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REVIEW

The Prognostic and Predictive Value of Dihydropyrimidine Dehydrogenase-Related Indicators in Clinical Outcomes of Chemotherapy in Colorectal Cancer Patients: a Systematic Review and Meta-Analysis

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Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide. Predictive biomarkers are needed to predict patients' outcomes and to select a chemotherapy regimen. We assessed whether dihydropyrimidine dehydrogenase (DPD)-related indicators can predict CRC patients' outcomes. We searched the studies in PubMed, EmBase, and the Cochrane Library up to March 4, 2018. We mainly analyzed different CRC patients' outcomes according to specific DPD-related indicators. Twenty-five articles were included in the meta-analysis. The results showed that for disease-free survival (DFS), low DPD expression was significantly superior to high expression ($I^2 = 72\%$; HR: 1.59; 95%CI: 1.21–2.09; $p = 0.001$). However, this result had a potential publication bias (Begg's test: $p = 0.007$; Egger's test: $p = 0.004$). Among patients treated with chemotherapy, a high thymidylate phosphorylase (TP)/DPD ratio was advantageous for DFS ($I^2 = 63.7\%$; HR: 0.65; 95%CI: 0.46–0.92; $p = 0.015$), and this result did not have a publication bias. For overall survival (OS), low DPD expression was superior to high expression ($I^2 = 74.4\%$; HR: 2.11; 95%CI: 1.48–3.00; $p < 0.001$), although this result had a publication bias (Egger's test: $p = 0.003$; Begg's test: $p = 0.010$). There was no difference in OS according to the TP/DPD ratio ($I^2 = 0\%$; HR: 0.92; 95%CI: 0.75–1.13; $p = 0.420$). DFS and OS were better in CRC patients with low DPD expression than in those with high DPD expression. However, because of publication bias, more DPD indicator-related studies, especially with negative results, are still needed. Patients with a high TP/DPD ratio have better DFS but not OS.

Keywords Dihydropyrimidine dehydrogenase · Thymidylate phosphorylase · Colorectal cancer · Meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of death. Since 2004, oxaliplatin combined with fluorouracil has become the standard adjuvant chemotherapy for stage 3 colon cancer [1]. In addition, disease-free survival (DFS) and overall survival (OS) can be prolonged by adjusting the choice and route of administration of the cytotoxic drug 5-fluorouracil (5-FU) and its derivatives, which are still the main drugs used for CRC treatment [2, 3].

Biomarkers that are associated with cytotoxic drug metabolism as an indicator to reveal drug reactions could also be potential prognostic and predictive indicators in personalized and precision medicine. Dihydropyrimidine dehydrogenase (DPD) is the initial rate-limiting enzyme in endogenous pyrimidine catabolism and is responsible for the reduction of the pyrimidine analog 5-FU [4]. A previous study suggested that low expression of DPD in tumor tissue reduces the decomposition of 5-FU and increases the concentration of 5-FU in tumor cells [5]. However, because of the application of different 5-FU derivatives and different chemotherapy strategies, it

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is still controversial to predict the prognosis of patients based on DPD expression. Additionally, because of differences in DPD expression patterns, the metabolism of 5-FU differs among patients. Expression of DPD is also important in guiding cytotoxic drug applications [6]. Therefore, it is still necessary to study which chemotherapy strategy has the greatest benefit to CRC patients classified specifically according to DPD expression. In this study, a meta-analysis was first used to evaluate whether DPD-related indicators can predict CRC patients' outcomes. In addition, whether different DPD-related indicators could guide chemotherapy strategies and provide evidence for individualized medicine was investigated.

Methods

Search Strategy

We searched relevant studies in PubMed, EmBase, and the Cochrane Library. The publication date of searched studies was in the range of January 1, 1984 to March 4, 2018. The following keywords were used: "colon", "rectum", "colorectal", "bowel", "cancer", "neoplasm", "carcinoma", "tumor", "phyma", "dihydropyrimidine dehydrogenase", "DPYD", and "DPD". The detailed search strategy is presented in Supplementary Table 1. Only English articles were included in our search. We also scrutinized related reviews and meta-analyses to identify additional eligible studies.

Data Extraction and Management

Two authors extracted the details from eligible studies independently, with disagreements resolved by discussion. The studies included in the meta-analysis had to meet all the following inclusion criteria: (1) cancer was confirmed as CRC; (2) the report introduced a definitive chemotherapy regimen or a controlled study of chemotherapy regimens; (3) the study had a before chemotherapy DPD expression indicator-related case-control design; and (4) the study reported DFS and/or OS stratified by DPD expression indicators.

Studies that met any of the exclusion criteria listed below were excluded from our analysis: (1) the study included other types of cancer patients without a separate report on the CRC patients; (2) the study did not report a definitive chemotherapy regimen; (3) the study did not compare the patients according to DPD expression; and (4) the study did not provide indispensable data such as DFS or OS. Reviews, case reports, and basic research articles were also excluded.

The following information was extracted from each of the eligible studies: first author, publication year, country, sample size, age, stage of disease, DPD assessment method, intervention, and the 5-year (or maximum follow-up period) DFS and OS. The quality of each study was also assessed by two authors using two predefined criteria based on the Cochrane Collaboration tool for randomized controlled trial (RCT) design [7] and the Newcastle-Ottawa Scale (NOS) [8]. The quality criteria were determined with the following factors: for the Cochrane tool, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias; and for the NOS, selection (4 items, 4 stars), comparability (1 item, 2 stars), and exposure (3 items, 3 stars). This research first analyzed the different CRC patients' outcomes according to specific DPD-related indicators. In addition, further post hoc research was performed to analyze which chemotherapy regimen was better in specific populations stratified by DPD expression.

Statistical Analysis

We extracted DFS and OS directly from the raw data of the included articles or indirectly from Kaplan-Meier (KM) curves. Pooled hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated for DFS and OS. The heterogeneity between studies was estimated by χ^2-based Q-tests and the I^2 index. P-values<0.10 and/or $I^2 > 50\%$ were considered to indicate heterogeneity between studies. However, the median of the DPD-related indicator is not a defined value, and a random-effects model is considered to be a more natural choice than a fixed-effects model in a medical decision-making context [9]. Therefore, this study prioritized the results of the random-effects model. The subgroup analysis was performed according to whether a study included patients with metastasis and the methods of DPD expression detection. A sensitivity analysis was performed to evaluate the stability of the results by changing the effect models and by subsequently excluding individual studies. The publication bias of the literature was examined by Begg's funnel plot and Egger's linear regression method. If there was publication bias, the results were corrected by a trim-and-fill method [10]. All tests were two-sided, and p-values<0.05 were considered statistically significant. All analyses were conducted using STATA software (version 14.0; STATA Corporation, College Station, TX, USA).

Results

Study Selection and Characteristics

A total of 1069 publications were found after excluding the duplications. After screening the titles and abstracts, 994 of these articles were excluded. The full texts of 75 articles were assessed. Studies were excluded for the following reasons: nondesired outcome (20); not a DPD indicator-related

comparison study (13); review (7); basic research article (5); included other cancer patients (4); and protocol (1). Ultimately, 25 articles were included in the meta-analysis [11–35]; these articles included three chemotherapy comparison studies [14–16] and three post hoc studies of RCTs [11–13] (Fig. 1, Table 1).

The ages of the included patients were 22 to 90, the median/mean ages were 58 to 70, and five studies did not report the patients' ages. In the staging of patients, eight studies involved metastatic CRC patients. All the DPD-related indicators were detected in tumor tissue before chemotherapy. For the cut-off value selection, except for the cut-off values of one study that were calculated by the maximal χ^2 statistic method [20], the median measured DPD expression level or ratio was selected. The treatment regimens included 5-FU-based and 5-FU derivative-based chemotherapies. The five-year (or maximum follow-up period) DFS and OS were 55.1% to 80.9% and 62% to 88.2%, respectively (Table 1).

From the quality assessment, three studies were post hoc studies of RCTs, and three were comparison studies (Supplementary Fig. 1). Eleven studies did not have a uniform chemotherapy regimen in a single group. Five studies included CRC patients with a uniform stage of disease. None of the studies reported raw data of DFS and OS, and the results were

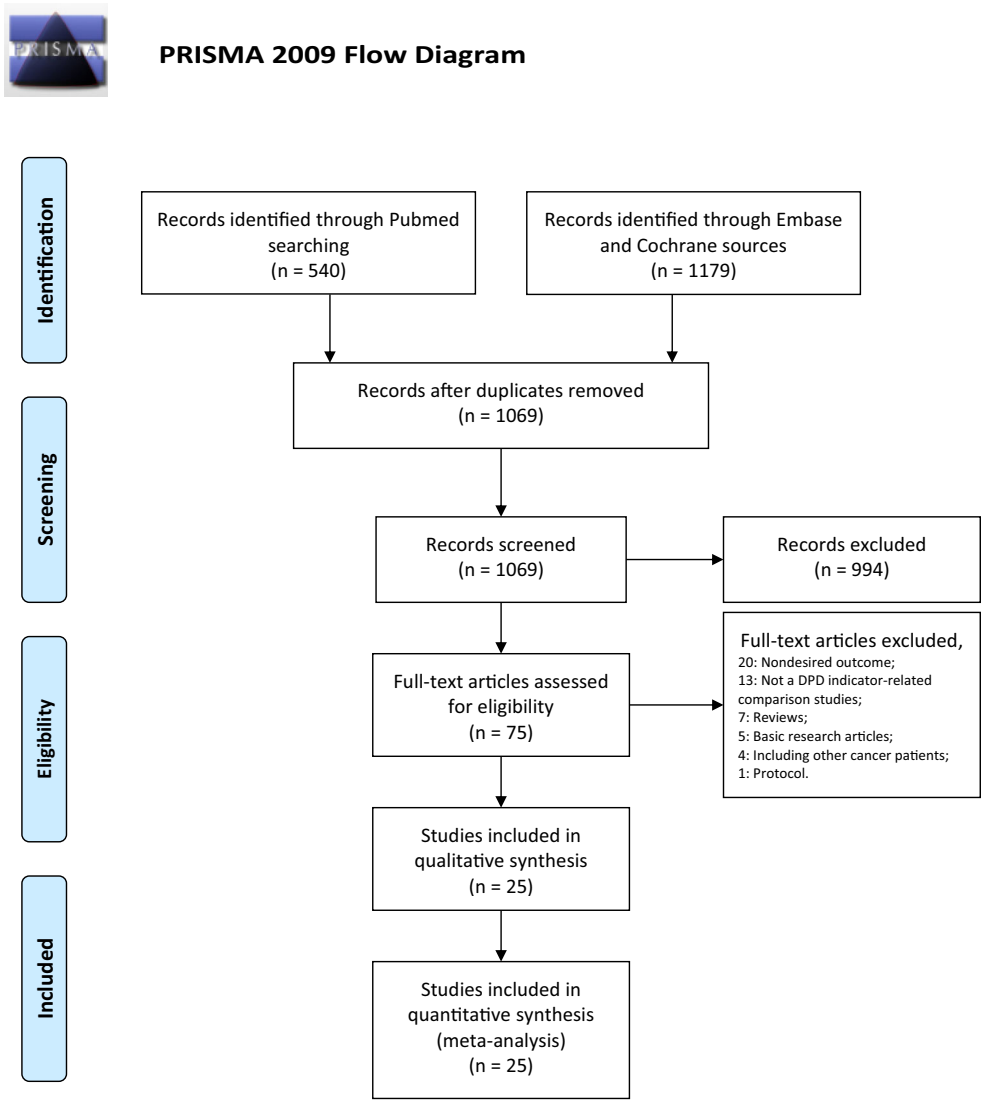

Fig. 1 PRISMA flowchart illustrating the selection of studies included in our analysis

Table 1 Characteristics of the included studies

Author, year	Sample size	Age#	Stage of Disease	Main treatment regimen##	5-year DFS	5-year OS	NOS
Koda et al. 2016 [11]	131	68(27–79)	TNM:III	UFT + LV	66.90%	79.50%	8
				S-1	75.70%	88.20%	
Schmoll et al. 2015 [12]	498	61(22–83)	TNM:III	XELOX	67.00%	77.00%	8
				5-FU + LV	61.00%	74.00%	
Mori et al. 2013 [13]	195	63(26–75)	TNM:III	Doxifluridine	69.39%	NA	8
				UFT	59.79%	NA	
Soong et al. 2008 [14]	788	NA	TNM:II-III	5-FU + LV	NA	NA	7
				No chemotherapy	NA	NA	
Lassman et al. 2006 [15]	92	62(NA)	TNM:I-III	5-FU(+LV;+Levamisol;+Mitomycin C)	55.10%*	NA	6
				No chemotherapy	72.50%*	NA	
Tsuji et al. 2004A [16]	182	64(29–90)	TNM:II-III	UFT	79%	NA	7
				No chemotherapy	72%	NA	
Kataoka et al. 2015 [17]	36	66(27–81)	TNM:II-IV	mFOLFOX6 + XELOX(;+bevacizumab;+cetuximab)	NA	NA	6
Shigeta et al. 2014 [18]	101	62(55–70)	TNM:II-III	LV+(5-FU;UFT)	NA	NA	6
Koumarianou et al. 2014 [19]	126	70(32.5–90)	TNM:I-III	5-FU + LV;FOLFOX;FOLFIRI	67.90%*	76.90%*	6
Ochiai et al. 2014 [20]	68	66(35–75)	Dukes' stage B/C	5-FU + LV	72.05%	86.76%	7
Donada et al. 2011 [21]	55	62.9 ± 9.1	TNM:II-III	5-FU + LV	66%*	71%*	7
Jensen et al. 2009 [22]	340	NA	TNM:II-IV	5-FU + Isovorin	64%*	62%*	7
Gustavsson et al. 2009 [23]	144	65(33–84)	Duke's stage A-D	FOLFIRI;FOLFOX;Capecitabine;5-FU + LV;5-FU + LV + MTX	NA	NA	6
Yamada et al. 2008 [24]	103	66(31–80)	Duke's stage B-C	UFT(;+LV)	NA	NA	6
Tokunaga et al. 2007 [25]	150	66.7 ± 10.3	TNM:II-IV	UFT	NA	66.60%	7
Ochiai et al. 2006 [26]	90	67(30–81)	Duke's stage A-C	5-FU	71.11%	75.56%	7
Hotta et al. 2006 [27]	22	66 ± 10	UICC:II-IV	5-FU + LV	NA	NA	7
Ciaparrone et al. 2006 [28]	62	62.2(21–81)	Duke's stage B-C	5-FU + LV	70.97%	72.58%	7
Westra et al. 2005 [29]	220	58(18–75)	Duke's stage C	5-FU + Levamisol(;+LV)	56.45%	68.95%	7
Tsuji et al. 2004B [30]	89	61(29–74)	TNM:II-III	UFT	80.90%	NA	7
Oi et al. 2004 [31]	64	NA	Duke's stage C	Carmofur;Doxifluridine;UFT	57.80%	NA	7
Kommann et al. 2003 [32]	295	NA	UICC:II-III	5-FU + Levamisol(;+LV;+IFN-α)	74.92%*	NA	6
Ichikawaet al. 2003A [33]	37	62(38–80)	ECOG score > 2	UFT + LV	NA	NA	7
Ichikawaet al. 2003B [34]	37	62(38–80)	ECOG score > 2	UFT + LV	NA	NA	7
Ikeguchiet al. 2002 [35]	189	NA	Duke's stage A-D	5-FU;UFT	72%	NA	6

Abbreviations: *5-FU* 5-fluorouracil, *DPD* dihydropyrimidine dehydrogenase *ECOG* Eastern Cooperative Oncology Group, *ELISA* The enzyme-linked immunosorbent assay, *FOLFIRI* 5-Fluorouracil, leucovorin, and irinotecan *FOLFOX* 5-Fluorouracil, leucovorin, and oxaliplatin, *IHC* Immunohistochemistry, *INF* Interferon, *LV* Leucovorin, *MA* Metabolic activity, *MTX* Methotrexate *NA* Not available, *NOS* Newcastle-Ottawa Scale, *PCR* Polymerase chain reaction, *S-1* Tegafur, gimeracil and oteracil, *TNM* TNM classification of malignant tumors, *UFT* tegafur and uracil, *UICC* Union for International Cancer Control, *XELOX* Capecitabine and Oxaliplatin

#: Mean ± standard deviation; Median (Minimum-Maximum)

*: Maximum follow-up period

reported as HRs or were calculated from KM curves. The minimum population size in the included studies was 22, and the maximum was 788. NOS scores ranged from six to eight. In total, the quality of the studies was acceptable (Table 1).

The DFS results in CRC patients with different DPD expression levels showed that low DPD expression was significantly superior to high expression ($I^2 = 72\%$; HR: 1.59; 95%CI: 1.21–2.09; $p = 0.001$) (Fig. 2). The sensitivity analysis of the results from patients who received chemotherapy showed that ignoring an individual study did not affect the overall results. For the subgroup analysis, in the study population not including patients with metastasis, the low DPD expression group also had a significant advantage in terms of DFS ($I^2 = 70.8\%$; HR: 1.41; 95%CI: 1.04–1.90; $P = 0.027$). In the population including patients with metastasis, low DPD expression was still superior ($I^2 = 64.1\%$; HR: 2.49; 95%CI: 1.30–4.80; $p = 0.006$). With respect to the different methods of DPD expression detection, the results of studies performing PCR showed that the population with low DPD expression had an advantage in terms of DFS ($I^2 = 71.2\%$; HR: 1.41; 95%CI: 1.02–1.95; $p = 0.036$). When DPD expression was detected by IHC, there was no difference in DFS among the different groups ($I^2 = 84.8\%$; HR: 1.64; 95%CI: 0.82–3.28; $p = 0.159$). Only one study assessed DPD by metabolic activity, and there was no difference in DFS among the groups (HR: 2.56; 95%CI: 0.95–6.89; $p = 0.063$). When expression was detected by ELISA, the low DPD expression group had a significant advantage in terms of DFS ($I^2 = 0\%$; HR: 3.34; 95%CI: 1.70–6.56; $p < 0.001$). In addition, it should be noted that the results had publication bias (Begg's test: $p = 0.007$; Egger's test: $p = 0.004$). By the trim-and-fill method, the results changed after supplementing six correct results (HR: 1.20; 95%CI: 0.90–1.60; $p = 0.206$) (Fig. 3a), indicating

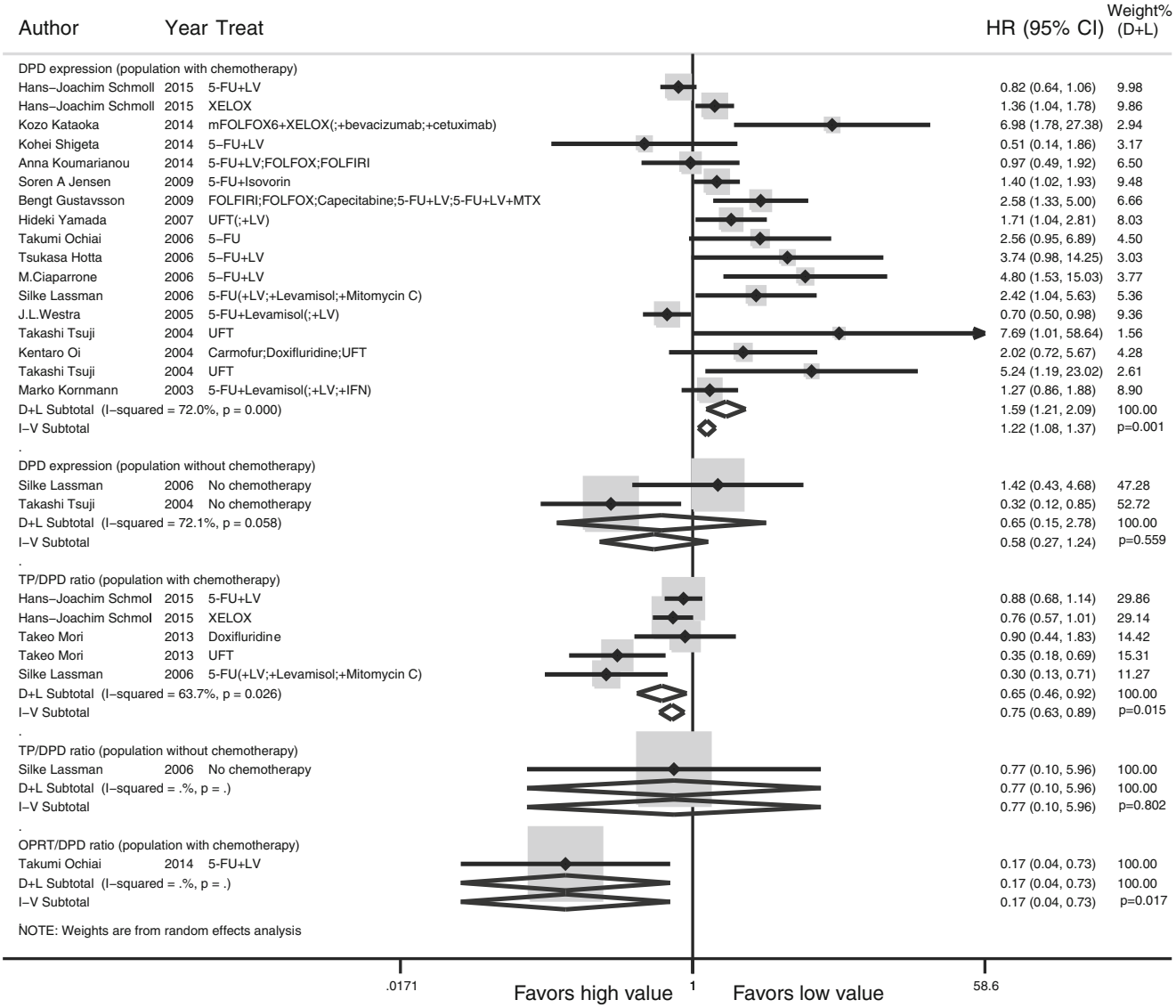

Fig. 2 Forest plot of disease-free survival of colorectal cancer patients stratified according to different DPD expression indicators

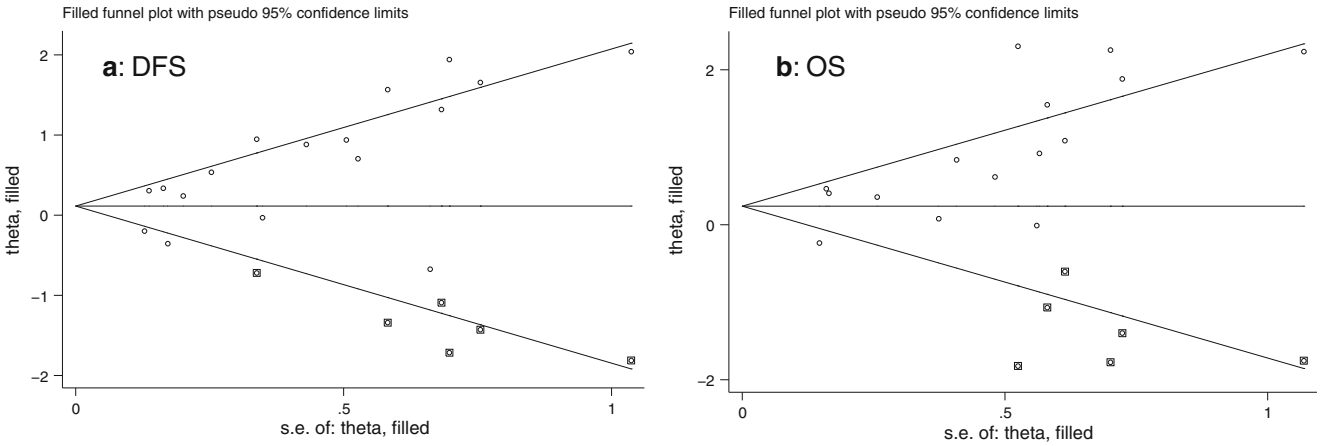

Fig. 3 Funnel plots of disease-free survival (**a**) and overall survival (**b**) between low and high DPD expression groups that were corrected by trim-and-fill methods. The squares represent supplemented results

that publication bias may exist and that some negative results were unpublished, which might have impacted the overall results.

In the population without chemotherapy, there was no significant difference in DFS among patients with different DPD expression levels ($I^2 = 72.1\%$; HR: 0.65; 95%CI: 0.15–2.78; $p = 0.559$). In the population treated with chemotherapy, a high thymidylate phosphorylase (TP)/DPD ratio was advantageous for DFS ($I^2 = 63.7\%$; HR: 0.65; 95%CI: 0.46–0.92; $p = 0.015$), and this result did not have a publication bias (Egger's test: $p = 0.151$; Begg's test: $p = 0.462$). In the population without chemotherapy, the results based on only one study showed no difference in DFS according to the TP/DPD ratio (HR: 0.77; 95%CI: 0.10–5.96; $p = 0.802$). For the orotate phosphoribosyl transferase (OPRT)/DPD ratio, only one study included this measurement, and its results showed that the high OPRT/DPD ratio group had superior DFS (HR: 0.17; 95%CI: 0.04–0.73; $p = 0.017$) (Fig. 2).

For OS, in the population treated with chemotherapy, low DPD expression was superior to high expression ($I^2 = 74.4\%$; HR: 2.11; 95%CI: 1.48–3.00; $p < 0.001$) (Fig. 4). In addition, the sensitivity analysis showed that ignoring individual studies did not change the overall results. In the subgroup analysis, within the population without metastatic CRC, the low DPD expression group had significantly better OS than the high expression group ($I^2 = 65.1\%$; HR: 1.57; 95%CI: 1.10–2.25; $p = 0.014$). In the population that contained metastatic CRC patients, low DPD expression was still superior to high expression in terms of OS ($I^2 = 80.4\%$; HR: 2.11; 95%CI: 1.48–3.00; $p = 0.003$). With respect to the different methods of DPD expression detection, the results from PCR assays showed that low DPD expression was superior to high expression for OS ($I^2 = 81.2\%$; HR: 2.08; 95%CI: 1.22–3.53; $p = 0.007$). For IHC detection, low DPD expression also had an advantage ($I^2 = 60.2\%$; HR: 2.06; 95%CI: 1.21–3.52; $p = 0.008$). Only one study included metabolic activity detection, and it showed no difference in OS according to DPD expression (HR: 2.52; 95%CI: 0.83–7.62; $P = 0.103$). There was also no difference in OS among DPD expression groups via ELISA detection (HR: 2.96; 95%CI: 0.89–9.87; $p = 0.077$). In addition, a publication bias existed (Egger's test: $p = 0.003$; Begg's test: $p = 0.010$). By the trim-and-fill method, the results changed after supplementing six correct results (HR: 1.36; 95%CI: 0.93–1.97; $p = 0.110$). Other stratified analyses showed that low DPD expression was associated with superior OS in the population not receiving chemotherapy ($I^2 = 0\%$; HR: 0.60; 95%CI: 0.45–0.80; $p < 0.001$). There was no difference in OS between groups stratified by the TP/DPD ratio ($I^2 = 0\%$; HR: 0.92; 95%CI: 0.75–1.13; $p = 0.420$) or the OPRT/DPD ratio ($I^2 = 91.0\%$; HR: 0.57; 95%CI: 0.02–20.25; $p = 0.756$) (Fig. 4).

We further investigated which chemotherapy strategy had greatest benefit to CRC patients classified specifically according to DPD expression. One comparison study showed that in the population with lower DPD expression, XELOX was superior to FU/FA for DFS (HR: 0.70; 95%CI: 0.54–0.91; $p = 0.007$), but there was no difference in DFS according to whether or not patients received 5-FU-based chemotherapy ($I^2 = 88.2\%$; HR: 0.42; 95%CI: 0.03–6.10; $p = 0.525$). In the group with higher DPD expression, patients who did not receive chemotherapy had better DFS than patients who did receive chemotherapy ($I^2 = 0\%$; HR: 2.28; 95%CI: 1.19–4.37; $p = 0.013$). Only one comparison study showed that in the population with a lower TP/DPD ratio, doxifluridine treatment led to better DFS than tegafur/uracil (UFT) (HR: 2.06; 95%CI: 1.12–3.79; $p = 0.02$)(Fig. 5). One comparison study showed that in the population with lower DPD expression, XELOX was superior to FU/FA in terms of OS (HR: 0.61; 95%CI: 0.45–0.83; $p = 0.002$) (Fig. 6).

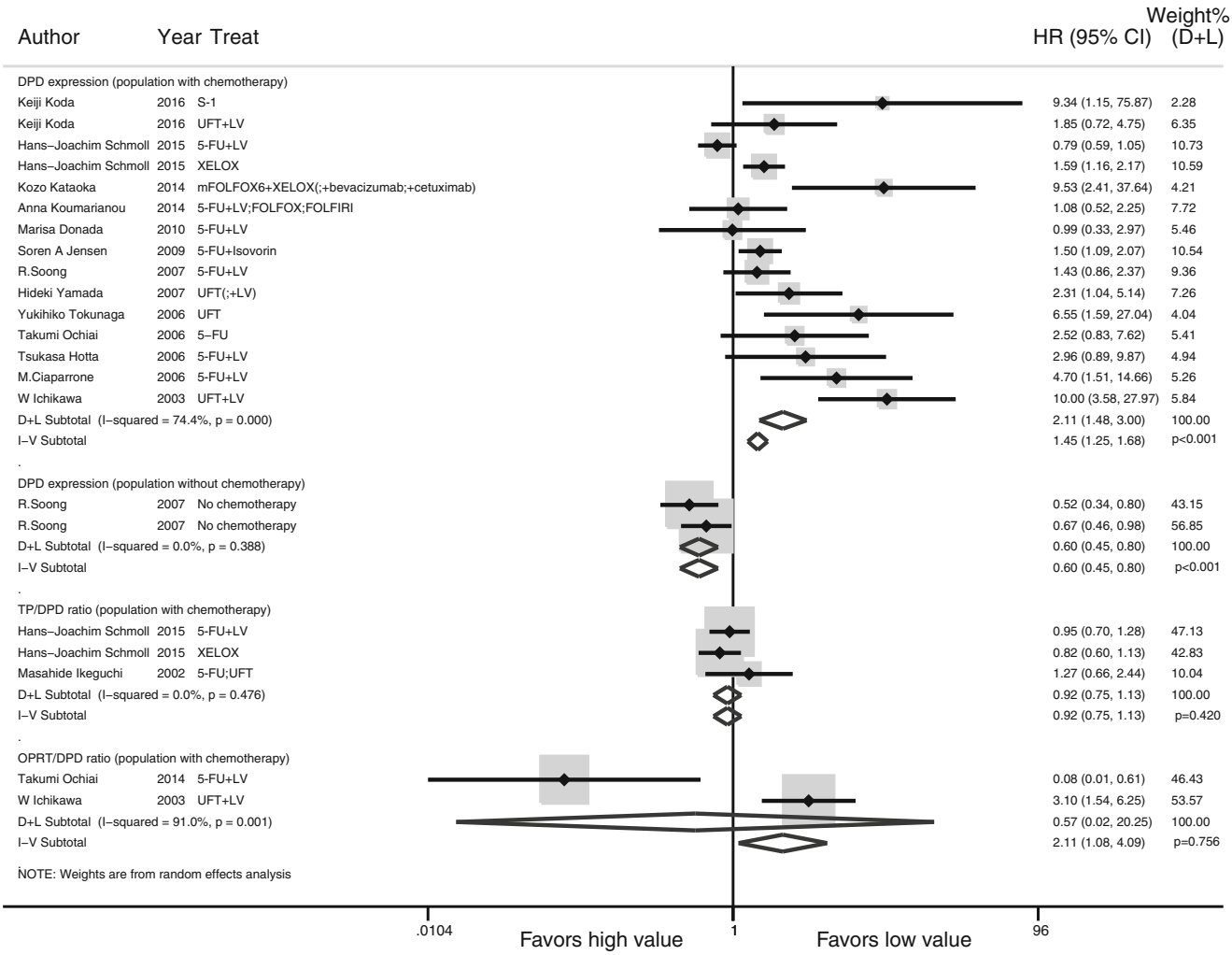

Fig. 4 Forest plot of overall survival of colorectal cancer patients stratified according to different DPD expression indicators

Discussion

In the results of this study, the population with lower DPD expression had better DFS and OS. When the median TP/DPD ratio was set as the cut-off value, the population with a higher TP/DPD ratio had better DFS but not OS. In the analysis, the study heterogeneity was relatively robust; therefore, the random-effects model was mainly adopted. The main source of heterogeneity among studies might be the differences in cut-off values and DPD expression detection methods used.

The post hoc analysis of the population with low DPD expression showed that patients had better DFS and OS with XELOX treatment than with FU/FA treatment. In addition, in the population with high DPD expression, no chemotherapy was superior to chemotherapy. The above result was interesting but nonrobust because it was based on only two studies [15, 16]. However, this result also provided some clues for individualized clinical medicine. In the population with a low TP/DPD ratio, patients had better DFS when treated with doxifluridine than when treated with UFT. Overall, the above results could not be pooled due to the diversity of chemotherapy regimens. Therefore, this post hoc analysis can only be used as a cue for further clinical studies, not as evidence to guide clinical applications.

In this study, DPD expression showed a predictive association with patient prognosis; however, publication bias existed, and some negative results might not have been reported. Therefore, more DPD-related comparison studies, especially studies with negative results, are needed to verify the reliability of the present results. In addition, the median value might not be the optimal cut-off value. The selection of cut-off values by another method, such as the maximal χ^2 statistic method, might increase the significance of DPD-related indicators in predicting patients' outcomes. Therefore, the specific cut-off value of DPD-related indicators should be defined by more comparison studies. This research analyzed populations with low and high DPD expression measured before chemotherapy, and the level of DPD might have been altered by chemotherapy or the time point after treatment. Therefore,

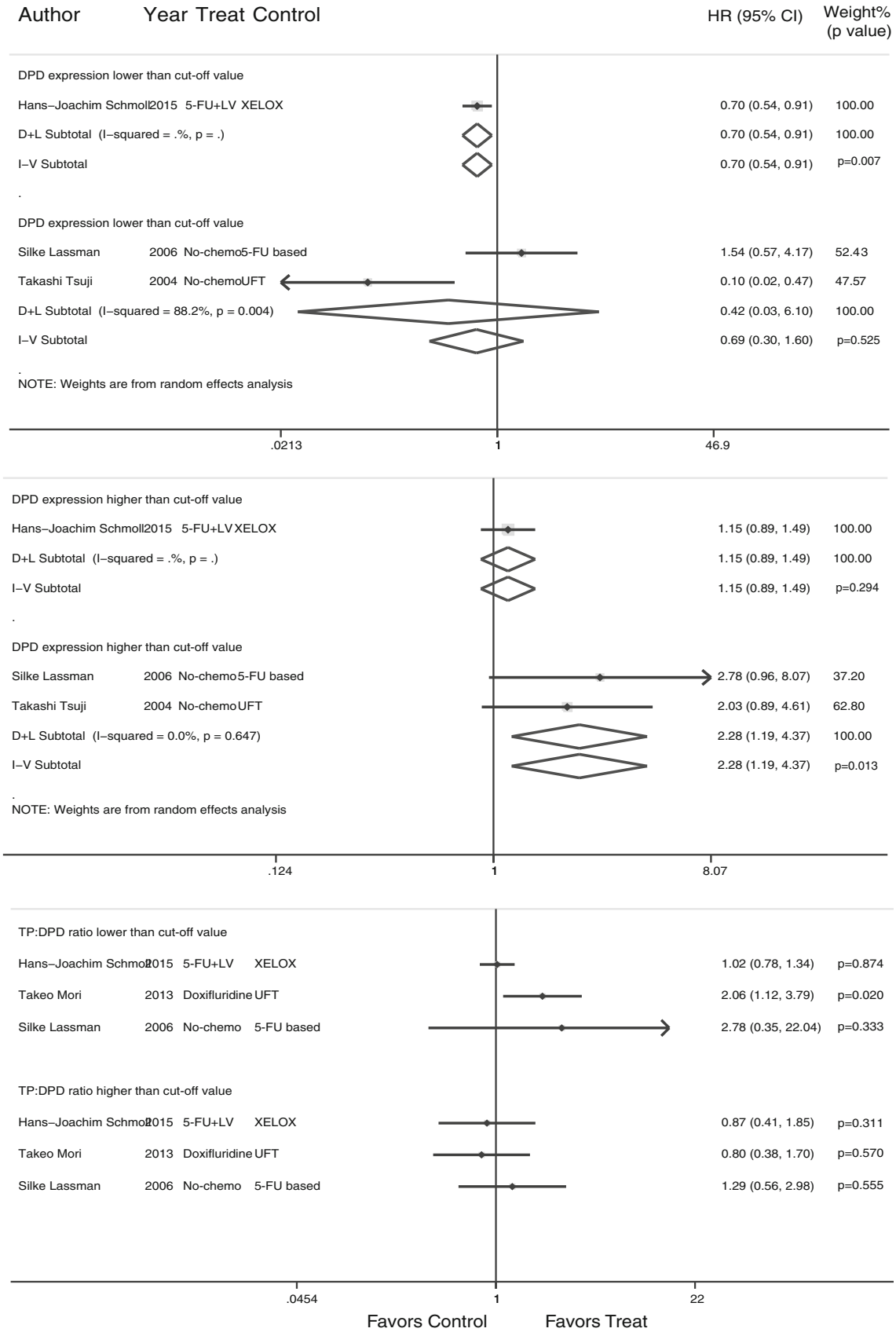

Fig. 5 Forest plots of disease-free survival between treatment regimens among populations stratified by specific DPD indicators

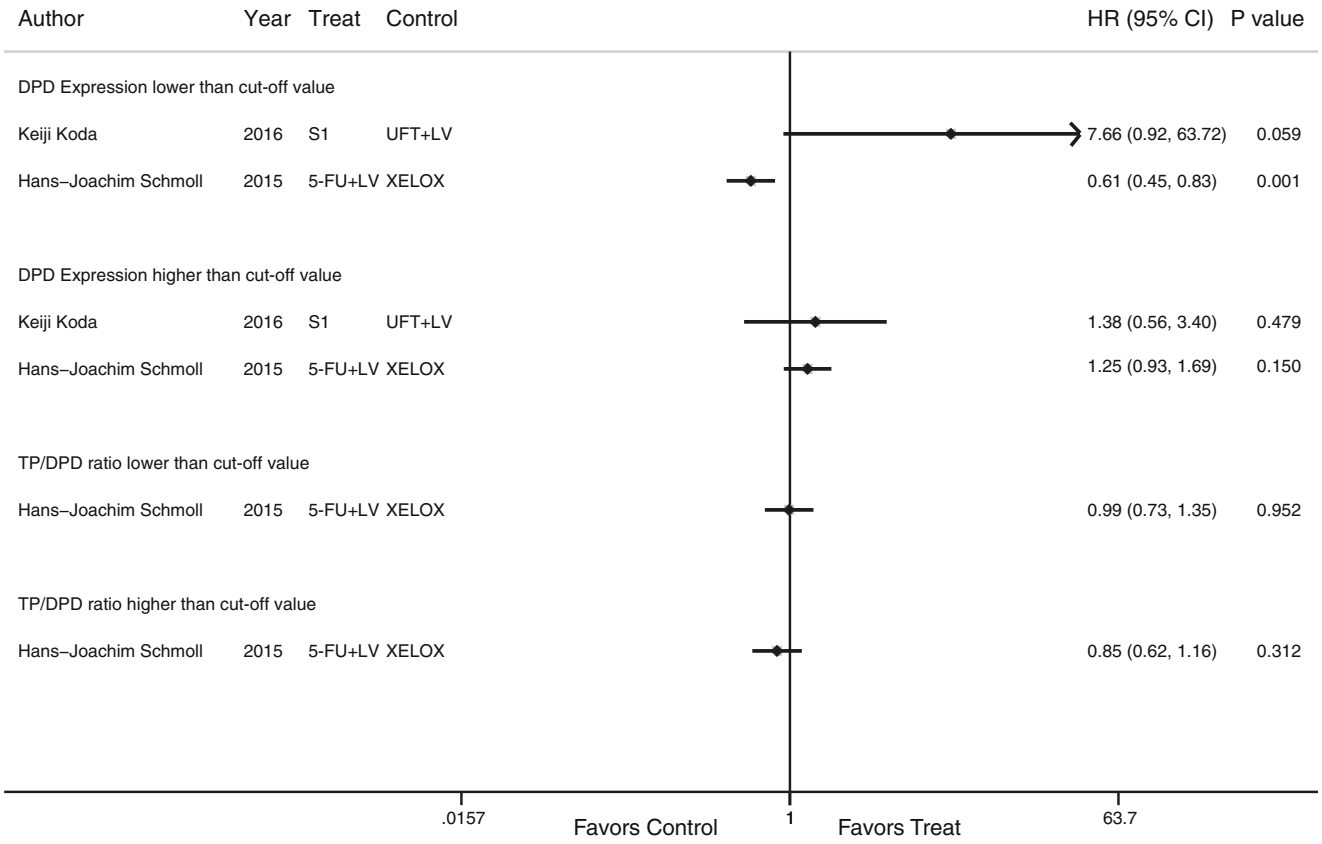

Fig. 6 Forest plots of overall survival between treatment regimens among populations stratified by specific DPD indicators

how to use the change in DPD expression to predict prognosis and choose a chemotherapy regimen remains a challenge.

DPD is the rate-limiting enzyme of 5-FU metabolism, but different chemotherapeutic drugs may affect its predictive value. For example, gimeracil in S-1 can selectively inhibit DPD activity to reduce 5-FU degradation [36]. Therefore, the impact of the chemotherapy strategy needs to be considered when researching the predictive value of DPD for CRC patients' outcomes. The TP/DPD ratio was also a predictive indicator in CRC patients. TP expression at both the protein and mRNA levels was higher in colorectal tumor tissue than in normal tissue. High TP expression is related to increased cancer cell proliferation and angiogenesis [37]. In particular, TP is important in the transformation of capecitabine into 5-FU in tumors [38]. Our results indicated that the TP/DPD ratio can be used as a predictor of DFS in CRC patients who receive chemotherapy. However, these results might confirm that high TP activity enhances the anticancer effect of 5-FU-based treatments [39]. In addition, OPRT is another phosphorylase that is important in the metabolism of 5-FU and in its anticancer activity [11]. A previous study showed that high expression of OPRT is related to high tumor invasiveness and high 5-FU sensitivity [40]. The OPRT/DPD ratio also showed a relationship with the prognosis of CRC patients in this study. However, the results need further confirmation because of the small number of included studies.

Limitations

There are several limitations in this research. First, this study is based on other studies but not an individual study. Second, heterogeneity was generally robust in the analysis; therefore, we prioritized a random-effects model to pool the results. The study heterogeneity may be attributable to differences in DPD expression detection methods and cut-off values. Third, publication bias may have affected the accuracy of the results. Fourth, in the post hoc analysis, advantageous chemotherapy regimens were not confirmed for specific populations stratified by DPD expression. Therefore, the results can only be used as a cue for further clinical studies.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that there is no conflict of interests in this work.

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