# Predicting survival in pulmonary arterial hypertension in the United Kingdom

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## ONLINE DATA SUPPLEMENT

## CATEGORISATION OF CONTINUOUS UNIVARIATE MORTALITY PREDICTORS IN THE DERIVATION COHORT

Meaningful thresholds of continuous univariate mortality predictors were identified by exploratory analysis. Each variable was dichotomised into 2 subgroups starting from a low threshold and analysed in a univariate Cox model as a categorised variable. This was carried out repeatedly with the threshold increasing by fixed increments. Care was taken to ensure there were sufficient patient numbers and deaths in each subgroup. The threshold that yielded the most significant hazard ratio was used to categorise the variable into two subgroups. If more than one meaningful threshold was identified, they were used to divide the variable into 3 or more subgroups. Different combinations were explored and the one that yielded the best separation of hazard ratios between subgroups was used to categorise the variable. The analyses on age, right atrial pressure (RAP), cardiac output (CO), percent predicted carbon monoxide diffusing capacity (DLco), six-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NTproBNP) and

Cambridge Pulmonary Hypertension Review (CAMPHOR) score are outlined as follows.

**Age**

Step 1 (Table 1)

The subgroup above the threshold was defined as the reference group. Thresholds of 40 years, 50 years, 60 years and 70 years yielded significant results. Age 70 years was chosen to be the upper threshold and further dichotomised Cox analysis was performed in patients aged <70 years to identify a lower threshold.

Step 2 (Table 2)

No further significant thresholds were identified for age <70 years. So age was categorised into 2 subgroups, ≥70 years and <70 years.

**RAP**

Step 1 (Table 3)

The subgroup above the threshold was defined as the reference group. Thresholds of 5 mmHg and 10 mmHg yielded significant results. Right atrial pressure 10 mmHg was chosen to be the upper threshold and further dichotomised Cox analysis was performed in patients with RAP <10mmHg to identify a lower threshold.

Step 2 (Table 4)

No further significant thresholds were identified for RAP <10mmHg. So RAP was categorised into 2 subgroups, ≥10 mmHg and< 10 mmHg.

**CO**

Step 1 (Table 5)

The subgroup above the threshold was defined as the reference group. Threshold of 3.0 L/min yielded the most significant result. It was chosen to be the lower threshold and further dichotomised Cox analysis was performed in patients with CO >3.0 L/min to identify an upper threshold.

Step 2 (Table 6)

No further significant thresholds were identified for CO >3.0 L/min. So CO was categorised into 2 subgroups, ≥3.0 L/min and <3.0 L/min.

**DLco (% predicted)**

Step 1 (Table 7)

The subgroup above the threshold was defined as the reference group. Thresholds of 30%, 35%, 40%, 45%, 50%, 55% and 60% yielded similarly significant results. DLco 60% predicted was chosen to be the upper threshold and further dichotomised Cox analyses were performed in patients with DLco <60% to identify a lower threshold.

Step 2 (Table 8)

Thresholds of 30% and 40% yielded similarly significant results. So DLco % was categorised into 3 subgroups differently, ≥60, 40-59, <40 or ≥60, 30-59, <30. Both were assessed in the multivariate model sequentially.

**6MWD**

Step 1 (Table 9)

The subgroup above the threshold was defined as the reference group. Thresholds of 50 metres,100 metres, 150 metres, 200 metres, 250 metres and 300 metres yielded similarly significant results. A 6MWD of 300 metres was chosen to be the upper threshold and further dichotomised Cox analyses were performed in patients with 6MWD <300 metres to identify a lower threshold.

Step 2 (Table 10)

Thresholds of 150 metres and 50 metres yielded the most significant results.

Step 3 (Figure 1)

Dividing 6MWD into 4 subgroups, <50 metres, 50-149 metres, 150-299 metres and ≥300 metres and using ≥300 metres subgroup as the reference group, there was an incremental increase in HR with each subgroup. The 6MWD <50 metres subgroup had the worst outcome and the ≥300 metres subgroup the best outcome.

**NTproBNP**

Step 1 (Table 11)

NTproBNP was log transformed and thresholds of $10^{2.9}$ pg/mL, $10^{3.0}$ pg/mL, $10^{3.1}$ pg/mL, $10^{3.2}$ pg/mL and $10^{3.3}$ pg/mL yielded significant results. These thresholds corresponded to NTproBNP 794 pg/mL, 1000 pg/mL, 1259 pg/mL, 1585 pg/mL and 1995 pg/mL respectively.

Step 2 (Table 12)

Dichotomised Cox analysis was repeated using thresholds at 100 pg/mL increments from 900 to 2000 pg/mL. The subgroup above the threshold was defined as the reference group. All yielded significant results.

Step 3 (Table 13)

Using 2000 pg/mL as an upper threshold, no lower threshold was identified.

Step 4 (Table 14)

Using 900 pg/mL as a lower threshold, no upper threshold was identified. So NTproBNP was categorised into 2 subgroups, using thresholds at 100 pg/mL increments from 900 to 2000 pg/ml, each of which was tested in the multivariate model sequentially.

**CAMPHOR**

Step 1 (Table 15)

The subgroup above the threshold was defined as the reference group. Threshold of 55 yielded the most significant result. It was chosen to be the upper threshold and further dichotomised Cox analysis was performed in patients with CAMPHOR <55 to identify a lower threshold.

Step 2 (Table 16)

No further significant thresholds were identified for CAMPHOR <55. So CAMPHOR was categorised into 2 subgroups, ≥55 and <55.

**Table 1. Dichotomised univariate Cox analysis of age (Step 1)**

| Threshold (years) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <30 | 8/174 (3/78) | 0.80 | 0.702 |
| <40 | 25/157 (6/75) | 0.42 | 0.039 |
| <50 | 48/134 (14/67) | 0.55 | 0.043 |
| <60 | 83/99 (28/53) | 0.57 | 0.016 |
| <70 | 126/56 (47/34) | 0.41 | <0.001 |
| <80 | 176/6 (79/2) | 0.80 | 0.752 |

**Table 2. Dichotomised univariate Cox analysis of age in patients <70 years (Step 2)**

| Threshold (years) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <30 | 8/118 (3/44) | 1.07 | 0.913 |
| <40 | 26/100 (7/40) | 0.62 | 0.237 |
| <50 | 48/78 (14/33) | 0.76 | 0.380 |
| <60 | 83/43 (28/19) | 0.87 | 0.647 |

**Table 3. Dichotomised univariate Cox analysis of RAP (Step 1)**

| Threshold (mmHg) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <5 | 53/129 (17/64) | 0.53 | 0.021 |
| <10 | 126/56 (50/31) | 0.51 | 0.003 |
| <15 | 156/26 (68/13) | 0.65 | 0.161 |
| <20 | 177/5 (80/1) | 1.94 | 0.511 |

**Table 4. Dichotomised univariate Cox analysis of RAP in patients with RAP<10 mmHg (Step 2)**

| Threshold (mmHg) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <1 | 13/113 (4/46) | 0.88 | 0.807 |
| <2 | 21/105 (7/43) | 0.94 | 0.885 |
| <3 | 35/91 (11/39) | 0.72 | 0.334 |
| <4 | 40/86 (12/38) | 0.67 | 0.221 |
| <5 | 53/73 (17/33) | 0.67 | 0.175 |
| <6 | 72/54 (25/25) | 0.65 | 0.123 |
| <7 | 84/42 (32/18) | 0.70 | 0.219 |
| <8 | 101/25 (38/12) | 0.60 | 0.125 |

**Table 5. Dichotomised univariate Cox analysis of CO (Step 1)**

| Threshold (L/min) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <2.0 | 4/176 (2/77) | 0.87 | 0.844 |
| <2.5 | 17/163 (11/68) | 1.77 | 0.080 |
| <3.0 | 46/134 (28/51) | 2.05 | 0.002 |
| <3.5 | 82/98 (43/36) | 1.59 | 0.042 |
| <4.0 | 108/72 (53/26) | 1.44 | 0.132 |
| <4.5 | 126/54 (59/20) | 1.36 | 0.233 |
| <5.0 | 142/38 (64/15) | 1.20 | 0.519 |
| <5.5 | 161/19 (70/9) | 0.99 | 0.981 |
| <6.0 | 168/12 (75/4) | 1.52 | 0.415 |

**Table 6. Dichotomised univariate Cox analysis of CO in patients with CO≥ 3.0 L/min (Step 2)**

| Threshold (L/min) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <3.5 | 36/98 (15/36) | 1.10 | 0.760 |
| <4.0 | 62/72 (25/26) | 1.06 | 0.844 |
| <4.5 | 80/54 (31/20) | 1.04 | 0.882 |
| <5.0 | 96/38 (36/15) | 0.92 | 0.792 |
| <5.5 | 115/19 (42/9) | 0.77 | 0.487 |
| <6.0 | 122/12 (47/4) | 1.23 | 0.691 |

**Table 7. Dichotomised univariate Cox analysis of DLco (Step 1)**

| Threshold (% predicted) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <20 | 13/145 (8/58) | 2.19 | 0.038 |
| <25 | 28/130 (15/51) | 1.91 | 0.028 |
| <30 | 42/116 (23/43) | 2.27 | 0.002 |
| <35 | 58/100 (32/34) | 2.11 | 0.003 |
| <40 | 70/88 (37/29) | 2.35 | <0.001 |
| <45 | 87/71 (44/22) | 2.35 | 0.001 |
| <50 | 95/63 (48/18) | 2.60 | <0.001 |
| <55 | 108/50 (51/15) | 2.32 | 0.005 |
| <60 | 115/43 (55/11) | 2.52 | 0.006 |
| <65 | 127/31 (57/9) | 1.89 | 0.082 |
| <70 | 137/21 (59/7) | 1.52 | 0.294 |
| <75 | 144/14 (62/4) | 2.03 | 0.170 |
| <80 | 149/9 (64/2) | 2.46 | 0.210 |

**Table 8. Dichotomised univariate Cox analysis of DLco in patients with DLco <60% predicted (Step 2)**

| Threshold (% predicted) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <20 | 13/102 (8/47)) | 1.76 | 0.142 |
| <25 | 28/87 (15/40) | 1.50 | 0.183 |
| <30 | 42/73 (23/32) | 1.79 | 0.035 |
| <35 | 58/57 (32/23) | 1.63 | 0.076 |
| <40 | 70/45 (37/18) | 1.85 | 0.034 |
| <45 | 87/28 (44/11) | 1.79 | 0.086 |
| <50 | 95/20 (48/7) | 2.14 | 0.061 |
| <55 | 108/7 (51/4) | 1.47 | 0.461 |

**Table 9. Dichotomised univariate Cox analysis of 6MWD (Step 1)**

| Threshold (metres) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <50 | 27/175 (21/66) | 4.02 | <0.001 |
| <100 | 36/166 (27/60) | 4.17 | <0.001 |
| <150 | 49/153 (36/51) | 3.93 | <0.001 |
| <200 | 80/122 (49/38) | 2.94 | <0.001 |
| <250 | 105/97 (63/24) | 3.63 | <0.001 |
| <300 | 130/72 (73/14) | 4.13 | <0.001 |
| <350 | 164/38 (79/8) | 3.12 | 0.002 |
| <400 | 188/14 (85/2) | 3.74 | 0.066 |
| <450 | 195/7 (86/1) | 3.10 | 0.261 |

**Table 10. Dichotomised univariate Cox analysis of 6MWD in patients with 6MWD <300 metres (Step 2)**

| Threshold (metres) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <50 | 27/103 (21/52) | 2.76 | <0.001 |
| <100 | 36/94 (27/46) | 2.43 | <0.001 |
| <150 | 49/81 (36/37) | 2.52 | <0.001 |
| <200 | 80/50 (49/24) | 1.74 | 0.026 |
| <250 | 105/25 (63/10) | 2.03 | 0.039 |

**Table 11. Dichotomised univariate Cox analysis of log NTproBNP (Step 1)**

| Threshold (pg/mL) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| $<10^{2.0}$ | 7/19 (2/37) | 0.47 | 0.294 |
| $<10^{2.1}$ | 12/84 (4/35) | 0.58 | 0.307 |
| $<10^{2.2}$ | 14/82 (6/33) | 0.83 | 0.672 |
| $<10^{2.3}$ | 17/79 (7/32) | 0.75 | 0.501 |
| $<10^{2.4}$ | 20/76 (7/32) | 0.61 | 0.232 |
| $<10^{2.5}$ | 26/70 (8/31) | 0.49 | 0.075 |
| $<10^{2.6}$ | 29/67 (10/29) | 0.59 | 0.148 |
| $<10^{2.7}$ | 33/63 (12/27) | 0.64 | 0.201 |
| $<10^{2.8}$ | 35/61 (13/26) | 0.70 | 0.305 |
| $<10^{2.9}$ | 41/55 (13/26) | 0.49 | 0.038 |
| $<10^{3.0}$ | 48/48 (15/24) | 0.44 | 0.013 |
| $<10^{3.1}$ | 51/45 (15/24 ) | 0.40 | 0.006 |
| $<10^{3.2}$ | 58/38 (18/21) | 0.42 | 0.007 |
| $<10^{3.3}$ | 66/30 (22/17) | 0.45 | 0.013 |
| $<10^{3.4}$ | 70/26 (26/13) | 0.61 | 0.148 |

**Table 12. Dichotomised univariate Cox analysis of NTproBNP (Step 2)**

| Threshold (pg/mL) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <900 | 43/53 (13/26) | 0.41 | 0.009 |
| <1000 | 48/48 (15/24) | 0.44 | 0.013 |
| <1100 | 49/47 (15/24) | 0.43 | 0.012 |
| <1200 | 50/46 (15/24) | 0.41 | 0.007 |
| <1300 | 53/43 (16/23) | 0.42 | 0.009 |
| <1400 | 53/43 (16/23) | 0.42 | 0.009 |
| <1500 | 54/42 (17/22) | 0.45 | 0.013 |
| <1600 | 58/38 (18/21) | 0.42 | 0.007 |
| <1700 | 60/36 (20/19) | 0.47 | 0.020 |
| <1800 | 62/34 (20/19) | 0.45 | 0.013 |
| <1900 | 64/32 (21/18) | 0.44 | 0.012 |
| <2000 | 66/30 (22/17) | 0.45 | 0.013 |
| <2100 | 66/30 (22/17) | 0.45 | 0.013 |

**Table 13. Dichotomised univariate Cox analysis of NTproBNP in patients with NTproBNP <2000 pg/mL (Step 3)**

| Threshold (pg/mL) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <900 | 43/23 (13/9) | 0..49 | 0.114 |
| <1000 | 48/18 (15/7) | 0.56 | 0.225 |
| <1100 | 49/17 (15/7) | 0.55 | 0.204 |
| <1200 | 50/16 (15/7) | 0.42 | 0.118 |
| <1300 | 53/13 (16/6) | 0.52 | 0.182 |
| <1400 | 53/13 (16/6) | 0.52 | 0.182 |
| <1500 | 54/12 (17/5) | 0.57 | 0.289 |
| <1600 | 58/8 (18/4) | 0.46 | 0.168 |
| <1700 | 60/6 (20/2) | 0.76 | 0.717 |
| <1800 | 62/4 (20/2) | 0.62 | 0.514 |
| <1900 | 64/2 (21/1) | 0.54 | 0.550 |

**Table 14. Dichotomised univariate Cox analysis of NTproBNP in patients with NTproBNP ≥900 pg/mL (Step 4)**

| Threshold (pg/mL) | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <1000 | 5/48 (2/24) | 0.85 | 0.830 |
| <1100 | 6/47 (2/24) | 0.80 | 0.762 |
| <1200 | 7/46 (2/24) | 0.57 | 0.446 |
| <1300 | 10/43 (3/23) | 0.69 | 0.540 |
| <1400 | 10/43 (3/23) | 0.69 | 0.540 |
| <1500 | 11/42 (4/22) | 0.78 | 0.645 |
| <1600 | 15/38 (5/21) | 0.62 | 0.342 |
| <1700 | 17/36 (7/19) | 0.81 | 0.640 |
| <1800 | 19/34 (7/19) | 0.73 | 0.482 |
| <1900 | 21/32 (8/18) | 0.70 | 0.404 |
| <2000 | 23/30 (9/17) | 0.70 | 0.401 |

**Table 15. Dichotomised univariate Cox analysis of CAMPHOR score (Step 1)**

| Threshold | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <15 | 5/71 (1/28) | 0.34 | 0.287 |
| <20 | 9/67 (3/26) | 0.70 | 0.556 |
| <25 | 18/58 (5/24) | 0.46 | 0.115 |
| <30 | 23/53 (6/23) | 0.48 | 0.112 |
| <35 | 28/48 (8/21) | 0.41 | 0.041 |
| <40 | 39/37 (11/18) | 0.38 | 0.016 |
| <45 | 44/32 (13/16) | 0.42 | 0.026 |
| <50 | 48/28 (14/15) | 0.61 | 0.098 |
| <55 | 55/21 (16/13) | 0.30 | 0.002 |
| <60 | 62/14 (22/7) | 0.43 | 0.060 |
| <65 | 68/8 (25/4) | 0.61 | 0.369 |

**Table 16. Dichotomised univariate Cox analysis of CAMPHOR score in patients with CAMPHOR <55 (Step 2)**

| Threshold | Number of patients below/above threshold (number of deaths below/above threshold) | Hazard ratio | p value |
|---|---|---|---|
| <15 | 5/50 (1/15) | 0.51 | 0.517 |
| <20 | 9/46 (3/13) | 1.07 | 0.918 |
| <25 | 18/37 (5/11) | 0.72 | 0.544 |
| <30 | 23/32 (6/10) | 0.76 | 0.601 |
| <35 | 28/27 (8/8) | 0.73 | 0.535 |
| <40 | 39/16 (11/5) | 0.72 | 0.542 |
| <45 | 44/11 (13/3) | 1.00 | 0.999 |

**Figure 1. Distribution of hazard ratios among 6MWD subgroups**