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.

Influence of chronic corticosteroids and calcineurin inhibitors on COVID-19 clinical outcomes: Analysis of a nationwide registry.

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Highlights.

- Chronic IS therapies entail different risk profiles and clinical outcomes in COVID-19.
- Chronic Corticosteroid use before admission confer higher mortality and complications risk.
- Chronic calcineurin inhibitors treatment does not seem to have any effect on mortality.

Influence of chronic corticosteroids and calcineurin inhibitors on COVID-19 clinical outcomes: Analysis of a nationwide registry.

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ABSTRACT

Objectives. To analyze whether subgroups of immunosuppressive (IS) medications confer different outcomes in COVID-19.

Methods. Multicenter retrospective cohort of consecutive immunosuppressed patients (ISP) hospitalized with COVID-19 from March to July 2020. The primary outcome was in-hospital mortality. A propensity score-matched (PSM) model comparing ISP and non-ISP was planned, as well as specific PSM models comparing individual IS medications associated with mortality.

Results. Out of 16,647 patients, 868 (5.2%) were on chronic IS therapy prior to admission and were considered ISP. In the PSM model, ISP had greater in-hospital mortality (OR 1.25, 95%CI 0.99-1.62), which was related to a worse outcome associated with chronic corticoids (OR 1.89, 95%CI 1.43-2.49). Other IS drugs had no repercussion on mortality risk (including calcineurin inhibitors (CNI), OR 1.19, 95% CI 0.65-2.20). In the pre-planned specific PSM model within patients on chronic IS treatment before admission, corticosteroids were associated with an increased risk of mortality (OR 2.34, 95%CI 1.43-3.82).

Conclusions: Chronic IS therapies pose a heterogeneous group of drugs with different risk profiles for severe COVID-19 and death. Chronic systemic corticosteroid is associated with increased mortality. On the contrary, CNI and other IS treatments prior to admission do not seem to convey different outcomes.

Keywords: COVID-19; immunocompromised host; prognosis factors; solid organ transplantation; autoimmune diseases; immune-mediated inflammatory diseases

Abbreviations

AHF: Acute heart failure.

AKI: Acute kidney injury

ARDS: Acute respiratory distress syndrome

CCI: Charlson Comorbidity Index

CHF: Chronic heart disease

CI: Confidence interval

CNI: Calcineurin inhibitors

COPD: chronic obstructive pulmonary disease

CRF: Chronic renal failure

CRP: C-reactive protein.

DIC: Diffuse intravascular coagulopathy

LDH: Lactate Dehydrogenase

HR: Hazard ratio

ICU: Intensive care unit.

IHD: Ischemic heart disease

IQR: Interquartile range

IS: Immunosuppressive

ISP: Immunosuppressed patients

IMID: Immune-mediated inflammatory diseases

MOF: Multiple organ dysfunction syndrome

OR: Odds ratio.

RT-PCR: Real-time polymerase chain reaction

SOT: Solid organ transplant

INTRODUCTION

Since the beginning of 2020, the world has faced the coronavirus disease 2019 (COVID-19) pandemic. As of November 11, 2021, more than 250 million people have had COVID-19 and more than 5 million have died worldwide [Dong et al., 2020].

COVID-19 progresses with an initial viral replication phase followed by a viral clearance phase as a result of the immune response. In some patients, SARS-CoV-2 replication in the lungs may trigger a cytokine storm that leads to the development of uncontrolled inflammation, an acute respiratory distress syndrome (ARDS) and respiratory failure, which are the main causes of death in these patients [Rodríguez-Baño et al., 2020]. This uncontrolled inflammation has prompted the use of several anti-inflammatory drugs in severe cases [Horby et al., 2020].

It has been speculated that patients receiving chronic systemic corticosteroids or other immunosuppressive (IS) therapies are likely to have a lower risk of this uncontrolled inflammation [D'Antiga; 2020]. In this regard, special attention should be paid to calcineurin inhibitors (CNI), including cyclosporine and tacrolimus [Gálvez-Romero et al., 2021; Solanich et al; 2021], which are the foundation of immunosuppression in solid organ transplant (SOT) recipients and are also used in some patients with immune-mediated inflammatory diseases (IMID). *In vitro* studies have shown that cyclosporine and tacrolimus inhibit viral replication of several coronaviruses through binding to intracellular cyclophilins, inactivating peptidyl-prolyl cis/trans isomerase function [Ma-Lauer et al., 2020]. Therefore, chronic treatment with CNI could reduce the severity of SARS-CoV-2 infection [Belli et al., 2021]. On the other hand, as in other viral infections, IS therapies may lead to an uncontrolled initial viral replication [Urra et al., 2020], viral immune evasion, and higher risk of mortality [Belsky et al., 2021]. Data on the natural course of COVID-19 in chronically immunosuppressed patients (ISP), compared to what is available on the general population, are scarce and inconsistent. Some studies suggest that ISP have higher rates of severe COVID-19 and mortality compared to the general population, while others show just the opposite: a lower incidence of severe

COVID-19 and lower mortality [Suárez-García I et al., 2021; Minotti et al., 2020; Martínez-Urbistondo et al., 2021)

In the light of the foregoing, we aimed to assess whether certain IS treatments — corticosteroids and CNI in particular—may be at different risk of severe COVID-19 and adverse outcomes compared to the non-immunosuppressed population.

PATIENTS AND METHODS

Study population and participants

This work is a retrospective cohort study of all adult patients (18 years of age or older) admitted to the hospital for the first time due to COVID-19, in 150 hospitals across Spain from March to July, 2020, who reached a hard endpoint (death or hospital discharge). Information on the SEMI-COVID-19 registry and data collection procedures have been described in previously published works [Suárez-García et al., 2021].

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Provincial Research Ethics Committee of Málaga (Spain) pursuant to the recommendation of the Spanish Agency of Medicines and Medical Products (AEMPS, for its initials in Spanish). All patients gave their informed consent.

Definition and variables

SARS-CoV-2 infection was confirmed by a positive real-time polymerase chain reaction (RT-PCR) test of a nasopharyngeal exudate sample, sputum, or bronchoalveolar lavage.

Patients were defined as on IS treatment if they were receiving any immunosuppressive medication, including systemic corticosteroids, CNI (tacrolimus and cyclosporine), antimetabolites (mycophenolate, azathioprine), mTOR inhibitors (sirolimus, everolimus), and/or other immunosuppressive treatments at the time of admission. ISP were classified either as SOT recipients or IMID patients. Due to limitations in the database, we could not identify the specific IMID disease. Patients with hematological (active lymphoproliferative, myeloproliferative disorders, or bone marrow transplantation) or solid

organ malignancies were not included in this study. ARDS and severity were defined according to the Berlin definition [Ranieri et al., 2012]. Patients nor receiving IS treatments prior to admission (non-IS population) were used as controls.

Study outcomes

The primary endpoint was in-hospital all-cause mortality. Secondary endpoints were 30-day mortality and in-hospital complications, including bacterial pneumonia, sepsis, septic shock, acute kidney injury (AKI), acute heart failure (AHF), myocarditis, stroke or multiple organ dysfunction syndrome (MOF).

Statistical analysis

Quantitative variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as percentages and absolute frequencies.

Clinical presentation and complications were compared between each group of ISP and controls, using the chi-square test for qualitative variables (or Fisher's exact test when appropriate) and Student's t test for quantitative variables (or the Mann-Whitney U test when appropriate).

The influence of belonging to either ISP group (SOT recipients or IMID patients) as well as specific IS medications on mortality were analyzed by including demographic and comorbidity variables in a single-step multivariate logistic regression model, which also included the aforementioned groups (model 1) or medications (model 2). The corrected odds ratio (OR) and 95% confidence intervals (CI) were calculated for statistically significant variables.

A survival analysis was also performed, comparing time-to-death between groups with data censored at 30 days of clinical progress (30-day mortality). Time-to-death was modeled using Kaplan-Meier curves and differences were assessed by stratified Cox regression models. Hazard ratios (HR) and 95% CI were determined.

In order to better estimate the influence of chronic immunosuppressive medication on clinical course and mortality, a 1:1 propensity score analysis was performed comparing ISP with non-IS population after matching, according to sex, age, and comorbidities. We also

conducted a propensity score matching analysis within ISP on specific medications found to be associated with mortality, comparing with ISP who were receiving other medications. All models were required to have only exact matches. The validity of all propensity score matching models was assessed by comparing demographic and comorbidity variables between the groups. Clinical course and mortality were compared between groups, using the same analytical method as described above. OR and 95% CI were provided for all variables with a *p* value < 0.10.

For all statistical analysis, two-tailed *p*-values < 0.05 were considered significant. The statistical analyses were performed using the SPSS version 25 software package (IBM SPSS Statistics).

RESULTS

A total of 16,647 consecutive adult patients hospitalized with COVID-19 were included in the registry. 1,674 patients with malignancy were excluded from the analysis. Of the remaining 14,973 evaluable patients, 868 (5.79%) were considered ISP and 14,105 patients (94.2%) were not. Among ISP, 654 patients had a prior history of IMID (4.36% overall) and 214 were SOT recipients (1.42% overall, 151, 32, 16, and 15 had kidney, liver, lung, and heart transplantation, respectively). There were 1,243 prescriptions for immunosuppressive medications among the 868 ISP. The most common treatments were glucocorticoids (593 patients, 68.3%), followed by antimetabolites as mycophenolate, azathioprine or methotrexate (369 patients, 42.5%), CNI (155 patients, 17.9%) and m-TOR inhibitors (65 patients, 7.5%).

The demographic characteristics, general baseline data, comorbidities, clinical presentation and outcomes in ISP and controls are summarized in **table 1**. Overall, the mean age was 69 years and 8,460 patients (56.5%) were male. The hospital mortality rate was 19.1% (2,857 deaths). In the multivariate logistic regression analysis, after adjustment by age and comorbidities (**table 2**), higher in-hospital mortality was found both in SOT recipients (OR 2.46, 95% CI 1.73-3.49) and IMID patients (OR 1.38, 95% CI 1.10-1.72). Among specific chronic IS treatments, only corticoids use at admission was associated with in-hospital

mortality (OR 2.24 95% CI 1.41-3.55). Interestingly, after adjusting for chronic glucocorticoid use at admission in the survival analysis (**figure 1**), SOT recipients remained at higher risk of 30-day mortality (HR 1.69, 95% CI 1.23-2.35), while IMID patients had a similar risk than the general non-IS population (HR 0.86, 95% CI 0.76-1.15). On the other hand, chronic glucocorticoid use was strongly associated with 30-day mortality (HR 2.00, 95% CI 1.43-2.79)

Propensity score matched analysis

We performed a propensity score matching analysis of a total of 636 pairs of ISP patients and controls. Difference in clinical course and complications between the groups are shown in **table 3**. **Figure 2** shows the time-to-death analysis for the groups. Although their clinical presentation was similar, in-hospital mortality was higher in patients receiving any immunosuppressive medications compared to controls (25% vs 21.1%; HR 1.21, 95% CI 1.01-1.52). In this model, glucocorticoid use was associated with higher in-hospital mortality than in general non-IS population (OR 1.89, 95%CI 1.43-2.49), while CNI (OR 1.19, 95%CI 0.65-2.20), antimetabolites (OR 1.09, 95%CI 0.59-2.00), and mTOR inhibitors (OR 0.76, OR 0.23-2.61) were not associated with worse outcomes.

Chronic glucocorticoid treatment

A specific propensity score matched analysis regarding chronic systemic glucocorticoid therapy confirmed that their use before admission was associated with mortality in all the study population (OR 1.89, 95%CI 1.43-2.49). Furthermore, patients under corticoid treatment presented more in-hospital complications, such as severe ARDS (OR 1.75, 95% CI 1.05-2.91), sepsis (OR 1.99, 95% CI 1.06-4.38), septic shock (OR 3.67, 95% CI 1.19-11.36, AKI (OR 2.28, 95% CI 1.37-3.80) and MOF (OR 2.43, 95% CI 1.41-4.26). Finally, chronic systemic corticoid treatment was also associated with worse outcomes within SOT recipients (OR 1.82, 95% CI 1.01-3.30).

As planned, a separate propensity score matching analysis of a total of 212 ISP with systemic glucocorticoids, paired to ISP without glucocorticoids, was performed. Differences in the clinical course and complications between patients with and without systemic

glucocorticoids are summarized in **table 4**. **Figure 3** shows the time-to-death analysis for the groups. In-hospital mortality was higher in IS patients with glucocorticoids (27.8% vs 14.2%, HR 2.08, 95% CI 1.30-3.31). Interestingly, in this model, patients without glucocorticoids but with other immunosuppressive treatments had similar in-hospital mortality rates than general non-IS population (14.2% vs 18.6%, respectively), although the groups were not statistically comparable.

Chronic calcineurin inhibitors

In the propensity score analysis, chronic CNI therapy before hospital admission was not associated with worse outcomes (OR 1.19, 95%CI 0.65-2.20). To note, the majority of patients on CNI were SOT recipients (85.2%, 132/155). Consequently, a sub-analysis was performed to analyze the role of CNI treatment before admission in SOT patients. When chronic CNI treatment was considered, no differences regarding mortality were found (31.7% vs 32.6%, p=1.000).

DISCUSSION

A recent study published from the Spanish cohort showed that immunosuppression and immunosuppressant drugs conferred a higher death risk because of COVID-19 [Suárez-García et al., 2021]. After these findings, we sought to evaluate which immunosuppressant drugs in particular were associated with this greater risk by a propensity-score analysis. Therefore, the main finding of our study is that chronic systemic glucocorticoid therapy at admission was the strongest risk factor for death in immunosuppressed COVID-19 patients. We also found that immunosuppression with CNI was not associated with favorable outcomes.

Our results indicate that not all chronic immunosuppressive treatments may be comparable in regard to COVID-19 severity risk, as previously postulated by other authors [Pablos et al., 2020; FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors, 2021]. Of special relevance is the deleterious effect found of chronic glucocorticoid treatment at admission on immunosuppressed patients with COVID-19,

confirming that, in our previous study, the impact of immunosuppressant drugs on mortality was probably attributable to chronic corticoids [Suárez-García et al., 2021]. In our population, patients receiving chronic glucocorticoid therapy prior to hospital admission had similar clinical presentations, but they developed more complications, including severe ARDS, sepsis, AKI and MOF. In addition, mortality rates were clearly higher in patients with glucocorticoids after adjusting for comorbidity and in propensity score-matched analysis. Moreover, when analyzing the different patients subgroups, we found that chronic glucocorticoid treatment was, at least, partly responsible of the higher mortality seen in ISP since it was the strongest risk factor for death. In fact, in our study, patients with IMID who were not on chronic systemic glucocorticoids had a comparable in-hospital mortality to non-immunocomprimised patients. Moreover, among SOT recipients (which had higher in-hospital mortality compared to general non-IS population after adjusting for chronic corticosteroid therapy), chronic corticoid was also associated with and increased risk of mortality and complications.

These results may be shocking, considering that glucocorticoids are, to date, the most effective treatment for this disease [Rodríguez-Baño et al., 2021; Horby et al., 2021]. However, some small series have shown that, when analyzing patients with chronic immunosuppressive medications, patients receiving glucocorticoids seemed to be at higher risk of death than those not receiving them [Ayala-Gutiérrez et al., 2021; Anikhindi et al., 2020; Pablos et al., 2020; Schulze-Koops et al., 2021]. As a matter of fact, higher mortality rates have been found even in patients with chronic inhaled glucocorticoids [Schultze et al., 2020]. It has been described that patients on chronic glucocorticoids have a longer incubation period and present with atypical symptoms [Han et al., 2020], probably due to a decrease in SARS-CoV-2 RNA clearance [Ma et al., 2020]. Besides, some authors have found a harmful effect of glucocorticoid treatment on COVID-19 when they are administered too soon in the disease's clinical course [Li et al., 2020]. This has led to some experts to theorize that glucocorticoids should indeed be administered, but only at the right time [Fernández-Cruz et al., 2020]. Our results support the theory that glucocorticoids should only be prescribed in the inflammatory phase of COVID-19 [Griffin et al., 2021 Ngo et al, 2021], as it

has been demonstrated that patients with chronic glucocorticoids at the initial stages of the infection are at high risk of severe COVID-19, complications, and death

Another point of interest is the hypothesized protective role of calcineurin inhibitors by suppressing SARS-CoV-2 viral replication [Poulsen et al., 2020]. This effect may provide benefits both during the inflammatory and the first phase of COVID-19, where there is a predominance of viral replication [Griffin at Al, 2021, Ngo et al, 2021]. Some authors have reported favorable results treating COVID-19 patients with cyclosporine [Guisado-Vasco et al., 2020, Gálvez-Romero et al., 2021). It has also been reported that chronic CNI treatment prior to COVID-19 may entail a better prognosis [Belli et al. 2021]. However, other studies [Yin et al., 2021] failed to corroborate this finding. Our data also suggest that CNI treatment is not associated with favorable outcomes. Indeed, SOT recipients on chronic immunosuppressive treatment with CNI at admission presented similar in-hospital mortality than those without CNI. The lack of benefic found could be related to the fact that CNI clinically targeted concentration are much lower than the concentrations required to inhibit viral replication [Poulsen et al., 2020, Solanich et al, 2021]. Therefore, these findings supports that immunosuppression with CNI at early stages of COVID-19 is not associated with favorable outcomes.

Additionally, we did not find a higher in-hospital mortality in patients with other immunosuppressive medications, including antimetabolites, methotrexate, mTOR inhibitors, tyrosine-kinase inhibitors, and anti-TNF-alpha monoclonal antibodies. After adjusting for confounding factors, none of these medications were associated with worse outcomes in hospitalized COVID-19 patients. Other authors have also noted that some immunosuppressive medications may not result in more severe COVID-19 disease [Pablos et al., 2021; Schultze et al., 2021; Han et al., 2020]. This may be a result of either the different biological effects of these medications and/or the different baseline characteristics of the patients receiving the different treatments [Suárez-García et al., 2021; Calderón-Parra et al., 2021; Ward et al., 2021].

Our study is based on a large, multicenter cohort and has the strengths inherent to these types of works but it also has several limitations. The main limitation is that the database was not specifically designed to analyze COVID-19 prognosis in ISP. Therefore, some relevant variables, such as immunosuppressive medication management during hospital admission, specific IMID condition, date of transplant in SOT patients, etc., were not available. Secondly, not knowing the cumulative doses of steroids and the dose before the admission were also a pitfall since the risk of death might depend on these [Ward et al., 2021]. Finally, the low number of non-SOT patients treated with CNI limits the external validity of our conclusion regarding this therapy outside SOT recipients. Finally, the paucity of patients treated with some drugs, including mTOR inhibitors, tyrosine-kinase inhibitors, anti-TNF-alpha monoclonal antibodies and anti-CD20 monoclonal antibodies, prevent us from drawing any robust conclusion about the influence of these therapies on COVID-19 clinical outcomes. However, our results emphasize that we should identify and carefully monitor patients at special risk of severe COVID-19 among ISP, which may include SOT recipients and those on chronic glucocorticoid therapy.

In conclusion, immunosuppressed therapies are a heterogeneous group of drugs with different risk profiles for severe COVID-19 and death. While corticosteroids present a well-established benefit during the inflammatory phase in COVID-19, chronic treatment with glucocorticoids at the time of admission entails a special risk of severe COVID-19, complications, and death. On the contrary, chronic CNI treatment at the time of admission does not seem to have any effect on mortality. More studies are needed to clarify the profile of COVID-19 in different immunosuppressed patients and the influence of specifics immunosuppressive drugs on their outcomes.

Potential conflicts of interest. The authors declare no conflicts of interest.

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Ethical Approval Statement. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Provincial Research Ethics Committee of Málaga (Spain) pursuant to the recommendation of the Spanish Agency of Medicines and Medical Products (AEMPS, for its initials in Spanish). All patients gave their informed consent.

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Contributions

- Jorge Calderon: Study concept and design, statistical analysis, interpretation of results, drafting of manuscript, critical revision of manuscript, approval the final version of the manuscript.
- Valentin Cuervas-Mons: Study concept and design, interpretation of results, drafting of manuscript, critical revision of manuscript, approval the final version of the manuscript.
- Victor Moreno-Torres: data acquisition, drafting of manuscript, critical revision of manuscript, approved the final version of the manuscript.
- All other authors: data acquisition, critical revision of manuscript, approved the final version of the manuscript.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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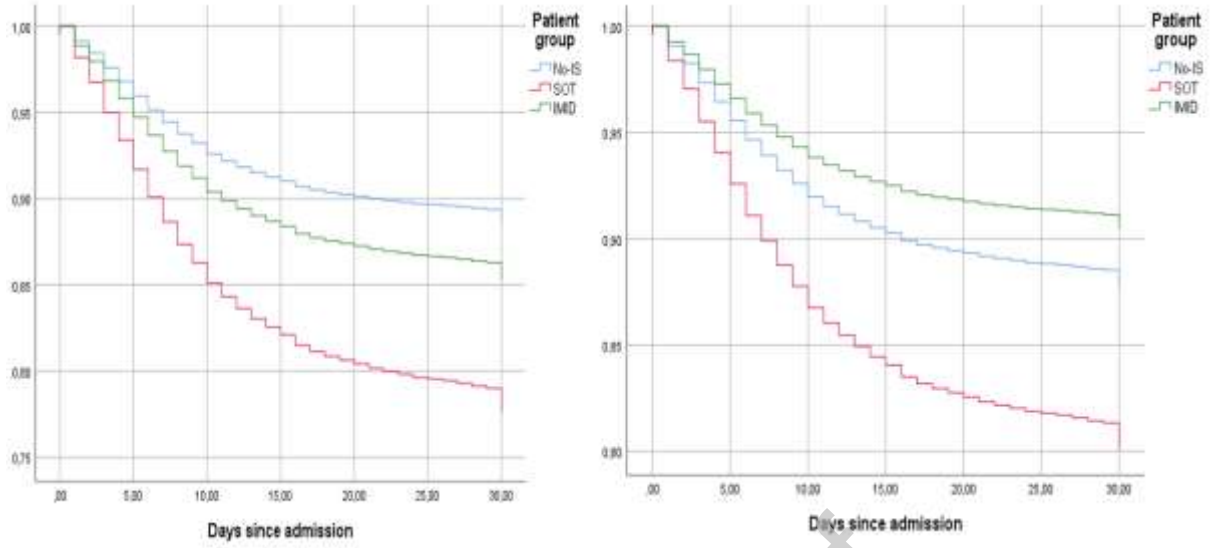

Figure 1: Time-to-death according to patient's group (no-IS, SOT and IMID)

Kaplan-Meier curves was used to shown survival curve and stratified Cox regression was used to estimate hazard ratio and their 95% confident interval. Cox regression models were adjusted for: A: Cox regression model adjusted by sex, age, obesity, cognitive decline, anticoagulation, chronic renal failure, liver cirrhosis, cardiac failure, COPD. HR IMID 1.31 (95% CI 1.11-1.55, p=0.002). HR SOT 2.10 (95% CI 1.63-2.70 p<0.001). B: Model A plus corticoid. HR IMID 0.86 (95% CI 0.76-1.15, p=0.306). HR SOT 1.69 (95% CI 1.23-2.35, p=0.001), HR corticoid 2.00 (95% CI 1.43-2.79, p<0.001).

IS: Immunosuppressed. SOT: Solid organ transplant. IMID: Immune-mediated inflammatory disease. HR: Hazard ratio. COPD: Chronic obstructive pulmonary disease.

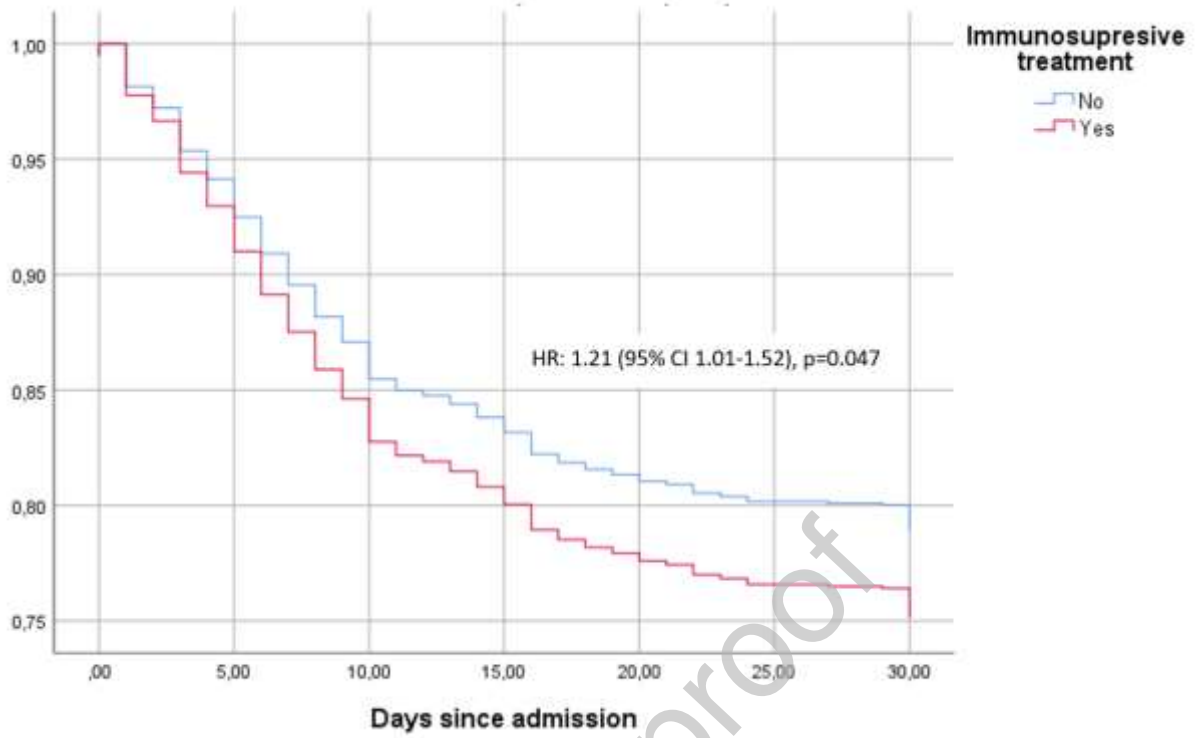

Figure 2: Time-to-death according to patient's group.

Kapplan-Meier curves was used to shown survival curve and stratified Cox regression was used to estimate hazard ratio and their 95% confident interval. HR: Hazard ratio. CI: Confidence interval.

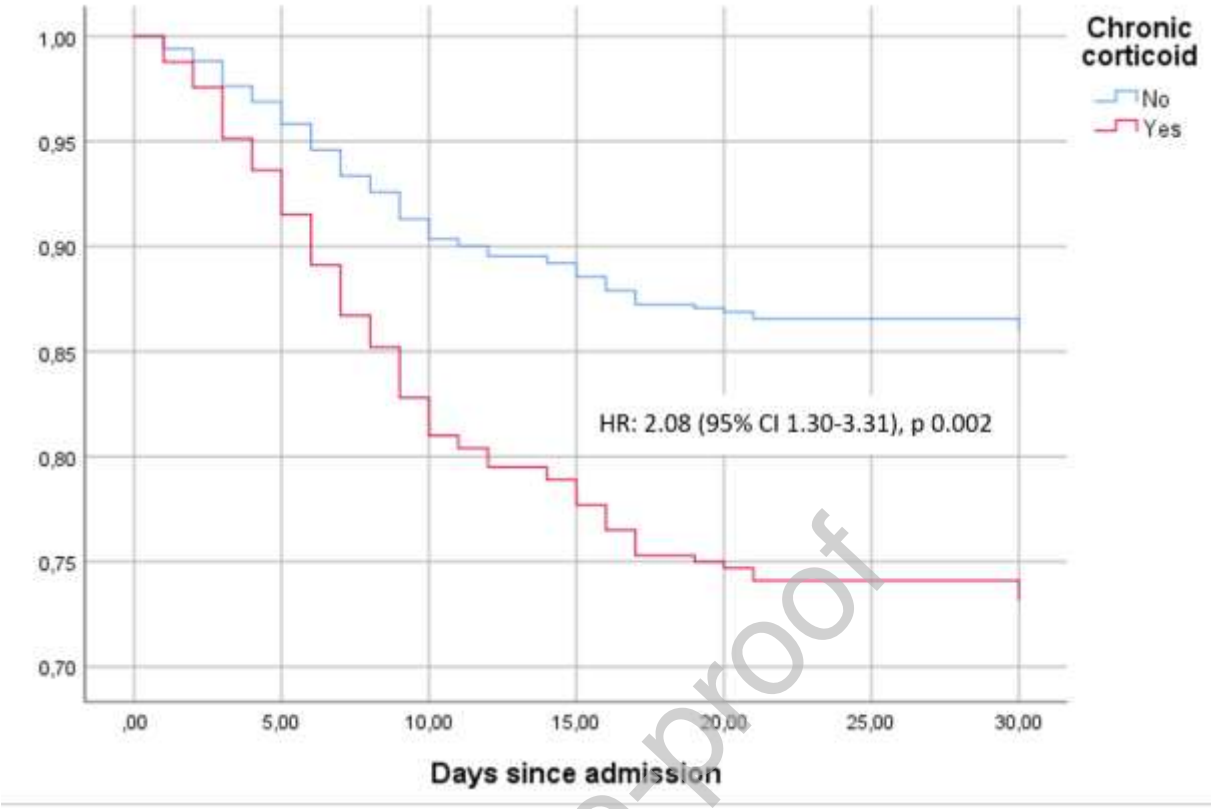

Figure 3. Time-to-death according to chronic corticoid treatment.

Kapplan-Meier curves was used to shown survival curve and stratified Cox regression was used to estimate hazard ratio and their 95% confident interval. Cox regression models were adjusted for other IS treatments (including CNI, mTOR inhibitors, and antimetabolite), none of which showed a significant association with time-to-death.

HR: Hazard ratio. CI: Confidence interval. CNI: Calcineurin inhibitors.

Table 1. Multivariant analysis, by logistic multivariant regression, of association with mortality of demographical factors and comorbidity.

Variable	OR	95% CI
Demographical and comorbidity		
Age	1.08	1.07-1.09
Sex (Female)	0.58	0.52-0.65
Obesity	1.35	1.20-1.53
Charlson Index	1.15	1.09-1.23
Alcoholism	1.10	0.86-1.39
Active smoking	1.05	0.95-1.16
Hypertension	1.10	0.98-1.24
Dyslipidemia	1.04	0.93-1.16
Diabetes Mellitus	1.02	0.89-1.17
Cardiac Failure	1.06	0.88-1.27
Atrial fibrillation	0.84	0.69-1.04
Acute IHD	0.89	0.73-1.10
Chronic IHD	1.11	0.87-1.41
Peri. vasc. disease	1.04	0.83-1.29
COPD	1.15	0.95-1.38
Asthma	0.75	0.60-0.94
Stroke	1.25	0.97-1.61
Cognitive decline	1.32	1.13-1.55
Depression	1.24	1.07-1.45
CRF	1.18	0.93-1.48
Liver Cirrhosis	1.03	0.62-1.68
Anticoagulation	1.30	1.12-1.50
Antiagregation	1.21	1.06-1.39
Model 1		
SOT	2.46	1.73-3.49
IMID	1.38	1.10-1.72
Model 2		
Corticoids	2,24	1,41-3,55
CNI	1,46	0,84-2,54
Methotrexate	0,86	0,45-1,60
Antimetabolite	1,44	0,89-2,34
mTOR	0,78	0,30-1,97

Model 1: demographical factors, comorbidity and patient's group. Model 2: demographical factors, comorbidity and immunosuppressive treatment drug. All demographical and comorbidity variables are included in both models. Adjusted Odds ratio and their 95% confidence intervals (CI) are apported.
IHD: Ischemic heart disease. COPD: Chronic Obstructive Pulmonary Disease. CRF: Chronic renal failure. SOT: Solid Organ Transplantation. IMID: Inmune-mediated inflammatory disease. CNI: Calcineurin Inhibitor.

Table 2. Multivariant analysis, by logistic multivariant regression, of association with mortality of demographical factors and comorbidity.

Variable	OR	95% CI
Demographical and comorbidity		
Age	1.08	1.07-1.09
Sex (Female)	0.58	0.52-0.65
Obesity	1.35	1.20-1.53
Charlson Index	1.15	1.09-1.23
Alcoholism	1.10	0.86-1.39
Active smoking	1.05	0.95-1.16
Hypertension	1.10	0.98-1.24
Dyslipidemia	1.04	0.93-1.16
Diabetes Mellitus	1.02	0.89-1.17
Cardiac Failure	1.06	0.88-1.27
Atrial fibrillation	0.84	0.69-1.04
Acute IHD	0.89	0.73-1.10
Chronic IHD	1.11	0.87-1.41
Peri. vasc. disease	1.04	0.83-1.29
COPD	1.15	0.95-1.38
Asthma	0.75	0.60-0.94
Stroke	1.25	0.97-1.61
Cognitive decline	1.32	1.13-1.55
Depression	1.24	1.07-1.45
CRF	1.18	0.93-1.48
Liver Cirrhosis	1.03	0.62-1.68
Anticoagulation	1.30	1.12-1.50
Antiagregation	1.21	1.06-1.39
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SOT	2.46	1.73-3.49
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Model 2		
Corticoids	2,24	1,41-3,55
CNI	1,46	0,84-2,54
Methotrexate	0,86	0,45-1,60
Antimetabolite	1,44	0,89-2,34
mTOR	0,78	0,30-1,97

Model 1: demographical factors, comorbidity and patient's group. Model 2: demographical factors, comorbidity and immunosuppressive treatment drug. All demographical and comorbidity variables are included in both models. Adjusted Odds ratio and their 95% confidence intervals (CI) are apported.
IHD: Ischemic heart disease. COPD: Chronic Obstructive Pulmonary Disease. CRF: Chronic renal failure. SOT: Solid Organ Transplantation. IMID: Inmune-mediated inflammatory disease. CNI: Calcineurin Inhibitor.

Table 3: Analysis of patients with chronic immunosuppressive treatment at admission, matched by propensity score to non-IS patients.

Variable	IS (n= 636)	Non-IS (n=636)	p	OR	95% CI
Demographical and comorbidity					
Age	70 (59-78)	70 (59-78)	1.000		
Sex (Male)	47.6% (303)	47.6% (303)	1.000		
Obesity	21.2% (135)	21.2% (135)	1.000		
CCI	1 (0-2)	1 (0-2)	0.102		
Age-adjusted CCI	4 (2-5)	3 (2-5)	0.123		
Alcoholism	3.1% (20)	4.4% (28)	0.190		
Smoking	4.1% (26)	5.0% (32)	0.180		
Hypertension	61.6% (392)	61.6% (392)	1.000		
Dyslipidemia	50.0% (318)	43.6% (277)	0.251		
Diabetes mellitus	13.8% (88)	13.8% (88)	1.000		
CHF	8.8% (56)	8.8% (56)	1.000		
Atrial fibrillation	12.9% (82)	12.3% (78)	0.736		
Acute IHD	8.2% (52)	7.7% (49)	0.836		
Chronic IHD	4.1% (26)	3.8% (24)	0.885		
Peri. Vasc. Dis.	8.0% (51)	7.4% (47)	0.753		
COPD	7.9% (50)	7.9% (50)	1.000		
Asthma	8.2% (52)	8.2% (52)	1.000		
Stroke	4.6% (29)	3.0% (19)	0.185		
Cognitive decline	6.6% (42)	6.6% (42)	1.000		

Depression	12.1% (77)	12.5% (79)	0.865		
CRF	10.1% (64)	10.1% (64)	1.000		
Liver cirrhosis	0.8% (5)	0.8% (5)	1.000		
Antiaggregation	21.1% (134)	20.0% (127)	0.627		
Anticoagulation	13.1% (83)	13.1% (83)	1.000		
Clinical presentation					
Cough	70.9% (457)	68.2% (432)	0.210		
Arthromyalgia	27.3% (172)	30.1% (190)	0.290		
Asthenia	43.1% (271)	42.2% (267)	0.776		
Fever	59.6% (378)	57.2% (362)	0.599		
Dyspnea	56.8% (361)	60.4% (382)	0.190		
Diarrhea	26.4% (167)	23.6% (149)	0.270		
Rx infiltrate	63.9% (403)	67.7% (423)	0.342		
Lymphocytes	0.8 (0.5-1.2)	1.0 (6.9-1.4)	<0.001	1.00	1.00-1.01
CRP	62 (22-129)	68 (18-134)	0.687		
LDH	319 (241-433)	327 (240-442)	0.627		
Ferritin	568 (284-1054)	569 (260-1156)	0.912		
D-Dimer	688 (370-1362)	737 (376-1310)	0.487		
Complications and outcomes					
Severe distress	18.7% (119)	20.8% (131)	0.247		
Bact. pneumonia	10.7% (68)	12.6% (80)	0.336		
Sepsis	8.5% (54)	9.0% (57)	0.767		
Septic shock	4.6% (29)	6.8% (43)	0.091	0.83	0.68-1.01
ARI	19.0% (121)	17.6% (112)	0.562		
ACF	7.7% (49)	6.5% (41)	0.444		
Myocarditis	2.2% (14)	1.3% (8)	0.142		

Stroke	0	0.2% (1)	-		
MOF	9.0% (57)	7.2% (46)	0.304		
DIC	1.1% (7)	1.1% (7)	1.000		
ICU admission	7.9% (50)	11.2% (71)	0.045	0.83	0.71-0.98
Hospital mortality	25.0% (159)	21.1% (134)	0.055	1.25	0.99-1.62
COVID-related mortality	93.7% (149/159)	93.2% (123/134)	1.000		

Variables included in propensity score: Sex, Age, hypertension, obesity, CHF, COPD, asthma, liver cirrhosis, CRF, diabetes mellitus, cognitive decline, and anticoagulation. Only exact matched were allowed. Qualitative variables are expressed as percentage (absolute number). Quantitative variables as median (interquartile range). Qualitative variables were compared by Chi2 test. Quantitative variables were compared by Mann-Whitney's U. Odds Ratio and their 95% confident interval are provided for variables with p-value inferior to 0.10

Table 4. Analysis of patients with chronic corticoid treatment at admission matched by propensity score to immunosuppressed patients due to other medications.

Variable	CE (n= 212)	No CE (n=212)	p	OR	95% CI
Demographical and comorbidity					
Age	66 (57-75)	66 (56-75)	0.999		
Sex (male)	53.8% (114)	53.8% (114)	1.000		
Obesity	21.2% (45)	21.2% (45)	1.000		
CCI	1 (0-2)	1 (0-2)	0.190		
Age-adjusted CCI	3 (2-5)	3 (2-5)	0.681		
Alcoholism	3.9% (8)	1.9% (4)	0.234		
Smoking	6.5% (13)	2.5% (5)	0.111		
Hypertension	53.8% (114)	53.8% (114)	1.000		
Dyslipidemia	47.2% (100)	43.4% (92)	0.495		
Diabetes Mellitus	16.6% (35)	13.7% (29)	0.498		
CHF	3.3% (7)	3.3% (7)	1.000		
Atrial fibrillation	5.2% (11)	8.0% (17)	0.328		
Acute IHD	6.6% (14)	3.8% (8)	0.185		
Chronic IHD	4.2% (9)	5.2% (11)	0.819		
Peri. Vasc. Dis.	6.2% (13)	4.7% (10)	0.529		
COPD	10.8% (23)	7.1% (15)	0.173		
Asthma	10.4% (22)	11.8% (25)	0.757		
Stroke	2.4% (5)	0.9% (2)	0.449		
Cognitive decline	3.3% (7)	4.7% (10)	0.622		
Depression	10.9% (23)	14.2% (30)	0.378		
CRF	14.6% (31)	14.6% (31)	1.000		
Liver cirrhosis	1.4% (3)	1.4% (3)	1.000		
SOT	24.1% (51)	24.1% (51)	1.000		
IMID	75.9% (161)	75.9% (161)			
Anticoagulation	7.5% (16)	7.5% (16)	1.000		
Antiaggregation	18.9% (40)	15.2% (32)	0.365		
Clinical presentation					
Cough	71.3% (151)	72.6% (154)	0.699		
Arthromyalgia	29.7% (62)	28.0% (59)	0.747		
Asthenia	42.3% (88)	40.5% (85)	0.766		
Fever	60.7% (128)	62.7% (133)	0.617		
Dyspnea	63.2% (134)	48.6% (103)	0.003	1.82	1.23-2.68
Diarrhea	30.8% (65)	33.0% (70)	0.625		
Rx infiltrate	66.2% (139)	64.5% (135)	0.731		
Lymphocytes	0.8 (0.5-1.1)	0.8 (0.6-1.2)	0.191		
CPR	69 (24-141)	52 (17-111)	0.030	1.01	1.00-1.01
LDH	319 (246-404)	301 (240-389)	0.354		
Ferritin	681 (301-1174)	570 (264-1024)	0.157		
D-Dimer	710 (396-1273)	615 (361-1298)	0.224		
Complications and outcomes					
Severe distress	21.7% (46)	13.7% (29)	0.041	1.75	1.05-2.91
Bact. pneumonia	10.4% (22)	9.0% (19)	0.743		
Sepsis	9.0% (19)	3.7% (8)	0.029	1.99	1.06-4.38
Septic shock	6.6% (14)	1.9% (4)	0.027	3.67	1.19-11.36
AKI	25.0% (53)	12.7% (27)	0.002	2.28	1.37-3.80
AHF	6.1% (13)	3.8% (8)	0.371		
Myocarditis	2.8% (6)	0.9% (2)	0.089	1.51	0.87-5.44

Stroke	0	0.5% (1)	-	-	-
DIC	1.4% (3)	0.5% (1)	0.312		
MOF	7.5% (16)	1.9% (4)	0.012	2.43	1.41-4.26
ICU admission	14.6% (31)	4.7% (10)	0.001	3.46	1.65-7.26
Hospital Mortality	27.8% (59)	14.2% (30)	<0.001	2.34	1.43-3.82
COVID-related mortality	96.6% (57/59)	96.7% (29/30)	1.000		

Variables included in propensity score: Sex, Age, hypertension, obesity, CHF, liver cirrhosis, CRF, and anticoagulation. Only exact matched were allowed. Qualitative variables are expressed as percentage (absolute number). Quantitative variables as median (interquartile range). Qualitative variables were compared by Chi2 test. Quantitative variables were compared by Mann-Whitney's U. Odds Ratio and their 95% confidence intervals (CI) are provided for variables with p-value inferior to 0.10
CCI: Charlson Comorbidity Index. CHF: Chronic heart disease. IHD: Ischemic heart disease COPD: Chronic Obstructive Pulmonary Disease. CRF: Chronic renal failure. SOT: Solid Organ Transplantation. IMID: Inmuno-mediated inflammatory disease. CRP: C-reactive protein. LDH: Lactate Dehydrogenase AKI: Acute kidney injury AHF: Acute heart failure. DIC: Diffuse intravascular coagulopathy.MOF: Multiple organ dysfunction syndrome. ICU: Intensive care unit.