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Clinical Research

Gastrointestinal Bleeding in Extracorporeal Membrane Oxygenation Patients: A Comprehensive Analysis of Risk Factors and Clinical Outcomes

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Background: Extracorporeal membrane oxygenation (ECMO) is an intervention for severe heart and lung failure; however, it poses the risk of complications, including gastrointestinal bleeding (GIB). Comprehensive analyses of GIB in patients undergoing ECMO are limited, and its impact on clinical outcomes remains unclear.
Methods: This retrospective study included 484 patients who received venovenous and venoarterial ECMO between January 2015 and December 2022. Data collected included patient characteristics, laboratory results, GIB details, and interventions. Statistical analyses were performed to identify risk factors and assess the outcomes.
Results: GIB occurred in 44 of 484 patients (9.1%) who received ECMO. Multivariable analysis revealed that older age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01–1.06; p=0.0130) and need to change the ECMO mode (OR, 3.74; 95% CI, 1.75–7.96; p=0.0006) were significant risk factors for GIB, whereas no association was found with antiplatelet or systemic anticoagulation therapies during ECMO management. Half of the patients with GIB (22/44, 50%) underwent intervention, with endoscopy as the primary modality (19/22, 86.4%). Patients who underwent ECMO and developed GIB had higher rates of mortality (40/44 [90.9%] vs. 262/440 [59.5%]) and ECMO weaning failure (38/44 [86.4%] vs. 208/440 [47.3%]).
Conclusion: GIB in patients undergoing ECMO is associated with adverse outcomes, including increased risks of mortality and weaning failure. Even in seemingly uncomplicated cases, it is crucial to avoid underestimating the significance of GIB.

Keywords: Gastrointestinal bleeding, Extracorporeal membrane oxygenation, Complication, Endoscopy, Embolization

Introduction

Extracorporeal membrane oxygenation (ECMO) refers to the use of mechanical devices for cardiopulmonary support in patients with severe heart and/or lung failure who are unresponsive to optimal conventional care [1]. Although ECMO serves as a last-resort lifesaving measure for some patients, similar to any other medical procedure, it is not without complications. Hemorrhage is the most frequently encountered complication during ECMO, and among these cases, gastrointestinal bleeding (GIB) occurs in approximately 3%–19% [2-6]. Dealing with GIB in patients undergoing ECMO is especially challenging because of the patients' critical condition and the limitations of conventional diagnostic and therapeutic approaches.

However, despite its high incidence, comprehensive analyses concerning the risk factors, clinical outcomes, and management strategies associated with GIB in patients undergoing ECMO are scarce. Previous studies have primarily focused on upper GIB or have considered GIB as just one of multiple bleeding or gastrointestinal complications associated with ECMO. This retrospective study, conducted at a single center, sought to fill this gap in the literature and contribute to a more comprehensive understanding by

investigating various aspects of GIB in patients who underwent ECMO, identifying associated risk factors, and examining the impact of GIB on clinical outcomes. Furthermore, we share our center's experience with the management of patients who develop GIB while undergoing ECMO.

Methods

Study design

This retrospective study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (IRB no., 2023-09-011-001). Given the retrospective nature of this study, the requirement for informed consent was waived. The study population comprised 599 patients who underwent ECMO treatment for various reasons at Hallym University Sacred Heart Hospital between January 2015 and December 2022. The exclusion criteria included patients aged <19 years, those with an ECMO support duration <24 hours, individuals who received ECMO support in the context of cardiac surgery, and patients transferred to another hospital during ECMO management. Ultimately, 484 patients were included in the analysis, and their characteristics and clinical outcomes were retrospectively assessed by analyzing their electronic medical records.

Initial laboratory data were acquired immediately after ECMO initiation. Patients who received antiplatelet therapy during ECMO support were categorized as having single, dual, or triple therapy. Stroke was confirmed by computed tomography (CT) scans indicating acute infarction or hemorrhage, while limb ischemia was defined by symptomatic changes (decreased skin temperature and loss of arterial pulsation), along with the absence of peripheral Doppler flow signals [7].

The primary endpoint was all-cause mortality in patients with or without GIB. The secondary endpoints were the demographics, clinical characteristics, and complications of patients who received ECMO support.

Definition of bleeding

GIB was defined as evident bleeding with manifestations such as hematemesis, melena, or hematochezia, and all incidents that occurred during ECMO management were reviewed. Other bleeding complications were defined in accordance with the following criteria established by the International Society on Thrombosis and Hemostasis: (1) fatal bleeding and/or (2) symptomatic bleeding in a critical area or organ, such as the intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial areas, or intramuscular bleeding with compartment syndrome; and/or (3) bleeding that causes a fall in the hemoglobin level of ≥2 g/dL (1.24 mmol/L) or leads to transfusion of 2 or more units of whole blood or red cells, and/or (4) surgical site bleeding that requires a second intervention [8,9].

General management

At our institution, routine systemic anticoagulation is not performed in ECMO patients to reduce the risk of bleeding [10-12]. Intravenous anticoagulation is only considered in the following situations: (1) pulse pressure <10 mm Hg, (2) echocardiographic confirmation of aortic valve opening failure, (3) presence of a left ventricular thrombus in the imaging work-up, (4) presence of pulmonary embolism confirmed by CT, and (5) prior administration of oral-anticoagulants in accordance with established guidelines, regardless of ECMO mode. Under these circumstances, intravenous heparin is used with a target activated partial thromboplastin time of 60–80 seconds. The administration of antiplatelet agents follows established guidelines. The discontinuation of anticoagulation and antiplatelet agents is considered in cases of planned intervention or surgery, as well as in the event of bleeding complications.

During ECMO management, for non-bleeding-related anemia, such as iron deficiency anemia and anemia of chronic disease, we consider transfusion when the hemoglobin level falls to 7 g/dL. In cases of thrombocytopenia, potential causes such as drugs and antibiotics are initially addressed, and transfusion is considered when the platelet count drops below 30,000/μL.

Upon ECMO initiation, all patients are administered 40 mg of intravenous esomeprazole daily, which is continued throughout ECMO support. Enteral feeding commences once a high dose of intravenous norepinephrine is weaned below 0.3 μg/kg/min.

Gastrointestinal bleeding management

When a GIB event occurs, we monitor vital signs, laboratory data such as hemoglobin and coagulation profiles, and the rate of GIB and transfusion. If the patient is on antiplatelet and/or anticoagulation therapy, discontinuation is considered. Emergent endoscopy is primarily considered when it is decided that an intervention is needed. If endoscopy fails to control bleeding or GIB persists despite a successful procedure, angiography is then performed. In cases where endoscopic intervention is not feasible due to re-

source shortages or the patient's instability, angiography becomes the primary consideration. Additionally, the possibility of surgery is discussed in a multidisciplinary meeting regarding the patient's general condition, suspected bleeding focus, and the cause of GIB, such as bowel ischemia.

To evaluate the interventions performed on patients who received ECMO and developed ECMO, reports written by endoscopists or interventional radiologists were utilized. Reports stating outcomes such as "successful bleeding control," "no active bleeding," "successful embolization," and "no extravasation" were classified as technical successes. Furthermore, an intervention was considered clinically successful when GIB subsided for 48 consecutive hours without additional interventions.

Statistical analysis

Continuous variables are reported as either mean (standard deviation) or median with interquartile range (IQR), as appropriate. The Student t-test or Mann-Whitney U test was used to compare continuous variables between groups. Categorical variables were expressed as percentages (%) and assessed using the chi-square or Fisher exact test for comparison. Statistical significance was set at $p<0.05$.

To identify the risk factors associated with mortality, a multivariable logistic regression analysis was conducted, including variables with $p<0.05$ from the univariate analysis. All statistical analyses were performed using R statistical software ver. 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics

Patient demographics are presented in Tables 1 and 2, and Supplementary Tables 1 and 2 provide the demographic characteristics stratified by mortality and ECMO weaning outcomes, respectively. Among the 484 patients, 44 (9.1%) experienced GIB. Of the total cohort, 353 (72.9%) were supported with venoarterial ECMO and 131 (27.1%) with venovenous ECMO. In total, 182 patients (37.6%) were discharged from the hospital and classified as survivors, whereas 302 (62.4%) died during hospitalization. Successful weaning from ECMO was achieved in 238 patients (49.2%), whereas weaning failed in 246 (50.8%). Among the 44 patients who experienced GIB during ECMO, 4 (9.1%) survived and were discharged, whereas 40 (90.9%) died.

The primary reason for initiating ECMO in patients with GIB was acute respiratory failure in most cases (23/44, 52.3%), followed by myocardial infarction (12/44, 27.3%). Additionally, 4 patients (9.1%) required ECMO support for sepsis, and ECMO was initiated in 5 cases owing to miscellaneous causes, such as pulmonary embolism, ventricular arrhythmia, myocarditis, diabetic ketoacidosis, and chronic thromboembolic pulmonary hypertension. Systemic heparinization was administered during ECMO before the GIB event in 14 out of 44 patients (31.8%), with a duration ranging from 1 to 77 days. The median usage period was 8 days (IQR, 3.0–12.0 days) (Table 3). The leading cause of death among these patients was sepsis (31/44, 70.5%); however, GIB was considered a direct cause of death in 4 patients.

Risk factors and clinical impact of GIB

Compared with patients who underwent ECMO and did not develop GIB, the patients in the GIB group were older (median, 61.0 years [IQR, 55.0–70.0 years] versus 58.0 years [IQR, 49.0–67.0 years]; $p=0.015$), more frequently needed the ECMO mode to be changed (12 [27.3%] versus 43 [9.8%], $p=0.001$), and experienced a higher incidence of other bleeding complications (10 [22.7%] versus 45 [10.4%], $p=0.028$), all of which were statistically significant. The GIB group also demonstrated poorer outcomes in terms of ECMO weaning (38 [86.4%] versus 208 [47.3%], $p<0.001$) and mortality (40 [90.9%] versus 262 [59.5%], $p<0.001$). The initial laboratory data obtained after ECMO initiation showed no differences in any category regarding blood count, coagulation indices, and kidney or liver function (Tables 1, 2).

Univariate logistic regression analysis indicated that older age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01–1.06; $p=0.0129$), and need to change the ECMO mode (OR, 3.46; 95% CI, 1.66–7.22; $p=0.0009$) were associated with the occurrence of GIB. Subsequent multivariable logistic regression analysis found that older age (OR, 1.04; 95% CI, 1.01–1.06; $p=0.0130$) and need to change the ECMO mode (OR, 3.74; 95% CI, 1.75–7.96; $p=0.0006$) were independently associated with the occurrence of GIB in patients who received ECMO (Table 4).

Furthermore, after adjusting for confounding factors, GIB was found to be independently associated with ECMO weaning failure (OR, 4.59; 95% CI, 1.75–12.07; $p=0.0020$) and mortality (OR, 4.17; 95% CI, 1.38–12.57; $p=0.0113$) (Table 5).

The median ECMO period during which patients were

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Table 1. Baseline characteristics and laboratory data of patients according to the occurrence of a GIB event

Characteristic	GIB (n=44)	Non-GIB (n=440)	p-value
Age (yr)	61.0 (55.0–70.0)	58.0 (49.0–67.0)	0.015
Male sex	33 (75.0)	311 (70.7)	0.669
Hypertension	13 (29.5)	186 (42.3)	0.140
Diabetes	11 (25.0)	119 (27.0)	0.910
Coronary disease	4 (9.1)	51 (11.6)	0.803
Cerebrovascular accident	1 (2.3)	25 (5.7)	0.545
Chronic kidney disease	2 (4.5)	19 (4.3)	1.000
COPD	0	10 (2.3)	0.649
Asthma	1 (2.3)	12 (2.7)	1.000
Gastric ulcer	1 (2.3)	5 (1.1)	1.000
Liver cirrhosis	0	10 (2.3)	0.649
Autoimmune disease	2 (4.5)	13 (3.0)	0.901
ECPR	11 (25.0)	104 (23.7)	0.993
SOFA score	11.0 (9.0–14.0)	12.0 (10.0–14.0)	0.378
SAPS score	68.0 (43.0–84.0)	68.0 (48.0–83.0)	0.636
ECMO machine			0.360
EBS	1 (2.3)	40 (9.1)	
PLS	41 (93.2)	374 (85.0)	
HLS	1 (2.3)	20 (4.4)	
Others	1 (2.3)	6 (1.4)	
Initial ECMO mode			0.357
Venoarterial	29 (65.9)	324 (73.6)	
Venovenous	15 (34.1)	116 (26.4)	
Initial laboratory data			
Hemoglobin (g/dL)	10.6 (8.7–12.1)	10.3 (8.6–12.2)	0.943
Platelet (×10³/μL)	148.0 (68.0–194.5)	150.0 (97.0–213.0)	0.318
INR	1.5 (1.2–1.9)	1.5 (1.2–2.0)	0.753
aPTT (sec)	125.1 (61.4–150.0)	108.7 (59.0–150.0)	0.439
Fibrinogen (mg/dL)	307.5 (171.0–430.0)	285.0 (178.0–442.5)	0.937
Antithrombin (%)	57.0 (42.5–70.0)	58.0 (43.0–75.0)	0.455
BUN (mg/dL)	22.5 (17.3–33.0)	21.5 (15.8–30.1)	0.442
Creatinine (mg/dL)	1.2 (0.9–1.8)	1.1 (0.8–1.7)	0.911
Albumin (mg/dL)	2.2 (1.8–3.0)	2.5 (2.0–3.0)	0.097
AST (IU/L)	138.5 (50.0–406.5)	122.5 (49.0–456.5)	0.923
ALT (IU/L)	56.5 (24.5–159.5)	64.0 (27.5–178.5)	0.510
Lactate	4.2 (2.3–8.8)	4.1 (2.3–8.8)	0.713

Values are presented as median (interquartile range) or number (%).
GIB, gastrointestinal bleeding; COPD, chronic obstructive pulmonary disease; ECPR, extracorporeal cardiopulmonary resuscitation; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score; ECMO, extracorporeal membrane oxygenation; EBS, emergency bypass system; PLS, permanent life support; HLS, cardiohelp; INR, international normalized ratio; aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase.

free from GIB was 13.0 days (IQR, 4.0–33.0 days), ranging from the day of cannulation to a maximum of 122 days (Table 3). The receiver operating characteristic analysis of GIB occurrence and the free-from-GIB ECMO period resulted in an area under the curve (AUC) of 0.521, with a median sensitivity of 0.5227 and a median specificity of 0.5523, indicating no discriminative value. A Kaplan-Meier analysis showed an even distribution of GIB events throughout the ECMO period (Supplementary Fig. 1).

Intervention results

Notably, half of the patients underwent an intervention for GIB management (22/44 [50.0%]). Among these cases, endoscopy was the primary choice of intervention (19/22 [86.4%]), with 12 being esophagogastroduodenoscopy (EGD), 2 sigmoidoscopy, and 1 colonoscopy. Four patients underwent both EGD and sigmoidoscopy. Besides that, 2 patients (9.1%) underwent angiography, and 1 (4.5%) un-

Table 2. Clinical outcomes of patients according to the occurrence of a GIB event

Variable	GIB (n=44)	Non-GIB (n=440)	p-value
Systemic heparinization during ECMO	17 (38.6)	183 (42.0)	0.789
Antiplatelet therapy during ECMO[a]			
Single	4 (9.1)	17 (3.9)	0.217
Dual	5 (11.4)	73 (16.6)	0.494
Triple	0	16 (3.6)	0.399
Transfusion, pack	28.0 (16.0–52.5)	7.0 (3.0–14.0)	<0.001
Transfusion rate (pack/day)	1.1 (0.6–1.5)	0.5 (0.3–0.9)	<0.001
Complications			
Other bleeding	10 (22.7)	45 (10.4)	0.028
Limb ischemia	4 (9.1)	16 (3.6)	0.182
Stroke			
Ischemic	3 (6.8)	37 (8.4)	0.934
Hemorrhagic	0	12 (2.7)	0.547
ECMO mode change	12 (27.3)	43 (9.8)	0.001
ECMO duration (day)	28.0 (15.0–56.0)	12.0 (6.0–20.0)	<0.001
ICU stay (day)	40.0 (25.0–65.5)	23.0 (12.5–39.0)	<0.001
Hospital stay (day)	44.0 (27.5–70.0)	31.0 (16.5–50.0)	0.006
ECMO weaning failure	38 (86.4)	208 (47.3)	<0.001
Mortality	40 (90.9)	262 (59.5)	<0.001

Values are presented as number (%) or median (interquartile range).
GIB, gastrointestinal bleeding; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.
[a]Antiplatelet therapy was administered using a combination of aspirin, clopidogrel and ticagrelor.

Table 3. Clinical characteristics and management of patients with GIB (n=44)

Variable	Value
Indication for ECMO	
ARDS	23 (52.3)
AMI	12 (27.3)
Sepsis	4 (9.1)
Others	5 (11.4)
Systemic heparinization during ECMO before GIB event	14 (31.8)
Minimum use (day)	1
Maximum use (day)	77
Median (IQR) (day)	8 (3.0–12.0)
"Free from GIB" ECMO period (day)	13.0 (4.0–33.0)
GIB amount (mL)	2,520.0 (1,020.0–4,990.0)
GIB duration (day)	4.0 (2.0–7.0)
GIB rate (mL/day)	611.2 (348.3–1,011.7)
Bleeding focus	
Upper gastrointestinal	17 (38.6)
Lower gastrointestinal	27 (61.4)
Conservative treatment	22 (50.0)
Intervention	22 (50.0)
Endoscopy	19 (86.4)
Endovascular	2 (9.1)
Surgery	1 (4.5)
Re-intervention	11 (50.0)
Clinical success	10 (45.5)

Values are presented as number (%) or median (IQR).
GIB, gastrointestinal bleeding; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; AMI, acute myocardial infarction; IQR, interquartile range.

Table 4. Univariate and multivariable logistic regression analysis of risk factors for gastrointestinal bleeding

	OR (95% CI)	p-value
Univariate logistic regression analysis		
Age	1.03 (1.01–1.06)	0.0129
ECMO mode change	3.46 (1.66–7.22)	0.0009
Multivariable logistic regression analysis		
Age	1.04 (1.01–1.06)	0.0130
ECMO mode change	3.74 (1.75–7.96)	0.0006

OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.

Table 5. Univariate and multivariable logistic regression analysis of risk factors for mortality and ECMO weaning failure

	Univariate logistic regression analysis		Multivariable logistic regression analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality				
Age	1.02 (1.01–1.03)	0.0068	1.03 (1.01–1.05)	0.0009
SOFA score	1.08 (1.02–1.14)	0.0126	1.09 (1.01–1.18)	0.0249
SAPS score	1.01 (1.00–1.02)	0.0187	1.00 (0.99–1.02)	0.4778
ECMO mode change	5.68 (2.38–13.55)	0.0001	5.24 (1.98–13.89)	0.0009
GIB	6.79 (2.39–19.32)	0.0003	4.17 (1.38–12.57)	0.0113
Other bleeding	2.09 (1.09–4.02)	0.0262	2.53 (1.06–6.05)	0.0363
Ischemic stroke	8.36 (2.54–27.54)	0.0005	7.20 (2.05–25.21)	0.0020
ECMO weaning failure				
Age	1.01 (1.00–1.03)	0.0362	1.03 (1.01–1.05)	0.0020
Hypertension	0.66 (0.46–0.95)	0.0251	0.59 (0.36–0.97)	0.0365
Autoimmune disease	4.02 (1.12–14.41)	0.0329	3.12 (0.77–12.69)	0.1112
SOFA score	1.08 (1.02–1.14)	0.0081	1.08 (1.00–1.17)	0.0486
SAPS score	1.01 (1.00–1.02)	0.0135	1.01 (0.99–1.02)	0.2922
ECMO mode change	4.50 (2.26–8.94)	<0.0001	4.63 (1.97–10.90)	0.0004
GIB	7.06 (2.93–17.05)	<0.0001	4.59 (1.75–12.07)	0.0020
Other bleeding	2.60 (1.41–4.81)	0.0022	3.10 (1.36–7.08)	0.0071
Ischemic stroke	6.17 (2.54–15.00)	0.0001	6.58 (2.28–18.96)	0.0005
Hemorrhagic stroke	11.14 (1.43–86.91)	0.0214	1.98 (0.20–19.62)	0.5587

ECMO, extracorporeal membrane oxygenation; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score; GIB, gastrointestinal bleeding.

derwent surgery as the primary intervention. The technical success rate was 72.7% (16/22), and the clinical success rate was 45.5% (10/22) for the primary intervention, and re-intervention was performed in 11 out of 22 patients (50%) (Table 3).

Four patients underwent subsequent angiography after an initial endoscopy for various reasons, such as the inability to identify or specify the bleeding site or the challenge of controlling excessive bleeding. One patient underwent endoscopy followed by two subsequent embolizations; however, GIB persisted, ultimately necessitating surgical intervention. One of the 2 patients who primarily underwent angiography showed no extravasation, but continued to bleed and subsequently underwent a hemoclip procedure via endoscopy to address duodenal ulcer bleeding. In the other patient, extravasation was not detected on initial angiography; however, endoscopy revealed ongoing bleeding. The bleeding was not controlled by endoscopy, but was eventually controlled by embolization. GIB subsided in 8 patients, 3 of whom ultimately survived (Fig. 1).

Discussion

Patients undergoing ECMO exhibit elevated susceptibility to bleeding influenced by multiple factors such as the patient's underlying illness, the utilization of antiplatelet and/or anticoagulation therapies during ECMO, and the ECMO procedure itself. Although bleeding at the cannulation site is the most common hemorrhagic complication, GIB also accounts for a significant proportion of bleeding

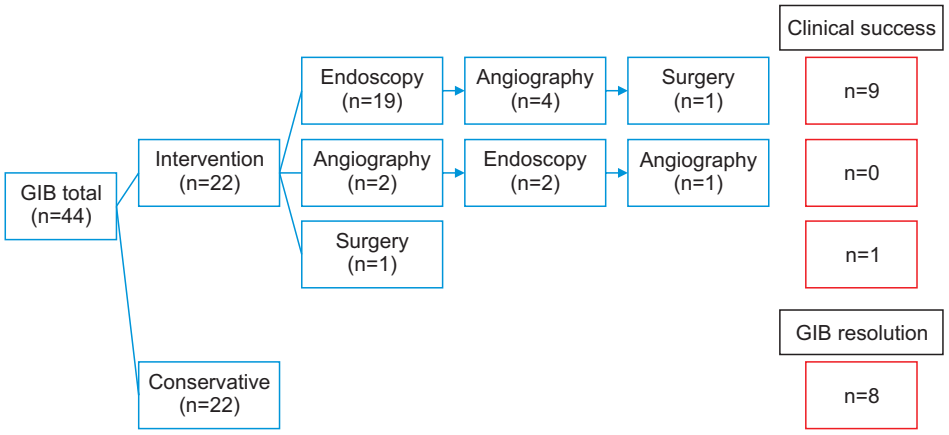

Fig. 1. A schematic diagram of the management and outcomes of patients undergoing extracorporeal membrane oxygenation who developed gastrointestinal bleeding (GIB), showing 22 interventions, with endoscopy (n=19) being the most frequent primary intervention method, and 6 patients subsequently requiring another method of intervention.

events [4,13]. However, despite its high incidence, GIB in patients undergoing ECMO has long been overlooked as merely a bleeding or gastrointestinal complication. Only recently has there been a growing recognition of the importance of studying GIB in patients undergoing ECMO. Nevertheless, the existing studies on GIB in patients undergoing ECMO remain fragmented and lack consistency and comprehensiveness.

The majority of the previous studies reported a higher mortality rate in patients experiencing GIB; however, most of those studies did not specifically focus on the impact of GIB on mortality and ECMO weaning. Therefore, we investigated the effects of GIB on the clinical outcomes of patients undergoing ECMO. Our study involved a review of 490 patients over an 8-year period at a single center, including both venoarterial and venovenous ECMO cases. In our patient cohort, the incidence of GIB was 9.1%, which falls within the previously reported range of 3%–19%. Through multivariable analysis, we identified a significant association between GIB and mortality, as well as a correlation between GIB and ECMO weaning failure, regardless of the ECMO type. In line with our findings, Mazzeffi et al. [2] analyzed 132 patients who underwent venovenous and venoarterial ECMO and revealed an independent association between GIB and in-hospital mortality [2]. These consistent results further support the possibility that GIB has a critical impact on patient outcomes during ECMO.

Moreover, there is limited knowledge regarding the risk factors that predispose patients receiving ECMO to GIB. Stern et al. [6] reported that in patients on venoarterial ECMO, a history of peptic ulcer disease, dual antiplatelet therapy, and extracorporeal cardiopulmonary resuscitation were significant independent risk factors for GIB. Our research also considered the patients' history of gastroduodenal ulcers, although the incidence was relatively low (6/490 [1.2%]). However, a review of reports of patients who underwent endoscopy for GIB clearly showed that ulcer bleeding constituted a significant proportion of cases (7/17 upper GIB cases). Although it remains uncertain whether these ulcers existed before ECMO initiation, considering that the lifetime prevalence of peptic ulcer disease is estimated to be around 5%–10% in the general population [14], the recognition of peptic ulcer disease in patients may have been underestimated, leading to limited data in this regard.

Regarding the influence of antiplatelet and anticoagulation therapies, our study did not identify any association with GIB. Low-dose aspirin usage increases the risk of major GIB, with dual antiplatelet therapy approximately doubling this risk compared to single antiplatelet therapy [15-17]. Similarly, oral anticoagulants have an overall incidence of major GIB ranging from 0.5–1.9 events per 100 patient-years [18]. However, our study's statistical power may have been affected by the small sample size.

Notably, our study revealed a previously unreported association between the need to change the ECMO modes and GIB. However, these findings should be carefully considered. An ECMO mode change is typically considered when there is a need for enhanced cardiac or pulmonary support, implying an even more complex and critical patient condition. Factors such as underlying coagulopathy, systemic inflammation, and multi-organ failure, which are ever-changing, may contribute to this association. Rather than suggesting that the ECMO mode change directly causes GIB, it would be more reasonable to assert that a patient's deteriorating condition necessitating an ECMO mode change is associated with GIB. Therefore, conducting additional research using more extensive data through

multicenter analyses to investigate specific factors requiring ECMO mode changes, such as right ventricular failure in patients receiving venovenous ECMO, will contribute to a better understanding of the risk factors associated with GIB.

Prolonged ECMO can contribute to coagulopathy, leading to bleeding complications [13]. In line with our findings, most studies on GIB in patients receiving ECMO have reported longer ECMO durations in patients with GIB than in those without [5,6]. However, the unclear temporal order of events makes it difficult to determine whether the ECMO duration should be considered a risk factor or outcome.

To address this issue, we analyzed GIB and ECMO durations using the ECMO duration during which patients were free from GIB. However, our analysis revealed an AUC of 0.521 and a gradual curve in the Kaplan-Meier analysis, suggesting that the ECMO duration itself may not directly correlate with the risk of GIB. Instead, GIB appears to be closely associated with the patient's general condition, and deterioration of the patient's condition can occur independently of the ECMO duration. Therefore, it seems reasonable to conclude that GIB is evenly distributed throughout the entire duration of ECMO support.

Managing patients receiving ECMO who develop GIB presents distinct challenges compared with patients without ECMO support. These challenges arise from limitations in conducting standard diagnostic and therapeutic procedures, largely attributable to difficulties associated with patient transport and positioning. To our best knowledge, this is the first to investigate the management of GIB in patients with ECMO and evaluate its outcomes.

Routine computed tomography was not performed at our center because of the risks of transporting patients undergoing ECMO. Endoscopy remains the primary intervention, although performing endoscopy in patients undergoing ECMO poses challenges related to patient positioning. Proper positioning typically requires the involvement of approximately 4 nurses, with the attending physician overseeing patient monitoring. Recently, as our center expanded its angiography and embolization capabilities, endovascular interventions have been enthusiastically integrated into our protocol. In cases where bleeding could not be identified or controlled through endoscopy or when lower GIB was suspected, an endovascular intervention was considered as the primary subsequent intervention approach.

Limitations

This study has some limitations. First, this was a retrospective study, which has the potential for bias. Certain patient information relevant to GIB, such as a history of peptic ulcer, might have been inadvertently omitted, as it may not have been deemed a critical data point at the time of the initial medical record documentation. Moreover, limitations in obtaining highly credible medical records related to the use of antiplatelet or anticoagulation agents before hospitalization are acknowledged. Consequently, our analysis focused on the impact of using these agents during ECMO support. Unfortunately, the effects of previous antiplatelet and anticoagulant use on GIB could not be evaluated due to data constraints. Second, because this study was conducted at a single center, the generalizability of the findings to a broader population may be limited. Third, to the best of our knowledge, this study represents one of the largest study populations regarding GIB and ECMO; however, the sample size remains relatively small, potentially limiting the statistical power and its ability to detect smaller associations or risk factors. Therefore, in light of the diverse reasons to change the ECMO mode and the subsequent adjustments to different modes, we encountered limitations in further categorizing these changes based on the various combinations of ECMO modes. The need for larger multicenter studies to elucidate the impact of ECMO mode changes cannot be overstated.

Conclusion

In conclusion, significant associations were found between GIB and adverse outcomes, including mortality and ECMO weaning failure. Even in seemingly uncomplicated cases of GIB, it is crucial not to underestimate its significance, but to approach it with attention and care to optimize patient outcomes.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.5090/jcs.23.136. **Supplementary Table 1**. Demographics of patients according to the mortality outcome. **Supplementary Table 2**. Demographics of patients according to the result of weaning from ECMO. **Supplementary Fig. 1**. A Kaplan-Meier analysis of GIB events throughout the extracorporeal membrane oxygenation period.

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