Clinical, Dose-Exposure, and Pharmacogenetic Factors Associated with Clinically Significant Capecitabine-Induced Hand-Foot Syndrome in Iraqi Cancer Patients: An Observational Study

Mahmoud Kamil Ismaeil[1], Ayad Rateb Al-Asadi[2,*] and Mahmood Sh. Abdulrahman[3]

[1]*Al-Yarmuk Oncology Center, Baghdad, Iraq*

[2]*Al-Amal National Hospital of Oncology, Baghdad, Iraq*

[3]*Oncology Teaching Hospital, Medical City Complex, Baghdad, Iraq*

Abstract: Capecitabine-induced hand-foot syndrome (HFS) can impair function and derail treatment. We recruited patients from February to June 2026 in a prospective observational study and studied clinical, dose related inflammatory renal pharmacogenetic associations with clinically significant HFS in Iraqi adults on capecitabine containing regimens (180). The recorded outcome classification was no or mild HFS 97 (46.1%) vs clinically significant HFS 83 (46.1%); six had nonstandard severity code making grading interpretation difficult. Group comparisons multivariable logistic regression single marker ROC analyses were used for analysis. Cumulative dose recorded was higher in the group with clinically significant HFS (311.47 ± 83.36 versus 254.39 ± 84.14 g; P < 0.001).Adjusted associations were observed for cumulative dose (odds ratio [OR] 1.01 per g, 95% confidence interval [CI] 1.00–1.01; P < 0.001), diabetes (OR 3.46, 95% CI 1.34–8.92; P = 0.010), and the cytidine deaminase variant category (OR 2.56, 95% CI 1.06–6.16; P = 0.036). Recorded cumulative dose had an apparent area under the curve of 0.683, with an exploratory cut-off of 289.10 g. These findings identify associations within the analyzed sample. Uncertainty in outcome grading, exposure timing, and genotype classification, together with the absence of demonstrated model validation, precludes use of the cut-off or genetic categories for clinical decisions. Studies with standardized outcome assessment and exposure measured before HFS onset are needed.

Keywords: Capecitabine, CDA, cumulative dose, diabetes, DPYD, hand-foot syndrome, palmar-plantar erythrodysesthesia, pharmacogenetics.

INTRODUCTION

Capecitabine is an oral fluoropyrimidine prodrug used in colorectal, breast, gastric and other gastrointestinal malignancies. It is frequently complicated by toxicities that impact adherence, quality of life and chemotherapy delivery [1]. Hand-foot syndrome (HFS) (palmar-plantar erythrodysesthesia) is a well recognized and treatment limiting adverse event associated with capecitabine containing regimens [2]. Clinical trials are ongoing to determine dose related susceptibility and preventive interventions [3, 4]. Capecitabine-induced HFS is characterized by erythema, swelling, dysesthesia, pain, fissuring, desquamation, blistering and functional limitation of the palms and soles. Clinically significant toxicity can affect walking, manual activity and self care and may require treatment interruption or dose modification [2, 5]. Because capecitabine is administered in outpatient settings early recognition and education of patients are important aspects of toxicity management [1, 2]. The frequency and severity of capecitabine-induced HFS vary among populations, types of cancer, regimens, duration of treatment and grading methods. Clinical studies have looked at dose, number of cycles and patient factors as possible determinants of HFS [6, 7, 8]. A 2026 cohort used time to grade 2–3 HFS and competing-risk analysis for prescribed capecitabine dose (see Figure **1**) to show how baseline dose must be distinguished from exposure accumulated during follow-up [3]. The initial prescribed dose, daily dose, relative dose intensity, planned cycles and total cumulative dose all refer to different aspects of treatment. Cumulative dose is dose x duration but not plasma drug exposure measure (cumulative dose = dose + time). A course-level total can include treatment given after toxicity occurs; HFS reductions or interruptions then affect the measure itself. Prospective interpretation thus depends on temporal relationship between dosing and onset of HFS. Patient-related factors may also be involved in HFS susceptibility. Renal function is related to capecitabine dosing but creatinine-clearance criteria used for dose adjustment are not an indexed eGFR category [1]. Diabetes has been associated with more severe capecitabine hand-foot toxicity in a previous observational study [9]. Local inflammation signalling and epidermal barrier injury provide reasons to look at host inflammatory characteristics as well: experimental work implicated interleukin-6 and interleukin-8 pathways, a 2025 single-

*Address correspondence to this author at the Al-Amal National Hospital of Oncology, Baghdad, Iraq; E-mail: dr.ayadoncology@gmail.com

ISSN: 1929-2260 / E-ISSN: 1929-2279/26 © 2026 Neoplasia Research

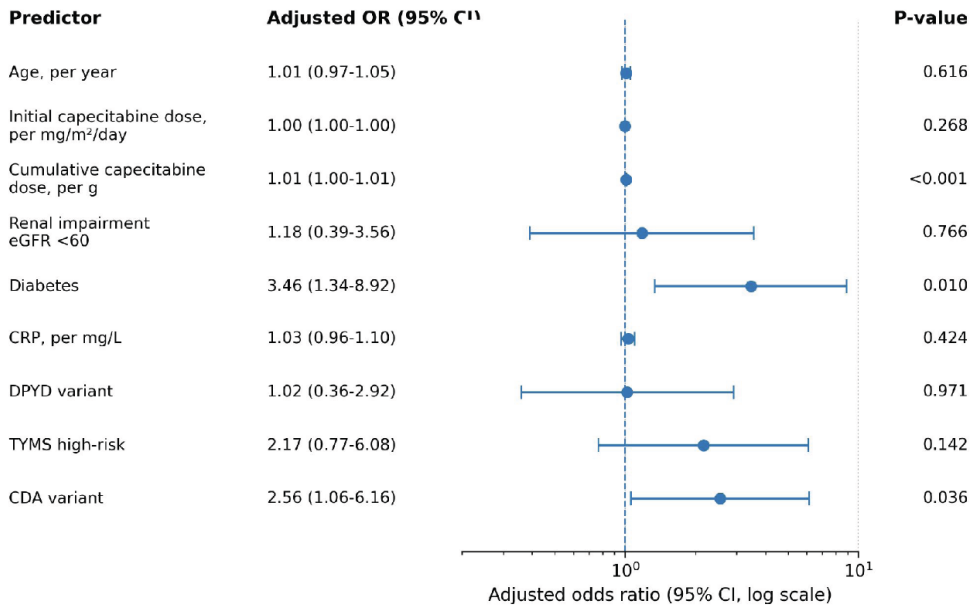

Figure 1: Forest plot of independent predictors of clinically significant capecitabine-induced handfoot syndrome.

arm study looked at topical hydrocortisone prevention and a 2026 human study described altered stratum-corneum lipids and local fluorouracil accumulation [10, 11, 12]. None of these findings establish circulating CRP, NLR, PLR or SII as validated predictors of HFS. Pharmacogenetic susceptibility is another component of fluoropyrimidine toxicity. Variants that are functionally important for DPYD (encoding dihydropyrimidine dehydrogenase) safety and dosing recommendations are known [13, 14]. Other candidate genes include TYMS (thymidylate synthase), MTHFR (methylenetetrahydrofolate reductase) and CDA (cytidine deaminase). They relate to drug activation or pharmacological target or folate metabolism. Variant specific studies on CDA and CDH4 show HFS susceptibility goes beyond DPYD but also emphasize the need for precise allele definitions [15, 16, 17]. An Iraqi oncology cohort can inform on treatment patterns, comorbidity and candidate pharmacogenetic associations in this population. Patient selection, cancer distribution, dosing, supportive care and genetic background may impact transferability of associations across settings. In this study clinical, dose related, renal inflammatory and pharmacogenetic factors associated with recorded classification of clinically significant capecitabine-induced HFS in Iraqi cancer patients were assessed. Treatment modification, hospitalization and supportive management were described as well as apparent discriminatory performance of individual dose and laboratory variables. The aim was exploratory association assessment not a clinically validated prediction rule development.

METHODS

Study Design Recruitment and Population

This prospective observational clinical pharmacology study included adults with cancer on capecitabine-containing regimens in Iraq from February through June 2026. Eligible patients were screened consecutively during oncology visits; clinical, treatment, laboratory, pharmacogenetic and HFS information was recorded on a standardized data-collection form. Treatment selection, capecitabine dosing and supportive management were the responsibility of treating oncology team members. Analysis was exploratory. Adults with histologically confirmed cancer treated with capecitabine were eligible. HFS status had to be ascertainable and sufficient clinical, dosing, renal, laboratory and pharmacogenetic information available for the principal analyses (capecitabine monotherapy; CAPOX [capecitabine plus oxaliplatin]; radiotherapy combined with capecitabine). Patients were excluded if key treatment-exposure data were not available, HFS status was not known, follow-up was too short to assess dermatologic toxicity or missing pharmacogenetic and laboratory information precluded inclusion in the principal analysis. The final analytic cohort consisted of 180 patients (97 no/grade 1 HFS group; 83 recorded clinically significant HFS group). The sample size was based on the number of eligible patients recruited during the study period and availability of information needed for analysis (no hypothesis-based sample size calculation). The study was exploratory in nature to assess clinical, treatment-related and pharmacogenetic associations. Cohort size

was not interpreted as evidence that power is adequate for small effects or uncommon genotype categories.

Clinical and Laboratory Variables

Baseline variables were age, BMI, sex, cancer type, diabetes, serum creatinine and eGFR. Cancer type was breast, colorectal or gastric cancer. Renal impairment was an analytical category defined as eGFR <60 mL/min/1.73 m^2.Diabetes status was based on documented medical history, physician diagnosis, or antidiabetic medication use. Inflammatory variables were CRP, NLR, PLR, and SII. Definitions of the derived indices are provided in Supplementary Methods S1.

Capecitabine Dose Assessment

Treatment characteristics were regimen, body surface area, initial capecitabine dose (mg/m^2/day), daily dose (mg), planned cycles, relative dose intensity and recorded cumulative dose (g). Cumulative dose was calculated from prescriptions and changes in treatment. For each interval with unchanged prescribed dose the total daily dose (mg) was multiplied by number of days at that dose to get total daily dose in mg; totals for each interval were summed over the recorded course of treatment and divided by 1000 to express cumulative dose in g. Dose changes defined intervals; scheduled treatment-free days and interruptions counted as zero dose. Prescribed exposure adjusted for documented changes not confirmation of tablet ingestion. Relative dose intensity was documented prescribed dose intensity over the observed period divided by planned dose intensity over the same period. Initial dose, planned cycles and cumulative dose were analyzed separately as treatment descriptors. Cumulative dose was calculated as a course-level total and not restricted to exposure before first onset of clinically significant HFS. Dose prescribed after HFS onset was not separated in the current analysis and exposure was not modelled as time varying covariate; longer treatment duration and dose reductions or interruptions related to HFS could thus affect final cumulative total. The association reported is recorded treatment-course exposure and HFS classification only (it does not show that total dose preceded HFS or an exposure threshold prior to toxicity). Prescription records do not establish adherence nor measured pharmacokinetic exposure.

HFS Classification and Management Outcomes

The primary comparison was between recorded no/grade 1 HFS versus clinically significant HFS (originally coded as grade ≥2). CTCAE version 5.0 defines palmar-plantar erythrodysesthesia only using grades 1–3; grades 4 and 5 are not available for this event [18]. Grade 1 skin changes without pain, grade 2 painful changes affecting instrumental daily activities and grade 3 severe painful changes affecting self-care. Grade 0 denotes absence of HFS in this analysis. Six cases had a nonstandard grade 4 code and were included in the recorded clinically significant group. This category is not equivalent to a CTCAE version 5.0 HFS grade. The severity distribution and all outcome-based estimates therefore reflect the recorded classification and are subject to outcome misclassification. Secondary descriptive outcomes were HFS-related dose reduction, treatment delay, treatment interruption, hospitalization, topical management, and pyridoxine or systemic supportive management.

Pharmacogenetic Methods and Coding

DPYD, *TYMS*, *MTHFR*, and *CDA* were examined as candidate pharmacogenetic factors because of their roles in fluoropyrimidine metabolism, drug targeting, and folate biology [13, 14, 15, 17]. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood using a silica-membrane method. DPYD, MTHFR, and *CDA* single-nucleotide variants were genotyped by real-time PCR with TaqMan allelic discrimination. The TYMS promoter repeat was analyzed by conventional PCR and fragment sizing, with sequence confirmation of ambiguous repeat calls. Specimen handling, assay procedures, marker definitions, and laboratory quality-control procedures are described in Supplementary Methods S2 and S3 and Table **S3**.

The DPYD panel comprised rs3918290 (c.1905+1G>A), rs55886062 (c.1679T>G), rs67376798 (c.2846A>T), and rs75017182 (c.1129−5923C>G). DPYD status distinguished the reference category at the tested loci from a heterozygous variant category. *TYMS* categories were based on the 28-bp repeat rs34743033: 3R/3R, 2R/3R, and 2R/2R were coded as low, intermediate, and high categories, respectively. MTHFR rs1801133 (C677T; c.665C>T) was coded as CC, CT, or TT, corresponding to the wild-type, heterozygous, and variant categories. CDA rs532545, conventionally designated −451C>T, was coded as CC versus CT/TT. These category definitions were used for exploratory association analysis; the TYMS labels do not constitute validated dosing groups and the reference categories do not imply absence of untested variants.

The adjusted model included the DPYD variant, TYMS high-risk, and CDA variant indicators. These indicators were used to explore associations, rather than to assign a DPYD activity score or a genotype-directed dose. Laboratory personnel were blinded to HFS classification during genotype calling; control samples, duplicate testing, and repeat evaluation of ambiguous calls were incorporated as detailed in Supplementary Methods S3.

Statistical Analysis

Statistical analyses were conducted utilizing IBM SPSS Statistics version 29.0. The distributions of continuous variables were evaluated through the examination of histograms and quantile–quantile plots.Continuous variables were summarized as mean ± standard deviation and categorical variables as counts and percentages. The principal comparison was between the no/grade 1 HFS group and the recorded clinically significant HFS group.

Welch independent-samples t tests were used for continuous variable comparisons; Pearson chi square tests with Yates continuity correction for two by two tables were used for categorical comparisons. The HFS grade distribution was described without a between group significance test because the grades themselves defined group membership. Two sided P values were reported; $P < 0.05$ was treated as nominal significance threshold. Multiple exploratory comparisons and candidate gene analyses increase chance findings. Multivariable binary logistic regression summarized adjusted associations with the recorded clinically significant HFS classification. The model had nine terms: age, initial capecitabine dose, cumulative capecitabine dose, renal impairment, diabetes, CRP, DPYD variant status, TYMS high-risk status and CDA variant status. All terms were entered simultaneously as they were relevant to study objectives and biologically plausible (not statistically significant in unadjusted comparisons) but not because of their importance. They represented demographic characteristics, treatment exposure, renal function, comorbidity, inflammation and candidate pharmacogenetic categories. Continuous effects were expressed per year of age, per mg/m²/day of initial dose, g of cumulative dose and per mg/L of CRP respectively. Adjusted ORs, 95% CIs and P values are given for every term. ORs describe relative odds and were not interpreted as risk ratios or evidence of causality. Renal impairment, diabetes and the three genetic indicators were modeled as binary variables. Reference categories were eGFR ≥60 mL/min/1.73 m², absence of diabetes, DPYD reference status at the tested loci, combined TYMS low/intermediate categories and CDA CC respectively. The adjusted model did not include treatment regimen, cancer type or MTHFR category so residual confounding by these characteristics remains possible. ROC analyses were performed for individual variables (initial dose, cumulative dose, CRP, NLR and eGFR) in the recorded inverse-risk orientation. Area under the curve (AUC), exploratory cut-off, sensitivity and specificity were summarized for each variable. Cut-offs were interpreted according to Youden-index principles (sensitivity + specificity − 1) [19]. These same-sample analyses summarized the apparent discrimination of individual markers; they did not assess the performance of the nine-variable logistic model. Calibration, optimism-corrected performance, and clinical utility of a multivariable prediction model were not established [20].

Complete-case analysis served as the primary method for the main comparisons and multivariable regression. Patients whose HFS status could not be determined or who had missing values for variables needed for a specific analysis were omitted from that analysis. Missing values were not imputed. Selection on data availability may introduce bias if patients with incomplete information differ systematically from those included.

Institutional Approval and Informed Consent

Baghdad Medical City (Ministry of Health) Republic of Iraq granted institutional authorization to the study. Center of Training and Human Development, Baghdad Medical City issued official no objection letter (no. 2646). All participants provided written informed consent before enrollment, including consent for the collection and storage of blood samples, pharmacogenetic testing, and the use of de-identified clinical and laboratory data for research purposes.

RESULTS

Clinical Characteristics

A total of 180 patients receiving capecitabine-containing treatment were included. The recorded classification was as follows: 97 patients with no/grade 1 HFS and 83 (46.1%) clinically significant HFS. Baseline characteristics are shown in Table **1**. No statistically significant differences were detected for age, body mass index, sex, cancer type, serum

creatinine, eGFR, or renal impairment. Diabetes was more frequent in the clinically significant HFS group (18/83, 21.7%) than in the no/grade 1 group (10/97, 10.3%; P = 0.058).

Data are mean ± standard deviation or n (%); percentages use the indicated column denominators. P values compare the two HFS groups and refer to the overall distribution for multilevel categories. eGFR, estimated glomerular filtration rate; HFS, hand-foot syndrome. The clinically significant group includes six cases with a nonstandard severity code, as described in Methods.

Capecitabine Dosing and Treatment Characteristics

Treatment characteristics are summarized in Table **2**. Regimen distribution differed between groups (P = 0.040). Capecitabine plus radiotherapy accounted for 22.9% of the clinically significant HFS group and 12.4% of the no/grade 1 group; capecitabine monotherapy accounted for 22.9% and 38.1%, respectively.

Table 1: Clinical Characteristics According to Recorded HFS Classification

Variable	Total (N=180)	No/grade 1 HFS (n=97)	Clinically significant HFS (n=83)	P value
Age, years	55.72 ± 10.40	56.33 ± 10.95	55.01 ± 9.73	0.394
Body mass index, kg/m²	26.39 ± 4.22	26.55 ± 4.01	26.21 ± 4.46	0.602
Sex: Female	94 (52.2)	51 (52.6)	43 (51.8)	1.000
Male	86 (47.8)	46 (47.4)	40 (48.2)	
Cancer type: Breast	53 (29.4)	34 (35.1)	19 (22.9)	0.165
Colorectal	92 (51.1)	44 (45.4)	48 (57.8)	
Gastric	35 (19.4)	19 (19.6)	16 (19.3)	
Diabetes: No	152 (84.4)	87 (89.7)	65 (78.3)	0.058
Yes	28 (15.6)	10 (10.3)	18 (21.7)	
Creatinine, mg/dL	1.02 ± 0.25	1.03 ± 0.23	1.01 ± 0.27	0.682
eGFR, mL/min/1.73 m²	67.59 ± 12.12	66.95 ± 12.94	68.33 ± 11.13	0.441
eGFR <60 mL/min/1.73 m²: No	131 (72.8)	68 (70.1)	63 (75.9)	0.482
Yes	49 (27.2)	29 (29.9)	20 (24.1)	

Table 2: Capecitabine Dosing and Treatment Characteristics

Variable	Total (N=180)	No/grade 1 HFS (n=97)	Clinically significant HFS (n=83)	P value
Treatment regimen: CAPOX	93 (51.7)	48 (49.5)	45 (54.2)	0.040
Capecitabine + radiotherapy	31 (17.2)	12 (12.4)	19 (22.9)	
Capecitabine monotherapy	56 (31.1)	37 (38.1)	19 (22.9)	
Body surface area, m²	1.72 ± 0.17	1.70 ± 0.17	1.73 ± 0.17	0.275
Initial capecitabine dose, mg/m²/day	2215.56 ± 323.61	2160.82 ± 332.17	2279.52 ± 302.89	0.013
Daily capecitabine dose, mg	3800.72 ± 651.90	3680.20 ± 652.53	3941.58 ± 626.05	0.007
Planned cycles	5.88 ± 1.43	5.56 ± 1.51	6.25 ± 1.24	<0.001
Relative dose intensity	0.90 ± 0.10	0.90 ± 0.10	0.90 ± 0.09	0.535
Recorded cumulative capecitabine dose, g	280.71 ± 88.29	254.39 ± 84.14	311.47 ± 83.36	<0.001

Recorded initial dose was higher in the clinically significant HFS group (2279.52 ± 302.89 versus 2160.82 ± 332.17 mg/m²/day; P = 0.013), as was daily dose (3941.58 ± 626.05 versus 3680.20 ± 652.53 mg; P = 0.007). This group also had more planned cycles (6.25 ± 1.24 versus 5.56 ± 1.51; P < 0.001) and a higher recorded cumulative dose (311.47 ± 83.36 versus 254.39 ± 84.14 g; P < 0.001). Relative dose intensity did not differ significantly (P = 0.535).

Data are mean ± standard deviation or n (%). CAPOX, capecitabine plus oxaliplatin; HFS, hand-foot syndrome. Relative dose intensity is the ratio of documented prescribed to planned dose intensity over the corresponding treatment period, with 1.00 representing 100%. Cumulative dose is the prescription-based course-level total adjusted for documented treatment changes. Actual tablet ingestion was not known and exposure before HFS onset was not separated from subsequent exposure.

Inflammatory Indices

CRP, NLR, PLR and SII were numerically similar between groups (no statistically significant differences in the unadjusted comparisons; Table S1). These results do not rule out absence of a clinically relevant association or local inflammatory mechanisms.

Pharmacogenetic Category Distributions

Pharmacogenetic distributions are shown in Table **3**. No statistically significant group differences were detected for *DPYD* status (P = 0.731) or *TYMS* category (P = 0.279).

MTHFR category distribution differed between groups (P = 0.012). The recorded wild-type category was more frequent in the clinically significant group, whereas the variant category contained 2/83 (2.4%) versus 13/97 (13.4%) patients. *CDA* variant status was recorded in 20/83 (24.1%) versus 12/97 (12.4%) patients (P = 0.064). These unadjusted comparisons do not establish an allele-specific or clinically actionable genetic effect.

Data are n (%). P values compare the full category distribution for each gene. *CDA*, cytidine deaminase; *DPYD*, dihydropyrimidine dehydrogenase; HFS, hand-foot syndrome; *MTHFR*, methylenetetrahydrofolate reductase; *TYMS*, thymidylate synthase. Marker definitions and genotype-to-category coding are described in Methods and Table **S3**. TYMS risk labels are exploratory study categories and are not validated dosing groups.

Recorded HFS Severity and Management

The recorded severity distribution was grade 0 in 49 patients (27.2%), grade 1 in 48 (26.7%), grade 2 in 46 (25.6%) and grade 3 in 31 (17.2%). Six patients (3.3%) had a nonstandard grade 4 code. These six (7.2% of the 83-patient clinically significant group) introduced uncertainty into the severity classification (Table **4**). HFS-related dose reduction was recorded in 60

Table 3: Recorded Pharmacogenetic Categories According to HFS Classification

Variable	Total (N=180)	No/grade 1 HFS (n=97)	Clinically significant HFS (n=83)	P value
DPYD status: Wild-type	160 (88.9)	85 (87.6)	75 (90.4)	0.731
Heterozygous variant	20 (11.1)	12 (12.4)	8 (9.6)	
TYMS category: Low-risk	96 (53.3)	55 (56.7)	41 (49.4)	0.279
Intermediate	63 (35.0)	34 (35.1)	29 (34.9)	
High-risk	21 (11.7)	8 (8.2)	13 (15.7)	
MTHFR status: Wild-type	85 (47.2)	39 (40.2)	46 (55.4)	0.012
Heterozygous	80 (44.4)	45 (46.4)	35 (42.2)	
Variant	15 (8.3)	13 (13.4)	2 (2.4)	
CDA status: Wild-type	148 (82.2)	85 (87.6)	63 (75.9)	0.064
Variant	32 (17.8)	12 (12.4)	20 (24.1)	

Table 4: Recorded HFS Severity and Clinical Management

Outcome/management indicator	Total (N=180)	No/grade 1 HFS (n=97)	Clinically significant HFS (n=83)	P value
HFS grade: 0	49 (27.2)	49 (50.5)	0 (0.0)	—
HFS grade: 1	48 (26.7)	48 (49.5)	0 (0.0)	
HFS grade: 2	46 (25.6)	0 (0.0)	46 (55.4)	
HFS grade: 3	31 (17.2)	0 (0.0)	31 (37.3)	
Nonstandard severity category	6 (3.3)	0 (0.0)	6 (7.2)	
Dose reduction due to HFS	60 (33.3)	0 (0.0)	60 (72.3)	<0.001
Treatment delay due to HFS	39 (21.7)	0 (0.0)	39 (47.0)	<0.001
Treatment interruption due to HFS	22 (12.2)	0 (0.0)	22 (26.5)	<0.001
Hospitalization due to HFS	13 (7.2)	0 (0.0)	13 (15.7)	<0.001
Emollient/topical management	119 (66.1)	49 (50.5)	70 (84.3)	<0.001
Pyridoxine/systemic support	71 (39.4)	21 (21.6)	50 (60.2)	<0.001

Table 5: Multivariable Associations with Recorded Clinically Significant HFS

Variable and unit	Adjusted OR	95% CI	P value
Age, per year	1.01	0.97–1.05	0.616
Initial capecitabine dose, per mg/m^2/day	1.00	1.00–1.00	0.268
Recorded cumulative capecitabine dose, per g	1.01	1.00–1.01	<0.001
Renal impairment, eGFR <60 mL/min/1.73 m^2	1.18	0.39–3.56	0.766
Diabetes	3.46	1.34–8.92	0.010
CRP, per mg/L	1.03	0.96–1.10	0.424
DPYD variant indicator	1.02	0.36–2.92	0.971
TYMS high-risk indicator	2.17	0.77–6.08	0.142
CDA variant indicator	2.56	1.06–6.16	0.036

patients (33.3% of the full cohort; 72.3% of the clinically significant group), delay in 39 (21.7%; 47.0%), interruption in 22 (12.2%; 26.5%), and hospitalization in 13 (7.2%; 15.7%). Each occurred only in the clinically significant group (all $P < 0.001$). Topical management and pyridoxine/systemic supportive management were also more frequent in this group. These observations describe management patterns and do not estimate the effectiveness of supportive treatments.

Data are n (%). HFS, hand-foot syndrome; CTCAE, Common Terminology Criteria for Adverse Events. The nonstandard category contains six cases coded as grade 4 (not a CTCAE version 5.0 grade for HFS). Their binary group assignment is retained without regrading. No P value is shown for severity because severity defines the comparison groups. Management indicators are reported separately and not summed to obtain a patient total.

Adjusted Associations

Adjusted estimates for all nine model terms are presented in Table **5**. Recorded cumulative dose was associated with clinically significant HFS (adjusted OR 1.01 per g, 95% CI 1.00–1.01; P < 0.001). Two-decimal rounding limits interpretation of this small per-unit effect; a displayed confidence limit of 1.00 must not be interpreted as an exact boundary at the null. Diabetes was associated with higher adjusted odds (OR 3.46, 95% CI 1.34–8.92; P = 0.010), as was the recorded *CDA* variant category (OR 2.56, 95% CI 1.06–6.16; P = 0.036).

No statistically significant adjusted associations were detected for age, initial dose, renal impairment, CRP, *DPYD* variant status, or *TYMS* high-risk status. Wide confidence intervals for several categorical terms indicate substantial uncertainty.

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HFS, hand-foot syndrome. Estimates are adjusted for the nine terms displayed. Dose effects are per 1 mg/m2 day of initial dose and per 1 g cumulative dose. ORs displayed and confidence limits have two decimal places; values shown as 1.00 do not imply an exact null effect or zero width interval. These rounded dose estimates are not sufficient to accurately rescale to larger increments. Genetic coding is described in Methods and Table **S3**.The outcome includes the six nonstandard severity codes described in Methods.

Exploratory Single-Marker Discrimination

The single-marker ROC summaries are presented in Table **S2**. Recorded cumulative dose had the highest observed AUC (0.683), exploratory cut-off 289.10 g, sensitivity 0.627 and specificity 0.680. Initial dose had an AUC of 0.602. These are apparent estimates from the analyzed sample; there was no formal difference between AUCs. CRP and NLR had AUCs of 0.531 and 0.518 respectively; the eGFR analysis (inverse risk) had an AUC of 0.464 and did not discriminate in that orientation. The cumulative-dose cut-off was not interpreted as a threshold for changing treatment or initiating a monitoring intervention.

DISCUSSION

In this observational analysis associations were found between recorded cumulative capecitabine dose, diabetes and CDA variant category with recorded clinically significant HFS classification after adjustment for the covariates included. These results describe associations in the analyzed cohort but do not establish causal determinants, a validated prediction model or genotype-directed dosing strategy. The patients in the clinically significant HFS group had higher recorded initial and daily doses, more planned cycles and greater cumulative dose. The dose-related pattern is consistent with previous clinical findings [3, 5, 7, 8]. But a total dose recorded across a course combines intensity (treatment) with time on therapy (exposure). Longer exposure gives more opportunity for both dose and toxicity to accumulate; HFS can interrupt or reduce subsequent dose through interruptions or reductions. The course level association therefore cannot rule out that the total dose preceded HFS or identify an exposure threshold. The event-time approach used in the recent competing-risk study highlights a design requirement for future dose-toxicity analyses [3].

Cumulative dose showed modest apparent single-marker discrimination, with an AUC of 0.683. The 289.10-g cut-off was derived and assessed in the same sample and is susceptible to optimism. It cannot be used as a treatment threshold, a validated monitoring trigger, or evidence that the multivariable model predicts individual outcomes accurately. Future evaluation should distinguish discrimination, calibration, and clinical utility and should include appropriate internal and external validation [20, 21].

The diabetes association is clinically relevant and similar to an earlier capecitabine based cohort [9]. Nevertheless, only 28 patients had diabetes, and the adjusted CI was wide. Diabetes may also correlate with vascular, neurological, renal, or treatment-related characteristics that were not fully represented in the model. It may warrant attention during routine toxicity assessment, but this study did not test whether diabetes-specific monitoring or preventive intervention improves outcomes.

The *CDA* association merits further investigation. CDA is activated by capecitabine and studies have previously looked at specific CDA variants in relation to HFS [15, 17]. The association in this small candidate gene analysis does not prove causality or support CDA dose modification. Lack of a statistically significant DPYD association does not refute established fluoropyrimidine safety recommendations related to DPYD because the outcome here was HFS classification rather than full spectrum severe systemic toxicity [1, 13, 14]. MTHFR category frequencies differed in the unadjusted analysis but only 15 patients

were in the variant category and two of them were in the clinically significant HFS group. Direction cannot be interpreted as general harmful-variant effect. There is no adjusted MTHFR estimate, small genotype subgroups and multiple comparisons so interpretation is limited. Studies that measure folate pathway biology should also consider measured folate and nutritional characteristics; earlier work linked folate status to HFS susceptibility [5]. No statistically significant differences were found for the systemic inflammatory indices. That does not rule out inflammation as a cause of local skin toxicity: Capecitabine-specific experimental studies point to local inflammatory pathways; human work supports disruption of skin barrier with local fluorouracil accumulation [10, 12]. The hydrocortisone study in 2025 looked at a local preventive approach but because it was single arm did not establish comparative preventive efficacy (11). Mechanisms and interventions like these should be distinguished from prediction using circulating CRP or blood cell ratios. The frequency of dose reduction, delay, interruption and hospitalization highlights how treatment burden of HFS can be. Patient education, early symptom reporting, skin care and toxicity-guided dose modification are still clinically relevant [1, 2]. A 2025 randomized trial showed lower grade ≥2 HFS with methylcobalamin in women with HER2-negative early breast cancer (proof that preventive strategies need direct comparison) [4]. That result cannot be applied to the pyridoxine/systemic-support category in this cohort because it combined recorded management practices and was not a randomized intervention. The study combines dose descriptors, comorbidity, inflammatory indices and candidate pharmacogenetic categories in an Iraqi oncology cohort. Its main contribution is description of these associations with clinically relevant treatment-management outcomes. Several limitations limit interpretation. The observational design precludes causal inference. Selection was based on available clinical, laboratory and pharmacogenetic information so selection bias is possible. Follow-up differences and incomplete covariate information may affect estimates. Treatment regimen differed between groups but was not included in the adjusted model; cancer type, treatment duration, cancer stage, concurrent therapy and supportive care confound associations as well. The small cohort size, nine-term model and small genotype strata reduce precision of multivariable estimates. The number of participants and outcome events do not provide information for all adjusted associations [21]. Wide confidence intervals, uncertain exposure timing, six nonstandard severity codes and limited genotype-group sizes affect stability and reproducibility of the findings. Candidate panel does not cover variation in genes examined comprehensively. This analysis does not establish model calibration, optimism-corrected performance or external validity. Reproducible genetic association reporting also requires laboratory quality control results and transparent reporting of genotype failures [22].

CONCLUSION

Cumulative capecitabine dose recorded, diabetes and CDA variant category were associated with clinically significant HFS classification in this exploratory observational study. Exposure timing, outcome grading and pharmacogenetic characterization uncertainty and limited model evaluation preclude use of the reported cut-offs or genetic categories as clinical decision rules; future studies should define exposure before onset of HFS, assess outcomes standardized to patients' groups, control for treatment-related confounding and evaluate reproducibility before application to clinical practice.

AUTHOR CONTRIBUTIONS

Mahmoud Kamil Ismaeil, Ayad Rateb Al-Asadi, and Mahmood Sh. Abdulrahman contributed to the study, participated in the preparation or critical revision of the manuscript, and reviewed and approved the final version.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICAL STATEMENT

Baghdad Medical City, Ministry of Health, Republic of Iraq, granted institutional authorization for this study through the Center of Training and Human Development (no-objection letter No. 2646). All participants provided written informed consent before enrollment, including consent for blood collection and storage, pharmacogenetic testing, and use of de-identified clinical and laboratory data for research purposes.

SUPPLEMENTARY MATERIALS

The supplementary materials can be downloaded from the journal website along with the article.

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Received on 01-10-2026 Accepted on 29-10-2026 Published on 23-11-2026

https://doi.org/10.30683/1929-2279.2026.15.36

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