Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

The association between pre-exposure to glucocorticoids and other immunosuppressant drugs with severe COVID-19 outcomes

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ABSTRACT

Objectives: Whether preinfection use of immunosuppressant drugs is associated with COVID-19 severity remains unclear. The study was aimed to determine the association between preinfection use of immunosuppressant drugs with COVID-19 outcomes within 1 month after COVID-19 diagnosis.

Methods: This cohort study included individuals aged ≥18 years with underlying conditions associated with an immunocompromised state and diagnosed with COVID-19 between February 2020 and January 2021 at Karolinska University Hospital, Stockholm.

Exposure to immunosuppressant drugs was defined based on dose and duration of drugs (glucocorticoids and drugs included in L01 or L04 chapter of Anatomical Therapeutic Chemical classification) before COVID-19 diagnosis. Outcomes included hospital admission, ICU admission, mechanical ventilation, mortality, renal failure, stroke, pulmonary embolism, and cardiac event. ORs were calculated using logistic regression and baseline covariate adjustment for confounding with inverse probability of treatment weights.

Results: Of 1067 included individuals, 444 were pre-exposed to immunosuppressive treatments before COVID-19 diagnosis (72 high-dose glucocorticoids, 255 L01 drugs (antineoplastics), 198 L04 (other immunosuppressants) and 78 to multiple drugs). There was no association between pre-exposure and hospital admission (OR 0.83, 95% CI 0.64 to 1.09) because of COVID-19. Pre-exposure to L01 or L04 drugs were not associated with hospital admission (adjusted ORs (aORs): 1.23, 0.86 to 1.76 and 1.31, 0.77 to 2.21) or other outcomes. High-dose glucocorticoids (≥20 mg/day prednisolone equivalent) were associated with hospital admission (aOR 2.50, 1.26 to 4.96), cardiac events (aOR 1.93, 1.08 to 3.46), pulmonary embolism (aOR 2.78, 1.08 to 7.15), and mortality (aOR 3.48, 1.77 to 6.86) due to COVID-19.

Discussion: Antineoplastic and other immunosuppressants drugs were not associated with COVID-19 severity whereas high-dose glucocorticoids were associated. Further studies should evaluate the effect of pre-exposure of different dose of glucocorticoids on COVID-19 prognosis. **Rakel Brodin, Clin Microbiol Infect 2022;28:1477**

Introduction

Since December 2019, SARS-CoV-2, the cause of COVID-19, has rapidly spread worldwide, with more than 314 million cases of COVID-19 and 5.5 million deaths [1].

There is a complex relationship between SARS-CoV-2 and the immune response, with an exaggerated immune response in some patients, leading to cytokine storms [2]. Glucocorticoids have been

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demonstrated to reduce COVID-19 mortality, being recommended in severe cases [3]. It has been hypothesized that patients being in an immunocompromised state, either caused by the underlying disease or by immunosuppressive treatment, are less likely to experience an exaggerated immune response [4].

Whether preinfection use of immunosuppressive treatment is a risk or protective factor for COVID-19 remains unclear and previous studies have reported conflicting results. Some studies indicated an increased risk of hospitalization [5] and higher mortality rates [6] among immunosuppressed patients whereas other cohort studies did not observe higher mortality compared to the general population [7,8] or were reported to be less likely to develop COVID-19-associated severe Acute respiratory distress syndrome (ARDS) [8]. To our knowledge, the effect of immunosuppressant drugs in patients with underlying conditions has not been evaluated previously.

The aim of our study was to determine the association of exposure of immunosuppressant drugs prior to SARS-CoV-2 infection with the risk of severe outcomes within the first month after COVID-19 diagnosis.

Methods

We conducted a cohort study from 21 February 2020 to 15 January 2021, with ≥18-years-old patients being followed-up at the tertiary-care level Karolinska University Hospital (Stockholm) because of an underlying disease that may be treated with immunosuppressants and diagnosed with COVID-19. COVID-19 diagnosis was identified through U071 and U072 codes of International Statistical Classification of Diseases 10th Revision (ICD-10) (Appendix S1) or through a positive polymerase chain reaction test.

Underlying conditions were identified using ICD-10 codes registered in the electronic health records during the 5 years prior to COVID-19 diagnosis and were categorized as cancer, solid organ transplant, autoimmune diseases, and haematological disorders including hematopoietic cell transplant (ICD-10 codes detailed in Appendix S1). Patients with multiple underlying conditions were classified in a mutually exclusive manner using the following order: solid-organ transplant, haematology, cancer, and autoimmune disease. To ensure access to data on exposure and outcomes, patients transferred from other hospitals because of COVID-19 were excluded and study subjects had to have at least one elective inpatient admission or outpatient visit at the hospital within 1 year before COVID-19 diagnosis. Patients with asthma and chronic obstructive pulmonary disease, usually treated with glucocorticoids, were excluded as these conditions are major predictor for COVID-19 severity [9]. Patients with treatment restrictions due to terminal diseases and those already hospitalized before the time of COVID-19 diagnosis were also excluded.

The follow-up period started when patients were diagnosed with COVID-19 and ended after 1 month, discharge from the hospital, or death, whatever came first.

Data were extracted from a research database containing pseudo-anonymized clinical data from electronic health records over the period 2010 to 2021. This includes data from both in- and outpatients at the hospital on age, sex, drug treatments using the Anatomical Therapeutic Chemical classification (ATC), laboratory results, ICD-10 code diagnoses, medical records, clinical data, and radiology findings.

Outcomes

COVID-19 severity was defined as outcomes considered severe or critical by WHO [9]. The primary outcome was hospital admission. Secondary outcomes were mortality, ICU admission, mechanical ventilation, acute kidney injury (based on the Kidney Disease: Improving Global Outcomes criteria, but without urine volume measurements) [10], pulmonary embolism, acute cardiac event, (Troponin (TnT) > 14 ng/L [11]) and stroke. All outcomes were assessed during the first 30 days after COVID-19 diagnosis to ensure association with COVID-19 diagnosis.

Exposure

Exposure definition was based on the definition provided in the CDC Yellow-book [12], which considers the expected time for duration of immunosuppression after ending therapy (Appendix S2).

- Use of >15 days of prednisolone ≥20 mg/day or equivalent (ATC-class H02) during the past month.
- Rituximab and alemtuzumab during the past 6 months.
- All others (ATC classes L01 and L04) <3 months.

All other individuals were considered as nonexposed

Covariates

We controlled for confounding by including covariates for the exposure and the outcomes. We included demographic variables (age, sex), body mass index, number of visits within the past year before COVID-19 diagnosis, and comorbidities that are considered to increase the risk for COVID-19 severity (chronic kidney disease, lung disease, diabetes mellitus (DM), liver disease, cardiac disease, and hypertension), using ICD-10 codes (Appendix S3).

Statistical methods

Dichotomous variables were described as frequencies and percentages. Age was included as a continuous variable, but a restriction to those aged <70 years was predetermined. Clinical characteristics of the cohort were assessed, with standardized mean difference <0.1 considered as well balanced. Logistic regression models were used to estimate unadjusted and adjusted (weighted) ORs (95% CI) of the outcomes for exposed compared to unexposed patients. We analysed subgroups of immunosuppressant drugs fitting separate models, including the exposure to different doses of glucocorticoids.

Inverse probability of treatment weighting (IPTW) model was used to adjust for observed differences between the exposed and unexposed cohorts. Each individual's propensity score (PS) was estimated based on known confounders (age, sex, underlying conditions, and other comorbidities such as hypertension cardiac disease, or DM) (Appendix S3).

Missing data were considered for the outcomes evaluated with laboratory parameters (acute kidney injury and acute cardiac event), and a complete case analysis approach was planned.

In the sensitivity analysis, we restricted the cohort to individuals with underlying conditions diagnosed <2.5 years before COVID-19; a stricter definition of cardiac events was used (TnT >50 ng/l) considering potential elevation of TnT for other reasons, and differences between first and second phase of the pandemic (cut-off 15 August 2020)were investigated [13].

Data management and analysis were performed using Stata-16.1(StataCorp-LLC).

Ethical approval was obtained by the Stockholm Ethical Review Board (Dnr-2018/1030-31) with amendment for COVID-19 (Dnr-2020-01385). The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (Appendix S4).

Results

Between 27 February 2020 and 15 January 2021, 7929 patients were diagnosed with COVID-19. Of them, 1735 patients had underlying diseases associated with an immunocompromised state. After screening for eligibility, 668 patients were excluded because they did not fulfill inclusion criteria, leaving 1067 individuals for the final study population (Fig. 1).

The median age was 64 years (IQR 51 to 75) and 45.2% (482/1067) were female. A cancer diagnosis was identified among 46.1% (492/1067), autoimmune diseases in 28.6% (305/1067), haematological conditions in 15.0% (160/1067), and solid organ transplants in 10.3% (110/1067). Among 41.5% (444/1067) patients fulfilling the criteria for exposure to immunosuppressive treatment (immunosuppressant drugs detailed in Appendix S5), 45.7% (203/444) were female, the median age was 61(IQR 50 to 71 years), and 78 (17.6%) were exposed to multiple immunosuppressant drugs. Patients without any immunosuppressive treatment were slightly older (median age 66, IQR 53 to 78 years) and had a nonsignificant lower proportion of female patients (44.8% (279/623, p value = 0.762) (Table 1).

There were 772 hospitalized patients, with a median temperature of 37.4C° (36.8 to 38.1), median respiratory rate of 20 breaths/minute (17 to 24), and median oxygen saturation of 96% (94 to 98).

Pre-exposure to any immunosuppressant drug and COVID-19 outcomes

No significant association was found between exposure to immunosuppressive treatments and hospital admission, ICU admission, mechanical ventilation, acute renal failure, cardiac events, pulmonary embolism, or mortality, in both unadjusted and adjusted analyses (Table 2). Similarly, after IPTW, there were no statistically significant differences in the odds of any of the outcomes among individuals with chronic immunosuppression and their counterparts, compared to unexposed individuals (Appendix S6). When limiting the cohort to individuals <70 years, acute cardiac events were significantly associated with exposure to immunosuppressive treatments (adjusted OR (aOR) 1.77, 95% CI 1.10 to 2.83), independently of age, sex, DM, hypertension, number of visits, and belonging to a group with underlying conditions (Table 2). In the subanalysis by categories of underlying categories, no association was found with immunosuppression exposure and any of the outcomes (Appendices 7 and 8).

Pre-exposure to glucocorticoids and COVID-19 outcomes

High-dose glucocorticoids (equivalent to ≥20 mg/day prednisolone >15 days within the month prior to COVID diagnosis) was associated with an increased odds of hospital admission (aOR 2.50, 95% CI 1.26 to 4.96]), cardiac events (aOR 1.93, 95% CI 1.08 to 3.46]), pulmonary embolism (aOR 2.78, 95% CI 1.08 to 7.15]) and mortality (aOR 3.48, 95% CI 1.77 to 6.86) compared to no glucocorticoid usage after adjusting for age, sex, cardiac disease, hypertension, number of visits, underlying condition, and treated with other immunosuppressant drugs (Fig. 2). Similarly, when restricting the analysis to <70-year-old individuals, exposure to high-dose glucocorticoids was associated with increased odds of hospital admission (aOR 2.34, 95% CI 1.08 to 5.08), ICU admission (aOR 2.91, 95%CI 1.09 to 7.79), mortality (aOR 6.12, 95% CI 2.12 to 17.64), and cardiac events (aOR 2.62, 95% CI 1.23 to 5.56]) (Table 3, Fig. 2).

Exposure to low-dose or to high-dose but recurrent and short treatment with glucocorticoids (i.e. cancer patients administered glucocorticoids before chemotherapy) was not significantly associated with any of the outcomes in the adjusted analysis. However, the test for trend showed an increasing odd of hospital admission, ICU admission, cardiac event, and mortality when increasing the dose of glucocorticoids (Table 3).

In the analysis by categories of underlying categories, high dose of glucocorticoids was associated with higher mortality in cancer and autoimmune diseases patients; hospital and intensive care admission were also associated with autoimmune diseases (Appendix S8).

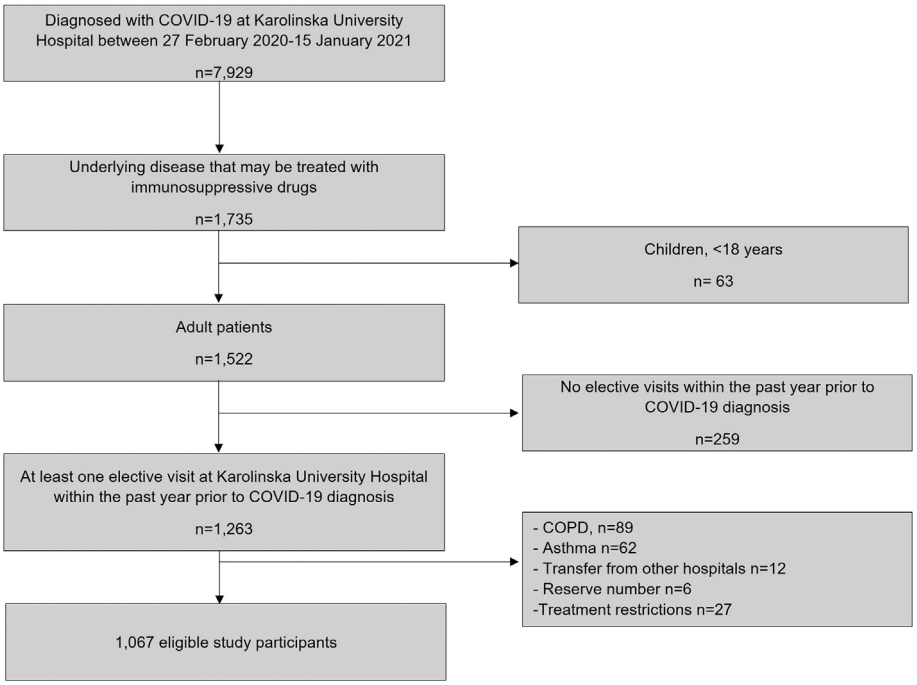

Fig. 1. Flow chart of the individuals included in the study.

Table 1
Baseline characteristics of patients with underlying conditions associated with an immunocompromised state, between February 2020 and January 2021 at Karolinska University Hospital, Stockholm, on date of hospitalization with COVID-19, by pre-exposure to immunosuppressant treatments prior to COVID-19 diagnosis ($n = 1067$)

Variables	Immunosuppressant drugs								
	Steroids high dose $n = 72$	Steroids low dose $n = 262$	L01 $n = 255$	L04 $n = 198$	Pre-exposure[a] $n = 444$	Non pre-exposure[a] $n = 623$	p	Absolute standardized mean difference between exposed and non-exposed	Total $n = 1067$
Demographics									
Female	31 (43.1)	140 (53.4)	127 (49.8)	82 (41.4)	203 (45.7)	279 (44.8)	0.762	0.02	482 (45.2)
Age (y)	63 (54–74)	62 (51–72)	65 (51–74)	56 (42–64)	61 (50–71)	66 (53–78)	**0.004**	0.35	64 (51–75)
Underlying diseases									
Solid organ transplant	10 (13.9)	80 (30.5)	1 (0.4)	105 (53.0)	106 (23.9)	4 (0.6)[b]	**<0.001**	0.75	110 (10.3)
Cancer	25 (34.7)	70 (26.7)	133 (52.2)	12 (6.1)	148 (33.4)	344 (55.1)		0.45	492 (46.1)
Autoimmune	21 (29.2)	87 (33.2)	57 (22.4)	63 (31.8)	117 (26.4)	188 (30.1)		0.08	305 (28.6)
Haematological	16 (22.2)	25 (9.5)	64 (25.1)	18 (9.1)	73 (16.5)	87 (13.9)		0.07	160 (15.0)
Comorbidities									
Diabetes mellitus	9 (12.5)	58 (22.1)	23 (9.0)	58 (29.3)	79 (17.8)	101 (16.2)	0.497	0.04	180 (16.9)
BMI	2 (2.9)	5 (2.1)	8	3	12 (2.9)	17 (3.2)	0.559	0.060	29
Underweight	26	97	(3.4)	(1.6)	165	194			(3.1)
Normal weight	(37.7); 41	(40.3); 139	103	68	(40.3)	(36.8)			359
Overweight	(59.4)	(57.7)	123 (52.6)	114 (61.6)	(56.7)	(60.0)			549 (58.6)
Hypertension	24 (33.3)	108 (41.2)	52 (20.4)	90 (45.5)	138 (31.1)	226 (36.3)	0.078	0.11	364 (34.1)
Cardiac disease	14 (19.4)	79 (30.2)	43 (16.9)	60 (30.3)	106 (23.9)	180 (28.9)	0.068	0.11	286 (26.8)
Lung disease	16 (22.2)	25 (9.5)	20 (7.8)	27 (13.6)	52 (11.7)	36 (5.8)	**0.001**	0.21	88 (8.3)
Kidney disease	13 (18.1)	79 (30.2)	12 (4.7)	82 (41.4)	93 (21.0)	75 (12.0)	**<0.001**	0.24	168 (15.8)
Liver disease	4 (5.6)	26 (9.9)	9 (3.5)	34 (17.2)	42 (9.5)	30 (4.8)	**0.003**	0.18	72 (6.8)
Stroke	1 (1.4)	5 (1.9)	4 (1.6)	2 (1.0)	5 (1.1)	8 (1.3)	0.817	0.01	13 (1.2)
Laboratory parameters									
Leucocyte count ($n = 771$)	7.4 (5.2–11.1)	6.8 (4.9–9)	5.6 (3.8–7.8)	6.8 (5.4–8.9)	6.2 (4.4–8.5)	6.7 (5.5-9)	**0.016**	0.23	6.4 (5–8.8)
Severe neutropenia ($n = 419$)	1 (2.0)	1 (0.8)	4 (2.1)	0 (0.0)	4 (1.5)	2 (1.3)	0.805	0.03	6 (1.4)
Lymphopenia ($n = 183$)	1.3 (0.7–1.9)	1.4 (1–2.1)	1.3 (0.9–2)	1.4 (0.9–2)	101 (55.2)	56 (47.5)	0.190	0.12	157 (52.2)
Haemoglobin ($n = 782$)	121 (103–134)	124 (112–136)	120 (106–132)	129 (115–143)	123 (110–137)	126 (112–140)	0.515	0.11	124 (111–138)
Creatinine ($n = 778$)	68 (57–98)	79 (65–114)	68 (59–85)	94 (73–126)	80 (64–105)	77 (63–104)	0.412	0.11	78 (64–105)
AST ($n = 534$)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.4 (0.4–0.6)	0.4 (0.3–0.5)	0.4 (0.4–0.6)	0.4 (0.3–0.6)	0.332	0.10	0.4 (0.3–0.6)
ALT ($n = 626$)	0.4 (0.3–0.8)	0.4 (0.3–0.6)	0.4 (0.3–0.7)	0.4 (0.3–0.5)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.119	0.001	0.4 (0.3–0.6)
($n = 418$)	1.6 (1.1–2.4)	1.3 (1–1.8)	1.4 (1–1.8)	1.4 (1–1.7)	1.4 (1–1.9)	1.3 (1–1.9)	0.391	-0.09	1.4 (1-1.9)
Vital signs in hospitalized patients ($n = 772$)	$n = 58$	n = 188	$n = 129$	$n = 158$	n = 308	n = 440			
Fever	23 (39.7)	101 (53.7)	66 (51.2)	83 (52.5)	155 (50.3)	194 (44.1)	0.093	0.13	349 (46.7)
Respiratory rate (IQR)	20 (17–25)	20 (17–25)	20 (16–25)	21 (17–24)[c]	20 (17–24)[d]	20 (17–24)[e]	0.842	−0.04	20 (17–24)
Saturation (IQR)	96 (94–97)	96 (94–98)	96 (94–98)[f]	96 (94–98)	96 (94–98)[g]	96 (94–98)[h]	0.242	−0.08	96 (94–98)
Other									
Number of visits in the year previous to COVID-19	16 (7–33)	16 (6–30)	21 (10–38)	12 (5–27)	16 (7–32)	5 (2–13)	**<0.001**	−0.359	8 (3–21)

Bold: $P < 0.05$.
Categorical variables described as frequency (%); Continuous variables are described as median (IQR). Lab parameters refers to pre COVID-19 value. L01 represents the antineoplastic agents included in the L01 chapter of the ATC classification. L04 represents other immunosuppressants drugs included in the chapter L04 of the ATC classification.
Leucocytes x 109/L; severe neutropenia considered with those under 0.5 × 109/L neutrophils; lymphopenia <0.1 × 109/L lymphocytes; haemoglobin g/L; creatinine μmol/L; AST μkat/L; ALT μkat/L; ALP μkat/L; vital signs refers to first value at hospital admission; body temperature: degree Celsius; Respiratory rate: breaths/minute; saturation; % oxygen; number of visits refers to total amount of hospitalization or visits to outpatient clinic within past year before COVID-19.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATC, anatomical therapeutic chemical; BMI, body mass index.

[a] Pre-exposure definition: prednisolone ≥20 mg/day or equivalent (ATC class H02) for at least 15 days during past month, rituximab and alemtuzumab during the past 6 months, all others (ATC classes L01 and L04, excluding rituximab and alemtuzumab) during the past 3 months.

[b] Three individuals with a history of organ transplant, organ rejection, and now on the waiting list for a new transplant, therefore unexposed. For the other individual, the reason for unexposed treatment could not be further evaluated.

[c] $n = 157$.

[d] $n = 307$.

[e] $n = 435$.

[f] $n = 130$.

[g] $n = 309$.

[h] $n = 441$.

Table 2
Association between exposure to immunosuppressive treatment and COVID-19 severity outcomes in all cohort ($n = 1067$) and among participants aged less than 70 years ($n = 664$)

Outcome	Pre-exposure[a] $n = 444$	Non pre-exposure $n = 623$	p value[c]	Unadjusted		Adjusted[b]	
	n (%)	*n*(%)		OR	95% CI	aOR	95% CI
Hospital admission[d]; All age groups; <70 years	311 (70.1)	461 (74.0)	0.155	0.83	0.64–1.09	1.31	0.94–1.80
	201 (63.8)	225 (64.5)	0.859	0.99	0.72–1.36	1.26	0.86–1.85
ICU admission[d]; All age groups; <70 years	40 (9.0)	46 (7.4)	0.336	1.25	0.80–1.94	1.07	0.64–1.78
	31 (9.8)	22 (6.3)	0.093	1.63	0.92–2.89	1.58	0.80–3.13
Mechanical ventilation[d]; All age groups; <70 years	29 (6.5)	39 (6.3)	0.858	1.05	0.64–1.73	0.92	0.52–1.63
	22 (7.0)	21 (6.0)	0.613	1.18	0.62–2.05	1.09	0.52–2.28
Acute kidney injury[e]; All age groups; <70 years	30 (9.7)	54 (11.7)	0.366	0.80	0.50–1.29	0.62	0.35–1.10
	22 (11.0)	23 (10.2)	0.808	1.08	0.58–2.00	0.70	0.32–1.51
Cardiac event; All age groups; <70 years	158 (35.6)	239 (38.4)	0.355	0.89	0.69–1.15	1.21	0.87–1.69
	86 (27.3)	64 (18.3)	**0.006**	**1.69**	**1.17–2.43**	**1.77**	**1.10–2.83**
Pulmonary embolism[d]; All age groups; <70 years	21 (4.7)	30 (4.8)	0.948	0.99	0.56–1.74	1.60	0.84–3.05
	13 (4.1)	19 (5.4)	0.429	0.75	0.37–1.55	1.69	0.69–4.14
Mortality; All age groups; <70 years	55 (12.4)	87 (14.0)	0.455	0.87	0.61–1.26	1.43	0.94–2.19
	22 (7.0)	15 (4.3)	0.132	1.68	0.86–3.30	2.00	0.93–4.30

Bold: P < 0.05.
Unadjusted and adjusted logistic regression calculating odds ratio (OR) and 95% CI for severe outcomes of COVID-19 according to exposure to any immunosuppressive treatment, H02, L01, and L04.
[a] Pre-exposure definition: prednisolone ≥20mg/day or equivalent (ATC class H02) for at least 15 days during past month, rituximab and alemtuzumab during the past 6 months, all others (ATC classes L01 and L04, excluding rituximab and alemtuzumab) during the past 3 months.
[b] Adjusted for age, sex, diabetes, cardiac disease, hypertension, number of outpatient visits within past year, and underlying condition.
[c] p value calculated using chi-square test.
[d] Including age as quadratic variable in adjusted model.
[e] Analysis on acute renal failure was restricted to hospitalized patients was performed using the KDIGO algorithm.

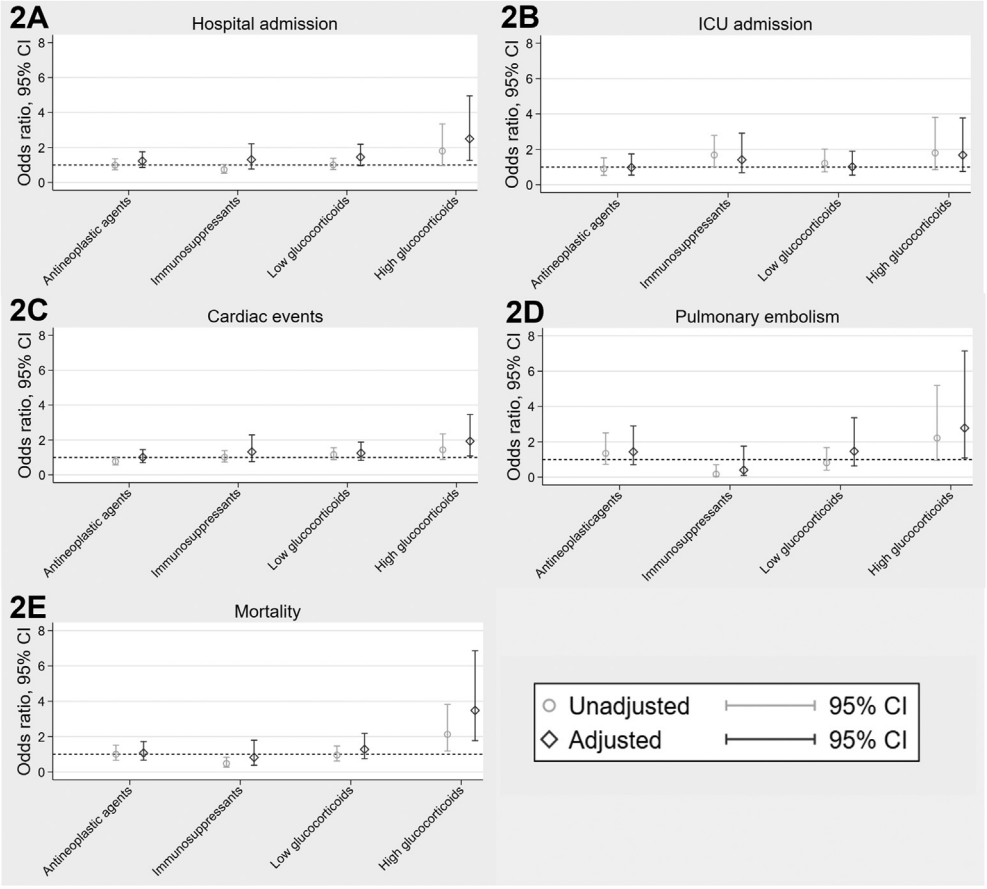

Fig. 2. Association between COVID-19 outcomes (hospital admission (2A), ICU admission (2B), cardiac event (2C), pulmonary embolism, (2D) and mortality (2E)) and pre-exposure to immunosuppressant drugs.

Pre-exposure to antineoplastic and other immunosuppressants and COVID-19 outcomes

No association was found between treatment with antineoplastic drugs (L01) and COVID-19 outcomes, neither in unadjusted nor adjusted logistic regression (Fig. 2 and Table 4).

Exposure to immunosuppressants (L04) was associated with a higher ICU admission in the entire cohort (OR 1.69, 95% CI 1.02 to 2.81]) and with a lower percentage of pulmonary embolism (OR 0.17, 95% CI 0.04 to 0.71). However, these findings were not observed in the adjusted analysis. No associations were found in the adjusted analysis in <70-year-old individuals (Table 4).

Sensitivity analyses

Using a stricter definition of a cardiac event (TnT >50), no association was found between exposure to immunosuppressive treatments and cardiac events in unadjusted analysis (OR 0.73, 95% CI 0.53 to 1.07) nor adjusted analysis (aOR 0.78, 95% CI 0.50 to 1.22]) (Appendix S9). No association was found between immunosuppressive treatments and COVID-19 outcomes when restricting the cohort to receiving their underlying diagnosis within 2.5 years of COVID-19 diagnosis (Appendix S10). Dividing the cohort to first and second phase of the pandemic yielded a significant association between immunosuppressive treatment and hospital admission (OR 0.58, 95% CI 0.40 to 0.84]) in the first phase. No further significant associations were found (Appendix S11).

Underlying conditions and COVID-19 outcomes

Information of underlying conditions with other covariates are detailed in Appendix S12.

When comparing the COVID-19 outcomes among the different groups of underlying conditions, 67 (60.9%) of transplant patients were hospitalized compared with 365 (74.2%) with cancer, 22 (74.1%) autoimmune diseases, and 114 (71.3%) with haematological disorders. The odds of hospital admission in the entire cohort among cancer patients was 1.84 (95% CI 1.20 to 2.84) and in patients with autoimmune disease 1.84 (95% CI 1.16 to 2.91) times higher compared to transplant patients, being consistent with the adjusted analysis. Conversely, the aOR of acute kidney injury was 0.35 (95% CI 0.14 to 0.89) and the aOR of cardiac events 0.51 (95% CI 0.29 to 0.91) among cancer patients compared to transplant patients (Appendix S13).

Discussion

In this cohort study, antineoplastic agents (L01 chapter of ATC classification) and other type of immunosuppressant drugs (L04 chapter) were not associated with worse COVID-19 outcomes.

Table 3
Association between different pre-exposure to glucocorticoids and COVID-19 outcomes in the entire cohort ($n = 1067$, no glucocorticoids; $n = 733$, low dose; $n = 262$, high dose; $n = 72$) and among participants less than 70 years of age ($n = 664$, no glucocorticoids; $n = 439$, low dose; $n = 177$, high dose; $n = 48$)

Outcome	Entire cohort				<70 years old group			
	n (%)	p value[a]	OR (95% CI)	aOR (95% CI)[b]	*n* (%)	p value[a]	OR (95% CI)	aOR (95% CI)[b]
Hospital admission[c] $n = 772$								
No treatment	525/733 (71.6)		1	1	274 (62.4)		1	1
Low	188/262 (71.8)	0.169	1.01 (0.74–1.38)	1.45 (0.96–2.19)[d]	115 (65.0)	0.128	1.12 (0.78–1.61)	1.51 (0.94–2.44)[d]
High	59/72 (81.9)		1.80 (0.97–3.35)	**2.50(1.26–4.96)**	37 (77.1)		**2.03 (1.01–4.08)**	**2.34 (1.08–5.08)**
ICU admission [c] $n = 86$								
No treatment	54/733 (7.4)		1	1	27 (6.2)		1	1
Low	23/262 (8.8)	0.276	1.21 (0.73–2.01)	1.01 (0.54–1.90)	18 (10.2)	0.018	1.73 (0.93–3.)[d]	1.42 (0.61–3.31)[d]
High	9/72 (12.5)		1.80 (0.85 –3.81)	1.68 (0.75–3.77)	8 (16.7)		**3.05 (1.30–7.16)**	**2.91 (1.09–7.79)**
Mechanical ventilation[c] $n = 68$								
No treatment	45/733 (5.76)		1	1	23 (5.2)		1	1
Low	17/262 (6.27)	0.465	1.09 (0.61–1.94)	1.03 (0.51–2.10)	15 (8.5)	0.173	1.67 (0.85–3.29)	1.76 (0.72–4.34)
High	7/72 (9.33)		1.69 (0.73–3.89)	1.62 (0.66–3.97)	5 (10.4)		2.10 (0.76–5.81)	2.26 (0.73–7.01)
Acute kidney injury[e] $n = 85$								
No treatment	54/733 (10.3)		1	1	25 (9.1)		1	1
Low	23/262 (12.2)	0.739	1.22 (0.72–2.04)	1.32 (0.69–2.54)	15 (13.0)	0.429	1.49 (0.76–2.95)	1.60 (0.63–4.06)
High	7/72 (11.9)		1.17 (0.51–2.71)	1.44 (0.58–3.56)	5 (13.5)		1.56 (0.56–4.35)	1.71 (0.54–5.37)
Cardiac event $n = 397$								
No treatment	262/733 (35.7)		1	1	**80 (18.2)**		1	1
Low	103/262 (39.3)	0.249	1.16 (0.87–1.56)	1.25(0.83–1.88)[d]	**52 (29.4)**	**<0.001**	**1.87(1.25–2.80)**[d]	1.55 (0.87–2.77)[d]
High	32/72 (44.4)		1.44 (0.88–2.34)	**1.93 (1.08–3.46)**	**18 (37.5)**		**2.69 (1.43–5.07)**	**2.62 (1.23–5.56)**
Pulmonary embolism[c] $n = 51$								
No treatment	34/733 (4.6)	0.109			24 (5.5)		1	1
Low	10/262 (3.8)	0.109	0.82 (0.40–1.68)	1.46 (0.64–3.36)	4 (2.6)	0.121	0.40 (0.14–1.17)	1.21 (0.34–4.13)
High	7/72 (9.7)		2.21 (0.94–5.19)	**2.78 (1.08–7.15)**	4(8.3)		1.57 (0.52–4.74)	2.64 (0.72–9.71)
Mortality $n = 142$								
No treatment	**93/733 (12.7)**		1	1	18 (4.1)		1	1
Low	**33/262 (12.2)**	**0.028**	0.96 (0.62–1.47)	1.28 (0.75–2.18)[d]	11 (6.2)	0.001	1.54 (0.72–3.35)[d]	2.14 (0.77–5.93)[d]
High	**17/72 (23.6)**		**2.12 (1.18–3.82)**	**3.48 (1.77–6.86)**	8 (16.7)		**4.68 (1.91–11.43)**	**6.12 (2.12–17.64)**

Bold: P < 0.05.
Unadjusted and adjusted logistic regression calculating OR and 95% CI between nonexposed to glucocorticoids, low and high dose. Doses of glucocorticoids defined as: No treatment: Treatment with L01, L04, or no treatment; Low dose: <20 mg/day equivalent to prednisone or recurrent high dose (>20 mg equivalent to prednisone) but not daily (i.e.: high-dose glucocorticoids provided before the chemotherapy); High dose: ≥20 mg/day equivalent to prednisone. aOR, adjusted OR.

[a] p value calculated using chi-square test.

[b] Adjusted for age, sex, cardiac disease, hypertension, number of outpatient visits within past year, underlying condition, and if treated with other immunosuppressant drugs (L01 or L04).

[c] Including age as quadratic variable in adjusted model.

[d] Test for trend showed significant increasing trend of the association between dose of glucocorticoids with hospital admission (p value = 0.008), cardiac event (p value = 0.029), and mortality (p value = 0.01) in the entire cohort and with hospital admission (p value = 0.020), ICU admission (p value = 0.041), cardiac event (p value = 0.10) and mortality (p value = 0.001) in the <70-years-old cohort.

[e] Analysis on acute renal failure was restricted to hospitalized patients and was performed using the KDIGO algorithm.

Table 4
Association between COVID-19 outcomes and the pre-exposure to antineoplastic agents (L01 chapter) ($n = 255$) and other immunosuppressants (L04 chapter) L04 ($n = 198$) in the entire cohort and in the subgroup of <70 years

Outcome	Exposed n (%)	Nonexposed	p value [c]	Unadjusted		Adjusted[a]	
				OR	95% CI	aOR	95% CI
L01 (Antineoplastic agents)	n = 255	n = 812					
Hospital admission[b] n = 772							
Entire cohort	184 (23.8)	71 (24.1)	0.936	0.99	0.72–1.35	1.23	0.86–1.76
<70 years	102 (23.9)	56 (23.5)	0.904	1.02	0.70–1.49	1.13	0.74–1.73
ICU admission[b] n = 86							
Entire cohort	19 (22.1)	236 (24.1)	0.682	0.90	0.53–1.52	0.97	0.54–1.74
<70 years	10 (18.9)	148 (24.2)	0.380	0.73	0.36–1.48	0.95	0.42–2.13
Mechanical ventilation[b] n = 68							
Entire cohort	13 (19.1)	242 (24.2)	0.339	0.74	0.40–1.38	0.67	0.34–1.32
<70 years	7 (16.3)	151(24.3)	0.213	0.61	0.26–1.39	0.64	0.26–1.61
Acute kidney injury[b] n = 85							
Entire cohort	14 (7.6)	70 (11.9)	0.102	0.61	0.33–1.11	0.79	0.42–1.49
<70 years	10 (9.8)	35 (10.8)	0.775	0.90	0.43–1.88	1.26	0.55–2.88
Cardiac event n = 397							
Entire cohort	83 (20.9)	172 (25.7)	0.078	0.77	0.57–1.03	1.00	0.70–1.45
<70 years	33 (22.0)	125 (24.3)	0.557	0.88	0.57–1.36	1.15	0.68–1.96
Pulmonary embolism[b] n = 51							
Entire cohort	15 (5.9)	36 (4.4)	0.344	1.35	0.73–2.50	1.43	0.71–2.90
<70 years	8 (5.1)	24 (4.7)	0.870	1.07	0.47–2.43	1.62	0.61–4.26
Mortality n = 142	15 (5.9)	36 (4.4)	0.344				
Entire cohort	34 (23.9)	221 (23.9)	0.989	1.00	0.66–1.52	1.07	0.68–1.72
<70 years	11 (29.7)	147 (23.4)	0.383	1.38	0.67–2.86	1.21	0.52–2.83
L04 (Immunosuppressants)	n = 198	n = 869					
Hospital admission[b] n = 772							
Entire cohort	133 (17.2)	64 (21.7)	0.093	0.75	0.54–1.05	1.31	0.77–2.21
<70 years	104 (24.4)	60 (25.2)	0.819	0.96	0.66–1.38	1.39	0.78–2.48
ICU admission[b] n = 86							
Entire cohort	23 (26.7)	174 (17.7)	0.039	1.69	1.02–2.81	1.40	0.67–2.91
<70 years	21 (39.6)	143 (23.4)	0.009	2.15	1.20–3.84	1.98	0.82–4.76
Mechanical ventilation[b] n = 68							
Entire cohort	17 (25.0)	180 (18.0)	0.151	1.52	0.86–2.69	1.68	0.74–3.78
<70 years	14 (32.6)	150 (24.2)	0.217	1.52	0.78–2.94	1.46	0.53–4.05
Renal failure[b] n = 85							
Entire cohort	16 (8.1)	69 (7.9)	0.929	1.03	0.58–1.81	0.43	0.15–1.26
<70 years	13 (7.9)	33 (6.6)	0.561	1.22	0.62–2.38	0.29	0.07–1.29
Cardiac event n = 397							
Entire cohort	74 (18.6)	123 (18.4)	0.909	1.02	0.74–1.40	1.32	0.76–2.29
<70 years	52 (34.7)	112 (21.8)	0.001	1.90	1.28–2.82	1.77	0.90–3.49
Pulmonary embolism[b] n = 51							
Entire cohort	2 (1.02)	49 (5.6)	0.006	0.17	0.04–0.71	0.40	0.09–1.75
<70 years	2 (1.2)	30 (6.0)	0.013	0.19	0.05–0.82	0.61	0.13–2.95
Mortality n = 142							
Entire cohort	15 (10.6)	182 (19.7)	0.009	0.48	0.28–0.84	0.82	0.38–1.80
<70 years	10 (27.0)	154 (24.6)	0.735	1.14	0.54–2.40	1.68	0.54–3.23

[a] Adjusted by sex age, underlying diseases, hypertension, number of outpatient visits with past year cardiac or diabetes, and exposure to other immunosuppressant drugs.
[b] Including age as quadratic variable in adjusted model.
[c] p value calculated using chi-square test.

However, we observed that high-dose glucocorticoids were associated with an increased odds of hospital admission, cardiac events, pulmonary embolism, and mortality independently of the treatment with other immunosuppressant drugs. These results were also consistent in individuals <70 years old, although an association between low-dose glucocorticoids and COVID-19 outcomes did not reach statistical significance.

Overall, we did not find any association between immunosuppressed individuals with severe COVID-19 outcomes. However, in individuals <70 years old, the exposure to immunosuppressant drugs was significantly associated with the odds of having a cardiac event. This association was not observed in the sensitivity analysis restricted to higher cut-off (TnT >50 ng/l). Other factors may also contribute to mild increase of TnT, such as the viral disease per se that may exerts temporary cardiac disfunction as described in other viral infections such as H7N9 [14] or H1N1 [15].

Most studies in the field of the immunocompromised state and COVID-19 severity were initially focused on underlying medical conditions, such as cancer [16], HIV [17], or transplants [18,19], with contradictory results. However, only few studies have specifically evaluated COVID-19 outcomes in relation to the exposure to different immunosuppressant drugs.

The lack of association between immunosuppressant drugs and severe COVID-19 outcomes has been also reported in another study [7]. However, grouping the drugs into only two classes may have precluded detection of associations with individual drugs. Also, although the concomitant use of immunosuppressant drugs and the elderly age further increases the risk of infections [20], we did not find this association in the adjusted regression analysis.

One study on individuals with inflammatory bowel disease found an association between glucocorticoid exposure and a poor outcome, although the cut-off dose of glucocorticoids was not indicated [21]. Another cohort study also found a worsened prognosis of SARS-CoV-2 infection in those exposed to >7.5 mg/day equivalent of prednisolone [22]. In our study, we defined the exposure to high-dose glucocorticoids based on CDC recommendations, which state that below

20 mg/day, there is no major increased risk of developing severe complications from a viral infection and therefore allowing the use of attenuated live vaccines [12].

The harmful effect of chronic exposure to glucocorticoids could be particularly related to the suppression of immune T-cell response; consequently, patients may not manifest common signs and symptoms of infection as clearly [23] leading to failure in early recognition of infection [24]. However, the association with glucocorticoids but not with other immunosuppressants and COVID-19 may be driven by the severity of the underlying disease stage. This may differ depending on the type of disease, since multiple studies reported a higher mortality in transplant patients [25] and haematological cancer [26]. In our study, transplant patients were less likely to be hospitalized, whereas they were associated with an increased odds of ICU admission. This discrepancy could be justified because we included outpatient visits and phone call from long-term and well-controlled transplant patients who did not require hospitalization and also because advanced cancer patients are not usually candidates for intensive care.

Limitations

First, although the study included over 1000 individuals, the sample size precluded a proper analysis among different categories of underlying conditions, which may increase the hospitalization risk itself. We tried to overcome this bias by including only individuals with underlying conditions, and we also considered IPTW adjustment, finding consistent results regardless of analytic strategy.

While we adjusted for a range of covariates, other unmeasured factors may drive the association between steroid use and the COVID-19 outcome (residual cofounding). We did not study other outcomes associated with the use of glucocorticoids such as sepsis [27,28].

Data were not collected for the purpose of this study. Hence, the reasons of the outcomes were not ascertained and could be other than COVID-19. We added other indirect indicators of COVID-19 such as blood temperature, respiratory rate, or oxygen in hospitalized patients, what did not show any difference among exposed and nonexposed patients. Furthermore, by limiting the follow-up period to 1 month from COVID-19 diagnosis, overestimation of COVID-19 outcome is assumed to be minimal. Finally, a potential misclassification of exposed individuals for which the immunosuppressant therapy was not properly registered cannot be ruled out.

Our cohort contains local data from a Swedish tertiary centre but it includes outpatients and telephonically followed-up patients.

Conclusions

The use of antineoplastic or other immunosuppressants prior to COVID-19 diagnosis was not associated with worsened outcomes in patients with cancer, solid-organ transplants, haematological, and autoimmune diseases in our study. The use of high-dose of glucocorticoids was associated with a worsened prognosis of SARS-CoV-2, although more studies are warranted to evaluate the effect of the underlying disease severity and the pre-exposure of different doses of glucocorticoid regimens on the prognosis of COVID-19.

Transparency declaration

The authors declare no conflict of interest.

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Author contributions

RB, ARM, and PB conceived and designed the study. RB and ARM performed the data analysis including the manual annotation and drafted the manuscript. SVW and PH were responsible for the data extraction of the research dataset, collected and analysed the data, and reviewed the manuscript. PN, PB, and AF collaborated in the study design and data analysis and reviewed the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.05.014.

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