Treatment-Related Coronary Disorders of Fluoropyrimidine Administration: A Systematic Review and Meta-Analysis

Yajie Lu†, Shizhou Deng†, Qiongyi Dou, Wei Pan, Qingqing Liu, Hongchen Ji, Xiaowen Wang and Hong-Mei Zhang*

Department of Clinical Oncology, Xijing Hospital, Air Force Medical University of PLA, Xi’an, China

Background: Coronary disorders are recognized as the most common manifestation of fluoropyrimidine-related cardiotoxicity in clinical practice. However, there are limited and conflicting data on the incidence and profiles of fluoropyrimidine-related coronary disorders. In this meta-analysis, we aimed to systematically assess the incidence of all-grade and grade 3 or higher fluoropyrimidine-related coronary disorders, and further explore the factors that influence its occurrence.

Methods: Studies reporting the fluoropyrimidine-related coronary disorders were retrieved from a systematic search of English literature in the PubMed, Web of Science, Medline, and Cochrane database from 1 Jan 2001, to 1 Jan 2022. The NIH assessment tool was used to evaluate the quality of each study. The data of basic study characteristics, treatment details, and results of coronary toxicities were extracted. According to the results of the heterogeneity test ($I^2$ and $p$-value statistic), a random-effect model or fixed-effect model was selected for the pooled analysis of the incidence of adverse coronary events. Subgroup analysis was conducted to further explore the risks influencing the occurrence of fluoropyrimidine-related coronary disorders. The stability and publication bias of our results were evaluated by sensitivity analysis and Egger test, respectively.

Results: A total of 63 studies were finally included in our pooled analysis, involving 25,577 patients. The pooled cumulative incidence of all-grade and grade 3 or higher coronary disorders was $2.75\%$ (95% CI $1.89\%$–$3.76\%$) and $1.00\%$ (95% CI $0.62\%$–$1.47\%$), respectively. The coronary disorders were most reported as myocardial ischemia ($1.28\%$, 95% CI $0.42\%$–$2.49\%$) and angina/chest pain ($1.1\%$, 95% CI $0.54\%$–$1.81\%$). Subgroup analysis revealed that studies in the female-only population seemed to have a lower incidence of fluoropyrimidine-related coronary disorders. The occurrence of adverse coronary events varied among different tumor types. Patients with esophageal cancer have the highest coronary toxicity ($6.32\%$), while those with breast cancer have a relatively lower incidence ($0.5\%$). Coronary disorders induced by 5-FU monotherapy are more frequent than that induced by capecitabine ($3.31\%$ vs. $1.21\%$, $p < 0.01$). Fluoropyrimidine combination therapy, whether combined with other chemotherapy drugs, targeted...
therapy drugs, or radiotherapy, significantly increased the incidence of coronary complications ($p < 0.01$).

**Conclusion:** This meta-analysis has defined the incidence of fluoropyrimidine-related coronary disorders and depicted its epidemiological profiles for the first time, which may provide a reference for clinical practice in cancer management.

**Keywords:** coronary disorder, 5-FU, capecitabine, meta-analysis, fluoropyrimidine

## INTRODUCTION

With the continuous development of chemotherapy, radiotherapy, and new treatment technologies, the survival of cancer patients has been greatly improved. Meanwhile, the cardiovascular toxicity related to anti-tumor therapy has become increasingly prominent, which is one of the important causes of death due to treatment-related complications (Curigliano et al., 2016). Cardio-Oncology, an emerging interdisciplinary field, focuses on cardiovascular disease in cancer patients, and has developed rapidly in recent years (Koutsoukis et al., 2018). The incidence and spectrum of cardiotoxicity vary widely by chemotherapeutic regimens. The cardiotoxicity of anthracyclines has been extensively studied and highly concerned over the past 2 decades (Lotrionte et al., 2013; Smith et al., 2010). However, fluoropyrimidine (5-fluorouracil (5-FU), capecitabine, S-1, Tasi02, etc.) induced cardiotoxicity has not been attracted equal attention.

The coronary disorder is one of the typical adverse reactions induced by chemotherapy agents, such as 5-FU and capecitabine, which often refers to the transient contraction of coronary artery and thrombus formation, causing varying degrees of myocardial ischemia, and resulting in the clinical syndrome of angina pectoris, myocardial infarction, even sudden death (More et al., 2021). Chest pain with typical or atypical angina pectoris is the most prominent manifestation of the coronary disorder, which has directly been visualized during coronary angiography (Baldeo et al., 2018; Das et al., 2019; Gao et al., 2019).

Despite some studies that have focused on fluoropyrimidine-induced coronary disorder, most of them were conducted with small samples or just case reports (Karakulak et al., 2016; Ben-Yakov et al., 2017; Sedhom et al., 2017). The reported incidence of fluoropyrimidine-related coronary disorder varies from 0% to 35% (Pai and Nahata, 2000; Sara et al., 2018; Lestuzzi et al., 2020), which is a too wide range to provide valuable reference for clinical practice. In addition, some studies suggested that the occurrence of coronary disorder depended on the different fluoropyrimidine drugs, route of administrations, dosage schedules, and co-administered agents (Depetris et al., 2018; Kanduri et al., 2019). However, there is no consensus on the incidence, profiles, and risk factors of fluoropyrimidine-related coronary disorders. An accurate description of the incidence and epidemiological characteristics of coronary vasospasm is the basis for guiding clinical practice and is very crucial for the early identification and prevention of ischemic events caused by fluoropyrimidines. Obviously, the currently available data are not yet sufficient for drawing definite conclusions. Therefore, in this systematic review and meta-analysis, we are dedicated to comprehensively and systematically evaluating the incidence and epidemiological characteristics of fluoropyrimidine-induced coronary disorders and to further exploring the factors influencing its occurrence using a method of single-rate meta-analysis.

## MATERIALS AND METHODS

### The Definition of Coronary Disorder

The coronary disorder of interest in this study was defined as a group of symptoms represented by chest pain syndrome, including angina pectoris, myocardial ischemia, myocardial infarction, and acute coronary syndrome. The fluoropyrimidine-related coronary disorders were recognized by the new occurrence of a chest pain at rest in the presence of recent fluoropyrimidine administration with or without electrocardiogram (ECG) or biomarker changes.

### Search Strategy and Selection Criteria

Literature search and study selection were conducted under the PRISMA guidelines. Studies reporting the fluoropyrimidine-related coronary disorders were retrieved from a systematic search of English literature in the PubMed, Web of Science, Medline, and Cochrane database from 1 Jan 2001 to 1 Jan 2022. The search strategy was determined after several pre-retrievals and finally combined the following two sorts of items: 1) “fluoropyrimidine” OR “5-FU” OR “capecitabine” OR “S-1” OR “Tas102”; 2) “cardiotoxicity” OR “coronary vasospasm” OR “chest pain” OR “angina” OR “myocardial ischemia” OR “myocardial infarction” OR “acute coronary syndrome.” Studies had to meet the following inclusion criteria: 1) patients with a diagnosis of solid malignances; 2) articles explicitly reported the coronary disorders as defined above, and it is associated with fluorouracil-containing treatment; 3) the sample size was greater than 20; 4) the full-text was available; 5) prospective or retrospective clinical studies. Reviews, letters, comments, case report, meeting abstract were excluded.

### Methodological Quality Assessment and Data Extraction

The quality of included studies was assessed using the quality assessment tool of the National Institutes of Health (NIH) (Nhlbi Study Quality Assessment Tools, 2020, Supplementary Table S1). The reviewers could select “YES,” “NO,” or “Cannot Determine/Not
Applicable/Not Reported” for each item in the list. Based on their responses, the quality of each study was graded as “good,” “fair,” or “poor.” The incidences of fluoropyrimidine-related coronary disorders of all-grade and grade 3 or higher were the main outcomes in this meta-analysis. The data of basic characteristics (first-author, publication year, study design, country or region, age, gender, tumor type, and sample size), treatment details (treatment type, line, regimen, and dosage), and the incidence of fluoropyrimidine-related coronary disorders were extracted and documented. Two authors (Lu and Deng) independently searched the literature, assessed the quality of included studies, and extracted and cross-checked the data.

**Statistical Analysis**

The incidence of fluoropyrimidine-related coronary disorders in each study was shown as a percentage calculated using a division method \( \left( \frac{\text{the sum of coronary disorder}}{\text{the sum of total patients}} \times 100\% \right) \). The Cochran’s chi-squared test reporting I² statistic and p-value was used to test heterogeneity, and if heterogeneity exists (I² > 50% or p < 0.1), a random-effect model was conducted, otherwise, a fixed-effect model was adopted. The pooled incidence was achieved by a single rate meta-analysis method, shown as a proportion and 95 confidence intervals (CI). Subgroup analyses were performed based on study-level characteristics (e.g., publication period, study design, gender, age, tumor, treatment type, regimen, and so on) for all-grade and grade 3 or higher adverse coronary events. Sensitivity analyses were conducted to evaluate the stability of our results. Publication bias was shown by funnel plot symmetry and statistically checked using the Egger test. For all tests, p-values less than 0.05 were considered statistically significant. All the statistical process of this meta-analysis was performed using R software (version 4.0.6, MathSoft, Massachusetts) with “meta,” “rmeta,” and “metafor” packages.

**RESULTS**

**Eligible Studies and Characteristics**

A total of 1818 initial records were identified through a literature search. After title and abstract screening and full-text screening, 63 studies were finally included in this meta-analysis, involving 25,577 patients (Figure 1). The included populations covered more than 30 countries around the world, of which 5 were multi-country collaborations. Forty-seven (74.6%) of the 63 included articles were prospective studies, while the remaining 16 (25.4%) were retrospective in design. The tumor spectrum included colorectal cancer (number of studies: \( n = 25, 39.7% \)), breast cancer (\( n = 11, 17.5% \)), esophagus cancer (\( n = 4, 6.3% \)), gastric cancer (\( n = 3, 4.8% \)), and others (\( n = 9, 14.3\% \)), the remaining 11 (17.5%) studies focused on mixed solid malignancies without distinguishing specific tumor categories. The included 63 studies consisted of 92 treatment arms, and their regimens included 5-FU/capecitabine mono chemotherapy (\( n = 20, 21.7\% \)), 5-FU/capecitabine combined chemotherapy (\( n = 33, 35.9\% \)), 5-FU/capecitabine based chemotherapy plus targeted therapy (\( n = 25, 27.2\% \)), 5-FU/capecitabine based chemotherapy plus radiotherapy (\( n = 6, 6.5\% \)), and the modified fluoropyrimidine agents S1 or TAS 102 (\( n = 2, 2.2\% \)). According to the NIH quality assessment tools, 29 studies (46%) were rated as high quality, 34 (54%) fair
# Table 1: The characteristics of the included 64 studies.

| No | Author          | Year | Country/Region | Sample size | Study design | Age       | Gender (female %) | Tumor type                        | Regimen | Quality | References                           |
|----|-----------------|------|----------------|-------------|--------------|-----------|------------------|-----------------------------------|---------|---------|-------------------------------------|
| 1  | Zafar A         | 2021 | United States  | 4,019       | retro        | 58 ± 13   | 0.425            | Mixed malignancies                | 5-FU or Cap based Cap             | Good    | Zafar et al. (2021)                |
| 2  | Mayer IA        | 2021 | United States  | 198         | pros         | 52 (95–76)| 0.414            | Breast cancer                     | Cap     | Good    | Mayer et al. (2021)                |
| 3  | Chakravarthy AB | 2020 | United States  | 355         | pros         | 54.3 ± 11.7| 0.348            | Rectal cancer                     | mFOLFOX + Bev                       | Fair    | Chakravarthy et al. (2020)        |
| 4  | Dyhl-Polk A (1) | 2020 | Denmark        | 108         | retro        | 66 (35–81)| 0.454            | Colorectal or anal cancer         | Cap     | Fair    | Dyhl-Polk et al. (2020a)          |
| 5  | Delaloge S      | 2020 | Multi-country  | 628         | pros         | 18–70     | 1                | Breast cancer                     | TX      | Good    | Delaloge et al. (2020)            |
| 6  | Grierson P      | 2020 | United States  | 16          | pros         | 66 (42–73)| 0.563            | Pancreatic ductal adenocarcinoma  | Cap + Tosedostat                    | Fair    | Grierson et al. (2020)            |
| 7  | Dyhl-Polk A (2) | 2020 | Denmark        | 2,236       | retro        | 65 (21–85)| 0.447            | Colorectal cancer                 | S-FU based                          | Good    | Dyhl-Polk et al. (2020b)          |
| 8  | Raber I         | 2019 | United States  | 177         | retro        | 54–77     | 0.452            | Mixed malignancies                | S-FU or Cap based                   | Fair    | Raber et al. (2019)               |
| 9  | Jin X           | 2019 | China          | 129         | retro        | >18       | 0.217            | Gastric cancer                    | S-FU or Cap or S-1 based           | Fair    | Jin et al. (2019)                 |
| 10 | Primrose JN     | 2019 | United Kingdom | 213         | pros         | 62 (55–68)| 0.5                | Biliary tract cancer              | Cap     | Good    | Primrose et al. (2019)            |
| 11 | Abdel-Rahman O  | 2019 | Canada         | 3,223       | pros         | 60.7 (11.4)| 0.403            | Colorectal cancer                 | FOLFOX or 5-FU based + Bev or Pan  | Good    | Abdel-Rahman, (2019)              |
| 12 | Hayashi Y       | 2019 | Japan          | 80          | pros         | 66.5 (62–73)| 0.113            | Esophageal cancer                 | 5-FU/cisplatin + RT                | Fair    | Hayashi et al. (2019)             |
| 13 | Peng J          | 2018 | China          | 527         | pros         | 57 (23–87)| 0.339            | Mixed malignancies                | S-FU or Cap based                   | Good    | Peng et al. (2018)                |
| 14 | Chen EY         | 2018 | China          | 47          | pros         | 59.7 (21.14–80.1)| 0.276| Mixed malignancies | Colorectal cancer                 | FOLFOX + Celecoxib                   | Good    | Chen et al. (2018)                |
| 15 | Kwakman JJJM    | 2017 | Netherlands    | 1973        | pros         | NA        | NA               | Colorectal cancer                 | Cap mono or S-FU based ± Bev       | Good    | Kwakman et al. (2017)             |
| 16 | Turan T         | 2017 | Turkey         | 32          | pros         | 57        | 0.303            | Mixed malignancies                | S-FU based                          | Good    | Turan et al. (2017)               |
| 17 | Leicher LW      | 2017 | Netherlands    | 86          | retro        | 69 (45–83)| 0.523            | Colorectal cancer                 | Cap                               | Fair    | Leicher et al. (2017)             |
| 18 | Zhang P         | 2017 | China          | 397         | pros         | 25–70     | 1                | Breast cancer                     | Cap + Udfeline                      | Good    | Zhang et al. (2017)               |
| 19 | Kerr RS         | 2016 | Multi-country  | 1941        | pros         | 65 (58–71)| 0.427            | Colorectal cancer                 | Cap + Bev                          | Good    | Kerr et al. (2016)                |
| 20 | Winther SB      | 2016 | Norway         | 71          | retro        | 67–87     | 0.408            | Colorectal cancer                 | Sox or S-1                         | Fair    | Winther et al. (2016)             |
| 21 | Polk A          | 2016 | Denmark        | 452         | retro        | 63 (28–88)| 1                | Breast cancer                     | Cap + Tra                          | Fair    | Polk et al. (2016)                |
| 22 | Mayer RJ        | 2015 | United States  | 534         | pros         | 63 (27–82)| 0.389            | Colorectal cancer                 | Cap + Tra                          | Fair    | Mayer et al. (2015)               |
| 23 | Lestuzzi C      | 2014 | Germany        | 358         | pros         | 57.5 (23–80)| NA     | Mixed malignancies | Breast cancer                     | 5-FU or 5-FU based                 | Fair    | Lestuzzi et al. (2014)            |
| 24 | Tonyali O       | 2013 | Turkey         | 37          | retro        | 46 (30–75)| 1                | Gastro-esophageal adenocarcinoma  | ECX                               | Good    | Tonyali et al. (2013)             |
| 25 | Okines AFC      | 2013 | United Kingdom | 120         | pros         | 62 (56–67)| 0.321            | Gastro-esophageal adenocarcinoma  | ECX + Bev                         | Good    | Okines et al. (2013)              |

(Continued on following page)
| No | Author     | Year | Country/Region | Sample size | Study design | Age (range) | Gender (female %) | Tumor type | Regimen | Quality | References |
|----|------------|------|----------------|-------------|--------------|-------------|------------------|------------|---------|---------|------------|
| 26 | Khan MA    | 2012 | Pakistani      | 301         | retro        | 47 (18–81) | 0.249            | Mixed malignancies | S-FU or S-FU/ Cap based | Fair | Khan et al. (2012) |
| 27 | Martin M   | 2012 | Multi-country  | 88          | Pros         | 53 (32–82) | 0.988            | Breast cancer     | Cap + Bev + Tra | Fair | Martin et al. (2012) |
| 28 | Petruini L | 2012 | Italy          | 39          | pros         | 67 (41–83) | 0.154            | Hepatocellular carcinoma | S-FU + Sorafenib | Good | Petruini et al. (2012) |
| 29 | Koca D     | 2011 | Turkey         | 52          | pros         | 59          | 0.75             | Mixed malignancies | Cap or Cap based + Lap | Fair | Koca et al. (2011) |
| 30 | Jensen SA  | 2010 | Denmark        | 106         | pros         | 64 (37–81) | 0.556            | Colorectal cancer  | FOLFOX4        | Good | Jensen et al. (2010) |
| 31 | Masi G     | 2010 | Italy          | 57          | pros         | 61 (34–75) | 0.4              | Colorectal cancer  | FOLFOXIRI + Bev | Good | Masi et al. (2010) |
| 32 | Michalaki V| 2010 | Greece         | 29          | pros         | 52 (34–70) | 1                | Breast cancer      | S-FU based + Tra | Fair | Michalaki et al. (2010) |
| 33 | Chua YJ    | 2010 | Australia      | 105         | pros         | 64 (54–70) | 0.46             | Rectal cancer      | XELOX          | Good | Chua et al. (2010) |
| 34 | Baur M     | 2010 | Austria        | 71          | pros         | 62 (39–84) | 0.394            | Rectal cancer      | S-FU based + Cap + Tra | Good | Baur et al. (2010) |
| 35 | Joensuu H  | 2009 | Multi-country  | 231         | pros         | ≤65         | 1                | Breast cancer      | CapIRI + Bev     | Good | Joensuu et al. (2009) |
| 36 | Skof E     | 2009 | Slovenia       | 87          | pros         | 63 (47–75) | 0.366            | Colorectal cancer  | FOLFOX4         | Good | Skof et al. (2009) |
| 37 | Ardavanis A| 2008 | Greece         | 34          | retro        | 69.5 (57–83)| 0.47            | Colorectal cancer  | CapIRI + Bev | Fair | Ardavanis et al. (2008) |
| 38 | Kosmas C   | 2008 | Greece         | 644         | pros         | 66 (56–70) | NA               | Mixed malignancies | S-FU based or Cap based | Good | Kosmas et al. (2008) |
| 39 | Yamamoto D | 2008 | Japan          | 59          | pros         | 55 (42–70) | 1                | Breast cancer      | 5-FU based + Cap + Tra | Good | Yamamoto et al. (2008) |
| 40 | Machiels JP| 2007 | Belgium        | 40          | pros         | 61 (34–78) | 0.33             | Rectal cancer      | Cap + RT         | Fair | Machiels et al. (2007) |
| 41 | Giantonio BJ| 2007 | United States  | 572         | pros         | 62 (21–85) | 0.396            | Colorectal cancer  | FOLFOX4 + Bev | Good | Giantonio et al. (2007) |
|    |            |      |                |             |              | 60.8 (25–84) | 0.392            |                      |                |        |                      |
| 42 | Yilmaz U   | 2007 | Turkey         | 27          | pros         | 54 (19–70) | 0.444            | Gastrointestinal cancer | LV5FU2        | Fair | Yilmaz et al. (2007) |
| 43 | Emmanouilides C | 2007 | Greece         | 53          | pros         | 65 (18–78) | 0.434            | Colorectal cancer  | FOLFOX + Bev | Fair | Emmanouilides et al. (2007) |
| 44 | Geyer CE   | 2006 | United States  | 324         | pros         | 54 (26–80) | 1                | Breast cancer      | Cap + Lap Cape | Good | Geyer et al. (2006) |
| 45 | Mambrini A | 2006 | Italy          | 211         | pros         | 61 (21–79) | NA               | Pancreatic cancer  | FEC            | Good | Mambrini et al. (2006) |
| 46 | Koopman M  | 2006 | Netherland     | 293         | pros         | 64 (27–84) | 0.373            | Colorectal cancer  | CapIRI          | Good | Koopman et al. (2006) |
| 47 | Jensen SA  | 2006 | Denmark        | 668         | retro        | 63 (35–79) | 0.396            | Colorectal or gastric cancers | Cap/Capatin/Docetaxel | Good | Jensen and Sorensen, (2006) |
|    |            |      |                |             |              | NA            | NA               |                      |                |        |                      |
| 48 | Yerushalmi R| 2006  | Israel         | 89          | retro        | 66 (25–82) | 0.418            | Rectal cancer      | Cap + RT         | Fair | Yerushalmi et al. (2006) |
| 49 | Giordano KF| 2006 | United States  | 44          | pros         | 57 (32–77) | 0.114            | Gastric or gastro-esophageal junction adenocarcinoma | TX | Fair | Giordano et al. (2006) |
| 50 | Jatoi A    | 2006 | United States  | 46          | pros         | 61 (32–80) | 0.116            | Esophageal or gastro-esophageal cancer | XELOX | Fair | Jatoi et al. (2006) |

(Continued on following page)
quality, and none was classified as poor (high risk of bias). The detailed characteristics of each included study are shown in Table 1.

**The Incidence of 5-Fluorouracil Associated Coronary Artery Disorders**

Using a random-effect model, the pooled incidence of all-grade fluoropyrimidine-related coronary disorders among 22,939 cases from 59 studies was 2.75% (95% CI 1.89%–3.76%) (Figure 2A). Thirty-three studies reported the incidence of grade 3 or higher fluoropyrimidine-related coronary disorders, involving a total of 14,135 cases. The pooled incidence of grade 3 or higher coronary disorders by meta-analysis was 1.00% (95% CI 0.62%–1.47%) (Figure 2B).

**Specific Reported Events of Coronary Disorders**

Coronary disorders were frequently reported as angina/chest pain, myocardial infarction, myocardial ischemia, and acute coronary syndrome in our included literature. As shown in Figure 3, myocardial ischemia and angina/chest pain were the two most common adverse events, which have a pooled incidence of 1.28% (95% CI 0.42%–2.49%) and 1.1% (95% CI 0.54%–1.81%), respectively. Myocardial infarction and the acute coronary syndrome were less reported, with a pooled incidence of 0.38% (95% CI 0.16%–0.67%) and 0.14% (0.0%–0.56%), respectively. Fourteen studies reported the typical ST-T changes on ECG with or without symptomatic coronary toxicities. A random-effect meta-analysis gave a pooled incidence of ST-T changes of 4.77% (95% CI 3.12%–7.28%), significantly higher than the incidence of adverse coronary events (2.75%).

**Subgroup Analyses**

Subgroup analyses were conducted to compare the incidence of all-grade and grade 3 or higher coronary disorders among different study-level moderators, and further identify the factors influencing the occurrence of adverse coronary events. The pooled incidence and 95% CI of coronary events in each subgroup were shown in Table 2, as well as the results of statistical comparisons between subgroups. A significant difference was identified among different publication periods (p = 0.02) for the incidence of all-grade coronary events, but

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**TABLE 1** (Continued) The characteristics of the included 64 studies.

| No | Author | Year | Country/Region | Sample size | Study design | Age (female %) | Gender (female %) | Tumor type | Regimen | Quality | References |
|----|--------|------|----------------|-------------|--------------|----------------|------------------|------------|---------|---------|------------|
| 51 | Baghi M| 2006 | Germany        | 24          | pros         | 60 (23–79)    | 0.042           | Junction adenocarcinoma | TPF       | Fair    | Baghi et al. (2006) |
| 562| Meydan N| 2005 | Turkey         | 231         | retro        | 59 (23–87)    | 0.402           | Mixed malignancies     | LV5FU2    | Fair    | Meydan, (2005) |
| 53 | Lordick F| 2005 | Germany        | 48          | pros         | 62 (41–75)    | 0.187           | Gastric cancer         | FUFOX     | Fair    | Lordick et al. (2005) |
| 54 | Ng M     | 2005 | United Kingdom | 153         | pros         | 33–81          | 0.412           | Colorectal cancer      | CapeOx    | Good    | Ng et al. (2005) |
| 55 | Felu J   | 2005 | Spain          | 51          | pros         | 76 (71–89)    | 0.392           | Colorectal cancer      | Cap       | Fair    | Felu et al. (2005) |
| 56 | Wacker A | 2003 | Germany        | 102         | pros         | 61.7 (39–78)  | 0.311           | Mixed malignancies     | S-FU or S-FU based | Fair    | Wacker et al. (2003) |
| 57 | Vaishampayan UN | 2002 | United States | 32         | retro        | 67.5 (45–84) | 0.375           | Gastrointestinal cancer | Cap + RT | Fair    | Vaishampayan et al. (2002) |
| 58 | Tsavaris N| 2002 | Greece         | 427         | retro        | NA             | NA              | Mixed malignancies     | 5-Fu based | Fair    | Tsavaris et al. (2002) |
| 59 | Van Cutsem E| 2002 | Switzerland | 1,425      | pros         | NA             | NA              | Colorectal cancer      | LV5FU2    | Fair    | Van Cutsem et al. (2002) |
| 60 | Hartung G | 2001 | Germany        | 51          | pros         | 60 (24–77)    | 0.25            | Colorectal cancer      | Cap       | Fair    | Hartung et al. (2001) |
| 61 | Dencausse Y | 2001 | Germany        | 21          | pros         | 30–80          | 0.333           | Breast cancer          | Cap       | Fair    | Dencausse et al. (2001) |
| 62 | Peiffert D | 2001 | France         | 80          | pros         | ≤75            | 0.837           | Colorectal cancer      | LV5FU2    | Fair    | Peiffert et al. (2001) |
| 63 | Hoff PM  | 2001 | Multi-country  | 605         | pros         | 64 (23–86)    | 0.40            | Colorectal cancer      | Cap       | Good    | Hoff, (2001) |

Notes: a, Mixed malignancies: including two or more tumor types, such as breast cancer, colorectal cancer, gastric cancer, head and neck cancer, and so on; NA: not available; RT: radiotherapy; Cap: Capecitabine; Bev: Bevacizumab; Cet: Cetuximab; Pan: Panitumumab; Tra, Trastuzumab; Lap, Lapatinib.

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not statistically significant for grade 3 or higher events ($p = 0.65$). We did not observe an obvious difference between prospective and retrospective study designs (all-grade: $p = 0.58$, grade 3 or higher: $p = 0.21$), nor between phase II and phase III clinical trials (all-grade: $p = 0.24$, grade 3 or higher: $p = 0.18$). There was also no significant difference between studies with good-quality and fair-quality ($p = 0.43$) for all-grade events, however, the good-quality studies had lower pooled incidence than fair-quality studies for...
| Subgroup                          | All-grade adverse coronary events | Grade 3 or higher adverse coronary events |
|---------------------------------|----------------------------------|----------------------------------------|
| **Publication period**          |                                  |                                        |
| 2001–2005                       | 1,196                            | 1,329                                  |
| 2006–2010                       | 3,190                            | 1,767                                  |
| 2011–2015                       | 1,635                            | 810                                    |
| 2016–2022                       | 16,978                           | 8,804                                  |
| **Study design**                |                                  |                                        |
| Prospective study               | 13,950                           | 11,739                                 |
| Retrospective study             | 9,049                            | 971                                    |
| Phase for clinical trials       |                                  |                                        |
| II                              | 938                              | 711                                    |
| III                             | 7,617                            | 8,576                                  |
| **Study quality**               |                                  |                                        |
| Good                            | 18,385                           | 10,970                                 |
| Fair                            | 4,162                            | 1,740                                  |
| **Age**                         |                                  |                                        |
| No limitation                   | 22,797                           | 12,639                                 |
| Old                             | 202                              | 71                                     |
| **Gender**                      |                                  |                                        |
| All                             | 20,556                           | 11,204                                 |
| Female-only                     | 2,355                            | 1,418                                  |
| **Tumor type**                  |                                  |                                        |
| Esophageal cancer               | 244                              | 290                                    |
| Colorectal cancer               | 12,553                           | 10,403                                 |
| Gastric cancer                  | 177                              | 177                                    |
| Pancreatic cancer               | 227                              | 16                                     |
| Breast cancer                   | 2,443                            | 1,506                                  |
| Bilary tract cancer             | 223                              | 223                                    |
| **Others**                      |                                  |                                        |
| **Treatment type**              |                                  |                                        |
| Adjuvant                        | 3,703                            | 3,366                                  |
| Neoadjuvant                     | 549                              | 380                                    |
| For advanced/metastasis/relapse disease | 925     | 933                                    |
| **Regimen**                     |                                  |                                        |
| 5-FU monotherapy                | 484                              | 1,380                                  |
| Capecitabine monotherapy        | 2,627                            | 3,059                                  |
| 5-FU combined chemotherapy      | 2,993                            | 706                                    |
| Capecitabine combined chemotherapy | 3,956                        | 1,711                                  |
| 5-FU based/targeted therapy     | 336                              | 623                                    |
| Capecitabine based/targeted therapy | 3,177                    | 2,483                                  |
| 5-FU based/radio                | 181                              | 21                                     |
| Capecitabine based/radio        | 75                               | 32                                     |
| S-1                             | 71                               | 71                                     |
| TAS 102                         | 534                              | 534                                    |

Notes: *p < 0.05; a, “others” including liver cancer, gastrointestinal cancer, and head and neck cancer.

the assessment of grade 3 or higher coronary events (*p < 0.01*). Notably, the female-only population (with breast cancer) reported lower pooled incidence than general populations, both in the assessment of all-grade (*p < 0.01*) and grade 3 or higher (*p < 0.01*) coronary disorders.

The pooled incidence of coronary disorders for all-grade or grade 3 or higher varied between tumor types (all-grade: *p < 0.01*, grade 3 or higher: *p < 0.01*). Fluoropyrimidine-related coronary disorders were most frequently in the treatment of esophageal cancer, with the all-grade incidence of 6.32% (95% CI 3.62%–9.71%). Fluoropyrimidines in the treatment of breast cancer, however, occupied the relatively lower coronary complications (all-grade: 0.50%, 95% CI 0.11%–1.16%) than colorectal cancer (all-grade: 2.69%, 95% CI 1.57%–4.09%) and esophageal cancer.
The effect of treatment parameters on the incidence of coronary events was also analyzed. As a result, the administrations of fluoropyrimidine as neoadjuvant chemotherapy, adjuvant chemotherapy, or palliative treatment for advanced/metastasis/relapse disease did not significantly affect the occurrence of coronary events (all-grade: \( p = 0.37 \); grade 3 or higher: \( p = 0.15 \)). However, the treatment regimen is closely related to the occurrence of coronary disorders (all-grade: \( p < 0.01 \); grade 3 or higher: \( p = 0.07 \)). Coronary disorder induced by 5-FU is more frequent than that induced by capecitabine, both for all-grade (3.31% vs. 1.21%) and grade 3 or higher (0.92% vs. 0.75%). The 5-FU or capecitabine combined chemotherapy had a higher incidence of coronary events than 5-FU or capecitabine monotherapy (5-FU: 4.31% vs. 3.31%; capecitabine: 2.69% vs. 1.21%). The addition of targeted therapy drugs (e.g., bevacizumab, cetuximab, and trastuzumab) to capecitabine increased the risk of coronary disorder (all-grade; 2.85% vs. 1.21%; grade 3 or higher: 1.22% vs. 0.75%). Similarly, the addition of radiotherapy resulted in a significant increase in coronary toxicity, both for 5-FU (all-grade: 5.1% vs. 3.3%, grade 3 or higher: 4.76% vs. 0.92%) and capecitabine (all-grade: 2.65% vs. 1.21%, grade 3 or higher: 3.12% vs. 0.75%). Novel fluoropyrimidines, S-1 and Tas 102, demonstrated lower coronary toxicity (S-1: 0; Tas102: 0.56%), however, such data were derived from a limited number of studies.

### Sensitive Analyses and Publication Bias

Sensitivity analyses were performed for the main outcome measures, all-grade and grade 3 or higher incidence of coronary disorders. In the all-grade and grade 3 or higher analyses, the variation of the pooled results after removing studies one by one was 2.64%–2.86% and 0.92%–1.07%, respectively (Figure 4), indicating that the conclusions of this meta-analysis were stable and reliable. The funnel plots and Egger tests did not show existing significant publication bias in the

![FIGURE 4](https://example.com/figure4.png)

**FIGURE 4** | The results of sensitive analysis. (A) the sensitive analysis of the incidence of all-grade coronary disorders indicated a variation between 2.64% and 2.86%; (B) the sensitive analysis of the incidence of grade 3 or higher coronary disorders indicated a variation between 0.92% and 1.07%.
DISCUSSION

Fluoropyrimidine, as a well-known class of pyrimidine antimetabolites, has been used in cancer treatment for more than half a century. Although numerous therapeutic strategies have been introduced in recent years, such as targeted therapy (Bedard et al., 2020), antiangiogenic therapy, and immunotherapy (Hegde and Chen, 2020), fluoropyrimidines are still one of the most effective and frequently used agents in the treatment of colorectal cancer, breast cancer, gastric cancer, and head and neck cancers, whether for neoadjuvant, adjuvant, advanced or maintenance therapy. Cardiotoxicity, especially coronary disorders caused by 5-FU and capecitabine remains a critical issue in cancer therapy that threatens patient survival and leads to the discontinuation of the medication. Unfortunately, there is no solid evidence worldwide about the incidence of fluoropyrimidine-related coronary disorders and the risk factors affecting its occurrence (Deac et al., 2020; Li et al., 2021). In this study, we systematically evaluated the incidence and profile of coronary disorder associated with fluoropyrimidines administration. To our best knowledge, this is the first comprehensive systematic review and meta-analysis on this topic.

The mechanism of fluoropyrimidine-induced cardiotoxicity has not yet been fully elucidated. Although several theories have been proposed, including vasoconstriction, endothelial injury, direct myocardial toxicity, and so on, the most predominant and important clinicopathological change was the disorder of coronary artery (Depetris et al., 2018; Mohammed et al., 2018; Chong and Ghosh, 2019). The coronary disorders defined in this study mainly refers to reversible cardiac ischemia caused by coronary vasospasm, and coronary atherosclerosis due to fluorouracil-induced coagulation problems was also included. There are several reported presentations of fluoropyrimidine-related coronary disorders, including atypical chest pain to typical angina, ACS, myocardial ischemia, and myocardial infarction.

According to our results, myocardial ischemia (1.28%) and angina/chest pain (1.1%) are the most frequently reported. In fact, ischemia and angina/chest pain are not two independent adverse events. Chest pain with or without typical angina is often the primary clinical manifestation of acute cardiac ischemia or ACS, both of which are outcomes of coronary disorders. Thus, in this analysis, we focused on the overall coronary disorders consisting of angina/chest pain, myocardial ischemia and infarction, and ACS, rather than one of them.

Our results generated reliable data on the overall incidence of fluoropyrimidine-related coronary disorder of 2.7%, which revised the previous over-or under-estimation of 0–35%. The incidence of grade 3 or higher fluoropyrimidine reached 1%, accounting for 37% of the overall incidence, indicating that coronary disorder is one of the high-risk complications, which deserves special attention. The pooled results in our study were close to the data reported by Zafar et al. (2021), in which coronary disorders occurred in 2.16% of 4,019 patients treated with 5-FU. It should be noted that 14 of the 63 included studies observed ECG changes during fluoropyrimidine administration, with a pooled incidence of ST-T changes of 4.77%, remarkably exceeding the incidence of adverse coronary events (2.16%). Such inconsistency may be derived from the presence of asymptomatic ischemic ECG changes in some populations (Lounsbery et al., 2017). Therefore, continuous ECG monitoring should be recommended during fluoropyrimidine use, as early ST-T changes often indicate an impending adverse coronary event.

The results of our subgroup analysis showed a lower incidence of the coronary disorder in the female-only population, a phenomenon that has also been observed in other studies (Peng et al., 2018). Delaloge et al. (2020) reported 5 (0.8%) of 628 breast cancer patients treated with capecitabine developed coronary disorders in a phase III clinical trial. A similar low incidence (0.5%, 2/397) was also reported by Zhang et al. (2017) in 2017. Such gender differences may be associated with the protective effect of female hormones on the heart (Kurokawa et al., 2009; Gowd and Thompson, 2012; Costa et al., 2021). However, in this pooled analysis, the female-only population were breast cancer patients with capecitabine administration. We
believed that the characteristics in tumor type and medication should be mainly accounted for the lower coronary toxicity in the female-only population. In addition, a significant difference on the incidence of all-grade adverse coronary events was also observed among different publication periods. This discrepancy could be partly related to the way of drug administration, increased concomitant targeted therapy, and increased attention to cardiotoxicity.

We had observed a significant difference in fluoropyrimidine-related coronary disorders among different tumor types. However, these differences, to a great extent, should be attributed to the variability in treatment regimens among tumors. Capecitabine is an oral prodrug of 5-FU designed to be converted selectively in tumors. It is rapidly absorbed from the gut as an unchanged drug and then converted to the active form of 5-FU by carboxylesterase and thymidine phosphorylase (O’Connell et al., 2014). Therefore, the effect of capecitabine on the coronary is indirect, and our results seem to show that the incidence of capecitabine-caused coronary disorders is significantly lower than that of intravenous 5-FU. However, due to the lack of evidence of direct comparison between 5-FU and capecitabine, such a conclusion needs further confirmation. The coronary toxicity was distinctly varied from formulations or administration protocols of 5-FU or capecitabine. Combination therapy significantly increases coronary toxicity, whether combined with other chemotherapeutics or targeted therapy. The increased incidence of the coronary disorder in combination therapy may result from additive and synergistic toxic effects of different agents on the heart. As we know, anti-angiogenic targeted drugs (e.g., bevacizumab) also had adverse effects on the cardiovascular system (Economopoulou et al., 2015). Therefore, when combination regimens containing these agents were considered, more attention should be paid to the occurrence of coronary adverse events. On the other hand, radiotherapy covering or adjacent to the heart also significantly increases coronary toxicity of fluoropyrimidines. As in our meta-analysis, patients with esophageal cancer who received 5-FU combined with radiotherapy had the highest incidence of coronary disorder at 6.32%. Some studies further showed that radiotherapy increases not only short-term cardiotoxicity, but also long-term cardiotoxicity, such as pericarditis and pericardial effusion (Saunders and Anwar, 2019). Other fluoropyrimidine drugs, such as S-1 and TAS102, have shown a lower incidence of coronary disorders in our study and may be a safer option for patients. However, due to the limited number of cases included in the TAS102 and S1 analyses, more evidence is needed.

Admittedly, there were some limitations in this meta-analysis. First, heterogeneity was observed among the included studies. Although we have performed subgroup analyses and adopted a random-effect model to minimize the effects of the heterogeneity, its influence on the stability of the results cannot be eliminated. Second, it is difficult to clearly define and distinguish “coronary disorder,” although in this study we included various manifestations such as angina, chest pain, myocardial infarction, myocardial ischemia, and ACS. Not all included studies have undertaken a comprehensive and targeted examination to identify these conditions, so the result may be an inevitable underestimation of the incidence. Furthermore, it is difficult to determine whether the referred coronary disorder was related to fluoropyrimidine-containing treatment. Although we only included studies that clearly indicated such a correlation, there is still a possibility that patients with spontaneous coronary disorder could be counted in the original study. Finally, several previous studies have reported the effects of age, race, smoking, history of heart disease, and other factors on fluoropyrimidine-related coronary toxicity. However, limited by the characteristics of the included studies in this meta-analysis, we did not have enough data to further analyze all possible moderators. Owing to the above limitations, the findings of this meta-analysis should be interpreted with carefully, and subsequent large-sample clinical studies are necessary.

CONCLUSION

In conclusion, this meta-analysis, which used a single-rate pooled analysis model, has defined the incidence of coronary disorders induced by fluoropyrimidine-based treatment, and depicted its epidemiological profiles. The occurrence of fluoropyrimidine-related coronary disorders is not a rare condition during fluoropyrimidine administration, which needs to be highly concerned. It varies among tumor types, and different treatment regimens may be associated with different incidence of adverse coronary events. This comprehensive overview of fluoropyrimidine-related coronary disorders can provide a reference for clinical practice in cancer management.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YL: literature retrieval, data extraction, literature quality evaluation, and article writing; SD: literature retrieval, data extraction, literature quality evaluation; QD, WP, and QL: data verification; HJ and XW: statistical analysis; H-MZ: study design and quality supervision.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.885699/full#supplementary-material
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