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MAIN TEXT ARTICLE

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A bi-centric experience of extracorporeal carbon dioxide removal ($ECCO_2R$) for acute hypercapnic respiratory failure following allogeneic hematopoietic stem cell transplantation

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Abstract

Acute respiratory failure (ARF) is the main reason for ICU admission following allogeneic hematopoietic stem cell transplantation (HSCT). Extracorporeal CO_2 removal ($ECCO_2R$) can be used as an adjunct to mechanical ventilation in patients with severe hypercapnia but has not been assessed in HSCT recipients. Retrospective analysis of all allogeneic HSCT recipients ≥18 years treated with $ECCO_2R$ at two HSCT centers. 11 patients (m:f = 4:7, median age: 45 [IQR: 32-58] years) were analyzed. Acute leukemia was the underlying hematologic malignancy in all patients. The time from HSCT to ICU admission was 37 [8-79] months, and 9/11 (82%) suffered from chronic graft-versus-host disease (GVHD) with lung involvement. Pneumonia was the most frequent reason for ventilatory decompensation ($n = 9$). $ECCO_2R$ was initiated for severe hypercapnia (P_aCO_2: 96 [84-115] mm Hg; pH: 7.13 [7.09-7.27]) despite aggressive mechanical ventilation (invasive, $n = 9$; non-invasive, $n = 2$). $ECCO_2R$ effectively resolved blood gas disturbances in all patients, but only 2/11 (18%) could be weaned off ventilatory support, and one (9%) patient survived hospital discharge. Progressive respiratory and multiorgan dysfunction were the main reasons for treatment failure. $ECCO_2R$ was technically feasible but resulted in a low survival rate in our cohort. A better understanding of the prognosis of ARF in patients with chronic GVHD and lung involvement is necessary before its use can be reconsidered in this setting.

KEYWORDS

extracorporeal CO_2 removal, hematology, hematopoietic stem cell transplantation, intensive care unit

1 | INTRODUCTION

Despite recent improvements, non-relapse mortality due to toxic, infectious, and immunologic complications remains a substantial risk following allogeneic hematopoietic stem cell transplantation (HSCT).[1] In fact, up to every third HSCT recipient requires admission to the intensive care unit (ICU) at least once during his/her peri- or post-transplant course.[2] Pulmonary organ dysfunction presenting as an acute hypoxemic respiratory failure (ie, the acute respiratory distress

syndrome; ARDS) is the reason for clinical deterioration in most of these patients. In a study by Yadav et al, the authors found that the incidence of ARDS may be as high as 16% during the first year following allogeneic HSCT and that 80% of the cases had a severe course.[3] In 2017, our group conducted a retrospective multicenter study of 37 HSCT recipients rescued with extracorporeal membrane oxygenation (ECMO) for severe ARDS.[4] When processing our data, we came across a series of patients treated with extracorporeal carbon dioxide removal ($ECCO_2R$) for acute hypercapnic respiratory failure in two participating HSCT centers. In contrast to ECMO, $ECCO_2R$ provides artificial respiratory support by removing CO_2 only with no or minimal effects on the systemic oxygenation. This is achieved by lower blood flow and different technical devices and setups than ECMO, which requires a blood flow of ≥60% of the cardiac output (ie, >2000-3000 mL/min) to provide systemic oxygenation.[5] $ECCO_2R$ is an experimental technique, although its use has been implicated in decompensated asthma or chronic obstructive pulmonary disease (COPD), as a bridge to lung transplantation, or as an adjunct to achieve ultraprotective mechanical ventilation.[6-8] The purpose of this first report in the literature is to describe the characteristics and outcomes of HSCT recipients treated with $ECCO_2R$ for acute hypercapnic respiratory failure in two tertiary care HSCT centers and to highlight important gaps of knowledge in presented clinical scenarios.

2 | PATIENTS AND METHODS

We retrospectively analyzed the clinical course of all adult (≥18 years) allogeneic HSCT recipients treated with $ECCO_2R$ in the ICUs of two HSCT centers (Medical University of Vienna, Austria [$n = 7$]; University Hospital Essen, Germany [$n = 4$]) between 2009 and 2018. The study was approved by the ethics committees of the Medical University of Vienna (EC 1979/2019) and the University of Duisburg-Essen (EC 15-6446-BO) and conducted following Good Clinical Practice guidelines and the amended Declaration of Helsinki.

Patients were included if they had a history of allogeneic HSCT and were treated with extracorporeal life support for the primary purpose of CO_2 removal. $ECCO_2R$ was defined as extracorporeal blood flow of <2000 mL/min via either a pumpless arterio-venous setup (AV-$ECCO_2R$) or a pump-driven veno-venous (VV-$ECCO_2R$) configuration using a setup including specifically designed cannulas for lower blood flows as well as gas exchange membranes designed for $ECCO_2R$. Patients were treated with one of the following devices and setups: (i) the Interventional Lung Assist (iLA; Xenios), a pumpless AV-$ECCO_2R$ system which uses the arterio-venous pressure gradient to maintain blood flow in the circuit; for cannulation, a 13-15 Fr arterial drainage and a 15-17 venous return cannula were used (NovaPort One, Xenios); (ii) a pump-driven veno-venous circuit operated by an iLA activve (Xenios) or a Cardiohelp (Getinge) console equipped with a low-resistance membrane ventilator (iLA, Xenios; HLS 5.0, Getinge); for cannulation, a 22-24 Fr double-lumen cannula was used in a jugular or femoral approach (NovaPort Twin, Xenios); or (iii) the Hemolung Respiratory Assist System (ALung Technologies), which uses a pump-driven ultra low-flow (300-550 mL/min) veno-venous setup including a specially designed 15.5 Fr double-lumen cannula. According to institutional standards in both centers, patients received 5000 units of unfractionated heparin immediately after cannulation, followed by a continuous infusion to keep the activated partial thromboplastin time (aPTT) between 50 seconds and 60 seconds.

Baseline data were recorded for the time immediately before the initiation of $ECCO_2R$. Organ dysfunction was graded using the SOFA score,[9] the Simplified Acute Physiology Score II (SAPSII)[10] was used to assess the severity of illness, and the Charlson Comorbidity Index (CCI)[11] to account for comorbidities at ICU admission, respectively. The performance status was graded according to the Eastern Cooperative Oncology Group (ECOG) scale.[12] Chronic graft-versus-host disease (GVHD) was defined according to the NIH criteria.[13,14] P_aCO_2 and P_aO_2 indicate partial pressures of carbon dioxide and oxygen obtained from arterial blood gas analysis. Major bleeding was defined as the requirement of two or more units of packed red blood cells due to a bleeding event, in case a surgical or interventional procedure for bleeding was required, as well as in cases of intracerebral hemorrhage or fatal outcome. We obtained the source data from the original study on ECMO in HSCT recipients[4] to identify possible selection criteria for $ECCO_2R$ and to compare complications and outcomes between both cohorts. Continuous data are presented as the median and interquartile range (25%-75%), dichotomous data as number and percentage. The Fisher's exact test and the Mann-Whitney *U* test were used to compare dichotomous and continuous variables, respectively. The Wilcoxon rank-sum test was used to compare variables of invasive ventilation and gas exchange prior, and 8 hours after the initiation of $ECCO_2R$. A two-sided P value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Incidence of $ECCO_2R$ and patient characteristics

We identified 11 (m:f = 4:7, age: 45 [32-58] years) patients following allogeneic HSCT having received $ECCO_2R$. The included patients corresponded to 3.4% of all allogeneic HSCT recipients admitted to the ICUs in both centers during the study period. The patient characteristics are shown

in Table 1. Acute leukemia was the underlying hematologic malignancy in all patients, and all but one patient (91%) were in remission of the disease. The median time from HSCT to ICU admission was 37 [8-79] months. Nine out of the 11 (82%) patients had moderate/severe chronic GVHD, and lung involvement had been documented in all cases. Other organs involved in chronic GVHD were the skin ($n = 9$; 100%), the liver ($n = 4$; 44%), the eyes ($n = 3$; 33%), and the gastrointestinal tract ($n = 2$; 22%). All patients had had a significantly impaired performance status (≥2; median score: 3 [2-3]) before developing the acute illness but had been ambulatory and lived at home.

TABLE 1 Patient characteristics

	All patients ($n = 11$)
Sex	
Male	4 (36)
Female	7 (64)
Age at ICU admission (years)	45 (32-58)
Body mass index at ICU admission	18 (17-21)
Charlson comorbidity index	3 (3-5)
Performance status before acute illness	3 (2-3)
Underlying malignancy	
Acute lymphoblastic leukemia	6 (55)
Acute myeloid leukemia	5 (45)
Donor type	
Matched related	2 (18)
Matched unrelated	8 (73)
Mismatched unrelated	1 (9)
Time from HSCT to ICU admission (months)	37 (8-79)
GVHD at ICU admission	
Acute GVHD	1 (9)
Chronic GVHD	9 (82)
Bronchiolitis obliterans syndrome	9 (82)
Immunosuppression at ICU admission	10 (91)
Steroids	9 (82)
Calcineurin inhibitor	5 (45)
Others	5 (45)
SAPS II at ICU admission	33 (28-35)
SOFA score at ICU admission	6 (2-9)
Documented pulmonary infection	9 (82)
Identified pathogen	5 (45)
Infiltrates on chest X-ray (# of quadrants)	4 (2-4)
Life supporting interventions during ICU stay	
Non-invasive mechanical ventilation	7 (64)
Invasive mechanical ventilation	11 (100)
Vasopressors	11 (100)
Renal replacement therapy	6 (55)
ICU survival	2 (18)
Hospital survival	1 (9)

3.2 | Characteristics and causes of respiratory failure

The time from hospital to ICU admission was 3 [1-10] days. Respiratory failure with the predominant pattern of severe hypercapnia and ventilatory decompensation was the reason for ICU admission in our cohort. Pneumonia was deemed the underlying cause of respiratory failure in nine (82%) patients, of which five had a pathogen identified (*Pneumocystis jirovecii*, $n = 3$; *Stenotrophomonas maltophilia* and *Klebsiella pneumoniae*, $n = 1$; *Aspergillus fumigatus*, $n = 1$). Exacerbation of bronchiolitis obliterans syndrome without pulmonary infiltrates and idiopathic pneumonia syndrome concurrent with acute GVHD were the underlying causes of respiratory failure in the remaining two patients. $ECCO_2R$ was mostly used as an adjunct to invasive mechanical ventilation (IMV) ($n = 9$; 82%), but also as a possible means to avoid endotracheal intubation in two (18%) patients undergoing non-invasive mechanical ventilation (NIV). The physiologic parameters at the initiation of $ECCO_2R$ are shown in Table 2. Patients suffered from severe hypercapnia (P_aCO_2: 96 [84-115] mm Hg; pH: 7.13 [7.09-7.27]) despite aggressive ventilator settings (respiratory rate: 26 [24-32]/min; P_{max} 28 [27-35] mbar; PEEP: 5 [5-6] mbar; tidal volume: 292 [215-392] mL; P_{max}, PEEP and tidal volume given for invasively ventilated patients only) and from a moderate impairment in oxygenation (P_aO_2/F_iO_2: 170 [131-248]).

3.3 | Configuration, efficacy, and complications of $ECCO_2R$

The majority of patients (7/11; 64%) received $ECCO_2R$ using a pump-driven device in veno-venous configuration through a double-lumen cannula inserted in the femoral ($n = 4$) or jugular ($n = 2$) vein. One patient had two single lumen-cannulas placed in the femoro-jugular configuration. Three patients were treated with the iLA system in arterio-venous configuration, and one patient was initiated on the Hemolung device. $ECCO_2R$ effectively resolved hypercapnia in all patients within 8 hours from its initiation (Table 2) at a median blood flow of 1100 [750-1200] mL/min without overt differences between the different devices and configurations (Supplementary Figure S1). Systemic anticoagulation was provided with heparin in all cases. The median duration of $ECCO_2R$ treatment was 11 [4-32] days. Major bleeding occurred in three (27%) patients (pulmonary, insertion site, retroperitoneal hematoma), none of which was deemed fatal. Other complications included hemolysis or clotting requiring

TABLE 2 Characteristics of $ECCO_2R$ and respiratory failure

	All patients ($n = 11$)		
$ECCO_2R$ configuration			
Arterio-venous	3 (27)		
Veno-venous pump-driven	8 (73)		
Cannulation			
Femoro-femoral	4 (36)		
Double-lumen femoral	5 (45)		
Double-lumen jugular	2 (18)		
Blood flow (L/min)	1.1 (0.75-1.2)		
NIV at start of $ECCO_2R$	2 (18)		
Days from ICU admission to $ECCO_2R$	3 (1-3)		
Days form IMV start to $ECCO_2R$	0 (0-6)		
Leukocytes (G/L)	12.2 (8.4-16)		
Thrombocytes (G/L)	177 (65-205)		
Hemoglobin (g/dL)	11.1 (10.1-12.9)		
Days of $ECCO_2R$ treatment	17 (7-26)		
Successful weaning from $ECCO_2R$	2 (18)		
Parameters before and 8 hours after $ECCO_2R$	**Prior**	**8 hours after**	***P***
Pmax (mbar)[a]	28 (27-35)	26 (25-28)	.06
PEEP (mbar)[a]	5 (5-6)	5 (5-8)	.18
ΔP (mbar)[a]	23 (21-27)	20 (15-23)	.06
Tidal volume (mL)[a]	247 (205-349)	197 (180-324)	.50
Respiratory rate	26 (24-32)	16 (14-22)	.01
PaO_2/FiO_2	170 (131-248)	187 (126-302)	.61
pH	7.13 (7.09-7.27)	7.44 (7.35-7.49)	<.01
P_aCO_2 (mm Hg)	96 (84-115)	49 (36-55)	<.01
P_aO_2 (mm Hg)	83 (73-88)	81 (70-115)	.29
SaO_2 (%)	94 (92-97)	93 (92-97)	.86
Standard bicarbonate (mmoL/L)	30 (24-32)	29 (23-34)	.92
Lactate (mmoL/L)	1 (0.8-1.6)	1.1 (0.9-1.9)	.72

[a]Analyzed for invasively ventilated patients ($n = 9$).

a system change ($n = 2$), ischemic stroke ($n = 1$), and accidental decannulation ($n = 1$). Supplementary Table S3 lists all complications according to the carbon dioxide removers and configurations of $ECCO_2R$.

3.4 | Outcome

Of the two patients who received NIV, both had to be intubated after 12 and 20 days of $ECCO_2R$ due to accidental decannulation and progressive hypoxemia, respectively. The latter patient ultimately required escalation to ECMO due to refractory hypoxemic respiratory failure 12 days after intubation and died 25 days later. Two (18%) patients could successfully be weaned from $ECCO_2R$. One patient had a second ICU referral 52 days after discharge during the hospital stay and eventually succumbed to sepsis and multiorgan failure. One patient survived hospital discharge and lived for another 18 months, but ultimately died from chronic GVHD (wasting syndrome, recurrent pulmonary infections). In the remaining patients, the reason for death was worsening respiratory failure and progressive hypoxemia in four patients, progressive multiorgan failure in three patients, and therapy withdrawal due to the inability to wean from $ECCO_2R$ in two patients.

3.5 | Comparison between HSCT recipients treated with $ECCO_2R$ and ECMO

Supplementary Tables S1 and S2 compare baseline characteristics, complications, and outcomes between HSCT

recipients treated with $ECCO_2R$ and ECMO in the original study. There were no differences regarding demographic and transplant-related characteristics between the cohorts. The time from HSCT to ICU admission was significantly longer in the $ECCO_2R$ cohort (37 [8-79] vs. 5 [1-10] months, $P < .01$). Chronic GVHD was present in 82% ($n = 9$) of $ECCO_2R$ patients versus 22% ($n = 8$) in the ECMO cohort ($P < .01$). Only 2/37 (5%) patients had bronchiolitis obliterans syndrome in the original ECMO study. Patients treated with $ECCO_2R$ had a higher burden of comorbidities (CCI: 3 [3-5] vs. 0 [0-1], $P < .01$), but a lower severity of the acute illness as indicated by the SAPSII (33 [28-35] vs. 56 [42-67], $P < .01$) and the SOFA (6 [2-9] vs. 12 [9-15], $P < .01$) score, respectively. Blood counts were significantly higher in the $ECCO_2R$ group. Patients treated with ECMO suffered from a profound impairment in oxygenation (P_aO_2/F_iO_2: 66 [53-82] vs. 170 [131-248]) with only moderate hypercapnia ($P_{aC}O_2$: 57 [47-71] vs. 96 [84-115]) and acidosis (pH: 7.29 [7.18-7.37] vs. 7.13 [7.09-7.27]) ($P < .01$ for all comparisons). The driving pressure (ΔP) in the $ECCO_2R$ group was higher (23 [21-27] vs. 20 [17-24] mbar, $P = .04$) than in the ECMO patients. Utilization of other life-supporting interventions, bleeding events (27% vs. 38%, $P = .72$), and the risk of ischemic stroke (9% vs. 8%, $P = 1.0$) did not differ between the two groups. ICU survival (18% vs. 19%, $P = 1.0$) and hospital survival (9% vs. 19%, $P = .66$) were similar in both cohorts.

4 | DISCUSSION

To our knowledge, this is the first report of the use of $ECCO_2R$ to treat hypercapnic respiratory failure in patients following allogeneic HSCT. Ventilatory decompensation mostly occurred due to pulmonary infection based on lung involvement by chronic GVHD in our cohort. $ECCO_2R$ was technically able to resolve hypercapnia and acidosis but enabled weaning from the respirator in only two cases, and only one (9%) patient survived hospital discharge.

$ECCO_2R$ was instituted in two of our patients undergoing non-invasive mechanical ventilation to obviate the need for intubation and IMV. NIV failure and the need for IMV are strong adverse prognostic factors in patients with exacerbation of COPD, which inspired several retrospective and non-randomized prospective studies of $ECCO_2R$ as a means to avoid intubation in this group.[15-18] Both of our patients initiated on $ECCO_2R$ during NIV suffered from bronchiolitis obliterans syndrome, which may have led the treating physicians to similar considerations regarding the avoidance of IMV as in COPD. Additionally, our patients had low body mass indices and impaired performance status due to chronic GVHD, both factors that predispose to harmful consequences from analgosedation, including loss of respiratory muscle tone and general muscle wasting. Both patients had to be intubated during their further course due to accidental decannulation and progressive hypoxemia, respectively. Worsening hypoxemia is a well-recognized "complication" of $ECCO_2R$, either due to the worsening of the respiratory failure itself (eg, progressive infiltrates) or due to the excessive removal of CO_2 (reduction of tidal volume, lower partial pressure of alveolar oxygen, and increased risk of atelectasis during spontaneous ventilation).[19] Notably, while NIV has long been considered the first-line therapy of hypoxemic respiratory failure in immunocompromised patients, this paradigm has recently been overturned by a large prospective randomized trial[20] and data from a large observational study.[21] We think that the registered attempts to prevent intubation by extracorporeal life support in both of our cohorts reflect a sign of the times when these new techniques inspired hope to improve dismal outcomes of immunocompromised and hematologic patients otherwise requiring IMV. Based on our observations[4] and recent data from randomized trials,[20,22] we believe that augmented efforts to avoid IMV are not justified in this patient population or may even put patients at unnecessary risks of harm. In the context of extracorporeal life support, our case of accidental decannulation is one example of these risks, alongside bleeding complications registered in our and other cohorts (see below).

In the majority of our patients, $ECCO_2R$ was used as an adjunct to enable less invasive ventilator settings during IMV and protect patients from the deleterious effects of hypercapnia. The median driving pressure (ΔP) in invasively ventilated patients was 23 (21-27) mbar and, thus, in a range in which a negative effect on survival due to the infliction of ventilator-induced lung injury (VILI) has to be assumed and weaning cannot be performed.[23] Despite aggressive mechanical ventilation, our patients suffered from severe hypercapnia with only moderate metabolic compensation. Excessive hypercapnia and acidosis have several adverse consequences on pulmonary and extrapulmonary organ function, including pulmonary vasoconstriction leading to increased right ventricular afterload and cerebral edema due to increased intracranial blood flow.[19] Indeed, one of our patients was deemed to have died from right ventricular failure despite the correction of hypercapnia and acidosis.

There are limited reports in the literature on the use of $ECCO_2R$ to reduce ventilatory pressures and correct gas exchange alterations in patients undergoing IMV for hypercapnic respiratory failure.[24,25] Only 2/11 patients could be weaned in our cohort, and only one patient survived hospital discharge. Worsening of respiratory failure with progressive hypoxemia and multiorgan dysfunction were the leading causes of death in our patients. The failure to control the underlying pulmonary infection in these severely immunocompromised individuals and an unclear contribution of alloreactivity in patients with underlying GVHD may have

accounted for the observed outcome.[26] Bronchiolitis obliterans syndrome caused by chronic GVHD leads to a progressive decline in lung function despite treatment in many patients.[27] Extracorporeal life support in other forms of chronic progressive lung disease has only proven effective as a bridge to lung transplantation, as recovery from acute respiratory failure seldomly occurs.[28] This circumstance might also apply to patients with chronic GVHD and lung involvement, as the underlying lung pathology might be too severe or irreversible. Of note, several large cohort studies have proven the feasibility of lung transplantation following HSCT,[29] but so far, none have addressed bridging with extracorporeal life-support in these patients. It is noteworthy that three of our patients had pneumonia caused by *P. jirovecii*, a pathogen that by itself induces or aggravates bronchiolitis. Progressive hypoxemia during the early phase of treatment is a recognized phenomenon of this infection,[30] and, hence, ECMO may be preferred over $ECCO_2R$ in these situations if extracorporeal life support is required.

The comparison between HSCT recipients having received $ECCO_2R$ and ECMO in the original study delineates two different patient types and clinical scenarios associated with the use of the respective technique. $ECCO_2R$ was used to enable more protective ventilation and correct hypercapnia and acidosis in long-term HSCT survivors with lung involvement by chronic GVHD, whereas ECMO served as a rescue for refractory ARDS in patients early after HSCT. Both complications are well recognized following HSCT and typically occur at the observed time-points.[31] The burden of comorbidities was higher in the $ECCO_2R$ group, and ECMO patients were more severely affected by acute illness and multiorgan dysfunction. Demographics and HSCT-related characteristics (eg, donor type, remission status) did not differ between groups. Given these findings, we do not think that factors other than the primary pattern of gas exchange disturbance and ventilatory requirements influenced the selection between $ECCO_2R$ and ECMO in our patients. As the frequency of other life-supporting interventions did not differ between the two cohorts, the selection of $ECCO_2R$ as a less invasive technique in the context of a more restrictive or reluctant ICU management strategy also seems unlikely.

Given previously reported dismal outcomes in allogeneic HSCT recipients with GVHD requiring IMV and our patients' reduced performance status, the question arises whether the aggressive ICU measures taken in our cohort were disproportional.[32,33] In this context, it is important to recognize that studies analyzing critically ill allogeneic HSCT patients have so far almost exclusively focused on the early post-transplant period and acute GVHD. There is evidence that the chances of surviving the ICU increase with longer time from transplantation, and that outcome may be much more favorable than in the early post-transplant period.[2] Supporting this notion, the hospital survival of allogeneic HSCT patients requiring ECMO for ARDS was 6/13 (46%) when treated after 240 days from HSCT in the original study.[4] Despite these clues supporting a more aggressive ICU strategy in the late than in the early post-transplant period, critical long-term HSCT survivors, including those with chronic GVHD, are blank pages in the available literature, precluding informed statements about expected trajectories and outcomes when considering ICU measures. Hence, we think that there is an urgent need to collect the respective data in this patient population. All of the included patients had acute leukemia as their underlying hematologic disease, which might be interpreted as an adverse prognostic factor regarding the expected post-ICU outcomes. However, the median time from HSCT to ICU admission was 37 months, indicating long-term remission in all but one patient. Leukemia relapse beyond two years after HSCT in the presence of chronic GVHD is an infrequent event.[34] Hence, the majority of the included patients had the perspective of remaining disease-free lifelong. The performance status, another prognostic factor regarding long-term outcomes, was significantly impaired in all of our patients before the acute illness, but all had been ambulatory before hospital admission and lived at home.

$ECCO_2R$ is considered a less invasive technique than ECMO due to smaller sized or double-lumen cannulas and lower blood flow. However, there are several risks associated with its use. Most strikingly, three (27%) of our patients had major bleeding complications, with similar bleeding rates also reported in other studies[35] and in the original ECMO study (38%).[4] Device -related complications, such as hemolysis or clotting as in two of our patients, require constant monitoring, a high level of familiarity with the technique, and rapid action in case of system failure. Hence, we think that the use of any form of extracorporeal life support should be limited to experienced centers with access to multidisciplinary teams (eg, surgery, interventional radiology). Complications attributable to $ECCO_2R$ may vary between different carbon dioxide removers, configurations, and devices.[6] Due to substantial heterogeneity in these aspects and the small sample size, our study could not specifically address this critical issue. When interpreting the complications observed in our cohort and other reports, the used devices and methodology should be considered before making broad interferences about the risks and benefits of $ECCO_2R$ other than those related to the patient type.

Our study has several limitations. First, the sample size was small. However, as it is the first report of its kind, our data contribute to the knowledge on extracorporeal life-support in HSCT recipients and might stimulate research on critically ill patients with chronic GVHD and respiratory failure. Second, four different devices were used for $ECCO_2R$, but three of them were also applied in a recent pilot study of $ECCO_2R$ in ARDS.[35] Third, this was a retrospective study that shares all the inherent limitations of this method.

5 | CONCLUSION

$ECCO_2R$ was used in 11 patients with hypercapnic respiratory failure following HSCT, mostly in the context of chronic GVHD with lung involvement exacerbated by pulmonary infection requiring IMV. While the technique could resolve hypercapnia and acidosis, only two patients could be weaned, and only one patient survived hospital discharge. Progressive respiratory failure and multiorgan failure were the main reasons for treatment failure. Further research is needed to justify the use of $ECCO_2R$ in this patient population.

CONFLICT OF INTEREST

PW, AH, AT, and TL declare no conflicts of interest related to the submitted work. PS reports lecture fees from Getinge. TS reports lecture fees from Getinge and Xenios.

AUTHORS CONTRIBUTIONS

All authors substantially contributed to the study and the manuscript and met the requirements for authorship defined by the International Committee of Medical Journal Editors (ICMJE). PW and TL designed the study, collected data, analyzed the data, and wrote the manuscript; AT and AT collected the data and critically revised the manuscript; PS, TS, WR, AH, and NB contributed to the writing and critically revised the manuscript. All authors read and approved the final version of the manuscript prior to its submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the first author, upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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