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Letter to the Editor

The value of FDP/FIB and D-dimer/FIB ratios in predicting high-risk APL-related thrombosis

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ABSTRACT

Hemorrhage is the typical manifestation of APL-related coagulopathy while thrombosis is infrequently reported. In a retrospective analysis with 33 patients with hyperleukocytic APL, we found 6 out of 33 hyperleukocytic APL patients presented with thrombosis rather than hemorrhage. A notable feature in these high-risk APL patients with thrombosis is that there were no significant abnormalities in fibrinogen (FIB), prothrombin time (PT) and activated partial thromboplastin time (APTT). Compared with the normal ranges, both the high-risk APL patients with thrombosis and the high-risk APL patients with hemorrhage had a significant increase in fibrinogen degradation product (FDP) and D-dimer levels. However, the group with hemorrhage had noticeably higher plasma levels of FDP and D-dimer than the group with thrombosis. To find a close relationship between coagulation markers and the onset of thrombotic events in patients with high-risk APL, the potential effects of FDP/FIB and D-dimer/FIB ratios as risk markers were investigated. We demonstrated that FDP/FIB and D-dimer/FIB ratios in the patients with high-risk APL with thrombosis showed higher ratios than the normal range but significantly lower ratios than the patients with high-risk APL-related hemorrhage. Our data demonstrated that the alteration in FDP/FIB and D-dimer/FIB ratios have more significant relevance than the levels of FIB, FDP or D-dimer as potential factors for predicting thrombosis and may help with designing more appropriately risk-adapted treatment protocols or personalized therapy.

Acute promyelocytic leukemia (APL) is characterized by a t(15;17) translocation, which results in the to PML–RARα fusion gene [1]. According to the white blood cell count (WBC) and platelet count (PLT), patients are divided into low-risk APL (WBC $< 10 \times 10^9$/L, PLT $> 40 \times 10^9$/L), intermediate-risk APL (WBC $< 10 \times 10^9$/L, PLT $< 40 \times 10^9$/L) and high-risk APL (WBC $\geq 10 \times 10^9$/L) [2,3]. Despite major advances in the treatment of APL, high-risk APL remains associated with higher early mortality rates due to lethal complications [4,5]. Patients with high-risk APL are prone to both bleeding and thrombosis [6]. Bleeding complications from APL are well known. In contrast, APL-associated thrombosis is relatively underappreciated because of its significantly lower incidence. APL-associated thrombosis, although low in incidence, is one of the most critical cause of early death in this otherwise curable leukemia [6,7]. Therefore, an understanding of potential factors predicting fatal thrombotic complications in patients with APL might be useful for designing more appropriate risk-adapted treatment protocols or personalized therapy aimed at reducing the considerable problem of induction mortality in APL. Several studies [6–11] have already identified some risk factors associated with higher rates of thrombosis in APL, such as higher WBC count, type of PML/RARa transcript, FLT3/ITD mutation, positive finding of CD2 or CD15 and all-trans retinoic acid (ATRA) therapy.

In our study, we retrospectively analyzed 33 patients newly diagnosed with high-risk APL (WBC $\geq 10 \times 10^9$/L) at Zhengzhou University People's Hospital and Hospital League from January 2013 to September 2018. Based on the clinical data, the 33 patients were divided into two groups: 6 patients who developed high-risk APL-related thrombosis and 27 patients who developed high-risk APL-related hemorrhage (Table 1). In the high-risk APL patients who developed thrombosis (thrombosis: patients 1–6 in Supplementary Table 1), 4 out of the 6 patients experienced confirmed life-threatening cerebrovascular accidents, including 2 patients (patients 3 and 5) who developed a cerebral infarction within a week of starting ATRA treatment, 1 patient (patient 4) who initially presented with subcutaneous hemorrhage and later developed thrombosis after 25 days of ATRA therapy, and one particularly critical patient (patient 2) who developed a cerebral infarction even before ATRA therapy and 7 days after ATRA treatment expired from uncontrolled increased intracranial pressure. An additional 2 out of 6 patients developed lower-limb deep vein thrombosis, including 1 patient (patient 1) who developed lower-limb deep vein thrombosis within 7 days after ATRA treatment and 1 patient (patient 6) who developed deep vein thrombosis even before arsenic trioxide-based induction therapy. Except for case 6, the rest of the high-risk APL patients with thrombosis were immediately administered with ATRA at the time of suspected diagnosis. In high-risk APL thrombotic group, coagulation data shown in Table1 were taken at the onset of thrombosis. Notably, we found that there were no significant abnormalities in fibrinogen (FIB), prothrombin time (PT) or activated partial thromboplastin time (APTT) in these high-risk APL patients with thrombosis. In other words, their coagulation profile did not reflect the tendency of hemorrhage and disseminated intravascular coagulation (DIC) that is observed in most APL patients with hemorrhage. Compared with the normal range, both the high-risk APL patients with thrombosis and the high-risk APL patients with hemorrhage had significant increase in fibrinogen degradation product (FDP) and D-dimer levels. However, the group with hemorrhage had noticeably higher plasma levels of FDP and D-dimer than the group with thrombosis ($p < 0.002$ and $p < 0.001$, respectively, Table 1 and Supplementary Table 1). Therefore, significant differences in FIB, PT, FDP, and D-dimer levels were observed between the two groups (Table 1 and Supplementary Table 1). Although there was a

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Table 1
Comparison of the clinical parameters between high-risk APL-related thrombosis and high-risk APL-related hemorrhage.

	Normal Range	Thrombosis (N = 6)	Hemorrhage (N = 27)	P value
Age, years		47 (7-53)	27 (5-76)	0.123
Male, n (%)		5 (83.3%)	15 (55.56%)	0.215
WBC ($\times 10^9$/L)	3.5-9.5	58.23 (23.9-127.57)	43.8 (11.6-258.01)	0.427
HGB (g/L)	130-175	87.5 (46-94)	78 (50-135)	0.726
PLT ($\times 10^9$/L)	125-350	43 (9-82)	24 (8-65)	0.243
PT (s)	11-17	13.05(12.1-15.5)	15.2 (13.0-25.4)	0.021
APTT (s)	28-43.5	32.15 (29.0-37.1)	27.6 (19.3-42)	0.036
FIB (g/L)	2-4	3.42 (1.73-5.24)	1.24 (0.31-4.99)	0.001
FDP (mg/L)	0-5	26.3 (13.55-54.6)	77.1 (29.4-183.2)	0.002
D-dimer (mg/L)	0-0.5	4.27 (3.8-10.28)	12.5 (3.9-46.2)	0.001
FDP/FIB		7.74 (4.07-15.6)	58.16 (18.72-384.19)	< 0.0005
D-dimer/FIB		1.69 (0.77-2.93)	9.23 (3.28-97.48)	< 0.0002

We retrospectively analyzed the clinical data of 33 patients newly diagnosed with high-risk APL (6 patients with high-risk APL-related thrombosis, 27 patients with high-risk APL-related hemorrhage) at Zhengzhou University People's Hospital and Hospital League from January 2013 to September 2018.

significant difference in the coagulation profile between these two groups, the alteration of FIB, PT, APTT, FDP, and D-dimer levels was not useful for predicting thrombosis. While both groups showed increased FDP and D-dimer levels (Table 1 and Supplementary Table 1), some high-risk APL patients with hemorrhage also showed normal FIB levels.

To find a close relationship between coagulative-fibrinolytic abnormalities and the onset of thrombotic events in patients with high-risk APL, the potential effects of FDP/FIB and D-dimer/FIB ratios as risk markers were investigated. We demonstrated that the ratios of FDP/FIB and D-dimer/FIB in the patients with high-risk APL with thrombosis were higher than the normal range but significantly lower than the patients with high-risk APL-related hemorrhage (Table 1, Fig. 1 and Supplementary Table 1). The ratio of FDP/FIB in the patients with high-risk APL-related thrombosis ranged from 4.07 to 15.6, while the ratio of FDP/FIB in the patients with high-risk APL-related hemorrhage ranged from 18.72 to 384.19. Likewise, the ratios of D-dimer/FIB in the patients with high-risk APL-related thrombosis range from 0.77 to 2.93, while the ratio of D-dimer/FIB in the patients with high-risk APL-related hemorrhage range from 3.28 to 97.48. Thus, FDP/FIB and D-dimer/FIB ratios can be used for predicting thrombosis. To the best of our knowledge, this observation is the first to identify FDP/FIB and D-dimer/FIB ratios as possible markers for distinguishing or differentiating subgroups for the development of high-risk APL-related thrombosis and high-risk APL-related hemorrhage. Further research is needed to confirm these findings prospectively and in a larger cohort of patients.

To further emphasize the potential effect of FDP/FIB and D-dimer/FIB ratios on predicting thrombotic events in patients with high-risk APL, we highlighted all of the high-risk APL patients with thrombosis (6 cases) showing the continuously monitored dynamic coagulation profiles, including the data obtained before or at the onset of thrombosis, compared with the control group with 6 age- and gender-matched high-risk APL patients with hemorrhage (Fig. 2). As mentioned above, we concluded that there were no significant abnormalities in FIB and PT in these high-risk APL patients with thrombosis. Both the patients with thrombosis and the patients with hemorrhage showed noticeably higher levels of FDP and D-dimer. Therefore, FDP and D-dimer are not sufficient to be used for predicting fatal thrombotic complications in these high-risk APL patients. In contrast, before or at the onset of thrombosis, FDP/FIB and D-dimer/FIB ratio in the patients of high-risk APL with thrombosis were remarkably lower than in the patients with high-risk APL-related hemorrhage (Fig. 2). Especially in patient 4 who initially complained of subcutaneous hemorrhage and later developed thrombosis after ATRA therapy for 25 days, the decreased FDP/FIB and D-dimer/FIB ratios were consistent with the onset of thrombosis. Hence, FDP/FIB and D-dimer/FIB ratio can be used to predict fatal thrombotic complications in these high-risk APL patients. Our data demonstrated that the alteration in FDP/FIB and D-dimer/FIB ratio have more significant relevance than the levels of FIB, FDP or D-dimer in drawing a clear distinction between the two groups (Fig. 2).

ATRA has a profound impact on the hemostatic system, and it can rapidly correct fibrinolysis and reverse coagulopathy with prothrombotic function [12,13]. In our 6 cases of high-risk APL-related thrombosis, 4 out of 6 patients developed thrombosis after ATRA administration associated with an increased WBC count. This finding was consistent with a previous report in which thrombotic events appeared to be higher in patients who received ATRA compared to those in the pre-ATRA period [12,13], suggesting the imbalance between procoagulant and anticoagulant factors is caused by treatment with ATRA, which might increase the risk of thrombosis. Therefore, the dose and timing of ATRA administration might need to be adjusted in this small distinct subtype of high-risk APL trending to thrombosis. Future large-

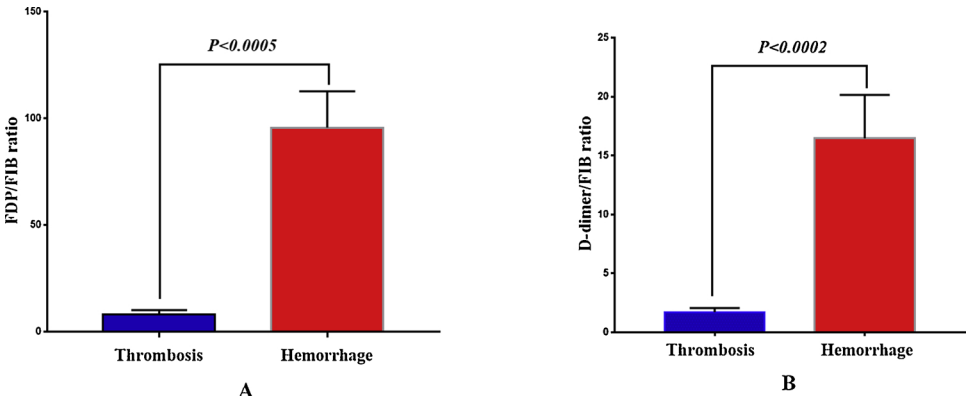

Fig. 1. Comparison of the FDP/FIB and D-dimer/FIB ratios between high-risk APL-related thrombosis and high-risk APL-related hemorrhage.
We retrospectively analyzed 33 patients newly diagnosed with high-risk APL (6 patients with high-risk APL-related thrombosis, 27 patients with high-risk APL-related hemorrhage) at Zhengzhou University People's Hospital and Hospital League from January 2013 to September 2018.
(A)The FDP/FIB ratio was lower in high-risk APL-related thrombosis than in high-risk APL-related hemorrhage ($P < 0.0005$).
(B)The D-dimer/FIB ratio was lower in high-risk APL-related thrombosis than in high-risk APL-related hemorrhage ($P < 0.0002$).

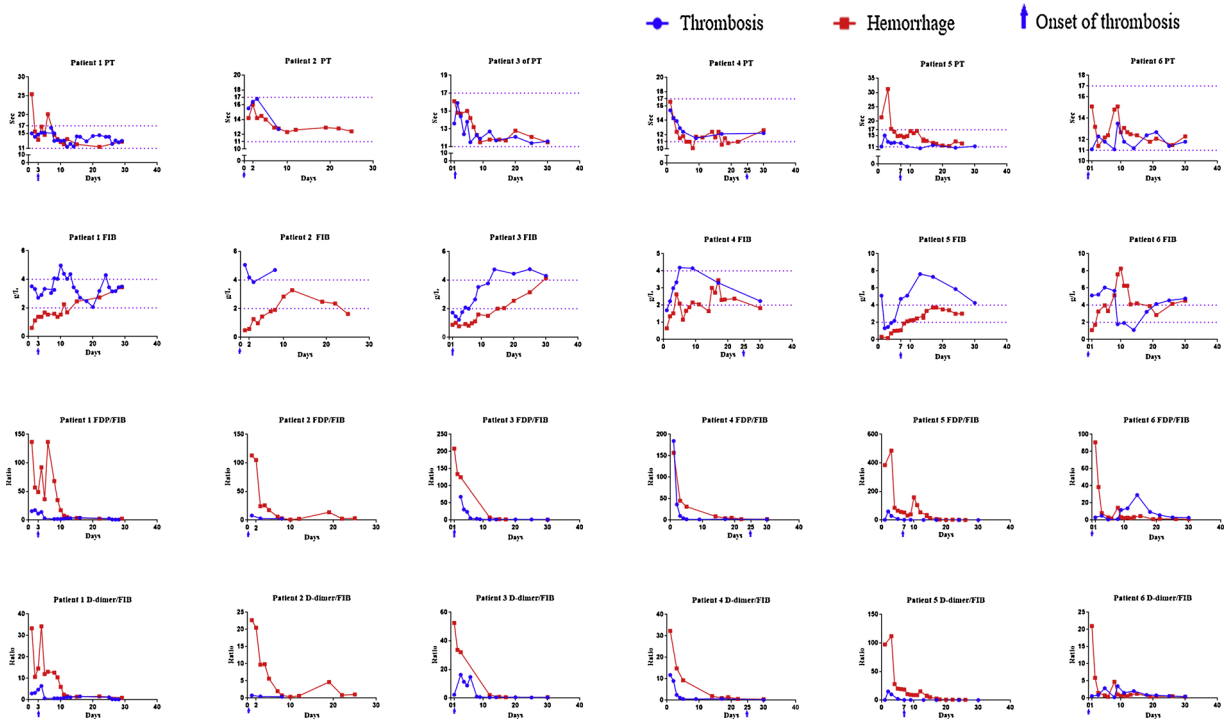

Fig. 2. Dynamic coagulation profiles of the high-risk APL patients with thrombosis compared with high-risk APL patients with hemorrhage.
We highlighted all of the high-risk APL patients with thrombosis (6 cases) showing the continuously monitored dynamic coagulation profile including the data obtained before or at the time of onset of the thrombosis, compared with the control group of 6 age- and gender-matched high-risk APL patients with hemorrhage.

scale investigation to explore the predictive markers and individualized therapy for the disregarded high-risk APL-related thrombotic events is warranted.

In comparison with APL-related hemorrhage, APL-related thrombosis is an infrequent yet important complication. Notably, in the high-risk APL population, with or without ATRA therapy, thrombotic complications have become more frequent and are one of the most critical causes of early death in this otherwise curable leukemia. Among the 6 patients with high-risk APL-related thrombosis in our study, 1 death was attributed to thrombotic complication. Therefore, early detection of a clear distinction between the two groups of hemorrhage or thrombosis is life-saving. FDP/FIB and D-dimer/FIB ratio have more significant relevance than the levels of FIB, FDP or D-dimer in predicting fatal thrombotic complications in these high-risk APL patients.

Conflicts of interest

The authors have no relevant conflict of interest to disclose.

Author contributions

Drs. Xiawan Yang and Wanjun Zhang performed the clinical research and contributed vital clinical data.

Drs. Lijuan Duan, Chenghua Wang, Hafiz Abdul Waqas Ahmed and Lei Huo performed research and contributed to analyzed data.

Drs. Yuqing Chen and Fangfang Xu performed the clinical research and contributed vital clinical data.

Drs. Ruyu Yang, Xiuli Wei, Xudong Wei, and Depei Wu helped design the research.

Drs. Yanliang Bai, Mingyue Shi and Kai Sun performed the clinical research, designed the research, contributed to analyzed data and wrote the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.02.007.

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