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Strategies to optimise the treatment of community-acquired pneumonia

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Citation
Wittermans, E. (2023, September 28). *Strategies to optimise the treatment of community-acquired pneumonia*. Retrieved from https://hdl.handle.net/1887/3642455

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3642455

Note: To cite this publication please use the final published version (if applicable).

CHAPTER 6

Overweight and obesity are not associated with worse clinical outcomes in COVID-19 patients treated with fixed-dose 6 mg dexamethasone

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INT J OBES (LOND). 2022;46(11):2000-2005.

ABSTRACT

Objective

A fixed 6 mg dexamethasone dose for 10 days is the standard treatment for all hospitalised COVID-19 patients who require supplemental oxygen. Yet, the pharmacokinetic properties of dexamethasone can lead to diminishing systemic dexamethasone exposure with increasing body mass index (BMI). The present study examines whether this translates to overweight and obesity being associated with worse clinical outcomes, defined as ICU admission or in hospital death, in COVID-19 patients treated with fixed-dose dexamethasone.

Methods

We conducted a single centre retrospective cohort study in COVID-19 patients who were admitted to a non-ICU ward and were treated with dexamethasone (6 mg once daily for a maximum of ten days) between June 2020 and January 2021. Univariable and multivariable logistic regression analyses were conducted to assess the association between BMI-categories and an unfavourable clinical course (ICU admission and/or in hospital death). Analyses were adjusted for age, comorbidities, inflammatory status, and oxygen requirement at admission. For reference, similar analyses were repeated in a cohort of patients hospitalised before dexamethasone was introduced (March 2020 through May 2020).

Results

In patients treated with dexamethasone (n= 385) an unfavourable clinical course was most prevalent in patients with normal weight (BMI < 25) compared to patients with overweight (BMI 25–30) and patients with obesity (BMI ≥ 30) with percentages of 33, 26 and 21% respectively. In multivariable analyses, there was no association between BMI-category and an unfavourable clinical course (respectively with aORs of 0.81 (0.43–1.53) and 0.61 (0.30–1.27) with normal weight as reference). In the reference cohort (n = 249) the opposite was observed with an unfavourable clinical course being most prevalent in patients with overweight (39% vs 28%; aOR 2.17 (0.99–4.76)). In both cohorts, CRP level at admission was higher and lymphocyte count was lower in patients with normal weight compared to patients with obesity.

Conclusions

Overweight and obesity are not associated with an unfavourable clinical course in COVID-19 patients admitted to a non-ICU ward and treated with 6 mg dexamethasone once daily.

INTRODUCTION

The RECOVERY TRIAL and the WHO REACT meta-analysis showed that corticosteroids reduced mortality and the need for mechanical ventilation in patients with severe COVID-19.[1,2] After these publications, a course of 6 mg dexamethasone for 10 days was added to the WHO and Dutch national COVID-19 guidelines as standard treatment for hospitalised COVID-19 patients requiring supplemental oxygen.[3,4] The rationale being that severe COVID-19 (defined as an oxygen saturation <94% on ambient air), is caused by dysregulation of the host immune response. This dysregulation can lead to inflammatory organ injury and subsequently unfavourable clinical outcomes.[5] Dexamethasone and other corticosteroids are potent non-specific inhibitors of the immune system.[6] Therefore, they are thought to attenuate the dysregulated immune response in severe COVID-19 and thereby prevent (further) organ damage. Yet even with widespread use of dexamethasone, COVID-19 related morbidity and mortality remain high, and COVID-19 is still a severe burden on healthcare systems.[7–9] A high body mass index (BMI) has been identified as an important risk factor for ICU admission and mortality in hospitalised COVID-19 patients.[10,11] It is therefore important to identify opportunities for improvement of treatment for COVID-19 patients with overweight and obesity. Considering the lipophilic nature of dexamethasone and its relatively large volume of distribution, one might argue that a fixed dose of dexamethasone is less effective in individuals with obesity compared to individuals with normal weight because of lower serum blood levels.[12–14] Besides pharmacokinetic differences, obesity has also been linked to higher inflammatory states in COVID-19 further adding to a potential diminishing relative effectiveness of dexamethasone with increasing body mass index.[15] To the best of our knowledge, none of the dexamethasone trials in COVID-19 patients have conducted subgroup analyses based on BMI. It remains unclear if individuals with overweight or obesity respond differently to the currently recommended fixed dose of dexamethasone 6 mg compared to individuals with normal weight.

The aim of the present study was to examine whether overweight and obesity are associated with worse clinical outcomes (ICU admission and/or in hospital death) in non-ICU patients treated with fixed-dose dexamethasone for COVID-19 compared to patients with normal weight.

METHODS

Study design and study population

We conducted a retrospective cohort study including hospitalised adults (≥18 years of age) with confirmed COVID-19 in a 750-bed teaching hospital (St. Antonius Hospital, Nieuwegein, the Netherlands). We identified two cohorts. First, a cohort with patients who were admitted between June 1st 2020 and January 17th 2021, and were treated with dexamethasone 6 mg in accordance with local and national guidelines.[3] As of June 2020, guidelines stated that treatment with dexamethasone 6 mg once daily (oral or intravenously) should be given to all hospitalised patients with an oxygen saturation <94% on ambient air for 10 days or until hospital discharge. Patients who were admitted to the ICU on the date of emergency department presentation, patients who were transferred to our hospital from a different hospital and patients with missing BMI data were excluded.

The second cohort consisted of patients who were admitted prior to the implementation of the dexamethasone protocol (from March 1st 2020 thru May 31st 2020) and did not receive corticosteroid treatment but did require supplemental oxygen, thus patients who would have had an indication for corticosteroid treatment according to the guidelines implemented after June 1st 2020. Also in this cohort, we excluded patients who were directly admitted to the ICU and patients who were transferred from another hospital. In the remainder of the manuscript, we will refer to the cohorts as the dexamethasone cohort and the historical cohort.

The study was reviewed by the Medical Ethics Committee at the St. Antonius Hospital (No. W21.127), and the need for informed consent was waived due to the retrospective nature of the study and anonymous handling of data.

Data collection

All data analysed in this study were extracted from the hospital's COVID-19 database. This database contains clinical and outcome data for all patients admitted to our hospital with COVID-19. Data was available from time of hospital admission to time of hospital discharge. For patients who were admitted multiple times with COVID-19, we only included the data from the first hospital admission. All records in the database were manually checked to ensure that COVID-19 was the main reason for hospital admission and that patients either had a positive PCR test for COVID-19 prior to hospital admission or upon hospital admission. All variables except Charlson Comorbidity Index (CCI) were directly available from the COVID-19 database. The CCI was calculated using ICD-10 codes from the COVID-19 database for which the coding algorithm by Quan et al.[16] was used.

Data analysis

The primary study outcome was an unfavourable clinical course, which was defined as ICU admission and/or in hospital death. We explored the association between BMI, inflammatory state at admission and an unfavourable clinical course. Lymphocyte count and C-reactive protein (CRP) concentration were used as indicators of inflammation as a lower lymphocyte count and higher CRP concentration have both been associated with a higher level of systemic inflammation in COVID-19 patients.[17,18] Analyses were primarily conducted in the dexamethasone cohort. The historical cohort was used as a reference cohort to put the findings in the dexamethasone cohort into perspective of a non-treated population.

Statistical analyses were conducted using SPSS 26.0. Overall, continuous variables are shown as mean (SD) or median [IQR] depending on distribution. Categorical variables are shown as n (%). Patients were divided into three subgroups based on BMI: patients with normal weight (BMI < 25 kg/m^2), patients with overweight (BMI 25–29.9 kg/m^2), and patients with obesity (BMI > 30 kg/m^2). First, differences in inflammatory state at admission between BMI subgroups was explored. We calculated the median lymphocyte count and median CRP concentration for each BMI subgroup. A Kruskall-Wallis test was used to compare medians. Next, we calculated percentages of patients with an unfavourable clinical course within each BMI subgroup. Subsequently, logistic regression analysis was done with unfavourable clinical course as dependent variable. Associations with BMI-categories were adjusted for age, CCI, CRP level, lymphocyte count and oxygen requirement at admission. CRP was stratified using a cut-off of 75 mg/L this was based on the cut-off used by other COVID-19 studies as a criterion for a heightened inflammatory response.[19] Lymphocyte count was stratified using a cut-off of 0.70 10^9 cells/L (indicating more severe lymphocytopenia). Due to lack of a homogenous cut-off value in literature, this value was determined by ROC analysis of lymphocyte count and an unfavourable clinical course. Oxygen requirement was based on the method of oxygen delivery at admission and was grouped into three groups: (1) Nasal cannula (<6 L O_2) or mask (2) Venturi mask or nasal cannula (≥6 L O_2) and (3) Non-rebreathing mask or high flow nasal cannula (Optiflow).

RESULTS

Patient selection and baseline characteristics for both cohorts

Between June 2020 and January 2021, 715 patients with confirmed COVID-19 were admitted to our hospital of which 385 met the inclusion criteria for the dexamethasone cohort (Figure 1). Median duration of corticosteroid therapy was 6 days (IQR 4.0–10.0 days). Prior to June 2020, 391 patients with confirmed COVID-19 were admitted to our hospital of which 249 met the inclusion criteria for the historical cohort (Figure 1). Baseline characteristics for both cohorts are shown in Table 1. Demographics and baseline clinical characteristics of the historical cohort were similar to the dexamethasone cohort.

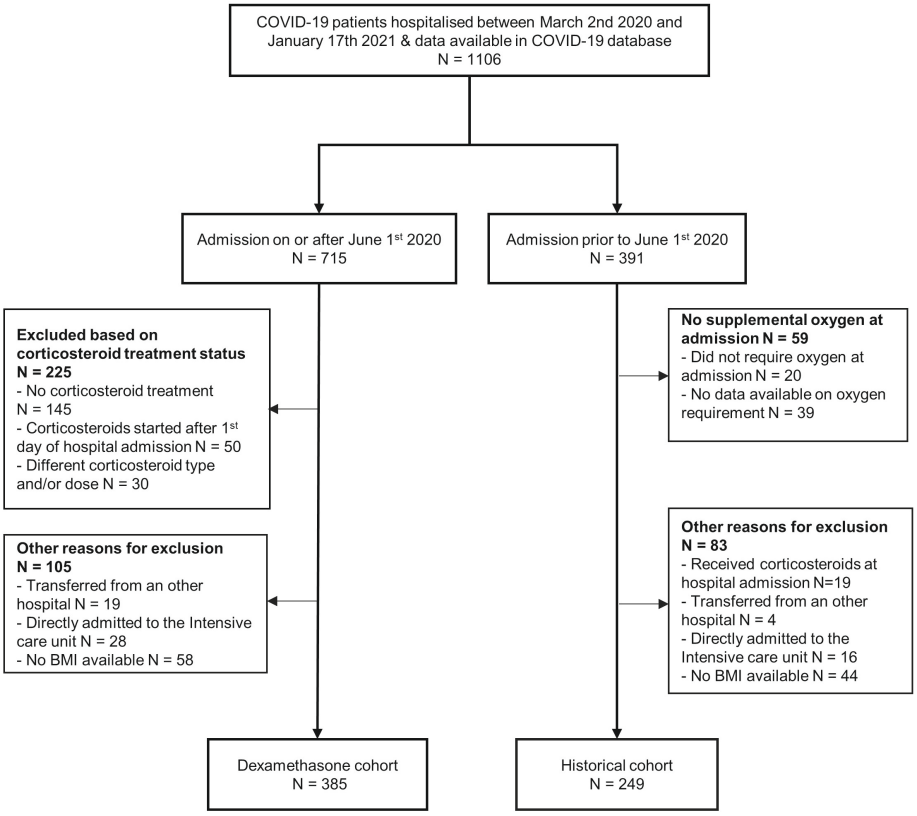

Figure 1 Flowchart showing the process of patient selection for the dexamethasone cohort and the historical cohort.

Table 1 Population characteristics

	Dexamethasone cohort N = 385	**Historical cohort N = 249**
Demographics		
Age (years)	67 (13)	64 (16)
Male	235 (61.0)	162 (65.1)
Body mass index mean (kg/m^2)	28.6 (5.1)	28.5 (5.2)
Body mass index <25 kg/m^2	86 (22.3)	58 (23.3)
Body mass index 25-29.9 kg/m^2	176 (45.7)	109 (43.8)
Body mass index ≥ 30 kg/m^2	123 (31.9)	82 (32.9)
Comorbidities		
Hypertension	113 (29.4)	70 (28.1)
Diabetes Mellitus	92 (23.9)	57 (22.9)
Chronic pulmonary disease	59 (15.3)	27 (10.8)
Charlson comorbidity index score ≥ 3	80 (20.8)	46 (18.5)

Table 1 Continued

	Dexamethasone cohort N = 385	Historical cohort N = 249
Measurement at admission		
Oxygen saturation (%)	94 [92 - 96]	95 [93-97]
Respiratory rate (breaths/min)*	23 (6)	23 (6)
Heartrate (bpm)	92 (18)	93 (17)
Systolic blood pressure (mmHg)	136 (22)	136 (23)
Diastolic blood pressure (mmHg)*	75 (12)	78 (14)
Body temperature (°C)	37.8 (1.9)	37.9 (1.1)
Presence of ≥ 2 SIRS criteria*	193 (50.1)	151 (60.6)
Method of oxygen delivery*		
None	3 (0.8)	-
Nasal Cannula <6L O2	333 (86.5)	203 (81.5)
Mask	11(2.9)	18 (7.2)
Venturi mask	2 (0.5)	1 (0.4)
Nasal cannula ≥ 6L O2	8 (2.1)	1 (0.4)
Non rebreathing mask	23 (6.0)	24 (9.6)
Optiflow/airvo	1 (0.3)	1 (0.4)
Laboratory results at admission*		
C-reactive protein concentration (mg/L)	82 [46 - 134]	79 [39 - 139]
White blood cell count (10^9 cells/L)	6.8 [5.0 – 9.1]	6.9 [5.3 – 9.3]
Lymphocyte count (10^9 cells/L)	0.84 [0.62 - 1.18]	0.85 [0.59 – 1.20]
Estimated glomular filtration rate (EPI)	76 [54 - 90]	78 [54 - 90]

Data are shown as n (%), mean (SD) or median [IQR]. *Missing data for dexamethasone cohort n (%): respiratory rate 1 (0.3%), diastolic blood pressure 1 (0.3%), SIRS criteria 2 (0.5%), Method of oxygen delivery 4 (1.0%), C-reactive protein 7 (1.8%), White blood cell count 6 (1.6%), lymphocyte count 16 (4.2%), Kidney function 6 (1.6%). Missing data for historical cohort n (%): Lymphocyte count 11 (4.4%), White blood cell count 2 (0.8%), eGFR 3 (1.2%), SIRS 1 (0.4%)

Clinical outcomes

In the dexamethasone cohort 65 (16.9%) patients were admitted to the ICU, and 46 (11.9%) patients died in hospital. Eleven patients died after ICU admission. A total of 100 (26.0%) patients met the combined outcome of ICU admission and/or in hospital death. In the historical cohort, 43 (17.3%) patients were admitted to the ICU and 57 (22.9%) died in hospital. Eighteen patients died after ICU admission. A total of 82 (32.9%) patients met the combined outcome of ICU admission and/or in hospital death.

Body mass index, inflammatory state at admission and clinical course

In the dexamethasone cohort, median CRP concentration was lowest in patients with obesity and highest in patients with normal weight. For lymphocyte count the

opposite was observed, patients with obesity had higher lymphocyte counts compared to patients with normal weight. Although not statistically significant, numerically, the same trend was seen in the historical cohort (Table 2).

Table 2 Inflammatory parameters at admission by body mass index category

	Dexamethasone cohort				Historical cohort			
	CRP	**P**	**Lymphocyte count**	**P**	**CRP**	**P**	**Lymphocyte count**	**P**
BMI < 25 kg/m^2	97 [54-150]	0.018	0.68 [0.52-0.96]	<0.001	96 [62-133]	0.25	0.74 [0.47-1.21]	0.075
BMI 25 to 29.9 kg/m^2	81 [52-146]		0.85 [0.64-1.18]		82 [39-144]		0.85 [0.59-1.16]	
BMI ≥ 30 kg/m^2	69 [37-118]		0.89 [0.70 -1.33]		61 [35-138]		0.97 [0.69-1.34]	

Data are shown as Median [IQR]. *P*-values(Kruskall-wallis) represent difference in median CRP or Lymphocyte count between BMI categories within each cohort.

In the dexamethasone cohort, the percentage of ICU admission and/or in hospital death was higher in patients with normal weight than in patients with overweight and patients with obesity (33% vs 26% vs 21%; p for trend = 0.07), though this difference between groups did not reach statistical significance (Figure 2). The unadjusted odds ratio for an unfavourable clinical course was 0.73 (95% CI 0.41–1.29; p = 0.28) for patients with overweight compared to patients with normal weight, and 0.56 (95% CI 0.30–1.04; p = 0.07) for patients with obesity compared to patients with normal weight. In the multivariable model, there was also no association between BMI and an unfavourable clinical course after adjusting for age, CCI, inflammatory status and oxygen requirement (Table 3). In the historical cohort, the rate of ICU admission and/or in hospital death was higher in patients with overweight (39%), compared to patients with normal weight (28%) or patients with obesity (29%) (Figure 2). The unadjusted odds ratio for an unfavourable clinical course was 1.65 (95% CI 0.82–3.29; p = 0.16) for patients with overweight compared to patients with normal weight, and 1.09 (95% CI 0.52–2.29; p = 0.83) for patients with obesity compared to patients with normal weight. In the multivariable model, there was no association between BMI subgroups and ICU admission and/or in hospital death (Table 3).

Regarding inflammatory state at admission, in the multivariable model both the presence of a CRP concentration ≥75 mg/L and lymphocyte count <0.70 10^9 cells/L at admission were associated with an unfavourable clinical course in the dexamethasone cohort but not in the historical cohort (Table 3).

Table 3 Multivariable analysis of the association between BMI subgroups, C-reactive protein, lymphocyte count and ICU admission and/or in hospital death

	Dexamethasone cohort		**Historical cohort**	
	Odds ratio (95% CI)	**P**	**Odds ratio (95% CI)**	**P**
Body mass index				
Body mass index <25 kg/m^2 (ref)				
Body mass index 25 to 29.9 kg/m^2	0.81 (0.43 – 1.53)	0.52	2.17 (0.99 – 4.76)	0.054
Body mass index ≥ 30 kg/m^2	0.61 (0.30 – 1.27)	0.19	1.79 (0.75 – 4.23)	0.19
C-reactive protein concentration				
CRP <75 mg/L (ref)				
CRP ≥75 mg/L	1.73 (1.01 – 2.96)	0.046	1.69 [0.91 – 3.17]	0.10
Lymphocyte count				
Lymphocyte count ≥0.7 10^9 cells/L (ref)				
Lymphocyte count <0.7 10^9 cells/L	1.95 (1.15 – 3.31)	0.013	0.78 [0.41 – 1.50]	0.46

Analysis was adjusted for age, CCI and oxygen requirement upon admission. Numbers analysed: dexamethasone cohort 363; Historical cohort 238. CRP: C-reactive protein.

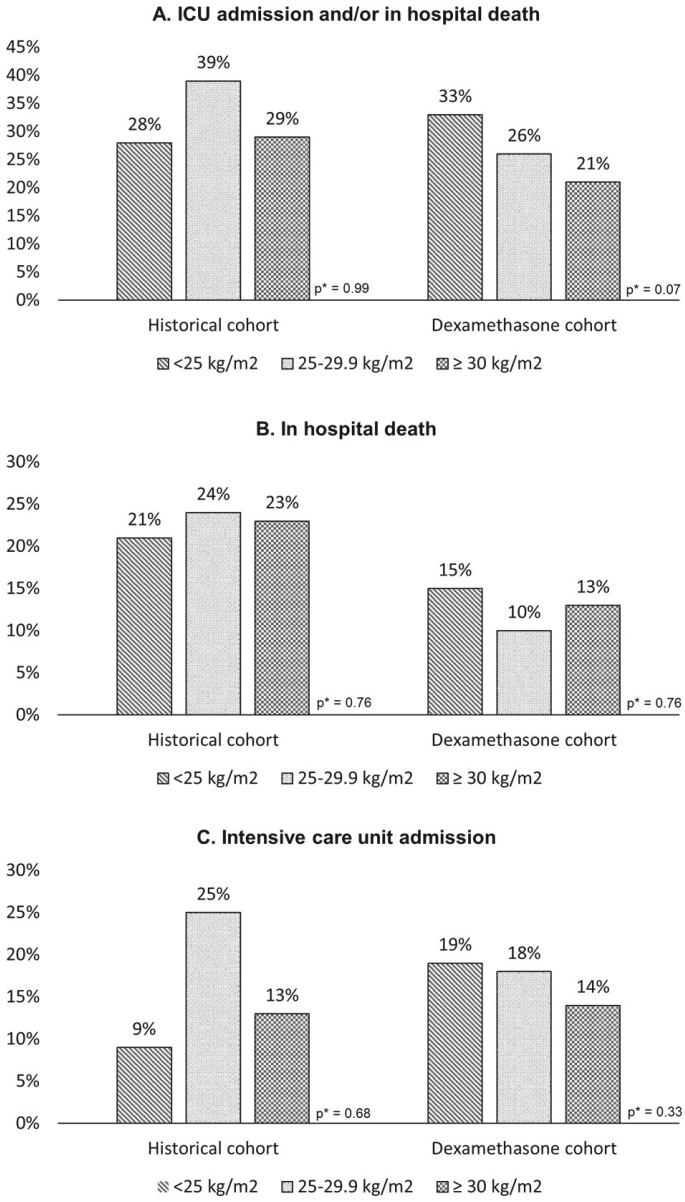

Figure 2 Clinical outcomes by BMI subgroup and cohort **A** shows the percentage of patients with an unfavourable clinical course during admission for each BMI subgroup by cohort. **B** shows the percentage of patients who died in hospital for each BMI subgroup by cohort. **C** shows the percentage of patients who required intensive care unit admission for each BMI subgroup by cohort. Numbers analysed; Historical cohort BMI < 25 kg/m^2 N = 58, BMI 25–29.9 kg/m^2 N = 109, ≥30 kg/m^2 N = 82. Dexamethasone cohort BMI < 25 kg/m^2 N = 86, BMI 25–29.9 kg/m^2 N = 176, ≥30 kg/m^2 N = 123. *Chi-square for trend.

DISCUSSION

This study showed that in COVID-19 patients admitted to a non-ICU ward and treated with dexamethasone, patients with overweight and patients with obesity do not experience worse clinical outcome compared to patients with normal weight. Interestingly, the percentage of secondary ICU admission and/or in hospital mortality was higher in patients with normal weight compared to patients with obesity. Yet, both univariable and multivariable analysis did not show a statistically significant difference in odds of an unfavourable clinical course between BMI subgroups. Furthermore, we observed lower inflammatory status at admission in patients with overweight and those with obesity.

When designing the study, we hypothesised that patients with obesity and patients with overweight would benefit less from a fixed 6 mg dexamethasone dose compared to normal weight patients. Yet, we could not confirm this hypothesis. For this we propose two possible explanations. First this could mean that the systemic dexamethasone exposure from a fixed-dose is not affected or only minimally affected by total body weight. Thus that, contrary to our hypothesis, the systemic exposure of dexamethasone is similar in individuals with and individuals without obesity. However, this would contradict what we know from community-acquired pneumonia patients. In a pharmacokinetic study of dexamethasone in community-acquired pneumonia patients a volume of distribution of 1 L/kg was observed. This indicates a linear decrease in peak serum dexamethasone concentrations with increase in total body weight.[14] Unfortunately, we were not able to measure dexamethasone serum concentrations in the present study to explore this further. But there is a Swiss trial underway that compares dexamethasone pharmacokinetics between COVID-19 patients with normal weight and COVID-19 patients with obesity which might shed more light on the matter.[20]

A second, and more likely, explanation for why we did not observe worse clinical outcomes in patients with obesity may lie in differences in baseline inflammatory state. Our finding of a lower inflammatory status in patients with obesity was unexpected. In general, obesity is linked to higher expressions of CRP and pro-inflammatory cytokines such as TNF-a, and interleukin-6.[21] In an analysis of 781 hospitalised COVID-19 patients McNeill et al. also showed that initial CRP was higher in individuals with obesity than in individuals without obesity.[15] In the present study, higher CRP and lower lymphocyte counts were associated with worse outcome, but it were the patients with normal weight who had the highest baseline inflammatory status. Possibly, the lower state of inflammation in our patients with obesity means that these patients require lower serum peak dexamethasone concentrations compared to patients with normal weight as there is less inflammation to dampen. This would result in a null effect difference between patients with obesity and those with normal weight. The fact that we observed worse outcomes for patients with overweight not treated with dexamethasone compared to patients with healthy weight not treated with dexamethasone could support this hypothesis.

In general, it remains uncertain what dexamethasone dose is optimal for COVID-19 patients, especially for non-ICU patients. Several studies are underway that compare the effectiveness of high vs low dose dexamethasone for COVID-19 patients, however results have not yet been published.[22,23] To our knowledge, as of yet there is only one published randomised controlled trial that has compared low (6 mg) vs high (12 mg) dose dexamethasone. This study did not show a statistically significant difference in days alive without life support and 28-day mortality between patients treated with 12 mg dexamethasone and those treated with 6 mg dexamethasone.[24] However, a secondary Bayesian analysis of the same trial showed higher probability of benefit in patients treated with 12 mg compared to 6 mg.[25] Because, this study only included patients requiring ≥10 L of oxygen or those on mechanical ventilation and there was no baseline information available on BMI (only body weight), it is difficult to relate the results of this trial to the findings in the present study.

The data in the present study represent the time between the start of the SARS-CoV-2 outbreak in the Netherlands in March 2020 and January 2021. Overall, we found that the prognosis for COVID-19 patients improved during this period, as shown by the lower overall mortality rate in the dexamethasone cohort compared to the historical cohort (which coincided with the first wave of the pandemic). Although the introduction of standard corticosteroid treatment was a major improvement of care for COVID-19 patients, it should be noted that other improvements of care were also made between March 2020 and January 2021. An important example is awareness about the increased risk of thromboembolic complications in COVID-19 patients.[26] Furthermore other medications such as remdesivir and tocilizumab became available.[27,28] However, in our hospital tocilizumab was only prescribed in ICU patients and remdesivir was only prescribed during a short two-week period. Considering this, we do not expect that these medications influenced clinical outcomes in our cohort with non-ICU patients.

The main strength of the present study is our well-defined cohort of patients not admitted to the ICU. Though, ICU admission rate is high in COVID-19, the majority of hospitalised COVID-19 patients are still admitted to a regular ward.[29] Optimising non-ICU treatment might help in reducing secondary ICU admissions which is better for both the patient and the health care system. The present study also has several limitations. First, this was a retrospective study in which we had to rely on available data from the COVID-19 database. Because we only included patients for whom a BMI was available, we cannot exclude the possibility that some selection bias may exist due to missing BMI data in the COVID-19 database. Second, it is important to note that due to increasing pressure on the Dutch health care system during the second and third COVID-19 wave, a national system was implemented to equally distribute COVID-19 patients between Dutch hospitals. We cannot exclude the possibility that a patient died or was admitted to the ICU after being transferred to a different hospital. However, only 21 (5.5%) patients in the dexamethasone cohort were transferred to a different hospital

and patients had to be clinically stable to be transferred. Last, the number of patients in the historical cohort was quite small which may have led to insufficient statistical power in this cohort.

In conclusion, overweight and obesity both are not associated with secondary ICU admission and/or in hospital death in patients admitted to a non-ICU ward and treated with dexamethasone 6 mg once daily.

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