International Journal of General Medicine

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ORIGINAL RESEARCH

A Prediction Model for Chemotherapy-Induced Thrombocytopenia Based on Real-World Data and a Close Relationship Between AST/ALT Ratio and Platelet Count in Patients with Solid Tumors

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Objective: Chemotherapy-induced thrombocytopenia (CIT) can lead to chemotherapy dose delay or reduction, and even serious bleeding. This study aimed to develop a CIT-predicting model based on the laboratory indices of cancer patients undergoing chemotherapy.

Material and Methods: From Jun 1, 2017 to Dec 30, 2021, a total of 2043 patients who had received 7676 cycles of chemotherapy were retrospectively enrolled. A logistic regression analysis was performed to identify predictive factors, on the basis of which a nomogram model for predicting CIT was established. A bootstrapping technique was applied for internal validation. A generalized additive mixed model (GAMM) was constructed to analyze the trends in the changes of aspartate aminotransferase (AST), ratio of AST to alanine transaminase (ALT) (AST/ALT ratio), and platelet (PLT) count in patients with solid tumors. P values ≤0.05 were considered statistically significant.

Results: The patient-based incidence of CIT was 20.51% and the cycle-based incidence was 10.01%. The multivariate analysis showed that AST level, AST/ALT ratio, and total bilirubin (Tbil), white blood cell (WBC), platelet (PLT), hemoglobin (Hb) levels were significantly associated with the risk of CIT. The GAMM analysis showed that PLT level was inversely associated with AST/ALT ratio and AST level, more significantly with AST/ALT ratio. And both exhibited statistically predictive abilities for CIT. The model achieved an area under the receiver operating characteristic curve (AUC) of 0.793, a sensitivity of 0.543 and a specificity of 0.930.

Conclusion: The AST/ALT ratio was inversely associated with the CIT risk in cancer patients. The GAMM model based on laboratory indices presented a high accuracy in predicting the risk of CIT, and a potential to be translated into clinical management.

Keywords: chemotherapy-induced thrombocytopenia, solid tumors, AST/ALT-ratio, prediction model

Introduction

Chemotherapy-induced thrombocytopenia (CIT), a most common complication in cancer patients receiving myelosuppressive chemotherapy, emerges as the peripheral platelet count falls below 100×10^9/L, with or without bleeding.[1] In the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE 4.03) established by the National Institute of Health (NIH), thrombocytopenia refers to a decrease in the number of platelets (PLT) in the blood specimen, involving four grades: grade 1, PLT count < low limit of normal (LLN) of 75,000/mm^3 or 75.0×10^9/L; grade 2, PLT count <75,000–50,000/mm^3 or <75.0–50.0×10^9/L; grade 3, PLT count <50,000–25,000/mm^3 or <50.0–25.0×10^9/L; grade 4, PLT count

Received: 2 August 2022
Accepted: 10 October 2022
Published: 1 November 2022

<25,000/mm^3 or <25.0×10^9/L. Prior studies estimated that more than 30% of patients with solid tumors experienced thrombocytopenia,[2] while the incidence of CIT in hematological tumors reached 75%.[3] CIT may lead to chemotherapy dose delay or reduction, and even serious bleeding, which increases the expenditure and worsens the prognosis.[4]

Serum transaminases aspartate transaminase (AST) and alanine transaminase (ALT) are routinely measured to evaluate liver function. ALT is involved in the glucose-alanine cycle, interchange between alanine and pyruvate, and regeneration of glucose consumed by muscle. AST acts in aerobic glycolysis through relocating nicotinamide adenine dinucleotide (NADH) within the mitochondria. These transaminase reactions are essential to the metabolism in muscle and liver cells.[5] AST/ALT ratio, also termed as De Ritis ratio, has also been proven as an efficient index to diagnose many non-hepatic diseases.[6] Moreover, it is also an independent prognostic factor for several cancer entities.[7–11] Besides, a recent study has suggested that AST/ALT ratio is inversely associated with palette (PLT) count in severe fever with thrombocytopenia syndrome (SFTS).[12] However, the efficiency of AST/ALT ratio in predicting CIT is unclear.

Cytotoxic chemotherapy can decrease PLT count through several pathophysiological mechanisms. Cytotoxic drugs repress the production of megakaryocytes and PLTs.[13] In addition, chemotherapeutic drugs can enhance PLT clearance through various immune mechanisms. For example, idiopathic thrombocytopenic purpura (ITP) has been reported in patients receiving fludarabine monotherapy.[14] Currently, treatment options of CIT and related therapeutic benefits are limited. An efficient model based on various variables is needed to predict high-risk CIT groups. Some studies have clarified the relationship between CIT and demographic characteristics, such as the body mass index.[15–17] However, these variables were relatively simple subjective and some show region-related differences.

Therefore, based on objective laboratory indexes, we constructed a model and evaluated its accuracy to predict CIT in a cohort of cancer patients receiving chemotherapy.

Materials and Methods

Patients and Data Collection

This was a retrospective study that included 2043 patients receiving chemotherapy for solid tumor in the Oncology Department of Jinhua Municipal Central Hospital from June 2017 to December 2021. In this study, the primary endpoint was chemotherapy-induced thrombocytopenia predicted by the model. Basic information of the cancer patients, including epidemiological, demographic, clinical, and laboratory data, were obtained from the electronic medical records of the hospital (the Guide Patients Support Care [GPS] information system).

The inclusion criteria were as follows: (1) solid malignant tumors were confirmed by pathological findings; (2) the patient was followed up during all chemotherapy cycles; (3) the patient had blood routinely tested within 1–2 months after the occurrence of CIT; (4) the patient had no other liver diseases, except for malignancies.

The exclusion criterions were as follows: (1) a history of hematologic malignancy confirmed by fluorescence in situ hybridization (FISH) from a bone marrow aspirate and biopsy or peripheral blood review test performed in the prior three months; (2) a history of symptomatic venous thromboembolic events (VTEs) or arterial events; (3) abnormal liver and kidney function confirmed by laboratory indicators within the past three months.

The PLT count test was performed at the beginning of every chemotherapy cycle. A single episode of thrombocytopenia was considered as CIT. The diagnosis of thrombocytopenia was based on the PLT count during chemotherapy. The diagnosis of CIT was made based on the lowest platelet value.

This study complied with the ethical standards of the Institutional Research Council and the Declaration of Helsinki.

Variables Definitions

According to the CTCAE 4.03, thrombocytopenia was divided into four grades: Grade 1, 75×10^9-99×10^9/L; Grade 2, 50×10^9-74×10^9/L; Grade 3, 25×10^9-49×10^9/L; Grade 4, <25×10^9/L. Anemia was defined as hemoglobin (Hb) concentration <110 g/L. Decreased white blood cell (WBC) count was defined as a WBC count <4000/mL, increased C-reactive protein (CRP) as a CRP level >8 mg/dL, decreased total bilirubin (Tbil) as a Tbil level <25 μmol/L. Hypoalbuminemia was considered as an albumin (Alb) level <30g/L. Increased ALT was defined as an ALT level >50 U/L and increased AST was defined as an AST level >35 U/L. AST/ALT ratio >1 was regarded as abnormal.

Tumors in less than 30 patients were classified as "other tumors", and those with two or more primary sites were defined as multiple primary cancers (MPC).

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation (SD) if in normal distribution, or median (interquartile range) if in skewed distribution; categorical variables were described as frequency or percentage. In addition, the Chi-square test (categorical variables) and two-tailed test (continuous variables) were employed to determine differences in means and proportions between groups. Univariate and multivariate logistic regression analyses were applied to identify factors associated with CIT.

A generalized additive mixed model (GAMM) was constructed to explore the relationship between AST, AST/ALT-ratio and PLT. The accuracies of the two variables were compared according to their receiver operating curves (ROCs).

Variables with a p-value less than 0.05 in the multivariate logistic regression analysis were selected. Using them, a nomogram was established to display the predictive accuracy of the final model. The discrimination and calibration of the model were calculated using the area under the ROC curve. A bootstrapping technique was applied using 1000 random data sets (validation set) generated from the original data. All statistical analyses were performed by R software (version 4.1.2) with the "survival", "survminer", "rms", "pROC" and "rmda" packages. P values ≤0.05 were considered statistically significant.

Results

Demographics and Clinical Characteristics of Patients

A total of 2043 patients (1224 [59.91%] males and 819 [40.09%]) females with solid tumors who received chemotherapy during the study period were included. The patients' detailed demographic and clinical characteristics are summarized in Table 1. Thrombocytopenia occurred in 419 patients, with a frequency of 20.51%. The 5 most common types were (in a downtrend of frequency) cervical (10/27, 37.04%), biliary (13/37, 35.14%), gastric (45/136, 33.09%), ovarian (12/41, 29.27%) and bladder (9/32, 28.12%) cancers.

The patients' laboratory results were analyzed. In all patients with CIT, the WBC count decreased in 161 (38.42%) patients. The Hb level dropped below the normal range in 285 (68.02%) patients. The AST level rose above the normal range in 142 (33.89%) patients, and the ALT level in 45 (10.84%) patients. The Tbil level exceeded the upper limit in 57 (13.60%) patients, while the Alb level decreased in 39 (9.31%) patients.

Univariate and Multivariate Analyses Based on Chemotherapy Cycles

A total of 7676 cycles were administered. CIT occurred in 768 (10.01%) cycles (Table 2). The univariate logistic analysis showed that tumor site (P<0.001), AST/ALT ratio (P<0.001), AST (P<0.001), Tbil (P<0.001), Alb (P=0.002), PLT (P<0.001), Hb (P<0.001), WBC (P<0.001), CRP (P=0.020) were associated with CIT of patients with solid tumors (Table 3). In the multivariate logistic analysis, we found that AST/ALT-ratio (P<0.001), AST (P<0.001), Tbil (P=0.04), PLT (P<0.001), WBC (P=0.001) and Hb (P<0.001) were independent predictive factors for CIT.

Predictive Values of AST/ALT Ratio and AST for CIT

Given that the levels of myeloid, erythroid, and megakaryocytic cells can reflect the hematopoietic function of bone marrow, it has been expected that WBC and Hb are associated with PLT. We further explored whether AST influences the count of PLT. An abnormal AST/ALT ratio was detected after a median of 4 cycles of chemotherapy. The GAMM model showed that both AST/ALT ratio and AST were inversely associated with PLT count (Figures 1 and 2), and the relationship between AST/ALT ratio and PLT showed a stronger linear negative correlation. As shown by the ROC curves, the AUC of AST/ALT ratio was 0.604, while the AUC of AST was 0.569 (Figure 3). Obviously, AST/ALT ratio was more accurate than AST in predicting CIT (P=0.045).

Table 1 Demographics and Clinical Characteristics of Cancer Patients

Variables	Total 2043	PLT.Low (%) 419(20.51)	PLT.normal (%) 1624(79.49)	*P*-value
Gender				0.104
Male	1224	236(19.28)	988(80.72)	
Female	819	183(22.34)	636(77.66)	
Age				0.494
40–49	191	31(16.23)	160(83.77)	
50–59	526	108(20.53)	418(79.47)	
60–69	763	165(21.63)	598(78.37)	
70–79	427	89(20.84)	338(79.16)	
≥80	74	17(22.97)	57(77.03)	
<40	62	9(14.52)	53(85.48)	
Site				<0.001
Bladder	32	9(28.12)	23(71.88)	
Breast	183	34(18.58)	149(81.42)	
Cervix	27	10(37.04)	17(62.96)	
Colorectal	685	140(20.44)	545(79.56)	
Oesophagus	76	15(19.74)	61(80.26)	
Biliary	37	13(35.14)	24(64.86)	
Gastric	136	45(33.09)	91(66.91)	
Head	37	6(16.22)	31(83.78)	
Lung	397	56(14.11)	341(85.89)	
Ovarian	41	12(29.27)	29(70.73)	
Pancreas	62	14(22.58)	48(77.42)	
Sarcoma	25	4(16)	21(84)	
mpc	128	24(18.75)	104(81.25)	
Other	121	28(23.14)	93(76.86)	
Unknown	56	9(16.07)	47(83.93)	
Liver metastases				<0.001
Yes	586	157(26.79)	429(73.21)	
Unknown	1457	262(17.98)	1195(82.02)	
PLT				<0.001
Low	419	419(100)	0(0)	
Normal	1624	0(0)	1624(100)	
WBC				<0.001
Low	490	161(32.86)	329(67.14)	
Normal	1553	258(16.61)	1295(83.39)	
Hb				<0.001
Low	853	285(33.41)	568(66.59)	
Normal	1190	134(11.26)	1056(88.74)	
CRP				0.011
High	408	98(24.02)	310(75.98)	
Normal	451	72(15.96)	379(84.04)	
Unknown	1184	249(21.03)	935(78.97)	
Tbil				<0.001
High	125	57(45.6)	68(54.4)	
Normal	1779	335(18.83)	1444(81.17)	
Unknown	139	27(19.42)	112(80.58)	
Alb				<0.001
Low	98	39(39.8)	59(60.2)	
Normal	869	142(16.34)	727(83.66)	
Unknown	1076	238(22.12)	838(77.88)	

(*Continued*)

Table 1 (Continued).

Variables	Total 2043	PLT.Low (%) 419(20.51)	PLT.normal (%) 1624(79.49)	*P*-value
AST				<0.001
High	392	142(36.22)	250(63.78)	
Normal	1188	205(17.26)	983(82.74)	
Unknown	463	72(15.55)	391(84.45)	
ALT				0.666
High	198	45(22.73)	153(77.27)	
Normal	1790	364(20.34)	1426(79.66)	
Unknown	55	10(18.18)	45(81.82)	
AST/ALT-ratio	1.43 [1.07, 1.93]	1.60 [1.21, 2.20]	1.38 [1.03, 1.81]	<0.001

Abbreviations: PLT, platelet; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; Tbil, total bilirubin; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine transaminase; AST/ALT-ratio, aspartate aminotransferase/alanine transaminase ratio.

Table 2 Clinical Characteristics Based on Chemotherapy Cycles

Variables	Total 7676	PLT.Low (%) 768(10.01)	PLT.Normal (%) 6908(89.99)	*P*-value
Gender				0.515
Male	4208	412(9.79)	3796(90.21)	
Female	3468	356(10.27)	3112(89.73)	
Age				0.724
40–49	827	73(8.83)	754(91.17)	
50–59	2127	211(9.92)	1916(90.08)	
60–69	2953	300(10.16)	2653(89.84)	
70–79	1397	148(10.59)	1249(89.41)	
≥80	148	17(11.49)	131(88.51)	
<40	224	19(8.48)	205(91.52)	
Site				<0.001
Appendix	15	1(6.67)	14(93.33)	
Bladder	128	7(5.47)	121(94.53)	
Breast	981	62(6.32)	919(93.68)	
Cervix	101	16(15.84)	85(84.16)	
Colorectal	3104	322(10.37)	2782(89.63)	
Oesophagus	153	15(9.8)	138(90.2)	
Biliary	121	22(18.18)	99(81.82)	
Gastric	416	91(21.88)	325(78.12)	
Head	81	6(7.41)	75(92.59)	
Liver	19	9(47.37)	10(52.63)	
Lung	1288	74(5.75)	1214(94.25)	
Ovarian	200	41(20.5)	159(79.5)	
Pancreas	192	17(8.85)	175(91.15)	
Sarcoma	79	4(5.06)	75(94.94)	
mpc	445	34(7.64)	411(92.36)	
Other	248	30(12.1)	218(87.9)	
Unknown	105	17(16.19)	88(83.81)	
Liver metastases				0.143
Yes	3055	325(10.64)	2730(89.36)	
Unknown	4621	443(9.59)	4178(90.41)	

(*Continued*)

Table 2 (Continued).

Variables	Total 7676	PLT.Low (%) 768(10.01)	PLT.Normal (%) 6908(89.99)	*P*-value
PLT				<0.001
Low	609	360(59.11)	249(40.89)	
Normal	6804	380(5.58)	6424(94.42)	
Unknown	263	28(10.65)	235(89.35)	
WBC				<0.001
Low	1698	255(15.02)	1443(84.98)	<0.001
Normal	5714	485(8.49)	5229(91.51)	
Unknown	264	28(10.61)	236(89.39)	
Hb				<0.001
Low	2900	405(13.97)	2495(86.03)	
Normal	4512	335(7.42)	4177(92.58)	
Unknown	264	28(10.61)	236(89.39)	
CRP				0.020
High	820	77(9.39)	743(90.61)	
Normal	1825	154(8.44)	1671(91.56)	
Unknown	5031	537(10.67)	4494(89.33)	
Tbil				<0.001
High	200	45(22.5)	155(77.5)	
Normal	6945	661(9.52)	6284(90.48)	
Unknown	531	62(11.68)	469(88.32)	
Alb				0.002
Low	147	25(17.01)	122(82.99)	
Normal	3163	285(9.01)	2878(90.99)	
Unknown	4366	458(10.49)	3908(89.51)	
AST				<0.001
High	1375	225(16.36)	1150(83.64)	
Normal	4816	414(8.6)	4402(91.4)	
Unknown	1485	129(8.69)	1356(91.31)	
ALT				0.249
High	627	53(8.45)	574(91.55)	
Normal	6670	671(10.06)	5999(89.94)	
Unknown	379	44(11.61)	335(88.39)	
AST/ALT-ratio	1.36[1.03, 1.81]	1.58 [1.20, 2.00]	1.34 [1.02, 1.78]	<0.001

Abbreviations: PLT, platelet; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; Tbil, total bilirubin; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine transaminase; AST/ALT-ratio, aspartate aminotransferase/alanine transaminase ratio.

Table 3 Univariate and Multivariate Analysis

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Male	1	–	1	–
Female	1.05(0.91–1.22)	0.49	0.89(0.71–1.11)	0.3
Age				
<40	1		1	–
40–49	1.04(0.62–1.77)	0.87	1.03(0.52–2.14)	0.93
50–59	1.19(0.73–1.94)	0.49	1.17(0.62–2.32)	0.64
60–69	1.22(0.75–1.98)	0.42	1.19(0.64–2.36)	0.6

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
70–79	1.28(0.78–2.11)	0.34	1.05(0.55–2.13)	0.88
≥80	1.4(0.7–2.79)	0.34	1.12(0.30–3.01)	0.83
Site				
Unknown	1	–	1	–
Appendix	0.37 (0.05–3)	0.35	0.79(0.04–5.4)	0.84
Bladder	0.3 (0.12–0.75)	0.01	0.42(0.13–3.17)	0.15
Breast	0.35 (0.2–0.62)	<0.001	0.29(0.12–0.76)	0.01
Cervix	0.97 (0.46–2.05)	0.95	1.06(0.36–3.23)	0.92
Colorectal	0.6 (0.35–1.02)	0.06	0.62(0.28–1.55)	0.27
Oesophagus	0.56 (0.27–1.18)	0.13	0.5(0.18–1.5)	0.2
Biliary	1.15 (0.57–2.3)	0.69	0.83(0.29–2.49)	0.74
Gastric	1.45(0.82–2.56)	0.2	0.98(0.42–2.54)	0.97
Head	0.41(0.16–1.1)	0.08	0.31(0.06–1.28)	0.12
Liver	4.66(1.65–13.17)	<0.001	2.82(0.64–12.42)	0.17
Lung	0.32(0.18–0.56)	<0.001	0.4(0.17–1.03)	0.04
mpc	0.43(0.23–0.8)	0.01	0.43(0.18–1.17)	0.08
Other	0.71(0.37–1.36)	0.3	0.66(0.26–1.8)	0.39
Ovarian	1.33(0.72–2.49)	0.36	1.26(0.5–3.43)	0.63
Pancreas	0.5(0.24–1.03)	0.06	0.52(0.19–1.51)	0.22
Sarcoma	0.28(0.09–0.86)	0.03	0.56(0.13–2.02)	0.39
Liver metastases				
No	1	–	1	–
Yes	1.12(0.97–1.31)	0.13	0.94(0.75–1.16)	0.54
PLT				
Normal		–		–
Low	24.44(20.17–29.61)	<0.001	17.78(14.27–22.19)	<0.001
WBC				
Normal	1	–	1	–
High	1.91(1.62–2.24)	<0.001	1.49(1.19–1.84)	<0.001
Hb				
Normal	1	–	1	–
Low	2.02(1.74–2.36)	<0.001	1.43(1.16–1.76)	<0.001
CRP				
Normal	1	–	1	–
High	1.12(0.84–1.5)	0.42	0.86(0.58–1.24)	0.44
Unknown	1.3(1.07–1.56)	0.01	1.06(0.84–1.35)	0.62
Tbil				
Normal	1	–	1	–
High	2.76(1.96–3.88)	<0.001	1.68(1.01–2.71)	0.04
Unknown	1.26(0.95–1.66)	0.11	1.15(0.27–3.65)	0.84
Alb				
Normal	1	–	1	–
Low	2.07(1.32–3.24)	<0.001	1.23(0.66–2.18)	0.5
Unknown	1.18 (1.01–1.38)	0.03	1.07(0.87–1.32)	0.51
AST				
Normal	1	–	1	–
High	2.08(1.75–2.48)	<0.001	1.69(1.33–2.14)	<0.001

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
ALT				
Normal	1	–	1	–
High	0.83(0.62–1.11)	0.2	0.77(0.51–1.15)	0.2
AST/ALT-ratio	1.42(1.28–1.56)	<0.001	1.23(1.08–1.41)	<0.001

Abbreviations: PLT, platelet; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; Tbil, total bilirubin; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine transaminase; AST/ALT-ratio, aspartate aminotransferase/alanine transaminase ratio.

Predictive Value of Nomogram for CIT

In the multivariate logistic regression model, AST/ALT ratio, AST, PLT, WBC and Hb were statistically significant predictors for CIT. Therefore, a nomogram containing AST/ALT-ratio, Tbil, Alb, PLT, WBC and Hb was established to predict CIT of chemotherapy-treated patients (Figure 4). The AUC value of the model was 0.793 (sensitivity 0.543, specificity 0.930), which indicated that the prediction model has a high accuracy (Figure 5). In addition, the calibration plots revealed a good match between the CIT frequencies predicted by the nomogram model and observed in the real setting (Figure 6).

Discussion

In this study, we found that baseline laboratory parameters, including PLT, WBC, Hb, AST, Tbil and AST/ALT-ratio, were significantly associated with CIT risk. There was an inversely relationship between AST/ALT ratio and PLT count,

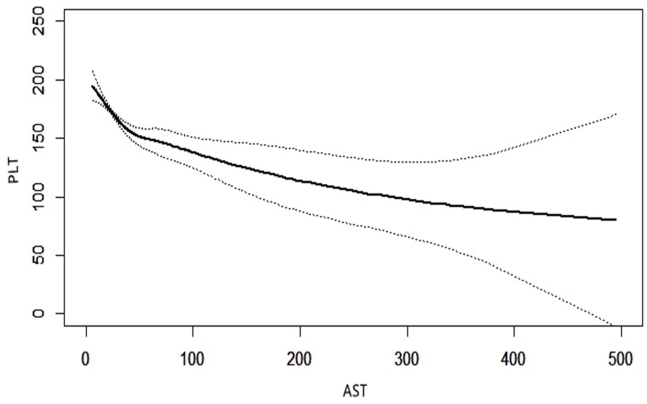

Figure 1 Shift trend of AST and PLT of cancer patients analyzed by GAMM.

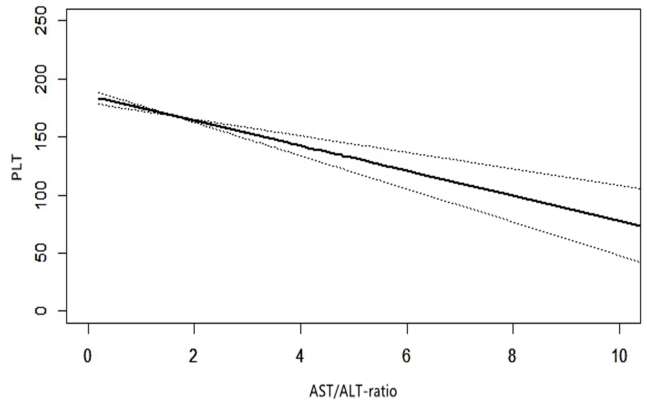

Figure 2 Shift trend of AST/ALT-ratio and PLT of cancer patients analyzed by GAMM.

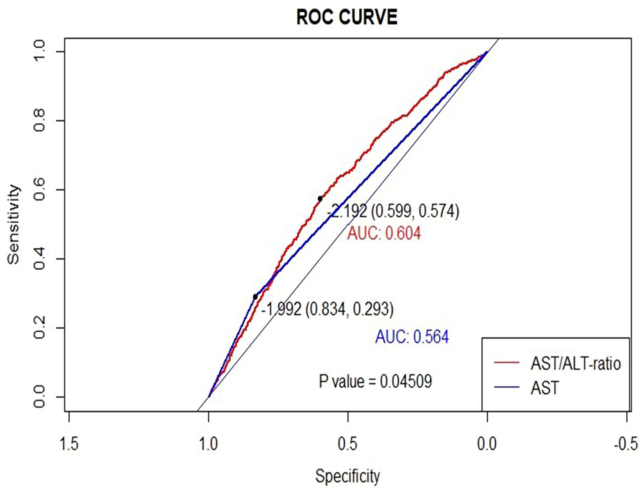

Figure 3 The compared ROC between AST/ALT-ratio and AST.

as well as between AST and PLT count. Besides, a nomogram incorporating the six significant parameters demonstrated a strong predictive ability.

In our cohort, the incidence of CIT during the chemotherapy course was 20.51%, higher than those in previous studies.[18,19] The incidences in different cancer types were slightly different from other investigations.[20–24]

To the best of our knowledge, our study was the first to evaluate the potential predictive value of AST/ALT ratio and AST for CIT. Furthermore, we found AST/ALT-ratio and AST were both inversely associated with PLT. In a prognostic study of severe fever with SFTS, an evident inverse correlation was found between AST/ALT ratio and PLT count.[12] In other studies of SFTS, some inflammatory factors were up-regulated in infected HepG2 cells. Proinflammatory cytokines, including IL-6 and tumor necrosis factor-alpha (TNF-α), increase dramatically with disease severity.[25] Patients who received allogeneic hematopoietic stem cell transplantation exhibited high levels of TNF-α, interferon-gamma (IFN-γ), and IL-2, as well as ALT and AST.[26] These indicate that the immune system is disrupted in liver injury. Previous studies have highlighted that PLTs are essential to cellular inflammation and can be used to score hepatic fibrosis. Xu et al have found that a low PLT count is associated with cirrhosis and progression to hepatic decompensation among patients with chronic hepatitis C.[27] In patients receiving chemotherapy, the AST/ALT ratio increases and the PLT count decreases, indicating the damage to hepatic function. Chemotherapy-induced liver injury (CALI) is also a common adverse event in cancer patients. The evolution of CALI is usually accompanied by elevations of ALT, AST, and Tbil. Idiosyncratic CALI has been explained as a result from adaptive immune attack in previous reports, with immune cell-mediated liver injury playing a critical role.[28]

Some molecules trigger the adaptive immune attack on the liver by up-regulating costimulatory factors on professional antigen-presenting cells and promoting the release of cytokines and chemokines. In addition, some cytokines, such as TNF-α and IFN-γ, can make hepatocytes more susceptible to drug-induced stress by shifting cellular responses away from cell survival towards cell death.[29] Considering that CIT involves specific immune responses induced by chemotherapeutic drugs, we propose that the link between elevated AST and CIT may be mediated by immune-related mechanisms. Currently, the immune-related mechanisms underlying CIT have not been fully clarified. No immunosuppressive agents have been used in the routine treatment of CIT. However, in some cases whose thrombocytopenia is known to be caused by immune mechanisms, such as ITP caused by fluadabine, corticosteroids or gamma globulin can be used to treat thrombocytopenia, and the therapeutic effect is significant.[30]

Interestingly, serum AST/ALT ratio has been found related to a high mortality rate in previous cancer models. In patients with oral and oropharyngeal cancer, AST/ALT ratio >1.44 is an independent prognostic factor for poor cancer-specific survival and overall survival (OS).[31] Furthermore, AST/ALT ratio has been validated as a prognostic marker for disease-free survival (DFS) in stage II–III non-cancer patients.[32] Besides, it can also predict the prognosis of gastric,

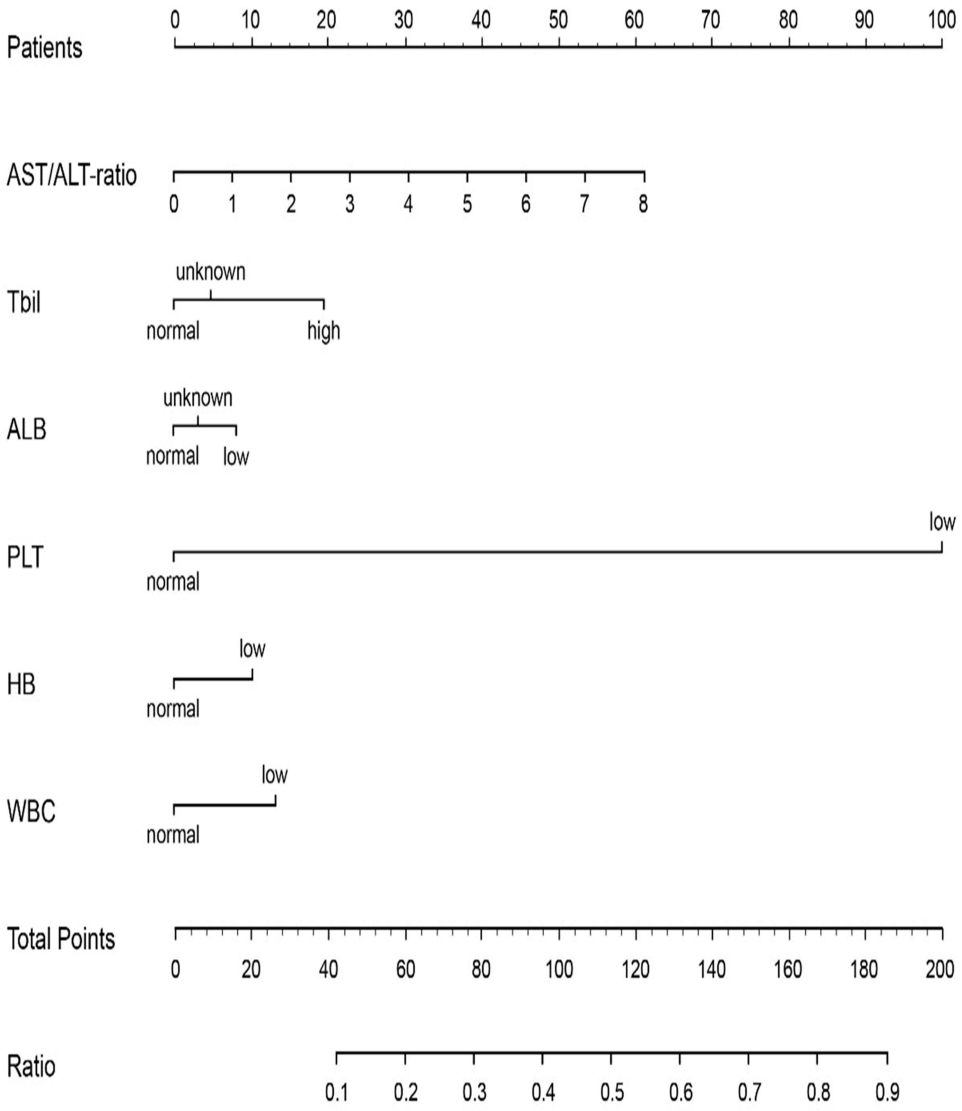

Figure 4 The nomogram model for CIT probability prediction based on laboratory indicators.
Abbreviations: Tbil, total bilirubin; Alb, albumin; PLT, platelet; WBC, white blood cell; Hb, hemoglobin; AST/ALT-ratio, aspartate aminotransferase/alanine transaminase ratio; Risk; Risk probability of developing thrombocytopenia.

prostate and advanced-stage pancreatic cancer.[33–35] In the current study, we addressed that the AST/ALT ratio tightly correlates with CIT risk. However, the mechanism contributing to the increase in AST/ALT ratio and the decrease in PLT after chemotherapy is still unclear, and should be uncovered by future studies.

Severe thrombocytopenia may lead to bleeding, which require platelet transfusion. Few models have been developed to predict CIT risk based on clinical and laboratory variables.[36] These predictive models only incorporate specific predictors and their application is limited to a certain cancer type. In the present study, our model was based on the data from a whole spectrum of cancers, thus largely expanding its clinical applicability. Compared with previous models, our model absorbed real-time laboratory indicators measured in those who had passed the myelosuppression phase but not received the next cycle of chemotherapy. These indicators, easily measurable, can efficiently help to distinguish the patients at a high risk of CIT.

However, several limitations should be mentioned. First, our study lacked external data validation. Second, our study was a retrospective and single-center study, and therefore, the potential biases could not be avoided. Such drawbacks will be addressed in our future studies.

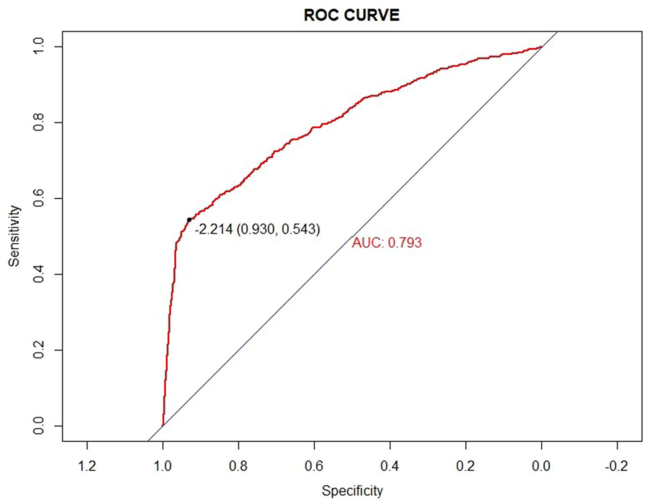

Figure 5 The area under the ROC curve (AUC). AUC:0.793, Sensitivity: 0.543, Specificity: 0.930.

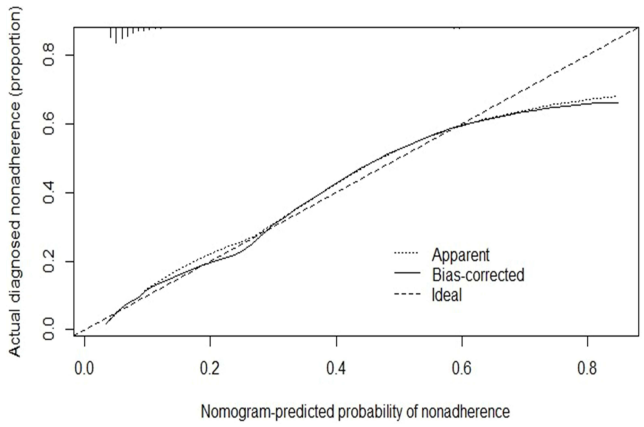

Figure 6 The calibration curve for predicting CIT in the validation set: the ideal prediction curve has a good fit with the actual observations.

In conclusion, our model was accurate in predicting CIT risk, and AST/ALT ratio was closely associated with PLT count in patients with solid tumors. Our model may provide a possibility to design individualized treatment for cancer patients.

Studies Involving Animal Subjects

Generated Statement: No animal studies are presented in this manuscript.

Studies Involving Human Subjects

Generated Statement: The studies involving human participants were reviewed and approved by Medical Ethics Committee of Jinhua Central Hospital. The patients/participants provided their written informed consent to participate in this study.

Inclusion of Identifiable Human Data

Generated Statement: No potentially identifiable human images or data are presented in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Jianfei Fu and Huixian Hu are co-corresponding authors for this study. Jianfei Fu has received research support from Company Jiangsu Hengrui Medicine Co., Ltd. The authors have no other relevant financial or non-financial interests to disclose for this work.

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