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Factors affecting thrombohemorrhagic early death in patients with acute promyelocytic leukemia treated with arsenic trioxide alone

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ABSTRACT

Acute promyelocytic leukemia (APL) is often accompanied by a potentially devastating coagulopathy. Predictors of thrombohemorrhagic early death (TH-ED)/early bleeding death are not well characterized. In this retrospective study, eleven baseline clinical variables that can be assessed easily and promptly were chosen for evaluation in a cohort of 364 patients with APL who were administered arsenic trioxide (ATO) alone as remission induction therapy. TH-ED was defined as death from bleeding or thrombosis within 30 days after hospital admission. Cox proportional hazards regression model was used for both the univariate and multivariate analyses. Totally, 53 patients died from severe bleeding (51 cases) or thrombosis (2 cases), and at 30 days the cumulative incidences of TH-ED were 14.6%. Six independent risk factors for TH-ED were identified, including relapse, male, white blood cell (WBC) count above 10×10^9/L, fibrinogen level below 1 g/L, D-dimer level above 4 mg/L and increased creatinine level. Increased creatinine level was the most powerful risk factor, followed by WBC count $> 10 \times 10^9$/L. This study identified risk factors for TH-ED in a large cohort of patients with APL, which enriched clinical information on identifying patients at high risk of TH-ED.

1. Introduction

Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia characterized by a potentially devastating coagulopathy [1,2]. Differentiation therapy using all-trans retinoic acid (ATRA) and/or arsenic trioxide (ATO) has greatly improved the prognosis of APL. Nevertheless, multiple studies revealed that the early death (ED) rates have not declined as much as one had expected since the introduction of differentiation therapy. Now ED has become the major cause of treatment failure and the biggest barrier to beating the disease, and coagulopathy still accounts for the majority of such EDs. In large clinical trials (> 200 participants in each clinical trial) from the ATRA era, about 3–7% of patients suffered from early fatal bleeding [3–8].

Thrombosis is also a major clinical manifestation of APL coagulopathy, and occurred in 8–26% of cases in reports [9–12]. Since both are clinical manifestations of coagulopathy, bleeding and thrombosis should share some common pathogenic factors. Therefore, if the event of interest is fatal coagulopathy in a clinical study, it should also include deaths attributable to thrombosis. To show this more clearly, in this study early fatal coagulopathy are named thrombohemorrhagic early death (TH-ED).

In this retrospective study, we aimed to identify predictors for TH-ED in a large cohort of patients with APL who were induced with ATO alone.

2. Material and methods

2.1. Patients

Totally, 436 consecutive patients were diagnosed as APL during the period from December 2008 to March 2016 at The First Affiliated

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Table 1
Demographic and baseline characteristics of the patients with APL.

Characteristics		All patient cohort (n = 364)	Survival cohort (n = 294)	Thrombohemorrhagic ED (n = 53)
De novo/relapse	De novo	285	234	38
	Relapse	79	60	15
Age, years	Median (range)	40 (7–81)	40 (7–81)	38 (11–76)
	≤50	267	224	39
	> 50	97	70	14
Sex	Female	169	149	16
	Male	195	145	37
WBC count, $\times 10^9$/L	Median (range)	3.03 (0.27–211.1)	2.60 (0.27–153.11)	17.64 (0.53–211.1)
	≤10	256	223	19
	> 10	108	71	34
Platelet count, $\times 10^9$/L	Median (range)	25.1 (1 − 302)	25.5 (1–302)	22.5 (3.5–77)
	≥30	146	120	17
	< 30	218	174	36
Fibrinogen, g/L	Median (range)	1.25 (0.225–4.59)	1.30 (0.225–4.59)	0.85 (0.28–3.72)
	≥1.0	235	206	21
	< 1.0	129	88	32
D-dimer, mg/L	Median (range)	4.82 (0–40)	4.38 (0–40)	6.44 (0.228–40)
	≤4	160	140	13
	> 4	204	154	40
Creatinine, μmol/L	Median (range)	65.8 (4.8–183)	63 (4.8–143.3)	75.7 (34.9–183)
	≤Normal	349	288	45
	> Normal	15	6	8
Serum uric acid, μmol/L	Median (range)	261.3(4.2–892)	254.3 (4.2–583.9)	309.7 (26.7–892)
	≤Normal	340	278	45
	> Normal	24	16	8
AST, $U_{/L}$	Median (range)	21.5 (4.2–805.6)	19.9 (4.2–204)	31.9 (9.9–805.6)
	≤Normal	316	259	40
	> Normal	48	35	13
Albumin, g/L	Median (range)	40.8 (21.7–55.4)	41.25 (21.7–55.4)	39.7 (26.2–54.7)
	≥Normal	333	274	45
	< Normal	31	20	8

APL-acute promyelocytic leukemia, ED-early death, WBC-white blood cell, AST-aspartate aminotransferase.

Hospital (418 cases) and The Fourth Affiliated Hospital (18 cases) of Harbin Medical University. The diagnosis was confirmed genetically in all cases by the demonstration of reciprocal translocation between chromosomes 15 and 17 and/or the PML/RARα rearrangements. Among these patients, 364 (83.5%, 285 newly diagnosed and 79 relapsed cases) who were treated with ATO alone as induction therapy were included in this study. This study protocol was discussed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Harbin Medical University who waived the need for patient informed consent for this retrospective analysis.

2.2. Treatments

ATO (0.16 mg/kg per day for a maximum of 10 mg per day) was infused intravenously as differentiation induction therapy until visible leukemic blasts and promyelocytes were eliminated from the bone marrow and the blast and promyelocyte count was no > 5% of marrow mononuclear cells or for a maximum of 60 days. Platelet transfusions were given to maintain platelet counts > 30×10^9/L. Patients with coagulopathy or active bleeding were treated with fresh-frozen plasma repeatedly to maintain a fibrinogen level > 1.5 g/L. Cryoprecipitate or/and fibrinogen was given to patients with a fibrinogen level < 1 g/L.

2.3. Candidate predictors of TH-ED

In order to facilitate the application of our results in clinical practice, only those variables that can be assessed easily and promptly were included. Based on this principle and the results of previously reports, 11 baseline clinical variables were selected for the analysis, including age, sex, de novo/relapse, platelet count, white blood cell (WBC) count, and plasma level of fibrinogen, D-dimer, aspartate aminotransferase (AST), albumin, uric acid (UA) and creatinine.

2.4. Outcome definitions

TH-ED was defined as death from bleeding or thrombosis within 30 days of hospital admission. Patients alive after 30 days of hospital admission were censored at day 30. Death unrelated to hemorrhage and thrombosis within 30 days of hospital admission was treated as a competing event.

2.5. Statistical analysis

Less than 4% of values were missing for each variable. Missing data were replaced with the median values calculated using data from participants in whom data were available. To provide clinician with an easy and convenient access, all continuous variables were converted into binary variables. The cut-off values were set either at the borders between normal and abnormal or derived from a literature review [4,13].

Due to the presence of competing events, the 30-day cumulative incidence of TH-HD was estimated using cumulative incidence functions [14]. Univariate and multivariate Cox proportional hazards regression analyses were performed to assess predictive role of the 11 candidate predictors for TH-ED. Patients who died of causes other than hemorrhage and thrombosis within 30 days of hospital admission were censored at the time of death [14]. Before multivariate analysis, multicollinearity of candidate predictors was evaluated using the tolerance and the variance inflation factor. In the multivariate analysis, a backward stepwise variable selection was used to identify the independent predictors of TH-HD.

All P values were two-sided and variables with P values < 0.05 were considered statistically significant. All analyses were performed using SAS, Version 9.4.

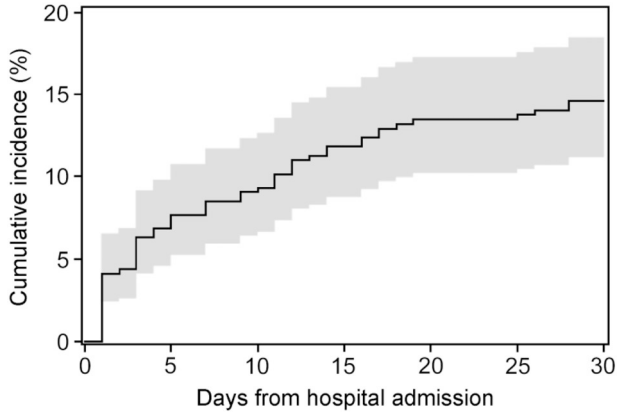

Fig. 1. Cumulative incidence of thrombohemorrhagic early death in patients with APL (n = 364).
APL-acute promyelocytic leukemia.
The corresponding band represents the 95% confidence interval. At 30 days, the cumulative incidence was 14.6% (95% CI, 11.2–18.4%).

3. Results

3.1. The incidence and causes of TH-ED

The study cohort consisted of 364 patients, 195 males (53.6%), and 169 (46.4%) females. The median age of the patients was 40 years (range 7–81). Totally 70 patients (19.2%; 95% confidence interval [CI], 15.3–23.7%) died within the first 30 days of hospital admission, and 53/70 (75.7%, 95% CI, 64.0–85.2%) of the subjects died from severe bleeding (51 cases) or thrombosis (2 cases). Table 1 gives patient baseline characteristics for all patient cohort, TH-ED cohort and survival cohort. Notably, 10 patients were involved in this study who died due to bleeding < 12 h from hospital admission, before ATO treatment was given.

At 30 days, the cumulative incidences of TH-ED and ED attributable to non- thrombohemorrhagic causes were 14.6% (95% CI, 11.2–18.4%) and 4.7% (95% CI, 2.8–7.2%), respectively. It can be seen from Fig. 1 that the cumulative incidence of TH-ED was the highest during the first 3 days, then stayed relatively stable at a reduced level during 4–19 days, and dropped to a lower level after 20 days. Correspondingly, there were 23, 26 and 4 patients died during 1–3 days, 4–19 days and 20–30 days, respectively. The median time from hospital admission to TH-ED was 5 days (range, 1–28 days).

Eight out of 53 patients with TH-ED died due to multiple causes with bleeding as one of the causes, because it was so hard to ascribe ED to a particular cause in them (Table 2). Among 53 TH-EDs, 44 (83.0%) were due to cerebral bleeding, 5 (9.4%) were attributable to disseminated intravascular coagulation (DIC), and the other 4 were because of gastrointestinal tract hemorrhage, pulmonary hemorrhage, cerebral infarction and pulmonary embolism, respectively (Table 2). The median time to death due to cerebral bleeding was 3.5 days (range, 1–28 days), and that to death due to DIC was 15 days (range, 8–24 days).

3.2. Predictive role of the 11 candidate predictors for TH-ED

The univariate Cox proportional hazard regression analysis identified the following 8 risk factors for TH-ED: male, WBC count > 10×10^9/L, fibrinogen < 1 g/L, D-dimer > 4 mg/L, creatinine level > Normal, UA level > Normal, AST level > Normal and albumin level < Normal (Table 3). No significant association was found between TH-ED and de novo/relapse, age or platelet count (all $P > 0.05$).

Only variables with P values < 0.25 in the univariate analysis were further analyzed in a multivariate Cox proportional hazard regression model, and the multivariate analysis identified 6 independent risk factors for TH-ED (Table 4): relapse, male, WBC count > 10×10^9/L,

Table 2
Causes of early death in this study.

Cause of early death	n	Median time, days (range)
Cerebral bleeding	39	3 (1–28)
Cerebral bleeding + DS	3	3 (1–5)
Cerebral bleeding + DS + infection	1	14
Cerebral bleeding + CNS leukemia	1	26
Gastrointestinal tract hemorrhage + DS	1	7
Pulmonary hemorrhage	1	28
DIC	3	18 (14–25)
DIC + DS	1	9
DIC + DS + infection	1	16
Cerebral infarction	1	1
Pulmonary embolism	1	7
DS	4	11(7–12)
Infection	5	21 (5–30)
DS + infection	3	19 (14–23)
CNS leukemia	3	6 (4–14)
Severe liver injury	1	4
Unknown	1	10
Total	70	7 (1–30)

DS-differentiation syndrome, CNS-central nervous system, DIC-disseminated intravascular coagulation.

Table 3
Univariate cause-specific Cox proportional hazards models for the risk of thrombohemorrhagic death within the first 30 days.

Variables	Unfavorable category	Hazard ratio	95% CI	P^a
De novo/relapse	Relapse	1.445	0.795–2.627	0.2273
Age, years	> 50	1.023	0.556–1.885	0.9407
Sex	Male	2.122	1.181–3.815	**0.0119**
WBC count, $\times 10^9$/L	> 10	5.049	2.879–8.856	< **0.001**
Platelet count, $\times 10^9$/L	< 30	1.478	0.830–2.632	0.1840
Fibrinogen, g/L	< 1	3.071	1.770–5.328	< **0.001**
D-dimer, mg/L	> 4	2.641	1.412–4.938	**0.0024**
Creatinine, μmol/L	> Normal	6.358	2.989–13.522	< **0.001**
Uric acid, μmol/L	> Normal	2.913	1.373–6.180	**0.0053**
AST, U/L	> Normal	2.353	1.259–4.400	**0.0074**
Albumin, g/L	< Normal	2.209	1.041–4.688	**0.0389**

WBC-white blood count, AST-aspartate aminotransferase, CI-confidence interval.
A value of P < 0.05 is defined in bold.
[a] Univariate cause-specific Cox proportional hazards models was used.

Table 4
Multivariate cause-specific Cox proportional hazards models for the risk of thrombohemorrhagic death within the first 30 days.

Variables	Unfavorable category	Hazard ratio	95% CI	P^a
De novo/relapse	Relapse	2.996	1.576–5.696	< 0.001
Sex	Male	2.109	1.165–3.816	0.0137
WBC count, $\times 10^9$/L	> 10	4.536	2.465–8.347	< 0.001
Fibrinogen, g/L	< 1	2.018	1.138–3.577	0.0163
D-dimer, mg/L	> 4	3.552	1.825–6.917	< 0.001
Creatinine, μmol/L	> Normal	7.955	3.527–17.939	< 0.001

WBC-white blood count, CI-confidence interval.
[a] Multivariate cause-specific Cox proportional hazards models was used.

fibrinogen < 1 g/L, D-dimer > 4 mg/L and creatinine level > Normal. Creatinine level > Normal was the strongest independent risk factor for TH-ED (hazard ratio [HR] = 7.955; 95% CI, 3.527–17.939; $P < 0.001$), followed by WBC count > 10×10^9/L (HR = 4.536; 95% CI, 2.465–8.347; $P < 0.001$). After adjusting for sex, WBC count, fibrinogen, D-dimer and creatinine level, relapse became statistically significant at predicting TH-ED (HR = 2.996; CI, 1.576–5.696; $P < 0.001$).

4. Discussion

A distinctive coagulopathy associated with APL remains the most important cause of ED although great progress has been made in the management of this disease. Population-based studies revealed that the true rate of ED in large unselected cohorts of patients with newly diagnosed APL were high up to 17%–30%, and the majority of which is correlated with coagulopathy [13,15–17]. Currently, the mainstay of treatment for APL coagulopathy is aggressive blood product transfusion which is clearly inadequate for patients with high risk of TH-ED. For this subset of patients, more effective therapies for rapidly reversing coagulopathy need to be developed, while promptly and accurately identifying this subset of patients lays a foundation for clinical trials to explore more effective treatment methods.

There is very limited knowledge on how to identify high-risk TH-ED patients. To our knowledge, there are only one published study [5] identified risk factors for TH-ED, and another 4 studies [3,4,18,19] explored risk factors for early bleeding death in APL (Table 5). Among the 4 studies, two involved no patients died from thrombosis, one included two cases with early lethal thrombosis, while the other study did not provide relevant information. All five studies concentrated on patients receiving ATRA-based induction therapy, and none have focused on patients treated with ATO alone, although ATO is a very promising agent. Only three of the five patient cohorts have > 200 participants [3–5].

In our study the cumulative incidence of TH-ED at 30 days (14.6%) was somewhat higher than that in 3 large clinical trials (3.7–5.1%) [3–5]. Among the 3 studies, two [3,4] excluded patients with poor clinical condition, and the other [5] only involved child and adolescent patients. In addition, none of the studies involved relapsed patients. However, our study involved unselected patients, even including ten patients (7 de novo and 3 relapsed cases) died before therapy initiation and 79 relapsed patients who had a somewhat higher TH-ED rate (19.0%) than de novo cases (13.3%, $P = 0.227$; Tables 1 and 3). It can also be seen that studies on independent baseline predictors for TH-ED/early lethal bleeding often give inconsistent results. Several factors may contribute to the lack of consistency. (a) Differences in total numbers of patients and TH-EDs/early lethal bleeding. Compared with number of patients, number of deaths is more important for screening for risk factors. (b) Differences in candidate variables among various studies. Actually almost all baseline variables are more or less related one to another, therefore, overall constitution of candidate variables often has a great influence on whether or not a certain variable is included in the final multivariate model. Here is an extreme example. Both our study and study by Mantha et al. [3] revealed that WBC count and peripheral blast count were highly correlated in APL ($P = 0.928$ and 0.68, respectively), and De la Serna et al. [4] mentioned that the inclusion of peripheral blast count in multivariate analysis prompted WBC count to be removed from the regression model. (c) Differences in the cut-offs for continuous variables among different studies. (d) Differences in statistical methods. Three statistical methods were used in these studies, including logistic regression model, Cox's proportional regression models and cause-specific Cox proportional hazards regression, and the latter is the most appropriate method for such analysis [14].

In accordance with previous studies [3,5,18], our study also found that high WBC count was an independent risk factor for TH-ED. The results are easy to understand considering that APL cells are the direct

Table 5
Studies assessing predictors of thrombohemorrhagic early death/hemorrhagic mortality in patients with APL.

Publication time	Author	Number of patients (age range)	Induction regimen	Endpoint	Number of TH-EDs/bleeding deaths (%)	Candidate predictors (cutoff point for dichotomizing numerical variables/categories for categorical variables or ranked variables)	Statistical methods
2008	De la Serna et al. [4]	732 (2–83 years)	ATRA + idarubicin	Hemorrhagic induction death	37 (5.1)	PB blast counts (30×10^9/L)[a,b], coagulopathy (no, yes)[a,b], creatinine (1.4 mg/dL)[a,b], age (70 years)[a], WBC counts (10×10^9/L)[a], sex, ECOG PS (0–1, 2–3), fever (no, yes), platelet counts (40×10^9/L), HB (10g/dL), fibrinogen (170 mg/dL), UA (7 mg/dL), albumin (3.5 g/dL), *PML/RARA* isoform (BCR1/BCR2, BCR3), FAB classification (M3, M3v)	Univariate Chi-square/Fisher exact test; multivariate logistic regression model
2011	Kim et al. [19]	90 (15–80 years)	ATRA + idarubicin/(cytarabine + daunorubicin)	Hemorrhagic induction death	15 (16.7)	Platelet counts (30×10^9/L)[a,b], fibrinogen (1.0 g/L)[a], LDH (2 × UNL)[a], age (41 years), WBC counts (10×10^9/L), PB blast counts (10×10^9/L), PT (1.3 × UNL), APTT (35.3 s), D-dimer (32 mg/L), UA (3.7 mg/dL), secondary chromosome abnormalities (no, yes)	Univariate and multivariate logistic regression model
2013	Mitrovic et al. [18]	56 (19–78 years)	ATRA + anthracyclines	Fatal bleeding within 30 days of therapy initiation	8 (14.3)	ISTH DIC Score (0–5, 6)[a,b], WBC counts (20×10^9/L)[a], PT (50%)[a], ECOG PS (1–2, 3–4)[a], fibrinogen (2 g/L)[a], age (55 years), sex, HB, platelet counts (30×10^9/L), APTT, D-dimer, coagulopathy (no, yes)*	Univariate and multivariate Cox's proportional regression models
2017	Abla et al. [5]	683 (0.4–19 years)	ATRA + chemotherapy	TH-ED within 30days of presentation	25 (3.7)	BMI (95th percentile)[b], WBC counts (10×10^9/L)[a,b], ethnicity (Caucasian, Asian, Hispanic, Black, unknown)[a], PB blast counts (30×10^9/L)[a], FAB classification (M3, M3v)[a], age (10 years), sex, platelet counts (10×10^9/L), HB, treatment period (1993–2002, 2003–2013), cytarabine use in induction (no, yes), use of steroids as DS prophylaxis (no, yes)	Univariate and multivariate cause-specific Cox proportional hazard regression
2017	Mantha et al. [3]	995 (19–73 years)	ATRA + chemotherapy	Fatal bleeding within 30 days of APL diagnosis	37 (3.7)	WBC counts (20×10^9/L)[a,b], ECOG PS (0–2, 3–4)[a], PB blast count[a], age, sex, platelet counts (30×10^9/L), HB, APTT, fibrinogen, creatinine clearance, FAB classification (M3, M3v)[#]	Univariate and multivariate cause-specific Cox proportional hazards regression
2019	Hou et al.	364 (4–81 years)	ATO alone	TH-ED within 30days of hospital admission	53 (14.6)	De novo/relapse[b], sex[ab], WBC counts (10×10^9/L)[a,b], fibrinogen (1 g/L)[a,b], D-dimer (4 mg/L)[a,b], creatinine (normal, above normal)[a,b], UA (normal, above normal)[a], AST (normal, above normal)[a], albumin (normal, below normal)[a], age (50 years), platelet count (30×10^9/L)	Univariate and multivariate cause-specific Cox proportional hazards regression

APL-acute promyelocytic leukemia, PB-peripheral blood, WBC-white blood cell, PS-performance status, HB-hemoglobin, UA-uric acid, LDH-lactate dehydrogenase, UNL-upper normal limit, PT-prothrombin time, APTT-activated partial thromboplastin time, BMI-body mass index, DS-differentiation syndrome, AST-aspartate aminotransferase.

[a]Significant predictors in univariate analysis.

[b]Significant predictors in multivariate analysis.

*For some of the numerical variables that are statistically insignificant, the cutoff points were not given by the authors.

[#]The numerical variables age, PB blast count, HB, APTT, fibrinogen and creatinine clearance were not dichotomized.

The variables in shadows are statistically significant in neither univariate nor multivariate analysis.

cause of coagulopathy. WBC count instead of peripheral blood blast count was chosen as candidate variable because the two variables were strongly correlated, while WBC count is more easily accessible to clinician. In the study by De la Serna et al., high WBC count would also be recognized as independent prognostic factor for early hemorrhagic mortality if peripheral blood blast count was excluded from the multiple regression analysis [4].

In accordance with the study by De la Serna et al. [4], our study also found that a high creatinine level was the most robust independent predictor among all the candidate variables, whereas the variable was absent from the other 4 studies. There is no evidence showing that increased creatinine level could aggravate APL coagulopathy. But significant correlation does not mean causality at all. Increased creatinine level might merely reflect a state of disease progression, for example, it could be a reflection of DIC compromising the glomerular microcirculation, and patients in such a state are more likely to suffer fatal bleeding.

Prognostic factors for TH-ED in relapse patients have never been studied before. Our study indicated that although relapse was not associated with TH-ED in the univariate analysis, it acquired predictive significance for TH-ED after adjustment for sex, WBC count, fibrinogen, D-dimer and creatinine in the multivariable Cox regression, which suggested that some or all of the 5 variables were confounding factors when the predictive role of de novo/relapse classification for TH-ED was assessed.

It was taken for granted that coagulation parameters would be powerful predictors of fatal coagulopathy, but studies revealed that coagulation parameters provided only weak power to predict early hemorrhagic mortality. D-dimer and fibrinogen were evaluated in 2 [18,19] and 4 [3,4,18,19] of the 5 studies, respectively. Neither of the 2 studies found D-dimer was associated with early hemorrhagic death, while 2 [18,19] of the 4 studies found fibrinogen level was a significant predictor in univariate analysis. Blood product administration at least partly negated these parameters' effect on the risk of TH-ED. However, both variables are significant multivariate predictors in our study. Maybe this is because there are more TH-EDs in our study, which is favorable for the identification of weak predictors.

All previous studies showed that sex was not related to TH-ED/early lethal bleeding. But our study found that male was a weak predictor of TH-ED. Maybe ATO induced therapy is more effective for female patients than male ones.

One limitation of the study is that in this retrospective study some data that was intended to be collected, such as Eastern Cooperative Oncology Group (ECOG) performance status and lactate dehydrogenase, was unavailable. Despite this limitation, our study represents the first large clinical trial where unselected patients with APL were included, and contains the largest number of TH-EDs among the published studies for identifying the predictors of TH-ED/fatal bleeding (Table 5). As mentioned above, the greater the number of deaths, the more favorable for the identification of prognostic factors. In addition, this is also the first study for identifying predictors of TH-ED/fatal bleeding in APL patients receiving ATO alone as induction therapy. As a very promising agent, ATO deserves more exploration. Both ATRA combined with chemotherapy and ATO alone are regimes of targeted differentiation therapy, therefore patients receiving the two different treatment regimes share some common risk factors, such as high WBC count, high creatinine level.

5. Conclusion

The rates of TH/ED are still high to this day, and TH/ED is the major barrier to curing APL. This study identified risk factors affecting TH-ED in a large cohort of APL patients who were treated with ATO alone as induction therapy. The results enriched clinical information on the determinants of TH/ED in APL, which can potentially lead to significant improvements in the prognosis for patients with APL.

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Declaration of competing interest

The authors report no conflicts of interest in this work.

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