The correlation factors and prognostic significance of coagulation disorders after chimeric antigen receptor T cell therapy in hematological malignancies: a cohort study

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Background: Along with cytokine release syndrome (CRS) and neurotoxicity, coagulation disorder is a common early complication of chimeric antigen receptor (CAR)-T cell therapy. However, the mechanisms and prognostic significance of CAR-T-related coagulation disorders are not fully known. This study explored the possible correlation factors and prognostic significance of coagulation disorders after CAR-T cell infusion in patients with relapsed/refractory hematological malignancies.

Methods: This cohort study included 56 patients with relapsed/refractory hematological malignancies who were treated with CAR-T cells between April 2017 and February 2022. The median follow-up was 26.8 months. Coagulation disorders were defined as the abnormality in at least one coagulation parameters, including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, and D-dimer. The correlation factors of coagulation disorders were analyzed using Wilcoxon rank-sum test, Fisher's exact test, paired *t*-test and Spearman correlation coefficient. The prognostic significance of coagulation disorders was analyzed using Kaplan-Meier method and stepwise multivariate Cox regression model.

Results: The incidence of coagulation disorders was 59% within 1 month of CAR-T cell infusion. PT prolongation, APTT prolongation, TT prolongation, and D-dimer increase peaked at a median of 6–9 days, and fibrinogen decreased to its lowest value at a median of 12 days. Coagulation disorders in patients with severe CRS were more significant (P<0.001). Abnormality of coagulation parameters was closely related to cytokines, CAR-T cells, liver function parameters, and von Willebrand Factor (VWF) in both peak level and peak time (P<0.05). Statistical analysis showed that coagulation disorders were associated with higher initial response rates (TT, P=0.006; D-dimer, P=0.010) and also longer progression-free survival (PFS) (PT, P=0.017; APTT, P=0.018; TT, P=0.001; Fibrinogen, P=0.003; D-dimer, P<0.001) in CAR-T therapy, with TT prolongation (HR =0.279, 95% CI: 0.099–0.782, P=0.015) and D-dimer increase (HR =0.218, 95% CI: 0.087–0.548, P=0.001) independent predictors for PFS.

Conclusions: The protection of liver and endothelial cells may reduce CAR-T-related coagulation disorders. Further, coagulation disorders occurring within 1 month of CAR-T cell infusion can serve as a new predictor for prognosis in patients with hematological malignancies.

Keywords: Chimeric antigen receptor T cells; coagulation disorders; liver function; endothelial cells; prognosis

Page 2 of 10

Dong et al. Coagulation disorders in CAR-T therapy

Introduction

Chimeric antigen receptor (CAR)-T cells have shown promising efficacy for the treatment of relapsed/refractory (r/r) hematologic malignancies, including acute lymphoblastic leukemia (ALL) (1,2), non-Hodgkin lymphoma (NHL) (3-6), and multiple myeloma (MM) (7,8). Consequently, 5 CAR-T products have been approved by the Food and Drug Administration (FDA) (2,3,5,6,8), which paved the way for the application of CAR-T treatment to a greater number of patients. However, CAR-T treatment-associated toxicities, which may be severe and life-threatening, cannot be disregarded. Thus far, most studies have focused on CAR-T-related cytokine release syndrome (CRS) and neurotoxicity (9-11).

Coagulation disorder is another common adverse reaction of CAR-T treatment. It has been reported that more than 50% of patients with hematological malignancies suffer from a coagulation disorder after CAR-T treatment (12,13), with some patients progressing to disseminated intravascular coagulation (DIC) (7–28%) (12,13) and pulmonary embolism (PE) (2–8%) (14), which seriously endangers the life of patients.

At present, there are few studies on the mechanisms and influencing factors of coagulopathy in CAR-T therapy. Wang *et al.* (12) and Shao *et al.* (15) found that the severity of coagulation disorders was positively correlated with CRS grade during CAR-T therapy. We know that most chemotherapeutic agents produce coagulopathy through induction of endothelial injury and decrease of coagulation factors synthesis in the liver in cancer patients (16). However, the association of coagulation disorders with endothelial and liver injury in CAR-T therapy has not been investigated yet. In addition, the prognostic significance of CAR-T-related coagulation disorders are not fully known.

Here, we explored the possible correlation factors and prognostic significance of coagulation disorders after CAR-T cell infusion in patients with r/r hematological malignancies. This study may provide new targets for the prevention of CAR-T-related coagulation disorders and new predictor for the prognosis of CAR-T therapy. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3814/rc).

Methods

Patients

In this retrospective cohort study, patients with r/r hematological malignancies who were treated with CAR-T cells between April 2017 and February 2022 at The First Affiliated Hospital of Wenzhou Medical University were eligible. The following exclusion criteria were used: (I) patients with coagulation disorders and abnormal liver function before CAR-T cell infusion, (II) patients treated with anticoagulant drugs, and (III) patients who had clear signs of infection or other disorders known to cause coagulation disorders. The follow-up ended in April 2022. The number of cases in our hospital during the study period determined the sample size. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The First Affiliated Hospital of Wenzhou Medical University (No. 2016-220 and 2017-159) and informed consent was taken from all the patients or the patients' guardians.

CAR-T cell manufacture and infusion

In our study, CAR-T cell infusion was set on day 0. On approximately day-11, peripheral blood mononuclear cells were obtained from patients by leukapheresis, and CD3+ T cells were sorted for CAR-T cell preparation. The CAR included an anti-CD19 or B-cell maturation antigen (BCMA) single-chain variable fragment, 4-1BB or CD28 co-stimulatory domain, and CD3ζ T cell activation domain (Hrain Biotechnology and CARsgen Therapeutic, Shanghai, China). Prepared CAR-T cells were stored in liquid nitrogen until the day of infusion. Before infusion, all patients received lymphodepletion chemotherapy with fludarabine and cyclophosphamide (FC) regimen (fludarabine 25–30 mg/m^2 on day-4 to -2, cyclophosphamide 500 mg/m^2 on day-4 to -3).

CAR-T cell proliferation, CRS, and efficacy assessment

After CAR-T cell infusion, the patients' physical condition was closely monitored for 14 days. On days 1, 3, 6, 9, 14, 21, and 28, peripheral blood was drawn for the assessment of circulating CAR-T cell and cytokine levels. From day 29 to 6 months post-infusion, CAR-T cell level and treatment response were assessed monthly. After 6 months, follow-up was performed at an interval of 3 months. CRS was diagnosed and graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system (17). Grade ≥3 CRS was considered to be severe CRS. CAR-T cell levels

were measured by quantitative polymerase chain reaction (qPCR), and treatment response was assessed according to the National Comprehensive Cancer Network (NCCN) guidelines by bone marrow blasts examination for ALL (18), the Lugano criteria by computed tomography (CT) and positron emission tomography (PET)/CT examination for NHL (19), and the International Myeloma Working Group (IMWG) criteria for MM (20). Response evaluation for MM included bone marrow plasma cells, serum paraprotein, immunofixation electrophoresis, and free immunoglobulin light chains. Progression-free survival (PFS) was defined as the time from CAR-T infusion to disease progression, death, or last follow-up.

Coagulation parameters, liver function, and von Willebrand Factor (VWF) monitoring

Coagulation disorders were defined as the abnormality in at least one coagulation parameters, including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, and D-dimer. These coagulation parameters were monitored closely within 1 month of CAR-T cell infusion. To further analyze the relationship of liver and endothelial cell damage with coagulation disorders in CAR-T treatment, we monitored liver function in all patients and measured the VWF level in 12 patients with coagulopathy. The above parameters of all patients were tested in the same laboratory.

Statistical analyses

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Two-tailed P<0.05 was considered statistically significant. PFS was evaluated using Kaplan-Meier curves and compared using the log-rank test. Continuous variables and categorical variables were compared using Wilcoxon rank-sum test and Fisher's exact test, respectively. The paired *t*-test was used to compare coagulation parameters and VWF level before and after CAR-T treatment. The correlation of 2 continuous variables was analyzed by Spearman correlation coefficient. To evaluate the independent predictors of PFS, variables with P<0.05 in the univariate analysis were included in the stepwise multivariate Cox regression analysis.

We analyzed whether PFS was related to sex, age, diagnosis, number of relapses, transplant history, tumor burden, CAR-T infusion dose, peak CAR-T cells, CAR-T expansion duration, and coagulation disorders. The cut-off values of CAR-T infusion dose, peak CAR-T cells, and CAR-T expansion duration were established based on the medians. PT, APTT, and TT prolongation were defined as exceeding the upper limit of normal by ≥3, ≥10, and ≥3 seconds, respectively. Fibrinogen concentration ≤1.5 g/L was defined as fibrinogen decrease, and D-dimer concentration ≥5 mg/L was defined as D-dimer increase.

Results

Patient characteristics

Between April 2017 and February 2022, 59 patients with r/r hematological malignancies were treated with CAR-T cells. A total of 56 patients [B-cell acute lymphoblastic leukemia (B-ALL), n=14; diffuse large B-cell lymphoma (DLBCL), n=15; MM, n=27] were included in our cohort study, and the remaining 3 patients were excluded. The median age was 52 years (range, 16–70 years). Comparisons of clinical characteristics among different coagulation disorder groups are listed in *Table 1*, and no significant differences were observed.

Incidence of coagulation disorders

Within 1 month of CAR-T cell infusion, 59% of patients had at least 1 abnormal coagulation parameter. The medians of maximum PT, APTT, TT, and D-dimer were 15.4 seconds (13.5–26.4 seconds), 47.8 seconds (31.7–131.1 seconds), 17.5 seconds (14.5–27.1 seconds), and 3.04 mg/L (0.31–20.00 mg/L), respectively, and the median of minimum fibrinogen was 2.43 g/L (0.55–6.78 g/L). The incidence of prolonged PT, prolonged APTT, prolonged TT, decreased fibrinogen, and elevated D-dimer were 23%, 48%, 27%, 36%, and 39%, respectively. PT prolongation, APTT prolongation, TT prolongation, and D-dimer increase peaked at a median of 9 days (2–16 days), 6 days (1–16 days), 9 days (4–16 days), and 8 days (3–16 days), respectively, and fibrinogen decreased to its lowest value at a median of 12 days (7–21 days). There was a significant statistical difference for all values compared with their respective baseline level (*Figure 1A-1E*).

Association of coagulation disorders with CRS and CAR-T cell proliferation

The all-grade CRS rate and grade ≥3 CRS rate were 82% and 36%, respectively. We found that there were significant

Page 4 of 10

Dong et al. Coagulation disorders in CAR-T therapy

Table 1 Baseline characteristics of patients

Characteristics	PT			APTT			TT			Fibrinogen			D-dimer		
	Normal (n=43)	Prolonged (n=13)	P	Normal (n=29)	Prolonged (n=27)	P	Normal (n=41)	Prolonged (n=15)	P	Normal (n=36)	Decreased (n=20)	P	Normal (n=34)	Elevated (n=22)	P
Sex			1			0.789			0.227			0.575			0.577
Male	26 [60]	8 [61]		17 [59]	17 [63]		27 [66]	7 [47]		23 [64]	11 [55]		22 [65]	12 [54]	
Female	17 [40]	5 [39]		12 [41]	10 [37]		14 [34]	8 [53]		13 [36]	9 [45]		12 [35]	10 [45]	
Age			1			0.795			1			1			0.414
<50 years	20 [47]	6 [46]		14 [48]	12 [44]		19 [46]	7 [47]		17 [47]	9 [45]		14 [41]	12 [54]	
≥50 years	23 [53]	7 [54]		15 [52]	15 [56]		22 [54]	8 [53]		19 [53]	11 [55]		20 [59]	10 [46]	
Diagnosis			0.656			0.736			0.681			1			0.492
MM	20 [47]	7 [54]		15 [51]	12 [44]		20 [49]	7 [47]		17 [47]	10 [50]		16 [47]	11 [50]	
B-ALL	10 [23]	4 [31]		6 [21]	8 [30]		9 [22]	5 [33]		9 [25]	5 [25]		7 [21]	7 [32]	
DLBCL	13 [30]	2 [15]		8 [28]	7 [26]		12 [29]	3 [20]		10 [28]	5 [25]		11 [32]	4 [18]	
Number of relapses			1			0.43			0.768			0.785			0.581
<2	18 [42]	6 [46]		14 [48]	10 [37]		17 [42]	7 [47]		16 [44]	8 [40]		16 [47]	8 [36]	
≥2	25 [58]	7 [54]		15 [52]	17 [63]		24 [58]	8 [53]		20 [56]	12 [60]		18 [53]	14 [64]	
Transplant history			0.514			1			0.524			0.552			0.573
Yes	28 [65]	10 [77]		20 [69]	18 [67]		29 [71]	9 [60]		23 [64]	15 [75]		22 [65]	16 [73]	
No	15 [35]	3 [23]		9 [31]	9 [33]		12 [29]	6 [40]		13 [36]	5 [25]		12 [35]	6 [27]	
Tumor burden			1			0.361			0.736			1			0.762
Low	11 [26]	3 [23]		9 [31]	5 [19]		11 [27]	3 [20]		9 [25]	5 [25]		8 [24]	6 [27]	
High	32 [74]	10 [77]		20 [69]	22 [81]		30 [73]	12 [80]		27 [75]	15 [75]		26 [76]	16 [73]	
CAR-T infusion dose			1			0.422			1			0.412			0.423
<3×10^6/kg	21 [49]	6 [46]		12 [41]	15 [56]		20 [49]	7 [47]		19 [53]	8 [40]		18 [53]	9 [41]	
≥3×10^6/kg	22 [51]	7 [54]		17 [59]	12 [44]		21 [51]	8 [53]		17 [47]	12 [60]		16 [47]	13 [59]	

Numbers are presented as n [%]. PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; B-ALL, B-cell acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma; CAR-T, chimeric antigen receptor T cells.

differences in maximum PT, APTT, TT, D-dimer, and minimum fibrinogen levels between severe and mild CRS patients (*Figure 1A-1E*). Moreover, patients with grade ≥3 CRS had more abnormal coagulation parameters than those with grade <3 CRS (*Figure 1F*). In our study, increased cytokines were mainly interleukin (IL)-6 and interferon (IFN)-γ; thus, the total peak level of cytokines was defined as the sum of the peak levels of IL-6 and IFN-γ. Further analysis showed that cytokine levels were correlated with the levels of maximum PT, APTT, TT, D-dimer, and minimum fibrinogen (*Figure 1A-1E*) and also with the number of abnormal coagulation parameters (*Figure 1F*). In addition, the peak time of coagulation parameters and

cytokines was positively correlated (*Figure 1G*).

All CAR-T cells were derived from recipients, and the median infusion dose was 3×10^6/kg (1–28.2×10^6/kg). The median peak level, peak time, and expansion duration of CAR-T cells were 1.1×10^5 copies/µg genomic DNA (gDNA) (0.0009–18×10^5 copies/µg gDNA), 9 days (6–36 days), and 1.9 months (0–14.1 months), respectively. We found that the level of peak CAR-T cells was related to the levels of maximum PT, TT, D-dimer, minimum fibrinogen, and the number of abnormal coagulation parameters but not related to the level of maximum APTT (*Figure 1A-1F*). Moreover, the peak time of coagulation parameters was positively associated with CAR-T cells (*Figure 1H*).
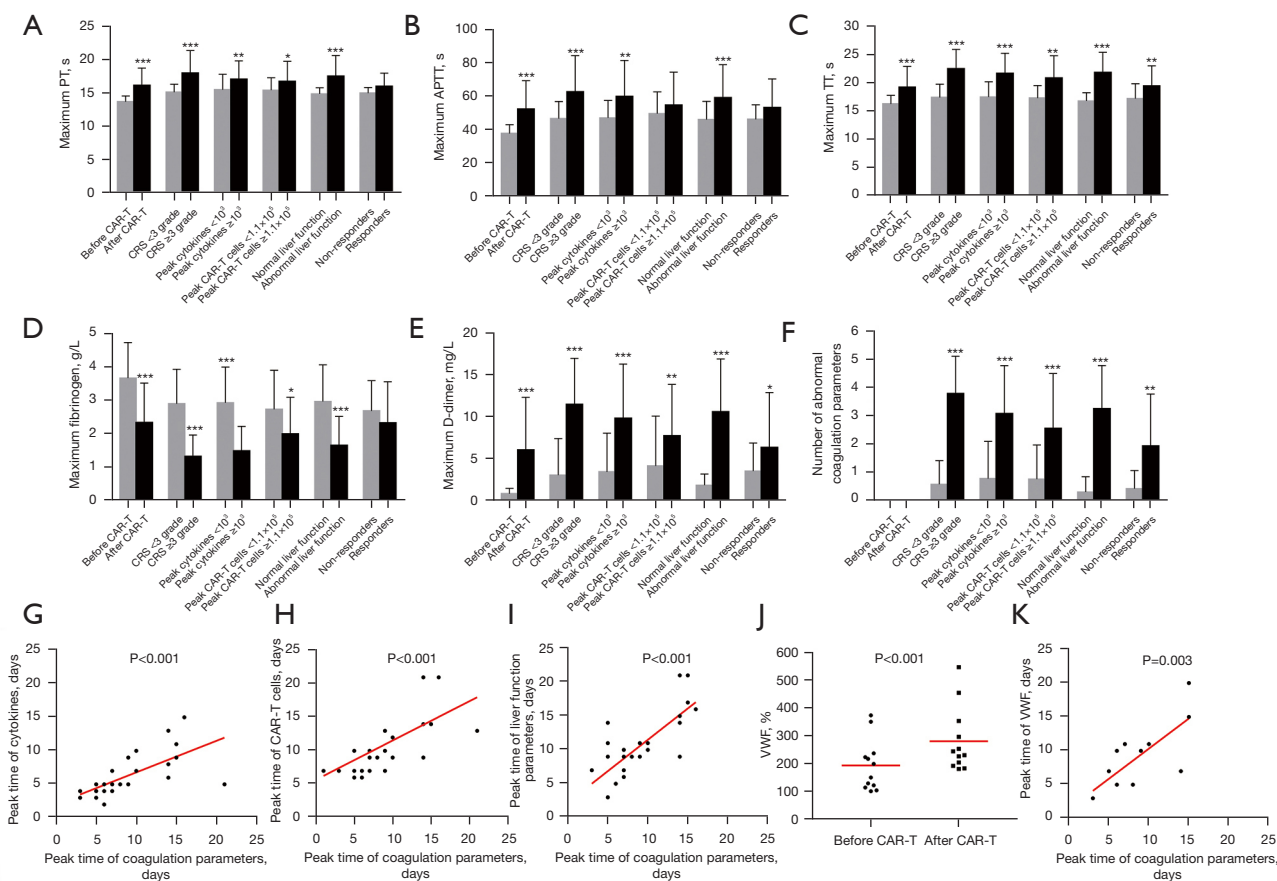
Figure 1 The relationship of coagulation disorders after CAR-T cell infusion with CRS severity, cytokine level, CAR-T cell level, liver function, initial response rate, and VWF level. The relationship of maximum PT (A), maximum APTT (B), maximum TT (C), minimum fibrinogen (D), maximum D-dimer (E), and number of abnormal coagulation parameters (F) after CAR-T cell infusion with coagulation parameters before CAR-T cell infusion, CRS severity, peak cytokine level, peak CAR-T cell level, liver damage, and initial response. The correlation of peak time of coagulation parameters after CAR-T cell infusion with peak time of cytokines (G), CAR-T cells (H), liver function parameters (I), and VWF (K). Change in VWF levels before and after CAR-T cell infusion (J). *, P<0.05, **, P<0.01, ***, P<0.001. CAR-T, chimeric antigen receptor T; CRS, cytokine release syndrome; VWF, von Willebrand Factor; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time.

Association of the coagulation disorders with liver damage and VWF increase

The incidence of abnormal liver function was 48% within 1 month of CAR-T cell infusion. The medians of maximum alanine aminotransferase and aspartate aminotransferase were 35 U/L (10–401 U/L) and 35 U/L (16–755 U/L), respectively. Further analysis showed that liver function was related to all coagulation parameters (*Figure 1A-1F*). Furthermore, the peak time of coagulation parameters and liver function parameters was positively correlated (*Figure 1I*). For endothelial cells, we found that the serum

levels of VWF after CAR-T cell infusion was higher than baseline levels in the patients with coagulopathy (*Figure 1J*). Similarly, the peak time of coagulation parameters was positively associated with VWF (*Figure 1K*).

Association of the coagulation disorders with initial response rates and PFS

Fifty-three out of 56 patients (95%) survived for more than 1 month and were evaluated for response. The remaining 3 patients died of severe CRS or cerebral hemorrhage within 1 month of CART cell infusion. The overall response rate

Table 2 Univariate and multivariable analyses for PFS

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Sex (male *vs.* female)	0.755	0.402–1.418	0.357	–	–	–
Age (years) (<50 *vs.* ≥50)	1.029	0.547–1.936	0.922	–	–	–
Diagnosis (B-ALL *vs.* DLBCL *vs.* MM)						
B-ALL *vs.* DLBCL	1.93	0.763–4.887	0.098	–	–	–
B-ALL *vs.* MM	1.294	0.577–2.900	0.531	–	–	–
DLBCL *vs.* MM	0.695	0.318–1.521	0.266	–	–	–
Times of relapse (<2 *vs.* ≥2)	0.918	0.478–1.762	0.779	–	–	–
Transplant history (yes *vs.* no)	1.284	0.649–2.541	0.412	–	–	–
Tumor burden (low *vs.* high)	1.094	0.513–2.334	0.808	–	–	–
CAR-T infusion dose (×10^6/kg) (<3 *vs.* ≥3)	1.29	0.688–2.419	0.394	–	–	–
Peak CAR-T cells (×10^5 copies/μg gDNA) (<1.1 *vs.* ≥1.1)	0.417	0.208–0.837	0.001*	–	–	–
CAR-T expansion duration (months) (<1.9 *vs.* ≥1.9)	0.475	0.247–0.914	0.007*	–	–	–
Coagulation disorders						
PT (normal *vs.* prolonged)	0.363	0.181–0.725	0.017*	–	–	–
APTT (normal *vs.* prolonged)	0.516	0.274–0.974	0.018*	–	–	–
TT (normal *vs.* prolonged)	0.326	0.172–0.619	0.001*	0.279	0.099–0.782	0.015*
Fibrinogen (normal *vs.* decreased)	0.373	0.198–0.701	0.003*	–	–	–
D-dimer (normal *vs.* elevated)	0.304	0.162–0.573	<0.001*	0.218	0.087–0.548	0.001*

*, P<0.05. PFS, progression-free survival; B-ALL, B-cell acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma; CAR-T, chimeric antigen receptor T cells; gDNA, genomic DNA; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time.

and complete remission rate without additional therapy after CAR-T infusion were 74% and 58%, respectively. Further analysis showed that initial response was associated with maximum TT and D-dimer but not associated with maximum PT, APTT and minimum fibrinogen levels (*Figure 1A-1E*). In addition, responders had more abnormal coagulation parameters than non-responders (*Figure 1F*).

To avoid the impact of hematopoietic stem cell transplantation (HSCT) on the long-term efficacy of CART treatment, the 6 patients with CAR-T treatment bridging HSCT were excluded in the analysis of PFS. At a median follow-up of 26.8 months, the median PFS among the 47 evaluated patients was 4.1 months. To explore the relevant factors affecting PFS, we analyzed whether PFS was related to sex, age, diagnosis, number of relapses, transplant history, tumor burden, CAR-T infusion dose, peak CAR-T cells, CAR-T expansion duration, and coagulation disorders.

In univariate analysis, we found that PFS was associated with peak CAR-T cells [hazard ratio (HR) =0.417, 95% confidence interval (CI): 0.208–0.837], CAR-T expansion duration (HR =0.475, 95% CI: 0.247–0.914), and also coagulation disorders, including PT prolongation (HR =0.363, 95% CI: 0.181–0.725), APTT prolongation (HR =0.516, 95% CI: 0.274–0.974), TT prolongation (HR =0.326, 95% CI: 0.172–0.619), fibrinogen decrease (HR =0.373, 95% CI: 0.198–0.701), and D-dimer increase (HR =0.304, 95% CI: 0.162–0.573) (*Table 2*). However, multivariable Cox regression analysis showed that only TT prolongation (HR =0.279, 95% CI: 0.099–0.782) and D-dimer increase (HR =0.218, 95% CI: 0.087–0.548) were independent predictors for PFS (*Table 2*). Patients with prolonged PT, prolonged APTT, prolonged TT, decreased fibrinogen, elevated D-dimer, or more abnormal coagulation parameters exhibited longer PFS (*Figure 2*).
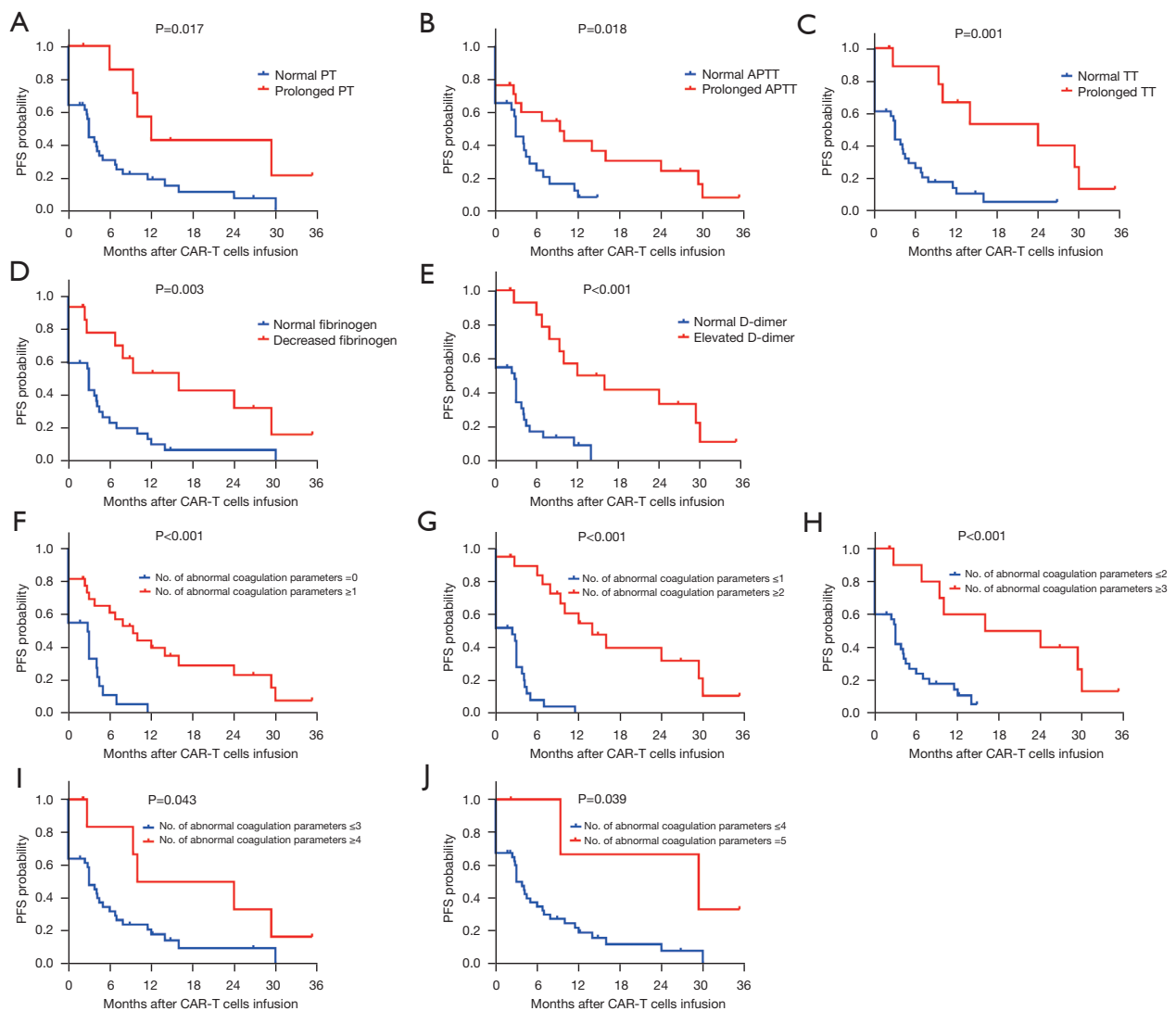
Figure 2 The relationship of coagulation disorders after CAR-T cell infusion with PFS. (A-E) Kaplan-Meier analysis showed that patients with prolonged PT, prolonged APTT, prolonged TT, decreased fibrinogen, or elevated D-dimer exhibited longer PFS. (F-J) Kaplan-Meier analysis showed that patients with more abnormal coagulation parameters exhibited longer PFS. CAR-T, chimeric antigen receptor T; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; PFS, progression-free survival.

Discussion

Despite CAR-T cell therapy showing promising response rates, treatment-associated toxicities are still a major concern. Along with CRS and neurotoxicity, coagulation disorder is a common early complication of CAR-T treatment. In our study, the incidence of coagulation disorders was 59% within 1 month of CAR-T cell infusion in patients with r/r hematological malignancies. PT prolongation, APTT prolongation, TT prolongation, and D-dimer increase peaked at a median of 6–9 days, and

fibrinogen decreased to its lowest value at a median of 12 days. The changes in coagulation parameters we observed were similar to previous reports (12,13). Therefore, it is important to be alert to the occurrence of coagulation disorders in patients treated with CAR-T cells, particularly in the second week after infusion.

To our knowledge, the mechanisms of CAR-T-related coagulation disorders remain unclear. Consistent with previous research (12,13,15), we found that coagulation disorders in patients with severe CRS were more significant.

Page 8 of 10

Dong et al. Coagulation disorders in CAR-T therapy

Our previous study found that CRS severity was associated with levels of cytokines and CAR-T cells (21), so we further investigated the relationship of cytokines and CAR-T cells with coagulation disorders. The results showed that abnormality of coagulation parameters was closely related to cytokines and CAR-T cells in both peak level and peak time.

We then considered the mechanism by which high levels of cytokines and CAR-T cells induced coagulation disorders. We know that many coagulation-related proteins are synthesized in the liver, and thus the liver plays an important role in the regulation of coagulation function (22). Our study showed that abnormality of coagulation parameters was also closely associated with liver function parameters in both peak level and peak time. Therefore, we speculated that high levels of cytokines and CAR-T cells may induce coagulation disorders, at least in part, by injuring the liver.

Besides the liver, we know that endothelial activation is also closely related to coagulation disorders (23). It has been demonstrated that high levels of cytokines (24,25) and CAR-T cells (26) can cause activation and damage of endothelial cells. In this study, we explored the presence of endothelial activation after CAR-T cell infusion in patients with coagulation disorders by detecting the serum levels of VWF, an important marker of endothelial activation (27). The results showed that the serum level of VWF after CAR-T cell infusion was higher than baseline levels in the patients with coagulopathy. Moreover, the peak time of coagulation parameters was positively associated with VWF. The above results suggested that CAR-T-related coagulation disorders may have been secondary to endothelial activation induced by high levels of cytokines and CAR-T cells.

In addition to the correlation factors of CAR-T-related coagulation disorders, we also explored the prognostic significance of coagulation disorders in patients treated with CAR-T cells. The results showed that coagulation disorders were associated with higher initial response rates and also longer PFS in CAR-T therapy, with TT prolongation and D-dimer increase independent predictors for PFS.

In conclusion, we propose the following possible mechanisms of CAR-T-related coagulation disorders: (I) high levels of cytokines cause liver damage and impair the production of coagulation-related proteins; (II) the liver damage caused by off-target effects of CAR-T cells also affects the production of coagulation-related proteins; (III)

high levels of cytokines cause activation and damage of vascular endothelial cells, thereby activating coagulation pathway; (IV) CAR-T cells directly damage vascular endothelial cells, resulting in activation of coagulation. Further, our results suggested that coagulation disorders occurring within 1 month of CAR-T cell infusion could serve as a new predictor for prognosis in patients with r/r hematological malignancies. However, due to the limited number of cases in this study, our findings need to be further validated with larger, multicenter, and prospective studies.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3814/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The First Affiliated Hospital of Wenzhou Medical University (No. 2016-220 and 2017-159) and informed consent was taken from all the patients or the patients' guardians.

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Page 10 of 10

Dong et al. Coagulation disorders in CAR-T therapy

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