

Routine Use of Immunosuppressants is Associated with Mortality in Hospitalised Patients with COVID-19

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Abstract

Background: Whilst there is literature on impact of the SARS viruses in the severely immunosuppressed, and those who develop exaggerated immune response, less is known about the link between routine immunosuppressant use and outcome in COVID-19. Consequently, guidelines on their use vary depending on specific patient populations.

Methods: The study population was drawn from the COPE Study (COVID-19 in Older People), a multicentre observational cohort study, carried out in UK and Italy. Data were collected between 27th February and 28th April 2020 by trained data collectors and included all unselected consecutive admissions with Covid-19. Load (name/number of medications) and dosage of immunosuppressant were collected along with other covariate data. The primary outcome was time-to-mortality from the date of admission (or) date of diagnosis, if diagnosis was five or more days after admission. Secondary outcomes were Day-14 mortality and time-to-discharge (length of stay). Data were analysed with mixed-effects, Cox proportional hazards and Logistic regression models using non-users of immunosuppressants as the reference group.

Results: 1184 patients were eligible for inclusion. The median (IQR) age was 74(62-83), 676(57%) were male, and 299(25.3%) died in hospital (total person follow-up 15,540 days). Most patients exhibited at least one comorbidity, and 113(~10%) were on immunosuppressants. We found that any immunosuppressant use was associated with increased mortality: aHR 1.87,95%CI:1.30,2.69 (time to mortality) and aOR1.71,95%CI:1.01-2.88 (14-day mortality). There also appeared to be a dose-response relationship.

Conclusion: Despite the possibility of indication bias, until further evidence emerges we recommend adhering to public health measures stringently, a low threshold to seek medical advice and close monitoring of worsening symptoms in those who take immunosuppressants routinely regardless of their indication.

Key Messages

What is already known about this subject?

- Many international guidelines recognise the potential increase in risk of COVID-19 infection in those who routinely use immunosuppressants
- Recently published RECOVERY trial showed the benefit of Dexamethasone in severe COVID-19 cases
- However, the potential impact of routine use of these drugs on COVID-19 outcomes independent of other risk factors is associated with poor outcomes.

What does this study add?

- This is the first study to report that routine immunosuppressant use in unselected patients admitted to hospital was associated with increased mortality risk.
- The observed effect sizes are large with a clinically meaningful increase in the risk of in-patient and early (Day 14) mortality with a likely load- and dose-response relationship, in COVID-19 setting.

How might this impact on clinical practice?

- A low threshold to seek medical advice and close monitoring of worsening symptoms should be exercised in those who take immunosuppressants regardless of their indication.

Introduction

SARS-CoV-2 (COVID-19) infection triggers local inflammatory and immune responses in the respiratory tract with resultant release of cytokines and priming of adaptive T and B cell immune responses. In most cases, this process helps to resolve the infection. However, a dysfunctional immune response can occur in some causing systemic damage [1].

Whilst it is well recognised that immunosuppression may render an individual more susceptible to viral illnesses, [2] mild to moderate immunosuppression may have beneficial impact on outcomes of viral illnesses which can cause exaggerated immune response (cytokine storms) such as that caused by SARS-CoV-2 (commonly referred as COVID-19) [3].

The beneficial effect of low dose dexamethasone (glucocorticoids) on survival in severe COVID-19 infection has been reported very recently [4]. Prior to the current pandemic, studies have suggested that using inhaled corticosteroids may be a potentially therapeutic option in viral infections, especially coronaviruses in asthmatic patients, although good quality evidence is lacking. The potential benefit of immunosuppression in such illnesses may stem from their anti-inflammatory effects which could diminish the clinical expression of disease including exaggerated immune response to viral illness.

Therefore, it is not surprising that immunosuppressants usage during the COVID-19 pandemic is the centre of interest from several viewpoints with regard to: [1] susceptibility to viral infection, [2] plausibility of atypical presentation and un-recognised spread of infection, [3] their role as a potential therapeutic option, and [5] their impact on prognosis in people who routinely require some form of immunosuppression for their pre-existing conditions.

Whilst current recommendations are to shield people taking immunosuppressive treatment, this has its own limitation as the level of immunosuppression varies hugely among this population. The RECOVERY trial excluded patients, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial.

Evidence is lacking for those who use immunosuppressants for several conditions and have COVID-19 to a severity which requires hospital and/or intensive care admission. The primary aim of this study is to examine the association between immunosuppressant usage and in-hospital mortality, and length of hospital stay.

Methods

Setting

In order to enable timely collection of data, our existing network of clinical facilities with experience in collecting data for academic and service evaluation purposes Older Persons Surgical Outcome Collaborative (OPSOC; www.opsoc.eu) was utilised, with the addition of one Italian site. Data gathering occurred in ten centres in the United Kingdom (Aberdeen Royal Infirmary, Glasgow Royal Infirmary, Nevill Hall Hospital, Abergavenny, Royal Alexandra Hospital, Paisley, Inverclyde Royal Infirmary, Inverclyde, Royal Gwent Hospital, Newport, Salford Royal Infirmary, Southmead Hospital, Bristol, University Hospital of Wales, Cardiff, and Ysbyty Ystrad Fawr, Caerphilly) and one Italian hospital (University Hospital of Modena Policlinico). Each of these hospitals delivered urgent, in-patient care to patients with COVID-19. Data were gathered between 27th February and 28th April 2020, however UK data collection began on the 6th of March. All methods were carried out in accordance with relevant guidelines and regulations.

Study Design

The COPE study (COVID-19 in Older People study) is a multicentre international observational study co-ordinated by OPSOC and provided this study population. Informed consent was not required due to nature of the project. The Health Research Authority (20/HRA/1898) granted permission to conduct the study in the United Kingdom, and in Italy this was granted by the Ethics Committee of Policlinico Hospital Modena (Reference 369/2020/OSS/AOUMO). Cardiff University sponsored the study.

Routinely recorded hospital data for patients with COVID-19 were collected prospectively using a standardised electronic case report format. This was supplemented by patient paper records, medication prescription charts and information from electronic records as required. All study personnel completed specific data collection training prior to capturing data. This was supervised locally by the site's principal investigator. We adhered to data protection policy in order to record data securely at each site, and each site subsequently transferred anonymised data to King's College London for statistical analysis.

Participants

Consecutive, unselected patients aged 18 years or older who were admitted to hospital with a diagnosis of COVID-19 were included. Diagnosis was made on the basis of laboratory-confirmed SARS-CoV-2 positive swabs, or a clinical diagnosis (made by the clinical team at each site and based on signs, symptoms and/or radiology) consistent with COVID-19. No additional exclusion criteria were applied. In-patient admission lists were screened by clinical teams at each site for eligibility.

Patient and public involvement

No specific patient and public involvement was sought due to nature of the research which requires urgent data collection and analysis.

Exposure

Data on routine use of immunosuppressive agents including number and class of immunosuppressants that each patient was taking prior to admission were collected from admission records. Topical or inhaled immunosuppressants such as corticosteroid creams, enemas and inhalers were not included in this data. Immuno-suppressants were grouped according to their therapeutic action as below:

- Glucocorticoids (e.g. prednisolone, dexamethasone)
- Antimetabolites (e.g. azathioprine, mycophenolate mofetil, leflunomide, methotrexate)
- T-cell inhibitors (e.g. ciclosporin, tacrolimus)
- Monoclonal antibodies (e.g. rituximab, infliximab)
- Cytotoxic agents (e.g. cyclophosphamide, chemotherapy regimens)
- Tyrosine kinase inhibitors (e.g. ibrutinib, afatinib)

Each patient's prescription was then defined as high or low dose for each drug they were taking (Supplementary Table 1). Patients' weights were not recorded in our data, hence where the literature suggested dose ranges in mg/kg we assumed a 70kg bodyweight. Data were collected for patients taking sulfasalazine, mesalazine and hydroxychloroquine, however these are not widely felt to have significant immunosuppressive effects and thus these were coded separately.

Supplementary Table 1 shows each immunosuppressant drug and their high/low dose cut off ranges based on prior studies throughout several specialities and current national guidelines which identify patient cohorts who are at higher risk of COVID-19 infection.

For the purposes of our analyses, we classified patients as having been prescribed any immunosuppressant versus none. In addition, we examined two different dosing variables. First, because it is known that patients on more than one immunosuppressant agent will be at a higher risk of infection due to cumulative effect, we also coded each patient's overall immunosuppressant load as none, low (one immunosuppressant) or high (2 or more immunosuppressants). Second, we examined dose-response as follows: none; low dose (one immunosuppressant at a low or standard dose); moderate/high dose (one immunosuppressant at a high dose, or more than one immunosuppressant).

Covariates

We included variables with prognostic utility which included: patient age group (under 65, 65–79, or 80 years and over); sex; C-reactive protein (CRP) on admission; reduced renal function using estimated glomerular filtration rate (eGFR) on admission; smoking status (never, previous, or current), COPD on admission, frailty, and previous or current history of: coronary artery disease, diabetes mellitus, and hypertension [6][7][8][69]. Frailty was measured using the pre-admission Clinical Frailty Score (CFS) [10]. The CFS is being used as an ordinal hierarchical scale that numerically ranks frailty from 1 to 9, with a score of 1 being very fit, 2 well, 3 managing well, 4 vulnerable, 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail and 9 terminally ill. The CFS has been used globally to aid clinical management [11] and frailty has been found to be independently associated with poorer outcomes in COVID-19 disease [12]. Clinical Frailty Scores were grouped 1–2, 3–4, 5–6 and 7–9 for purposes of the analyses.

End points

The primary end point was the time to mortality from the date of admission (or date of diagnosis, if diagnosis was five or more days after admission). Secondary end points were Day-14 mortality and the time-to-discharge (herein described as the length of stay). For patients with a positive diagnosis of COVID-19 after 5 days from their date of the admission, their length of stay was calculated from the date of diagnosis so as not to be biased by length of stay independent of COVID status. All outcomes were assessed up to 28th April, 2020.

Statistical analysis

Baseline demographic and clinical characteristics were partitioned by mortality, and patients who were prescribed an immunosuppressant versus those without. Time to mortality (primary end point) and length of stay (secondary endpoint) were analysed with mixed-effects multivariable Cox's proportional hazards models. The analyses were fitted with a random intercept to account for hospital variation, and adjusted for the base model of: immunosuppressant prescribed (yes/no; and supplemented by the number of prescribed immunosuppressants); patient age group; sex; smoking status; CRP; diabetes; hypertension; coronary artery disease; reduced renal function (eGFR<60); COPD; and the clinical frailty score. The adjusted hazard ratios (aHR) were estimated with associated 95% confidence intervals (95%CI). The baseline proportionality assumption was tested visually with log-log residuals. Each time to event analysis was reported with a Kaplan Meier survival plot.

The secondary end point of Day-14 mortality was analysed using a mixed-effects multivariable logistic model, fitting each hospital as a random intercept effect, and adjusted with covariates consistent with the primary end point. The adjusted odds ratio (aOR) were estimated and presented with corresponding 95% confidence interval (95%CI). Missing data were explored for patterns of missingness. Subgroup analyses were carried out to explore potentially moderating effects of immunosuppressant use within different subgroups stratified by: age group; sex; smoking status; diabetes; hypertension; coronary artery disease; and renal impairment. Analysis was carried out using Stata version 15 [13] Kaplan Meier survival plots were visualised in R [14], with packages survival [15] (REF) and survminer [16].

Results

A total of 1,184 hospitalised adult patients with COVID-19 were included. Of them 1,121 (94.7%) were diagnosed via laboratory testing by PCR and the remaining 63 (5.3%) via clinical diagnosis only. There were 7 patients taking a single immunosuppressant of unknown dose, whose overall immunosuppression was imputed as 'low' for dose-response analysis. There were 222 cases of missing COPD that were imputed as not cases, 22 cases of missing smoking status, which were imputed as never smokers, and 32 with missing CRP, which were median imputed. There were no more than 14 patients missing for each of the remaining covariates. The complete case population was used within each analysis, and the number included shown as the population under investigation.

Descriptive data

The median (IQR) age of the sample was 74 (62–83) years, and 676 were male (57%). The overall in-hospital mortality rate was 25.3% (299/1184), and this varied between 11.1% and 43.9% between sites (Table 1). The proportion of patients with pre-existing comorbidities were hypertension (52.6%), diabetes (26.3%), coronary artery disease (23.1%), COPD (11.2%) and 36.2% of them had reduced renal function at the time of admission. There were 113 patients who routinely used immunosuppressant constituting 9.5% of the sample (11.2% in women and 8.3% in men) (Supplementary Table 2). Among the immunosuppressant users, corticosteroids were the most commonly prescribed immunosuppressant with 103 prescriptions (91.2% of users), followed by antimetabolites (37 prescriptions; 32.7% of users). With regards to steroids, 84 (74.3% of immunosuppressant users) were prescribed a low-dose, whilst 11

(9.7%) were prescribed a high dose (unknown dose $n = 8$, 7.1%). A full breakdown of immunosuppressant prescription by type and dose are shown in Supplementary Table 3.

Prevalence of immunosuppressant use was more than two-fold among current smokers compared to never smokers (16.7% vs. 8.1%). Of those patients that were not frail (CFS 1 to 4) 8.4% routinely used immunosuppressant compared to 10.7% in those who were frail. Full patient demographics and clinical characteristics are shown in Supplementary Table 2. In patients prescribed one or more immunosuppressants 31.9% and 40.9% died, compared to 24.4% of patients without any immunosuppressants during median (IQR) follow-up of 11 days (5–19) (total person follow-up 15,540 days).

In the crude analysis, it was found that use of any immunosuppressant agent was associated with increased mortality, hazard ratio (95%CI) for time to mortality was 1.74, (1.23–2.46, $p < 0.002$; Table 2). There was also a likely load response: one drug versus none, HR 1.66, 95%CI 1.13–2.46, $p < 0.01$; two or more drugs versus none, HR 2.03 95%CI 1.03–3.98, $p < 0.04$ (see Figure 1). Other important covariates which are known to be associated with an increased mortality in COVID–19 showed expected results. These included: older age (compared to under 65 year olds: patients aged 65–79, HR 3.28, $p < 0.001$; patients aged over 80 years, HR 4.46, $p < 0.001$); CRP (HR 1.003; $p < 0.001$); reduced renal function (HR 2.08, $p < 0.001$); CAD (HR 1.62, $p < 0.001$), hypertension (HR 1.27, $p < 0.05$), COPD (HR 1.67, $p = 0.002$), and frailty (CFS 3–4, HR 2.77, $p < 0.001$; CFS 5–6, HR 3.63, $p < 0.001$; CFS 7–9, HR 5.83, $p < 0.001$) (see Table 2).

In the multivariable analysis, we found that any immunosuppressant use was associated with an increased risk of mortality, aHR (95%CI) for time to mortality was (1.87, 1.30–2.69, $p < 0.001$; Table 2), with a likely load and dose-response: one immunosuppressant (versus none), aHR 1.77, 95%CI 1.18–2.65, $p = 0.006$; two or more immunosuppressants (versus none), aHR 2.29, 95%CI 1.15–4.53, $p < 0.02$; low dose (versus none) aHR 1.88, 95%CI 1.23–2.88, $p = 0.004$; moderate-high dose (versus none) aHR 1.85, 95%CI 1.01–3.37, $p = 0.05$. Of the other covariates, it was also found that frailty (CFS = 3–4, aHR 2.04, 95%CI 1.17–3.57, $p < 0.01$; CFS 5–6, aHR 2.16, 95%CI 1.21–3.88, $p < 0.009$; CFS 7–9 aHR 3.22, 95%CI 1.80–5.77, $p < 0.001$), renal failure (aHR 1.40; 1.08–1.81, $p < 0.01$) and CRP (aHR 1.004, 95%CI 1.003–1.005, $p < 0.001$) also independently increased the risk of mortality.

For secondary endpoints, any immunosuppressant use was associated with a 70% increase in the odds of Day–14 mortality (aOR 1.71, 95%CI 1.01–2.88, $p < 0.04$, Table 3), with a likely load-response (one immunosuppressant, aOR 1.46, 95%CI 0.82–2.61, $p < 0.20$; two or more immunosuppressants aOR 3.34, 95%CI 1.13–9.87, $p < 0.03$), dose-response (low dose, aOR 1.64, 95%CI 0.90–3.00, $p = 0.11$; moderate/high dose, aOR 1.90, 95%CI 0.76–4.80, $p = 0.17$). Day–14 mortality was also associated with: older age (65–75 vs. under 65; aOR 2.91, $p < 0.001$; over 80 vs. under 65; aOR 4.66, $p < 0.001$); CRP (aOR 1.006, $p < 0.001$); reduced renal function (aOR 1.66, $p < 0.005$); and increasing frailty (CFS 3–4 aOR 1.88, $p = 0.08$; CFS 5–6 aOR 2.76, $p < 0.006$; CFS 7–9 aOR 5.74, $p < 0.001$). There was no association between any immunosuppressant use and the time to discharge (aHR 0.92, 95%CI 0.68–1.26, $p < 0.62$). Variables associated with an increased length of hospital stay were older age, higher CRP, and increasing level of frailty (see Table 3).

Supplementary Figures 1–3 show the forest plots demonstrating the adjusted hazards or odds ratios for different age groups, sex, smoking status and four major co-morbidities. Overall, the results are largely consistent and as expected, and those variables which showed point estimates in an un-expected direction showed no statistically significant differences.

Discussion

This study has shown that prior, routine immunosuppressant use in unselected patients admitted to hospital with COVID–19 was associated with increased mortality risk, with a likely load- and dose-response relationship. The observed effect sizes are large with a clinically meaningful increase in the risk of in-patient and day 14 mortality. Whilst the prevalence of immunosuppressant use is higher in women in this study, the mortality risk appears to be more pronounced in men, which is consistent with other COVID–19 studies [17]. We did not find any significant association between routine immunosuppressant usage and length of hospital stay.

The prevalence of routine immunosuppressant use in our sample was approximately 10%. The equivalent figures for general populations vary by countries, perhaps reflecting the different health care systems and challenges in obtaining accurate prescription data nationwide as well as frequency and chronicity of conditions that require use of immunosuppressants (e.g. autoimmune conditions) among the population. US studies estimated 2.7% to 6.2% prevalent use of immunosuppressants among American adults. The former figure came from a study which estimated the prevalence through self-report (2013 data) from NHIS [18] and the latter was derived from the national claims database MarketScan that included 47.2 million unique enrollees, representing 115 million person-years of observation during 2012–2017, and identified immunosuppressive conditions in 6.2% adults 18–64 years of age [19]. Therefore, apparently high prevalence usage of these drugs as routinely prescribed medication in our sample may be related to age and co-morbidity profile of patients admitted to hospitals in UK and Italy.

Guidance on use of immunosuppressant agents during COVID–19 pandemic has been produced by a variety of national bodies and professional societies.

In transplant patients with confirmed or suspected COVID–19, the recommendation is to withhold immunosuppressant agents, with the exclusion of steroids [20]. This recommendation stems from the balance between Cyclophilins' potential antiviral activity inhibition of peptidyl-prolyl isomerase (PPIase) activity [21] vs. their additional immunosuppression. Regarding the use of steroids in transplant patients, guidelines have been based on currently available evidence regarding corticosteroid treatment in COVID–19 which has suggested a possibility that steroid treatment may promote an exaggerated pro-inflammatory response or result in increased viral shedding [22], however following the recent pre-publication results from the RECOVERY trial [4] demonstrating the prognostic benefit of short-term dexamethasone in severe COVID–19 infection, this guidance may evolve.

The National Institute for Health & Care Excellence (NICE) in the UK recommend continuing corticosteroids, hydroxychloroquine, chloroquine, mepacrine, dapson and sulphasalazine in those using these agents for dermatological conditions but to consider temporarily stopping all other oral immunosuppressive

therapies, novel small molecule immunosuppressants, biological therapies and monoclonal antibodies in the event of suspected or proven COVID-19 infection [23], advice which is reflected in guidelines from the American Association of Dermatologists [24].

NICE recommends that patients with rheumatological, autoimmune, inflammatory and metabolic bone disorders are advised to continue with steroids, hydroxychloroquine and sulphasalazine but to temporarily stop other disease modifying anti-rheumatic drugs, JAK inhibitors and biological therapies if they have COVID-19 [25]. The American College of Rheumatology makes similar recommendations but includes sulphasalazine in the drugs that should be temporarily withheld [26]. Hydroxychloroquine has been used to treat COVID-19 cases in hospitalised patients without rheumatological disorders, however a recently reported observational study in NEJM failed to show significant benefit [25].

Current advice on the use of steroids, which were the most commonly used immunosuppressant in this study, and are frequently used for a variety of conditions is somewhat unclear. Many guidelines advise against abruptly stopping steroids [NICE 167, NICE 169, AAD], however some guidelines recommend usual dose [26], or not to increase steroid dosing in mild symptomatic COVID-19 infection, whilst some recommend increasing dose or even giving high dose steroids (methylprednisolone 1mg/kg IV in severe cases) [27]. On the other hand, the British Society of Gastroenterology recommend avoidance of steroids if possible or if not possible "shielding" while prednisolone dose is 20mg or more [28]. The cautious cessation of immunomodulators (azathioprine, mercaptopurine, thioguanine, methotrexate) in stable patients was advised with careful discussion of risk and benefit on a case-by-case basis is currently recommended especially for those >65 or those with significant comorbidity [28].

Given the current uncertainties around the use of these agents during COVID-19 pandemic and lack of evidence of the impact of routine use of these drugs, our study provides novel insight and better understanding into the prognostic value of being a routine user of these agents in hospitalised patients with COVID-19. The findings are particularly important in busy clinical settings on several fronts. First, recognition by clinicians about the clinically important increased mortality risk associated with immunosuppressants should prompt them to carefully and closely monitor the patient's symptoms. Secondly, prognostic information is important for patients and their significant others, especially when hospitalised with COVID-19 infection, and even more so for patients who need immunosuppressant agents for their pre-existing medical condition(s) due to wide general knowledge of concern of impact of these drugs on outcome. Our results provide robust early (Day 14) and in-patient mortality risks associated with COVID-19 infection independently of other known important prognostic indicators including age, sex, frailty, smoking status, major co-morbidities (hypertension, diabetes, renal function, and coronary artery disease) and disease severity marker (CRP). Our results also provide much needed evidence in the literature, which specifically lacks prognostic information generalisable to majority of the population and therefore provide useful new knowledge to prescribers (general practitioners as well as specialists) and guideline developers, committees and panels.

One of the key purposes of this study was to provide much needed evidence with regards to impact of immunosuppressants on prognosis during the pandemic to support clinicians in advising the risk associated with routine use of these medications in their patients. The lessons learned may be particularly relevant and useful for future waves of the pandemic. It appears that in an unselected hospitalised patient population with COVID-19 infection, prior immunosuppression has important prognostic value. We are also first to report dose-response relationship between the number of agents and mortality. We did not observe significant differences in length of stay outcome but this could be biased by early mortality.

Our findings should be considered in the light of a number of limitations. First, we did not collect data on the underlying condition for which immunosuppression was prescribed and were therefore unable to adjust for this, resulting in a the potential for indicator bias. Second, we did not check the compliance but it was likely to be high or very high during the incubation period and aside from corticosteroids, these drugs would be unlikely to be started during a period acute infection. Third, we did not collect detailed information on invasive management and dosing changes (withholding/increasing) of these agents, nor such immunosuppressant usage acutely for those who did not use immunosuppressant agents routinely as advised by some international [29], and local guidelines. Nevertheless, current management of COVID-19 in UK and Europe are somewhat similar, and the internal relationship between the exposure and outcome we observed in this study is unlikely to be affected by this. Fourth, the study has intrinsic limitations associated with any observational study such as indication bias, i.e. the impact of underlying condition requiring immunosuppressant therapy. However, the prospective relationship observed reduces the possibility of reverse causality, and selection bias was reduced by our unselected consecutive data collection methods.

Our study findings should be considered in the context of recently reported RECOVERY trial results which showed benefit of low dose dexamethasone in seriously ill patients with COVID-19 [4]. Some of the patients included in our study also participated in the RECOVERY trial in UK. However, the allocation to trial arms would have happened randomly and thus this would not have major impact on our results. Eligibility criteria for RECOVERY states that if "the attending clinician believes... that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient" [4], which would indicate that patients already prescribed corticosteroids would not be included in this arm of the trial. Further, to be eligible to the trial, participants would require to be suitable for all six different regimens and thus people using immunosuppressants are more likely to be deemed unsuitable for clinical trial participation. Thus, the results in our study may be overestimation of real impact associated with routine use of immunosuppressants.

The study population was predominantly Caucasian, however, there is no reason to believe the relationship between immunosuppressant use and outcome would be differ by ethnicity and thus the results are most likely to be generalisable regardless of ethnicity. Day-14 mortality was chosen over day-7 mortality, as previous studies have demonstrated that the clinical course of COVID-19 disease comprises a longer time to mortality, particularly among patients who are ventilated [30] [31].

It is always possible that inaccuracies may have occurred in data collection, however, training in data collection was provided to all study personnel and the research team are experienced in collecting observation data in frail people from multiple UK sites (www.OPSOC.eu). These factors should have helped minimise bias. Even with a large sample, the proportion of people using the immunosuppressants was relatively low (just over 100) and thus it was not possible to analyse the exposure-outcome relationships for each and individual classes of immunosuppressants. A final limitation is that patients were only

included if admitted to hospital. That will have excluded patients who were discharged from or died in emergency departments, and excluded cases managed in the community. Nevertheless, internal relationships we found between immunosuppressant usage and COVID-19 outcomes is unlikely to be different.

There are several strengths in our study. This was a large, multi-centre prospective study involving front line clinicians to gather a large dataset from patient records (paper form, electronic records or both) which minimised missing data. These data were collected from representative hospitals situated widely across England, Scotland and Wales, and 13% of the sample was derived from Italy. The demographic findings, such as the increased mortality demonstrated with a raised CRP and prevalence rates of comorbidities (hypertension, diabetes and ischaemic heart disease) are also in line with other estimates, suggesting that our data is comparable to other populations.

In summary, using a large unselected cohort of hospitalised adult patients with COVID-19 infection, we found that routine use of any immunosuppressant agents was associated with increased in-patient and early (within day 14) mortality. The effect sizes observed are substantial with almost doubling of poor outcomes. Although this study is limited by indicator bias, our study shows that this patient group is at increased risk of mortality regardless of whether the driver of worse outcomes is the immunosuppressant or the underlying condition for which it is prescribed. We therefore recommend that people who are on these agents for any condition abide by stringent social distancing measures, have a low threshold to seek early medical advice for COVID-19 symptoms and for professionals to be aware of the prognostic impact of these agents and that close monitoring of worsening symptoms should be exercised in those who take immunosuppressants regardless of their indication.

Declarations

Contributorship

JH and KM are PIs of COPE study. PKM conceived the study. AGE and FB-P performed literature search. BC and RS analysed the data. PKM, BC, RS, AGE and FB-P drafted the paper. All authors contributed to data collection, interpretation of results and writing of the manuscript. PKM is the guarantor.

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Competing interest

None for all authors

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Tables

Table 1. Demographic and clinical characteristics, by primary end point of in-patient mortality

	Dead	Alive	Total
Sites	299 (25.3)	885 (74.7)	1,184
Hospital A	15 (13.0)	100 (87.0)	115 (9.7)
Hospital B	14 (28.0)	36 (72.0)	50 (4.2)
Hospital C	34 (22.2)	119 (77.8)	153 (12.9)
Hospital D	10 (23.3)	33 (76.7)	43 (3.6)
Hospital E	15 (12.2)	108 (87.8)	123 (10.4)
Hospital F	23 (14.9)	131 (85.1)	154 (13.0)
Hospital G	36 (32.1)	76 (67.9)	112 (9.5)
Hospital H	108 (43.9)	138 (56.1)	246 (20.8)
Hospital I	43 (24.0)	136 (76.0)	179 (15.1)
Hospital J	1 (11.1)	8 (88.9)	9 (0.8)
Age			
Under 65 yrs	35 (10.0)	314 (90.0)	349 (29.5)
65 to 79 yrs	116 (27.9)	300 (72.1)	416 (35.1)
Over 80 yrs	148 (35.3)	271 (64.7)	419 (35.4)
Sex			
Female	119 (23.4)	389 (76.6)	508 (42.3)
Male	180 (26.6)	496 (73.4)	676 (57.7)
Smoking Status			
Never smokers	142 (22.5)	488 (77.5)	630 (53.2)
Ex smokers	127 (29.1)	309 (70.9)	436 (36.8)
Current smokers	22 (22.9)	74 (77.1)	96 (8.1)
Missing	8	14	22
CRP&&	112, (58-181)	68, (29-136)	79, (33.5-150)
eGFR < 60			
No	135 (18.1)	612 (81.9)	747 (63.1)
Yes	159 (37.1)	270 (62.9)	429 (36.2)
Missing	5	3	8
Hypertension			
No	122 (21.9)	434 (78.1)	556 (47.0)
Yes	174 (27.9)	449 (72.1)	623 (52.6)
Missing	3	2	5
Coronary Artery disease			
No	195 (21.6)	710 (78.5)	905 (76.4)

Yes	101 (36.9)	173 (63.1)	274 (23.1)
Missing	3	2	5
COPD			
No	645 (77.8)	184 (22.2)	829 (70.0)
Yes	89 (66.6)	44 (33.1)	133 (11.2)
Missing	71	151	222
Diabetes			
No	203 (23.4)	665 (76.6)	868 (73.3)
Yes	94 (30.2)	217 (69.8)	311 (26.3)
Missing	2	3	5
Immunosuppressant			
None	261 (24.4)	810 (75.6)	1071 (90.5)
1	29 (31.9)	62 (68.1)	91 (7.7)
2	9 (40.9)	13 (59.1)	22 (1.9)
Clinical Frailty Score (CFS)			
1, Very Fit	4 (4.8)	79 (95.2)	83 (7.0)
2, Fit	15 (10.3)	131 (89.7)	146 (12.3)
3, Managing well	29 (15.4)	159 (84.6)	188 (15.9)
4, Vulnerable	40 (27.8)	104 (72.2)	144 (12.2)
5, Mildly frail	31 (21.7)	112 (78.3)	143 (12.1)
6, Frail	61 (32.3)	128 (67.7)	189 (16.0)
7, Severely frail	70 (36.1)	124 (63.9)	194 (16.4)
8, Very severely frail	35 (51.5)	33 (48.5)	68 (5.7)
9, Terminally ill	11 (45.8)	13 (54.2)	24 (2.0)
Missing	3	2	5

Table 2. Primary End Point: Crude and Adjusted Time-to-mortality, from admission or diagnosis, for patients with a diagnosis five or more days after admission

	Crude Hazard ratio (HR)		Adjusted HR (aHR) ^{&}	
	(n=1,150) ^{&&}		(n=1,136) ^{&&&}	
	HR, (95%CI)	p-value	aHR, (95%CI)	p-value
Immunosuppressant				
None (Ref)	Reference Category		Reference Category	
Any immunosuppressant	1.74 (1.23-2.46)	0.002	1.87 (1.30-2.69)	0.001
One immunosuppressant [^]	1.66 (1.13-2.46)	0.01	1.77 (1.18-2.65)	0.006
Two immunosuppressants [^]	2.03 (1.03-3.98)	0.04	2.29 (1.15-4.53)	0.02
Low - Dose [^]	1.87 (1.19-2.75)	0.003	1.88 (1.23-2.88)	0.004
Moderate/High - Dose [^]	1.61 (0.91-2.84)	0.33	1.85 (1.01-3.37)	0.05
Age				
Under 65	Reference Category		Reference Category	
65 to 79	3.28 (2.20-4.90)	<0.001	2.23 (1.43-3.49)	p<0.001
Over 80	4.46 (2.99-6.65)	<0.001	3.11 (1.95-4.97)	p<0.001
Sex (Female)				
Male	1.01 (0.79-1.28)	0.96	1.14 (0.88-1.48)	0.32
Smoking status (Never)				
Ex-smokers	1.30 (1.01-1.66)	0.04	1.02 (0.79-1.33)	0.86
Current smokers	1.01 (0.64-1.60)	0.97	1.04 (0.64-1.70)	0.88
CRP [§]	1.003 (1.002-1.004)	<0.001	1.004 (1.003-1.005)	p<0.001
Patients with diabetes	1.22 (0.95-1.58)	0.12	1.10 (0.83-1.44)	0.52
Patients with CAD	1.62 (1.26-2.09)	<0.001	1.28 (0.98-1.69)	0.08
Patients with hypertension	1.27 (1.00-1.61)	0.05	1.01 (0.78-1.30)	0.97
Patients with COPD	1.67 (1.20-2.33)	0.002	1.30 (0.91-1.85)	0.14
Patients with reduced renal function	2.08 (1.63-2.64)	<0.001	1.40 (1.08-1.81)	0.01
Clinical Frailty Scale				
CFS 1 to 2	Reference Category		Reference Category	
CFS 3 to 4	2.77 (1.62-4.72)	<0.001	2.04 (1.17-3.57)	0.01
CFS 5 to 6	3.63 (2.13-6.16)	<0.001	2.16 (1.21-3.88)	0.009
CFS 7 to 9	5.83 (3.46-9.84)	<0.001	3.22 (1.80-5.77)	p<0.001

&The multivariable mixed-effects Cox regression was adjusted for: age group; sex; smoking; CRP; diabetes; CAD; eGFR, hypertension; COPD; and the Clinical Frailty Scale

&&34 Cases were not included in the analysis due to patient death on admission.

&&&14 Cases were not included in the analysis due to missing covariate data-see Table 1.

§fitted as a slope parameter

^Fitted in replacement of “Any immunosuppressant” to demonstrate the load and dose response, respectively

Survival is estimated with a crude hazard ratio (HR), and adjusted Hazards Ratio (aHR), using a crude and adjusted mixed-effects multivariable Cox proportional hazards regression.

Table 3. Secondary End Points. Outcome 1: Day-14 mortality (Left panel), and Outcome 2: Length of hospital stay (Right panel)

	Day 14 Mortality		Length of Hospital Stay	
	Adjusted Odds ratio (aOR)^{&}		Adjusted HR (aHR)^{&}	
	(n=1,066) ^{&&&}		(n=1,136) ^{&&}	
	HR, (95%CI)	p-value	aHR, (95%CI)	p-value
Immunosuppressant				
None	Reference Category		Reference Category	
Any	1.71 (1.01-2.88)	0.04	0.92 (0.68-1.26)	0.62
One immunosuppressant[^]	1.46 (0.82-2.61)	0.20	1.03 (0.74-1.44)	0.84
Two immunosuppressants[^]	3.34 (1.13-9.87)	0.03	0.56 (0.26-1.20)	0.14
Low - Dose[^]	1.64 (0.90-3.00)	0.11	1.18 (0.81-1.72)	0.39
Moderate/High- Dose[^]	1.90 (0.76-4.80)	0.17	0.64 (0.39-1.08)	0.09
Age				
Under 65	Reference Category		Reference Category	
65 to 79	2.91 (1.65-5.14)	p<0.001	0.72 (0.57-0.91)	0.005
Over 80	4.66 (2.53-8.58)	p<0.001	0.49 (0.37-0.66)	p<0.001

Sex (Female)	Reference Category		Reference Category	
Male	1.17 (0.82-1.66)	0.39	1.00 (0.83-1.21)	0.99
Smoking status (Never)	Reference Category		Reference Category	
Ex-smokers	0.93 (0.65-1.35)	0.72	0.93 (0.77-1.13)	0.49
Current smokers	0.80 (0.41-1.59)	0.53	0.96 (0.67-1.37)	0.83
CRP [§]	1.006 (1.004-1.008)	p<0.001	0.997 (0.996-0.998)	p<0.001
Patients with diabetes	1.11 (0.76-1.62)	0.60	0.99 (0.80-1.23)	0.92
Patients with CAD	1.19 (0.81-1.74)	0.38	1.19 (0.94-1.52)	0.15
Patients with hypertension	1.06 (0.74-1.51)	0.76	0.84 (0.70-1.01)	0.07
Patients with COPD	1.50 (0.90-2.48)	0.12	0.99 (0.73-1.35)	0.96
Patients with reduced renal function	1.66 (1.17-2.36)	0.005	0.88 (0.71-1.08)	0.22
Clinical Frailty Scale				
CFS 1 to 2	Reference Category		Reference Category	
CFS 3 to 4	1.88 (0.94-3.78)	0.08	1.06 (0.83-1.35)	0.64
CFS 5 to 6	2.76 (1.33-5.71)	0.006	0.71 (0.53-0.95)	0.02
CFS 7 to 9	5.74 (2.75-11.98)	p<0.001	0.67 (0.48-0.93)	0.02

& The multivariable mixed-effects logistic and cox regressions were adjusted for: age group; sex; smoking; CRP; diabetes; CAD; hypertension; COPD; and the Clinical Frailty Scale

&& 104 cases were excluded from the analysis as the patient was followed up for less than 14 Days and alive and in hospital

&& 34 Cases were not included in the analysis due to patient death on admission , and 14 cases were not included in the analysis due to missing covariate data-see Table 1.

^Fitted in replacement of "Any immunosuppressant" to demonstrate the load and dose response, respectively

Day-14 mortality (Left panel), estimated with an adjusted Odds Ratio (aOR) and analysed using an adjusted mixed-effects multivariable logistic model. Outcome 2: Length of hospital stay (Right panel) (measured as the time to discharge from admission, or diagnosis for patients with a diagnosis five or more days after admission), estimated with an adjusted Hazards Ratio (aHR) and analysed with an adjusted mixed-effects multivariable Cox proportional hazards regression.

Figures

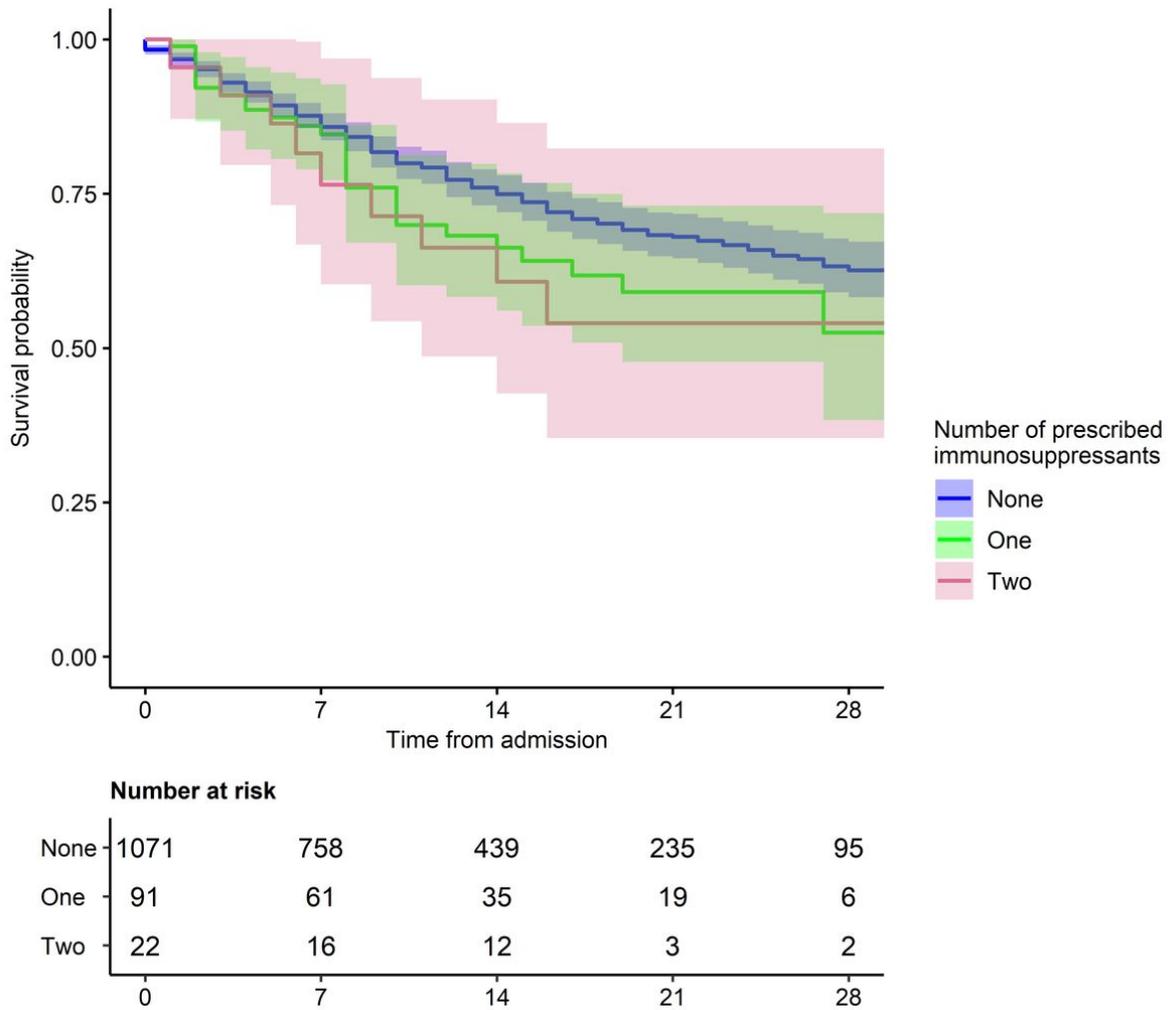


Figure 1
Kaplan Meier Survival plot for patients prescribed with no, one or two immunosuppressants (immunosuppressant load), presented with 95% Confidence intervals.

Supplementary Files

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