Trauma Surgery & Acute Care Open

Risk factors for severe lower extremity ischemia following venoarterial extracorporeal membrane oxygenation: an analysis using a nationwide inpatient database

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/tsaco-2021-000776).

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Received 24 May 2021
Accepted 31 March 2022

To cite: Honda A, Michihata N, Iizuka Y, *et al*. *Trauma Surg Acute Care Open* 2022;**7**:e000776.

ABSTRACT

Objectives Venoarterial extracorporeal membrane oxygenation is increasingly being used as a life-saving modality in critically ill patients. Despite its necessity, severe lower extremity ischemia associated with venoarterial extracorporeal membrane oxygenation remains a potentially devastating complication. We aimed to investigate the incidence and risk factors for severe lower extremity ischemia requiring fasciotomy or amputation following venoarterial extracorporeal membrane oxygenation.

Methods All patients who received venoarterial extracorporeal membrane oxygenation during hospitalization were identified in a Japanese national inpatient database from July 1, 2010 to March 31, 2018. The primary outcome was occurrence of severe lower extremity ischemia that required fasciotomy or amputation. We used cause-specific proportional hazard models to examine the associations between potential risk factors and outcomes. We also performed a competing-risk analysis to estimate the cause-specific HR for severe lower extremity ischemia using a multivariable competing-risk Cox proportional hazard model with adjustment for potential risk factors.

Results A total of 29 231 patients who underwent venoarterial extracorporeal membrane oxygenation during hospitalization were identified. Of these, 98 patients (0.3%) had lower extremity ischemia requiring fasciotomy or amputation. The young group (≤18 years) had a significantly higher proportion of severe lower extremity ischemia cases than the adult (19–59 years) and elderly (≥60 years) groups (1.4%, 0.5%, and 0.2%, respectively; $p<0.001$). In a multivariable competing-risk Cox proportional hazards regression model, younger age (HR 3.06; 95% CI 1.33 to 7.02; $p<0.008$) and consciousness disturbance on admission (HR 2.53; 95% CI 1.60 to 3.99; $p<0.001$) were significantly associated with higher likelihood of severe lower extremity ischemia.

Conclusion In this study using a nationwide database, younger age and consciousness disturbance on admission were associated with higher risk of severe lower extremity ischemia following venoarterial extracorporeal membrane oxygenation.

Level of evidence Level III—prognostic and epidemiological.

Key messages

What is already known on this topic

- Lower extremity ischemia is one of the potentially devastating complications associated with venoarterial extracorporeal membrane oxygenation (VA-ECMO).
- Fasciotomy or amputation may require when acute compartment syndrome occurs following VA-ECMO of the affected limbs.

What this study adds

- Our study revealed that 1.4% of young patients required invasive treatment following VA-ECMO in Japan.
- Younger age and consciousness disturbance on admission were possible risk factors for severe lower extremity ischemia.

How this study might affect research, practice or policy

- Understanding the possible risk factors might help better management of VA-ECMO therapy and reduce invasive treatment, especially in younger patients.

BACKGROUND

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used as a life-saving modality in critical patients with refractory cardiopulmonary failure that is potentially reversible or treatable cardiac disease.[1,2] During the past decade, the annual numbers of ECMO procedures in the USA and Germany have increased by more than threefold.[3,4] Despite its pivotal role as a life-saving modality, VA-ECMO has grave complications including bleeding, acute kidney injury, and vascular structure insult.[5–7]

Lower extremity ischemia (LEI) is one of the potentially devastating complications associated with VA-ECMO. LEI can lead to acute compartment syndrome that requires emergency fasciotomy or—in more severe conditions—amputation of the affected limb.[8,9] In previous studies, the proportions of fasciotomy and amputation following VA-ECMO were 9%–13% and 2%–3.9%, respectively.[10–12] However, the risk factors for LEI following VA-ECMO remain largely elusive. Prior studies indicated potential risk factors such as young age, female sex, diabetes mellitus, respiratory disease, and atherosclerotic disease[6 13 14]; however, their sample sizes were insufficient to draw solid conclusions.

To address this issue, we conducted an observational study using a nationwide inpatient database in Japan. The aims of the present study were to: (1) investigate the occurrence of severe LEI following VA-ECMO requiring fasciotomy or amputation and (2) examine its risk factors.

METHODS

Data source

We used the Diagnosis Procedure Combination database, which covers approximately 90% of all tertiary-care emergency hospitals in Japan.[15–18] The database includes national administrative claims data and discharge data for all inpatients at >1000 participating hospitals. The database includes the following patient information: age and sex, body weight and height, diagnosis, comorbidities at admission, complications after admission, medical procedures, length of hospital stay, discharge status, and in-hospital death. Diagnosis, comorbidities, and complications are recorded using International Classification of Diseases, Tenth Revision (ICD-10) codes. Dates of hospital admission, surgery, bedside procedures, drugs administered, VA-ECMO initiation, weaning from VA-ECMO, and hospital discharge are recorded using a uniform data submission form. The validity of diagnoses and procedures in the database has been established.[19] The specificity and sensitivity for diagnoses were 96% and 50%–80%, respectively, while the specificity and sensitivity for procedures were both >90%.[19]

Participants

We included all patients who received VA-ECMO during hospitalization from July 1, 2010 to March 31, 2018 (figure 1). We excluded patients who: (1) were admitted with pneumonia, (2) had multiple injuries, (3) underwent fasciotomy or amputation prior to VA-ECMO, or (4) were admitted with diabetes mellitus-related gangrene. We excluded patients who were admitted with pneumonia because venovenous (VV)-ECMO is the first choice of treatment in these patients, and we were unable to distinguish between VA-ECMO and VV-ECMO in the present data. The primary outcome was occurrence of severe LEI that

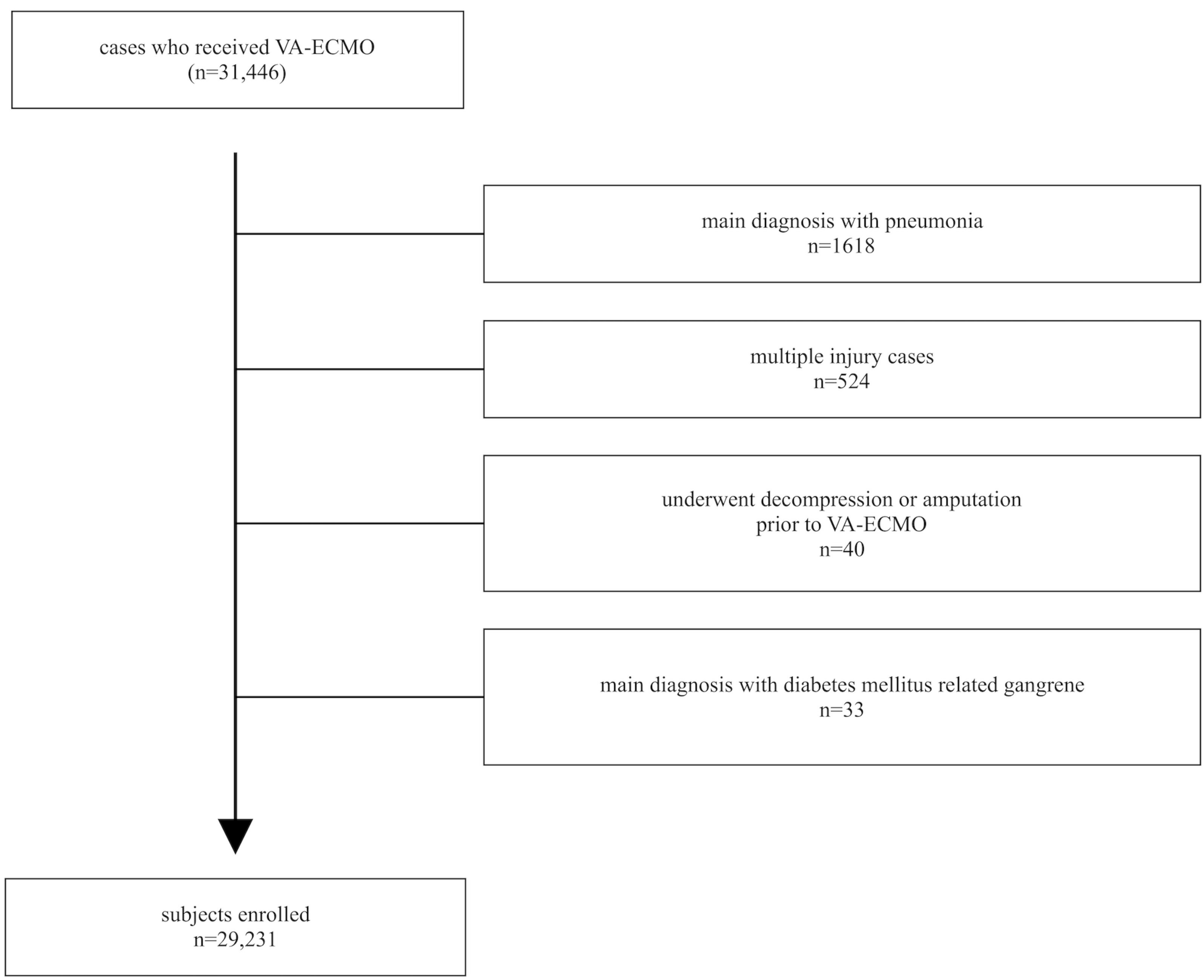

Figure 1 Flow chart of the study. Patients who were admitted with pneumonia, had multiple injuries, underwent fasciotomy or amputation prior to venoarterial extracorporeal membrane oxygenation, or were admitted with diabetes mellitus-related gangrene were excluded. VA-ECMO, venoarterial extracorporeal membrane oxygenation.

required fasciotomy or amputation. We identified complications of LEI and compartment syndrome using ICD-10 codes (M62.2, T79.6) and fasciotomy, amputation, or disarticulation using Japanese original codes.

Baseline variables included age, sex, body mass index (BMI), diabetes mellitus (E10–14), chronic lung disease (J40–47), history of cerebrovascular disease (I60–69), history of cardiac disease (I60–69), pre-ECMO cardiac arrest, use of anticoagulation (heparin, nafamostat, and argatroban) at the start of VA-ECMO, Charlson Comorbidity Index,[20] hospital volume, consciousness disturbance on admission, and ambulance use. We divided the eligible patients into three groups according to age: ≤18 years (young group), 19–59 years (adult group), and ≥60 years (elderly group). BMI was categorized into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), and overweight (≥25.0 kg/m^2). Hospital volume of VA-ECMO was categorized into tertiles (low, medium, and high) such that the numbers of patients in the three categories were almost equal. We used the Japan Coma Scale (JCS) score (0, alert consciousness; 1–3, dizziness; 10–30, somnolence; 100–300, coma) to categorize consciousness disturbance on admission into binomial valuables of alert (JCS score, 0) or not (JCS score >0).[21] JCS status is well correlated with Glasgow Coma Scale scores.[22]

Statistical analysis

We used a t-test for comparisons of continuous variables, and the χ^2 test or Fisher's exact test for categorical variables. Patient demographic data were compared between the young (≤18 years), adult (19–59 years), and elderly (≥60 years) groups. The log-rank test was used to compare cause-specific hazard functions among the groups. We further carried out cause-specific proportional hazard models to examine the associations between potential risk factors and outcomes.[23 24] In the present study, occurrence of in-hospital death was regarded as a competing risk for fasciotomy or amputation. We therefore estimated the cumulative incidences of severe LEI and competing risk using a cause-specific hazard function.[23 24] The cumulative incidence was defined as the probability of experiencing the outcome within a certain time and not experiencing a competing event within the same period. We compared the cumulative incidence using the log-rank test. We also performed a competing-risk analysis to estimate the cause-specific HR for severe LEI using a multivariable competing-risk Cox proportional hazard model with adjustment for potential risk factors.[24 25] The following sensitivity analyses were performed. First, because it was difficult to completely remove the bias arising from the competing risk of death, we performed a sensitivity analysis on surviving patients who were discharged. Second, to make the indications for VA-ECMO clearer, we excluded patients who were weaned from ECMO within 2 days, were aged <12 years, or died within 2 days after admission. Third, we excluded patients who did not receive anticoagulants at the start of VA-ECMO. Fourth, we excluded patients who underwent cardiac surgery, as there may have been an option for central cannulation. All statistical analyses were performed with STATA V.15 software (StataCorp, College Station, Texas, USA). A two-tailed significance level of $p<0.05$ was used in all analyses.

RESULTS

We identified 29 231 eligible patients who received VA-ECMO from July 1, 2010 to March 31, 2018 (males, 71%; mean age±SD, 62±18 years). The average annual number of patients who received VA-ECMO was 2.9 per 100 000 inhabitants (online supplemental table S1). Cardiogenic shock was the most common diagnosis at admission (85%). Table 1 shows the demographic characteristics of the patients. In the sample, 948 patients (3.2%) were in the young group, but the majority of patients (65%) were in the elderly group. The young group was less likely to have consciousness disturbance on admission than the adult and elderly groups (online supplemental table S2).

Table 2 shows the outcomes according to age categories. The proportions of overall in-hospital death and 30-day death were 70% and 61%, respectively. A total of 98 patients (0.3%) received fasciotomy or amputation. Seven patients (0.7%) in the young group underwent amputation. Regarding age categories, the young group had significantly lower occurrence of death than the adult and elderly groups (overall in-hospital death, 55%, 66%, and 72%, $p<0.001$; 30-day death, 36%, 59%, and 64%, $p<0.001$), higher proportion of severe LEI (1.4%, 0.5%, and 0.2%, $p<0.001$), longer duration of VA-ECMO (4 days, 1 day, and 1 day, $p<0.001$), and longer hospital stay (72 days, 29 days, and 25 days, $p<0.001$).

Figure 2 shows the cumulative incidences of severe LEI and competing risk among the age categories. Overall, median observation period was 11 days (IQR, 2–35 days). During the observation period, 17 911 patients (61%) died. The majority of fasciotomy or amputation procedures were performed within 1 week after starting VA-ECMO (median, 6 days; IQR, 2–19 days). Data for the observational period, timing of fasciotomy or amputation after starting VA-ECMO, timing of death after starting VA-ECMO, proportion of patients who underwent leg intervention during ECMO, and proportion of patients who underwent cardiac surgery are shown in online supplemental table S3.

Table 3 shows the multivariable competing-risk Cox proportional hazards regression model for severe LEI. Younger age (HR, 3.06; 95% CI, 1.33 to 7.02; p=0.008) and consciousness disturbance on admission (HR, 2.53; 95% CI, 1.60 to 3.99; $p<0.001$) were significantly associated with higher likelihood of severe LEI. The sensitivity analyses produced similar results to those in the main analysis (online supplemental tables S4–S9).

DISCUSSION

The present study using a nationwide inpatient database revealed that severe LEI requiring fasciotomy or amputation occurred in 0.3% of patients who received VA-ECMO. Notably, 1.4% of young patients required invasive treatment including amputation because of severe LEI. After adjustment for patient demographic and clinical characteristics, younger age and impaired consciousness on admission were risk factors for severe LEI.

To the best of our knowledge, this is the first nationwide study to focus on the risk factors for severe LEI in patients who received VA-ECMO during hospitalization. In previous nationwide studies, the annual incidence of VA-ECMO was 4.4 per 100 000 inhabitants in the USA[26] and 3.5 per 100 000 inhabitants in Germany.[4] Consistent with these studies, our study revealed that the average annual incidence of VA-ECMO was 2.9 per 100 000 inhabitants and increased by almost threefold from 2010 and 2017 (online supplemental table S1). Despite the pivotal role of VA-ECMO as a life-saving modality, its mortality rate remains high, and its risk of severe complications should be acknowledged.

Severe LEI has been increasingly recognized as a devastating complication following VA-ECMO, particularly in those with refractory cardiogenic shock after cardiac surgery.[6 10–12] In previous studies, the reported proportions of severe LEI following

Table 1 Demographic data of patients who received venoarterial extracorporeal membrane oxygenation

	Patient age				
	Overall	Young (≤18 years)	Adult (19–59 years)	Elderly (≥60 years)	
Demographic data	(n=29 231)	(n=948)	(n=9195)	(n=19 088)	P value
Sex, n (%)					<0.001
Male	20 860 (71)	520 (55)	6955 (76)	13 385 (70)	
Female	8371 (29)	428 (45)	2240 (24)	5703 (30)	
Body mass index (kg/m²), n (%)					<0.001
Underweight (<18.5)	2585 (11)	625 (78)	566 (8.0)	1394 (9.1)	
Normal weight (18.5–24.9)	13 127 (57)	143 (18)	3496 (50)	9488 (62)	
Overweight (≥25)	7413 (32)	29 (3.6)	2974 (42)	4410 (29)	
Comorbid conditions at admission, n (%)					
Diabetes mellitus	4904 (17)	8 (0.8)	1198 (13)	3698 (19)	<0.001
Hypertension	5858 (20)	20 (2.1)	1337 (15)	4501 (24)	<0.001
Chronic lung disease	566 (1.9)	18 (1.9)	116 (1.3)	432 (2.3)	<0.001
Cerebrovascular disease	1145 (3.9)	11 (1.2)	262 (2.8)	872 (4.6)	<0.001
Cardiac disease	18 300 (63)	159 (17)	3432 (37)	5472 (29)	<0.001
Atherosclerotic disease	6649 (23)	24 (2.5)	1639 (18)	4986 (26)	<0.001
At least one comorbidity	21 571 (74)	477 (50)	6465 (70)	14 629 (77)	<0.001
Episode of arrest at admission, n (%)	4150 (14)	75 (7.9)	1612 (18)	2463 (13)	<0.001
Use of anticoagulants, n (%)	19 617 (67)	424 (45)	6824 (74)	12 369 (65)	<0.001
Charlson Comorbidity Index update category, n (%)					<0.001
≤2	27 476 (94)	931 (98)	8776 (95)	17 769 (93)	
≥3	1755 (6.0)	17 (1.8)	419 (4.6)	1319 (6.9)	
Consciousness on admission, n (%)					<0.001
Alert	13 624 (47)	596 (63)	3406 (37)	9622 (50)	
Disturbance	15 607 (53)	352 (37)	5789 (63)	9466 (50)	
Ambulance use, n (%)	20 141 (69)	425 (45)	7021 (76)	12 695 (67)	<0.001
Hospital volume (per year), n (%)					<0.001
Low (0.75–17.4)	10 146 (35)	214 (23)	3105 (34)	6827 (36)	
Medium (17.5–41.4)	9884 (34)	389 (41)	3081 (34)	6414 (34)	
High (≥41.5)	9201 (31)	345 (36)	3009 (33)	5847 (31)	

VA-ECMO in adult and pediatric patients ranged from 8.6% to 33%[6 10–12 27] and from 9.5% to 19%,[28–30] respectively. However, these prior studies lacked a unanimous definition of severe LEI and were mostly associated with small sample sizes or conducted in limited settings. Conversely, our results showed that severe LEI occurred in <1% of patients who received VA-ECMO. This marked difference may be attributable, at least in part, to increased recognition of this complication and improved management of VA-ECMO. In Japan, ultrasound-guided cannulation[31 32] and monitoring of lower extremity blood flow using near-infrared spectroscopy (NIRS)[33] have been widely used for ECMO and management of LEI. NIRS is used to determine whether distal perfusion catheter is needed.

The precise mechanism and risk factors for LEI following VA-ECMO remain unclear. Previous reports have proposed two mechanisms for severe LEI: peripheral circulation insufficiency on the same side as the cannulation[6] and raised intracompartment pressure within a fascial or osteofascial compartment caused by

Table 2 Adverse outcomes among age categories

		Patient age			
	Overall	Young (≤18 years)	Adult (19–59 years)	Elderly (≥60 years)	
Adverse outcomes	(n=29 231)	(n=948)	(n=9195)	(n=19 088)	P value
In-hospital death, n (%)	20 370 (70)	521 (55)	6037 (66)	13 812 (72)	<0.001
Died within 30-day, n (%)	17 910 (61)	339 (36)	5410 (59)	12 161 (64)	<0.001
Severe lower extremity ischemia, n (%)	98 (0.3)	13 (1.4)	42 (0.5)	43 (0.2)	<0.001
Fasciotomy	42 (0.1)	6 (0.6)	20 (0.2)	16 (0.1)	<0.001
Amputation at any level	60 (0.2)	7 (0.7)	25 (0.3)	28 (0.1)	<0.001
VA-ECMO duration (days), mean (±SD)	2.9 (8.6)	8.6 (19)	3.3 (12)	2.4 (5.2)	<0.001
Length of hospital stay, (days), mean (±SD)	28 (54)	72 (125)	29 (61)	25 (42)	<0.001

VA-ECMO, venoarterial extracorporeal membrane oxygenation.

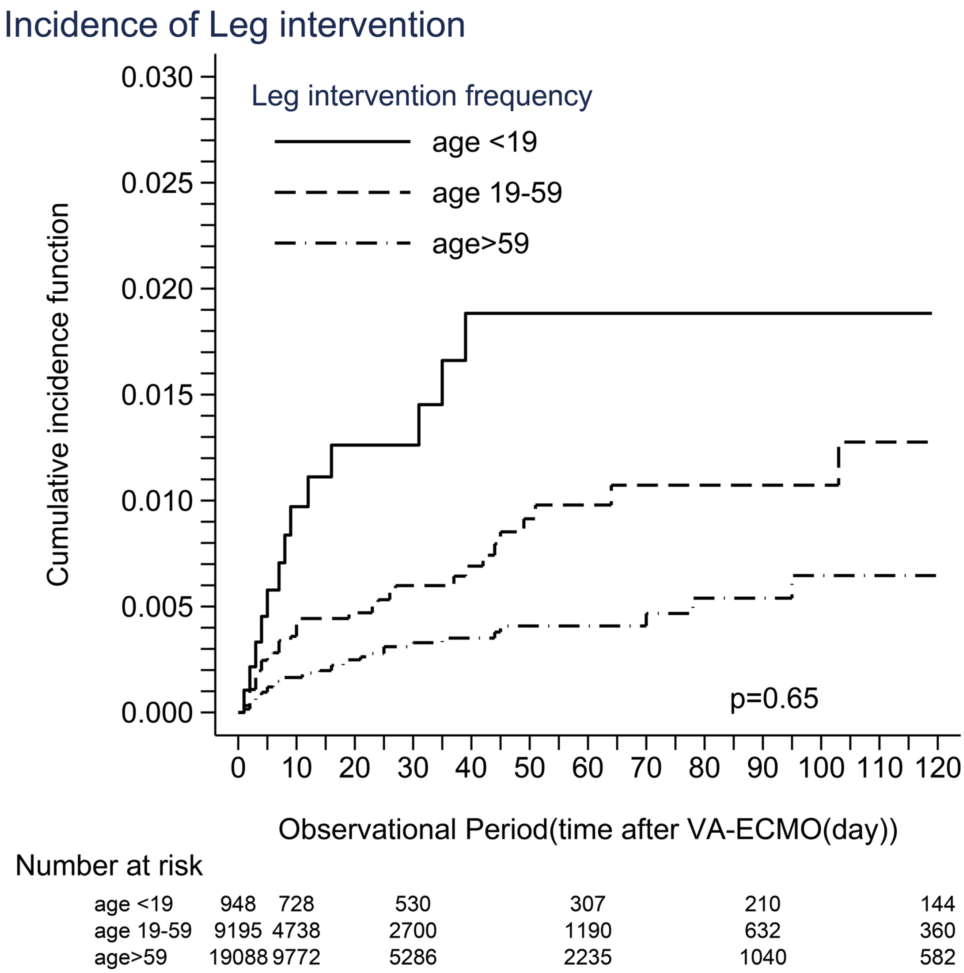

Figure 2 Kaplan-Meier curves of fasciotomy or amputation among the age categories during the observation period. VA-ECMO, venoarterial extracorporeal membrane oxygenation.

an increased volume within a fixed compartment size.[9] Children and women were reported to be at high risk for LEI through immature development of arteries and collateral blood flow.[34, 35] Other conditions like diabetes mellitus, atherosclerotic disease, and respiratory disease were also reported as risk factors for LEI, presumably arising from degenerative changes to peripheral arteries and states of chronic hypoxia.[6 13] In the present study, children and adolescent patients were at higher risk of severe LEI than adult or elderly patients. Prior studies showed that a relative lack of collateral circulation in young patients may accelerate ischemic compartment syndrome.[34 35] Furthermore, McQueen *et al*[36] described that the stronger fascial structures, which the younger patients have, may lead to exacerbation of compartment syndrome. Because of the difficulties associated with proper cannulation of immature arteries, young patients are at risk of vascular structure insults (such as hemorrhage, vascular injury, mismatch between diameter of femoral artery and cannula size) .[13 37] However, many elderly people are also at risk because they have relatively small vessel diameters owing to calcification. Smaller catheters are routinely placed under ultrasound guidance when the vessel diameter appears small in patients such as young people, women, and elderly people with calcified vessels. Considering that ultrasound-guided cannulation is a relatively safe procedure, musculoskeletal structural reasons such as stronger fascia in younger patients, rather than difficulty in cannulation, may be a possible reason.

The present study showed that consciousness disturbance on admission was another factor associated with high risk of severe LEI. Presumably, patients with consciousness disturbance are likely to have more severe systemic conditions (such as severe cardiogenic shock) than those without consciousness disturbance. The lack of consciousness was presumably due to the severity and presence of shock on admission. Notably, in-hospital death was significantly higher in patients with consciousness disturbance on admission than in those without (online supplemental table S2). Such patients with more severe conditions are considered a priority for life-saving management regardless of their local condition, including suboptimal peripheral blood flow and leg ischemia. Although these patients are less likely to survive, closer attention should be paid to possible occurrence of severe LEI.

Several limitations should be acknowledged in the present study. First, we were unable to obtain data on the indications for VA-ECMO. In Japan, as in the USA and other Western countries, the indications for VA-ECMO are based on the Extracorporeal Life Support Organization guidelines. However, based on our sensitivity analysis, we believe that the indication bias may have had little influence on the evaluation of severe complications following VA-ECMO. Second, we were unable to obtain information on catheter size, insertion technique, side for catheter insertion, use of central cannulation, use of distal perfusion catheter, and whether VV-ECMO or VA-ECMO was performed. Although variations in technique may affect outcomes, a

Table 3 Risk factors for severe lower extremity ischemia following VA-ECMO using a multivariable competing-risk Cox regression model

Risk factor	Cause-specific HR	95% CI	P value
Age (years)			
19–59	Reference		
≤18	**3.08**	**1.34 to 7.07**	**0.008***
≥60	**0.57**	**0.36 to 0.92**	**0.021***
Sex			
Female	Reference		
Male	1.06	0.66 to 1.70	0.812
Body mass index (kg/m^2)			
Normal weight (18.5–24.9)	Reference		
Underweight (<18.5)	0.93	0.45 to 1.96	0.865
Overweight (≥25.0)	1.26	0.78 to 2.04	0.352
Comorbid conditions			
Diabetes mellitus	1.21	0.70 to 2.10	0.498
Atherosclerotic disease	0.64	0.36 to 1.18	0.152
Episode of arrest at admission	0.82	0.43 to 1.59	0.564
VA-ECMO duration (days)	0.97	0.93 to 1.01	0.166
Consciousness on admission			
Alert	Reference		
Disturbance	**2.50**	**1.58 to 3.95**	**<0.001***

*P<0.05.
VA-ECMO, venoarterial extracorporeal membrane oxygenation.

previous large-population study found that percutaneous techniques had similar rates of limb ischemia to surgical techniques.[38] As we adjusted for hospital volume of VA-ECMO and performed a sensitivity analysis, we believe that the insertion techniques had little influence on the outcomes. Third, even with the competing-risk analysis, the effects of confounding bias cannot be entirely adjusted, and therefore the risk of LEI may have been underestimated. Thus, we performed a sensitivity analysis on surviving patients only, and the results were confirmed to be robust. Fourth, the incidence of severe complications among younger patients was extremely low. Because of the anonymity of our database, we were unable to disclose the ages of the younger patients due to the low incidence of severe LEI. However, most of the patients who experienced severe LEI in the young group were aged >12 years, and their heights were almost equal to or taller than the average height of Japanese women. Finally, errors in data entry and coding may have occurred. However, we believe that miscoding is rare in the Diagnosis Procedure Combination database because the diagnoses are recorded by the attending physicians. Despite these limitations, we believe that the present study can provide an overview of the complications and interventions related to VA-ECMO and help to reduce this potentially disabling complication.

CONCLUSIONS

In this study using a nationwide database, younger age and consciousness disturbance on admission were associated with higher risk of severe LEI following VA-ECMO. The findings of the present study have important implications for better management of VA-ECMO therapy.

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Contributors All authors contributed to the study conception and design. AH and YI designed and executed the experiments and wrote the manuscript. NM and YI were a major contributor to in writing the manuscript. NM, KU, and KM contributed to introduce the clinical epidemiology and helped to conduct statistical analysis and to write the manuscript. YI, TM, ET, SI, and TT contributed to introduce the concept of orthopaedic surgery and helped to write the manuscript. HM and KF contributed to construct the database. HY and HC are supervisors and edited the manuscript. All authors reviewed and approved the final manuscript. AH accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (19AA2007 and 20AA2005) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Institutional Review Board of The University of Tokyo (approval number: 3501-(3) (December 25th, 2017)). Because all data were de-identified, the requirement for patient informed consent was waived. This study was approved by the Institutional Review Board of The University of Tokyo.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets analyzed during the current study are not publicly available due to contracts with the hospitals providing data to the database.

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REFERENCES

1 Rihal CS, Naidu SS, Givertz MM, Szeto WY, Burke JA, Kapure NK, Kern M, Garratt KN, Goldstein JA, Dimas V. SCAI/ACC/ HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care. Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol* 20152015;5:e7–26.
2 Smedira NG, Moazami N, Golding CM, McCarthy PM, Apperson-Hansen C, Blackstone EH, Cosgrove DM. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. *J Thorac Cardiovasc Surg* 2001;122:92–102.
3 Sanaiha Y, Bailey K, Downey P, Seo Y-J, Aguayo E, Dobaria V, Shemin RJ, Benharash P. Trends in mortality and resource utilization for extracorporeal membrane oxygenation in the United States: 2008-2014. *Surgery* 2019;165:381–8.
4 Karagiannidis C, Brodie D, Strassmann S, Stoelben E, Philipp A, Bein T, Müller T, Windisch W. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med* 2016;42:889–96.
5 Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, Esmailian F, Azarbal B. Complications of extracorporeal membrane oxygenation for treatment of

cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014;97:610–6.
6 Bisdas T, Beutel G, Warnecke G, Hoeper MM, Kuehn C, Haverich A, Teebken OE. Vascular complications in patients undergoing femoral cannulation for extracorporeal membrane oxygenation support. *Ann Thorac Surg* 2011;92:626–31.
7 Thomas J, Kostousov V, Teruya J. Bleeding and thrombotic complications in the use of extracorporeal membrane oxygenation. *Semin Thromb Hemost* 2018;44:020–9.
8 Long B, Koyfman A, Gottlieb M. Evaluation and management of acute compartment syndrome in the emergency department. *J Emerg Med* 2019;56:386–97.
9 Marchesi M, Marchesi A, Calori GM, Cireni LV, Sileo G, Merzagora I, Zoia R, Vaienti L, Morini O. A sneaky surgical emergency: acute compartment syndrome. retrospective analysis of 66 closed claims, medico-legal pitfalls and damages evaluation. *Injury* 2014;45 Suppl 6:S16–20.
10 Bakhtiary F, Keller H, Dogan S, Dzemali O, Oezaslan F, Meininger D, Ackermann H, Zwissler B, Kleine P, Moritz A. Venoarterial extracorporeal membrane oxygenation for treatment of cardiogenic shock: clinical experiences in 45 adult patients. *J Thorac Cardiovasc Surg* 2008;135:382–8.
11 Hsu P-S, Chen J-L, Hong G-J, Tsai Y-T, Lin C-Y, Lee C-Y, Chen Y-G, Tsai C-S. Extracorporeal membrane oxygenation for refractory cardiogenic shock after cardiac surgery: predictors of early mortality and outcome from 51 adult patients. *Eur J Cardiothorac Surg* 2010;37:328–33.
12 Rastan AJ, Dege A, Mohr M, Doll N, Falk V, Walther T, Mohr FW. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg* 2010;139:302–11.
13 Bonicolini E, Martucci G, Simons J, Raffa GM, Spina C, Lo Coco V, Arcadipane A, Pilato M, Lorusso R. Limb ischemia in peripheral veno-arterial extracorporeal membrane oxygenation: a narrative review of incidence, prevention, monitoring, and treatment. *Crit Care* 2019;23:266.
14 Yau P, Xia Y, Shariff S, Jakobleff WA, Forest S, Lipsitz EC, Scher LA, Garg K. Factors associated with ipsilateral limb ischemia in patients undergoing femoral cannulation extracorporeal membrane oxygenation. *Ann Vasc Surg* 2019;54:60–5.
15 Chikuda H, Yasunaga H, Takeshita K, Horiguchi H, Kawaguchi H, Ohe K, Fushimi K, Tanaka S. Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database. *Emerg Med J* 2014;31:201–6.
16 Chikuda H, Ohya J, Horiguchi H, Takeshita K, Fushimi K, Tanaka S, Yasunaga H. Ischemic stroke after cervical spine injury: analysis of 11,005 patients using the Japanese diagnosis procedure combination database. *Spine J* 2014;14:2275–80.
17 Chikuda H, Yasunaga H, Horiguchi H, Takeshita K, Kawaguchi H, Matsuda S, Nakamura K. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. *J Bone Joint Surg Am* 2012;94:433–8.
18 Ohya J, Chikuda H, Oichi T, Kato S, Matsui H, Horiguchi H, Tanaka S, Yasunaga H. Seasonal variations in the risk of reoperation for surgical site infection following elective spinal fusion surgery: a retrospective study using the Japanese diagnosis procedure combination database. *Spine* 2017;42:1068–79.
19 Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol* 2017;27:476–82.
20 Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel J-M, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–82.
21 Ono K, Wada K, Takahara T, Shirotani T. Indications for computed tomography in patients with mild head injury. *Neurol Med Chir* 2007;47:291–8.
22 Shigematsu K, Nakano H, Watanabe Y. The eye response test alone is sufficient to predict stroke outcome--reintroduction of Japan Coma Scale: a cohort study. *BMJ Open* 2013;3:e002736.
23 Beyersmann J, Schumacher M. Time-dependent covariates in the proportional subdistribution hazards model for competing risks. *Biostatistics* 2008;9:765–76.
24 Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009;170:244–56.
25 Tullio A, Magli A, Moretti E, Valent F. Why we should take care of the competing risk bias in survival analysis: a phase II trial on the toxicity profile of radiotherapy for prostate cancer. *Rep Pract Oncol Radiother* 2019;24:511–9.
26 Nasr DM, Rabinstein AA. Neurologic complications of extracorporeal membrane oxygenation. *J Clin Neurol* 2015;11:383–9.
27 Pozzi M, Koffel C, Djaref C, Grinberg D, Fellahi JL, Hugon-Vallet E, Prieur C, Robin J, Obadia JF. High rate of arterial complications in patients supported with extracorporeal life support for drug intoxication-induced refractory cardiogenic shock or cardiac arrest. *J Thorac Dis* 2017;9:1988–96.
28 Gander JW, Fisher JC, Reichstein AR, Gross ER, Aspelund G, Middlesworth W, Stolar CJ. Limb ischemia after common femoral artery cannulation for venoarterial extracorporeal membrane oxygenation: an unresolved problem. *J Pediatr Surg* 2010;45:2136–40.
29 Kurkluoglu M, Hynes CF, Alfares FA, El-Sayed Ahmed MM, Peer SM, Zurakowski D, Jonas RA, Nath DS. Choice of peripheral venoarterial extra-corporeal membrane oxygenation cannulation site in patients above 15 kilograms. *J Card Surg* 2015;30:461–5.
30 Schad CA, Fallon BP, Monteagudo J, Okochi S, Cheung EW, Morrissey NJ, Kadenhe-Chiweshe AV, Aspelund G, Stylianos S, Middlesworth W. Routine use of distal arterial perfusion in pediatric femoral venoarterial extracorporeal membrane oxygenation. *Artif Organs* 2017;41:11–16.
31 Ahn HJ, Lee JW, Joo KH, You YH, Ryu S, Lee JW, Kim SW. Point-of-care ultrasound-guided percutaneous cannulation of extracorporeal membrane oxygenation: make it simple. *J Emerg Med* 2018;54:507–13.
32 Son AY, Khanh LN, Joung HS, Guerra A, Karim AS, McGregor R, Pawale A, Pham DT, Ho KJ. Limb ischemia and bleeding in patients requiring venoarterial extracorporeal membrane oxygenation. *J Vasc Surg* 2021;73:593–600.
33 Steffen RJ, Sale S, Anandamurthy B, Cruz VB, Grady PM, Soltesz EG, Moazami N. Using near-infrared spectroscopy to monitor lower extremities in patients on venoarterial extracorporeal membrane oxygenation. *Ann Thorac Surg* 2014;98:1853–4.
34 Foley PJ, Morris RJ, Woo EY, Acker MA, Wang GJ, Fairman RM, Jackson BM. Limb ischemia during femoral cannulation for cardiopulmonary support. *J Vasc Surg* 2010;52:850–3.
35 Lamb KM, DiMuzio PJ, Johnson A, Batista P, Moudgill N, McCullough M, Eisenberg JA, Hirose H, Cavarocchi NC. Arterial protocol including prophylactic distal perfusion catheter decreases limb ischemia complications in patients undergoing extracorporeal membrane oxygenation. *J Vasc Surg* 2017;65:1074–9.
36 McQueen MM, Gaston P, Court-Brown CM. Acute compartment syndrome. *J Bone Joint Surg* 2000;82:200–3.
37 Tanaka D, Hirose H, Cavarocchi N, Entwistle JWC. The impact of vascular complications on survival of patients on venoarterial extracorporeal membrane oxygenation. *Ann Thorac Surg* 2016;101:1729–34.
38 Danial P, Hajage D, Nguyen LS, Mastroianni C, Demondion P, Schmidt M, Bouglé A, Amour J, Leprince P, Combes A, *et al*. Percutaneous versus surgical femoro-femoral veno-arterial ECMO: a propensity score matched study. *Intensive Care Med* 2018;44:2153–61.