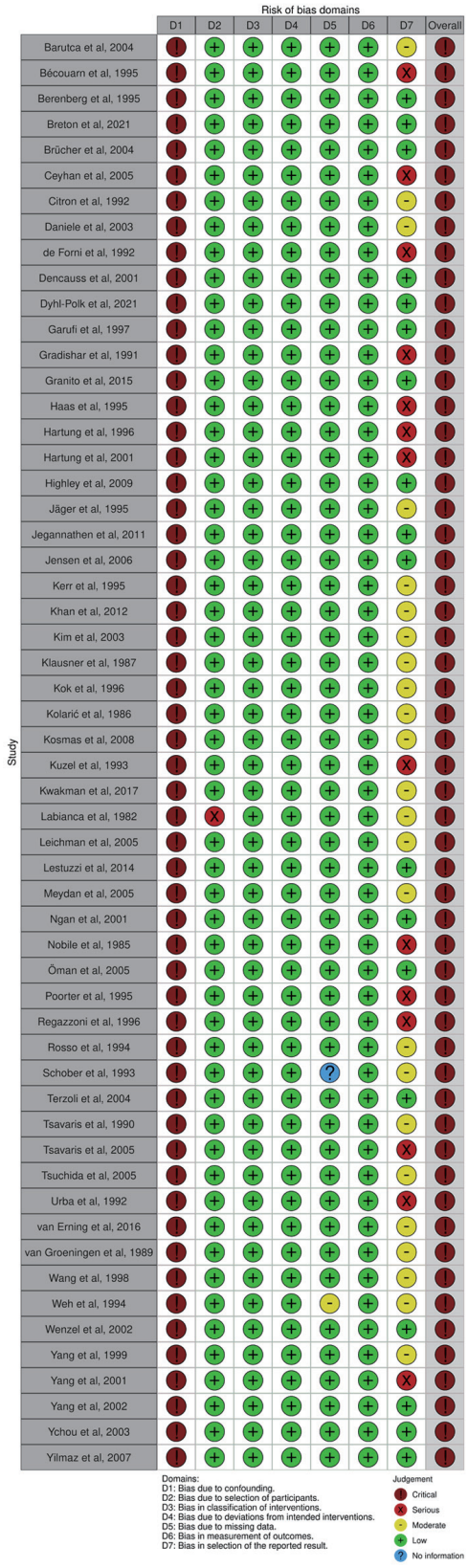

Figure 3. The evaluation of the risk of bias in non-randomized studies using The Risk Of Bias In Non-randomized Studies (ROBINs).

Prevalence of 5-FU and capecitabine cardiotoxicity

Of 80 included studies, 70 reported the prevalence of cardiotoxicity in 5-FU users. The pooled prevalence of cardiotoxicity was 3.5% (95% CI: 2.7 - 4.2; $P < 0.001$; $I^2 = 73.86\%$; Fig. 4). In addition, 14 studies reported the prevalence of cardiotoxicity in capecitabine users. The pooled prevalence of cardiotoxicity was 2.8% (95% CI: 1.6 - 4.0; $P < 0.001$; $I^2 = 72.62\%$; Fig. 5). Cardiotoxicity from 5-FU and capecitabine was classified as common by the Council for International Organizations of Medical Sciences criteria. The funnel plot showed that most included studies were small. The symmetry was not evaluable since the pooled prevalence was close to zero causing the plot to distribute at the positive side of the funnel (Fig. 6).

Meta-regression

Meta-regression revealed that the heterogeneity in the analysis of cardiotoxicity in 5-FU users was not caused by age, cumulative dose, place of study, sex, and year of study (P-value ≥ 0.099 in all analyses). The heterogeneity in the analysis of cardiotoxicity in capecitabine users was caused by place of study (P-value = 0.001) but not age, cumulative dose, sex, and year of study (P-value > 0.1 in all analyses). Details of the meta-regression analysis are shown in Supplementary Materials 5 and 6 (www.wjon.org).

Discussion

The prevalence of any cardiotoxic events in 5-FU users was 3.5% and 2.8% in capecitabine users. Although cardiotoxicity was classified as common, the prevalence was still lower than other common ADRs. For example, the most common ADRs to 5-FU were diarrhea (64%), stomatitis (60%), and nausea/vomiting (51%), while the most common ADRs to capecitabine were hand-foot syndrome (62%), diarrhea (46%), and nausea/vomiting (36%) [103]. The prevalence of cardiotoxicity from 5-FU and capecitabine was lower than drugs well-known for cardiotoxicity such as anthracyclines, cyclophosphamide, and docetaxel which have a prevalence of, approximately 9% [104], 7-28%, and 2.3-8% [105], respectively. While our meta-analysis reported the estimated prevalence of cardiotoxicity from fluoropyrimidine monotherapy regimen as approximately 3%, a systematic review of cardiotoxicity from 5-FU and capecitabine as either monotherapy or combination regimens reports the prevalence as 0-20% and 3-35%, respectively [106].

Cardiotoxicity from fluoropyrimidines may be considered type A since evidence supporting pharmacological mechanisms is available. First, the most recognized mechanism is that fluoropyrimidines induce the release of vasoconstrictive mediators. For example, kinase C causes endothelium-independent vasoconstriction [107], and endothelin-1 is a potent vasoconstrictor that can induce coronary artery disease [108, 109]. Second, fluoropyrimidines induce vascular endothelial dysfunction and impaired oxygen delivery. Animal studies have shown that 5-FU can have direct toxic effects on vascu-

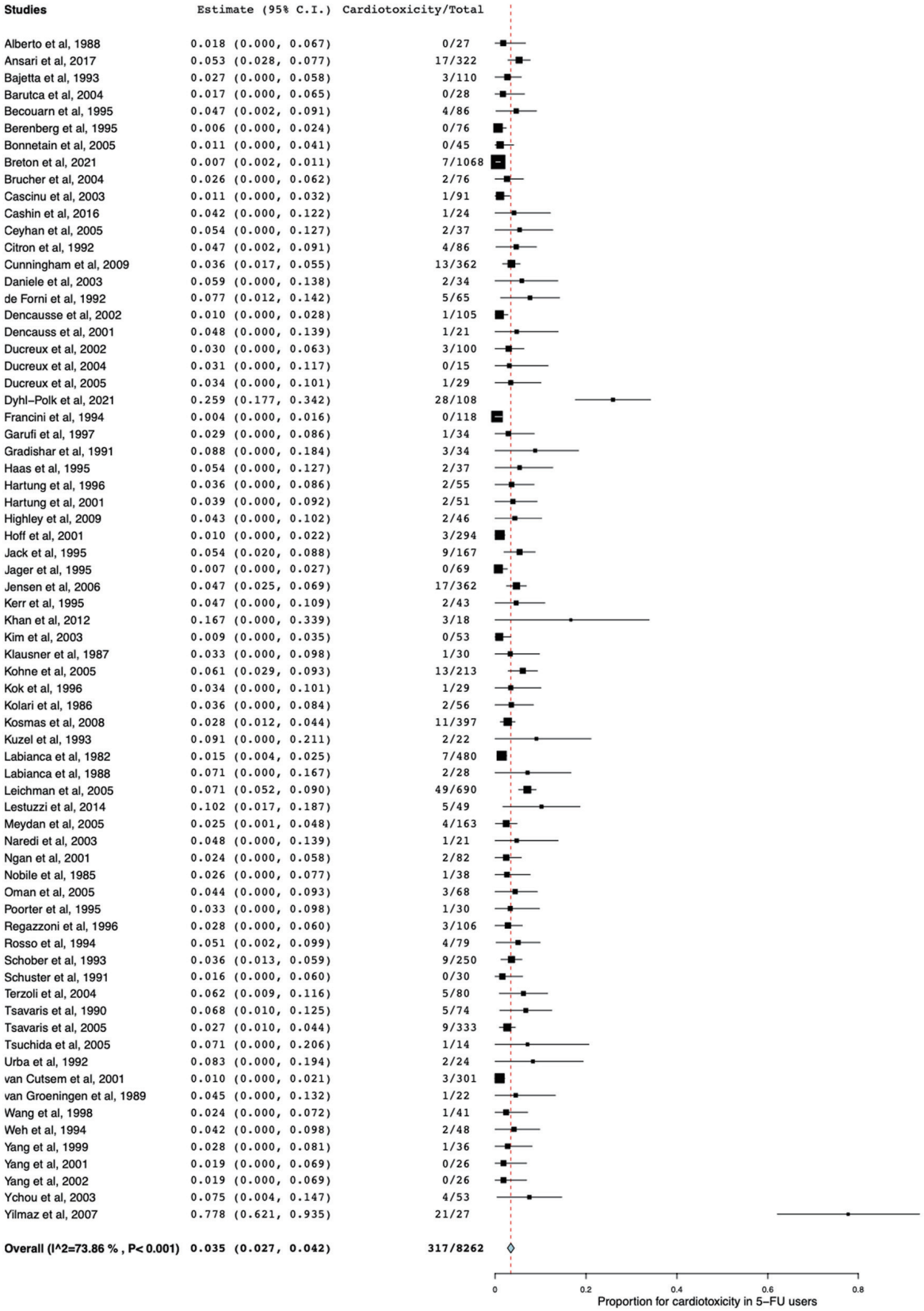

Figure 4. Forest plot of cardiotoxicity in patients receiving 5-FU monotherapy. 5-FU: 5-fluorouracil.

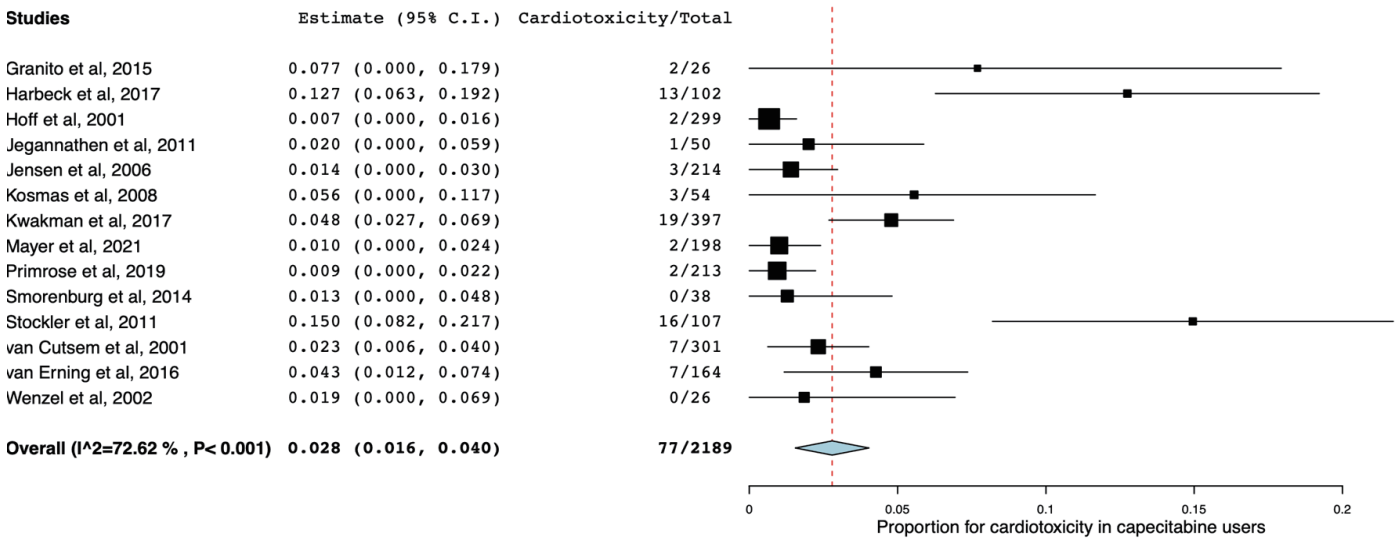

Figure 5. Forest plot of cardiotoxicity in patients receiving capecitabine monotherapy.

lar endothelial cells. This results in direct endothelial damage, fibrin, and platelet accumulation. Additionally, studies have shown that 5-FU can alter erythrocyte membranes, resulting in decreased oxygen transport in the blood and myocardial ischemia [110, 111]. Third, fluoropyrimidines degrade to alpha-fluoro-beta-alanine (FBAL) which causes a direct toxic effect on cardiomyocytes [112, 113]. From these mechanisms, clinical symptoms from the most common cardiotoxicity are angina and the less common are arrhythmias, myocardial infarction, heart failure, acute pulmonary edema, and cardiac arrest [114].

The cardiotoxicity of 5-FU and capecitabine can occur in the first cycle of use, 12 - 48 h after receiving the first dose [115]. The risk factors are not well understood. For example, the effect of pre-existing cardiovascular diseases [8, 25, 26, 116] on cardiotoxicity is inconclusive. Anyhow, there are some limitations in our study. First, our study analyzed the data from fluoropyrimidine monotherapy only. This may not reflect the cardiotoxicity in patients who used combination regimens with fluoropyrimidine and other drugs. Second, the risk of bias in the included studies was high. This is expected since prevalent studies are highly affected by biases in nature. Third, most studies did not report the severity of cardiotoxicity so the

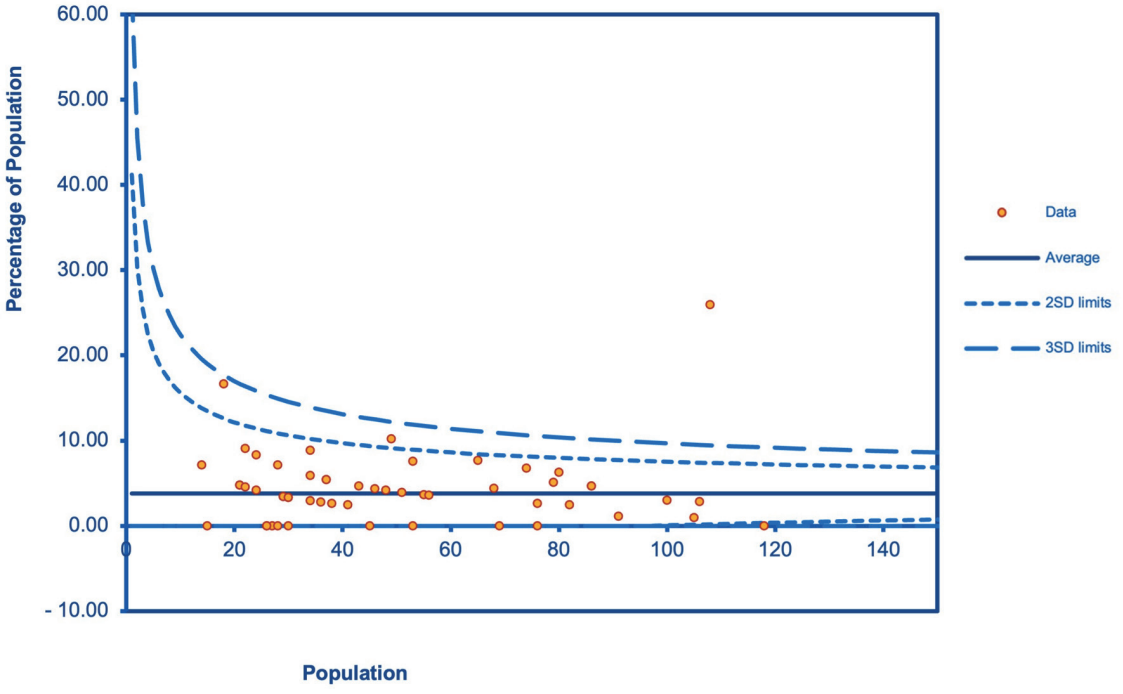

Figure 6. A funnel plot for the publication bias.

authors could not incorporate the severity data in the meta-analysis. Next, we cannot distinguish the cardiotoxicity from bolus versus continuous 5-FU since most studies used both types of administration. Last, we included seven studies [15, 26, 41, 47, 52, 74, 83] whose minor fraction of participants had pre-existing cardiac conditions. These studies did not specify whether the cardiotoxicity occurred in patients with pre-existing cardiac conditions. In addition, the small number of studies discouraged the meta-regression to determine the effect of pre-existing cardiac conditions on the pooled estimate.

This is the first systematic review and meta-analysis that identifies the prevalence of cardiotoxicity in 5-FU and capecitabine monotherapy users. The number of included participants is large so the prevalence can be reported more accurately. There are several applications for this study. First, although cardiotoxicity from fluoropyrimidines may be dose-dependent, this study did not support the association between the cumulative dose of 5-FU or capecitabine and the cardiotoxicity prevalence. The management of cardiotoxicity should be based on how type B reactions are managed including discontinuation. Non-dihydropyridine calcium channel blockers and nitrates should also be provided [114]. Second, cardiotoxicity is common and can include serious events. Therefore, patients should be followed up from the first cycle until the end of treatment. The follow-up should include an electrocardiography (EKG) which allows the detection of subclinical cardiotoxicity. Patients with underlying heart diseases should be closely monitored. Some studies suggest that colorectal cancer patients with dihydropyrimidine dehydrogenase (DPD) deficiency have an increased risk of cardiotoxicity, and therefore pretreatment screening of DPD activity may be considered [117]. Future studies should include studies that evaluate risk factors for cardiotoxicity from 5-FU or capecitabine more accurately.

Conclusion

The prevalence of cardiotoxicity from 5-FU and capecitabine was 3.5% and 2.8%, respectively. We did not find evidence that cardiotoxicity was associated with the cumulative dose of 5-FU or capecitabine.

Supplementary Material

Suppl 1. Search term.

Suppl 2. Additional baseline characteristics of the included studies.

Suppl 3. Details of the dosage regimen and cardiotoxicity outcomes in patients who received 5-FU monotherapy.

Suppl 4. Details of the dosage regimen and cardiotoxicity outcomes in patients who received capecitabine monotherapy.

Suppl 5. Meta-regression for an association between the cardiotoxicity prevalence in 5-FU users and demographic data (age, cumulative dose, place of study, sex, and year of study).

Suppl 6. Meta-regression for an association between the cardiotoxicity prevalence in capecitabine users and demographic data (age, cumulative dose, place of study, sex, and year of study).

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Conflict of Interest

There is nothing to declare.

Informed Consent

Not applicable.

Author Contributions

BS and NL contributed to the research idea and design. BS, PT, AnP, SK, and TT contributed to data collection. BS and NL contributed to the statistical analysis and interpretation of data. BS wrote the first draft of the manuscript. NL and ArP edited the draft of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and approved and reviewed the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

ADRs: adverse drug reactions; 95% CI: 95% confidence interval; CCRT: concurrent chemoradiation; EKG: electrocardiography; FBAL: alpha-fluoro-beta-alanine; 5-FU: 5-fluorouracil; NCCN: National Comprehensive Cancer Network; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoB 2.0: the Cochrane Risk-of-Bias tool 2.0; ROBINs: the Risk Of Bias In Non-randomized Studies; WHO: World Health Organization

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