Supplement : Discriminating between between CPAP success and failure in COVID-19 patients with severe respiratory failure

The UCL Critical Care COVID-19 Research Group

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Supplementary Figure 1: ICU patient flow chart and hospital outcome

Supplementary Figure 2: Model combining CRP and NT-proBNP predicting CPAP failure
CRP = C-reactive protein; NT-proBNP = N type -pro B-natriuretic peptide.

Supplementary Figure 3: Other biochemical and physiological markers taken on ICU admission in patients receiving CPAP
ALT = Alanine Aminotransferase, INR = international normalised ratio.

Supplementary Figure 4: PaO$_2$/FiO$_2$ and respiratory rate measured at baseline and at 6 hours after commencement of CPAP.

Modelling data

Separate univariable logistic regression models were fitted for each potential predictor measured at ICU admission. Five had p-values <0.05, namely log(SpO$_2$), CRP, log(NT-Pro-BNP), log(Troponin-T), log(creatinine). These predictors were fitted into a multivariable logistic regression mode and backwards elimination omitted creatinine (p=0.52), Troponin-T (p=0.33) and SpO$_2$ (p=0.062). The selected predictors were CRP (p=0.003) and NT-proBNP (p=0.003). Applying the Hosmer-Lemeshow test to each imputed dataset suggested no obvious problems with goodness of fit (p-values ranging from 0.25 to 0.85).

Bootstrapping produced an optimism-corrected ROC area of 0.804 (95% CI: 0.728 to 0.880) and calibration slope of 0.72, the latter suggestive of model-overfitting. The selected model was re-fitted using the lasso generating a final model of:

$$\log\left(\frac{p}{1-p}\right) = -4.160 + 0.006186 \times CRP + 0.6305 \times \log(NTProBNP)$$

where p is the probability of CPAP failure.

The ROC curve for this model is shown. Using a cut-point of 0.635 (chosen to maximise Youden's index) the sensitivity of the model is 0.75 (95% CI: 0.62 to 0.86) and specificity 0.83 (95% CI: 0.61 to 0.95). The equivalent cut-point for the approximate model above is at a total score of 1.5. That is, the optimal balance of sensitivity and specificity (using Youden's index) is obtained using the following rule: total score of 0 or 1 = success; total score of 2 and above = failure. The corresponding positive predictive value (PPV) is 0.91 (95% CI: 0.78 to 0.97) and negative predictive value (NPV) 0.59 (95%: 0.41 to 0.76). The positive and negative likelihood ratios were 4.34 and 0.29, respectively.

Because of the relatively small dataset and number of events., only a few variables were included in the multivariable model (after applying univariable screening), with backward elimination applied to reduce the number further. The model was then re-fitted, obtaining the presented regression coefficients, using the lasso estimation procedure to further guard against overfitting. The potential performance of this model was then investigated using a bootstrap internal validation procedure. All aspects of model development were included in the validation procedure including univariable screening and backward elimination. This validation exercise produced a 'corrected' ROC area of 0.804, suggesting that the final model has potentially good discrimination. As a sensitivity exercise, the lasso procedure was applied to all 16 of the initial predictors. This approach led to a very similar final model.

Supplementary Table 1: Demographics

	CPAP success	CPAP failure
n	32	61
Age (y)	56 [46-64]	61[47-70]
Male (%)	24 (75%)	44 (72%)
Body mass index	28 [24-34]	26 [24-30]

Past medical history
  Hypertension
  Diabetes
  Chronic respiratory disease
  Chronic cardiovascular disease
  Active cancer
  Immunosuppressed
	
	9 (28%)
	4 (13%)
	4 (13%)
	2 (6%)
	2 (6%)
	3 (9%)
		
		23 (38%)
		12 (20%)
		13 (21%)
		10 (16%)
		9 (15%)
		18 (30%)

Ceiling of treatment	2	14
Hours in hospital pre-ICU admission	8 [4-14]	8 [4-14]
Days in ICU	3 [2-7]	12 [5-25]*
Days on CPAP	2 [1-6]	3 [1-5]
Days on mechanical ventilation	n/a	15 [7-25]
Hospital survival	32	21 [†]

Data shown as n (%) or median (IQR).

* Includes CPAP ceiling of treatment patients

[†] 14 died with CPAP as their ceiling of treatment, and 26 died on invasive ventilation.

n/a not applicable

Supplementary Table 2: Requirement for organ support and thromboembolic complications

	CPAP success	CPAP failure	p
N	32	61	
Vasopressor support	0	46	<0.0001
Renal replacement therapy	0	28	<0.0001
Acute kidney injury (KDIGO score ≥1)	8	47	<0.0001
Patients with known thromboembolic complications (deep venous/pulmonary)	5 (4/2)*	20 (6/16)†	0.089

* One patient had both pulmonary embolus and DVT diagnosed
† Two patients had both pulmonary embolus and DVT diagnosed

Supplementary Table 3: Values in dataset (N (%)) and normal range

Values	N (%)	Normal Range
SpO_2	87 (94%)	96 - 100 %
FiO_2	85 (92%)	0.21
Respiratory Rate on ICU admission	85 (92%)	12 – 20 breaths/min
PaO_2/FiO_2 on ICU admission	61 (66%)	kPa
Temperature	93 (100%)	36.2 – 37.2 °C
C-reactive protein	93 (100%)	0 – 5 mg/L
Neutrophils	93 (100%)	2 - 7.5 x 10^9/L
Lymphocytes	93 (100%)	1.2 – 3.65 x 10^9/L
Platelets	91 (98%)	150 – 450 x 10^3/µL
Fibrinogen	64 (69%)	1.5 – 4 g/L
International normalised ratio (INR)	91 (98%)	0.9 – 1.1
D-Dimers	75 (81%)	0 - 550 µg/L
Ferritin	90 (97%)	30 - 400 µg/L
Lactate dehydrogenase	82 (88%)	135 - 214 IU/L
NT-proBNP	76 (82%)	<40 ng/L
Troponin-T	67 (72%)	0 - 14 ng/L
Creatinine	91 (98%)	50 – 120 µmol/L
SOFA Score	63 (68%)	
Bilirubin	91 (98%)	2 – 17 µmol/L
Alanine transaminase	93 (100%)	10 – 35 UI/L
Respiratory rate post-CPAP	87 (94%)	12 – 20 breaths/min
PaO_2/FiO_2 6 h post-CPAP	59 (63%)	kPa

Supplementary Table 4: Numerical predictive score

The numerical variables of CRP and log (NT-proBNP) were converted into categorical variables, each with 5 groups of equal width. For an individual, the total score is the sum of two component scores (CRP and NT). The corresponding risks are shown in the (b) below.

(a)

Predictor		Score
CRP	> 120	1
	> 240	2
	> 320	3
	> 480	4
NT-proBNP	> 221	1
	> 992	2
	> 4447	3
	> 19930	5

(b)

Total Score	Risk (%)
0	31
1	50
2	69
3	83
4	92
≥ 5	97