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High mortality among patients with severe COVID-19 and Do Not Intubate orders

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ABSTRACT

INTRODUCTION. Moderate to severe respiratory distress among patients with COVID-19 is associated with a high mortality. This study evaluated ventilator support and mortality by Do Intubate (DI) or Do Not Intubate (DNI) orders.

METHODS. This was a retrospective study of patients with COVID-19 and a supplemental oxygen requirement of ≥ 15 l/min. The patients were divided into two groups corresponding to the first and second wave of COVID-19 and were subsequently further divided according to DI and DNI orders and analysed regarding need of ventilator support and mortality.

RESULTS. The study included 178 patients. The mortality was 24% for patients with DI orders (n = 115) and 81% for patients with DNI orders (n = 63) increasing to 98% (n = 46) for patients with DNI orders and very high flow oxygen requirements (≥ 30 l/min.). From the first to the second wave of COVID-19, the use of constant continuous positive airway pressure (cCPAP) increased from 71% to 91% ($p < 0.001$), whereas the use of mechanical ventilation decreased from 54% to 28% (odds ratio = 0.38 (95% confidence interval: 0.17-0.85)).

CONCLUSION. The mortality was high for patients with DNI orders and respiratory distress with very high levels in supplemental oxygen in both the first and second wave of COVID-19 despite an increase in use of cCPAP and treatment with dexamethasone and remdesivir during the second wave. Hence, careful evaluation on transition to palliative care must be considered for these patients.

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TRIAL REGISTRATION. The study was approved by the Danish Patient Safety Authority (record no. 31-1521-309) and the Regional Data Protection Centre (record no. P-2020-492).

A key feature of COVID-19 caused by SARS-CoV-2 is respiratory distress among hospitalised patients [1]. Respiratory distress may be mild and corrected by low-flow supplemental oxygen, whereas moderate distress requires high-flow or non-invasive ventilation, e.g., constant, continuous positive airway pressure (cCPAP). Severe respiratory failure requires mechanical ventilation (MV) or extracorporeal membrane oxygenation [1]. Medical treatment includes dexamethasone and remdesivir; both of which were introduced as standard treatments in the second wave of COVID-19 in Denmark for patients with moderate to severe respiratory distress [2, 3] along with prophylactic anticoagulation due to an increased risk of thrombotic events [4]. Use of

tocilizumab was recommended in March 2021 for individuals with respiratory failure and inflammation based on clinical trial evidence [5, 6].

Multiple studies have demonstrated high mortality rates in patients with COVID-19 and moderate to severe respiratory distress, but the majority of studies were performed on patients with Do Intubate (DI) orders in intensive care unit (ICU) settings [3, 7, 8]. Only few smaller studies have described the mortality among patients with Do Not Intubate (DNI) orders and moderate to severe respiratory distress [9, 10].

This study examined the use of ventilator support and mortality in the first and second wave of COVID-19 for patients with a supplemental oxygen requirement of ≥ 15 l/min. We evaluated the mortality dependent on the DI or DNI order.

METHODS

This was a retrospective single-centre study of adult patients (≥ 18 years of age) admitted with COVID-19 at the Department of Infectious Diseases, Copenhagen University Hospital – Amager and Hvidovre, from 15 March to 30 December 2020. Part of the patient group included in this study is a subset of a previously described cohort [11]. All patients were confirmed SARS-CoV-2 positive by reverse-transcriptase polymerase-chain-reaction performed on a oropharyngeal swab or a lower respiratory tract specimen. Acceptable oxygen saturation was defined as 92-96% for patients with no previous record of lung disease and 88-92% for patients with chronic obstructive pulmonary disease (COPD). All patients who required ≥ 15 l/min. of supplemental oxygen to meet the defined criteria for acceptable oxygen saturation were included in this study.

Patients were treated with high-flow nasal cannula (HFNC) using Optiflow and/or cCPAP. cCPAP was tested on all patients with a supplemental oxygen requirement of ≥ 10 l/min and discontinued in case of intolerance or lack of effect. A proportion of patients who progressed despite these treatments were transferred to the ICU for MV.

The patients were divided into two groups depending on their time of admission. Dexamethasone and remdesivir were standard treatments as from 17 June 2020. Hence, patients admitted before this date were categorised as Group 1 (admission from 15 March to 16 June 2020), and patients admitted after this date were categorised as Group 2 (17 June to 30 December 2020). The majority of patients in Group 1 were admitted during the first wave of the COVID-19 pandemic in Denmark, and Group 2 correlates with the second wave. Tocilizumab was introduced as standard treatment after this study period and was therefore not available for use in the included patients.

Based on age, comorbidities and daily activity level, each patient was assessed by a medical doctor for a DI or DNI order at hospital admission. DNI was assigned to patients who were excluded from MV due to an expected poor outcome. These criteria remained unchanged during the study period. For patients with a DI order, initiation of MV was indicated by 1) unacceptable blood oxygen saturation despite maximum supplemental oxygen by HFNC and/or cCPAP, 2) if the patient was unsuitable for cCPAP, e.g., due to intolerance of the mask or exhaustion or 3) if a second organ system failed. The principles of treatment at the ICU remained unchanged during the study period.

The registered outcomes included in-hospital mortality and ventilator support: cCPAP and MV. Patients with a supplemental oxygen requirement of ≥ 30 l/min. were analysed as a subgroup.

Data regarding age, sex, comorbidity, treatment code (DI/DNI), need of supplemental oxygen with HFNC, cCPAP and/or MV, medical treatment of COVID-19 and in-hospital death/survival were transferred from the electronic healthcare records to the secure online data platform RedCap hosted by the Capital Region of Denmark.

The study population was characterised using descriptive statistics. Categorical variables were reported as frequencies with percentages. Continuous variables were presented as medians with interquartile range. Comparisons were performed using the χ^2 test and the Mann-Whitney U test, as appropriate. Logistic regression was used to compute odds ratios with 95% confidence intervals for in-hospital mortality or MV between Group 1 and Group 2.

Data sharing statement

The data that support the findings of this study are available on reasonable request from the corresponding author, NH. The data are not publicly available as they contain information that could compromise the privacy of research participants. The data will remain available until one year after publication.

Trial registration: The study was approved by the Danish Patient Safety Authority (record no. 31-1521-309) and the Regional Data Protection Centre (record no. P-2020-492).

RESULTS

The study included 178 patients with SARS-CoV-2 infection and a need for supplemental oxygen of ≥ 15 l/min.; 82 patients in Group 1 and 96 patients in Group 2. The characteristics of the two groups are listed in **Table 1**. The groups were comparable in terms of demographic factors and comorbidities with no significant differences across any variables. The proportion of patients with DNI orders was higher in Group 1, though not significantly so, whereas the use of cCPAP was significantly higher in Group 2.

TABLE 1 Characteristics of patients in Group 1 and Group 2.

	Group 1	Group 2	p value
Patients, n	82	96	
Age, median (IQR), yrs	71 (60-79)	69 (55-76)	0.1
Males, n (%)	54 (66)	70 (73)	0.3
BMI[a], kg/m^2, median (IQR)	28 (24-33)	29 (25-32)	0.8
Any comorbidity[b], n (%)	76 (93)	82 (85)	0.1
CVD, n (%)	57 (70)	64 (66)	0.7
Hypertension, n (%)	43 (52)	41 (42)	0.2
Diabetes, n (%)	31 (38)	34 (35)	0.7
COPD, n (%)	9 (11)	12 (12)	0.8
Asthma, n (%)	7 (9)	10 (10)	0.7
DNI orders, n (%)	34 (41)	29 (30)	0.1
HFNC, all, n (%)	81 (99)	95 (99)	0.9
cCPAP, n (%)			
All	58 (71)	87 (91)	< 0.001
DI orders	38 (79)	63 (94)	0.02
DNI orders	20 (59)	24 (83)	0.2

cCPAP = constant continuous positive airway pressure; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DI = Do Intubate; DNI = Do Not Intubate; HFNC = high-flow nasal cannula; IQR = interquartile range.
a) Data were only available for 156 patients (88%).
b) Includes the listed variables and chronic kidney or liver disease and cancer.

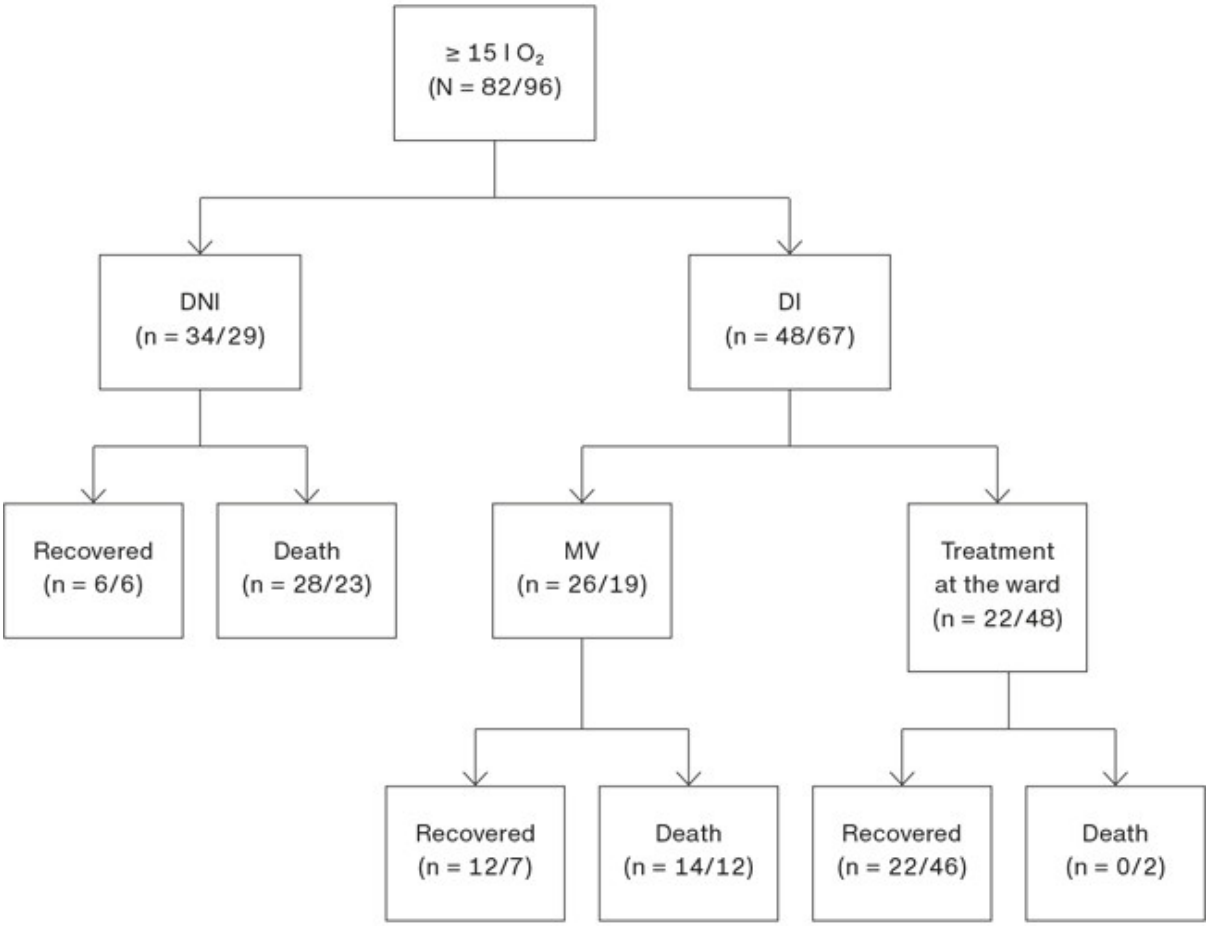
The decision on DI or DNI orders was not changed during hospital admission with very few exceptions where the patient's DI order was changed to DNI (the DNI status would then be registered for use in this study).

Treatment with dexamethasone and/or remdesivir was given to few patients in Group 1 as part of a clinical trial. In Group 2, all patients but one (99%) were treated with dexamethasone, and 91 patients (95%) were treated with remdesivir.

In-hospital mortality and use of mechanical ventilation in Group 1 and Group 2

Mortality and use of MV in Group 1 and Group 2 are shown in **Figure 1** and **Table 2.** In Group 1, 26 patients (57%) with DI orders were transferred to the ICU for MV, and no patients with DI orders died on the ward. The in-hospital mortality was 51%; 14 patients (29%) with DI orders and 28 patients (82%) with DNI orders ($p < 0.001$).

FIGURE 1 Outcome for patients in Group 1/Group 2.



DI = Do Intubate; DNI = Do Not Intubate; MV = mechanical ventilation.

TABLE 2 Mortality rates and use of mechanical ventilation in Group 1 and Group 2.

	n/N (%)		OR (95% CI)	
	Group 1	Group 2	crude	adjusted[a]
In-hospital mortality				
All	42/82 (51)	37/96 (39)	0.60 (0.33-1.09)	0.65 (0.33-1.28)
Subgroups:				
DI	14/48 (29)	14/67 (21)	0.64 (0.27-1.51)	0.60 (0.24-1.52)
DNI	28/34 (82)	23/29 (79)	0.82 (0.23-2.89)	0.83 (0.21-3.26)
Mechanical ventilation				
DI	26/48 (54)	20/67 (30)	0.36 (0.17-0.78)	0.38 (0.17-0.85)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DI = Do Intubate; DNI = Do Not Intubate; OR = odds ratio.

a) Adjusted for age, sex and any comorbidities including CVD, hypertension, diabetes, COPD, asthma and chronic kidney or liver disease.

In Group 2, 19 patients (28%) with DI orders were transferred to the ICU for MV. Two patients with DI orders died before intubation was performed. The in-hospital mortality was 39%; 14 patients (21%) with DI orders and 23 patients (79%) with DNI orders ($p < 0.001$).

The use of MV was significantly higher in Group 1 than in Group 2 (Table 2).

The overall mortality was higher in Group 1 than in Group 2, although this difference was not significant.

Patient characteristics and in-hospital mortality by Do Not Intubate and Do Intubate orders

Table 3 compares patients with DI and DNI orders. Patients with DNI orders were older, generally had more comorbidities and were more often women. COPD was more frequent in patients with DNI orders, whereas patients with DI orders were more often diagnosed with asthma.

TABLE 3 Characteristics and mortality in patients with Do Not Intubate and Do Intubate orders.

	DNI	DI	p value
Patients, n	63	115	
Age, median (IQR), yrs	79 (74-83)	64 (53-72)	< 0.001
Males, n (%)	37 (59)	87 (76)	0.02
BMI, kg/m², median (IQR)	27 (23-32)	29 (25-32)	0.5
Any comorbidity[a], n (%)	61 (97)	99 (86)	0.02
CVD, n (%)	44 (70)	77 (67)	0.7
Hypertension, n (%)	34 (54)	49 (43)	0.1
Diabetes, n (%)	28 (44)	36 (31)	0.08
COPD, n (%)	12 (19)	10 (9)	0.04
Asthma, n (%)	2 (3)	15 (13)	0.03
In-hospital mortality, n (%)	51 (81)	28 (24)	< 0.001

COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DI = Do Intubate; DNI = Do Not Intubate; IQR = interquartile rage.
a) Includes the listed variables and chronic kidney or liver disease.

The mortality among patients with DNI orders was 81%, and was comparable between Group 1 and Group 2 (Table 2).

Patients with DNI orders and a supplemental oxygen requirement of ≥ 30 l/min (n = 46) demonstrated a very high mortality rate of 98% as 45/46 patients passed away; 25/26 patients in Group 1 and 20/20 patients in Group 2.

DISCUSSION

In this study, we showed a continued high mortality for patients with severe COVID-19 and DNI orders requiring high-flow supplemental oxygen despite the introduction of remdesivir and dexamethasone treatment and increased use of cCPAP. However, progression to MV was halved for patients with severe COVID-19 and DI orders in Group 2.

The very high mortality for patients with DNI orders (81%) is comparable in Group 1 and Group 2 and in line with two previous reports from the first wave of COVID-19 in Italy of patients with DNI orders and a need for non-invasive ventilation which reported mortality rates of 89% (n = 27) and 88% (n = 25), respectively [9, 10]. In comparison, a study of hospitalised patients with COVID-19 and DNI orders who were not treated with high-flow oxygen (10% received dexamethasone) found a mortality of 49% [12], which is still higher than an in-hospital mortality rate of 44% found in a systematic review of patients with non-COVID-19 acute respiratory failure and DNI orders treated with non-invasive ventilation [13].

For individuals with DNI orders requiring very high levels of supplemental oxygen (≥ 30 l/min.), the in-hospital mortality was 98%. This leads us to recommend careful evaluation of these patients for transition to palliative care in open dialogue with the patient and relatives to avoid prolonged struggle and suffering.

The use of cCPAP increased from 71% during the first wave of COVID-19 to 91% in the second wave. This may have contributed to the decrease in the need of MV in the second wave together with the introduction of dexamethasone and remdesivir which we showed in a study that included the subset of the individuals included here [14]. It is not possible to distinguish between the effects of cCPAP and medical treatment in this study. In patients with severe COVID-19, a recent study found that initial cCPAP significantly reduced the risk of intubation and mortality compared with low-flow oxygen therapy [15], whereas the effect of HFNC on these outcomes is more questionable [15, 16].

Though we did not find a significant decrease in overall mortality for patients with severe COVID-19 from the first to the second wave, this has previously been documented in Denmark for hospitalised patients with COVID-19 [14, 17]. However, for patients in ICU settings, the mortality may be more comparable between the two waves [17-19].

The results of this study must be interpreted in the light of the retrospective design with its inherent limitations. In addition, this is a single-centre study, which limits its generalisability. The study was performed when other variants of SARS-CoV-2 than now were dominating and before vaccines against SARS-CoV-2 had been introduced; hence, the clinical situation and management of patients with severe COVID-19 may have changed as fewer patients now progress to acute respiratory failure. However, regardless of SARS-CoV-2 variant, we believe that the results are useful for informing the decision of palliation for elderly comorbid patients with COVID-19 and DNI and in need of very high levels of supplemental oxygen.

CONCLUSION

The mortality was high for patients with DNI orders and respiratory distress with very high levels in supplemental oxygen in both the first and second wave of COVID-19 despite increased use of cCPAP and antiviral and anti-inflammatory treatments, whereas we observed an improved prognosis for patients with DI orders. Hence, careful evaluation of the need for transition to palliative care must be considered for patients with severe COVID-19 and DNI orders irrespective of the available treatment options.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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