European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-023-03466-8

RESEARCH

Dihydropyrimidine dehydrogenase phenotype in peripheral blood mononuclear cells is related to adverse events of fluoropyrimidine-therapy

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Received: 16 March 2022 / Accepted: 2 February 2023

Abstract

Purpose The primary objective of this study was to determine if dihydropyrimidine dehydrogenase (DPD) activity measured in peripheral blood mononuclear cells (PBMCs) is related to adverse events during fluoropyrimidine therapy.

Methods A retrospective cohort study was conducted. The study population included 481 patients who received fluoropyrimidine treatment and for whom relevant patient characteristics were known and adverse events were noted in the electronic health records. Factors besides DPD phenotype that could affect the incidence of adverse events were corrected for using log regression. These log regression models were used to identify an association between the DPD phenotype measured in PBMCs and adverse events.

Results Patients with a decreased DPD activity measured in PBMCs suffered more adverse events. Results from log regression data show that this effect remains significant after correcting for dosage, chemotherapy regimen and relevant patient characteristics.

Conclusion A significant correlation was found between reduced DPD enzyme activity in PBMCs and adverse events. The findings in this paper support further exploring DPD phenotyping as a method for preventing fluoropyrimidine-related adverse events. Further assessment of DPD phenotyping will require clinical validation in a prospective study.

Keywords Chemotherapy · Fluoropyrimidine therapy · DPD · Adverse events · 5FU · Capecitabine

Introduction

The fluoropyrimidine (FP) 5-fluorouracil (5FU) and its oral prodrugs capecitabine and tegafur are the backbone of several treatment regimens for solid tumours including colorectal-, stomach- and breast cancers [1]. Although FP treatment significantly improves patients' overall survival, severe adverse events are common, with toxicity of grades 3–5 on the Common Terminology Criteria for Adverse Events (CTC-AE) scale occurring in approximately 30% of patients [2, 3]. The most common adverse events attributed to FP include diarrhoea, nausea, vomiting, mucositis, neutropenia and hand-foot syndrome [4]. FP-related adverse events can be fatal in up to 1% of patients [5]. Considering that approximately 2 million patients are treated with FP every year, adverse events of these therapies pose a substantial challenge in cancer treatment. A well-known cause for severe adverse reactions is a deficiency of the dihydropyrimidine dehydrogenase (DPD) enzyme, which is responsible for approximately 80% of FP catabolism [6]. This enzyme converts 5FU to 5-dihydrofluorouracil (5FUH2) which forms the rate-limiting step in its metabolism into non-cytotoxic metabolites. Lower activity of DPD increases exposure to 5FU and its cytotoxic metabolites which can result in severe adverse events.

To prevent FP-related adverse events, various methods have been developed to screen patients for DPD deficiency. These methods utilize different strategies such as genotyping the *DPYD* gene which encodes the DPD enzyme, activity assays of DPD obtained from blood samples and challenge tests with uracil or other substances converted by DPD. Currently, genotyping of *DPYD* is the only method that has

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Published online: 09 February 2023

been validated in prospective clinical trials [7]. Due to the prevalence of DPD deficiency and the severity of FP adverse events in deficient patients, the EMA recommends that all patients receiving FP therapy should be tested for DPD deficiency before starting treatment [8].

Although genotyping is effective in reducing the incidence of toxicity, it also has limitations. Only up to 17% of CTC-AE grades 3–5 adverse events can be predicted using the four *DPYD* variants currently tested for using genotyping [9]. Therefore, improvement of existing methods and development and validation of other methods to detect DPD deficiency are needed. An alternative method is DPD phenotyping in peripheral blood mononuclear cells (PBMCs). This method is currently used in Tergooi Medical Center in the Netherlands. When using this method, FP starting dosages are adjusted based on measured DPD activity. In the current study, we aim to establish an association between reduced DPD activity determined through this method and adverse events of FP therapy.

Materials and methods

We performed a single centre, retrospective cohort study. Patients treated with FP therapy between January 1, 2017 and January 1, 2021 in Tergooi Medical Center were included in the study. All patients within this group above the age of 18 were eligible for inclusion. Written informed consent was not required due to the study's retrospective nature and the coding of patient data.

Patient data relevant for the study were collected using the electronic patient health records (EHR). The following data were collected: sex, age, weight, height, FP dosage, chemotherapy regimen, estimated glomerular filtration rate (eGFR), aspartate aminotransaminase (ASAT), alanine aminotransferase (ALAT), DPD activity in PBMCs and adverse events during FP therapy. DPD activity in PBMCs was determined prior to treatment start using a radiochemical analysis method previously described by Kuilenburg et al. [10]. For the laboratory results ASAT, ALAT and eGFR, multiple entries from different dates within the study period were available for each patient. In the case of an FP-related adverse event, the last laboratory results measured before the occurrence were used. The ASAT/ALAT ratio, also known as the De Ritis ratio, was calculated to interpret the hepatic function [11]. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [12]. Data on adverse events were collected using the program Clinical Data Collector (CDC; CTcue B.V., Amsterdam, The Netherlands) by searching through the EHR data using a list of search terms. The adverse events were noted in Dutch; the English translations for the terms used in this search can be found in the supplement. The SmPC texts of FP drugs were used to determine which terms to use when searching for adverse events using the application CtCue [13–15]. After the initial search was completed, the data was reviewed manually, and adverse events were graded on a 5-point scale according to the CTCAE v5.0 [16]. Adverse events were categorized into the following groups: cardiovascular, haematological, gastrointestinal, neurological, or dermatological. Adverse events that did not fall into one of these categories were categorized as 'Other'. Adverse events unrelated to FP use were excluded based on the reporting date relative to the start of the treatment cycle. Events occurring more than 10 weeks after the start of the previous treatment cycle were assumed to have a cause other than FP-related toxicity. The 10-week limit was set based on an earlier finding that adverse events appear on average 19.1 +/− 15.3 days after the start of treatment [17].

Statistical analysis

All statistical analyses were performed using SPSS version 25 (IBM Corp., New York, USA). DPD activity measure in PBMCs has been shown to follow a circadian rhythm [18]. DPD activities used in this study were measured between 8 a.m. and 5:30 p.m. To test if this affects the reliability of the data, a one-way between-groups analysis of variance was used to determine if the average measured activity differed significantly based on the timing of sampling.

Univariate log regression was used to determine if patients who suffered adverse events differed in the characteristics of sex, age, BSA and had higher rates of abnormal liver or kidney

Table 1 Patient characteristics and adverse events found in patient records

Characteristics	Value		
Number of participants	481 (47.2% male)		
Median age, *IQR* (years)	66 (58–73) years		
Mean BSA (m^2)	1.89 ± 0.21		
Mean DPD, *SD*	9.7 (2.85)		
Adverse event	None	Grade 1/2	Grade ≥ 3
Cardiovascular	369 (76.7%)	90 (18.7%)	22 (4.6%)
Haematological	381 (79.2%)	58 (12.1%)	42 (8.7%)
Gastrointestinal	234 (48.6%)	161 (33.5%)	86 (17.9%)
Neurological	384 (79.8%)	95 (19.8%)	2 (0.4%)
Dermatological	372 (77.3%)	97 (20.1%)	12 (2.5%)
Other	276 (57.4%)	162 (33.7%)	43 (8.9%)
Any	119 (24.7%)	216 (44.9%)	146 (30.4%)

The number of adverse events is shown as a percentage of the total population in brackets

IQR interquartile range, *BSA* body surface area, *SD* standard deviation, *DPD* dihydropyrimidine dehydrogenase

Table 2 Univariate log regression results showing differences in patient characteristics and lab values found between patients with different types of adverse events

Adverse event type	Grade	Associated with	Odds ratio	*CI* (95%)
Cardiovascular	Any	BSA in bottom 33% of patients	0.473	0.282–0.793
	Grade ≥ 3	Capecitabine used instead of 5FU	0.413	0.172–0.993
		Irinotecan used	2.875	1.006–8.218
Haematological	Any	Male sex	1.732	1.109–2.705
		Capecitabine used instead of 5FU	0.492	0.303–0.797
		Oxaliplatin used	2.048	1.164–3.602
		Irinotecan used	3.546	1.927–6.525
		ASAT > 30	1.713	1.081–2.716
		DPD activity < 70%	1.798	1.014–3.189
	Grade ≥ 3	Capecitabine used instead of 5FU	0.207	0.108–0.397
		Oxaliplatin used	3.122	1.531–6.366
		Irinotecan	10.846	5.338–22.036
Gastrointestinal	Any	BSA in top 33% of patients	0.668	0.452–0.985
		BSA in bottom 33% of patients	1.492	1.010–2.205
		Capecitabine used instead of 5FU	0.486	0.313–0.755
		Oxaliplatin used	3.061	1.727–5.426
		Bevacizumab used	1.551	1.005–2.392
		Irinotecan used	2.694	1.412–5.138
		ASAT > 30	1.815	1.242–2.652
		ALAT > 35	1.921	1.230–3.002
		DeRitis > 2	1.665	1.014–2.734
		DPD activity < 70%	2.148	1.245–3.706
	Grade ≥ 3	BSA in top 33% of patients	0.502	0.282–0.894
		Capecitabine used instead of 5FU	0.395	0.240–0.652
		Oxaliplatin	3.079	1.748–5.423
		Irinotecan	4.066	2.186–7.562
		eGFR < 60	2.985	1.508–5.909
		ASAT > 30	1.824	1.114–2.985
		ALAT > 35	2.282	1.358–3.834
Neurological	Any	Bevacizumab used	2.357	1.450–3.832
Dermatological	Any	Capecitabine used instead of 5FU	2.932	1.542–5.572
		Oxaliplatin used	0.411	0.190–0.888
		Bevacizumab used	2.134	1.330–3.423
		FP dose < 95% of normal	1.925	1.233–3.006
		ASAT > 30	1.71	1.098–2.662
Other	Any	Capecitabine used instead of 5FU	0.574	0.375–0.881
		Oxaliplatin used	1.993	1.186–3.350
		Bevacizumab used	2.209	1.431–3.409
		Irinotecan used	2.4	1.314–4.386
		ASAT > 30	1.906	1.302–2.790
		ALAT > 35	1.61	1.041–2.492
	Grade ≥ 3	Male sex	2.008	1.052–3.832
		Capecitabine used instead of 5FU	0.336	0.176–0.64
		Oxaliplatin used	3.881	1.947–7.737
		Irinotecan used	3.008	1.381–6.552
		eGFR < 60	2.72	1.167–6.339
		ALAT > 45	2.074	1.058–4.064
		DPD activity < 70%	2.43	1.143–5.167
All (combined)	Any	Capecitabine used instead of 5FU	0.475	0.270–0.836
		Oxaliplatin used	3.905	1.644–9.279
		Bevacizumab used	2.052	1.166–3.612

Table 2 (continued)

Adverse event type	Grade	Associated with	Odds ratio	*CI* (95%)
		Irinotecan used	3.247	1.258–8.382
		ASAT > 30	1.972	1.246–3.119
		ALAT > 35	1.996	1.131–3.521
		DPD activity < 70%	2.045	1.006–4.156
	Grade ≥ 3	Male sex	1.49	1.008–2.201
		Capecitabine used instead of 5FU	0.271	0.174–0.422
		Oxaliplatin	3.882	2.288–6.589
		Irinotecan	8.486	4.349–16.557
		ASAT > 30	1.724	1.147–2.593
		ALAT > 35	2.064	1.312–3.248

Only differences significant at the $p < 0.05$ level are listed

function, were more likely to use specific chemotherapy drugs, or were more likely to have DPD deficiency. In these tests, an eGFR below 60 and 30 ml/min was considered indicative of moderate and severe kidney dysfunctions, respectively. For liver function, ASAT above 30 IU/ml, ALAT above 35 IU/ml, or a De Ritis ratio above 2 were used as markers of liver dysfunction. Patients were considered to have minor or moderate DPD deficiency if their DPD activity in PBMCs was between 50 and 70% or < 50% of the population average of 9.6 nmol/mg/h [19]. The cut-offs for DPD activity were selected based on the recommendations for dose adjustments set by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [20]. The CPIC recommends dose corrections for patients with a DPD activity between 30 and 70% of the population average. Univariate log regression was also used to determine the effects of dose adjustments on the incidence of adverse events. For this test, the population was split into groups receiving > 95%, 70–95% and < 70% of the normal dosage. These intervals were selected because dose corrections cluster in three groups, with most patients receiving either 100, 75 or 50% of the normal dose.

To assess the relationship between DPD activity and adverse events, multivariate log regression models were generated to correct for the dose adjustments and other potential confounding factors. Covariates included in all models were DPD activity and dose correction used during the therapy. Lab results indicative of liver or kidney dysfunction as well as potentially confounding factors such as sex, age, BSA and other chemotherapy drugs used were included in the initial model and removed if the Wald test statistic had a *p*-value above 0.1, as this indicates that the variable does not contribute to the model significantly. Lastly, ROC curves were made to test the predictive value of the generated models on our dataset.

Results

A total of 481 patients received FP therapy with 5FU or capecitabine at Tergooi Medical Center within the study period. Only two patients received Tegafur in this period. This group was excluded from the study since its population size is not large enough to find statistically significant associations. A DPD phenotype was known for 442 patients. For the remaining 39 patients, no phenotype had been determined because the patient had either been genotyped previously, had received FP therapy at a different hospital without serious adverse events or the risk associated with delaying treatment outweighed the risk of adverse events due to DPD deficiency. In the latter case, half a standard dose was used when starting treatment. Out of 442 patients, 373 had a DPD activity greater than 6.7 nmol/mg/h and were determined not to be DPD deficient. A total of 53 patients had a minor DPD deficiency with an activity between 6.7 and 4.8 nmol/mg/h. The remaining 16 patients had a moderate DPD deficiency with an activity below 4.8 nmol/mg/h. For 75.3% of patients, at least one adverse event had been recorded in the EHR. Patient characteristics and the number of adverse events of each type are presented in Table 1.

Statistical analysis

Univariate log regression was used to identify differences in lab results and patient characteristics between patients for whom different adverse events had been noted. Between these groups, differences significant at the $p < 0.05$ level were found in BSA, FP drug used, FP dosage, other chemotherapeutics used, DPD activity, sex, eGFR, ASAT, ALAT and DeRitis ratio. A reduced DPD activity was associated with more haematological and gastrointestinal adverse events as well as more adverse events in general. All associations significant at the $p < 0.05$ level per adverse event category can be found in Table 2. An analysis of variance showed no significant difference between the measured DPD activities based on what hour of the day samples were collected ($p = 0.602$). Because of this, corrections for the time of sampling to take into account the circadian rhythm were not needed.

Multivariate log regression models were generated for each adverse event category to determine if DPD activity

Table 3 Mutlivariate log regression models showing significant associations between DPD deficiency and adverse events in different categories

Covariate	Odds ratio	95% *CI*	*p*
Cardiovascular adverse events			
DPD activity normal	-	-	0.098
DPD activity < 70%	2.090	1.067–4.092	0.032
DPD activity < 50%	1.320	0.390–4.463	0.655
Dose normal	-	-	0.868
Dose 70–95%	1.143	0.666–1.961	0.627
Dose < 70%	0.998	0.501–1.985	0.995
BSA in middle 33%			0.004
BSA in bottom 33%	0.363	0.187–0.704	0.003
BSA in top 33%	1.028	0.603–1.754	0.919
Constant	0.304	-	< 0.0001
Gastrointestinal adverse events			
DPD activity normal	-	-	0.009
DPD activity < 70%	2.917	1.459–5.832	0.002
DPD activity < 50%	1.623	0.516–5.099	0.407
normal	-	-	0.385
Dose 70–95%	0.797	0.500–1.270	0.340
Dose < 70%	1.188	0.650 –2.174	0.575
ASAT ≥ 30	1.891	1.233–2.899	0.003
BSA in middle 33%	-	-	0.078
BSA in bottom 33%	1.177	0.707–1.957	0.531
BSA in top 33%	0.666	0.404–1.096	0.109
Received oxaliplatin	2.328	1.070–5.063	0.033
Received bevacizumab	1.619	0.973–2.694	0.064
Received irinotecan	2.152	0.878–5.278	0.094
Constant	0.621	-	0.053
Neurological adverse events			
DPD activity normal	-	-	0.067
DPD activity < 70%	2.249	1.135–4.459	0.020
DPD activity < 50%	1.383	0.362–5.282	0.636
Dose normal	-	-	0.593
Dose 70–95%	0.989	0.566–1.726	0.969
Dose < 70%	0.687	0.321–1.471	0.334
Received bevacizumab	1.944	1.113–3.395	0.020
Constant	0.189	-	< 0.0001
Grade ≥ 3 haematological adverse events			
DPD activity normal	-	-	0.100
DPD activity < 70%	0.939	0.276–3.189	0.919
DPD activity < 50%	5.252	1.124–24.543	0.035
Dose normal	-	-	0.524
Dose 70–95%	0.988	0.417–2.340	0.978
Dose < 70%	0.439	0.099–1.944	0.278
Received irinotecan	12.831	5.543–29.702	< 0.0001
Constant	0.053	-	< 0.0001
Grade ≥ 3 other adverse events			
DPD activity normal	-	-	0.049
DPD activity < 70%	3.166	1.244–8.057	0.016
DPD activity < 50%	2.223	0.412–11.982	0.353
Dose normal	-	-	0.805
Dose 70–95%	0.768	0.330–1.792	0.542
Dose < 70%	0.770	0.259–2.292	0.639
ASAT ≥ 30	2.043	0.976–4.278	0.058
BSA in middle 33%	-	-	0.071
BSA in bottom 33%	0.364	0.141–0.936	0.036
BSA in top 33%	0.493	0.211–1.153	0.103
Received irinotecan	2.432	0.920–6.430	0.073
Constant	0.086	-	< 0.0001

Only models in which DPD deficiency contributed significantly at the $p < 0.05$ level are listed

measured in PBMCs remains associated with adverse events when correcting for dose adjustments and other factors that might affect the rate of adverse events. In these models, gastrointestinal, cardiovascular and neurological adverse events were significantly associated with DPD deficiency in PBMCs. DPD deficiency was also associated with more grade ≥ 3 adverse events in the haematological and other categories. Odds ratios and 95% confidence intervals of all covariates included in models where DPD deficiency was significantly associated with adverse events are shown in Table 3. In addition to DPD deficiency, choice of FP, other chemotherapy drugs used, sex, increased ASAT, increased ALAT, reduced eGFR and BSA were independently associated with adverse events. ROC curves were generated for the models where DPD activity contributed significantly ($p < 0.05$) (Fig. 1). In each of these models, the *AUC* of the corresponding ROC curve was significantly larger than 0.5 ($p < 0.05$). The *AUCs* for these ROC curves including the confidence interval are shown in Table 4.

Discussion

The data in our study shows a clear link between reduced DPD activity measured in PBMCs and cardiovascular, gastrointestinal, neurological and haematological adverse events of FP therapy. To our knowledge, this is the first study to show a statistically significant association between DPD deficiency in PBMCs and multiple types of adverse events. Aside from DPD deficiency, univariate log regression analysis found associations between adverse events and the FP drug used, chemotherapy regimen, patient characteristics indicative of kidney and liver dysfunction as well as a high body surface area. To better assess the association between DPD activity in PBMCs and adverse events, possible causes for these associations were evaluated, and multivariate log regression models were made to adjust for these factors.

Though the link between DPD deficiency and adverse events of FP therapy is well established, little research has been done to investigate the association between DPD activity in PBMCs and the incidence of adverse events using real-world therapy records. Some studies have linked low DPD activity in PBMCs to different adverse events, but these typically study only a small patient population (< 100 patients) [21, 22]. To better investigate associations between activity in PBMCs and the incidence of adverse events, data from a large number of patients is needed. For this purpose, we performed a cohort study using retrospective data collected over 3 years. This study design allows for a large patient group to be studied, enabling us to establish statistically significant associations with various types of adverse events, which could not be achieved in previous studies.

Poor kidney function was significantly associated with adverse events classified as 'other'. A possible explanation for this finding is that poor kidney function increases exposure to metabolites of 5FU that are cleared renally [23]. These could potentially contribute to an increased incidence of adverse events.

Markers for liver damage were also expected to be associated with an increased incidence of adverse events, since an impaired liver function is known to affect 5FU metabolism [24, 25]. This association is also seen in this study, as increased ASAT and ALAT levels and a DeRitis ratio above two were associated with more haematological, gastrointestinal, dermatological, 'other' adverse events, more adverse events in general as well as more grade ≥ 3 adverse events.

It was also found that men suffered more grade ≥ 3 'other' adverse events. This is an unexpected finding since previous studies reported more adverse events in women [26]. Furthermore, a higher BSA was associated with cardiovascular adverse events. This association could be due to these patients receiving a higher dosage since this is BSA-guided, or because patients with a higher body mass have both a higher BSA and a higher risk of cardiovascular problems. Patients receiving 5FU suffered more blood count-related, gastrointestinal and uncategorized adverse events as well as more grade ≥ 3 cardiovascular adverse events and adverse events generally. Capecitabine was instead associated with more dermatological adverse events. These findings match earlier studies finding that capecitabine use is associated with fewer adverse events compared to 5FU but causes more hand-foot syndrome [27].

Lastly, concurrent use of other chemotherapeutics significantly increased the incidence of adverse events. This is an expected result, considering that these drugs have side effects that are similar to those of FP.

To establish if the relation between DPD activity and adverse events persists after correcting for the therapy received and relevant patient characteristics, multivariate log regression models were made correcting for FP dosage given and the factors described above. In these models, the association between reduced DPD activity measured in PBMCs and adverse events remained significant for cardiovascular, gastrointestinal, neurological and 'other' adverse events. Reduced DPD activity was also associated with more grade 3 + adverse events in the haematological and 'other' categories. ROC curves were generated for these models to see if they could correctly classify patients in the study population as having specific types of adverse events. ROC curves obtained in this manner underestimate the predictive capabilities of DPD activity in practice. This is because the available data consists of patients who had their dosages adjusted based on the measured DPD activity. Bias is also introduced by the fact that the models are tested using the same data used to create them. An *AUC* significantly higher than 0.5 would however show that patients can be correctly classified within this dataset, indicating that DPD phenotyping likely can be used to predict adverse events during FP therapy. In our results, the *AUC* for every model that DPD phenotype significantly contributed to was significantly higher than 0.5 (Table 4).

Limitations of this study design are the inability to gather additional patient data due to the retrospective design and that the fluoropyrimidine dosages all patients received were adjusted based on the measured activities. Because of these dose adjustments, the efficacy of using measured DPD activity to prevent adverse events cannot be assessed properly.

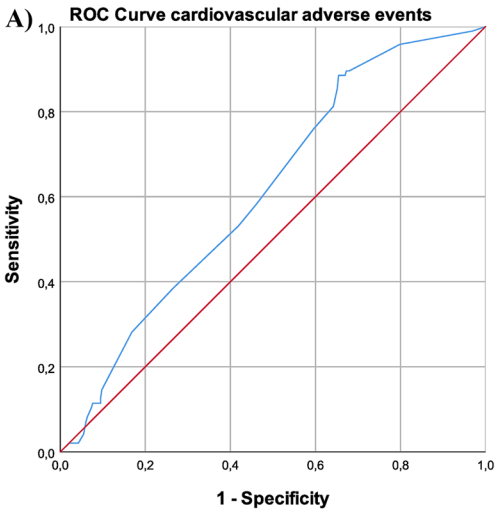
Fig. 1 ROC curves for predicting different types of adverse events where a significant association with DPD activity in PBMCs was found. **A** Cardiovascular adverse events predicted using a log regression model containing DPD activity, dose and BSA as covariates. (*AUC* = 0.613). **B** Gastrointestinal adverse events predicted using a log regression model containing DPD activity, dose, ASAT, BSA and whether oxaliplatin and bevacizumab were used as covariates. (*AUC* = 0.692). **C** Neurological adverse events predicted using a log regression model containing DPD activity, dose, FP Drug used and whether bevacizumab was used as covariates. (*AUC* = 0.618). **D** Grade ≥ 3 haematological adverse events predicted using a log regression model containing DPD activity, dose and whether irinotecan was used as covariates. (*AUC* = 0.736). **E** Grade ≥ 3 'other' adverse events predicted using a log regression model containing DPD activity, dose, ASAT, BSA and whether irinotecan was used as covariates. (*AUC* = 0.697)

Table 4 *AUC* with confidence interval for each ROC curve generated for multivariate log regression models where DPD was significantly associated with adverse events

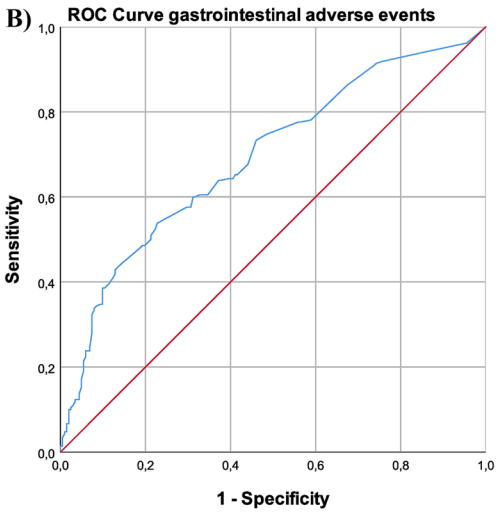
Adverse event type	*AUC*	95% *CI*	*p*
Cardiovascular	0.613	0.554–0.673	0.001
Gastrointestinal	0.692	0.641–0.743	< 0.0001
Neurological	0.618	0.552–0.684	0.001
Haematological grade ≥ 3	0.736	0.641–0.832	< 0.0001
Other grade ≥ 3	0.697	0.599–0.794	< 0.001

All curves had an area that differed significantly from 0.5 at the $p < 0.05$ level

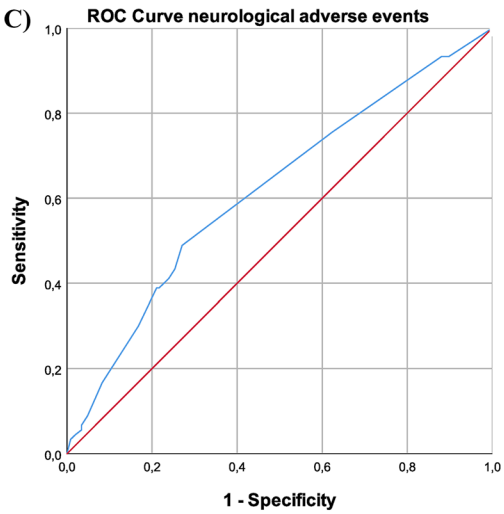
A)


ROC Curve cardiovascular adverse events
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
Diagonal segments are produced by ties.

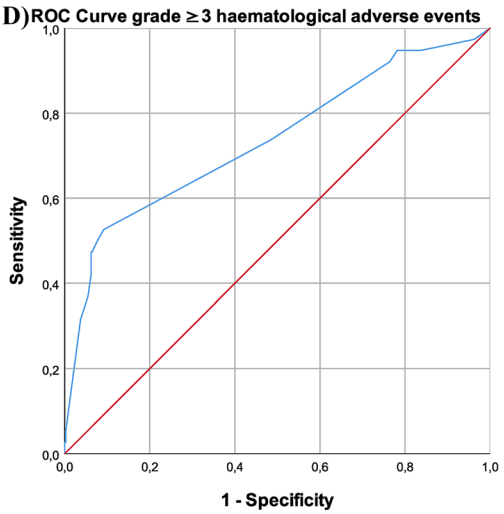
B)


ROC Curve gastrointestinal adverse events
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
Diagonal segments are produced by ties.

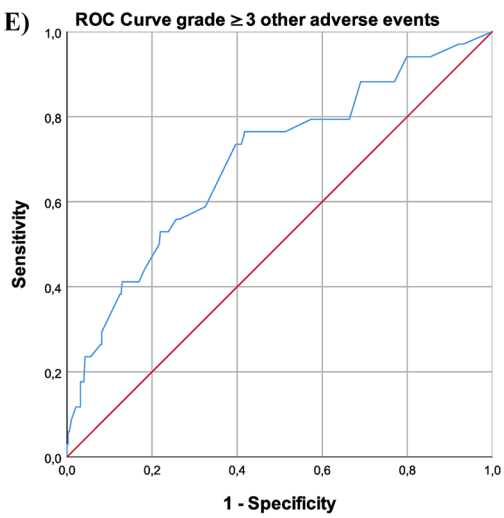
C)


ROC Curve neurological adverse events
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
Diagonal segments are produced by ties.

D)


ROC Curve grade ≥ 3 haematological adverse events
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
Diagonal segments are produced by ties.

E)


ROC Curve grade ≥ 3 other adverse events
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
Diagonal segments are produced by ties.

Nevertheless, the results of this study show a clear association between DPD activity and multiple types of adverse events. Compared to genotyping, DPD phenotyping provides a much more direct method to determine the rate at which a patient can catabolize FPs. Because of this, our findings suggest that DPD phenotyping in PBMCs can estimate the risk of adverse events in a way that *DPYD* genotyping alone cannot. Further investigation through prospective studies is warranted and could show how DPD phenotyping can be applied to prevent adverse events and optimize the treatment of patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-023-03466-8.

Author contribution Conceptualization: A. D. and P. L.; methodology: A. D., P. L., and A. W.; formal analysis and investigation: K. D., P. L. and A. D.; writing original draft preparation: K. D.; manuscript review and editing: K. D., P. L., G. B., A. W. and A. D.; supervision: A. D.

Data availability The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval This research study was conducted retrospectively from the data obtained for clinical purposes. We consulted extensively with the local scientific committee of Tergooi Medical Center which determined that our study did not need ethical approval.

Consent to participate Informed consent was deemed unnecessary due to anonymized data and due to the observational nature of the study.

Consent for publication Informed consent was deemed unnecessary due to anonymized data and due to the observational nature of the study.

Conflict of interest The authors declare no competing interests.

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