Prevalence of Thrombocytopenia among Chinese Adult Antiretroviral-naïve HIV-positive Patients

Hong-Wei Fan, Fu-Ping Guo, Yi-Jia Li, Ning Li, Tai-Sheng Li

Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

Abstract

Background: The prevalence of thrombocytopenia among Chinese antiretroviral therapy (ART)-naïve HIV-infected adults has not been well-described. The aim of this study was to investigate the prevalence and associated risk factors of thrombocytopenia among Chinese ART-naïve HIV-infected adults.

Methods: We performed a cross-sectional study of Chinese adult ART-naïve HIV-infected patients from September 2005 through August 2014. Socio-demographic variables and laboratory results including platelets, CD4+ cell count, and viral load were obtained from medical records. Factors and outcomes associated with thrombocytopenia were assessed using logistic regression.

Results: A total of 1730 adult ART-naïve HIV-infected patients was included. The mean age was 38 years. The prevalence of thrombocytopenia was 4.5%. There were significant differences in the prevalence of thrombocytopenia between patients <30 years of age (2.8%) and 30–39 years (4.0%) compared with patients greater than 50 years (7.0%) (P = 0.006 and P = 0.044, respectively). The prevalence of thrombocytopenia was also significantly different between patients with CD4+ counts of 200–349 cells/mm³ (3.3%) and >350 cells/mm³ (2.8%) compared with patients with CD4+ counts of 50–199 cells/mm³ (7.1%) (P = 0.002 and P = 0.005, respectively). The prevalence of thrombocytopenia was significantly different by hepatitis C virus antibody (HCV-Ab) seropositivity (10.2% for HCV-Ab positive vs. 3.9% for HCV-Ab negative, P = 0.001). We observed differences in prevalence of thrombocytopenia by mode of transmission (10.7%) versus men who have sex with men (3.9%) (P = 0.002) and versus heterosexual transmission (3.9%) (P = 0.001). In binary logistic regression analyses, age \geq 50 years, HCV-Ab positivity and having a CD4+ cell count of 50–199 cells/mm³ were significantly associated with thrombocytopenia with adjusted odds ratio of 2.482 (95% confidence interval [CI]: 1.167, 5.281, P = 0.018), 2.091 (95% CI: 1.078, 4.055, P = 0.029) and 2.259 (95% CI: 1.028, 4.962, P = 0.042), respectively. **Conclusions:** Thrombocytopenia is not common among adult ART-naïve HIV-infected patients in China. Older age (age over 50 years), HCV-Ab negative, and adult ART-naïve HIV-infected patients in China. Older age (age over 50 years), HCV-Ab negative, and adult ART-naïve HIV-infected patients in China. Older age (age over 50 years), HCV-Ab negative, and adult ART-naïve HIV-infected patients in China. Older age (age over 50 years), HCV-Ab negative, and adult ART-naïve HIV-infected patients in China. Older age (age over 50 years), HCV-Ab negative probability and have see years).

HCV-Ab positivity and lower CD4+ cell count are associated with an increased risk of thrombocytopenia. Therefore, early diagnosis and treatment of thrombocytopenia in these patients are necessary.

Key words: HIV; Prevalence; Thrombocytopenia

INTRODUCTION

Hematologic abnormalities are common manifestations of advanced HIV infection and AIDS.^[1,2] The prevalence of thrombocytopenia in adult antiretroviral therapy (ART)-naïve HIV-infected patients ranges from 5.9% to 40%.^[3-6] Furthermore, race and ethnicity may affect the prevalence of thrombocytopenia.^[4] Thrombocytopenia may be the first clinical manifestation in asymptomatic HIV-infected patients and may progress over time resulting in severe bleeding.^[7] Thrombocytopenia is characterized by a platelet (PLT) count <100 × 10⁹/mm³,^[8] and also frequently occurs in HIV-infected patients.^[5,9] To our knowledge, the prevalence of thrombocytopenia among ART-naïve

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HIV-infected patients in China has not been extensively studied. We combined data from three large HIV cohorts in China to evaluate the prevalence of and associated risk factors for thrombocytopenia among Chinese ART-naïve HIV-infected adults.

Methods

Study population

This was a cross-sectional study with data retrieved from three multicenter prospective studies^[10-13] in China, established in 2005, 2009, and 2012, respectively. The research centers are from several different regions of China, including Beijing, Shanghai, Guangdong, Fujian, Yunnan, Henan, Zhejiang, Jiangxi, Guangxi, and Shanxi province. The patients represent a broad cross section of Chinese HIV-infected patients. HIV infection was determined by

> Address for correspondence: Prof. Tai-Sheng Li, Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing 100730, China E-Mail: litsh@263.net

standard serum enzyme-linked immunosorbent assays and also confirmed by Western blotting analyses. Patients were only considered for enrollment in this study if they were ART-naïve and at least 18 years of age at the time of enrollment. The protocols were approved by independent ethics committees and institutional review boards, and the clinical trials were carried out in accordance with the principles of *Good Clinical Practice* and *Declaration of Helsinki*.

Study-outcome definitions

Thrombocytopenia was defined as PLT count $<100 \times 10^{9}$ /L. Mild thrombocytopenia was defined as a PLT count between 99 × 10⁹/L and 50 × 10⁹/L, and severe thrombocytopenia as $<50 \times 10^{9}$ /L. Besides, anemia was defined as hemoglobin <100 g/L, and neutropenia was defined as neutrophil count <1500 cells/mm³.

Data collection

Medical records were reviewed to ascertain demographic, clinical, and laboratory characteristics. Variables included age, sex, HIV transmission route, cytomegalovirus (CMV) antibody (Ab), hepatitis B surface antigen (HBsAg) and hepatitis C virus Ab (HCV-Ab), CD4+ T-cell count, and HIV viral load (VL). Age was categorized as <30, 30–39, 40–49, and over 50 years. HIV transmission routes were defined as homosexual transmission (men who have sex with men [MSM]), heterosexual transmission, blood transmission, or unknown transmission risk. CD4 cell count was categorized as <50, 50–199, 200–349, and over 350 cells/mm³. VL was categorized as <5log₁₀ copies/ml and >5log₁₀ copies/ml.

Statistical analysis

All statistical analyses were performed using the SPSS 19.0 statistical package (IBM Corporation, Armonk, New York, USA). We assessed the frequency of thrombocytopenia by baseline demographic and clinical factors, including age at enrollment, sex, HIV transmission route, opportunistic infections (OIs), HBsAg positivity, HCV-Ab positivity, CMV-Ab positivity, baseline CD4 cell count, and baseline VL. Noncategorical variables were assessed by Student's t-test, and categorical variables were assessed by Chi-square test. Bonferroni correction was used in multiple comparisons. Odds ratios and 95% confidence intervals (CI) were calculated to assess the relationship between each risk factor and the thrombocytopenia. To adjust for potential confounders, we used both univariate and multivariate binary logistic regression models. Variables included in the models were age, sex, transmission route, history of OIs, HBsAg positivity, HCV-Ab positivity, CMV-Ab positivity, CD4 cell count, and VL. The statistical test was two-tailed, and a P < 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

We included 1730 Chinese adult ART-naïve HIV-infected patients. Baseline characteristics are summarized in

Table 1. Most patients were men (69.8%), mean age was 38 years, mean CD4 count was 229 cells/mm³, and mean VL load was $4.7\log_{10}$ copies/ml. The prevalence of thrombocytopenia was 4.5%, while the prevalence of mild thrombocytopenia was 4.1%, and severe thrombocytopenia was 0.4%. Twenty-nine patients (1.7%) had both neutropenia and thrombocytopenia, 3 (0.2%) had both anemia and thrombocytopenia, and 6 (0.3%) had pancytopenia.

Prevalence of thrombocytopenia by age groups

Figure 1 describes the prevalence of thrombocytopenia among patients according to age. The prevalence of thrombocytopenia was 2.8%, 4.0%, 5.2%, and 7.0% among patients younger than 30, 30–39, 40–39 and over 50 years of age, respectively. There was significant difference in the prevalence of thrombocytopenia between patients younger than 30 years of age and those aged over 50 years (P = 0.006); while the difference between patients aged 30–39 years and those aged over 50 years was marginally significant (P = 0.044, according to Bonferroni correction).

Table	1:	Demographic	characteristics	of	1730	HIV/AIDS
patier	ıts	in China (n (°	%))			

Characteristics	Values
Age (years)	
<30	432 (25.0)
30–39	594 (34.3)
40–49	402 (23.2)
>50	302 (17.5)
Sex	
Male	1207 (69.8)
Female	523 (30.2)
Route of transmission	
MSM	689 (39.8)
Heterosexual	765 (44.2)
Blood	150 (8.7)
Other/unknown	126 (7.3)
HBs-Ag+*	180 (10.6)
$HCV-Ab^{+\dagger}$	167 (9.9)
CMV-IgM [‡]	50 (3.7)
OI history [§]	287 (16.7)
CD4+ count (cells/mm ³)	
<200	745 (43.1)
200–349	695 (40.2)
Over 350	290 (16.8)
Viral load (log ₁₀ copies/ml)	
<5	1154 (66.7)
Over 5	576 (33.3)
Thrombocytopenia	
Overall	78 (4.5)
Mild (PLT 50-99×109/L)	71 (4.1)
Severe (PLT <50×10 ⁹ /L)	7 (0.4)

*32 patients missing data; *50 patients missing data; *369 patients missing data; *13 patients missing data. MSM: Men who have sex with men; HBs-Ag: Hepatitis B surface antigen; HCV-Ab: Hepatitis C virus antibody; CMV-IgM: Cytomegalovirus immunoglobulin M; OI: Opportunistic infection; PLT: Platelet.

Prevalence of thrombocytopenia by CD4 cell counts

The prevalence of thrombocytopenia was 3.8%, 7.1%, 3.3%, and 2.8% among patients with CD4 cell counts of <50, 50-199, 200–349, and >350 cells/mm³, respectively [Figure 2]. The prevalence of thrombocytopenia was significantly different between patients with CD4 cell counts of 50–199 cells/mm³ compared with 200–349 cells/mm³ (P = 0.002), and between patients with CD4 cell counts of 50–199 cells/mm³ versus >350 cells/mm³ (P = 0.005).

Prevalence of thrombocytopenia by hepatitis C virus seropositivity

The prevalence of thrombocytopenia was significantly different between patients who were HCV-Ab positive (10.2%) and those who were HCV-Ab negative (3.9%) (P = 0.001) [Figure 3].

Prevalence of thrombocytopenia by transmission route

The prevalence of thrombocytopenia was 3.9%, 3.9%, and 10.7% among the patients with homosexual (MSM), heterosexual, and the blood transmission (P = 0.001) [Figure 4]. The prevalence of thrombocytopenia differed between patients with blood transmission and MSM patients (P = 0.002), and between patients with blood transmission and those with heterosexual transmission (P = 0.001).

Prevalence of thrombocytopenia by other risk factors

Among 1207 male patients, 60 (5.0%) patients had thrombocytopenia compared with 18 (3.5%) out of



Figure 1: Prevalence of thrombocytopenia among patients with different age.



Figure 3: Prevalence of thrombocytopenia among patients with different serum biomarkers.

523 female patients. The prevalence of thrombocytopenia did not differ significantly by sex (P = 0.098). The prevalence of thrombocytopenia was 4.6% among patients with VL < 5log₁₀ copies/ml and 4.3% among those with VL \geq 5log₁₀ copies/ml (P = 0.459). The prevalence of thrombocytopenia also did not differ significantly by HBsAg positivity (4.4% among HBsAg- patients vs. 5.0% among HBsAg+ patients, P = 0.415), by CMV-Ab positivity (3.9% among CMV-immunoglobulin M [IgM]- patients vs. 4.0% among CMV-IgM+ patients, P = 0.590), nor by history of OIs (4.3% for those without OIs vs. 5.6% for those with a history of OIs, P = 0.218) [Figure 3].

Risk factors for thrombocytopenia among antiretroviral therapy-naïve patients

In a multivariate logistic regression model, we analyzed factors associated with the thrombocytopenia among Chinese adult ART-naïve HIV-infected patients. Table 2 demonstrates the results of the logistic regression analysis. Age \geq 50 years, HCV-Ab positivity and lower CD4+ cell count (50–199 cells/mm³) were significantly associated with thrombocytopenia. We did not find a statistically significant association between VL and the presence of thrombocytopenia.



Figure 2: Prevalence of thrombocytopenia among patients with different CD4 + count.



Figure 4: Prevalence of thrombocytopenia among patients with different transmission routes.

Table 2: Association of thrombocytopenia with related factors among Chinese adult ART-naïve HIV-infected patients							
Variables	Thrombocytopenia (n (%))		Crude OR	Р	Adjusted OR*	Р	
	Yes	No	(95% CI)		(95% CI)		
Age, years							
<30	12 (2.8)	420 (97.2)	Reference	Reference	Reference	Reference	
30–39	24 (4.0)	570 (96.0)	1.474 (0.729, 2.980)	0.281	1.370 (0.671, 2.796)	0.387	
40-49	21 (5.2)	381 (94.8)	1.929 (0.936, 3.974)	0.075	1.688 (0.805, 3.539)	0.166	
>50	21 (7.0)	281 (93.0)	2.616 (1.267, 5.402)	0.009	2.482 (1.167, 5.281)	0.018	
Sex							
Male	60 (5.0)	1147 (95.0)	1.468 (0.858, 2.511)	0.161			
Female	18 (3.4)	505 (96.6)	Reference	Reference			
Route of transmission							
MSM	27 (3.9)	662 (96.1)	Reference	Reference	Reference	Reference	
Heterosexual sex	30 (3.9)	735 (96.1)	1.001 (0.589, 1.701)	0.998	0.872 (0.501, 1.517)	0.627	
Blood	16 (10.7)	134 (89.3)	2.928 (1.535, 5.583)	0.001	1.790 (0.850, 3.770)	0.125	
Other/unknown	5 (4.0)	121 (96.0)	1.013 (0.383, 2.683)	0.979	0.821 (0.304, 2.218)	0.697	
HBs-Ag							
Negative	67 (4.4)	1451 (95.6)	Reference	Reference			
Positive	9 (5.0)	171 (95.0)	1.140 (0.558, 2.327)	0.719			
Unknown	2 (6.3)	30 (93.7)	1.444 (0.338, 6.168)	0.620			
HCV-Ab							
Negative	1454 (96.1)	59 (3.9)	Reference	Reference	Reference	Reference	
Positive	17 (10.2)	150 (89.8)	2.793 (1.587, 4.915)	< 0.001	2.091 (1.078, 4.055)	0.029	
Unknown	2 (4.0)	48 (96.0)	1.027 (0.244, 4.326)	0.971	0.859 (0.199, 3.713)	0.839	
CMV-IgM							
Negative	51 (3.9)	1260 (96.1)	Reference	Reference			
Positive	2 (4.0)	48 (96.0)	1.029 (0.243, 4.353)	0.969			
Unknown	25 (6.8)	344 (93.2)	1.795 (1.097, 2.940)	0.020			
OIs							
Negative	62 (4.3)	1368 (95.7)	Reference	Reference			
Positive	16 (5.6)	271 (94.4)	1.303 (0.741, 2.292)	0.358			
Unknown	0 (0)	13 (100)	NA	0.978			
CD4+ count, cells/mm ³							
<50	7 (3.8)	175 (96.2)	1.410 (0.502, 3.956)	0.514	1.255 (0.440, 3.581)	0.671	
50-199	40 (7.1)	523 (92.9)	2.696 (1.245, 5.839)	0.012	2.259 (1.028, 4.962)	0.042	
200-349	23 (3.3)	672 (96.7)	1.206 (0.533, 2.730)	0.652	1.069 (0.466, 2.450)	0.875	
Over 350	8 (2.8)	282 (97.2)	Reference	Reference	Reference	Reference	
Viral load, log ₁₀ copies/ml							
<5	53 (4.6)	1101 (95.4)	1.061 (0.652, 1.726)	0.812			
Over 5	25 (4.3)	551 (95.7)	Reference	Reference			

 <5</th>
 53 (4.6)
 1101 (95.4)
 1.061 (0.652, 1.726)
 0.812

 Over 5
 25 (4.3)
 551 (95.7)
 Reference
 Reference

 OR:Oddsratio;MSM:Menwhohavesex with men;HBs-Ag: Hepatitis B surface antigen;HCV-Ab: Hepatitis C virus antibody;CMV-IgM: Cytomegalovirus immunoglobulin M; OI: Opportunistic infections; CI: Confidence interval; ART: Antiretroviral therapy; NA: not applicable. *Factors with statistical significance in univariate analyses were included in multivariate regression.

DISCUSSION

We found an overall low prevalence of thrombocytopenia, and in particular severe thrombocytopenia, among Chinese adult ART-naïve HIV-infected patients. To our knowledge, this is the first study in China to determine the prevalence of thrombocytopenia in adult ART-naïve HIV-infected patients.

A previous study of the Taiwanese population receiving periodic health examinations found the prevalence of thrombocytopenia to be 0.5%.^[8] There are no data regarding the prevalence of thrombocytopenia in the mainland of China. In our study, the prevalence of thrombocytopenia among Chinese adult ART-naïve HIV-infected patients was 4.5%, which was higher than the general population. This

suggests that thrombocytopenia occurs more frequently in ART-naïve HIV-infected patients in China compared with the general population. In addition, 22% of adults diagnosed with immune thrombocytopenia are HIV-positive.^[14] As such, HIV infection should be considered as a differential diagnosis for individuals presenting with thrombocytopenia. Thrombocytopenia in HIV-infected patients is likely to be multifactorial, with contributions from splenic PLT sequestration, immune-mediated PLT destruction, and decreased PLT production related to direct infection of megakaryocytes by HIV.^[15-17]

The prevalence of thrombocytopenia observed in this study is consistent with several previous published studies.^[3,4,18-21] However, other studies have demonstrated a higher prevalence of thrombocytopenia.^[5,22] Prior to the advent of highly active ART, the prevalence of HIV-associated thrombocytopenia was estimated to be 10-30%.^[23,24] Ambler *et al.*^[5] investigated the prevalence of thrombocytopenia (< $100 \times 10^{9}/L$) in HIV positive ART-naïve patients in Australia. In that study, the overall prevalence of thrombocytopenia was 26%. The discrepancy between the prevalence observed in their study and ours may be explained by varying definitions of thrombocytopenia and differences in characteristics between the two study population.

We found that thrombocytopenia was significantly associated with CD4+ counts between 50 and 200 cells/mm³. Other studies have also found a lower CD4+ count (CD4 < 200 cells/mm³) to be a risk factor for thrombocytopenia.^[19,20,25] Muñoz *et al.*^[26] found a decrease in PLT number predicted a steep decline of CD4 + T cell counts in homosexual men. Patients with more severe immunodeficiency (CD4+<200 cells/mm³) presented with a lower PLT count. However, these studies did not further divide CD4+ cells into <50 and 50–200 cells/mm³. We found a CD4+ count between 50 and 200 cells/mm³ but not <50 cells/mm³, was significantly associated with an increased risk of thrombocytopenia. The mechanism for this is unclear and needs to be studied further.

We found an association between HCV-Ab positivity and thrombocytopenia among Chinese adult ART-naïve HIV-infected patients, which is in line with previous studies.^[8,27-29] An association between chronic immune thrombocytopenic purpura and HCV has been described previously;^[27] cryoglubulins,^[28] and anti-PLT autoantibodies^[29] have been detected in thrombocytopenic patients with HCV. Lai *et al.* found that anti-HCV antibodies in the setting of thrombocytopenia may be associated with hepatocellular damage, hepatic fibrosis, liver cirrhosis, and inadequate production of thrombopoietin.^[8,30]

We found older age (age >50 years) was a risk factor for thrombocytopenia, similar to previous studies.^[8] The increase in the prevalence of thrombocytopenia with age may be due to a higher incidence of myelodysplasia in older patients, but this requires further evaluation.

Our study has some limitations. First, it was a retrospective observational study which has inherent limitations. Second, selection bias may have affected the findings. However, the results of this large cohort study likely still reflect the true prevalence of thrombocytopenia in this population of Chinese HIV-infected adults. This study provides the basis for recommendations to improve the clinical care of HIV-infected persons and lays the groundwork for further studies on the pathophysiology of HIV-associated thrombocytopenia.

In conclusion, thrombocytopenia is not common among adult ART-naïve HIV-infected patients in China. Older age, HCV-Ab positivity and lower CD4+ cell count are associated with an increased risk of thrombocytopenia. Routine assessment for thrombocytopenia among this HIV-infected population should be performed to optimize clinical management.

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