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Supplementary appendix

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Supplement to: Bos LDJ, Sjoding M, Sinha P, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohort studies. *Lancet Respir Med* 2021; published online Oct 12. https://doi.org/10.1016/S2213-2600(21)00365-9.

Online supplement

Longitudinal respiratory subphenotypes in patients with COVID-19 related acute respiratory distress syndrome

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Online method description.

Code used for latent class analysis:

```
### Normalise variables to mean and SD
predictors.list.mean<-apply(cluster.matrix.lca, 2, mean)
predictors.list.sd<-apply(cluster.matrix.lca, 2, sd)
cluster.matrix.lca.normalised<-cluster.matrix.lca

for(j in list.predictor.variables[1:length(list.predictor.variables)]){
  cluster.matrix.lca.normalised[,j]<-
    (cluster.matrix.lca[,j]-
predictors.list.mean[which(names(predictors.list.mean)==j)])/predictors.list.sd[which(names(predictors.list.sd)
==j)]
}

set.seed(999)

FORMULA <- cbind(driving_pressure,compliance, minute_ventilation,
              ph,pf_ratio, CO2_difference,
              VR,mechpower) ~ 1
CONTROL <- list(tolerance = 10^-12, iter.max = 500)
cheatMix <- stepFlexmix(FORMULA, k = 1:5,
                    model = FLXMCmvbinary(), data = data.frame(cluster.matrix.lca.normalised),
                    control = CONTROL, nrep = 100)
cheatMix
getModel(cheatMix, "BIC")
plot(cheatMix)
```

Online only tables

Table S1: Regression coefficients for mixed model analysis of input variables in the derivation cohort .

Variable	Names	Beta estimate	2.5% CI	97.5% CI
Pdriving	Intercept	13.6814	13.3904	13.9723
Pdriving	Hours since admission	-0.0125	-0.0153	-0.0098
Pdriving	**Phenotype 2**	**1.0713**	**0.5684**	**1.5742**
Pdriving	**Interaction term**	**0.0084**	**0.0037**	**0.0131**
Crs	Intercept	35.3532	34.08	36.6267
Crs	Hours since admission	0.0632	0.0497	0.0766
Crs	Phenotype 2	1.1838	-1.033	3.4006
Crs	Interaction term	0.0078	-0.0153	0.0308
Minute ventilation	Intercept	8.9914	8.8504	9.1323
Minute ventilation	Hours since admission	0.0098	0.0008	0.0116
Minute ventilation	**Phenotype 2**	**1.803**	**1.5601**	**2.046**
Minute ventilation	**Interaction term**	**0.0158**	**0.0127**	**0.019**
pH	Intercept	7.355	7.3497	7.3603
pH	Hours since admission	2E-04	1E-04	2E-04
pH	**Phenotype 2**	**-0.014**	**-0.0232**	**-0.0048**
pH	**Interaction term**	**2E-04**	**2E-04**	**3E-04**
PaO2/FiO2	Intercept	167.8197	163.8172	171.8218
PaO2/FiO2	Hours since admission	0.0052	-0.0378	0.0483
PaO2/FiO2	Phenotype 2	6.4494	-0.4242	13.3232
PaO2/FiO2	Interaction term	0.0243	-0.0478	0.0964
VR	Intercept	1.5136	1.4683	1.5588
VR	Hours since admission	0.0048	0.0044	0.0052
VR	**Phenotype 2**	**0.3862**	**0.3077**	**0.4648**
VR	**Interaction term**	**0.0017**	**0.0001**	**0.0024**
Mechanical Power	Intercept	17.1377	16.7418	17.5334
Mechanical Power	Hours since admission	0.005	5E-04	0.0096
Mechanical Power	**Phenotype 2**	**4.353**	**3.6641**	**5.0419**
Mechanical Power	**Interaction term**	**0.04**	**0.0322**	**0.0478**
A-etCO2 difference	Intercept	6.2746	5.6286	6.9206
A-etCO2 difference	Hours since admission	0.0343	0.0278	0.0407
A-etCO2 difference	**Phenotype 2**	**2.6403**	**1.5253**	**3.7555**
A-etCO2 difference	**Interaction term**	**0.0128**	**0.0018**	**0.0237**

Online figures

Figure S1: Patient recruitment in derivation and replication cohorts

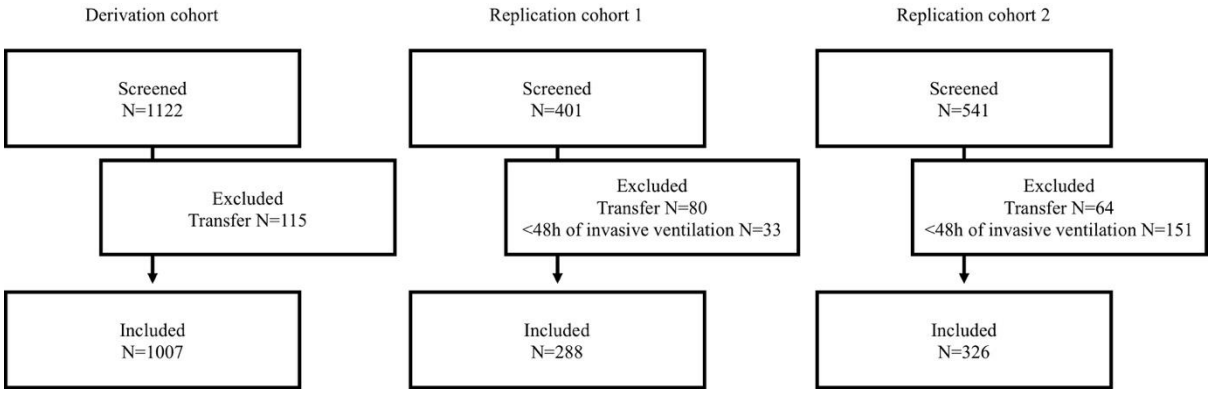
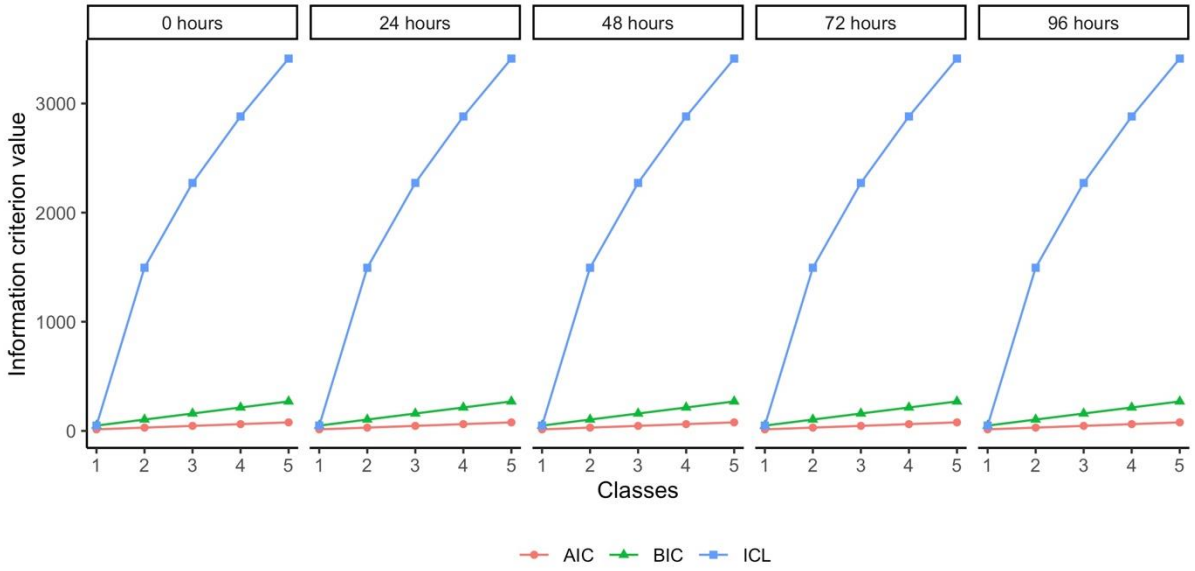
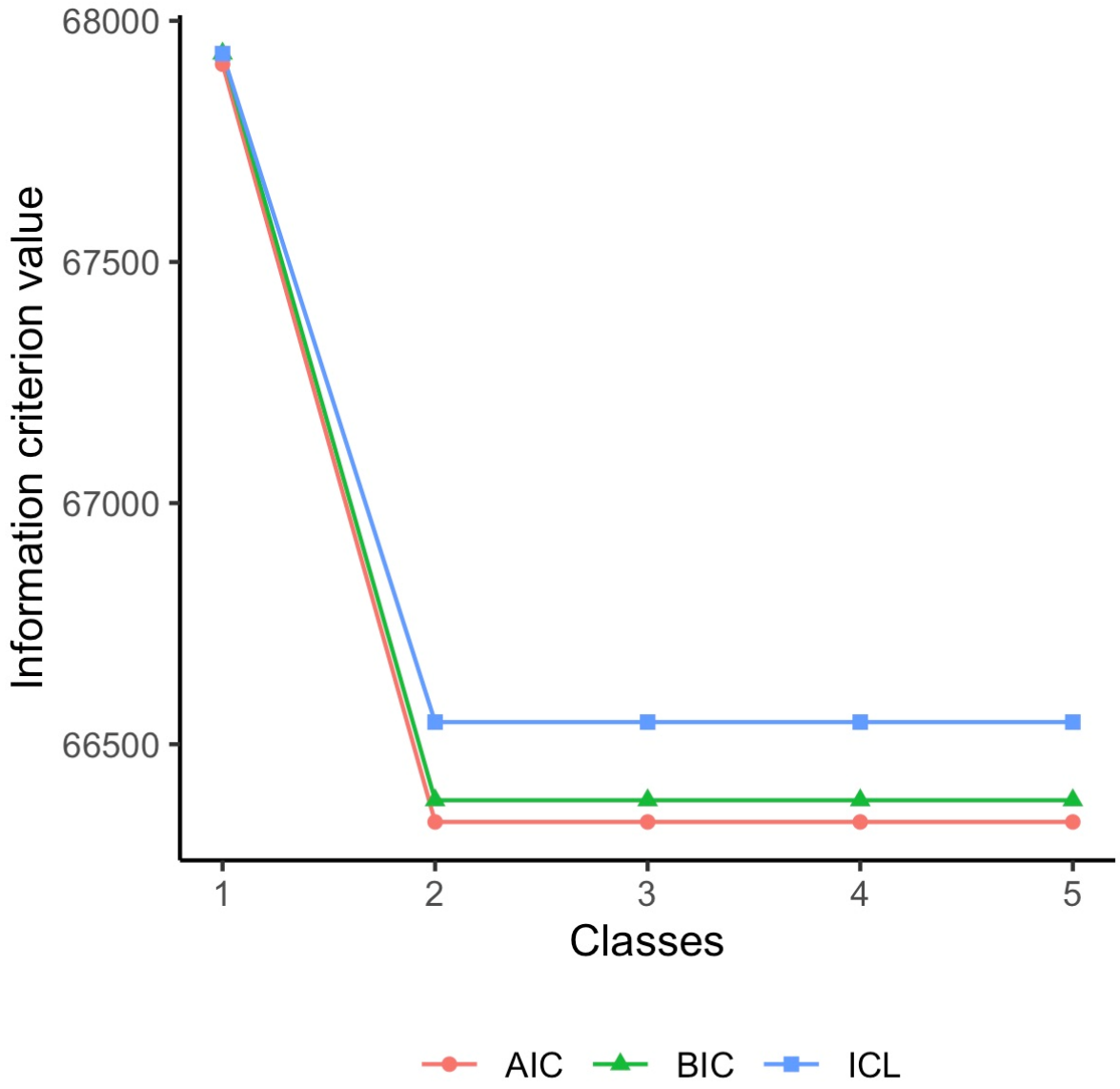


Figure S2: Model fit for cross-sectional analysis, repeated for data every 24 hours in derivation cohort



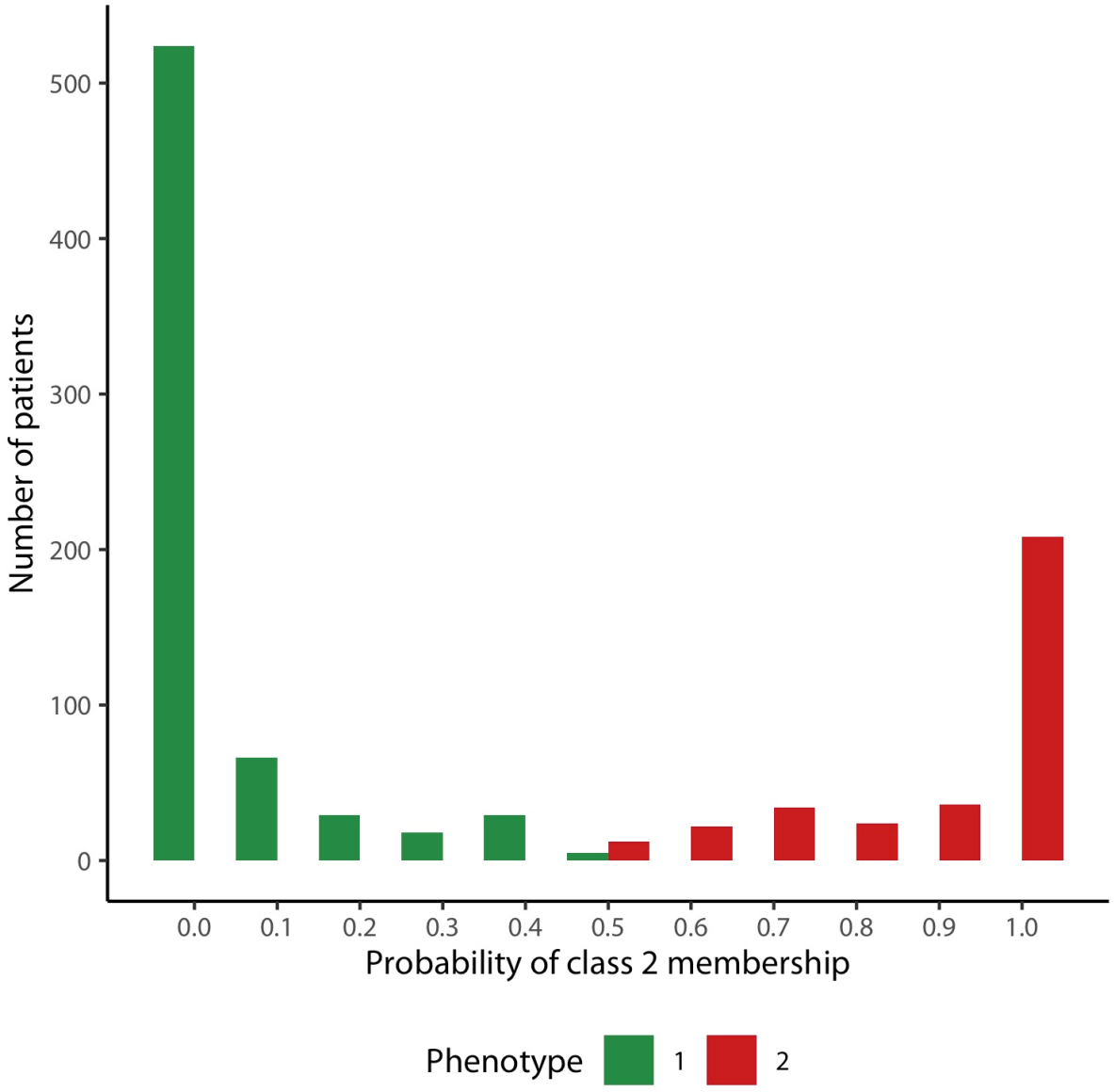
Legend: AIC = Akaike information criterion, BIC = Bayesian information criterion, ICL = Integrated completed likelihood criterion. For AIC, BIC and ICL a lower value indicates a better fit.

Figure S3: Model fit between 1 to 5 classes using longitudinal LCA.



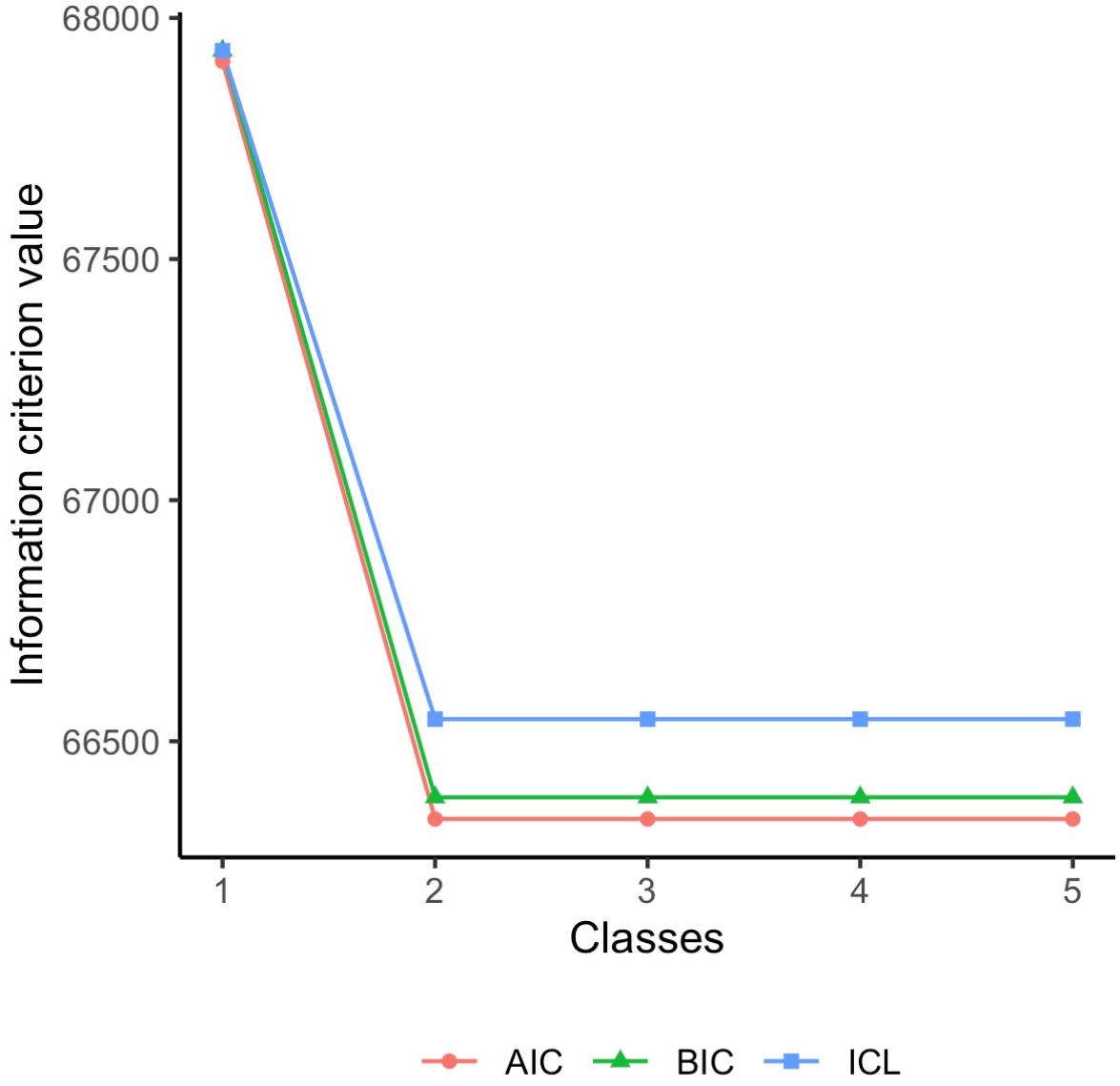
Legend: AIC = Akaike information criterion, BIC = Bayesian information criterion, ICL = Integrated completed likelihood criterion. For AIC, BIC and ICL a lower value indicates a better fit.

Figure S4: Probability of class membership for longitudinal LCA in derivation cohort



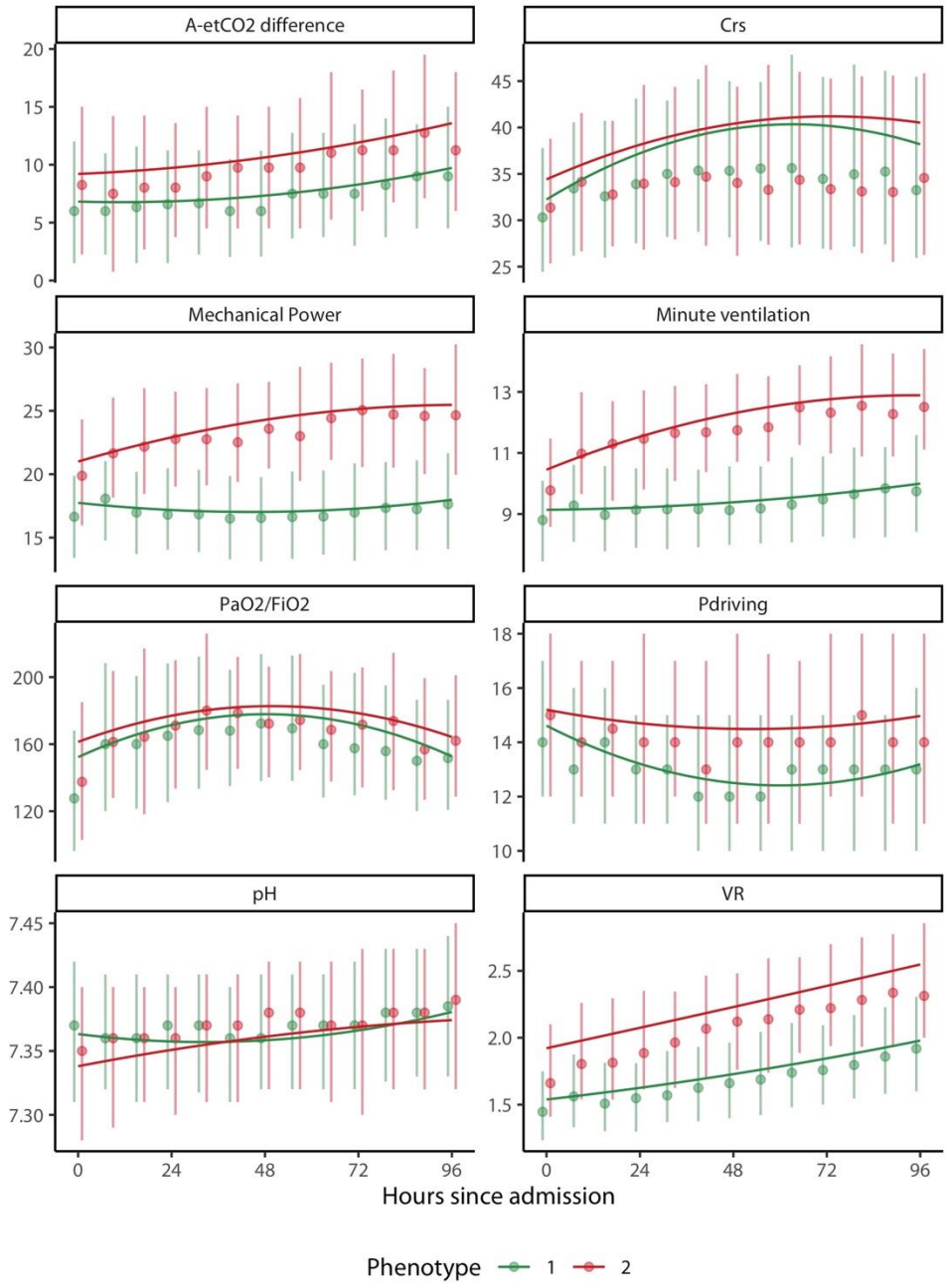
Legend: X-axis shows the probability of phenotype membership binned per 0.1 steps probability. Y-axis shows number of patients per bin.

Figure S5: Model fit between 1 to 5 classes using longitudinal LCA for patients who remained on invasive mechanical ventilation for more than 96 hours



Legend: AIC = Akaike information criterion, BIC = Bayesian information criterion, ICL = Integrated completed likelihood criterion. For AIC, BIC and ICL a lower value indicates a better fit.

Figure S6: Dynamics of variables that were used to define subphenotypes in the derivation cohort



Legend: Y-axis shows the value of the variable and the X-axis the hours since start of mechanical ventilation. Per timepoint the median and inter-quartile range is shown for the two subphenotypes. The green fitted line shows the modelled mean values for subphenotype 1 and the red line for subphenotype 2. The curves are fitted with the formula: *y ~ poly(x, 2)*.

Figure S7: ventilator free days in between time-dependent LCA subphenotypes in original analysis and sensitivity analysis for patients with >96h of MV alone

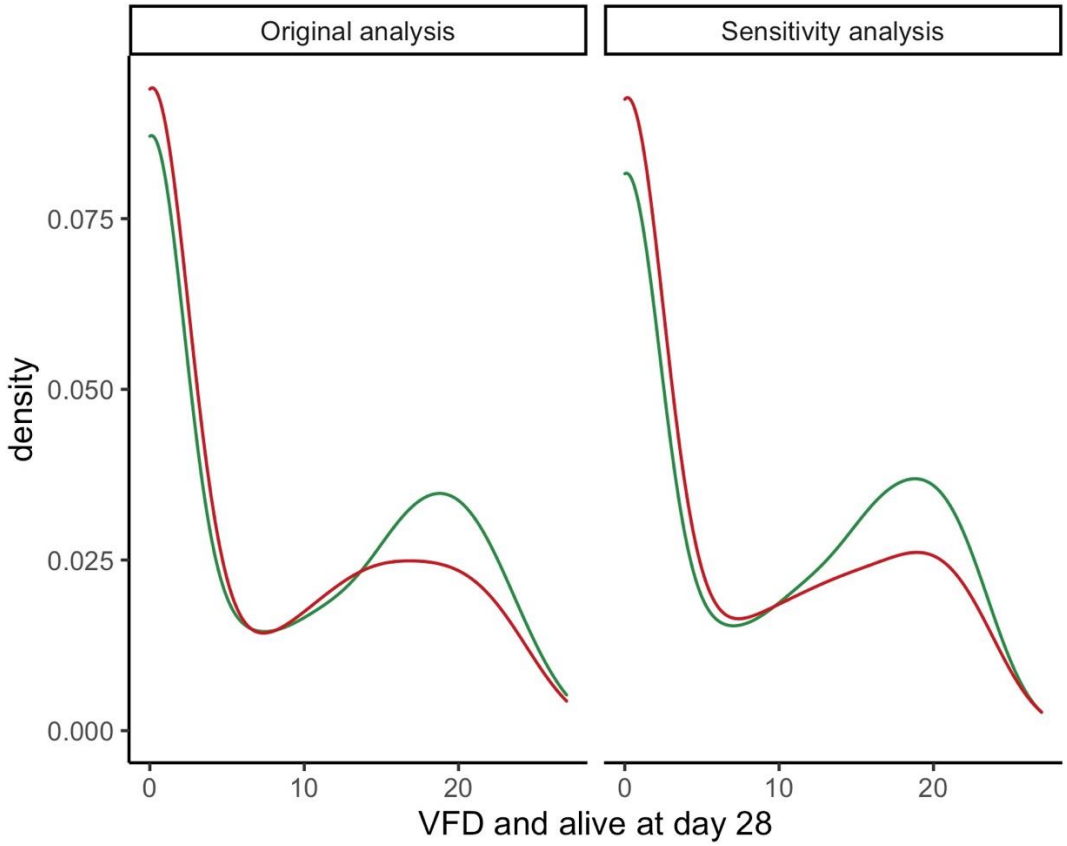


Figure S8: VR trajectories in replication cohort 1

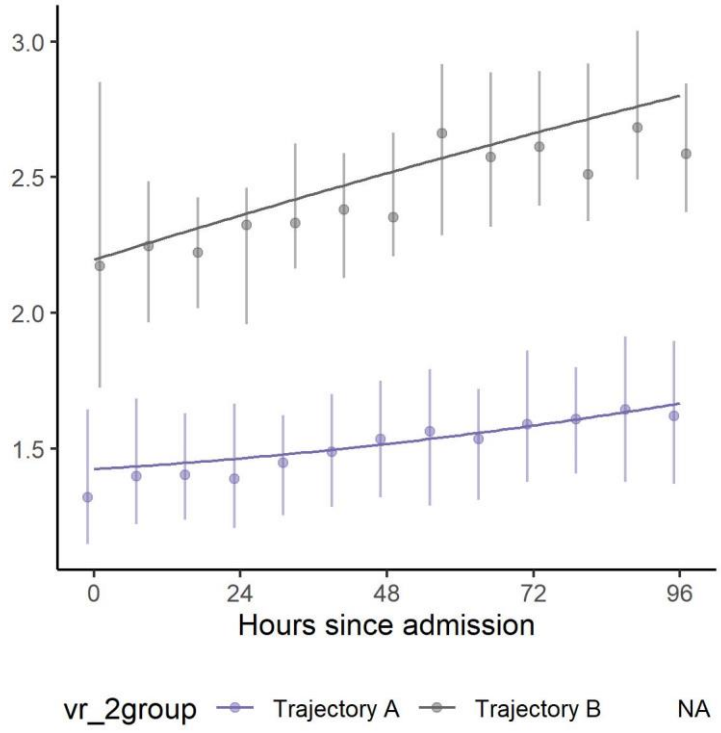


Figure S9: Mechanical power trajectories in replication cohort 1.

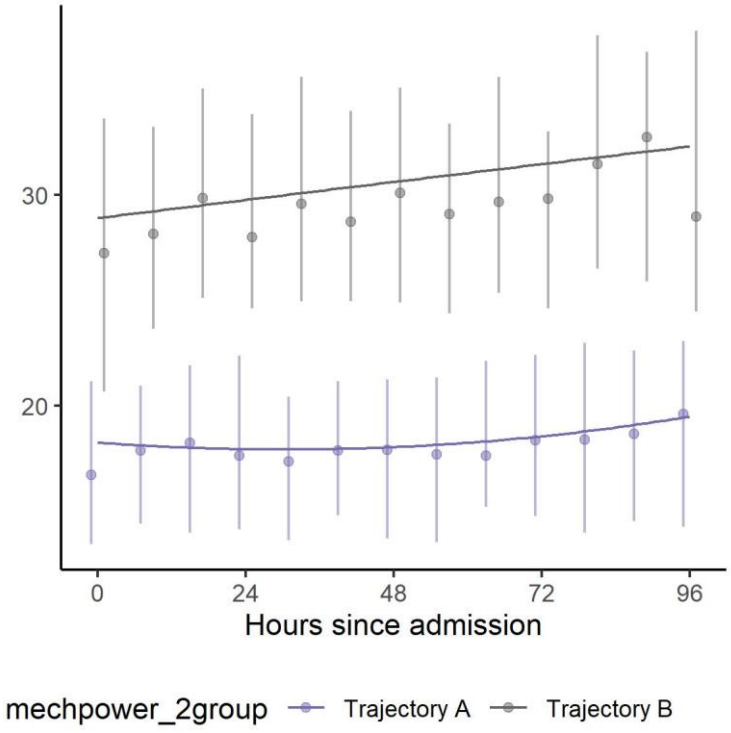


Figure S10: VR trajectories in replication cohort 2

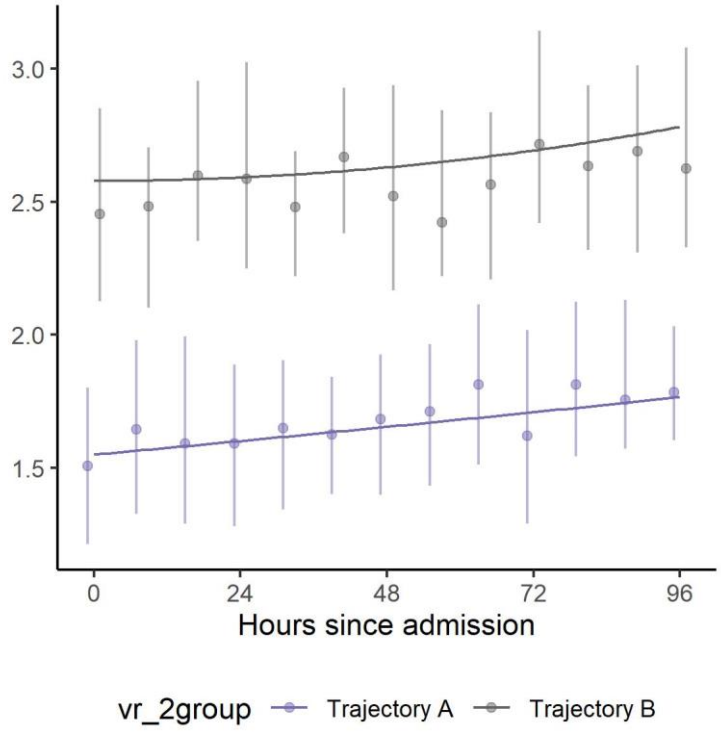


Figure S11: Mechanical power trajectories in replication cohort 2.