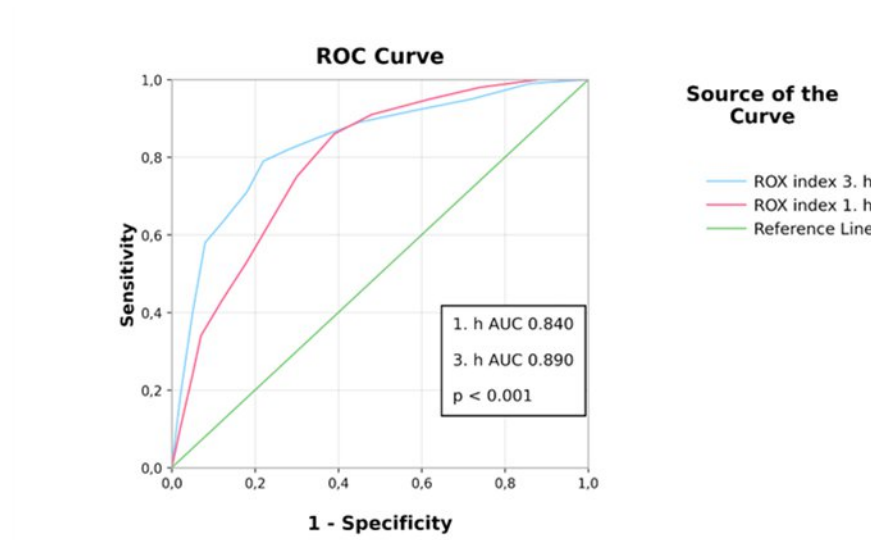


Supplementary Figure 1 : ROX index composite ROC

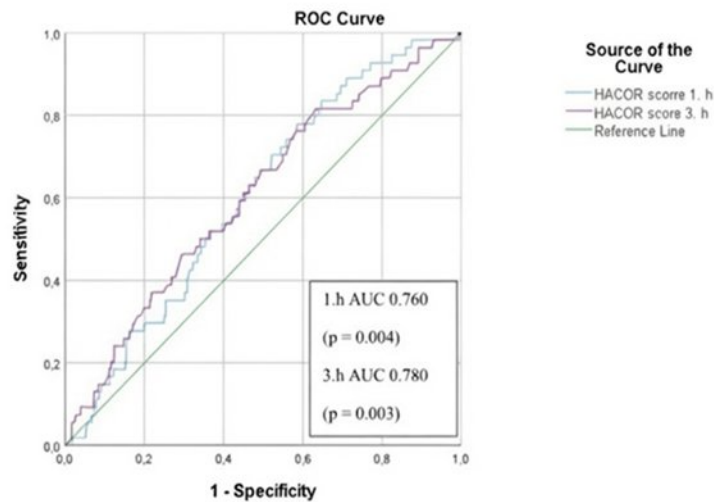


Supplementary Figure 1. ROC curves of the ROX index measured at 1 hour and 3 hours after HFNC initiation for prediction of composite HFNC failure, performed as an exploratory secondary analysis.

Composite HFNC failure was defined as clinical deterioration requiring endotracheal intubation, transition to non-invasive ventilation, or HFNC intolerance. The area under the ROC curve (AUROC) was 0.840 (95% CI 0.720–0.960) at 1 hour and 0.890 (95% CI 0.790–0.980) at 3 hours. The diagonal line represents the reference line (no discrimination).

Abbreviations: HFNC, high-flow nasal cannula; ROC, receiver operating characteristic; AUROC, area under the receiver operating characteristic curve.

Supplementary Figure 2 : HACOR score composite ROC



Supplementary Figure 2. ROC curves of the HACOR score measured at 1 hour and 3 hours after HFNC initiation for prediction of composite HFNC failure, performed as an exploratory secondary analysis.

Composite HFNC failure was defined as clinical deterioration requiring endotracheal intubation, transition to invasive ventilation, or HFNC intolerance. The area under the ROC curve (AUROC) was 0.760 (95% CI 0.620–0.900) at 1 hour and 0.780 (95% CI 0.640–0.920) at 3 hours. The diagonal line represents the reference line (no discrimination).

Abbreviations: HFNC, high-flow nasal cannula; ROC, receiver operating characteristic; AUROC, area under the receiver operating characteristic curve.

Supplementary Table 1. Baseline Clinical Characteristics of the Study Population

Variable	HFNC Success (n = 126)	HFNC Failure ^a (n = 50)	p-value
Demographics			
Male sex, n (%)	82 (65.1)	33 (66.0)	0.912
Age, years (mean ± SD)	66.9 ± 12.5	70.3 ± 14.4	0.151
SOFA score (mean ± SD)	5.7 ± 2.4	8.2 ± 3.0	0.001

APACHE II score (mean $\pm$ SD)	16.0 $\pm$ 5.5	22.1 $\pm$ 6.3	<0.001
Underlying disease			
Respiratory disease, n (%)	89 (70.6)	36 (72.0)	0.853
Cardiovascular disease, n (%)	75 (59.5)	30 (60.0)	0.952
Diabetes mellitus, n (%)	54 (42.9)	21 (42.0)	0.910
Hypertension, n (%)	46 (36.5)	22 (44.0)	0.362
Chronic kidney disease, n (%)	36 (28.6)	16 (32.0)	0.662
Initial Vital Signs			
Systolic blood pressure (mmHg, mean $\pm$ SD)	141.4 $\pm$ 24.1	138.0 $\pm$ 26.8	0.432
Diastolic blood pressure (mmHg, mean $\pm$ SD)	77.5 $\pm$ 15.4	77.5 $\pm$ 15.2	1.000
Pulse rate (bpm, mean $\pm$ SD)	86.3 $\pm$ 14.2	102.1 $\pm$ 15.6	<0.001
Respiratory rate (breaths/min, mean $\pm$ SD)	27.8 $\pm$ 4.1	33.3 $\pm$ 5.2	<0.001
Pulse oximetry (% SpO ₂ , mean $\pm$ SD)	87.9 $\pm$ 5.5	83.1 $\pm$ 6.7	<0.001
Glasgow Coma Scale (median, IQR)	15 (15-15)	14 (14-15)	0.031
Initial Arterial Blood Gas			
pH (mean $\pm$ SD)	7.42 $\pm$ 0.02	7.41 $\pm$ 0.03	0.030
PaO ₂ (mmHg, mean $\pm$ SD)	89.3 $\pm$ 31.8	82.2 $\pm$ 30.7	0.176
PaCO ₂ (mmHg, mean $\pm$ SD)	34.5 $\pm$ 6.7	35.2 $\pm$ 5.9	0.400
HFNC Settings			
Flow (L/min, mean $\pm$ SD)	38.4 $\pm$ 7.1	40.7 $\pm$ 8.2	0.009
FiO ₂ (mean $\pm$ SD)	0.62 $\pm$ 0.12	0.65 $\pm$ 0.19	0.252
Total HFNC exposure duration (hours, median, IQR)	18.5 (12.0-30.0)	12.0 (6.0-20.0)	0.005
Co-Treatments			
Diuretics, n (%)	77 (61.1)	17 (34.0)	0.001
Antibiotics, n (%)	90 (71.4)	36 (72.0)	0.932
Bronchodilators, n (%)	39 (31.0)	14 (28.0)	0.705
Outcomes			
Hospital Length of Stay (days, median, IQR)	12.0 (8.0-20.0)	16.0 (10.0-25.0)	0.020
ICU Length of Stay (days, median, IQR)	5.0 (3.0-8.0)	10.0 (6.0-16.0)	<0.001
Early oxygenation response			
SpO ₂ at 1 h (%), Median [IQR]	95 (93-97)	92 (90-94)	<0.001
SpO ₂ at 3 h (%), Median [IQR]	95 (94-96)	91 (88-93)	<0.001

^a HFNC failure was defined as clinician-determined endotracheal intubation within 48 hours after HFNC initiation.

Note: Data are presented as mean $\pm$ standard deviation, median (interquartile range), or n (%), as appropriate. Percentages were calculated using the corresponding column totals (n=126 and n=50). Continuous variables were compared using the independent-samples t test or the Mann-Whitney U test according to distribution, and categorical variables using the chi-square or Fisher's exact test, as appropriate. All tests were two-sided, and a p value <0.05 was considered statistically significant. Total HFNC exposure duration was defined as the cumulative time during which HFNC was actually administered, excluding interruptions. In

patients who underwent intubation, this differed from the elapsed time from HFNC initiation to endotracheal intubation, which included interruptions.

Abbreviations: HFNC, high-flow nasal cannula; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; SpO₂, peripheral oxygen saturation; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide; FiO₂, fraction of inspired oxygen; SD, standard deviation; IQR, interquartile range.

Supplementary Table 2. Temporal Distribution of Intubation Events After HFNC

Initiation

Time from HFNC initiation	Number of intubations	Percentage
<3 hours	5	10.0%
3–12 hours	14	28.0%
12–48 hours	31	62.0%
Total	50	100%

Supple. Table 2. Temporal distribution of endotracheal intubation events within the 48-hour outcome window following HFNC initiation.

Supplementary Table 3. Comparison of patients included in and excluded from the complete-case time-point analysis

Variable	Included in the complete-case analysis (n=88)	Excluded from the time-point analysis (n=88)	Absolute SMD	p-value
Demographic and clinical characteristics				
Age, years	67.92 ± 13.20	67.82 ± 13.04	0.01	0.960
Male sex, n (%)	58 (65.9)	57 (64.8)	0.02	0.870
Underlying respiratory disease, n (%)	63 (71.6)	62 (70.5)	0.02	0.860
Cardiovascular disease, n (%)	53 (60.2)	52 (59.1)	0.02	0.870
Diabetes mellitus, n (%)	38 (43.2)	37 (42.0)	0.02	0.870

Chronic kidney disease, n (%)	27 (30.7)	25 (28.4)	0.05	0.740
Baseline illness severity				
SOFA score	6.58 ± 2.86	6.24 ± 2.76	0.12	0.420
APACHE II score	18.21 ± 6.45	17.25 ± 6.25	0.15	0.320
Baseline physiological variables				
Respiratory rate, breaths/min	29.74 ± 5.18	28.98 ± 4.98	0.15	0.320
Pulse rate, beats/min	91.83 ± 16.50	89.75 ± 15.93	0.13	0.400
SpO ₂ , %	86.06 ± 6.32	87.02 ± 6.16	0.15	0.310
Glasgow Coma Scale score	14 (13–15)	15 (14–15)	0.12	0.400
Arterial pH	7.414 ± 0.028	7.417 ± 0.026	0.11	0.460
PaO ₂ , mmHg	85.34 ± 31.85	89.22 ± 31.28	0.12	0.420
PaCO ₂ , mmHg	34.92 ± 6.55	34.48 ± 6.39	0.07	0.650
Initial HFNC settings				
Flow rate, L/min	39.54 ± 7.55	38.56 ± 7.41	0.13	0.380
FiO ₂	0.638 ± 0.148	0.620 ± 0.138	0.13	0.400
Outcome and reasons for non-inclusion				
HFNC failure within 48 h, n (%)	39 (44.3)	11 (12.5)	0.75	<0.001
Reason for non-inclusion in the time-point analysis				
Intubation before the 3-h assessment, n (%)	—	5 (5.7)	—	Not applicable†
Missing ≥1 physiological variable required for score calculation at 1 or 3 h, n (%)	—	83 (94.3)	—	Not applicable†

Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. The complete-case analytical cohort comprised patients with all physiological variables required to calculate both ROX and HACOR at the 1- and 3-hour assessments. Absolute standardized mean differences (SMDs) were used to quantify the magnitude of between-group differences; an absolute SMD <0.10 was considered negligible, 0.10–0.19 small, and ≥0.20 potentially meaningful. For the GCS score, the SMD was calculated using the underlying continuous values, whereas the variable is presented as median (interquartile range). HFNC failure was defined as endotracheal intubation within 48 hours after HFNC initiation.

†Among the 88 patients not included in the complete-case time-point analysis, 83 had one or more missing physiological variables required for score calculation at the 1- or 3-hour assessment, whereas 5 underwent endotracheal intubation before the scheduled 3-hour measurement. These rows represent the reasons for non-inclusion and were therefore not subjected to statistical comparison.

Supplementary Table 4. Sensitivity analyses of the associations of 3-hour ROX and HACOR values with HFNC success after adjustment for baseline illness severity

Predictor	Original adjusted model* aOR (95% CI); p	SOFA-adjusted sensitivity model† aOR (95% CI); p	APACHE II-adjusted sensitivity model‡ aOR (95% CI); p
ROX index at 3 h, per 1-unit increase	1.38 (1.05–1.82); 0.022	1.35 (1.03–1.77); 0.029	1.32 (1.01–1.74); 0.044
HACOR score at 3 h, per 1-unit increase	0.77 (0.63–0.94); 0.011	0.79 (0.64–0.96); 0.021	0.82 (0.67–0.99); 0.045

*Original adjusted models included age, sex, and underlying respiratory disease.

†SOFA-adjusted models included the respective 3-hour score, age, sex, underlying respiratory disease, and baseline SOFA score.
‡APACHE II-adjusted models included the respective 3-hour score, age, sex, underlying respiratory disease, and baseline APACHE II score. SOFA and APACHE II were entered into separate models to avoid redundancy between global illness-severity measures. All models included 88 patients (49 HFNC successes and 39 HFNC failures). HFNC success was coded as the dependent outcome; therefore, an aOR >1 indicates a greater likelihood of HFNC success, whereas an aOR <1 indicates a lower likelihood of success.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HFNC, high-flow nasal cannula; ROX, ratio of SpO₂/FiO₂ to respiratory rate; HACOR, heart rate, acidosis, consciousness, oxygenation, and respiratory rate; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Supplementary Table 5. Sedative and opioid analgesic exposure during the first 3 hours after HFNC initiation and in relation to the 1- and 3-hour ROX and HACOR assessments

Panel A.

Variable	Overall (n=88)	HFNC success (n=49)	HFNC failure (n=39)	Absolute SMD	p value
Any sedative or opioid before either assessment, n (%)	16 (18.2%)	9 (18.4%)	7 (17.9%)	0.011	1.000
Exposure before the 1-hour assessment, n (%)	11 (12.5%)	6 (12.2%)	5 (12.8%)	0.017	1.000

Exposure after the 1-hour but before the 3-hour assessment, n (%)	5 (5.7%)	3 (6.1%)	2 (5.1%)	0.043	1.000
Ongoing infusion at the 1-hour assessment, n (%)*	2 (2.3%)	1 (2.0%)	1 (2.6%)	0.035	1.000
Ongoing infusion at the 3-hour assessment, n (%)*	2 (2.3%)	1 (2.0%)	1 (2.6%)	0.035	1.000
Number of administrations per exposed patient, median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)	—	0.780
Time from the last bolus administration or completion of infusion to the subsequent ROX/HACOR assessment among patients without an ongoing infusion (n=14), min, median (IQR)	45 (30–60)	45 (30–60)	40 (30–55)	—	0.652
Glasgow Coma Scale at the 1-hour assessment, median (IQR)	15 (14–15)	15 (14–15)	15 (14–15)	0.050	0.850
Richmond Agitation–Sedation Scale at the 1-hour assessment, median (IQR)	0 (–1 to 0)	0 (–1 to 0)	0 (–1 to 0)	0.030	0.920
Glasgow Coma Scale at the 3-hour assessment, median (IQR)	15 (14–15)	15 (14–15)	15 (14–15)	0.040	0.890
Richmond Agitation–Sedation Scale at the 3-hour assessment, median (IQR)	0 (–1 to 0)	0 (–1 to 0)	0 (–1 to 0)	0.025	0.950

* No patient received continuous deep sedation during the 3-hour assessment window. The ongoing infusions recorded at the assessment times consisted of low-dose dexmedetomidine. The same two patients had ongoing dexmedetomidine infusions at both assessments.

Note: Data are presented as n (%) or median (interquartile range), as appropriate. Categorical variables were compared using the two-sided Fisher's exact test, and continuous or ordinal variables were compared using the Mann–Whitney U test. Absolute standardized mean differences were calculated using the underlying patient-level values.

Panel B. Agent and dose details

Agent	Overall (n=88)	Success (n=49)	Failure (n=39)	Dose or infusion rate	Administration	Timing relative to assessment
Fentanyl	9 (10.2%) **	5 (10.2%)	4 (10.3%)	25 µg (25–50) per dose	11 IV bolus doses in total	30–45 min before the subsequent assessment

Dexmedetomidine	4 (4.5%)	2 (4.1%)	2 (5.1%)	Infusion rate, median (range): 0.3 µg/kg/h (0.2–0.4)	4 infusion episodes; duration, median (range): 90 min (40–150)	Ongoing at both assessments in 2 patients; infusion completed before the 1-hour assessment in 2 patients
Midazolam	3 (3.4%)	2 (4.1%)	1 (2.6%)	1 mg (1–2) per dose	3 IV bolus doses in total	45–60 min before the subsequent assessment

**** Among the 16 exposed patients, 9 (56.3%) received fentanyl. Percentages in Panel B were calculated using the corresponding column totals (n=88, n=49, and n=39).**

Abbreviations: HFNC, high-flow nasal cannula; ROX, ratio of oxygen saturation as measured by pulse oximetry to fractional inspired oxygen, divided by respiratory rate; HACOR, heart rate, acidosis, consciousness, oxygenation, and respiratory rate; SMD, standardized mean difference; IQR, interquartile range; IV, intravenous.