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

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Letter to the Editor

Co-infection with SARS-CoV-2 and *Pneumocystis jirovecii* in liver transplant recipients: A double whammy

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Abbreviations

ACLF	Acute-on-Chronic-Liver Failure
AKI	Acute Kidney Injury
BAL	Bronchoalveolar Lavage
BDG	Beta-D-Glucan
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CT	Computed Tomography
CVVHDF	Continuous Veno-Venous Haemodiafiltration
HAT	Hepatic Artery Thrombus
HFNO	High Flow Nasal Oxygen
HRS-AKI	Hepatorenal Syndrome Acute Kidney Injury
ICU	Intensive Care
IgA	Immunoglobulin A
LDH	Lactate Dehydrogenase
LT	Liver Transplant
MMF	Mycophenolate Mofetil
PCP	Pneumocystis Pneumonia
PCR	polymerase chain reaction
P	*jirovecii Pneumocystis jirovecii*
PSC	Primary Sclerosing Cholangitis
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOT	Solid Organ Transplant
TMP-SMX	Trimethoprim-Sulfamethoxazole
V-V ECMO	Veno-Venous Extracorporeal Membrane Oxygenation

Dear editor,

We describe two cases of co-infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and *Pneumocystis jirovecii (P. jirovecii)* in liver transplant (LT) recipients, causing coronavirus disease 19 (COVID-19) and pneumocystis pneumonia (PCP) respectively, during the second wave of the COVID-19 pandemic. Both patients became critically unwell and required intensive care (ICU) admission, with one receiving veno-venous extracorporeal membrane oxygenation (V-V ECMO) for 29 days for refractory type 1 respiratory failure (further clinical details are summarised in **Table 1**).

P. jirovecii is an opportunistic fungus that causes PCP in the immunocompromised, including solid organ transplant (SOT) recipients, and carries a high morbidity and mortality. Studies have suggested it occurs in less than 3% of LT recipients not receiving prophylaxis [1]. In the absence of prophylaxis, PCP risk is highest in the first 6-months post transplantation. Other risks factors include cytomegalovirus (CMV) infection, hypogammaglobulinaemia, lymphopenia, treated graft rejection and increasing age [2].

We report the first two documented cases of concurrent severe COVID-19 and PCP in LT recipients. There are several case reports in the literature describing co-infection in immunocompromised patients, such as those with HIV [3]. One of our cases had multiple risk factors for *P. jirovecii* infection, including timing post-transplant and hypogammaglobulinaemia, and the other was on an anti-metabolite. Whilst both patients have survived 3-months post diagnosis, they remain in ICU, highlighting the grave morbidity associated with severe COVID-19 and PCP co-infection.

Severe COVID-19 and PCP share many clinical characteristics, including profound hypoxaemia and bilateral pulmonary infiltrates on imaging, creating a diagnostic dilemma. A raised beta-D glucan (BDG) and serum lactate dehydrogenase (LDH) should raise suspicion for concurrent PCP [2]. Whilst COVID-19 testing is now readily available via nasopharyngeal swab PCR, PCP is notoriously difficult to diagnose, and gold standard remains via bronchoalveolar lavage (BAL) fluid. The use of steroids in the treatment of severe COVID-19 may further delay PCP diagnosis, due to their favourable effect on PCP leading to transient clinical improvement [3].

Lymphocyte count at time of concurrent PCP diagnosis was 0.36×10^9/L and 0.39×10^9/L in our patients. Lymphopenia is common in SARS-CoV-2 infection [4], and $CD4^+$T lymphocytes play a crucial role in the immune response against *P. jirovecii* [2]. SARS-CoV-2 infection may result in a further functional immune suppression in already immunocompromised LT recipients, increasing the risk of *P. jirovecii* infection.

The incidence and outcome of COVID-19 in LT recipients remain a matter of debate. Nonetheless, vaccination in this patient group is of

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Table 1
Patient characteristics at time of COVID-19 and PCP co-diagnosis and subsequent treatment.

	Case 1	Case 2
Age (years)	28	51
Indication for OLT	Decompensated AIH cirrhosis	Re-do OLT for HAT, initial OLT for PSC
Co-morbidities	T1DM, IgA deficiency, HRS-AKI at time of OLT requiring CVVHDF	CKD, UC (pan-proctocolectomy and ileostomy)
Time post OLT	1 month	8 years
COVID-19 vaccination	No	No
PCP prophylaxis	No	No
Immunosuppression at diagnosis	Basiliximab induction, tacrolimus (trough levels of 6–8μg/L), prednisolone (10 mg/day)	Tacrolimus (trough levels of 2–5μg/L), MMF (750 mg BD)
COVID-19 diagnosis	Positive nasopharyngeal swab PCR	Positive nasopharyngeal swab PCR
PCP diagnosis	Positive BAL PCR	Positive BAL PCR
CT thorax findings	Multifocal peripheral ground glass changes	Multifocal peripheral ground glass changes
BDG level (pg/ml)	266	227
WCC (x 10^9)	13.03	4.71
Lymphocyte count (x 10^9)	0.36	0.39
CRP (mg/L)	32	96
LDH (IU/L)	495	–
COVID-19 treatment	Dexamethasone (6 mg/day) escalated to methylprednisolone (1.5 mg/kg/day) plus remdesivir (200 mg loading then 100 mg/day for 4 days)	Prednisolone (40 mg/day)
PCP treatment	TMP-SMX, switched to primaquine and clindamycin due to pancytopaenia and methylprednisolone (1.5 mg/kg/day)	TMP-SMX, switched to primaquine and clindamycin due to pancytopaenia plus prednisolone (40 mg/day)
Immunosuppression changes	Prednisolone held whilst on IV steroids, low normal trough tacrolimus levels (5–7μg/L)	MMF held
ICU-specific treatment	Intubation and ventilation, V-V ECMO for 29 days, CVVHDF	Intubation and ventilation for 3 days, CVVHDF
3-month outcome	Remains in ICU	Remains in ICU

Abbreviations: AIH, autoimmune hepatitis; BAL, bronchoalveolar lavage; BD, twice daily; BDG, beta-D glucan; CRP, C-reactive protein; CKD, chronic kidney disease; COVID 19, coronavirus disease 19; CT, computed tomography; CVVHDF, continuous veno-venous haemodiafiltration; HAT, hepatic artery thrombus; HRS-AKI, hepatorenal syndrome acute kidney injury; ICU, intensive care unit; IgA, immunoglobulin A; IV, intravenous; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; OLT, orthotopic liver transplantation; PCP, pneumocystis pneumonia; PCR, polymerase chain reaction; PSC, primary sclerosing cholangitis; T1DM, type 1 diabetes mellitus; TMP-SMX, trimethoprim-sulfamethoxazole; UC, ulcerative colitis; VV-ECMO, veno-venous extracorporeal membrane oxygenation; WCC, white cell count.

paramount importance. However, SOT recipients are at risk for lower vaccine immunogenicity, due to impaired immune response, and were excluded from clinical trials. Recent real-world data has revealed lower immunological response, with both reduced serological antibody production (SARS-CoV-2 IgG antibodies against Spike-protein (S)) and antibody titre, amongst LT patients to the BNT162b2 vaccine [5].

We highlight the importance of a high index of suspicion for co-infection with SARS-CoV-2 and *P. jirovecii* in LT recipients. Additional investigations, such as serum LDH, BDG and ultimately BAL, should be considered. With the continuing pandemic, and reduced level of protection vaccination offers LT recipients, co-infection with PCP requires attention. Should further data on co-infection be reported, PCP prophylaxis in LT patients with severe COVID-19, especially with other risk factors, may require consideration given our experience of significant morbidity in this patient cohort.

Conflicts of Interest

The authors of this manuscript have no conflicts of interest to disclose. K.A. was sub-investigator in the Gilead Remdesivir and RECOVERY trial. KA is P.I. of the MK-4482-002 trial (Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19).

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Authors' contribution

V.T.K. is the guarantor of the article. V.T.K. collected the data, and drafted the manuscript with K.A.'s input and supervision. S.P., T.P., V.A. and K.A. edited and revised the manuscript. All authors were involved in the clinical care of the patients described. All co-authors approved the final version of the submitted manuscript.

Consent for publication

Signed consent has been obtained to publish the anonymised clinical details of both patients in this letter.

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