Mortality and Severity of Coronavirus Disease 2019 in Patients with Long-Term Glucocorticoid Therapy: A Korean Nationwide Cohort Study

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Background: The severity of coronavirus disease 2019 (COVID-19) among patients with long-term glucocorticoid treatment (LTGT) has not been established. We aimed to evaluate the association between LTGT and COVID-19 prognosis.

Methods: A Korean nationwide cohort database of COVID-19 patients between January 2019 and September 2021 was used. LTGT was defined as exposure to at least 150 mg of prednisolone (≥ 5 mg/day and ≥ 30 days) or equivalent glucocorticoids 180 days before COVID-19 infection. The outcome measurements were mortality, hospitalization, intensive care unit (ICU) admission, length of stay, and mechanical ventilation.

Results: Among confirmed patients with COVID-19, the LTGT group ($n=12,794$) was older and had a higher proportion of comorbidities than the control ($n=359,013$). The LTGT group showed higher in-hospital, 30-day, and 90-day mortality rates than the control (14.0% vs. 2.3%, 5.9% vs. 1.1%, and 9.9% vs. 1.8%, respectively; all $P<0.001$). Except for the hospitalization rate, the length of stay, ICU admission, and mechanical ventilation proportions were significantly higher in the LTGT group than in the control (all $P<0.001$). Overall mortality was higher in the LTGT group than in the control group, and the significance remained in the fully adjusted model (odds ratio [OR], 5.75; 95% confidence interval [CI], 5.31 to 6.23) (adjusted OR, 1.82; 95% CI, 1.67 to 2.00). The LTGT group showed a higher mortality rate than the control within the same comorbidity score category.

Conclusion: Long-term exposure to glucocorticoids increased the mortality and severity of COVID-19. Prevention and early proactive measures are inevitable in the high-risk LTGT group with many comorbidities.

Keywords: COVID-19; Glucocorticoids; Long term adverse effects; Mortality

INTRODUCTION

Since the first case of new coronavirus called severe acute respiratory syndrome coronavirus 2, also known as coronavirus disease 2019 (COVID-19), occurred in December 2019, there have been 605 million cumulative cases worldwide and 6.49 million deaths [1,2]. Although the number of infected people is gradually decreasing because of the availability of COVID-19 vaccines and the application of the treatment, it is still too early to overlook the fact that the number of confirmed cases exceeds 450,000 per day worldwide, negatively affecting the health of the global population [1].

As the risk of severe COVID-19 and adverse outcomes continues to increase, special care is needed, particularly for the elderly population and those at high-risk with underlying medical conditions, including diabetes mellitus, chronic kidney disease (CKD), cardiovascular disease (CVD), and other various chronic diseases [3-5]. Several guidelines for these populations have been released [6-9].

In various chronic diseases such as rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), and asthma, long-term use of glucocorticoids inevitably leads to adrenal insufficiency [10,11]. Patients with adrenal insufficiency are considered at an increased risk of infection due to an altered immune system and an increased risk of infection-induced adrenal crisis, which can lead to death and serious complications [12]. As reported in a small case-control study, patients with adrenal insufficiency who were well-trained with an appropriate replacement strategy following "sick day rules" had similar rates and severity of COVID-19 infection as controls with intact adrenal function [13]. Nevertheless, considering the various adverse effects caused by the prolonged use of glucocorticoids and the underlying diseases of patients who need to continue long-term or/and high-dose regimens, concerns persist that people receiving long-term glucocorticoid treatment (LTGT) are vulnerable to infectious diseases. Moreover, the association between LTGT with a high-risk of adrenal insufficiency and the risk of mortality and severe outcomes among patients with COVID-19 remains unclear. Therefore, this study aimed to determine the mortality and other severe outcomes of COVID-19 in patients with LTGT compared to a control group using a Korean nationwide population-based database.

METHODS

Ethical considerations

This study was approved by the Institutional Review Board

Committee of the Korean Health Insurance Review and Assessment Service as an exemption study (HIRA IRB 2022-054). The need for informed consent was waived as all data used in the National Health Insurance Service (NHIS) database were anonymized and de-identified before being provided.

Data sources and study population

In this retrospective cohort study, all patients with COVID-19 infection from January 2020 to September 2021 in the Korea NHIS database were included to evaluate outcomes of COVID-19 in patients with LTGT. In brief, the NHIS has secured nationwide COVID-19 cohort data by providing public health insurance to the entire population of South Korea. Heretofore, the government has provided free medical care by assigning a special code—"3/02" in MT043—to the type of National Disaster Medical Expense Subsidy when a patient is diagnosed with COVID-19 to prevent the spread of it via thorough infection control. Therefore, under the International Classification of Diseases, Tenth Revision (ICD-10), the following ICD-10 codes and specially assigned claim codes simultaneously were used to identify patients with COVID-19: B34.2 (coronavirus infection, unspecified site), U18.1 (novel coronavirus infection), U07.1 (COVID-19, virus identified), and U07.2 (COVID-19, virus not identified).

Underlying diseases, including diabetes mellitus, hypertension, CVD, cerebral infarction or transient ischemic accident, CKD, COPD, asthma, and RA, were defined as at least one claim of either outpatient, inpatient, or both using each appropriate ICD-10 code within 1 year prior to the date of COVID-19 diagnosis.

Operational definitions of the LTGT group and control group

Given the National Institute for Health and Care Excellence guideline for patients at risk of systemic side effects from oral corticosteroids, LTGT was defined as a prescription of oral prednisolone ≥5 mg/day or the equivalent for at least 30 days from the previous 180 days to the time of diagnosis of COVID-19 [14]. The control group consisted of patients who had not been prescribed glucocorticoids for 180 days before the date of confirmed COVID-19 infection.

Outcome measurements

The primary outcome of this study was overall mortality among patients with LTGT compared with the control group after a diagnosis of COVID-19. The secondary endpoints included the

following other severe COVID-19 results that were compared between the LTGT group and control group: hospitalization rates, need for admission to the intensive care unit (ICU), length of stay, and need for oxygen therapy, including mechanical ventilation.

Statistical analysis

Baseline characteristics and clinical outcomes of the study population are expressed as a number with percentage (%) and mean with standard deviation (SD). Continuous variables were compared between the two groups using the *t* test, whereas categorical variables were analyzed using the chi-square test or Fisher exact test as appropriate. The odds ratio (OR) with 95% confidence interval (CI) of mortality in patients with LTGT was calculated using logistic regression analysis. To further strengthen the mortality risk in the LTGT group, a multivariable-adjusted OR was generated in logistic regression analysis to compare the mortality rate between the groups after data were adjusted for age, sex, Charlson comorbidity index (CCI), and the following comorbidities: diabetes mellitus, hypertension, CVD, cerebrovascular disease, CKD, COPD, asthma, and RA. Kaplan-Meier survival curves were compared between the groups using the log-rank test, and subgroups were analyzed according to the CCI index (0, 1, and ≥2) of both groups to adjust the multiple comorbidities related to survival. The CCI score was calculated based on ICD-10 codes [15].

Statistical significance was set at a two-sided *P*<0.05. All statistical analyses were performed using R version 4.1.1 (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Among the total 509,216 patients diagnosed with COVID-19 from January 2019 to September 2021, there were 12,794 and 359,013 patients in LTGT group and control group, respectively, after excluding those with a lack of baseline information (*n*=22) and patients who did not meet the inclusion criteria (*n*=137,387) (Fig. 1). The baseline characteristic of the study population at the time of diagnosis of COVID-19 are summarized in Table 1. The LTGT group was older than the control group (mean±SD age, 57.8±21.3 years vs. 40.7±21.3 years, *P*<0.001), and the proportion of men was slightly lower in the LTGT group than in the control group (50.3% vs. 52.5%, *P*<0.001). There were also significant differences in comorbidities between the groups. The
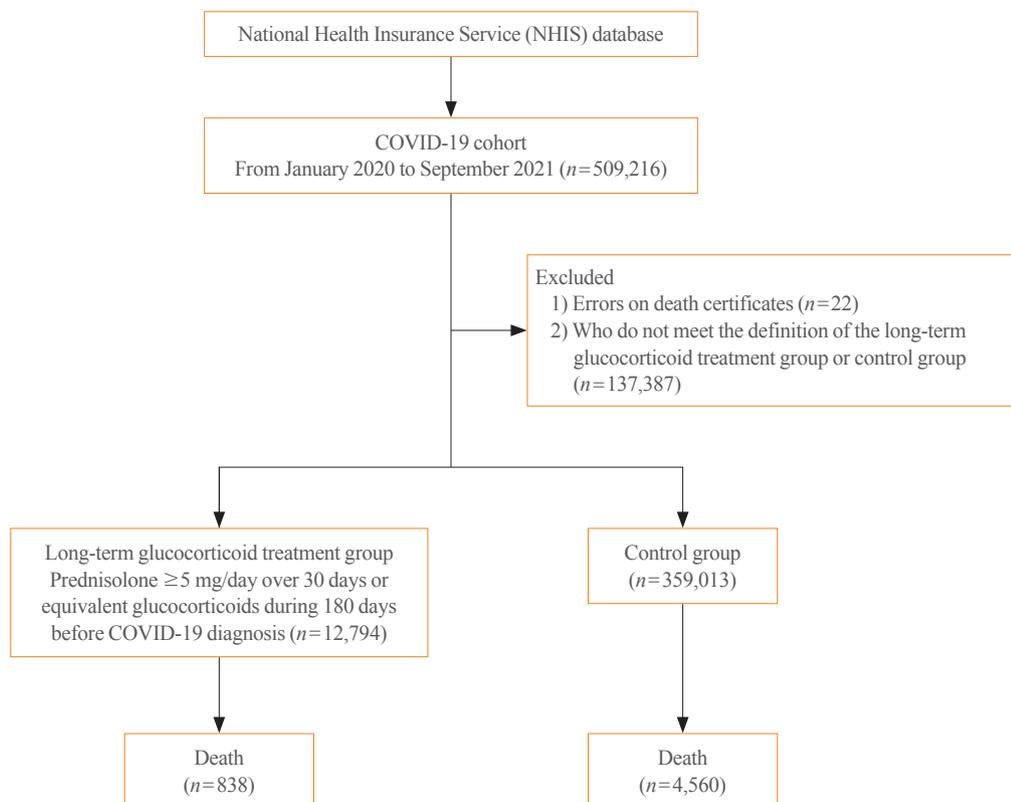
Fig. 1. Flow chart showing the study population. COVID-19, coronavirus disease 2019.

Table 1. Baseline Characteristics of the LTGT Group and Control Group in the NHIS COVID-19 Database Cohort Study (n=371,807)

Characteristic	LTGT (n=12,794)	Control (n=359,013)	P value
Age, yr	57.8±21.3	40.7±21.3	<0.001
Age group, yr			<0.001
<40	2,445 (19.1)	178,506 (49.7)	
40–64	4,951 (38.7)	130,607 (36.4)	
65–74	2,483 (19.4)	25,175 (7.0)	
≥75	2,915 (22.8)	24,725 (6.9)	
Male sex	6,438 (50.3)	188,641 (52.5)	<0.001
Comorbidity			
Diabetes mellitus	4,362 (34.1)	42,534 (11.8)	<0.001
Hypertension	5,709 (44.6)	58,917 (16.4)	<0.001
Cardiovascular disease	268 (2.1)	1,542 (0.4)	<0.001
Cerebrovascular disease	1,102 (8.6)	9,525 (2.7)	<0.001
Chronic kidney disease	949 (7.4)	4,729 (1.3)	<0.001
COPD	1,333 (10.4)	4,033 (1.1)	<0.001
Asthma	2,782 (21.7)	17,054 (4.8)	<0.001
Rheumatoid arthritis	2,007 (15.7)	4,467 (1.2)	<0.001
CCI score			<0.001
0	3,471 (27.1)	254,271 (70.8)	
1	2,407 (18.8)	53,345 (14.9)	
≥2	6,916 (54.1)	51,397 (14.3)	

Values are expressed as mean±standard deviation or number (%). The Fisher exact test or t test was performed to compare data between the two groups. P<0.05 is considered significant.
LTGT, long-term glucocorticoid treatment; NHIS, National Health Insurance Service; COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index.

Table 2. Outcomes of COVID-19 in the LTGT Group Compared with the Control Group

Variable	LTGT (n=12,794)	Control (n=359,013)	P value
Mortality within 30 days after diagnosis	754 (5.9)	3,867 (1.1)	<0.001
Mortality within 90 days after diagnosis	1,271 (9.9)	6,337 (1.8)	<0.001
In-hospital mortality	1,788 (14.0)	8,260 (2.3)	<0.001
Mortality by the CCI score			
0	53 (1.5)	584 (0.2)	<0.001
1	71 (2.9)	580 (1.1)	<0.001
≥2	630 (9.1)	2,703 (5.3)	<0.001
Hospitalization rate	5,869 (45.9)	203,924 (56.8)	<0.001
Length of hospitalization stay, day	19.2±26.7	13.6±26.7	<0.001
ICU occupancy rate	627 (4.9)	7,240 (2.0)	<0.001
Length of ICU stay, day	22.8±32.1	19.0±32.1	0.017
Oxygen therapy	2,058 (16.1)	26,923 (7.5)	<0.001
Mechanical ventilation	378 (3.0)	2,934 (0.8)	<0.001

Values are expressed as number (%) or mean±standard deviation. Mortality by the CCI score was 30-day mortality, expressed as a percentage of the number of deaths related to the number of patients in the CCI score category in each group. The Fisher exact test or t test was performed to compare data between the two groups. P<0.05 is considered significant.
COVID-19, coronavirus disease 2019; LTGT, long-term glucocorticoid treatment; CCI, Charlson comorbidity index; ICU, intensive care unit.

LTGT group had a higher rate of accompanying diabetes mellitus, hypertension, CVD, and CKD than the control group. Additionally, the incidences of chronic inflammatory diseases such as COPD, asthma, and RA, each disease that requires glucocorticoids as treatment, were more than five times higher in the LTGT than in the control group (COPD, asthma, and RA: 10.4% vs. 1.1%, 21.7% vs. 4.8%, and 15.7% vs. 1.2%, respectively; all P<0.001).

Table 2 shows the treatment outcomes for COVID-19, including mortality. The hospitalization rate for COVID-19 was lower in the LTGT group than in the control group, but the ICU admission rate was more than doubled in the LTGT group than in the control group. The application of mechanical ventilation and simple oxygen therapy was also significantly higher in the

LTGT group than in the control group. The length of hospitalization in the LTGT group was 19.2±26.7 days overall, which was longer than the 13.6±26.7 days in the control group, and the length of stay in the ICU was significantly longer in the LTGT group than in the control group (22.8±32.1 days vs. 19.0±32.1 days, P=0.017). In-hospital mortality was approximately 6.1 times higher in the LTGT group than in the control group (14.0% vs. 2.3%, P<0.001), and 30- and 90-day mortalities were 5.4 and 5.5 times higher in the LTGT group than in the control group, respectively (both P<0.001). The mortality rate, according to the CCI score, was significantly higher in the LTGT group than in the control group in all categories. Especially in the group with a CCI score ≥2, the LTGT group had a mortality rate of 6.1 times higher than the control group (P<0.001). Overall mortality in the LTGT group was higher (5.75; 95% CI, 5.31 to 6.23; P<0.001) than that in the control group, and the adjusted OR was significant at 1.82 (95% CI, 1.67 to 2.00; P<0.001) after adjusting for confounding factors
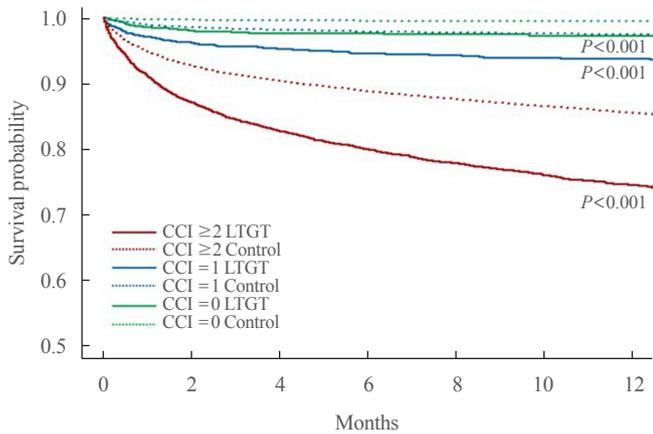
Fig. 2. Kaplan-Meier survival curves showing data of the long-term glucocorticoid treatment (LTGT) group compared with the control group stratified by the Charlson comorbidity index (CCI) score. Survival probability is plotted on the Y-axis against time after coronavirus disease 2019 (COVID-19) infection on the X-axis. Different colors (green, blue, and red) represent different CCI scores (CCI=0, CCI=1, and CCI ≥2, respectively). The solid and dotted lines represent the LTGT and control groups, respectively. Within the same CCI score category, comparisons between the groups were considered as significant if $P<0.05$.

including age, sex, the CCI score, and underlying comorbidities. The Kaplan-Meier curves for each CCI category in both groups are shown in Fig. 2. In the same CCI category, the LTGT group showed a significantly higher mortality than the control group (both $P<0.001$).

DISCUSSION

This study evaluated the association between long-term glucocorticoid use and COVID-19 severity and mortality in patients diagnosed with COVID-19 in South Korea from January 2020 to September 2021. In this nationwide population-based study, the patients with LTGT showed significantly high mortality and severe COVID-19 outcomes. After adjusting for various confounding factors, the LTGT group showed a significantly higher proportion of comorbidities than the control group. Even taking this into account, it was important that the group treated with glucocorticoids for a long time had a 1.8-fold higher mortality rate than the control group. Especially in the high-risk group with a CCI score ≥2, the mortality gap between the LTGT group and control group widened by >6 times.

Since the outbreak of the COVID-19 pandemic, several studies have shown an increased risk of adverse COVID-19 outcomes in patients with Cushing syndrome, a condition of ele-

vated endogenous cortisol, and in patients receiving high-dose glucocorticoid therapy for chronic diseases, such as asthma and inflammatory bowel disease [16-18]. Prolonged exposure to iatrogenic glucocorticoids suppresses the hypothalamus-pituitary-adrenal axis, leading to secondary adrenal insufficiency [10,11]. The pivotal role of glucocorticoids in the deterioration of the immune system increase susceptibility to infection [19,20]. Additionally, patients with adrenal insufficiency are more likely to have an infection-induced adrenal crisis than those without, which is a serious complication that may lead to death [21,22]. In Italy, a tertiary center study of 279 patients with primary or secondary adrenal insufficiency who were properly trained with regular follow-up found that COVID-19 infection and severity had a similar pattern in those patients compared to controls [13]. However, as hypothesized, LTGT has been reported to be associated with a poor prognosis for COVID-19 [16-18,23]. According to a study of >80,000 patients with asthma in Israel, recent exposures to chronic systemic corticosteroids within approximately 4 months prior to COVID-19 infection were independent risk factors for severity and all-cause mortality [16]. Considering that the proportion of pre-existing chronic diseases, including COPD, asthma, and RA, were significantly higher in the LTGT group than in the control group in our study, recent previous long-term glucocorticoid exposure could lead to poor outcomes of COVID-19.

To date, risk factors associated with COVID-19 mortality are older age, male sex, and underlying chronic diseases, e.g., hypertension, diabetes mellitus, COPD, renal disease, CVD, and malignancy [24-27]. We showed that patients who were exposed to at least 150 mg of prednisolone (≥5 mg/day and ≥30 days) or equivalent doses of glucocorticoids 180 days before the onset of COVID-19 had a mortality rate approximately 2-fold higher than the controls, even after controlling for various possible confounding factors. Our subgroup analysis by CCI category, a predictive indicator for mortality, highlighted adverse outcomes of COVID-19 with LTGT.

Meanwhile, in our study, the hospitalization rate of LTGT was lower than that of the control group. At the beginning of the study period, the Korean government had a policy of hospitalizing and isolating all COVID-19-infected patients, regardless of the severity of their symptoms. Moreover, during the early period of the COVID-19 pandemic, many young and healthy people, including religious groups, were hospitalized after cluster infections in a local city [28]. These environmental factors surrounding COVID-19 may have contributed to the relatively higher hospitalization rate in the control group.

There are some limitations to this study. First, since this study used claim data, information on laboratory results or vital signs was unavailable, so the operational definition of severe COVID-19 could only be determined by the application of oxygen therapy and invasive mechanical ventilation or admission to the ICU. Second, the cause of death provided by the National Statistical Office was not linked. However, mortality within 30 days after the diagnosis of COVID-19 is more likely to mean death due to COVID-19 rather than other diseases. Therefore, it is difficult to undermine the significance of our study results. Third, we were not able to identify the underlying diseases for LTGT. In particular, the results of this study did not include all chronic metabolic or inflammatory diseases. For example, dyslipidemia was not considered an independent variable. However, we tried to identify as many underlying conditions associated with the severity and mortality from COVID-19 in individuals as possible. The prevalence in Korea is estimated to be 300, 30, and 10 per 100,000 population for RA, systematic lupus erythematosus, and ankylosing spondylitis, respectively [29-31]. Therefore, in this study, RA was included as a representative autoimmune disease with a high possibility of LTGT. Even so, it is noteworthy that the mortality rate of the LTGT group was significantly higher than that of the control group, even after adjusting for age, sex, CCI score, and various comorbidities. Finally, the results should be carefully interpreted because not all long-term glucocorticoid users have adrenal insufficiency, and not all routes of administration of glucocorticoids other than oral, e.g., topical or inhaled, have been analyzed. Moreover, it is unknown whether the proper replacement measure by the sick day rule has been applied. Nevertheless, this study's findings have important clinical implications in terms of raising awareness among clinicians and patients that various chronic diseases are prone to prolonged exposure to glucocorticoids, which can worsen the matter.

In conclusion, this nationwide population-based case-control study showed that patients exposed to LTGT had severe COVID-19 outcomes, including increased mortality. Especially as the risk of LTGT increased greatly in the higher risk group with various underlying comorbidities, preemptive measures should be taken to overcome the COVID-19 pandemic.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: E.J.K. Acquisition, analysis, or interpretation of data: E.J.K., K.S., K.M.K., G.H.S., S.J.Y. Drafting the work or revising: E.J.K., G.H.S. Final approval of the manuscript: E.J.K., K.S., K.M.K., G.H.S., S.J.Y.

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