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Extracorporeal membrane oxygenation in traumatic brain injury – A retrospective, multicenter cohort study

Marius Marc-Daniel Mader[a,b], Rolf Lefering[c], Manfred Westphal[a], Marc Maegele[c,d], Patrick Czorlich[a,*]

[a] Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Hamburg 20246, Federal Republic of Germany
[b] Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA
[c] Institute for Research in Operative Medicine (IFOM), University Witten/Herdecke, Cologne, Federal Republic of Germany
[d] Department for Trauma and Orthopedic Surgery, Cologne-Merheim Medical Center (CMMC), University Witten/Herdecke, Federal Republic of Germany

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ABSTRACT

Introduction: Patients with traumatic brain injury (TBI) regularly require intensive care with prolonged invasive ventilation. Consequently, these patients are at increased risk of pulmonary failure, potentially requiring extracorporeal membrane oxygenation (ECMO). The aim of this work was to provide an overview of ECMO treatment in TBI patients based upon data captured into the TraumaRegister DGU® (TR-DGU).
Methods: A retrospective multi-center cohort analysis of patients registered in the TR-DGU was conducted. Adult patients with relevant TBI ($AIS_{Head} \geq 3$) who had been treated in German, Austrian, or Swiss level I or II trauma centers using ECMO therapy between 2015 and 2019 were included. A multivariable logistic regression analysis was used to identify risk factors for the need for ECMO treatment.
Results: 12,247 patients fulfilled the inclusion criteria. The overall rate of ECMO treatment was 1.1% (134 patients). Patients on ECMO had an overall hospital mortality rate of 38% (51/134 patients) while 13% (1523/12,113 patients) of TBI patients without ECMO therapy died. Male gender ($p = 0.014$), AIS_{Chest} 3+ ($p<0.001$), higher Injury Severity Score ($p<0.001$) and packed red blood cell (pRBC) transfusion ($p<0.001$) were associated with ECMO treatment.
Conclusion: ECMO therapy is a potentially lifesaving modality for the treatment of moderate-to-severe TBI when combined with severe chest trauma and pulmonary failure. The in-hospital mortality is increased in this high-risk population, but the majority of patients is surviving.

Introduction

The global incidence of traumatic brain injury (TBI) is the highest in North America and Europe [1]. Moderate and severe TBI only make up a small proportion of all TBI but are usually associated with treatment in an intensive care unit (ICU) and in many cases with invasive ventilation therapy [1,2]. Due to the severity of the injury, TBI is one of the leading causes of death in young adults worldwide. In addition to the primary injuries, complications during the course of ICU treatment, such as hypoxemia due to acute respiratory distress syndrome (ARDS), also determines mortality [3]. As a rescue option for therapy-refractory ARDS, extracorporeal membranous oxygenation (ECMO) has been introduced back in the early 1970ies [4]. Although this method has developed into an established ICU therapy over the last two decades, data on ECMO treatment in patients with TBI are sparse. Most studies published are single-center case series, which, however, due to their methodological nature, can neither provide epidemiological data on the rate of the need for ECMO nor can they identify risk factors associated with the need for ECMO in TBI patients [5]. Such questions can only be solved by systematically recorded data, e.g. from registries, and are highly relevant for optimum governmental health care planning with only a limited number of ECMO treatment places available, especially in the context of the current COVID-19 pandemic [6].

The aim of this work was to determine the incidence, potential risk factors and mortality in patients with severe to moderate TBI in need of ECMO treatment by using systematically recorded data into the TraumaRegister DGU® (TR-DGU) from German, Austrian and Swiss hospitals.

* Corresponding author.
E-mail address: p.czorlich@uke.de (P. Czorlich).

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List of abbreviations

AIS	Abbreviated Injury Scale
ASA	American Society of Anesthesiologists
AUC	Akademie der Unfallchirugie GmbH (Academy for Trauma Surgery)
CI	Confidence Interval
CPR	Cardiopulmonary Resuscitation
ECMO	Extracorporeal Membrane Oxygenation
ER	Emergency Room
ICU	Intensive Care Unit
ISS	Injury Severity Scale
OR	Odds Ratio
pRBC	packed red blood cell
RISC	Reversed Injury Severity Score
SD	Standard Deviation
SMR	Standardized Mortality Ratio
TBI	Traumatic Brain Injury
TR-DGU	TraumaRegister DGU®

Patients and methods

Trauma register DGU®

The TR-DGU was founded in 1993. The aim of this multi-center database is a pseudonymized and standardized documentation of severely injured patients. Data are collected prospectively in four consecutive time phases from the site of the trauma until discharge from hospital: (A) prehospital phase, (B) emergency room (ER) and initial surgery, (C) intensive care unit (ICU) and (D) discharge. The documentation includes detailed information on demographics, injury pattern, comorbidities, pre- and in-hospital management, ICU course, relevant laboratory findings including data on transfusion and outcome of each individual. The inclusion criterion is admission to hospital *via* emergency room with vital signs and subsequent transfer to ICU or intermediate care unit or death before admission to ICU.

The infrastructure for documentation, data management, and data analysis is provided by the AUC - *Academy for Trauma Surgery*, a company affiliated to the *German Trauma Society*. The scientific leadership is provided by the *Committee on Emergency Medicine, Intensive Care and Trauma Management* (*Sektion NIS*) of the German Trauma Society. The participating hospitals submit their pseudonymized data into a central database *via* a web-based application. Scientific data analysis is approved according to a peer review procedure established by *Sektion NIS*.

The participating hospitals are primarily located in Germany (90%), but a rising number of hospitals of other countries contribute data as well. Currently, approximately 30,000 cases from over 650 hospitals are entered into the database per year. Participation in the TR-DGU is voluntary. For hospitals associated with TraumaNetzwerk DGU® however, the entry of at least a basic data set is obligatory for reasons of quality assurance. The basic data set is mostly provided by smaller hospitals and contains only a limited range of variables, e.g. no surgical procedures and no information on ECMO treatment. The standard data set with more detailed information is mostly submitted by high-level trauma centers.

The present study is in line with the publication guidelines of the TraumaRegister DGU® and registered as TR-DGU project ID 2019-041. Furthermore, it was approved by the local ethic committee (WF-059-18).

Study cohort and variables

Although the TR-DGU database comprises a wide range of information for each case captured, only patients $\geq$ 16 years of age treated in participating German, Austrian, and Swiss level I and II hospitals between 2015 and 2019 with a predominately moderate-to-severe TBI (Abbreviated Injury Scale $(AIS)_{head} \geq 3$) requiring intensive care on a corresponding unit were potentially eligible for analysis. Patients documented by using the basic TR-DGU documentation were excluded a-priori as this format does not include information on ECMO treatment. Early transfers from other hospitals (<48 h) were not considered because no outcome information for these patients can be retrieved from the TR-DGU database. Patients who died within 48 h after admission were excluded in order to control for the effect of initial withdrawal of care. Missing data of ECMO was an exclusion criterion on patient level. Finally, hospitals that did not perform any ECMO therapy during the observation period (in any patient, also non-TBI) were excluded since it was assumed that this treatment is not available there.

The primary outcome parameter in this analysis was in-hospital mortality. Secondary outcome parameter was the Glasgow Outcome Scale at discharge. Variables extracted from the TR-DGU included basic demographic data, trauma mechanism, pre-injury American Society of Anesthesiologists (ASA) Physical Status Classification, and packed red blood cell (pRBC) transfusion until 48 h after admission to the ICU. Parameters of trauma severity were Injury Severity Score (ISS), AIS of different body regions, Eppendorf–Cologne-Scale, and the Revised Injury Severity Classification, version II (RISC-II) predicting the risk of death [7–9].

Statistical methods

Statistical analyses were performed using SPSS statistical software (SPSS Version 24.0, IBM Inc., Armonk, New York, USA). Data are presented as mean with standard deviation (SD) for continuous variables, and as numbers and/or percentages for categorical variables. In case of skewed data, median with inter-quartile range (IQR) was used instead of mean/SD. Differences in frequencies were evaluated with Fisher's exact test (2×2 tables) and chi-squared test with Yates correction (larger tables), and differences in ordinal or continuous measurements were evaluated with Mann–Whitney U-test. The significance level has been set at 0.05, but due to multiple testing significant results have to be interpreted with caution. Finally, a multivariable logistic regression analysis was used to identify risk factors for the need of ECMO treatment. The model included the following predictors: age, sex, overall injury severity (ISS), severity of chest trauma, polytrauma according to the Berlin definition [10], pRBC transfusion, unconsciousness (GCS $\leq$ 8), ventilation required on ICU, interhospital transfer, and hospital level of care. From all predictors suggested by experts only those with $p<0.20$ were left in the final model. Results are presented as odds ratios with 95% confidence interval (CI).

Results

The inclusion criteria were met by 12,247 patients from 73 hospitals including 134 patients (1.1%) treated with ECMO (Fig. 1). ECMO treatment was performed in 49 participating hospitals; out of these, 47 provided care for 1–6 patients and two for 10 or more patients within the observation period (Fig. 2). The remaining 24 hospitals had the capability to perform ECMO but did not apply this technology in TBI patients.

Patients who were treated with ECMO were younger (49.8 vs 56.6 years of age; $p < 0.001$), more frequently male (81% vs 71%; $p = 0.014$) and had a higher median ISS (34vs 24 points;

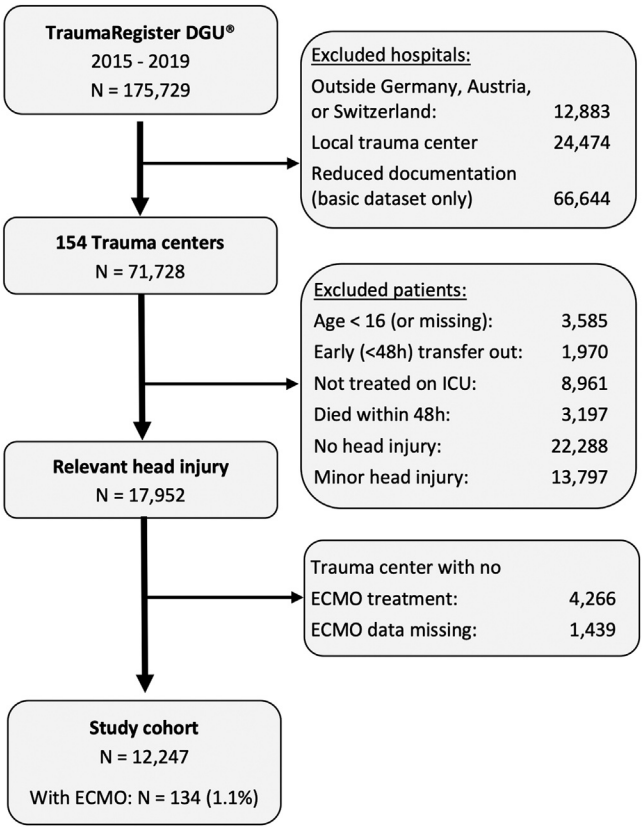

Fig. 1. Flow Chart of excluded and included patients of the study cohort.
ECMO Extracorporeal Membrane Oxygenation; *ICU* Intensive Care Unit.

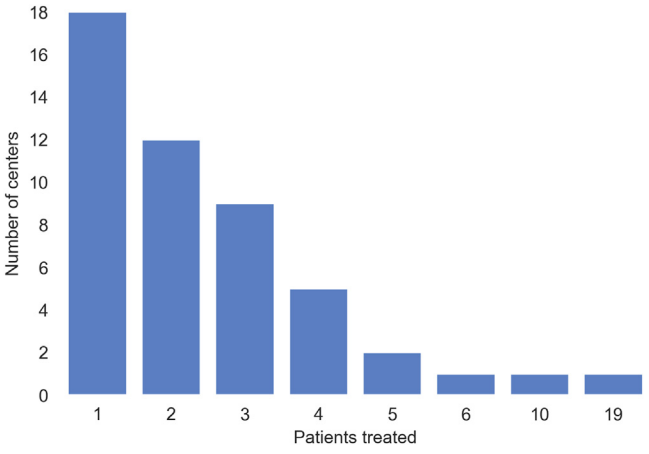

Fig. 2. Number of TBI patients with ECMO therapy per trauma center, during the whole study period
ECMO Extracorporeal Membrane Oxygenation.

$p < 0.001$). They had suffered less often from an isolated TBI (13% vs 35%, $p < 0.001$) but had sustained more often a polytrauma (58% vs 27%, $p < 0.001$) and injuries to the chest (64% vs. 30%; $p < 0.001$). The most common mechanism of injury in patients in need for ECMO was a road traffic crash (58%) while patients not in need for ECMO had equally been involved in road traffic crashes (40%) and low falls (39%).

Patients requiring ECMO who had been directly admitted to a trauma center presented more often in shock (20% vs 8%, $p < 0.001$), were more often unconscious with a Glasgow Coma Scale ≤ 8 (53% vs. 38%, $p = 0.001$), had a higher rate of pre-hospital intubation (69% vs 45%, $p < 0.001$), required more cardio-pulmonary

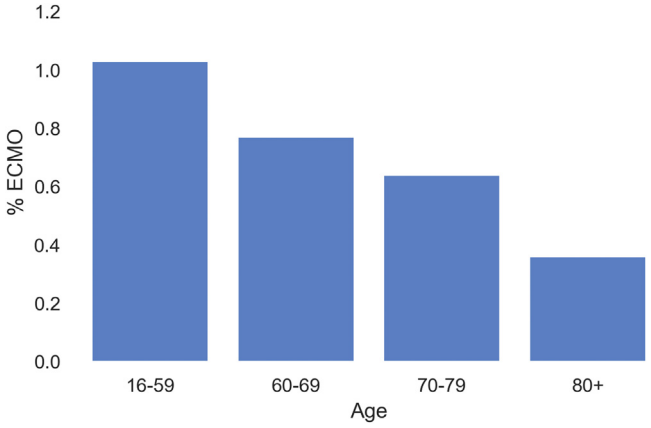

Fig. 3. Prevalence of ECMO treatment in different age groups.
ECMO Extracorporeal Membrane Oxygenation.

resuscitation (11% vs 3%, $p < 0.001$), and had an increased need for vasopressors (29% vs. 12%, $p < 0.001$). They also required more packed red blood cell transfusions (39% vs 9%, $p < 0.001$) and had an increased risk of death based on the RISC II score (29% vs 16%, $p < 0.001$).

ECMO patients spent longer on ventilators (median 9 days [IOR 4–24 days] vs 1 day [IQR 0–10 days] $p < 0.001$), were treated longer on the ICU (median 15 days [IQR 7–29 days] vs 7 days [IQR 2–17] $p < 0.001$) and had a longer overall hospital stay (median 20 days [IQR 10–40] vs 15 days [IQR 8–25 days] $p < 0.001$). Sepsis was more often documented for patients on ECMO (33% vs 9%, $p < 0.001$) and the overall in-hospital mortality was significantly higher (38% vs 13%, $p < 0.001$; see Table 1). The reasons for the death of the patients were primarily organ failure/ARDS in the ECMO group and TBI in the non-ECMO group (Table 3). A favorable outcome at discharge defined as a Glasgow Outcome Scale of 4 and 5 was documented for 39 patients (48% of survivors) in the ECMO group and 7725 patients (74% of survivors) in the non-ECMO group.

The rate of ECMO treatment differed between different age groups and was highest in the age group of 16–59 years with 1.4% and decreased to 0.5% in the age group over 80 years (see Fig. 3).

The annual incidence of ECMO treatment per 1000 TBI cases, considering also treatment in trauma centers without ECMO availability, between 2016 and 2019 is presented in Fig. 4.

The following risk factors for an ECMO therapy were identified in multivariable analysis (Table 2): younger age, male sex, higher Injury Severity Score, severity of thoracic trauma, polytrauma, pRBC transfusion, requirement for ventilation on ICU, and unconsciousness. The predicted probability for ECMO ranged from 0.01% to 23%.

Finally, we analyzed factors that might be associated with a higher risk for a case fatality in patients undergoing an ECMO therapy and summarized our findings in Table 3. Detailed information about the time of death can be found in the Kaplan–Meier plot in Fig. 5.

Discussion

The present study systematically describes frequencies, risk factors and outcomes of patients with moderate-to-severe TBI in need for ECMO treatment based upon prospectively collected data into a standardized multinational and multicenter registry. The results may add to the planning and allocation of resources in times of a pandemic in which different entities may compete for this treatment option. An optimum allocation of resources is also important in this context as patients with trauma-related ARDS may display

Table 1
Demographic, clinical and outcome data of the study cohort.

	Missing Data	ECMO $n = 134$	No ECMO $n = 12{,}113$	p-value
Age (years)*	0%	49.8 (20.1)	56.6 (21.2)	<0.001
Male patients	0%	108 (80%)	8554 (70%)	0.014
Injury Severity Score*	0%	35.9 (14.6)	24.6 (11.2)	<0.001
Penetrating trauma	4%	1 (0.8%)	189 (1.6%)	0.73
Severe head injury (AIS 4+)	0%	87 (65%)	7453 (62%)	0.47
Isolated head injury	0%	17 (13%)	4294 (35%)	<0.001
Chest trauma (AIS 3+)	0%	86 (64%)	3674 (30%)	<0.001
Abdominal trauma (AIS 3+)	0%	25 (19%)	594 (5%)	<0.001
Extremity/pelvic trauma (AIS 3+)	0%	45 (34%)	1673 (14%)	<0.001
Polytrauma (Berlin definition)	0%	78 (58%)	3285 (27%)	<0.001
Injury mechanism: road traffic	2%	74 (55%)	4814 (40%)	<0.001
Injury mechanism: low fall	2%	28 (21%)	4583 (39%)	<0.001
Injury mechanism: high fall	2%	22 (17%)	1666 (14%)	0.38
Pre-injury ASA 3/4	10%	30 (25%)	2463 (22%)	0.52
Surgical intervention for head injury	0%	59 (44%)	4925 (40%)	0.43
Number of surgical procedures#	0%	2 [1 - 5]	1 [0 - 3]	<0.001
Primary admitted patients only				
No. of patients	not applicable	105	9863	
Unconscious (GCS ≤ 8)	7%	51 (53%)	3482 (38%)	0.004
Pre-hospital intubation	3%	69 (69%)	4284 (45%)	<0.001
Thorax drainage	3%	6 (6.0%)	309 (3.2%)	0.143
Catecholamines	3%	29 (29%)	1156 (12%)	<0.001
Cardio-pulmonary resuscitation	3%	11 (11%)	287 (3%)	<0.001
Pre-hospital volume (ml) #	3%	1000 [500–1000]	500 [500–1000]	0.001
Eppendorf Cologne Scale#	10%	2 [1 - 4]	1 [0 - 3]	<0.001
Normal light reaction	8%	60 (61%)	6809 (75%)	0.008
Normal pupil size	5%	70 (70%)	7513 (79%)	0.081
Shock prehospital (BP≤90 mmHg)	14%	17 (20%)	681 (8%)	<0.001
pRBC transfusion	0%	41 (39%)	913 (9%)	<0.001
Outcome (all patients)				
Ventilation days#	0%	9 [4 - 24]	1 [0 - 10]	<0.001
ICU days#	0%	15 [7 - 29]	7 [2 - 17]	<0.001
Days in hospital#	0%	20 [10 - 40]	15 [8 - 25]	<0.001
Sepsis	2%	43 (33%)	1106 (9%)	<0.001
Multiple organ failure	1%	88 (68%)	3585 (30%)	<0.001
Hospital mortality	0%	51 (38%)	1523 (13%)	<0.001
Risk of death (based on RISC II)	0%	29%	16%	<0.001
Glasgow Outcome Scale (survivor only)	1%			<0.001
2 persistent vegetative state		7 (9%)	595 (6%)	
3 severe disability		35 (43%)	2161 (21%)	
4 moderate disability		27 (33%)	3052 (29%)	
5 minor/no disability		12 (15%)	4673 (45%)	

ASA American Society of Anesthesiologists; BP Blood Pressure; ECMO Extracorporeal Membrane Oxygenation; GCS Glasgow Coma Scale; ICU Intensive Care Unit; pRBC Packed Red Blood Cell; RISC Reversed Injury Severity Score.
* Mean with standard deviation.
# Median with interquartile range.

Table 2
Multivariable logistic regression analysis for risk of an ECMO treatment.

	Coefficient	Odds ratio [95% CI]	p-value
Age (reference 16–59 years of age)			
60–69 years of age	−0.12	0.89 [0.53 - 1.48]	0.65
70–79 years of age	−0.18	0.84 [0.50 - 1.42]	0.51
80 years of age and older	−0.56	0.59 [0.30 - 1.15]	0.12
Gender (reference: female)			
male	0.53	1.70 [1.09 - 2.64]	0.018
Chest injury severity (reference: AIS 0–2)			
AIS_{Chest} 3	0.49	1.63 [1.01 - 2.62]	0.045
AIS_{Chest} 4	0.91	2.48 [1.36 – 4.54]	0.003
AIS_{Chest} 5	1.28	3.59 [1.75 - 7.38]	0.001
Abdominal injury severity (reference: AIS 0–2)			
$AIS_{Abdominal}$	0.20	1.23 [0.73 - 2.07]	0.45
Extremities injury severity (reference: AIS 0–2)			
$AIS_{Extremities/Pelcic}$	0.12	1.13 [0.72 - 1.77]	0.61
Injury Severity Score (per point)	0.02	1.02 [1.00 - 1.04]	0.02
Number of operative interventions (reference: no interventions)			
1–2 operative interventions	0.14	1.16 [0.71 - 1.87]	0.56
≥ 3 operative interventions	−0.28	0.76 [0.44 - 1.30]	0.32
pRBC transfusions until ICU admission (reference: no transfusion)			
1–9 pRBC transfusions	1.07	2.91 [1.83 - 4.64]	<0.001
≥ 10 pRBC transfusion	1.38	3.99 [1.79 - 8.87]	<0.001
Constant	−6.34		<0.001

AIS Abbreviates Injury Scale; CI Confidence Interval; ECMO Extracorporeal Membrane Oxygenation; ISS Injury Severity Scale; pRBC Packed Red Blood Cell.

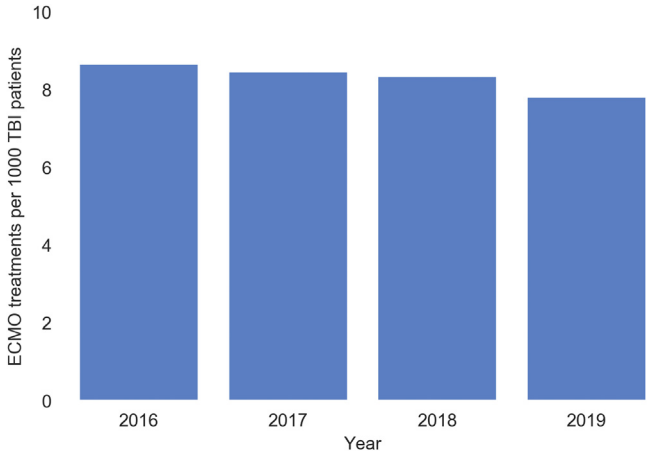

Fig. 4. Prevalence of ECMO treatment per 1000 TBI patients between 2016 and 2019.
The bar chart is based on all TBI patients irrespective of the availability of ECMO therapy in the treating trauma center. The year 2015 is not shown because of incomplete patient inclusion from this year.
ECMO Extracorporeal Membrane Oxygenation; *TBI* Traumatic Brain Injury.

Table 3
Cause of death for TBI patients with and without ECMO treatment.

	ECMO $n = 51$	No ECMO $n = 1523$
TBI related	14 (28%)	1005 (66%)
Hemorrhage	0 (0%)	19 (1%)
Organ failure / ARDS	32 (63%)	319 (21%)
Other reasons	3 (6%)	142 (9%)
Unknown / missing	2 (4%)	38 (3%)

ARDS Acute Respiratory Distress Syndrome; ECMO Extracorporeal Membrane Oxygenation; TBI Traumatic Brain Injury.

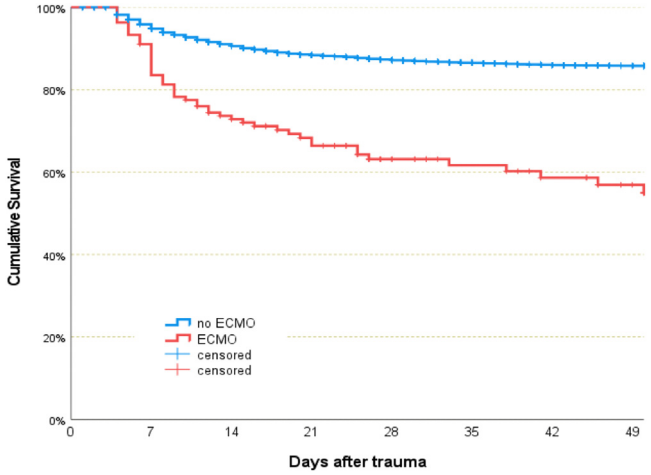

Fig. 5. Kaplan–Meier plot.
Kaplan–Meier plot of survival times in patients with and without ECMO therapy. Patients transferred alive to another hospital were considered as censored. Patients discharged home, or transferred to a rehabilitation center, or those who died, were considered to have their outcome observed (no censoring). At day 50, 84 patients were still at risk in the ECMO group. Regard that only patients who survived the first 48 h were included here.
We only censored those cases who were transferred alive to another hospital. Those patients had a similar risk of death as those still under observation. Patients discharged home, or transferred to a rehabilitation center, or those who died, were considered to have their outcome observed (no censoring).

a better prognosis while on ECMO as compared to patients with any another underlying disease [5,6,11,12].

A total of 1.1% of all patients included in this analysis received ECMO treatment. As previously shown, the majority of patients in need of ECMO were male but far older compared to other studies with an average age of 49.8 years [5,13–16]. Interestingly, the most common cause of injury in this cohort was traffic related as reported before despite the fact that the overall most common cause for moderate-to-severe TBI in the TR-DGU are low falls [16,17]. The rate of moderate-to-severe chest trauma with 64.2% and the mean ISS with 35.9 points were also comparable to the systematic review published by Wang and co-workers but lower than in other published series [5,13,16]. Of the 134 patients in need for ECMO, 51 (38.1%) died in-hospital during their later courses. This mortality rate may indicate that despite TBI with potential intracranial hemorrhage and anticoagulation to successfully perform ECMO treatment, this treatment does not necessarily lead to poor outcome. Our mortality rate is slightly higher than the 30.3% in a recently published systematic review investigating ECMO in trauma patients but within the range of 21% to 61.5% of other publications [14,16,18–20]. In particular, treatment with extracorporeal devices such as ECMO or pumpless extracorporeal lung assistance in TBI patients is not necessarily associated with a poor prognosis, but rather is survived in a relevant number of cases and allows a lung-protective ventilation which leads to better control of the intracranial pressure (ICP) [21].

In the current study cohort, most hospitals (82%) were large level 1 trauma centers but with a rather limited number of patients treated with ECMO; most centers contributed only 1–2 patients during the observation period. However, this does not necessarily reflect the overall number of ECMO cases and experience of these centers. It might be worth to be discussed, whether ECMO therapy in high-risk populations like TBI-patients could benefit from treatment in dedicated centers with higher caseloads. Moreover, it should be pointed out that the majority of patients of the study cohort were treated in Germany and country-specific handling of ECMO indications has been previously discussed. It was shown that in the context of the COVID-19 pandemic, ECMO patients in Germany were older on average and demonstrated a higher mortality rate than in other western European countries, possibly reflecting more liberal ECMO indications leading to a broader availability of ECMO therapy [22]. Interestingly, although the age of ECMO patients in the current TBI cohort was significantly higher than in comparative studies from other countries, the mortality rate was not increased.

ECMO patients had an increased need for ventilation on intensive care and early pRBC transfusions as well as more severe thoracic injuries. These factors have also been identified as risk factors for ARDS over the recent years [13–15,23–25]. The association between pRBC transfusion and an increased risk for ARDS in trauma patients is well established [26–28]. Moreover, it has been reported that almost all patients on ECMO also required pRBC transfusions [29]. As expected, patients in the present cohort treated with ECMO spent significantly longer on ventilation as well as on the intensive care unit (ICU), which corresponds to the current literature of ARDS after TBI [30].

The analysis showed that ECMO patients had a worse outcome than patients without ECMO. This association should not be interpreted as a causal relation. Often ECMO is applied when the situation of the patient deteriorates, as shown with a higher rate of sepsis and multiple organ failure. Thus, ECMO might rather be an indicator for a worsening of the patient's clinical course. It is a limitation of our study that TR-DGU neither includes a daily monitoring on ICU, nor is the day of onset of ECMO documented. This limits the use of classical analyses like matched pairs or propensity score matching.

The present study has some further limitations. Although data is prospectively captured into the TR-DGU database, the data anal-

ysis is retrospective. Well-known limitations of the TR-DGU are that the participation is voluntary despite the fact that the TR-DGU captures data from almost all German trauma centers, lack of details regarding outcome, especially long-term outcome, and the dominance of German hospitals within the TR-DGU. Due to the structure of the TR-DGU, causation on time and implementation of ECMO treatment remains somewhat speculative. In contrast to single center reports, detailed information on interval and type of ECMO applied, e.g. VV or VA ECMO, therapeutic effects and complications, e.g. oxygenator thrombosis, ventilation modes and settings, anticoagulation, bleeding complications including hemorrhagic progression, and causes of mortality remain elusive. In particular, information on anticoagulation would be relevant given reports that longer heparin-free time may be possible with ECMO therapy in TBI patients [31].

Conclusions

Patients with moderate-to-severe TBI were treated with ECMO in about 1% of all cases, representing a potentially lifesaving modality for the treatment of moderate-to-severe TBI when combined with severe chest trauma, packed red blood cell transfusion and pulmonary failure. The in-hospital mortality is increased in this high-risk population, but the majority of patients is surviving. TBI-patients with ECMO treatment presented with a higher rate of multiple organ failure and sepsis compared to TBI patients without ECMO treatment. Nevertheless, the indication for an ECMO treatment in TBI patients remains a case-by-case decision.

Declarations

Funding / conflict of interest

Rolf Lefering declares that his institution (IFOM) has an ongoing service agreement with AUC GmbH, the owner of the TraumaRegister DGU database, which includes statistical support for scientific analyses using registry data. All other authors declare that they have no conflicts of interest.

Ethics approval / consent

The present analysis is in line with the publication guidelines of the TraumaRegister DGU® and registered as TR-DGU project ID 2019-041. Furthermore, the analysis plan was approved by the local ethic committee (WF-059-18).

Data availability

The publication guideline of the TraumaRegister DGU®, at present, denies external access to raw data captured in the registry.

Code availability

Statistical operations are reported in the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Marius Marc-Daniel Mader: Conceptualization, Investigation, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Rolf Lefering:** Formal analysis, Data curation, Supervision, Methodology, Writing – review & editing. **Manfred Westphal:** Supervision, Writing – review & editing. **Marc Maegele:** Conceptualization, Investigation, Formal analysis, Data curation, Supervision, Writing – review & editing. **Patrick Czorlich:** Conceptualization, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.

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