General Psychiatry

New role of platelets in schizophrenia: predicting drug response

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ABSTRACT

Background Elevated platelet count (PLTc) is associated with first-episode schizophrenia and adverse outcomes in individuals with precursory psychosis. However, the impact of antipsychotic medications on PLTc and its association with symptom improvement remain unclear.

Aims We aimed to investigate changes in PLTc levels following antipsychotic treatment and assess whether PLTc can predict antipsychotic responses and metabolic changes after accounting for other related variables.

Methods A total of 2985 patients with schizophrenia were randomised into seven groups. Each group received one of seven antipsychotic treatments and was assessed at 2, 4 and 6 weeks. Clinical symptoms were evaluated using the positive and negative syndrome scale (PANSS). Additionally, we measured blood cell counts and metabolic parameters, such as blood lipids. Repeated measures analysis of variance was used to examine the effect of antipsychotics on PLTc changes, while structural equation modelling was used to assess the predictive value of PLTc on PANSS changes.

Results PLTc significantly increased in patients treated with aripiprazole (F=6.00, p=0.003), ziprasidone (F=7.10, p<0.001) and haloperidol (F=3.59, p=0.029). It exhibited a positive association with white blood cell count and metabolic indicators. Higher baseline PLTc was observed in non-responders, particularly in those defined by the PANSS-negative subscale. In the structural equation model, PLTc, white blood cell count and a latent metabolic variable predicted the rate of change in the PANSS-negative subscale scores. Moreover, higher baseline PLTc was observed in individuals with less metabolic change, although this association was no longer significant after accounting for baseline metabolic values.

Conclusions Platelet parameters, specifically PLTc, are influenced by antipsychotic treatment and could potentially elevate the risk of venous thromboembolism in patients with schizophrenia. Elevated PLTc levels and associated factors may impede symptom improvement by promoting inflammation. Given PLTc's easy measurement and clinical relevance, it warrants increased attention from psychiatrists.

Trial registration number ChiCTR-TRC-10000934.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent studies have identified the potential of platelet count (PLTc) in predicting cancer diagnosis and survival.

⇒ Additionally, PLTc has been linked to poorer outcomes in individuals referred for early intervention in psychosis services; however, it remains unclear whether antipsychotic medications influence PLTc or if there may be a correlation between PLTc changes and symptom improvement following antipsychotic treatment.

WHAT THIS STUDY ADDS

⇒ We found that PLTc increased slightly with certain antipsychotic drugs in a large longitudinal cohort of patients with schizophrenia who were receiving antipsychotic monotherapy.

⇒ We reported for the first time that PLTc could predict changes in negative symptoms in a structural model that also included baseline negative symptoms, white blood cell counts and a latent metabolic variable.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest the possibility that elevated PLTc may contribute to the increased risk of venous thromboembolism (VTE) following antipsychotic treatment.

⇒ To validate this inference, future research should incorporate assessments of platelet parameters and VTE, while extending the follow-up period for individuals with schizophrenia.

⇒ A positive outcome could emphasise the importance of regular monitoring of platelet parameters after antipsychotic treatment to identify VTE risk.

⇒ Our findings further suggest that high PLTc and other markers of chronic inflammation may impede the alleviation of negative symptoms, potentially requiring adjunctive anti-inflammatory drugs for a subgroup of patients.

INTRODUCTION

Platelets, traditionally known for their roles in haemostasis and thrombosis, are increasingly implicated in diverse disorders, including tumours, autoimmune diseases and psychiatric disorders.[1] In schizophrenia research, platelets serve as model cells because of their involvement in schizophrenia-related biochemical processes,[2 3] including inflammation, oxidative stress and neurotransmitter

activities. Platelet count (PLTc) is commonly used to assess initial haemostasis in clinical practice, but recent studies reveal its clinical significance in other diseases. For example, elevated PLTc is associated with cancer risk and poor survival, likely attributed to cancer-induced inflammation and platelet-mediated cytokine release.[4 5] Similarly, PLTc levels are elevated in first-episode patients with schizophrenia[6] and linked to poorer outcomes for patients who were referred to early intervention in psychosis services.[7] While these findings highlight the relevance of PLTc in the context of schizophrenia, there is a notable absence of related studies in this area.

Antipsychotic exposure has been linked to increased venous thromboembolism (VTE) risk, with elevated platelet aggregation as an underlying biological mechanism.[8] Patients with schizophrenia show increased platelet aggregation after taking antipsychotics,[9–11] and a positive correlation exists between PLTc and platelet aggregation.[12] Consequently, antipsychotic treatment may lead to changes in PLTc, with opposing evidence suggesting both an increase because of platelet aggregation and a decrease because of anti-inflammatory effects. For example, it was previously found that white blood cell count (WBCc) decreased significantly after a 6-week treatment with risperidone, olanzapine, quetiapine, perphenazine and haloperidol.[13] This corresponds to the anti-inflammatory effects of antipsychotics because WBCc can be used as an index of chronic and low-grade inflammation. Therefore, an investigation into PLTc changes after antipsychotic treatment in a large longitudinal cohort of patients with schizophrenia is warranted.

The association between elevated PLTc and poor clinical outcomes in patients with first-episode psychosis raises the question of whether PLTc can predict antipsychotic drug responses.[7] Previous studies have suggested the predictive value of several biomarkers associated with PLTc. For example, clinical symptom improvement following antipsychotic treatment is reported to be associated with increases in blood lipids,[14] which are positively associated with PLTc.[15] Additionally, it was previously found that a greater improvement in negative symptoms after taking antipsychotics could be predicted by a lower WBCc at baseline.[13] White blood cells have profound interactions with platelets, for example, the concentrations of platelet–leucocyte aggregates are positively correlated with interleukin (IL)-6, IL-8 and IL-10.[16] Therefore, in this study, we investigated whether PLTc could predict antipsychotic drug responses independently of WBCc and metabolic measures. Furthermore, a prior study has highlighted an association between PLTc and lipid levels following antipsychotic treatment.[17] A previous analysis also identified significant alterations in metabolic measures after a 6-week course of antipsychotic treatment, including changes in body mass index (BMI), waist circumference (WC), glucose levels, triglycerides and low-density lipoprotein (LDL).[18] Consequently, we also aimed to investigate whether PLTc could predict metabolic changes following antipsychotic treatment.

In this study involving 2985 patients with schizophrenia, we aimed to address two key questions. First, we aimed to understand how PLTc levels change following treatment with seven different antipsychotics, including atypical (risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone) and typical (perphenazine and haloperidol) antipsychotics. Second, we sought to understand whether PLTc can predict antipsychotic responses and metabolic changes after accounting for baseline WBCc and metabolic measures.

METHODS

Participants

The participants in this study were recruited from a clinical trial conducted on 3030 Han Chinese patients with schizophrenia. The protocol for the clinical trial is provided in the online supplemental materials. In this clinical trial, patients aged 18–45 years and diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) were recruited from the inpatient wards of 32 different hospitals with psychiatric departments across China between 6 July 2010 and 30 November 2011. After a 1-week washout period, participants were randomly assigned (2:2:2:2:2:1:1) to one of the seven groups, including five atypical antipsychotic groups (risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone) and two typical antipsychotic (perphenazine and haloperidol) groups. Patients were followed up after 2, 4 and 6 weeks. Interviews with trained psychiatrists were conducted at baseline and every 2 weeks. Fasting blood samples were collected at baseline and after 4 and 6 weeks. Patients with missing PLTc values at baseline were excluded. The trial profile is presented in figure 1.

The study was registered at the Chinese Clinical Trial Registry (https://www.chictr.org.cn/showproj.html?proj=8604) and the trial number is ChiCTR-TRC-10000934.

Clinical and laboratory assessments

Demographic and clinical characteristics were collected at baseline, including age, sex, years of education, family history of mental illness, age at onset, duration of illness (DOI) and psychiatric medication history. DOI (years) was defined as the period between the onset of psychosis and the pretrial clinical interviews. Body weight and height were measured by a trained investigator, and BMI was calculated as weight divided by height squared (kg/m^2). WC was measured at the end of a normal expiration by measuring the minimum circumference at the level of the umbilicus to the nearest 0.5 cm. Psychiatrists assessed clinical symptoms using the positive and negative syndrome scale (PANSS). Fasting blood samples were collected between 07:00 and 09:00 hours and used to assess prolactin levels; blood cell counts, including PLTc, WBCc and red blood cell counts and metabolic measures, including glucose, total cholesterol

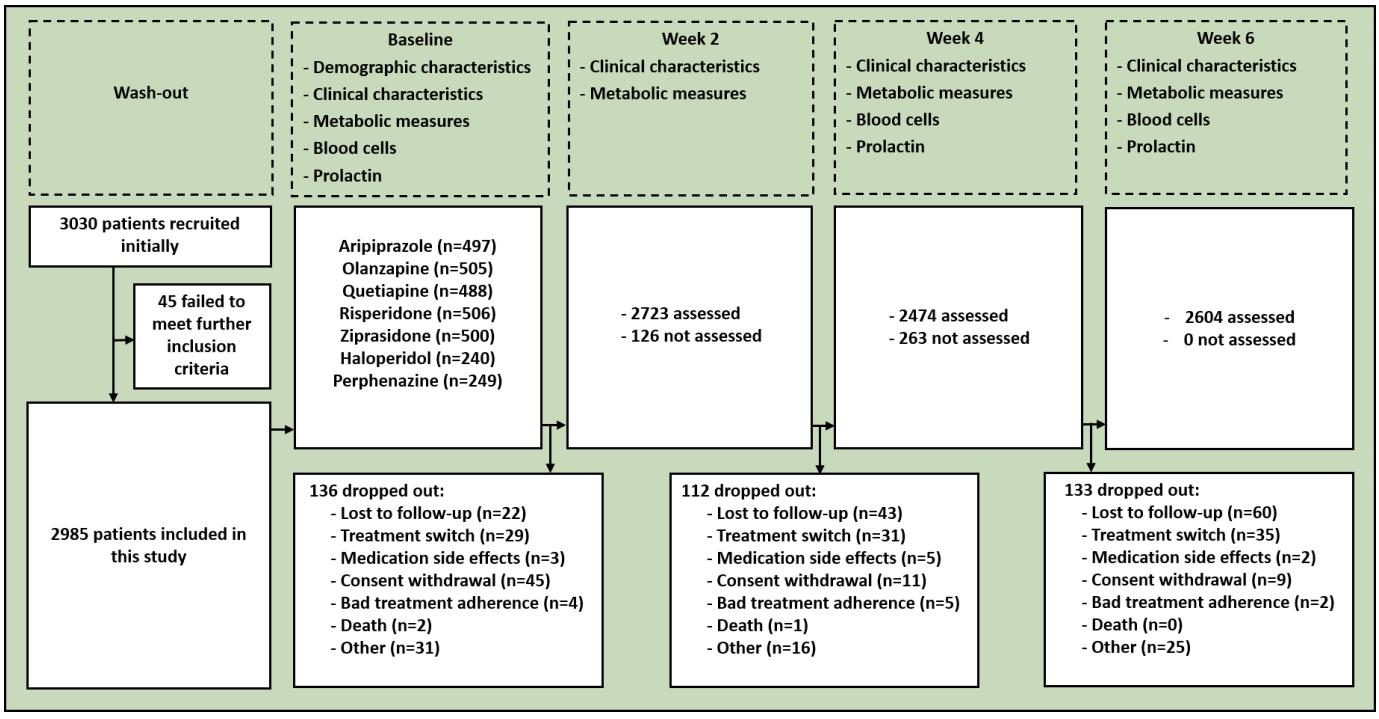

Figure 1 Trial profile. The number of patients not assessed at each time point is the number of patients who did not drop out but with missing data for analysis at the according time point.

(TC), triglycerides, high-density lipoprotein and LDL. Blood laboratory analyses were performed at the hospital where the blood samples were collected using a unified protocol. Prolactin was assessed in 16 centres, and qualified data were available for 1048 patients. During the 6-week follow-up period, BMI, WC and PANSS scores were assessed at the end of weeks 2, 4 and 6. Blood samples were collected at the end of weeks 4 and 6. The medical reference range for PLTc is 100×10^9–300×10^9 for Chinese patients. Patients were divided into three groups based on their PLTc at baseline: low ($<100\times10^9$), normal (100×10^9–300×10^9) and high ($>300\times10^9$). Responders and non-responders were categorised based on PANSS score changes of ≥50% and <50%, respectively.[19]

Statistical analysis

Comparisons among the three PLTc groups were conducted using either analysis of variance (ANOVA) for continuous variables or the χ^2 test for categorical variables. Tukey's honest significant difference method was used to compute pairwise differences after the ANOVA showed statistical significance. Pairwise differences between categorical variables were tested using pairwise χ^2 tests with the Bonferroni correction. Repeated measures ANOVA was used to compare changes in PLTc over time. Univariate logistic models were fitted for changes in PANSS and metabolic measures, which were converted into binary variables using 50% as the cut-off for PANSS and the median for metabolic measures. Specifically, changes in PANSS total, positive subscale and negative subscale scores, as well as changes in metabolic variables that showed significant differences among the three PLTc groups were outcome variables of interest. Before fitting the structural equation model (SEM) model, a latent growth curve model (LGM) was used to estimate the longitudinal trajectories of the outcome variables that can be predicted by PLTc in the univariate logistic analysis. Demographic and clinical characteristics that were associated with the outcome variables were also included in the LGM model. Model fit was assessed using the comparative fit index (CFI), goodness-of-fit index (GFI), standardised root mean square residual (SRMR) and root mean square error of approximation (RMSEA). Values of >0.90 for CFI and GFI, and <0.08 for SRMR and RMSEA, respectively, indicate a reasonable model fit. For the LGM, the time scores were originally fixed at 0, 1, 2 and 3. When misfit (CFI/GFI ≤0.90 or SRMR/RMSEA ≥0.08) was observed, parameters were freed one by one until goodness-of-fit was acceptable. The predicted values of the intercept (average level at baseline) and slope (rate of change) were entered into a new SEM to study the parallel changes in these variables. In addition, PLTc, WBCc and a latent variable of metabolism were also included in the SEM model to address the second key question that we aim to answer in this study. The latent variable of metabolism was created from metabolic measures that were associated with outcome variables or showed significant differences among the three PLTc groups. Because metabolic variables were correlated with each other, we further deleted

those with small coefficients to improve the model fit indices.

Before the statistical analysis, extreme outlying data were winsorised at the 1% or 99% level for all laboratory assessments. The drug dose was scaled within each antipsychotic group, resulting in a mean dose of zero for any single antipsychotic group. The false discovery rate (FDR) method was used to correct for multiple comparisons among different groups. The significance level was set at p<0.05 for SEM. Complete-case analyses were adopted for all statistical models and were performed using R V.4.1.0 (https://www.R-project.org/). The SEM and LGM were fitted using the R package 'lavaan'.

RESULTS

Association between PLTc and demographic, clinical and metabolic measures

We included 2985 patients with available PLTc data at baseline. The mean (SD) age of all the patients was 31.77 (7.96) and 1530 (51.26%) were men. We divided the patients into the following three groups: patients with low PLTc levels (n=56, 1.88%), normal PLTc levels (n=2637, 88.34%) and high PLTc levels (n=292, 9.78%). The percentage of male patients was lower in the high PLTc group compared with that in the other two groups (χ^2=30.45, FDR<0.001). No significant differences were identified in the percentage of drug-naïve patients between the three groups. PLTc levels were not associated with PANSS scores. WBCc (F=67.24, FDR<0.001), BMI (F=20.32, FDR<0.001), TC (F=18.57, FDR<0.001) and LDL (F=10.92, FDR<0.001) were significantly increased in the low–to–high platelet group. Prolactin levels were assessed in 1048 patients and were not significantly different among the three groups (table 1).

Longitudinal change of PLTc

Significant changes in PLTc levels were observed in patients treated with aripiprazole (F=6.00, p=0.003), ziprasidone (F=7.10, p<0.001) and haloperidol (F=3.59, p=0.029). There was an obvious increase in PLTc levels in the first 4 weeks of treatment in all three groups, but PLTc did not continue to increase after that according to figure 2A.

Association between PLTc and longitudinal changes in PANSS and metabolic measures

In the univariate model, PLTc was significantly higher in non-responders than in responders, as defined by changes in PANSS-negative subscale scores (online supplemental table 1, figure 2B). No significant difference was found between non-responders and responders as defined by changes in the positive PANSS subscale or total scores. We then fitted an LGM for PANSS-negative subscale scores (GFI=0.98, CFI=0.99, SRMR=0.02, RMSEA=0.06) and adjusted for years of education, DOI and age at onset (figure 3A), which were also associated with changes in PANSS-negative subscale scores. The slope (change rate) of the PANSS-negative subscale scores was considered the outcome of the final SEM. The model fit indices for SEM were acceptable (GFI=0.97, CFI=0.93, SRMR=0.04 and RMSEA=0.06). In the model, the rate of change in the PANSS-negative subscale scores was moderately associated with the intercept (average level at baseline) (figure 3B). The correlations between change rate and PLTc, WBCc and metabolic measures were significant, although with weaker associations. Positive coefficients indicated that elevated PLTc levels were associated with less symptom improvement, as the change rate was negative, signifying symptom improvement post-treatment. Consequently, higher PLTc levels corresponded to larger negative values, indicating a relatively smaller reduction in the PANSS-negative subscale scores following antipsychotic treatment.

Out of the three metabolic measures that exhibited a positive association with baseline PLTc, patients with lesser changes (<median) in TC and LDL levels had higher PLTc levels (online supplemental table 1, figure 2C). Nevertheless, when adjusting for baseline blood lipid levels and other variables in SEM, PLTc was not predictive of changes in any of these blood lipid levels.

DISCUSSION

Main findings

In a cohort comprising 2985 patients with schizophrenia, we conducted a novel analysis of longitudinal changes in PLTc following monotherapy with 7 different antipsychotics. For the first time, our study revealed a significant increase in PLTc compared with baseline after a 6-week treatment with aripiprazole, ziprasidone and haloperidol. Furthermore, we observed associations between baseline PLTc and both WBCc and various metabolic parameters. In our SEM model encompassing these variables, we found that baseline PLTc had predictive value for the improvement of negative symptoms, in conjunction with baseline PANSS-negative subscale scores, WBCc and metabolic parameters. It is worth noting that in univariate models without covariate adjustments, PLTc exhibited associations with metabolic changes.

We observed a significant increase in PLTc following a 6-week treatment with certain antipsychotics, which aligns with prior studies reporting increased platelet aggregation in patients treated with antipsychotics.[9 10] Another study measured platelet aggregation as changes in the optical density of platelet-rich plasma from six patients treated with chlorpromazine for >6 months.[11] While limited by its small sample size, this study stands as the sole direct assessment of platelet aggregation in patients treated with antipsychotics. In a recent study, mean platelet component levels, serving as an indirect measure of platelet activation, demonstrated a significant reduction following administration of atypical antipsychotics, indicative of increased platelet aggregation.[9] However, this study included only 16 patients and did not

Table 1 Characteristics of the patients in the three PLTc groups

	Total	Low PLTc ($<100\times10^9$)	Normal PLTc (100×10^9–300×10^9)	High PLTc ($>300\times10^9$)				
	(n=2985)	(n=56, 1.88%)	(n=2637, 88.34%)	(n=292, 9.78%)	F/χ^2	P value	FDR	Pairwise comparison
Demography								
Age, mean (SD)	31.77 (7.96)	33.93 (8.34)	31.69 (7.94)	32.08 (8.00)	2.41	0.090	0.163	
Men, n (%)	1530 (51.26)	31 (55.36)	1 394 (52.86)	105 (35.96)	30.45	<0.001	<0.001	High<normal; high<low
Educational years, mean (SD)	10.41 (3.29)	9.57 (3.70)	10.40 (3.26)	10.59 (3.39)	2.24	0.106	0.163	
Clinical characteristics								
Family history, n (%)	637 (21.34)	10 (17.86)	555 (21.05)	72 (24.66)	2.38	0.304	0.395	
Age at onset, mean (SD)	25.30 (6.99)	27.62 (8.09)	25.28 (6.97)	25.03 (6.88)	3.32	0.036	0.087	
DOI, mean (SD)	6.17 (5.94)	6.04 (5.86)	6.09 (5.89)	6.95 (6.43)	2.77	0.063	0.115	
Drug-naïve, n (%)	863 (28.91)	16 (28.57)	770 (29.20)	77 (26.37)	1.03	0.598	0.656	
PANSS, mean (SD)								
Total score	89.48 (15.32)	89.82 (16.81)	89.45 (15.46)	89.66 (13.67)	0.04	0.961	0.964	
Positive subscale	25.52 (4.70)	26.04 (6.08)	25.54 (4.72)	25.24 (4.21)	0.89	0.410	0.455	
Negative subscale	21.77 (6.75)	21.32 (7.04)	21.72 (6.79)	22.26 (6.30)	0.96	0.385	0.454	
General subscale	42.16 (8.44)	42.46 (8.72)	42.15 (8.50)	42.16 (7.79)	0.04	0.964	0.964	
Blood cells, mean (SD)								
PLTc	216.61 (63.82)	81.15 (16.53)	206.01 (48.00)	338.36 (37.64)	–	–	–	
WBCc	6.72 (1.98)	5.65 (1.79)	6.61 (1.92)	7.90 (2.12)	67.24	<0.001	<0.001	Low<normal<high
RBCc	15.72 (6.04)	14.80 (5.23)	15.66 (6.07)	16.40 (5.94)	2.29	0.096	0.079	
Metabolism, mean (SD)								
BMI	22.22 (3.71)	20.48 (3.03)	22.14 (3.62)	23.34 (4.26)	20.32	<0.001	<0.001	Low<normal < high
WC	79.59 (11.38)	77.06 (8.76)	79.50 (11.33)	80.92 (12.10)	3.46	0.032	0.087	
Systolic BP	115.99 (11.61)	115.16 (10.11)	115.92 (11.61)	116.83 (11.84)	0.95	0.386	0.454	
Diastolic BP	75.65 (8.38)	74.23 (7.11)	75.60 (8.38)	76.39 (8.54)	1.98	0.138	0.197	
GLU	4.84 (0.77)	4.79 (0.76)	4.84 (0.77)	4.92 (0.81)	1.74	0.176	0.235	
TC	4.18 (0.92)	3.78 (0.88)	4.16 (0.91)	4.46 (0.98)	18.57	<0.001	<0.001	Low<normal<high
TG	1.23 (0.72)	1.25 (0.80)	1.22 (0.71)	1.33 (0.81)	3.00	0.050	0.100	
HDL	1.32 (0.36)	1.24 (0.35)	1.31 (0.35)	1.36 (0.38)	3.24	0.039	0.872	
LDL	2.36 (0.86)	1.96 (0.85)	2.35 (0.85)	2.52 (0.89)	10.92	<0.001	<0.001	Low<normal<high
Prolactin*, mean (SD)	32.88 (37.88)	38.45 (35.12)	33.06 (38.78)	28.30 (24.44)	0.84	0.432	0.483	

Continued

Table 1 Continued

	Total	Low PLTc (<100×10⁹)	Normal PLTc (100×10⁹–300×10⁹)	High PLTc (>300×10⁹)	F/χ^2	P value	FDR	Pairwise comparison
	(n=2985)	(n=56, 1.88%)	(n=2637, 88.34%)	(n=292, 9.78%)				

*Data were available for 1048 patients, 28, 948 and 72 patients in the low, normal and high platelet groups, respectively.
BMI, body mass index; BP, blood pressure; DOI, duration of illness; FDR, false discovery rate; GLU, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PANSS, positive and negative syndrome scales; PLTc, platelet count; RBCc, red blood cell count; SD, standard deviation; TC, total cholesterol; TG, triglycerides; WBCc, white blood cell count; WC, waist circumference.

differentiate between various treatments. Additionally, mean platelet volume (MPV), another platelet parameter that is involved in several mental disorders[20] and can be used as a surrogate biomarker of platelet activity because of the greater activity of larger platelets, exhibited significantly higher MPV levels in patients taking atypical antipsychotic drugs compared with those in drug-naïve patients.[10] Conversely, Lee *et al* found no significant MPV changes in 100 patients with schizophrenia receiving clozapine for 1 year.[21] These disparate results may be attributed to variations in the antipsychotics studied.

In summary, our study contributes novel evidence indicating that increased platelet aggregation can be identified through the measurement of platelet parameters following antipsychotic treatment. Given the potential role of increased platelet aggregation in the reduced life expectancy of individuals with schizophrenia, primarily because of excess mortality due to VTE, timely identification holds paramount importance. Easily accessible platelet parameters may prove valuable in this regard.

We also observed variations in how different antipsychotics influenced PLTc. While the precise mechanisms underlying this phenomenon are unknown, we can infer some insights into how antipsychotics might increase platelet aggregation. First, platelets possess serotonin receptors (5-HT2A), to which antipsychotics can bind and act as receptor antagonists.[22] This binding may lead to increased serotonin levels, which, in turn, can induce platelet activation. Antipsychotics vary in their affinity for platelet 5-HT2A receptors, with one study ranking them by pKI (the negative log10 of the inhibition constant), a measure of affinity (higher values indicating stronger affinity): risperidone (pKI=9.62), ziprasidone (pKI=8.85), olanzapine (pKI=8.48), aripiprazole (pKI=8.15), haloperidol (pKI=7.30) and quetiapine (pKI<6.1).[22] The relatively low pKI for quetiapine may explain why PLTc did not increase in patients treated with this drug. However, the three drugs for which we observed significant PLTc changes did not significantly differ from the other drugs tested in terms of 5-HT2A affinity. Therefore, this alone cannot account for our findings. Second, in some patients, antipsychotics can cause hyperprolactinemia, which is a potent platelet aggregation co-activator.[23] The propensity of antipsychotics to cause hyperprolactinemia varies because of differences in dopamine D (2) receptor-binding affinity and the ability to cross the blood-brain barrier.[24] Among the three antipsychotics that cause a significant increase in PLTc, haloperidol is associated with a higher risk of hyperprolactinemia.[24] However, this does not explain why aripiprazole increases PLTc, as it is a partial D2 receptor agonist and prolonged binding suppresses prolactin secretion.[25] Third, antipsychotic treatments can induce oxidative stress, which, in turn, increases platelet aggregation through several mechanisms such as reduced nitric oxide synthase expression in epithelial cells and platelets.[26] Previous studies have reported that risperidone treatment can increase nitric oxide metabolite levels.[27] This may explain why PLTc did

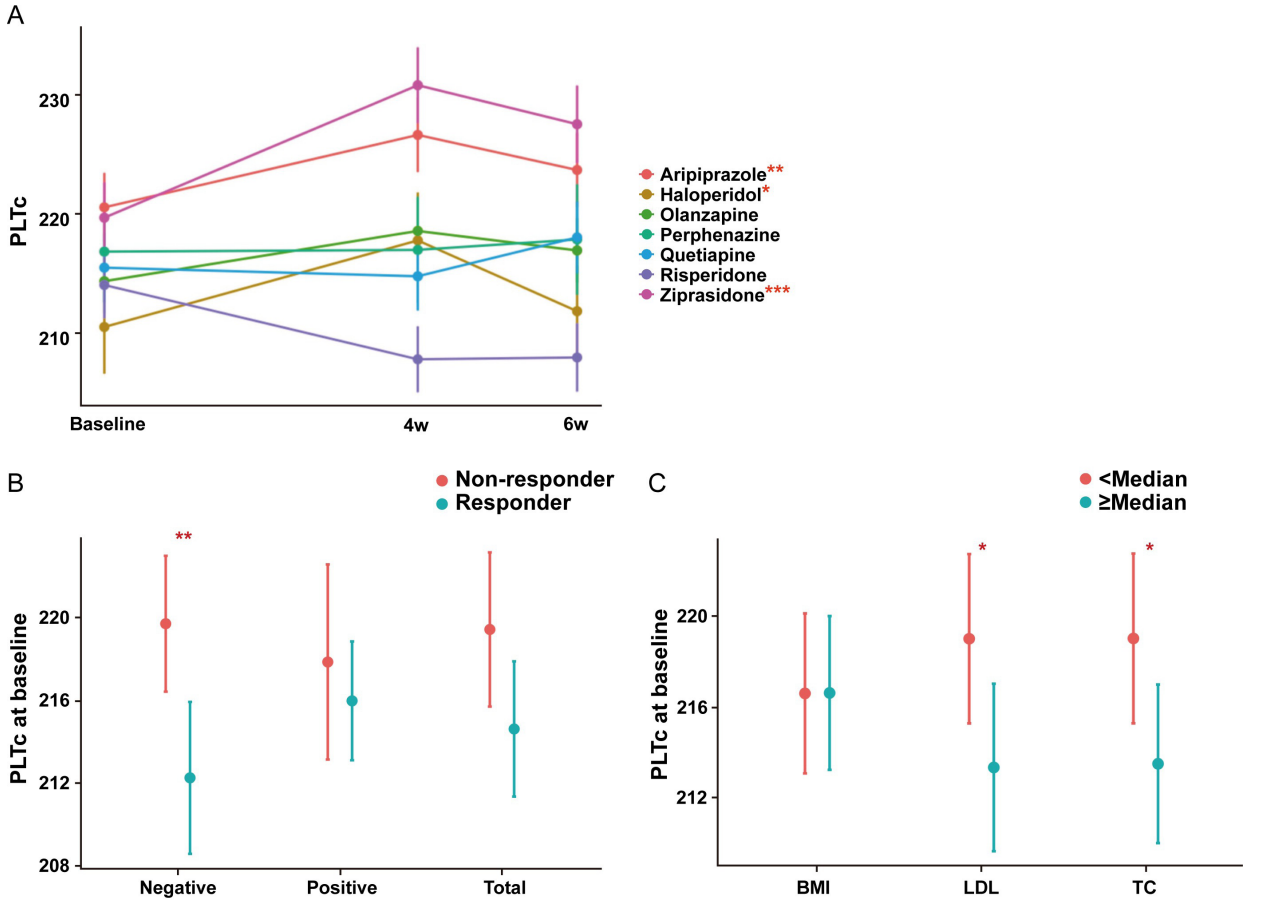

Figure 2 Longitudinal changes of PLTc and differences in baseline PLTc between groups based on drug response and metabolic changes. (A) Longitudinal changes of PLTc among the different antipsychotic groups. (B) Differences in baseline PLTc between different drug response groups. (C) Differences in baseline PLTc between groups based on different metabolic changes. Metabolic variables that showed significant differences in table 1 were selected. *p<0.05; **p<0.01; ***p<0.001. BMI, body mass index; LDL, low-density lipoprotein; PLTc, platelet count; TC, total cholesterol.

not significantly increase with risperidone, despite its higher risk of hyperprolactinemia compared with other antipsychotic drugs.[24]

Furthermore, our observation that PLTc did not continue to increase after the first 4 weeks—a novel finding—requires validation in future studies. The underlying biological mechanism remains unclear but may be associated with the anti-inflammatory effects of antipsychotics, as discussed in the introduction. In summary, antipsychotics influence platelet aggregation through diverse pathways, and the predominant effect might vary among different antipsychotics at different stages of treatment. Our findings suggest that the long-term effects of antipsychotics on platelets are complex and the relevant mechanisms require further exploration.

After accounting for baseline negative symptoms, we predicted changes in negative symptoms by considering PLTc, WBCc and a latent metabolic factor involving blood lipid levels. We anticipated that patients with elevated baseline PLTc, WBCc and metabolic levels would exhibit less improvement in negative symptoms. Additionally, we observed positive correlations between PLTc, WBCc and metabolic levels, suggesting a shared underlying mechanism among these three parameters. We propose that the potential biological mechanism driving this association is linked to elevated PLTc as a response to heightened inflammation levels in individuals with schizophrenia, similar to observations in patients with cancer.[4 5] First, WBCc serves as an inflammatory index since white blood cells are major producers of inflammatory mediators. Second, platelets play a significant role in both the innate and adaptive immune responses to inflammatory stimuli, interacting directly with various types of immune cells, including white blood cells, dendritic cells and T cells, among others.[28] Activated platelets also serve as sources of many pro-inflammatory factors. In the present study, we established a positive correlation between PLTc and WBCc. Third, metabolic disturbances and inflammation are positively associated, consistent with reports characterising a pro-inflammatory state as a component of metabolic syndrome.[29] The fact that these variables exclusively predict changes in negative symptoms, as opposed to the positive symptom subscale, aligns with previous research indicating that numerous inflammatory markers are associated with negative symptoms but not necessarily positive symptoms.[30] Given that negative symptoms in schizophrenia are often more challenging to treat and contribute to poor functional outcomes, identifying

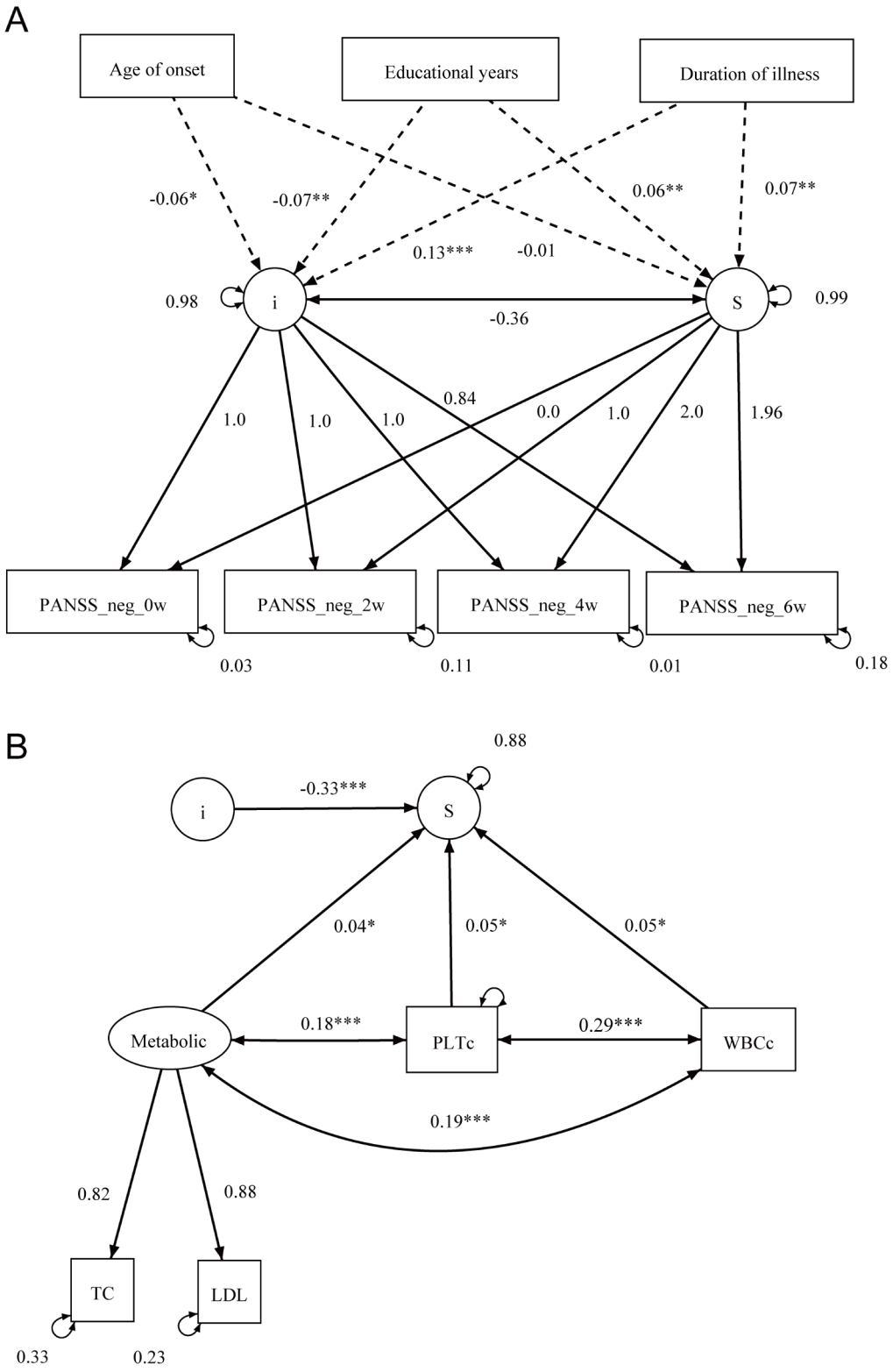

Figure 3 Latent growth curve model and structural equation model for PANSS-negative subscale scores. (A) Diagram of latent growth curve model. (B) Diagram of structural equation model. Note: squares represent the observed variables; ovals represent latent variables; lines with double arrows represent covariances and variances; lines with single arrows represent regressions; dashed lines stand for the effect of covariants on i and S. *p<0.05; **p<0.01; ***p<0.001. i, intercept (average level at baseline of PANSS negative subscale scores); LDL, low-density lipoprotein (baseline); PANSS_neg_0w, negative subscale of positive and negative syndrome scales at zero week or baseline; PLTc, platelet count (baseline); S, slope (rate of change in the PANSS negative subscale scores); TC, total cholesterol (baseline); WBCc, white blood cell count (baseline).

biological predictors of negative symptom improvement holds substantial clinical relevance.

Limitations

Although this study has a large sample size, a longitudinal design and a comprehensive patient assessment, it also presents certain limitations. First, the primary focus of this clinical trial was not the exploration of platelet functions or inflammation in schizophrenia; consequently, only PLTc and WBCc but no other platelet parameters or white blood cell parameters, were documented in the case report form. This constraint limits our ability to investigate additional platelet or inflammatory parameters. Second, our follow-up period was limited to 6 weeks, preventing us from assessing the long-term impact of antipsychotics on platelet parameters.

Implications

Platelet parameters associated with platelet aggregation, notably PLTc, are influenced by antipsychotic treatments. These variables offer simplicity in measurement and may warrant routine monitoring for identifying the risk of developing VTE. PLTc, WBCc and metabolic levels hold predictive value for tracking longitudinal shifts in negative PANSS subscale scores. While the exact biological mechanisms remain unknown, all these factors have roles in inflammation and could potentially impede the improvement of negative symptoms by elevating inflammation levels. This insight may suggest the need for adjunctive medications in a subset of patients to mitigate inflammation levels.

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Contributors TL is responsible for the overall content as the guarantor. QW, WG and TL designed, supervised the study and revised the article. YZhang, YZheng, PN and SL did the statistical analyses and prepared the tables and figures. YZhang, YZheng and TL wrote and revised the manuscript. XL, HY, WW, XQ, XY, RX, LZ and WD provided further data interpretation and revised the manuscript. XL, HY, WW and RX were responsible for patient recruitment and revised the manuscript.

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Competing interests None declared.

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Ethics approval The study was approved by the Ethical Committee of the Sixth Hospital, Peking University and the approval ID is Ethics Review No. 23 in 2009. The study was conducted in accordance with Good Clinical Practice guidelines and the Helsinki Declaration. All participants and their legal guardians gave written informed consent before taking part.

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