Outcomes of SARS-CoV-2 infection in patients under treatment with pharmacological immunosuppression. A Swiss cohort study.

Keywords

cancer, immunosuppression, autoimmunity, rheumatology, chronic obstructive pulmonary disease, liver disease, COVID-19, SARS-CoV-2, solid organ transplant

Abstract

Introduction
The impact of pharmacological immunosuppression (IS) on COVID-19 outcomes is unclear. This study aimed at investigating the outcomes of hospitalised patients undergoing IS and focussed on length of hospital stay, admission to intensive care unit (ICU) and mortality.

Material and methods
Patients admitted to public hospitals in Southern Switzerland with SARS-CoV-2 infection (n = 442) were prospectively included, and their data were collected and analysed. Immunosuppressed patients were compared to patients from the same cohort but without any IS.

Results
Thirty-five patients (7.9%, 65.7% male, median age 70.6 years) were treated with IS at the time of hospital admission. Compared with patients without IS, immunosuppressed patients showed higher mortality (n = 16 / 35, 45.7% vs n = 95 / 407, 23.3% p = 0.003) and longer hospital stay (median = 15.5 days vs median = 11, p = 0.0144). Moreover, in the univariate and multivariable logistic regression analysis, IS was independently associated with mortality (OR = 2.76 (95%-CI: 1.37-5.59) and 2.66 -95%-CI: 1.19-5.94 -) and in the linear univariate and multivariable regression analysis with the length of stay (p = 0.005 and p = 0.007). Furthermore, patients under IS were more often admitted to the ICU, although the association was not significant (p = 0.069).

Conclusions
Patients under IS were at a significantly higher risk of severe and prolonged COVID-19 disease, with higher mortality and more extended hospital stay than patients without IS.

Explanation letter

Dear Editor,
Thank you for your interest in our manuscript. We received your decision letter, and we thank the referees for their comments. Please find below the responses to the comments brought forth by the reviewers. We have revised our manuscript accordingly, and hope that our revisions satisfactorily address all comments. Moreover, we added some further references, partially of papers already published on Archives of Medical Science, and we thank you for this valuable advice. Please find below our detailed answer (in red) to each referee's comment (in black). Changes on the manuscript are highlight in red.
Best Regards
Antonio Galante
(on behalf the authors of the manuscript)

Reviewer 1:
The paper is interesting and well written. I suggest to improve references adding papers by Ferri et al concerning SarsCov2 and rheumatic diseases and by Murdaca et al concerning SarsCov2, rheumatic

diseases, microbioma and vitamin D

Accordingly, we modified the Introduction paragraph as it follows:

1. ☐"First, a higher prevalence of COVID-19 has been observed in patients with autoimmune systemic diseases, who usually are treated with immunosuppressive medications [20]."

2. ☐"In addition, conditions frequently associated with autoimmune diseases, as vitamin D deficiency and dysbiosis, could have an impact on systemic inflammation, increasing the risk for more severe COVID-19 [29]."

Reviewer 2:

The manuscript "Outcomes of SARS-CoV-2 infection in patients under treatment with pharmacological immunosuppression. A Swiss cohort study" by Galante et al. addressed a critical issue in caring for patients with COVID-19. There were concerns about the evolution of COVID-19 in patients with immunosuppression, and data from the literature are controversial.

The study included 442 patients with COVID-19, and among them, 35 with immunosuppression. Even though this group is small, the study revealed interesting data regarding the lengths of stay and mortality higher in IS patients.

The paper is, in general, well written and needs minor improvements before publishing it:

We answered to the reviewer's comments and applied the suggested changes to the manuscript as it follows.

- Abstract: the methods must include more about what was done in this study;

We agree with her/him that the abstract's methods section had to be implemented. Consequently, although being aware of not exceeding the recommended number of words for this section (250), we modified it as it follows:

"Patients admitted to public hospitals in Southern Switzerland with SARS-CoV-2 infection (n= 442) were prospectively included, and their demographic, clinical, laboratory and treatment data were collected and analysed. Patients under IS at hospital admission or during the six months prior to hospitalisation for a minimum of four weeks were compared to patients from the same cohort but without any history of IS."

- use IS in a uniform way around the manuscript as sometimes the authors used IS, other Immunsupresion or immunosuppression treatment or IS treatment;

We applied the suggested changes to the manuscript.

- correct or complete "Di of IS in ..." on page 5;

Thanks for drawing our attention on this typing error, which has been finally adjusted with: "The distribution of IS in…".

- some English language corrections: see "founded" on page 7 instead of "funded";

We applied the suggested correction to the manuscript.

Besides these minor changes, there should be no more corrections.

Reviewer 3:

"Outcomes of SARS-CoV-2 infection in patients under treatment with pharmacological immunosuppression. A Swiss cohort study." is an interesting paper. I think it only needs a little revision.

Please, move lines 156-161 ("Among comorbidities that are considered relevant in COVID-19"... "the presence of cirrhosis is

associated with higher mortality [31–36]") from Results to Introduction section.

Accordingly, we applied the suggested changes to the Introduction section of the manuscript.

Reviewer 4:

In the present study, the authors assess outcomes of COVID-19 in patients with or without IS treated. Based on their findings, they claim that immunosuppressed patients hospitalised with COVID-19 experience longer hospital stays and higher in-hospital deaths than non-IS patients. Here are some specific concerns the authors should consider to improve the relevance and impact of their study.

We answered to the reviewer's comments and applied the suggested changes to the manuscript as it follows.

1. Too few immunosuppressed patients were included for comparison, which has limitations. It is well established that age and underlying conditions affect the outcome of COVID-19 patients. The age of immunosuppressed patients is higher, and the Number of comorbidities has a higher proportion in immunosuppressed patients, especially diabetes. These factors will affect the outcome of patients to a

certain extent, and a small sample size may lead to biased results.

We agree with the reviewer that the number of immunosuppressed patients included in this study is limited, and older age and more comorbidities could therefore impact on outcome of these patients. However, as already commented in the discussion section, we didn't find any statistically significant differences in age between immunosuppressed and non-immunosuppressed patients. The number of comorbidities is similar in the two groups too, resulting finally in two homogeneous groups although the IS group is much smaller. Nevertheless, diabetes was reported more commonly in patients under IS, although univariate and multivariable logistic regression adjustment for diabetes confirmed IS as independently associated with mortality and length of stay in this group of patients, as reported on the manuscript's results and discussion. However, we agree on this additional limitation of our study, which she/he correctly pointed out. Therefore, we added a further comment to the discussion section of the manuscript, following the indications we received by the reviewer:

"Furthermore, although no significant difference was found in comparison with patients not under IS, patients under IS were slightly older and reported more commonly certain comorbidities as diabetes, which are both known risk factors for more severe COVID-19 disease."

2. Whether the patient has always been hospitalized because of COVID-19, or if the COVID-19 has turned negative but there are complications that require hospitalization.

As by the Materials and Methods paragraph, 2.1. Study design and Setting section, all 442 patients have been hospitalized with symptomatic SARS-CoV-2 infection, confirmed by PCR nasopharyngeal swab at admission.

3. Previous studies provided conflicting results regarding the impact of immunosuppression on COVID-19 outcomes. The author should discuss the reasons for the contradictory results and how this study differs from previous studies.

Following this advice, we have added a further comment in our Discussion in order to better support the relevance of our findings:

"However, looking at overall available data in immunosuppressed patients, which remain conflicting in terms of outcome of COVID-19 with respect to IS, those patients with the most severe disease are more likely to have several concomitant comorbidities and older age, and their outcomes do not relate only to degree of IS. This report brings new added value, first because it is based on information from a fully detailed, multicenter centralised clinical data management system, providing accurate and reliable results. Furthermore, IS was confirmed to be independently associated with worse outcomes also after univariate and multivariable logistic regression adjustments for comorbidities."

4. Treatment with immunosuppressants in patients with concomitant CLD was not associated with worse outcomes. This is also inconsistent with previous studies, which require specific discussion of different reasons.

Concerning patients with CLD, we have added a further comment in our Discussion in order to argument the limited impact of chronic liver disease in our population:

"Although limited information is available on the impact of SARS-CoV-2 infection in patients with CLD, our finding is inconsistent with previous studies, where a higher risk for more severe disease has been described in patients with CLD when compared with patients without CLD [49]. However, individuals with CLD under IS because of underlying autoimmune hepatitis and even liver transplant recipients show comparable outcomes of COVID-19 with matched controls [50,51]. Besides specific considerations regarding the known immune dysregulation in patients with CLD, the severity of COVID-19 in this populations is mostly influenced by comorbidities rather than additional factors like IS. However, because of the very small number of patients with CLD and IS included in our analysis, no inference could be draw."

We hope the above responses adequately address the reviewers' comments. Thank you for your interest in our manuscript, and please let us know if any further changes are required.

Antonio Galante

Reply letter AMS 30062022.docx

Outcomes of SARS-CoV-2 infection in patients under treatment with pharmacological immunosuppression. A Swiss cohort study.

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Abbreviations

BMI	Body mass index
CLD	Chronic liver disease
CNI	Calcineurin inhibitors
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
IS	Pharmacological immunosuppression
MMF	Mycophenolate mofetil
mTori	mTOR inhibitors
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Abstract

Background: The impact of pharmacological immunosuppression (IS) on COVID-19 outcomes is unclear. This study aimed at investigating the outcomes of hospitalised patients undergoing IS and focussed on length of hospital stay, admission to intensive care unit (ICU) and mortality.

Methods: Patients admitted to public hospitals in Southern Switzerland with SARS-CoV-2 infection (n= 442) were prospectively included, and their demographic, clinical, laboratory and treatment data were collected and analysed. Patients under IS at hospital admission or during the six months prior to hospitalisation for a minimum of four weeks were compared to patients from the same cohort but without any history of IS.

Results: Thirty-five patients (7.9%, 65.7% male, median age 70.6 years) were treated with IS at the time of hospital admission. Compared with patients without IS, immunosuppressed patients showed higher mortality (n= 16/35, 45.7% vs n= 95/407, 23.3% p= 0.003) and longer hospital stay (median= 15.5 days vs median= 11, p= 0.0144). Moreover, in the univariate and multivariable logistic regression analysis, IS was independently associated with mortality (OR= 2.76 (95%-CI: 1.37-5.59) and 2.66 -95%-CI: 1.19-5.94 -) and in the linear univariate and multivariable regression analysis with the length of stay (p= 0.005 and p= 0.007). Furthermore, patients under IS were more often admitted to the ICU, although the association was not significant (p= 0.069).

Conclusion: Patients under IS were at a significantly higher risk of severe and prolonged COVID-19 disease, with higher mortality and more extended hospital stay than patients without IS.

1. Introduction

Since its outbreak [1–3], Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has raised concern for immunosuppressed patients usually identified as vulnerable to viral infections [4,5]. Potentially life-threatening SARS-CoV-2 infection complications, including acute respiratory distress syndrome (ARDS), are suspected to be linked with the cytokine storm causing hyperinflammation, hypercoagulability and severe hypoxemia [6,7]. Although the lack of a hyperimmune response to the SARS-CoV-2 may be protective in patients receiving pharmacological immunosuppression (IS), available studies provide conflicting results about the disease course in this group of patients [8–18].

As the pandemic continues to impact the medical management of all categories of patients and the emergence of new variants changes clinical impact and transmissions rates [19], data regarding the outcome of COVID-19 in immunosuppressed individuals are partially controversial. First, a higher prevalence of COVID-19 has been observed in patients with autoimmune systemic diseases, who usually are treated with immunosuppressive medications [20]. Furthermore, these patients seem to be more likely to have a more serious course of disease, even if results differ between cohorts [21,22], whereas the impact of comorbidities, known to affect COVID-19 outcomes negatively, has to be considered [23–28]. In addition, conditions frequently associated with autoimmune diseases, as vitamin D deficiency and dysbiosis, could have an impact on systemic inflammation, increasing the risk for more severe COVID-19 [29]. Finally, data regarding impaired immune responses to anti-COVID-19 vaccines in these populations cause uncertainty in their management and confirm their vulnerability [30,31].

Among comorbidities that are considered relevant in COVID-19, it has been hypothesised that patients with CLD may be particularly prone to severe COVID-19 because of the immune dysregulation associated with this chronic condition [32]. However, published studies provide divergent results regarding CLD impact on COVID-19 disease progression and outcome, although the presence of cirrhosis is associated with higher mortality [33–38]. Accordingly, we focused on this subpopulation of patients for additional analysis.

Therefore, the aim of this study was to assess outcomes of COVID-19 in patients on IS who required hospitalisation, compared to patients without IS treated in the same time period and in the same hospitals. Therefore, we investigated whether IS was associated with the development of severe COVID-19, defined as longer hospitalisation, admission to an intensive care unit (ICU) or death in a cohort consisting of all individuals from Southern Switzerland who were admitted to our institution with confirmed COVID-19.

2. Materials and Methods

2.1. Study design and Setting

We carried out a prospective observational cohort study evaluating 442 patients who were admitted to Ente Ospedaliero Cantonale, the primary health institution in

Southern Switzerland, with confirmed SARS-CoV-2 infection, as determined by PCR nasopharyngeal swabs. Patients were consecutively included from February 25th to May 11th, 2020, with their demographic, clinical, laboratory and treatment information that was daily collected and analysed until death or hospital discharge. Immunosuppressed patients were identified based on whether they were under IS at the time of hospital admission or had received prescriptions for immunosuppressants for at least four consecutive weeks during the six months prior to hospitalisation. Immunosuppressive treatment included cytotoxic agents (chemotherapics, calcineurin inhibitors, mTOR inhibitors, folate antagonists, inosine monophosphate dehydrogenase inhibitors, purine analogues, alkylating agents and Janus kinase inhibitors), interleukin inhibitors, tumour necrosis factor inhibitors, or systemic corticosteroids (with a dosage higher than or equal to 5 mg/day of prednisone or equivalent). Relevant baseline medical conditions such as diabetes, hypertension, and chronic liver disease (CLD) accounted for comorbidities. Clinical outcomes such as length of hospital stay, admission to ICU and mortality were monitored until May 11th, 2020.

2.2. Statistical Analysis

The different random variables between patients with and without IS were compared with the parametric (Student t-test) or the non-parametric tests (Mann-Whitney, Chi-square test or Fisher exact test), as appropriate. To assess the potential role of pre-existing IS on different outcomes (mortality; length of hospital stay; ICU-admission), univariate and multivariable regression models were used. Only random variables with a p-value < 0.1 identified in the univariate analysis were entered in the multivariable models. All tests were performed two-sided, and p-values < 0.05 were considered statistically significant. Statistical analysis was performed using Stata version 15 (StatCorp. LP, College Station, TX, USA).

2.3. Ethical statement

The Ethics Committee approved the study of canton Ticino (Project-ID CE 3743), which was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from all participants.

3. Results

Among 442 adult patients with COVID-19 included in this study, we found 35 patients (7.9%) who were on IS at the time of hospital admission or in the previous six months for at least four consecutive weeks. The median age was 70.6 (IQR 65.9 - 75.4) years, and 23 patients (65.7%) were men, while 407 patients (92.1%) were not under IS at admission nor had a recent history of IS. Immunocompromised COVID-19 patients were older than patients without IS (mean age: 70.6 vs 68.9, p = 0.48), while both groups had higher proportions of male patients (65.7 % vs 61.7%, p = 0.22). Characteristics of patients with or without IS are detailed in Table 1.

The most significant number of patients on IS (n = 19, 54.3%) suffered from autoimmune diseases, while 4 (11.4%) were solid organ transplant recipients, 4

(11.4%) had malignancy, 4 (11.4%) had a chronic obstructive pulmonary disease (COPD), and 4 (11.4%) had other chronic conditions. Oral corticosteroids (n = 30, 85.7%), specifically prednisone or equivalent on a dosage higher than or equal to 5 mg/day, were the most common immunosuppressive medication. Other used immunosuppressants are detailed in Table 1. Among the patients who were still under IS at hospital admission (n = 16/35, 45.7%), 4 (25%) patients underwent reduction or discontinuation of IS. The most common strategy of managing IS at admission was continuing the treatment in 12 out of 16 patients (75%). 14 patients (40%) had received IS six months before admission and were off treatment at the time of hospitalisation. No data regarding IS management were available in 5 patients (14.3%).

Immunosuppressed patients showed similar rates of baseline comorbidities as compared to patients who were off IS (median number of comorbidities = 2 for both groups, p = 0.06), showing a higher incidence of diabetes (n = 14/35, 40% p = 0.01) although BMI was lower in patients under IS (25.8 (23.9-27.7) vs 28 (27.2-28.8), p = 0.10). Compared with patients without IS, immunosuppressed patients showed higher mortality (n = 16/35, 45.7% vs n = 95/407, 23.3% p = 0.003) and a longer hospital stay (median = 15.5 days vs median = 11 days, p = 0.0144), while their admission at ICU was not significantly increased (n = 11/35, 31.4% vs n = 76/407, 18.7% p = 0.069). Moreover, in the univariate and multivariable logistic regression (Table 2), IS was associated both with mortality (OR = 2.76, p = 0.005 and 2.66, p < 0.001) and length of stay (OR = 6.14, p = 0.005 and 5.98, p = 0.007), but not with ICU admission (OR = 2.01, p = 0.08 and 1.88, p = 0.11). No gender differences were observed for mortality in the group of patients under IS (male, n = 10/23, 56.5% vs female n = 6/12, 50% p = 0.71).

Treatment with immunosuppressants in patients with concomitant CLD (n = 8/35, 22.9%), primarily fatty liver (n = 6/8, 75%) and mild disease, only 1/8 being cirrhotic, was not associated with worse outcomes (Table 2). The distribution of IS in this subgroup of patients was similar to the whole group under IS, most patients (6/8, 75%) were on steroids, and one patient each was receiving methotrexate and tacrolimus for previous liver transplantation. However, due to the limited number of patients with CLD within our cohort, no further assertions could be possible.

4. Discussion

In the present prospective observational study, IS in patients with COVID-19 was associated with increased mortality and a more extended hospital stay. Although previous studies provided conflicting results regarding the impact of IS on COVID-19 outcomes, our findings clearly showed that patients on IS were significantly at higher risk of severe and prolonged COVID-19 disease. In our cohort, IS was found to be an independent risk factor for longer hospitalisation and in-hospital mortality from COVID-19.

Managing patients on IS who become infected with SARS-CoV-2 has been challenging since the COVID-19 pandemic began. Specifically, the assumption that poor antiviral immunity in immunocompromised patients entails an increased risk for COVID-19 complications, as seen for other respiratory viruses, diverged from some

initial observations in chronically immunosuppressed patients who showed no association with more severe COVID-19 disease or even protection from SARS-CoV-2 infection due to their reduced immune response [8].

These findings indicate that IS is a risk factor for more severe COVID-19, in line with previously reported results from other patient cohorts suggesting that immunocompromised patients have a higher risk of worse outcomes than the general population [39–44]. However, looking at overall available data in immunosuppressed patients, which remain conflicting in terms of outcome of COVID-19 with respect to IS, those patients with the most severe disease are more likely to have several concomitant comorbidities and older age, and their outcomes do not relate only to degree of IS. This report brings new added value, first because it is based on information from a fully detailed, multicenter centralised clinical data management system, providing accurate and reliable results. Furthermore, IS was confirmed to be independently associated with worse outcomes also after univariate and multivariable logistic regression adjustments for comorbidities.

Confirmation that immunosuppressed patients are more likely to develop a severe disease is relevant to their management and suggests a need for early COVID-19 vaccination in these patient categories [31]. In addition, individualised IS adjustments and prioritisation of COVID-19 treatments for infected subjects on IS, such as monoclonal antibody therapy [45,46], are required. Indeed, immunosuppressed patients with COVID-19 reported longer hospital stays and higher mortality than non-immunosuppressed patients. Nonetheless, patients under IS were more often admitted to ICU due to the severe course of COVID-19, although this finding was not statistically significant.

Due to the broader proportion of patients under corticosteroids, we can assume that poor outcomes were further associated with steroid-based IS. This finding is actually broadly consistent with other published studies [16,39,44,47]. Moreover, most patients in our cohort continued their immunosuppressive medications once admitted. Although the population size is too small to estimate the impact of this strategy adequately, this would suggest that there are no protective benefits of IS in the long term. However, none of the patients in our cohort, who were under IS after solid organ transplantation (4/35), underwent a reduction in IS. This resulted in no rejection episodes during this time and a good outcome, with no ICU admission or death.

In our cohort, we found no significant differences in sex, age and BMI between immunosuppressed and non-immunosuppressed patients, resulting in two homogeneous groups. Male gender confirmed to represent a predictor of higher mortality in hospitalized adults with COVID-19 (Table 2A), and this finding is in line with previous studies [48]. However, further analysis didn't show any gender differences for mortality in the group of patients under IS, more probably because of the small number of patients in this group. Although diabetes was more frequent in patients under IS, applying univariate and multivariable logistic regression adjustments for comorbidities like diabetes, hypertension, and CLD allowed us to confirm IS as independently associated with mortality and length of stay. This observation suggests that IS should always be considered as a risk factor similar to well-known risk factors that favour a more severe disease course. However, in a separate analysis of comorbidities, the presence of CLD was not associated with

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worse outcomes in immunosuppressed patients. Although limited information is available on the impact of SARS-CoV-2 infection in patients with CLD, our finding is inconsistent with previous studies, where a higher risk for more severe disease has been described in patients with CLD when compared with patients without CLD [49]. However, individuals with CLD under IS because of underlying autoimmune hepatitis and even liver transplant recipients show comparable outcomes of COVID-19 with matched controls [50,51]. Besides specific considerations regarding the known immune dysregulation in patients with CLD, the severity of COVID-19 in this populations is mostly influenced by comorbidities rather than additional factors like IS. However, because of the very small number of patients with CLD and IS included in our analysis, no inference could be draw.

Our study includes the following limitations: first, it is a prospective observational study, but it was initially designed to describe COVID-19 in all admitted patients. Therefore, no data were collected to specifically assess immunosuppressed patients, which may have resulted in a significant percentage of missing information. Second, we could include only a small, heterogenous group of patients under IS, which precluded related subgroup analyses (e.g., with respect to type of organ transplant and autoimmune disease, dosage and duration of IS). Furthermore, although no significant difference was found in comparison with patients not under IS, patients under IS were slightly older and reported more commonly certain comorbidities as diabetes, which are both known risk factors for more severe COVID-19 disease. Third, outcomes were analysed in a short-term setting, whereas more information would also be needed on long-term morbidity and mortality in immunosuppressed patients. Forth, the proportion of in-hospital deaths in patients under IS was very high in our cohort. This finding could be attributed eventually to the overloaded healthcare system during the first wave of the pandemic, which might have risen thresholds for admission to the ICU for certain categories of patients as patients with older age and/or severe comorbidities. However, this does not fully explain the higher mortality in our immunosuppressed patients. Indeed, the proportion of patients admitted to the ICU was at least not lower among patients under IS when compared to the patients not under IS. In addition, the management of COVID-19 changed constantly since the period in which our study has been conducted, namely the first pandemic wave. Data suggest now the benefit on mortality of vaccinations and COVID-19 specific therapies, including systemic corticosteroids, tocilizumab, remdesivir and anti-SARS-CoV-2 monoclonal antibodies on the general population [52–54], as well as in immunosuppressed individuals [55]. Finally, although our analyses were adjusted, we cannot completely exclude some residual confounding due to non-measured variables, and the number of testable variables in our multivariable models is limited by the number of patients under IS.

In conclusion, this study provides evidence that immunosuppressed patients hospitalised with COVID-19 experience longer hospital stays and higher in-hospital deaths than non-IS patients. Therefore, the impact of COVID-19 on this vulnerable population remains critical, and further data regarding disease severity and vaccine response are required to improve the management of these patients.

Author contributions

Galante, Terziroli Beretta-Piccoli and De Gottardi developed the concept and designed the study. Ruinelli, Leo and Galante collected data. Pagnamenta, Galante and De Gottardi participated in statistical analysis and interpretation of data. Galante, Terziroli Beretta-Piccoli and De Gottardi wrote the manuscript. All authors contributed to the critical discussion of the results and approved the final version of the article.

Conflict of interest

Funding

Institutional Review Board Statement

The study was approved by the Ethics Committee of the Canton of Ticino (Project-ID CE 3743) and it was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent Statement

Written informed consent was obtained from all participants.

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Table 1. Characteristics of patients sorted by history of pharmacological immunosuppression at admission. Statistically significancy differences are highlighted in bold.

Variable	Total (n= 442)	IS (n= 35)	Non-IS (n= 407)	p-value
Male, n (%)	274 (62)	23 (65.7)	251 (61.7)	0.22
Age, mean (IQR)	69.1 (67.7-70.4)	70.6 (65.9-75.4)	68.9 (67.6-70.3)	0.48
BMI, mean (IQR)	27.84 (27.1-28.6)	25.8 (23.9-27.7)	28 (27.2-28.8)	0.10
Underlying disease responsible for IS (%)				
Autoimmune disease		19 (54.3)		
Solid-organ Transplantation		4 (11.4)		
Malignancy		4 (11.4)		
COPD		4 (11.4)		
Others		4 (11.4)		
Baseline IS (%)				
Steroids (prednisone or equivalent ≥ 5 mg/day)		30 (85.7)		
Mycophenolate mofetil (1 to 2 g/daily)		3 (8.6)		
CNI		2 (5.7)		
mTori		2 (5.7)		
Methotrexate		1 (2.9)		
Comorbidities				
Number of comorbidities, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.06
Diabetes, n (%)	101 (22.9)	14 (40)	87 (21.4)	0.01
Hypertension, n (%)	205 (46.4)	18(51.4)	187 (45.9)	0.53
Chronic liver disease, n (%)	108 (24.4)	8 (22.9)	100 (24.6)	0.05
Outcome				
Death, n (%)	111 (25.1)	16 (45.7)	95 (23.3)	**0.003**
Admission to ICU, n (%)	87 (19.7)	11 (31.4)	76 (18.7)	0.069
Length of stay, median (IQR)	15.1(13.9-16.3)	15.5 (8.71-33.4)	11 (6.8-17.9)	**0.0144**

Abbreviations: BMI, body mass index; IS, pharmacological immunosuppression; COPD, chronic obstructive pulmonary disease; CNI, calcineurin inhibitors; mTori, mTOR inhibitors; ICU, intensive care unit; IQR, interquartile range.

Table 2. Potential risk factors associated with outcome (A. death, B. length of stay) in univariable and in multivariable logistic regression analysis. Statistically significancy comparisons are highlighted in bold.

A. Potential risk factors associated with death as outcome

Variable	Univariate logistic regression		Multivariable logistic regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (male as reference)	1.31 (0.83-2.06)	0.24	1.72 (1.04-2.86)	**0.035**
Age (per year)	1.08 (1.05-1.10)	**< 0.001**	1.07 (1.05-1.10)	**< 0.001**
BMI (per kg/m^2)	1.00 (0.96-1.04)	0.84		
Diabetes	1.96 (1.21-3.17)	**0.006**	0.66 (0.34-1.27)	0.212
Hypertension	1.58 (1.03-2.44)	**0.037**	0.51 (0.29-0.92)	**0.026**
Chronic liver disease	1.44 (0.89-1-33)	0.135		
Number of comorbidities	1.61 (1.37-1.88)	**< 0.001**	1.60 (1.25-2.04)	**< 0.001**
Immunosuppression	2.76 (1.37-5.59)	**0.005**	2.66 (1.19-5.94)	**< 0.001**

B. Potential risk factors associated with length of stay

Variable	Univariate linear regression		Multivariable linear regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (male as reference)	0.96 (-1.47-3.38)	0.78	0.91 (-1.51-3.33)	0.46
Age (per year)	0.034 (-0.06-0.11)	0.61	-0.005 (-0.10-0.09)	0.92
BMI (per kg/m^2)	0.12 (-0.12-0.36)	0.96		
Diabetes	0.90 (-1.91-3.70)	0.63	-0.62 (-4.08-2.83)	0.73
Hypertension	1.89 (-0.47-4.25)	0.12	1.37 (-1.53-4.27)	0.35
Chronic liver disease	2.67(-0.65-5.40)	0.06	3.12 (-0.14-6.39)	0.06

Number of comorbidities	0.60 (-0.22-1.42)	0.16	0.37 (-0.89-1.63)	0.56
Immunosuppression	6.14 (1.82-10.47)	**0.005**	5.98 (1.61-10.35)	**0.007**

Abbreviations: BMI, body mass index; IQR, interquartile range; OR, odds ratio.