

# Risk factors associated with failure of high-flow nasal cannula oxygen therapy in patients with severe COVID-19 in Wuhan, China

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## Research article

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# Abstract

**Background:** Acute hypoxemic respiratory failure is prevalent in severe Coronavirus Disease 2019 (COVID-19). High-flow nasal cannula oxygen therapy (HFNC) is currently one of the most common ventilation strategies for COVID-19 patients with respiratory failure. This study is to analyze the risk factors associated with HFNC failure in patients with severe COVID-19.

**Methods:** In this single-center, retrospective, observational study, we enrolled patients with confirmed severe COVID-19 admitted to Renmin Hospital of Wuhan university (Wuhan, China) from 1 February 2020 to 26 March 2020. Epidemiological, clinical, and laboratory data, and treatments and outcomes upon hospital admission, were obtained from electronic medical records. Sequential organ failure assessment (SOFA) scores were calculated.

**Results:** Of 54 patients with severe COVID-19, HFNC was successful in 28 (51.9%) and unsuccessful in 26 (48.1%). HFNC failure was seen more commonly in patients aged  $\geq 60$  years and in men. In addition, compared with patients successfully treated with HFNC, patients with HFNC failure had the following characteristics: higher percentage of fatigue and anorexia as well as cardiovascular disease; increased time from onset to diagnosis and SOFA scores; elevated body temperature, respiratory rate, and heart rate; more complications including ARDS, septic shock, myocardial damage, and acute kidney injury; increased C-reactive protein, neutrophil counts and prothrombin time; and decreased arterial partial pressure of oxygen/fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) (all  $P < 0.05$ ). However, binary logistic regression analysis showed that only male,  $\text{PaO}_2/\text{FiO}_2$  and SOFA scores were independent risk factors significantly associated with HFNC failure (all  $P < 0.05$ ).

**Conclusion:** Patients with severe COVID-19 had a high HFNC treatment failure rate. Male, low  $\text{PaO}_2/\text{FiO}_2$  and SOFA scores were independent risk factors associated with HFNC failure in severe COVID-19 patients. However, studies with larger sample sizes or multi-center studies are warranted.

## Background

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious disease caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV) [1, 2]. Patients with severe COVID-19 may develop dyspnea and hypoxemia within 1 week after the onset of COVID-19, which may quickly progress to acute respiratory distress syndrome (ARDS) or end-organ failure [3]. In three pooled studies of 278 patients with COVID-19, 56 (20.1%) developed ARDS [3-5]. Considering that acute hypoxemic respiratory failure is prevalent in severe COVID-19, the large-scale, safe delivery of respiratory support is needed to resolve the key healthcare challenge of the COVID-19 pandemic [6].

High-flow nasal cannula oxygen therapy (HFNC) is a non-invasive therapy where heated, humidified oxygen is delivered via a large-bore nasal cannula at flow rates up to 60 L/min [7]. HFNC may be considered a first-line therapy in acute respiratory failure, including in patients with ARDS [8]. The major

goal of HFNC in treating ARDS is to achieve sufficient oxygenation to avoid endotracheal intubation. Compared with standard oxygen therapy, HFNC can improve oxygenation, decrease respiratory rate, increase lung volumes, and improve patient comfort [7]; HFNC may also be better tolerated than non-invasive ventilation. Therefore, HFNC may be an appropriate therapy for many COVID-19 patients for whom tracheal intubation has not yet become a necessity but for whom low-flow nasal oxygen or facemask oxygen is not providing adequate respiratory support [6]. HFNC is currently one of the most common ventilation strategies for COVID-19 patients with respiratory failure [9]. To avoid HFNC failure and intubation delay, it is essential to know how to select appropriate COVID-19 patients for HFNC. However, little attention has been paid to evaluating the risk factors associated with HFNC failure. This retrospective, observational study was performed to analyze the risk factors associated with HFNC failure in severe COVID-19 patients with hypoxic respiratory failure.

## Materials And Methods

### Patients

We collected data for patients with COVID-19 admitted to the Infectious Disease Department of the Renmin Hospital of Wuhan University (Wuhan, China) from 1 February 2020 to 26 March 2020. The selected patients met the following inclusion criteria: (1) aged  $\geq 18$  years; (2) diagnosis of severe COVID-19; and (3) treated with HFNC for hypoxic respiratory failure. Severe COVID-19 was defined according to the Chinese management guidelines for COVID-19 (version 6.0) [10]. COVID-19 was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay [11]. The retrospective analysis of data was approved by the ethics committee of First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2020-88). As this was a retrospective study, the need for informed consent from study participants was waived.

### HFNC

HFNC (Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) was used in severe COVID-19 patients with the aim of reaching and maintaining a target pulse blood oxygen saturation ( $\text{SpO}_2$ )  $> 90\%$  only when dyspnea (respiratory rate  $\geq 30$  breaths/min) and/or hypoxemia ( $\text{SpO}_2 < 90\%$ ) were not improved after treatment with standard oxygen therapy (oxygen inhalation by nasal tube or facemask) [10]. The temperature was set at  $31^\circ\text{C}$  to  $37^\circ\text{C}$ , the flow was set at 30 L/min to 60 L/min, and the fraction of inspired oxygen concentration ( $\text{FiO}_2$ ) was set to maintain a  $\text{SpO}_2$  of  $> 93\%$ . HFNC was used continuously for all enrolled patients in the initial phase of treatment. When respiratory failure was reversed, HFNC was used intermittently. The time of standard oxygen therapy was gradually increased, and the duration of HFNC was gradually shortened until the patient was totally weaned from HFNC. However, if dyspnea (respiratory rate  $\geq 30$  breaths/min) and/or hypoxemia ( $\text{SpO}_2 < 90\%$ ) were not improved within 1–2 hours after treatment with HFNC, the attending physicians determined whether to use either noninvasive ventilation (NIV) or invasive mechanical ventilation as rescue therapy; early endotracheal intubation and invasive mechanical ventilation were immediately considered in patients who failed to maintain arterial

partial pressure of oxygen ( $\text{PaO}_2$ )/ $\text{FiO}_2 > 150$  within 1–2 hours after treatment with HFNC [10]. Patients who were changed from HFNC to conventional oxygen therapy were defined as successful HFNC treatment (Success group), and patients who required NIV or intubation as rescue therapy, or who died, were defined as HFNC treatment failure (Failure group).

## Data collection

Epidemiological data, demographics, medical history, contact history, signs and symptoms, comorbidities, and laboratory results were collected from patients' clinical records. Disease severity was assessed with the sequential organ failure assessment (SOFA) score. We also recorded outcomes within 28 days of HFNC treatment.

## Statistical Analysis

Data were analyzed with SPSS 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were described as medians (ranges), while categorical variables were expressed as frequencies (%). Categorical data were compared using the  $\chi^2$  test or Fisher's exact test; continuous variables were compared by the Mann–Whitney  $U$  test. We performed binary logistical regression analysis to determine the risk factors associated with HFNC failure, and the odds ratios and 95% confidence intervals were reported. All tests were two-sided, and  $P$ -values  $< 0.05$  were considered statistically significant.

## Results

We enrolled 54 severe COVID-19 patients treated with HFNC (Fig. 1). Twenty-eight cases (51.9%, 28/54) were successfully treated by HFNC (Success group); 26 cases (48.1%, 26/54) experienced HFNC treatment failure (Failure group). Among patients in the Failure group, 9 cases received noninvasive ventilation as rescue therapy, and 15 cases received endotracheal intubation and invasive mechanical ventilation as rescue therapy. In addition, among 9 cases receiving noninvasive ventilation, 6 cases received endotracheal intubation and invasive mechanical ventilation as rescue therapy. Among 10 cases that died in the Failure group, 2 COVID-19 cases with a long time of coronary heart disease died during HFNC therapy because of sudden cardiac arrest induced by the initial rhythm of ventricular fibrillation, 6 cases died during invasive mechanical ventilation therapy because of severe ARDS, and 2 cases died during noninvasive ventilation therapy because of the relative's refusal to early intubation and invasive mechanical ventilation.

The clinical characteristics of severe COVID-19 patients treated with HFNC in the Success and Failure groups are summarized in Table 1. Patients in the Failure group were older than those in the Success group, but without significant difference; whereas the percentage of patients older than 60 years of age in the Failure group was higher than that in the Success group (69.2% vs. 30.8%, respectively;  $P = 0.001$ ). Male patients were more common in the Failure group, with a higher proportion than that in the Success group (61.5% vs. 38.5%, respectively;  $P < 0.001$ ). Notably, patients in the Failure group had a significantly higher percentage of fatigue, anorexia, and the comorbidity of cardiovascular disease than patients in the

Success group. In addition, the time from onset to diagnosis was longer in the Failure group than that in the Success group, indicating delayed hospitalization and treatment in the Failure group. Body temperature, respiratory rate, and heart rate were also significantly higher in the Failure group than in the Success group. Furthermore, patients in the Failure group had significantly higher SOFA scores, with a significantly higher percentage of ARDS, septic shock, and acute myocardial and kidney injury than those in the Success group, indicating greater disease severity in the patients in the Failure group. Patients in the Failure group had significantly higher neutrophil counts, prothrombin time, creatinine level and C-reactive protein, a significantly lower  $\text{PaO}_2 / \text{FiO}_2$  than the Success group (all  $P<0.05$ ).

**Table 1** Characteristics of severe COVID-19 patients treated with HFNC

|  | Normal range | Total<br>( <i>n</i> = 54) | Success<br>group<br>( <i>n</i> = 28) | Failure<br>group<br>( <i>n</i> = 26) | $\chi^2/F$ | <i>P</i> * |
|--|--------------|---------------------------|--------------------------------------|--------------------------------------|------------|------------|
| <b>Age</b> (years)                           | —            | 64 (27- 95)               | 57 (27-87)                           | 74 (34-95)                           | 1.951      | 0.057      |
| ≤60 [ <i>n</i> (%)]                          | —            | 23 (42.6)                 | 15 (53.6)                            | 8 (30.8)                             | 10.824     | 0.001      |
| ≥60 [ <i>n</i> (%)]                          | —            | 31 (57.3)                 | 13 (46.4)                            | 18 (69.2)                            | 10.824     | 0.001      |
| <b>Male</b> [ <i>n</i> (%)]                  | —            | 25 (46.3)                 | 9 (32.1)                             | 16 (61.5)                            | 18.602     | < 0.001    |
| <b>Source of infection</b> [ <i>n</i> (%)]   |              |                           |                                      |                                      |            |            |
| No   | —            | 44 (81.5)                 | 23 (82.1)                            | 20 (77.0)                            | 116.114    | < 0.001    |
| Family gathering                             | —            | 6 (11.1)                  | 3 (10.7)                             | 3 (11.5)                             | 116.114    | < 0.001    |
| Hospital contacting                          | —            | 4 (7.4)                   | 2 (7.1)                              | 3 (11.5)                             | 116.114    | < 0.001    |
| <b>Signs and symptoms</b> [ <i>n</i> (%)]    |              |                           |                                      |                                      |            |            |
| Fever  | —            | 20 (30.0)                 | 13 (46.4)                            | 7 (26.9)                             | 2.200      | 0.138      |
| Dyspnea                                      | —            | 36 (66.7)                 | 18 (64.3)                            | 18 (69.2)                            | 0.561      | 0.454      |
| Dry cough                                    | —            | 26 (48.1)                 | 15 (53.6)                            | 11 (42.3)                            | 0.685      | 0.408      |
| Fatigue                                      | —            | 28 (51.9)                 | 10 (35.7)                            | 18 (69.2)                            | 8.026      | 0.005      |
| Anorexia                                     | —            | 19 (35.2)                 | 6 (21.4)                             | 13 (50.0)                            | 4.826      | 0.028      |
| Dizzy  | —            | 1 (1.9)                   | 0 (0)                                | 1 (3.8)                              | 1.097      | 0.295      |
| Diarrhea                                     | —            | 1 (1.9)                   | 1 (3.6)                              | 0 (0)                                | 0.946      | 0.331      |
| <b>Comorbidities</b> [ <i>n</i> (%)]         |              |                           |                                      |                                      |            |            |
| Hypertension                                 | —            | 21 (38.9)                 | 9 (32.1)                             | 12 (46.2)                            | 1.114      | 0.291      |
| Diabetes                                     | —            | 10 (18.5)                 | 7 (25.0)                             | 3 (11.5)                             | 1.619      | 0.203      |
| Cardiovascular disease                       | —            | 11 (20.4)                 | 2 (7.1)                              | 9 (34.6)                             | 6.273      | 0.012      |
| Cerebrovascular disease                      | —            | 4 (7.4)                   | 1 (3.6)                              | 3 (11.5)                             | 1.248      | 0.264      |
| Chronic kidney injury                        | —            | 2 (3.7)                   | 1 (3.6)                              | 1 (3.8)                              | 0.003      | 0.957      |
| COPD   | —            | 6 (11.1)                  | 3 (10.7)                             | 3 (11.5)                             | 0.009      | 0.923      |
| Cancer                                       | —            | 1 (1.9)                   | 0 (0)                                | 1 (3.8)                              | 1.097      | 0.295      |
| Hyperthyroidism                              | —            | 1 (1.9)                   | 0 (0)                                | 1 (3.8)                              | 1.097      | 0.295      |
| <b>Time from onset to diagnosis</b> (days)   | —            | 4 (0-9)                   | 3 (0-9)                              | 5 (1-9)                              | 19.505     | 0.021      |
| <b>SOFA</b> (scores)                         | —            | 3.0 (0-14)                | 2.5 (0-5)                            | 5.0 (2-14)                           | 4.186      | < 0.001    |
| <b>Vital signs</b>                           |              |                           |                                      |                                      |            |            |
| Temperature (°C)                             | 36-37        | 37.5 (35.5-39.2)          | 37.4 (36.0-39.2)                     | 37.7 (35.5-39.0)                     | 2.064      | 0.031      |
| Respiratory rate (/min)                      | 12-20        | 28 (16-40)                | 25 (16-32)                           | 31 (16-40)                           | 1.688      | 0.042      |
| Heart rate (/min)                            | 60-90        | 88 (55-146)               | 87 (55-130)                          | 98 (70-146)                          | 1.429      | 0.027      |
| MAP (mmHg)                                   | 70-105       | 93 (75-123)               | 94 (75-123)                          | 93 (77-123)                          | 1.892      | 0.062      |
| <b>Organ function injury</b> [ <i>n</i> (%)] |              |                           |                                      |                                      |            |            |
| ARDS   | —            | 32 (59.3)                 | 11 (39.3)                            | 21 (80.8)                            | 9.610      | 0.002      |
| Septic shock                                 | —            | 8 (14.8)                  | 0 (0)                                | 8 (30.8)                             | 10.114     | 0.001      |
| Myocardial damage                            | —            | 11 (20.4)                 | 1 (3.6)                              | 10 (38.5)                            | 10.117     | 0.001      |
| Liver injury                                 | —            | 16 (29.6)                 | 7 (25.0)                             | 9 (34.6)                             | 0.598      | 0.439      |
| AKI  | —            | 8 (14.8)                  | 0 (0)                                | 8 (30.8)                             | 10.114     | 0.001      |

|   |           |                   |                   |                   |        |       |
|---|-----------|-------------------|-------------------|-------------------|--------|-------|
| Gastrointestinal hemorrhage               | —         | 1 (1.9)           | 0 (0)             | 1 (3.8)           | 1.058  | 0.304 |
| <b>Whole blood cell analysis</b>          |           |                   |                   |                   |        |       |
| White blood cells (×10 <sup>9</sup> /L)   | 3.5-9.5   | 7.01 (2.01-21.03) | 5.62 (2.01-14.02) | 8.85 (3.02-21.03) | 21.430 | 0.065 |
| Neutrophils count (×10 <sup>9</sup> /L)   | 1.8-6.3   | 5.51 (2.02-20.14) | 3.61 (2.02-13.25) | 7.57 (2.03-20.27) | 17.850 | 0.013 |
| Lymphocytes (×10 <sup>9</sup> /L)         | 1.1-3.2   | 0.87 (0-2.02)     | 1.01 (0-2.02)     | 0.79 (0-2.02)     | 5.582  | 0.061 |
| Red blood cells (×10 <sup>12</sup> /L)    | 3.8-5.1   | 4.12 (3.02-5.02)  | 4.11 (3.03-5.03)  | 4.13 (3.22-4.91)  | 2.407  | 0.492 |
| Hemoglobin (g/L)                          | 115-150   | 128 (72-157)      | 128 (72-157)      | 128 (104-157)     | 36.947 | 0.334 |
| Platelets (×10 <sup>9</sup> /L)           | 125-350   | 176 (20-396)      | 205 (59-396)      | 149 (20-326)      | 50.072 | 0.391 |
| <b>Coagulation function parameters</b>    |           |                   |                   |                   |        |       |
| Prothrombin time (seconds)                | 9-13      | 12.4 (10.5-20.2)  | 12.0 (10.5-15.3)  | 13.5 (10.8-20.2)  | 17.069 | 0.009 |
| APTT (seconds)                            | 25.0-31.3 | 28.8 (22.7-63.2)  | 28.3 (22.7-55.8)  | 29 (23.9-63.2)    | 15.638 | 0.269 |
| Fibrinogen (g/L)                          | 2-4       | 4.50 (0.28-7.45)  | 4.56 (2.48-7.45)  | 3.72 (0.28-6.78)  | 12.610 | 0.082 |
| D-dimer (mg/L)                            | 0-0.55    | 1.3 (0.2-179.7)   | 0.9 (0.2-13.5)    | 10.0 (0.3-179.7)  | 21.082 | 0.275 |
| <b>Liver injury markers</b>               |           |                   |                   |                   |        |       |
| ALT (U/L)                                 | 9-50      | 25.1 (7.3-532.6)  | 22.1 (7.3-532.6)  | 27.2 (8.9-102.2)  | 37.144 | 0.326 |
| AST(U/L)                                  | 15-40     | 33.3 (13.5-768.0) | 25.2 (13.0-768.5) | 43.2 (21.5-139.5) | 44.148 | 0.195 |
| Albumin (g/L)                             | 40-55     | 34.0 (27.9-61.1)  | 35.2 (27.9-61.1)  | 33.4 (27.9-40.6)  | 15.606 | 0.481 |
| Total bilirubin (μmol/L)                  | 0-23      | 10.0 (6.1-411.3)  | 9.7 (6.1-21.3)    | 12.4 (7.5-411.3)  | 17.222 | 0.371 |
| <b>Kidney injury marker</b>               |           |                   |                   |                   |        |       |
| Creatinine (μmol/L)                       | 59-104    | 67 (13-293)       | 64 (42-139)       | 75 (13-293)       | 2.482  | 0.027 |
| BUN (mmol/L)                              | 3.6-9.5   | 5.7 (2.0-31.5)    | 4.9 (2.0-14.6)    | 7.4 (2.9-31.5)    | 1.877  | 0.175 |
| <b>Blood gas analysis</b>                 |           |                   |                   |                   |        |       |
| PH  | 7.35-7.45 | 7.43 (7.72-7.14)  | 7.43 (7.33-7.54)  | 7.43 (7.14-7.72)  | 1.603  | 0.112 |
| PaCO <sub>2</sub> (mmHg)                  | 35-48     | 37 (25-68)        | 36 (25-53)        | 34 (25-68)        | 1.683  | 0.090 |
| PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg) | 400-500   | 186 (49-475)      | 223 (98-475)      | 143 (49-273)      | 10.385 | 0.032 |
| <b>C-reactive</b>                         | 0-10      | 61.3 (5.2-        | 52.6 (5.5-        | 102.3 (5.0-       | 7.975  | 0.007 |

|                       |       |                      |                      |                      |       |       |
|-----------------------|-------|----------------------|----------------------|----------------------|-------|-------|
| <b>protein</b> (mg/L) |       | 200.0)               | 200.0)               | 200.0)               |       |       |
| <b>PCT</b> (ng/mL)    | 0-0.1 | 0.12 (0.01-<br>2.96) | 0.11 (0.02-<br>2.96) | 0.17 (0.01-<br>2.01) | 1.323 | 0.516 |

Note: Values are the medians (ranges). **P\*** indicates the *P*-values for the comparisons of the Success group and Failure group.  $\chi^2/F$ , chi-square/Fisher's exact test; HFNC, high-flow nasal cannula; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; SOFA, sequential organ failure assessment; MAP, mean arterial pressure; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; PCT, procalcitonin; PaO<sub>2</sub>/FiO<sub>2</sub>, arterial partial pressure of oxygen/fraction of inspired oxygen; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Considering the small sample size in our study ( $n = 54$ ) and to avoid overfitting in the model, we chose five independent variables for binary logistic regression analysis according to previous findings and clinical constraints. We used HFNC failure as a dependent variable, and age, sex, time from onset to diagnosis, PaO<sub>2</sub>/FiO<sub>2</sub>, and SOFA scores as independent variables. Binary logistic regression analysis showed that only male, low PaO<sub>2</sub>/FiO<sub>2</sub> and SOFA scores were independent risk factors significantly associated with HFNC failure in patients with severe COVID-19 (Table 2).

**Table 2** Risk factors associated with HFNC failure in severe COVID-19 patients

|                      | <b>β value</b> | <b>Wald value</b> | <b>P value</b> | <b>OR value</b> | <b>95% CI</b> |
|----------------------|----------------|-------------------|----------------|-----------------|---------------|
| . onset to diagnosis | 0.005          | 0.024             | 0.877          | 1.005           | 0.948-1.064   |
|                      | 1.821          | 4.880             | 0.027          | 6.178           | 1.228-31.089  |
|                      | 0.057          | 0.111             | 0.739          | 1.058           | 0.758-1.477   |
|                      | -0.019         | 4.995             | 0.025          | 0.981           | 0.965-0.998   |
|                      | 0.790          | 4.288             | 0.038          | 2.202           | 1.043-4.650   |
| res                  | 0.158          | 0.003             | 0.954          | 1.171           |               |

Note: CI, confidence interval; COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; OR, odds ratio; PaO<sub>2</sub>/FiO<sub>2</sub>, arterial partial pressure of oxygen/fraction of inspired oxygen; SOFA, sequential organ failure assessment.

## Discussion

This study retrospectively investigated the clinical characteristics of COVID-19 patients with HFNC failure and the risk factors associated with HFNC failure. We observed that patients with severe COVID-19 had a high failure rate with HFNC treatment (48.1%, 26/54), which is similar to results in a study by Wang et al. (41.2%, 7/17) [9]. Notably, HFNC failure was seen more commonly in patients aged  $\geq 60$  years and in men. In addition, patients experiencing HFNC failure had the following characteristics: higher percentage of fatigue and anorexia as well as cardiovascular disease; increased time from onset to diagnosis and SOFA scores; elevated body temperature, respiratory rate, and heart rate; more complications such as



ARDS, septic shock, myocardial damage, and acute kidney injury; increased C-reactive protein, neutrophil counts and prothrombin time; and decreased  $\text{PaO}_2/\text{FiO}_2$ . However, only male,  $\text{PaO}_2/\text{FiO}_2$  and SOFA scores were independent risk factors significantly associated with HFNC failure.

Increasing data show that the severity of SARS-CoV-2 infection is gender-related [12]. Two studies have reported a higher rate of severe cases in adult men compared with women, with rates ranging from 58% to 67% [13, 14]. A retrospective cohort study in China also showed that male is a major risk factor for higher disease severity and mortality [15]. This association of male with disease severity and high mortality may be explained by high expression of type 2 angiotensin converting enzyme (ACE2) and serine-protease TMPRSS2 in male patients, which are two major host proteins involved in cell–virus entry and in triggering the viral cell cycle. Previous studies of SARS-CoV-2 showed that only serine-protease TMPRSS2 is essential for viral spread and pathogenesis [16, 17]. In addition, estrogen can enhance TMPRSS2 expression through the binding of their respective receptors to their responsive elements because the androgen-responsive element is the only known transcription promoter for TMPRSS2 [12]. Data from murine models showed that androgenic control of TMPRSS2 expression is also maintained in lung tissue [18]. Therefore, male patients with COVID-19 have a possibility of more severe lung injury resulting from SARS-CoV-2 infection. In the present study, we found that male COVID-19 patients had a higher possibility of HFNC failure, which was consistent with the tendency toward more severe disease and higher mortality in male patients with COVID-19 [4, 5, 14, 19, 20]. This higher possibility of HFNC failure may be because of the greater disease severity and poorer tolerance to HFNC treatment in male patients, especially older male patients. Thus, early monitoring with high-quality supportive care is needed for these patients, and HFNC treatment should be implemented as early as possible to avoid treatment delay for older male patients with COVID-19 at high risk.

We also found that low  $\text{PaO}_2/\text{FiO}_2$  and SOFA scores were independent risk factors significantly associated with HFNC failure. Our observations showed that  $\text{PaO}_2/\text{FiO}_2$ , as one of six variables, constituted a large proportion when assessing SOFA scores in patients with severe COVID-19 because other variables (namely platelets, bilirubin, mean arterial blood pressure, Glasgow coma score, and creatinine) were not as affected in these patients. Increasing evidence also shows that patients with severe COVID-19 are characterized by classic ARDS, as indicated by the signs of dyspnea and decreased  $\text{PaO}_2/\text{FiO}_2$  [4, 5, 14, 19–22]. Indeed, from a therapy perspective, positive end-expiratory pressure (PEEP) ventilation is optimally used to increase functional residual capacity and open collapsed alveoli, thereby improving ventilation–perfusion matching and reducing intrapulmonary shunting, as well as improving lung compliance and thus, reducing respiratory load. In addition, PEEP assists respiratory muscles during inspiration, reducing the work of breathing and dyspnea. From a theoretical and physiological point of view, HFNC may also be beneficial in patients with ARDS. However, HFNC is only a “partial support” therapy. This is mainly because HFNC generates only a small positive pressure spike at end-expiration that depends on the nasal airflow and the extent of mouth opening. HFNC appears to improve oxygenation primarily by flushing the nasal airspaces, reducing anatomical dead space. As such, HFNC does not sufficiently address the underlying pathology of ARDS, such as the ventilation–perfusion

mismatch caused by atelectasis or consolidation in the dependent areas when patients are supported with HFNC [23]. Therefore, HFNC is more likely to be unsuccessful when used in COVID-19 patients with low  $\text{PaO}_2/\text{FiO}_2$ . A recent study showed that HFNC alone could be offered for mild cases ( $\text{PaO}_2/\text{FiO}_2$  between 200 mmHg and 300 mmHg) [22]. Therefore, COVID-19 patients with severe ARDS are not appropriate candidates for HFNC [24], and invasive mechanical ventilation is an optimal choice. This is because invasive mechanical ventilation may result in better physiological effects on ventilation–perfusion mismatch and greater homogeneity in ARDS mechanics during positive pressure support [24]

## Limitations

There were two limitations in the present study. First, this was a retrospective study, which may limit the strength and reliability of our results. Second, this was a single-center study with a relatively small sample size. The small sample size was prone to generating bias, yielding spurious findings on statistical analysis and thus, limiting the reliability of our results. Increasing the sample size by enrolling more cases in future studies may avoid this limitation.

## Conclusions

Patients with severe COVID-19 had a high failure rate with HFNC treatment. Male, low  $\text{PaO}_2/\text{FiO}_2$  and SOFA scores were independent risk factors associated with HFNC failure in severe COVID-19 patients. However, studies with larger sample sizes or multi-center studies are warranted.

## Abbreviations

ACE2: type 2 angiotensin converting enzyme; ARDS: acute respiratory distress syndrome; COVID-19: Coronavirus Disease 2019;  $\text{FiO}_2$ : inspired oxygen concentration; HFNC: High-flow nasal canula; NIV: noninvasive ventilation;  $\text{PaO}_2$ : arterial partial pressure of oxygen; PEEP: positive end-expiratory pressure; RT-PCR: real-time reverse transcription polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SOFA: sequential organ failure assessment;  $\text{SpO}_2$ : pulse arterial oxygen saturation.

## Declarations

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### Authors' contributions

PG and HG conceived and designed the study. XH-M, MM-A and PG participated in patient management and data collection. XH-M, MM-A, FY, JZ, HG, and PG analyzed the data. XH-M and PG wrote the manuscript. HG and PG took overall responsibility for the manuscript. All authors approved the final version of the manuscript.

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## **Availability of data and materials**

All data generated or analyzed during this study are included in this manuscript.

## **Ethics approval and consent to participate**

The present study was approved by the ethics board of First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2020-88). The need for written informed consent was waived owing to the rapid emergence of this infectious disease.

## **Consent for publication**

Not applicable.

## **Competing interests**

The authors declare that they have no competing interests.

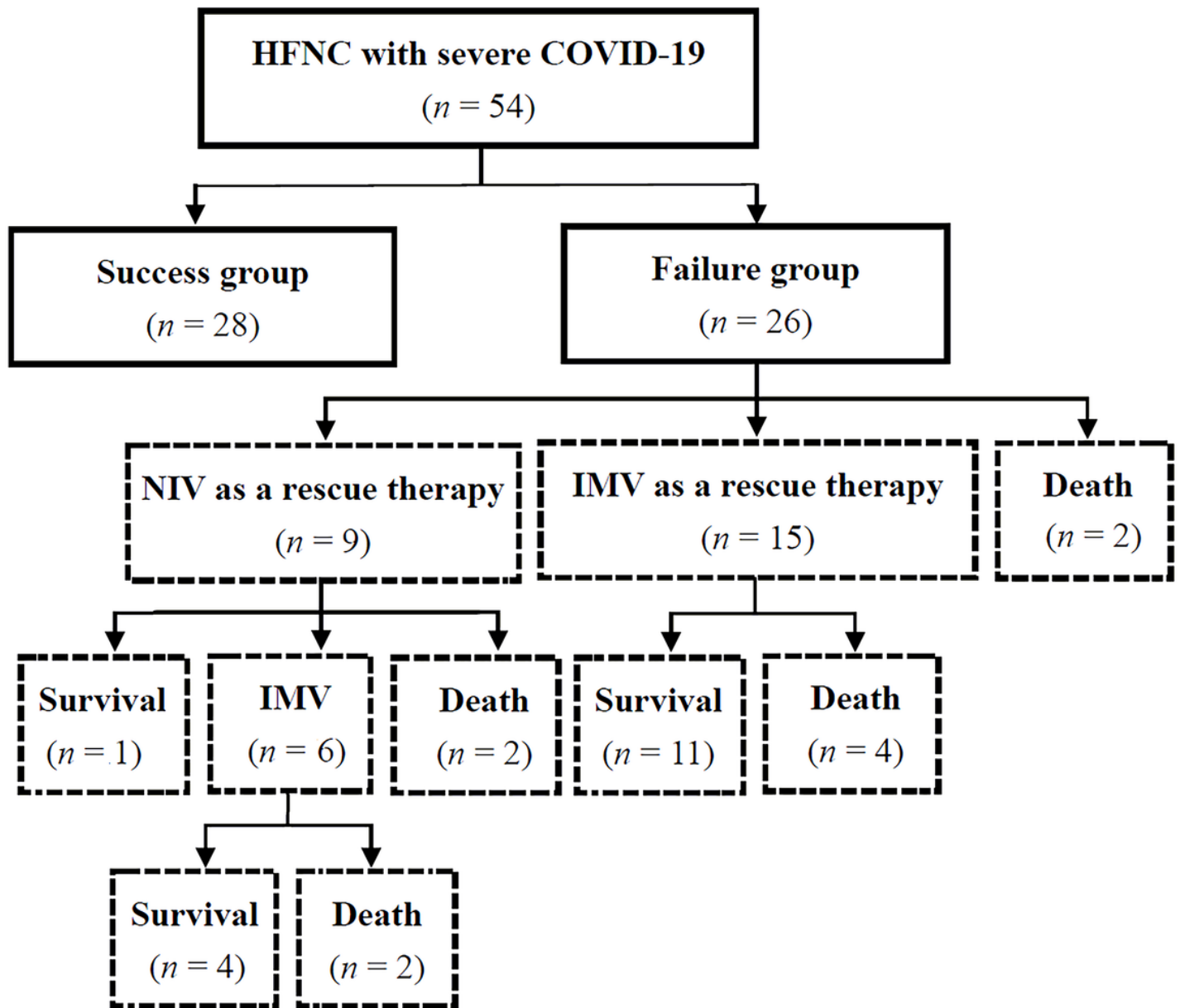
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## Figures



**Figure 1**

Flowchart of participant enrolment in this study HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; COVID-19, coronavirus disease 2019.