Oseltamivir improved thrombocytopenia during veno-arterial extracorporeal membrane oxygenation in adults with refractory cardiac failure: A single-center retrospective real-world study

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Research article

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Abstract

Background

Severe thrombocytopenia is a common complication of extracorporeal membrane oxygenation (ECMO). Oseltamivir can be used to treat infection-associated thrombocytopenia.

Objective

To evaluate the effect of oseltamivir on attenuating severe thrombocytopenia during ECMO.

Methods

This was a single-center real-world study in critically ill patients supported with venous-arterial extracorporeal membrane oxygenation (VA-ECMO). Patients suspected or confirmed with influenza received oseltamivir according to the Chinese guidelines. Thrombocytopenia and survival were compared between the oseltamivir-treated and -untreated groups. The factors associated with survival were analyzed by multivariable Cox analysis.

Results

A total of 82 patients were included. All patients developed thrombocytopenia after initiating VA-ECMO. Twenty-three patients received oseltamivir (O^+ group), and 59 did not (O^- group). During the first 8 days of VA-ECMO initiation, the platelet counts in the O^+ group were higher than in the O^- group (all $P < 0.05$). The patients in the O^+ group had higher median platelet counts at the nadir (77,000/μL, 6,000-169,000/μL), compared with the O^- group (49,000/μL, 2,000-168,000/μL; $P = 0.04$). A platelet count nadir < 50,000/μL was seen in 26% of the patients in the O^+ group, compared with 53% in the O^- group ($P = 0.031$). No significant differences in survival to discharge were seen between the O^+ and O^- groups (48% vs. 56%, $P = 0.508$). Only the Sequential Organ Failure Assessment (SOFA) scores at the time of VA-ECMO initiation were independently associated with survival (OR = 1.12, 95% confidence interval (95% CI): 1.02–1.22, $P = 0.015$).

Conclusions

Oseltamivir could ameliorate VA-ECMO-related thrombocytopenia. These findings suggest the prophylactical potential of oseltamivir on severe thrombocytopenia associated with the initiation of VA-ECMO.

Background

Extracorporeal membrane oxygenation (ECMO) is increasingly used as rescue therapy in patients with refractory cardiac/respiratory failure for temporary support or bridge to decision-making in both adult and pediatric patients [1–4]. Venous blood is removed peripherally (via the femoral vein) or centrally (via cannulation near the right atrium), oxygenated, and returned to the venous system peripherally (via the femoral vein) or centrally (via cannulation near the right atrium) in veno-venous (VV) ECMO, or to the arterial system peripherally (via the femoral artery) or centrally (via the ascending aorta) in veno-arterial (VA) ECMO [1–4]. Clinical trial data supporting the use of ECMO in adults is limited but suggests that ECMO may reduce mortality when compared to conventional ventilation [1–4].

Platelets are activated and even impaired due to biological incompatibility and high shear stress within 15 min after starting ECMO and last throughout ECMO until it is discontinued [5]. Severe and very severe thrombocytopenia is a common complication in patients supported with ECMO. Persistent severe thrombocytopenia independently predicts 90-day mortality [6]. The recovery of platelet count over time discriminates between survivors and non-survivors. Thus, the correction of thrombocytopenia is a key issue for clinicians during ECMO. With the exception of emergent platelet transfusion when necessary, there is no effective method to prevent severe thrombocytopenia currently.

Nevertheless, an increasingly better understanding of platelets' functions and biology could yield some hints to improve platelet levels during ECMO. Indeed, recent studies highlighted the role of platelet desialylation in platelet clearance. Desialylation leads to the exposure of β-galactose residues on platelets, which can be recognized by Ashwell-Morell receptors (AMRs) on hepatocytes, resulting in platelet phagocytosis in the liver [7]. Furthermore, platelet desialylation can be caused by exogenous neuraminidases from pathogens [8] and by intracellular neuraminidase (Neu1) translocation to the platelet surface during platelet activation [9]. Therefore, desialylation could be responsible, at least in part, for the pathogenesis of thrombocytopenia in many diseases and the clearance of transfused platelets after storage in circulation [10]. Inhibition of platelet desialylation has been shown to extend the lifespan of circulating platelets, increasing their overall number [9, 11].

Oseltamivir is an antiviral agent commonly used to prevent and treat influenza A and B. It is a viral sialidase inhibitor that prevents the release of progeny virions [12]. Oseltamivir can be used to treat infection-associated thrombocytopenia by inhibiting platelet desialylation [13, 14].

Therefore, this study was designed to evaluate the effect of oseltamivir on attenuating severe thrombocytopenia during ECMO. The results could provide a novel method to prevent ECMO-related thrombocytopenia in patients who are already in critical condition.

Methods

Study design and patients

This was a single-center real-world study in critically ill patients supported with venous-arterial extracorporeal membrane oxygenation (VA-ECMO) to evaluate whether oseltamivir administration would ameliorate VA-ECMO-related thrombocytopenia. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of Qilu Hospital of Shandong University before the study began. The patients or their legal representative signed the informed consent form.

The study was conducted among adults (≥ 18 years of age) who received VA- ECMO because of cardiac failure due to cardiogenic shock (CS), cardiac arrest (CA), or acute right ventricular dysfunction for more than 24 h and were cared for at the intensive care unit (ICU) at Qilu Hospital of Shandong University, between May 2016 and July 2020. Day (D) 0 was defined as the day when VA-ECMO was initiated. None of the enrolled patients showed thrombocytopenia on D1 just before cannulation. The patients who were suspected or confirmed with influenza received oseltamivir phosphate (Kewei, Yichang East Sunshine Changjiang Pharmaceutical, China, H20065415) orally or through a feeding tube at 75 mg once every 12 h for 10 days before and during VA-ECMO support. Patients developed influenza-like symptoms before and after ECMO was initiated and were treated with oseltamivir phosphate.

The Guidelines for the diagnosis and treatment of influenza developed by the Ministry of Health of the People's Republic of China (2011 edition) state that the course of oseltamivir can be extended to 10 days in severely ill patients. Influenza was diagnosed with a rapid serum antigen detection method.

Data collection

For each enrolled patient, the following variables were collected: 1) general characteristics including age, sex, and comorbidities; 2) severity of illness as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II [15] and the Sequential Organ Failure Assessment (SOFA) [16] scores; 3) laboratory data; 4) interventions including continuous renal replacement therapy (CRRT) and oxygenator circuit changes; 5) comorbidity such as disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), sepsis, hepatic dysfunction (defined as a ≥ 2-fold increase in alanine aminotransferase [17]), acute kidney injury (defined as ≥ 1.5-fold increase in creatinine) [18], bleeding, and thrombotic events; and 6) platelet transfusions (in units of platelets).

ECMO

Based on patients' blood vessel diameter and estimated cardiac output, the ECMO cannula sizes were 21-23 Fr for venous drainage and 15-17 Fr arterial reinfusion, without bicaval dual-lumen cannulae. The Rotaflow centrifugal pump (Maquet, Rastatt, Germany) and Quadrox D or I oxygenator (Maquet, Rastatt, Germany) were used. Unfractionated heparin (100 units/kg) was given at the time of cannulation, followed by a continuous intravenous infusion of unfractionated heparin for a target activated partial thromboplastin time (aPTT) of 50-70 s, unless there was an indication for a higher level of anticoagulation.

Statistical analysis

Statistical analyses were conducted using SPSS 17.0 (IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). The continuous variables are presented as medians (interquartile range (IQR)) or means ± standard deviations, based on data normality distribution tested using the Kolmogorov-Smirnov test. The continuous variables were analyzed using the Mann-Whitney U-test. The categorical data are presented as n (%) and were analyzed using the chi-square test. Survival analysis was performed using the Kaplan-Meier method, and the curves were compared using the log-rank test. A multivariable Cox proportional hazards regression model was used to evaluate the predictors of out-hospital survival. All tests were two-sided. P-values < 0.05 were considered statistically significant.

Results

Characteristics of the patients

A total of 82 patients without thrombocytopenia before cannulation were included (Fig. 1). They all underwent VA-ECMO support due to refractory cardiac failure, including 59 patients with CS, 13 patients with CA, and 10 patients with acute right ventricular dysfunction. Among them, 23 patients were suspected of influenza infection with flu-like symptoms, including cough, fatigue, sore throat, headache, and fever. Although only nine patients were confirmed with influenza by later rapid serum antigen detection, all patients received a full course of oseltamivir anti-influenza treatment empirically, from 2-3 days before until 7-8 days after VA-ECMO, for a total of 10 days, because they were admitted during a seasonal influenza pandemic period. Table 1 describes the clinical characters of the patients treated (O^+ group) and untreated (O^- group) with oseltamivir. No differences were found on any demographic variable between the two groups. The APACHE II score, SOFA score, and baseline platelet count at the time of VA-ECMO initiation were not statistically different between the two groups. One patient in the O^+ group developed HIT on day 12 and was weaned from VA-ECMO successfully on day 14.

Table 1. Characteristics of adults who received VA-ECMO for refractory cardiac failure (n = 82)

Variables	Oseltamivir- untreated group (n = 59)	Oseltamivir-treated group (n = 23)	*P*
Age	55 (10-81)	47 (13-76)	0.060*
Female, n (%)	19 (32)	6 (26)	0.589**
Days on ECMO treatment	8 (6-15)	10 (7-13)	0.399*
APACHE II	26 ± 8	27 ± 5	0.682*
SOFA	11 ± 3	10 ± 4	0.072*
Platelet counts on day 1 before cannulation ($\times 10^3/\mu L$)	179 (134-247)	199 (144-278)	0.329*
Complications during the first 8 days of ECMO treatment			
Sepsis, n (%)	5 (8)	2 (3)	0.531**
Hepatic dysfunction, n (%)	3 (5)	4 (17)	0.073**
CRRT, n (%)	37 (62)	3 (9)	0.832**
DIC, n (%)	17 (29)	2 (9)	0.079**
Circuit exchange, n (%)	3 (5)	1 (4)	0.832**
Thrombosis, n (%)	0 (0)	0 (0)	0.324**
HIT, n (%)	0 (0)	0 (0)	0.324**

Continuous data are presented as mean ± standard deviation or median (interquartile range).

VA-ECMO: venous-arterial extracorporeal membrane oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRRT: continuous renal replacement therapy; DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia.

* Mann-Whitney U test.

** Fisher exact or chi-square test.

Clinical outcomes

Overall, 85% of the patients developed thrombocytopenia, and 44% developed severe thrombocytopenia (platelet count < 50,000/μL). As shown in Fig. 2, the decrease of platelet counts was observed < 24 h after initiating VA-ECMO. The nadir platelet count was observed on day 4, and the platelet started to increase on day 8. The biphasic temporal pattern was seen in both groups (Fig. 2).

During the first 8 days of VA-ECMO initiation, the platelet counts in the O^+ group were higher than in the O^- group on day 2 (113,000 ± 62,700 vs. 85,700 ± 42,800/μL, P = 0.04), day 4 (94,800 ± 60,800 vs. 65,000 ± 39,800/μL, P = 0.02), day 6 (105,500 ± 64,600 vs. 71,500 ± 36,100/μL, P < 0.001), and day 8 (113,000 ± 71,800 vs. 68,000 ± 30,400/μL, P = 0.01). The patients in the O^+ group had higher median platelet counts at the nadir (77,000/μL, 6,000-169,000/μL), compared with the O^- group (49,000/μL, 2,000-168,000/μL; P = 0.04). A platelet count nadir < 50,000/μL was seen in 26% of the patients in the O^+ group, compared with 53% in the O^- group (P = 0.031). There was no difference in the time to platelet recovery. Platelet transfusions were administered in 4% of the patients in the O^+ group, compared with 32% in the O^- group (P = 0.022), and the O^+ group received small amounts of platelets (0.09 ± 0.42 vs. 0.95 ± 2.41 apheresis units; P = 0.007). There was a tendency towards fewer bleeding events in the O^+ group compared with the O^- group (9% vs. 29%, P = 0.052) (Table 2). In the O^+ group, there were no differences in the changes in platelet counts regardless of influenza status (P > 0.05) (Table 3).

Table 2. Changes in platelet count and outcomes of patients during the first 8 days of ECMO

Variables	Oseltamivir-untreated group (n = 59)	Oseltamivir-treated group (n = 23)	*P*
Platelet nadir ($\times 10^3/\mu L$)	49 (31-66)	77 (48-102)	0.040*
Day to platelet nadir	4 (3-6)	4 (2-7)	0.657*
Percentage of patients with platelet nadir < $50\times 10^3/\mu L$, n (%)	31 (53%	6 (26)	0.031**
Percentage of patients with platelet nadir < $100\times 10^3/\mu L$, n (%)	50 (85)	17 (74)	0.254**
Recovery time to platelet ≥ 100×103/μL (days)	4 (2-6)	3 (0-5)	0.134*
Administration of platelet transfusion (apheresis unit), n (%)	19 (32%)	1 (4%)	0.022**
Platelet transfusion times	1 (0-15)	0 (0-2)	0.002*
Amount of platelet transfusion	1 (0-17)	0 (0-2)	0.007*
Bleeding, n (%)	17 (29)	2 (9)	0.052**
Survival to discharge, n (%)	33 (56)	11 (48)	0.508**

Continuous data are presented as median (interquartile range).

ECMO: extracorporeal membrane oxygenation.

* Mann-Whitney U test.

** Fisher exact or chi-square test.

Table 3. Characteristics of the patients treating with oseltamivir during hospital stay (n = 23)

Variables	Influenza (n = 9)	No influenza (n = 14)	*P*
Days on ECMO treatment	13 (11-15)	9 (5-10)	0.014*
Hospital stay (days)	21 (15-29)	11 (5-26)	0.185*
APACHE II	27 ± 4	28 ± 6	0.165*
SOFA	9 ± 3	11 ± 5	0.776*
Platelet counts on d1 before cannulation ($\times 10^3/\mu L$)	147 (114-321)	221 (173-254)	0.777*
Platelet nadir ($\times 10^3/\mu L$)	77 (50-97)	78 (35-101)	0.753*
Day to PLT nadir	6 (3-7)	4 (2-5)	0.237*
Percentage of patients with platelet nadir < $50\times 10^3/\mu L$, n (%)	5 (56%)	3 (23%)	0.708**
Percentage of patients with platelet nadir < $100\times 10^3/\mu L$, n (%)	6 (67%)	9 (69%)	0.537**
Recovery time to platelet ≥ $100\times 10^3/\mu L$ (days)	4 (1-6)	3 (0-5)	0.481*
Administration of platelet transfusion (apheresis units), n (%)	1 (11)	0 (0)	0.391**
Platelet transfusion times, n (%)	0 (0-2)	0 (0-0)	0.212*
Amount of platelet transfusion, n (%)	0 (0-2)	0 (0-0)	0.212*
Survival to discharge, n (%)	5 (54)	6 (43)	0.433**

Continuous data are presented as mean ± standard deviation or median (interquartile range).

ECMO: extracorporeal membrane oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRRT: continuous renal

replacement therapy; DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia.

* Mann-Whitney U test.

** Fisher exact or chi-square test.

Prognosis analysis

No significant differences in survival to discharge were seen between the O^+ and O^- groups (48% vs. 56%, P = 0.508) (Fig. 3). Table 4 shows that among the variables possibly associated with survival, only the SOFA scores at the time of VA-ECMO initiation were independently associated with survival (OR = 1.12, 95% confidence interval (95% CI): 1.02-1.22, P = 0.015).

Table 4. Multivariate Cox proportional hazard analysis of factors influencing survival in all patients who received ECMO

Variables	Hazard ratio	95% CI		*P*
		Lower	Upper	
Univariable Analysis				
Age	1.017	0.998	1.037	0.083
Female	0.783	0.395	1.555	0.485
Oseltamivir treat	0.796	0.401	1.579	0.513
APACHE score	1.035	0.991	1.081	0.123
SOFA score	1.11	1.022	1.204	0.013
Sepsis	1.052	0.407	2.717	0.917
CRRT	0.915	0.489	1.713	0.782
DIC	1.318	0.675	2.575	0.418
Hepatic dysfunction	1.023	0.316	3.317	0.97
Multivariable analysis				
Age	1.012	0.99	1.035	0.281
Female	0.612	0.293	1.279	0.192
Oseltamivir treat	1.119	0.516	2.429	0.776
APACHE score	1.027	0.976	1.08	0.301
SOFA score	1.116	1.017	1.225	0.021
Sepsis	1.127	0.397	3.196	0.822
CRRT	0.767	0.377	1.563	0.466
DIC	1.294	0.629	2.644	0.484
Hepatic dysfunction	0.918	0.277	3.046	0.889
Final multivariable prediction model				
Age	1.014	0.993	1.035	0.199
Oseltamivir	1.051	0.509	2.168	0.893
SOFA score	1.118	1.022	1.223	0.015
CRRT	0.748	0.373	1.502	0.415

APACHE score, SOFA score, and DIC were obtained at ICU admission.

95% CI: 95% confidence interval; ECMO: extracorporeal membrane oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRRT: continuous renal replacement therapy; DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia.

Discussion

Severe thrombocytopenia is a common complication of ECMO [6]. Oseltamivir can be used to treat infection-associated thrombocytopenia [13, 14]. This study aimed to evaluate the effect of oseltamivir on attenuating severe thrombocytopenia during ECMO. The results suggest that oseltamivir could ameliorate VA-ECMO-related thrombocytopenia. These findings suggest the prophylactical potential of oseltamivir on severe thrombocytopenia associated with the initiation of VA-ECMO. This is the first study to provide evidence suggesting the effect of oseltamivir on the prophylaxis of severe thrombocytopenia induced by VA-ECMO.

The prevailing view has been that platelets are activated by the artificial surface of ECMO and impaired by high shear stress in the extracorporeal circuit, leading to an early decline in platelet count [19–21]. It could be hypothesized that platelet desialylation participates in this process through the translocation of intracellular Neu1 to the platelet surface, which contributes to increased clearance of the platelets. As observed in this study, platelet count dropped dramatically after the beginning of VA-ECMO, followed by a period until day 8–10, except for one patient in the O^+ group who developed HIT on day 12.

Oseltamivir, as a viral neuraminidase inhibitor, has been shown to significantly increase platelet counts in mouse models of anti-GPIba-mediated ITP by inhibiting platelet desialylation [22]. Oseltamivir was also successfully used to treat an adult ITP patient who responded poorly to conventional therapies, including corticosteroids, intravenous immunoglobulin (IVIG), recombinant human thrombopoietin, rituximab, danazol, and vindesine [23]. A multicenter and randomized controlled trial showed that platelet desialylation levels were increased significantly in septic patients and that the administration of oseltamivir attenuated thrombocytopenia associated with sepsis [14]. Recently, a retrospective analysis showed that oseltamivir increased the platelet counts regardless of influenza status [13], supporting the present study.

Aside from the platelet-reducing effect of the extracorporeal circuit, critical illness severity, and comorbid conditions have been shown to be associated with the development of thrombocytopenia in critically ill patients [24]. In this study, none of the examined complications (hepatic dysfunction, renal dysfunction, sepsis, HIT, thrombosis, and DIC) were associated with patient outcomes. Only the SOFA scores were associated with survival.

Thrombocytopenia increases the bleeding risk during ECMO, especially because of the need for anticoagulation to avoid circuit clogging, which leads to a higher threshold for platelet transfusion in

patients receiving ECMO compared with other critically ill patients [25]. Maintenance of platelet count above 100,000/μL has been recommended by the Extracorporeal Life Support Organization (ELSO) [26]. So far, platelet transfusion is often the only readily available treatment. In China, a platelet-count threshold of less than 50,000/μL is used for prophylactic platelet transfusion during ECMO. However, platelet transfusion is extremely costly and of a limited resource. More than that, the benefit of multiple platelet transfusions for patients undergoing ECMO remains unknown. Platelet transfusion is associated with increased risks of thrombosis and in-hospital mortality in large retrospective studies involving patients with platelet consumptive disorders [27]. Recently published studies suggest that a more restrictive platelet transfusion practice could be appropriate in critically ill neonates [28, 29]. In this study, oseltamivir attenuated thrombocytopenia during VA-ECMO and reduced the requirement for platelet transfusion. A trend towards fewer bleeding events was also seen in the O^+ group.

In this study, oseltamivir had no effect on out-hospital survival, although it led to significantly higher platelet counts by day 8 on ECMO, which is considered as a predictor of poor outcome in ECMO patients after cardiac surgery [6]. The reason for this contradiction might be the small number of patients treated with oseltamivir.

This study has some limitations and must be interpreted with care. First, the observational nature of the study relied on the availability of recorded data and was prone to selection bias. Second, the small number of ECMO patients treated with oseltamivir limited the statistical power of the analysis. Since oseltamivir has been shown to attenuate severe thrombocytopenia, regardless of influenza status, it might be widely used in ECMO patients in future prospective clinical trials if not contraindicated. We only evaluated the effect of oseltamivir on preventing severe thrombocytopenia in patients receiving VA-ECMO, and the findings might not be generalizable to veno-venous extracorporeal membrane oxygenation (VV-ECMO).

Third, although the expression of platelet activation markers by flow cytometry is considered as an alternative indicator for platelet function [30–33], this was not performed in this study, since platelet aggregation and adherence results need to be interpreted with caution during thrombocytopenia [34].

Conclusions

Oseltamivir increased the median platelet count nadir, decreased the prevalence of severe thrombocytopenia, and reduced platelet transfusions. Those results support the clinical effect of oseltamivir as a prophylaxis to prevent VA-ECMO-induced severe thrombocytopenia. Future studies are necessary to confirm this benefit.

Abbreviations

ECMO
extracorporeal membrane oxygenation

VA-ECMO
venous-arterial extracorporeal membrane oxygenation
SOFA
Sequential Organ Failure Assessment
VV
veno-venous
VA
veno-arterial
AMRs
Ashwell-Morell receptors
Neu1
neuraminidase
CS
cardiogenic shock
CA
cardiac arrest
ICU
intensive care unit
D
day
APACHE
Acute Physiology and Chronic Health Evaluation
CRRT
continuous renal replacement therapy
DIC
disseminated intravascular coagulation
HIT
heparin-induced thrombocytopenia
aPTT
activated partial thromboplastin time
IQR
interquartile range
VV- ECMO
veno-venous ECMO
APACHE II
Acute Physiology and Chronic Health Evaluation II
95% CI
95% confidence interval

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Qilu Hospital of Shandong University before the study began. The patients or their legal representative signed the informed consent form.

Consent for publication

Written informed consent was obtained from the patients or their legal representative for publication of this article and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YL designed the study and drafted the manuscript.

LW participated in the design of the study helped to draft the manuscript.

JZ collected the medical data.

HH performed the statistical analysis.

HL participated in coordination and helped to collect the medical data.

CL participated in the statistical analysis and data curation.

HG embellished the manuscript.

YC conceived of the study and helped to draft the manuscript.

XC proofread the manuscript.

All authors read and approved the final manuscript.

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Figures

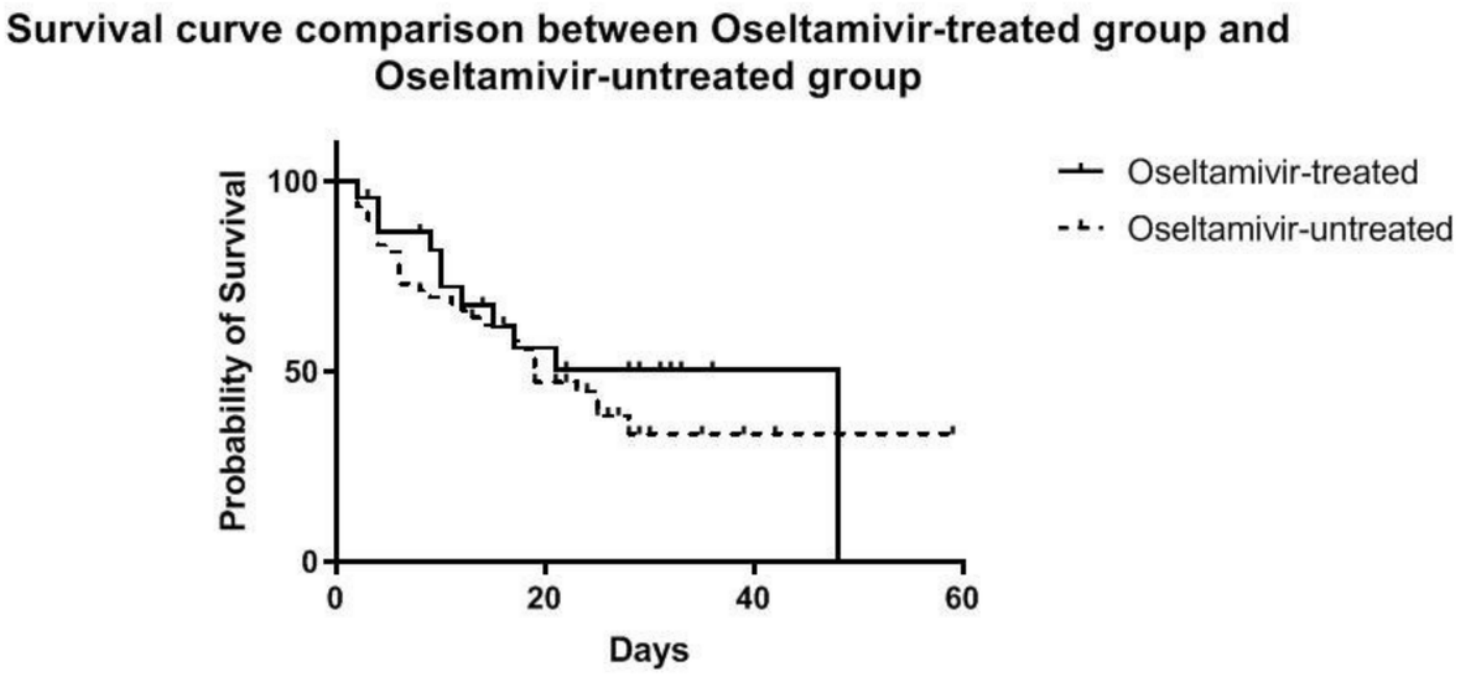

Figure 3

Estimated survival of patients during veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support and until discharge stratified by the oseltamivir -treated and -untreated groups.