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MAIN TEXT

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Outcome after veno-venous extracorporeal membrane oxygenation in elderly compared to younger patients: A 14-year retrospective observational study

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Abstract

Background: The outcome after veno-venous extracorporeal membrane oxygenation in elderly patients is supposed to be unsatisfactory. Our primary aim was to determine the influence of advanced age on short- and long-term outcomes; the secondary aim was to analyze risk factors for impaired outcomes.

Methods: Between January 2006 and June 2020, 755 patients received V-V ECMO support at our department. Patients were grouped according to age (18–49.9, 50–59.9, 60–69.9, ≥70 years old), and then retrospectively analyzed for short- and long-term outcomes. Risk factors for in-hospital mortality and death during follow-up were assessed using multivariate regression analysis.

Results: Duration of V-V ECMO support was comparable between all groups median (8–10 days, $p = 0.256$). Likewise, the weaning rate was comparable in all age groups 68.2%–76.5%; ($p = 0.354$), but in-hospital mortality was significantly climbing with increasing age (<50 years 30.1%/n = 91 vs. 50–59.9 years 37.1%/n = 73, vs. 60–69.9 years 45.6%/n = 78 vs. ≥70 years 51.8%/n = 44; $p < 0.001$). Older age groups also showed significantly reduced cerebral performance category scores. The multivariate logistic analysis yielded age, acute and chronic hemodialysis, bilirubin on day 1 of support, malignancy, and primary lung disease as relevant risk factors for in-hospital mortality. Age, coronary artery disease, presence of another primary lung disease, malignancy, and immunosuppression were risk factors for death during follow-up.

Conclusion: In V-V ECMO patients, advanced age is associated with more comorbidity, impaired short- and long-term outcome, and worse neurological outcome.

KEYWORDS

extracorporeal membrane oxygenation, long-term outcome, respiratory failure, survival

1 | INTRODUCTION

After evolving from cardiopulmonary bypass and first applications in young adult and pediatric patients,[1-3] V-V ECMO was adopted as a reasonable tool for respiratory support in patients of almost any age who do not respond to conventional treatment.

Age per se is not a contraindication for V-V ECMO, its use in elderly patients remains controversial because of increased morbidity and potentially poor prognosis.[4] It is common sense that advanced age represents a relative contraindication for V-V ECMO in patients with respiratory failure. The risk of death seems to increase with age, although there is no defined threshold[5]. Thus, decisions with regard to support should be made on a patient-by-patient basis. This retrospective analysis includes 14 years of experience gained at the Regensburg University Medical Center in supporting elderly patients with V-V ECMO. Our primary aim was to determine the influence of advanced age on short- and long-term outcomes; the secondary aim was to analyze risk factors for impaired outcomes.

2 | MATERIALS AND METHODS

This retrospective observational study was approved by the ethics committee of the University Regensburg (study number 20-2058-104) and followed STROBE guidelines. We used data from our institutional database and medical records. Between January 2006 and June 2020, 1525 patients were supported with ECMO at our department, of whom 755 had V-V ECMO support. Patients who switched to other ECMO configurations were excluded from the study. The patients were divided into 2 cohorts: patients with lung failure due to a pulmonary pathology (LF due to pulmonary reason) and patients with lung failure due to an extrapulmonary etiology (LF due to extrapulmonary reason). In addition, the patients were categorized into four age groups: 18–49.9, 50–59.9, and elderly 60–69.9 or ≥70 years. Regarding the definition of respiratory failure requiring ECLS and ECMO circuit composition, we refer to previous publications[6,7].

In most patients, cannulation was achieved via a femoral or a jugular vein using the Seldinger technique. Vessel diameters were examined with ultrasound prior to implantation, whenever possible. Correct cannula placement was controlled by chest x-ray and CT scan.

The prospectively acquired data were retrospectively analyzed. Follow-up data were obtained by contacting survivors, their relatives, or their general practitioners, median follow-up time was 1104.5 days (IQR 388.0–2278.3). At hospital discharge, the neurological outcome was evaluated by means of the cerebral performance category (CPC) score[8]. The performance status during follow-up was assessed with the Eastern Co-operative of Oncology Group (ECOG) score.[9]

2.1 | Statistical methods

Continuous data are presented as mean (standard deviation [SD]) or as median (interquartile range [IQR: q1–q3]) depending on the underlying distribution. Percentage values in the running text are related to the entire cohort or the subgroup as 100%. In the tables, percentage values either relate to the entire cohort or subgroups. Categorical variables are presented as absolute and relative frequencies. Comparisons between groups were done with the Mantel–Haenszel test for ordinally scaled variables, and the Chi-squared test of independence for dichotomous and nominally scaled variables. The Kruskal-Wallis-Test was used for continuous data.

Risk factors for hospital mortality and death during follow-up were identified by means of multivariable logistic regression analysis and Cox's regression analysis. Prior to multivariate analysis, univariate risk factor analysis was carried out; relevant variables were chosen for the analysis. Collinearity was ruled out. The follow-up was assessed with Kaplan–Meier analysis. A p-value of <0.05 was considered statistically significant. Statistical analyses were done with IBM SPSS software (version 26; IBM Corp., Armonk, NY, USA).

3 | RESULTS

The 755 patients in the study group included 302 patients aged 18–49.9 (mean 36.5 years), 197 patients aged 50–59.9 (mean 54.6 years), 171 patients aged 60–69.9 (mean 64 years), and 85 patients aged ≥70 years (mean 73 years; 62 patients aged 70–74.9 years, 21 patients aged 75–79.9 years, and 2 patients aged ≥80 years). As depicted in Table 1, patient morbidity was rising along with age. In 59.5%, lung failure was caused by a pulmonary pathology (predominantly in patients aged 50–69.9 years). The most common pulmonary cause was bacterial pneumonia with comparable incidences in all age groups. However, aspiration pneumonia was more common in the patients aged over 60 years (60–69.9 years 10.5%, $n = 18$ and ≥70 years 10.6%, $n = 9$ vs. <50 years 5.3%, $n = 16$, and 50–59.9 6.1%, $n = 12$; $p = 0.021$). The most frequent non-pulmonary condition leading to acute lung failure was surgical trauma (predominantly in patients aged ≥70 years 27.1%, $n = 23$, vs. 60–69.9 years 19.9%, $n = 34$ vs. 50–59.9 years 16.8%, $n = 33$ vs. <50 years 11.9%, $n = 36$; $p < 0.001$). In contrast, trauma etiology of acute

TABLE 1 Characteristics and comorbidities, causes of respiratory failure

	All	<50 years	50–59.9 years	60–69.9 years	≥70 years	*p*-value
Characteristics and comorbidities						
Male sex	508/67.3%	184/60.9%	139/70.6%	121/70.8%	64/75.3%	0.216
Body-mass-index (median kg/m^2 [IQR])		27.7 (24.20–33.10)	27.7 (25.40–33.90)			0.05
Diabetes	126/16.7%	27/8.9%	46/23.4%	33/19.3%	20/23.5%	**<0.001**
Arterial hypertension	222/29.4%	30/9.9%	74/37.6%	69/40.4%	49/57.6%	**<0.001**
History of stroke	21/2.8%	2/0.7%	4/2.0%	11/6.4%	4/4.7%	0.002
Peripheral artery disease	28/3.7%	2/0.7%	5/2.5%	13/7.6%	8/9.4%	**<0.001**
Atrial fibrillation	124/16.4%	22/7.3%	38/19.3%	41/24.0%	23/27.1%	**<0.001**
COPD	77/10.2%	12/4.0%	24/12.2%	31/18.1%	10/11.8%	**<0.001**
Bronchial asthma	26/3.4%	13/4.3%	3/1.5%	6/3.5%	4/4.7%	0.350
Coronary artery disease	92/12.2%	9/3.0%	23/11.7%	34/19.9%	26/30.6%	**<0.001**
Hyperlipidemia	35/4.6%	1/0.3%	9/4.6%	14/8.2%	11/12.9%	**<0.001**
Smoking	124/16.4%	44/14.6%	46/23.4%	24/14.1%	10/11.8%	**0.022**
Another chronic lung disease	67/8.9%	24/7.9%	13/6.6%	17/9.9%	13/15.3%	0.104
Malignant disease	76/10.1%	26/8.6%	20/10.2%	18/10.5%	12/14.1%	0.159
Immunosuppression	82/10.9%	38/12.6%	17/8.6%	22/12.9%	5/5.9%	0.185
Chronic hemodialysis	184/24.4%	59/19.5%	51/25.9%	46/26.9%	28/32.9%	**0.006**
Causes of respiratory failure						
ALF due to pulmonary reason	449/59.5%	162/53.6%	127/64.5%	114/66.7%	46/54.1%	**0.012**
ALF due to extrapulmonary reason	306/40.5%	140/46.4%	70/35.5%	57/33.3%	39/45.9%	**0.012**
Pneumonia bacterial	279/37.0%	101/33.4%	79/40.1%	68/39.8%	31/36.5%	0.388
Pneumonia viral	115/15.2%	45/14.9%	36/18.3%	28/16.4%	6/7.1%	0.111
Aspiration pneumonia	55/7.3%	16/5.3%	12/6.1%	18/10.5%	9/10.6%	**0.021**
ALF post trauma	59/7.8%	42/13.9%	8/4.1%	6/3.5%	3/3.5%	**<0.001**
ALF after surgery	126/16.7%	36/11.9%	33/16.8%	34/19.9%	23/27.1%	**<0.001**
ALF post chemotherapy	19/2.5%	10/3.3%	6/3.0%	2/1.2%	1/1.2%	0.118
Other	102/13.5%	52/17.2%	23/11.7%	15/8.8%	12/14.1%	0.059

Note: Bold indicates *p*-value <0.05.

Abbreviations: ALF, acute lung failure; COPD, chronic obstructive pulmonary disease.

lung failure in elderly patients was rare (≥70 years 3.5%, $n = 3$, and 60–69.9 years 3.5%, $n = 6$ vs. <50 years 13.9%, $n = 42$ and 50–59.9 4.1%, $n = 8$, $p < 0.001$). An overview of the indications and comorbidities of the entire V-V ECMO cohort is shown in Table 1.

The subgroup analysis focusing on morbidity in patients aged ≥70 years showed comparable demographic data. Only the incidence of atrial fibrillation was significantly rising with age (70–74.9 years 22.6%, $n = 14$ vs. 75–79.9 years 33.3%, $n = 7$ vs. ≥80 years 100%, $n = 2$; $p = 0.042$). Seven patients (11.3%) aged 70–74.9 years suffered from malignant disease (1 lung cancer, 3 lymphoma or leukemia, 2 bladder cancer, 1 esophagus cancer), and 5 patients (23.8%) aged 75–79.9 years suffered from an oncological disease (1 lung cancer, 1 lymphoma or leukemia, 2 colon cancer, and 1 melanoma). None of the two patients aged ≥80 years had any malignancy.

Weaning was successful in 74.4% ($n = 562$) of all patients receiving V-V ECMO and it was comparable in all age groups (<50 years 76.5%, $n = 231$ vs. 50–59.9 years 76.1%, $n = 150$ vs. 60–69.9 years 71.9%, $n = 123$ vs. ≥70 years 68.2%, $n = 58$; $p = 0.354$; Table 2).

Likewise, the median duration of support was comparable between all groups too (<50 years 8 days IQR 6–15, vs. 50–59.9 years 10 days, IQR 6–15 vs. 60–69.9 years 9 days IQR 6–18 vs. ≥70 years 9 days IQR 4–5-13.5; $p = 0.256$).

Overall, in-hospital mortality was 37.9% ($n = 286$) rising significantly with age (<50 years: 30.1%, $n = 91$ vs. 50–59.9 years: 37.1%, $n = 73$ vs. 60–69.9 years: 45.6%, $n = 78$ vs. ≥70 years: 51.8%, $n = 44$; $p < 0.001$; Table 2). The more frequent cause of death in the younger age groups was multi-organ-failure (<50 years: 32.3, $n = 30$ vs. 50–59.9 years: 26%, $n = 19$ vs. 60–69.9 years: 26.6%, $n = 21$ vs. ≥70 years:

TABLE 2 Weaning, hospital mortality

V-V ECMO	All	<50 years	50–59.9 years	60–69.9 years	≥70 years	p-value
Overall						
Weaning	562/74.4%	231/76.5%	150/76.1%	123/71.9%	58/68.2%	0.354
In-hospital mortality	286/37.9%	91/30.1%	73/37.1%	78/45.6%	44/51.8%	**<0.001**
ALF due to pulmonary reason						
Weaning	343/76.4%	132/81.5%	97/76.4%	84/73.7%	30/65.2%	**0.017**
In-hospital mortality	155/34.5%	41/25.3%	41/32.3%	48/42.1%	25/54.3%	**<0.001**
ALF due to extrapulmonary reason						
Weaning	219/71.6%	99/70.7%	53/75.7%	39/68.4%	28/71.8%	0.821
In-hospital mortality	131/42.8%	50/35.7%	32/45.7%	30/52.6%	19/48.7%	**0.031**

Note: Bold indicates *p*-value <0.05.
Abbreviation: ALF, acute lung failure.

TABLE 3 Place of cannulation

	All	<50 years	50–59.9 years	60–69.9 years	≥70 years	p-value
ICU	372/49.3%	133/44.0%	96/48.7%	94/55.0%	49/57.6%	**0.005**
Another hospital	354/46.9%	153/50.7%	97/49.2%	75/43.9%	29/34.1%	**0.007**
Operating room	21/2.8%	11/3.6%	3/1.5%	2/1.2%	5/3.2%	0.084
Emergency room	8/1.1%	5/1.7%	1/0.5%	0/0%	2/2.4%	0.188

Note: Bold indicates *p*-value <0.05.
Abbreviation: ICU, intensive care unit.

TABLE 4 Complications on ECMO

	All	<50 years	50–59.9 years	60–69.9 years	≥70 years	p-value
Vessel injury with bleeding	5/0.7%	4/1.3%	1/0.5%	0/0%	0/0%	0.285
Major bleeding	90/11.9%	38/12.6%	17/8.6%	25/14.6%	10/11.8%	0.341
Cannula thrombosis	51/6.8%	19/6.3%	15/7.6%	10/5.8%	7/8.2%	0.837
Pericardial tamponade	3/0.4%	0/0%	3/1.5%	0/0%	0/0%	0.372
New AKF requiring hemodialysis	153/20.3%	60/19.9%	45/22.8%	31/18.1%	17/20.0%	0.723
CPR on ECMO	7/0.9%	5/1.0%	1/0.5%	1/0.6%	0/0%	0.371
Surgical implantation	6/0.8%	4/1.3%	2/1.0%	0/0%	0/0%	0.355

Abbreviations: AKF, acute kidney failure; CPR, cardiopulmonary resuscitation.

15.9%, $n = 7$; $p = 0.067$). Patients in the older age groups mostly died due to respiratory insufficiency after ECMO weaning (<50 years: 20.4%, $n = 19$ vs. 50–59.9 years: 13.7%, $n = 10$ vs. 60–69.9 years: 29.1%, $n = 23$ vs. ≥70 years: 31.8%, $n = 14$; $p = 0.48$).

Because ECMO management, weaning protocols, and other therapeutic strategies had changed over the study period of 14 years, we performed a subgroup analysis of the outcomes in the periods 2006 to 2013 and 2014 to 2020. In both periods, the weaning rate was comparable in all age groups. Between 2006 and 2013, the weaning rate was in patients aged <50 years 77%, $n = 123$ vs. 50–59.9 years 69.6%, $n = 55$ vs. 60–69.9 years 66.7%, $n = 38$ vs. ≥70 years 71.7%, $n = 33$; $p = 0.397$. Between 2014 and 2020, the weaning rate was in patients aged <50 years 75.9%, $n = 107$ vs. 50–59.9 years 80.5%, $n = 95$ vs. 60–69.9 years 74.6%, $n = 85$ vs. ≥70 years 65.8%, $n = 25$; $p = 0.307$. The trend of higher hospital mortality in elderly patients was evident in both periods: Between 2006 and 2013, in-hospital mortality in patients <50 years was 30.4%, $n = 49$ vs. 50–59.9 years 40.5%, $n = 32$ vs. 60–69.9 years 56.1%, $n = 32$ vs. ≥70 years 47.8%, $n = 22$; $p = 0.001$. Between 2014 and 2020 the mortality in patients aged <50 years was 29.8%, $n = 48$ vs. 50–59.9 years 34.7%, $n = 41$ vs. 60–69.9 years 40.4%, $n = 46$ vs. ≥70 years 55.3%, $n = 21$; $p = 0.004$.

The most common complication of ECMO was acute kidney failure requiring hemodialysis. Similarly to other ECMO-related complications, its incidence was comparable between all age groups (Table 4).

Table 3 illustrates, older patients received V-V ECMO mostly in our own ICU, whereas the younger patients were transferred frequently from another hospital after V-V ECMO implantation there to undergo further therapy in our institution.

In most patients, the cannulation was performed using the Seldinger technique (97.2%, $n = 734$; $p =$ n.s.), in 15 patients (2%), prior placed introducer was used and only in 6 patients, surgical implantation was performed (Table 4).

Most cannulations were uneventful. Significant bleeding occurred during 13 cannulations (<50 years 3%, $n = 9$ vs. 50–59.9 years 1%, $n = 2$ vs. 60–69.9 years 0.6%, $n = 1$ vs. ≥70 years 1.2%, $n = 1$; $p = 0.597$), and in 26 patients vessel punction was prolonged and difficult (<50 years 3.3%, $n = 10$ vs. 50–59.9 years 2.5%, $n = 5$ vs. 60–69.9 years 3.5%, $n = 6$ vs. ≥70 years 5.9%, $n = 5$; $p = 0.597$).

As an outflow vessel, the mostly femoral vein was used (84.2%, $n = 636$). The internal jugular vein was used in 15.5% of patients and the subclavian vein was cannulated rarely. The most common inflow cannula position was the internal jugular vein (83.8%, $n = 633$, subclavian vein 8.5%, and femoral vein 7.6%). In 10.3% of cannulations ($n = 78$), Avalon cannula was used.

Multivariate logistic regression analysis confirmed age as a significant risk factor for in-hospital mortality (OR 1.028; 95% CI: 1.1016–1.041, $p < 0.001$). Further relevant risk factors were chronic hemodialysis, acute kidney failure requiring dialysis, bilirubin on day 1 after ECMO implantation, malignancy, and another primary lung disease (including lung fibrosis, cystic fibrosis, vasculitis, and others: Table 5). The CRP level on day 1 was protective.

The cerebral performance status at hospital discharge differed between the older and the younger age groups ($p = 0.001$), showing better outcomes for younger patient groups (Table 7).

During follow-up, Kaplan–Meier analysis yielded better long-term survival in the younger age groups (Log Rang < 0.001; Figure 1).

According to multivariate Cox's regression, significant risk factors for death during follow-up were age, relevant comorbidities (CAD, another primary pulmonary disease, and malignancy), and immunosuppressive therapy (Table 6).

During follow-up, the ECOG score deteriorates with rising age as demonstrated in Table 7 ($p = 0.013$).

3.1 | Subgroup analysis: Lung failure due to pulmonary vs. extrapulmonary reason

Overall, the weaning rates of patients with lung failure due to pulmonary reason (76.4%, $n = 343$) and extrapulmonary reason (71.6%, $n = 219$) were comparable

TABLE 5 Multivariate logistic regression models on hospital mortality multivariate Cox's regression models on death at follow-up; other primary lung diseases = fibrosis, cystic fibrosis, vasculitis, and others

	Univariate logistic regression models on hospital mortality		**Multivariate logistic regression models on hospital mortality**	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Age	1.035 (1.014–1.036)	**0.001**	1.028 (1.016–1.041)	**<0.001**
Another primary lung disease	1.783 (1.077–2.949)	**0.024**	2.068 (1.156–3.699)	**0.014**
Malignancy	3.385 (2.062–5.555)	**<0.001**	3.183 (1.771–5.723)	**<0.001**
Noradrenalin level before ECMO (μg/kg/min)	1.227 (1.040–1.719)	**0.023**	1.182 (0.865–1.615)	0.295
Chronic hemodialysis	2.779 (1.977–3.906)	**<0.001**	2.730 (1.741–4.281)	**<0.001**
Acute kidney failure requiring hemodialysis	1.457 (1.018–2.087)	**0.04**	2.115 (1.351–3.309)	**0.001**
Bilirubin day 1	1.105 (1.044–1.169)	**0.001**	1.109 (1.035–1.188)	**<0.003**
CRP day 1	0.998 (0.996–0.999)	**0.001**	0.997 (0.995–0.998)	**<0.001**
Lactate before ECMO	1.012 (1.007–1.016)	**<0.001**	1.006 (1.000–1.012)	0.716
Immunosuppression	1.951 (1.230–3.094)	**0.004**	1.097 (0.612–1.966)	0.755
Extrapulmonary ALF	1.420 (1.053–1.914)	**0.021**	1.138 (0.786–1.648)	0.494

Note: Bold indicates *p*-value <0.05.

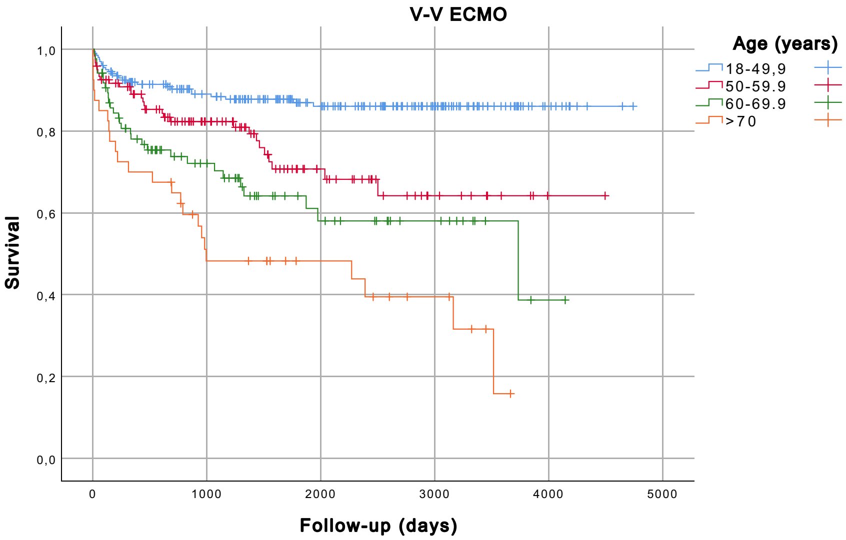

FIGURE 1 Survival in follow-up.

TABLE 6 Multivariate Cox's regression models on death at follow-up; other primary lung diseases = fibrosis, cystic fibrosis, vasculitis, and others

	HR (95% CI)	*p*-value
Age	1.044 (1.028–1.061)	**<0.001**
Chronic obstructive pulmonary disease	1.591 (0.966–2.620)	0.068
Coronary artery disease	1.740 (1.054–2.874)	**0.030**
Another primary lung disease	1.839 (1.011–3.311)	**0.046**
Malignancy	2.831 (1.605–4.992)	**<0.001**
Chronic hemodialysis	0.926 (0.569–1.508)	0.757
Acute kidney failure requiring hemodialysis	1.113 (0.667–1.857)	0.681
History of stroke	2.110 (0.898–4.956)	0.87
Immunosuppression	2.612 (1.481–4.606)	**0.001**

Note: Bold indicates *p*-value <0.05.

TABLE 7 Cerebral performance status (CPC) score and Eastern Co-operative of Oncology Group (ECOG) score at follow-up

	All	<50 years	50–59.9 years	60–69.9 years	≥70 years	*p*-value
CPS score						**<0.001**
CPC1	57/12.1%	41/19.4%	11/8.8%	3/3.2%	2/4.9%	
CPC2	346/73.3%	147/69.7%	100/80%	70/73.7%	29/70.7%	
CPC 3	64/13.6%	21/10%	14/11.2%	19/20%	10/24.4%	
CPC4	3/0.6%	1/0.5%	0/0%	2/2.1%	0/0%	
CPC5	2/0.4%	1/0.5%	0/0%	1/1.1%	0/0%	
ECOG at follow-up						**0.013**
0–1	281/78.7%	146/81.1%	78/81.3%	45/72.6%	12/63.2%	
2	63/17.6%	30/16.7%	17/17.7%	10/16.1%	6/31.6%	
3	13/3.6%	4/2.2%	1/1%	7/11.3%	1/5.3%	

Note: Bold indicates *p*-value <0.05.

($p = 0.136$). Regardless of age, however, hospital mortality was higher in patients with lung failure due to extrapulmonary reason (extrapulmonary reason 42.8%, $n = 131$, vs. pulmonary reason 34.5%, $n = 155$; $p = 0.21$).

In most cases, patients with lung failure due to pulmonary reason had developed both bacterial and viral pneumonia. In patients with lung failure due to pulmonary reason, the weaning rates significantly deteriorated with age (<50 years: 81.5%, $n = 132$ vs. 50–59.9 years: 76.4%, $n = 97$ vs. 60–69.9 years: 73.7%, $n = 84$ vs. ≥70 years: 65.2%, $n = 30$; $p = 0.017$), whereas in patients with lung failure due to extrapulmonary reason (mostly acute lung failure after surgery) the weaning rates were comparable ($p = 0.821$, Table 2). The in-hospital mortality rate of patients with lung failure due to pulmonary reason raised continuously across the age groups as well (<50 years: 25.3%, $n = 41$ vs. 50–59.9 years: 32.3%, $n = 41$ vs. 60–69.9 years: 42.1%, $n = 48$ vs. ≥70 years: 54.3%, $n = 25$; $p < 0.001$). In contrast, lung failure patients due to extrapulmonary reason aged <50 years presented with significantly lower hospital mortality (35.7%, $n = 50$, $p = 0.031$) but in the patients aged 50 and more, the difference was not significant (Table 2).

The CPC score at discharge and the ECOG score at follow-up were worse in older patients in both subgroups.

3.2 | Comment

During the current COVID-19 pandemic, veno-venous extracorporeal membrane oxygenation has become a better-known treatment modality, not only among medical stuff but also in the general population. In case of failure of conventional therapy, V-V ECMO represents a rescue option to achieve stable gas exchange. The use of ECLS in the United States alone increased by 433% between 2006 and 2011.[10] V-V ECMO is used in different clinical contexts, for different indications, and in different patient populations, which results in heterogeneous patient outcomes. V-V ECMO is an invasive support modality, which involves risks that must be balanced against benefits for each individual patient because large randomized controlled trials showing the efficacy of V-V ECMO in improving outcomes are still lacking.[11] ECMO indication is guided by three general principles: The presence of a high risk of death despite optimization of conventional treatment, potential reversibility of the primary disease, and the absence of contraindications.[12] In this study, we primarily focused on age as a potential contraindication or risk factor for worse long- and short-term outcomes.

Age can negatively influence the treatment course because of associated comorbidities and patients' reduced biological ability to recover and deal with ECMO complications.[13] When stratifying V-V ECMO support by age, Deatrick et al. found a lower survival rate at discharge for patients aged >65 years, who had been treated with V-V ECMO for respiratory failure. The authors suggested age to be an independent predictor of survival at discharge and an incremental increase in in-hospital mortality from the age of 45 years onwards.[14] Baek et al. showed in a multicenter study of 209 patients that elderly patients have higher mortality; the authors also found that age is a predictor of mortality compared to the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.[15] Other studies described advanced age and immunosuppression to contribute to the weakening of functional reserves, resulting in more comorbidities.[16-19]

Over the entire study period of 14 years and in accordance with the above-mentioned studies, we consistently registered higher hospital mortality rates in the V-V ECMO group of elderly patients, especially in patients with lung failure due to pulmonary reason. In patients with lung failure due to pulmonary reason, age was obviously stronger associated with respiratory performance, which predisposes to infection and consecutively to respiratory failure and corresponds to a worse in-hospital outcome.

The decrease in respiratory performance of elderly patients is mirrored in the fact that respiratory insufficiency after ECMO weaning is the main cause of death in elderly patients in contrast to younger patients, who frequently die of multiple-organ failure.

Of note, another actual analysis of our team shows that the use of V-A ECMO can achieve the same hospital mortality rates, neurological status at hospital discharge and during follow-up, and thus quality of life during follow-up in elderly patients as in younger patients.

Non-respiratory comorbidities have a greater impact on elderly patients receiving V-V ECMO. Although hemodialysis was not associated with increased mortality in adult patients supported with V-V/V-A ECMO in a study by Antonucci et al., chronic renal failure requiring hemodialysis has a higher prevalence in elderly patients and is a strong risk factor for mortality in critically ill patients with or without extracorporeal support.[20] This fact was also evident in our multivariate regression analysis, in which chronic hemodialysis was a strong risk factor for hospital mortality than acute kidney failure requiring hemodialysis.

According to Masha et al., bilirubin levels were associated with worse outcomes in ECLS.[21] In our study, bilirubin levels on the first day played the same role.

The duration of ECMO support is another factor with a negative impact on mortality[22] but did not contribute to the worse outcome of elderly patients in our study because it was comparable in all age groups.

Interestingly, multivariate logistic regression analysis showed higher C-reactive protein (CPR) values on day 1 to be a protective factor. Enger et al. reported similar findings: In their analysis, a lower CPR value was associated with an increased risk of mortality.[23] In this context, CRP levels before and after initiation of extracorporeal support represent a surrogate marker of activation or exhaustion of a patient's immune reaction.

Our current study pointed out, the rising age is not only an independent risk factor for hospital mortality, but older age correlates with worse neurological status and so quality of life in follow-up.

4 | CONCLUSIONS

In patients on V-V ECMO, the strong association of advanced age with comorbidities and reduced biological ability to recover lead to impaired short- and long-term outcomes, and worse neurological outcomes. Chronic and acute hemodialysis, bilirubin, malignancy, and primary lung disease represent risk factors for in-hospital mortality in addition to age. Age, CAD, another primary lung disease, malignancy, and immunosuppression are risk factors for death of ECMO survivors during follow-up.

4.1 | Limitations

This study has several limitations such as its retrospective observational design. Although most data were obtained prospectively, some data were collected retrospectively. Despite the division of patients into two subgroups, patient heterogeneity could not be completely avoided.

AUTHOR CONTRIBUTION

Zdenek Provaznik: Concept/design, data analysis/interpretation, statistics. **Alois Philipp:** Concept/design, data collection. **Thomas Müller:** Data collection. **Kozakov Kostiantyn:** Data collection. **Dirk Lunz:** Data collection. **Christof Schmid:** Critical revision of article. **Bernhard Floerchinger:** Concept/design, critical revision of article.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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