**Supplementary appendix**

1. **STROBE statement**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Item No | Recommendation | Page No |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 1 |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4 |
| (*b*)For matched studies, give matching criteria and number of exposed and unexposed |  |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 4 |
| Study size | 10 | Explain how the study size was arrived at | 4 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 4/5 |
| (*b*) Describe any methods used to examine subgroups and interactions | 4/5 |
| (*c*) Explain how missing data were addressed | 5 |
| (*d*) If applicable, explain how loss to follow-up was addressed | N/A |
| (*e*) Describe any sensitivity analyses | 4/5 |
| Results | | |  |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5 |
| (b) Give reasons for non-participation at each stage | 5 |
| (c) Consider use of a flow diagram | Fig1 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 5 |
| (b) Indicate number of participants with missing data for each variable of interest | Tab1 |
| (c) Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | 15\* | Report numbers of outcome events or summary measures over time | 5 |



|  |  |  |  |
| --- | --- | --- | --- |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6 |
| (*b*) Report category boundaries when continuous variables were categorized | 6 |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 6 |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 7 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 9  9 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8,9 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 |
| Other information | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 10 |

1. **Methods**
   1. Additional methodology regarding latent class analysis

Continuous TTE and haemodynamic data were tested for normality and those with a skewed distribution underwent log / square root transformation prior to inclusion in the LCA model. Continuous variables were then placed on a z-scale. Correlation was examined using the Pearson Correlation co-efficient and any one of two co-linear variables (co-efficient >0.5) were excluded. Sensitivity analyses were performed with inclusion of each of the excluded variables and are described below. Categorical variables included LVEF (normal, depressed, hyperdynamic), septal dyskinesia (present or absent), tricuspid regurgitation (none, mild, moderate-severe). Vasopressor dose was included as a categorical variable (0, >0 – <0.1, 0.1 micrograms kg-1 min-1), due to a persistent non-normal distribution despite transformation. Missing data was handled using the full information maximum likelihood function in Latent Gold v 6.0. Class allocation was based on a posterior probability of class assignment >50%.

1. **Results**
   1. Exclusion of parameters due to co-linearity

Continuous variables were tested for normality, and non-normal variables were transformed. Subsequently normalised variables were standardized by placement on a z-scale. Parameters were tested for co-linearity using Pearson correlation co-efficient. This is demonstrated in the correlation matrix below. The following variables were included in the correlation matrix: right ventricular end-diastolic area:left ventricular end-diastolic area (RV:LVEDA), RVEDAi, LVEDAi, RVESAi, LVESAi, LVEF = left ventricular ejection fraction, vasopressor dose, IVC = inferior vena cava diameter, c-IVC = collapsibility of IVC, TAPSE = tricuspid annular plane systolic excursion, MAP = mean arterial pressure, HR = heart rate, CVP = central venous pressure, LVOT VTI = left ventricular outflow tract velocity time integral, SVi = stroke volume index, CI = cardiac index, SVRI = systemic vascular resistance index.

Correlation between each of the variables was examined using the Pearson Correlation co-efficient. If the correlation co-efficient was >0.5, one of the two parameters displaying correlation was excluded. A high number of parameters were excluded on these grounds: RVEDA, RVESA correlated with RV:LVEDA, RVESA correlated with RVFAC, LVESAi correlated with LVEDA, CI correlated with LVOTVTI, SVI and LVEF. This was expected given their similarity and co-dependency in clinical practice. Due to their co-dependency, exclusion of one and inclusion of the other almost always had little effect on model selection and characteristics of the classes defined, as demonstrated below.

Figure 3.1.1: Correlation between cardiovascular parameters



Figure 3.1.1 Legend: RV = right ventricular, LV = left ventricular; EDA = end-diastolic area; ESA = end-systolic area; EF = ejection fraction; IVC = inferior vena cava diameter; c-IVC = collapsibility of IVC, TAPSE = tricuspid annular plane systolic excursion, LVOT VTI = left ventricular outflow tract velocity time integral, SVi = stroke volume index, CI = cardiac index, SVRI = systemic vascular resistance index MAP = mean arterial pressure, HR = heart rate, CVP = central venous pressure, VP = Vasopressor dose. Values denote pearson correlation co-efficient on scale of red (-1) to blue (+1).

3.2. Sensitivity analyses of excluded co-linear variables

Sensitivity analyses were performed with inclusion of each of the excluded variables (e.g. RVEDA in place of RVESA). This was performed to ascertain the effects of exclusion of these parameters on model fit / selection.

3.2.1 RVEDA vs RV:LVEDA

RVEDA was included and RV:LVEDA was excluded. This had little effect on fit statistics: the four-class model was deemed to have the best fit due to a lower BIC, higher entropy, improvement in VLMR compared to the three class model. Although the BIC was lower for the 5 class model, the rate of decrease in BIC was low (difference of 4 points), therefore the 4 class model was chosen. For RVEDA four class model, the maximum bivariate residual was higher (51), which led to inclusion of RV:LVEDA over RVEDA.

Table 3.2.1.1 RVEDA inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9664.2923 | 19448.9301 | 19364.5846 | 19382.5846 | 18 | 140.7025 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9386.3162 | 19013.3234 | 18844.6324 | 18880.6324 | 36 | 94.0300 | 555.9522 | 0.0000 | 0.1241 | 0.5974 |
| 3-Cluster | -9207.8881 | 18776.8126 | 18523.7761 | 18577.7761 | 54 | 85.6622 | 356.8562 | 0.0000 | 0.1224 | 0.6837 |
| 4-Cluster | -9093.2987 | 18667.9794 | 18330.5974 | 18402.5974 | 72 | 51.2307 | 229.1788 | 0.0000 | 0.1572 | 0.7010 |
| 5-Cluster | -9030.9297 | 18663.5868 | 18241.8594 | 18331.8594 | 90 | 23.5791 | 124.7380 | 0.0000 | 0.1717 | 0.7072 |

Table 3.2.1.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of cluster characteristics of the four-cluster model that was generated through use of RVEDA demonstrated that the clusters were highly similar to the original model. Therefore, the use of RV:LVEDA or RVEDA had little effect on subphenotype characterisation.

Table 3.2.1.2 Cluster characteristics with use of RVEDA

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3383 | 0.2959 | 0.2497 | 0.1149 |  |
| **Indicators** |  |  |  |  |  |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1406 | 0.0322 | 0.4455 | -1.4632 | -0.0003 |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0422 | 0.2538 | 0.3091 | -1.1217 | 0.0089 |
| **lvedai** |  |  |  |  |  |
| **Mean** | -0.2214 | 0.8109 | -0.4490 | -0.4638 | -0.0001 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.3972 | -0.0826 | 1.0873 | -0.9817 | -0.0007 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0523 | 0.2164 | -0.6235 | 0.9434 | -0.0004 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.3450 | -0.2703 | 0.7372 | 0.1122 | 0.0000 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.1950 | 0.0108 | 0.0348 | 0.5469 | 0.0089 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4458 | 0.4989 | 0.2585 | 0.1941 | 0.3858 |
| **2** | 0.3090 | 0.2977 | 0.3116 | 0.2945 | 0.3046 |
| **3** | 0.2452 | 0.2034 | 0.4299 | 0.5115 | 0.3096 |
| **Mean** | 1.7994 | 1.7045 | 2.1714 | 2.3174 | 1.9238 |
| **rvedai** |  |  |  |  |  |
| **Mean** | -0.5001 | 0.6929 | -0.6334 | 1.0604 | 0.0002 |

Table 3.2.1.2 Legend: RVEDA = right ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* + 1. RVESA vs RV:LVEDA

RVESA was included and RV:LVEDA was excluded. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to the lowest BIC and improvement in VLMR compared to the three class model. However, the maximum bivariate residual was higher (49), which led to inclusion of RV:LVEDA over RVESA. Furthermore, RV:LVEDA has been used in many studies to characterise RV dysfunction.

Table 3.2.2.1 RVESA inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9664.2923 | 19448.9301 | 19364.5846 | 19382.5846 | 18 | 390.2434 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9268.8178 | 18778.3267 | 18609.6357 | 18645.6357 | 36 | 127.1701 | 790.9489 | 0.0000 | 0.0638 | 0.7408 |
| 3-Cluster | -9046.4170 | 18453.8705 | 18200.8340 | 18254.8340 | 54 | 70.4221 | 444.8017 | 0.0000 | 0.1174 | 0.7261 |
| 4-Cluster | -8930.5009 | 18342.3838 | 18005.0018 | 18077.0018 | 72 | 49.1849 | 231.8322 | 0.0000 | 0.1384 | 0.7369 |
| 5-Cluster | -8873.2552 | 18348.2378 | 17926.5104 | 18016.5104 | 90 | 26.6102 | 114.4915 | 0.0002 | 0.1537 | 0.7344 |

Table 3.2.2.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of RVESA and exclusion of RV:LVEDA, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of RV:LVEDA vs. RVESA had little effect on subphenotype characterisation. RV:LVEDA was chosen due to its use in numerous studies to characterise RV dilation.

Table 3.2.2.2 Cluster characteristics with use of RVEDA

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3945 | 0.2397 | 0.2385 | 0.1273 |  |
| **Indicators** |  |  |  |  |  |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.2325 | -0.3985 | 0.8135 | -1.4976 | -0.0003 |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0014 | 0.2283 | 0.3285 | -0.9796 | 0.0077 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.0880 | 0.6402 | -0.5904 | -0.3719 | -0.0001 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.3541 | 0.1971 | 0.8658 | -0.8857 | 0.0010 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0246 | 0.1342 | -0.5759 | 0.9042 | 0.0002 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.3657 | -0.0024 | 0.5595 | 0.0939 | 0.0003 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.1678 | 0.0801 | -0.0434 | 0.5273 | 0.0097 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4666 | 0.4302 | 0.3007 | 0.2108 | 0.3858 |
| **2** | 0.3013 | 0.3075 | 0.3123 | 0.2953 | 0.3046 |
| **3** | 0.2322 | 0.2623 | 0.3870 | 0.4939 | 0.3096 |
| **Mean** | 1.7656 | 1.8322 | 2.0863 | 2.2831 | 1.9238 |
| **rvesai** |  |  |  |  |  |
| **Mean** | -0.3476 | 0.6124 | -0.8971 | 1.6092 | 0.0003 |

Table 3.2.2.2 Legend: RVESA = right end-systolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* + 1. RVFAC vs RVESA

RVESA was included and RVFAC was excluded. this had little effect on fit statistics: the four-class model

was deemed to have the best fit due to a lower BIC, higher entropy, improvement in VLMR compared to the three class model. Although the BIC was lower for the 5 class model, the rate of decrease in BIC was low (difference of 9 points), therefore the 4 class model was chosen. For the 4 class model for RVESA, the maximum bivariate residual was higher (55), which led to inclusion of RVFAC over RVESA. Furthermore, RVFAC has been used in many studies to characterise RV systolic function.

Table 3.2.3.1 RVESA inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9664.2923 | 19448.9301 | 19364.5846 | 19382.5846 | 18 | 379.2936 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9114.9316 | 18470.5541 | 18301.8631 | 18337.8631 | 36 | 101.6239 | 1098.7214 | 0.0000 | 0.0536 | 0.7706 |
| 3-Cluster | -8897.1301 | 18155.2968 | 17902.2603 | 17956.2603 | 54 | 72.4710 | 435.6029 | 0.0000 | 0.1117 | 0.7408 |
| 4-Cluster | -8742.7939 | 17966.9697 | 17629.5877 | 17701.5877 | 72 | 54.8421 | 308.6725 | 0.0000 | 0.1223 | 0.7560 |
| 5-Cluster | -8677.6808 | 17957.0890 | 17535.3615 | 17625.3615 | 90 | 42.3388 | 130.2262 | 0.0000 | 0.1306 | 0.7699 |

Table 3.2.3.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of RVESA and exclusion of RVFAC, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of RVFAC vs. RVESA had little effect on subphenotype characterisation. RVFAC was chosen due to its use in numerous studies to characterise RV systolic function.

Table 3.2.3.2 Cluster characteristics with use of RVESA

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3720 | 0.3146 | 0.2147 | 0.0986 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0265 | 0.1491 | 0.2962 | -0.9750 | 0.0049 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.1630 | 0.2840 | -0.5332 | -0.3668 | -0.0001 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.4052 | 0.0487 | 1.0329 | -0.8699 | 0.0006 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0416 | 0.2468 | -0.7366 | 0.9912 | 0.0017 |
| **ZZZHR** |  |  |  |  |  |
| **Mean** | -0.3410 | -0.1427 | 0.7333 | 0.1531 | 0.0004 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2121 | 0.1068 | -0.0019 | 0.5636 | 0.0097 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4679 | 0.4286 | 0.2693 | 0.1914 | 0.3858 |
| **2** | 0.3020 | 0.3088 | 0.3098 | 0.2900 | 0.3046 |
| **3** | 0.2302 | 0.2627 | 0.4208 | 0.5186 | 0.3096 |
| **Mean** | 1.7623 | 1.8341 | 2.1515 | 2.3271 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5522 | 0.3435 | -0.5079 | 2.1034 | 0.0004 |
| **rvesai** |  |  |  |  |  |
| **Mean** | -0.3758 | 0.4001 | -0.8331 | 1.9627 | 0.0004 |

Table 3.2.3.2 Legend: RVESA = right end-systolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* + 1. LVEDA vs LVESA

LVESA was included and LVEDA was excluded. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to the lowest BIC and improvement in VLMR compared to the three class model. However, the maximum bivariate residual was slightly higher (10.7), which led to inclusion of LVEDA over LVESA.

Table 3.2.4.1 LVESA inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9664.2923 | 19448.9301 | 19364.5846 | 19382.5846 | 18 | 105.2806 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9301.5168 | 18843.7245 | 18675.0335 | 18711.0335 | 36 | 53.6125 | 725.5510 | 0.0000 | 0.0528 | 0.7271 |
| 3-Cluster | -9050.5428 | 18462.1222 | 18209.0857 | 18263.0857 | 54 | 15.0120 | 501.9479 | 0.0000 | 0.1165 | 0.7198 |
| 4-Cluster | -8933.2419 | 18347.8659 | 18010.4839 | 18082.4839 | 72 | 10.7288 | 234.6018 | 0.0000 | 0.1352 | 0.7283 |
| 5-Cluster | -8892.3904 | 18386.5084 | 17964.7809 | 18054.7809 | 90 | 6.4811 | 81.7030 | 0.0033 | 0.1779 | 0.7031 |

Table 3.2.4.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of LVESA and exclusion of LVEDA, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of LVEDA vs. LVESA had little effect on subphenotype characterisation. LVEDA was chosen due to its use in our previous study to characterise RV dysfunction in COVID-19 ARDS.

Table 3.2.4.2 Cluster characteristics with use of LVESA

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3908 | 0.2596 | 0.2360 | 0.1136 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0651 | 0.2851 | 0.3507 | -1.0767 | 0.0091 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.4281 | 0.0491 | 1.1266 | -0.9958 | -0.0016 |
| **ivc** |  |  |  |  |  |
| **Mean** | 0.0192 | 0.2306 | -0.7255 | 0.9087 | -0.0004 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.3575 | -0.1629 | 0.7154 | 0.1139 | -0.0000 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2029 | 0.1222 | -0.0131 | 0.5300 | 0.0098 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4670 | 0.4482 | 0.2747 | 0.1951 | 0.3858 |
| **2** | 0.3029 | 0.3064 | 0.3115 | 0.2922 | 0.3046 |
| **3** | 0.2301 | 0.2454 | 0.4138 | 0.5127 | 0.3096 |
| **Mean** | 1.7632 | 1.7973 | 2.1392 | 2.3175 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5590 | 0.5125 | -0.4477 | 1.6775 | 0.0004 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1138 | -0.0081 | 0.5180 | -1.4489 | -0.0003 |
| **lvesai** |  |  |  |  |  |
| **Mean** | 0.3692 | 0.0603 | -0.6329 | -0.0913 | -0.0001 |

Table 3.2.4.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVESA = left ventricular end-systolic area, CI = cardiac index, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* + 1. CI vs LVOT VTI

LVOT VTI was included and CI was excluded. This had little effect on fit statistics: the four-class model was deemed to have the best fit due to the lowest BIC and improvement in VLMR compared to the three class model. However, the maximum bivariate residual was slightly higher (11.6), which led to inclusion of CI over LVOT VTI.

Table 3.2.5.1 LVOT VTI inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9661.4544 | 19443.2543 | 19358.9088 | 19376.9088 | 18 | 105.2806 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9296.6917 | 18834.0745 | 18665.3835 | 18701.3835 | 36 | 20.4501 | 729.5253 | 0.0000 | 0.0440 | 0.7614 |
| 3-Cluster | -9157.0604 | 18675.1574 | 18422.1209 | 18476.1209 | 54 | 15.4423 | 279.2626 | 0.0000 | 0.1524 | 0.6461 |
| 4-Cluster | -9076.5932 | 18534.5685 | 18297.1865 | 18369.1865 | 72 | 11.5166 | 160.9344 | 0.0000 | 0.1686 | 0.6545 |
| 5-Cluster | -8993.5307 | 18588.7889 | 18167.0614 | 18257.0614 | 90 | 9.2977 | 166.1251 | 0.0000 | 0.1698 | 0.6880 |

Table 3.2.5.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of LVOT VTI and exclusion of CI, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of LVOT VTI vs. CI had little effect on subphenotype characterisation. CI was chosen.

Table 3.2.5.2 Cluster characteristics with use of LVOT VTI

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.4320 | 0.2896 | 0.1798 | 0.0986 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0684 | 0.2328 | 0.4611 | -1.1337 | 0.0085 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0460 | 0.3433 | -0.9309 | 0.8894 | 0.0005 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.1480 | -0.2379 | 0.5739 | 0.3063 | 0.0004 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2331 | 0.1623 | 0.0773 | 0.4731 | 0.0070 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4503 | 0.4124 | 0.2918 | 0.1963 | 0.3858 |
| **2** | 0.3032 | 0.3086 | 0.3101 | 0.2892 | 0.3046 |
| **3** | 0.2465 | 0.2790 | 0.3981 | 0.5146 | 0.3096 |
| **Mean** | 1.7962 | 1.8666 | 2.1062 | 2.3183 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5533 | 0.4815 | -0.4147 | 1.7633 | 0.0004 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1480 | -0.0898 | 0.6000 | -1.4745 | -0.0003 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.2410 | 0.1540 | -0.4572 | -0.6771 | -0.0002 |
| **lvotvti** |  |  |  |  |  |
| **Mean** | -0.2113 | 0.1499 | 0.8243 | -1.0195 | -0.0008 |

Table 3.2.5.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVESA = left ventricular end-systolic area, LVOT VTI = left ventricular outflow tract velocity time integral, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* + 1. CI vs SVI

SVi was included and CI was excluded. This had little effect on fit statistics: the four-class model was deemed to have the best fit due to the lowest BIC and improvement in VLMR compared to the three class model. However, the maximum bivariate residual was higher (12.0), which led to inclusion of CI over SVI.

Table 3.2.6.1 SVi inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9664.2923 | 19448.9301 | 19364.5846 | 19382.5846 | 18 | 105.2806 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9288.2910 | 18817.2731 | 18648.5821 | 18684.5821 | 36 | 20.0304 | 752.0025 | 0.0000 | 0.0393 | 0.7778 |
| 3-Cluster | -9147.1702 | 18655.3769 | 18402.3404 | 18456.3404 | 54 | 15.5914 | 282.2417 | 0.0000 | 0.1408 | 0.6620 |
| 4-Cluster | -9079.4017 | 18540.1854 | 18302.8034 | 18374.8034 | 72 | 11.9684 | 135.5370 | 0.0000 | 0.1689 | 0.6613 |
| 5-Cluster | -9000.8585 | 18603.4444 | 18181.7169 | 18271.7169 | 90 | 9.6580 | 157.0865 | 0.0000 | 0.1734 | 0.6887 |

Table 3.2.6.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of SVi and exclusion of CI, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of CI vs. SVi had little effect on subphenotype characterisation. CI was chosen.

Table 3.2.6.2 Cluster characteristics with use of SVI

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.4170 | 0.2909 | 0.1498 | 0.1423 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0525 | 0.3763 | 0.3968 | -0.9632 | 0.0097 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0831 | 0.2653 | -1.0171 | 0.7592 | -0.0008 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.1311 | -0.3168 | 0.7835 | 0.2133 | 0.0003 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2322 | 0.1182 | 0.0453 | 0.4411 | 0.0073 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4702 | 0.4230 | 0.2420 | 0.2131 | 0.3858 |
| **2** | 0.3023 | 0.3104 | 0.3058 | 0.2983 | 0.3046 |
| **3** | 0.2275 | 0.2665 | 0.4522 | 0.4886 | 0.3096 |
| **Mean** | 1.7573 | 1.8435 | 2.2103 | 2.2755 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5608 | 0.2728 | -0.4044 | 1.5071 | 0.0003 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1473 | 0.1098 | 0.6064 | -1.2907 | -0.0001 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.2058 | 0.2538 | -0.5573 | -0.5388 | -0.0002 |
| **svi** |  |  |  |  |  |
| **Mean** | -0.2259 | 0.4404 | 0.6957 | -0.9735 | -0.0008 |

Table 3.2.6.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVESA = left ventricular end-systolic area, SVI = stroke volume index, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* + 1. CI vs LVEF

LVEF was included and CI was excluded. This had little effect on fit statistics: the four-class model was deemed to have the best fit due to the lowest BIC and improvement in VLMR compared to the three class model. However, the maximum bivariate residual was higher (12.9), which led to inclusion of CI over LVEF.

Table 3.2.7.1 LVEF inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9277.8895 | 18676.1244 | 18591.7789 | 18609.7789 | 18 | 105.2806 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -8938.1233 | 18110.2517 | 17946.2465 | 17981.2465 | 35 | 56.3268 | 679.5324 | 0.0000 | 0.0515 | 0.7360 |
| 3-Cluster | -8812.7557 | 17973.1761 | 17729.5113 | 17781.5113 | 52 | 15.0799 | 250.7352 | 0.0001 | 0.1534 | 0.6484 |
| 4-Cluster | -8720.5821 | 17902.4885 | 17579.1641 | 17648.1641 | 69 | 12.9313 | 184.3472 | 0.0000 | 0.1545 | 0.6803 |
| 5-Cluster | -8674.1045 | 17923.1931 | 17520.2091 | 17606.2091 | 86 | 9.0826 | 92.9551 | 0.0002 | 0.1722 | 0.6914 |

Table 3.2.7.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of LVEF and exclusion of CI, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of LVEF vs. CI had little effect on subphenotype characterisation. CI was chosen as LVEF is influenced greatly by loading conditions.

Table 3.2.7.2 Cluster characteristics with use of LVESA

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.4507 | 0.2821 | 0.1710 | 0.0961 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0389 | 0.2226 | 0.4161 | -1.1282 | 0.0086 |
| **mivc** |  |  |  |  |  |
| **Mean** | -0.0178 | 0.2843 | -0.9432 | 0.9606 | 0.0027 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.2317 | -0.2149 | 0.8190 | 0.2603 | 0.0002 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.1892 | 0.1171 | 0.0082 | 0.6133 | 0.0081 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4489 | 0.4219 | 0.2774 | 0.1762 | 0.3858 |
| **2** | 0.3046 | 0.3088 | 0.3099 | 0.2828 | 0.3046 |
| **3** | 0.2464 | 0.2694 | 0.4127 | 0.5410 | 0.3096 |
| **Mean** | 1.7975 | 1.8475 | 2.1353 | 2.3648 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5496 | 0.5098 | -0.4099 | 1.8186 | 0.0004 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1713 | -0.1061 | 0.5701 | -1.5152 | -0.0003 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.2895 | 0.0904 | -0.5844 | -0.5850 | -0.0002 |
| **lvefcat** |  |  |  |  |  |
| **depressed** | 0.2247 | 0.1131 | 0.0037 | 0.1933 | 0.1523 |
| **normal** | 0.6891 | 0.7068 | 0.2592 | 0.7026 | 0.6217 |
| **hyperdynamic** | 0.0861 | 0.1802 | 0.7371 | 0.1041 | 0.2260 |
| **Mean** | 1.8614 | 2.0671 | 2.7334 | 1.9108 | 2.0737 |

Table 3.2.7.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVESA = left ventricular end-systolic area, LVEFcat = left ventricular ejection fraction category, VP cat = vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate, RVFAC = right ventricular fractional area change

* 1. Exclusion due to local dependence after latent class analysis

Parameters were also excluded due to local dependence after LCA analysis, denoted by high bivariate residual (BVR) values >20 generated in the fit statistics. Again, this was expected given the co-dependency of many of the parameters used in clinical practice (e.g. MAP and vasopressor dose). Local dependence within classes was assessed through the use of bivariate residuals. Maximum BVR values <20 were deemed to be locally independent. The final model, after exclusion of the below parameters, had a maximum BVR of 10.6 and all class-defining variables were deemed to have conditional independence. Models with maximum BVR values >20 led to exclusion of either one of the class defining variables that were co-dependent. Sensitivity analyses were performed on excluded co-dependent variables.

3.3.1 C-IVC vs IVC diameter

When collapsibility of IVC (c-IVC) was included alongside IVC diameter, the BVR amongst the two variables was 23.2. This led to exclusion of c-IVC. In sensitivity analyses, c-IVC was included and IVC was excluded. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the two class model. However, the maximum bivariate residual was higher (11), which led to inclusion of LVEID over LVEIS.

Table 3.3.1.1 c-IVC inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9664.2923 | 19448.9301 | 19364.5846 | 19382.5846 | 18 | 105.2806 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -8995.0465 | 18230.7840 | 18062.0930 | 18098.0930 | 36 | 49.6874 | 1338.4916 | 0.0000 | 0.0259 | 0.8787 |
| 3-Cluster | -8730.3037 | 17821.6439 | 17568.6074 | 17622.6074 | 54 | 28.3179 | 529.4856 | 0.0000 | 0.0911 | 0.7893 |
| 4-Cluster | -8573.2388 | 17627.8595 | 17290.4775 | 17362.4775 | 72 | 14.9031 | 314.1299 | 0.0000 | 0.1093 | 0.7789 |
| 5-Cluster | -8443.1185 | 17687.9645 | 17166.2370 | 17256.2370 | 90 | 9.9187 | 260.2406 | 0.0000 | 0.1104 | 0.7995 |

Table 3.3.1.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of c-IVC and exclusion of IVC, demonstrated that the classes were highly similar to the original model. Therefore, the inclusion of c-IVC vs. IVC had little effect on subphenotype characterisation. IVC was chosen due to the lower BVR when it was included in the model.

Table 3.3.1.2 Cluster characteristics with use of c-IVC

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3146 | 0.3096 | 0.1935 | 0.1835 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.3200 | 0.0406 | 0.4024 | 0.0979 | 0.0076 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.0028 | -0.3564 | 0.7452 | -0.1816 | -0.0002 |
| **cvp** |  |  |  |  |  |
| **Mean** | 0.1062 | -0.2508 | 0.0325 | 0.2161 | 0.0017 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.3134 | 0.5214 | 0.2813 | 0.3915 | 0.3858 |
| **2** | 0.3131 | 0.2883 | 0.3102 | 0.3118 | 0.3046 |
| **3** | 0.3736 | 0.1904 | 0.4085 | 0.2967 | 0.3096 |
| **Mean** | 2.0602 | 1.6690 | 2.1273 | 1.9052 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | 0.3830 | -0.5342 | -0.4202 | 0.6878 | 0.0000 |
| **rvfac** |  |  |  |  |  |
| **Mean** | -0.3064 | 0.1733 | 0.5144 | -0.3094 | 0.0000 |
| **lvedai** |  |  |  |  |  |
| **Mean** | -0.0797 | 0.2773 | -0.2429 | -0.0750 | -0.0000 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.3263 | -0.3449 | 1.2337 | -0.1579 | 0.0004 |
| **civc** |  |  |  |  |  |
| **Mean** | -0.9897 | 0.2828 | 0.9599 | 0.2355 | 0.0049 |

Table 3.3.1.2 Legend: RV:LVEDA = right: left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, LVEF = left ventricular ejection fraction, RVFAC = right ventricular fractional area change, VPcat = vasopressor dose category, c-IVC = collapsibility of inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CI = cardiac index

* + 1. CI vs SVRI

When CI was included alongside SVRI category, the BVR amongst the two variables was 41. This led to exclusion of SVRI. In sensitivity analyses, SVRI was included and CI was excluded. This had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three class model. With inclusion of SVRI, the maximum bivariate residual was higher (21), which led to inclusion of CI over SVRI.

Table 3.3.2.1 SVRI inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9194.6234 | 18509.5923 | 18425.2468 | 18443.2468 | 18 | 105.2806 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -8839.6415 | 17919.9740 | 17751.2830 | 17787.2830 | 36 | 68.5449 | 709.9638 | 0.0000 | 0.0500 | 0.7417 |
| 3-Cluster | -8710.3044 | 17781.6453 | 17528.6088 | 17582.6088 | 54 | 42.3022 | 258.6742 | 0.0000 | 0.1536 | 0.6507 |
| 4-Cluster | -8609.6500 | 17707.6819 | 17363.3000 | 17435.3000 | 72 | 21.0699 | 201.3089 | 0.0000 | 0.1723 | 0.6671 |
| 5-Cluster | -8560.8199 | 17723.3673 | 17301.6398 | 17391.6398 | 90 | 17.5698 | 97.6602 | 0.0000 | 0.1661 | 0.6840 |

Table 3.3.2.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of SVRI and exclusion of CI, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of SVRI vs. CI had little effect on subphenotype characterisation. CI was chosen due to the lower BVR.

Table 3.3.2.2 Cluster characteristics with use of SVRI

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.4120 | 0.2722 | 0.2010 | 0.1149 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0311 | 0.2369 | 0.3738 | -1.0152 | 0.0099 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.2610 | -0.2191 | 0.7405 | 0.1602 | 0.0001 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2320 | 0.1225 | 0.0683 | 0.4803 | 0.0068 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.5067 | 0.3995 | 0.2012 | 0.2426 | 0.3858 |
| **2** | 0.2973 | 0.3173 | 0.2991 | 0.3106 | 0.3046 |
| **3** | 0.1960 | 0.2832 | 0.4997 | 0.4469 | 0.3096 |
| **Mean** | 1.6893 | 1.8837 | 2.2985 | 2.2043 | 1.9238 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5615 | 0.4325 | -0.4006 | 1.6900 | 0.0004 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1468 | -0.0957 | 0.5420 | -1.2472 | -0.0002 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.2642 | 0.1258 | -0.3546 | -0.6257 | -0.0002 |
| **mivc** |  |  |  |  |  |
| **Mean** | -0.0539 | 0.3006 | -0.7789 | 0.8369 | -0.0006 |
| **svri** |  |  |  |  |  |
| **Mean** | 0.4029 | -0.1797 | -1.0445 | 1.1826 | 0.0433 |

Table 3.3.2.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, LVEF = left ventricular ejection fraction, vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, SVRI = systemic vascular resistance index, CVP = central venous pressure.

3.3.3 MAP vs VP dose category

When MAP was included alongside VP dose category, the BVR amongst the two variables was 71. This led to exclusion of MAP. In sensitivity analyses, MAP was included and VP dose category removed. The four-class model was deemed to have the best fit. This was because the cluster 3 to 4 had a greater decrease in BIC and AIC compared to the transition from cluster 4 to 5. However, the maximum bivariate residual was higher (83) when MAP was included. VP Category was chosen due to the lower BVR and because MAP targets can be 65mmHg in ICU patients but vasopressor requirements can vary considerably. VP category was therefore deemed to be more sensitive at describing the degree of shock compared to MAP.

Table 3.3.3.1 MAP inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9911.0396 | 19942.4246 | 19858.0791 | 19876.0791 | 18 | 526.0146 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -9464.1531 | 19175.6830 | 19002.3062 | 19039.3062 | 37 | 264.2630 | 893.7729 | 0.0000 | 0.0825 | 0.6805 |
| 3-Cluster | -9114.2931 | 18602.9945 | 18340.5863 | 18396.5863 | 56 | 147.2761 | 699.7199 | 0.0000 | 0.0906 | 0.7750 |
| 4-Cluster | -8967.0221 | 18435.4837 | 18084.0442 | 18159.0442 | 75 | 83.4391 | 294.5421 | 0.0000 | 0.1185 | 0.7759 |
| 5-Cluster | -8892.5430 | 18413.5569 | 17973.0860 | 18067.0860 | 94 | 80.2089 | 148.9581 | 0.0000 | 0.1314 | 0.7774 |

Table 3.3.3.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of MAP and exclusion of VP dose category, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of MAP vs. VP dose category had little effect on subphenotype characterisation. VP dose category was chosen for reasons mentioned above.

Table 3.3.3.2 Cluster characteristics with use of MAP

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3521 | 0.3508 | 0.1498 | 0.1473 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0537 | 0.2675 | -0.8760 | 0.4547 | 0.0116 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.1927 | -0.1400 | 0.1116 | 0.6795 | 0.0002 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2566 | 0.0847 | 0.3774 | 0.0740 | 0.0068 |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5478 | 0.1316 | 1.3753 | -0.3973 | 0.0002 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1412 | 0.1281 | -1.1915 | 0.5621 | -0.0001 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.1845 | 0.1306 | -0.5348 | -0.2102 | -0.0001 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0637 | 0.0154 | 0.7197 | -0.6295 | -0.0026 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.4955 | 0.1873 | -1.0192 | 1.7498 | -0.0019 |
| **map** |  |  |  |  |  |
| **Mean** | 0.5284 | 0.3350 | -1.1349 | -0.9203 | -0.0018 |

Table 3.3.3.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, MAP = mean arterial pressure, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CVP = central venous pressure.

3.3.4 Septal dyskinesia vs RVLVEDA

When septal dyskinesia was included alongside RVLVEDA, the BVR amongst the two variables was 25. This led to exclusion of Septal dyskinesia. In sensitivity analyses, septal dyskinesia was included and RVLVEDA was excluded. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three-class model. However, the maximum bivariate residual was higher (31), which led to inclusion of RVLVEDA over septal dyskinesia.

Table 3.3.4.1 Septal dyskinesia inclusion and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -8731.2065 | 17576.0727 | 17496.4130 | 17513.4130 | 17 | 89.5103 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -8527.5637 | 17282.4468 | 17123.1275 | 17157.1275 | 34 | 53.2481 | 407.2855 | 0.0000 | 0.1024 | 0.5955 |
| 3-Cluster | -8353.6263 | 17048.2315 | 16809.2526 | 16860.2526 | 51 | 32.3328 | 347.8749 | 0.0000 | 0.1270 | 0.6709 |
| 4-Cluster | -8308.2698 | 17001.1781 | 16752.5396 | 16820.5396 | 68 | 31.3806 | 90.7130 | 0.0003 | 0.1998 | 0.6183 |
| 5-Cluster | -8224.8070 | 17017.9123 | 16619.6141 | 16704.6141 | 85 | 31.7064 | 166.9255 | 0.0000 | 0.1963 | 0.6720 |

Table 3.3.4.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of septal dyskinesia and exclusion of RVLVEDA, demonstrated that the classes were slightly similar to the original model. Cluster 3 is likely the same as previous, with low RVFAC, TAPSE and CI and high VP dose requirements. Cluster 4 is likely the same as previous, with high CI high HR, and small IVC diameter. Cluster 1 and 2 are slightly different to previous ones. Cluster 2 is defined by high TAPSE, normal CI, dilated IVC, high LVEDA. Cluster 1 was defined by low HR, low CVP, and mildly low CI. It is unclear why these new clusters were formed. This could be because RVLVEDA is likely crucial to cluster development. Septal dyskinesia presence is binary and therefore unlikely to provide much information to cluster development. RVLVEDA was therefore included over septal dyskinesia.

Table 3.3.4.2 Cluster characteristics with use of septal dyskinesia

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.4207 | 0.2285 | 0.2072 | 0.1436 |  |
| **Indicators** |  |  |  |  |  |
| **tapse** |  |  |  |  |  |
| **Mean** | 0.0012 | 0.3182 | 0.4148 | -1.0355 | 0.0099 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.4603 | 0.8092 | 0.0200 | 0.0271 | -0.0004 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.2495 | -0.0701 | 0.2165 | 0.5633 | 0.0050 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1670 | 0.4508 | 0.0211 | -1.2343 | -0.0002 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.1720 | -0.3806 | 0.3963 | -0.4673 | -0.0001 |
| **ivc** |  |  |  |  |  |
| **Mean** | -0.0016 | -0.7415 | 0.2253 | 0.8452 | -0.0019 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.4014 | 1.1069 | 0.2587 | -0.9623 | -0.0007 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.5138 | 0.2754 | 0.3822 | 0.1925 | 0.3858 |
| **2** | 0.2950 | 0.3158 | 0.3183 | 0.2954 | 0.3046 |
| **3** | 0.1912 | 0.4089 | 0.2994 | 0.5121 | 0.3096 |
| **Mean** | 1.6774 | 2.1335 | 1.9172 | 2.3196 | 1.9238 |
| **Septal dyskinesia** |  |  |  |  |  |
| **0** | 0.9573 | 0.9994 | 0.9035 | 0.7788 | 0.9301 |
| **1** | 0.0427 | 0.0006 | 0.0965 | 0.2212 | 0.0699 |
| **Mean** | 0.0427 | 0.0006 | 0.0965 | 0.2212 | 0.0699 |
|  |  |  |  |  |  |

Table 3.3.4.2 Legend: LVEDA = left ventricular end-diastolic area, LVEF = left ventricular ejection fraction, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CVP = central venous pressure. HR = heart rate.VP cat = vasopressor category.CI = cardiac index.

* 1. Exclusion of additional patient cohorts

3.4.1 Exclusion of spontaneously ventilating patients

Patients that were spontaneously ventilating on CPAP at the time of TTE may have influenced subphenotype characterization. Therefore repeat LCA was performed after exclusion of spontaneously ventilating patients. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three-class model.

Table 3.4.1.1 Exclusion of spontaneously ventilating patients and effect on fit statistics

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **Max. BVR** | **VLMR p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -8376.0372 | 16869.7610 | 16788.0745 | 108.1854 |  | 0.0000 | 1.0000 |
| 2-Cluster | -8023.1707 | 16281.7143 | 16118.3413 | 51.7747 | 0.0000 | 0.0401 | 0.7791 |
| 3-Cluster | -7842.2276 | 16037.5147 | 15792.4552 | 18.1320 | 0.0000 | 0.1149 | 0.7219 |
| 4-Cluster | -7736.8385 | 15944.4230 | 15617.6769 | 12.4590 | 0.0000 | 0.1381 | 0.7233 |
| 5-Cluster | -7701.8121 | 15992.0569 | 15583.6243 | 7.0958 | 0.0015 | 0.1748 | 0.7085 |

Table 3.4.1.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through exclusion of spontaneously ventilating patients, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of spontaneously ventilating patients had little effect on subphenotype characterisation.

Table 3.4.1.2 Cluster characteristics with exclusion of spontaneously ventilating patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3583 | 0.2834 | 0.2360 | 0.1236 |  |
| **Indicators** |  |  |  |  |  |
| **RVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5747 | 0.4115 | -0.4591 | 1.7012 | 0.0116 |
| **rvfac** |  |  |  |  |  |
| **Mean** | 0.1595 | 0.0108 | 0.5162 | -1.4243 | 0.0065 |
| **tapse** |  |  |  |  |  |
| **Mean** | -0.0334 | 0.2796 | 0.2926 | -1.0796 | 0.0032 |
| **lvedai** |  |  |  |  |  |
| **Mean** | 0.3107 | 0.1477 | -0.3152 | -0.5932 | 0.0060 |
| **ci** |  |  |  |  |  |
| **Mean** | -0.4606 | 0.1155 | 1.1578 | -0.9748 | 0.0203 |
| **ivc** |  |  |  |  |  |
| **Mean** | 0.0247 | 0.1823 | -0.7282 | 0.8884 | -0.0018 |
| **HR** |  |  |  |  |  |
| **Mean** | -0.4268 | -0.0934 | 0.7523 | 0.1406 | 0.0150 |
| **cvp** |  |  |  |  |  |
| **Mean** | -0.1308 | 0.1774 | 0.0123 | 0.4961 | 0.0673 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.3944 | 0.4096 | 0.1923 | 0.1403 | 0.3198 |
| **2** | 0.3432 | 0.3410 | 0.3250 | 0.2992 | 0.3329 |
| **3** | 0.2624 | 0.2494 | 0.4828 | 0.5605 | 0.3473 |
| **Mean** | 1.8680 | 1.8399 | 2.2905 | 2.4202 | 2.0275 |

Table 3.4.1.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CVP = central venous pressure, VP cat = vasopressor category, CVP = central venous pressure, HR = heart rate

3.4.2 Exclusion of patients with liver disease

Patients that had history of liver disease at the time of TTE may have influenced subphenotype characterization. This is because cluster 2 of the LCA was characterized by a high cardiac output state, with hyperdynamic LVEF, high lactate, low platelets, increased white blood cell count and increased incidence of patients with history of liver disease (25%). It could be that a high prevalence of liver disease in our single-centre ICU population, which is associated with a high cardiac output state, influenced the identification of cluster 4 that otherwise would not exist in ARDS patients without liver disease. Therefore repeat LCA was performed after exclusion of patients with liver disease. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three-class model.

Table 3.4.2.1 Exclusion of patients with liver disease and effect on fit statistics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **AIC3(LL)** | **Npar** | **Max. BVR** | **VLMR** | **p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -8203.1359 | 16523.6959 | 16442.2718 | 16460.2718 | 18 | 87.6877 |  |  | 0.0000 | 1.0000 |
| 2-Cluster | -7856.5976 | 15948.0435 | 15785.1953 | 15821.1953 | 36 | 45.1389 | 693.0765 | 0.0000 | 0.0439 | 0.7699 |
| 3-Cluster | -7652.8265 | 15657.9254 | 15413.6530 | 15467.6530 | 54 | 14.8932 | 407.5423 | 0.0000 | 0.1074 | 0.7345 |
| 4-Cluster | -7558.2711 | 15586.2388 | 15260.5423 | 15332.5423 | 72 | 10.5048 | 189.1107 | 0.0000 | 0.1296 | 0.7270 |
| 5-Cluster | -7514.9941 | 15617.1089 | 15209.9883 | 15299.9883 | 90 | 8.7220 | 86.5540 | 0.0000 | 0.1608 | 0.7248 |

Table 3.4.2.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through exclusion of patients with liver disease, demonstrated that the classes were highly similar to the original model. The hyperdynamic subtype, Class 4 (denoted as cluster 3 here) had a similar prevalence and similar characteristics (high cardiac index, heart rate, vasopressor requirements). This indicates that the cluster was not driven by the presence of liver disease and exists in ARDS cohorts without liver disease. Therefore the inclusion of patients with liver disease had little effect on subphenotype characterisation.

Table 3.4.2.2 Cluster characteristics with exclusion of patients with liver disease

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.4270 | 0.2559 | 0.1848 | 0.1323 |  |
| **Indicators** |  |  |  |  |  |
| **VPcat** |  |  |  |  |  |
| **1** | 0.4767 | 0.4964 | 0.2708 | 0.2197 | 0.4097 |
| **2** | 0.3045 | 0.2999 | 0.3156 | 0.3048 | 0.3054 |
| **3** | 0.2187 | 0.2037 | 0.4136 | 0.4755 | 0.2849 |
| **Mean** | 0.3710 | 0.3536 | 0.5714 | 0.6279 | 0.4376 |
| **ZRVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5498 | 0.4360 | -0.4725 | 1.5969 | 0.0004 |
| **ZRVFAC** |  |  |  |  |  |
| **Mean** | 0.1057 | 0.0902 | 0.6068 | -1.3638 | -0.0002 |
| **ZTAPSE** |  |  |  |  |  |
| **Mean** | -0.0050 | 0.3459 | 0.3571 | -1.0566 | 0.0123 |
| **ZLVEDA** |  |  |  |  |  |
| **Mean** | 0.2716 | 0.1349 | -0.3920 | -0.5920 | -0.0002 |
| **ZCI** |  |  |  |  |  |
| **Mean** | -0.3684 | 0.1916 | 1.2484 | -0.9398 | -0.0023 |
| **ZIVC** |  |  |  |  |  |
| **Mean** | -0.0164 | 0.2106 | -0.8124 | 0.7877 | 0.0010 |
| **ZHR** |  |  |  |  |  |
| **Mean** | -0.3539 | -0.0569 | 0.8050 | 0.1304 | 0.0001 |
| **ZCVP** |  |  |  |  |  |
| **Mean** | -0.1696 | 0.0953 | -0.0390 | 0.4876 | 0.0092 |

Table 3.4.2.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CVP = central venous pressure, VP cat = vasopressor category, CVP = central venous pressure, HR = heart rate

* + 1. Exclusion of patients with ischaemic heart disease

Patients that had history of ischaemic disease at the time of TTE may have influenced subphenotype characterization. This is because these patients may have had a higher incidence of undiagnosied LV or RV dysfunction. Therefore repeat LCA was performed after exclusion of patients with ischaemic heart disease disease. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three-class model.

Table 3.4.3.1 Exclusion of patients with ischaemic disease and effect on fit statistics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **Max. BVR** | **VLMR p-value** | **Entropy R²** |
| 1-Cluster | -8270.1547 | 16657.8652 | 16576.3094 | 112.8508 |  | 1.0000 |
| 2-Cluster | -7926.7459 | 16088.6035 | 15925.4919 | 51.6201 | <0.0001 | 0.8229 |
| 3-Cluster | -7777.6991 | 15908.0656 | 15663.3982 | 8.9523 | <0.0001 | 0.7153 |
| 4-Cluster | -7703.6671 | 15807.5575 | 15551.3343 | 9.9313 | <0.0001 | 0.7008 |
| 5-Cluster | -7671.7721 | 15931.3233 | 15523.5443 | 8.2118 | 0.0020 | 0.7167 |

Table 3.4.3.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through exclusion of patients with ischaemic disease, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of patients with ischaemic heart disease had little effect on subphenotype characterisation.

Table 3.4.3.2 Cluster characteristics with exclusion of patients with ischaemic heart disease

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3727 | 0.2563 | 0.2535 | 0.1175 |  |
| **Indicators** |  |  |  |  |  |
| **ZRVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5793 | -0.4147 | 0.5242 | 1.6147 | 0.0004 |
| **ZRVFAC** |  |  |  |  |  |
| **Mean** | 0.1949 | 0.4382 | -0.0065 | -1.5627 | -0.0003 |
| **ZCI** |  |  |  |  |  |
| **Mean** | -0.3538 | 1.0816 | -0.0166 | -1.2181 | -0.0021 |
| **ZTAPSE** |  |  |  |  |  |
| **Mean** | 0.0026 | 0.2768 | 0.3017 | -1.1757 | 0.0102 |
| **ZLVEDAi** |  |  |  |  |  |
| **Mean** | 0.2585 | -0.2222 | 0.1077 | -0.5689 | -0.0002 |
| **ZMIVC** |  |  |  |  |  |
| **Mean** | 0.0313 | -0.7377 | 0.2863 | 0.8746 | -0.0020 |
| **Zheartrate** |  |  |  |  |  |
| **Mean** | -0.3467 | 0.7168 | -0.2829 | 0.1462 | -0.0000 |
| **Vpcat** |  |  |  |  |  |
| **1** | 0.4805 | 0.2587 | 0.4549 | 0.1931 | 0.3834 |
| **2** | 0.2940 | 0.3013 | 0.2989 | 0.2838 | 0.2959 |
| **3** | 0.2255 | 0.4400 | 0.2462 | 0.5230 | 0.3207 |
| **Mean** | 1.7451 | 2.1813 | 1.7913 | 2.3299 | 1.9373 |
| **ZCVP1\_A** |  |  |  |  |  |
| **Mean** | -0.2387 | 0.0211 | 0.0865 | 0.6310 | 0.0125 |

Table 3.4.3.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CVP = central venous pressure, VP cat = vasopressor category, CVP = central venous pressure, HR = heart rate

* + 1. Exclusion of patients with chronic respiratory conditions

Patients that had history of chronic respiratory conditions at the time of TTE may have influenced subphenotype characterization. This is because these patients may have had a higher incidence of undiagnosied LV or RV dysfunction. Therefore repeat LCA was performed after exclusion of patients with chronic respiratory disease disease. Again, this had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three-class model.

Table 3.4.4.1 Exclusion of patients with chronic respiratory disease and effect on fit statistics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **Max. BVR** | **VLMR p-value** | **Entropy R²** |
| 1-Cluster | -7228.9563 | 14561.9572 | 14489.9125 | 98.7860 |  | 1.0000 |
| 2-Cluster | -6925.9222 | 14059.9336 | 13915.8443 | 50.2304 | <0.0001 | 0.8271 |
| 3-Cluster | -6779.0435 | 13870.2208 | 13654.0869 | 11.5905 | <0.0001 | 0.7161 |
| 4-Cluster | -6719.8836 | 13855.9457 | 13567.7672 | 7.2808 | <0.0001 | 0.6999 |
| 5-Cluster | -6691.0246 | 13902.2723 | 13542.0491 | 5.5980 | 0.0228 | 0.7142 |

Table 3.4.4.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through exclusion of patients with chronic respiratory disease, demonstrated that the classes were highly similar to the original model. Therefore the inclusion of patients with chronic respiratory disease had little effect on subphenotype characterisation.

Table 3.4.4.2 Cluster characteristics with exclusion of patients with chronic respiratory disease

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3663 | 0.2585 | 0.2505 | 0.1247 |  |
| **Indicators** |  |  |  |  |  |
| **ZRVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5646 | 0.5131 | -0.4753 | 1.5524 | 0.0004 |
| **ZRVFAC** |  |  |  |  |  |
| **Mean** | 0.1269 | 0.1073 | 0.4449 | -1.4913 | -0.0003 |
| **ZCI** |  |  |  |  |  |
| **Mean** | -0.4431 | 0.1587 | 1.0420 | -1.1204 | 0.0001 |
| **ZTAPSE** |  |  |  |  |  |
| **Mean** | -0.0376 | 0.3988 | 0.2912 | -1.1913 | 0.0137 |
| **ZLVEDAi** |  |  |  |  |  |
| **Mean** | 0.2901 | 0.1077 | -0.2673 | -0.5394 | -0.0002 |
| **ZMIVC** |  |  |  |  |  |
| **Mean** | 0.1075 | 0.1317 | -0.7442 | 0.8886 | -0.0022 |
| **Zheartrate** |  |  |  |  |  |
| **Mean** | -0.4284 | -0.1429 | 0.7347 | 0.0773 | -0.0001 |
| **Vpcat** |  |  |  |  |  |
| **1** | 0.4433 | 0.4570 | 0.2517 | 0.1668 | 0.3643 |
| **2** | 0.3067 | 0.3043 | 0.3071 | 0.2799 | 0.3028 |
| **3** | 0.2500 | 0.2387 | 0.4413 | 0.5533 | 0.3328 |
| **Mean** | 1.8068 | 1.7817 | 2.1896 | 2.3865 | 1.9685 |

Table 3.4.4.2 Legend: RV:LVEDA = right:left ventricular end-diastolic area, LVEDA = left ventricular end-diastolic area, CI = cardiac index, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, CVP = central venous pressure, VP cat = vasopressor category, CVP = central venous pressure, HR = heart rate

1. **Reasons for choosing 4 cluster model**

4.1 Rejection of three cluster model

BIC decreased from classes 1 – 4, but increased when class 5 was added. AIC decreased sequentially, however the rate of decrease was less with the addition of class 5. Compared to the three-class model, the four-class model had an improved model fit (VLMR = p<0.0001) and equivalent entropy indicating good class separation and was therefore judged to be the best fit for the population. Furthermore, cluster 3 of the three-class model outlined below has characteristics consistent with the cluster 3 of the four-class model (RV failure: with high RVLVEDA, low RVFAC, low CI and high IVC and CVP). However, cluster 1 and 2 in the three-cluster model make less pathophysiological sense. Cluster 2 in the three-cluster model is characterized by low RVLVEDA, but low CI, low HR, and low CVP. Its closest corresponding cluster in the four-cluster model is cluster 1 (normal LV / RV function). Cluster 1 in the three-cluster model is characterized by normal RVLVEDA, high RVFAC, high CI, high HR and relatively high VP requirements and most closely resembles Cluster 4 of the four-cluster cohort. The RV dysfunction subphenotype subphenotype (cluster 2) in the four-cluster model does not exist in this three-cluster model.

Table 4.1.1 Characteristics of the three-cluster model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Overall** |
| **Cluster Size** | 0.4195 | 0.4057 | 0.1748 |  |
| **Indicators** |  |  |  |  |
| **RVLVEDA** |  |  |  |  |
| **Mean** | -0.0826 | -0.5249 | 1.4258 | 0.0003 |
| **rvfac** |  |  |  |  |
| **Mean** | 0.3342 | 0.1326 | -1.1163 | -0.0003 |
| **tapse** |  |  |  |  |
| **Mean** | 0.3921 | -0.0440 | -0.7929 | 0.0086 |
| **lvedai** |  |  |  |  |
| **Mean** | -0.0961 | 0.2883 | -0.4417 | -0.0001 |
| **ci** |  |  |  |  |
| **Mean** | 0.7167 | -0.4053 | -0.7929 | -0.0020 |
| **ivc** |  |  |  |  |
| **Mean** | -0.3825 | 0.0288 | 0.8313 | -0.0040 |
| **HR** |  |  |  |  |
| **Mean** | 0.3830 | -0.3710 | -0.0588 | -0.0003 |
| **cvp** |  |  |  |  |
| **Mean** | 0.0611 | -0.2107 | 0.3985 | 0.0094 |
| **vpcat** |  |  |  |  |
| **1** | 0.3499 | 0.4829 | 0.2457 | 0.3858 |
| **2** | 0.3128 | 0.2969 | 0.3031 | 0.3046 |
| **3** | 0.3374 | 0.2203 | 0.4512 | 0.3096 |
| **Mean** | 1.9875 | 1.7374 | 2.2056 | 1.9238 |

* 1. Rejection of five cluster model

Whilst the VLMR test demonstrated an improved model fit with the addition of a fifth class (p<0.0001) the increase in BIC and decreased reduction in AIC with the addition of a fourth class resulted in rejection of this model.

Table 4.2.1: Cluster characteristics of five cluster model

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Cluster5** | **Overall** |
| **Cluster Size** | 0.2772 | 0.2584 | 0.2197 | 0.1261 | 0.1186 |  |
| **Indicators** |  |  |  |  |  |  |
| **RVLVEDA** |  |  |  |  |  |  |
| **Mean** | -0.6494 | 0.4811 | -0.4914 | 1.5991 | -0.3224 | 0.0002 |
| **rvfac** |  |  |  |  |  |  |
| **Mean** | 0.1400 | 0.0661 | 0.4901 | -1.3897 | 0.0953 | -0.0001 |
| **tapse** |  |  |  |  |  |  |
| **Mean** | -0.1027 | 0.3224 | 0.3111 | -1.0170 | 0.1233 | 0.0100 |
| **lvedai** |  |  |  |  |  |  |
| **Mean** | 0.3931 | 0.1365 | -0.2795 | -0.5564 | -0.1060 | -0.0001 |
| **ci** |  |  |  |  |  |  |
| **Mean** | -0.5190 | 0.1090 | 1.1758 | -0.9738 | -0.1911 | -0.0018 |
| **ivc** |  |  |  |  |  |  |
| **Mean** | 0.1083 | 0.2122 | -0.7364 | 0.8633 | -0.2691 | -0.0002 |
| **HR** |  |  |  |  |  |  |
| **Mean** | -0.5162 | -0.1478 | 0.7708 | 0.0810 | 0.0091 | -0.0001 |
| **cvp** |  |  |  |  |  |  |
| **Mean** | -0.0264 | 0.1341 | 0.0242 | 0.4747 | -0.6958 | 0.0102 |
| **vpcat** |  |  |  |  |  |  |
| **1** | 0.4304 | 0.4523 | 0.2488 | 0.2062 | 0.5818 | 0.3858 |
| **2** | 0.3122 | 0.3085 | 0.3106 | 0.2995 | 0.2728 | 0.3046 |
| **3** | 0.2574 | 0.2392 | 0.4406 | 0.4943 | 0.1454 | 0.3096 |
| **Mean** | 1.8270 | 1.7869 | 2.1917 | 2.2881 | 1.5635 | 1.9238 |

Table 4.2.1 Legend: RVESA = right end-systolic area, LVEDA = left ventricular end-diastolic area, LVEF = left ventricular ejection fraction, vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, LVEID = left ventricular eccentricity index in diastole.

* 1. Rejection of the 2-cluster model

BIC decreased from classes 1 – 4, but increased when class 5 was added. AIC decreased sequentially, however the rate of decrease was less with the addition of class 5. Compared to the two-class model, the three-class model had an improved model fit (VLMR = p<0.0001) and a considerably lower BIC. The two-class model could therefore be rejected on the basis of the fit statistics. Furthermore, with the two-class model there is considerable loss of information. The two clusters correspond to normal (cluster 1) and abnormal (cluster 2) cardiovascular function, the latter being dictated solely by dilated RV size and systolic function (high RV:LVEDA, low RVFAC, low CI). This is overly simplistic and provides poor insight into the complex haemodynamics present in ARDS.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Overall** |
| **Cluster Size** | 0.8056 | 0.1944 |  |
| **Indicators** |  |  |  |
| **ZRVLVEDA** |  |  |  |
| **Mean** | -0.3278 | 1.3618 | 0.0006 |
| **ZZZrvfac** |  |  |  |
| **Mean** | 0.2413 | -1.0025 | -0.0005 |
| **ZZZtapse** |  |  |  |
| **Mean** | 0.1787 | -0.7095 | 0.0060 |
| **ZZZlvedai** |  |  |  |
| **Mean** | 0.1087 | -0.4516 | -0.0002 |
| **ZZZci** |  |  |  |
| **Mean** | 0.1711 | -0.7060 | 0.0005 |
| **ZZZmivc** |  |  |  |
| **Mean** | -0.1904 | 0.7648 | -0.0047 |
| **ZZZHR** |  |  |  |
| **Mean** | 0.0093 | -0.0388 | -0.0001 |
| **ZZZcvp** |  |  |  |
| **Mean** | -0.0776 | 0.3605 | 0.0076 |
| **vpcat** |  |  |  |
| **1** | 0.4186 | 0.2499 | 0.3858 |
| **2** | 0.3055 | 0.3011 | 0.3046 |
| **3** | 0.2760 | 0.4491 | 0.3096 |
| **Mean** | 1.8574 | 2.1992 | 1.9238 |

1. **Derivation and validation cohorts**

In latent class analysis methodology, it is often recommended to perform clustering analyses in derivation cohorts and subsequently validating the findings in external validation cohorts (Sinha et al, 2021, Critical Care Medicine). We were unable to identify an appropriate external validation cohort to confirm the findings of this study. The findings therefore require prospective validation in multicenter cohorts.

We performed the LCA in a derivation and validation cohort by splitting our cohort of patients from date of admission to the ICU: derivation cohort before 1st January 2020 (n=471) and validation cohort after 1st January 2020 (n=330). The fit statistics for both cohorts favour selection of 4-class models. Furthermore, the 4-classes generated by the derivation and validation cohorts closely resemble the 4-classes generated in the overall cohort.

Whilst we do not have an external validation cohort for ARDS, we have conducted LCA in patients with COVID-19 ARDS and identified 3 subphenotypes that closely resemble the first 3 classes of the 4-class model presented here. Although a different disease process, both cohorts of patients met criteria for ARDS and the similarity of the subphenotypes between them increases the generalisability of the findings presented here.

Table 5.1 Derivation cohort fit statistics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **Max. BVR** | **VLMR p-value** | **Entropy R²** |
| 1-Cluster | -5615.9332 | 11342.6156 | 11267.8664 | 41.1983 |  | 1.0000 |
| 2-Cluster | -5494.3810 | 11210.2603 | 11060.7619 | 26.7933 | 0.0000 | 0.5469 |
| 3-Cluster | -5392.8270 | 11117.9016 | 10893.6540 | 7.9246 | 0.0000 | 0.6603 |
| 4-Cluster | -5338.3348 | 11019.6663 | 10820.6696 | 4.2962 | 0.0001 | 0.7010 |
| 5-Cluster | -5314.2337 | 11182.2134 | 10808.4675 | 4.6988 | 0.0057 | 0.7403 |

Table 5.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Table 5.2 Cluster characteristics of the four-cluster model in the derivation cohort

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3800 | 0.3318 | 0.1966 | 0.0916 |  |
| **Indicators** |  |  |  |  |  |
| **Vpcat** |  |  |  |  |  |
| **1** | 0.5317 | 0.5437 | 0.2351 | 0.2215 | 0.4489 |
| **2** | 0.2510 | 0.2483 | 0.2555 | 0.2521 | 0.2511 |
| **3** | 0.2174 | 0.2080 | 0.5094 | 0.5264 | 0.3000 |
| **Mean** | 1.6857 | 1.6643 | 2.2743 | 2.3048 | 1.8511 |
| **ZRVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5534 | 0.5163 | -0.5140 | 1.5343 | 0.0005 |
| **ZRVFAC** |  |  |  |  |  |
| **Mean** | 0.0589 | 0.0538 | 0.4319 | -1.3714 | -0.0004 |
| **ZTAPSE** |  |  |  |  |  |
| **Mean** | -0.1093 | 0.2459 | 0.3520 | -1.0768 | 0.0107 |
| **ZLVEDAi** |  |  |  |  |  |
| **Mean** | 0.2163 | 0.0267 | -0.2490 | -0.4620 | -0.0002 |
| **ZCI** |  |  |  |  |  |
| **Mean** | -0.5423 | 0.1067 | 1.3220 | -1.0185 | -0.0039 |
| **ZMIVC** |  |  |  |  |  |
| **Mean** | 0.1429 | 0.0963 | -0.8177 | 0.8004 | -0.0012 |
| **Zheartrate** |  |  |  |  |  |
| **Mean** | -0.3035 | -0.0970 | 0.7239 | 0.0560 | -0.0000 |
| **ZCVP** |  |  |  |  |  |
| **Mean** | -0.0631 | -0.0292 | 0.0004 | 0.3603 | -0.0006 |

Table 5.2 Legend: RVESA = right end-systolic area, LVEDA = left ventricular end-diastolic area, LVEF = left ventricular ejection fraction, vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, LVEID = left ventricular eccentricity index in diastole.

Table 5.3 Validation cohort fit statistics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **Max. BVR** | **p-value** | **Entropy R²** |
| 1-Cluster | -4032.8548 | 8170.1476 | 8101.7095 | 94.8079 |  | 1.0000 |
| 2-Cluster | -3876.8164 | 7762.5091 | 7725.6328 | 41.0164 | 0.0000 | 0.8748 |
| 3-Cluster | -3693.5368 | 7700.3879 | 7595.0735 | 10.7316 | 0.0000 | 0.7913 |
| 4-Cluster | -3652.8362 | 7623.4249 | 7449.6724 | 6.2582 | 0.0064 | 0.7735 |
| 5-Cluster | -3672.3828 | 7666.9564 | 7424.7657 | 6.6884 | 0.0092 | 0.8270 |

Table 5.4 Cluster characteristics of the four-cluster model of the validation cohort

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3399 | 0.3236 | 0.2284 | 0.1080 |  |
| **Indicators** |  |  |  |  |  |
| **ZRVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5750 | -0.2387 | 0.3572 | 1.7783 | 0.0010 |
| **ZRVFAC** |  |  |  |  |  |
| **Mean** | 0.3935 | 0.4194 | -0.3708 | -1.7193 | -0.0010 |
| **ZCI** |  |  |  |  |  |
| **Mean** | -0.1017 | 0.9505 | -0.6630 | -1.1320 | -0.0007 |
| **Zheartrate** |  |  |  |  |  |
| **Mean** | -0.3339 | 0.7753 | -0.7758 | 0.3686 | 0.0000 |
| **ZCVP1\_A** |  |  |  |  |  |
| **Mean** | -0.4669 | 0.0548 | 0.4635 | 0.6077 | 0.0305 |
| **ZTAPSE** |  |  |  |  |  |
| **Mean** | 0.2066 | 0.3860 | -0.1807 | -1.4213 | 0.0003 |
| **ZLVEDAi** |  |  |  |  |  |
| **Mean** | 0.3378 | -0.2312 | 0.1417 | -0.6729 | -0.0003 |
| **ZMIVC** |  |  |  |  |  |
| **Mean** | -0.2380 | -0.4700 | 0.4566 | 1.2290 | 0.0040 |
| **Vpcat** |  |  |  |  |  |
| **1** | 0.4110 | 0.2814 | 0.2162 | 0.1473 | 0.2961 |
| **2** | 0.3792 | 0.3917 | 0.3811 | 0.3511 | 0.3807 |
| **3** | 0.2098 | 0.3269 | 0.4027 | 0.5016 | 0.3233 |
| **Mean** | 1.7989 | 2.0454 | 2.1864 | 2.3543 | 2.0272 |

Table 5.4 Legend: RVESA = right end-systolic area, LVEDA = left ventricular end-diastolic area, LVEF = left ventricular ejection fraction, vasopressor dose category, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, LVEID = left ventricular eccentricity index in diastole.

1. **Logistic regression analysis for 3-variable models for each subphenotype**

We determined the three most important variables for each class on the basis of the greatest difference in the mean standardized values when compared to other classes. The diagnostic performance of the 3-variable model in identifying latent CV subphenotypes was evaluated using area under the receiver operating curve (AUROC) of a multivariate logistic regression analysis with the dependent variable being cluster allocation and the 3-variables as independent variables. The 3-variable models and their corresponding AUROC following multivariate logistic regression analysis are outlined in the table below. Using optimal cut offs for each of the parameters that elicited maximum balanced sensitivity and specificity, the diagnostic accuracy of the 3-variable models in identifying each subphenotype were then assessed.

Table 6.1 Area under the receiver operator curves following multivariate logistic regression analysis of 3-variable models

|  |  |  |
| --- | --- | --- |
| Class | 3-variable models | AUROC of MVLRA |
| Class 1 | RV:LVEDA, CI, HR | 0.95 (0.93 – 0.96) |
| Class 2 | RV:LVEDA, RVFAC, TAPSE | 0.83 (0.79 – 0.86) |
| Class 3 | RV:LVEDA, RVFAC, CI | 0.97 (0.94 – 0.99) |
| Class 4 | CI, HR, IVC | 0.99 (0.99 – 0.99) |

Table 6.1 Legend: RV:LVEDA = right:left ventricular end-diastolic area, CI = cardiac index, IVC = inferior vena cava diameter, TAPSE = tricuspid annular plane systolic excursion, HR = heart rate.

1. **Posterior probabilities for class assignment**

Median (interquartile range) for all four classes for posterior probabilities of class assignment.

|  |  |
| --- | --- |
| Class | Median IQR |
| 1 | 90.5 (79.2 – 96.5) |
| 2 | 91.8 (76.8 – 98.6) |
| 3 | 95.5 (80.4 – 99.6) |
| 4 | 96.4 (85.6 – 100) |

1. **Timing of TTE and effect on subhphenotype prevalence and mortality**

8.1 Latent class analysis of patients that received a TTE

To assess subphenotype stability across ICU admission, analysis of patients that received a 2nd TTE during the first 7 days of ARDS was performed. A small cohort of patients (n=44, ~6%) received a 2nd TTE during the first 7 days of ARDS. We included data from their 2nd TTE and excluded data from their 1st TTE and performed an LCA. This had little effect on fit statistics: the four-class model was deemed to have the best fit due to lowest BIC, improvement in VLMR compared to the three-class model.

Table 8.1.1 Inclusion of patients with a 2nd TTE and the effect on fit statistics

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LL** | **BIC(LL)** | **AIC(LL)** | **Max. BVR** | **VLMR p-value** | **Class.Err.** | **Entropy R²** |
| 1-Cluster | -9663.161 | 19446.6684 | 19362.3229 | 105.6107 |  | 0.0000 | 1.0000 |
| 2-Cluster | -9281.0803 | 18802.8517 | 18634.1607 | 54.0748 | 0.0000 | 0.0453 | 0.7593 |
| 3-Cluster | -9059.4786 | 18479.9937 | 18226.9572 | 17.2435 | 0.0001 | 0.1144 | 0.7232 |
| 4-Cluster | -8949.8549 | 18381.0917 | 18043.7098 | 10.6500 | 0.0001 | 0.1343 | 0.7230 |
| 5-Cluster | -8905.1809 | 18412.0893 | 17990.3618 | 7.0290 | 0.0001 | 0.1642 | 0.7214 |

Table 9.1.1 Legend: LL = likelihood ratio. BIC = Bayesian information criteria. AIC = akaike information criteria. MaxBVR = maximum bivariate residual. VLMR = Vuoung-Lo-Mendell-Rubin test p value

Analysis of class characteristics of the four-class model that was generated through inclusion of patients that received a 2nd TTE, demonstrated that the classes were highly similar to the original model.

Table 8.1.2 Cluster characteristics of four class model after including patients with a 2nd TTE

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cluster1** | **Cluster2** | **Cluster3** | **Cluster4** | **Overall** |
| **Cluster Size** | 0.3934 | 0.2607 | 0.2191 | 0.1268 |  |
| **Indicators** |  |  |  |  |  |
| **ZRVLVEDA** |  |  |  |  |  |
| **Mean** | -0.5565 | 0.4641 | -0.4729 | 1.5929 | 0.0003 |
| **ZZZrvfac** |  |  |  |  |  |
| **Mean** | 0.1431 | 0.0611 | 0.4763 | -1.3871 | 0.0008 |
| **ZZZtapse** |  |  |  |  |  |
| **Mean** | -0.0513 | 0.3430 | 0.3169 | -1.0165 | 0.0098 |
| **ZZZlvedai** |  |  |  |  |  |
| **Mean** | 0.2626 | 0.1158 | -0.2932 | -0.5473 | -0.0001 |
| **ZZZci** |  |  |  |  |  |
| **Mean** | -0.4222 | 0.1116 | 1.1822 | -0.9720 | -0.0012 |
| **ZZZmivc** |  |  |  |  |  |
| **Mean** | 0.0011 | 0.1900 | -0.7345 | 0.8676 | -0.0010 |
| **ZZZHR** |  |  |  |  |  |
| **Mean** | -0.3668 | -0.1405 | 0.7843 | 0.0715 | 0.0000 |
| **ZZZcvp** |  |  |  |  |  |
| **Mean** | -0.2168 | 0.1156 | 0.0169 | 0.4820 | 0.0097 |
| **vpcat** |  |  |  |  |  |
| **1** | 0.4741 | 0.4562 | 0.2470 | 0.2068 | 0.3858 |
| **2** | 0.3030 | 0.3066 | 0.3088 | 0.2982 | 0.3046 |
| **3** | 0.2229 | 0.2372 | 0.4442 | 0.4950 | 0.3096 |
| **Mean** | 1.7488 | 1.7810 | 2.1972 | 2.2882 | 1.9238 |

We then compared class assignment from 1st to 2nd TTE data. The majority of patients (n=38, 86.4%) were assigned to the same subphenotype class. However, given the marked selection bias involved in this analysis, we cannot comment on subphenotype stability for the majority of patients and this requires assessment in prospective studies.

Figure 8.1.1 Sankey plot of class assignment for patients from their first TTE (left) to their 2nd TTE on the right



8.2 Comparing subphenotype prevalence and associated mortality in early vs late TTE

We compared subphenotype prevalence in patients that had an early TTE (<72 hours) to patients that had a late TTE (>72 hours). There was no significant difference in subphenotype proportion when TTE was performed early vs late. There was also no significant difference in the associated mortality rates of the subphenotypes derived from early vs late TTE. This suggests that these cardiovascular subphenotypes are present in equal proportion both early on in ARDS, and at a later stage. Given that the TTE parameters and associated mortality rates of the subphenotypes are similar in both early and late ARDS, there is no evidence to suggest that their treatment implications would also differ.

Figure 8.2.1 Subphenotype proportion in TTEs performed before and after 72 hours after ARDS onset



Figure 8.2.1 Legend: TTE = transthoracic echocardiogram; ns = non-significant

Figure 8.2.2 90-day mortality associated with Subphenotypes when TTE was performed before or after 72 hours



Figure 8.2.2 Legend: TTE = transthoracic echocardiogram; ns = non-significant

Table 8.2.1 TTE characteristics of Subphenotypes before and after 72 hours after ARDS onset

|  |  |  |  |
| --- | --- | --- | --- |
|  | <72 hours | >72 hours | P value |
| **Class 1** |  |  |  |
| RV:LVEDA | 0.53 (0.48 – 0.57) | 0.53 (0.47 – 0.58) | 0.533 |
| RVFAC | 0.42 (0.36 – 0.47) | 0.41 (0.36 – 0.48) | 0.940 |
| TAPSE | 21 (19 – 23) | 20 (19 – 23) | 0.975 |
| LVEDAi | 17 (15 – 19) | 17 (15 – 20) | 0.092 |
| CI | 2.9 (2.5 – 3.4) | 3.0 (2.6 – 3.5) | 0.309 |
| IVC diameter | 1.8 (1.6 – 2.1) | 1.8 (1.5 – 2) | 0.175 |
| Heart rate | 80 (69 – 90) | 80 (70 – 90) | 0.281 |
| CVP | 9 (6 – 11) | 9 (4 – 11) | 0.987 |
| VP dose | 0.05 (0 – 0.14) | 0 (0 – 0.13) | 0.0052 |
| **Class 2** |  |  |  |
| RV:LVEDA | 0.73 (0.65 – 0.80) | 0.74 (0.66 – 0.83) | 0.322 |
| RVFAC | 0.39 (0.33 – 0.46) | 0.43 (0.34 – 0.49) | 0.054 |
| TAPSE | 23 (20 – 27) | 22 (19 – 24) | 0.177 |
| LVEDAi | 17 (14 – 19) | 17 (14 – 19) | 0.831 |
| CI | 3.6 (3.2 – 4.3) | 3.9 (3.2 – 4.5) | 0.211 |
| IVC diameter | 2 (1.5 – 2.2) | 2 (1.6 – 2.2) | 0.673 |
| Heart rate | 81 (70 – 95) | 83 (75 – 95) | 0.621 |
| CVP | 10 (8 – 12) | 9 (7 – 11) | 0.092 |
| VP dose | 0.09 (0 – 0.28) | 0.07 (0 – 0.25) | 0.091 |
| **Class 3** |  |  |  |
| RV:LVEDA | 0.53 (0.48 – 0.6) | 0.55 (0.47 – 0.58) | 0.525 |
| RVFAC | 0.45 (0.39 – 0.51) | 0.47 (0.37 – 0.55) | 0.365 |
| TAPSE | 22 (19 – 24) | 22 (20 – 26) | 0.268 |
| LVEDAi | 15 (12 – 17) | 15 (12 – 17) | 0.410 |
| CI | 5.2 (4.0 – 6.3) | 5.3 (4.3 – 6.4) | 0.232 |
| IVC diameter | 1.5 (1.4 – 1.8) | 1.4 (1.3 – 1.8) | 0.414 |
| Heart rate | 100 (90 – 112) | 100 (93 – 113) | 0.536 |
| CVP | 9 (7 – 13) | 10 (5 – 13) | 0.817 |
| VP dose | 0.20 (0.05 – 0.43) | 0.16 (0 – 0.45) | 0.098 |
| **Class 4** |  |  |  |
| RV:LVEDA | 0.93 (0.78 – 1.05) | 0.9 (0.74 – 1.14) | 0.903 |
| RVFAC | 0.22 (0.17 – 0.28) | 0.23 (0.16 – 0.27) | 0.673 |
| TAPSE | 16 (12 – 20) | 17 (13 – 21) | 0.359 |
| LVEDAi | 15 (13 – 17) | 14 (13 – 16) | 0.434 |
| CI | 2.0 (1.6 – 2.7) | 2 (1.5 – 2.5) | 0.557 |
| IVC diameter | 2.2 (2 – 2.5) | 2.2 (2 – 2.5) | 0.831 |
| Heart rate | 87 (75 – 102) | 89 (70 – 108) | 0.566 |
| CVP | 11 (7 – 15) | 12 (8 – 16) | 0.554 |
| VP dose | 0.2 (0.1 – 0.48) | 0.18 (0.08 – 0.47) | 0.106 |

Table 8.2.1 Legend: RV:LVEDA = right ventricular: left ventricular end-diastolic area; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular plane systolic excursion; LVEDAi = left ventricular end-diastolic area index; CI = cardiac index; IVC = inferior vena cava; CVP = central venous pressure; VP dose = vasopressor dose

1. **Multivariate logistic regression analysis**

Following univariate analysis, the following clinical variables were included in a multivariable logistic regression analysis: age, P/F ratio, lactate, temperature, platelet count, bilirubin, alkaline phosphatase (ALP), international normalized ration (INR), charlson comorbidity index, performance status, need for intubation and renal replacement therapy. Other than the OR presented for the RV dysfunction phenotypes, the following parameters also independently associated with mortality: age, RRT, P/F ratio, Lactate, bilirubin, intubation (Table 9.1).

Table 9.1 Other parameters associated with mortality after multivariate logistic regression analysis

|  |  |  |
| --- | --- | --- |
| **Non-CV parameters** | OR (95% CI) | P value |
| Age | 1.04 (1.03 – 1.05) | <0.001 |
| Renal replacement therapy | 1.72 (1.13 – 2.63) | 0.012 |
| P/F ratio | 0.96 (0.94 – 0.98) | <0.001 |
| Lactate | 1.23 (1.09 – 1.38) | <0.001 |
| Bilirubin | 1.01 (1.00 – 1.01) | <0.001 |
| Tracheal intubation | 1.91 (1.14 – 3.17) | 0.013 |