Role of advanced respiratory support in acute respiratory failure in clinically frail patients with COVID-19

Iftikhar Nadeem*,1, Louise Jordon1, Masood Ur Rasool2, Noor Mahdi1, Ritesh Kumar1, Zahra Rehman3, Craig J Tilley1, Simran Kang3, Amrita Rai3, She Lok1 & Alison McMillan1

1Department of Respiratory Medicine, East & North Hertfordshire NHS Trust, Stevenage, UK
2Department of Respiratory Medicine, Norfolk & Norwich University Hospital NHS Trust, Norwich, UK
3Department of Internal Medicine, East & North Hertfordshire NHS Trust, Stevenage, UK

* Author for correspondence: iftikharnadeem49@gmail.com

Background: The main aim of this study was to assess the efficacy of advanced respiratory support (ARS) for acute respiratory failure in do-not-attempt cardiopulmonary resuscitation order (DNACPR) COVID-19 patients. Methods: In this single-center study, the impact of different types of ARS modality, PaO2/FiO2 (PF) ratio, clinical frailty score (CFS) and 4C score on mortality was evaluated. Results: There was no significant difference in age, type of ARS modality, PF ratio and 4C scores between those who died and those who survived. Overall survival rates/hospital discharge of patients still requiring ARS at 5 and 7 days post admission were 20 and 17%, respectively. Conclusion: Our study showed that ARS can be a useful tool in frail, elderly and high-risk COVID-19 patients irrespective of high 4C mortality score.

First draft submitted: 25 August 2021; Accepted for publication: 4 November 2021; Published online: 17 December 2021

Keywords: acute respiratory support • clinical frailty score (CFS) • COVID-19 • invasive mechanical ventilation • ISARIC 4C mortality score • noninvasive mechanical ventilation (CPAP & HFNO) • PaO2/FiO2 Ratio

Since the outbreak of COVID-19 in December 2019, the approach for managing acute respiratory failure (ARF) in COVID-19 has been under continuous review by various research and medical communities. According to initial studies, 67% of the patients admitted to intensive care developed acute respiratory distress syndrome (ARDS) [1] and that 2–17% of the patients hospitalized with COVID-19 required invasive mechanical ventilation [2–4]. Over the course of the pandemic, there has been a steady increase in the use of advanced respiratory support in ARF due to COVID-19 by around 15% as compared to ARF due to other causes (30% vs 15%) [5,6]. Advanced respiratory support (ARS) is defined as the use of non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO).

Although much of the evidence surrounding ARS use in COVID-19 has been to delay or bridge to invasive mechanical ventilation [7], its use has been increasing in patients where escalation to invasive mechanical ventilation would not be appropriate (‘do-not-intubate’, which frequently accompanies a ‘do-not-attempt cardiopulmonary resuscitation order’; DNACPR). In practice, these decisions represent a clinical judgement based on the perceived benefit of treatment, the patient’s frailty, co-morbidities and wishes. The tools that have been utilized as decision aids include the clinical frailty score (CFS) [8] and International Severe Acute Respiratory and Emerging Infection Consortium-4C Score (ISARIC 4C) [9–11]. The ISARIC 4C mortality score is a good predictor of 30-days mortality in COVID-19 (and other common respiratory tract infections).

Patients with ARF in COVID-19 where a ‘do-not-intubate’ and DNACPR decision have been made presented an important and prevalent group. A comprehensive review of available literature on the use of noninvasive ventilation in these patients showing evidence on the outcomes and predictors of mortality was scarce and suboptimal.

The main aim of this study was to evaluate the outcomes of ARS for ARF in COVID-19 patients who were not suitable candidates for invasive ventilation and had a DNACPR order in place. The secondary aims were to investigate any predictors of survival outcome such as clinical frailty score (CFS), ISARIC 4C score, age and admission PaO2/FiO2 (PF) ratio.
Methods

Study setting & patient selection
This was a retrospective, observational single-center study conducted at the district general hospital in UK. We included all patients who were admitted to the respiratory support unit (RSU) with ARF for treatment with ARS from 1 March 2020 to 28 February 2021 with COVID-19 pneumonia. ARS modalities included continuous positive airways pressure ventilation (CPAP), bi-level ventilation (BiPAP) or high-flow nasal oxygen (HFNO). Different ARS types were selected by clinicians depending on patient tolerability and clinical indications. Pharmacological treatment for COVID-19 was given in accordance with the latest available evidence-based national guidelines. The average time from swab positivity to admission to RSU was 11 days.

Inclusion criteria
- Adults over the age of 18 with a valid DNACPR on admission and whose ceiling of care was ARS, excluding invasive mechanical ventilation;
- At least one positive reverse transcriptase (RT) PCR nasopharyngeal swab confirming COVID-19 infection. In addition at least one of criteria C, D and E needed to be met:
  - ARS was required to treat Type 1 respiratory failure, in patients who despite maximal pharmacological and oxygen therapy were unable to maintain oxygen saturations over 92%. Maximal oxygen therapy is defined as a flow rate of 15 l/min delivered via non-rebreath mask or humidified FiO₂ of 60%;
  - ARS was required to treat compensated hypercapnic respiratory failure in patients who were unable to maintain oxygen saturations over 88% despite maximal pharmacological and oxygen therapy;
  - ARS was required to treat decompensated hypercapnic respiratory failure.

Exclusion criteria
- All patients who were eligible for escalation to ITU for invasive ventilation if they did not respond to ARS;
- Patients in whom ARS was discontinued prematurely due to poor compliance and tolerability. Poor tolerability was defined as anyone who was not able to use the ARS for more than 24 h or in which ARS type had to be changed from the initial modality.

Sample size
A total of 454 patients were admitted to our RSU during the above time frame, 198 patients with COVID-19. 100 fulfilled the inclusion criteria. This has also been explained in flow chart (Figure 1).

Data collection
The baseline characteristics included age, sex, clinical frailty scale, reason for DNACPR, comorbidities, date of admission, PF ratio before starting advanced respiratory support, type of advanced respiratory support, urea, respiratory rate, C-reactive protein (CRP), Glasgow coma score (GCS) and ISARIC 4C mortality score at the time of initiation of advanced respiratory support. All patients’ data were also included in our ICNARC data base as standard.

Study objective
Primary outcomes included death or discharge from hospital post ARS initiation. Secondary outcomes included outcomes at 48 h, 5 days and 7 days of ARS treatment, respectively. Other secondary outcomes included the effect of ARS modality, PF ratio, CFS and ISARIC 4C score on the primary outcome.

Statistical measure
All data analyses were performed using the JASP software package version 0.14.1. Data analysis was conducted in a pre-specified manner, and appropriate parametric and non-parametric tests were applied as per the data distribution. Where appropriate, p-values (p < 0.05) were calculated to determine significance.

Ethical approval
In view of the observational and retrospective nature of this study, a formal ethical approval was not required as the study fell under the category of service evaluation. The data were collected as per NHS health research authority (HRA) guidance. Results are reported in accordance with the strengthening of the reporting of observational studies.
Role of advanced respiratory support in acute respiratory failure in clinically frail patients with COVID-19  

Short Communication

Results

Population demographics

From 1 March 2020 to 28 February 2021, 100 patients (39 females) meeting the inclusion criteria were admitted to our respiratory support unit requiring advanced respiratory support. The median age was 78 years (SEM 0.92; range 48–96 years), and median clinical frailty score (CFS) was 5 (SEM 0.09, range 3–7). The median ISARIC 4C score was 12.57 (SEM 0.29, range 2–18) which when stratified corresponded to two patients in the low-risk group, three in the intermediate-risk group, 69 in the high-risk group and 26 in the very high-risk group.

At the point of admission, 44 patients were started on high-flow nasal oxygen (HFNO), 53 on continuous positive airway pressure (CPAP) and three on BiPAP. The mean PaO₂/FiO₂ (PF) ratio at admission was 124.7.

Overall outcomes

Patients were included in the study at admission to RSU and followed through until hospital discharge or death. Of the 100 patients, 72 patients died (72%) and 28 patients survived to hospital discharge (28%) (Table 1).

Table 2 describes the different co-morbidities of patients included in the study.

There was no significant difference in age between those who died and those who survived (W = 1059, p = 0.70). There was no difference in survival rates between ISARIC 4C groups (Chi square X² = 6.54, df 3, p = 0.88). There was also no difference in survival rates based on the type of ARS the patient was started on (Chi square X² = 3.094, df 3, p = 0.142). There was no significant difference in PF ratio at admission between those who survived and those who died (t = -0.448, p = 0.655).

When grouped by clinical frailty score, there was a significant difference in survival rates between groups (Chi square X² = 11.802, df 4, p = 0.019).

Tables 3, 4 & 5 demonstrate the differences in survival rates by grouped CFS, ISARIC 4C score and ARS type (Table 3, 4 & 5).
Table 1. Comparison of mean age, mean clinical frailty score, \( \text{mean PaO}_2/\text{FiO}_2 \) ratio and mean international severe acute respiratory infection consortium-coronavirus clinical characterization consortium (ISARIC 4C) score on admission to the respiratory support unit, in patients who were discharged from hospital and in those who died.

| Parameters                        | Survived (n = 28) | Died (n = 72) |
|-----------------------------------|-------------------|--------------|
| Mean age (years)                  | 75.9              | 76.8         |
| Mean CFS                          | 4.7               | 5.1          |
| Mean ISARIC 4C score              | 12.3              | 12.7         |
| Mean PF ratio at admission        | 126.7             | 123.9        |
| ARS type (count, %):              |                   |              |
| High-flow nasal oxygen (HFNO)     | 9 (32.1)          | 35 (48.6)    |
| Continuous positive airway pressure (CPAP) | 17 (60.7) | 36 (50)      |
| Bi-level positive airway pressure (BiPAP) | 2 (7.2)  | 1 (1.4)      |

The table also shows the outcomes according to the modality of advanced respiratory support.

Table 2. The prevalence of co-morbidities in patients admitted to the respiratory support unit requiring advanced respiratory support for COVID-19 infection.

| Co-morbidity                         | Patients with co-morbidity (%) |
|--------------------------------------|-------------------------------|
| Hypertension                         | 43                            |
| Diabetes mellitus                    | 36                            |
| Atrial fibrillation or atrial flutter| 24                            |
| Chronic obstructive pulmonary disease| 24                            |
| Ischemic heart disease               | 21                            |
| Cancer                               | 19                            |
| CKD                                  | 12                            |
| Hypercholesterolemia                 | 8                             |
| Asthma                               | 7                             |
| Congestive cardiac failure           | 6                             |
| Dementia                             | 5                             |

Table 3. Displaying the survival rate and death rate by Dalhousie clinical frailty scale.

| CFS | Status  | Count | %     |
|-----|---------|-------|-------|
| 3   | Died    | 1     | 16.7  |
|     | Survived| 5     | 83.3  |
|     | Total   | 6     |       |
| 4   | Died    | 17    | 77.3  |
|     | Survived| 5     | 22.7  |
|     | Total   | 22    |       |
| 5   | Died    | 34    | 75.6  |
|     | Survived| 11    | 24.4  |
|     | Total   | 45    |       |
| 6   | Died    | 15    | 68.1  |
|     | Survived| 7     | 31.8  |
|     | Total   | 22    |       |
| 7   | Died    | 5     | 100   |
|     | Survived| 0     | 0     |
|     | Total   | 5     |       |

Predicting outcomes

Determining outcomes after a specified time on ARS is important for prognostication and relative communications. Data from the 100 patients were examined at three time points: 48 h post admission, 5 days post admission and 7 days post admission.

Figure 2 shows a Kaplan–Meier curve demonstrating survival to hospital discharge for the total study participants. Overall, 28% of patients survived to discharge. Data from one patient were censored, due to prolonged hospital admission.
### Table 4. Displaying the survival rate and death rate according to International severe acute respiratory infection consortium – coronavirus clinical characterization consortium (ISARIC 4C) score.

| ISARIC 4C score | Status | Count | %  |
|-----------------|--------|-------|----|
| Low             | Died   | 0     | 0  |
|                 | Survived | 2   | 100.0|
|                 | Total   | 2   | 100.0|
| Intermediate    | Died   | 3     | 100|
|                 | Survived | 0   | 0  |
|                 | Total   | 3   | 100|
| High            | Died   | 51    | 73.9|
|                 | Survived | 18  | 26.1|
|                 | Total   | 69   | 100|
| Very high       | Died   | 18    | 69.2|
|                 | Survived | 8   | 30.8|
|                 | Total   | 26   | 100|

Only three patients were present in intermediate group and 100% mortality in this group is likely due to small number. Low risk (ISARIC 4C 0–3), intermediate risk (ISARIC 4C 4–8), high risk (ISARIC 4C 9–14) and very high risk (ISARIC 4C ≥ 15).

### Table 5. Displaying survival rate and death rate according to the modality of advanced respiratory support (CPAP, BIPAP and HFNO).

| ARS type                                  | Status | Count | %  |
|-------------------------------------------|--------|-------|----|
| High-flow nasal oxygen (HFNO)             | Died   | 35    | 79.5|
|                                           | Survived | 9   | 20.5|
|                                           | Total   | 44   | 100|
| Continuous positive airway pressure (CPAP)| Died   | 36    | 67.9|
|                                           | Survived | 17  | 32.1|
|                                           | Total   | 53   | 100|
| Bi-level positive airway pressure (BIPAP) | Died   | 1     | 33.3|
|                                           | Survived | 2   | 66.7|
|                                           | Total   | 3    | 100|

### Figure 2. Kaplan–Meier curve to show survival to hospital discharge of study participants.

At the 48 h time point, 21 patients had died, leaving 79 patients remaining in the cohort. When data for these 79 patients were re-assessed at 5 days, 35 patients remained on ARS (44.3%), 28 had been de-escalated to oxygen or air (35.4%) and 18 patients had died (22.8%). Of the 35 patients who were on ARS at the 5 day time point,
their eventual overall outcomes were as follows: 28 patients died (80%) and seven patients survived (20%). From our cohort, overall survival rates of patients still requiring ARS at 5 days post admission is thus 20%.

When data for patients were re-assessed at 7 days, 23 patients remained on ARS (38.9%), 25 patients were stepped down to oxygen or room air (42.3%), ten patients died (16.9%) and one patient was discharged (1.7%).

Of those still requiring ARS at 7 days post admission (23 patients), their eventual overall outcomes were: 19 died (83%) and 4 survived (17%). From our cohort, overall survival rates of patients still requiring ARS at 7 days post admission is thus 17%, suggesting that if a patient still requires ARS at 7 days post admission, then their percentage chance of survival is 17% (Table 6).

Discussion

In this single-center study of COVID-19 patients who were started on ARS as their ceiling of care for acute hypoxic respiratory failure, we observed that 72% died and 28% survived to hospital discharge. Of those still requiring ARS at 5 days and 7 days, the in-hospital survival rates were 20% and 17%, respectively. Patient age, PF ratio on admission, type of ARS (HFNO/CPAP/BiPAP) and ISARIC 4C score were not significantly different in those who survived and those who died, whereas increasing CFS was associated with a poorer survival rate.

These data will be of benefit in informing discussions with patients and relatives regarding prognosis when commencing ARS in this patient group.

The benefit of ARS in ARF in COVID-19

Worldwide, the majority of patients in first wave with moderate-to-severe ARF were treated by IMV, based on criteria generally used for typical ARDS [13,14] with 49–60% mortality [15,16]. IMV is not without risks [17] and capacity is extremely limited and as such ARS has been used with increasing frequency in subsequent waves. It is not yet clear which form of ARS (if any) provides the greatest benefit. Intensive care national audit and research care’s (ICNARC) data do not include patient’s CFS and DNACPR status [18]. Burns GP et al. described a 50% survival rate (14/28 patients with median ARS duration of 5 days) which was almost same as of invasive mechanical ventilation in appropriate COVID-19 pneumonitis patients having respiratory failure [19]. In contrary, Elsheikh A et al. reported a 90% mortality (9/10 patients from a cohort of 45) with CPAP alone used as ceiling of care [20]. Similarly, another single-center experience stated an 83% mortality (20/24 patients with a median duration on ARS of 3 days) [21].

As seen in previous work, we observed that patients who required ARS for a longer duration (>5 days or >7 days) had significantly higher mortality [22]; potentially suggesting that ongoing ARS requirements at these time points could be an early indication of treatment failure.

Type of ARS & mortality

We did not observe a survival difference between patients in our cohort commenced on HFNO, CPAP or BiPAP. Both HFNO and CPAP have been shown independently to reduce risk of all-cause mortality and tracheal intubation compared with supplemental oxygen alone [23], but few studies compare the two modalities, particularly in groups where ARS is the ceiling of care. A study by Brusasco et al. [24] showed that usefulness of CPAP in moderate to severe acute respiratory failure. Demoule et al. [25] revealed HFNC reduced intubation and subsequent invasive mechanical ventilation. One previous single-center RCT showed no difference in respiratory support-free days between HFNO and CPAP in COVID-19-related ARF. Procopio et al. [26] proposed HFNC a better treatment option than CPAP frail COVID-19 patients with respiratory failure. All these studies included patients who were for possible intubation in case the treatment with ARS failed. Notably, Recovery-RS, a global multicenter RCT, is currently recruiting to compare use of HFNC, CPAP and standard oxygen in COVID-19 patients, our center was also enrolled in this trial although it excluded patients who not suitable for invasive ventilation [27].
Possible reasons for no difference being observed between ARS types may reflect the heterogeneity in clinical and operational rationale for decisions over which modality to use e.g. concerns over hospital oxygen supply and possible heart failure element driving CPAP use and cognitive impairment favoring HFNO use.

Clinical implications of CFS & ISARIC 4C mortality scoring
In our study patients with a premorbid frailty score of 3 were more likely to gain survival benefits from ARS compared to those with a CFS of 7. Labenz C et al. reported a strong positive relation between higher CFS score and the need for invasive mechanical ventilation [28]. MacMahon DP et al. evaluated the role of CFS scoring in predicting mortality of patients who required non-invasive ventilation due to acute hypercapnic respiratory failure in COPD/OHS/Kyphoscoliosis patients. They reported that the patients having remarkably high CFS score (7–9) had in-hospital mortality of 60% as compared to those having CFS score 1–6 (20%) [29]. Our study depicted the usefulness of CFS scoring while making treatment escalation decisions in selective patient group.

We observed a survival benefit (31%) in patients having ISARIC 4C score >14 (very high risk category) of patients who were supported by non-invasive ventilation. However, Ali R et al. [30] described a higher death rate (80%) without ARS support. The ISARIC 4C deterioration model developed by Gupta R K et al. [31] when implemented alongside ISARIC 4C mortality score has higher proportion of envisaging decline in clinical condition and hence supports in advance decision making i.e., escalating to intensive care units or non-invasive support in case of elderly and frail patients. Nevertheless, a more targeted clinical trial is required to establish the role of ISARIC 4C mortality scoring in making decisions for non-invasive ventilator support.

Correlation with previous work, strengths & limitations
Much of the existing data surrounding ARS in COVID-19 exclude patients who are not suitable for escalation to IMV in case of treatment failure [7,32–35]. To our knowledge, this is the biggest study to date to see the clinical benefit of ARS in ARF in COVID-19 in patients who were IMV is not an appropriate treatment escalation, and to explore survival rates by ARS type, patient CFS and ISARIC 4C score. This addresses a critical gap in our current knowledge and clinical practice of COVID-19 management. Strengths of our study include the complete data set and real-world patient group, representative of many seen across the nation.

Nonetheless, our study has a few limitations. It represents admissions to a single center, a small number of patients. 95% of patients had high or very high ISARIC 4C scores, and 94% had a CFS between 4 and 7, making differentiation between these groups challenging.

Survival rates may have been lower in our cohort compared to other populations due to high CFS, multiple underlying health conditions and PF ratio showing moderate to high level of ARDS. Additionally, this was an unselected patient population and all patient treated were included.

Conclusion
Our study showed that ARS can be a useful tool in frail, elderly and high-risk patient groups irrespective of ISARIC 4C mortality score. These findings combined with other studies will enable physicians to prognosticate in this selected patient group, to guide escalation decisions and to communicate effectively with relatives. Other measures such as patient age, admission PF ratio and ISARIC 4C score did not help to predict outcomes in this group.

On a local level, we hope this information helps guide conversations with patients and relatives. On a national and international scale, we anticipate that this work will guide larger studies to answer this question definitively.

Author contributions
Iftikhar Nadeem and Louise Jordon contributed equally as combined first author. Iftikhar Nadeem contributed in abstract writing, paper writing, data collection and editing. Louise Jordon contributed in paper writing, data analysis and editing. Masood Ur Rasool contributed in paper writing and editing. Noor Mahdi contributed in abstract writing, paper writing and editing. Ritesh Kumar contributed in paper writing and editing. Zahra Rehman contributed in data collection and paper writing. Craig J Tilley contributed in data collection and paper writing. Simran Kang contributed in data collection and paper writing. Amrita Rai contributed in data collection and paper writing. She Lok contributed in paper writing, editing and proof reading. Alison McMillan contributed in paper writing, editing and proof reading.
Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

Summary points
- Management of acute respiratory failure (ARDS) in COVID-19 has been under continuous review by the research and medical communities.
- There has been a steady increase in the use of advanced respiratory support in ARDS due to COVID-19 by around 15% as compared to ARDS due to other causes (30% vs 15%).
- Majority of the times, ARS use in COVID-19 has been to delay or bridge to invasive mechanical ventilation, it’s use has been increasing in patients where escalation to invasive mechanical ventilation would not be appropriate (‘do-not-intubate’, which frequently accompanies a ‘do-not-attempt cardiopulmonary resuscitation order’; DNACPR).
- Main aim of this retrospective single-center observational study was to evaluate the outcomes of ARS for ARDS in COVID-19 patients who were not suitable candidates for invasive ventilation and had a DNACPR order in place. Secondary aims were to investigate any predictors of survival outcome such as clinical frailty score (CFS), ISARIC 4C score, age and admission PaO2/FiO2 (PF) ratio.
- 100 patients met the inclusion criteria. Age, sex, clinical frailty scale, PF ratio before starting advanced respiratory support, type of advanced respiratory support and ISARIC 4C mortality score at the time of initiation of advanced respiratory support were calculated.
- We found that there was no significant difference in age, type of ARS modality, PF ratio and 4C scores between those who died and those who survived. Overall survival rates/hospital discharge of patients still requiring ARS at 5 and 7 days post admission was 20 and 17% respectively.
- This study addresses a critical gap in our current knowledge and clinical practice of COVID-19 management. Our study showed that ARS can be a useful and viable tool in frail, elderly and high-risk COVID-19 patient groups irrespective of ISARIC 4C mortality score. These findings combined with other studies will enable physicians to prognosticate in this selected patient group, to guide escalation decisions and to communicate effectively with relatives. Other measures such as patient age, admission PF ratio and ISARIC 4C score did not help to predict outcomes in this group.

References
1. Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 8(5), 475–481 (2020).
2. Guan W, Ni Z, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382(18), 1708–1720 (2020).
3. Richardson S, Hirsch J, Narasimhan M et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. J. Am Med. Assoc. 323(20), 2052–2059 (2020).
4. Karagiannidis C, Mostert C, Hentschker C et al. Case characteristics, resource use, and outcomes of 10021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir. Med. 8(9), 853–862 (2020).
5. Bellani G, Laffey J, Pham T et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. Am. J. Respir. Crit. Care 195(1), 67–77 (2017).
6. Guan W, Ni Z, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382(18), 1708–1720 (2020).
7. Walker J, Dolly S, Ng L, Prior-Ong M, Sabapathy K. The role of CPAP as a potential bridge to invasive ventilation and as a ceiling-of-care for patients hospitalized with Covid-19 – an observational study. PLoS ONE 15(12), e0244857 (2020).
8. Saberolles R, Lafeber M, van Kempen J et al. Association between clinical frailty scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicenter, retrospective, observational cohort study. Lancet Healthy Longev. 2(3), 163–170 (2021).
9. Knight S, Ho A, Pius R et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C mortality score. Br. Med. J. 370, m3339 (2020).
10. NICE. COVID-19 rapid guideline: managing COVID-19 (2021). www.nice.org.uk/guidance/ng191/chapter/Recommendations
Role of advanced respiratory support in acute respiratory failure in clinically frail patients with COVID-19

Short Communication

11. Rockwood K, Song X, Macknight C et al. A global clinical measure of fitness and frailty in elderly people. Can. Med. Assoc. J. 173(5), 489–495 (2005).

12. Wellbelove Z, Walsh C, Perinpanathan T, Lillie P, Barlow G. Comparing the 4C mortality score for COVID-19 to established scores (CURB65, CRB65, qSOFA, NEWS) for respiratory infection patients. J. Infection. 82(3), 414–451 (2021).

13. Rubenfeld G, Slutsky A, Thompson B. ARDS definition task force. Definition of acute respiratory distress syndrome. J. Am. Med. Assoc. 308(13), 1321 (2012).

14. Maiolo G, Collino F, Vasques F et al. Reclassifying acute respiratory distress syndrome. Am. J. Respir. Crit. Care 197(12), 1586–1595 (2018).

15. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy. J. Am. Med. Assoc. 323(16), 1545 (2020).

16. Bhatraju PK, Ghassemieh BJ, Nichols M et al. Covid-19 in critically ill patients in the Seattle region — case series. N. Eng. J. Med. 382(21), 2012–2022 (2020).

17. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Ann. Intensive Care 10, 78 (2020).

18. Intensive Care National Audit & Research center. ICNARC – reports. Covid-19 reports (2020). www.icnarc.org/Our-Audit/Audits/Cmp/Reports

19. Burns GP, Lane ND, Tedd HM et al. Improved survival following ward-based non-invasive pressure support for severe hypoxia in a cohort of frail patients with COVID-19: retrospective analysis from a UK teaching hospital. BMJ. Open Respir. Res. 7(1), e000621 (2020).

20. Elsheikh A, Karunanithi V, Mahalingam A, Shafig M, Setty N, Samuel J. Late breaking abstract – CPAP is effective in treating COVID-19 patients with type 1 respiratory failure. Eur. Respir. J. 56, 4410 (2020).

21. Sivaloganathan AA, Nasim-Mohi M, Brown MM et al. Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single center. Brit. J. Anaesth. 125(4), 368–371 (2020).

22. Ashish A, Unsworth A, Martindale J et al. CPAP management of COVID-19 respiratory failure: a first quantitative analysis from an inpatient service evaluation. BMJ Open. Respir. Res. 7(1), e000692 (2020).

23. Gorman E, Connolly B, Couper K, Perkins GD, McAuley DF. Non-invasive respiratory support strategies in COVID-19. Lancet Resp. Med. 9, 553–556 (2021).

24. Zafrani L, Girodias L, Labb´e V, Dres M, Far Toukh M, Azoulay E. High-flow nasal cannula in critically ill patients with severe COVID-19. Am. J. Respir. Crit. Care 202(7), 1039–1042 (2020).

25. Brusasco C, Corradi F, Di Domenico A et al. Oxygen therapy via high flow nasal cannula in severe respiratory failure caused by Sars-Cov-2 infection: a real-life observational study. Ther. Adv. Respir. Dis. 14, 1753466620963016 (2020).

26. Procopio G, Cancelliere A, Trecarichi E et al. Oxygen therapy via high flow nasal cannula in severe respiratory failure caused by Sars-Cov-2 infection: a real-life observational study. Ther. Adv. Respir. Dis. 14, 1753466620963016 (2020).

27. RECOVERY-RS Respiratory Support. https://warwick.ac.uk/fac/sci/med/research/ctu/trials/recovery-rs/