A comparison of long term outcomes in patients managed with VV-ECMO in the first and second waves of the COVID-19 pandemic in the UK

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Abstract

Background

Early studies of veno-venous extracorporeal membrane oxygenation (VV-ECMO) in COVID-19 have revealed similar outcomes to historical cohorts. Changes in the disease and treatments has led to differences in the patients supported on VV-ECMO in the 1st and 2nd waves. We aimed to compare these two groups in both the acute and follow-up phase.

Methods

In this retrospective study, we identified the differences between patients supported on ECMO for COVID-19 between wave 1 (17/03/2020-31/08/2020) and wave 2 (01/09/2020-25/05/2021). We examined mortality at censoring date (30/11/2021) and decannulation, patient characteristics, complications and lung function and quality of life (QOL – by EQ5D3L) at first follow-up.

Findings

One-hundred and twenty-three patients were included in our analysis. Survival at censoring date [Chi-sqaured 6.35, p=0.012] and decannulation [90.4% vs 70.0%, p<0.001], was significantly lower in the 2nd wave, whilst duration of ECMO run was longer [12.0(18.0-30.0) days vs. 29.5(15.5-58.3)] days (p=0.005)). Wave 2 patients had longer application of non-invasive ventilation (NIV) prior to ECMO and a higher incidence of barotrauma. Patient age and NIV use were independently associated with increased mortality [OR 1.07(1.01-1.14), p=0.025 and 3.37(1.12–12.60), p=0.043 respectively]. QOL and lung function, apart from KCOc was similar at follow up across the waves.

Conclusion

Most patients with COVID-19 supported on ECMO in both waves survived in the short and longer term. At follow-up patients had similar lung function and QOL across the 2 waves. This suggests that ECMO has an ongoing role in the management of a carefully selected group of patients with COVID-19.

Trial Registration

Research Ethics Committee (20/EM/0204)

Introduction

Veno-venous (VV) Extracorporeal Membrane Oxygenation (ECMO) is an established adjunctive salvage intervention in patients with refractory hypoxemic respiratory failure (1).

The use of ECMO support in patients presenting with COVID 19 related respiratory failure has been a matter of debate (2). However, initial analysis of a large multi-centre cohort of patients treated with ECMO during the first wave of the pandemic has shown outcomes comparable to that noted in large,

randomized control trials (3). Furthermore, our single centre 6-months outcome data suggest survival rates similar to our historical cohort of patients with viral pneumonia (4).

There has been a rapid expansion of knowledge around pathophysiology (5), management and outcome of patients with COVID-19. Throughout the pandemic we have seen the emergence of new more virulent variants (6, 7), discovery of effective immunomodulatory treatments including dexamethasone and interleukin (IL-6) inhibitors (8, 9) and the widespread use of non-invasive ventilation (NIV) (10). This has clearly been accompanied by a change in the effectiveness of ECMO on a global scale (11), with more recent cohorts experiencing lower survival to 90-days (12, 13).

Whilst 90 and 180-day survival in patients supported with ECMO for COVID-19 has been extensively documented (4, 12, 13) important outcomes like long-term survival, follow up pulmonary function and quality of life (QOL) have not been widely reported in the literature (14).

We aimed to compare the differences between the patients managed in our center across the 1st and 2nd waves of the pandemic in the UK, from referral through admission and in those who survived to recovery.

Methods

This is a single-centre retrospective cohort study of an intensive care unit providing ECMO services to 46 referring hospitals within a wider national network (15). All patients admitted with polymerase chain reaction proven COVID-19 ARDS requiring VV-ECMO support were identified. Patients with a known outcome of decannulation or death as of 30/11/2021 (censoring date) were included in the analysis.

The first wave was defined as cannulation for VV-ECMO between the 17/03/2020 and 31/08/2020. The 2nd wave was defined as those cannulated for VV-ECMO between the 01/09/2020 and 31/05/2021 as per the national intensive care audit system (ICNARC) in the UK (16).

Patients were excluded from the analysis if they were under 18 years of age or if they required veno-arterial ECMO. The study was approved by Research Ethics Committee (20/EM/0204) and the need for individual informed consent was waived due to the retrospective nature of the analysis. Patient's suitability for VV-ECMO was assessed in line with national United Kingdom (UK) National Health Service (NHS) commissioning criteria previously described by Camporota *et al.* (17). Data were collected from electronic patient records and referral documents as previously described (4). A full explanation of data collection methods can be found in the online supplement. Data on lung function, which was performed in keeping with current American thoracic society guidelines (18) and QOL, measured by EQ-5D-3L (19) was collected at first follow-up.

The primary outcome of the study was difference in mortality at censoring date between patients supported on VV-ECMO for COVID-19 ARDS in the 1st and 2nd waves. Secondary outcomes included differences in pulmonary function and quality of life at first follow up, mortality at decannulation and ECMO related complications. We also examined differences in duration of ECMO run. A long run was

defined as ≥ 30 days. Disparities in demographic and baseline characteristics between the 1st and 2nd waves were also investigated. Finally, we performed logistic regression to examine the predictors of mortality at decannulation in the cohort as a whole.

Data were analysed using Graphpad Prism (Graphpad, San Diego, USA) and R Studio (RStudio, Vienna, Austria). Normality of the data was assessed using Shapiro-Wilk and Kolmogorov-Smirov test and visually using histograms. Data are presented as mean and standard deviation or median and interquartile range. Differences between the 1st and 2nd waves were compared using student t-test or Mann-Whitney U test, whilst proportions in different groups were compared using Fisher's exact test or Chi squared depending on the number of groups. Mortality data was analysed as a proportion as described above and using Kaplan-Meier plots. A full explanation of the multivariate analysis which was performed on factors identified as different between those who survived and did not survive to decannulation can be found in the online supplement. There was no imputation undertaken for missing data, and we adopted a strategy of using all valid data to increase the sample size of our study as advocated by Dzuria and colleagues (20). As convention, statistical significance was set at a p value < 0.05.

Results

One-hundred and twenty-three patients with COVID-19 pneumonitis were admitted and supported with VV-ECMO during the study period. Fifty-three patients were managed in the 1st wave and seventy in the 2nd wave.

Patient demographics for waves 1 and 2 are shown in Table 1. Body mass index (BMI) was significantly higher in the 2nd wave compared to the 1st. There was no other significant difference in any demographics between the two groups.

Table 1

Differences in demographics between patients with COVID-19 admitted to the Royal Brompton hospital for veno-venous extra-corporeal membrane oxygenation in the 1st and 2nd waves of the pandemic. Body mass index (BMI).

	1st wave (N = 53)	2nd Wave (N = 70)	p Value
Age years (Mean and SD)	46.0 (7.8)	46.4 (10.5)	0.821
Sex male n (%)	39 (73.6)	46 (65.7)	0.431
BMI kg/m^2 (Median and IQR)	29.4 (25.6–34.2)	32.6 (29.0–39.6)	0.008
Asthma n (%)	10 (18.9)	14 (20.0)	1.000
COPD n (%)	0 (0.0)	1 (1.4)	1.000
Cardiovascular disease n (%)	0 (0.0)	2 (2.9)	1.000
Chronic kidney disease n (%)	0 (0.0)	2 (2.9)	1.000
Hypertension n (%)	13 (22.6)	25 (35.7)	0.238
Diabetes Mellitus n (%)	9 (17.0)	16 (22.9)	0.501
Immunosuppression n (%)	1 (1.9)	2 (2.9)	1.000

Baseline referral characteristics are shown in Table 2. In the 2nd wave patients had longer duration of NIV prior to intubation as well as a lower Murray score. Patients in the 2nd wave also had a higher incidence of barotrauma, with pneumomediastinum being more common than pneumothorax. Those patient who had barotrauma at referral had a longer duration of NIV than those without [5 (2–7) days vs 1 (0–5) days, p = 0.007]. The treatments offered to the two groups were also significantly different, with patients in the 2nd wave being more likely to have been given dexamethasone, an IL-6 inhibitor and remdesivir prior to ECMO initiation.

Table 2

Baseline pre-veno-venous extracorporeal membrane oxygenation (VV-ECMO) characteristics in patients with COVID-19 admitted to the Royal Brompton hospital in wave 1 and wave 2 of the pandemic. Non-invasive ventilation (NIV) (defined as continuous positive airway pressure or bi-level positive airway pressure). Invasive mechanical ventilation (IMV). Positive end expiratory pressure (PEEP). Partial pressure of oxygen / fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio). Partial pressure of carbon dioxide ($PaCO_2$). Renal replacement therapy (RRT). Barotrauma is one of pneumothorax and / or pneumomediastinum.

	1st wave (N = 53)	2nd wave (N = 70)	P value
PRE-ECMO parameters			
RESP score (Median and IQR)	4 (3–5)	4 (3–5)	0.571
Days of NIV prior to intubation (Median and IQR)	0 (0–3)	3 (0–7)	0.002
Days of IMV prior to ECMO (Median and IQR)	3.5 (2.0–6.0)	3.0 (1.0–5.0)	0.071
Plateau pressure (cmH_2O) (Mean and SD)	29.1 (4.2)	27.5 (5.2)	0.113
PEEP (cmH_20) (Median and IQR)	12.5 (10.0–15.0)	12.0 (10.0–14.0)	0.270
pH (Median and IQR)	7.28 (7.18–7.38)	7.31 (7.26–7.37)	0.216
PaO_2/FiO_2 ratio (kPa) (Median and IQR)	9.3 (8.1–10.7)	9.8 (7.8–12.2)	0.328
$PaCO_2$ (kPa) (Median and IQR)	8.4 (6.8–10.3)	7.5 (6.4–9.3)	0.078
Murray Score (Median and IQR)	3.50 (3.25–3.75)	3.25 (3.0–3.5)	0.002
Prone ventilation n (%)	51 (96.2)	65 (92.9)	0.698
Inotropic / Vasopressor support n (%)	24/53 (45.3)	36/68 (52.9)	0.465
RRT n (%)	7/52 (13.5)	3/70 (4.3)	0.100
Barotrauma n (%)	4 (7.5)	17 (24.3)	0.016
Pneumothorax n (%)	1 (1.8)	10 (14.3)	0.023
Pneumomediastinum n (%)	3 (5.7)	13 (18.6)	0.056
COVID-19 treatments			
Dexamethasone n (%)	2 (3.8)	70 (100.0)	< 0.001
Other steroids n (%)	7 (13.2)	10 (15.2)	1.000
IL-6 inhibitor n (%)	3 (5.7)	19 (27.1)	0.002
Remdesivir n (%)	1/53 (1.9)	44/69 (63.8)	< 0.001

Admission characteristics after initiation of ECMO including ventilatory parameters in the first 24 hours across the two groups are shown in Table 3. Patients in the 2nd wave had lower admission sequential

organ failure assessment (SOFA) scores, creatinine levels, d-dimers, lactate dehydrogenase (LDH) and C-reactive protein (CRP). They also had higher albumin. There was no difference in ventilatory practice in the first 24 hours between the 1st and 2nd wave.

Table 3

Admission bloods and average ventilatory parameters in the first 24 hours in the first and second waves of the COVID-19 pandemic in patients requiring veno-venous extra-corporeal membrane oxygenation (VV-ECMO). Sequential organ failure assessment (SOFA), C-reactive protein (CRP), Lactate dehydrogenase (LDH), Alanine aminotransferase (ALT), Fraction of inspired oxygen (FiO2), Positive end expiratory pressure (PEEP), peak inspiratory pressure (PINSP).

	1st wave N = 53	2nd wave N = 70	P value
Admission to ECMO centre			
SOFA score (Median and IQR)	8 (7–11)	7 (5–8)	< 0.001
Creatinine ($mmolL^{-1}$) (Median and IQR)	77 (57–202)	71 (45–94)	0.033
CRP (mg/L) (Median and IQR)	240 (173–327)	156 (58–206)	< 0.001
D-dimer (ng/ml) (Median and IQR)	3506 (1921–6477)	2324 (1017–4611)	0.026
Ferritin (µg/L) (Median and IQR)	881 (476–1376)	549 (303–1180)	0.079
Troponin I (ng/L) (Median and IQR)	59.9 (26.1–98.7)	39.7 (15.8–154.0)	0.628
Albumin (g/L) (Median and IQR)	20 (19–25)	23 (20–26)	0.049
LDH (IU/L) (Median and IQR)	1089 (895–1335)	986 (730–1211)	0.004
ALT (IU/L) (Median and IQR)	44 (29–75)	45 (28–84)	0.798
First 24 hours after admission			
FiO2 (Median and IQR)	48.0 (37.8–59.3)	45.0 (37.4–55.1)	0.494
PEEP (cmH_2O) (Median and IQR)	10 (10–12)	10 (10–12)	0.502
Pinsp (cmH_2O) (Median and IQR)	22.3 (2.8)	23.3 (3.8)	0.137
Tidal volume (ml) (Median and IQR)	142 (93–212)	160 (100–245)	0.243

Differences in ECMO related complications, between the 1st and 2nd wave are shown in Table 4. The only significant differences between the groups was an increased incidence of pulmonary embolism (PE) in the 1st wave. Alongside this there was an increased proportion of patients in the 2nd wave being pulsed with iv methylprednisolone whilst on ECMO [47.2% vs 70.0%, p = 0.015].

Table 4

Number and percentage of patients with COVID-19 supported with veno-venous extra-corporeal membrane oxygenation (VV-ECMO) experiencing complications at any time during their ECMO run. Renal replacement therapy (RRT) was defined as having RRT at any time during the ECMO run. This includes patients who were established on RRT prior to ECMO initiation

	1st wave (N = 53)	2nd wave (N = 70)	p value
Requirement for RRT n (%)	24 (45.3)	25 (35.7)	0.353
Ischaemic stroke n (%)	6 (11.3)	5 (7.1)	0.528
Intracranial haemorrhage (%)	11 (20.8)	10 (14.3)	0.469
GI haemorrhage (%)	5 (9.4)	13 (18.6)	0.201
Pneumothorax (%)	9 (16.9)	22 (31.4)	0.093
Pulmonary Embolism (%)	37 (69.8)	34 (48.6)	0.027

The duration of ECMO run was significantly shorter in the 1st wave when compared to the 2nd [12 (18–30) vs. 30 (16–58) days (p = 0.005)] (Fig. 1A). In keeping with this data, a significantly lower proportion of patients in the 1st wave had a long ECMO run [18.9% vs. 48.6%, p < 0.001] (Fig. 1B).

[Figure 1]

Figure 1a) *Duration of ECMO run in the 1st and 2nd waves.* b) *Number of patients in the 1st and 2nd waves with short (< 30 days) and long (≥ 30 days) duration of ECMO run.*

Significantly more patients in the first wave of the pandemic survived to decannulation [(90.6% vs. 70.0% (p = 0.007)] (Fig. 2A) and to censoring date (Fig. 2B).

[Figure 2]

Figure 2a) *Differences in survival to decannulation in patients with COVID-19 supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) in the 1st and 2nd wave of the pandemic.* **b)** Differences in survival to censure date 30th November 2021 *in patients with COVID-19 supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) in the 1st and 2nd wave of the pandemic.*

The differences in referral and admission characteristics in those that survived and did not survive to decannulation are documented in supplementary table 1. Significant differences were found in the age of patients, the duration of NIV prior to ECMO and the RESP score. In logistic regression both age [OR 1.07 (1.01–1.14, p = 0.025] and use of NIV [OR 3.37 (1.12–12.60), p = 0.043] was independently associated with increased risk of mortality on ECMO.

Supplementary table 1.

At the time of writing, follow up lung function was available in 32 patients in wave 1 and 25 patients in wave 2 at a median time from admission of 7.6 (3.0–9.6) and 7.5 (7.0–7.9) months respectively. The transfer coefficient of carbon monoxide corrected for haemoglobin (KCOc) percent predicted was significantly higher in the patients followed up in wave 2 compared to wave 1. There were no other significant differences in lung function between the groups (Fig. 3A). Example CT scans showing development and then resolution of COVID-19 changes are shown in Fig. 3C. Follow up QOL was measured by the EQ5D3L in 27 patients in wave 1 and 25 patients in wave 2 at a median time from admission of 7.9 (5.8–8.6) months and 7.4 (6.3–8.2) months respectively. There was no difference in indexed quality of life scores between the two groups at follow up (Fig. 3B). Proportionally more patients in wave 2 had ongoing problems with mobility, self-care and usual activities but this did not reach statistical significance (Table 5).

[Figure 3]

Figure 3a) *Pulmonary function tests at follow in patients with COVID-19 supported on ECMO in the 1st and 2nd waves. Forced expiratory volume in 1 second (FEV1) [82.9 ± 20.1% vs.76.8 ± 15.6], Forced vital capacity (FVC) [80.4 ± 20.7% vs. 76.2 ± 15.6], transfer factor of carbon monoxide corrected for haemoglobin (TLCOc) [59.5 ± 17.8 vs. 60.2 ± 15.5], transfer coefficient of carbon monoxide corrected for haemoglobin (KCOc) [80.1 ± 16.2 vs. 90.7 ± 13.0].* b) *Follow up EQ5D3L quality of life index in patients with COVID-19 supported on ECMO in the 1st and 2nd waves (note the normalised value for this age group in the UK is 0.8).* c) *Representative admission and follow up CT scans of 2 patients supported on ECMO for COVID-19, one from the 1st wave and one from the 2nd wave.*

Table 5
Proportion of patients reporting problems (1 - none, 2 - some, 3 - severe) with mobility, self-care, usual activities, pain/discomfort, anxiety/depression in the 1st and 2nd waves of the pandemic as measured by the EQ5D3L.

	Mobility		**Self-care**		**Usual Activities**		**Pain / Discomfort**		**Anxiety / Depression**	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
1	63.0%	40.0%	44.4%	24.0%	66.7%	48.0%	29.6%	32.0%	44.4%	44.0%
2	37.0%	60.0%	51.9%	72.0%	33.3%	52.0%	63.0%	60.0%	44.4%	44.0%
3	0.0%	0.0%	3.7%	4.0%	0.0%	0.0%	7.4%	8.0%	11.1%	12.0%
p value	0.164		0.297		0.173		0.976		0.995	

Discussion

This report is the first to present a comprehensive view of the similarities and differences between patients with COVID-19 managed with VV-ECMO in the 1st and 2nd waves of the pandemic from referral

to follow-up. We have shown that patients with COVID-19 supported on VV-ECMO in the 2nd wave had an increased mortality and longer ECMO runs than patients managed in the 1st wave. We have confirmed the results of our previous work (4), which revealed that the patients who survive their ECMO run for COVID-19 also tend to survive in the long term. We have also, for the first time as far as we can tell, demonstrated that pulmonary function and quality of life is similar, between survivors of the 2 waves at an average of 7 months follow up.

In the UK, ICNARC reported a new increase in ICU admissions due to COVID-19 after 01/09/2020, defining the 2nd wave of the pandemic (16). The results of several studies, particularly the REMAP-CAP trial, have changed the standard of care for patients with COVID-19 admitted to hospital between the 1st and 2nd waves. Dexamethasone (8), and anti-IL-6 drugs (9, 21), have been shown to improve mortality, whilst remdesivir (22) reduced time to recovery. The adoption of these treatments is well represented in our baseline characteristics. These interventions have undoubtedly improved global outcomes in patients presenting to hospital with COVID-19 (16) but are not universally effective in preventing some patients from requiring extra-corporeal support.

Patients in the 2nd wave had lower inflammatory markers at cannulation, likely due to an alteration in host response to different COVID-19 variants and previous steroid treatment (23). Despite a dampening of the measured inflammatory response they continued to deteriorate to require VV-ECMO. They were also more likely to receive a pulse of methylprednisolone once on ECMO, for non-resolving COVID-19 pneumonitis. Whilst the optimum timing of immunomodulation remains uncertain (24) our data suggests that patients in the 2nd wave were less likely to respond to steroid treatment but were still susceptible to their side-effects (12). This may have had a significant impact on the duration of ECMO run and mortality seen in the 2nd wave.

A further difference seen between the 1st and 2nd waves is a reduction in the incidence of PE. This is probably due to more patients receiving treatment dose anticoagulation very early in the disease (25). This along with the increase use of immunomodulators (8, 9) may explain the reduction in documented PEs. This reduction in burden of vascular disease in the 2nd wave may also be a factor in the significant difference in KCOc between the 1st and 2nd waves at follow up.

As well as changes in pharmacological interventions, studies have suggested that NIV could prevent intubation and reduce mortality in COVID-19 ARDS (10). We found a longer duration of NIV in patients supported on ECMO in the 2nd wave. These findings were mirrored across the rest of the National ECMO service (17). Duration of invasive mechanical ventilation prior to ECMO represents a well-established risk factor for increased mortality (26), whilst duration of NIV is less well studied. Our findings suggest that in COVID-19 acute respiratory distress syndrome (ARDS) duration of NIV but not invasive mechanical ventilation may be associated with reduced survival in patients going on to require VV-ECMO. These findings are supported in the wider literature (27, 28).The increased duration of NIV in patients in the 2nd wave meant these individuals may have been more likely to be exposed to self-induced lung injury and delayed institution of prone positioning (29). This hypothesis is supported by the association between

barotrauma and NIV duration in our cohort. Our work highlights the need for urgent studies of the optimal timing of intubation in COVID-19 ARDS.

The survival data, although showing a difference in outcome between the 1st and 2nd waves to date of censure and decannulation also suggest that very few patients who survived to 90-days died during the follow up period. This finding was independent of whether the patient was supported in the 1st or 2nd wave and is in keeping with data on longer term survival after ECMO from other causes of ARDS (1). The increased mortality was despite a decrease in SOFA and Murray scores seen in the 2nd wave. Importantly, traditional ICU severity scores have been shown to be poorly predictive of outcomes in COVID-19 related critical illness (30).

Despite the reduction in survival between the 1st and 2nd waves, mortality in both groups remains similar to historical cohorts (3, 4). The better survival rates reported in our cohort than in the general literature could be partly due to the high volume of patients supported in our center, a factor associated with low mortality in other studies (31). In contrast to our data a study reporting the outcomes of patients referred but deemed not suitable for ECMO has shown a mortality of 80% at 90 days (32). With mortality in our 2nd wave cohort of just more than 30%, our findings highlight the importance of VV-ECMO in supporting a carefully selected group of patients with COVID-19 ARDS.

As well as showing the differences in outcome over the pandemic our data also sheds some light on who might benefit most from support with VV-ECMO for COVID-19. Age is an important predictor of mortality in patients with COVID-19 who are managed with VV-ECMO both in our study and the wider literature (3). Whilst there is no upper age-limit to consider ECMO in COVID-19 it remains an important consideration, with the original studies of ECMO excluding patients over 65 years of age (1). The RESP score was developed to predict outcomes on ECMO (26) and despite the narrow score range seen in our population, was still significantly higher in those who survived compared to those who died. Our data therefore validates the RESP score as a tool which can predict survival on ECMO even within a narrow window.

The median duration of ECMO was 11 days longer in the 2nd wave than the 1st. This has been verified in a number of other studies (33). As well as implication for individuals and families these longer runs have economic implications on healthcare provision with every day of ECMO support costing over $7500 in one study (34), making it a huge financial burden particularly in resource poor healthcare settings.

Follow up data on patients supported on VV-ECMO for COVID-19 is lacking (14). Here we present a well characterized unique cohort of patients who had lung function and quality of life measured at an average of between 7 and 8 months after the initiation of their ECMO run. We have demonstrated that there is very little difference in the follow up parameters of patients supported in the 1st and 2nd waves of the pandemic. This suggests that despite the reduction in survival across the 2 waves patients who survive to follow up have similar physiological reserve and quality of life. This adds weight to the argument that ECMO is a worthwhile treatment in a carefully selected group of patients with COVID-19. Whilst there was no statistical difference in QOL between the 2 waves there were some numerical differences in the proportion of patients reporting mobility, self-care and usual activity issues. This may relate to an

increase in critical care-neuro-myopathy precipitated by a longer duration of ECMO run, ICU stay and increased use of steroids (35). The QOL in our survivors is typical of that seen in patients after ARDS due to COVID-19 and other causes (36, 37) and is lower, numerically at least, than a healthy population of the same age who have an expected EQ5D3L index score of 0.8 (38). As well as the aforementioned increased KCOc in the 2nd wave the lung function parameters at follow up in our group as a whole show a disproportionate reduction in transfer factor of carbon monoxide (TLCOc) with relatively preserved spirometry. This is in keeping with follow up data from the wider ARDS and COVID-19 literature (36, 37).

Limitations And Strengths

This study's limitations include its single-center and retrospective design. There is also the issue of missing data. Data was collected from referral forms which included both data entry boxes and free text, a potential source of bias. Due to the nature of the study it was not possible to control for multiple comparisons, accepting that this may cause more type 1 error.

Despite these limitations this is a large single-center ECMO study incorporating a homogenous group of patients, with a similar disease profile and a uniform approach to clinical management. Only BMI was different between the 1st and 2nd waves, a factor which has not been shown to be a risk factor for mortality in large registry studies (3).

Conclusions

Our study shows a reduced survival in the 2nd wave of patients receiving VV-ECMO support for COVID-19 ARDS. These patients also had significantly longer ECMO runs. Importantly we have shown no significant difference in QOL or lung function in those who were followed up at just over 6 months. Data presented here support the hypothesis that age at cannulation and prolonged use of NIV prior to ECMO might represent the main factors influencing survival. This data supports the current position taken by the Nationally commissioned ECMO service in the UK on the patients most likely to benefit from ECMO support (17).

Despite the poorer outcomes as the pandemic progresses, our results support the continued provision of ECMO in a carefully selected population of patients with ARDS secondary to COVID-19. Further work should aim define those who are likely to benefit most from this important but sometimes scarce and resource intense intervention.

Abbreviations

Veno-venous extracorporeal membrane oxygenation (VV ECMO)

Quality of life (QOL)

Non-invasive ventilation (NIV)

Interleukin 6 (IL-6)

Intensive care national audit and research centre (ICNARC)

United Kingdom (UK)

National health service (NHS)

Sequential organ failure assessment (SOFA)

Lactate dehydrogenase (LDH)

C-reactive protein (CRP)

Pulmonary embolism (PE)

Transfer coefficient of carbon monoxide (KCOc)

Acute respiratory distress syndrome (ARDS)

Transfer factor of carbon monoxide (TLCOc)

Declarations

Ethics approval and consent to participate

The study was approved by Research Ethics Committee (20/EM/0204) and the need for individual informed consent was waived due to the retrospective nature of the analysis.

Consent for publication

Not applicable

Availability of data and materials

Anonymised datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

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Author contributions

B.G., P.B., S.S. and S.L. designed the project. All authors contributed to collection of the data. B.G., P.B., S.S. S.L. and B.P. analysed and interpreted the data. All authors contributed to the writing and editing of the final manuscript.

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Figures

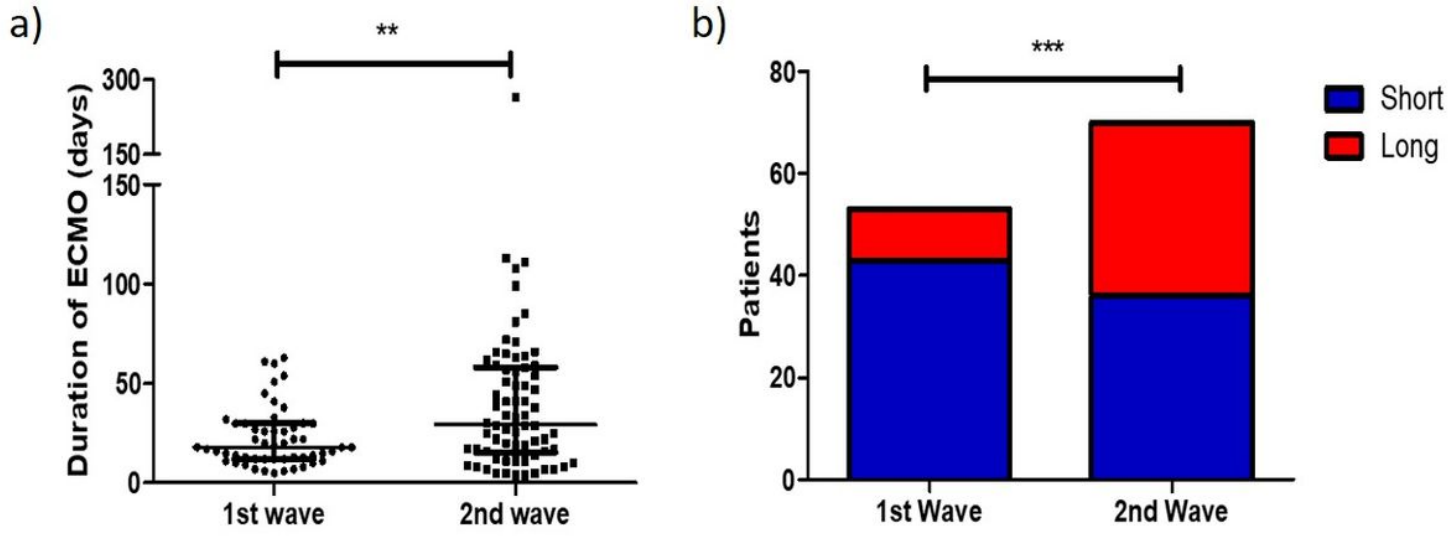

Figure 1

a) *Duration of ECMO run in the 1st and 2nd waves.* ***b)*** *Number of patients in the 1st and 2nd waves with short (< 30 days) and long (≥ 30 days) duration of ECMO run.*

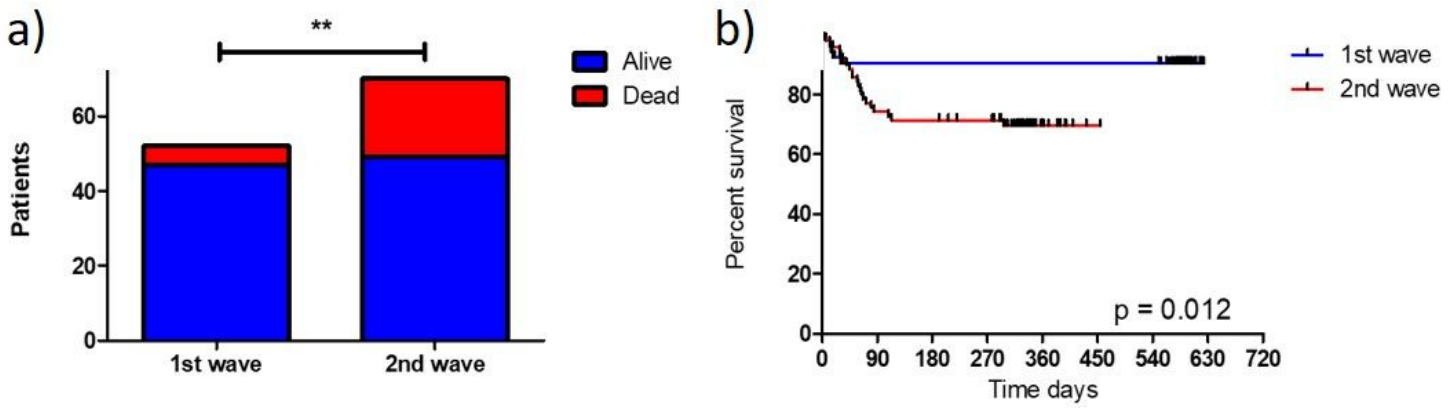

Figure 2

a) *Differences in survival to decannulation in patients with COVID-19 supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) in the 1st and 2nd wave of the pandemic.* **b)** Differences in survival to censure date 30th November 2021 *in patients with COVID-19 supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) in the 1st and 2nd wave of the pandemic.*

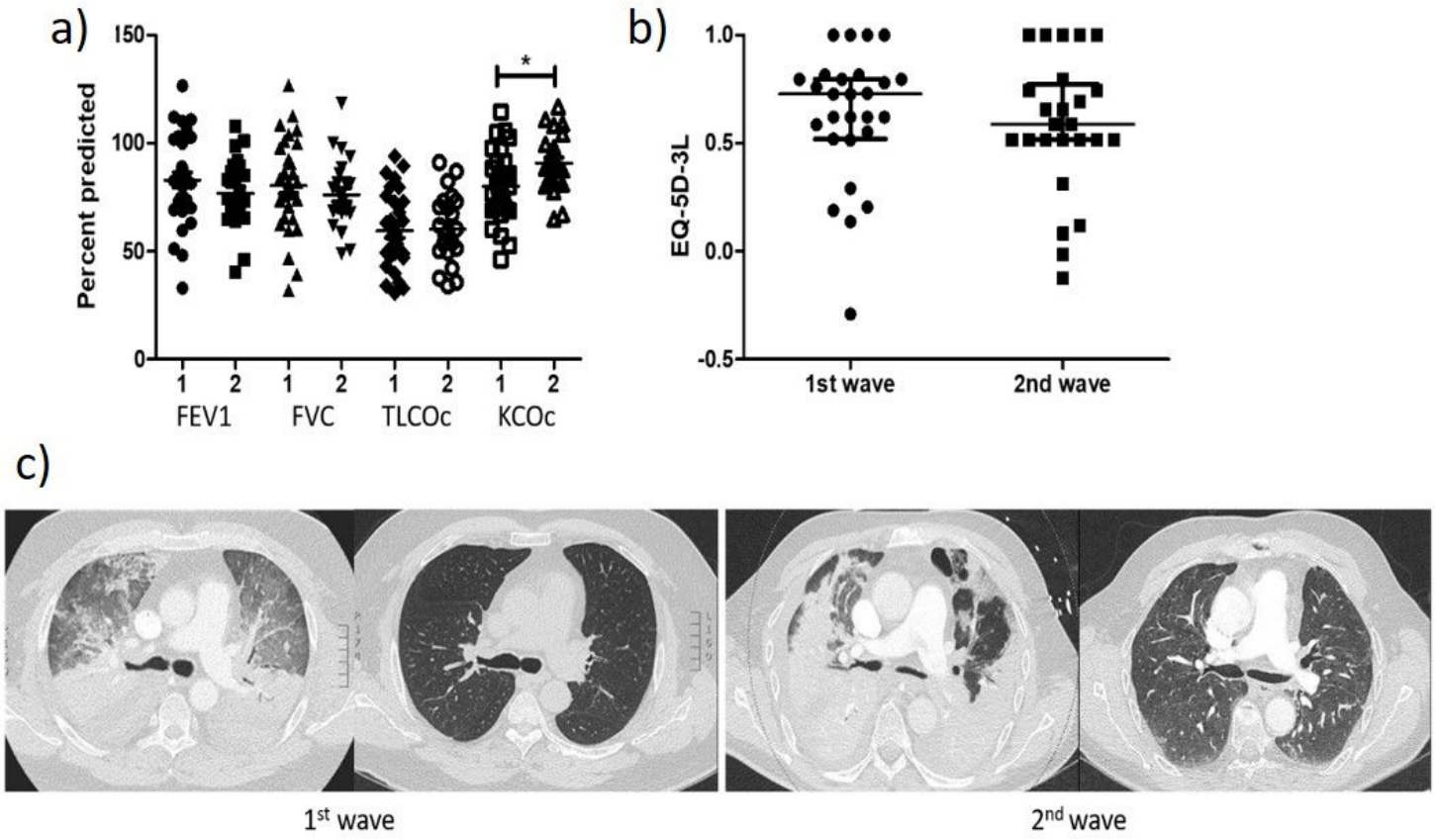

Figure 3

a) *Pulmonary function tests at follow in patients with COVID-19 supported on ECMO in the 1st and 2nd waves. Forced expiratory volume in 1 second (FEV1) [82.9±20.1% vs.76.8±15.6], Forced vital capacity (FVC) [80.4±20.7% vs. 76.2±15.6], transfer factor of carbon monoxide corrected for haemoglobin (TLCOc) [59.5±17.8 vs. 60.2±15.5], transfer coefficient of carbon monoxide corrected for haemoglobin (KCOc) [80.1±16.2 vs. 90.7±13.0].* ***b)*** *Follow up EQ5D3L quality of life index in patients with COVID-19 supported on ECMO in the 1st and 2nd waves (note the normalised value for this age group in the UK is 0.8).* ***c)*** *Representative admission and follow up CT scans of 2 patients supported on ECMO for COVID-19, one from the 1st wave and one from the 2nd wave.*

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