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Development of a risk prediction nomogram model of pyrotinib-induced severe diarrhea

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Abstract

Background To identify the factors influencing pyrotinib-induced severe diarrhea and to establish a risk prediction nomogram model.

Methods The clinical data of 226 patients received pyrotinib from two medical institutions from January 2019 to December 2023 were analysed retrospectively. A training set was made up of 167 patients from Hainan Cancer Hospital, and the external validation set was made up of 59 patients from Hainan West Central Hospital. Univariate and multivariate logistic regression analysis were used to identify independent factors influencing pyrotinib-induced severe diarrhea, and a risk prediction nomogram model was constructed, which was verified on patients in the external validation set.

Results History of adverse reactions (ADRs), initial dose of pyrotinib, combination with capecitabine, thrombocytopenia, aspartate transaminase (AST), and use of probiotics or other drugs that regulate the gut microbiota were identified as independent influencing factors for pyrotinib-induced severe diarrhea (all $P<0.05$). Based on these, a risk prediction nomogram model of pyrotinib-induced severe diarrhea was established. The area under the receiver operating characteristic curve was 0.794 and 0.863 in the training set and the external validation set, respectively. The calibration curve of the prediction model displayed good consistency both the two sets, which indicated that the model could have favourable predictive ability.

Conclusion The risk prediction nomogram model of pyrotinib-induced severe diarrhea constructed in this study may identify high risk populations earlier so that clinicians can make appropriate decisions in time.

Keywords Pyrotinib, Severe diarrhea, Prediction model, Nomogram

Introduction

Pyrotinib was approved for marketing in August 2018 as an irreversible small-molecule receptor tyrosine kinase inhibitor (TKI) of human epidermal growth factor receptor-2 (HER-2). It was independently developed in China. Pyrotinib has demonstrated excellent therapeutic effects in the treatment of HER-2-positive breast cancer [1]. Diarrhea is the most common adverse effect of pyrotinib, having an incidence rate of 85.7–98.4% and the incidence rate of grade 3 diarrhea is 10.7–31% [2–6]. Diarrhea not only impairs quality of life and therapy compliance but also leads to dehydration, electrolyte imbalance, and even

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a potential threat to life in severe cases. Diarrhea has become an obstacle to the clinical application of pyrotinib. Therefore, early intervention against diarrhea is crucial for improving patient compliance with pyrotinib, quality of life and treatment outcomes [6]. This study aims to identify the factors influencing pyrotinib-induced severe diarrhea and establish a risk prediction nomogram model that will serve as a reference for identifying high risk populations and clinicians can take corresponding measures early.

Materials and methods

General data

Patients treated with pyrotinib at Hainan West Central Hospital and Hainan Cancer Hospital from January 2019 to December 2023 were enrolled in this study.

Inclusion criteria: (1) patients were treated with pyrotinib for the first time, and (2) patients' age must be between 18 and 80 years. Exclusion criteria: (1) pyrotinib was used prior; (2) pyrotinib was used for diseases other than breast cancer; (3) diarrhea was caused by anything else; and (4) incomplete medical records affecting the data relevant to this study or the missing rate ≥ 10% [7].

According to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [8], diarrhea was ranked as grade 0–4. grade 0–2 was as non-severe diarrhea subgroup and grade 3–4 was as severe diarrhea subgroup.

Data collection

This study used electronic medical records to collect medical records retrospectively. The data were put into Excel tables and verified by another person.

Medical records before pyrotinib included: (1) general information, including sex, age, body mass index (BMI), body surface area (BSA), family history of breast cancer, underlying disease such as hypertension or diabetes, chronic intestinal disease, oral or intravenous use of antibiotics within three months, and history of (ADRs); (2) disease status: hormone receptor status, pathological type, disease stage, and Ki-67 index; (3) laboratory examination: white blood cells, platelets, hemoglobin (Hb), blood natrium, blood chloride, blood potassium, albumin, lactate dehydrogenase, alkaline phosphatase (ALP), AST, alanine transaminase (ALT), total bilirubin, creatinine, and CA-153. Medical records received pyrotinib included: (1) treatment plans: treatment objectives, initial dose of pyrotinib, and combination with capecitabine; (2) combined drugs, including potassium/ sodium ion channel inhibitors, strong inhibitors of Share Cytochrome P3A4 Enzymes (CYP3A4), antibiotics, probiotics or other drugs that regulate the gut microbiota.

Statistical methods

SPSS 22.0 software was used for univariate and multivariate logistic regression analysis to screen influencing factors and it was also used to compare the consistency of variables between the training set and the external validation set. Normally distributed continuous variables are given as mean ± standard deviation, and Student's t test was used to analyse their intergroup differences. Categorical variables are described as n (%), and the chi-squared test or Fisher's exact probability test was used to find intergroup differences. The R (version 4.2) software packages car, rms, pROC, and rmda were used to construct a nomogram prediction model. The bootstrap method was used to resample the model 1000 times for internal validation, and external validation was conducted using data from the external validation set. The discrimination and consistency of the model were tested using receiver operating characteristic (ROC) curves and calibration curves. The level of significance was $\alpha = 0.05$.

Results

Basic characteristics of patients

A total of 226 patients received pyrotinib from two medical centres were included in this study. Medical data of 167 patients from Hainan Cancer Hospital were used for the training set and 59 patients from Hainan West Central Hospital were used for the external validation set. The flow chart of analysis in this study was shown in Fig. 1. In the training set, the cases of grade 0–4 diarrhea were 13, 58, 44, 46 and 6, respectively. 52 patients (31.14%) suffered severe diarrhea, and 165 patients (98.81%) were female. In the external validation set, the cases of grade 0–4 diarrhea were 6, 17, 20, 13 and 3, respectively. 16 patients (27.11%) suffered severe diarrhea, and all 59 patients (100%) were female. The basic characteristics of the two sets are summarized in Table 1.

Construction and validation of the risk prediction nomogram model for patients with pyrotinib-induced severe diarrhea

Univariate logistic regression analysis was used to screened out potentially meaningful variables preliminarily. Through univariate logistic regression analysis, we identified eight predictors from 35 variables, including BMI>24, History of ADR, initial dose of pyrotinib, combination with capecitabine, thrombocytopenia, AST, ALT and combination with probiotics or other drugs that regulate the intestinal flora (all $P < 0.05$). They were presented in Supplementary Material 1. Then, multivariate logistic regression analysis was used to further determine the meaningful variables. Finally, we confirmed six meaningful variables related to pyrotinib-induced severe diarrhea, including history of ADR, initial dose of pyrotinib, combination with capecitabine, thrombocytopenia,

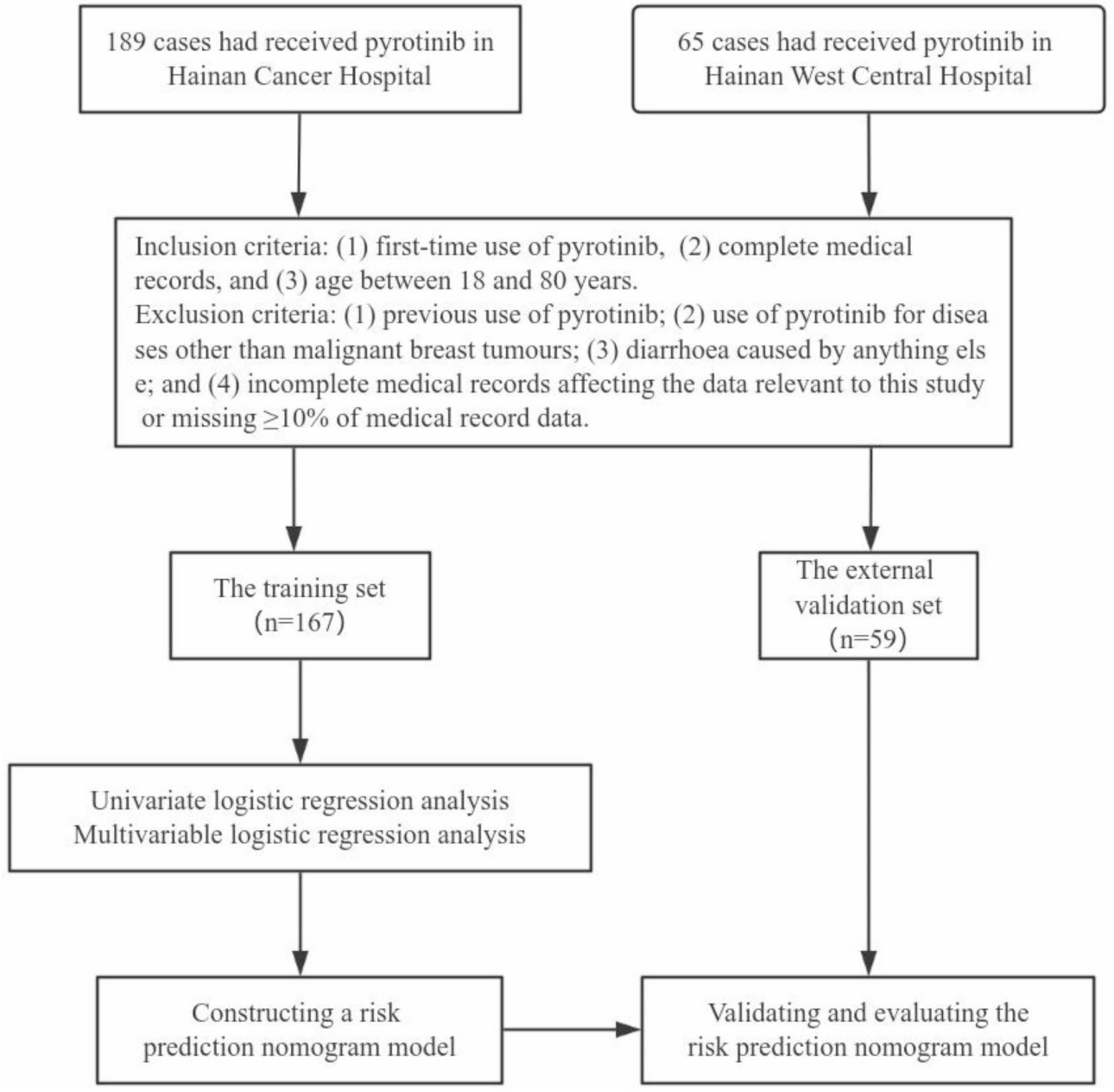

Fig. 1 The flow chart of analysis in this study

AST, and combination with probiotics or other drugs that regulate the intestinal flora (all $P<0.05$), as shown in Table 2 and the Forest plots in Fig. 2A. By incorporating independent risk factors above into the prediction model, we constructed a risk prediction nomogram model for pyrotinib-induced severe diarrhea with the R (version 4.2) software packages. The risk prediction nomogram model was presented in Fig. 2B. As we can see, in the nomogram model, each level of each predictor has a corresponding point, the longer the bar, the higher the score; the higher the total score, and the greater the probability of severe diarrhea. It can visually predict the probability of severe diarrhea after receiving pyrotinib and is easier to apply in the clinical practice.

The area under the ROC curve in the training set was 0.794, with a 95% confidence interval (CI) of 0.724–0.864, a sensitivity of 0.635, a specificity of 0.817, and the Youden index of 0.452, as shown in Fig. 3A. It had an area under the ROC curve in the external validation set of 0.863, with a 95% CI of 0.767–0.959 and the Youden index of 0.503, as shown in Fig. 3B. These data indicated that the model has good prediction accuracy for distinguishing those at risk of severe diarrhea caused by pyrotinib. The Hosmer-Lemeshow test analysis for the

Table 1 Baseline demographic and clinicopathological characteristics in the training set and external validation set

Characteristics	Training set			External validation set		
	No severe diarrhea	Severe diarrhea	*p*	No severe diarrhea	Severe diarrhea	*p*
	n = 115 (%)	*n* = 52 (%)		*n* = 43(%)	*n* = 16(%)	
Gender			0.850			-
Male	2 (1.74)	0 (0.00)		0 (0.00)	0 (0.00)	
Female	113 (98.26)	52(100.00)		43 (100.00)	16 (100.00)	
Age			0.268			0.300
≤50	45 (39.13)	15 (28.85)		16 (37.21)	3 (18.75)	
>50	70 (60.87)	37 (71.15)		27 (62.79)	13 (81.25)	
BSA[a]	1.51[1.45; 1.60]	1.52[1.43; 1.62]	0.902	1.50[1.45; 1.57]	1.47[1.42; 1.58]	0.550
BMI			0.011			0.444
≤24	90 (78.26)	30 (57.69)		33 (76.74)	10 (62.50)	
>24	25 (21.74)	22 (42.31)		10 (23.26)	6 (37.50)	
Family history of breast cancer			0.850			-
No	113 (98.26)	52(100.00)		43 (100.00)	16 (100.00)	
Yes	2 (1.74)	0 (0.00)		0 (0.00)	0 (0.00)	
Underlying disease			0.925			0.565
No	93 (80.87)	41 (78.85)		32 (74.42)	10 (62.50)	
Yes	22 (19.13)	11 (21.15)		11 (25.58)	6 (37.50)	
Chronic intestinal disease			0.683			-
No	114 (99.13)	52(100.00)		43 (100.00)	16 (100.00)	
Yes	1 (0.87)	0 (0.00)		0 (0.00)	0 (0.00)	
Oral or intravenous use of antibiotics within three months			0.257			0.421
No	102 (88.70)	42 (80.77)		35 (81.40)	15 (93.75)	
Yes	13 (11.30)	10 (19.23)		8 (18.60)	1 (6.25)	
History of ADRs			0.026			1.000
No	24 (20.87)	3 (5.77)		11 (25.58)	4 (25.00)	
Yes	91 (79.13)	49 (94.23)		32 (74.42)	12 (75.00)	
Hormone receptor status			0.820			1.000
HR-Negative HER2-Positive	94 (81.74)	41 (78.85)		36 (83.72)	13 (81.25)	
HR-Positive HER2-Positive	21 (18.26)	11 (21.15)		7 (16.28)	3 (18.75)	
Pathological type			0.862			0.604
Invasive carcinoma	114 (99.13)	52(100.00)		43 (100.00)	15 (93.75)	
Micropapillary carcinoma	1 (0.87)	0 (0.00)		0 (0.00)	1 (6.25)	
Disease stage			0.072			0.368
Stage I-III;	17 (14.78)	2 (3.85)		5 (11.63)	0 (0.00)	
Stage IV	98 (85.22)	50 (96.15)		38 (88.37)	16 (100.00)	
Ki-67 index			1.000			0.943
<30%	37 (32.17)	17 (32.69)		13 (30.23)	4 (25.00)	

Table 1 (continued)

Characteristics	Training set			External validation set		
	No severe diarrhea	Severe diarrhea	*p*	No severe diarrhea	Severe diarrhea	*p*
	n = 115 (%)	*n* = 52 (%)		*n* = 43(%)	*n* = 16(%)	
≥30%	78 (67.83)	35 (67.31)		30 (69.77)	12 (75.00)	
Treatment objectives			0.096			1.000
Postoperative treatment	0 (0.00)	2 (3.85)		1 (2.33)	0 (0.00)	
Salvage treatment	115(100.00)	50 (96.15)		42 (97.67)	16 (100.00)	
Initial dose of pyrotinib			< 0.001			< 0.001
Normal	27 (23.48)	44 (84.62)		11 (25.58)	16 (100.00)	
Reduce	88 (76.52)	8 (15.38)		32 (74.42)	0 (0.00)	
Combination with capecitabine			< 0.001			< 0.001
No	68 (59.13)	15 (28.85)		28 (65.12)	2 (12.50)	
Yes	47 (40.87)	37 (71.15)		15 (34.88)	14 (87.50)	
Leukopenia			1.000			0.086
No	26 (22.61)	12 (23.08)		12 (27.91)	9 (56.25)	
Yes	89 (77.39)	40 (76.92)		31 (72.09)	7 (43.75)	
Hb decreased			0.925			0.568
No	93 (80.87)	41 (78.85)		27 (62.79)	12 (75.00)	
Yes	22 (19.13)	11 (21.15)		16 (37.21)	4 (25.00)	
Thrombocytopenia			0.069			0.086
No	90 (78.26)	33 (63.46)		31 (72.09)	7 (43.75)	
Yes	25 (21.74)	19 (36.54)		12 (27.91)	9 (56.25)	
Hyperlipidaemia			0.332			0.962
No	79 (68.70)	31 (59.62)		28 (65.12)	11 (68.75)	
Yes	36 (31.30)	21 (40.38)		15 (34.88)	5 (31.25)	
Hypochloremia			0.517			0.538
No	97 (84.35)	41 (78.85)		37 (86.05)	12 (75.00)	
Yes	18 (15.65)	11 (21.15)		6 (13.95)	4 (25.00)	
Hyponatremia			0.048			0.880
No	115(100.00)	49 (94.23)		40 (93.02)	14 (87.50)	
Yes	0 (0.00)	3 (5.77)		3 (6.98)	2 (12.50)	
Hypokalemia			0.097			0.153
No	93 (80.87)	48 (92.31)		35 (81.40)	16 (100.00)	
Yes	22 (19.13)	4 (7.69)		8 (18.60)	0 (0.00)	
Other blood electrolyte were normal			0.569			0.716
No	82 (71.30)	40 (76.92)		34 (79.07)	14 (87.50)	
Yes	33 (28.70)	12 (23.08)		9 (20.93)	2 (12.50)	
Hypoproteinemia			0.176			0.961
No	96 (83.48)	38 (73.08)		36 (83.72)	14 (87.50)	
Yes	19 (16.52)	14 (26.92)		7 (16.28)	2 (12.50)	

Table 1 (continued)

Characteristics	Training set			External validation set		
	No severe diarrhea	Severe diarrhea	*p*	No severe diarrhea	Severe diarrhea	*p*
	n = 115 (%)	*n* = 52 (%)		*n* = 43(%)	*n* = 16(%)	
Lactate dehydrogenase increased			0.073			0.335
No	80 (69.57)	28 (53.85)		34 (79.07)	10 (62.50)	
Yes	35 (30.43)	24 (46.15)		9 (20.93)	6 (37.50)	
Total bilirubin increased			0.189			0.916
No	84 (73.04)	32 (61.54)		31 (72.09)	12 (75.00)	
Yes	31 (26.96)	20 (38.46)		12 (27.91)	4 (25.00)	
AST increased			< 0.001			< 0.001
No	102 (88.70)	26 (50.00)		41 (95.35)	8 (50.00)	
Yes	13 (11.30)	26 (50.00)		2 (4.65)	8 (50.00)	
ALT increased			< 0.001			0.020
No	105 (91.30)	28 (53.85)		32 (74.42)	6 (37.50)	
Yes	10 (8.70)	24 (46.15)		11 (25.58)	10 (62.50)	
ALP increased			1.000			0.147
No	106 (92.17)	48 (92.31)		40 (93.02)	12 (75.00)	
Yes	9 (7.83)	4 (7.69)		3 (6.98)	4 (25.00)	
Creatinine increased			0.586			0.583
No	94 (81.74)	45 (86.54)		33 (76.74)	14 (87.50)	
Yes	21 (18.26)	7 (13.46)		10 (23.26)	2 (12.50)	
CA153 increased			0.149			0.828
No	79 (68.70)	29 (55.77)		30 (69.77)	10 (62.50)	
Yes	36 (31.30)	23 (44.23)		13 (30.23)	6 (37.50)	
Combination with strong inhibitors of CYP3A4						0.604
No	115(100.00)	51 (98.08)	0.683	43 (100.00)	15 (93.75)	
Yes	0 (0.00) (19.13)	1 (1.92)		0 (0.00)	1 (6.25)	
Combination with antibiotics			0.285			0.676
No	107 (93.04)	45 (86.54)		40 (93.02)	16 (100.00)	
Yes	8 (6.96)	7 (13.46)		3 (6.98)	0 (0.00)	
Combination with probiotic or other gut microbiota			< 0.001			0.045
No	82 (71.30)	50 (96.15)		31 (72.09)	16 (100.00)	
Yes	33 (28.70)	2 (3.85)		12 (27.91)	0 (0.00)	

[a]The BSA was presented as mean ± standard deviation

Table 2 Multivariate logistic regression analyses of pyrotinib-induced severe diarrhea from training set

	Estimate	SE	Wald	*P*	OR	95%CI
(Intercept)	-3.205	1.043	-3.072	0.002	0.041	0.005–0.314
BMI>24	0.565	0.638	0.885	0.376	1.760	0.504–6.149
ADR_before Yes	2.565	1.023	2.507	0.012	12.998	1.749–96.570
Pyrotinib Reduce	-3.870	0.809	-4.784	< 0.001	0.021	0.004–0.102
Capecitabine Yes	1.405	0.651	2.160	0.031	4.077	1.139–14.595
Thrombocytopenia Yes	1.740	0.774	2.248	0.025	5.696	1.250-25.955
AST_increased Yes	2.971	0.957	3.105	0.002	19.511	2.992-127.237
ALT_increased Yes	1.416	0.946	1.498	0.134	4.123	0.646–26.315
Probiotic Yes	-3.251	1.198	-2.714	0.007	0.039	0.004–0.405

training set and the external validation set showed *P* values of 0.298 and 0.478, respectively ($P > 0.05$). It is demonstrated that the risk prediction nomogram model had a good fit. The calibration curve analysis showed that the prediction probability of the nomogram model for pyrotinib-induced severe diarrhea was close to the actual probability, as shown in Fig. 3C and D.

The results of the decision curve analysis showed that the net benefit of construction set and validation set was superior to both the all curve and none curve. The threshold probabilities of the training set and the external validation set were 0–85% and 0–92%, respectively, as shown in Fig. 3E. Patients who are likely to suffer from pyrotinib-induced severe diarrhea may benefit by early identification based on this prediction nomogram model, which has clinical significance.

Discussion

Pyrotinib is a novel irreversible TKI of the HER receptor that was independently developed in China. It significantly inhibits the expression of the epithelial growth factor receptor (EGFR) / HER-1, HER-2, and HER-4 receptors [9, 10]. Diarrhea is the most common adverse event during pyrotinib treatment, and severe diarrhea is the main cause of pyrotinib reduction and discontinuation [6, 11]. Studies have demonstrated that the implementation of an effective management strategy of diarrhea can improve the tolerance of pyrotinib and significantly reduce the incidence and duration of severe diarrhea [6, 11, 12]. Therefore, how to accurately identify high-risk individual for severe diarrhea caused by pyrotinib early has become an urgent clinical problem.

This study retrospectively analysed the clinical data of 226 patients from January 2019 to December 2023, who took pyrotinib at Hainan West Central Hospital or Hainan Cancer Hospital. Univariate and multivariable logistic regression analysis revealed that a history of ADRs, initial dose of pyrotinib, combination with capecitabine, thrombocytopenia, AST, and combination with probiotics or other drugs that regulate the intestinal flora were independent risk factors associated with pyrotinib-induced severe diarrhea ($P < 0.05$). However, the results of another study showed that factors such as age and BMI are not associated with pyrotinib-induced diarrhea, while the Eastern Cooperative Oncology Group (ECOG) score is a risk factor for the occurrence of diarrhea during the first week of pyrotinib [13]. This is inconsistent with the results of our study, which may be related to the incomplete inclusion of factors in the models, different subgroup designs, and small sample sizes.

In China, pyrotinib combined with capecitabine has been used as a commonly recommended treatment regimen for patients who failed to be treated with trastuzumab [1]. Capecitabine is an analogue of fluoropyrimidine nucleosides, and diarrhea is also one of its most common adverse effect [14–16]. The results of this study indicated that combination with capecitabine is an independent risk factor for pyrotinib-induced severe diarrhea. In other words, the severity of diarrhea may be higher when pyrotinib is combined with capecitabine. The results of this study was similar to other relevant studies [2, 17] on pyrotinib combined with capecitabine.

This study found the risk of severe diarrhea would increase by 2.565-fold for the patients who experienced ADRs during previous antitumour treatments. Compared with patients with normal platelet counts, the risk of severe diarrhea increased by 1.740-fold in patients with low platelet counts. No other research ever reported a direct correlation between thrombocytopenia and diarrhea. However, when patients undergo antitumour treatment, they often experience ADRs due to mistaken injury of normal cells and tissues. When immune cells are injured, they inhibit the function of the whole body's immune system. Therefore, most patients with malignant tumours experience a decreased immune function after undergoing multiline antitumour treatment [18–20]. The immune microenvironment would be changed after the occurrence of thrombocytopenia. The patients are more likely to suffer adverse drug reactions such as diarrhea in subsequent treatment.

Pyrotinib is highly bound to plasma proteins, ranging from 86.9 to 99.7%, and mainly metabolized by hepatic cytochrome P450 3A4 enzymes. Ultimately, 90.9% of pyrotinib and its metabolites are excreted from the body

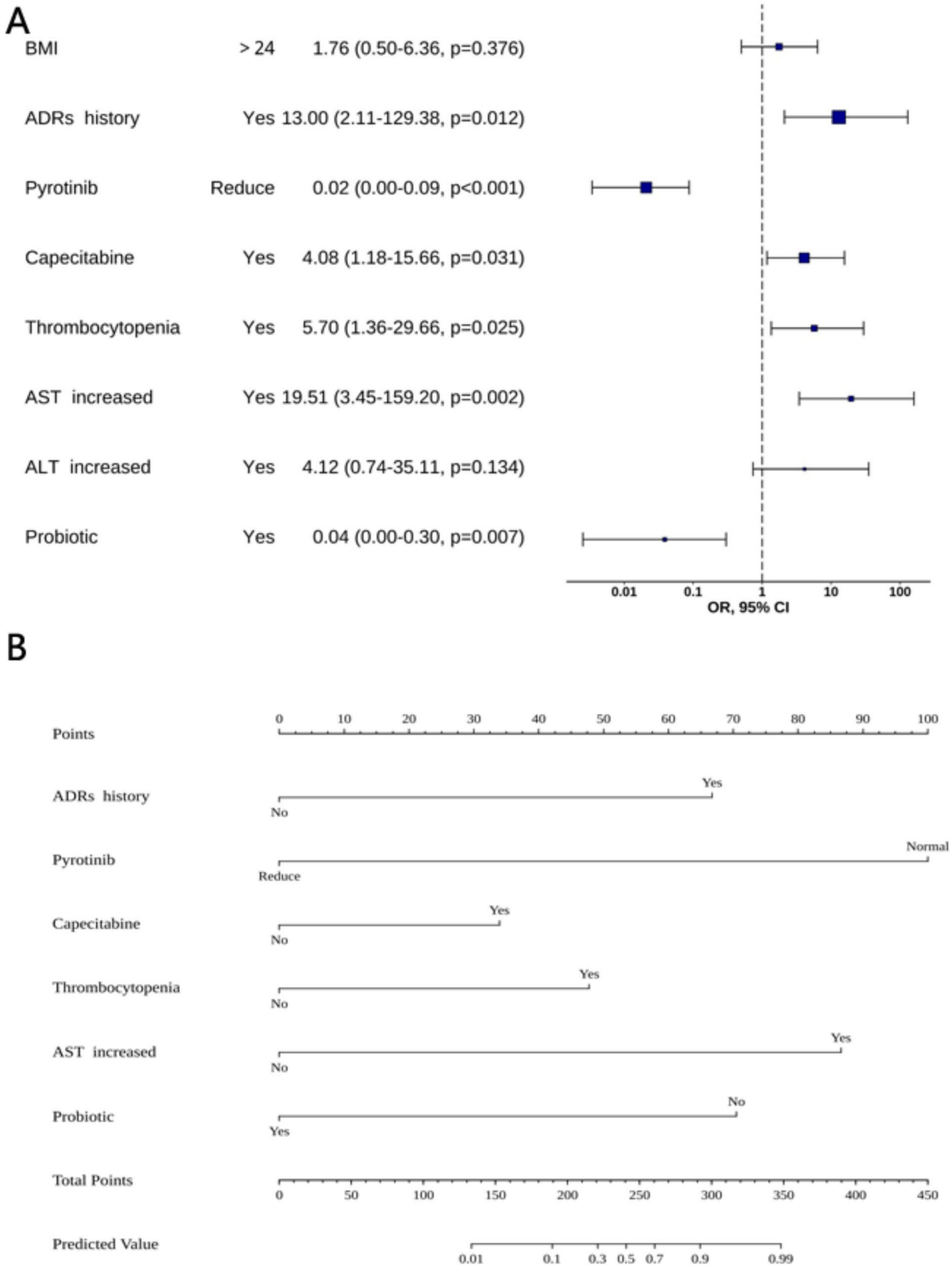

Fig. 2 Prediction nomogram model for risk of pyrotinib-induced severe diarrhea. (**A**) Forest plots of the multivariate logistic regression analysis. (**B**) Nomogram of the prediction model for pyrotinib-induced severe diarrhea in the training set. To estimate the risk of pyrotinib- induced severe diarrhea, the points for each variable were calculated by drawing a straight line from the patient's variable value to the axis labeled "points". The total points were converted to "probability of pyrotinib- induced severe diarrhea" on the lowest axis

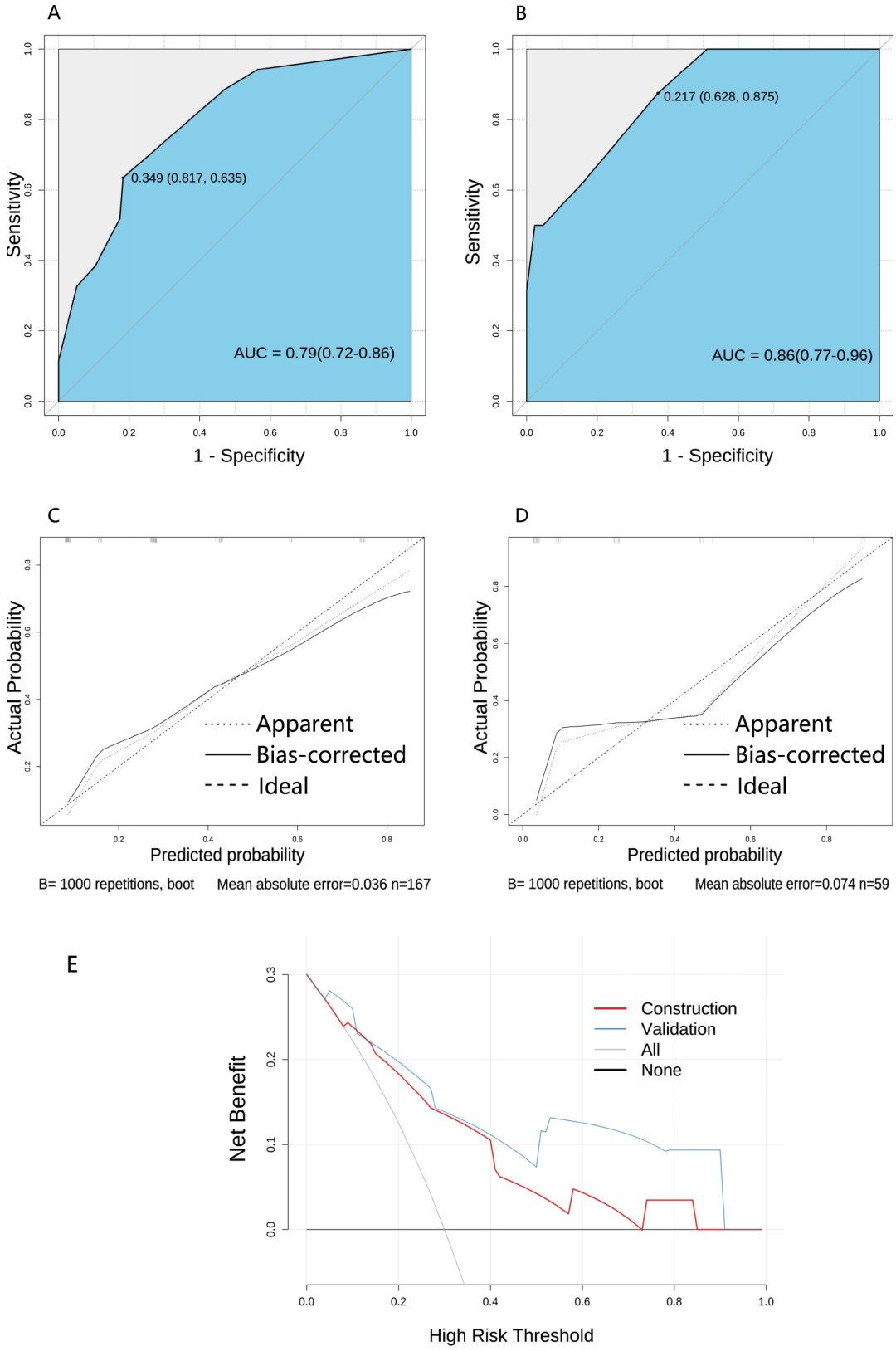

Fig. 3 The performance of the nomogram model to predict the probability of pyrotinib-induced severe diarrhea. ROC curves and AUCs to evaluate the prediction accuracy in training set (**A**), and the external validation set (**B**), the AUC was 0.794 and 0.863, respectively.Calibration curves to assess the agreement of actual probabilities and predicted probabilities for prediction accuracy in the training set (**C**) and the external validation set (**D**). The decision curve analysis of the risk prediction nomogram model of pyrotinib-induced severe diarrhea was in (**E**)

in the faeces, and 1.7% are excreted in the urine [21, 22]. Therefore, the combination of strong CYP3A4 inhibitors such as itraconazole, fluconazole, and grapefruit juice during pyrotinib can affect the metabolism of pyrotinib. There is an elevated risk and increased severity of adverse reactions once pyrotinib accumulates in the body. Since only two of the 226 patients in this study used strong CYP3A4 inhibitors while taking pyrotinib, it was impossible to determine the relationship between the combination of strong CYP3A4 inhibitors and severe diarrhea. In addition, the results of this study showed that elevated AST was an independent risk factor for severe diarrhea associated with pyrotinib. Compared to patients with normal AST levels, patients with elevated AST levels had a 2.971-fold greater risk of severe diarrhea. This means that impaired liver function may also affect the metabolism of pyrotinib, resulting in its accumulation in the body and increasing the incidence and severity of adverse reactions. As for other liver function indicators, such as ALT and ALP, this study did not find any correlation between them and pyrotinib-induced severe diarrhea.

In a single-centre, open-label, dose-escalation phase I clinical study [23], 2 patients in the 480 mg group experienced dose-limiting toxicity grade 3 diarrhea, and most patients who experienced diarrhea in the 80–400 mg dose group experienced symptom relief without interruption of treatment or reduction in the dose of pyrotinib. According to this study, when the daily dose of pyrotinib taken by patients was lower than their maximum tolerable dose of 400 mg/day, the probability of severe diarrhea decreased by 3.87-fold. Therefore, the initial daily dose of pyrotinib could be appropriately reduced and closely monitor the patient's response to the medicine. Clinician will adjust the maintenance dose to 400 mg if the patient does not experience intolerable adverse reactions such as severe diarrhea. It is possible to increase the tolerance of pyrotinib and decrease the occurrence of severe diarrhea, when the patient is susceptible to severe diarrhea predicted by this model.

Patients who received probiotics or other gut microbiota regulators during pyrotinib had a 3.251-fold lower risk of severe diarrhea. The occurrence of pyrotinib-induced diarrhea may lead to an imbalance in the gastrointestinal microbial environment [24–27], while probiotics can alleviate diarrhea by balance of the gut microbiota [28, 29]. In addition, some studies have shown that the risk of breast cancer may be related to the species composition and biological function of the microbiota located in the breast and intestines [30–34]. Except for regulating intestinal function, probiotics can prevent or treat breast cancer by regulating the gastrointestinal microbiota and the immune system [35–38]. Therefore, patients may consider taking probiotics or other gut microbiota regulators during pyrotinib treatment or experienced diarrhea.

Based on the multivariate logistic regression analysis, we constructed a risk prediction nomogram model for severe diarrhea induced by pyrotinib. The areas under the ROC curves of the training set and the external validation set were 0.794 and 0.863, respectively. It is suggested that the nomogram model possesses a good predictive ability for identifying patients at high risk of pyrotinib-induced severe diarrhea. The Hosmer-Lemeshow goodness-of-fit test showed that the fit of the nomogram model was good. The calibration curve analysis showed that the prediction probability of the nomogram model for pyrotinib-induced severe diarrhea was close to the actual probability.

The advantage of this study is that we have constructed a visual nomogram model based on the logistic regression analysis, making it easier for clinicians to identify individual at high risk of pyrotinib-induced severe diarrhea. Therefore, this risk prediction nomogram model is suitable for generalization in patients who are taking pyrotinib. However, This study did have certain limitations. Firstly, the influencing factors were distinguished baesd on binary classification method, which was not rigorous enough. Secondly, although this study has been taken into various medical records and demographic variables, there are still potential confounding factors that have not been incorporated, such as genetic factors and lifestyle factors. Thirdly, this was a retrospective study with a small sample, and the potential significant correlations between variables may be obscured. At last, the participants are Asians, which may affect the applicability of the model. This study still requires validation through prospective, multi-center, and large-sample clinical research before it can be widely used in medical practice.

Summary

In a word, this study established a risk prediction nomogram model for pyrotinib-induced severe diarrhea. It can help clinicians identify patients at high risk of severe diarrhea early so that they make timely clinical decisions. In the future, this model still needs to be validated and optimized to improve its predictive value through multicentre prospective studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13427-2.

Supplementary Material 1

Author contributions

QC and YL conceptualized, designed the images and drafted the entire manuscript.YL and HZ collected and verified the training set data from Hainan

Cancer Hospital.QC and YZ collected and verified the external validation set data from Hainan West Central Hospital.QC, GH and XYcontributed to guide data analysis, and interpretation and manuscript writting. All authors contributed to the article and approved the final manuscript.

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Data availability
The significant statistics used and/or analysed during this study are included in this published article.The raw data available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was approved by the Ethics Committee of Hainan West Central Hospital (NO.LLKY-2023-18) and complied with the Declaration of Helsinki, and our Institutional Review Board has waived for informed consent due to the data of this retrospective study are anonymous.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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References

1. The Chinese Society of Clinical Oncology. Guidelines of Chinese society of clinical oncology breast Cancer. Beijing: People's Medical Publishing House; 2023.
2. Li Q, Guan XW, Chen SS, et al. Safety, efficacy,and biomarker analysis of pyrotinib in combination with capecitabine in HER2-positive metastatic breast cancer patients: a phase I clinical trial. Clin Cancer Res. 2019;25(17):5212–20.
3. Ma F, Ouyang Q, Li W, et al. Pyrotinib or Lapatinib Combined with Capecitabine in ER2-Positive metastatic breast Cancer with prior taxanes, anthracyclines, and/or trastuzumab: a randomized, phase II study. J Clin Oncol. 2019;37(29):2610–9.
4. Yan M, Bian L, Hu X, et al. Pyrotinib plus capecitabine for human epidermal growth factor receptor 2-positive metastatic breast cancer after trastuzumab and taxanes(PHENIX): a randomized,double-blind,placebo-controlled phase 3 study. Transl Breast Cancer Res. 2020;1:13.
5. Xu B, Yan M, Ma F, et al. PHOEBE investigators. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(3):351–60.
6. Wang SY, Zou JQ, Chen Y. Research progress of pyrotinib-associated diarrhea in patients with HER2-positive breast cancer. J Cancer Control Treat. 2023;36(10):887–91.
7. Barzi F, Woodward M. Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. Am J Epidemiol. 2004;160(1):34–45.
8. Freites-Martinez A, Santana N, Arias-Santiago S, et al. Using the common terminology criteria for adverse events (CTCAE-Version 5.0) to evaluate the severity of adverse events of Anticancer therapies. Actas Dermosifiliogr (Engl Ed). 2021;112(1):90–2.
9. Li X, Yang CY, Wan H, et al. Discovery and development of pyrotinib: a novel irreversible EGFR/HER2 dual tyrosine kinase inhibitor with favorable safety profiles for the treatment of breast cancer. Eur J Pharm Sci. 2017;110:51–61.
10. Blair HA. Pyrotinib: First Global approval. Drugs. 2018;78(16):1751–5.
11. Qi X, Shi Q, Xuhong J, et al. Pyrotinib-based therapeutic approaches for HER2-positive breast cancer: the time is now. Breast Cancer Res. 2023;25(1):113.
12. Wu J, Jiang ZF, Liu ZZ, et al. Neoadjuvant pyrotinib, trastuzumab, and docetaxel for HER2-positive breast cancer (PHEDRA): a double-blind, randomized phase 3 trial. BMC Med. 2022;20(1):498.
13. Tang YJ. Correlation analysis of diarrhea in patients with advanced breast cancer treated with pyrotinib.Nanning:Guangxi medical university. 2021.
14. Natori A, Ethier JL, Amir E, et al. Capecitabine in early breast cancer: a meta-analysis of randomised controlled trials. Eur J Cancer. 2017;77:40–7.
15. Huo X, Li J, Zhao F, Ren D, et al. The role of capecitabine-based neoadjuvant and adjuvant chemotherapy in early-stage triple-negative breast cancer: a systematic review and meta-analysis. BMC Cancer. 2021;21(1):78.
16. Hoon SN, Lau PK, White AM, et al. Capecitabine for hormone receptor-positive versus hormone receptor-negative breast cancer. Cochrane Database Syst Rev. 2021;5(5):CD011220.
17. Yan M, Ouyang Q, Sun T, et al. Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial. Lancet Oncol. 2022;23(3):353–61.
18. Lu Y, Zhao Q, Liao JY, et al. Complement signals determine Opposite effects of B cells in Chemotherapy-Induced immunity. Cell. 2020;180(6):1081–97.
19. Wang L, Simons DL, Lu X, et al. Breast cancer induces systemic immune changes on cytokine signaling in peripheral blood monocytes and lymphocytes. EBioMedicine. 2020;52:102631.
20. Liu YY. An observational study of the effect of chemotherapy and targeted therapy on immune status in patients with HER-2-positive breast cancer. Xinxiang: Xinxiang Medical University; 2023.
21. Meng J, Liu XY, Ma S, et al. Metabolism and disposition of pyrotinib in healthy male volunteers: covalent binding with human plasma protein. Acta Pharmacol Sin. 2019;40(7):980–8.
22. Zhu Y, Li L, Zhang G, et al. Metabolic characterization of pyrotinib in humans by ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2016;15(1033–1034):117–27.
23. Ma F, Li Q, Chen S, et al. Phase I study and Biomarker Analysis of Pyrotinib, a Novel irreversible Pan-ErbB receptor tyrosine kinase inhibitor, in patients with human epidermal growth factor receptor 2-Positive metastatic breast Cancer. J Clin Oncol. 2017;35(27):3105–12.
24. Tang X, Liu H, Yang S, et al. Epidermal growth factor and intestinal barrier function. Mediators Inflamm. 2016;2016:1927348.
25. Lai J, Zhuo X, Yin K, et al. Potential mechanism of pyrotinib-induced diarrhea was explored by gut microbiome and ileum metabolomics. Anticancer Drugs. 2023;34(6):747–62.
26. Secombe KR, Van Sebille YZA, Mayo BJ, et al. Diarrhea Induced by small molecule tyrosine kinase inhibitors compared with chemotherapy: potential role of the Microbiome. Integr Cancer Ther. 2020;19:1534735420928493.
27. Lai J, Jiang F, Zhuo X, et al. Effects of Shenling Baizhu powder on pyrotinib-induced diarrhea: analysis of gut microbiota, metabonomics, and network pharmacology. Chin Med. 2022;17(1):140.
28. Wei D, Heus P, van de Wetering FT, van Tienhoven G, et al. Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer. Cochrane Database Syst Rev. 2018;8(8):CD008831.
29. Da X, Cao B, Mo J, et al. Inhibition of growth of hepatocellular carcinoma by co-delivery of anti-PD-1 antibody and sorafenib using biomimetic nanoplatelets. BMC Cancer. 2024;24(1):273.
30. Plaza-Díaz J, Álvarez-Mercado AI, Ruiz-Marín CM, et al. Association of breast and gut microbiota dysbiosis and the risk of breast cancer: a case-control clinical study. BMC Cancer. 2019;19(1):495.
31. Terrisse S, Derosa L, Iebba V, et al. Intestinal microbiota influences clinical outcome and side effects of early breast cancer treatment. Cell Death Differ. 2021;28(9):2778–96.
32. Wu AH, Tseng C, Vigen C, et al. Gut microbiome associations with breast cancer risk factors and tumor characteristics: a pilot study. Breast Cancer Res Treat. 2020;182(2):451–63.
33. Ma J, Sun L, Liu Y, et al. Alter between gut bacteria and blood metabolites and the anti-tumor effects of Faecalibacterium prausnitzii in breast cancer. BMC Microbiol. 2020;20(1):82.
34. Li Y, Dong B, Wu W, et al. Metagenomic analyses reveal distinct gut microbiota signature for Predicting the Neoadjuvant Chemotherapy responsiveness in breast Cancer patients. Front Oncol. 2022;12:865121.
35. Ranjbar S, Seyednejad SA, Azimi H, et al. Emerging roles of Probiotics in Prevention and treatment of breast Cancer: a Comprehensive Review of their therapeutic potential. Nutr Cancer. 2019;71(1):1–12.

36. Yazdi MH, Soltan Dallal MM, Hassan ZM, et al. Oral administration of Lactobacillus acidophilus induces IL-12 production in spleen cell culture of BALB/c mice bearing transplanted breast tumour. Br J Nutr. 2010;104(2):227–32.
37. Imani Fooladi AA, Yazdi MH, Pourmand MR, et al. Th1 Cytokine Production Induced by Lactobacillus acidophilus in BALB/c mice bearing transplanted breast tumor. Jundishapur J Microbiol. 2015;8(4):17354.
38. Legesse Bedada T, Feto TK, Awoke KS, et al. Probiotics for cancer alternative prevention and treatment. Biomed Pharmacother. 2020;129:110409.

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