Additional file 1: supplementary materials

Contents

1. Formulas used
2. Figure S1: correlation plots
3. Stepwise description of discarded variables due to correlation
4. Missing data
5. Figure S2a: density plots of imputed variables. Figure S2b: strip plots of imputed variables
6. Table S1: main outcomes and transitions between complete case and imputation models
7. Figure S3a: profile plot of all recruitable subphenotypes
8. Figure S3b: profile plot of all non-recruitable subphenotypes
9. Figure S4: alluvial plot of patient flow in complete case and imputation models
10. Table S2: changes per lung region
11. Figure S5a: changes in in end-expiratory lung volumes before and after recruitment
12. Figure S5b: changes in lung weight before and after recruitment
13. Figure S6a: volumes in different aeration regions before and after recruitment
14. Figure S6b: weight in different aeration regions before and after recruitment
15. Table S3: LASSO regression results
16. Table S4: GLM results of nested variable models.
17. Table S5: AUROCs for variable subsets
   Figure S7: ROC curves for variable subsets
18. Table S6a: Fine and Gray regression results of subphenotype membership and duration of MV.
   Table S6b: Cox regression results of subphenotype membership and survival
19. Figure S8: Kaplan-Meier plot of survival.
20. Table S7. Goodness-of-fit tests.
   Figure S9: Shoenfeld plots for covariates used in survival analysis.
21. Figure S10: Cumulative incidence plot using only complete case analyses
22. Figure S11: Kaplan-Meier using only complete cases
23. Table S8a: Fine and Gray regression results of subphenotype membership and duration of MV using complete cases only.
   Table S8b: Cox regression results of subphenotype membership and survival using complete cases only.
24. References of supplementary materials
Formulas

**Ideal Body Weight**
- Male: $50 + (0.91 \times (\text{Height} - 152.4))$
- Female: $45.5 + (0.91 \times (\text{Height} - 152.4))$

**Mechanical Power**
$$Respiratory \ Rate \times Tidal \ Volume \times \frac{p_{\text{Max}}}{1000}$$

**$CO_2$ difference**
$$paCO_2 - etCO_2$$

**Ventilatory Ratio**
$$\frac{Respiratory \ Rate \times Tidal \ Volume \times (paCO_2 \times 7.50062)}{Weight \times 100 \times 37.5}$$

**Oxygenation index**
$$\frac{p_{Map} \times FiO_2 \times \frac{100}{paO_2}}{\text{lung volume}}$$

**Lung weight /volume/aeration**
$$\sum_{i=1}^{N-1} \left( d \cdot \frac{M_i + M_{i+1}}{2 \cdot t} \right) + \frac{M_1 + M_N}{2}$$

In which $N$ is the number of slices, $t$ is the slice thickness, $d$ is the distance between slices and $M_i$ is the lung mass in the $i_{th}$ slice.

**Lung weight**
$$\left( 1 - \frac{\text{mean CT number}}{1000} \right) \times \text{lung volume}$$

**End-expiratory lung volume**
$$\left( \frac{\text{mean CT number}}{1000} \right) \times \text{lung volume}$$

**Percentage recruitment**
$$\frac{M_{\text{non-aerated (before RM)}} - M_{\text{non-aerated (after RM)}}}{M_{\text{total (before RM)}}} \times 100\%$$

In which $M$ is as lung weight in grams and RM indicating recruitment manoeuvre.

**Data collection**

Clinical respiratory parameters: last values before transport to CT-scan (estimated maximum 30 minutes prior)

Blood gas results: values used in decision making for the recruitment manoeuvre (estimated maximum 3 hours prior)

Laboratory results: morning round (maximum 24 hours prior)
Figure S1. Correlation plots of all variables used in the latent class analysis (left) compared to all available variables before selecting (right). The size of the dots represents the p-value of the correlation (bigger dot equals lower p-value) and the colour represents the correlation coefficient (legend included). Spearman rank-order correlation coefficient was used for calculation. The stars plotted correspond with significance levels; * > 0.05, ** > 0.01, *** > 0.001.
Stepwise selection of variables

At each step, a single strongly correlated variable (correlation coefficient > 0.7, p-value < 0.05) was deleted followed by a recalculation of correlations. In a correlated pair/group, there was a preference for: variables that were clinically more relevant, variables that were used more in comparable literature, more compound variables.

1. Deleted arterial pH (correlation with: CO₂ difference, ventilatory ratio, paCO₂)
   Preference for other more used and/or more compound variables: CO₂ difference, ventilatory ratio, paCO₂
2. Deleted PaCO₂ (correlation with: CO₂ difference)
   Preference for other more used and more compound variable: CO₂ difference
3. Deleted etCO₂ (correlation with: CO₂ difference, poorly aerated lung mass)
   etCO₂ is used in another variable. Preference for other more used and more compound variable: CO₂ difference.
4. Deleted PaO₂ (correlation with: oxygenation index, PaO₂ / FiO₂)
   Preference for other more used and more compound variables: oxygenation index, PaO₂ / FiO₂
5. Deleted oxygenation index (correlation with: PaO₂ / FiO₂)
   Preference for other more used variable: PaO₂ / FiO₂
6. Deleted plateau pressure (correlation with: compliance, driving pressure, mechanical power)
   Preference for other more used and more compound variables: compliance, driving pressure, mechanical power
7. Deleted driving pressure (correlation with: compliance, mechanical power)
   Preference for other more used and more compound variables: compliance, mechanical power
8. Deleted peak airway pressure (correlation with: mechanical power, compliance, mean airway pressure)
   Preference for other more used and more compound variables: mechanical power, compliance, mean airway pressure
9. Deleted mean airway pressure (correlation with: mechanical power, compliance)
   Preference for other more used and more compound variables: mechanical power, compliance
10. Deleted minute volume (correlation with: poorly aerated lung volume, mechanical power, ventilatory ratio)
   Preference for other more used and more compound variables: mechanical power, ventilatory ratio
11. Deleted ventilatory ratio (correlation with: mechanical power, CO₂ difference)
   Preference for other more used and more compound variables: mechanical power, CO₂ difference
12. Deleted I/E ratio
    Homogenous variable, not well distributed, not used in comparable literature
13. Deleted hyper aerated lung volume (correlation with normally aerated lung volume)
    Although both important, hyper aerated lung volume is less reliable.
Missing data

As LCA requires complete datasets, missing data was imputed by fully conditional specification with predictive mean matching under the missing at random assumption\(^1,2\). Imputation was limited to the variables used in the LCA, other variables and outcomes were not imputed. Prediction of imputed variables was based only on variables used in the LCA. Five imputation models with a maximum of 50 iterations each were created. The quality of the imputation models was visually assessed using stripplots and density plots for each imputed variable\(^2,3\). The effects of imputation on latent class assignment were tested by calculating class transitions between complete case and imputation models. Outcomes and class characteristics were compared among complete case and imputation models.
Figure S2a. Density plots of variables in complete case dataset compared to imputed datasets. Complete case is plotted in black, colored lines are different imputation sets. Only imputed variables are included.

Figure S2b. Stripplots of imputed variables only. Complete case data is displayed with grey dots, imputed datapoints are colored.
**Table S1**: Main outcomes and transitions between complete case and imputation models. Data is displayed according to distribution.

| Class | N | Recruitability % | Duration of mechanical ventilation | Duration of ICU stay | Extubation success (%) | ICU mortality (%) | Transitions between classes, compared to model 1 |
|-------|---|------------------|-------------------------------|---------------------|-----------------------|------------------|-----------------------------------------------|
|       |   |                  | N                             | N                  | Percent              | Percent          |                                                   |
|       |   |                  | p                             | p                  | p                    | p               | 2      | 5      | 1      | 0      | 2      | 0      | 3      | 4      | 2      | 0      |
| 1     | 52 | 9.22             | 18.50                         | [9.75, 29.25]      | 24 (54.5)            | 19 (43.2)       | 2      | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      |
| 2     | 38 | 12.02            | 18.00                         | [13.00, 28.00]     | 13 (31.5)            | 22 (59.5)       | 5      | -      | -      | -      | -      | -      | -      | -      | -      | -      | -      |
| 1     | 62 | 8.95             | 18.00                         | [13.00, 28.00]     | 27 (52.9)            | 23 (45.1)       | 1      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 2     | 37 | 12.56            | 17.50                         | [10.00, 32.50]     | 12 (25.9)            | 20 (58.8)       | 1      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 1     | 61 | 9.11             | 19.00                         | [10.00, 31.00]     | 27 (54.0)            | 22 (44.0)       | 1      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 2     | 38 | 12.02            | 17.00                         | [12.50, 31.00]     | 12 (25.9)            | 21 (58.8)       | 2      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 1     | 60 | 9.22             | 19.00                         | [10.00, 31.00]     | 27 (54.0)            | 22 (44.0)       | 3      | 4      | 4      | -      | -      | -      | -      | -      | -      | -      | -      |
| 2     | 39 | 11.48            | 17.00                         | [12.50, 31.00]     | 12 (25.9)            | 21 (58.8)       | 3      | 4      | 4      | -      | -      | -      | -      | -      | -      | -      | -      |
| 1     | 63 | 14.61            | 17.00                         | [10.00, 31.00]     | 26 (51.0)            | 24 (47.1)       | 2      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 2     | 36 | 8.95             | 16.00                         | [10.00, 31.00]     | 12 (29.4)            | 19 (55.9)       | 2      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 1     | 60 | 15.50            | 20.00                         | [10.00, 31.00]     | 26 (51.0)            | 24 (47.1)       | 2      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
| 2     | 39 | 22.00            | 20.00                         | [10.00, 31.00]     | 12 (29.4)            | 19 (55.9)       | 2      | 0      | 0      | -      | -      | -      | -      | -      | -      | -      | -      |
**Figure S3a:** profile plot of all recruitable subphenotypes in complete case (CC) and imputation models (I1 – I5). Variables used in the LCA are displayed on the X-axis and their corresponding standardized mean difference (SMD) on the Y-axis.
Figure S3b: Profile plot of all non-recruitable subphenotypes in complete case (CC) and imputation models (I1 – I5). Variables used in the LCA are displayed on the X-axis and their corresponding standardized mean difference (SMD) on the Y-axis.
Figure S4. Alluvial plot of complete case (left) and imputation models (subsequent 5). Patient flow is coloured according to class membership in complete case analysis.
Table S2. Changes per lung region. All values displayed according to distribution.

|                      | Subphenotype 1 (n=62) | Subphenotype 2 (n=37) | Between subphenotypes p-value |
|----------------------|-----------------------|-----------------------|-----------------------------|
|                      | Before                | “Non-recruitable” After | p-value                     | Before                | “Recruitable” After | p-value        |
| PEEP                 | 10.00 [10.00, 10.00]  | 20.00 [20.00, 20.00]  | <0.001                      | 10.00 [10.00, 10.00]  | 20.00 [20.00, 20.00]  | <0.001        |
| Total lung volume    | 2843.10 [2175.11, 3736.62] | 3667.68 [2687.67, 4347.86] | 0.002                        | 2597.61 [2258.73, 3220.69] | 3272.79 [2653.50, 3917.91] | 0.004          |
| Total lung mass      | 1326.56 [1030.22, 1619.78] | 1360.51 [1086.23, 1614.42] | 0.640                        | 1613.68 [1429.67, 1884.76] | 1724.21 [1511.19, 1927.12] | 0.240          |
| Lung volume non-aerated | 259.36 [181.03, 406.27] | 140.72 [85.60, 227.96] | <0.001                      | 576.96 [392.14, 735.77] | 341.78 [234.89, 466.79] | <0.001        |
| Lung mass normal     | 439.04 [322.85, 612.25] | 674.27 [477.25, 780.09] | <0.001                      | 260.05 [161.19, 420.02] | 444.24 [301.73, 693.93] | 0.001          |
| Percentage volume non-aerated | 11.29 [6.09, 15.17] | 3.65 [2.46, 6.53] | <0.001                      | 22.96 [14.11, 30.96] | 9.05 [6.96, 13.91] | <0.001        |
| Change %             | -4.09 [-7.78, -1.65] |                        |                             | -8.12 [-12.31, -3.75] |                        | 0.002          |
| Percentage volume poorly aerated | 26.40 [19.42, 35.25] | 20.63 [13.47, 28.64] | <0.001                      | 35.19 [30.06, 51.63] | 38.04 [28.95, 51.69] | 0.698          |
| Change %             | -1.85 [-5.82, 0.62] |                        |                             | 6.47 [1.01, 12.50] |                        | <0.001         |
| Percentage volume normally aerated | 56.01 [45.89, 65.36] | 66.71 [58.81, 76.27] | <0.001                      | 35.42 [19.51, 45.36] | 46.88 [36.21, 58.85] | <0.001        |
| Change %             | 24.10 [14.80, 43.24] |                        |                             | 22.83 [12.35, 31.00] |                        | 0.360          |
| Percentage volume hyper aerated | 1.31 [0.20, 3.91] | 2.97 [0.69, 6.81] | <0.001                      | 0.16 [0.03, 0.80] | 0.62 [0.20, 1.64] | <0.001        |
| Change %             | 1.09 [0.37, 3.81] |                        |                             | 0.27 [0.15, 1.32] |                        | 0.009          |
| Percentage mass non-aerated | 22.21 [14.69, 30.24] | 10.01 [6.46, 15.30] | <0.001                      | 35.81 [24.88, 43.74] | 17.53 [13.94, 25.33] | <0.001        |
| Change %             | -8.95 [-14.25, -3.68] |                        |                             | -12.56 [-18.17, -6.72] |                        | 0.024          |
| Percentage mass poorly aerated | 38.56 [31.40, 45.99] | 33.37 [26.32, 41.86] | <0.001                      | 43.47 [30.83, 54.68] | 47.43 [36.47, 57.94] | 0.017          |
| Change %             | -3.38 [-8.60, 0.90] |                        |                             | 6.09 [0.97, 10.75] |                        | <0.001         |
| Percentage mass normally aerated | 33.17 [27.19, 44.76] | 50.28 [39.79, 60.81] | <0.001                      | 15.01 [11.38, 24.07] | 27.22 [18.88, 39.03] | <0.001        |
| Change %             | 13.53 [7.44, 22.81] |                        |                             | 11.56 [6.45, 16.93] |                        | 0.231          |
| Percentage mass hyper aerated | 0.21 [0.03, 0.76] | 0.59 [0.15, 1.62] | <0.001                      | 0.02 [0.00, 0.12] | 0.06 [0.02, 0.28] | <0.001        |
| Change %             | 0.18 [0.06, 0.66] |                        |                             | 0.03 [0.01, 0.22] |                        | 0.002          |
**Figure S5a.** Changes in end-expiratory lung volumes before and after the recruitment manoeuvre. Data is stratified per lung aeration category and per subphenotype. Lung regions were classified according to Hounsfield Units (HU) with normally aerated ranging from −900 to −501 HU, poorly aerated from −500 to −101 HU, non-aerated from −100 to 100 HU and hyper-inflated from -1000 to -901 HU.
Figure S5b. Changes in lung weight before and after the recruitment manoeuvre. Data is stratified per lung aeration category and per subphenotype. Lung regions were classified according to Hounsfield Units (HU) with normally aerated ranging from −900 to −501 HU, poorly aerated from −500 to −101 HU, non-aerated from −100 to 100 HU and hyper-inflated from -1000 to -901 HU.
**Figure S6a.** End-expiratory lung volume (in mL) of different aeration regions displayed before and after the recruitment manoeuvre. Corresponding patient data points are connected by a line. Data is stratified and coloured by subphenotype. The p-values before and after recruitment (bottom p-values) compare relative amounts (mL / total mL) by the recruitment manoeuvre and are derived by Wilcoxon signed-rank tests. The p-values between subphenotypes (upper p-values) compare the changes in relative amounts by the recruitment manoeuvre (change in mL / total mL) between subphenotypes and are derived by Mann-Whitney U tests (table S2).
**Figure S6b.** Mass (in grams) of different aeration regions displayed before and after the recruitment manoeuvre. Corresponding patient data points are connected by a line. Data is stratified and coloured by subphenotype. The p-values before and after recruitment (bottom p-values) compare relative amounts (grams / total grams) by the recruitment manoeuvre and are derived by Wilcoxon signed-rank tests. The p-values between subphenotypes (upper p-values) compare the changes in relative amounts by the recruitment manoeuvre (change in grams / total grams) between subphenotypes and are derived by Mann-Whitney U tests (table S2).
Subphenotype identification using variable subsets and standard ICU severity scores.

**Table S3.** LASSO coefficient estimates, with the lambda parameter tuned in order to arrive at 4 variables.

| Prediction model considering all variables | S0 |
|-------------------------------------------|----|
| Intercept                   | 0.5655465 |
| CRP                        | - |
| D-Dimer                    | - |
| HCO3-                      | - |
| Clinical PEEP              | - |
| Compliance                 | - |
| TV / IBW                   | - |
| PaO2 / FiO2                | 0.2533840 |
| CO2 difference             | - |
| Non-aerated lung mass      | -0.2732269 |
| Poorly aerated lung mass   | -0.3070397 |
| Normally aerated lung volume | 0.0665896 |
| Prediction model without CT-derived parameters | S0 |
| Intercept                   | 0.63997659 |
| CRP                        | -0.02684768 |
| D-Dimer                    | - |
| HCO3-                      | - |
| Clinical PEEP              | - |
| Compliance                 | 0.10852415 |
| TV / IBW                   | - |
| PaO2 / FiO2                | 0.71079442 |
| CO2 difference             | - |
| Mechanical Power           | -0.60568786 |
| Intercept                   | 0.63997659 |
| CRP                        | -0.02684768 |
| D-Dimer                    | - |
Table S4. GLM results (validated with 5-fold cross validation) of selected variable models in terms of subphenotype prediction.

| Prediction model (n=4) considering all variables | Estimate  | St. Error | Z-value | P-value |
|-------------------------------------------------|-----------|-----------|---------|---------|
| Intercept                                       | 1.3157    | 0.4071    | 3.232   | 0.00123* |
| Non-aerated lung mass                          | -1.4833   | 0.5438    | -2.728  | 0.00638* |
| Mechanical power                                | -1.7986   | 0.4963    | -3.240  | 0.00029* |
| PaO\textsubscript{2} / FiO\textsubscript{2}     | 1.1801    | 0.4312    | 2.737   | 0.00620* |
| Normally aerated lung volume                    | 1.0497    | 0.3922    | 2.677   | 0.00744* |

| Prediction model (n=4) considering all variables excluding CT-derived parameters | Estimate  | St. Error | Z-value | P-value |
|---------------------------------------------------------------------------------|-----------|-----------|---------|---------|
| Intercept                                                                       | 1.1848    | 0.3675    | 3.224   | 0.00126* |
| Mechanical power                                                                | -1.2666   | 0.4065    | -3.116  | 0.00183* |
| PaO\textsubscript{2} / FiO\textsubscript{2}                                     | 1.8136    | 0.4388    | 4.133   | < 0.0001* |
| Compliance                                                                      | 0.8463    | 0.3638    | 2.326   | 0.02001* |
| CRP                                                                             | -0.5871   | 0.3509    | -1.673  | 0.09427  |
| PaO\textsubscript{2} / FiO\textsubscript{2}                                     | 0.7453    | 0.2595    | 2.872   | 0.00408  |
| Apache II                                                                       | 1.4467    | 0.3219    | 4.494   | < 0.00001 |
| Intercept                                                                       | 0.57260   | 0.62810   | 0.912   | 0.3620   |
| Apache II                                                                       | -0.06558  | 0.03641   | -1.801  | 0.0716   |
| SOFA                                                                            | -0.96399  | 0.57954   | -1.663  | 0.0962   |
| SOFA                                                                            | 0.06650   | 0.07576   | 0.878   | 0.3801   |
Table S5. Areas under the receiver operating curves (AUROCs) for the variable subsets and standard severity scores, in terms of subphenotype prediction. 95% confidence intervals are derived by means of bootstrapping the AUROCs.

| Prediction model (n=4) considering all variables | AUROC (95% CI) |
|-------------------------------------------------|----------------|
| Non-aerated lung mass, mechanical power, PaO₂/FiO₂, normally aerated lung volume | 0.93 (0.88-0.98) |
| Prediction model (n=3) considering all variables excluding CT-derived parameters | |
| Mechanical power, PaO₂/FiO₂, compliance | 0.87 (0.79-0.91) |
| Standard severity score | |
| PaO₂/FiO₂ | 0.79 (0.56-0.82) |
| Apache II | 0.62 (0.48-0.72) |
| SOFA | 0.51 (0.34-0.58) |

Figure S7. Receiver operating characteristic (ROC) curves for variable subsets in terms of phenotype prediction. AUROC are listed in table S5.
Table S6b. Fine and Grey regression results of subphenotype membership and duration of mechanical ventilation

|                      | SHR (95% CI)       | P-value |
|----------------------|--------------------|---------|
| **Univariate analysis of subphenotype and Mechanical ventilation duration** |                     |         |
| Subphenotype 2 (recruitable) | 0.56 (0.23 – 1.07) | p = 0.077 |
| **Multivariate analysis of subphenotype + Confounders, and mechanical ventilation duration** |                     |         |
| Subphenotype 2 (recruitable) | 0.46 (0.23 - 0.91) | p = 0.026 |
| Age                  | 0.97 (0.94 – 1.00) | p = 0.073 |
| Gender (male)        | 0.74 (0.34 - 1.59) | p = 0.430 |
| Apache II score      | 0.97 (0.92 - 1.03) | p = 0.320 |

Table S6b. Cox regression results of subphenotype membership and survival

|                      | HR (95% CI)       | P-value |
|----------------------|--------------------|---------|
| **Univariate analysis of subphenotype, and mortality** |                     |         |
| Subphenotype 1 (non-recruitable) | 1.08 (0.58 - 1.98) | p = 0.814 |
| **Multivariate analysis of subphenotype + confounders, and mortality** |                     |         |
| Subphenotype 1 (non-recruitable) | 1.18 (0.6 - 2.34)  | p = 0.629 |
| Age                  | 1.02 (0.97 - 1.07) | p = 0.461 |
| Gender (male)        | 0.91 (0.43 - 1.92) | p = 0.799 |
| Apache II score      | 1.01 (0.95 - 1.07) | p = 0.816 |
Figure S8. Kaplan-Meier plot of survival.
Table S7. Goodness-of-fit tests; tests correlation between Schoenfeld residuals and time. A p-value above 0.05 indicates a high likelihood that hazards are proportional.

| Subphenotype | Chi-square | df | p  |
|--------------|------------|----|----|
| Subphenotype | 0.0407     | 1  | 0.840 |
| Age          | 0.2439     | 1  | 0.621 |
| Gender       | 4.8818     | 1  | 0.027 |
| Apache 2     | 0.9898     | 1  | 0.320 |
| Global       | 8.5271     | 4  | 0.074 |

Figure S9. Shoenfeld residuals plots for covariates used in the survival analysis. For each moment in time, residuals are displayed by the black line with the 95% CI in dotted lines around it. A good proportional model is centered (with its 95% CI) around zero most of the time.
Figure S10. Cumulative incidence plot using only complete cases of time-to-event analysis (time = MV duration, event = successful extubation) in the presence of survival.
**Figure S11.** Kaplan-Meier plot using only complete cases of survival analysis.

OR = 1.16 (0.63-1.89), p = 0.823

adj. OR = 1.27 (0.68-2.47), p = 0.478
### Table S8a. Fine and Gray regression results of subphenotype membership and outcomes in complete case patients only

|                          | HR (95% CI)       | P-value |
|--------------------------|-------------------|---------|
| Univariate analysis of subphenotype and Mechanical ventilation duration |                   |         |
| Subphenotype 1 (non-recruitable) | 0.52 (0.27 - 0.99) | p = 0.045 |
| Multivariate analysis of subphenotype + Confounders, and mechanical ventilation duration |                   |         |
| Subphenotype 1 (non-recruitable) | 0.44 (0.22 - 0.87) | p = 0.018 |
| Age                       | 0.98 (0.95 - 1.01) | p = 0.210 |
| Gender (male)             | 0.69 (0.32 - 1.52) | p = 0.360 |
| Apache II score           | 0.96 (0.90 - 1.02) | p = 0.230 |

### Table S8b. Cox regression results of subphenotype membership and outcomes in complete case patients only

|                          | HR (95% CI)       | P-value |
|--------------------------|-------------------|---------|
| Univariate analysis of subphenotype, and mortality |                   |         |
| Subphenotype 1 (non-recruitable) | 1.16 (0.63 - 2.18) | p = 0.623 |
| Multivariate analysis of subphenotype + confounders, and mortality |                   |         |
| Subphenotype 1 (non-recruitable) | 1.27 (0.66 - 2.47) | p = 0.478 |
| Age                       | 1.03 (0.98 - 1.08) | p = 0.309 |
| Gender (male)             | 0.97 (0.46 - 2.05) | p = 0.939 |
| Apache II score           | 1 (0.94 - 1.06)    | p = 0.977 |
References (supplementary materials)

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