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Lithium in the time of COVID: forever vigilant

Frances N. Adiukwu[1,2*], Anastasia K. Yocum[2], Brittany M. Wright[2], Ian Gesler[2] and Melvin G. McInnis[2]

Abstract

Background There have been case reports of renal dysfunction with lithium toxicity among severely ill COVID-19 patients. Lithium levels may be affected by comorbid conditions and the presence of infective disease states like the SARS-CoV-2 which clearly adds systemic health burden. This study aimed to review the effect SARS-CoV-2 has on serum Li levels and the possible mechanism underlying it.

Methods Retrospective data from all clinical service encounters within the University of Michigan health system between September 2019 and September 2023 were reviewed. The study cohort included 98 patients with an average age of 45 years (62% female) who were diagnosed with any subtype of bipolar disorder, actively taking Li, and infected with SARS-CoV-2 during the study timeframe.

Results There was no overarching effect of a SARS-CoV-2 infection on Li chemistry in the overall sample. Higher serum Li levels were not significantly associated with SARS-CoV-2 infection nor total comorbidity index. However, higher Li levels were observed in males while infected with SARS-CoV-2 when compared with no infection. eGFR remained unassociated with serum Li level. Receiving COVID vaccination was associated with lower serum Li levels (*Coeff.* = − *0.88*, *p* = *0.048*).

Conclusions Patients with a diagnosis of BD, treated with Li, and infected with SARS-CoV-2 were not likely to present with elevated Li levels unless they are male or unvaccinated. Elevated serum Li level was not associated with significant renal dysfunction in this cohort. The case reports of severe renal complications and Li toxicity may be among cases of greater overall clinical severity of COVID-19. These findings are reassuring that Li may be used in the context of a COVID-19 illness but emphasize the ongoing need for clinical vigilance.

Keywords Lithium levels, SARS-COV-2, Bipolar disorder, Renal indices

Introduction

Lithium (Li) is an established first-line treatment for bipolar disorder (BD) (Yatham et al. 2018) yet has been a subject of ongoing controversy since the early studies emerged (Blackwell and Shepherd 1968; Schou 1968). The original description of Li use in BD by John Cade (Cade 1949) emerged around the time that reports of severe Li toxicity among cardiac patients who were treated with Li salts as a substitute for sodium were published (Corcoran et al. 1949), unwittingly setting a stage of embroilment fueled in part by marketing campaigns that Li is dangerous; therefore, use alternatives. Enduring anxieties around the narrow therapeutic window remain and are invoked when highlighting the risks and dangers associated with Li therapy, with the unfortunate result of diminished use, e.g., lower prescription rates in America and Europe (Malhi et al. 2023) and low confidence in its use among psychiatry trainees (Rakofsky and Dunlop 2012). This therapeutic inertia notwithstanding, lithium was established in the USA as an anti-manic drug over 40 years ago (Fieve 1977; Burgess et al. 2001) and is recommended as the gold standard for the treatment and maintenance of bipolar disorder (BD) (Bowden et al. 1994; Licht 2012; Yatham et al. 2018). The strengths of Li are manifold and include both anti-manic

*Correspondence:
Frances N. Adiukwu
Frances.adiukwu@uniport.edu.ng
[1] Department of Mental Health, University of Port Harcourt, Port Harcourt, Rivers State, Nigeria
[2] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

and anti-depressive effects, reduction in suicidal behaviors, and as well preventative maintenance management in the long-term care of BD aimed towards sustaining a euthymic mood (Lewitzka et al. 2015; Del Matto et al. 2020). Lithium has also been observed to have neurotrophic, anti-oxidant, and neuroprotective properties, and may reduce cognitive decline (Malhi et al. 2013; Wen et al. 2019). While the precise mechanism of action of Li remains unknown, it is thought to produce its therapeutic effect through its targeting of cellular, intracellular, and molecular pathways that ultimately decrease neuronal excitability (Malhi et al. 2013).

Lithium, like many therapeutic agents, is affected by concomitant illnesses and a range of human conditions from dehydration, fluid imbalance, and cardiac dysfunction, to intercurrent infections (Baird-Gunning et al. 2017). The emergence of any systemic illness in an individual taking Li demands increased therapeutic vigilance with careful monitoring of Li levels, electrolyte panel, and kidney functioning especially with infections that have been associated with negative renal effects. Like the individual side-effect profile of Li, the complications and interactions between systemic illness and Li at the personal level are difficult if not impossible to predict. Once complications manifest, they are easily and logically attributed, but the lack of biologically relevant predictive markers reduces the clinician to subjective empirical statements cached in probability.

The COVID-19 illness caused by the SARS-CoV-2 virus which results predominantly in a respiratory illness presented with a range of clinical manifestations from an insignificant and passing finding of exposure, mild and fleeting respiratory symptoms, to severe illness that led to death in severe cases. It was also found to affect other body systems (Vindegaard and Benros 2020). These included the cardiac, renal, the central and peripheral nervous systems, and the musculoskeletal system (Bridwell et al. 2020; Long et al. 2020; Barrantes 2021). Despite knowledge of the viral sequence emerging very soon after the pathogen was identified, it remained notoriously difficult to predict the course of the illness (Tjendra et al. 2020), regardless of the perceived underlying risk conditions (Galanter et al. 2021). This is further complicated by the fact that people with pre-existing mental health conditions were, frequently but not always, at an overall increased risk for a multitude of health-related disparities including an increased risk of SARS-CoV-2 infection (Moreno et al. 2020; Yocum et al. 2021). A complex pattern ensued. SARS-CoV-2 infection was reported to have a negative effect on psychotropic medication, i.e., drug–drug interactions between psychotropic medications and those used in the treatment of COVID-19 (Ostuzzi et al. 2020). It was found that the SARS-CoV-2 virus has an affinity to the ACE2 receptors of the kidneys (Samavati and Uhal 2020; Fan et al. 2021) and infection resulted in acute kidney injury (AKI), of which in the majority (i.e. not all) of cases is mild, but with elevated creatinine and electrolyte abnormalities. Some cases, SARS-CoV-2 infection resulted in acute tubular necrosis associated with increased mortality for reasons unknown (Liakopoulos et al. 2022). Patients on long-term treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARB) with comorbid SARS-CoV-2 infection had an increased risk of developing acute kidney injury, highlighted the focal point of the ACE receptors (Oussalah et al. 2020). Furthermore, the systemic inflammatory response of SARS-CoV-2 also affects the kidneys (Ostuzzi et al. 2020). Thus, the effect of a SARS-CoV-2 infection on the kidney through any of the various mechanisms above had the potential to alter the serum concentration of psychotropic medication, such as Li, which are primarily excreted through the kidney.

A series of case reports of Li toxicity in patients with BD who developed SARS-CoV-2 infection raised concerns of specific interactions between Li, the SARS-CoV-2 virus, and the kidney (Almadani et al.; Suwanwongse and Shabarek 2020; Pai et al. 2022; McInnis and Yocum 2022; Malyam et al. 2023). The cases represented patients diagnosed with BD, who were maintained on Li at therapeutic doses and levels, and in the context of a SARS-CoV-2 infection, presented in Li toxicity and compromised renal function. Proposed mechanisms included SARS-CoV-2 binding on ACE 2 receptors in the kidney compromising Li excretion (Pai et al. 2022; McInnis and Yocum 2022), presence of systemic immune response causing acute renal injury (Malyam et al. 2023), and the presence of medical and metabolic comorbidities that could precipitate or worsen renal impairment (McInnis and Yocum 2022; Malyam et al. 2023). The need for further study of the relationship between Li, SARS-CoV-2, and its consequences were apparent.

This current study aims to retrospectively examine the influence of comorbidities, COVID-19 infection, and SARS-CoV-2 vaccination on Li treatment and management in individuals diagnosed with Bipolar Disorder (BD). The limited understanding of the mood stabilizing mechanisms of Li, the difficulty in predicting exactly who will experience specific side-effects is further complicated by the variability of the clinical patterns and course of the COVID-19 illness. This investigation examines clinical data of individuals with BD, treated with Li, who developed COVID-19 as diagnosed in a tertiary health system and aims to provide insights that inform clinical decision-making and enhance patient care in the face of evolving healthcare challenges.

Methods

Participants

Patients were drawn retrospectively from all clinical service encounters within the University of Michigan Health System (U-M Health) between September 1, 2019, and September 1, 2023. Participants included 98 patients diagnosed with BD and being managed with Lithium, who during the study time frame had a diagnosis of COVID-19 (SARS-COV-@ infection).

Procedure and assessment

Every clinical encounter, an average of 92 distinct encounters per patient, was gathered and tabulated for the date of SARS-CoV-2 vaccination, SARS-CoV-2 illness, laboratory values including lithium level (log2 transformed), estimated glomerular filtration rate (eGFR), urea, and Charlson comorbidity index total and individual binary presence or absence for Charlson or Elixhauser comorbidity of congested heart failure (CHF), high blood pressure (HBP), diabetes, liver disease and renal disease. Both comorbidity indices, Charlson and Elixhauser, were aggregated for either presence or absence at each encounter and then collapsed when the original index segregated for mild, moderate, severe, complicated or uncomplicated disease. For example, if either hypertension uncomplicated and hypertension complicated was indicated in either Charlson or Elixhauser, that encounter for that patient was positive for high blood pressure.

Statistical analysis

Linear mixed-effects modeling (LMM) was used to predict if serum lithium levels as a response are affected by the fixed effects of SARS-CoV-2 infection, eGFR, urea, age at measurement, sex, Charlson comorbidity index sum, and the random effect of the patient identifier to account for the correlation among repeated measurements within the same patient. To tease out the specific comorbidities contributing to the effect in model above, LMM was used to predict if serum lithium levels were affected by the fixed effects of CHF, liver and renal disease, diabetes, SARS-CoV-2 infection, serum urea, eGFR, age at measurement, gender and random effect of the patient, again to account for the correlation among repeated measurements within the same patient. Lastly, LMM was used again to predict if serum lithium levels as a response are affected by the fixed effects of SARS-CoV-2 infection, SARS-CoV-2 vaccination, sex, age at measurement, and the random effect of repeated patient measurements. In all regression models, missing values are handled by omission; that is observations are removed if they contain any missing values in the regression model variables.

All analyses were completed using the R software (https://cran.r-project.org/) (v4.2.0: Vigorous Calisthenics) using packages dplyr (v1.0.9), stringr (1.5.0), lubridate (1.8.0), lme4 (1.1–34), and lmerTest (3.1–3) for analysis and ggplot2 (v3.3.6), sjPlot (v2.8.10) and ggsignif (0.6.4) for visualizations. All analysis scripts used in this project are available in an open and transparent manner and will be available upon request from the authors.

Results

The study cohort included 98 patients with an average age of 46 years (62% female) who were diagnosed with any subtype of bipolar disorder, actively taking some form of lithium salts, and infected with SARS-CoV-2 at some point during the study timeframe. Four of the 98 patients died during the timeframe studied. Additional demographics are provided in Table 1. The retrospective collection of encounters started on September 1, 2019. For some participants, their first encounter collected was later, after January of 2020, in which they tested positive for SARS-CoV-2. Thus, 12 of the 98 patients tested positive or were diagnosed with SARS-CoV-2 or COVID at their first encounter in this collection. This increased to 100% of the 98 patients by their last encounter. By the end of data collection, September 1, 2023, there were 17 patients not vaccinated for SARS-CoV-2. Eighty-one (82.7%) participants received at least one dose of the SARS-CoV-2 vaccination during the study period with a mean of 2.58 (± 1.62) doses at the end of the study period.

Segregated by sex, male patients on average have a significantly higher level of serum Li (Wilcoxon $p = 0.048$), if infected with SARS-CoV-2, see Fig. 1. The first LMM model, results in Table 2, found that higher serum Li levels were only significantly associated with a slight increase in serum urea levels ($Coeff. = 0.02$, $p = 0.048$). There were no significant findings for COVID-19 infection, serum eGFR, age, sex, nor any comorbidities. Separately, we analyzed the presence of specific medical comorbidities and found no significant associations with serum Li levels. Only participants' higher serum Li levels were again associated with a small increase in serum urea ($Coeff. = 0.02$, $p < 0.001$), Table 3. Finally, receiving SARS-CoV-2 vaccines was associated with lower serum Li levels ($Coeff. = -0.88$, $p = 0.048$) in participants who had SARS-CoV-2 illness (Table 4).

Discussion

In this study, patients with a diagnosis of BD, treated with Li, and who developed SARS-CoV-2 did not result in elevated serum Li levels or significant kidney complications. Only males showed a significant increase

Table 1 Demographic and clinical variables of study participants

	Overall (N = 98)	
Age		
Mean (SD)	46.6 (18.3)	
Median [Min, Max]	46.0 [21.0, 86.0]	
Sex		
Male	37 (37.8%)	
Female	61 (62.2%)	
Ethnicity		
Hispanic	8 (8.2%)	
Non-Hispanic	90 (91.8%)	
Race		
Caucasian	80 (81.6%)	
Non-Caucasian	18 (18.4%)	
Congestive heart failure		
No	92 (93.9%)	
Yes	6 (6.1%)	
High blood pressure		
No	54 (55.1%)	
Yes	44 (44.9%)	
Diabetes		
No	79 (80.6%)	
Yes	19 (19.4%)	
Liver disease		
No	79 (80.6%)	
Yes	19 (19.4%)	
Renal disease		
No	78 (79.6%)	
Yes	20 (20.4%)	
	Start (N = 98)	**End (N = 98)**
COVID infection		
No	86 (87.8%)	0 (0%)
Yes	12 (12.2%)	98 (100%)
COVID vaccination		
No	56 (57.1%)	17 (17.3%)
Yes	42 (42.9%)	81 (82.7%)
Number of COVID vaccinations		
Mean (SD)	0.429 (0.497)	2.58 (1.62)
Median [Min, Max]	0 [0, 1.00]	3.00 [0, 6.00]

in serum Li levels when infected with SARS-CoV-2 compared with males who are not infected. Investigating several hypothesized associations; only serum urea showed a significant positive, yet very little, association with increased serum Li levels. Total number of comorbidities, several individual comorbidities, sex, age, and serum eGFR did not significantly associate with serum Li levels. Importantly, serum Li level was not associated with SARS-CoV-2 infection however the SARS-CoV-2 vaccination status was negatively associated with serum Li levels. That is, serum Li levels decreased with vaccination.

Serum Li levels and SARS-CoV-2 infection

At the group level, linear mixed-effects modelling found no significant effect of the SARS-CoV-2 infection on serum lithium levels, when controlling for covariates, including sex (Table 2). There was, however, a small effect when comparing males and females that suggested elevated Li levels in males while infected vs. the

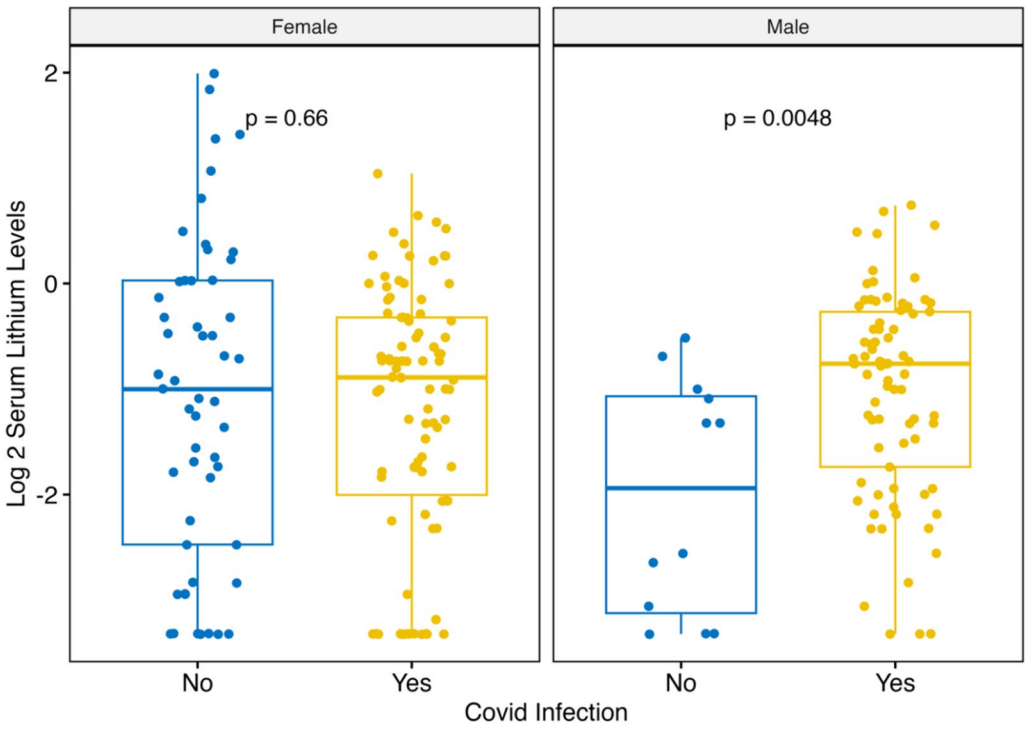

Fig. 1 The relationship between SARS-CoV-2 infection and serum lithium levels

Table 2 Linear mixed effect regression of the effect of SARS-CoV-2 infection, renal function indices, and multiple medical comorbidities on serum lithium level

Coefficient	Log2 lithium levels		
	Estimates	Conf. Int (95%)	P-value
Infection with COVID	0.21	−0.24–0.66	0.359
Serum eGFR	0	−0.01–0.01	0.989
Serum urea	0.02	0.01–0.03	< 0.001
Age at measurement	−0.02	−0.05–0.00	0.051
Sex	−0.25	−0.93–0.43	0.468
Total number of comorbidities	0.06	−0.03–0.16	0.194

Table 3 Linear mixed effect regression of SARS-CoV-2 infection and specific medical comorbidities on serum lithium levels

Coefficient	Log2 lithium levels		
	Estimates	Conf. Int (95%)	P-value
Infection with COVID	0.02	−0.43–0.47	0.925
Congestive heart failure	0.2	−0.68–1.08	0.654
Diabetes	0.27	−0.30–0.85	0.349
Liver disease	0.3	−0.17–0.77	0.211
Renal disease	−0.38	−1.05–0.29	0.268
Serum eGFR	0	−0.01–0.01	0.504
Serum urea	0.02	0.01–0.02	< 0.001
Sex	−0.14	−0.83–0.54	0.68
Age at measurement	−0.02	−0.03–0.00	0.117

non-infected state. These findings are contrary to those of other psychotropic medications during SARS-CoV-2 infection; elevated clozapine serum levels and clinical features of clozapine toxicity were observed in patients when infected with SARS-CoV-2 (Chengappa et al. 2022). Further, a systematic review identified elevated serum levels and evidence of toxicity of Li, clozapine, risperidone, haloperidol, and valproate among patients who subsequently developed COVID-19 of which, the majority of the patients were male (Sabe et al. 2021). The basis for these differences are not clear. The variability of the side-effect profile of Li is considerable, as is the range of clinical illness severity of the COVID-19 disease state. SARS-CoV-2 may act as a third agent, or promoter, in an already unstable system, either severe psychiatric illness and / or near toxic serum drug concentration, thereby exacerbating the already perilous clinical illness (Evans 1982). Other viral infections such as HIV have also been shown to increase the risk of adverse drug reactions (Levy 1997). Viral infections lead to systemic inflammatory states causing acute phase response (Petrovic et al. 2007) which may lead to dysregulation of metabolizing

Table 4 Effect of SARS-CoV-2 infection and vaccination on serum lithium levels

Coefficient	Log2 lithium level		
	Estimates	Conf. Int (95%)	P-value
Infection with COVID	0.03	−0.35–0.42	0.868
Sars-CoV-2 vaccinated	−0.88	−1.75 to −0.01	0.048
Number of Sars-CoV-2 vaccinations	0.18	−0.12–0.49	0.243
Sex	0.05	−0.49–0.58	0.866
Age at measurement	−0.01	−0.02–0.01	0.292

and transport proteins, acute renal injury, and direct liver damage. The variability in clinical states and the inconsistent increased serum levels of psychotropics in people with COVID-19 emphasize the need for closer monitoring of psychotropic medications and clinical vigilance during viral or, most likely, any infectious illness, especially those medications with a narrow therapeutic window (Sabe et al. 2021).

SARS-CoV-2 infection and renal indices

We found at the group level in this study, people with BD and treated with Li, SARS-CoV-2 infection did not negatively affect renal function, i.e. a decline in mean eGFR was not observed, however a slight, but significant, increase in serum urea was found. Trabulus et al., found that impaired renal function (defined as eGFR < 60 ml/min) was found in only 18.2% of COVID-19-diagnosed in-patients at admission baseline (Trabulus et al. 2020). A second study reported 63% of in-patients with COVID-19 had eGFR values > 60 ml/min, and that the patients with impaired renal function (< 60 ml/min) had a history of chronic kidney disease *before* the SARS-CoV-2 infection, and evidence of AKI was present in approximately 10% of all study participants (Mirijello et al. 2021). Further, impaired renal function was associated with older age, polypharmacy, and the presence of other medical comorbidities. (Trabulus et al. 2020; Mirijello et al. 2021). In our results, total number comorbidities, shown in Table 2, as well as specific renal disease comorbidity, shown in Table 3, was not significantly associated with higher serum Li levels. This implies a complex interaction between the pre-COVID-19 health status, the systemic effects of SARS-CoV-2 infection, and the serum Li levels, resulting in difficulties establishing causality. The lack of reliable predictable markers emphasizes the importance of clinical vigilance and a complete understanding of prior renal comorbidity for those on Li and SARS-CoV-2 infection.

Lithium is excreted largely unchanged through the kidneys and as a result, may have the potential for renal side effects. The most common renal side effect is polyuria which is due to the association of Li with nephrogenic diabetes insipidus (NDI) which decreases renal concentrating ability. The risk of NDI in Li users is increased with longer duration of Li use, frequent number of episodes of Li toxicity, concomitant use of antipsychotics, and high serum Li levels (Gitlin and Bauer 2023). With time, Li use may be associated with chronic tubulointerstitial nephritis resulting in decreased glomerular filtration rate (eGFR) (van Melick et al. 2008; Schoot et al. 2020). The controversies around Li and chronic kidney disease (CKD) remain, and while it has been long clear that CKD is associated with Li use (Fieve 1977), the continuation of Li even in the context of established CKD does not convincingly lead to end-stage kidney disease (Clos et al. 2015). Further, when age and medical comorbidities are taken into account, the evidence to link Li use to end-stage renal disease (ESRD) remains controverted (McKnight et al. 2012; Aiff et al. 2014; Clos et al. 2015; Gitlin 2016; Nielsen et al. 2018).

In the current sample, increases in urea were associated with a minimal increase in serum Li levels. No other index of renal function such as eGFR, had significant effects on serum Li levels when we controlled for age, SARS-CoV-2 infection, and the presence of medical comorbidities. This finding indicates that overall, an elevated serum urea level was not the result of impairment in renal function. Variability in serum urea levels between and within individuals can arise from non-intrinsic renal causes that lead to changes in renal perfusion such as fever, vomiting, and diarrhea (Gitlin 2016) which are common and early symptoms of COVID-19 (Larsen et al. 2020; Trabulus et al. 2020; Alimohamadi et al. 2020).

Serum Li levels and COVID vaccination

We investigated the effect of SARS-CoV-2 vaccination on serum Li levels and found that patients who received vaccination had lower serum Li levels. SARS-CoV-2 vaccinations have been shown to decrease illness severity (use of an invasive mechanical ventilator and progression to death) as well as the rate of hospitalization among vaccine breakthrough infections compared to the absence of vaccination (Tenforde et al. 2021, 2022).

Strengths and limitations and implications of findings

Using a retrospective study design, we were able to look at multiple measurements within patients and between patients providing evidence on the relative safety of Li in the treatment of BD during an acute systemic infective illness, specifically with SARS-CoV-2.

However, our study is limited by a small sample size, narrow socio-demographic diversity, and inability to draw causal inferences. There were substantially fewer males compared to females. The data are drawn from medical records with the range of challenges therein, patients receiving partial care, vaccinations, or management in other systems, i.e. a comprehensive clinical picture of many patients may be missing. We were unable to account for several confounding factors such as the severity of SARS-CoV-2 infection and the nature, severity, complications of, and treatment for medical comorbidities present. The sample included only those BD individuals who were *actively* receiving lithium *and* diagnosed with SARS-CoV-2 during the time frame of the study. It did not include those for whom Li was immediately discontinued in the management of severe SARS-CoV-2 (McInnis and Yocum 2022). The patient group for whom Li was continued through the SARS-CoV-2 illness may represent a moderate or lower illness severity. This is supported by the observation that the eGFR was relatively stable.

Conclusion

In conclusion, this retrospective study using the electronic health record investigated the interplay between comorbidities, SARS-CoV-2 infection and vaccination status effect on serum lithium concentrations among patients diagnosed with BD. In the subset of patients studied, those with BD, taking Li, and diagnosed with COVID-19, the study did not confirm that SARS-CoV-2 infection increases the toxicity of Li, nor did it test any potential protective effect of Li on infection occurrence. However, severely ill patients in previous case reports had Li discontinued at the onset of medical treatment. This study shows that Li serum levels, beyond a slight positive association with serum urea, does not associate with another renal insufficiency measure, eGFR, nor comorbid renal disease in this patient cohort. We conclude that the BD patient who becomes infected SARS-CoV-2 (or any infective condition) should be monitored with increased vigilance as it is impossible to predict who will experience severe forms of the infection. In severe conditions, the case reports clearly delineate a range of complications that may be associated with disrupted Li chemistry and kidney function. In the case of BD individuals that are exposed to SARS-CoV-2 and continue Li, the overall impact appears to be modest and can be managed with careful vigilance.

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Author contributions
Frances Adiukwu (FA): supervision, writing—original draft, writing—review and editing. Anastasia K. Yocum (AKY): data curation, formal analysis, methodology, writing—review and editing, visualization. Brittany M. Wright: data curation. Ian Gesler (IG): writing—original draft. Melvin G. McInnis (MGM): resources, writing—review and editing, funding acquisition, project administration, and supervision.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to privacy restrictions, but are available, deidentified, from Melvin G. McInnis (mmcinnis@med.umich.edu) upon reasonable request.

Declarations

Ethics approval and consent to participate
The IRBMED, HUM00227871, approved secondary use of the electronic medical record data, which includes Waiver of Informed Consent (45 CFR 46.116), for secondary use of the electronic medical record data. This study is in accordance of US Department of Health and Human Services, 45CFR Part 46, Common Rule Signatory.

Competing interests
MGM has consulted for Janssen and Otsuka Pharmaceuticals and received research support from Janssen. All other authors report no conflicts related to this work.

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