High Mortality Among Patients With Severe COVID-19 and Do-not-intubate Orders Despite Use of Remdesivir and Dexamethasone

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1 **High mortality among patients with severe COVID-19 and do-not-intubate orders**
2 **despite use of remdesivir and dexamethasone**

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23

24 **Abstract**

25 **Background**

26 Moderate to severe respiratory distress among patients with coronavirus disease 2019 (COVID-19)
27 is associated with a high mortality. Dexamethasone and remdesivir were introduced in the second
28 wave of COVID-19 in Denmark.

29 **Methods**

30 This is a retrospective study of patients with COVID-19 and a supplemental oxygen requirement of
31 ≥ 15 Liters per minute (L/min). The patients were divided in two groups corresponding to the first-
32 and second wave of COVID-19 and analysed regarding need of ventilator support and mortality
33 dependent on orders to Do Intubate (DI) or Do Not Intubate (DNI), respectively.

34 **Results**

35 The study included 178 patients. The mortality was 24% for patients with DI orders (n=115) and
36 81% for patients with DNI orders (n=63) increasing to 98% (n=46) for patients with DNI orders and
37 very high flow oxygen requirements (≥ 30 L/min). Use of constant continuous positive airway
38 pressure (cCPAP) increased from 71% in the first wave to 91% in the second wave ($p < 0.001$)
39 whereas the use of mechanical ventilation (MV) decreased from 54% to 28% ($p = 0.005$).

40 **Conclusion**

41 The mortality was high for patients with DNI orders and respiratory distress with very high levels in
42 supplemental oxygen in both the first and second wave of COVID-19 despite treatment with
43 dexamethasone and remdesivir and improved prognosis for patients with DI orders. Hence careful
44 evaluation on transition to palliative care must be considered for these patients.

45 **Study Registration**

46 The study was retrospectively registered and approved by the Danish Patient Safety Authority
47 (record no. 31-1521-309) and the Regional Data Protection Center (record no. WZ20017637-2020-
48 37).

49

50 Keywords: COVID-19, cCPAP, mechanical ventilation, mortality, Do-not-intubate orders.

51

52 **Background**

53 A key feature of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory
54 syndrome coronavirus-2 (SARS-CoV-2) is respiratory distress among hospitalized patients (1).
55 Respiratory distress may be mild and corrected by low-flow supplemental oxygen while moderate
56 distress requires high-flow or non-invasive ventilation e.g. constant, continuous positive airway
57 pressure (cCPAP). Severe respiratory failure requires mechanical ventilation (MV) or
58 extracorporeal membrane oxygenation (ECMO) (1). Medical treatment includes dexamethasone
59 and remdesivir both introduced as standard treatments in the second wave of COVID-19 in
60 Denmark for patients with moderate to severe respiratory distress (2, 3) together with
61 prophylactic anticoagulation due to increased risk of thrombotic events (4). Use of tocilizumab was
62 recommended in March of 2021 for individuals with respiratory failure and inflammation based on
63 clinical trial evidence (5, 6).

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

69 This study examines the use of ventilator support and mortality in the first- and second wave of
70 COVID-19 for patients with a supplemental oxygen requirement of ≥ 15 L/min. We evaluate the
71 mortality dependent on orders to DI or DNI.

72

73 **Methods**

74 This is a single center retrospective study of adult patients (≥ 18 years of age) admitted with
75 COVID-19 at the Department of Infectious Diseases, Copenhagen University Hospital – Amager and
76 Hvidovre from 15th of March to 30th of December 2020. All patients were confirmed SARS-CoV-2
77 positive by reverse-transcriptase polymerase-chain-reaction (RT-PCR) performed on
78 oropharyngeal swab or lower respiratory tract specimen. Acceptable oxygen saturation was
79 defined as 92-96% for patients with no previous record of lung diseases and 88-92% for patients
80 with chronic obstructive pulmonary disease (COPD). Only patients who required ≥ 15 L/min of
81 supplemental oxygen to meet the defined criteria for acceptable oxygen saturation were included
82 in this study.

83 The patients were treated with high flow nasal cannula (HFNC) by the use of Optiflow® and/or
84 cCPAP and a proportion of patients who progressed despite these treatments were transferred to
85 the ICU for MV.

86 The patients were divided in two groups dependent on their time of admission. Dexamethasone
87 and remdesivir were standard treatments from 17th of June 2020, hence patients admitted before
88 this date were categorized as Group 1 (admission from 15th of March to 16th of June 2020), and
89 patients after this date were categorized as Group 2 (17th of June to 30th of December 2020). The
90 majority of patients in Group 1 were admitted during the first wave of the COVID-19 pandemic in
91 Denmark and Group 2 correlates to the second wave. Tocilizumab was introduced as standard
92 treatment after this study period and therefore not available for the included patients.

93 Based on age, comorbidities and daily activity level each patient was assessed for a DI or DNI order
94 at hospital admission. DNI was assigned to patients who were excluded from MV due to an
95 expected poor outcome. For patients with a DI order initiation of MV was indicated by 1)
96 unacceptable blood oxygen saturation despite maximum supplemental oxygen by HFNC and/or
97 cCPAP, 2) if the patient was not suitable for cCPAP e.g. due to intolerance of the mask or
98 exhaustion or 3) if a second organ system failed.

99 The registered outcomes included in-hospital mortality, use of cCPAP and MV. Patients with
100 supplemental oxygen requirement of ≥ 30 L/min were analysed as a subgroup.

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

105 The study population was characterized using descriptive statistics. Categorical variables were
 106 reported as frequencies with percentages. Continuous variables were presented as medians with
 107 interquartile range (IQR). Comparisons were performed using χ^2 -test and Mann-Whitney *U* test,
 108 as appropriate.

109

110 Results

111 The study included 178 patients with SARS-CoV-2 infection and need of supplemental oxygen of
 112 ≥ 15 L/min; 82 patients in Group 1 and 96 patients in Group 2. Demographic factors and
 113 comorbidities for the two groups are listed in Table 1. The groups were comparable with no
 114 significant differences across in all variables (Table 1).

115 **Table 1. Baseline characteristics of patients in Group 1 and 2**

	Group 1	Group 2	p-value
Number of patients (n)	82	96	
Age (IQR)	71 (60-79)	69 (55-76)	p=0.1
Male, n (%)	54 (66%)	70 (73%)	p=0.3
BMI*, kg/m ² , median (IQR)	28 (24-33)	29 (25-32)	p=0.8
Any comorbidity, n (%)	76 (93%)	82 (85%)	p=0.1
CVD, n (%)	57 (70%)	64 (66%)	p=0.7
Hypertension, n (%)	43 (52%)	41 (42%)	p=0.2
Diabetes, n (%)	31 (38%)	34 (35%)	p=0.7
COPD, n (%)	9 (11%)	12 (12%)	p=0.8

Astma, n(%)	7 (9%)	10 (10%)	p=0.7
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116 **Data regarding Body Mass Index (BMI) was only available for 156 patients (88%). 'Any*
117 *comorbidity' includes the listed variables and chronic kidney- or liver disease and cancer. n =*
118 *number, IQR = interquartile range, BMI = Body Mass Index, CVD = cardiovascular disease. COPD =*
119 *chronic obstructive pulmonary disease.*

120

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

124

125 **Outcome in Group 1 and 2**

126 Mortality and need of MV in Group 1 and 2 are shown in Figure 1.

127 In Group 1, 26 patients (57%) with DI orders were transferred to ICU for MV and no patients with
128 DI orders died at the ward. The in-hospital mortality was 51%; 14 patients (29%) with DI orders
129 and 28 patients (82%) with DNI orders ($p < 0.001$).

130 In Group 2, 19 patients (28%) with DI orders were transferred to ICU for MV. Two patients with DI
131 orders died before intubation was carried out. The in-hospital mortality was 39%; 14 patients
132 (21%) with DI orders and 23 patients (79%) with DNI orders ($p < 0.001$).

133 **Figure 1. Outcome for patients in Group 1 and 2.**

134

135

136 *DNI = Do Not Intubate, DI = Do Intubate, MV = mechanical ventilation.*

137

138 *Use of cCPAP, mechanical ventilation and mortality in Group 1 and 2*

139 The use of cCPAP was significantly higher in Group 2, whereas the use of MV was significantly
140 higher in Group 1 (Table 2).

141 The proportion of patients with DNI orders and the overall mortality was higher in Group 1
142 although this was not significant, (p=0.1 and p=0.09, respectively). Mortality for patients with DNI
143 orders was comparable between the two groups (Table 2).

144 **Table 2. Use of HFNC, cCPAP, MV and mortality rates in Group 1 and 2.**

	Group 1	Group 2	p-value
HFNC, all	81 (99%)	95 (99%)	
cCPAP, all	58 (71%)	87 (91%)	p<0.001
DI order	38 (79%)	63 (94%)	p=0.02
DNI order	20 (59%)	24 (83%)	p=0.2
MV, DI order	26 (54%)	19 (28%)	p=0.005
In-hospital mortality, all	42 (51%)	37 (39%)	p=0.09
DI	14 (29%)	14 (21%)	p=0.3
DNI	28 (82%)	23 (79%)	P=0.8

145 *HFNC = high flow nasal cannula, cCPAP = constant, continuous positive airway pressure, MV =*
146 *mechanical ventilation, DI = Do Intubate, DNI = Do Not Intubate.*

147

148 ***Outcome for patients with DNI orders***

149 A comparison of patients with DI- and DNI orders is shown in Table 3. Patients with DNI orders
150 were older, had overall more comorbidities and were more often women. COPD was more
151 frequent in patients with DNI orders whereas patients with DI orders more often were diagnosed
152 with asthma.

153 **Table 3. Characteristics and mortality of patients with DNI and DI orders, respectively.**

	DNI	DI	p-value
Number of patients (n)	63	115	

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

Any comorbidity includes the listed variables and chronic kidney- or liver disease. IQR = interquartile range. BMI = Body Mass Index, CVD = cardiovascular disease. COPD = chronic obstructive pulmonary disease.

The in-hospital mortality for patients with DNI orders was 81%. 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

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

The very high mortality for patients with DNI orders (81%) is comparable in Group 1 and 2 and in accordance with two previous reports from the first wave of COVID-19 in Italy of patients with DNI orders and need of non-invasive ventilation (NIV) with mortality rates of 89% (n=27) and 88% (n=25), respectively (9, 10). In comparison, a study of hospitalized patients with COVID-19 and DNI

170 orders not treated with high-flow oxygen (10% received dexamethasone) found a mortality of 49%
171 (11).

172 For individuals with DNI orders requiring very high levels of supplemental oxygen (≥ 30 L/min) the
173 in-hospital mortality proportion was 98%. This leads us to recommend that these patients are
174 carefully evaluated for transition to palliative care in open dialogue with the patient and relatives
175 in order to avoid prolonged struggle and suffering.

176 The use of cCPAP increased from 71% in the first wave of COVID-19 to 91% in the second wave.
177 This may contribute to the decrease in need of MV in the second wave together with the
178 introduction of dexamethasone and remdesivir as we have shown in a recent study that included
179 the subset of individuals included here (12). HFNC and cCPAP have been associated with a
180 decrease in use of MV for patients with acute respiratory distress syndrome (ARDS) including
181 patients with COVID-19 (13-17), though the effect still awaits evaluation in randomized controlled
182 trials (18). However, it is still a challenge to identify the patients who would benefit from cCPAP
183 and the patients to whom early intubation should be preferred (19, 20).

184 Though we did not find a significant decrease in overall mortality for patients with severe COVID-
185 19 from the first to the second wave this was documented just recently for hospitalized patients
186 with COVID-19 (12, 21). However for patients in ICU settings the mortality may be more
187 comparable in the two waves (21-23).

188 In conclusion the mortality was high for patients with DNI orders and respiratory distress with very
189 high levels in supplemental oxygen in both the first and second wave of COVID-19 despite
190 treatment, while we observed improved prognosis for patients with DI orders. Hence careful
191 evaluation on transition to palliative care must be considered for these patients.

192

193 **Abbreviations**

194 COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-
195 2; RT-PCR, reverse-transcriptase polymerase-chain-reaction; L/min, Liters per minute; MV,
196 mechanical ventilation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit;

197 cCPAP, constant, continuous positive airway pressure; HFNC, high flow nasal cannula; NIV, non-
198 invasive ventilation; DI, Do intubate; DNI, Do Not Intubate; IQR, interquartile rage; BMI, Body Mass
199 Index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; ARDS, acute
200 respiratory distress syndrome.

201

202 **Declarations**

203 ***Ethics approval and consent to participate***

204 The study was approved by the Danish Patient Safety Authority (record no. 31-1521-309) and the
205 Regional Data Protection Center (record no. WZ20017637-2020-37).

206

207 ***Consent for publication***

208 Not applicable.

209

210 ***Availability of data and materials***

211 The data that support the findings of this study are available on reasonable request from the
212 corresponding author, NH. The data are not publicly available as they contain information that
213 could compromise the privacy of research participants.

214

215 ***Competing interests***

216 The authors declare to have no competing interests.

217

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219 No funding was received.

220

221 ***Authors' contributions***

222 NH, SI and TL collected data for the study. NH carried out data-analysis and wrote the manuscript.
223 GK, RM and TB supervised the work on data analysis and manuscript writing and KK reviewed and
224 contributed to the manuscript writing. All authors have read and approved the final manuscript.

225

226 ***Acknowledgement***

227 Not applicable.

228

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