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ORIGINAL RESEARCH

The Role of Plasma Trough Concentration of Voriconazole and Voriconazole N-Oxide in Its Hepatotoxicity in Adult Patients

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Objective: Hepatotoxicity is an important cause of early withdrawal of voriconazole (VCZ). The role of the plasma trough concentration of VCZ (C_0) in hepatotoxicity is confusion. VCZ N-oxide is the primary metabolite of VCZ in plasma. We investigated the role of VCZ C_0 and plasma trough concentration of VCZ N-oxide (C_N) in hepatotoxicity in adult patients.

Materials and Methods: This was a prospective study. VCZ C_0 and C_N were measured using liquid chromatography-tandem mass spectrometry.

Results: In total, 601 VCZ C_0 and C_N from 376 adult patients were included. The percentage of grade 1 or higher adverse events for ALP, ALT, AST, γ-GT, and TBIL were 35.4%, 21.0%, 30.1%, 56.2%, and 22.2%, respectively. Compared with younger adult patients, elderly patients (≥65 years) had a higher rate of grade 1 or higher adverse events of ALP. In the multivariate analysis, VCZ C_0 was a risk factor for grade 1 or higher adverse events of AST in elderly patients and TBIL in younger adult patients, and VCZ C_N was a risk factor for grade 1 or higher adverse events of ALT, AST, and TBIL. Results of the receiver operating characteristic curve analysis indicated that when the VCZ C_0 was higher than 4.0 μg/mL, or the VCZ C_N was lower than 1.7 μg/mL, the incidence of grade 1 or higher adverse events of AST and TBIL increased.

Conclusion: VCZ C_0 and C_N were associated with liver function-related adverse events. Measurement of VCZ C_N should be considered for VCZ therapeutic drug monitoring.

Keywords: voriconazole, voriconazole N-oxide, hepatotoxicity, therapeutic drug monitoring

Introduction

Voriconazole (VCZ), a broad-spectrum triazole antifungal drug, is widely used to prevent and treat invasive fungal infections (IFIs) caused by *Aspergillus* and *Candida*.[1] Compared with other triazole antifungal drugs such as isavuconazole and posaconazole for the treatment of IFIs, VCZ has similar therapeutic and preventive effects; however, the incidence of adverse events caused by VCZ is higher than that of isavuconazole and posaconazole.[2–4] According to the FDA Adverse Reaction Reporting System data from the first quarter of 2004 to the third quarter of 2021, the incidence of drug-induced liver injury (DILI) caused by antifungal drugs was 32.45% for VCZ.[5] Studies have also shown that the overall incidence of adverse events associated with VCZ in the treatment of IFIs is 40%, and common adverse events include elevated glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (γ-GT), as well as an increase in hallucinations, nausea, and blurred vision.[4] In allogeneic hematopoietic stem cell transplantation recipients, adverse events accounted for 68.7% of the early discontinuation of VCZ,[6] and liver toxicity was an important reason for the early withdrawal of VCZ, accounting for 22.8%.[4] Our previous study also showed that the incidence of abnormal liver function indicators among the adverse events caused by VCZ was 49.3% in elderly patients and 37.6% in younger adult patients.[7] Therefore, it is important to investigate factors associated with VCZ-induced hepatotoxicity for rational use.

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Previous studies have suggested a correlation between the plasma trough concentration of VCZ (C_0) and adverse events, and monitoring of VCZ C_0 has long been suggested to optimize its effectiveness and minimize toxicity.[8,9] However, these results remain confusion. The therapeutic window of VCZ recommended for most European patients is a trough level of 1–5.5 μg/mL,[1] which for Chinese patients is in the range of 0.5–5 μg/mL.[10] In a systematic review and meta-analysis, the incidence of hepatotoxicity was significantly increased with VCZ C_0>3.0, >4.0, >5.5 and >6.0 μg/mL.[8] In another systematic review and meta-analysis, the highest odds ratios for a significantly higher risk of hepatotoxicity were recorded at 4.0 μg/mL.[11] Steady-state VCZ C_0>3.61 μg/mL has also been reported to be associated with an increased incidence of hepatotoxicity in patients with pulmonary fungal diseases.[12] Furthermore, a lack of correlation between the serum VCZ level and the occurrence of hepatotoxicity has been observed in many patients.[13,14]

VCZ is mainly metabolized in the liver by isoenzymes cytochrome P450 2C19 (CYP2C19), CYP3A4, and CYP2C9. VCZ N-oxide is the primary metabolite of VCZ in the plasma.[15] Thus, the plasma concentration of VCZ N-oxide (C_N) and the ratio of VCZ C_N/C_0 may reflect the patient's metabolic capacity and liver function at a given time and have the potential to predict VCZ-induced hepatotoxicity. In the current study, we investigated the role of VCZ C_0, C_N, and C_N/C_0 in adverse events of liver function in adult patients. The basic characteristics of patients, fungal test results, administration route and dose of VCZ, duration of VCZ administration, VCZ C_0, C_N, and C_N/C_0, combined use of drugs, and laboratory test results, such as inflammatory indicators, renal function indicators, blood routine indicators, and electrolyte indicators, were included as influencing factors of adverse events of liver function. Considering the impaired liver function in the elderly[16] and limited data on VCZ-induced hepatotoxicity in the elderly, we also investigated factors associated with VCZ-induced hepatotoxicity in elderly patients (≥65 years).

Materials and Methods

Patients and Study Design

This single-center prospective study included adult patients receiving VCZ therapeutic drug monitoring in the Southwest Hospital of Chongqing from January 2021 to December 2023. Both patients with prophylactic and therapeutic uses of VCZ were included. The inclusion criteria for the patients were as follows: (a) receiving VCZ either intravenously or orally; (b) the measured VCZ $C_0$was under the steady state. In the case of the loading dose (6 mg/kg intravenously or 400 mg orally), the stable VCZ C_0 was achieved at the end of the second day of administration and before the fifth administration (day 3). In the absence of loading doses, VCZ C_0 was measure on day 5 or later;[10] (c) available liver function results in the early stage of administration, and the results measured on the same day of VCZ C_0 determination; (d) agreed to the use of their blood samples for VCZ C_N determination; and (e) signed informed consent forms. The exclusion criteria were (a) abnormal liver function before VCZ administration and (b) current pregnancy.

Data Collection

The following data were collected for each patient: (a) demographic characteristics, including age, sex, weight, underlying diseases, and fungal test results; (b)medication information, including VCZ dose and administration route, duration of VCZ administration, and combined use of antibiotics, corticosteroids, and proton-pump inhibitors (PPIs); (c) liver function indicators, including ALP, ALT, AST, γ-GT, and total bilirubin (TBIL); (d) inflammatory indicators, including procalcitonin (PCT) and interleukin 6 (IL-6); (e) kidney function, including serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR); (f) blood count, including white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), hematocrit (HCT) and platelet hematocrit; (g) and serum potassium, sodium and chloride levels.

VCZ C_0 and C_N Determination

VCZ C_N was measured together with VCZ C_0 using liquid chromatography-tandem mass spectrometry as previously described.[17] The limits of detection of VCZ C_0 and C_N were 8 and 10ng/mL, respectively. The lower limits of quantification for VCZ C_0 and C_N were 400 ng/mL.

Statistical Analysis

Statistical analysis was performed using IBM SPSS (version 26.0; IBM Corp., Armonk, NY, USA). Categorical data were compared using the chi-square test. Data conforming to a normal distribution from the two cohorts were compared using independent-sample *t*-tests. Data that did not conform to a normal distribution from the two cohorts were represented by the median and interquartile range (IQR) and compared using the Mann–Whitney *U*-test. The Common Terminology Criteria for Adverse Events (CTCAE) 5.0 was used to grade hepatotoxicity. The criteria for grade 1, 2, 3, and 4 adverse effects of ALT and AST were respectively >1.0–3.0×upper limit of normal (ULN), >3.0–5.0×ULN, >5.0–20.0×ULN, and >20.0×ULN. The criteria for grade 1, 2, 3, and 4 adverse effects of ALP and γ-GT were respectively >1.0–2.5×ULN, >2.5–5.0×ULN, >5.0–20.0×ULN, and >20.0×ULN. The criteria for grade 1, 2, 3, and 4 adverse effects of TBIL were respectively >1.0–1.5×ULN, >1.5–3.0×ULN, >3.0–10.0×ULN, and >10.0×ULN. Binary logistic regression was used to evaluate the risk factors for grade 1 or higher adverse events of ALP, ALT, AST, γ-GT, and TBIL levels. Covariates with a p value of <0.1 in the univariate analysis, were entered into the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive effect of VCZ C_0 and C_N on adverse events of liver function. Statistical significance was set at $p<0.05$.

Results

Patient Characteristics

A total of 601 VCZ C_0 and C_N from 376 adult patients were included, including 383 VCZ C_0 and C_N from 248 younger adult patients, and 218 VCZ C_0 and C_N from 128 elderly patients (Table 1). Male patients accounted for 62.0% of the

Table 1 Demographic and Clinical Characteristics of Patients

Variable	All Adult Patients (n=376)	Younger Adult Patients (n=248)	Elderly Patients (n=128)	p^a
Sex				0.017
Male (n [%])	233 (62.0)	143 (57.7)	90 (70.3)	
Female (n [%])	143 (38.0)	105 (42.3)	38 (29.7)	
Age (y)	55±18	46±13	74±7	<0.001
Underlying diseases				–
Hematological malignancy (no. [%])	122 (32.4)	111 (44.8)	11 (8.6)	
Pneumonia (no. [%])	258 (68.6)	142 (57.3)	116 (90.6)	
Cancer (no. [%])	52 (13.8)	16 (6.5)	36 (28.1)	
Organ transplantation (no. [%])	27 (71.8)	26 (10.5)	1 (0.8)	
Fungus category				–
Aspergillus (no. [%])	59 (15.7)	31 (12.5)	28 (21.9)	
Saccharomyces(no. [%])	55 (14.6)	26 (10.5)	29 (22.7)	
Candida (no. [%])	71 (18.9)	38 (15.3)	33 (25.8)	
Unidentified fungi (no. [%])	63 (16.8)	40 (16.1)	23 (18.0)	
Others (no. [%])	3 (0.8)	3 (1.2)	0	
Negative (no. [%])	131 (34.8)	110 (44.4)	21 (16.4)	
Combined use of antibiotics (no. [%])	507 (84.4)	324 (84.6)	183 (83.9)	0.833
Combined use of corticosteroid (no. [%])	164 (27.3)	118 (30.8)	46 (21.1)	0.010
Combined use of PPIs (no. [%])	231 (38.4)	143 (37.3)	88 (40.4)	0.463
Route of administration				0.130
Intravenous (n [%])	491 (81.7)	306 (79.9)	185 (84.9)	
Oral (n [%])	110 (18.3)	77 (20.1)	33 (15.1)	
VCZ dose (mg/kg/dose)	3.6±0.8	3.69±0.75	3.46±0.93	0.011
Duration of VCZ administration (d)	8 (5, 13)	7 (4, 13)	8 (5, 14)	0.038
VCZ C_0 (μg/mL)	3.41 (1.82, 5.43)	3.3 (1.8, 5.5)	3.6 (2.2, 5.4)	0.235
VCZ C_N (μg/mL)	2.10 (1.44, 3.17)	2.2 (1.5, 3.3)	2.1 (1.4, 3.0)	0.173
VCZ C_N/C_0	0.74 (0.38, 1.36)	0.77 (0.40, 1.55)	0.60 (0.35, 1.13)	0.014

Notes: A patient may have several underlying diseases or fungal categories. [a]A comparison between younger adult patients and elderly patients.
Abbreviations: VCZ, voriconazole; C_0, trough concentration of voriconazole; C_N, trough concentration of voriconazole N-oxide; PPIs, proton pump inhibitors.

patients. Pneumonia and hematological malignancies were the primary baseline diseases. Approximately one-third of the patients had negative fungal detection results. Most patients had combined use of antibiotics, and one-third of the patients received corticosteroids and PPIs. The major route of administration of VCZ is via intravenous administration. The median time for VCZ C_0 and C_N measurements was 8 days after VCZ administration. The median values of VCZ C_0, C_N and C_N/ C_0 were 3.41 μg/mL, 2.10 μg/mL and 0.74, respectively.

The proportion of men in the elderly patients was significantly higher than that in the younger adult patients ($p<0.05$). The VCZ dose in the elderly patients was significantly lower than that in the younger adult patients ($p<0.05$). The time for C_0 and C_N measurements after VCZ administration in the elderly patients was longer than that in the younger adult patients ($p<0.05$). The VCZ C_0 and C_N in the two cohorts were similar ($p>0.05$), but a lower VCZ C_N/C_0 was observed in the elderly patients ($p<0.05$).

The main antibiotics employed in combination were imipenem-cilastatin, cephalosporins, meropenem, cefoperazone, vancomycin, piperacillin, tigecycline, teicoplanin, levofloxacin, and moxifloxacin (Table 2). The proportion of the combined use of cephalosporins, cefoperazone, and levofloxacin in elderly patients was higher than that in younger adult patients, while the proportion of the combined use of imipenem-cilastatin and vancomycin in elderly patients was lower ($p<0.05$). The proportion of the combined use of antibiotics with potential hepatotoxicity in elderly patients, including cefoperazone, piperacillin, tigecycline, metronidazole, compound sulfamethoxazole, minocycline, and roxithromycin, was higher than that in younger adult patients (44.0% vs 35.2%, $p=0.033$).

The percentage of grade 1 or higher adverse events for ALP, ALT, AST, γ-GT, and TBIL were 35.4%, 21.0%, 30.1%, 56.2%, and 22.2%, respectively. Compared with younger adult patients, elderly patients had a higher rate of grade 1 or higher adverse events of ALP (Table 3).

Risk Factors of Grade 1 or Higher Adverse Events of Liver Function

A total of 27 factors were incorporated in the univariate analysis, encompassing sex, age, fungal test results, VCZ dose, route of VCZ administration, VCZ C_0, C_N, and C_N/C_0, duration of VCZ treatment, combined use of antibiotics with

Table 2 The Combined Use of Antibiotics in Patients

Combined use of Antibiotics	All Adult Patients (n=601)	Younger Adult Patients (n=383)	Elderly Patients (n=218)	p^a
Imipenem-cilastatin	137 (22.8)	108 (28.2)	29 (13.3)	<0.001
Cephalosporins	126 (21.0)	63 (16.4)	63 (28.9)	<0.001
Meropenem	98 (16.3)	59 (15.4)	39 (17.9)	0.428
Cefoperazone	97 (16.1)	52 (13.6)	45 (20.6)	0.024
Vancomycin	93 (15.5)	88 (23.0)	5 (2.3)	<0.001
Piperacillin	67 (11.1)	42 (11.0)	25 (11.5)	0.851
Tigecycline	57 (9.5)	34 (8.9)	23 (10.6)	0.501
Teicoplanin	54 (9.0)	31 (8.1)	23 (10.6)	0.311
Levofloxacin	45 (7.5)	17 (4.4)	28 (12.8)	<0.001
Moxifloxacin	45 (7.5)	27 (7.0)	18 (8.3)	0.589
Polymyxin B	27 (4.5)	13 (3.4)	14 (6.4)	0.085
Amikacin	20 (3.3)	12 (3.1)	8 (3.7)	0.724
Colistin	15 (2.5)	7 (1.8)	8 (3.7)	0.164
Metronidazole	4 (0.7)	2 (0.5)	2 (0.9)	0.959
Compound sulfamethoxazole	3 (0.5)	2 (0.5)	1 (0.5)	1.000
Minocycline	2 (0.3)	2 (0.5)	0	-
Norfloxacin	2 (0.3)	2 (0.5)	0	-
Azithromycin	1 (0.2)	1 (0.3)	0	-
Doxycycline	1 (0.2)	1 (0.3)	0	-
Linezolid	1 (0.2)	1 (0.3)	0	-
Roxithromycin	1 (0.2)	1 (0.3)	0	-

Notes: A patient may have one or more combined use of antibiotics. [a]A comparison between younger adult patients and elderly patients.

Table 3 Distribution of Adverse Events of Liver Function in Patients

Variable	All Adult Patients	Younger Adult Patients	Elderly Patients	p^a
ALP				0.050
Grade 0 (38–126 U/L)	250 (64.6)	163 (68.2)	87 (58.8)	
Grade 1 (>126-315 U/L)	123 (31.8)	65 (27.2)	58 (39.2)	
Grade 2 (>315-630 U/L)	11 (2.8)	8 (3.3)	3 (2.0)	
Grade 3 (>630-2520 U/L)	3 (0.8)	3 (1.3)	0	
ALT				0.471
Grade 0 (0–42 U/L)	327 (79.0)	197 (76.9)	130 (82.3)	
Grade 1 (>42-126 U/L)	78 (18.8)	53 (20.7)	25 (15.8)	
Grade 2 (>126-210 U/L)	5 (1.2)	4 (1.6)	1 (0.6)	
Grade 3 (>210-840 U/L)	4 (1.0)	2 (0.8)	2 (1.3)	
AST				0.556
Grade 0 (0–42 U/L)	288 (69.9)	179 (70.5)	109 (69.0)	
Grade 1 (>42-126 U/L)	105 (25.5)	63 (24.8)	42 (26.6)	
Grade 2 (>126-210 U/L)	12 (2.9)	9 (3.5)	3 (1.9)	
Grade 3 (>210-840 U/L)	6 (1.5)	3 (1.2)	3 (1.9)	
Grade 4 (>840 U/L)	1 (0.2)	0	1 (0.6)	
γ-GT				0.183
Grade 0 (12–58 U/L)	176 (43.8)	120 (48.0)	56 (36.8)	
Grade 1 (>58-145 U/L)	113 (28.1)	65 (26.0)	48 (31.6)	
Grade 2 (>145-290 U/L)	69 (17.2)	39 (15.6)	30 (19.7)	
Grade 3 (>290-1160 U/L)	44 (10.9)	26 (10.4)	18 (11.8)	
TBIL				0.231
Grade 0 (3–22 μmol/L)	327 (77.8)	204 (78.5)	123 (76.9)	
Grade 1 (>22-33 μmol/L)	40 (9.5)	20 (7.7)	20 (12.5)	
Grade 2 (>33-66 μmol/L)	33 (7.9)	25 (9.6)	8 (5.0)	
Grade 3 (>66-220 μmol/L)	15 (3.6)	8 (3.1)	7 (4.4)	
Grade 4 (>220 μmol/L)	5 (1.2)	3 (1.2)	2 (1.2)	

Notes: [a]Comparison between younger adult patients and elderly patients.
Abbreviations: ALP, alkaline phosphatase; ALT, glutamic-pyruvic transaminase; AST, glutamic-oxaloacetic transaminase; γ-GT, γ-glutamyl transferase; TBIL, total bilirubin.

potential hepatotoxicity and PPIs, levels of IL-6 and PCT, serum creatinine, BUN, eGFR, WBC, RBC, Hb, PLT, MPV, PDW, HCT, platelet hematocrit, serum potassium, sodium and chloride levels. Risk factors for grade 1 or higher adverse events of liver function ($p<0.1$) in the univariate analysis were shown in Figures 1–3. In the multivariate analysis, VCZ dose was a risk factor for grade 1 or higher adverse events of ALP and TBIL; duration of VCZ treatment was a risk factor for grade 1 or higher adverse events of ALP, ALT, and γ-GT; VCZ C_0 was a risk factor for grade 1 or higher adverse events of AST in elderly patients and TBIL in younger adult patients; and VCZ C_N was a risk factor for grade 1 or higher adverse events of ALT, AST, and TBIL. In addition, sex, combined use of PPIs and antibiotics with hepatotoxicity, MPV, PDW, RBC, Hb, serum sodium and chloride, BUN, and IL-6 were also identified as risk factors for grade 1 or higher adverse events of liver function (Table 4).

Prediction Value of VCZ C_0 and C_N for Grade 1 or Higher Adverse Events of Liver Function

In younger adult patients, the results of the ROC curve analysis indicated that when VCZ C_0 levels of ≥4.04 μg/mL and VCZ C_N levels of <1.71 μg/mL, the incidence of grade 1 or higher adverse events of TBIL increased (Figure 4A and B). In elderly patients, the results of the ROC curve analysis indicated that when VCZ C_0 levels of ≥4.26 μg/mL and VCZ C_N levels of <1.70 μg/mL, the incidence of grade 1 or higher adverse events of AST increased (Figure 4C and D).

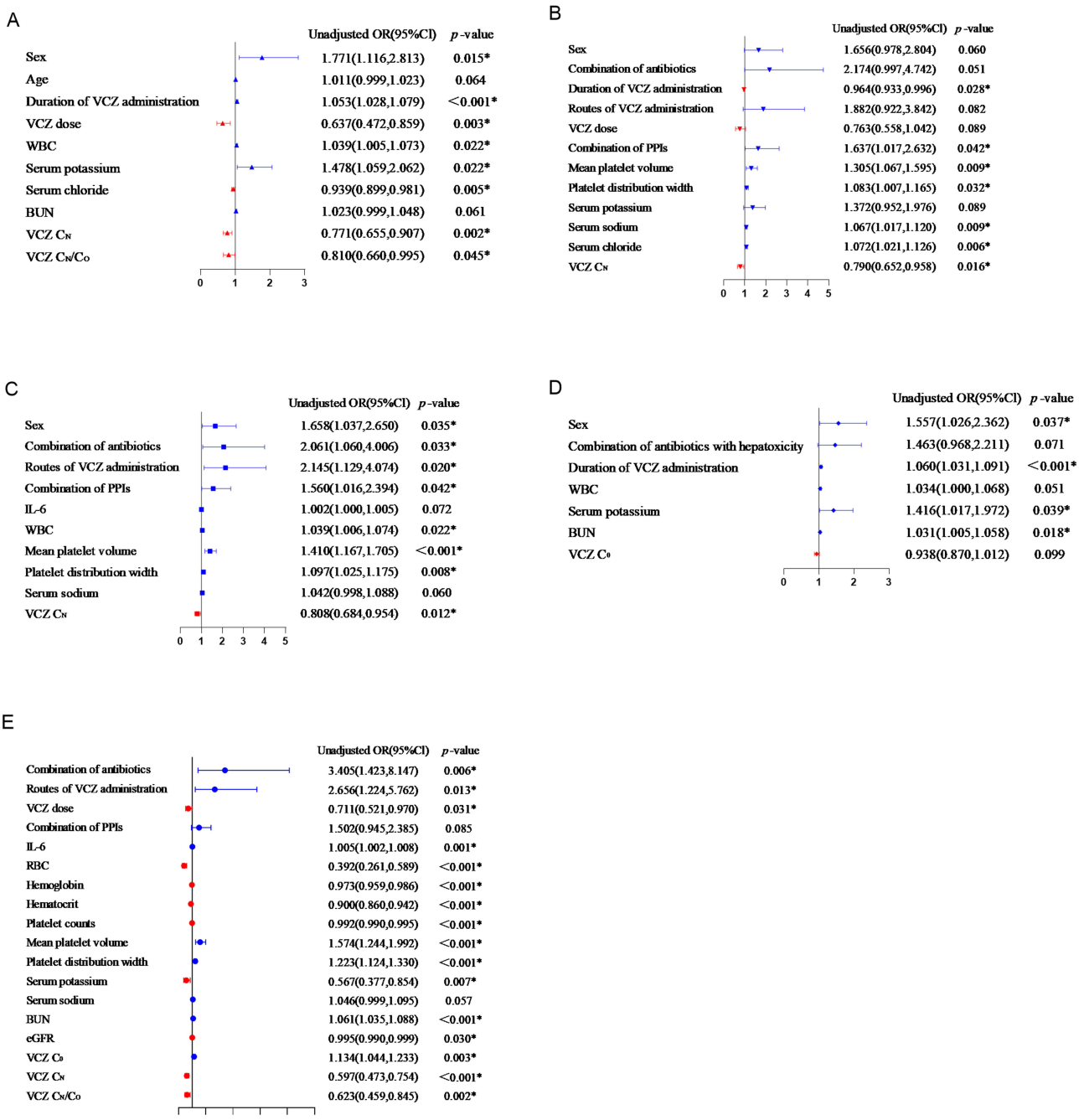

Figure 1 Risk factors for grade I or higher adverse events of liver function in all adult patients ($p<0.1$ in univariate analysis). (**A**) ALP, (**B**) ALT, (**C**) AST, (**D**) γ-GT, and (**E**) TBIL.

Discussion

VCZ is an important drug for the treatment of IFIs, especially those caused by *Aspergillus*. Hepatotoxicity has become an important cause of early withdrawal of VCZ, and VCZ C_0 has been suggested to be associated with hepatotoxicity. VCZ C_N is not routinely monitored in the clinic, and its role in hepatotoxicity remains unknown. In this study, we investigated the role of VCZ C_0 and C_N in its hepatotoxicity in adult patients. The median VCZ C_0 and C_N in our study were slightly higher than the values reported in two Japanese studies but with similar C_N/C_0.[18,19] VCZ C_N/C_0 was reported to be lower in Japanese patients who receiving VCZ with intravenous, with higher levels of C-reactive protein on the same day as VCZ C_0 measurement, CYP2C19 extensive metabolizer, and with old age.[18] Our previous study also showed that for

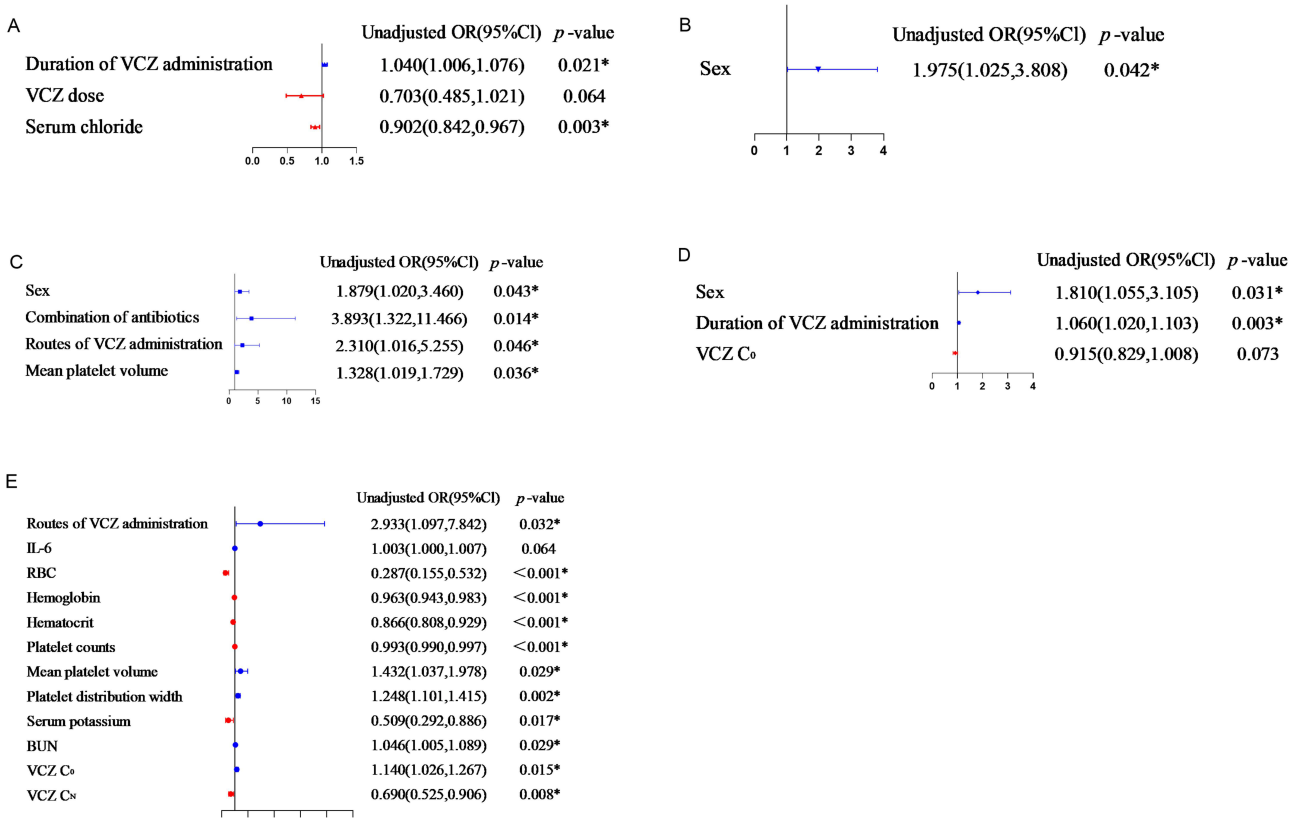

Figure 2 Risk factors for grade 1 or higher adverse events of liver function in younger adult patients (p<0.1 in univariate analysis). (**A**) ALP, (**B**) ALT, (**C**) AST, (**D**) γ-GT, and (**E**) TBIL.

patients with CYP2C19 normal metabolizer, VCZ C_0, C_0/dose, and C_0/C_N were significantly higher in the elderly patients.[17] The values of VCZ C_N/C_0 in younger adult patients and elderly patients in the current study were consistent with the results of previous studies.

To decrease VCZ-associated adverse events, C_0<4.0 μg/mL is strongly recommended for Asians, whereas C_0<5.5 μg/mL is generally recommended for non-Asians.[20] One study reported a significant difference in hepatotoxicity between patients with VCZ $C_0 \geq 4$ μg/mL and those with VCZ $C_0 < 4$ μg/mL.[21,22] In another study, liver enzyme abnormality was observed in 34.5% of patients with VCZ $C_0 >$ or = 3.9 μg/mL.[23] Similar results were also observed in our study. The cut off value of VCZ C_0 for grade 1 or higher adverse events of TBIL was 4.04 μg/mL in younger adult patients, while the cut off value of VCZ C_0 for grade 1 or higher adverse events of AST was 4.26 μg/mL in elderly patients.

In Yamada's study, VCZ C_N was correlated with a serum TBIL concentration.[19] We observed that VCZ C_N was a risk factor for grade 1 or higher adverse events of TBIL, ALT, and AST. Interestingly, the cutoff values of VCZ C_N for grade 1 or higher adverse events of TBIL in younger adult patients and for grade 1 or higher adverse events of AST in elderly patients were both 1.7 μg/mL. In general, when VCZ C_0 was higher than 4.0 μg/mL, or VCZ C_N was lower than 1.7 μg/mL, the incidence of grade 1 or higher adverse events of AST and TBIL increased. To the best of our knowledge, this is the first report of VCZ C_N as a risk factor for adverse events of liver function.

A previous study showed that hepatotoxicity occurred in 66.7% of patients within 7 days of the first dose of VCZ and in 94.4% within 15 days of the dose.[12] In another study, hepatotoxicity occurred in 6.0% of the patients after a median of 10 days.[24] Wang et al reported that the median time to hepatotoxicity was 3 days (range 1–24 days), and 83.2% of hepatotoxicity cases occurred within 7 days of VCZ initiation.[25] Taghvaye-Masoumi et al reported that only VCZ C_0 on day 14 is associated with hepatotoxicity.[26] We also found that the duration of VCZ administration was associated with grade 1 or higher adverse events of ALP, ALT, and γ-GT.

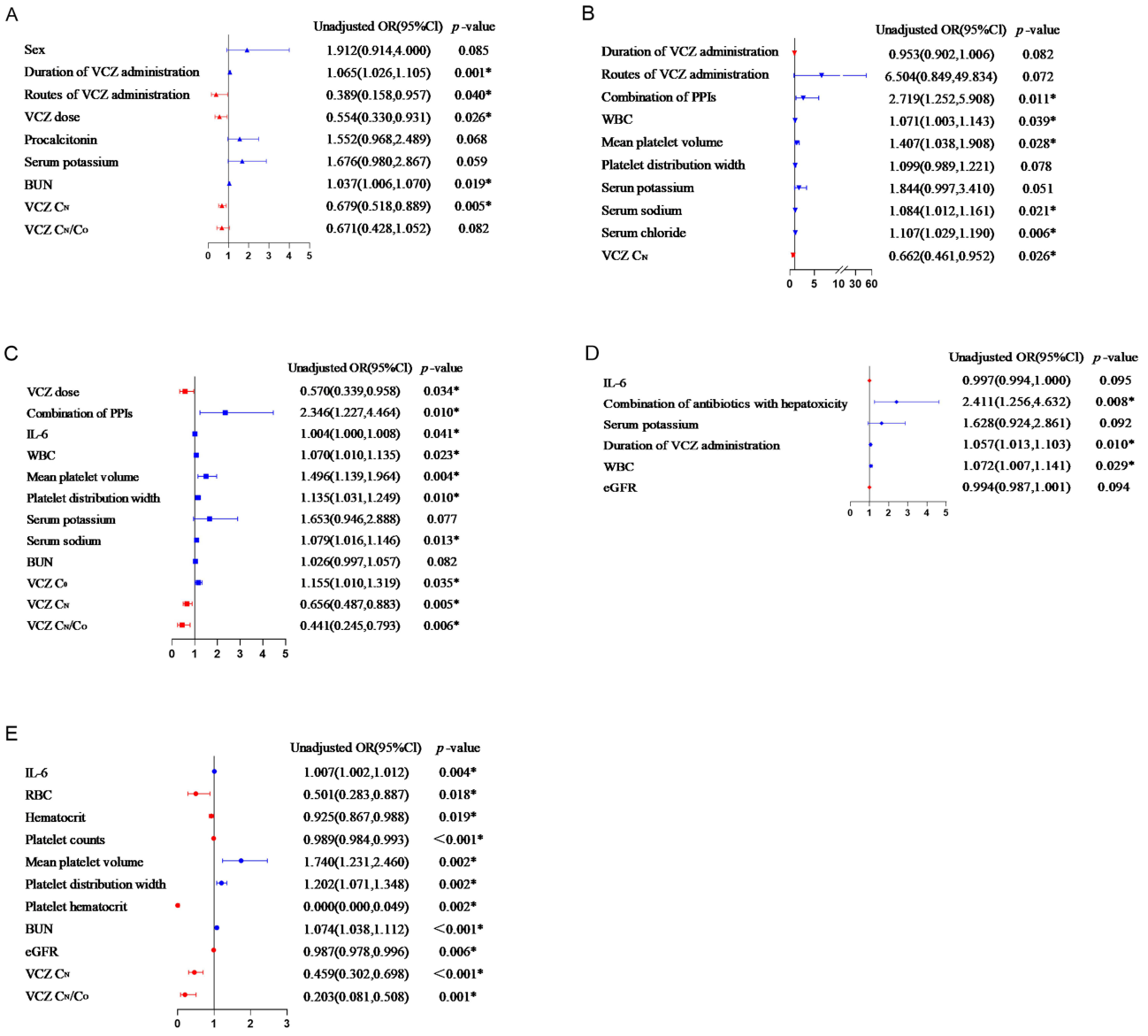

Figure 3 Risk factors for grade 1 or higher adverse events of liver function in elderly patients (p<0.1 in univariate analysis). (**A**) ALP, (**B**) ALT, (**C**) AST, (**D**) γ-GT, and (**E**) TBIL.

In the current study, approximately 84% of patients received antibiotics when using VCZ, which had potential hepatotoxicity or nephrotoxicity. PPIs are metabolized by the CYP2C19, CYP3A4, and CYP2C9 enzymes in the liver. The combined use of PPIs and VCZ can affect the C_0. We found that the combined use of antibiotics with hepatotoxicity and PPIs were risk factors for grade 1 or higher adverse events of ALT and γ-GT in elderly patients, which may be attributed to the higher proportion of combined use of antibiotics with hepatotoxicity, as well as the decreased CYP enzymes in these patients. To decrease the incidence of VCZ-associated adverse events of liver function in elderly patients, it is better not to combine antibiotics with potential hepatotoxicity. In addition, sex, MPV, PDW, RBC, Hb, serum sodium and chloride, BUN, and IL-6 levels were also associated with grade 1 or higher adverse events of liver function in our study, which should be considered when using VCZ.

This study has some limitations. First, it was a monocenter study, which could have led to a bias in the analysis. Second, pharmacogenetic data of patients were not included in the analysis, such as drug-metabolizing enzymes and genotype of CYP2C19. However, the effect of CYP2C19 genotypes on the incidence of adverse effects of VCZ has not been confirmed.[19,27,28] Based on our results, the risk of hepatotoxicity can be predicted by determining VCZ C_0 and C_N.

Table 4 Risk Factors for Adverse Events of Liver Function in Patients

Indicator	All Adult Patients				Younger Adult Patients				Elderly Patients			
	Factor	**Exp (B)**	**95% CI**	***p***	**Factor**	**Exp (B)**	**95% CI**	***p***	**Factor**	**Exp (B)**	**95% CI**	***p***
ALP	VCZ dose	0.710	0.511–0.988	0.042	Duration of VCZ administration	1.041	1.004–1.079	0.031	VCZ dose	0.578	0.339–0.985	0.044
	Serum chloride	0.944	0.892–0.999	0.048	Serum chloride	0.903	0.836–0.976	0.010				
ALT	Duration of VCZ administration	0.955	0.918–0.993	0.022	–	–	–	–	Combined use of PPIs	2.908	1.161–7.284	0.023
	MPV	1.325	1.060–1.657	0.014					Serum chloride	1.121	1.033–1.217	0.006
	VCZ C_N	0.805	0.644–1.007	0.058					VCZ C_N	0.583	0.357–0.954	0.032
AST	Sex	2.693	1.438–5.046	0.002	Sex	3.739	1.635–8.550	0.002	VCZ C_0	1.326	1.050–1.674	0.018
	MPV	1.375	1.130–1.672	0.001					VCZ C_N	0.566	0.339–0.945	0.030
	VCZ C_N	0.825	0.680–1.000	0.051								
γ-GT	Duration of VCZ administration	1.051	1.021–1.082	0.001	Sex	1.921	1.090–3.384	0.024	Combined use of antibiotics with hepatotoxicity	2.325	1.157–4.673	0.018
	Blood urea nitrogen	1.031	1.004–1.058	0.025	Duration of VCZ administration	1.065	1.024–1.109	0.002	Duration of VCZ administration	1.058	1.012–1.107	0.013
TBIL	VCZ dose	0.310	0.133–0.718	0.006	Red blood cells	0.272	0.082–0.897	0.032	Platelet distribution width	1.206	1.056–1.376	0.006
	IL-6	1.008	1.001–1.014	0.020	Platelet distribution width	1.183	1.014–1.380	0.033	VCZ C_N	0.361	0.188–0.695	0.002
	Hemoglobin	1.221	1.043–1.429	0.013	VCZ C_0	1.208	1.020–1.432	0.029				
	Serum sodium	1.319	1.088–1.598	0.005	VCZ C_N	0.576	0.344–0.967	0.037				

Abbreviations: VCZ, voriconazole; C_0, trough concentration of voriconazole; C_N, trough concentration of voriconazole N-oxide; ALP, alkaline phosphatase; ALT, glutamic-pyruvic transaminase; AST, glutamic-oxaloacetic transaminase; γ-GT, γ-glutamyl transferase; TBIL, total bilirubin; MPV, mean platelet volume; PPIs, proton pump inhibitor.

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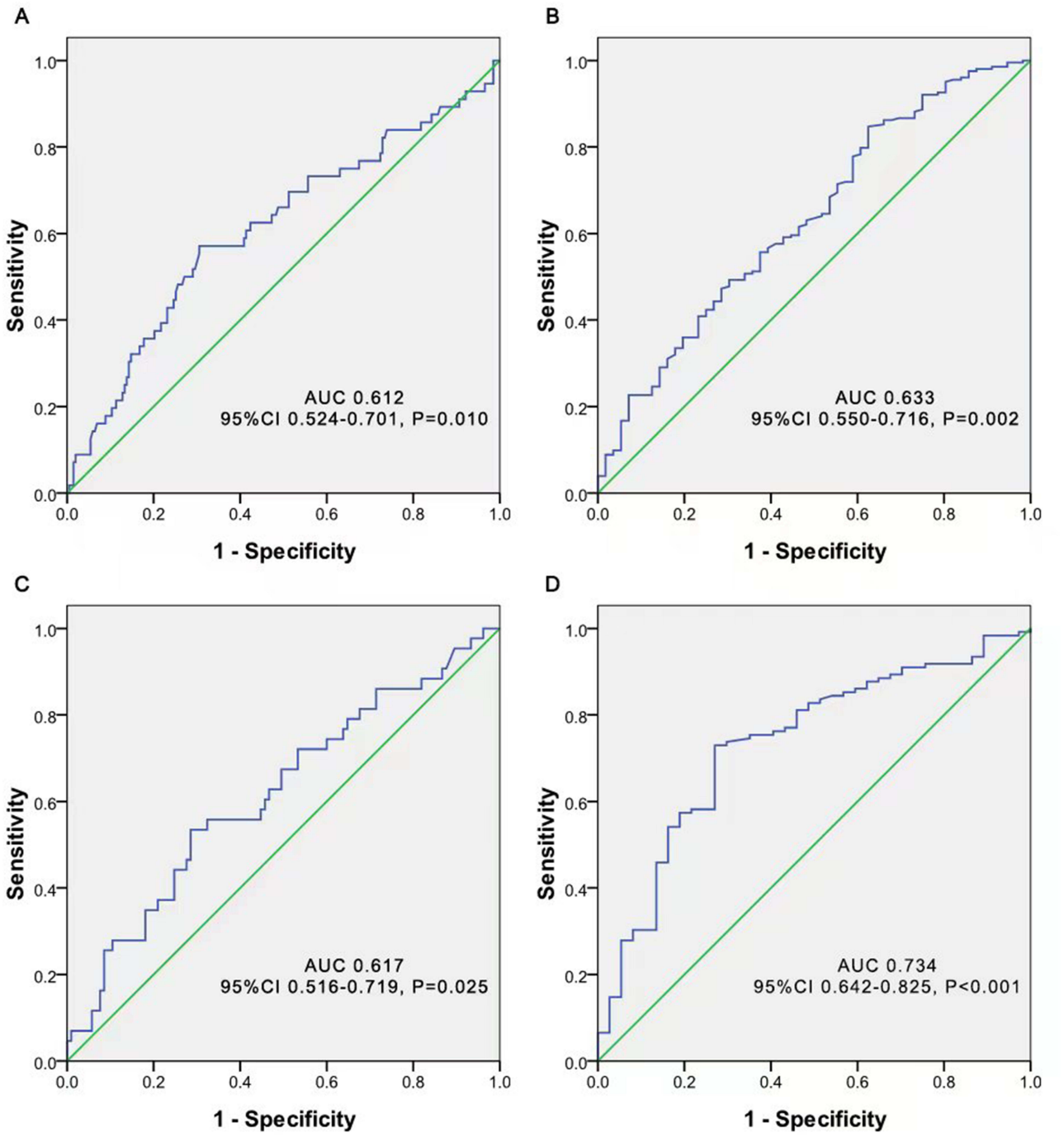

Figure 4 Receiver operating characteristic (ROC) curve for predicting grade 1 or higher adverse events of liver function. (**A**). Predicting grade ≥ 1 or higher adverse events of TBIL according to VCZ C_0 in younger adult patients; (**B**). Predicting grade ≥ 1 or higher adverse events of TBIL according to VCZ C_N in younger adult patients; (**C**). Predicting grade ≥ 1 or higher adverse events of AST according to VCZ C_0 in elderly patients; (**D**). Predicting grade ≥ 1 or higher adverse events of AST according to VCZ C_N in elderly patients.

Finally, since numerous variables demonstrated an influence on grade 1 or higher adverse events of liver function, VCZ C_0 and C_N ought to be combined with other indicators for thorough consideration when evaluating potential hepatotoxicity.

Conclusion

In summary, we report for the first time that VCZ C_N is a risk factor for its hepatotoxicity. Hepatotoxicity is more prevalent in the Asian population. The measurement of VCZ C_N may provide additional useful information in the early

phase of liver injury. VCZ C_0 and C_N should be monitored as early as the steady state concentration is achieved to avoid hepatotoxicity. It is possible to predict the onset of liver damage in advance. In practice, the VCZ C_N assay is relatively easy and inexpensive. It is necessary to determine VCZ C_N in VCZ therapeutic drug monitoring to limit its hepatotoxicity.

Data Sharing Statement

The original contributions presented in this study are included in the article, and further inquiries can be directed to the corresponding author.

Ethical Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of the Army Medical University (approval number: KY2023104). All organs were donated voluntarily with written informed consent, and that these were conducted in accordance with the Declaration of Istanbul.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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