haematologica
Journal of the Ferrata Storti Foundation

Dynamics and clinical significance of coagulation abnormalities following CAR T-cell therapy

by Christina Charlotte Rolling, Nigar Mammadova, Catherina Lück, Rolf Krause, Lennart Beckmann, Jochim Reinert, Carolina Berger, Boris Fehse, Florian Langer and Francis Ayuk

Received: September 16, 2026.
Accepted: October 21, 2026.

Citation: Christina Charlotte Rolling, Nigar Mammadova, Catherina Lück, Rolf Krause, Lennart Beckmann, Jochim Reinert, Carolina Berger, Boris Fehse, Florian Langer and Francis Ayuk. Dynamics and clinical significance of coagulation abnormalities following CAR T-cell therapy.
Haematologica. 2026 Oct 29. doi: 10.3324/haematol.2026.302009 [Epub ahead of print]

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.
E-publishing of this PDF file has been approved by the authors.
After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval, the final version of the manuscript will then appear in a regular issue of the journal.
All legal disclaimers that apply to the journal also pertain to this production process.

Dynamics and clinical significance of coagulation abnormalities following CAR T-cell therapy

Christina Charlotte Rolling[1*], Nigar Mammadova[1*], Catherina Lück[2], Rolf Krause[2], Lennart Beckmann[1], Jochim Reinert[2], Carolina Berger[2], Boris Fehse[2], Florian Langer[1], Francis Ayuk[2]

[*] CCR and NM share first authorship

1. Clinic and Policlinic of Oncology, Hematology, with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2. Clinic of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Corresponding author: Christina C. Rolling (c.rolling@uke.de)

Short title: Hypofibrinogenemia under tocilizumab-treated CRS

Data-sharing statement: The data underlying this study are available from the corresponding author upon reasonable request.

Acknowledgements: We sincerely thank all patients whose clinical and laboratory data contributed to our retrospective analysis. We also thank our clinical and nursing colleagues at the Department of Stem Cell Transplantation at the University Medical Center Hamburg-Eppendorf.

Authors' contributions: All authors contributed to data collection, critically revised the manuscript, and approved the final version. CCR, NM, and FA drafted the first version of the manuscript and analyzed the data.

Artificial intelligence: AI (ChatGPT, Open AI) was used for English-language proofreading only.

Conflicts of interest declarations: JR received travel grants from KITE/Gilead. CCR received honoraria for lectures and advisory boards from Novartis.

Funding: CCR was funded by the Margarete Clemes Stiftung, Essen, Germany.

Ethics statement: The study was approved by the local ethics committee of the city of Hamburg, Germany (PV7081).

Letter to the Editor

Chimeric antigen receptor (CAR) T-cell therapy is frequently complicated by cytokine release syndrome (CRS), a systemic inflammatory response associated with activation of the coagulation system.[1, 2] Coagulopathies, including hypofibrinogenemia, have been reported following CAR T-cell therapy, but their dynamics, risk factors, and clinical relevance remain incompletely understood. [3-6] This knowledge gap is particularly relevant as CAR T-cell therapy is expanding across hematologic malignancies and is being investigated in solid cancers and autoimmune disorders. We therefore retrospectively assessed coagulation abnormalities and thrombohemorrhagic complications in patients receiving CAR T-cell therapy, with a particular focus on hypofibrinogenemia and its association with CRS and CRS-directed therapies. We found hypofibrinogenemia to be common and closely associated with CRS severity and tocilizumab treatment, while clinically relevant bleeding complications remained rare.

We analyzed 150 consecutive patients treated with autologous CAR T-cells at the Clinic of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, between March 2019 and July 2025 after exclusion of patients treated within clinical trials, for autoimmune disorders, or with allogeneic CAR T-cell products. Our cohort included 113 patients (75.3%) with non-Hodgkin lymphoma (NHL), 34 (22.7%) with multiple myeloma (MM), and three (2.0%) with acute lymphoblastic leukemia (ALL). CRS and immune cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT criteria. Serial hematologic, coagulation, and inflammatory parameters were retrieved from electronic medical records. Severe hypofibrinogenemia was defined as fibrinogen < 1.0 g/L (CTCAE v.5.0 grade ≥3). Independent associations with severe hypofibrinogenemia were assessed using Firth-corrected multivariable logistic regression. The study was approved by the local ethics committee of the city of Hamburg, Germany (PV7081).

CRS occurred in 124 patients (82.7%), including grade ≥2 CRS in 73 (48.7%), and ICANS occurred in 57 (38%). All ALL patients developed CRS, and two of three ALL patients also developed ICANS. Tocilizumab was administered to 99 patients (66.0%), anakinra to 49 (33.0%), and dexamethasone to 63 (42.0%). Following CAR T-cell infusion, fibrinogen levels below the lower limit of normal (< 2.0 g/L) occurred in 80 patients (53.3%). Fibrinogen levels <1.5 g/L occurred in 57 (38%), and severe hypofibrinogenemia <1.0 g/L occurred in 33 patients (22%). Fibrinogen levels reached a median nadir of 1.92 g/L (IQR, 1.13–2.92) at 12 days (IQR, 9–15) after CAR T-cell infusion (**Table S1, Figure 1A**). Severe hypofibrinogenemia was more frequent in NHL than MM (30/113 [26.1%] vs. 2/34 [5.9%], p = 0.009)

Importantly, fibrinogen levels <2.0 g/L occurred exclusively in patients who developed CRS. Fibrinogen nadirs decreased with greater CRS (**Figure 1A**) and ICANS severity (**Figure 1B**), whereas peak IL-6 and D-dimer levels rose with CRS severity (**Figure 1C, D**). Accordingly, fibrinogen nadirs were inversely associated with peak IL-6 levels (ρ=−0.59), CRS grade (ρ=−0.56), ICANS grade (ρ=−0.43), and peak D-dimer (ρ=−0.42), while correlating positively with nadir platelet counts (ρ=0.41) (**Figure 2**). Among NHL patients receiving axi-cel, higher peak CAR T-cell levels were associated with

lower fibrinogen nadirs and greater CRS severity (**Figure S1A, B**). Together, these findings support a close relationship between CAR T-cell expansion, inflammation, and fibrinogen decline.

We next evaluated the impact of CRS-directed therapies tocilizumab, dexamethasone, and anakinra on plasma fibrinogen levels. Severe hypofibrinogenemia was rare in patients not receiving anti-inflammatory therapy. Tocilizumab treatment was associated with a more pronounced fibrinogen decline compared with no anti-inflammatory therapy, with the lowest nadirs observed in patients requiring treatment escalation with dexamethasone and/or anakinra (**Figure S2A**). In multivariable analysis, CRS requiring tocilizumab, NHL, and lower platelet nadirs were independently associated with severe hypofibrinogenemia (**Figure 3**).

Since IL-6 is a major regulator of hepatic fibrinogen synthesis[7] and tocilizumab blocks the IL-6 receptor, we assessed the temporal relationship between tocilizumab administration and fibrinogen, IL-6, and D-dimer levels. Fibrinogen declined shortly after tocilizumab administration (**Figure S2B**), beginning on day 1, while circulating IL-6 and D-dimer levels transiently increased. These temporal dynamics suggest a multifactorial mechanism involving inflammation-driven coagulation activation and fibrinogen consumption, together with impaired IL-6-mediated fibrinogen synthesis.

Our findings are consistent with previous reports linking CAR T-cell-associated coagulopathy to CRS.[3-5, 8] Similarly, Perl et al[6]. observed hypofibrinogenemia exclusively in patients receiving tocilizumab. Importantly, hypofibrinogenemia following tocilizumab treatment has also been reported in other inflammatory diseases outside the CAR T-cell setting, including rheumatoid arthritis, giant cell arteritis, Takayasu arteritis, and COVID-19, supporting an effect of IL-6 receptor blockade on fibrinogen dynamics.[9] However, treatment intensity is closely linked to CRS (and hence inflammation) severity, and our retrospective data cannot establish a causal effect of tocilizumab. The association should therefore be interpreted as reflecting both severe inflammation and a possible additional effect of IL-6 receptor blockade.

Importantly, laboratory abnormalities did not translate into a high rate of clinical thrombohemorrhagic complications. Only two minor bleeding events and three thromboembolic events occurred, none in patients with fibrinogen levels <1.0 g/L. Fibrinogen substitution and platelet transfusions were not systematically assessed and may have modified bleeding risk. Among patients with fibrinogen <1.0 g/L, 20 (61%) fulfilled updated ISTH laboratory criteria for overt disseminated intravascular coagulation (DIC)[10], which has been reported as a severe complication of CAR T-cell therapy and has been associated with an increased mortality rate.[11] However, interpretation of DIC scores in this setting is challenging, as thrombocytopenia may result from lymphodepleting chemotherapy, underlying disease, and CAR T-cell-associated hematotoxicity, while hypofibrinogenemia may, at least in part, reflect impaired fibrinogen synthesis following IL-6 receptor blockade. These findings emphasize the limitations of applying classical DIC criteria in CAR T-cell patients without considering treatment-related cytopenias and the effects of IL-6 receptor blockade. Consistent with the low rate of clinical complications, fibrinogen <1.0 g/L was not associated with inferior overall or relapse-free survival among patients with NHL.

In conclusion, hypofibrinogenemia is common after CAR T-cell therapy and is closely linked to CRS severity and CRS-directed treatment. The temporal decline following tocilizumab, together with increasing IL-6 and D-dimer levels and the independent associations with NHL, CRS requiring tocilizumab, and lower platelet nadirs, supports a model in which inflammation-driven consumption and reduced fibrinogen synthesis following IL-6 receptor blockade may act synergistically. Clinically relevant bleeding was rare in this cohort. Routine fibrinogen monitoring during CRS is warranted, particularly in patients requiring tocilizumab and additional anti-inflammatory therapy, while treatment decisions should consider the overall clinical bleeding risk rather than fibrinogen levels or DIC scores alone.

References

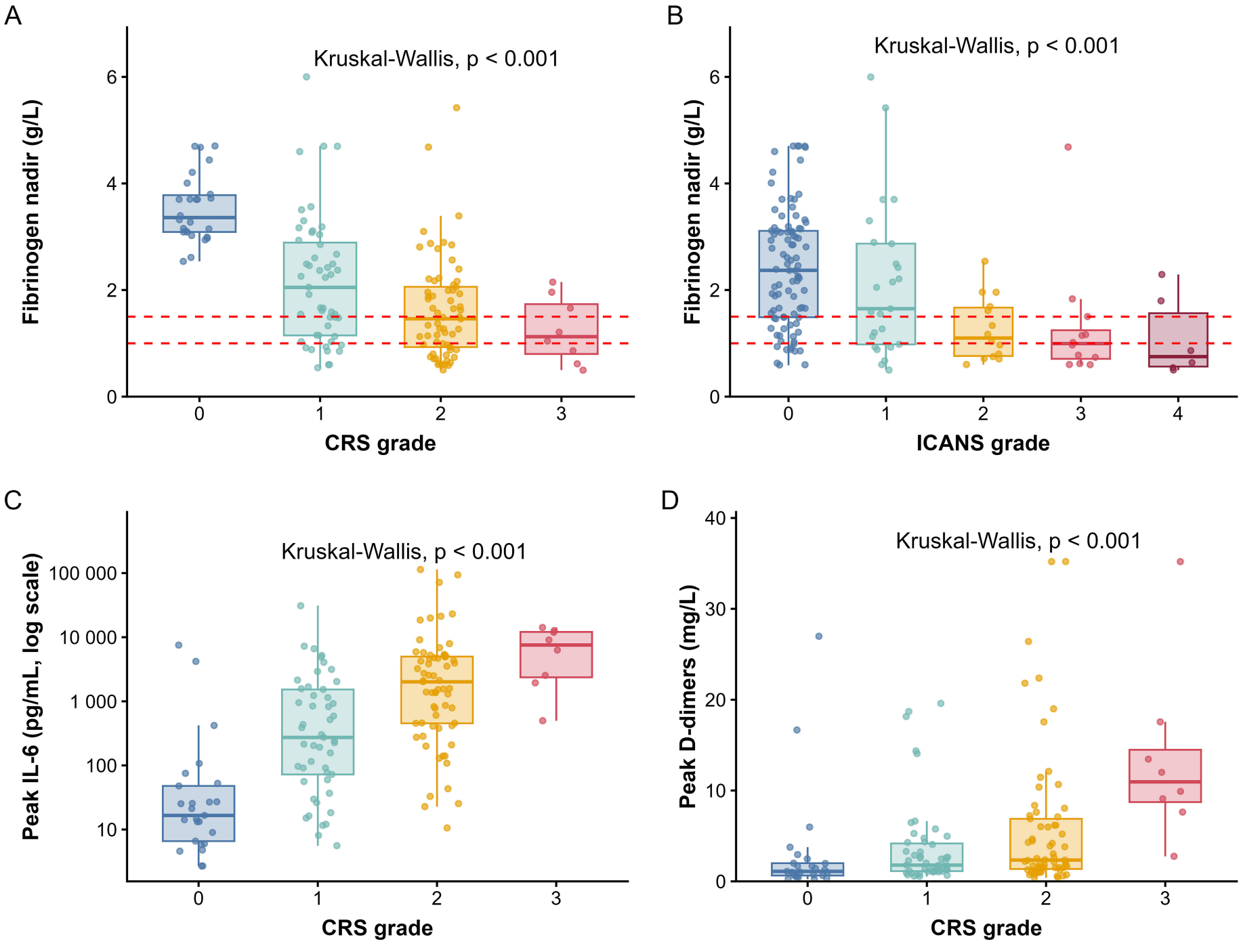
1. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med. 2010;38(2 Suppl):S26-34.
2. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020;383(23):2255-2273.
3. Jiang H, Liu L, Guo T, et al. Improving the safety of CAR-T cell therapy by controlling CRS-related coagulopathy. Ann Hematol. 2019;98(7):1721-1732.
4. Shao M, Yu Q, Teng X, et al. CRS-related coagulopathy in BCMA targeted CAR-T therapy: a retrospective analysis in a phase I/II clinical trial. Bone Marrow Transplant. 2021;56(7):1642-1650.
5. Wang Y, Qi K, Cheng H, et al. Coagulation disorders after chimeric antigen receptor T Cell therapy: analysis of 100 patients with relapsed and refractory hematologic malignancies. Biol Blood Marrow Transplant. 2020;26(5):865-875.
6. Perl M, Herfeld K, Harrer DC, et al. Tocilizumab administration in cytokine release syndrome is associated with hypofibrinogenemia after chimeric antigen receptor T-cell therapy for hematologic malignancies. Haematologica. 2024;109(9):2969-2977.
7. Dobson DA, Fish RJ, de Vries PS, Morrison AC, Neerman-Arbez M, Wolberg AS. Regulation of fibrinogen synthesis. Thromb Res. 2024;242:109134.
8. Buechner J, Grupp SA, Hiramatsu H, et al. Practical guidelines for monitoring and management of coagulopathy following tisagenlecleucel CAR T-cell therapy. Blood Adv. 2021;5(2):593-601.
9. An Q, Ma R, Yuan D, et al. Clinical observation of hypofibrinogenemia induced by the treatment of tocilizumab in rheumatic diseases and exploration of risk factor for hypofibrinogenemia. Clin Rheumatol. 2024;43(5):1491-1501.
10. Iba T, Levy JH, Maier CL, et al. Updated definition and scoring of disseminated intravascular coagulation in 2025: communication from the ISTH SSC Subcommittee on Disseminated Intravascular Coagulation. J Thromb Haemost. 2025;23(7):2356-2362.
11. Song Z, Tu D, Tang G, et al. Hemophagocytic lymphohistiocytosis and disseminated intravascular coagulation are underestimated, but fatal adverse events in chimeric antigen receptor T-cell therapy. Haematologica. 2023;108(8):2067-2079.

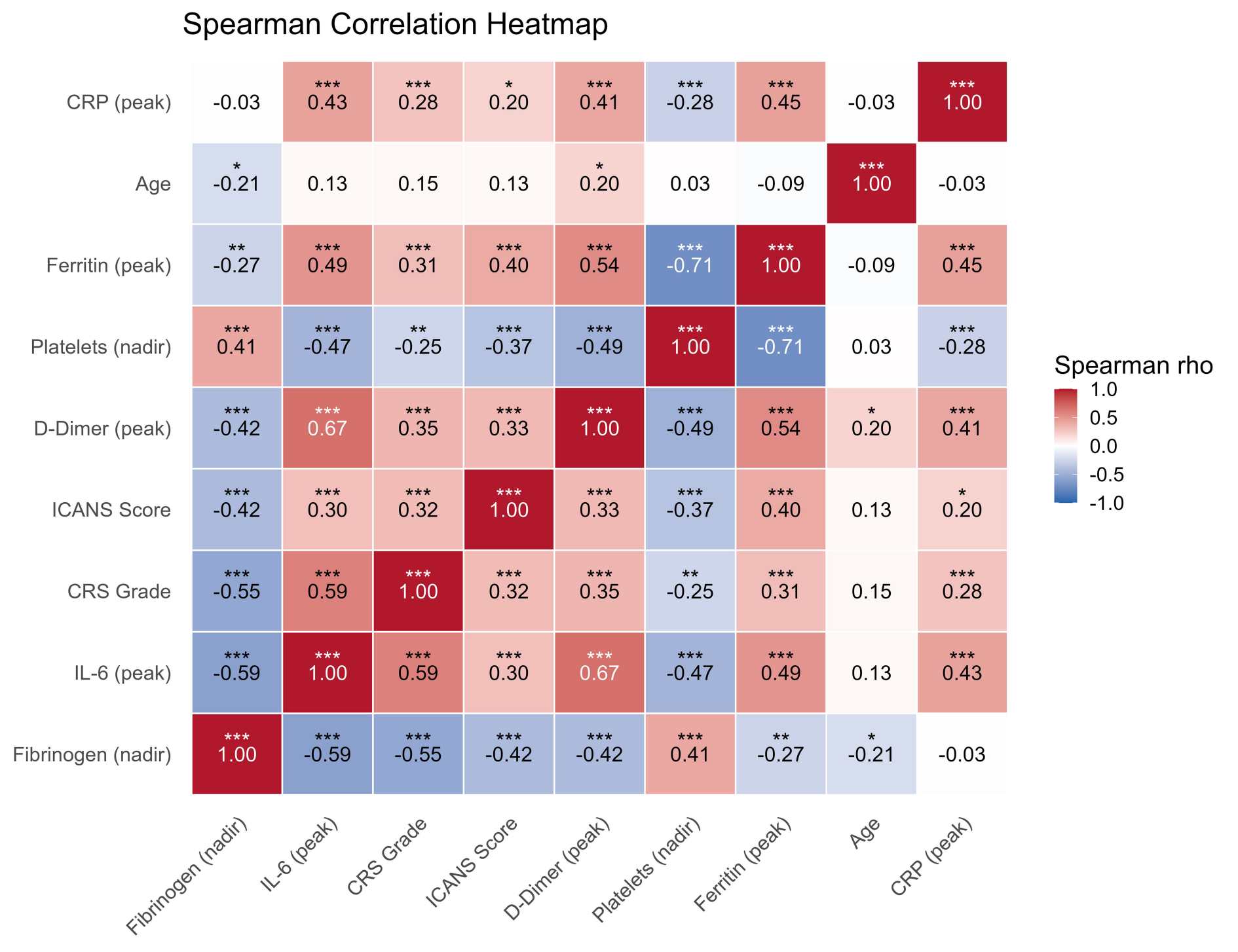
Figure Legends

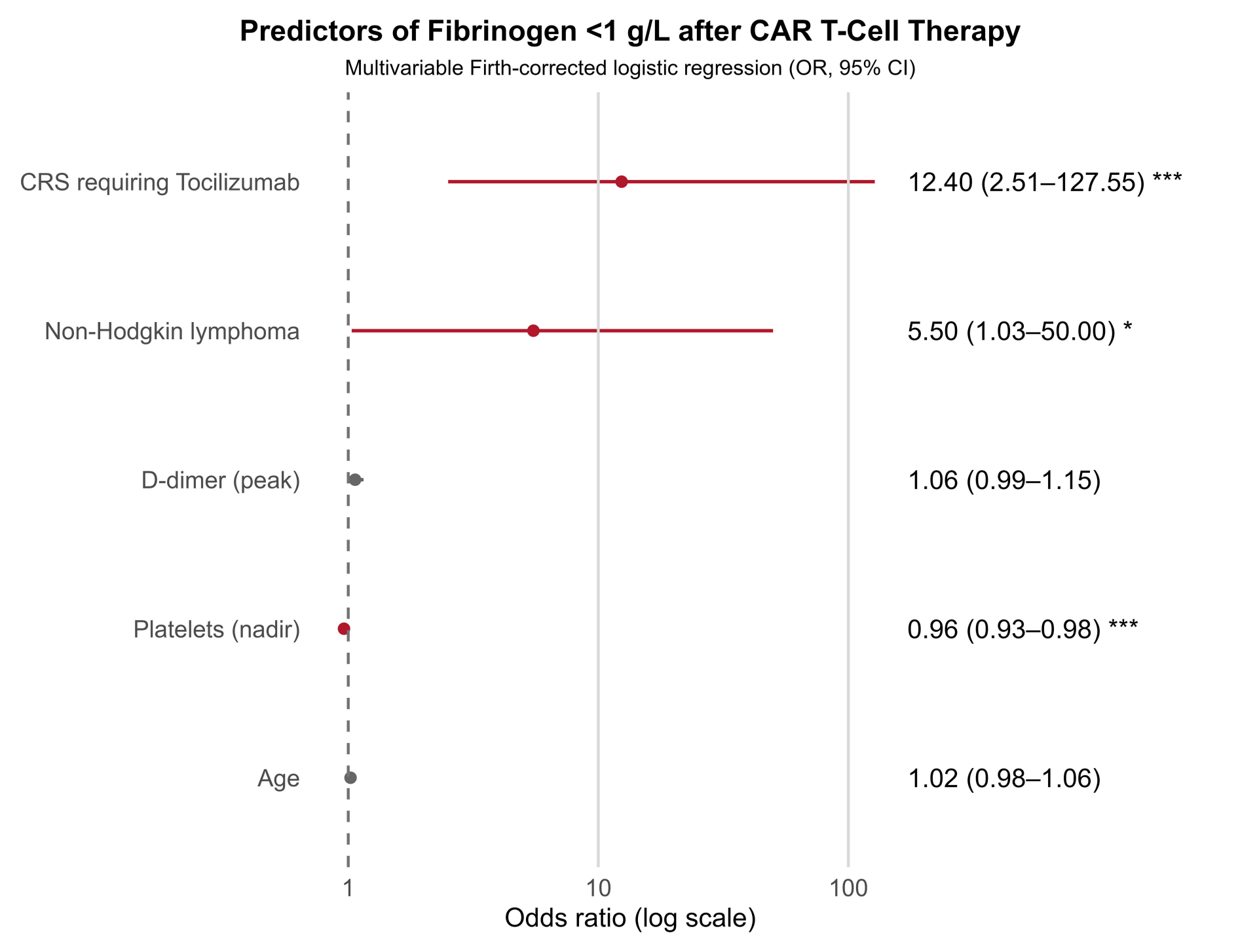
Figure 1. Association of CRS and ICANS with fibrinogen nadir and inflammatory markers following CAR T-cell therapy. **(A)** Plasma fibrinogen nadir levels according to CRS grade. **(B)** Plasma fibrinogen nadir levels according to ICANS grade. **(C)** Peak plasma IL-6 levels stratified by CRS grade. **(D)** Peak plasma D-dimer levels stratified by CRS grade. Each dot represents an individual patient, and boxplots indicate the median and interquartile range. Red dashed lines indicate clinically relevant thresholds (1.5 g/L and 1.0 g/L) in (**A**) and (**B**). Differences across groups were assessed using the Kruskal–Wallis test.

Figure 2. Correlation of fibrinogen with inflammatory and coagulation markers. Spearman correlation heatmap showing associations between fibrinogen nadir and markers of inflammation, disease severity, and coagulation following CAR T-cell therapy. Color intensity represents Spearman's ρ; significance levels are indicated (*p < 0.05, **p < 0.01, ***p < 0.001).

Figure 3. Fibrinogen < 1.0 g/L and tocilizumab exposure during CRS. Multivariable Firth-corrected logistic regression analysis of factors associated with severe hypofibrinogenemia (fibrinogen < 1.0 g/L) following CAR T-cell therapy. Points represent odds ratios with 95% confidence intervals on a logarithmic scale.


A
Kruskal-Wallis, p < 0.001
Fibrinogen nadir (g/L)
0
2
4
6
0
1
2
3
CRS grade
B
Kruskal-Wallis, p < 0.001
Fibrinogen nadir (g/L)
0
2
4
6
0
1
2
3
4
ICANS grade
C
Kruskal-Wallis, p < 0.001
Peak IL-6 (pg/mL, log scale)
10
100
1 000
10 000
100 000
0
1
2
3
CRS grade
D
Kruskal-Wallis, p < 0.001
Peak D-dimers (mg/L)
0
10
20
30
40
0
1
2
3
CRS grade


Spearman Correlation Heatmap
CRP (peak)
Age
Ferritin (peak)
Platelets (nadir)
D-Dimer (peak)
ICANS Score
CRS Grade
IL-6 (peak)
Fibrinogen (nadir)
Fibrinogen (nadir)
IL-6 (peak)
CRS Grade
ICANS Score
D-Dimer (peak)
Platelets (nadir)
Ferritin (peak)
Age
CRP (peak)
Spearman rho
1.0
0.5
0.0
-0.5
-1.0


Predictors of Fibrinogen <1 g/L after CAR T-Cell Therapy
Multivariable Firth-corrected logistic regression (OR, 95% CI)
CRS requiring Tocilizumab
12.40 (2.51–127.55) ***
Non-Hodgkin lymphoma
5.50 (1.03–50.00) *
D-dimer (peak)
1.06 (0.99–1.15)
Platelets (nadir)
0.96 (0.93–0.98) ***
Age
1.02 (0.98–1.06)
1
10
100
Odds ratio (log scale)

Supplementary Table 1

N	**150**
Age in years, median (IQR)	61.3 (52.8−70.3)
Female sex, n (%)	61 (40.7)
ECOG performance status, median (IQR)	1 (1−1)

Diagnosis, n (%)
- Non-Hodgkin lymphoma (NHL)
  o DLBCL
  o FL
  o MCL
  o DLCBL from CLL
  o PCNSL
  o PMBCL
- Multiple myeloma (MM)
- Acute lymphatic leukemia (ALL)
	
	- 113 (75.3)
	  o 93 (62.0)
	  o 7 (4.7)
	  o 10 (6.7)
	  o 1 (0.7)
	  o 1 (0.7)
	  o 1 (0.7)
	- 34 (22.7)
	- 3 (2)

CAR T-cell product, n (%) - axi-cel - tisa-cel - cilta-cel - ide-cel - brexu-cel - liso-cel	 - 85 (56.7) - 22 (14.7) - 21 (14) - 12 (8) - 5 (3.3) - 5 (3.3)
Complete blood count at CAR T cell infusion - Hemoglobin, g/dL - White blood counts, x 10^9/L - Platelets, x 10^9/L	Median (IQR) - 9.4 (8.7−10.2) - 1.10 (0.6−1.8) - 127 (76−178)
Hemostatic parameters at CAR T cell infusion - INR - APTT, sec - Thrombin time (TT), sec - Fibrinogen, g/L - D-dimers, mg/L	Median (IQR) - 1 (1−1.08) - 32 (29−34) - 16.4 (15.6−17.5) - 3.7 (3.49−3.82) - 0.85 (0.5−1.6)
Inflammatory markers at CAR T cell infusion - CRP, mg/L - Ferritin, µg/L - IL-6, pg/mL - LDH, IU/L	Median (IQR) - 11 (4−30) - 467.25 (218.1−1092.38) - 7.5 (2.9−29.2) - 211 (170−269.25)

Hemostatic alterations
- Fibrinogen <1.5 g/L, n (%)
  o Onset, days after CAR T, median (IQR)
- Fibrinogen < 1g/L, n (%)
  o Onset, days after CAR T, median (IQR)
- Peak D-dimers, mg/L, median (IQR)
  o Time to peak, days after CAR T, median (IQR)
- Fibrinogen nadir, g/L, median (IQR)
  o Time to nadir, days after CAR T, median (IQR)
- Platelet nadir, x 10^9/L, median (IQR)
	
	- 57 (38)
	  o 13 (10−16)
	- 33 (22)
	  o 11 (9−15)
	- 2.09 (1.1−5.98)
	  o 5 (4−8)
	- 1.92 (1.13−2.92)
	  o 12 (9−15)
	- 38.5 (11.75−95.75)

○ Time to nadir, days after CAR T, median (IQR)	○ 8.5 (5−17)
Inflammatory markers at peak - Ferritin (max), µg/L, median (IQR) ○ Onset, days after CAR T, median (IQR) - IL-6 (max), pg/mL, median (IQR) ○ Onset, days after CAR T, median (IQR) - CRP (max), mg/l, median (IQR) ○ Onset, days after CAR T, median (IQR)	 - 946.7 (430.53−2401.4) ○ 8 (5−13) - 605.4 (66.15−3887.3) ○ 5 (3−7) - 55 (28.0−124.0) ○ 4 (2−6)
CRS grades, n (%) - 0 - 1 - 2 - 3	 - 26 (17.3) - 51 (34.0) - 65 (43.3) - 8 (5.3)
ICAN grades, n (%) - 0 - 1 - 2 - 3 - 4	 - 93 (62) - 25 (16.7) - 14 (9.3) - 12 (8.0) - 6 (4.0)
Use of CRS and ICAN therapeutics - Tocilizumab in n (%) ○ Time to start, days after CAR T, median (IQR) - Anakinra, n (%) ○ Time to start, days after CAR T, median (IQR) - Dexamethason, n (%) ○ Time to start, days after CAR T, median (IQR)	 - 99 (66) ○ 3 (1−5) - 49 (33) ○ 5 (1−5) - 63 (42) ○ 5 (4−6)
Thrombohemorrhagic events in n (%) - Bleeding ○ Epistaxis ○ Localized bleeding - Thromboembolism ○ Pulmonary embolims ○ Upper extremity thrombosis ○ unknown	 2 (1.3) - 1 (0.7) - 1 (0.7) 3 (2) - 1 (0.7) - 1 (0.7) - 1 (0.7)

Table 1: Baseline characteristics, clinical and laboratory parameters of patients receiving CAR T-cell therapy.

Data are presented as median (interquartile range [IQR]) or number (percentage). Laboratory values were assessed at the time of CAR T-cell infusion unless otherwise specified. Time-to-event variables are reported as days after CAR T-cell infusion. Between-group comparisons were performed using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

Abbreviations: *ALL*, acute lymphoblastic leukemia; *APTT*, activated partial thromboplastin time; *CAR,* chimeric antigen receptor; *CLL*, chronic lymphocytic leukemia*; CRP*, C-reactive protein, *CRS*, cytokine release syndrome; *ECOG*, Eastern Cooperative Oncology Group performance status; *FL,* follicular lymphoma; *Hb*, hemoglobin; *ICANS*, immune effector cell–associated neurotoxicity syndrome; *IL-6*, interleukin-6; *INR*, international normalized ratio; *LDH*, lactate dehydrogenase; *MM*, multiple myeloma *; NHL,* non-Hodgkin lymphoma; *PCNS*L, primary CNS lymphoma; *PMBCL*, primary mediastinal B-cell lymphoma

Supplementary Material

Figure Legends

Figure S1: Association of CAR T-cell (axi-cel) expansion, assessed by droplet digital polymerase chain reaction (dPCR), with fibrinogen nadir and CRS severity. (**A**) Association between peak axi-cel levels and fibrinogen nadir in patients with NHL receiving axi-cel. Correlations were assessed using Spearman's rank correlation. Dashed red lines indicate fibrinogen levels of 1.5 and 1.0 g/L. (**B**) Peak axi-cel levels according to CRS grade. Differences across CRS grades were assessed using the Kruskal–Wallis test. Peak axi-cel levels are displayed on a logarithmic scale. Individual dots represent patients; boxes indicate the median and IQR.

Figure S2: Association of anti-inflammatory treatment with fibrinogen nadirs and fibrinogen kinetics following tocilizumab.(**A**) Fibrinogen nadirs according to anti-inflammatory treatment. Horizontal dashed lines indicate fibrinogen levels of 1.5 and 1.0 g/L. (**B**) Fibrinogen levels from day −5 to day +15 relative to tocilizumab administration (day 0). Gray lines represent individual patients; the red line indicates the estimated mean trajectory with 95% confidence interval. Horizontal lines indicate fibrinogen levels of 1.5 and 1.0 g/L. Asterisks indicate statistically significant differences between groups ($p<0.05$, *$p<0.01$, ***$p<0.0001$). Dexa, dexamethasone.

Figure S1:

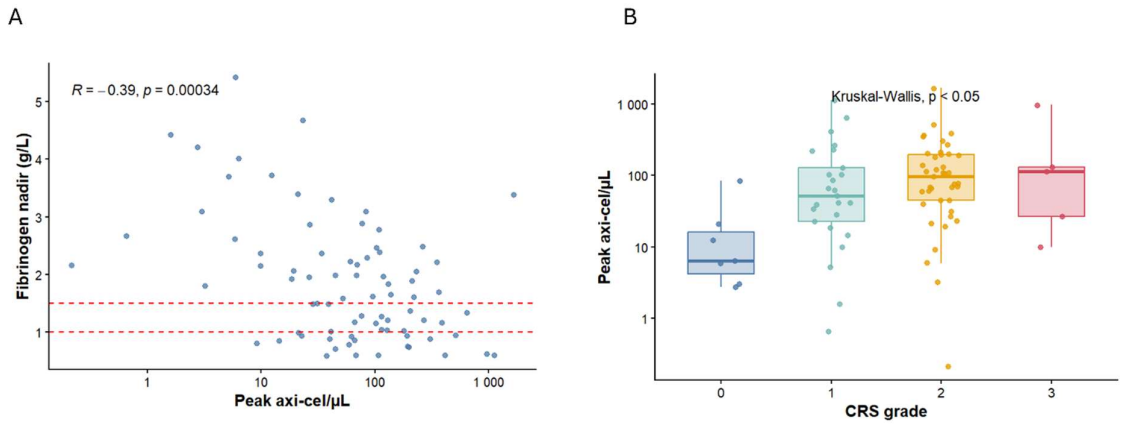


Figure S2:

