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RESEARCH LETTER

Fibrinogen levels and bleeding risk in adult extracorporeal cardiopulmonary resuscitation: multicenter observational study subanalysis

KEYWORDS
fibrinogen, hemorrhage, risk, heart arrest, cardiopulmonary resuscitation, extracorporeal membrane oxygenation

Essentials

- Hypofibrinogenemia frequently occurs in extracorporeal cardiopulmonary resuscitation (ECPR) and may heighten bleeding risk. This subanalysis of a multicenter observational study (SAVE-J II) included 2,100 adult patients receiving ECPR after out-of-hospital cardiac arrest at 36 facilities in Japan.
- Overall, 7.5% of patients experienced non-cannulation hemorrhagic complications, and those with fibrinogen levels below 140 mg/dL at ECPR initiation faced significantly higher bleeding risk. These findings underscore the importance of monitoring and managing fibrinogen levels in ECPR to mitigate hemorrhagic events and improve patient outcomes.

1 | INTRODUCTION

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is an essential life-support system in critical care specifically engineered to assist cardiac and respiratory function by externally maintaining blood perfusion and oxygenation [1].

However, the invasive nature of VA-ECMO introduces considerable risks, including fatal hemorrhagic complications that primarily result from consumptive coagulopathy, which significantly reduces the fibrinogen concentration [2,3]. These complications often necessitate further invasive procedures, underscoring the critical need for effective coagulation management [4].

The Extracorporeal Life Support Organization guidelines recommend maintaining fibrinogen at ≥150 mg/dL for VA-ECMO patients [5,6], with many institutions using 200 mg/dL as the standard [7]. Despite the guidelines, high-quality research supporting the recommendations is lacking. While one study found that 200 mg/dL fibrinogen does not pose a bleeding risk, the specific fibrinogen levels associated with bleeding risk have not been investigated [8]. Additionally, increased blood product use may worsen outcomes, suggesting a need for more conservative fibrinogen management strategies [9].

This study aimed to explore the association between initial fibrinogen at extracorporeal cardiopulmonary resuscitation (ECPR) initiation and subsequent bleeding complications in VA-ECMO patients following out-of-hospital cardiac arrest.

2 | METHODS

This study was a detailed subanalysis of the Study of Advanced life support for Ventricular fibrillation with Extracorporeal circulation in

Japan (SAVE-J II) study [10], which was a large-scale, multicenter, observational study exploring the efficacy of ECPR in Japanese patients who suffered out-of-hospital cardiac arrest. The SAVE-J II database includes intensive care unit records from 36 participating Japanese facilities over 6 years from January 1, 2013, to December 31, 2018.

Only adult patients aged ≥18 years who received ECPR immediately upon emergency admission to any of the participating centers after experiencing out-of-hospital cardiac arrest were included. For this study, we included all patients who were administered VA-ECMO after cardiac arrest. We meticulously recorded the fibrinogen concentration at ECPR initiation and monitored the patients to identify any hemorrhagic complications. The details of the variables used in the study in Supplementary Table S1.

The primary outcome of this study was the time from hospitalization to the onset of hemorrhagic complications. Hemorrhagic events were defined as computed tomography-confirmed intracerebral hemorrhage, mediastinal hemorrhage, intraabdominal organ hemorrhage, and gastrointestinal hemorrhage requiring transfusion or intervention. VA-ECMO insertion-related complications were recorded separately. Study endpoints included VA-ECMO discontinuation and death.

Fibrinogen levels measured at admission were categorized into 7 groups: ≤100 mg/dL, 101 to 120 mg/dL, 121 to 140 mg/dL, 141 to 160 mg/dL, 161 to 180 mg/dL, 181 to 200 mg/dL, and >200 mg/dL.

Continuous variables are presented as mean ± SD, and categorical variables as frequency (%). The cumulative incidence of hemorrhagic complications was calculated with mortality as a competing risk. Univariate and multivariate cause-specific Cox proportional hazards models were used to analyze time to bleeding complications, with predetermined fibrinogen cutoffs and other risk factors as covariates. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Variables with $P < .05$ in univariate analysis were considered potential risk factors. Spearman's correlation coefficient (≥.4 indicating correlation) was used to assess multicollinearity. Uncorrelated variables were included in the multivariate model, where significant variables were identified as risk factors. No sample size calculation or multiple testing adjustment was performed due to the study's exploratory nature. Missing data were neither imputed nor replaced. Analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing).

This retrospective study received ethics approval from the Clinical Ethics Committee of Fujieda Municipal General Hospital (approval number: R05-29). Participant data were anonymized, and an opt-out consent procedure was implemented at each facility due to the retrospective and preexisting nature of the data.

3 | RESULTS

Of the 2157 patients initially enrolled, 2100 were included in the final analysis after excluding 57 due to missing data on hemorrhagic complications. The demographic details and clinical outcomes segmented by the presence or absence of hemorrhagic complications are presented in Table 1.

Of the 2100 cases, hemorrhagic complications unrelated to VA-ECMO cannulation occurred in 158 cases (7.5%), with a median time of 1 day from admission to the onset of these complications, which was the focus of this study.

In the group with fibrinogen levels below 100 mg/dL, 21 of 144 patients (14.58%) developed hemorrhagic complications. The incidence of hemorrhagic complications in other groups was as follows: 2 of 69 patients (2.90%) in the 101 to 120 mg/dL group, 12 of 103 patients (11.65%) in the 121 to 140 mg/dL group, 10 of 124 patients (8.06%) in the 141 to 160 mg/dL group, 9 of 164 patients (5.49%) in the 161 to 180 mg/dL group, and 10 of 142 patients (7.04%) in the 181 to 200 mg/dL group. In the reference group (above 200 mg/dL), 68 of 1083 patients (6.28%) experienced hemorrhagic complications.

The univariate Cox regression analysis identified several potential risk factors for bleeding, including age ($P = .002$), adrenaline use ($P = .03$), return of spontaneous circulation before ECMO insertion ($P = .002$), arterial cannula size ($P = .04$), low flow time ($P = .001$), and platelet count on arrival ($P = .001$). Spearman's rank correlation coefficient was used to assess multicollinearity among these variables, revealing no correlations (Supplementary Table S2).

Using a multivariate Cox regression analysis with log-transformed fibrinogen levels, we found that lower fibrinogen levels were significantly associated with an increased risk of hemorrhagic complications (HR, 2.83; 95% CI, 1.19-2.83; $P = .008$).

Using a multivariate Cox regression analysis, HRs were calculated for 6 fibrinogen level groups (101 to 120 mg/dL, 121 to 140 mg/dL, 141 to 160 mg/dL, 161 to 180 mg/dL, and 181 to 200 mg/dL, as well as levels below 100 mg/dL), with levels equal to or above 200 mg/dL serving as the reference group.

Two fibrinogen level groups—below 100 mg/dL and 121 to 140 mg/dL—were associated with increased HRs (HR, 2.32; 95% CI, 1.24-4.36 and HR, 1.91; 95% CI, 0.97-3.76, respectively), suggesting a higher risk of hemorrhagic complications compared with the reference group (>200 mg/dL). The 101 to 120 mg/dL group demonstrated a lower HR (HR, 0.34; 95% CI, 0.05-2.52); however, due to the small sample size and few outcome events in this category, these findings should be considered preliminary and interpreted with caution (Table 2, Supplementary Figure S1).

4 | DISCUSSION

This study examined the association between fibrinogen at ECPR initiation and hemorrhagic complications in VA-ECMO patients following out-of-hospital cardiac arrest. Patients with fibrinogen below 140 mg/dL had a significantly higher risk of hemorrhage.

The incidence of hemorrhagic complications during ECPR has been reported to range from 8% to 70% in previous studies [11]. In contrast, our study observed an incidence of hemorrhagic complications of 7.5%, which is lower compared with prior research. This

TABLE 1 Characteristics of patients with out-of-hospital cardiac arrest who underwent extracorporeal cardiopulmonary resuscitation.

Variable	Category or (unit)	Overall n = 2,100	Bleed (−) n = 1,942	Bleed (+) n = 158	p value
Age	(y)	59.2 (14.0)	59.0 (14.1)	62.3 (12.5)	.20
Sex	Female	378 (17.8)	353 (18.2)	25 (15.8)	.47
	Male	1722 (82.2)	1589 (81.8)	133 (84.2)	
Medical history	Hypertension	648 (30.1)	590 (30.4)	57 (36.1)	.15
	Diabetes mellitus	406 (19.3)	374 (19.3)	32 (20.3)	.75
	Hyperlipidemia	221 (10.5)	202 (10.4)	19 (12.0)	.50
	Heart disease	494 (23.5)	448 (23.1)	46 (29.1)	.10
	Brain disease	137 (6.5)	125 (6.4)	12 (7.6)	.51
	Chronic renal failure	105 (5.0)	102 (5.3)	3 (1.9)	.08
	Dementia	406 (19.3)	374 (19.3)	32 (20.3)	.96
	Other	534 (25.4)	493 (25.4)	41 (25.9)	.85
Oral medication	Antiplatelet	238 (11.3)	214 (11.0)	24 (15.2)	.12
	Anticoagulant	103 (4.9)	94 (4.8)	9 (5.7)	.57
Onset to arrival	(min)	35.3 (18.5)	35.3 (18.6)	36.3 (17.5)	.58
Low flow time	(min)	61.2 (24.9)	60.4 (21.9)	70.8 (47.2)	<.001
Body temperature on arrival in case of ROSC	(°C)	34.3 (3.1)	34.3 (3.2)	34.6 (2.1)	.31
Systolic blood pressure on arrival in case of ROSC	(mm Hg)	109.4 (38.8)	112.0 (36.8)	97.8 (40.7)	.31
Diastolic blood pressure on arrival in case of ROSC	(mm Hg)	70.3 (28.9)	73.2 (27.9)	50.9 (21.9)	.05
Glasgow Coma Scale score on arrival		3.1 (1.3)	3.2 (1.3)	3.3 (1.3)	.40
Heart rate on arrival	(bpm)	103.0 (36.9)	104.2 (36.4)	97.3 (40.9)	.61
Performance status	0	1768 (87.5)	1644 (88.4)	124 (92.8)	.23
	1	187 (8.9)	178 (9.3)	9 (5.4)	
	2	30 (1.4)	29 (1.5)	1 (0.6)	
	3	14 (0.6)	12 (0.6)	2 (1.2)	
	4	1 (0.04)	1 (0.1)	0 (0.0)	
Bystander CPR	No	902 (43.0)	831 (43.0)	71 (41.5)	.75
	Yes	1202 (57.0)	1101 (57.0)	100 (58.5)	
Waveform on arrest	Asystole	207 (9.9)	193 (10.1)	14 (8.9)	.64
	Pulseless electrostatic activity	565 (26.9)	519 (27.1)	46 (29.1)	
	Ventricular fibrillation	1260 (60.0)	1163 (60.7)	97 (61.4)	
	Ventricular tachycardia	42 (2.0)	41 (2.1)	1 (0.6)	
Witness	No	472 (22.5)	432 (22.4)	40 (25.3)	.43
	Yes	1615 (76.9)	1497 (77.6)	118 (74.7)	
AED use	No	834 (39.7)	779 (40.6)	55 (34.8)	.18
	Yes	1244 (59.2)	1141 (59.4)	103 (65.2)	

(Continues)

TABLE 1 (Continued)

Variable	Category or (unit)	Overall n = 2,100	Bleed (−) n = 1,942	Bleed (+) n = 158	p value
Diagnosis	External	101 (4.8)	99 (5.1)	2 (1.3)	.05
	Cardiogenic	1395 (66.4)	1394 (71.9)	122 (77.2)	
	Noncardiogenic	183 (8.7)	166 (8.6)	17 (10.8)	
	Unknown	298 (14.2)	281 (14.5)	17 (10.8)	
Adrenaline use	No	1343 (64.0)	1254 (65.7)	89 (57.1)	.04
	Yes	723 (34.4)	656 (34.3)	67 (42.9)	
IABP insertion	No	920 (42.8)	885 (45.0)	35 (20.2)	.43
	Yes	1220 (58.1)	1082 (55.0)	138 (79.8)	
Portable X-ray	No	1260 (60.0)	1171 (63.1)	89 (59.7)	.43
	Yes	745 (35.4)	685 (36.9)	60 (40.3)	
Puncture method	Seldinger	2018 (96.0)	1865 (97.4)	153 (99.4)	.01
	Surgery	48 (2.3)	48 (2.5)	0 (0.0)	
ROSC before arrival	No	1799 (85.7)	1678 (87.9)	121 (77.6)	.001
	Yes	265 (12.6)	230 (12.1)	35 (22.4)	
Venous cannula size	(Fr)	20.6 (1.4)	20.6 (1.4)	20.6 (1.5)	.45
Arterial cannula size	(Fr)	15.9 (1.4)	15.9 (1.4)	16.1 (1.7)	.02
Fibrinogen on arrival	(mg/dL)	230.7 (108.8)	232.6 (108.5)	205.7 (114.6)	.006
aPTT on arrival	(s)	118.3 (64.1)	117.3 (64.1)	124.6 (62.5)	.28
Platelet count on arrival	($\times 10^3/\mu L$)	15.4 (7.4)	15.6 (7.5)	13.6 (5.8)	.002

AED, automated external defibrillator; aPTT, activated partial thromboplastin time; CPR, cardiopulmonary resuscitation; IABP, intraaortic balloon pump; Low flow time, the duration from cardiac arrest to the initiation of venoarterial extracorporeal membrane oxygenation, excluding patients who achieved return of spontaneous circulation upon hospital arrival and those who underwent venoarterial extracorporeal membrane oxygenation implementation outside the emergency department; ROSC, return of spontaneous circulation.

discrepancy may be due to the exclusion of hemorrhagic complications occurring during cannulation.

In out-of-hospital cardiac arrest, 62% of patients develop disseminated intravascular coagulation, and 22% show hyperfibrinolysis, indicating a common predisposition to hypofibrinogenemia, independent of ECPR [12]. This pattern persists in VA-ECMO, where disseminated intravascular coagulation and hyperfibrinolysis affect fibrinogen levels [13–15]. Postresuscitation hyperfibrinolysis is marked by increased tissue plasminogen activator and decreased α2-plasmin inhibitor [16–18] resulting from cardiac arrest conditions and adrenaline-induced tissue plasminogen activator secretion during resuscitation [19,20]. In our cardiac arrest patients, these mechanisms likely contributed to low fibrinogen levels. Beyond coagulation enhancement, fibrinogen is crucial for platelet aggregation [21] and wound healing [22], and its levels during VA-ECMO are determined by both coagulation consumption and fibrinolytic degradation.

TABLE 2 Results of the multivariate Cox proportional hazards analysis.

Fibrinogen on arrival	HR (reference above 200 mg/dL)	Lower 95% CI	Upper 95% CI	*P* value
Below 100 mg/dL	2.32	1.24	4.36	0.009
101-120 mg/dL	0.34	0.05	2.52	0.29
121-140 mg/dL	1.91	0.97	3.76	0.06
141-160 mg/dL	0.92	0.36	2.33	0.86
161-180 mg/dL	0.85	0.38	1.90	0.70
181-200 mg/dL	0.99	0.45	2.20	0.99

HR, hazard ratio; CI, confidence interval.

Our study identifies a specific fibrinogen threshold associated with increased bleeding risk, supporting guideline recommendations to maintain fibrinogen at ≥150 mg/dL [5,6]. However, we did not explore the underlying mechanisms of hypofibrinogenemia or evaluate therapeutic interventions like cryoprecipitate or antifibrinolytics. Future studies should investigate these aspects to inform clinical practice.

This study has several limitations. It was limited to ECPR patients after out-of-hospital cardiac arrest, so the findings may not apply to broader VA-ECMO cases. Bleeding mechanisms are complex; some events may stem from cardiopulmonary resuscitation-induced trauma or procedural interventions, complicating attribution solely to coagulation abnormalities like low fibrinogen. Factors not captured, such as

anticoagulation or thrombolytic therapy—especially in conditions like pulmonary embolism—may have influenced bleeding risk. Reverse causality, where bleeding lowers fibrinogen, is a potential concern. Moreover, early hepatic failure in severe cases may decrease fibrinogen synthesis, potentially confounding our findings. However, in our study, hemorrhagic complications occurred at a median of 1 day after ECMO initiation. This timing suggests that hepatic failure may not have fully manifested at the time of bleeding. Additionally, variations in the timing of fibrinogen measurements upon VA-ECMO initiation across facilities may have impacted the robustness of the results, and this factor should be considered when interpreting the study findings. Although most hemorrhagic events occurred within 3 days of admission, the inclusion of cases up to day 6 and daily fibrinogen measurements limited our ability to establish a clear link between initial fibrinogen and bleeding complications. The lack of day 2 fibrinogen data further restricted our analysis. Future studies should track fibrinogen dynamics more frequently during VA-ECMO to determine if maintaining specific levels reduces bleeding risk.

5 | CONCLUSIONS

This study showed that patients with fibrinogen levels at or below 140 mg/dL at the start of ECPR had a higher risk of hemorrhagic complications. Future studies should aim to continuously monitor fibrinogen levels after initiation of ECPR and develop comprehensive guidelines for fibrinogen management during the ECPR period to improve patient outcomes.

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AUTHOR CONTRIBUTIONS

S.K. was the principal author who conceived and designed the study, collected and analyzed data, and drafted the manuscript. E.N. helped conceive and design the study, analyzed and interpreted data, and revised the manuscript. Y.T. interpreted data and revised the manuscript. T.U. and H.S. revised the manuscript. A.I., T.H., T.S., and Y.K., on behalf of the Study of Advanced life support for Ventricular fibrillation with Extracorporeal circulation in Japan (SAVE-J II) Study Group, collected data. All authors read and approved the final manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

We utilized ChatGPT, a language model developed by OpenAI, to assist with grammar, word choice, and structural editing during the preparation of this manuscript.

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SUPPORTING INFORMATION

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