Pharmacogenetics of DPYD and treatment-related mortality on fluoropyrimidine chemotherapy for cancer patients: a meta-analysis and trial sequential analysis

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Abstract

Background Fluoropyrimidines are chemotherapy drugs utilized to treat a variety of solid tumors. These drugs predominantly rely on the enzyme dihydropyrimidine dehydrogenase (DPD), which is encoded by the DPYD gene, for their metabolism. Genetic mutations affecting this gene can cause DPYD deficiency, disrupting pyrimidine metabolism and increasing the risk of toxicity in cancer patients treated with 5-fluorouracil. The severity and type of toxic reactions are influenced by genetic and demographic factors and, in certain instances, can result in patient mortality. Among the more than 50 identified variants of DPYD, only a subset has clinical significance, leading to the production of enzymes that are either non-functional or impaired. The study aims to examine treatment-related mortality in cancer patients undergoing fluoropyrimidine chemotherapy, comparing those with and without DPD deficiency.

Methods The meta-analysis selected and evaluated 9685 studies from Pubmed, Cochrane, Embase and Web of Science databases. Only studies examining the main DPYD variants (DPYD*2A, DPYD p.D949V, DPYD*13 and DPYD HapB3) were included. Statistical Analysis was performed using R, version 4.2.3. Data were examined using the Mantel-Haenszel method and 95% CIs. Heterogeneity was assessed with I2 statistics.

Results There were 36 prospective and retrospective studies included, accounting for 16,005 patients. Most studies assessed colorectal cancer, representing 86.49% of patients. Other gastrointestinal cancers were evaluated by 11 studies, breast cancer by nine studies and head and neck cancers by five studies. Four DPYD variants were identified as predictors of severe fluoropyrimidines toxicity in literature review: DPYD*2A (rs3918290), DPYD p.D949V (rs67376798), DPYD*13 (rs55886062) and DPYD Hap23 (rs56038477). All 36 studies assessed the DPYD*2A variant, while 20 assessed DPYD p.D949V, 7 assessed DPYD*13, and 9 assessed DPYDHap23. Among the 587 patients who tested positive for at least one DPYD variant, 13 died from fluoropyrimidine toxicity. Conversely, in the non-carrier

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group there were 14 treatment-related deaths. Carriers of DPYD variants was found to be significantly correlated with treatment-related mortality (OR = 34.86, 95% CI 13.96–87.05; $p < 0.05$).

Conclusions This study improves our comprehension of how the DPYD gene impacts cancer patients receiving fluoropyrimidine chemotherapy. Identifying mutations associated with dihydropyrimidine dehydrogenase deficiency may help predict the likelihood of serious side effects and fatalities. This knowledge can be applied to adjust medication doses before starting treatment, thus reducing the occurrence of these critical outcomes.

Graphical abstract
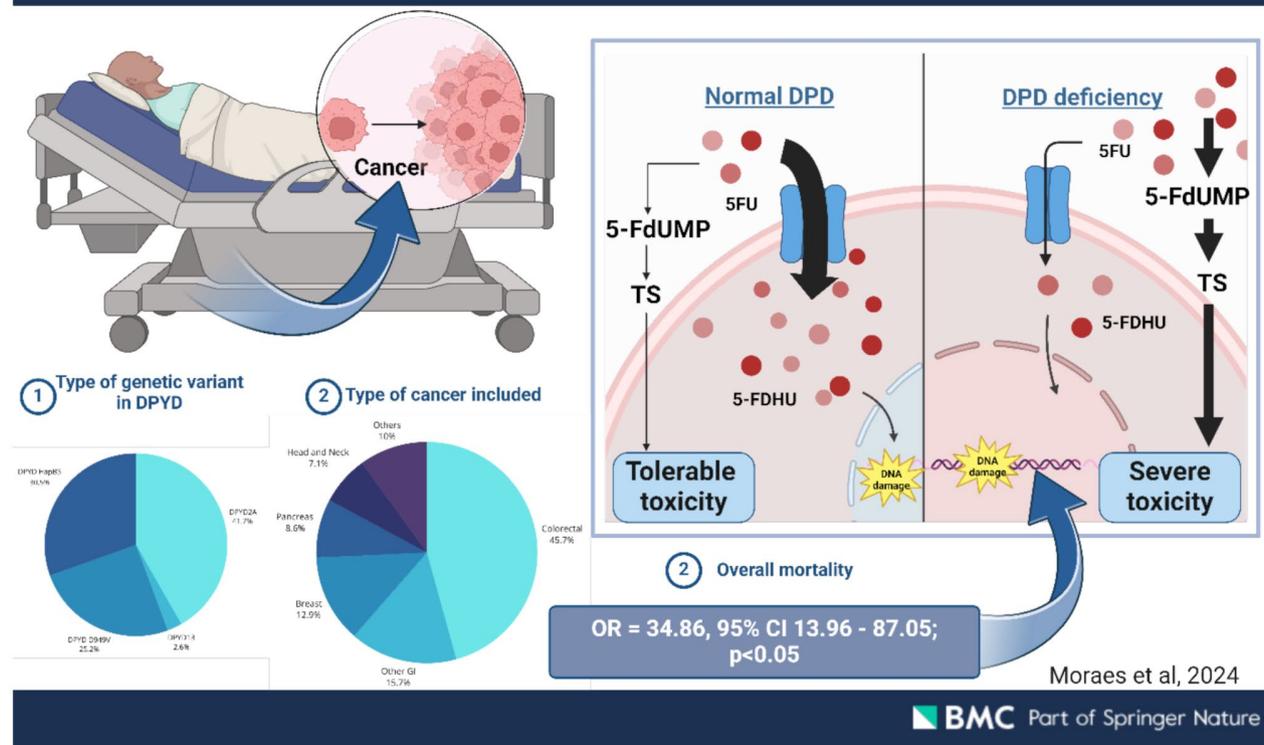
Introduction

Fluoropyrimidines are antimetabolic agents that form the basis of cytotoxic chemotherapy for various malignancies [1, 2]. This class comprises 5-fluorouracil (5-FU) and its oral prodrug capecitabine, which are mainly used to treat gastrointestinal, breast, and head and neck tumors, either as monotherapy or in combination [3, 4]. 5-FU is metabolized by dihydropyrimidine dehydrogenase enzyme (DPD) into dihydrofluorouracil (DHFU), which is an inactive metabolite of this drug [5]. Approximately 80% of the 5-FU administered is catabolized by DPD, which is highly expressed in the liver [6, 7]. Interindividual variability in DPD enzyme activity is well established in the literature [8, 9]. Approximately 3–5% of the general population have partially reduced DPD activity, whereas 0.2% have complete DPD deficiency [10, 11]. Patients with reduced enzyme activity often exhibit severe toxicity to cancer treatment with 5-FU-based cytotoxic chemotherapy [12].

Although changes in the administration and dosages of fluoropyrimidine have had an impact on reducing treatment-related toxicities in recent years, approximately 20% of patients receiving fluoropyrimidine monotherapy will experience serious effects (grade 3 or more) during treatment [13, 14]. Grade 3 toxicities are more common among patients receiving fluoropyrimidine in combination, affecting up to 56% of these patients [15, 16]. Deaths related to the administration of this drug (grade 5 toxic events) are rare events during treatment, accounting for approximately 1% of all cases [17]. However, uncommon

genetic variants in DPYD, which responsible for making the DPD enzyme through the process of transcription and translation. Previous studies identified in molecular analysis 128 polymorphisms in the DPYD that cause partial loss or total of activity of DPD [18], variants in DPYD represent factors recognized as a cause of severe or fatal fluoropyrimidine toxicity [17, 19, 20].

The DPYD gene is on chromosome 1p22, which is 843.32 kb long and has 23 exons, which are responsible for encoding DPD [21, 22]. Germline variants in DPYD are the main cause of DPD deficiency, and pathogenic variants are associated with an 8-fold increase in the risk of developing severe toxicities [23]. Four DPYD alleles are widely described as being highly associated with severe toxicities to fluoropyrimidine treatment, including rs75017182, rs55886062, rs3918290, and rs67376798 [24, 25]. The frequency of approximately 8% of these four alleles in European or North American populations has been previously described [26].

Although there has been extensive research into the risk of toxicity to fluoropyrimidine in cancer patients carrying genetic variants of DPYD, due to their rarity. A meta-analysis published in 2021 identified a significant association between allele status and treatment-related lethality, and provided estimates of lethality in carriers [27]. However, since then, numerous new studies have emerged, underscoring the need for an updated meta-analysis. Additionally, the previous meta-analysis did not address potential connections between ethnicity and DPD deficiency, an area that requires further exploration.

Therefore, we conducted a systematic review and meta-analysis to clarify the risk of death associated with the administration of a standard dose of fluoropyrimidine to patients with cancer.

Methods

Protocol and registration
This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered with the Prospective International Registry of Systematic Reviews (PROSPERO) under registration number CRD42024564336.

Eligibility criteria
Studies were eligible if they met the following criteria: (1) the population consisted of solid tumor (non-hematologic) cancer patients receiving standard dose of fluoropyrimidine chemotherapy; (2) at least one patient had one of the specified DPYD variants; (3) outcomes included analysis of the risk of treatment-related mortality.

Exclusions included studies with overlapping populations, qualitative or economic reviews, opinion pieces,

technical reports, guidelines, animal studies, in vitro experiments, studies lacking results, and studies not in English. Studies in which patients started treatment with reduced doses of fluoropyrimidine chemotherapy were also excluded.

Search strategy and data extraction
We systematically searched for published studies across PubMed, Cochrane Central, Embase, and Web of Science up to June 18, 2024. The search was restricted to English language papers and abstracts and conducted by two authors. Medical Subject Headings (MeSH) terms and specific syntax rules were used with Boolean connectors (OR, AND). Supplementary Table 5 provides a description of the terms used in search.

Our aim was to investigate treatment-related mortality in patients undergoing fluoropyrimidine chemotherapy, comparing those with and without DPYD deficiency. To achieve this, we identified key DPYD variants known to impact DPYD deficiency, as depicted in Supplementary Table 6.

Studies identified from databases and references were imported into Zotero (version 6.0.36) for deduplication and subsequently managed using Rayyan. Duplicate records were removed through automated and manual screening. Two authors independently assessed titles and abstracts of identified articles and extracted data based on predefined search criteria and quality assessment protocols. Any disagreements between reviewers were resolved through consensus.

Endpoints
The primary outcome of interest for a pooled analysis was the overall mortality on DPYD variants carriers attributed to fluoropyrimidines chemotherapy toxicity.

Risk of bias assessment
The quality assessment of individual observational studies utilized the Newcastle-Ottawa Scale, specifically tailored for non-randomized studies [28]. Two reviewers (A.B. and V.K.T.S) independently conducted the evaluation, resolving any discrepancies through consensus. Each study was evaluated across three main domains: selection of exposed cohorts, comparability of key factors, and assessment of outcomes including follow-up duration and adequacy. To explore potential publication bias, contour-enhanced funnel plots were visually inspected and assessed using Egger's regression asymmetry and Begg's rank correlation tests [29, 30].

Statistical analysis
Pertinent baseline characteristics of the sample were pooled to test the probability of their effects on outcome. Logit transformation was performed on the reported

events to compute the binary outcome of interest with a 95% confidence interval (CI) using the Mantel-Haenszel method. Heterogeneity was assessed with I^2 and Tau^2. We used DerSimonian and Laird random-effect models for the primary endpoint [31]. Statistical Analysis was performed using R software, version 4.2.3.

Results

Study selection and baseline characteristics

As described in PRISMA flow diagram (Fig. 1), a total of 9,685 studies were assessed in our systematic search. After the removal of duplicates and the screening of titles or abstracts, 93 manuscripts were eligible to be thoroughly reviewed for inclusion and exclusion criteria. Finally, 36 studies, encompassing a population of 16,005 patients, formed the scope of the analysis [32–67]. References for the excluded studies can be found in supplementary material Table 3.

The studies were divided into clinical trials and observational studies (prospectives and retrospectives), accounting for nine, 16 and 11 studies respectively. The baseline characteristics of included studies are summarized in Table 1.

The distribution by sex showed that 47% of the patients were male, 36% were female and 17% the sex was not identified, as shown in supplementary Table 4. Most studies studied groups of patients with different cancer sites,

but the majority of population consisted of colorectal cancer (86.49% of the studies and 78.67% of the population), followed by other gastrointestinal cancers (29.73% of the studies and 3.09% of the population), breast cancer (24.32% of the studies and 2.55% of the population), pancreas cancer (16.22% of the studies and 1.76% of the population), head and neck cancer (13.51% of the studies and 0.35% of the population), and other types of cancer (18.92% of the studies and 0.32% of the population).

In the meta-analysis, the genetic variants of interest were identified in 587 patients, which represents 3.62% of the total population of 16,005 patients studied. Specifically, DPYD2A (rs3918290) was found in 174 patients, DPYD13 (rs55886062) in 11 patients, DPYD D949V (rs67376798) in 105 patients, and DPYD HapB3 (rs75017182) in 127 patients. The remaining patients were classified as non-carrier for these variants.

Geographically, the majority of studies in this meta-analysis were conducted in Europe (78.38%), with smaller proportions in Asia (18.92%), Americas (2.7%), and Oceania (2.7%). This European predominance posed challenges in understanding the relationship between DPYD gene variants and ethnicity, as well as their clinical implications. In the Asian population, the rs3918290 variant appeared to be five times more prevalent (4,89%) compared to the European population (0.93%). Conversely, the rs75017182 variant was more prevalent among Europeans (0.82%) than Asians (0.17%). The other variants were not identified in Asian studies, as shown in supplementary Table 5.

Overall mortality

Twenty-seven deaths attributable to fluoropyrimidine toxicity were identified across all 36 studies. Thirteen of these deaths occurred in carriers of DPYD variants of interest (Table 2), while fourteen occurred in individuals non-carrier for these variants. This represents a 36-fold higher likelihood of death among DPYD variant carriers undergoing fluoropyrimidine chemotherapy compared to the general population.

The most prevalent variant identified in these fatalities was rs3918290, with seven patients being heterozygous. Two of these patients also carried the rs67376798 and rs55886062 alleles. The second most common variant was rs55886062, observed in three heterozygous patients including one previously mentioned. The only patient with the rs75017182 variant was homozygous. Only one patient was provenient from an American study, being all others from europeans studies. Five of these patients used capecitabine, while all the other eight patients received combined fluoropyrimidine chemotherapy.

Statistics showed the carriers of DPYD variants was found to be significantly correlated with treatment-related mortality (OR=34.86, 95% CI 13.96−87.05;
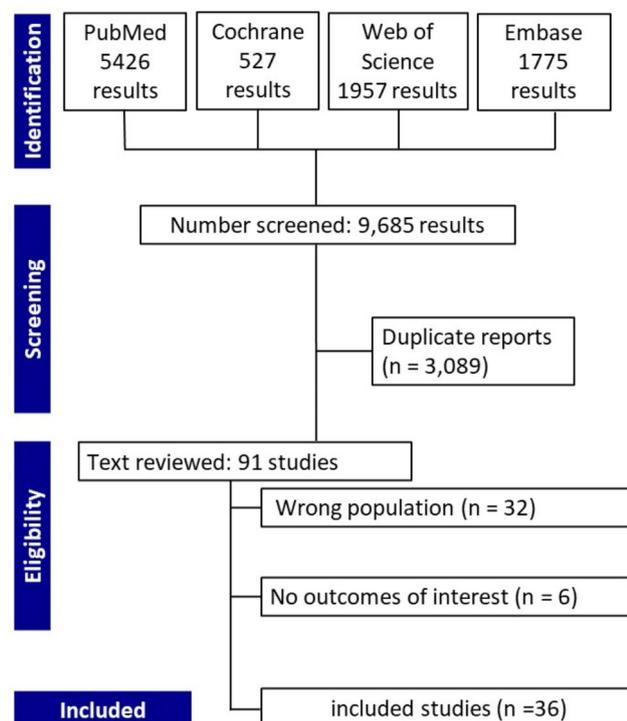

Fig. 1 PRISMA diagrams of included studies

Table 1 Summary characteristics of included studies. PS = prospective observational studies; RS = retrospective observational studies

Study	Study design	Study Origin	N	Variants	Total of DPYD variants carriers	Cancer types	NOS Score
Boisdron-Celle 2017 [36]	PS	Europe	1142	c.1905 + 1G > A; c.1679T > G; c.2846 A > T.	11	colorectal	9
Deenen 2011 [42]	RCT	Europe	568	c.1905 + 1G > A; c.1679T > G; c.2846 A > T; c.1129–5923 C > G	44	colorectal	8
Etienne-Grimaldi 2017 [45]	PS	Europe	243	c.1905 + 1G > A	11	breast	8
Froehlich 2015 [47]	PS	Europe	500	c.1905 + 1G > A; c.1679T > G; c.2846 A > T; c.1129–5923 C > G	32	colorectal, GI, breast, pancreas, head and neck, others	7
Jennings 2013 [49]	PS	Europe	254	c.1129–5923 C > G, c.1905 + 1G > A, c.2846 A > T	15	colorectal	9
Largillier 2006 [52]	PS	Europe	105	c.1905 + 1G > A	1	breast	7
Lee 2014 [67]	RCT	America	2886	c.1905 + 1G > A; c.2846 A > T.	133	colorectal	7
Morel 2006 [54]	PS	Europe	487	c.1905 + 1G > A; c.1679T > G; c.2846 A > T.	21	colorectal, GI, breast and head and neck	9
Rosmarin 2014 [57]	RCT	Europe and Oceania	927	c.1905 + 1G > A; c.2846 A > Tc.	18	colorectal	8
Toffoli 2015 [63]	RS	Europe	603	c.1905 + 1G > A; c.1679T > G; c.2846 A > T.	18	colorectal, breast and head and neck	7
Cremolini 2017 [41]	RCT	Europe	508	c.1905 + 1G > A; c.2846 A > T.	10	colorectal	5
Ceric 2010 [40]	PS	Europe	50	c.1905 + 1G > A.	1	colorectal, breast, pancreas and others	9
Gross 2008 [48]	RS	Europe	131	c.1129–5923 C > G; c.1905 + 1G > A; c.2846 A > T.	7	colorectal, GI, breast, others	8
Alvarado-Fernandez 2019 [32]	RS	Europe	89	c.1129–5923 C > G; 1679T > G; c.1905 + 1G > A; c.2846 A > T	3	colorectal, GI, pancreas, head and neck	8
Amirfallah 2018 [33]	RS	Asia	85	c.1905 + 1G > A	1	colorectal	9
Boige 2016 [34]	RCT	Europe	1545	c.1905 + 1G > A; c.1679T > G; c.2846 A > T.	89	colorectal	8
Boige 2010 [35]	RCT	Europe	349	c.1905 + 1G > A	2	colorectal	7
Botticelli 2017 [37]	RS	Europe	642	c.1905 + 1G > A	6	colorectal, GI, pancreas, others	9
Braun 2009 [38]	RCT	Europe	1188	c.1905 + 1G > A	4	colorectal	7
Dhawan 2013 [44]	PS	Asia	23	c.1905 + 1G > A; c.2846 A > T.	9	head and neck	7
Falvella 2015 [46]	PS	Europe	64	c.1129–5923 C > G	3	colorectal	9
Joerger 2015 [50]	PS	Europe	140	c.1905 + 1G > A; c.2846 A > T.	8	colorectal and GI	8
Kristensen 2010 [51]	RS	Europe	442	c.1905 + 1G > A; c.2846 A > T.	3	colorectal	7
Nahid 2017 [55]	PS	Asia	161	c.1905 + 1G > A	8	colorectal	9
Loganayagam 2013 [53]	RS	Europe	430	c.1905 + 1G > A; c.1679T > G; c.2846 A > T; c.1129–5923 C > G	25	colorectal, GI, others	9
Negarandeh 2020 [56]	PS	Asia	88	c.1905 + 1G > A	4	colorectal	9
Ohnuma 2014 [65]	RS	Asia	103	c.1905 + 1G > A	1	colorectal and GI	8
Ruzzo 2017 [58]	RCT	Europe	508	c.1905 + 1G > A; c.2846 A > T.	9	colorectal	7
Salgado 2007 [59]	PS	Europe	58	c.1905 + 1G > A	1	colorectal	9
Salgueiro 2004 [60]	PS	Europe	73	c.1905 + 1G > A	1	colorectal	8
Schwab 2008 [61]	RCT	Europe	683	c.1905 + 1G > A	13	colorectal, GI, breast and others	8
Toffoli 2019 [62]	RS	Europe	550	c.1905 + 1G > A; c.2846 A > T; c.1129–5923 C > G	37	colorectal	7
Vivaldi 2021 [64]	PS	Europe	167	c.1905 + 1G > A	1	pancreas	6
Detailleur 2021 [43]	RS	Europe	80	c.1905 + 1G > A; c.2846 A > T	10	colorectal, GI, breast, pancreas, others	9
Ghoche 2023 [66]	RS	Asia	53	c.1905 + 1G > A; c.1129–5923 C > G	6	GI	9
Cai 2012 [39]	PS	Asia	80	c.1905 + 1G > A	13	colorectal	9

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Table 2 Characteristics of grade 5 fluoropyrimidine toxicity in DPYD variants carriers. (aa) = heterozygous; (AA) = homozygous; FOLFOXIRI = folinic acid, fluorouracil (5FU), oxaliplatin and irinotecan; FOLFOX = folinic acid, fluorouracil and oxaliplatin

Study	Deaths	Genotype	Study Origin	Chemotherapy scheme
Boisdron-Celle 2017	1	c.2846 A > T (Aa)	European	FOLFOX
Deenen 2011	1	c.1905 + 1G > A (Aa)	European	capecitabine
Etienne-Grimaldi 2017	1	c.2846 A > T (Aa)	European	capecitabine
Froehlich 2015	1	c.1129–5923 C > G (AA)	European	5-FU combination therapy
Jennings 2013	1	TYMP rs11479 (Aa)	European	5-FU combination therapy
Largillier 2006	1	c.1905 + 1G > A (Aa)	European	capecitabine
Lee 2014	1	c.1905 + 1G > A / c.2846 A > T	American	FOLFOX
Morel 2006	1	c.1905 + 1G > A (Aa)	European	5-FU combination therapy
Rosmarin 2014	2	Not identified	European	capecitabine
Toffoli 2015	1	c.1905 + 1G > A / c.1679T > G	European	5-FU combination therapy
Cremolini 2017	1	c.1905 + 1G > A (Aa)	European	FOLFOXIRI combination therapy
Ceric 2010	1	c.1905 + 1G > A (Aa)	European	capecitabine

$p < 0.05$)|(Fig. 2A), as shown in Fig. 2. A Z-value for a test of the null hypothesis is 7.61 with a corresponding *p*-value < 0,000001. Between study variation of observed effects is estimated by an I-squared value of 2% along with an absolute true effect size variance estimated by a Tau-squared value of 0,3838.

Estimation of publication bias
Figure 3A shows the funnel plot of the included articles for publication bias assessment. The X-axis corresponds to the odds ratio, while the Y-axis represents the standard errors on either side of the mean effects. Each circle is representative of one study. Our results support that there seems to be a low risk of publication bias. Figure 3B shows the L'Abbé plot for comparison of studies' effect size to index of precision for analysis of publication bias. These data suggest low variability between the confidence interval and the number of deaths counted in each study.

Quality assessment
Our main outcome showed low heterogeneity (I2 = 2%). However, when we carried out the sensitive analysis, we observed that the omission of Gross 2008, Jennings 2013, Largillier 2006, Cremolini 2017, Rosmarin 2014 resulted in a total absence of heterogeneity (I2 = 0%). In addition, the evaluation of the NOS Scale showed that most of the studies scored highly, reflecting a low risk of bias (score 8–9).

Discussion
Our systematic review and meta-analysis support that genomic alterations in the DPYD gene are associated with increased mortality among cancer patients treated with fluoropyrimidine-based cytotoxic chemotherapy. We included 36 studies, totaling 16,005 patients from clinical trials and prospective and retrospective observational studies. The gender distribution of the patients showed that 47% were men, 36% were women and in
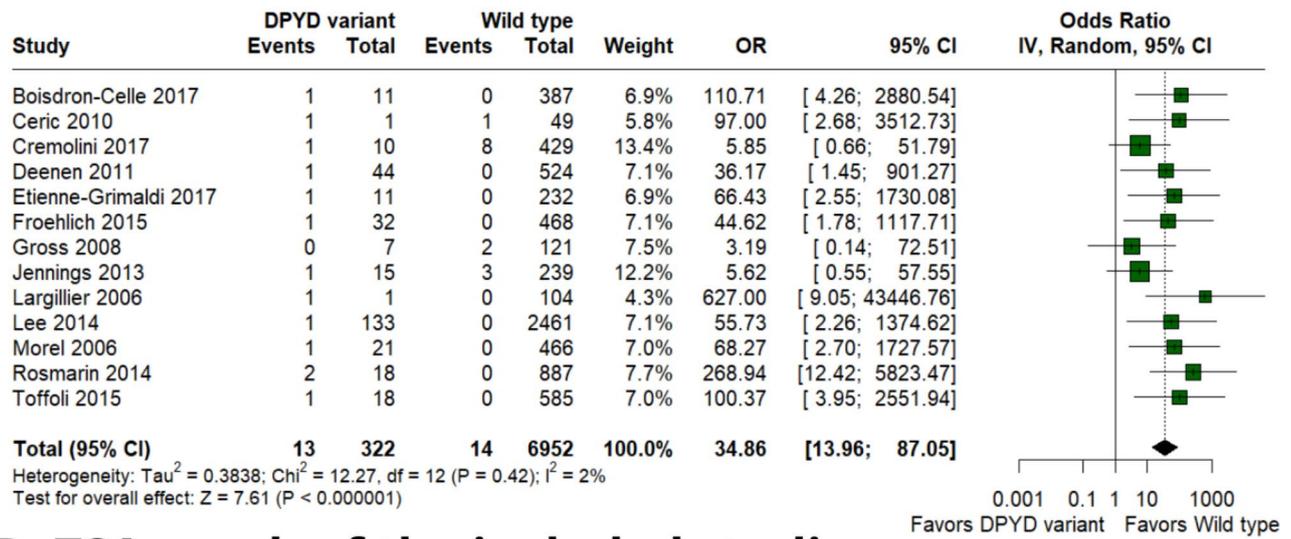
17% the sex was not identified. Most studies focused on colorectal cancer, representing 86.49% of the studies and 78.67% of the population.

Fluoropyrimidines have a narrow therapeutic index; even at standard doses, 30% of patients are expected to experience severe toxicities such as myelosuppression, gastrointestinal effects, and hand-foot syndrome [68]. It is estimated that DPD enzyme deficiency accounts for 61% of the severe toxicities to this chemotherapy regimen, typically developing within the first 1–2 cycles of treatment [69]. The DPD enzyme comprises 23 exons on chromosome 1, and only a small number of pathogenic variants have been identified as significantly increasing toxicity. These include DPYD*2A (rs3918290), D949V (rs67376798), HapB3 (rs75017182), and DPYD*13 (rs55886062) [70].

The clinical use of identifying pathogenic variants in DPYD is based on dose adjustments to minimize toxicities, guided by the variant status in this gene [71]. Dose adjustments improve tolerance and increase the safety of prescribing fluoropyrimidines for the treatment of solid tumors [72, 73]. Two pharmacogenetics expert groups, the Clinical Pharmacogenetics Implementation Consortium (CPIC) [74] and the Dutch Pharmacogenetics Working Group (DPWG) [75], recommend clinical stratification into poor, intermediate/partial, and normal metabolizers. They suggest dose reductions of up to 50% for patients carrying any of the four described variants [76]. Dose reductions above 50% or even the omission of fluoropyrimidines are indicated for heterozygous or compound heterozygous patients [77].

The results of this meta-analysis support the guidelines by reinforcing the evidence that patients with DPD deficiency experience a higher treatment-related mortality rate when undergoing fluoropyrimidine chemotherapy. We recommend testing patients for the key variants identified in this study: *DPYD*2A (rs3918290), D949V (rs67376798), HapB3 (rs75017182), and DPYD*13*

A- Overall Mortality

Study	DPYD variant Events	Total	Wild type Events	Total	Weight	OR	95% CI	Odds Ratio IV, Random, 95% CI
Boisdron-Celle 2017	1	11	0	387	6.9%	110.71	[4.26; 2880.54]	
Ceric 2010	1	1	1	49	5.8%	97.00	[2.68; 3512.73]	
Cremolini 2017	1	10	8	429	13.4%	5.85	[0.66; 51.79]	
Deenen 2011	1	44	0	524	7.1%	36.17	[1.45; 901.27]	
Etienne-Grimaldi 2017	1	11	0	232	6.9%	66.43	[2.55; 1730.08]	
Froehlich 2015	1	32	0	468	7.1%	44.62	[1.78; 1117.71]	
Gross 2008	0	7	2	121	7.5%	3.19	[0.14; 72.51]	
Jennings 2013	1	15	3	239	12.2%	5.62	[0.55; 57.55]	
Largillier 2006	1	1	0	104	4.3%	627.00	[9.05; 43446.76]	
Lee 2014	1	133	0	2461	7.1%	55.73	[2.26; 1374.62]	
Morel 2006	1	21	0	466	7.0%	68.27	[2.70; 1727.57]	
Rosmarin 2014	2	18	0	887	7.7%	268.94	[12.42; 5823.47]	
Toffoli 2015	1	18	0	585	7.0%	100.37	[3.95; 2551.94]	
Total (95% CI)	**13**	**322**	**14**	**6952**	**100.0%**	**34.86**	**[13.96; 87.05]**	

Heterogeneity: Tau^2 = 0.3838; Chi^2 = 12.27, df = 12 (P = 0.42); I^2 = 2%
Test for overall effect: Z = 7.61 (P < 0.000001)

0.001 0.1 1 10 1000
Favors DPYD variant Favors Wild type

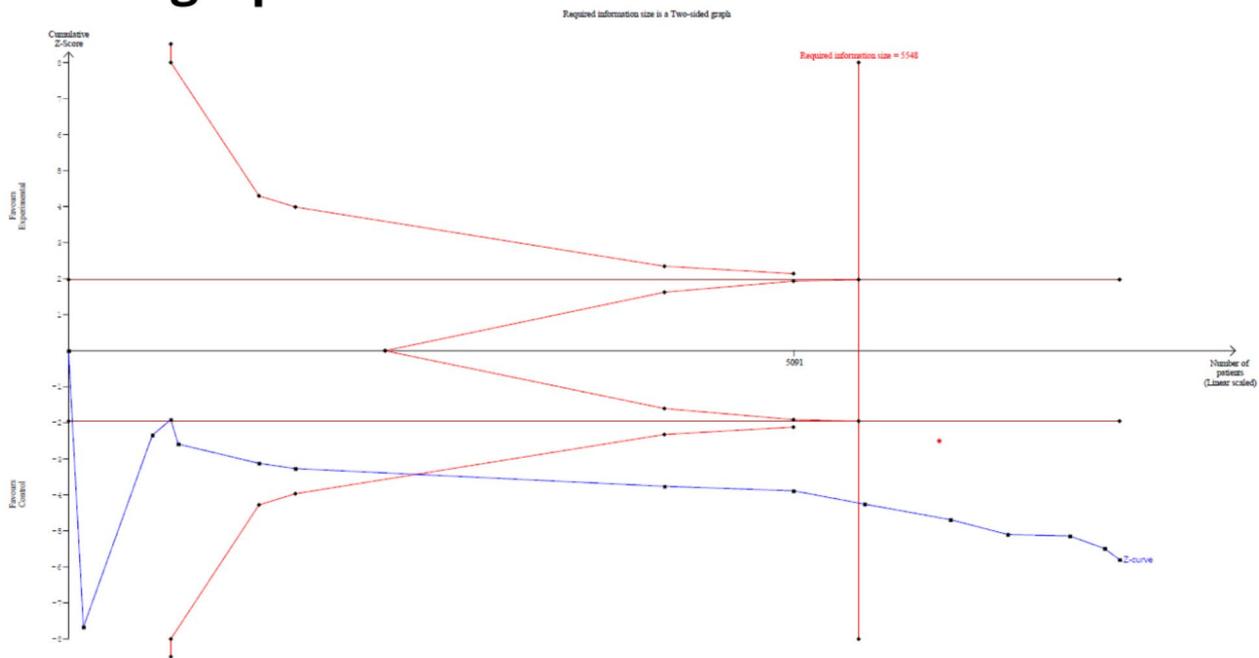## B- TSA graph of the included studies
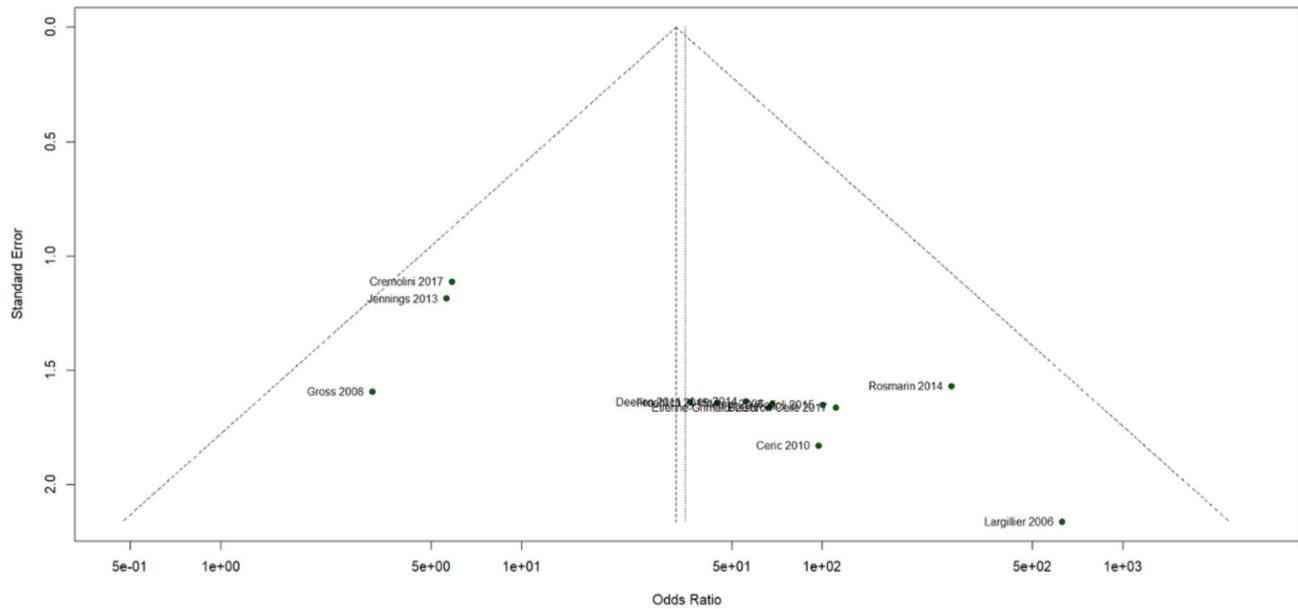

Fig. 2 Overall mortality

(rs55886062). However, this meta-analysis was unable to determine whether specific populations should be tested for additional variants due to the limited number of studies involving non-Caucasian groups.

Our meta-analysis identified 587 (3.62%) patients carrying variants in DPYD2A, DPYD13, DPYD D949V, and DPYD HapB3. Additionally, most studies were conducted in Europe (78.38%), with smaller proportions in Asia (18.92%), the Americas (2.7%), and Oceania (2.7%). These epidemiological data are expected since these four variants are well-described, primarily derived from studies
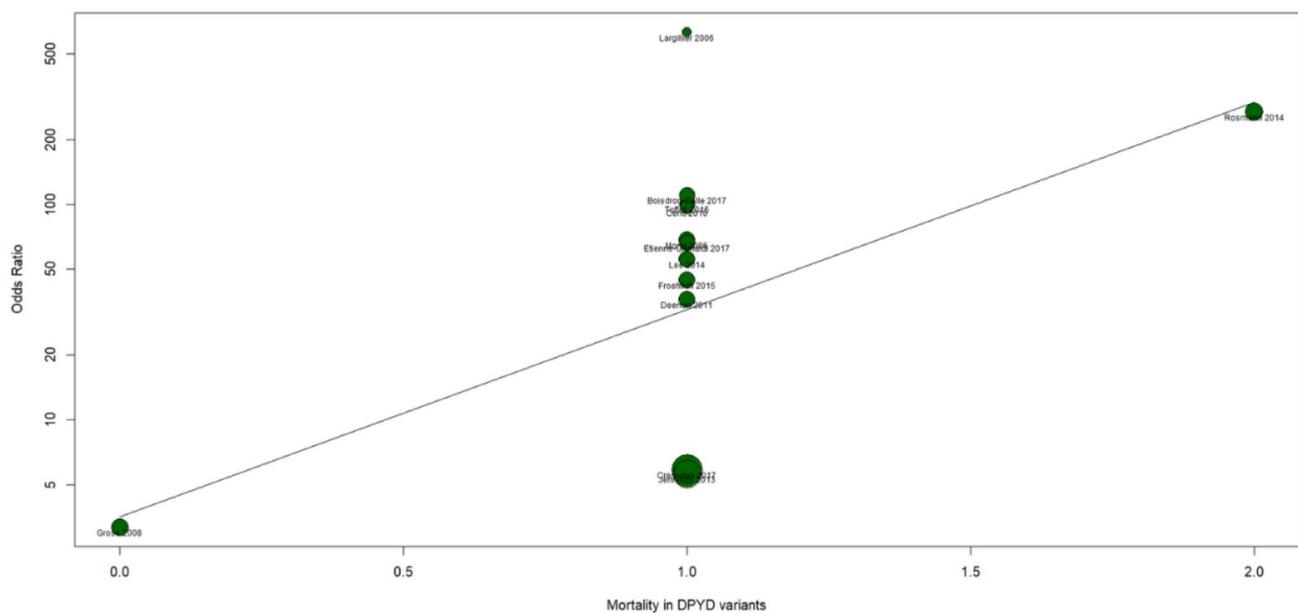
with Caucasian populations. The incidence of these four variants in the Caucasian population reaches 12%, and thus this European predominance may limit the understanding of genetic variants in different ethnicities [77–79]. Notably, the rs3918290 variant was five times more prevalent in the Asian population compared to the European one. In contrast, the rs75017182 variant was more prevalent among Europeans than Asians.

Our study identified 27 deaths attributed to fluoropyrimidine chemotherapy regimens, indicating that patients carrying variants in DPYD are at significant risk

A- Funnel plot

B- Meta-regression

Fig. 3 Funnel plot (**A**) and L'Abbé plot (**B**) for comparison of studies' effect size to index of precision for analysis of publication bias

of mortality during treatment. Notably, the rs3918290 variant was the most prevalent among fatalities, followed by rs55886062 and rs75017182. Additionally, our statistical analysis suggested a significant correlation between the carriers of variants in DPYD and treatment-related mortality (OR=34.86, 95% CI 13.96−87.05; $p<0.000001$). This result reinforces that genotyping is a crucial tool for

personalizing cancer treatment, especially for carriers of genetic variants in DPYD, and its use could minimize the risk of severe toxicity and mortality during cytotoxic chemotherapy treatment.

Sharma et al. (2021) conducted a meta-analysis that associated pathogenic variants in DPYD and increased the risk for treatment-related death [14]. Our

meta-analysis not only reinforces these results but also provides direct evidence, through TSA, that the studies currently available are sufficient to prove the direct relationship of 4 genetic variants in DPYD and mortality from 5FU exposure, different from the previous meta-analysis that didn't use TSA, also we evaluated a different result in overall mortality compared with the previous meta-analysis and made additionally sensitivity analysis with the funnel plot and meta-regression.

This meta-analysis has some limitations. First, most of the included studies consisted of patients with colorectal cancer, which could influence the generalization of the results. Second, the majority of the studies consisted of Caucasian patients from Europe; this ethnic and geographic limitation may reflect the absence of data in other global ethnicities and also influence the generalization of our findings [80, 81]. However, the low heterogeneity (I2=2%) reinforces, together with trial-sequential analysis (TSA), that our meta-analysis represents convincing evidence, and the number of patients has already exceeded the required number to prove (Z-score=5548) the association.

Conclusions

In conclusion, our systematic review and meta-analysis provide compelling evidence that genomic alterations in the DPYD gene significantly increase the risk of mortality among cancer patients undergoing fluoropyrimidine-based chemotherapy. The findings underscore the critical importance of genotyping for DPYD variants to personalize chemotherapy regimens, thereby enhancing treatment safety and efficacy. Although our analysis primarily reflects data from colorectal cancer patients and Caucasian populations, the strong correlation between DPYD variants and treatment-related mortality highlights the need for broader implementation of pharmacogenetic screening in diverse patient groups to mitigate severe toxicities and improve clinical outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12981-5.

Supplementary Material 1

Declarations

Institutional review board statement
No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. Furthermore, no patients or animals were involved in the design, conduct, or interpretation of our study.

Informed consent
Not aplicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors have no relevant financial or non-financial interests to disclose.

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