Supplementary Material

Methods

We performed a retrospective single-centre case-control study. Cases were identified using the West of Scotland Electronic Renal Patient Record database to search for all patients followed up by the Glasgow Renal and Transplant Unit who had a laboratory-confirmed positive SARS-CoV-2 polymerase chain reaction test and a functioning kidney transplant at the time of testing, from 1/3/2020 to 19/1/2021.

Controls were obtained using the same database to search for all kidney transplant patients in the unit who had an unplanned presentation to hospital or the renal assessment unit with any other infection from 1/1/2017 to 31/12/2020. Cases and controls were sorted into four groups stratified by place of care; 1) managed in high dependency or intensive care at any stage, 2) managed in the renal inpatient unit but not in high dependency or intensive care, 3) managed in a hospital inpatient unit but not the renal unit and 4) managed entirely as an outpatient. Control patients were assigned and sorted by a random number and they were analysed in sequence for exclusion criteria. Those who did not meet exclusion criteria were included until each place of care grouping had as many control patients as cases.

Cases and controls were analysed for baseline trough $[Tac]_b$ (defined as last $[Tac]_b$ more than 1 week prior to presentation or positive SARS-CoV-2 test), first $[Tac]_b$ after presentation and peak trough $[Tac]_b$ (defined as highest $[Tac]_b$ within 21 days of presentation or initial SARS-CoV-2 test positivity) and the time from symptom onset and presentation/ SARS-CoV-2 positive test to peak $[Tac]_b$. A 21-day period was used so that this would include the incubation period for SARS-CoV-2 infection (average 5-6, but up to 14 days[S1, S2]) and the period at which severe illness usually develops (approximately 7 days after onset of symptoms[S3]). Both groups were also analysed for length of hospital stay, presence of gastro-intestinal (GI) symptoms (vomiting or diarrhoea), presence of acute kidney injury (AKI) (defined by KDIGO 2012 AKI criteria), presence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (above upper limit of normal) and antibiotic usage.

Peak rise in $[Tac]_b$ was expressed as a percentage calculated by [(peak $[Tac]_b$-baseline $[Tac]_b$)/baseline $[Tac]_b$ x 100]. Peak rises were compared between groups using a Wilcoxon rank sum exact test through R statistics software.

Exclusion criteria were; patient not on tacrolimus, no $[Tac]_b$ checked within 21 days from presentation/ positive SARS-CoV-2 test, tacrolimus doses adjusted between peak and baseline $[Tac]_b$, no notes available and $[Tac]_b$ suspected to not be a trough. Medical case records, laboratory system collection times and medication charts were analysed to assess whether $[Tac]_b$ were true troughs.

Supplementary Table 1: Comparison of antibiotics used in the two groups.

	SARS-CoV-2 cases, n	Controls, n
Amoxicillin	9	7
Amoxicillin-Clavulanic acid	2	6
Piperacillin-Tazobactam	5	3
Levofloxacin	2	1
Doxycycline	1	4
Gentamicin	1	2
Temocillin	2	10
Ciprofloxacin	2	5
Metronidazole	1	4
Oseltamivir	0	3
Trimethoprim and Sulfamethoxazole (treatment dose)	0	2

Supplementary table 2: Comparison of changes in tacrolimus blood concentration between the SARS-CoV-2 and Control groups in selected sub-groups.

median % rise to peak $[Tac]_b$ from baseline in	SARS-CoV-2 cases	Control	P value
Outpatients only	23.6	7.8	0.3176
No AST/ ALT elevation	41	26.2	0.1411
AST/ ALT elevation	85.5	n/a	
No GI symptoms	24.1	13.7	0.1785
GI symptoms	104.7	37.1	0.1813

Abbreviations; $[Tac]_b$ – trough tacrolimus blood concentration, AST – aspartate aminotransferase, ALT – alanine aminotransferase, GI – gastrointestinal

Supplementary References

1. World Health Organisation. Coronavirus Disease 2019 (COVID-19): Situation Report – 73. 2020, April. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf. Accessed online 14/6/2021.

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3. Berlin, D. A., Gulick, R. M., Martinez, F. J. Severe Covid-19. New England Journal of Medicine. 2020; 383:2451-2460