The effect of immunosuppressants on the prognosis of SARS-CoV-2 infection

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In a nationwide cohort study of SARS-CoV-2 infections in Denmark, pre-morbid exposure to systemic glucocorticoids was associated with an increased risk of hospital admission and death, whereas other immunosuppressants were not https://bit.ly/3xRp7ZL

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Abstract

Background Immunosuppression may worsen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We conducted a nationwide cohort study of the effect of exposure to immunosuppressants on the prognosis of SARS-CoV-2 infection in Denmark.

Methods We identified all SARS-CoV-2 test-positive patients from February 2020 to October 2020 and linked healthcare data from nationwide registers, including prescriptions for the exposure (immunosuppressant drugs). We estimated relative risks of hospital admission, intensive care unit (ICU) admission and death (each studied independently up to 30 days from testing) with a log-linear binomial regression adjusted for confounders using a propensity score-based matching weights model.

Results A composite immunosuppressant exposure was associated with a significantly increased risk of death (adjusted relative risk 1.56 (95% CI 1.10–2.22)). The increased risk of death was mainly driven by exposure to systemic glucocorticoids (adjusted relative risk 2.38 (95% CI 1.72–3.30)), which were also associated with an increased risk of hospital admission (adjusted relative risk 1.34 (95% CI 1.10–1.62)), but not of ICU admission (adjusted relative risk 1.76 (95% CI 0.93–3.35)); these risks were greater for high cumulative doses of glucocorticoids than for moderate doses. Exposure to selective immunosuppressants, tumour necrosis factor inhibitors or interleukin inhibitors was not associated with an increased risk of hospitalisation, ICU admission or death, nor was exposure to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine.

Conclusions Exposure to glucocorticoids was associated with increased risks of hospital admission and death. Further investigation is needed to determine the optimal management of coronavirus disease 2019 (COVID-19) in patients with pre-morbid glucocorticoid usage, specifically whether these patients require altered doses of glucocorticoids.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifests with varying clinical severity [1, 2]. An inflammatory response with virus-specific T-cells clears the virus and leads to recovery in most patients; however, an aberrant

inflammatory response can lead to severe disease [3]. Severe cases are predominantly characterised by viral pneumonia and may feature multiorgan inflammatory involvement, including elevated pro-inflammatory cytokines such as interleukin (IL)-6/IL-8 and tumour necrosis factor (TNF) [3–5]. Patients receiving immunosuppressant therapies for conditions including inflammatory diseases and solid organ transplantation are susceptible to intercurrent viral and bacterial infections [6, 7], and although evidence is lacking regarding their effect on COVID-19, expert groups concerned that immunosuppression may worsen the prognosis have advised withholding or reducing immunosuppressants during intercurrent COVID-19 [8–10].

Immunosuppressants differ in their mechanisms of action and may therefore have differing effects on the disease course of COVID-19, and effects may vary with the severity of disease and timing in the disease course. Certain immunosuppressants may have beneficial effects in COVID-19 by regulating the elevated inflammatory response associated with severe disease. Randomised controlled trials (RCTs) have demonstrated improved survival of COVID-19 patients treated with corticosteroids [11, 12]. A number of clinical trials of biological immunosuppressants including anti-IL-6 agents have been performed without conclusive evidence of improved outcomes [13], but preliminary reports of a large RCT indicate improved survival in patients treated with tocilizumab [14]. The majority of RCTs and a meta-analysis of chloroquine or hydroxychloroquine to treat COVID-19 did not support efficacy [15].

In addition to efficacy studies of immunosuppressants as treatment for COVID-19, their safety also requires investigation to guide optimal management of comorbid diseases during the pandemic, as the presence of pre-existing immunosuppression may influence the prognosis of intercurrent COVID-19. Currently published studies of patients with COVID-19 receiving immunosuppressants for underlying conditions have been limited by small sample sizes or surveillance bias [16–19].

We therefore aimed to conduct a nationwide cohort study of the effect of exposure to immunosuppressants on the risk of hospital admission, intensive care unit (ICU) admission and death among all SARS-CoV-2 test-positive patients in Denmark from February 2020 to October 2020.

Methods

Data sources

We conducted a nationwide cohort study using the Danish COVID-19 cohort [20], based on data from the Danish Microbiology Register, a national register of all test results from all clinical microbiology departments in Denmark [21]. We defined the cohort as all individuals with a positive result for SARS-CoV-2 PCR on an oro- or nasopharyngeal swab or lower respiratory tract specimen, from the first detected case on 26 February 2020 until 18 October 2020 (30 days before data extraction on 18 November 2020). We used individuals' first positive test date in the Danish Microbiology Register (the index date) and a pseudonymised unique identifier to link individual-level healthcare data from other Danish national registers. We obtained information on prescription drugs dispensed at retail pharmacies from the Danish National Prescription Register [22], and information on diagnoses and medical procedures (including the administration of intravenous drugs) from the Danish National Patient Register, a register of hospital activities [23]. We obtained the date of death from the Danish Register of Causes of Death, if present [24].

Exposures and outcomes

The exposure was immunosuppressant drugs, including hydroxychloroquine and chloroquine (immunomodulators which are suspected to alter the immune response in COVID-19), and systemic glucocorticoids, which in moderate to high doses can cause immunosuppression (see supplementary table A1 for drug-level Anatomical Therapeutic Chemical (ATC) codes and procedure codes). The validity of the registration of immunosuppressants in our data sources has not been analysed, but studies have demonstrated a high validity of other procedures codes, such as antineoplastic procedures [25]. The exposure assessment window was 120 days preceding the index date, as packs contained up to 120 tablets and treatments given >120 days before infection are unlikely to cause ongoing immunosuppression. We used a minimum daily dose of systemic glucocorticoids equivalent to 7.5 mg prednisone per day to exclude doses unlikely to cause significant immunosuppression (supplementary table A2) [26]. As the prescribed daily dose is not available in the Danish National Prescription Register [22], we estimated the daily dose as the sum of the amount of glucocorticoids dispensed to an individual during the exposure assessment window divided by the number of days from the first prescription to the index date. Unexposed patients did not receive any immunosuppressant during the exposure assessment window.

We studied immunosuppressants as a composite exposure in our main analysis. In secondary analyses, seeking to investigate the effect of classes of immunosuppressants while maintaining sufficient sample size

to detect an effect, we broke down immunosuppressants into smaller categories. Biological and targeted immunosuppressants indicated in severe immune-mediated inflammatory diseases (IMIDs) or to prevent transplant rejection (TNF inhibitors, IL inhibitors, selective immunosuppressants and rituximab) comprised one group. Conventional disease-modifying antirheumatic drugs, as well as other immunosuppressants (calcineurin inhibitors, other immunosuppressants, hydroxychloroquine and chloroquine) formed a second group. Systemic glucocorticoids formed a third group.

The study outcomes were hospital admission, ICU admission and death, with each event studied separately and independently. We included events occurring up to 30 days from patients' first positive test date, as well as hospital and ICU admission up to 7 days before that date to include relevant events occurring before testing, while reducing unrelated events occurring after recovery. Previous studies have indicated that a small percentage of patients were hospitalised before testing [27] and ∼80% of deaths occur within 14 days of hospital admission [28].

Covariates

We controlled for confounding by including covariates for the exposure and outcomes in a propensity score model. These covariates were selected based on background knowledge, despite incomplete knowledge of the relation between all covariates, while excluding instrumental variables or mediators. We included demographic variables (age and sex), number of past hospital contacts, diagnoses and co-medications (including medications as proxies for disease, such as for diabetes) as covariates of immunosuppressive treatment and prognosis of SARS-CoV-2 infection (ATC and International Classification of Diseases, 10th Revision codes listed in supplementary table A3). To control for confounding by indication, we included diagnoses such as inflammatory diseases (included within the "skin disease" and "diseases of the gastrointestinal tract" categories), organ transplantation and certain malignancies that indicate treatment with immunosuppressants. Procedures and nonimmunosuppressant medications used to treat IMIDs were included as proxies of underlying disease severity.

Statistical methods

Clinical characteristics of the cohort were assessed, with standardised mean differences (SMDs) <0.1 considered well balanced. We estimated the propensity score as the probability of treatment conditional on observed covariates [29]. We used a propensity score (*PS*) weighting model where exposed subjects' weights were calculated as (minimum(*PS*, 1−*PS*))/*PS* and unexposed subjects' weights were calculated as (minimum(*PS*, 1−*PS*))/(1−*PS*), known as "matching weights". This gave a better covariate balance than inverse probability of treatment weighting as initially planned (supplementary figure A1 and supplementary tables A13–A20) [30]. Weights were truncated at the 1st and 99th centile. We removed antianaemic drugs from the final propensity score model due to imbalance; adjusting for this variable in the log binomial regression model gave similar results (supplementary tables A4–A12).

We estimated crude and adjusted (weighted) relative risks (and 95% confidence intervals with robust variance estimates) of the outcomes for exposed patients compared with unexposed patients using a log-linear binomial regression model. We preferred this model to a survival analysis with competing risks model because a high number of events such as death often occurred very close to the date of testing, and hospital and ICU admission could occur before testing, resulting in negative time to event. For the analyses of subgroups of immunosuppressants, we fitted separate propensity score models for each of the subgroups, selecting variables from the list of covariates (supplementary table A21). Exposure to combinations of the described groups of immunosuppressants was relatively rare and unlikely to alter results, so we did not study their effect. We performed a *post hoc* analysis of the dose effect of systemic glucocorticoids. To create two exposure groups of approximately equal size to maintain statistical power, we categorised the prednisolone-equivalent cumulative dose within 120 days preceding the index date as moderate dose (<2000 mg) or high dose (⩾2000 mg), which were each compared with unexposed patients.

Sensitivity analyses

To control for residual confounding, we performed an analysis comparing current users exposed 120 days preceding the index date to former users exposed to immunosuppressants 121–365 days preceding the index date. To study the effect of immunosuppressants in patients with more severe COVID-19, we restricted the cohort to hospital admissions coded with COVID-19 as the primary diagnosis, studying the outcomes ICU admission or death.

To reduce selection bias due to patients on immunosuppressants, among other clinically vulnerable people, being prioritised for testing (mainly before a policy change in Denmark on 21 April 2020), we undertook separate analyses of the cohort tested before or after 21 April 2020 and performed calculations to estimate

the effect of selection bias (see supplementary material). We used the statistical software Stata version 16.1 (StataCorp, College Station, TX, USA).

Results

Characteristics of SARS-CoV-2 test-positive patients

From 26 February 2020 to 18 October 2020, there were 36 727 individuals with positive SARS-CoV-2 PCR tests in Denmark, of which 527 were exposed to immunosuppressants and 36 200 were unexposed. There were 66 individuals exposed to selective immunosuppressants, 105 to TNF inhibitors, 25 to IL inhibitors, 29 to calcineurin inhibitors, 218 to other immunosuppressants, 31 to hydroxychloroquine or chloroquine, 136 to systemic glucocorticoids and none to rituximab. The median (interquartile range (IQR)) age of exposed patients was 57 (42–73) years and of unexposed patients was 39 (23–55) years, with a greater prevalence of comorbid diagnoses in the exposed population (table 1). In total, there were 715 deaths and 492 (69%) of those were during hospital stays. There were 425 ICU admissions and 105 (25%) of those patients died, all occurring within 28 days of ICU admission. Few patients were exposed to both glucocorticoids and selective immunosuppressants (n<5), TNF inhibitors (n<5), IL inhibitors (n<5), calcineurin inhibitors (n<5) or other immunosuppressants (n=14).

Composite immunosuppressant exposure: relative risk of severe outcomes of SARS-CoV-2 infection

Among patients exposed to the composite measure of immunosuppressants there were 165 hospital admissions, 25 ICU admissions and 57 deaths; among the unexposed there were 3373 hospital admissions, 400 ICU admissions and 658 deaths (table 2 and supplementary table A4). After weighting in our

TABLE 1 Characteristics of severe acute respiratory syndrome coronavirus 2 PCR test-positive patients in Denmark, 26 February 2020 to 18 October 2020, by exposure to immunosuppressants

Characteristics	Full cohort			Propensity score weighted dataset[#]		
	Exposed (n=527)	Unexposed (n=36 200)	SMD	Exposed (n=346)	Unexposed (n=339)	SMD
Age, years	57 (42–73)	39 (23–55)	0.80	57 (43–74)	56 (41–71)	0.11
Male	256 (48.6)	17 544 (48.5)	0.00	149 (43.1)	154 (45.4)	0.05
Admissions and outpatient contacts, n						
0	20 (3.8)	18 787 (51.9)	1.27	14 (4.0)	11 (3.4)	0.04
1–2	38 (7.2)	9574 (26.4)	0.53	36 (10.4)	47 (13.8)	0.10
3–5	113 (21.4)	4264 (11.8)	0.26	107 (30.9)	82 (24.2)	0.15
6+	356 (67.6)	3575 (9.9)	1.47	189 (54.6)	199 (58.7)	0.08
Diagnoses						
Cardiovascular disease	176 (33.4)	4269 (11.8)	0.53	111 (32.1)	98 (29.0)	0.07
Neoplasms, blood and blood-forming organs	27 (5.1)	101 (0.3)	0.30	<5[¶]	<5[¶]	0.09
Solid organ transplantation	24 (4.6)	27 (0.1)	0.30	<5[¶]	<5[¶]	0.12
Pulmonary disease	131 (24.9)	2742 (7.6)	0.48	73 (21.1)	66 (19.6)	0.04
Liver disease	15 (2.8)	302 (0.8)	0.15	11 (3.2)	7 (2.0)	0.07
Kidney disease	76 (14.4)	1049 (2.9)	0.42	34 (9.8)	30 (8.8)	0.04
Diseases of the gastrointestinal tract	91 (17.3)	365 (1.0)	0.59	17 (4.9)	12 (3.4)	0.07
Other gastrointestinal pathologies	94 (17.8)	1934 (5.3)	0.40	43 (12.4)	43 (12.5)	0.00
Neurological and musculoskeletal disease	353 (67.0)	8101 (22.4)	1.00	231 (66.8)	209 (61.7)	0.11
Skin disease	112 (21.3)	1399 (3.9)	0.54	51 (14.7)	35 (10.3)	0.13
Medications (ATC code)						
Antianaemic drugs (B03)[+]	276 (52.4)	2946 (8.1)	1.10	185 (53.5)	61 (18.0)	0.80
Cardiovascular drugs (C01–C10)	370 (70.2)	14 144 (39.1)	0.66	235 (67.9)	224 (66.2)	0.04
Antimicrobials (J01–J06)	515 (97.7)	32 201 (89.0)	0.36	335 (96.8)	329 (97.1)	0.02
Anticoagulants (B01AA)	39 (7.4)	633 (1.7)	0.27	19 (5.5)	19 (5.5)	0.00
Diabetes drugs (A10)	65 (12.3)	2211 (6.1)	0.22	44 (12.7)	39 (11.4)	0.04
Obstructive airway disease drugs (R03)	212 (40.2)	9502 (26.2)	0.30	135 (39.0)	126 (37.1)	0.04
Proxies for IMID severity						
Procedures for IMIDs	162 (30.7)	2239 (6.2)	0.67	82 (23.7)	78 (23.1)	0.01
IMID drugs	252 (47.8)	7651 (21.1)	0.58	156 (45.1)	144 (42.6)	0.05

Data are presented as mean (interquartile range) or n (%), unless otherwise stated. SMD: standardised mean difference; ATC: Anatomical Therapeutic Chemical; IMID: immune-mediated inflammatory disease. [#]: numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects; [¶]: due to data protection laws, exact counts of individuals between 1 and 4 are reported only as <5; [+]: due to imbalance of antianaemic drugs, this variable was removed from the final model.

TABLE 2 Relative risk of severe outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients exposed to immunosuppressants compared with unexposed

Outcome	Events		Relative risk (95% CI)	
	Exposed (n=527)	Unexposed (n=36 200)	Crude	Adjusted
Hospital admission	165	3373	3.36 (2.95–3.83)	1.13 (0.95–1.35)
ICU admission	25	400	4.29 (2.89–6.37)	1.16 (0.66–2.03)
Death	57	658	5.95 (4.60–7.69)	1.56 (1.10–2.22)

ICU: intensive care unit.

propensity score-based model, there were 346 patients exposed to immunosuppressants and 339 unexposed, with a well-balanced distribution of covariates (table 1 and supplementary figure A1). The distribution of antianaemic drug usage was not balanced in the weighting model, but including it as a variable in our regression model had little effect (supplementary table A4), so we removed it from the final model. The crude relative risk of hospital admission was 3.36 (95% CI 2.95–3.83), of ICU admission was 4.29 (95% CI 2.89–6.37) and of death was 5.95 (95% CI 4.60–7.69) (table 2). After weighting in our propensity score-based model, the adjusted relative risk of hospital admission was 1.13 (95% CI 0.95–1.33), of ICU admission was 1.16 (95% CI 0.66–2.03) and of death was 1.56 (95% CI 1.10–2.22) (table 2).

Subgroups of immunosuppressants: relative risk of severe outcomes of SARS-CoV-2 infection

For patients exposed to selective immunosuppressants, TNF inhibitors or IL inhibitors, compared with unexposed patients, the adjusted relative risk of hospital admission was 0.83 (95% CI 0.51–1.34), of ICU admission was 0.92 (95% CI 0.23–3.71) and of death was 1.17 (95% CI 0.38–3.62) (table 3 and supplementary tables A5–A7). For patients exposed to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine, compared with unexposed patients, the adjusted relative risk of hospital admission was 0.82 (95% CI 0.60–1.12), of ICU admission was 1.03 (0.43–2.49) and of death was 0.93 (95% CI 0.47–1.85). For patients exposed to systemic glucocorticoids, compared with unexposed patients, the adjusted relative risk of hospital admission was 1.34 (95% CI 1.10–1.62), of ICU admission was 1.76 (95% CI 0.93–3.35) and of death was 2.38 (95% CI 1.72–3.30).

When cumulative glucocorticoid dose was categorised as moderate or high, compared with unexposed patients, the adjusted relative risk of hospital admission was 1.20 (95% CI 0.89–1.62) and 1.47 (95% CI 1.15–1.89), of ICU admission was 1.92 (95% CI 0.82–4.46) and 1.58 (95% CI 0.62–4.04), and of death was 1.84 (95% CI 1.08–3.13) and 2.91 (95% CI 1.92–4.39), respectively (table 4 and supplementary table A8).

TABLE 3 Relative risk of severe outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients exposed to subgroups of immunosuppressants compared with unexposed

Outcome	Events		Relative risk (95% CI)	
	Exposed	Unexposed	Crude	Adjusted
Selective immunosuppressants, TNF inhibitors or IL inhibitors	(n=192)	(n=36 200)		
Hospital admission	33	3373	1.84 (1.35–2.52)	0.83 (0.51–1.34)
ICU admission	6	400	2.83 (1.28–6.25)	0.92 (0.23–3.71)
Death	5	658	1.43 (0.60–3.41)	1.17 (0.38–3.62)
Calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine	(n=268)	(n=36 200)		
Hospital admission	77	3373	3.08 (2.55–3.73)	0.82 (0.60–1.12)
ICU admission	16	400	5.40 (3.33–8.78)	1.03 (0.43–2.49)
Death	17	658	3.49 (2.19–5.56)	0.93 (0.47–1.85)
Systemic glucocorticoids	(n=136)	(n=36 200)		
Hospital admission	83	3373	6.55 (5.71–7.52)	1.34 (1.10–1.62)
ICU admission	10	400	6.65 (3.64–12.18)	1.76 (0.93–3.35)
Death	42	658	16.99 (13.07–22.09)	2.38 (1.72–3.30)

TNF: tumour necrosis factor; IL: interleukin; ICU: intensive care unit.

TABLE 4 Relative risk of severe outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients exposed to glucocorticoids, by cumulative prednisolone-equivalent dose <2000 mg (moderate) or ⩾2000 mg (high)

Outcome	Dose	Events		Relative risk (95% CI)	
		Exposed	Unexposed	Crude	Adjusted
Hospital admission	Moderate	38 (n=69)	3373 (n=36 200)	5.91 (4.76–7.33)	1.20 (0.89–1.62)
	High	45 (n=67)	3373 (n=36 200)	7.21 (6.08–8.55)	1.47 (1.15–1.89)
ICU admission	Moderate	5 (n=69)	400 (n=36 200)	6.56 (2.80–15.34)	1.92 (0.83–4.46)
	High	5 (n=67)	400 (n=36 200)	6.75 (2.89–15.78)	1.60 (0.62–4.14)
Death	Moderate	18 (n=69)	658 (n=36 200)	14.35 (9.58–21.50)	1.83 (1.08–3.11)
	High	24 (n=67)	658 (n=36 200)	19.71 (14.18–27.39)	2.96 (2.00–4.37)

ICU: intensive care unit.

Sensitivity analyses: relative risk of severe outcomes of SARS-CoV-2 infection

Comparing current users of immunosuppressants to former users, the adjusted relative risk of hospital admission was 1.13 (95% CI 0.83–1.52), of ICU admission was 1.21 (95% CI 0.68–2.15) and of death was 1.21 (95% CI 0.68–2.15) (table 5 and supplementary table A9). When restricting to admitted patients with COVID-19 as their primary diagnosis, the risk of death was not significantly increased in patients exposed to immunosuppressants (adjusted relative risk 1.30, 95% CI 0.94–1.82) nor was the risk of ICU admission (adjusted relative risk 0.89, 95% CI 0.50–1.56) (supplementary table A10).

Prior to the change in testing strategy on 21 April 2020, there were 199 patients exposed to immunosuppressants and 7794 unexposed; from 21 April 2020 to 18 October 2020, there were 328 patients exposed and 28 406 unexposed (supplementary tables A11 and A12). In the first and second period, the adjusted relative risk of hospital admission was 0.99 (95% CI 0.82–1.20) and 1.34 (95% CI 1.00–1.80), of ICU admission was 0.65 (95% CI 0.29–1.46) and 3.23 (95% CI 1.50–6.98), and of death was 1.06 (95% CI 0.70–1.63) and 2.60 (95% CI 1.52–4.46), respectively.

Discussion

Using a nationwide cohort of 36 727 individuals who tested positive for SARS-CoV-2, of whom 527 were exposed to immunosuppressants, we assessed the effect of immunosuppressants on the prognosis of intercurrent SARS-CoV-2 infection. A composite immunosuppressant exposure was associated with a significantly increased risk of death, which was mainly driven by a doubling of risk associated with systemic glucocorticoids. Glucocorticoids were also associated with a 34% increased risk of hospital admission, while the risk of ICU admission was not significantly increased (table 3). The risks of hospitalisation, ICU admission or death associated with selective immunosuppressants, TNF inhibitors or IL inhibitors were not significantly increased or decreased, nor were they in patients exposed to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine (table 3). These findings are in agreement with two multinational studies of COVID-19 patients: glucocorticoids were associated with increased risk of ICU admission or death in patients with comorbid inflammatory bowel diseases; glucocorticoids were associated with greater risk of hospital admission in patients with comorbid rheumatic diseases [18, 20].

The finding of an increased risk of death associated with glucocorticoids early in the course of COVID-19 contrasts with studies finding that high-dose glucocorticoids reduce mortality in patients with severe

TABLE 5 Relative risk of severe outcomes of severe acute respiratory syndrome coronavirus 2 infection in current users compared with former users of immunosuppressants

Outcome	Events		Relative risk (95% CI)	
	Current users (n=527)	Former users (n=177)	Crude	Adjusted
Hospital admission	165	43	1.29 (0.96–1.72)	1.13 (0.83–1.52)
ICU admission	<5	<5	2.80 (0.85–9.17)	2.39 (0.71–8.11)
Death	57	14	1.37 (0.78–2.39)	1.21 (0.68–2.15)

ICU: intensive care unit.

disease [10, 11]. Nonetheless, patients not requiring supplemental oxygen in the RECOVERY trial did not benefit from dexamethasone and the effect could be compatible with harm (rate ratio 1.19, 95% CI 0.91–1.55) [10]. This deleterious effect of glucocorticoids early in the disease course could be due to a suppressed adrenal stress response, as well as their suppressive effect on interferon production, resulting in impaired innate responses to viral infection. Chronic glucocorticoid exposure also has pleiotropic metabolic effects, including impaired glucose handling and skeletal muscle catabolism among other effects, which may contribute to adverse outcomes. By contrast, the initiation of glucocorticoids in severe disease appears to suppress the dysregulated inflammatory response which otherwise leads to multiorgan involvement and coagulation. The effect seen in our study appears to be dose related, but these subgroups were small, so interpretation of dose effects must be tentative. By contrast, treatment with high-dose glucocorticoids reduces mortality in patients with severe COVID-19 disease. The majority of patients in our study were not admitted to hospital and would have had milder COVID-19 not requiring oxygen therapy, similar to that subset of the RECOVERY trial. These findings prompt the important question of how to improve outcomes of COVID-19 in patients taking glucocorticoids. Whether patients on glucocorticoids require increased doses during COVID-19, as in other intercurrent illnesses, or reduced doses requires further investigation.

Important strengths of this nationwide cohort study include the use of prescription and hospital activity data from national registers. Our study reduced surveillance bias, which is the limitation of studies based on spontaneously reported cases, by including all SARS-CoV-2 test-positive persons in Denmark. We maximised power by using the full cohort, without restricting to specific patient populations. This facilitated extensive control of confounders, including the diverse diseases that indicate the use of immunosuppressants and glucocorticoids, further improving the reliability of our results. Controlling for covariates using a propensity score weighting model optimised the covariate distribution in a subset of the population with clinical equipoise for immunosuppressant exposure. Our analysis of bias suggested that the risk associated with immunosuppressants may be greater than estimated, as selection bias attenuated the relative risk estimates (see supplementary material). Selection bias had a greater effect in the period before 21 April 2020, when patients on immunosuppressants were prioritised for testing, which may have contributed to the lower relative risks estimated compared with after that date (supplementary table A9 and A10).

We also recognise limitations to our study. Our conclusions on the effects of classes of immunosuppressants are cautious, as the selected groups (other than glucocorticoids) included a number of drug classes that may have divergent effects, impairing our ability to detect associations with individual drugs. As the number of exposed subjects was small, the matching weights model targeted the population average treatment effect in the treated and this hinders the generalisability of the risk estimates to people without an underlying condition that could require immunosuppressant therapy. The number of covariates in our model was statistically limited by the number of outcome events, so there may be residual confounding caused by unmeasured disease severity. Residual confounding is suggested by the attenuation in the risk estimate for death associated with immunosuppressants when current users were compared with former users, which remained numerically increased but no longer statistically significant. Diagnostic coding is affected by differences in practices among clinicians, an inherent limitation when nationwide register data are used. Further studies may benefit from more detailed measures of severity. However, this is unlikely to completely account for the association of glucocorticoid exposure and severe outcomes, as other immunosuppressants such as TNF inhibitors are also treatments for severe IMIDs, but by contrast, those exposures were not significantly associated with severe outcomes.

In our cohort the majority of people with COVID-19 who died were never admitted to the ICU and a substantial number were not receiving hospital-based care when they died. Frailty may account for the greater number of deaths and greater relative risks associated with immunosuppressants compared with ICU admissions. Admission to the ICU depends not only on clinical assessment of the admitted patient, but also on factors such as frailty, short life expectancy, as well as patient and family preferences, *e.g.* a care home resident with such conditions might not be moved to hospital and thus would not be assessed for ICU admission. Further health system factors may also be important in the context of the pandemic [31].

In conclusion, this nationwide cohort study found that pre-morbid exposure to glucocorticoids was associated with a worsened prognosis of SARS-CoV-2 infection [18, 19]. Studies are warranted to determine whether altered doses are beneficial, with attention to the severity of COVID-19 at treatment initiation. While other pharmacological interventions remain relevant research candidates, evidence from multiple sources indicates the importance of glucocorticoids on prognosis, the effect of which may depend on timing in the disease course. Our findings that other immunosuppressants were not significantly associated with severe outcomes are tentative, but in context they support the continued use of

steroid-sparing immunosuppressants for a broad patient population with ongoing healthcare needs during the pandemic.

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