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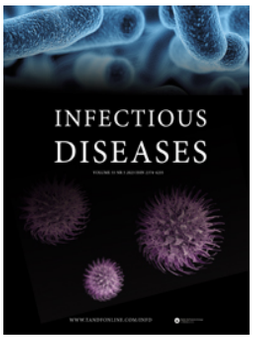

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Treatment effect modifiers in hospitalised patients with COVID-19 receiving remdesivir and dexamethasone

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ABSTRACT

Background: The combined effectiveness of remdesivir and dexamethasone in subgroups of hospitalised patients with COVID-19 is poorly investigated.

Methods: In this nationwide retrospective cohort study, we included 3826 patients with COVID-19 hospitalised between February 2020 and April 2021. The primary outcomes were use of invasive mechanical ventilation and 30-day mortality, comparing a cohort treated with remdesivir and dexamethasone with a previous cohort treated without remdesivir and dexamethasone. We used inverse probability of treatment weighting logistic regression to assess associations with progression to invasive mechanical ventilation and 30-day mortality between the two cohorts. The analyses were conducted overall and by subgroups based on patient characteristics.

Results: Odds ratio for progression to invasive mechanical ventilation and 30-day mortality in individuals treated with remdesivir and dexamethasone compared to treatment with standard of care alone was 0.46 (95% confidence interval, 0.37–0.57) and 0.47 (95% confidence interval, 0.39–0.56), respectively. The reduced risk of mortality was observed in elderly patients, overweight patients and in patients requiring supplemental oxygen at admission, regardless of sex, comorbidities and symptom duration.

Conclusions: Patients treated with remdesivir and dexamethasone had significantly improved outcomes compared to patients treated with standard of care alone. These effects were observed in most patient subgroups.

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Introduction

Early in the COVID-19 pandemic, randomised clinical trials showed that two pharmacological interventions were effective in the treatment of patients hospitalised with COVID-19 [1, 2]. In the Adaptive COVID-19 Treatment Trial-1, the antiviral drug remdesivir was superior to placebo in time to recovery, and the Randomised Evaluation of COVID-19 Therapy trial showed that the corticosteroid, dexamethasone, reduced 28-day mortality compared to placebo [1,2]. Based on these trials, Danish guidelines have recommended the use of remdesivir and dexamethasone in patients with COVID-19 and hypoxaemia since May and June 2020, respectively (https://infmed.dk/guidelines#covid19_retningslinje_2022v20.pdf). Other pharmacological interventions recommended in Denmark include the anti-interleukin-6 receptor monoclonal antibody, tocilizumab, that has shown to be associated with improved outcomes for patients with COVID-19 and respiratory distress [3,4]. Tocilizumab was added to the guideline in February 2021. Further, prophylactic anticoagulation has been recommended since April 2020 to all hospitalised patients with COVID-19 (https://infmed.dk/guidelines#covid19_retningslinje_2022v20.pdf).

The role of remdesivir in treatment of hospitalised individuals with COVID-19 was initially controversial due to conflicting results in clinical trials [1,5–9]. However, the final analysis of the Solidarity trial showed a reduction in 28-day mortality albeit modest [10]. Dexamethasone treatment of hypoxic individuals with COVID-19 has been less controversial. Little is known about the mechanisms behind the reduced mortality in hospitalised patients with COVID-19. We reported that the overall risk of invasive mechanical ventilation and 30-day mortality was markedly reduced during the second wave when remdesivir and dexamethasone were widely used as compared to the first wave prior to the recommendation of using these drugs [11]. Here, we extend the analysis to include an assessment of baseline factors associated with reduced use of invasive mechanical ventilation and 30-day mortality during an extended study period with more than 3800 hospitalised patients in Denmark between February 2020 and April 2021 treated with or without remdesivir and dexamethasone.

Study design and methods

Setting

The distribution of remdesivir and criteria for treatment in hospitalised patients with COVID-19 in Denmark have been described previously [11]. Treatment was initially administered through the Adaptive COVID-19 Treatment Trial-1 and later through an early access program. Prior to June 2020, less than 25 individuals in Denmark received remdesivir through the Adaptive COVID-19 Treatment Trial-1. From August 2020, remdesivir was widely available in Denmark.

This study was approved by the Danish Board of Health (record no. 31–1522–84 and 31–1521–309), the Capital Regional Data Protection Centre (record no. P-2020–492), the Region Zealand Data Protection Agency (record no. 070–2020), the Region of Southern Denmark (record no. 10.960 and 20/16169) and the legal authorities in North Denmark Region (record no. 2020–045). By Danish legislation, this type of study is exempted from ethical committee approval.

Study cohort

To evaluate the effect of the combination therapy with remdesivir and dexamethasone on clinical outcomes in patients hospitalised with COVID-19, we compared a cohort hospitalised from June 2020 through April 2021, all treated with standard of care plus remdesivir and dexamethasone (the RD cohort), to a previous cohort hospitalised from February through May 2020 receiving standard of care without remdesivir and dexamethasone (the SOC cohort). Our primary outcomes were use of invasive mechanical ventilation during hospitalisation and 30-day mortality. A secondary outcome was length of hospitalisation. Patients in the RD and SOC cohorts

were included from thirteen and eight different centres across Denmark, respectively. Corticosteroids were infrequently used prior to the Randomised Evaluation of COVID-19 Therapy trial press release on June 16, 2020.

For both cohorts, data were obtained through manual review of electronic health records and included demographic variables, comorbidities, radiographic infiltration on chest X-ray and baseline respiratory support. Chest X-ray infiltrate was ascertained within 24 h of admission, and baseline respiratory support (no oxygen, oxygen or invasive mechanical ventilation) was ascertained as the highest level of respiratory support on day of admission. In both cohorts, SARS-CoV-2 was confirmed by reverse transcriptase polymerase chain reaction on an oropharyngeal swab or lower respiratory tract specimen.

Variant analysis of SARS-CoV-2 was not implemented on an individual level during the study period. Based on population surveillance sampling, the Wuhan strain was dominating until the beginning of 2021 where Alpha (B.1.1.7) gradually became the dominant variant. Alpha was detected in more than 50% of sequenced samples by week 7 of 2021 and more than 90% by week 10 of 2021 and throughout the study period (https://covid19.ssi.dk/virusvarianter/varianter-i-danmark/opgoerelse-over-udvalgte-af-sars-cov-2-virusvarianter).

Statistical analysis

Baseline characteristics are presented as numbers with percentages or medians with an IQR. Comparisons of baseline variables between the SOC and RD cohorts were performed using χ^2- test, Fisher's exact test or Mann–Whitney U-test, as appropriate.

As data were collected retrospectively, imbalance in baseline characteristics between the two cohorts could have confounded our effect estimate of treatment with remdesivir and dexamethasone. Therefore, we used the stabilised inverse probability of treatment weighting method to create a pseudo-population in which covariates were independent of treatment selection. Inverse probability of treatment weighting estimates was computed using a multiple logistic regression model on the probability of receiving remdesivir and dexamethasone, and covariates in the model included age, sex, presence of comorbidities (arterial hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, cancer or other comorbidity), presence of radiographic infiltration and baseline respiratory support. Body mass index, symptom duration and type of oxygen at baseline (low or high flow) were not included in the model due to a high proportion (>10%) of missing values. The inverse probability of treatment weighting model was used to assess any association with progression to invasive mechanical ventilation or 30-day mortality in the RD and the SOC cohorts. As an exploratory analysis, we examined whether risk estimates of 30-day mortality differed between the two cohorts with regard to age (<50, 50–59, 60–69, 70–79 and ≥80 years), sex (female or male), coexisting comorbidity (arterial hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, cancer and other comorbidity), BMI (<25, 25–30 and >30 kg/m^2), symptom duration (0–3, 4–6, 7–9 and >9 days), radiographic evidence of pneumonic infiltration (yes and no), baseline respiratory support (no oxygen, oxygen and use of invasive mechanical ventilation) and type of oxygen at admission (oxygen through a low flow device and oxygen through a high flow device). The subgroup analyses were performed after inverse probability of treatment weighting. As a sensitivity analysis, we evaluated a potential time-dependent effect on 30-day mortality within the RD cohort by dividing the cohort into two groups (June through December 2020 and January through April 2021, respectively).

Risk estimates of use of invasive mechanical ventilation and 30-day mortality are presented as OR with 95% CI. Forest plots of point estimates and their 95% CI range were used for graphical analysis. Both normal and weighted absolute standardised mean difference between treatment groups were computed to validate the weighting procedure.

Duration of hospital stay in the RD cohort compared to the SOC cohort was calculated in each of the above-mentioned subgroups. The analyses were performed after applying the propensity score matching method to diminish potential heterogenicity of baseline characteristics between the two cohorts. Covariates in the model included age, sex, presence of comorbidity (yes or no), presence of radiographic infiltration and baseline respiratory support. For analyses of the duration of hospital stay, data on patients who died in hospital was censored.

P-values < .05 were considered statistically significant. Data analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population characteristics

The SOC cohort included 1044 and the RD cohort 2782 individuals. All patients in the RD cohort received remdesivir and dexamethasone.

Table 1. Characteristics of subjects included in the study.

	SOC cohort ($n = 1044$)	RD cohort ($n = 2782$)	p Value	SMD	SMD after IPTW[a]
Age, years, median [IQR]	71 [57, 80]	69 [57, 78]	.019	0.064	0.057
<0, *n* (%)	298 (28.5)	867 (31.2)			
60–69, *n* (%)	192 (18.4)	589 (21.2)			
70–79, *n* (%)	276 (26.4)	726 (26.1)			
≥80, *n* (%)	278 (26.6)	600 (21.6)	.004		
Sex					
Female, *n* (%)	472 (45.2)	1046 (37.6)			
Male, *n* (%)	572 (54.8)	1734 (62.4)	<.001	0.155	0.014
Comorbidity, *n* (%)	833 (79.8)	2199 (79.0)	.644		
Coexisting comorbidity					
Arterial hypertension, *n* (%)	407 (39.0)	1054 (37.9)	.558	0.021	0.012
Diabetes mellitus, *n* (%)	207 (19.8)	624 (22.4)	.090	0.065	0.019
Cardiovascular disease, *n* (%)	288 (27.6)	773 (27.8)	.934	0.006	0.039
COPD, *n* (%)	152 (14.6)	352 (12.7)	.134	0.055	0.020
Cancer, *n* (%)	127 (12.2)	274 (9.8)	.043	0.074	0.009
Others, *n* (%)	360 (36.3)	1290 (46.4)	<.001	0.208	0.010
BMI, median [IQR]	26.6 [23.5, 30.9]	27.8 [24.6, 32.0]	<.001		
<5, *n* (%)	288 (37.4)	634 (29.1)			
25–30, *n* (%)	257 (33.3)	779 (35.8)			
>30, *n* (%)	226 (29.3)	766 (35.2)	<.001		
Missing, *n*	273	603			
Radiographic evidence of pneumonic infiltration, *n* (%)	801 (80.7)	2567 (92.3)	<.001	0.343	0.010
Baseline respiratory support					
No oxygen, *n* (%)	577 (55.3)	671 (24.2)			
Oxygen, *n* (%)	443 (42.4)	2078 (74.9)			
IMV, *n* (%)	24 (2.3)	27 (1.0)	<.001	0.696	0.012
Type of oxygen at admission					
Low flow, *n* (%)	243 (91.7)	1803 (86.8)			
High flow, *n* (%)	22 (8.3)	275 (13.2)	<.030		
Missing, *n*	178	–			
Need of supplemental oxygen when receiving first dose of remdesivir, *n* (%)	–	2719 (97.7)	–		
Symptom duration, days, median [IQR]	7 [3, 10]	6 [3, 9]	<.001		
0–3, *n* (%)	226 (25.1)	736 (27.9)			
4–6, *n* (%)	158 (17.6)	670 (25.4)			
7–9, *n* (%)	234 (26.0)	750 (28.5)			
>9, *n* (%)	282 (31.3)	478 (18.1)	<.001		
Missing, *n*	144	148			
Time to IMV, days, median [IQR]	3 [1, 5]	3.5 [1.2, 7.0)	.018		
Use of IMV, *n* (%)	147 (14.1)	260 (9.3)	<.001		
Use of ECMO, *n* (%)	10 (1.0)	22 (0.8)	.759		
30-day mortality, *n* (%)	204 (19.5)	352 (12.7)	<.001		

BMI: body mass index; COPD: chronic obstructive pulmonary disease; ECMO: extra corporal membrane oxygenation; IPTW: inverse probability of treatment weighting; IQR: interquartile range; *n*: number; IMV: invasive mechanical ventilation; RD: remdesivir and dexamethasone; SMD: standardised mean difference; SOC: standard of care.

[a]covariates in the model included: age, sex, presence of comorbidity (arterial hypertension, diabetes mellitus, cardiovascular disease, COPD, cancer or other comorbidity), radiographic infiltration on chest X-ray and baseline respiratory support (no oxygen, oxygen or IMV).

Baseline and clinical characteristics of the patients in the two cohorts are presented in Table 1. Patients in the RD cohort were younger, more often male, had higher BMI and had one day shorter symptom duration at admission compared to patients in the SOC cohort. Patients in the RD cohort were more likely to have infiltration on chest X-ray at baseline and more often required supplemental oxygen at admission and with a higher proportion through a high flow device. About 80% of individuals in both cohorts suffered from comorbidities with a comparable distribution of each comorbidity except for cancer which was more frequent in the SOC cohort, and other comorbidity which was more common in the RD cohort. Use of invasive mechanical ventilation and 30-day mortality were significantly lower in the RD cohort than in the SOC cohort (9.3% vs 14.1%, $p < .001$, and 12.7% vs 19.5%, $p < .001$, respectively).

Unweighted standardised mean differences ranged from 0.006 to 0.696 for age, sex, each comorbidity, infiltration on chest X-ray and baseline respiratory support. After inverse probability of treatment weighting, the standardised mean differences ranged from 0.009 to 0.057 (Table 1).

Overall risk estimation

Odds ratios of use of invasive mechanical ventilation and 30-day mortality in the RD cohort compared to the SOC cohort overall and in subgroups after weighting are presented in Figures 1 and 2, respectively. Overall, odds

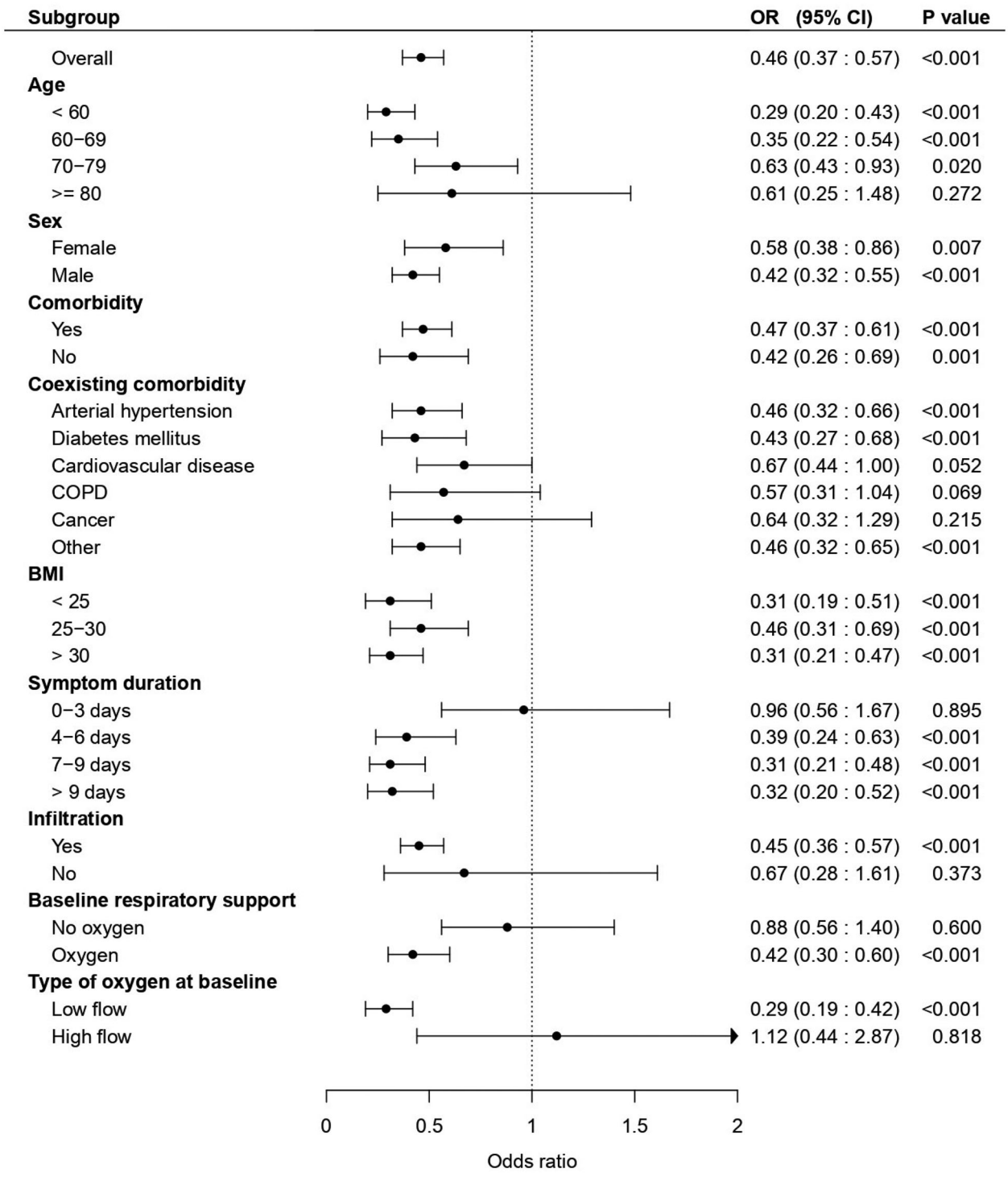

Figure 1. Odds ratios of use of IMV in patients with COVID-19 treated with SOC plus remdesivir and dexamethasone compared to patients treated with SOC alone overall and stratified by subgroups. BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; COVID-19 = Coronavirus Disease 2019; IMV: invasive mechanical ventilation; OR: odds ratio; SOC: standard of care.

of invasive mechanical ventilation and 30-day mortality was significantly lower after the introduction of remdesivir and dexamethasone (OR, 0.46; 95% CI, 0.37;0.57, and OR, 0.47; 95% CI, 0.39;0.56, respectively).

For patients treated with remdesivir and dexamethasone, the odds of use of invasive mechanical ventilation and 30-day mortality were lower in both the June–December 2020 period (OR, 0.50; 95% CI, 0.39;0.63, $p < .001$ and OR, 0.49; 95% CI, 0.40;0.60, $p < .001$, respectively) and the January–April 2021 period (OR, 0.44; 95% CI, 0.33;0.59, $p < .001$ and OR, 0.55; 95% CI, 0.43;0.69, $p < .001$, respectively) compared to the

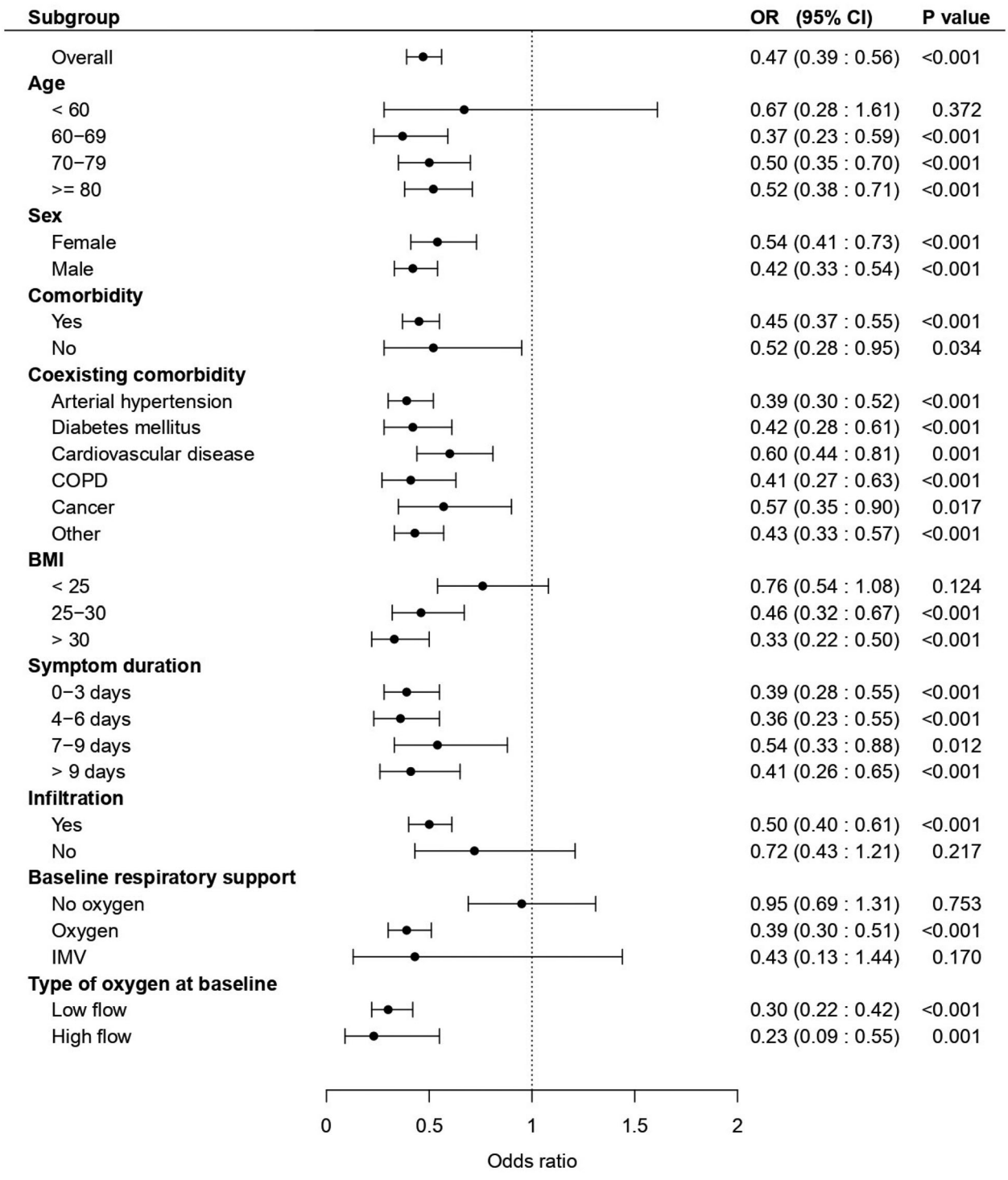

Figure 2. Odds ratios of 30-day mortality in patients with COVID-19 treated with SOC plus remdesivir and dexamethasone compared to patients treated with SOC alone overall and stratified by subgroups. BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; COVID-19: Coronavirus Disease 2019; OR: odds ratio; SOC: standard of care.

February–May 2020 period. Use of invasive mechanical ventilation and 30-day mortality did not differ within the second wave (January–April 2021 compared to June–December 2020) (OR, 0.88, 95% CI, 0.66;1.18, $p = 0.395$ and OR, 1.08; 95% CI, 0.85;1.36, $p = 0.535$, respectively).

Subgroup analysis of invasive mechanical ventilation

By subgroup analysis, the RD cohort had lower odds of use of invasive mechanical ventilation compared to the SOC cohort regarding individuals with infiltration on chest X-ray, with symptoms for more than three days

and with need of supplemental oxygen at admission, particularly those receiving low flow oxygen. Further, lower odds were observed in all age groups below 80 years, in both females and males, in all BMI subgroups, and in patients with and without coexisting comorbidity. Patients with arterial hypertension, diabetes and other comorbidity had significantly lower odds of use of invasive mechanical ventilation whereas patients with cardiovascular disease, chronic obstructive pulmonary disease and cancer did not (Figure 1).

Subgroup analysis of 30-day mortality

Odds of 30-day mortality were significantly lower in the RD cohort compared to the SOC cohort in patients older than 59 years, in the overweight and obese and in patients with radiographic infiltration. In addition, lower odds of 30-day mortality in the RD cohort compared to the SOC cohort were observed in all subgroups based on sex, comorbidity and symptom duration. Patients in the RD cohort requiring supplemental oxygen at admission, both low and high flow, had significantly lower odds of 30-day mortality, whereas patients breathing ambient air and patients requiring invasive mechanical ventilation did not have statistically significant lower odds of death (Figure 2).

Length of hospital stay

After propensity score matching, the SOC and RD cohorts included 677 and 676 individuals, respectively. The cohorts were well-balanced according to baseline characteristics after matching (see Supplementary Table S1). Median days from admission to discharge based on subgroups are presented in Table 2. Overall, patients in the SOC cohort had one day shorter hospital stay than

Table 2. Days from admission to discharge stratified by subgroups after propensity score matching[a].

	Time To discharge, days, median, [IQR]		
	SOC cohort ($n = 677$)	RD cohort ($n = 676$)	p Value
Overall	6 [3, 13]	7 [4, 11]	<.001
Age			
<60	5 [2, 11]	6 [4, 8]	.142
60–69	6 [3.0, 11.5]	7 [5, 15]	.042
70–79	7 [3, 14]	8 [5, 16]	.028
≥ 80	6 [3, 13]	7 [5, 13]	.061
Sex			
Female	6 [3.0, 12.2]	7 [5, 11]	.004
Male	6.5 [3, 13]	7 [4, 12]	.029
Comorbidity			
Yes	6 [3, 14]	7 [5, 13]	.001
No	6 [3.0, 9.8]	6 [4, 9]	.254
Coexisting comorbidity			
Arterial hypertension	7 [3, 14]	7 [4.0, 11.8]	.932
Diabetes mellitus	7 [3.2, 15.0]	7 [5, 12]	.973
Cardiovascular disease	8 [3, 15]	7 [5, 14]	.294
COPD	9 [4, 19]	8 [5, 11]	.292
Cancer	7 [3.0, 11.8]	9 [5, 14]	.034
Other	7 [3, 16]	7 [4, 12]	.607
BMI			
<25	8 [3, 16]	9 [5, 17]	.041
25–30	7 [3, 13]	6 [4, 11]	.842
>30	7.5 [3.0, 16.2]	7 [5, 11]	.624
Symptom duration, days, median [IQR]			
0–3	6 [3, 13]	7 [5, 13]	.041
4–6	8 [4, 14]	6 [4.2, 10.0]	.330
7–9	7 [2, 11]	6 [4, 9]	.485
>9	4.5 [2, 9]	6 [4.0, 8.2]	.029
Radiographic evidence of pneumonic infiltration			
Yes	6.5 [3, 14]	7 [5.0, 11.5]	.007
No	4 [2.0, 9.8]	6 [4.0, 9.2]	.003
Baseline respiratory support			
No oxygen	4 [2, 9]	7 [5, 13]	<.001
Oxygen	8 [5.0, 17.2]	5 [4, 9]	<.001
IMV	27 [20.5, 34.5]	35.5 [8.5, 58.0]	.957
Type of oxygen at admission			
Low flow	7 [4.0, 15.8]	5 [4, 8]	.001
High flow	8 [8, 37]	14 [8.2, 23.5]	.965

BMI: body mass index; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; IMV: invasive mechanical ventilation; RD: remdesivir and dexamethasone; SOC: standard of care.

[a]Covariates in the model included: age, sex, presence of comorbidity (yes or no), radiographic infiltration on chest X-ray and baseline respiratory support (no oxygen, oxygen or IMV).

patients in the RD cohort (6 vs. 7 days, respectively, $p < .001$). Significantly fewer days to discharge in the SOC cohort were demonstrated in patients between 60 and 80 years, with coexisting comorbidity and with a BMI below 25 (Table 2). Furthermore, individuals in the SOC cohort with symptoms for less than 4 days or more than 9 days or without need of supplemental oxygen at admission had a significantly shorter hospital stay than corresponding individuals in the RD cohort. In contrast, patients with need of oxygen at admission had three days shorter hospital stay in the RD cohort compared to the SOC cohort, driven by those requiring low flow oxygen.

Discussion

We previously reported that individuals hospitalised with COVID-19 had significantly reduced use of invasive mechanical ventilation and 30-day mortality in a cohort treated with remdesivir and dexamethasone compared to a cohort treated with initial SOC without these two drugs. In this expanded nationwide cohort study with more than 3800 patients hospitalised with COVID-19, we show that the reduced odds of mortality observed in the RD cohort was mainly driven by lower mortality among the elderly, the overweight and obese and in individuals with need of supplemental oxygen at admission and regardless of sex, comorbidities and duration of symptoms. To our knowledge, this is the first study to evaluate the effectiveness of combination therapy with remdesivir and dexamethasone based on specific subgroups of patient characteristics.

The overall decrease in 30-day mortality shown in this study is comparable with a recent comparative effectiveness study, showing a reduced 28-day mortality from 19.1% to 15.4% in patients treated with remdesivir compared to propensity score matched patients not treated with remdesivir [12]. The effect was seen in patients without need of supplemental oxygen at baseline, with need of low flow oxygen and with need of invasive mechanical ventilation/extracorporeal membrane oxygenation. We found a significantly lower 30-day mortality in patients requiring supplemental oxygen at admission treated with remdesivir and dexamethasone, and the effect was observed for both low and high flow requirements. The Adaptive COVID-19 Treatment Trial-1 was not powered to demonstrate an effect of remdesivir on mortality overall although individuals on low flow supplemental oxygen at baseline receiving remdesivir had significantly lower mortality at day 28 compared to placebo [1]. Based on these results, Danish and other guidelines recommend remdesivir for hypoxemic patients but not for patients requiring invasive mechanical ventilationor extracorporeal membrane oxygenation at admission (https://infmed.dk/guidelines#covid19_retningslinje_2022v20.pdf) [13]. A recent systematic review of randomised controlled trials of remdesivir in hospitalised patients with COVID-19 further supported this, as it concluded that there is a mortality benefit of remdesivir in nonventilated patients with need of oxygen [14]. It is unclear from previous trials whether remdesivir confers a clinical benefit in patients receiving oxygen through a high flow device. Patients requiring high flow nasal cannula are underrepresented in previous trials of remdesivir in COVID-19 and there is potential misclassification of oxygen requirements [14]. Danish guidelines do not distinguish between high and low flow oxygen, whereas American guidelines recommend remdesivir to certain patients requiring high flow oxygen (https://infmed.dk/guidelines#covid19_retningslinje_2022v20.pdf) [13]. In the Adaptive COVID-19 Treatment Trial-1, the effect of remdesivir on mortality was not seen in subgroups with more severe COVID-19, but CIs were wide in these groups and sample sizes small. Thus, the results should be interpreted with caution. The Randomised Evaluation of COVID-19 Therapy trial reported a 12.3% reduction in 28-day mortality in patients treated with dexamethasone compared to usual care in the subgroup requiring invasive mechanical ventilation at admission and a 4.2% reduction in patients receiving supplemental oxygen only at baseline [2]. We found a numerically but not statistically significant lower 30-day mortality in patients requiring invasive mechanical ventilation at admission, which could partly be explained by the small number of patients in this group. In patients not requiring supplemental oxygen at baseline, the Randomised Evaluation of COVID-19 Therapy trial did not demonstrate any efficacy of dexamethasone. Thus, in this subgroup of patients, dexamethasone is not recommended according to Danish guidelines (https://infmed.dk/guidelines#covid19_retningslinje_2022v20.pdf). This is in agreement with our results. A randomised placebo-controlled trial of remdesivir in outpatients at high risk of COVID-19 progression showed an 87% lower risk of hospitalisation or death in patients treated with remdesivir compared to placebo [15]. Based on these results, Danish guidelines criteria for treatment with remdesivir were changed to also include patients without need of supplemental oxygen after completion

of the present study (https://infmed.dk/guidelines#covid19_retningslinje_2022v20.pdf).

In this study, the overall duration of hospitalisation was one day shorter in the SOC cohort compared to the RD cohort, which should be taken into account considering the COVID-19 associated strain on health-care systems in many countries. However, in the RD cohort, patients requiring supplemental oxygen at admission, particularly low flow, had three days shorter stay than the corresponding patient group in the SOC cohort. This supports both the Adaptive COVID-19 Treatment Trial-1 and the Randomised Evaluation of COVID-19 Therapy trial, showing a faster recovery in patients with need of supplemental oxygen at baseline receiving remdesivir and dexamethasone, respectively.

From previous randomised trials, symptom duration seems to influence the efficacy of remdesivir as the Adaptive COVID-19 Treatment Trial-1 indicated that remdesivir was beneficial if administered in the early phase of COVID-19 (symptom duration $<$ 10 days) [1]. Another trial showed similar results although not statistically significant [7]. In contrast, the Randomised Evaluation of COVID-19 Therapy trial found that patients in the late phase (symptom duration $>$ 7 days) had a greater mortality benefit of dexamethasone compared to patients with shorter symptom duration [2]. We found reduced odds of 30-day mortality with the combined treatment regardless of symptom duration, which might indicate that the combination of remdesivir and dexamethasone is more advantageous than used separately. This assumption is supported by a recent study, showing improvement of different outcomes, including mortality, in patients treated with both remdesivir and dexamethasone compared to dexamethasone alone [16]. It is well known that COVID-19 is biphasic, the first stage of infection being characterised by viral replication with mild symptoms, and the second stage being characterised by an overactivation of the immune response leading to a deterioration of symptoms, and ultimately multiorgan failure and potentially death [17]. Collectively, this constitutes the rationale of inhibiting both viral replication and hyperinflammation in individuals with COVID-19.

The better outcome in June through December compared to February through May of 2020 did not improve further during January through April of 2021. The OR of 30-day mortality was nearly 1 when comparing the two latest time periods suggesting that major advances in treatment had occurred in the second half of 2020. However, the crude 30-day mortality in 2021 remained high at 12.7%, emphasising the need for better pharmacological and non-pharmacological therapies.

This study benefits from the large cohort, nationwide setting, standardised registration and complete follow-up. However, as our study was not randomised and although applying causal inference methods as inverse probability of treatment weighting and propensity score matching, we cannot mitigate all confounders. Furthermore, unmeasured variables could bias our effect estimates, and we cannot distinguish between individual effects of remdesivir and dexamethasone. Even so, the markedly reduced 30-day mortality coincided with the introduction of remdesivir and dexamethasone to standard of care in Denmark, and we observed no time-dependent effect on the mortality rate through the second wave after extending the period with four months.

In conclusion, our results show significantly reduced need of invasive mechanical ventilation and 30-day mortality for most subgroups in the cohort treated with remdesivir and dexamethasone compared to the cohort not receiving this treatment. We suggest that combined treatment with remdesivir and dexamethasone may not confer similar benefits in different patient groups based on demographic characteristics and on respiratory support at admission. Further randomised, controlled trials of combination therapy with remdesivir and dexamethasone in patients with COVID-19 are warranted.

Disclosure statement

C.B. reports honoraria from AstraZeneca outside the submitted work.

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All other authors report no potential conflicts.

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