

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 S1)

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 S2)

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 S3)

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 S4)

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 S5)

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 S6)

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 S7)

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 S8)

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 S9)

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 S10)

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

Step 3 (Figure S1)

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 S11)

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 S12)

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 S13)

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

Step 4 (Table S14)

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 S15)

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 S16)

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

Table S1. 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 S2. 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 S3. 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 S4. 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 S5. 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 S6. Dichotomised univariate Cox analysis of CO in patients with CO \geq 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 S7. 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 S8. 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 S9. 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 S10. 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 S11. 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 S12. 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 S13. 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 S14. 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 S15. 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 S16. 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 S1. Distribution of hazard ratios among 6MWD subgroups

