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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Liu L, Xie J, Wu W, et al. A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study. *Lancet Digit Health* 2021; published online Feb 8. https://doi.org/10.1016/S2589-7500(20)30316-2.

A Simple nomogram for predicting failure of non-invasive respiratory therapies in adults with COVID-19: A retrospective multicenter study

Online supplement

Method

The criteria for starting high flow nasal cannula, non-invasive ventilation and invasive mechanical ventilation

The criteria for starting HFNC, NIV and invasive MV were according to the suggestions of diagnosis and treatment of pneumonia and sever pneumonia patients with COVID-19 published by the National Health Commission of the People's Republic of China and the expert recommendation for sever pneumonia patients with COVID-19 published by Chinese Society of Critical Care Medicine- Chinese Medical Association, China critical care association and Chinese society of critical care medicine- Chinese Association of Pathophysiology [1,2].

Oxygen therapy should be started if one of the following situations occurs in COVID-19 patients with pneumonia to maintain the pulse oximetry SpO_2 :1) respiratory rate ≥ 30 breath/min; 2) SpO_2 ≤ 93%; 3） partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (F_IO_2) ≤ 300mmHg, 4) dyspnea or cyanosis.

If 200 mmHg < PaO_2/F_IO_2 ≤ 300 mmHg, high flow nasal cannula (HFNC) should be considered as first-line therapy when available. During HFNC, if PaO_2/F_IO_2 decline progressively to ≤ 200mmHg, or SpO_2 consistently below 93% with or without respiratory rate ≥ 30 breath/min, switching to non-invasive ventilation (NIV) should be considered when available. Invasive mechanical ventilation should start if the following situations occurs: 1) unconscious; 2) severe arrhythmia; 3) shock or the dose of norepinephrine more than 0.1ug/kg.min; 4) Acute respiratory acidosis (pH < 7·25); 5) Airway drainage difficulty.

If 150 mmHg < PaO_2/F_IO_2 ≤ 200 mmHg, NIV should be considered as initial therapy when available. During the first 2 hour of NIV, if tidal volume ≤ 9 ml/kg (predict body weight) and PaO_2/F_IO_2 maintained or improved, NIV should be continued. If tidal volume between 9 to 12 ml/kg and PaO_2/F_IO_2 maintained or improved, another 6 hours of NIV might be feasible with close monitoring. If tidal volume ≥ 12 ml/kg (predict body weight) or PaO_2/F_IO_2 decreased, invasive mechanical ventilation should start when.

If PaO_2/F_IO_2 ≤ 150 mmHg, invasive mechanical ventilation should start when available.

Table E1 List of participating hospitals

Training cohort		
Participating hospital	City	Province
Wuhan Jin-yintan Hospital	Wuhan	Hubei
Wuhan Pulmonary Hospital	Wuhan	Hubei
Union Hospital, Tongji Medical College Huazhong University of Science and Technology	Wuhan	Hubei
Tongji Hospital, Tongji Medical College Huazhong University of Science and Technology	Wuhan	Hubei
Wuhan ASIA General Hospital	Wuhan	Hubei
Zhongnan Hospital of Wuhan university	Wuhan	Hubei
Huangshi Hospital of Chinese Medicine	Huangshi	Hubei
Huangshi Central Hosptial	Huangshi	Hubei
The Third People`s Hospital of Shenzhen	Shenzhen	Guangdong
Huai`an NO.4 People`s Hosptial	Huai`an	Jiangsu
The First People`s Hospital of Lianyungang	Lianyungang	Jiangsu
The Second Hospital of Nanjing	Nanjing	Jiangsu
The Third Hospital of Nantong	Nantong	Jiangsu
The Fifth Hospital of Suzhou	Suzhou	Jiangsu
Wuxi No.5 People`s Hospital	Wuxi	Jiangsu
Xuzhou Infectious Disease Hospital	Xuzhou	Jiangsu
The Affiliated Hospital of Xuzhou Medical University	Xuzhou	Jiangsu
Yancheng No.1 People`s Hospital	Yancheng	Jiangsu
Affiliated Hospital of Yangzhou University	Yangzhou	Jiangsu
The Third Hospital of Yangzhou	Yangzhou	Jiangsu
External validation cohort		
Wuhan Third Hospital, Tongren Hospital of Wuhan university	Wuhan	Hubei
Wuhan Red Cross Hospital	Wuhan	Hubei

Table E2 Demographics and clinical respiratory variables of excluded patients

Demographics	Patients excluded for missing data in training cohort (n=87)	Patients excluded for missing data in validation cohort (n=17)
Age, years	68 (59, 78)	73 (62, 78)
Male, n (%)	55 (63)	16 (50)
APACHE II score	10 (7, 14)	10 (5, 12)
Hypertension, n (%)	38 (44)	7 (43)
Diabetes, n (%)	87 (18)	4 (25)
Coronary heart disease, n (%)	14 (16)	1 (6)
Chronic lung disease, n (%)	3 (3)	1 (6)
Other comorbidities, n (%)	2 (2)	1 (6)
SOFA score	2 (0, 4)	2 (0, 4)
GCS score	15 (15, 15)	15 (15, 15)
Heart rate, beats/min	91 (82, 107)	86 (75, 99)
Respiratory rate, breaths/min	23 (20, 30)	21 (20, 22)
Mean arterial pressure, mmHg	98 (83, 106)	98 (92, 102)
Number of comorbidities	1 (0, 1)	1 (0, 1)
Symptom onset to hospital admission, days	9 (5, 12)	-
Respiratory support and outcome		
NIV group, n (%)	34 (39)	7 (41)
Duration of NIV, days	3 (1, 7)	3 (1, 6)
HFNC group, n (%)	53 (61)	10 (59)
Duration of HFNC, days	4 (2, 7)	3 (3, 4)
Invasive MV, n (%)	28 (32)	1 (6)
Duration of Invasive MV, days	5 (3, 10)	1 (1, 1)
Use of steroids, n (%)	59 (68)	-
Use of antivirals, n (%)	57 (66)	-
Death before invasive MV, n (%)	28 (32)	8 (50)
Negative nucleic acid testing for SARS-CoV-2 within 28 days, n (%)	19 (44)	2 (22)
Mortality by 28-day, n (%)	48 (55)	9 (56)
Length of stay by 28-day, days	8 (3, 27)	12 (6, 28)

Data are provided as median (interquartile range) or frequency (%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow coma score, ROX, Respiratory rate-Oxygenation; HFNC high flow nasal cannula; NIV, non-invasive ventilation, MV, mechanical ventilation; NIRTs, non-invasive respiratory therapies

Table E3: Number of measurements for basic demographics and clinical features of patients

Demographics	Training cohort			External validation cohort		
	Overall (n=652)	NIRSs Success (n=237)	NIRSs Failure (n=415)	Overall (n=107)	NIRSs Success (n=33)	NIRSs Failure (n=74)
Age	652	237	415	107	33	74
Male	652	237	415	107	33	74
APACHE II	625	229	415	67	26	41
Hypertension	652	237	415	107	33	74
Diabetes	649	234	415	107	33	74
Coronary heart disease	652	237	415	107	33	74
Chronic lung disease	651	236	415	107	33	74
Other comorbidities	652	237	415	107	33	74
Data collected at the first day of non-invasive respiratory therapies						
SOFA score	622	229	393	68	26	42
GCS score	652	237	415	107	33	74
Heart rate	648	235	413	107	33	74
Respiratory rate	649	237	412	107	33	74
Mean arterial pressure	637	233	404	99	30	69
pH	420	171	249	71	22	49
PaO_2/FiO_2	422	173	249	74	30	44
$PaCO_2$	420	173	247	74	23	51
ROX index	652	237	415	107	33	74
Vasopressors use	652	237	415	107	33	74
Respiratory support and outcome						
NIV	652	237	415	107	33	74
Duration of NIV	379	100	279	77	18	59
HFNC	652	237	415	107	33	74
Duration of HFNC	356	143	213	46	20	26
Both of HFNC and NIV	652	237	415	107	33	74
Duration of HFNC+NIV, days	169	65	104	19	8	11
Invasive MV, n (%)	652	237	415	107	33	74
Duration of Invasive MV	264	-	264	31	-	31
Duration of NIRTs before invasive MV	270	-	270	31	-	31
Death before invasive MV	652	-	-	107	-	-
Negative nucleic acid testing for SARS-CoV-2 within 28 days	304	143	161	31	12	19
Death within 28 days after ICU admission	652	237	415	107	33	74
Length of stay by 28-day	652	237	415	107	33	74

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow coma score, ROX, Respiratory rate-Oxygenation; HFNC high flow nasal cannula; NIV, non-invasive ventilation, MV, mechanical ventilation; PaO_2, partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, $PaCO_2$, partial pressure of arterial oxygen carbon dioxide; NIRSs, non-invasive respiratory supports

Table E4 Demographics and clinical respiratory variables of patients with high-flow nasal cannula oxygen failure and success

	HFNC in Training cohort				HFNC in External validation cohort				p value [b]
Demographics	Overall (n=366)	HFNC S Success (n=162)	HFNC Failure (n=204)	p value [a]	Overall (n=48)	HFNC Success (n=22)	HFNC Failure (n=26)	p value [a]	
Age, years	64 (55, 73)	58 (48, 67)	69 (61, 76)	<0·0001	63 (53, 70)	56 (43, 67)	64 (57, 73)	0·065	0·36
Male, n (%)	241 (65.8)	100 (61.7)	141 (69·1)	0·14	31 (64·6)	14 (63·6)	17 (65·4)	0·90	0·86
APACHE II score	10 (6, 13)	7 (5, 9)	12.5 (10, 16)	<0·0001	10 (9, 12)	10 (9, 12)	12 (9, 17)	0·16	0·52
Hypertension, n (%)	154 (42·1)	65 (40·1)	89 (43·6)	0·500	23 (47·9)	9 (40·9)	14 (53·4)	0·37	0·44
Diabetes, n (%)	69 (18·9)	31 (19·1)	38 (18·6)	0·90	10 (20·8)	4 (18·2)	6 (23·1)	0·67	0·74
Coronary heart disease, n (%)	45 (12.3)	21 (13.0)	24 (11.7)	0.73	9 (18·8)	2 (9·1)	7 (26·9)	0·12	0·21
Chronic lung disease, n (%)	16 (2·3)	8 (5·0)	8 (3·9)	0·63	0 (0)	0 (0)	0 (0)	-	0.14
Other comorbidities, n (%)	29 (7·9)	14 (8·6)	15 (7·4)	0·65	7 (6·5)	1 (4·5)	6 (23·1)	0·070	0·12
Number of comorbidities	1 (0, 2)	1 (0, 1)	1 (0, 2)	<0·0001	1 (0, 2)	1 (0, 1)	1 (0, 2)	0·095	0·82
Duration of symptom onset to hospital admission, days	9 (5, 12)	7 (4, 11)	10 (7, 14)	<0·0001	8 (7, 11)	9 (5, 11)	8 (8, 10)	0·65	0·73
Data collected at the first day of non-invasive respiratory therapies									
SOFA score	3 (2, 5)	2 (1, 3)	4 (3, 6)	<0·0001	4 (3, 6)	3 (3, 4)	6 (4, 9)	0·011	0·13
GCS score	15 (15, 15)	15 (15, 15)	15 (15, 15)	0·001	15 (15, 15)	15 (15, 15)	15 (15, 15)	0·84	0·30
Heart rate, beats/min	92 (82. 102)	90 (82, 100)	95 (82, 107)	0·043	94 (84, 114)	91 (84, 112)	96 (81, 114)	0·90	0·21
Respiratory rate, breaths/min	22 (20, 26)	21 (20, 24)	24 (21, 30)	<0.0001	26(24, 33)	26 (24, 33)	29 (23, 34)	0·99	<0·0001
Mean arterial pressure, mmHg	95 (87, 103)	95 (89, 102)	96 (86, 103)	0·71	93 (87, 103)	90 (88, 95)	96 (87, 108)	0·19	0·74
pH	7·44 (7·41, 7·48)	7·44 (7.42, 7·47)	7·44 (7·37, 7·49)	0·30	7·45 (7·40, 7·49)	7·48 (7·43, 7·50)	7·43 (7·37, 7·48)	0·077	0·63
PaO_2/FiO_2, mmHg	116 (66, 252)	208 (123, 333)	83 (52, 126)	<0·0001	98 (77, 179)	171 (100, 208)	78 (76, 87)	0·005	0·72

$PaCO_{2,}$ mmHg	36 (32, 40)	37 (34, 39)	34 (30, 42)	0·27	36 (28, 40)	38 (35, 41)	30 (26, 37)	0·068	0·40
ROX index	6·39 (4·22, 12·53)	11·16 (6·88, 17·30)	4·72 (3·67, 6·82)	<0·0001	5·31 (3·75, 7·36)	6·96 (5·25, 9·51)	4·70 (3·38, 5·38)	0·0001	0·031
Vasopressors use, n (%)	17 (4·6)	1 (0·6)	16 (7·8)	0·001	3 (6·4)	0 (0)	3 (11.5)	0·11	0·34
Treatment and outcome									
Duration of HFNC, days	5 (2, 9)	7 (3, 11)	4 (2, 7)	<0·0001	7 (3, 8)	7 (6, 10)	3 (2, 8)	0·033	0·57
Switch to NIV, n (%)	120 (32·8)	36 (22·2)	84 (41·1)	<0·0001	19 (39·6)	1 (3·6)	1 (4·2)	0·675	0·35
Duration of HFNC+NIV, days	7 (4, 11)	9 (6, 13)	2 (2, 4)	<0·0001	7 (3, 11)	8 (7, 13)	5 (2, 10)	0·022	0·82
Invasive MV, n (%)	130 (35·6)	-	130 (63·7)	-	10 (20·8)	-	10 (38·5)	-	0·043
Duration of Invasive MV, days	7 (3, 11)	-	7 (3,11)	-	5 (2, 7)	-	5 (2, 7)	-	0·32
Use of steroids, n (%)	165 (70·6)	51 (70·8)	114 (69·0)	0·79	-	-	-	-	-
Use of antivirals, n (%)	276 (75·6)	143 (88·3)	133 (65·5)	<0·0001	-	-	-	-	-
Death before invasive MV, n (%)	74 (20·2)	-	74 (36·3)	-	16 (33·3)	-	16 (61·5)	-	0·038
Negative nucleic acid testing for SARS-CoV-2 within 28 days, n (%)	133 (73·5)	95 (86·3)	38 (53·5)	<0·0001	10 (47·6)	7 (63·6)	3 (30·0)	0·12	0·014
Death within 28 days after ICU admission, n (%)	178 (48·6)	-	178 (87·3)	-	20 (41·7)	-	20 (76·9)	-	0·36
Length of stay by 28-day, days	17 (7, 28)	28 (18, 28)	8 (4, 17)	<0·0001	14 (5, 26)	20 (16, 28)	7 (4, 13)	0·0001	0·28

Data are provided as median (interquartile range) or frequency (%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow coma score, ROX, Respiratory rate-Oxygenation; HFNC high flow nasal cannula; NIV, non-invasive ventilation, MV, mechanical ventilation; PaO_2, partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, $PaCO_{2,}$ partial pressure of arterial oxygen carbon dioxide; NIRSs, non-invasive respiratory therapies

[a] p for difference between HFNC failure vs. success

[b] p for difference between training cohort vs. validation cohort

Table E5 Demographics and clinical respiratory variables of patients with non-invasive ventilation failure and success

	NIV in Training cohort				NIV in External validation cohort				p value [b]
Demographics	Overall (n=286)	NIV Success (n=75)	NIV Failure (n=211)	p value [a]	Overall (n=59)	NIV Success (n=11)	NIV Failure (n=48)	p value [a]	
Age, years	65 (57, 72)	60 (52, 69)	67 (60, 73)	< 0·0001	66 (59, 74)	57 (53, 65)	68 (63, 74)	0·004	0·28
Male, n (%)	178 (62·2)	47 (62·7)	131 (62·1)	0·93	35 (59·3)	5 (45·5)	30 (62·5)	0·299	0·68
APACHE II score	11 (9, 15)	9 (6, 12)	12 (10, 16)	<0·0001	14 (9, 17)	8 (6, 9)	14 (12, 18)	0·002	0·13
Hypertension, n (%)	114 (39·9)	29 (38·7)	85 (40·3)	0·81	26 (44·1)	7 (63·6)	10 (40·0)	0·147	0·55
Diabetes, n (%)	55 (29·4)	10 (13·3)	45 (21·3)	0·13	13 (22·0)	3 (27·2)	10 (20·8)	0·642	0·59
Coronary heart disease, n (%)	39 (13·6)	10 (14·4)	29 (13·7)	0·93	8 (13·6)	0 (0)	8 (16·7)	0·145	0·11
Chronic lung disease, n (%)	15 (5·2)	2 (2·7)	13 (6·2)	0·22	6 (10·2)	0 (0)	0 (0)	0·216	0·99
Other comorbidities, n (%)	25 (8·7)	9 (12)	16 (7·6)	0·30	2 (3·4)	1 (9·1)	1 (2·1)	0·281	0·16
Number of comorbidities	1 (0, 2)	1 (0, 2)	1 (0, 2)	0·046	1 (0, 1)	1 (0, 1)	1（0, 1）	0·604	0·16
Duration of symptom onset to hospital admission, days	10 (6, 14)	9 (5, 11)	10 (7, 14)	0·017	10 (7, 13)	7 (6, 10)	11 (8, 13)	0·063	0·73
Data collected at the first day of non-invasive respiratory therapies									
SOFA score	4 (3, 5)	3 (1, 4)	4 (3, 6)	< 0·0001	5 (4, 7)	4 (3, 5)	6 (5, 7)	0·002	<0·0001
GCS score	15 (15, 15)	15 (15, 15)	15 (15, 15)	0.0010	15 (14, 15)	15 (15, 15)	15 (13, 15)	0·086	0·021
Heart rate, beats/min	92 (80, 105)	90 (81, 100)	92(80, 106)	0·27	97 (84, 113)	80 (75, 93)	100 (87, 115)	0·004	0·070
Respiratory rate, breaths/min	25 (20, 30)	22 (20, 26)	26 (22, 31)	< 0·0001	30 (27, 35)	28 (25, 33)	30 (28, 35)	0·204	<0·0001
Mean arterial pressure, mmHg	96 (87, 103)	96 (89, 104)	95 (86, 103)	0·31	96 (81, 105)	93 (82, 96)	97 (82, 109)	0·245	0·50
pH	7·45 (7·39, 7·48)	7·45 (7·40, 7·43)	7·44 (7·39, 7·48)	0·24	7·48 (7.40, 7.51)	7·47 (7.44, 7.49)	7·47 (7·40, 7·51)	0·937	0·046
PaO_2/FiO_2, mmHg	113 (68, 183)	165 (122, 269)	96 (56, 163)	< 0·0001	70 (50, 89)	92 (58, 112)	66 (49, 84)	0·053	< 0·0001

$PaCO_{2,}$ mmHg	36 (32, 42)	36 (32, 39)	36 (31, 44)	0·29	32 (26, 36)	35 (30, 41)	30 (26, 34)	0·339	<0·0001
ROX index	5·86 (3·79, 9·21)	8·94 (6·61, 13·93)	4.71 (3·32, 7·87)	< 0·0001	3·82 (3·14, 4·95)	5·04 (3·92, 7·93)	3·76 (3·11, 4·80)	0·035	<0·0001
Vasopressors use, n (%)	29 (10·1)	2 (2·7)	27 (12·8)	< 0·0001	2 (3.4)	0 (0)	2 (4.2)	0.491	0·099
Treatment and outcome									
Duration of NIV, days	5 (3, 9)	7 (4,10)	5 (2, 8)	0·27	4 (3, 7)	5 (3, 7)	4 (3, 7)	0·925	0·070
Switch to HFNC, n (%)	49 (17·1)	4 (5·3)	20 (9·5)	0·27	0 (0)	0 (0)	0 (0)	-	0.0010
Duration of HFNC+NIV, days	6 (3, 10)	8 (5, 12)	5 (3, 9)	< 0·0001	4 (3, 7)	5 (3, 7)	4 (3, 7)	0·925	0·11
Invasive MV, n (%)	158 (55·2)	-	158 (74·9)		21 (35·6)	-	21 (43·8)	--	0·0060
Duration of Invasive MV, days	8 (4, 14)	-	8 (5, 14)	0·0001	21 (1, 59)	-	4 (2, 6)	-	0·0030
Use of steroids, n (%)	140 (72·5)	25 (78·1)	115 (71·4)	0·44	-	-		-	-
Use of antivirals, n (%)	226 (79·6)	65 (89·0)	161 (76·3)	0·020	-	-	-	-	-
Death before invasive MV, n (%)	53 (18·5)	-	53 (25·1)	-	27 (45·8)	-	27 (56·2)	-	<0·0001
Negative nucleic acid testing for SARS-CoV-2 within 28 days, n (%)	81 (65·8)	27 (81·8)	54 (60)	0·024	4 (40)	1 (100)	3 (33·3)	0·197	0·10
Death within 28 days after ICU admission, n (%)	177 (61·9)	-	177 (83·9)	-	47 (79·7)	-	47 (97·9)	-	0·0090
Length of stay by 28-day, days	12 (6, 23)	19 (7, 28)	10 (6, 20)	0·0060	7 (3, 10)	9 (5, 14)	7 (3, 10)	0·278	<0·0001

Data are provided as median (interquartile range) or frequency (%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow coma score, ROX, Respiratory rate-Oxygenation; HFNC high flow nasal cannula; NIV, non-invasive ventilation, MV, mechanical ventilation; PaO_2, partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, $PaCO_{2,}$ partial pressure of arterial oxygen carbon dioxide;

[a] p for difference between NIV failure vs. success

[b] p for difference between training cohort vs. validation cohort

Table E6 Demographics and clinical respiratory variables of patients with high-flow nasal cannula oxygen and non-invasive ventilation

	Training cohort			External validation cohort		
Demographics	HFNC (n=366)	NIV (n=286)	p value	HFNC (n=48)	NIV (n=59)	p value
Age, years	64 (55, 73)	65 (57, 72)	0·43	63 (53, 70)	66 (59, 74)	0·056
Male, n (%)	241 (65·8)	178 (62·2)	0·34	31 (64·6)	35 (59·3)	0·59
APACHE II score	10 (6, 13)	11 (9, 15)	<0·0001	10 (9, 12)	14 (9, 17)	0·058
Hypertension, n (%)	154 (42·1)	114 (39·9)	0·57	23 (47·9)	26 (44·1)	0·69
Diabetes, n (%)	69 (18·9)	55 (29·4)	0·90	10 (20·8)	13 (22·0)	0·88
Coronary heart disease, n (%)	45 (12·3)	39 (13·6)	0·61	9 (18·8)	8 (13·6)	0·32
Chronic lung disease, n (%)	16 (2·3)	15 (5·2)	0·61	0 (0)	6 (10·2)	0·023
Other comorbidities, n (%)	29 (7·9)	25 (8·7)	0·71	7 (6·5)	2 (3·4)	0·038
Number of comorbidities	1 (0, 2)	1 (0, 2)	0·024	1 (0, 2)	1 (0, 1)	0·84
Symptom onset to hospital admission, days	9 (5, 12)	10 (6, 14)	0·041	8 (7, 11)	10 (7, 13)	0·059
Data collected at the first day of non-invasive respiratory therapies						
SOFA score	3 (2, 5)	4 (3, 5)	< 0·0001	5 (4, 7)	6 (5, 7)	0·0060
GCS score	15 (15, 15)	15 (15, 15)	0·023	15 (14, 15)	15 (13, 15)	0·075
Heart rate, beats/min	92 (82. 102)	92 (80, 105)	0·80	97 (84, 113)	100 (87, 115)	0·84
Respiratory rate, breaths/min	22 (20, 26)	25 (20, 30)	<0·0001	30 (27, 35)	30 (28, 35)	0.029
Mean arterial pressure, mmHg	95 (87, 103)	96 (87, 103)	0·97	96 (81, 105)	97 (82, 109)	0·67
pH	7·44 (7·41, 7·48)	7·45 (7·39, 7·48)	0·58	7·48 (7·40, 7·51)	7·47 (7·40, 7·51)	0·45
PaO_2/FiO_2, mmHg	116 (66, 252)	113 (68, 183)	0·13	70 (50, 89)	66 (49, 84)	<0·001
$PaCO_2$, mmHg	36 (32, 40)	36 (32, 42)	0·47	32 (26, 36)	30 (26, 34)	0·12
ROX index	6·39 (4·22, 12·53)	5·86 (3·79, 9·21)	0·0040	3·82 (3·14, 4·95)	3·76 (3·11, 4·80)	0·0010
Vasopressors use, n (%)	17 (4·6)	29 (10·1)	0·0010	2 (3·4)	2 (4·2)	0·47
Treatment and outcome						
Duration of NIRS, days	5 (2, 9)	5 (3, 9)	0·40	7 (3, 8)	4 (3, 7)	0·083
Both HFNC and NIV, n (%)	120 (32·8)	49 (17·1)	< 0·0001	19 (39·6)	0 (0)	<0·0001
Duration of HFNC+NIV, days	7 (4, 11)	6 (3, 10)	0·0020	7 (3, 11)	4 (3, 7)	0·011
Invasive MV, n (%)	130 (35·6)	158 (55·2)	<0·0001	10 (20·8)	21 (35·6)	0·094
Duration of Invasive MV, days	7 (3, 11)	8 (4, 14)	0·052	5 (2, 7)	21 (1, 59)	0·66
Use of steroids, n (%)	165 (70·6)	140 (72·5)	0·51	-	-	-
Use of antivirals, n (%)	276 (75·6)	226 (79·6)	0·23	-	-	-
Death before invasive MV, n (%)	30 (8·2)	53 (18·5)	<0·0001	16 (33·3)	27 (45·8)	0·19

Negative nucleic acid testing for SARS-CoV-2 within 28 days, n (%)	133 (73·5)	81 (65·8)	0·15	10 (47·6)	4 (40)	0·69
Death within 28 days after ICU admission, n (%)	178 (48·6)	177 (61·9)	0·0010	20 (41·7)	47 (79·7)	< 0·0001
Length of stay by 28-day, days	17 (7, 28)	12 (6, 23)	0·0020	14 (5, 26)	7 (3, 10)	0·0020

Data are provided as median (interquartile range) or frequency (%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow coma score, ROX, Respiratory rate-Oxygenation; HFNC high flow nasal cannula; NIV, non-invasive ventilation, MV, mechanical ventilation; PaO_2, partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, $PaCO_2$, partial pressure of arterial oxygen carbon dioxide; NIRSs, non-invasive respiratory therapies

Table E7 Factors associated with high flow nasal cannula failure in univariable and multivariate analyses

	Univariable models			Full multivariable model		
	OR	95% CI	p value	OR	95% CI	p value
ROX index	0·8	0·76, 0·84	<0·0001	0·8	0·76, 0·85	< 0·0001
Age	1·06	1·04, 1·08	<0.0001	1·05	1·03, 1·07	< 0·0001
GCS	0·8	0·67, 0·96	0·016	0·84	0·7, 1·01	0·069
Heart rate	1·02	1, 1·03	0·0080			
Respiratory rate	1·09	1·05, 1·14	<0·0001			
Symptom onset to hospital admission, days	1·07	1·03, 1·11	<0·0001			
Number of comorbidities	1·58	1·29, 1·93	<0·0001	1·31	1·03, 1·65	0·026

GCS, Glasgow coma score; ROX, Respiratory Rate-Oxygenation. Factors associated with overall non-invasive respiratory support failure in the final study model (main Article, table 2) were included in the multivariable analysis; although only 17 HFNC patients used vasopressors and the number was too small to calculate odds ratios.

Table E8 Factors associated with non-invasive ventilation failure in univariable and multivariate analyses

	Univariable models			Full multivariable model		
	OR	95% CI	p value	OR	95% CI	p value
ROX index	0·84	0·8, 0·89	<0.0001	0.84	0.79, 0.90	<0.0001
Age, years	1·04	1·02, 1·06	<0.0001	1·04	1·01, 1·07	0·0030
GCS	0·71	0·54, 0·95	0·020	0·70	0·52, 0·94	0·018
Vasopressor use	5·36	1·24, 23·1	0·024	5·19	1·12, 24.06	0·036
Heart rate, beats/min	1·01	0·99, 1·02	0·18			
Respiratory rate, breaths/min	1·09	1·05, 1·15	<0·0001			
Symptom onset to hospital admission, days	1·06	1·01, 1·11	0·022	1·04	0·98, 1·09	0·17
Number of comorbidities	1·27	1·00, 1·63	<0·0001			

GCS, Glasgow coma score; ROX, Respiratory Rate-Oxygenation. Factors associated with overall non-invasive respiratory support failure in the final study model (main Article, table 2) were included in the multivariable analysis.

Table E9 Comparison of C-statistics for the HFNC model

Model	Training cohort (n=366)		External validation cohort (n=48)	
	C-statistics (95%CI)	p value	C-statistics (95%CI)	p value
HFNC model	0·85 (0·81-0·89)	-	0·86 (0·75, 0·96)	-
ROX index	0·82 (0·77, 0·86)	0·038	0·78 (0·64, 0·92)	0·20
Age	0·71 (0·65, 0·76)	<0·0001	0·66 (0·49, 0·82)	0·014
GCS	0·55 (0·52, 0·58)	<0·0001	0·51 (0·41, 0·61)	<0·0001
Number of comorbidities	0·62 (0·57, 0·68)	<0·0001	0·63 (0·48, 0·78)	0·0037

GCS, Glasgow coma score; ROX, Respiratory Rate-Oxygenation; HFNC high flow nasal cannula.

Table E10 Comparison of C-statistics for the NIV model

Model	Training cohort (n=286)		External validation cohort (n=59)	
	C-statistics (95%CI)	p value	C-statistics (95%CI)	p value
NIV model	0·81 (0·76, 0·85)	-	0·88 (0·75, 1·00)	-
ROX index	0·76 (0·70, 0·82)	0·041	0·71 (0·52-0·90)	0·0060
Age	0·65 (0·57, 0·72)	<0·0001	0·78 (0·61-0·95)	0·041
GCS	0·57 (0·54, 0·61)	<0·0001	0·63 (0·54-0·73)	<0·0001
Vasopressor use	0·55 (0·52, 0·58)	<0·0001	0·52 (0·49-0·55)	<0·0001
Days from symptom onset to hospital admission	0·60 (0·52, 0·67)	<0·0001	0·68 (0·50-0·87)	<0·0001

GCS, Glasgow coma score; ROX, Respiratory Rate-Oxygenation; NIV, non-invasive ventilation,

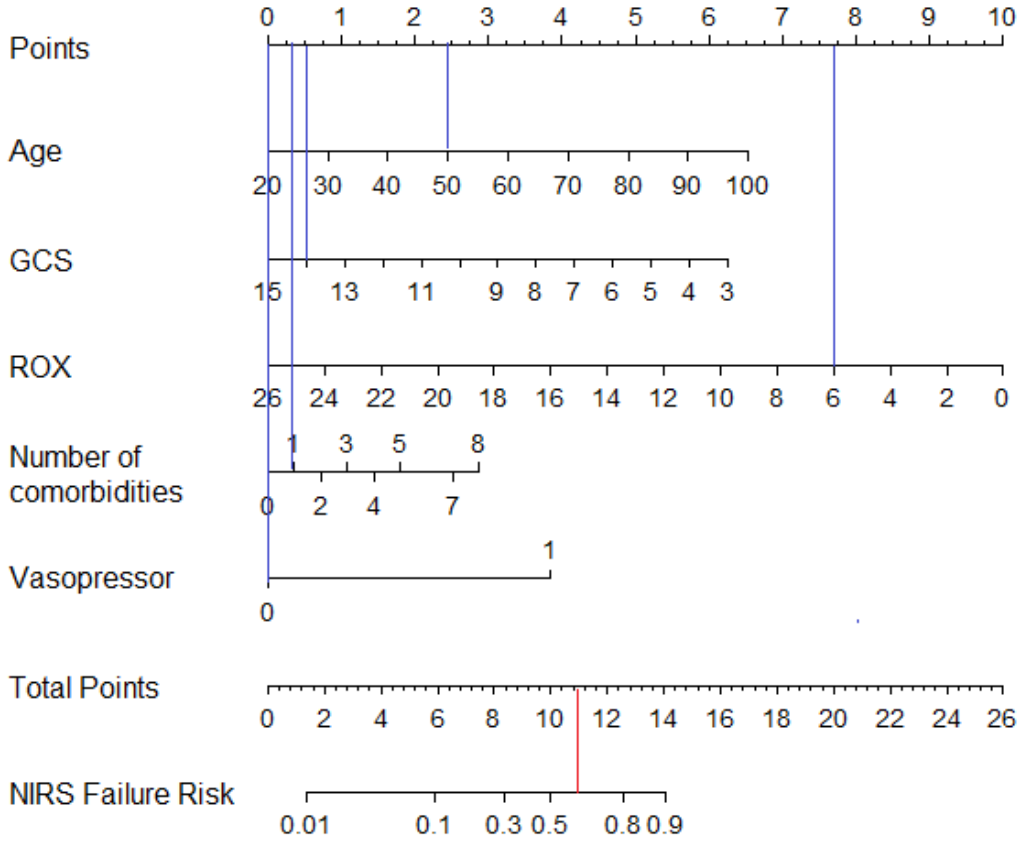

Figure E1 Example of practice of determining the risk of high flow nasal cannula (A) failure and non-invasive ventilation (B) by Nomogram

A: The blue line represent values of a randomly selected patient from the development dataset who is aged 50 years (2·45 points), with GCS score of 14 (0·52 point), ROX of 6 (7·69 points), one comorbidity (0·36 points) and no use of vasopressors (0 points). These values when plotted, correspond vertically to the points scale (top) and points are then summed to give a total point score (bottom). The presented patient has a total point's score of 11·02 with an associated probability of NIRS failure of 0·62 (red line). GCS, Glasgow coma score; ROX, Respiratory Rate-Oxygenation; HFNC high flow nasal cannula, NIV, non-invasive ventilation.

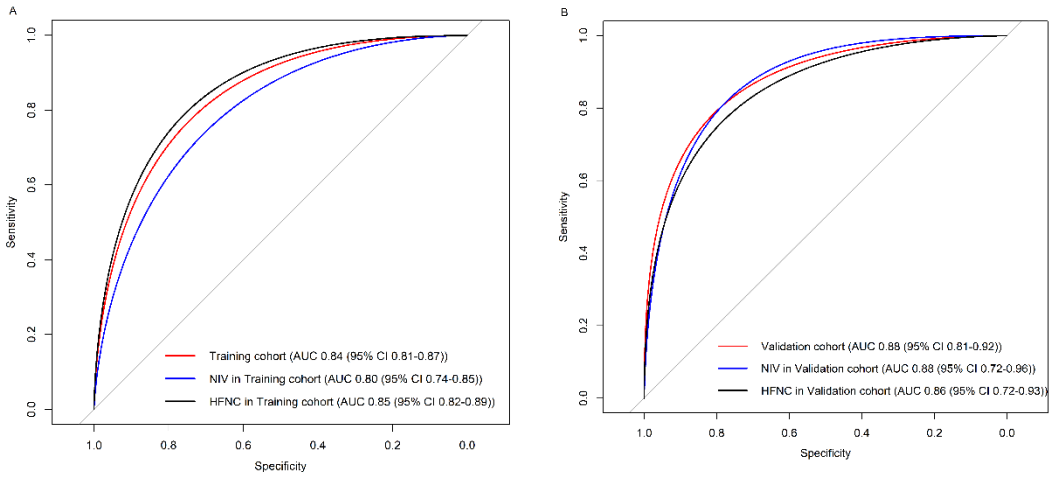

Figure E2 Receiver operating characteristic curve in the training cohort (A) and the in the validation cohort (B)

AUC, area under the receiver operating characteristic curve, equal to C-statistic value

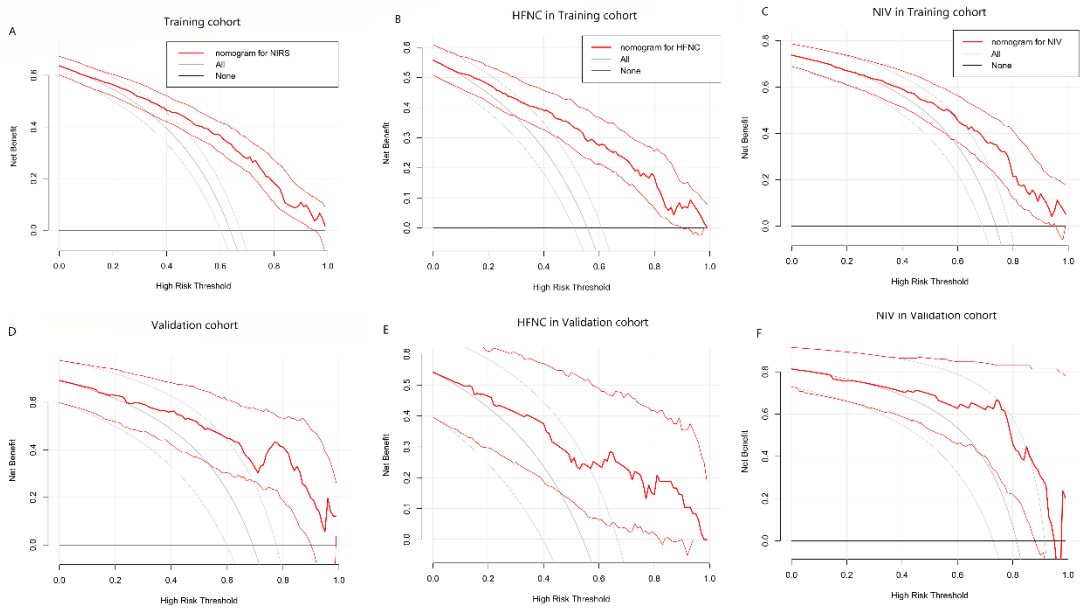

Figure E3 Decision curve analyses demonstrating the net benefit associated with the use of the nomogram on the detection of non-invasive respiratory support failure

A. training cohort, B. external validation cohort, C HFNC in validation cohort, D. NIV in validation cohort.

NIRS, non-invasive respiratory support

Reference

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