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Associations of Serum 25-Hydroxyvitamin D with Antipsychotic Concentrations and Metabolite-to-Parent Ratios: A Retrospective Therapeutic Drug Monitoring Study

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Associations of Serum 25-Hydroxyvitamin D with Antipsychotic Concentrations and Metabolite-to-Parent Ratios: A Retrospective Therapeutic Drug Monitoring Study

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Abstract

Background: Serum 25-hydroxyvitamin D [25(OH)D] may be associated with the pharmacokinetics of antipsychotic drugs. We examined the relationships between serum total 25(OH)D and therapeutic drug monitoring (TDM) outcomes, focusing on metabolite-to-parent ratios (MPRs).

Methods: In this single-center retrospective study, patients with serum total 25(OH)D measurements and eligible antipsychotic TDM records obtained within ±7 days were included. The first 25(OH)D measurement per patient was used for classification into four categories (≤10, >10–20, >20–30, and >30 ng/mL). Ten TDM outcomes across six antipsychotics were compared using Kruskal–Wallis tests; pairwise Mann–Whitney U tests were performed for significant outcomes. Spearman correlations were evaluated with Benjamini–Hochberg false discovery rate (FDR) correction. Aripiprazole MPR was further assessed using linear regression with HC3 robust standard errors, including sensitivity analyses of ln(MPR). Dose-adjusted models were restricted to inpatients with usable prescription-dose records.

Results: The cohort included 2,764 patients (731 with severe deficiency, 1,341 with deficiency, 515 with insufficiency, and 177 with sufficiency). Among ten TDM outcomes, only aripiprazole MPR differed across 25(OH)D categories after FDR correction (n=1,090; q=0.003), with median (interquartile range) values of 0.25 (0.18–0.34), 0.28 (0.20–0.37), 0.30 (0.22–0.38), and 0.31 (0.24–0.44), respectively. Serum 25(OH)D was weakly correlated with aripiprazole MPR (Spearman ρ=0.159; q<0.001). Per 10-ng/mL higher 25(OH)D, the fully adjusted inpatient model showed a positive but not statistically significant association with raw MPR (β=0.016, 95% CI 0.000–0.032; P=0.051; n=636). In the corresponding ln(MPR) model, the association was statistically significant (β=0.050, 95% CI 0.006–0.094; P=0.025), equivalent to a 5.1% higher MPR (95% CI 0.6%–9.8%). No other evaluated TDM outcome showed an FDR-significant association.

Conclusion: Higher serum total 25(OH)D was associated with a modestly higher aripiprazole MPR in categorical and correlation analyses. The association was attenuated in inpatient multivariable models and remained significant only when MPR was log-transformed. These observational findings do not establish causation, a specific enzyme mechanism, or a basis for dose adjustment; prospective validation is warranted.

Keywords: 25-hydroxyvitamin D; aripiprazole; therapeutic drug monitoring; metabolite-to-parent ratio; cytochrome P450; real-world study

Background

Antipsychotic drugs are a cornerstone of treatment for schizophrenia and other psychotic disorders. Nevertheless, substantial interindividual variability in serum concentrations, therapeutic response, and adverse effects can occur even among patients

receiving identical or similar doses. Drug exposure may be influenced by age, sex, hepatic and renal function, smoking, medication adherence, concomitant medications, and genetic or functional variation in drug-metabolizing enzymes. Therapeutic drug monitoring (TDM), which quantitatively measures drugs and active metabolites in blood and interprets these measurements in conjunction with dose, sampling time, and clinical information, can help assess adherence, identify drug–drug interactions and atypical pharmacokinetics, and support individualized dosing [1-3]. The clearance of several second-generation antipsychotics depends on the cytochrome P450 (CYP) enzyme system. for example, aripiprazole is metabolized primarily by CYP2D6 and CYP3A4, whereas quetiapine is metabolized predominantly by CYP3A4 [4,5].

In addition to its role in calcium and phosphate homeostasis, vitamin D has endocrine, immunomodulatory, and neurobiological functions. Serum 25(OH)D is the most widely used biomarker of vitamin D status [6]. Previous systematic reviews and meta-analyses have shown that vitamin D deficiency is common in patients with schizophrenia and that mean 25(OH)D levels are lower than those in healthy controls. However, the available evidence is derived largely from observational studies, and the direction of causality remains uncertain [7-9]. Reduced outdoor activity, insufficient sunlight exposure, dietary factors, obesity, hospitalization, and disease-related lifestyle factors may all contribute to variation in 25(OH)D levels among patients with psychiatric disorders [7].

The potential relationship between vitamin D and drug metabolism has received increasing attention. Active vitamin D can regulate the transcription of several drug-metabolizing enzymes through the vitamin D receptor (VDR). Studies in primary human

hepatocytes have shown that 1,25-dihydroxyvitamin D3 can induce CYP3A4 expression [10]. Subsequent research has suggested a bidirectional biological relationship between VDR and CYP3A4 and has highlighted marked tissue- and species-specificity in VDR-mediated regulation of CYP3A [11-13]. Thus, serum vitamin D status may be associated with in vivo exposure to, or metabolic phenotypes of, certain CYP3A-related drugs. However, serum 25(OH)D is not a direct measure of CYP3A activity, and its clinical relevance requires validation using real-world pharmacokinetic data.

A previous clinical study reported that higher vitamin D levels were associated with lower dose-related concentrations of antipsychotics, with more pronounced associations for aripiprazole and quetiapine, both of which involve CYP3A4-mediated metabolism [14]. However, that study had a relatively small sample and focused primarily on dose-related drug exposure. Evidence remains limited regarding whether vitamin D status is associated with clinically interpretable drug exposure, active-moiety concentrations, or metabolite-to-parent ratios (MPRs) in larger real-world TDM populations. Therefore, using single-center real-world TDM data, we systematically examined the associations of serum total 25(OH)D with serum concentrations,and MPRs of commonly used antipsychotics, with particular emphasis on the independent association between 25(OH)D and aripiprazole MPR and the robustness of this association.

Methods

Study design, setting, cohort construction, and ethics

This single-center retrospective study used hospital information-system and laboratory data from Beijing Anding Hospital, Capital Medical University, collected between December 2024 and February 2026. The source population comprised patients

with serum total 25(OH)D testing (n=8,221). Eleven patients without valid 25(OH)D results and 5,446 without an eligible antipsychotic TDM record within ±7 days of 25(OH)D measurement were excluded, leaving 2,764 patients (Figure 1). Eligible TDM records concerned aripiprazole, quetiapine, olanzapine, clozapine, risperidone, or paliperidone. For patient-level classification, the first valid 25(OH)D measurement was used, together with an eligible TDM record within the prespecified window. Outcome-specific samples differed according to the availability of the corresponding analyte measurements. The ±7-day window was prespecified to approximate vitamin D status at TDM sampling; it does not establish simultaneous measurement or pharmacokinetic steady state.

Patients were categorized by total 25(OH)D concentration as severe deficiency (≤10 ng/mL), deficiency (>10 to ≤20 ng/mL), insufficiency (>20 to ≤30 ng/mL), or sufficiency (>30 ng/mL). The ten outcomes tabulated for comparison were four parent-drug concentrations (olanzapine, paliperidone, clozapine, and quetiapine), two active-moiety concentrations (risperidone plus 9-hydroxyrisperidone; aripiprazole plus dehydroaripiprazole), and four metabolite-to-parent ratios (MPRs; risperidone, clozapine, quetiapine, and aripiprazole). MPR was defined as measured metabolite concentration divided by the corresponding parent-drug concentration. Dose-normalized serum concentrations (concentration-to-dose ratios, C/D ratios) were not evaluated because the retrospective records did not consistently provide sufficient information to verify stable dosing, treatment duration, and pharmacokinetic steady state at the time of TDM sampling. The ten outcomes were evaluated in categorical and continuous 25(OH)D analyses; regression analyses focused on aripiprazole MPR, which showed an FDR-

significant association in both. Dose-informed aripiprazole models used inpatient data because outpatient prescription records did not reliably establish actual daily dose. Daily aripiprazole dose was included as a covariate in the inpatient multivariable models when usable prescription records were available.

This retrospective study was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University. The requirement for informed consent was waived by the Ethics Committee because of the retrospective nature of the study. All patient data were de-identified prior to analysis. The study was conducted in accordance with the Declaration of Helsinki.

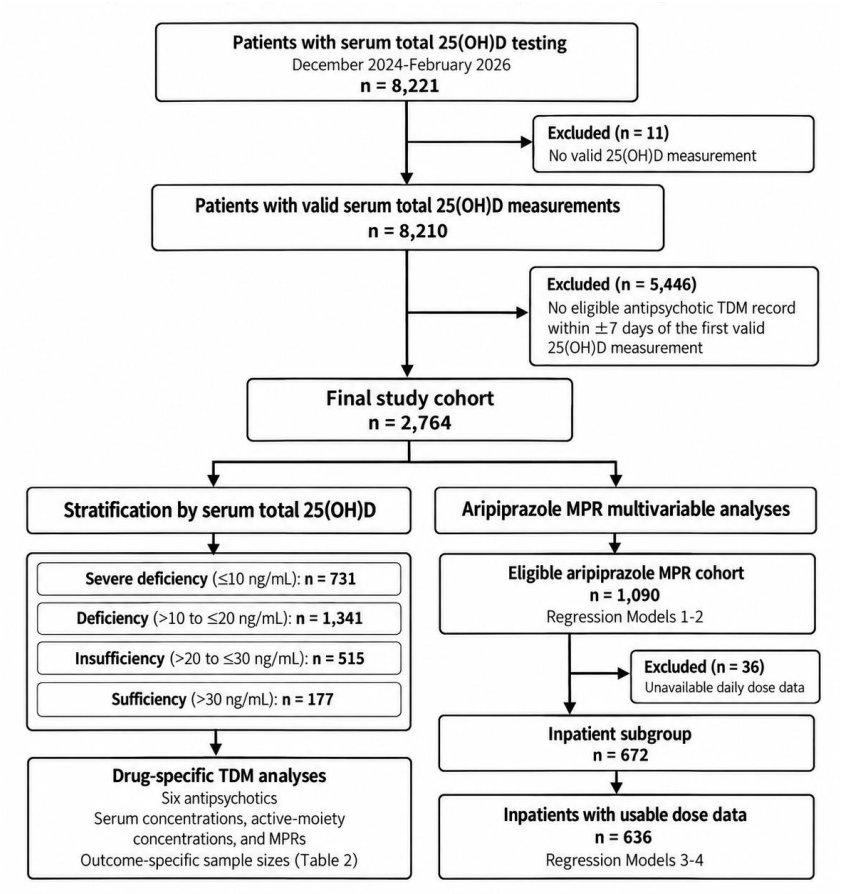

Figure 1. Flow diagram of study population selection

Measurement of antipsychotic drugs, metabolites, and total 25(OH)D

Serum drug and metabolite concentrations were measured using a validated ultra-performance liquid chromatography–tandem mass spectrometry method (Waters UPLC I-Class Xevo TQD). Serum samples were prepared by protein precipitation with methanol containing isotope-labeled internal standards, followed by chromatographic separation on a Waters BEH C_{18} column and detection by electrospray ionization in multiple-reaction-monitoring mode. The assay was validated in accordance with the Chinese Pharmacopoeia guideline for quantitative bioanalytical methods. The intra-assay and inter-assay coefficients of variation were <6.2% and <8.3%, respectively, and accuracy ranged from 85% to 115%.Routine analytical quality was ensured through internal quality control and external quality assessment.

Serum 25(OH)D2 and 25(OH)D3 concentrations were measured using liquid chromatography–tandem mass spectrometry (KLPMD-U; Hunan Calibra Biotechnology Co., Ltd., Hunan, China) and a fat-soluble vitamin assay kit (Zhejiang Diaseis Diagnostic Technology Co., Ltd., Zhejiang, China). The analytical performance of the assay met the predefined quality-control requirements.Total 25(OH)D was calculated as the sum of 25(OH)D2 and 25(OH)D3.

2.3 Statistical Analysis

Python (version 3.12; Python Software Foundation, Beaverton, OR, USA) was used for data processing and statistical analyses. GraphPad Prism 10.1.2 (GraphPad Software, Boston, MA, USA) was used for figure preparation. Continuous variables are presented as medians with interquartile ranges, and categorical variables as n (%). Baseline categorical characteristics were compared using Pearson’s chi-square test or Fisher’s

exact test, as appropriate. Cramér's V was calculated to quantify the strength of association between primary diagnostic category and serum 25(OH)D category. Differences in TDM outcomes across vitamin D groups were assessed using the Kruskal-Wallis test; when the overall test was significant, pairwise comparisons were performed using the Mann-Whitney U test. Rank-biserial correlations were reported as pairwise effect sizes for aripiprazole MPR. Associations between total 25(OH)D and TDM outcomes were evaluated using Spearman rank correlation. The Benjamini–Hochberg method controlled the false discovery rate across TDM-outcome tests and, separately, across the six pairwise aripiprazole MPR comparisons. FDR-adjusted $q<0.05$ was considered statistically significant for these multiple-comparison analyses. Regression results were interpreted using two-sided $P<0.05$.

Aripiprazole MPR was modelled as a continuous dependent variable in ordinary least-squares regression, with total 25(OH)D expressed per 10-ng/mL increment. To assess sensitivity to the right-skewed ratio outcome, corresponding models used the natural logarithm of MPR as the dependent variable. Heteroskedasticity-consistent HC3 standard errors were used to calculate 95% confidence intervals (CIs) and P values. For log-transformed models, $\exp(\beta)-1$ was used to express the association as a percentage difference in MPR; this interpretation does not imply a within-patient change.

Four models were specified: Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, restricted to inpatients with usable daily-dose records and adjusted for age, sex, daily aripiprazole dose, and the interval between 25(OH)D measurement and TDM; and Model 4, additionally adjusted for alanine aminotransferase, aspartate aminotransferase, CYP2D6 inhibitors, CYP3A4 inhibitors, CYP3A4 inducers, and

season. Concomitant medications with CYP2D6- or CYP3A4-inhibitory properties were identified according to Tables 3 and 4 of the AGNP consensus guidelines (2026), with Table 3 used for inhibitors and Table 4 for inducers. Medication exposure was assessed from inpatient prescription records in relation to the TDM sampling time. Models 1 and 2 used 1,090 patients with aripiprazole MPR data; among 672 inpatients, 636 had usable dose information and contributed to Models 3 and 4 (Figure 1; Table 5). Changes between Models 2 and 3 reflect both different adjustment sets and a different analytic population. Recorded prescriptions did not confirm administration, adherence, or steady state.

Results

Baseline Characteristics of the Study Population

As shown in Figure 1, 8,221 patients underwent serum total 25(OH)D testing during the study period; after exclusions, 2,764 were included in the final patient-level cohort. The distribution of the first qualifying 25(OH)D measurements was concentrated at lower values (Figure 2), with most patients meeting criteria for vitamin D deficiency or insufficiency.

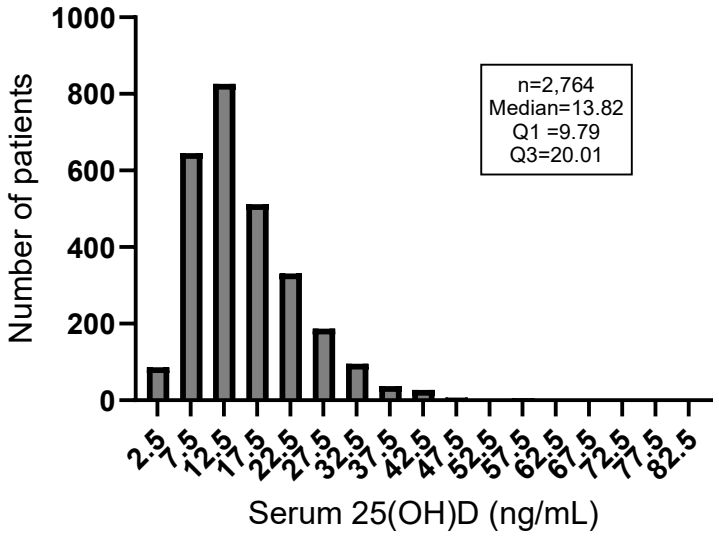

Figure2 Distribution of serum total 25(OH)D concentrations in the study population

Among 2,764 included patients, 731 (26.4%) had severe vitamin D deficiency, 1,341 (48.5%) had deficiency, 515 (18.6%) had insufficiency, and 177 (6.4%) had sufficiency. Overall serum total 25(OH)D was 13.82 (9.79–20.01) ng/mL; the corresponding group medians (interquartile ranges) were 7.70 (6.19–8.91), 13.98 (11.85–16.47), 23.87 (21.74–26.16), and 34.39 (31.84–40.11) ng/mL (Table 1).

Baseline characteristics varied across vitamin D groups. Median age decreased with increasing vitamin D status, from 27 years in the severe-deficiency group to 17 years in the sufficiency group. Sex distribution also differed: women accounted for 80.8% of the severe-deficiency group, compared with 58.1% and 58.2% of the insufficiency and sufficiency groups, respectively. The proportion of inpatients was highest in the severe-deficiency group (82.8%) and was 49.7% in the sufficiency group. The seasonal distribution of total 25(OH)D testing also varied across groups: winter testing was more common in the severe-deficiency group, whereas summer and autumn testing accounted for larger proportions in the insufficiency and sufficiency groups. Among the 2,764

patients included in the study, the most common primary diagnostic categories were schizophrenia spectrum and other psychotic disorders (560, 20.3%), other or unspecified mood disorders (503, 18.2%), depressive disorders (475, 17.2%), neurodevelopmental disorders (369, 13.4%), bipolar and related disorders (282, 10.2%), and childhood-onset behavioral and emotional disorders (169, 6.1%). The distribution of these diagnostic categories differed significantly across the four serum 25(OH)D groups (Pearson's χ^2 (18)= 74.120 , $P < 0.001$), although the overall association was weak (Cramér's V = 0.095).

Table 1. Baseline characteristics of the study population according to serum total 25(OH)D category

Variable	Overall	Severe deficiency ⩽10 ng/mL	deficiency >10 to ≤20 ng/mL	insufficiency >20 to ≤30 ng/mL	sufficiency >30 ng/mL	P value
No. of participants, n	2764	731	1341	515	177	—
Serum total 25(OH)D, ng/mL	13.82 (9.79, 20.01)	7.70 (6.19, 8.91)	13.98 (11.85, 16.47)	23.87 (21.74, 26.16)	34.39 (31.84, 40.11)	—
Age, years	22 (14, 43)	27 (15, 45)	21 (14, 42)	20 (14, 42)	17 (14, 35)	<0.001
Primary diagnostic category, n (%)						
Schizophrenia spectrum and other psychotic disorders	560 (20.3)	184 (25.2)	238 (17.7)	117 (22.7)	21 (11.9)	<0.001
Other or unspecified mood disorders	503 (18.2)	149 (20.4)	260 (19.4)	60 (11.7)	34 (19.2)	<0.001
Depressive disorders	475 (17.2)	109 (14.9)	255 (19.0)	83 (16.1)	28 (15.8)	0.091
Neurodevelopmental disorders	369 (13.4)	73 (10.0)	182 (13.6)	82 (15.9)	32 (18.1)	0.004
Bipolar and related disorders	282 (10.2)	91 (12.4)	128 (9.5)	49 (9.5)	14 (7.9)	0.115
Childhood-onset behavioral and emotional disorders	169 (6.1)	34 (4.7)	93 (6.9)	31 (6.0)	11 (6.2)	0.230
Other diseases	406 (14.7)	91 (12.4)	185 (13.8)	93 (18.1)	37 (20.9)	0.003
Sex, n (%)						<0.001
Male	819 (29.6)	140 (19.2)	389 (29.0)	216 (41.9)	74 (41.8)	
Female	1945 (70.4)	591 (80.8)	952 (71.0)	299 (58.1)	103 (58.2)	
Care setting, n (%)						<0.001
Inpatient	1940 (70.2)	605 (82.8)	946 (70.5)	301 (58.4)	88 (49.7)	
Outpatient	824 (29.8)	126 (17.2)	395 (29.5)	214 (41.6)	89 (50.3)	
Season of 25(OH)D testing, n (%)						<0.001
Spring	533 (19.3)	177 (24.2)	264 (19.7)	67 (13.0)	25 (14.1)	
Summer	627 (22.7)	103 (14.1)	309 (23.0)	165 (32.0)	50 (28.2)	
Autumn	682 (24.7)	130 (17.8)	314 (23.4)	176 (34.2)	62 (35.0)	
Winter	922 (33.4)	321 (43.9)	454 (33.9)	107 (20.8)	40 (22.6)	

Note. Values are median (IQR) or n (%), as appropriate. 25(OH)D, 25-hydroxyvitamin D.

Comparison of Antipsychotic TDM Parameters Across Vitamin D Groups

Ten TDM outcomes across six antipsychotics were compared across 25(OH)D categories (Table 2). Aripiprazole MPR was the only outcome with a significant between-category difference after FDR correction (n=1,090; Kruskal–Wallis $P<0.001$; $q=0.003$). The remaining parent-drug and active-moiety concentrations and MPRs did not meet the FDR threshold (all $q\geq0.270$).

Median (interquartile range) aripiprazole MPR increased from 0.25 (0.18–0.34) in severe deficiency to 0.28 (0.20–0.37) in deficiency, 0.30 (0.22–0.38) in insufficiency, and 0.31 (0.24–0.44) in sufficiency (Figure 3; Table 2). Aripiprazole active-moiety concentration had a nominal between-group P value of 0.032, but this was not significant after multiplicity correction ($q=0.270$).

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Drug	Outcome	n	Severe deficiency ⩽10 ng/mL	Deficiency >10 to ≤20 ng/mL	Insufficiency >20 to ≤30 ng/mL	Sufficiency >30 ng/mL	Kruskal-Wallis P	BH-FDR q
Olanzapine	Parent concentration	486	21.96 (11.45, 37.68) (n=145)	23.45 (13.02, 47.42) (n=241)	24.60 (11.94, 46.01) (n=81)	21.39 (12.57, 40.83) (n=19)	0.467	0.842
Risperidone	Active moiety concentration	346	27.11 (16.17, 38.12) (n=97)	22.80 (14.99, 35.53) (n=166)	22.70 (17.49, 33.84) (n=67)	23.21 (14.40, 34.02) (n=16)	0.632	0.842
Risperidone	MPR	224	3.04 (1.44, 5.33) (n=68)	3.03 (1.68, 5.88) (n=105)	3.01 (1.36, 4.95) (n=43)	1.63 (0.91, 3.48) (n=8)	0.579	0.842
Paliperidone	Parent concentration	324	23.75 (16.28, 32.46) (n=96)	25.05 (15.26, 40.95) (n=148)	22.18 (13.99, 30.29) (n=59)	24.35 (12.72, 35.50) (n=21)	0.732	0.842
Clozapine	Parent concentration	142	234.39 (129.67, 472.62) (n=51)	176.22 (107.39, 335.94) (n=62)	173.68 (57.89, 445.74) (n=26)	325.64 (212.06, 361.55) (n=3)	0.403	0.576
Clozapine	MPR	142	0.42 (0.33, 0.55) (n=51)	0.38 (0.32, 0.48) (n=62)	0.40 (0.24, 0.50) (n=26)	0.41 (0.39, 0.46) (n=3)	0.663	0.737
Quetiapine	Parent concentration	627	86.78 (41.16, 146.42) (n=183)	76.40 (40.22, 138.83) (n=327)	73.55 (45.63, 129.17) (n=87)	68.47 (37.95, 104.48) (n=30)	0.349	0.576
Quetiapine	MPR	582	0.64 (0.37, 1.02) (n=169)	0.66 (0.40, 1.05) (n=305)	0.63 (0.43, 1.05) (n=80)	0.66 (0.53, 1.27) (n=28)	0.798	0.798
Aripiprazole	Active moiety concentration	1119	175.65 (101.69, 278.76) (n=229)	174.21 (100.15, 265.55) (n=552)	195.53 (105.16, 329.40) (n=241)	142.83 (97.76, 207.30) (n=97)	0.032	0.27

Drug	Outcome	n	Severe deficiency ⩽10 ng/mL	Deficiency >10 to ≤20 ng/mL	Insufficiency >20 to ≤30 ng/mL	Sufficiency >30 ng/mL	Kruskal-Wallis P	BH-FDR q
Aripiprazole	MPR	1090	0.25 (0.18, 0.34) (n=222)	0.28 (0.20, 0.37) (n=538)	0.30 (0.22, 0.38) (n=235)	0.31 (0.24, 0.44) (n=95)	<0.001	0.003

Note. 25(OH)D, 25-hydroxyvitamin D; MPR, metabolite-to-parent ratio; BH-FDR, Benjamini-Hochberg false discovery rate. Risperidone active moiety was defined as risperidone + 9-hydroxyrisperidone, and aripiprazole active moiety as aripiprazole + dehydroaripiprazole.

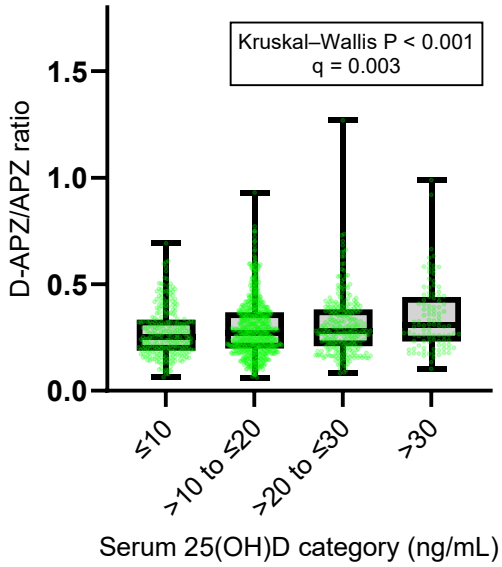

Figure 3. Aripiprazole metabolite-to-parent ratio across serum total 25(OH)D categories

Note: APZ:aripiprazole ;D-APZ: dehydroaripiprazole

Pairwise Comparisons of Aripiprazole MPR Across Vitamin D Groups

The six pairwise comparisons of aripiprazole MPR were corrected for multiple testing using the Benjamini–Hochberg procedure (Table 3). MPR was lower in severe deficiency than in insufficiency ($q=0.0048$) or sufficiency ($q<0.001$), and lower in deficiency than in sufficiency ($q=0.0048$). Severe deficiency versus deficiency, deficiency versus insufficiency, and insufficiency versus sufficiency did not differ significantly after correction (each $q=0.0741$).

Pairwise rank-biserial correlations indicated modest differences: the largest was for severe deficiency versus sufficiency ($r=0.289$), followed by deficiency versus sufficiency ($r=0.202$) and severe deficiency versus insufficiency ($r=0.164$). These findings describe differences in the distribution of MPR across vitamin D categories and should not be interpreted as a causal dose–response effect.

Table 3. Pairwise comparisons of aripiprazole MPR between serum total 25(OH)D categories

Pairwise comparison	Group 1: MPR Median (Q1, Q3)	Group 2: MPR Median (Q1, Q3)	Mann–Whitney U	Raw P value	BH-adjusted q value	Rank-biserial correlation r
Severe deficiency vs deficiency	0.25 (0.18, 0.34); n=222	0.28 (0.20, 0.37); n=538	54,724	0.0696	0.0741	0.084
Severe deficiency vs insufficiency	0.25 (0.18, 0.34); n=222	0.30 (0.22, 0.38); n=235	21,798	0.0024	0.0048	0.164
Severe deficiency vs sufficiency	0.25 (0.18, 0.34); n=222	0.31 (0.24, 0.44); n=95	7,496	<0.001	<0.001	0.289
Deficiency vs insufficiency	0.28 (0.20, 0.37); n=538	0.30 (0.22, 0.38); n=235	58,115	0.0741	0.0741	0.081
Deficiency vs sufficiency	0.28 (0.20, 0.37); n=538	0.31 (0.24, 0.44); n=95	20,401	0.0017	0.0048	0.202
Insufficiency vs sufficiency	0.30 (0.22, 0.38); n=235	0.31 (0.24, 0.44); n=95	9,732	0.0684	0.0741	0.128

Note. MPR, metabolite-to-parent ratio; BH, Benjamini-Hochberg.

Spearman Correlations Between 25(OH)D and TDM Parameters

In continuous analyses (Table 4; Figure 4), higher total 25(OH)D was weakly associated with higher aripiprazole MPR (Spearman $\rho=0.159$; n=1,090; raw $P<0.001$; FDR $q<0.001$). The scatterplot showed substantial between-patient dispersion, consistent with a small association rather than strong prediction at the individual level.

None of the other nine assessed TDM outcomes was significantly correlated with total 25(OH)D after FDR correction (Table 4). Quetiapine parent concentration showed a weak inverse correlation ($\rho=-0.076$; n=627), but neither its raw P value (0.059) nor FDR-adjusted q value (0.201) met the prespecified significance threshold.

Table 4. Correlations Between Serum 25(OH)D and Antipsychotic TDM Outcomes

Drug	Outcome	N	Spearman rho	Raw P	BH-FDR q
Olanzapine	Parent concentration	486	0.027	0.546	0.774
Risperidone	Active moiety concentration	346	-0.034	0.533	0.774

Drug	Outcome	N	Spearman rho	Raw P	BH-FDR q
Risperidone	MPR	224	-0.06	0.372	0.774
Paliperidone	Parent concentration	324	-0.048	0.392	0.774
Clozapine	Parent concentration	142	-0.100	0.235	0.458
Clozapine	MPR	142	-0.092	0.275	0.458
Quetiapine	Parent concentration	627	-0.076	0.059	0.201
Quetiapine	MPR	582	0.031	0.460	0.657
Aripiprazole	Active moiety concentration	1119	0.014	0.642	0.839
Aripiprazole	MPR	1090	0.159	**<0.001**	**<0.001**

Note. 25(OH)D, 25-hydroxyvitamin D; MPR, metabolite-to-parent ratio; BH-FDR, Benjamini-Hochberg false discovery rate. Risperidone active moiety was defined as risperidone + 9-hydroxyrisperidone, and aripiprazole active moiety as aripiprazole + dehydroaripiprazole.

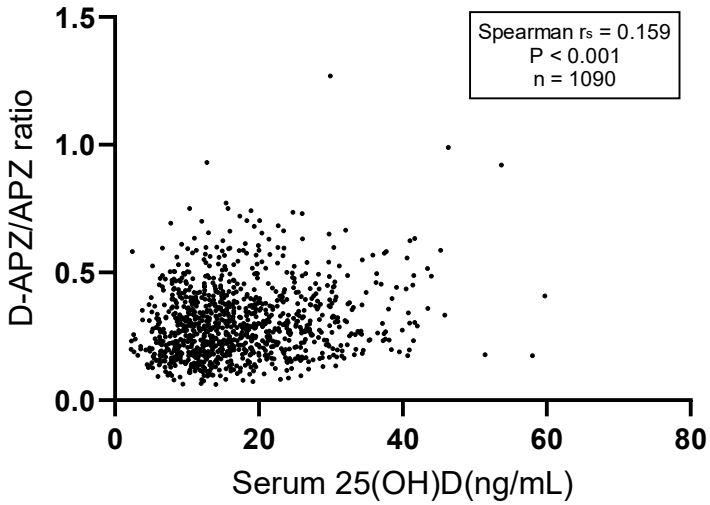

Figure 4. Correlation between serum total 25(OH)D level and aripiprazole metabolite-to-parent ratio

Multivariable Regression Analysis of Aripiprazole MPR

Regression estimates for the association of total 25(OH)D with aripiprazole MPR are presented in Table 5. For each 10-ng/mL increment in total 25(OH)D, the unadjusted

and age- and sex-adjusted models included 1,090 patients. Dose-adjusted Models 3 and 4 used 636 inpatients with usable prescription-dose information, rather than the complete aripiprazole MPR cohort.

With raw MPR as the outcome, the association was positive in Model 1 (β=0.029, 95% CI 0.017–0.040; P<0.001) and Model 2 (β=0.026, 95% CI 0.015–0.037; P<0.001). These coefficients represent absolute differences in the ratio per 10-ng/mL higher 25(OH)D, not percentage changes.

Among inpatients, the coefficient was smaller in Model 3 (β=0.017, 95% CI 0.002–0.033; P=0.027; n=636). After further adjustment for liver-function markers, CYP-related concomitant drugs, and season (Model 4), the association remained positive but did not reach the two-sided P<0.05 threshold (β=0.016, reported 95% CI 0.000–0.032; P=0.051; n=636). The lower confidence bound is rounded, and the P value should govern the significance interpretation.

The reduction in effect estimates across models must be interpreted with caution: Models 3 and 4 were restricted to inpatients, whereas Models 1 and 2 included both inpatients and outpatients. Thus, differences between Model 2 and Model 3 cannot be attributed to covariate adjustment alone.

Sensitivity Analysis Using ln(MPR)

Given the potentially skewed distribution of MPR, sensitivity analyses used ln(MPR) with the same four model specifications and analytic populations as the corresponding raw-MPR analyses (Table 5). Exponentiated coefficients are interpreted as relative differences in MPR per 10-ng/mL higher serum total 25(OH)D.

In Models 1 and 2 (n=1,090), the ln(MPR) coefficients were 0.092 (95% CI 0.061–0.123; P<0.001) and 0.087 (95% CI 0.055–0.119; P<0.001), respectively. These corresponded to estimated relative differences of 9.7% (95% CI 6.3%–13.1%) and 9.1% (95% CI 5.6%–12.7%) in MPR.

In the inpatient sample (n=636), the ln(MPR) coefficient was 0.056 (95% CI 0.012–0.099; P=0.013) in Model 3, or a 5.7% (95% CI 1.2%–10.5%) higher MPR. In fully adjusted Model 4, the coefficient was 0.050 (95% CI 0.006–0.094; P=0.025), equivalent to a 5.1% (95% CI 0.6%–9.8%) higher MPR for each 10-ng/mL higher 25(OH)D.

The association was consistently positive across the raw and log-transformed outcomes, but significance in the fully adjusted inpatient analysis depended on outcome transformation (raw MPR, P=0.051; ln[MPR], P=0.025). Together with the weak Spearman correlation, this indicates a small and model-sensitive association, rather than a robust effect across all model specifications.

Table 5. Multivariable associations between serum total 25(OH)D and aripiprazole metabolite-to-parent ratio

Model	Population	β (95% CI)	HC3 robust SE	P value	Relative change in MPR, % (95% CI)	N
Panel A. Aripiprazole MPR as the dependent variable						
Model 1	Full cohort	0.029 (0.017–0.040)	0.006	<0.001	—	1090
Model 2	Full cohort	0.026 (0.015–0.037)	0.006	<0.001	—	1090
Model 3	Inpatients only	0.017 (0.002–0.033)	0.008	0.027	—	636
Model 4	Inpatients only	0.016 (0.000–0.032)	0.008	0.051	—	636
Panel B. ln(MPR) as the dependent variable						
Model 1	Full cohort	0.092 (0.061–0.123)	0.016	<0.001	9.7 (6.3–13.1)	1090
Model 2	Full cohort	0.087 (0.055–0.119)	0.016	<0.001	9.1 (5.6–12.7)	1090
Model 3	Inpatients only	0.056 (0.012–0.099)	0.022	0.013	5.7 (1.2–10.5)	636
Model 4	Inpatients only	0.050 (0.006–0.094)	0.022	0.025	5.1 (0.6–9.8)	636

Note. 25(OH)D, 25-hydroxyvitamin D; MPR, metabolite-to-parent ratio; CI, confidence interval; HC3, heteroskedasticity-consistent covariance estimator. β coefficients represent the association per 10-ng/mL increase in serum total 25(OH)D. Model 1 was unadjusted. Model 2 adjusted for age and sex. Model 3 additionally included daily aripiprazole dose and the interval between 25(OH)D measurement and TDM sampling and was restricted to inpatients. Model 4 further adjusted for ALT, AST, CYP2D6 inhibitors, CYP3A4 inhibitors, CYP3A4 inducers, and season. Models 1 and 2 included the full aripiprazole MPR cohort (n=1,090). Of 672 inpatients in the unadjusted inpatient sensitivity cohort, 636 had usable recorded daily aripiprazole dose information and were included in Models 3 and 4. For Panel B, relative changes were calculated from exponentiated ln(MPR) coefficients. Retrospective prescription records do not establish medication administration or pharmacokinetic steady state; dose-adjusted models should therefore be interpreted cautiously.

Discussion

Using real-world TDM data, this study systematically evaluated the associations of serum total 25(OH)D with serum concentrations and MPRs of several antipsychotics. The principal findings were as follows. First, aripiprazole MPR increased across higher 25(OH)D categories, and the overall between-group difference remained statistically significant after FDR correction. Second, when 25(OH)D was analyzed as a continuous variable, it showed a weak positive correlation with aripiprazole MPR. Third, among all patients with available aripiprazole MPR data, both the unadjusted model and the model adjusted for age and sex showed significant positive associations between 25(OH)D and MPR. Fourth, after restriction to inpatients and further adjustment for dose, testing interval, liver-function markers, CYP-related concomitant medications, and season, the positive association was attenuated to borderline significance in the raw-MPR model, whereas it remained statistically significant in the ln(MPR) sensitivity analysis. Finally, apart from aripiprazole MPR, no other antipsychotic TDM parameter showed a consistently significant association with 25(OH)D after FDR correction. The categorical and continuous analyses of aripiprazole MPR therefore showed a consistent direction of association.

Aripiprazole is metabolized primarily in the liver by CYP2D6 and CYP3A4, and dehydroaripiprazole is one of its major active metabolites. The MPR may therefore partly

reflect the integrated balance between formation of the active metabolite from the parent drug and the subsequent clearance of both compounds [4,15]. Real-world TDM studies have demonstrated substantial interindividual pharmacokinetic variability in both aripiprazole and dehydroaripiprazole, with CYP2D6 functional variation representing an important source of this variability [15]. A systematic review and meta-analysis further showed that CYP2D6 metabolizer phenotype can materially affect aripiprazole exposure [16]. More recent evidence suggests that CYP3A4 may contribute not only to the formation of dehydroaripiprazole from aripiprazole but also to further elimination of dehydroaripiprazole. Accordingly, the parent-to-metabolite relationship cannot be considered a simple surrogate for the activity of a single CYP enzyme [17]. This pharmacokinetic complexity may help contextualize the observed association between 25(OH)D and aripiprazole MPR, although the underlying mechanisms remain uncertain. A recent cohort of 466 patients further demonstrated that CYP2D6 genotype and inhibitor-related phenoconversion were associated with aripiprazole and active-moiety dose-adjusted concentrations; poor metabolizer status was also associated with lower dehydroaripiprazole-to-aripiprazole ratios [18].

One potential mechanism linking vitamin D status to the aripiprazole metabolic phenotype is VDR-mediated regulation of CYP3A. Drocourt et al. demonstrated in primary human hepatocytes that active vitamin D can promote transcription of CYP3A4 and other drug-metabolizing enzymes through VDR-responsive elements [10]. Wang et al. reviewed the bidirectional relationship between vitamin D and CYP3A4, noting that active vitamin D can regulate CYP3A4 expression, whereas CYP3A4 itself participates in the metabolism of certain vitamin D compounds [11]. Qin and Wang further

emphasized the organ specificity of VDR-mediated CYP3A transcriptional regulation, with potentially prominent effects in the intestine, as well as important interspecies differences [12]. Thus, from a mechanistic perspective, higher vitamin D status could be associated with altered CYP3A-related metabolic capacity. Nevertheless, serum 25(OH)D cannot currently be used to infer hepatic or intestinal CYP3A4 activity directly.

Our findings are partly consistent with, but also importantly different from, the clinical observations reported by Gaebler et al. In 80 patients with schizophrenia, that study found an inverse association between vitamin D levels and dose-related antipsychotic concentrations, particularly for agents substantially metabolized by CYP3A4, including aripiprazole and quetiapine [14]. Dose-related concentration was an outcome of that previous study, not an outcome evaluated in our current analyses. In our cohort, the association was detected primarily for aripiprazole MPR, whereas aripiprazole active-moiety concentration was not significantly associated with vitamin D status after FDR correction. The studies therefore address related but different pharmacokinetic endpoints. Differences in cohort size and characteristics, vitamin D distributions, concomitant treatments, sampling conditions, and endpoint definitions may contribute to the divergent findings. Neither study alone establishes a causal effect of vitamin D on aripiprazole metabolism.

The biological interpretation of MPR requires particular caution. An increased MPR may reflect greater formation of metabolite from parent drug, but it can also be influenced by slower parent-drug clearance, altered downstream metabolite clearance, sampling time, degree of steady state, and individual genetic background [15–17]. Accordingly, the higher MPR observed in this study is better described as a modest shift

in the relative metabolic balance between aripiprazole and dehydroaripiprazole rather than direct evidence of increased CYP3A4 activity. In the absence of CYP2D6 and CYP3A4/5 genotype data, potential interactions between the vitamin D-associated signal and genetically determined metabolic phenotype cannot be disentangled. Recent pharmacogenetic findings further indicate that ABCB1 variants can be associated with the aripiprazole-to-dehydroaripiprazole ratio, suggesting that transporter-related variability may also complicate interpretation of the inverse metabolite-to-parent measure [19]. This evidence does not establish an effect of vitamin D on ABCB1.

The long elimination half-lives of aripiprazole and dehydroaripiprazole may also help explain why MPR showed a relatively stable pattern in real-world data. Studies in healthy volunteers indicate that aripiprazole and its active metabolite reach steady state after approximately 14 days of repeated dosing and that CYP2D6 functional variation can substantially affect aripiprazole half-life and clearance [20]. Long half-lives may reduce the impact of minor deviations in sampling time on concentration ratios, potentially making subtle differences in longer-term average metabolic phenotype easier to detect. Conversely, this also means that MPR reflects an integrated balance of formation and clearance over an extended time scale rather than enzyme activity at a single time point.

Quetiapine provides a useful comparator. It is extensively metabolized in the liver, with CYP3A4 serving as one of its most important metabolic enzymes, and its elimination half-life is substantially shorter than that of aripiprazole [4,21]. In vitro studies have shown that CYP3A4 generates multiple quetiapine metabolites, including quetiapine sulfoxide and N-desalkylquetiapine. CYP3A5 can also contribute to quetiapine metabolism, although its overall contribution appears smaller and its

metabolite profile may differ from that of CYP3A4 [22]. Consequently, a single quetiapine metabolite-to-parent ratio may not linearly reflect overall CYP3A activity. In addition, the shorter half-life of quetiapine makes both serum concentration and metabolite ratios more sensitive to the timing of the last dose, blood sampling, and dosing frequency. Such real-world variability may obscure small vitamin D-related effects.

Changes in CYP3A4 activity can, however, clearly influence aripiprazole exposure from a pharmacological perspective. For example, the CYP3A4 inducer carbamazepine substantially reduces systemic exposure to both aripiprazole and dehydroaripiprazole [23]. If vitamin D affected antipsychotic pharmacokinetics solely through broad and strong induction of CYP3A4, a consistent change in exposure or metabolic indices might be expected to be particularly evident for highly CYP3A4-dependent drugs such as quetiapine. We did not observe such a pattern. Our findings therefore favor an interpretation in which the vitamin D-associated signal is modest and shaped by drug-specific pharmacokinetic architecture, rather than a mechanism that can be generalized to all CYP3A4 substrates.

The statistical and clinical implications of these findings should be interpreted conservatively. The direction of association for aripiprazole MPR was consistent across categorical comparisons, Spearman correlation, multivariable regression, and the ln(MPR) sensitivity analysis, supporting internal consistency. Nevertheless, the Spearman correlation coefficient was only 0.159, and in the fully adjusted ln(MPR) model, each 10-ng/mL increase in 25(OH)D corresponded to an approximately 5.1% relative increase in MPR, indicating a small effect size. Moreover, active-moiety concentrations didn't show a consistent association either. Current evidence is therefore insufficient to support the

use of serum 25(OH)D as an independent basis for aripiprazole dose adjustment. A more appropriate clinical interpretation is that vitamin D status may be considered one of several background factors when interpreting aripiprazole TDM results, together with dose, sampling time, adherence, concomitant medications, liver function, and genetically determined metabolic phenotype. TDM itself emphasizes interpretation of drug concentrations within the full clinical context rather than mechanical dose adjustment based on a single parameter [1-3]. In a recent clinical cohort, CYP2D6 extreme metabolizer phenotypes were associated with a higher risk of aripiprazole treatment discontinuation, underscoring the distinction between an established pharmacogenetic determinant and the exploratory vitamin D association described here [18].

Future studies should prioritize prospective longitudinal designs in which within-patient changes in vitamin D status are used as a natural experiment, with repeated measurement of aripiprazole and dehydroaripiprazole concentrations and standardized assessment of sampling time, dose stability, and adherence. CYP2D6 and CYP3A4/5 genotype or phenotype information should also be incorporated, together with important covariates such as vitamin D supplementation, sunlight exposure, inflammatory status, and smoking. If within-patient increases in 25(OH)D after vitamin D supplementation are accompanied by corresponding changes in MPR, and this pattern remains reproducible after stratification by genetic metabolic phenotype, the causal relevance and clinical translatability of the association could be evaluated more rigorously.

Limitations

This study has several limitations. First, it was a single-center retrospective observational study. Although multiple statistical approaches yielded associations

between 25(OH)D and aripiprazole MPR in the same direction, causality cannot be established, and residual confounding from disease severity, healthcare-related factors, or other unmeasured variables cannot be excluded.

Second, although the multivariable models adjusted for age, sex, aripiprazole dose, testing interval, ALT, AST, CYP2D6/CYP3A4-related concomitant medications, and season, CYP2D6 and CYP3A4/5 genotype data and direct measures of enzyme phenotype were unavailable. Previous studies have shown that CYP2D6 phenotype substantially affects aripiprazole exposure and that CYP3A4 contributes to both formation and subsequent clearance of aripiprazole and dehydroaripiprazole [16,17]. Genetic variation may therefore represent an important source of residual confounding or effect modification. Recent pharmacogenetic data reinforce the relevance of CYP2D6 genotype and phenoconversion to both drug exposure and metabolite ratios [18]; ABCB1-related variability may represent an additional unmeasured influence [19].

Third, MPR reflects the combined effects of metabolite formation and the disposition of both the parent drug and its metabolite and is influenced by the degree of steady state, timing of the last dose, blood-sampling time, and analytical error [12,15]. An increased MPR therefore cannot be interpreted directly as increased CYP3A4 or CYP2D6 activity. Although measurements were matched within a predefined time window and daily dose and the interval between 25(OH)D measurement and TDM sampling were adjusted for in selected analyses, the influence of variations in real-world dosing and sampling conditions could not be fully eliminated. Furthermore, dose-normalized serum concentrations were not analyzed because pharmacokinetic steady state and dosing stability could not be reliably verified from the available retrospective records.

Consequently, the relationship between serum 25(OH)D and dose-normalized antipsychotic exposure could not be assessed, limiting direct comparisons with previous studies using C/D ratios.

Fourth, complete information was unavailable for smoking status, body weight or BMI, inflammatory status, diet, sunlight exposure, use of vitamin D supplements, and actual medication adherence. These factors may influence both 25(OH)D concentrations and antipsychotic pharmacokinetics and may therefore contribute to unmeasured confounding.

Fifth, effective sample sizes were uneven across antipsychotics and vitamin D groups. In particular, the higher-vitamin-D groups and some drug-specific outcomes had relatively small sample sizes, which may have limited statistical power and increased uncertainty in the estimates.

Conclusions

In this real-world TDM study, higher serum total 25(OH)D was weakly associated with higher aripiprazole MPR in categorical and correlation analyses. The association was attenuated after multivariable adjustment in the inpatient subgroup and remained statistically significant only in the ln(MPR) sensitivity model. No other evaluated antipsychotic TDM outcome, including aripiprazole active-moiety concentration, showed a statistically significant association with serum 25(OH)D after FDR correction.

These findings suggest a modest and model-sensitive association between vitamin D status and the relative metabolic profile of aripiprazole. However, causality and clinical significance remain uncertain, and the findings do not support vitamin D-based dose

adjustment. Prospective studies with standardized dosing and sampling conditions, pharmacogenetic data, and clinical outcomes are warranted.

List of abbreviations

25(OH)D, 25-hydroxyvitamin D; ALT, alanine aminotransferase; AST, aspartate aminotransferase;BH, Benjamini-Hochberg; CYP, cytochrome P450; HC3, heteroskedasticity-consistent covariance estimator; IQR, interquartile range; MPR, metabolite-to-parent ratio; TDM, therapeutic drug monitoring; VDR, vitamin D receptor.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University. The requirement for informed consent was waived by the Ethics Committee because of the retrospective nature of the study. All patient data were de-identified before analysis. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Data availability

The data used in this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JH and CL designed the study, GQ, XY and YY analyzed data, JH wrote the initial draft of the manuscript. All authors reviewed the manuscript.

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