PHIND

Clinical evaluation of a POC assay to identify PHenotypes IN the Acute Respiratory Distress Syndrome

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SAP Revisions:	Addition of sensitivity analysis regarding analysis restricted to patients with biosamples obtained within 24h of ARDS diagnosis

STATISTICAL ANALYSIS PLAN

V2.0_Final_23/07/2024

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This document and all preceding versions will be stored in the Trial Master File for this trial

Contents

ABBREVIATIONS

ABBREVIATION	DEFINITION
APACHE	Acute Physiology and Chronic Health Evaluation
AHRF	Acute Hypoxaemic Respiratory Failure
ARDS	Acute Respiratory Distress Syndrome
CI	Chief Investigator
CMP	Case Mix Programme
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTIMP	Clinical Study of an Investigative Medicinal Product
CTU	Clinical Trials Unit
DNAR	Do Not Attempt Resuscitation
ECMO	Extracorporeal Membrane Oxygenation
ECCO2R	Extracorporeal CO2 Removal
GCP	Good Clinical Practice
GP	General Practitioner
HSE	Health Service Executive
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Study Number
HFNO	High Flow Nasal Oxygen
LCA	Latent Class Analysis
LTA	Latent Transition Analysis
LPS	Lipopolysaccharide
MDM	Monocyte-derived Macrophages
MDT	Multi-Disciplinary Team
NHS	National Health Service
NICTU	Northern Ireland Clinical Trials Unit
NPV	Negative Predictive Value
PBW	Predictive Body Weight
PBMC	Peripheral Blood Mononuclear Cells
PEEP	Positive end-expiratory Pressure
PI	Principal Investigator
POC	Point of Care

QUB	Queen's University Belfast
REC	Research Ethics Committee
RR	Respiratory Rate
RMP	Registered Medical Practitioner
ROI	Republic of Ireland
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
SSC	Study Steering Committee
UK	United Kingdom
VFD	Ventilator Free Day

1. BACKGROUND AND DESIGN

Full details of the background to the study and its design are presented in the protocol.

The hypothesis that is under investigation is that patients prospectively classified to the hyper-inflammatory ARDS phenotype on the basis of clinical characteristics and a novel POC biomarker assay will have worse clinical outcomes than the hypo-inflammatory phenotype.

Aim:

The purpose of this project is to prospectively identify hyper- and hypo-inflammatory phenotypes in patients with ARDS and AHRF, and determine clinical outcomes associated with each phenotype.

Objectives:

Primary:

(i) Assess the clinical outcomes in patients with ARDS according to their prospectively defined inflammatory phenotype determined using a POC assay.

Secondary:

(i) Assess the agreement of the phenotype allocation using a POC assay and latent class analysis (LCA) from biomarkers and the clinical study dataset

(ii) Assess the stability of phenotype allocation over time

(iii) Feasibility of delivering a POC assay in the NHS intensive care setting

(iv) Identify if inflammatory phenotypes are present and influence outcomes in patients with AHRF

Patients will be eligible for the study if they meet the inclusion criteria.

Inclusion criteria

1. Patient is receiving mechanical ventilation, CPAP or high flow nasal oxygen (HFNO)
2. a) ARDS as defined by the Berlin definition [6]
   - Onset within 1 week of identified insult
   Within the same 24-hour time period:
   i. Hypoxaemic respiratory failure (PaO2/ FiO2 ratio ≤ 40kPa on PEEP ≥ 5 cmH2O*)
   ii. Bilateral infiltrates consistent with pulmonary oedema not explained by another pulmonary pathology
   iii. Respiratory failure not fully explained by cardiac failure or fluid overload

OR

   b) AHRF as defined by
   - Within the same 24-hour time period:
   i. Hypoxaemic respiratory failure (PaO2/ FiO2 ratio ≤ 40kPa on PEEP ≥ 5 cmH2O*)

ii. Unilateral infiltrates on chest imaging not fully explained by effusions, collapse, or nodules
iii. Respiratory failure not fully explained by cardiac failure or fluid overload

The time of onset of ARDS is when the last ARDS criterion is met.
*PEEP assumed ≥ 5 cmH_2O if on HFNO

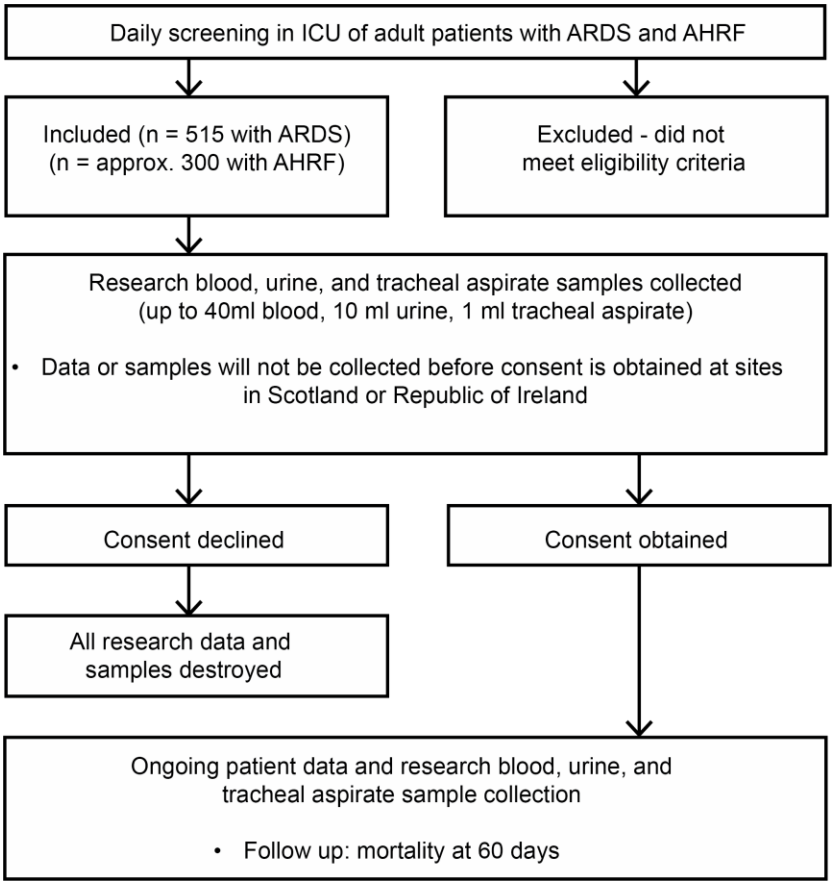
Patients will not be eligible for the study if they meet any of the exclusion criteria.

Exclusion criteria

1. Age <18 years of age
2. More than 72 hrs after onset of ARDS/AHRF
3. Receiving ECMO at the time of recruitment
4. Treatment withdrawal imminent within 24 hours
5. DNAR (Do Not Attempt Resuscitation) order (excluding advance directives) in place*
6. Declined consent
7. Prisoners

*Intended to only exclude patients who are not receiving active medical management and are receiving palliative care.

PHIND Schematic Diagram



2. OUTCOME MEASURES

2.1 Primary outcome measure(s)

The primary outcome is mortality at 60 days in the hyper-inflammatory and hypo-inflammatory phenotypes in patients with ARDS.

2.2 Secondary outcome measures

(i) Difference in time to extubation, intubation rate in patients on HFNO, re-intubation rate, ventilator free days at day 28, duration of ventilation, length of intensive care unit (ICU) and hospital stay as well as 28-day mortality, in the hyper-inflammatory and hypo-inflammatory phenotypes.

(ii) Agreement of phenotype classification using a POC assay and commercially-available assays

(iii) Agreement of phenotype classification using a POC assay and LCA

(iv) Agreement of phenotype classification between baseline and day 3

(v) Feasibility of delivering a POC assay in NHS/HSE intensive care setting as measured by assay technical failure rate.

(vi) Frequency of inflammatory phenotypes in patients with AHRF and difference in outcomes as described for ARDS phenotypes.

2.3 Study timeline

It is planned that the recruitment period will start in November 2019 and continue for at least 18 months. Following the completion of recruitment and follow-up, there will be a close out period.

2.4 End of study

For the purposes of submitting the end of study notification to the Sponsor and Research Ethics Committee (REC) the end of study will be considered to be when database lock occurs for the final analysis. The study will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC)
- Mandated by the Sponsor (e.g. following recommendations from the Study Steering Committee (SSC)
- Funding for the study ceases

The REC originally providing a favourable opinion of the study will be notified in writing once the study has been concluded or if terminated early

3. DATA

3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are described in the study protocol.
A copy of the CRFs is presented in the Trial Master File.

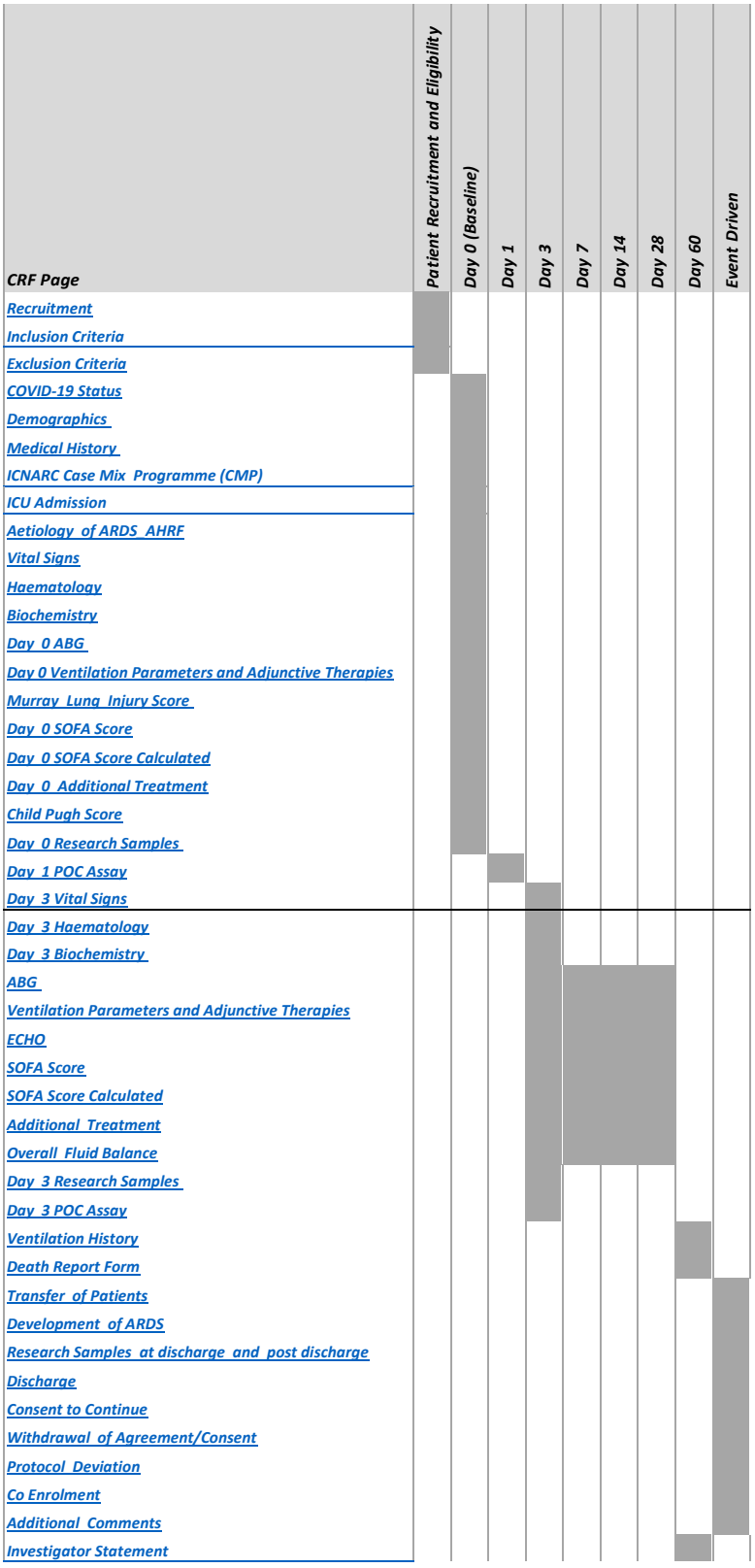
3.2 Management of datasets

Following the entry of patient data into the study database, the data will be processed as per the CTU SOPs. Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries within approximately 2 weeks. All queries will be responded to and resolved within the study database. Any amended information will then be entered in the study database.

The Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the SOP DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

3.3 Data completion schedule

The time points for completion of Case Report forms are reported in the table below.



3.4 Data verification

Study specific data validation checks will be implemented. The process of data validation ensuring the accuracy and quality of the data will be carried out according to SOP DM04 Data Validation and Discrepancy Management.

Data verification, consistency and range checks will have been performed at the data entry stage by the CTU, as well as checks for missing data (copies can be found in the TMF) according to SOP DM04. Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Given the thorough nature of our follow-up procedure we expect the issue of missing data to be relatively minimal. We anticipate high compliance with initial data collection as this is close to the time of patient registration.

Any problems with study data will be queried with the Trial Managers, Data Managers, or statisticians, as appropriate. If possible, data queries will be resolved, although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. This will be minimised.

Every effort will be made to minimise missing baseline and outcome data in this study. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate.

3.5 Data coding

The variable codings will be as specified on the CRF.

4. DEFINITION OF TERMS

Data will be censored at 60 days for all outcomes from the date of last patient recruited.

Term	Definition
Unassisted breathing	No ventilatory support is defined as; extubated with supplemental oxygen or room air, or open T-tube breathing, or tracheostomy mask breathing, or CPAP without inspiratory pressure support for 48 hours. Patients receiving pressure support via non-invasive ventilation (except for sleep disordered breathing) or extra-corporeal lung support will be defined as receiving ventilatory support.
Discharge from critical care	First discharge to a ward in the hospital or another hospital; a transfer between ICUs is not considered a discharge from critical care. Hospital discharge is the first date that the patient is discharged to home/community, a transfer between hospitals is not considered as a hospital discharge.
Ventilator free days (VFDs) to day 28	The number of days from the time of initiating unassisted breathing to day 28 after the date of commencing ventilatory support, assuming survival for at least 48 hours after initiating unassisted breathing and continued unassisted breathing to day 28. If the patient was receiving ventilatory support prior to ICU admission, the ICU admission date will be considered as the start of the VFD calculation. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint. The number of days alive and free from ventilation between final successful weaning and day 28 after study enrolment. $VFD = \{0, \quad \begin{matrix} (28-x), if\ patient\ alive\ at\ day\ 28\ and\ x \leq 27 \\ if\ patient\ requires\ mechanical\ ventilation\ for\ 28\ days\ or\ more \\ 0, if\ patient\ died\ within\ 28\ days\ or\ x > 27 \end{matrix}$ Where x is number of days until patient achieved unassisted breathing
Duration of ventilation (days)	From the date of commencing ventilatory support, or the date of ICU admission, if the patient was receiving ventilatory support prior to ICU admission, to the time of initiating unassisted breathing.

	$$Duration\ of\ ventilation = \begin{cases} Date\ of\ unassisted\ breathing - Date\ of\ commencing\ ventilatory\ support, if\ the\ pat\ achieved\ unassisted\ breathing \\ Date\ of\ death - Date\ of\ commencing\ ventilatory\ support, if\ the\ patient\ died\ prior\ to\ achieving\ unassisted\ breathing \end{cases}$$
Duration of ICU stay (days)	Duration of critical care and hospital stay will be counted from ICU admission to discharge. $$Duration\ of\ ICU\ stay = \begin{cases} Date\ of\ first\ ICU\ discharge - Date\ of\ ICU\ admission, if\ the\ patient\ is\ alive\ at\ ICU\ discharge \\ Date\ of\ death - Date\ of\ ICU\ admission, if\ the\ patient\ died\ prior\ to\ ICU\ discharge \end{cases}$$
Duration of hospital stay (days)	Duration of critical care and hospital stay will be counted from ICU admission to discharge. $$Duration\ of\ hospital\ stay = \begin{cases} Date\ of\ first\ hospital\ discharge - Date\ of\ ICU\ admission, if\ the\ patient\ is\ alive\ at\ hospital\ discharge \\ Date\ of\ death - Date\ of\ ICU\ admission, if\ the\ patient\ died\ prior\ to\ hospital\ discharge \end{cases}$$ Hospital discharge is the first date that the patient is discharged to home/community, a transfer between hospitals is not considered as a hospital discharge.
Extubation	First time being successfully free from an endotracheal tube or a tracheostomy tube for 48 hours
Time to extubation	From date of intubation to extubation, or from the date of ICU admission to successful extubation, if the patient was intubated prior to ICU admission.

5. SAMPLE SIZE CALCULATIONS

Data from several retrospective analyses have shown that the percentage of patients with ARDS in the hyper-inflammatory sub-group was 27-34% of the overall population, that the mortality in the hypo-inflammatory sub-group was 17-23%, with a mortality difference between the hyper-inflammatory and hypo-inflammatory sub-groups ranging from 15-32%. A conservative percentage of patients in the hyper-inflammatory sub-group of 25%, a mortality in the hypo-inflammatory sub-group of 17% and a difference in 28-day mortality between the hyper-inflammatory and hypo-inflammatory sub-groups of 15% was assumed. The mortality in the hyper-inflammatory group is assumed to be 17% under the null hypothesis and 32% under the alternative hypothesis [7-10].

Based on a two group chi-square test, group sizes of 347 in the hypo-inflammatory group and 116 in the hyper-inflammatory group achieves 90% power at a two-sided significance level of 0.05 to detect a mortality difference between the groups of 15%. Based on our previous experience the group sizes

have been inflated by 10% to allow for technical failure, drop-out or loss to follow-up giving group sizes of 386 in the hypo-inflammatory group and 129 in the hyper-inflammatory group. As such, at least 515 patients with ARDS will be recruited.

An additional exploratory cohort of patients with COVID-19 will be recruited. No formal sample size calculation for this cohort is feasible. An indicative sample of up to 100 patients will be recruited in this cohort during the course of the study, however it is recognized that this is an estimate which will be dependent on the duration of the COVID-19 pandemic.

A further exploratory cohort of up to 300 patients with AHRF will be recruited. No formal sample size calculation for this cohort is feasible as these subphenotypes have not been described in such AHRF patients before. A sample of 300 patients is required in order to provide a minimum sample to undertake latent class analysis.

6. RANDOMISATION AND BLINDING

6.1 Randomisation

No randomisation is required as this is an observational study.

6.2 Blinding and Allocation Concealment

Results of group allocation (hyper/hypo) will be blinded to clinical and research staff.

7. ANALYSIS PRINCIPLES

Baseline characteristics, and follow-up measurements will be described using the appropriate descriptive summary measures depending on the scale of measurement.

Analyes will be performed using the software STATA version 15.1. (StataCorp LLC, College Station, Texas) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Latent class analysis will be performed with Mplus version 8.8 (Muthen & Muthen, Los Angeles, California).

7.1 Primary Outcome

For the primary outcome of 60 day mortality, analysis will be conducted using the phenotype allocation defined by the POC assay. Absolute number and percentage by phenotype, unadjusted percentage point difference (95% confidence interval, CI) and risk ratio (95% CI) will be calculated.
Pearson's chi-square test will be used to compare the two phenotypes and p value will be reported.

7.2 Secondary Outcomes

A secondary analysis for the outcome of 60 day mortality using logistic regression to adjust for important variables (age, site, and gender) will be carried out. Odds ratio (95% CI) and p value will be reported.

Differences in 60 day mortality will also be evaluated using phenotype allocation as defined by i) commercially available assays in conjunction with a parsimonious logistic regression model and ii) LCA. For each i) and ii), analyses will be conducted by calculating: a) absolute number and percentage by phenotype, b) unadjusted percentage point difference (95%, CI), c) risk ratio (95% CI), and d) p value from Pearson's chi-square test (95% CI).

Further secondary outcomes will be analysed using both POC-derived phenotype allocation and LCA-derived phenotype allocation.

For secondary outcomes based on dichotomous variables (Re-intubation rate, 28-day mortality), absolute number and percentage by phenotype will be calculated, and p-value will be from Pearson's chi-square test.

For continuous secondary outcomes (Ventilator free days at day 28; Duration of ventilation; Length of ICU stay; Length of hospital stay), data will be reported as median (IQR) with p value derived from Mann-Whitney U test.

Analyses will be conducted to assess agreement of phenotype classification methods. Comparisons will be made between: (i) POC-derived phenotype versus phenotype from commercially available assays (defined by up to 8 different parsimonious logistic regression models [5]), (ii) POC-derived phenotype versus LCA-derived phenotype, and (iii) POC-derived phenotype versus phenotype derived from clinical classifier machine learning algorithm [11]. Cohen's kappa coefficient (95% CI) will be calculated and p-value will be from McNemar's test for agreement. All of these analyses will be performed for phenotype allocation at day 0 and at day 3. For additional comparisons between classification methods, LCA phenotype will be selected as the "gold standard" and sensitivity, specificity, negative predictive value, and positive predictive value will be calculated for all other methods. Area under the receiver operating curve (AUC) will also be calculated. These analyses will also be performed for phenotype allocation at day 0 and day 3.

Agreement of phenotype classification will also be assessed between day 0 and day 3 of study enrolment using POC-derived phenotype at day 0 and day 3, calculation Cohen's kappa coefficient (95% CI) and p-value from McNemar's test for agreement.

Stability of phenotype allocation over day 0 to day 3 and transition between phenotypes will be assessed by latent transition analysis (LTA).

The probabilities of phenotype allocation generated by parsimonious logistic regression models will be compared between those generated using data derived from POC assays to those generated using commercially available research-grade assays[5]. Comparisons will be made using Bland-Altman plots for the probabilities and McNemar's test for phenotype allocation using a probability cut-off of 0.5 to assign phenotypes.

For secondary outcomes related to feasibility of delivering a POC assay in NHS/HSE intensive care setting, assay technical failure rate will be calculated as absolute number and percentage of events. No inferential statistical analysis will be conducted.

7.3 Sensitivity analysis

Primary and secondary outcomes (except those related to agreement between phenotype allocation and those related to feasibility) will be analysed and reported separately (when pertinent) for:

- AHRF cohort
- patients receiving mechanical ventilation
- patients receiving non-invasive ventilation
- patients receiving high-flow nasal oxygen
- patients receiving high-flow nasal oxygen with a flow rate of at least 30 litres per minute
- analysis excluding COVID-19 patients
- analysis restricted to patients with biosamples obtained within 24h of ARDS diagnosis
- analysis restricted to patients with biosamples obtained within 48h of ARDS diagnosis

7.4 Additional analysis

To study the performance of the New Global Definition of ARDS [12], primary and secondary outcomes will be reported for the entire study cohort, the study cohort stratified by ARDS severity as defined by the New Global Definition of ARDS [12], and the study cohort stratified by ARDS severity as defined by the Berlin Definition of ARDS [6].

An additional analysis will be conducted on the cohort of patients with AHRF, to assess the proportion of patients developing ARDS by phenotype. This will be reported as absolute number and percentage, with p value for difference between phenotypes from Fisher's exact test. In AHRF developing ARDS, the median (IQR) number of days to ARDS development will be calculated by phenotype, with p value for difference between phenotypes from Mann Whitney U test.

Outcomes will be compared within a given phenotype with respect to ARDS/AHRF diagnosis. Primary and secondary outcomes will be compared for all hyperinflammatory patients (ARDS vs. AHRF) and all hypoinflammatory patients (ARDS vs. AHRF). Comparisons will be made using Fisher's exact test for categorical outcomes and Mann-Whitney U Test for continuous outcomes.

Subsequent analyses after study completion may explore the relationship between hyperinflammatory and hypoinflammatory phenotypes and other ARDS phenotypes [13] and sepsis phenotypes [14,15] as well as the use of varying probability cutpoints for phenotype assignment in comparison to full latent class analysis.

8. ANALYSIS DETAILS

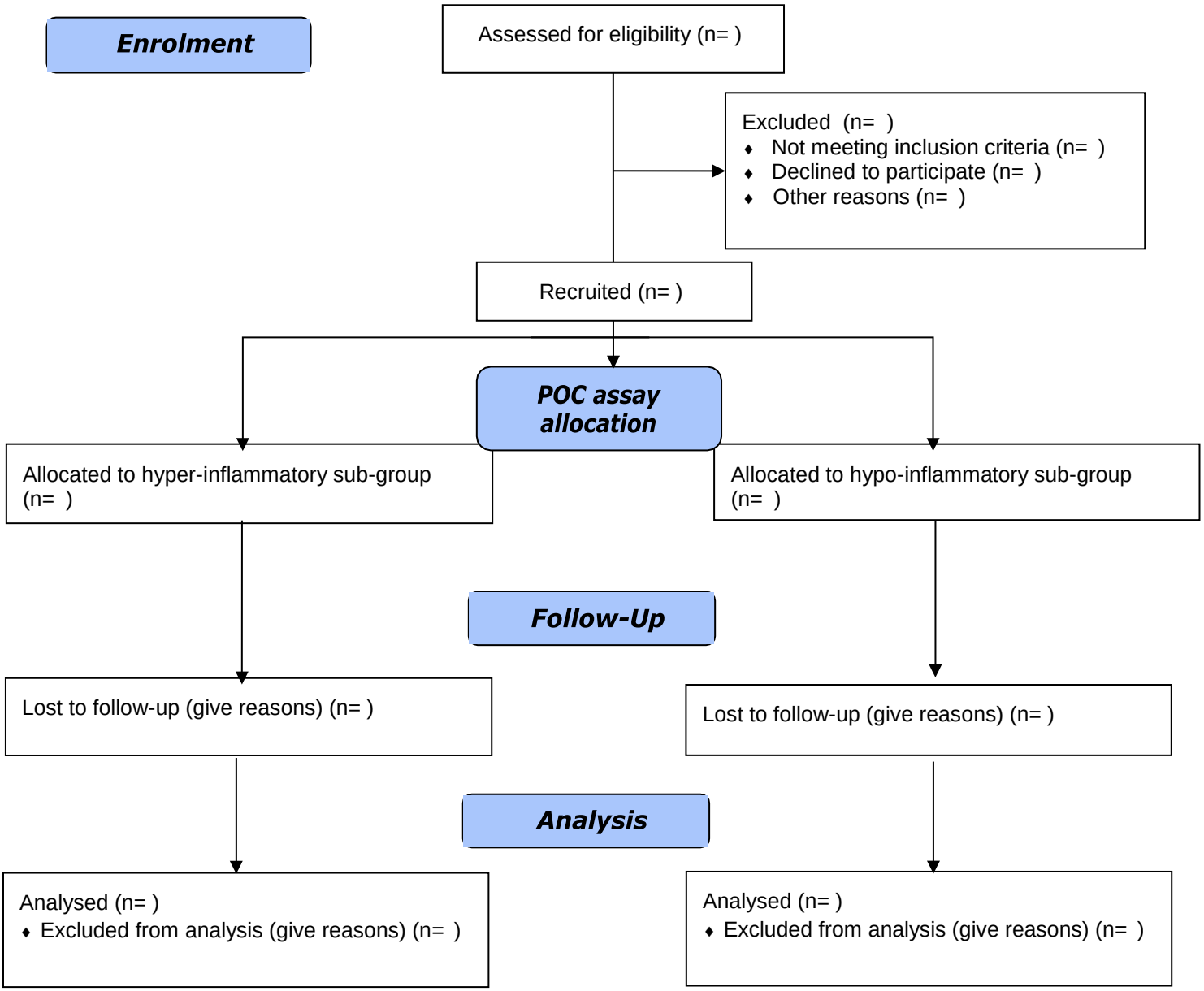
The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

8.1 Recruitment and withdrawal patterns

The recruitment and withdrawal patterns will be reported as follows:

- Recruitment by year, centre.
- Withdrawals by site - this should include the timing of withdrawals.

8.2 CONSORT Flow Diagram



8.3 Baseline Characteristics

Descriptive analysis will be conducted for the following baseline characteristics, by phenotype and total. Where mean (SD) is specified, median and interquartile range will also be calculated and presented if more appropriate based on the distribution:

- Age (years), mean (SD) by phenotype and total
- Sex, n (%) by phenotype and total
- Ethnicity, n. (%) by phenotype and total
- Height (cm), mean (SD) by phenotype and total
- Weight (kg), mean (SD) by phenotype and total
- Predicted body weight (kg), mean (SD) by phenotype and total
- Body mass index (kg/m2), mean (SD) by phenotype and total
- Cigarette smoking status (current smoker, past smoker and never smoked), n (%) by phenotype and total
- Current smokers (Number of years smoked and Average smoked per day), mean (SD) by phenotype and total
- Past smokers (Number of years smoked and Average smoked per day), mean (SD) by phenotype and total
- Past smokers (Not known), n (%) by phenotype and total
- Number of years e-smoking, mean (SD) by phenotype and total
- Type of e-smoking device (disposable, refillable, voltage variable, other, not known), n (%) by phenotype and total
- Amount of e-liquid used per day (mls), n (%) by phenotype and total
- Does the e-liquid used by the patient contain nicotine (Yes/No), n (%) by phenotype and total
- Nicotine content of e-liquid (Per Week) (5mg/ml, 10mg/ml, 15 mg/ml, 20 mg/ml, other, not known), n (%) by phenotype and total
- Past e-smokers (Number of years e-smoking and Number of years since stopped e-smoking), mean (SD) by phenotype and total
- Past e-smokers (Not known), n (%) by phenotype and total
- Alcohol use (Yes/No), n (%) by phenotype and total
- Average units of alcohol consumed per week, mean (SD) by phenotype and total
- Co-morbidities (Yes results for Congestive Heart Failure, Myocardial infarction, COPD, Asthma, Diabetes, Chronic Liver Disease, Cancer, Chronic Renal Failure, Other), n (%) by phenotype and total
- Aetiology of ARDS (Yes results for Smoke/toxin inhalation, Gastric content aspiration, Near drowning, Thoracic trauma, Pneumonia, Sepsis, Cardiopulmonary bypass, Pancreatitis, Non-thoracic trauma, Other), n (%) by phenotype and total
- APACHE II score, mean (SD) by phenotype and total
- Vital signs (Temperature (°C), Heart rate (bpm), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)), mean (SD) by phenotype and total

- Haematology (Haematocrit (L/L), White Cell Count (x109/L), PT (s), Fibrinogen (g/L)), mean (SD) by phenotype and total
- Biochemistry (Sodium (mmol/L), Glucose (mmol/L), Albumin (g/L), AST (U/L), ALT (U/L)), mean (SD) by phenotype and total
- First qualifying P/F ratio, mean (SD) by phenotype and total
- Worst P/F Ratio, mean (SD) by phenotype and total
- P/F Ratio closest to but prior to patient recruitment, mean (SD) by phenotype and total
- pH, mean (SD) by phenotype and total
- Lactate, mean (SD) by phenotype and total
- Bicarbonate, mean (SD) by phenotype and total
- PaCO2, mean (SD) by phenotype and total
- PaO2, mean (SD) by phenotype and total
- FiO2, mean (SD) by phenotype and total
- Mode of Ventilation (Yes results for SIMV, APRV, HFOV, BIPAP, PC, PRVC, PS, NIV, HFNO, CPAP/ASB, Other, None), n (%) by phenotype and total
- Minute Volume (ml), mean (SD) by phenotype and total
- Total Respiratory Rate, mean (SD) by phenotype and total
- Mean Airway Pressure (cmH2O), mean (SD) by phenotype and total
- Plateau Pressure (cmH2O), mean (SD) by phenotype and total
- PEEP (cmH2O), mean (SD) by phenotype and total
- Tidal Volume (Minute Volume/Total Respiratory Rate), mean (SD) by phenotype and total
- Tidal Volume (mls/kg PBW), mean (SD) by phenotype and total
- Respiratory Compliance (ml/cmH2O), mean (SD) by phenotype and total
- Oxygenation Index (OI), mean (SD) by phenotype and total
- Total SOFA score, mean (SD) by phenotype and total
- Use of Adjunctive Therapies (Yes results for Airway Pressure Release Ventilation (APRV), High-Frequency Oscillatory Ventilation (HFOV), Neuromuscular Blocking Drugs (NMBD), Nitric Oxide, Prone Position, ECCO2R, Other) n (%) by phenotype and total
- Murray Lung Injury Score, mean (SD) by phenotype and total
- Steroid Treatment on day 0 (Yes/No), n (%) by phenotype and total
- Type of steroid used (Hydrocortisone, Prednisolone, Dexamethasone, Methylprednisolone, Fludrocortisone, Other), n (%) by phenotype and total
- Total daily steroid dose, mean (SD) by phenotype and total
- Statin Treatment on day 0 or within last 7 days (Yes/No), n (%) by phenotype and total
- Type of statin used (Pravastatin, Atorvastatin, Simvastatin, Rosuvastatin, Other), n (%) by phenotype and total
- Total daily statin dose, mean (SD) by phenotype and total
- Insulin Treatment on day 0 (Yes/No), n (%) by phenotype and total
- Total daily insulin dose, mean (SD) by phenotype and total
- Enteral feeding on day 0 (Yes/No), n (%) by phenotype and total
- Total daily calories given, mean (SD) by phenotype and total

- Child Pugh Score, mean (SD) by phenotype and total
- Renal replacement therapy (Yes/No), n (%) by phenotype and total
- Does the patient have COVID-19? (Yes/No), n (%) by phenotype and total
- How was COVID-19 diagnosed? (Yes results for Clinical diagnosis, PCR diagnosis), n (%) by phenotype and total

8.4 Study withdrawal and protocol deviations

The withdrawal pattern will be analysed and reported using patients as unit of measure, as follows:

- Withdrawal of consent, n (%) by phenotype and total
- Type of consent withdrawn (Yes results for Use of data already collected, Ongoing data collection during hospital admission, Long term storage of research samples, Confirmation of vital status), n (%) by phenotype and total

The pattern of protocol deviations will be analysed and reported using both events and patients as unit of measure, as follows:

- Protocol deviations related to eligibility, n (%) by phenotype and total
- Protocol deviations related to consent, n (%) by phenotype and total
- Protocol deviations related to sample not taken, n (%) by phenotype and total
- Protocol deviations related to POC assay result not available, n (%) by phenotype and total
- Other protocol deviations, n (%) by phenotype and total

8.5 Study Outcomes

Primary outcome:

- Mortality at 60 days in patients with ARDS as defined by the POC assay, reported as n (%) by phenotype, unadjusted percentage point difference (95% CI), risk ratio (95% CI), and p value from Pearson's chi-square test

Secondary outcomes:

- Mortality at 60 days in patients with ARDS as defined by the POC assay, reported as odds ratio (95% CI) and p value from adjusted logistic regression (adjusted for age and gender)

- Mortality at 60 days in patients with ARDS defined by commercially-available laboratory assays and parsimonious models, reported as n (%) by phenotype, unadjusted percentage point difference (95%, CI), risk ratio (95% CI), and p value from Pearson's chi-square test (95% CI).

- Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis, reported as n (%) by phenotype, unadjusted percentage point difference (95%, CI), risk ratio (95% CI), and p value from Pearson's chi-square test (95% CI).

For further secondary analyses, the assumption of normal distribution will be checked graphically for each continuous variable, but we anticipate using the following tests (alternative in brackets).

- Time to extubation, mean (SD) by phenotype, difference in means (95% CI) and p value from two-sided t-test for unpaired data (Mann-Whitney test)

- Intubation rate in patients receiving HFNO, number (%) by phenotype, percentage point difference (95% CI), and p value from chi-square test

- Re-intubation rate, number (%) by phenotype, percentage point difference (95% CI), and p value from chi-square test

- Ventilator free days at day 28, mean (SD) by phenotype, difference in means (95% CI) and p value from t-test for unpaired data (Mann-Whitney test)

- Duration of ventilation, mean (SD) by phenotype, difference in means (95% CI) and p value from t-test for unpaired data (Mann-Whitney test)

- Length of ICU stay, median (IQR) by phenotype, p value from Mann-Whitney test

- Length of hospital stay, median (IQR) by phenotype, p value from Mann-Whitney test

- 28-day mortality, n (%) by phenotype, unadjusted percentage point difference (95% CI) and Risk ratio (95% CI) and p value from chi-square

- Time to extubation, difference in means (95% CI) adjusted for age, co-morbidity, aetiology of ARDS, vasopressor requirement and PF ratio. P-values will be from ANCOVA.

- Intubation rate in patients receiving HFNO, percentage point difference/ RR adjusted for age, co-morbidity, aetiology of ARDS, vasopressor requirement and PF ratio. P-values will be from log binomial regression.

- Re-intubation rate, percentage point difference/ RR adjusted for age, co-morbidity, aetiology of ARDS, vasopressor requirement and PF ratio. P-values will be from log binomial regression.

- Ventilator free days at day 28, difference in means (95% CI) adjusted for age, co-morbidity, aetiology of ARDS, vasopressor requirement and PF ratio. P-values will be from ancova

• Duration of ventilation, difference in means (95% CI) adjusted for age, co-morbidity, aetiology of ARDS, vasopressor requirement and PF ratio. P-values will be from ancova.

• 28-day mortality, percentage point difference/RR adjusted for age, co-morbidity, aetiology of ARDS, vasopressor requirement and PF ratio. P-values will be from log binomial regression.

Agreement of phenotype classification:

- Agreement of phenotype classification using POC-derived phenotype versus phenotype from commercially available assays (defined by up to 8 different parsimonious logistic regression models [5]), Cohen's kappa coefficient and p value from McNemars test
- Agreement of phenotype classification using POC-derived phenotype and LCA-derived phenotype, Cohen's kappa coefficient and p value from McNemars test
  Agreement of phenotype classification using POC-derived phenotype and phenotype from clinical classifier machine learning algorithm [11], Cohen's kappa coefficient and p value from McNemars test
- Agreement of phenotype classification between baseline and day 3, by (i) latent transition analysis (LTA) and (ii) POC-derived phenotype at day 0 and day 3, reporting Cohen's kappa coefficient and p value from McNemars test
- Probability of phenotype allocation generated by POC-derived classifier versus phenotype from commercially available assays and parsimonious logistic regression models [5]. Comparisons will be made using Bland-Altman plots

Feasibility outcomes:

Feasibility of delivering a POC assay in NHS/HSE intensive care setting as measured by assay technical failure rate, reported as absolute number and percentage of events. No inferential statistical analysis will be conducted.

Sensitivity analysis:

The primary outcome, secondary analyses of the primary outcome, and secondary outcomes (when pertinent) will be analysed as above for the following subgroups:

- AHRF cohort
- patients receiving mechanical ventilation
- patients receiving non-invasive ventilation
- patients receiving high flow nasal oxygen
- patients receiving high-flow nasal oxygen with a flow rate of at least 30 litres per minute
- analysis excluding COVID-19 patients
- analysis restricted to patients with biosamples obtained within 24h of ARDS diagnosis
- analysis restricted to patients with biosamples obtained within 48h of ARDS diagnosis

Additional analysis

- Primary and secondary outcomes for the total cohort
- Primary and secondary outcomes for the total cohort, stratified by severity as defined by the New Global Definition of ARDS [12]
- Primary and secondary outcomes for the total cohort, stratified by severity as defined by the Berlin Definition of ARDS [6]
- ARDS development among patients with AHRF, absolute number and percentage. Comparisons made stratified on phenotype allocation.
- Time to ARDS development in patients with AHRF developing ARDS, median (IQR) number of days. Comparisons made stratified on phenotype allocation.
- Primary and secondary outcomes within each phenotype with respect to ARDS/AHRF diagnosis
- Comparison of hyperinflammatory and hypoinflammatory phenotypes to other ARDS phenotypes [13]
- Comparison of hyperinflammatory and hypoinflammatory phenotypes to sepsis phenotypes [14,15]
- The use of varying probability cutpoints for phenotype assignment in comparison to full latent class analysis

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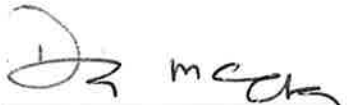
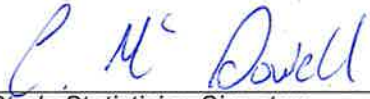
10. SIGNATURES OF APPROVAL

Date: 23/07/2024
Version: 2.0 Final
This document has completed a final review and is understood and approved by the following:

Danny McAuley		23.07.2024
Chief Investigator Name	*Chief Investigator Signature*	Date dd/mm/yyyy
Cliona McDowell		31.07.2024
Senior Statistician or designee Name	*Senior Statistician or designee Signature*	Date dd/mm/yyyy
Cliona McDowell		31.07.2024
Study Statistician Name	*Study Statistician Signature*	Date dd/mm/yyyy

APPENDIX 1: EXAMPLE SUMMARY TABLES

Table x.x.x.. Baseline Characteristics at study entry

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Total n = (%)
Age (years)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Gender			
Male	N (xx.x%)	N (xx.x%)	N (xx.x%)
Female	N (xx.x%)	N (xx.x%)	N (xx.x%)
Ethnicity			
Caucasian	N (xx.x%)	N (xx.x%)	N (xx.x%)
Black	N (xx.x%)	N (xx.x%)	N (xx.x%)
Asian	N (xx.x%)	N (xx.x%)	N (xx.x%)
Unknown	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Height (cm)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Weight (kg)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Predicted body weight (kg)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Body mass index (kg/m^2)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Cigarette smoking status			
Current smoker	N (xx.x%)	N (xx.x%)	N (xx.x%)
Past smoker	N (xx.x%)	N (xx.x%)	N (xx.x%)
Never smoked	N (xx.x%)	N (xx.x%)	N (xx.x%)
Current smokers			
Number of years smoked	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Average smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Not known	N (xx.x%)	N (xx.x%)	N (xx.x%)
Past smokers			

Number of years smoked	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Average smoked per day	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Not known	N (xx.x%)	N (xx.x%)	N (xx.x%)
Number of years e-smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Type of e-smoking device			
Disposable	N (xx.x%)	N (xx.x%)	N (xx.x%)
Refillable	N (xx.x%)	N (xx.x%)	N (xx.x%)
Voltage variable	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Not known	N (xx.x%)	N (xx.x%)	N (xx.x%)
Amount of e-liquid used per day (mls)			
0-4 mls	N (xx.x%)	N (xx.x%)	N (xx.x%)
5-9 mls	N (xx.x%)	N (xx.x%)	N (xx.x%)
10-14 mls	N (xx.x%)	N (xx.x%)	N (xx.x%)
15-19 mls	N (xx.x%)	N (xx.x%)	N (xx.x%)
20+ mls	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Does the e-liquid used by the patient contain nicotine?			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Nicotine content of e-liquid (Per Week)			
5mg/ml	N (xx.x%)	N (xx.x%)	N (xx.x%)
10mg/ml	N (xx.x%)	N (xx.x%)	N (xx.x%)
15mg/ml	N (xx.x%)	N (xx.x%)	N (xx.x%)
20mg/ml	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Not Known	N (xx.x%)	N (xx.x%)	N (xx.x%)
Past e-smokers			
Number of years e-smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Number of years since stopped e-smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Not known	N (xx.x%)	N (xx.x%)	N (xx.x%)
Alcohol use			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Average units of alcohol consumed per week	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Co-morbidities (Yes results)			
Congestive Heart Failure	N (xx.x%)	N (xx.x%)	N (xx.x%)
Myocardial Infarction	N (xx.x%)	N (xx.x%)	N (xx.x%)
COPD	N (xx.x%)	N (xx.x%)	N (xx.x%)
Asthma	N (xx.x%)	N (xx.x%)	N (xx.x%)
Diabetes	N (xx.x%)	N (xx.x%)	N (xx.x%)
Chronic Liver Disease	N (xx.x%)	N (xx.x%)	N (xx.x%)
Cancer	N (xx.x%)	N (xx.x%)	N (xx.x%)
Chronic Renal Failure	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Aetiology of ARDS			
Smoke/toxin inhalation	N (xx.x%)	N (xx.x%)	N (xx.x%)
Gastric content aspiration	N (xx.x%)	N (xx.x%)	N (xx.x%)
Near drowning	N (xx.x%)	N (xx.x%)	N (xx.x%)
Thoracic trauma	N (xx.x%)	N (xx.x%)	N (xx.x%)
Pneumonia	N (xx.x%)	N (xx.x%)	N (xx.x%)
Sepsis	N (xx.x%)	N (xx.x%)	N (xx.x%)
Cardiopulmonary bypass	N (xx.x%)	N (xx.x%)	N (xx.x%)
Pancreatitis	N (xx.x%)	N (xx.x%)	N (xx.x%)
Non-thoracic trauma	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
APACHE II score	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Vital Signs			
Temperature (°C)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Heart rate (bpm)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Systolic blood pressure (mmHg)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diastolic blood pressure (mmHg)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Haematology			
Haematocrit (L/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
White Cell Count ($x10^9$/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
PT (s)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Fibrinogen (g/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Biochemistry			
Sodium (mmol/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Glucose (mmol/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Albumin (g/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

AST (U/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
ALT (U/L)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
First qualifying P/F ratio	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Worst P/F Ratio	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
P/F Ratio closest to but prior to patient recruitment	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
pH	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Lactate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Bicarbonate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
$PaCO_2$	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
PaO_2	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
FiO_2	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mode of Ventilation			
SIMV	N (xx.x%)	N (xx.x%)	N (xx.x%)
APRV	N (xx.x%)	N (xx.x%)	N (xx.x%)
HFOV	N (xx.x%)	N (xx.x%)	N (xx.x%)
BIPAP	N (xx.x%)	N (xx.x%)	N (xx.x%)
PC	N (xx.x%)	N (xx.x%)	N (xx.x%)
PRVC	N (xx.x%)	N (xx.x%)	N (xx.x%)
PS	N (xx.x%)	N (xx.x%)	N (xx.x%)
NIV	N (xx.x%)	N (xx.x%)	N (xx.x%)
HFNO	N (xx.x%)	N (xx.x%)	N (xx.x%)
CPAP/ASB	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
None	N (xx.x%)	N (xx.x%)	N (xx.x%)
Minute Volume (ml)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Total Respiratory Rate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean Airway Pressure (cmH2O)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Plateau Pressure (cmH2O)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
PEEP (cmH2O)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Tidal Volume (Minute Volume/Total Respiratory Rate)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Tidal Volume (mls/kg PBW)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Respiratory Compliance (ml/cmH2O)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Oxygenation Index (OI)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Total SOFA score	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Use of Adjunctive Therapies			
Airway Pressure Release Ventilation (APRV)	N (xx.x%)	N (xx.x%)	N (xx.x%)

High-Frequency Oscillatory Ventilation (HFOV	N (xx.x%)	N (xx.x%)	N (xx.x%)
Neuromuscular Blocking Drugs (NMBD)	N (xx.x%)	N (xx.x%)	N (xx.x%)
Nitric Oxide	N (xx.x%)	N (xx.x%)	N (xx.x%)
Prone Position	N (xx.x%)	N (xx.x%)	N (xx.x%)
ECCO2R	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Murray Lung Injury Score	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Steroid Treatment on day 0			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Type of steroid used			
Hydrocortisone	N (xx.x%)	N (xx.x%)	N (xx.x%)
Prednisolone	N (xx.x%)	N (xx.x%)	N (xx.x%)
Dexamethasone	N (xx.x%)	N (xx.x%)	N (xx.x%)
Methylprednisolone	N (xx.x%)	N (xx.x%)	N (xx.x%)
Fludrocortisone	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Total daily steroid dose	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Statin Treatment on day 0 or within last 7 days			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Type of statin used			
Pravastatin	N (xx.x%)	N (xx.x%)	N (xx.x%)
Atorvastatin	N (xx.x%)	N (xx.x%)	N (xx.x%)
Simvastatin	N (xx.x%)	N (xx.x%)	N (xx.x%)
Rosuvastatin	N (xx.x%)	N (xx.x%)	N (xx.x%)
Other	N (xx.x%)	N (xx.x%)	N (xx.x%)
Total daily statin dose	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Insulin Treatment on day 0			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Total daily insulin dose	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Enteral feeding on day 0			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Total daily calories given	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Child Pugh Score	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Renal replacement therapy			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
Does the patient have COVID-19?			
Yes	N (xx.x%)	N (xx.x%)	N (xx.x%)
No	N (xx.x%)	N (xx.x%)	N (xx.x%)
How was COVID-19 diagnosed?			
Clinical diagnosis	N (xx.x%)	N (xx.x%)	N (xx.x%)
PCR diagnosis	N (xx.x%)	N (xx.x%)	N (xx.x%)

Mean (SD) presented for continuous variables and no. (%) for all categorical variables.

Table x.x.x. Withdrawal

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**
Withdrawal of consent	N (xx.x%)	N (xx.x%)
Use of data already collected	N (xx.x%)	N (xx.x%)
Ongoing data collection during hospital admission	N (xx.x%)	N (xx.x%)
Long term storage of research samples	N (xx.x%)	N (xx.x%)
Confirmation of vital status	N (xx.x%)	N (xx.x%)

Table x.x.x Protocol Deviations

	Number of Events			**Number of Patients**		
	Total N= (%)	**Hyper-inflammatory phenotype n = (%)**	**Hypo-inflammatory phenotype n = (%)**	**Total N= (%)**	**Hyper-inflammatory phenotype n = (%)**	**Hypo-inflammatory phenotype n = (%)**
Eligibility						
Consent						
Sample Not Taken						
POC Assay Result Not Available						
Other						

Table x.x.x Main Clinical Outcome variables

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Agreement of phenotype classifications (Secondary outcomes)

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Cohen's kappa coefficient (95% CI)**	**p-value[a]**
Agreement of phenotype classification using a POC assay and commercially-available assay (model 1) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 2) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 3) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 4) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 5) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 6) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 7) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC assay and commercially-available assay (model 8) [11]	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification using a POC-derived phenotype and LCA-derived phenotype	N agreed= N disagreed=	N agreed= N disagreed=		
Agreement of phenotype classification between day 1 and 3	N agreed= N disagreed=	N agreed= N disagreed=		

[a] p-value from McNemar's test used for agreement.

Table x.x.x Sensitivity analysis of the main clinical outcomes in patients with AHRF

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, AHRF cohort

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with AHRF defined by commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with AHRF defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcomes in patients receiving mechanical ventilation

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, mechanical ventilation cohort

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcomes in patients receiving non-invasive ventilation

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, non-invasive ventilation cohort

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcomes, patients receiving high-flow nasal oxygen

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, high flow nasal oxygen cohort

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by the standard laboratory assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcomes, patients receiving high-flow nasal oxygen at a rate of at least 30 litres per minute

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, high flow nasal oxygen (≥ 30 litres per minute) cohort

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by the standard laboratory assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcome variables, cohort excluding COVID-19 patients

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, cohort exluding COVID-19 patients

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcome variables, cohort restricted to patients with biosamples obtained within 24 hours of ARDS diagnosis

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, cohort restricted to patients with biosamples obtained within 24 hours of ARDS diagnosis

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.

Table x.x.x Sensitivity analysis of the main clinical outcome variables, cohort restricted to patients with biosamples obtained within 48 hours of ARDS diagnosis

	Hyper-inflammatory phenotype n = (%)	Hypo-inflammatory phenotype n = (%)	Unadjusted % Point or Mean Difference (95% CI)	Unadjusted risk ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Primary outcome [a]							
Mortality at 60 days in patients with ARDS as defined by the POC assay							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx		
Secondary outcomes							
Adjusted 60-day mortality (phenotype defined by POC assay)						xx.x (xx.x to xx.x)	x.xxx
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx		
28-day mortality [a]							
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)				
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx	xx.x (xx.x to xx.x)	x.xxx

[a] No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented and unadjusted p-value from chi-square and adjusted p-value from logistic regression adjusted for age, gender, and site.
[b] Mean(SD) for phenotypes and mean difference (95% CI) presented, unadjusted.
[c] Median[IQR] and p-value from Mann-Whitney test.

Table x.x.x Secondary analyses, cohort restricted to patients with biosamples obtained within 48 hours of ARDS diagnosis

	Hyper-inflammatory phenotype n = (%)	**Hypo-inflammatory phenotype n = (%)**	**Unadjusted % Point or Mean Difference (95% CI)**	**Unadjusted Risk ratio (95% CI)**	**p-value**
Mortality at 60 days in patients with ARDS defined by commercially-available assays and parsimonious model					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Mortality at 60 days in patients with ARDS defined by the complete data-set using latent class analysis					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx
Secondary outcomes using phenotype allocation defined by the complete dataset using latent class analysis					
Time to extubation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Intubation rate[a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Re-intubation rate [a]	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		x.xxx
Ventilator free days at day 28 [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Duration of ventilation [b]	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x to xx.x)		x.xxx
Length of ICU stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
Length of hospital stay [c]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]			x.xxx
28-day mortality [a]					
Alive	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)		
Dead	N (xx.x%)	N (xx.x%)	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xxx

No. (%) for phenotypes and mean difference and risk ratio (95% CI) presented.
Unadjusted p-value from chi-square.