

## SUPPLEMENTARY MATERIAL

### Non-invasive ventilation in COVID-19-related acute hypoxemic respiratory failure: a narrative review

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**Supplementary Table 1. A schematic and comparative table of clinical algorithms and guidelines cited.**

| <i>Aspect</i>                                       | <i>Weerakkody et al. [26]</i>                                     | <i>SIMEU [27]</i>                                                         | <i>COVID-19 Guidelines Panel</i>                    | <i>Prediletto &amp; Marra [49,50]</i>                             | <i>Scala et al. [48]</i>                                                                                                               |
|-----------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study Type</b>                                   | Meta-analysis (2 RCTs + 83 observational studies)                 | Clinical statement                                                        | position<br>Expert consensus guideline              | Observational studies                                             | algorithm<br>recommendation for ARF management                                                                                         |
| <b>Main NIRS Modalities Evaluated</b>               | HFNC, CPAP, BiPAP                                                 | HFNC, CPAP, NIPPV                                                         | HFNC, NIV, Mechanical Ventilation                   | STP/F, S/F ratio                                                  | HFNC, CPAP, NIV                                                                                                                        |
| <b>Initial Oxygen Therapy Criteria</b>              | Start with standard O <sub>2</sub> therapy                        | SpO <sub>2</sub> < 94%; FiO <sub>2</sub> titrated per range               | SpO <sub>2</sub> < 92%                              | SpO <sub>2</sub> < 92%                                            | Start COT if SpO <sub>2</sub> < 92%; reevaluate within 4 hrs                                                                           |
| <b>Escalation Criteria for NIRS</b>                 | Increased WOB, ↓ PaO <sub>2</sub> /FiO <sub>2</sub> , ↓ ROX index | SpO <sub>2</sub> < 92% after NRB 15 L/min or P/F 200–300                  | RR > 30, P/F < 300                                  | P/F < 300 or SpO <sub>2</sub> < 93%                               | P/F < 300 and/or RR > 30 → HFNC; P/F < 200 → CPAP; P/F < 100 or RR > 30 w/ distress → NIV                                              |
| <b>Preferred NIRS Modalities Based on Condition</b> | BiPAP if hypercapnic; CPAP/HFNC otherwise                         | HFNC preferred before NIV; NIPPV in COPD/acidosis                         | HFNC first-line; NIV if HFNC fails                  | S/F or STP/F used to stratify severity                            | HFNC (30–60 L/min); CPAP (PEEP 10); NIV (PEEP 12–16 + PS to get Vt 4–6 ml/kg/PBW)                                                      |
| <b>Monitoring Parameters</b>                        | Flowchart guided, clinical signs                                  | ABG, FiO <sub>2</sub> , Vt, SpO <sub>2</sub> , RR                         | Hourly ABG, RR, SpO <sub>2</sub> , FiO <sub>2</sub> | S/F ratio, STP/F ratio, lab and radiologic biomarkers             | Reassess: HFNC every 2, 6, 12 hrs; CPAP/NIV hourly                                                                                     |
| <b>Failure Indicators</b>                           | Hypoxemia, poor response                                          | Vt > 9 ml/kg PBW, P/F < 150, SpO <sub>2</sub> < 94%, RR > 25, intolerance | P/F < 150, SAPS II > 35, APACHE II > 17             | Persistent low S/F, poor clinical trend                           | Worsening SpO <sub>2</sub> or ↑ PaCO <sub>2</sub> , arrest, hemodynamic instability, NIRS intolerance → switch to invasive ventilation |
| <b>HFNC vs. NIV Recommendations</b>                 | HFNC + mask NIV ↓ intubation/mortality                            | HFNC before NIV; NIV in COPD or respiratory acidosis                      | HFNC preferred for initial therapy                  | HFNC for early ARF, S/F 200; STP/F used for mortality prediction  | Use HFNC first if P/F > 200; CPAP if P/F 100–200; NIV if P/F < 100                                                                     |
| <b>Use of P/F and S/F Ratios</b>                    | Not emphasized                                                    | S/F used for monitoring                                                   | Used in stratification                              | S/F correlates with severity; STP/F more physiologically accurate | P/F used for stepwise support; no S/F or STP/F specifically discussed                                                                  |
| <b>Role of STP/F Ratio</b>                          | Not addressed                                                     | Not discussed                                                             | Not discussed                                       | STP/F superior to P/F in mortality prediction                     | Not discussed                                                                                                                          |

RCT, randomized controlled trial; ARF, acute respiratory failure; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; NIPPV, noninvasive positive pressure ventilation; NIV, noninvasive ventilation; COT, continuous oxygen therapy; WOB, work of breathing; NRB, non-rebreather mask; RR, respiratory rate.

**Supplementary Table 2. Clinical trials of non-invasive ventilation in COVID-19-related acute respiratory failure.**

| PUBBLICATION               | PATIENT POPULATION                                                                                                                                                                                    | TREATMENT                                                                                                                                                                                                                                                         | INTUBATION RATE                                                                                                                                                                                                                                                                                                 | MORTALITY RATE                                                                                                                 |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Bellani et al. [58], 2021  | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 172 mmHg                                                                                                                                   | NIV + CPAP n=798<br>215 [27%] patients with limitations of treatment<br>Helmet was used for 617 patients, face mask for 248<br>Noninvasive respiratory support initiated 1 day after hospital admission<br>PEEP was 10.8 cmH <sub>2</sub> O, ranging from 2 to 20 | Noninvasive respiratory support failure 38%<br>[95% CI 34 to 41] in the overall cohort<br>Noninvasive respiratory support failure 27% [23 to 30] in patients with no limitations of treatment cohort<br>Noninvasive respiratory support failure 67% [61 to 73] in patients with limitations of treatment cohort | Overall mortality was 25% [95% CI 22 to 28]                                                                                    |
| Bertaina et al. [52], 2021 | COVID-19 AHRF<br>51% of patients had SpO <sub>2</sub> <92% on room air                                                                                                                                | NIV n= 390                                                                                                                                                                                                                                                        | NIV failure 44% [95% CI 40 to 49]<br>Received ETI 16% [95% CI 13 to 20]                                                                                                                                                                                                                                         | Overall cohort 38% [95% CI 33 to 43]<br>Among intubated patients 58% [95% CI 46 to 70%]                                        |
| Burns et al. [62], 2020    | COVID-19 AHRF<br>SpO <sub>2</sub> <94% in<br>Venturi Mask 40%                                                                                                                                         | CPAP n=23<br>BIPAP n=5<br>BIPAP settings: max PEEP=10.2 cmH <sub>2</sub> O max Pinsp=22.4 cmH <sub>2</sub> O<br>CPAP settings: Max PEEP=12.7 cmH <sub>2</sub> O                                                                                                   | Not reported                                                                                                                                                                                                                                                                                                    | BIPAP 40% [95% CI 12 to 77]<br>CPAP 52% [33 to 71]                                                                             |
| Duca et al. [53], 2020     | COVID-19 AHRF<br>CPAP Median PaO <sub>2</sub> /FiO <sub>2</sub> 131 mmHg<br>NIV Median PaO <sub>2</sub> /FiO <sub>2</sub> 87 mmHg<br>IMV at arrival Median PaO <sub>2</sub> /FiO <sub>2</sub> 76 mmHg | CPAP n=71<br>Helmet CPAP, PEEP=15cmH <sub>2</sub> O<br>NIV n=7<br>NIV, PEEP=16 cmH <sub>2</sub> O<br>IMV on arrival=7<br>IMV at arrival, PEEP=18 cmH <sub>2</sub> O                                                                                               | CPAP intubation rate 37% [95% CI 26 to 48]<br>NIV intubation rate 0% [95% CI 0 to 35]<br>CPAP failure 92% [95% CI 83 to 96]<br>NIV failure 57% [95% CI 25 to 84]                                                                                                                                                | CPAP 76% [95% CI 65 to 84]<br>NIV 57% [95% CI 25 to 84]<br>IMV at arrival 100% [95% CI 65 to 100]                              |
| Faraone et al. [54], 2020  | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 130 mmHg<br>25 [50%] patients had patients with limitations of treatment                                                                   | NIV n=25<br>CPAP n=25<br>Interface: full face or oronasal mask<br>PEEP started at 5 cmH <sub>2</sub> O, up to 12 cmH <sub>2</sub> O<br>IPAP set at 15cmH <sub>2</sub> O, up to 20–25 cmH <sub>2</sub> O                                                           | Patients with no limitations of treatment: 36% [95% CI 20 to 55]<br>CPAP failure 44% [95% CI 27 to 63]<br>NIV failure 68% [95% CI 48 to 83]                                                                                                                                                                     | Patients with limitations of treatment 88% [95% CI 70 to 96]<br>Patients with no limitations of treatment 12% [95% CI 4 to 30] |

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| Franco et al. [68], 2020   | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 138 mmHg                                                                                                               | HFNO n=163<br>CPAP n=330<br>PEEP 10.2 cmH <sub>2</sub> O<br>Helmet 149 [99%]<br>Face mask 2 [1%]<br>NIV n=177<br>PEEP 9.5 cmH <sub>2</sub> O<br>Pressure Support 17.3 cmH <sub>2</sub> O<br>Helmet 15<br>Face mask 57 | Received IMV: HFNO 29% [95% CI 24 to 36]<br>CPAP 25% [95% CI 20 to 30]<br>NIV 28% [95% CI 22 to 35]<br>HFNO Failure 38% [CI 31 to 47]<br>CPAP Failure 47% [95% CI 42 to 53]<br>NIV Failure 53% [95% CI 46 to 60] | 30-day mortality:<br>HFNO 16% [95% CI 11 to 22]<br>CPAP 30% [95% CI 26 to 35]<br>NIV 31% [95% CI 24 to 38]                        |
| Fu et al. [46], 2021       | COVID-19 AHRF<br>NIV as initial therapy<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 174.4 mmHg<br>NIV as rescue therapy<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 179.27 mmHg | NIV as initial therapy N=22<br>NIV as rescue therapy N=17<br>PEEP in NIV success: 6<br>PEEP in NIV failure: 6<br>Pressure Support in NIV success: 7<br>Pressure Support in NIV failure: 6                             | NIV as initial therapy 23% [95% CI 10 to 43]<br>NIV as rescue therapy 65% [95% CI 41 to 83]                                                                                                                      | NIV initial therapy 5% [95% CI 8 to 22]<br>NIV as rescue therapy 12% [95% CI 3 to 34]                                             |
| Grieco et al. [78], 2021   | COVID-19 AHRF<br>NIV PaO <sub>2</sub> /FiO <sub>2</sub> 105 mmHg<br>HFNO PaO <sub>2</sub> /FiO <sub>2</sub> 102 mmHg                                                              | Helmet NIV n=54<br>Continuous treatment<br>PEEP 12 cmH <sub>2</sub> O<br>Pressure Support 10 cmH <sub>2</sub> O<br>HFNO n=55                                                                                          | Helmet NIV 30% [95% CI 19 to 43]<br>HFNO 51% [95% CI 38 to 64]                                                                                                                                                   | HFNO 25% [16 to 38]<br>Helmet NIV 24% [95% CI 15 to 37]                                                                           |
| Hua et al. [55], 2020      | COVID-19 AHRF                                                                                                                                                                     | SOT n=204<br>IMV n=113<br>NIV n=152                                                                                                                                                                                   | Not reported                                                                                                                                                                                                     | SOT 6% [95% CI 4 to 11]<br>IMV 92% [95% CI 86 to 96]<br>NIV 41% [95% CI 33 to 49]                                                 |
| Liu et al. [76], 2021      | COVID-19 AHRF                                                                                                                                                                     | HFNO n=366<br>NIV n=286                                                                                                                                                                                               | HFNO 56% [95% CI 51 to 61]<br>NIV 74% 95% CI [68 to 78]                                                                                                                                                          | HFNO 49% [95% CI 44 to 54]<br>NIV 62% [95% CI 56 to 67]                                                                           |
| Menzella et al. [56], 2021 | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 120.1 mmHg                                                                                                             | NIV n=79<br>PEEP: 9.46 cmH <sub>2</sub> O<br>IPAP: 17.7 cmH <sub>2</sub> O                                                                                                                                            | ETI rate after the exclusion of patients with limitations of treatment and 2 sudden deaths<br>36% [95% CI 25 to 48]<br>NIV failure in the overall cohort 52% [95% CI 41 to 63]                                   | Mortality in the 20 intubated patients were 43% [95% CI 25 to 63]<br>18 [23%] patients had patients with limitations of treatment |

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|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
|                                  |                                                                                                                                                                                    |                                                                                                                                                  |                                                                                                                                                            | 2 [3%] patients died of sudden death                                                                                            |
| Mukhtar et al. [77], 2020        | COVID-19 AHRF                                                                                                                                                                      | NIV n=39                                                                                                                                         | Need for ETI 23% [13 to 38]<br>NIV failure 31% [95% CI 19 to 46]                                                                                           | 26% [15 to 41]                                                                                                                  |
| Rose'n et al. [89], 2021         | COVID-19 AHRF<br>Standard care n=39<br>PaO <sub>2</sub> /FiO <sub>2</sub> standard care 115 mmHg<br>Prone n=36<br>PaO <sub>2</sub> /FiO <sub>2</sub> prone 115 mmHg                | HFNO standard care n=29<br>HFNO prone n=31<br>NIV standard care n=27<br>PEEP 8 cmH <sub>2</sub> O<br>NIV prone n=21<br>PEEP 7 cmH <sub>2</sub> O | Standard care group 33% [95% CI 20 to 49]<br>Prone group 33% [95% CI 20 to 50]                                                                             | Control group 8% [95% CI 3 to 20]<br>Prone group 17% [95% CI 8 to 22]                                                           |
| Sivaloganathan et al. [79], 2020 | COVID-19 AHRF<br>Worst PaO <sub>2</sub> /FiO <sub>2</sub> ratio:<br>NIV only: 127.5 mmHg<br>NIV + MV: 104.26 mmHg<br>IMV only: 115 mmHg<br>NIV – limitations of treatment: 75 mmHg | NIV only n=31<br>NIV + MV n=27<br>IMV only n=21<br>NIV–limitations of treatment n=24                                                             | Patients with no limitations of treatment: 47% [95% CI 34 to 59]                                                                                           | Patients with no limitations of treatment: 5% [95% CI 2 to 14]<br>Patients with limitations of treatment: 83% [95% CI 64 to 93] |
| Vianello et al. [74], 2020       | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 108 mmHg                                                                                                                | HFNO n=28<br>Rescue NIV n=9                                                                                                                      | HFNO failure 32% [95% CI 18 to 51]<br>Rescue NIV failure 56% [95% CI 27 to 81]<br>ETI 18% [95% CI 8 to 36]                                                 | 11% [95% CI 4 to 27]                                                                                                            |
| Wang et al. [59], 2020           | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 209 mmHg in success patients<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 142 mmHg in failure patients                  | HFNO n=17<br>only IMV n=1<br>first line NIV n=9<br>rescue NIV n=7                                                                                | HFNO failure and rescue NIV 41% [95% CI 22 to 64]<br>HFNO 12% [95% CI 3 to 34]<br>First line NIV failure 11% [2 to 42]<br>Rescue NIV failure 29% [8 to 64] | Not reported                                                                                                                    |
| Wendel Garcia et al. [75], 2021  | COVID-19 AHRF<br>Median PaO <sub>2</sub> /FiO <sub>2</sub> 123 mmHg                                                                                                                | SOT n=87<br>HFNO n=87<br>NIV n=87<br>MV n=92                                                                                                     | SOT 64% [95% CI 53 to 63]<br>HFNO 52% [95% CI 41 to 62]<br>NIV 49% [95% CI 39 to 60]                                                                       | SOT 18% [95% CI 11 to 27]<br>HFNO 20% [95% CI 13 to 29]<br>NIV 37% [27 to 47]                                                   |

AHRF, acute hypoxemic respiratory failure; NIV, non-invasive ventilation; CPAP, continuous positive airway pressure.