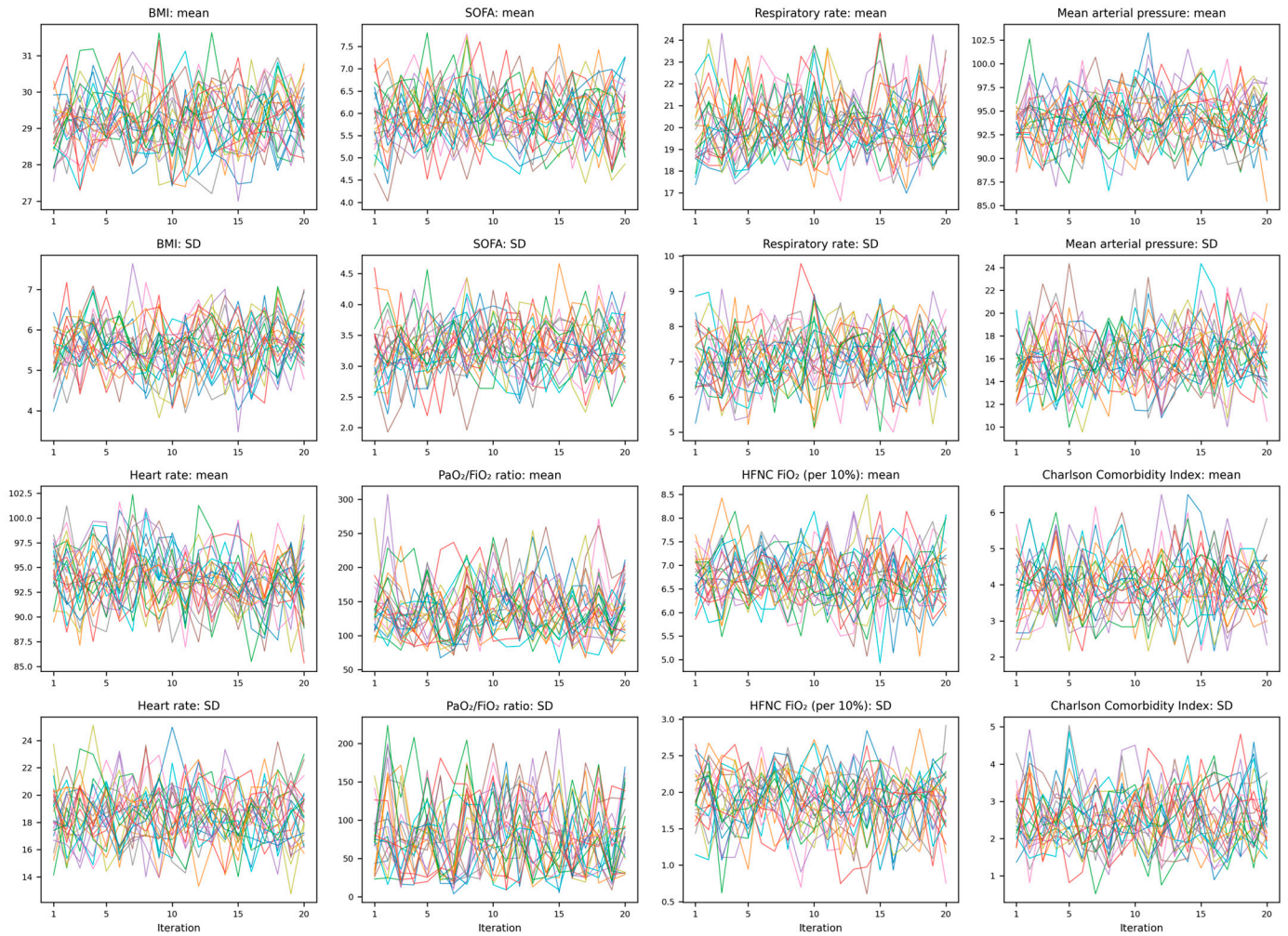




Supplementary Figure S1. Convergence diagnostics for multiple imputation. Trace plots of the mean and standard deviation of imputed values across 20 iterations for each variable with missing data; each line represents one of the 25 independent imputation chains. APACHE II (one missing value) is not shown. Abbreviations: BMI, body mass index; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

Table S1. Missing data for each variable, overall and according to outcome and awake prone positioning.

Variable	Overall (n = 222)	Successful (n = 72)	Unsuccessful (n = 150)	Prone (n = 139)	No prone (n = 83)
<i>Model covariates</i>					
BMI	75 (33.8)	21 (29.2)	54 (36.0)	53 (38.1)	22 (26.5)
APACHE II	1 (0.5)	1 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)
SOFA at ICU entry	79 (35.6)	15 (20.8)	64 (42.7)	53 (38.1)	26 (31.3)
PaO ₂ /FiO ₂ ratio	4 (1.8)	2 (2.8)	2 (1.3)	1 (0.7)	3 (3.6)
HFNC FiO ₂	7 (3.2)	0 (0.0)	7 (4.7)	0 (0.0)	7 (8.4)
Respiratory rate	74 (33.3)	30 (41.7)	44 (29.3)	52 (37.4)	22 (26.5)
<i>Other baseline variables</i>					
Charlson Comorbidity Index	6 (2.7)	2 (2.8)	4 (2.7)	3 (2.2)	3 (3.6)
HFNC flow	6 (2.7)	0 (0.0)	6 (4.0)	0 (0.0)	6 (7.2)
Heart rate	47 (21.2)	7 (9.7)	40 (26.7)	33 (23.7)	14 (16.9)
Systolic blood pressure	43 (19.4)	7 (9.7)	36 (24.0)	32 (23.0)	11 (13.3)

Variable	Overall (n = 222)	Successful (n = 72)	Unsuccessful (n = 150)	Prone (n = 139)	No prone (n = 83)
Mean arterial pressure	44 (19.8)	7 (9.7)	37 (24.7)	33 (23.7)	11 (13.3)
Lactate	72 (32.4)	18 (25.0)	54 (36.0)	48 (34.5)	24 (28.9)
<i>Laboratory parameters</i>					
CRP	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.2)
Procalcitonin	5 (2.3)	1 (1.4)	4 (2.7)	4 (2.9)	1 (1.2)
IL-6	178 (80.2)	54 (75.0)	124 (82.7)	120 (86.3)	58 (69.9)
Leukocytes	3 (1.4)	0 (0.0)	3 (2.0)	3 (2.2)	0 (0.0)
Ferritin	2 (0.9)	0 (0.0)	2 (1.3)	1 (0.7)	1 (1.2)
D-dimer	2 (0.9)	0 (0.0)	2 (1.3)	1 (0.7)	1 (1.2)
Blood glucose	4 (1.8)	1 (1.4)	3 (2.0)	2 (1.4)	2 (2.4)
AST	8 (3.6)	5 (6.9)	3 (2.0)	5 (3.6)	3 (3.6)
ALT	3 (1.4)	2 (2.8)	1 (0.7)	3 (2.2)	0 (0.0)
Total bilirubin	2 (0.9)	0 (0.0)	2 (1.3)	2 (1.4)	0 (0.0)
LDH	17 (7.7)	6 (8.3)	11 (7.3)	9 (6.5)	8 (9.6)
Pro-BNP	4 (1.8)	0 (0.0)	4 (2.7)	1 (0.7)	3 (3.6)
hs-Troponin T	8 (3.6)	2 (2.8)	6 (4.0)	7 (5.0)	1 (1.2)
Hemoglobin	4 (1.8)	1 (1.4)	3 (2.0)	3 (2.2)	1 (1.2)
Lymphocytes	5 (2.3)	1 (1.4)	4 (2.7)	4 (2.9)	1 (1.2)
Platelets	2 (0.9)	0 (0.0)	2 (1.3)	2 (1.4)	0 (0.0)
PT	1 (0.5)	1 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)
aPTT	2 (0.9)	0 (0.0)	2 (1.3)	2 (1.4)	0 (0.0)
AT-III	8 (3.6)	3 (4.2)	5 (3.3)	2 (1.4)	6 (7.2)
Fibrinogen	2 (0.9)	0 (0.0)	2 (1.3)	1 (0.7)	1 (1.2)

Values are number (%) of patients with missing data. No data were missing for age, sex, comorbidities, awake prone positioning, or outcome. One recorded HFNC FiO₂ value of 0 was considered implausible and counted as missing. IL-6 was not included in any model. Abbreviations: ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AT-III, antithrombin III; BMI, body mass index; CRP, C-reactive protein; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; hs-Troponin T, high-sensitivity troponin T; IL-6, interleukin-6; LDH, lactate dehydrogenase; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; Pro-BNP, pro-B-type natriuretic peptide; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

Table S2. Complete-case multivariable logistic regression for HFNC failure.

Parameter	APACHE II model, OR (95% CI)	<i>p</i>	SOFA model, OR (95% CI)	<i>p</i>
Awake prone positioning (yes vs. no)	0.24 (0.08–0.74)	0.013	0.27 (0.09–0.84)	0.024
Age, years	0.99 (0.95–1.03)	0.525	0.99 (0.95–1.03)	0.631
Sex (male vs. female)	1.20 (0.44–3.31)	0.725	1.36 (0.49–3.80)	0.561
BMI, kg/m ²	1.15 (0.95–1.38)	0.148	1.15 (0.92–1.45)	0.227
APACHE II (per point)	1.09 (1.01–1.19)	0.034	—	—
SOFA (per point)	—	—	1.35 (1.02–1.78)	0.036
PaO ₂ /FiO ₂ ratio (per unit)	0.993 (0.984–1.003)	0.152	0.994 (0.985–1.003)	0.192
HFNC FiO ₂ (per 10%)	1.45 (1.02–2.06)	0.040	1.23 (0.86–1.75)	0.251
Respiratory rate	0.97 (0.91–1.03)	0.324	0.98 (0.92–1.04)	0.416
Chronic heart failure	1.43 (0.50–4.11)	0.502	1.52 (0.50–4.58)	0.458
Chronic kidney disease	1.29 (0.26–6.38)	0.754	1.07 (0.19–6.12)	0.938

Values are odds ratios (95% CI) from multivariable binary logistic regression for HFNC failure (intubation), including only patients with complete data for all model covariates (APACHE II model:

n = 118, 78 events; SOFA model: n = 106, 65 events). Covariates were identical to the primary imputed models (Table 4). HFNC FiO₂ is expressed per 10% absolute increment. The reference category for awake prone positioning is "no prone positioning." Bold p-values denote p < 0.05 (two-sided). Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CI, confidence interval; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; OR, odds ratio; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

Table S3. Baseline characteristics according to awake prone positioning during HFNC.

Variable	Prone (n = 139)	No prone (n = 83)	p	SMD
Demographics and comorbidities				
Sex, male	96 (69.1)	52 (62.7)	0.327	0.14
Age, years	61.3 ± 12.0	68.3 ± 15.3	<0.001	-0.51
BMI, kg/m ²	25.5 (24.5–27.7)	26.2 (24.7–29.4)	0.221	-0.21
Charlson Comorbidity Index	3.0 (1.0–4.0)	5.0 (3.0–7.0)	<0.001	-0.67
Chronic heart failure	44 (31.7)	36 (43.4)	0.078	-0.24
Hypertension	73 (52.5)	43 (51.8)	0.918	0.01
Diabetes mellitus	45 (32.4)	35 (42.2)	0.141	-0.20
Chronic pulmonary disease	28 (20.1)	20 (24.1)	0.489	-0.10
Chronic kidney disease	14 (10.1)	18 (21.7)	0.017	-0.32
Cerebrovascular disease	6 (4.3)	9 (10.8)	0.061	-0.25
Malignancy	14 (10.1)	10 (12.0)	0.646	-0.07
Transplant recipient	5 (3.6)	4 (4.8)	0.731	-0.06
Calendar time				
Admission order	115 (71–177)	96 (33–161)	0.048	0.26
Early era (first 50 admissions)	19 (13.7)	31 (37.3)	<0.001	-0.56
Timing and treatment before ICU admission				
Symptom onset to ICU admission, days	9.0 (6.0–12.0)	8.0 (6.0–15.0)	0.509	-0.24
Hospital to ICU admission, days	3.0 (0.0–6.0)	3.0 (1.0–8.0)	0.133	-0.32
Corticosteroids	100 (71.9)	40 (48.2)	<0.001	0.50
Tocilizumab	21 (15.1)	4 (4.8)	0.019	0.35
Favipiravir	118 (84.9)	58 (69.9)	0.008	0.36
Hydroxychloroquine	18 (12.9)	28 (33.7)	<0.001	-0.51
Azithromycin	19 (13.7)	25 (30.1)	0.003	-0.41
Remdesivir	4 (2.9)	0 (0.0)	0.300	0.24
Anakinra	38 (27.3)	17 (20.5)	0.252	0.16
Illness severity				
APACHE II	12.0 (9.0–16.0)	17.0 (13.0–21.0)	<0.001	-0.65
SOFA at ICU entry	4.0 (3.0–5.0)	5.0 (3.0–8.0)	0.002	-0.62
Hemodynamic and respiratory status				
Heart rate, beats/min	90.0 (80.0–105.0)	98.0 (82.5–113.5)	0.051	-0.27
Systolic blood pressure, mmHg	131.0 (120.0–150.0)	125.0 (101.2–148.0)	0.037	0.36
Mean arterial pressure, mmHg	95.0 (86.7–100.0)	89.2 (75.0–100.0)	0.017	0.38
Lactate, mmol/L	1.8 (1.3–2.3)	1.5 (1.2–2.1)	0.146	0.15
Respiratory rate, breaths/min	30.0 (24.0–35.0)	30.0 (19.0–35.0)	0.576	0.13
PaO ₂ /FiO ₂ ratio	89.6 (70.9–112.8)	101.7 (74.2–149.5)	0.017	-0.39
HFNC FiO ₂ , %	80.0 (60.0–95.0)	70.0 (50.0–90.0)	0.045	0.32
HFNC flow, L/min	50.0 (45.0–55.0)	50.0 (50.0–60.0)	0.003	-0.22
Laboratory parameters				
CRP, mg/L	106.0 (43.6–177.0)	136.7 (80.0–201.6)	0.027	-0.27
Procalcitonin, ng/mL	0.19 (0.10–0.35)	0.30 (0.13–0.86)	0.006	-0.01
D-dimer, ng/mL	1610.0 (840.0–3835.0)	2500.0 (1462.5–4957.5)	0.003	-0.11
Ferritin, ng/mL	1064.0 (554.0–1682.2)	824.8 (349.9–1565.0)	0.122	-0.18

Variable	Prone (n = 139)	No prone (n = 83)	p	SMD
LDH, U/L	480.0 (388.0–624.8)	411.0 (294.0–588.0)	0.006	0.35
Lymphocytes, $\times 10^3/\mu\text{L}$	0.50 (0.30–0.70)	0.55 (0.40–0.90)	0.132	–0.14
Pro-BNP, pg/mL	678.1 (273.0–1574.1)	2280.2 (524.0–8909.1)	<0.001	–0.47
hs-Troponin T, ng/L	12.1 (6.4–25.7)	34.0 (15.9–95.5)	<0.001	–0.40

Data are n (%) for categorical variables and mean $\pm$ SD or median (IQR) for continuous variables. Categorical variables were compared with the χ^2 or Fisher exact test and continuous variables with the Student t-test or Mann–Whitney U test, as appropriate. Bold p-values denote $p < 0.05$ (two-sided). Admission order denotes the consecutive order of ICU admission; the early era comprises the first 50 admissions. SMD, standardized mean difference (prone minus no prone); absolute values > 0.1 indicate meaningful imbalance. Data were missing for BMI (n = 75), SOFA (n = 79), heart rate (n = 47), systolic blood pressure (n = 43), mean arterial pressure (n = 44), lactate (n = 72), respiratory rate (n = 74), and HFNC FiO₂ (n = 7). Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CRP, C-reactive protein; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; hs-Troponin T, high-sensitivity troponin T; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; Pro-BNP, pro-B-type natriuretic peptide; SD, standard deviation; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment.

Table S4. Sensitivity analyses restricted to patients in whom HFNC was initiated at ICU admission (n = 215; 143 events).

Analysis	Estimate (95% CI)	p
Multivariable logistic regression, APACHE II model		
Awake prone positioning (yes vs. no)	OR 0.25 (0.11–0.56)	<0.001
APACHE II (per point)	OR 1.09 (1.01–1.17)	0.018
PaO ₂ /FiO ₂ ratio (per unit)	OR 0.9946 (0.9897–0.9994)	0.029
HFNC FiO ₂ (per 10%)	OR 1.41 (1.15–1.73)	<0.001
Multivariable logistic regression, SOFA model		
Awake prone positioning (yes vs. no)	OR 0.26 (0.11–0.60)	0.002
Stabilized IPTW	OR 0.24 (0.11–0.52)	<0.001
Day-1 landmark, unadjusted (n = 161; 89 events)	HR 0.50 (0.32–0.77)	0.002
Day-1 landmark, adjusted (n = 158; 89 events)	HR 0.42 (0.26–0.69)	<0.001
Day-2 landmark, unadjusted (n = 132; 64 events)	HR 0.61 (0.36–1.05)	0.073
Day-2 landmark, adjusted (n = 129; 64 events)	HR 0.47 (0.25–0.88)	0.019

Models, covariates, imputation (m = 25), and weighting were identical to the primary analyses (Tables 4 and 5). Seven patients in whom HFNC was started after ICU admission (4 after extubation, 3 admitted for non-respiratory reasons) were excluded. Bold p-values denote $p < 0.05$ (two-sided). Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; HR, hazard ratio; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; OR, odds ratio; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

Table S5. Sensitivity analyses accounting for calendar time and COVID-19-specific treatments.

Analysis	n (events)	Estimate (95% CI)	p
<i>Whole cohort, additionally adjusted for calendar time*</i>			
Multivariable model	222 (150)	OR 0.18 (0.07–0.45)	<0.001
Multivariable model + corticosteroids, tocilizumab, anakinra	222 (150)	OR 0.17 (0.07–0.44)	<0.001
IPTW	222 (150)	OR 0.21 (0.09–0.46)	<0.001
Day-1 landmark, adjusted	158 (89)	HR 0.44 (0.26–0.74)	0.002
Day-2 landmark, adjusted	129 (64)	HR 0.47 (0.25–0.90)	0.022

Analysis	n (events)	Estimate (95% CI)	p
<i>Later era only†</i>			
Multivariable model	172 (119)	OR 0.24 (0.08–0.73)	0.011
IPTW	172 (119)	OR 0.22 (0.08–0.59)	0.003
Day-1 landmark, unadjusted	123 (70)	HR 0.54 (0.33–0.91)	0.020
Day-1 landmark, adjusted	118 (68)	HR 0.48 (0.27–0.87)	0.016
Day-2 landmark, unadjusted	109 (56)	HR 0.66 (0.36–1.21)	0.182
Day-2 landmark, adjusted	105 (55)	HR 0.48 (0.23–0.97)	0.041
<i>Alternative era boundaries (42nd–60th admission)‡</i>			
Multivariable model	162–180	OR 0.23–0.33	0.008–0.049
Day-1 landmark, adjusted	—	HR 0.48–0.53	0.016–0.040

Estimates refer to awake prone positioning (yes vs. no). Models, covariates, imputation (m = 25), and weighting were otherwise identical to the primary analyses (Tables 4 and 5). *Calendar time was modeled as consecutive admission order using a restricted cubic spline with four knots. †Admissions after the 50th, after corticosteroid use and routine awake proning were adopted. ‡The later era was redefined as starting after the 42nd, 45th, 48th, 50th, 53rd, 56th, or 60th admission; ranges across these definitions are shown. Bold p-values denote $p < 0.05$ (two-sided). Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OR, odds ratio.