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doi: 10.1016/j.bja.2020.12.017
Advance Access Publication Date: 23 December 2020

Phenotypes of severe COVID-19 ARDS receiving extracorporeal membrane oxygenation

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Keywords: ARDS; clustering analysis; COVID-19; ECMO; latent phenotypes

Editor—Patients with acute respiratory distress syndrome (ARDS) caused by coronavirus 2019 (COVID-19) have heterogeneous clinical presentation, inflammatory status,[1] and respiratory mechanics.[2] Although venous-venous extracorporeal membrane oxygenation (ECMO) is utilised in patients with COVID-19, international data include varied outcomes.[3] Some of these differences may reflect variable initiation criteria and case-mix, and the possibility of differing phenotypes in this population has not been explored. Identification of latent phenotypes using readily available clinical data can help identify patients at greater risk of deterioration,[4,5] or patients who might benefit from a particular therapy.

We used an unsupervised clustering algorithm to assess for the existence of distinct phenotypes of COVID-19 patients on ECMO, utilising data available on Day 0 of ECMO commencement. We hypothesised that distinct phenotypes may inform risk of mortality and organ failure. This retrospective study incorporated all adult COVID-19 ECMO patients admitted to Guy's and St Thomas' Foundation Trust (GSTFT), a regional ECMO centre in the UK, up to July 1, 2020 (n=56) with institutional ethics approval (reference number 10796). We selected 15 variables, representing typical data available at ECMO initiation. These included patient characteristics, respiratory parameters at time of ECMO referral, and ECMO Day 0 laboratory values (see Supplementary material). Primary outcome was survival to hospital discharge, with secondary outcomes of organ support requirements. A k-means clustering algorithm (see Supplementary material), used previously in critical care datasets,[6] was used to group patients based on similarities across all variables. Clusters were validated internally, on stability and cohesion metrics, and externally, based on association to outcomes. Multivariable models were constructed to test the association of cluster membership with distal outcomes when adjusted for baseline characteristics.

Three clusters were identified, demonstrating distinct phenotypes with significant differences in characteristics and outcomes (Table 1, Supplementary Figs S1 and S2). There was a significant survival difference between phenotypes (P=0.0023), with phenotype 1 membership having 96% survival to ICU discharge, and a significant difference in renal replacement requirements (P=0.0052).

Phenotype 1 (n=24 [42.8%], low mortality, hypoinflammatory, low organ support) included younger, mostly female patients, with low requirement for renal replacement characterised by lower pre-ECMO sequential organ failure assessment (SOFA) scores and markers of inflammation and thrombosis. More patients received steroids before ECMO (29.2% *vs* 5% and 16.7% in phenotypes 2 and 3, respectively, P=0.113). ICU mortality was 4.2%.

Phenotype 2 (n=20 [35.7%], intermediate mortality, hyperinflammatory, high organ support) patients required the most renal replacement therapy. Patients had a significantly longer time (median 5 days [inter-quartile range 5–6]) between start of invasive mechanical ventilation (IMV) and ECMO, the

Table 1 Characteristics and outcomes with comparisons between phenotypes

	All patients (*n*=56)	Phenotype 1 (*n*=24)	Phenotype 2 (*n*=20)	Phenotype 3 (*n*=12)	*P*-value
Patient characteristics					
Age, yr*	46.0 [37.5–52.2]	41 [34.8–48.0]	51 [45.2–53.0]	49 [44.8–54.2]	0.012
Body masss index (BMI)*	29.5 [27.0–34.0]	29.0 [26.8–34.2]	29.5 [27.0–33.5]	32.0 [29.0–34.0]	0.621
Female	15 (26.8)	10 (41.7)	3 (15)	2 (16.7)	0.093
Ethnicity	23 (41.1)	10 (41.7)	6 (30)	7 (58.3)	0.287
- White	11 (19.6)	1 (4.2)	8 (40)	2 (16.7)	0.011
- Black	22 (39.3)	13 (54.2)	6 (30)	3 (25)	0.137
- South/East Asian					
Comorbidity	8 (14.3)	1 (4.2)	4 (20)	3 (25)	0.160
- Diabetes mellitus	6 (10.7)	3 (12.5)	1 (5)	2 (16.7)	0.546
- Asthma	11 (19.6)	3 (12.5)	7 (35)	1 (8.3)	0.094
- Hypertension					
Clinical characteristics					
Days from ED to IMV*	2 [0.8–4.0]	1.0 [0.0–4.0]	1.0 [0.0–3.0]	6.0 [3.0–8.2]	<0.001
Days from IMV to ECMO*	4 [1.8–6.0]	3.5 [2.0–5.2]	6.0 [5.0–6.0]	1.0 [1.0–1.0]	<0.001
RESP score†	4 [3.0–5.0]	4.0 [4.0–5.0]	3.0 [2.8–4.2]	5.5 [4.0–6.2]	0.001
SOFA score*	6 [4.0–9.0]	4.5 [4.0–6.0]	8.0 [5.8–11.2]	6.5 [4.0–9.0]	0.006
PF ratio (kPa)*	9.19 [7.97–10.51]	9.85 [9.00–11.81]	8.74 [7.80–9.76]	7.99 [6.80–9.31]	0.004
P_{CO_2} (kPa)*	9.00 [7.20–9.89]	8.91 [7.11–9.40]	9.60 [7.80–11.60]	8.80 [7.51–9.91]	0.310
Plateau pressure (cm H_2O)*	30.0 [27.8–31.2]	30.0 [25.8–31.0]	31.0 [30.0–32.2]	29.2 [27.8–29.4]	0.020
Corticosteroids given pre-ECMO	10 (17.9)	7 (29.2)	1 (5.0)	2 (16.7)	0.113
Antimicrobials given pre-ECMO	56 (100)	24 (100)	20 (100)	12 (100)	1
ECMO Day 0 laboratory values					
Lymphocytes (10^9 L^{-1})*	0.6 [0.5–1.0]	0.6 [0.5–1.1]	0.8 [0.6–1.2]	0.4 [0.4–0.6]	0.013
N:L ratio*	13.9 [9.3–22.0]	11.8 [9.5–16.9]	10.6 [7.6–16.3]	23.2 [19.3–34.1]	<0.001
Procalcitonin (ng ml^{-1})*	3.6 [1.1–9.4]	1.2 [0.8–3.7]	8.1 [3.1–32.5]	5.3 [1.8–8.6]	0.005
Ferritin (μg L^{-1})*	1783.0 [997.5–3851.8]	1613 [846–2841]	1710 [1052–4328]	1932 [1619–4389]	0.340
CRP (mg L^{-1})*	310.5 [207.8–356.8]	194 [105–277]	355 [326–469]	333 [235–380]	<0.001
Fibrinogen (g L^{-1})*	6.8 [5.3–8.6]	5.4 [4.5–8.2]	8.2 [7.2–9.8]	6.3 [4.9–7.1]	0.001
D-dimer (mg L^{-1} FEU)*	9.2 [5.3–33.6]	5.2 [3.2–7.1]	30.1 [19.5–47.9]	31.6 [8.6–64.3]	<0.001
Outcome features					
Survival to 60 days	40 (71.4)	23 (95.8)	11 (55)	6 (50)	0.002
Peak norepinephrine requirement (μg kg^{-1} min^{-1})	0.1 [0.0–0.2]	0.07 [0–0.18]	0.19 [0.09–0.30]	0.14 [0.06–0.23]	0.098
Renal replacement therapy	22 (39.3)	4 (16.7)	13 (65)	5 (41.7)	0.005
Significant positive microbiology on admission BAL	10 (17.9)	4 (16.7)	6 (30.0)	0 (0.0)	0.098
Pulmonary embolism	15 (26.8)	7 (29)	4 (20)	4 (33)	0.670
Pneumothorax	15 (26.8)	6 (25.0)	6 (30.0)	3 (25.0)	0.921
Duration of ECMO (days)	13 [8.0–21.0]	16 [9–21]	13 [7–16]	12 [8–31]	0.330
Survivors only	13.5 [8.8–21.0]	16 [9–21.5]	13 [6–14.5]	12 [10–19]	
Causes of death					
Multi-organ failure	7 (12.5)	0 (0)	6 (30)	1 (8.3)	0.010
Intracranial bleed	2 (3.6)	0 (0)	1 (5)	1 (8.3)	0.407
Ischaemic stroke	2 (3.6)	1 (4.2)	0 (0)	1 (8.3)	0.459
Irreversible pulmonary fibrosis	2 (3.6)	0 (0)	0 (0)	2 (16.7)	0.022
Cardiac tamponade	2 (3.6)	0 (0)	1 (5)	1 (8.3)	0.407
Major haemorrhage	1 (1.8)	0 (0)	1 (5)	0 (0)	0.400

Values represented as median [inter-quartile range] or *n* (%). *P*-values represent significant difference across clusters 1, 2, and 3 when using the Kruskal-Wallis test (or Pearson's χ^2 test for categorical variables).
BAL, bronchoalveolar lavage; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ED, emergency department; IMV, invasive mechanical ventilation; L, lymphocyte; N, neutrophil; PF, partial pressure of arterial oxygen to fractional inspired oxygen; SOFA, sequential organ failure assessment.
* Input variables used in cluster analysis.
† Respiratory ECMO survival prediction (RESP) score was not included in cluster analysis and is shown for added informational value.

highest plateau pressures pre-ECMO, and the highest markers of inflammation. ICU mortality was 45%.

Phenotype 3 (*n*=12, 21.4%, intermediate mortality, hyperinflammatory, intermediate organ support) patients proceeded from IMV to ECMO in the shortest time (median 1 day, interquartile range 1–1). This phenotype was characterised by the worst pre-ECMO hypoxaemia, severe lymphopaenia, and highest neutrophil:lymphocyte (N:L) ratio. ICU mortality was 50%.

Phenotypes 2 and 3, which exhibited similar mortality, showed specific differences of interest. Six out of nine deaths (66.7%) in phenotype 2 occurred from multiorgan failure, with one out of six (16.7%) in phenotype 3. Admission bronchoscopy cultures showed significant growth (pathological organism requiring antimicrobials) in six (30%) patients in phenotype 2 and none in phenotype 3. Although both groups displayed elevated biochemical markers of inflammation, phenotype 2

had higher procalcitonin, which did not reach statistical significance.

In multivariable analysis, a hypoinflammatory phenotype was associated with survival (adjusted odds ratio 0.08, 97.5% confidence interval 0.01–0.65, P=0.019) and preserved renal function (adjusted odds ratio 0.22, 97.5% confidence interval 0.06–0.82, P=0.025) (Supplementary Table S1).

At the time of writing, no published study has investigated phenotypic differences in patients receiving ECMO. Identified differences indicate the persistence of factors associated with worse outcome in COVID-19 patients receiving ECMO. Patients in phenotypes 2 and 3 conform to recent definitions of COVID-19 hyperinflammation[7] that confers a higher risk for death. Hyperinflammation in phenotype 3 was primarily characterised by ferritin (in comparison to C-reactive protein and procalcitonin in phenotype 2), with bland microbiology at ECMO initiation. Severe lymphopaenia and high N:L ratio seen in phenotype 3 have been associated with severe COVID-19 activity.[8] Phenotype 2 may represent secondary, septic deterioration after prolonged IMV, with respiratory co-infection. This is supported by positivity in admission bronchoalveolar lavage and greater deaths from multiorgan failure. In contrast, phenotype 1, with relatively lower markers of inflammation, showed almost complete survival.

Understanding of the role of inflammation in COVID-19 is growing, with evidence supporting worse outcomes in hyperinflammatory phenotypes,[7] and demonstrable benefit of corticosteroid use in patients with respiratory failure.[9] Further exploration of treatment responses in hyperinflammatory phenotypes in COVID-19 ECMO may help guide the use of immunomodulation. Additionally, identifying patients who will derive benefit from ECMO is key. Phenotype 1, with high survival and greater steroid use pre-ECMO, warrants particular examination of immunomodulation use before ECMO initiation, and the added benefit of providing ECMO to patients belonging to a hypoinflammatory phenotype. The 10 (25%) survivors in our cohort were treated with a steroid before ECMO commencement, whereas no patients received a steroid pre-ECMO in the non-survivor group (P=0.048).

Phenotypes in this study were determined using available clinical data from a clinically important time point. The 'agnostic' approach used did not require definition of groups based on prior assumptions and can be applied to other datasets. This approach was recently used to show inflammatory phenotypes in traditional ARDS,[10] and in COVID-19.[4] The use of available clinical parameters for phenotyping is of particular interest given the evolving role of corticosteroid mediated immunomodulation in severe COVID-19.[9] Future validation of this model on a larger sample, using the standardised UK National ECMO databases, would allow testing of the treatment effect between phenotypes.

In conclusion, different phenotypes can be detected from routinely collected clinical data. A hypoinflammatory phenotype is associated with significantly better survival in a COVID-19 ECMO population, compared with hyperinflammatory phenotypes. The identification of novel phenotypes early in the course of ECMO support may have potential for informing treatment choice and outcomes in this highly specialised and resource intensive population, and for identifying populations that may benefit from future research on anti-inflammatory or immunomodulatory drugs.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.12.023.

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doi: 10.1016/j.bja.2020.12.023
Advance Access Publication Date: 26 December 2020