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Inflammatory and blood gas markers of COVID-19 delirium compared to non-COVID-19 delirium: a cross-sectional study

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ABSTRACT

Objectives: We aimed to find the association of inflammation and respiratory failure with delirium in COVID-19 patients. We compare the inflammatory and arterial blood gas markers between patients with COVID-19 delirium and delirium in other medical disorders.

Methods: This cross-sectional study used the CHART-DEL, a validated research tool, to screen patients for delirium retrospectively from clinical notes. Inflammatory markers C-reactive protein (CRP) and white cell count (WBC), and the partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2) were compared between patients with COVID-19 delirium and delirium in other medical disorders.

Results: In bivariate analysis, CRP (mg/L) was significantly higher in the COVID-19 group, (81.7 ± 80.0 vs. 58.8 ± 87.7, $p = 0.04$), and WBC (10^9/L) was significantly lower (7.44 ± 3.42 vs. 9.71 ± 5.45, $p = 0.04$). The geometric mean of CRP in the COVID-19 group was 140% higher in multiple linear regression (95% CI = 7–439%, $p = 0.03$) with age and sex as covariates. There were no significant differences in pO_2 or pCO_2 across groups.

Conclusion: The association between higher CRP and COVID-19 in patients with delirium may suggest an inflammatory basis for delirium in COVID-19. Our findings may assist clinicians in establishing whether delirium is due to COVID-19, which may improve management and outcomes of infected patients.

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Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection principally causes respiratory symptoms and fever when symptomatic. However, coronavirus disease 2019 (COVID-19) is considered a systemic disease with a complex pathophysiology, involving the ear, nose and throat, gastrointestinal, nervous and ocular systems (Grant et al., 2020).

Delirium is the most common acute neuropsychiatric condition in COVID-19 (Mcloughlin et al., 2020). According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, it is defined as a disturbance in attention and awareness with altered cognition developing over a short period of time with an identified organic cause, not better explained by another neurocognitive disorder or coma (American Psychiatric Association, 2013).

Incidence of delirium during hospital admission in COVID-19 patients compared to non-COVID-19 patients is relatively high on acute hospital wards (30% vs 18–35% respectively) and intensive care units (ICUs) (over 50% vs 32% respectively) (Emmerton & Abdelhafiz, 2020; Hawkins et al., 2021; Inouye et al., 2014; Salluh et al., 2015). Altered mental status and fluctuating levels of consciousness manifest following many acute infections (Kuswardhani & Sugi, 2017; Toovey, 2008). However the particularly deliriogenic nature of COVID-19 infection has meant new-onset delirium may be predictive of COVID-19 infection across both primary and secondary care, as it can be the sole symptom of infection in older patients (GOV.UK, 2020; Poloni et al., 2020; Zazzara et al., 2021).

Delirium in COVID-19 is associated with poorer outcomes, including a longer requirement for mechanical ventilation, a greater duration of ICU and hospital admission (Garcez et al., 2020; Kenerly et al., 2021; Khan et al., 2020), poorer physical function (Mcloughlin et al., 2020) and increased mortality (Garcez et al., 2020; Kenerly et al., 2021; Marengoni et al., 2020; Poloni et al., 2020; Rebora et al., 2021; Zerah et al., 2021). More widely, delirium is also associated with both an increased future risk of dementia and further neurocognitive decline in surviving patients (Davis et al., 2017; Fong et al., 2009). This is concerning given the large number of individuals infected with COVID-19.

The interaction of acute stressors such as systemic inflammation, respiratory failure, multiple organ failure, neurotransmitter imbalances and dehydration (Butterworth, 1999; Maldonado, 2018) on a background of predisposing risk factors such as old age, frailty, dementia and certain medications (Tay & Harwood, 2020; Vasilevskis et al., 2016) is known to be of key importance in precipitating delirium (Wilson et al., 2020). Systemic inflammation and respiratory failure are also known to correlate with severity of COVID-19 disease, which typically leads to a higher incidence of delirium (Asghar et al., 2021; Huang & Pranata, 2020; Izcovich et al., 2020; Santus et al., 2020; Zeng et al., 2020). Recently C-reactive protein (CRP) has also been associated with an increased risk of delirium in COVID-19 (Pranata et al., 2021). It is possible that these factors may be more associated with COVID-19 delirium to a greater extent than just severity of COVID-19 infection.

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This study aimed to ascertain whether delirium in COVID-19 is more associated with peripheral markers of inflammation and respiratory failure compared to delirium in other conditions. This may determine how COVID-19 increases the risk of delirium compared to other known causes, and whether there are unique or distinct pathophysiological features of delirium specific to COVID-19. Our objectives were:

1. To compare serum C-reactive protein (CRP) and total white cell count (WCC) between patients with COVID-19 delirium and delirium in the context of other disorders; and
2. To compare the partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) between patients with COVID-19 delirium and delirium in the context of other disorders.

Methods

We conducted a cross-sectional electronic record review to identify the differences in inflammatory and blood gas markers of patients with delirium with or without a diagnosis of COVID-19 at King's College Hospital (KCH), a large teaching hospital in South East London. We compared CRP, WBC, PO_2 and PCO_2 in patients with delirium in the context of COVID-19 to patients with delirium in the context of other medical disorders. The study was part of a quality improvement project aiming to improve identification and treatment of delirium in COVID-19 patients, which was approved by the South London and Maudsley NHS Foundation Trust Quality Improvement Department. This manuscript was written in accordance with the STROBE statement for cross-sectional studies (STROBE, 2021).

Selection criteria

Selection was carried out from an existing dataset of the 647 patients referred to KCH inpatient liaison psychiatry between 2/3/2020 and 10/5/2020, as described in a previous paper (Butler et al., 2021). From this dataset, patients were divided into two cohorts based on COVID-19 status, determined by reverse transcription polymerase chain reaction of a nasopharyngeal swab during hospitalisation. Patients with no recording of a swab were excluded.

The cohorts were retrospectively screened for delirium using the CHART-DEL (Chart-based Delirium Identification Instrument), a widely used and validated research tool for detecting the presence of delirium from analysis of patient notes (Helfand et al., 2021; Inouye et al., 2005). The CHART-DEL has a higher sensitivity than relying on clinical diagnosis, which is known to underestimate delirium prevalence and incidence in COVID-19 patients (Mcloughlin et al., 2020). The inclusion criteria were: admission to KCH between 2/3/2020 and 10/5/2020; SARS-CoV-2 PCR nasopharyngeal test result during admission; and probable or definite delirium within one week before or after the SARS-CoV-2 test result. According to the CHART-DEL, patients were described as having 'definite' delirium if a diagnosis in the patient notes was made by an experienced reference standard rater and 'probable' delirium if they showed evidence of all four Confusion Assessment Method (CAM) features within the notes: acute onset/fluctuation, inattention, disorganized thinking and altered of consciousness. The CHART-DEL assessment was performed on patient notes from seven days prior to seven days after recorded SARS-CoV-2 swab tests were taken. Patients were excluded if they did not meet the criteria for probably or definite delirium, or they did not have a result from a SARS-CoV-2 PCR test. Investigators underwent training for the use of the CHART-DEL alongside an experienced psychiatrist (JPR), which consisted of jointly reviewing the training manual (Inouye, 2011), reviewing 10 patient records together and periodic discussions between raters to agree on borderline cases.

Data extraction

Data for patients in these two cohorts with delirium (SARS-CoV-2 positive and SARS-CoV-2 negative) were manually extracted from the electronic healthcare record system and anonymised from 14/12/2020 to 12/1/2021. Extracted variables included demographics (age, sex and ethnicity), body mass index (BMI), baseline comorbidities (including a prior recorded episode of delirium) and complications of COVID-19, which were adapted from Brain Infections Global Network, used by the World Health Organisation (Brain Infections Global, 2020; WHO, 2020). Inflammatory markers (CRP and WBC), arterial blood gas measures (pO_2 and pCO_2), polypharmacy (number of medications taken on day of COVID-19 test) and clinical delirium presentation were also recorded. Data were extracted up to 48 h prior to the diagnosis of delirium, with data closest to the date and time of delirium diagnosis used when repeated measurements were taken.

Statistical analysis

Chi-squared tests and unpaired *t*-tests were used to compare demographic data, polypharmacy, comorbidities, and types of delirium between the two groups. Linear regression with age and sex as covariates was performed to assess whether COVID-19 status predicted inflammatory markers or blood gas values. Due to significant positive skew across all blood and gas markers, outcomes underwent logarithmic transformation prior to regression analyses (to reduce skewness and heteroscedasticity of the dataset). Homogeneity in the equality of variances between the two cohorts was then determined by an *F*-test. Pairwise correlation was undertaken to investigate multicollinearity between variables to best ascertain parameters to input into the multiple regression model. Missing data were excluded from analysis. Data analysis was performed on Stata (version 13.0) and the threshold for statistical significance was $p < 0.05$.

Results

Delirium was present in 33/130 (25.4%) patients referred to the liaison psychiatry service with COVID-19 compared to 43/68 (63%) patients without COVID-19. Figure 1 shows an overview of the selection process.

Characteristics of each cohort are summarised in Table 1. The COVID-19 positive group were significantly older, were taking more medications, had a higher prevalence of diabetes and a lower prevalence of alcohol misuse than the comparison group.

In the bivariate analyses (Table 2), CRP (mg/L) was significantly higher (81.7 ± 80.0 vs. 58.8 ± 87.7, $p = 0.04$) and WBC (10^9/L) significantly lower (7.44 ± 3.42 vs. 9.71 ± 5.45, $p = 0.04$) in the COVID-19 group than the comparison group. There were

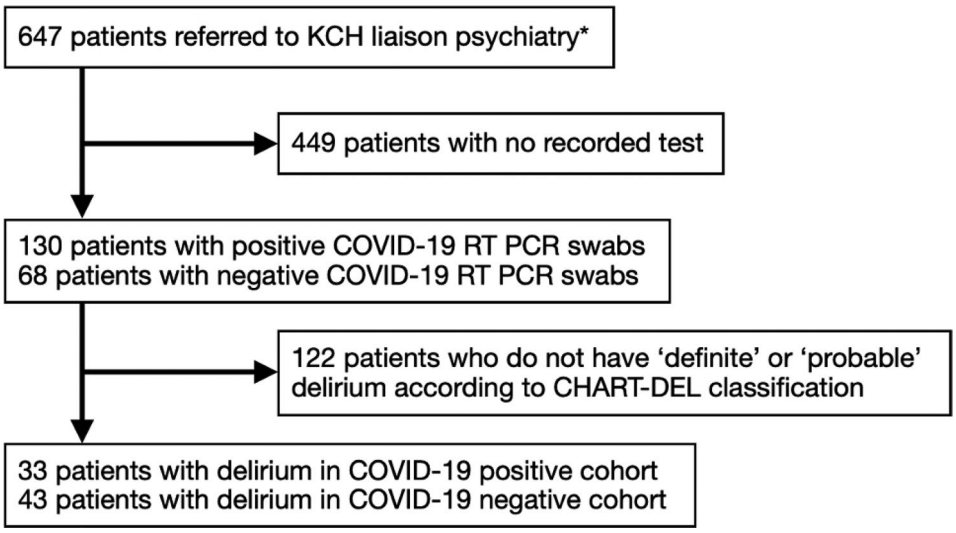

Figure 1. Overview of patient selection process. KCH = King's College Hospital. RT PCR = reverse transcription polymerase chain reaction. CHART-DEL = Chart-based Delirium Identification Instrument. COVID-19 = coronavirus disease 2019. *All patients who had been at King's College Hospital and had been referred to liaison psychiatry between 2/3/2020 and 10/5/2020

Table 1. Patient characteristics.

		COVID positive ($n=33$)	COVID negative ($n=43$)		P
Demographics	Age, mean (SD)	74.4 (14.5)	65.0 (15.8)		**0.01**
	Sex at birth, male (%)	18 (55)	28 (65)	0.35	
	BMI, mean (SD)	25.5 (7.0)	23.8 (4.9)	0.25	
	Ethnicity (%)			0.44	
	• White	• 16 (48)	• 27 (63)		
	• Mixed	• 0 (0)	• 0 (0)		
	• Asian	• 2 (6)	• 1 (2)		
	• Black	• 11 (33)	• 13 (30)		
	• Other	• 4 (12)	• 2 (5)		
Polypharmacy, mean (SD) [number of medications taken on day of COVID-19 test]		9.09 (5.28)	6.33 (5.89)		**0.04**
Baseline comorbidities (%)	Hypertension	22 (67)	22 (51)	0.18	
	Diabetes	21 (64)	11 (26)		**0.01**
	Dyslipidaemia	10 (30)	9 (21)	0.35	
	Renal disease	9 (27)	8 (19)	0.37	
	Heart disease	12 (36)	12 (28)	0.43	
	Respiratory disease	7 (21)	9 (21)	0.98	
	Liver disease	4 (12)	6 (14)	0.81	
	Previous delirium episode recorded	10 (30)	14 (33)	0.83	
	Dementia diagnosis	14 (42)	10 (24)	0.08	
	Other neurological disorder	9 (27)	13 (30)	0.78	
	Alcohol misuse	2 (6)	11 (26)		**0.03**
	Other psychiatric disorder	14 (42)	16 (38)	0.70	
Type of delirium (%)	Hypoactive	23 (70)	21 (49)	0.07	
	Hyperactive	10 (30)	22 (51)	0.07	
Complications of admission (%)	ICU admission across hospitalisation	0 (0)	2 (5)	0.21	
	Acute liver injury	0 (0)	2 (5)	0.21	
	Acute kidney injury	1 (3)	3 (7)	0.45	

Note: These bold values are those which are statistically significant ($p > 0.05$).

no significant differences in pO_2 or pCO_2 on bivariate analysis ($p=0.98$, $p=0.44$ respectively). As an additional exploratory analysis, to investigate the lower white cell count in the COVID-19 group, we compared the lymphocyte, neutrophil counts, and neutrophil:lymphocyte ratio (NLR) between the two groups, finding no significant differences on bivariate analysis ($p=0.42$, $p=0.10$, $p=0.55$ respectively). On multivariable analysis, the multiple regression adjusting for age and sex found that having COVID-19 was associated with a 140% higher geometric mean CRP (95% CI = 7–439%, $p=0.03$).

Discussion

We performed a case notes review to find associations with COVID-19 delirium compared to delirium of other aetiologies. Across the markers primarily investigated (CRP, WBC, PO_2 and PCO_2), we found a significantly higher serum CRP in COVID-19 delirium with age and sex as covariates, demonstrating a high CRP is particularly related to COVID-19 delirium.

In our study, the proportion of COVID-19 patients with delirium (25%) is consistent with other values reported for hospitalised COVID-19 patients (30%), despite the fact the small study population was derived from a cohort of psychiatric referrals (Aguilar-Navarro et al., 2020). A significantly lower incidence of delirium in the COVID-19 cohort compared to the non-COVID-19 cohort (25% vs 63% respectively) may be caused by an increase in severity of disease of non-COVID-19 patients attending hospital over this time. This would be supported by data showing increased in-hospital mortality incidences of non-COVID-19 patients in April 2020, thought to be due to people with milder conditions avoiding hospitals, which was similarly noted in the

Table 2. Comparison of inflammatory and blood gas markers for delirium patients.

	COVID-19 positive		COVID-19 negative		COVID status (unadjusted)		COVID status (age and sex adjusted)	
	n	Mean ± SD	n	Mean ± SD	% difference[a](95% CI)	P	% difference[a](95% CI)	P
CRP, mg/L[b]	29	81.7 ± 80.0	39	58.8 ± 87.7	**+121 (+3, +373)**	**0.04**	**+140 (+7, +439)**	**0.03**
WBC, 10^9/L[b]	27	7.44 ± 3.42	41	9.71 ± 5.45	**−21 (−37, −2)**	**0.04**	−20 (−37, +2)	0.08
Lymphocyte count, 10^9/L[b]	27	1.16 ± 0.53	41	1.35 ± 0.70	−10 (−32, +18)	0.42	+1 (−24, 35)	0.95
Neutrophil count, 10^9/L[b]	27	5.79 ± 3.07	41	7.71 ± 5.46	−21 (−40, 5)	0.10	−20 (−41, 8)	0.15
Neutrophil:lymphocyte ratio[b]	27	5.77 ± 3.25	41	8.93 ± 10.8	−12 (−41, 33)	0.55	−21 (−49, 23)	0.29
pO_2, kPa[b]	17	6.86 ± 4.05	31	6.62 ± 3.32	+0 (−27, +35)	0.98	+15 (−19, +62)	0.42
pCO_2, kPa[b]	18	5.41 ± 1.11	32	5.77 ± 1.36	−5 (−17, +8)	0.44	−5 (−19, +12)	0.51

Note: These bold values are those which are statistically significant ($p > 0.05$).

[a]Percentage difference of geometric means determined by value of $\left(e^{\beta}-1\right)\times 100$, whereby β was the correlation coefficient of COVID status on the natural logarithm of each outcome following linear/multiple regression.

[b]Untransformed, arithmetic mean and standard deviation (SD) provided for markers, with natural logarithmic transformations undertaken across regression analyses due to positive skew.

SARS epidemic (Birkmeyer et al., 2020; Office for National Statistics, 2020; Schull et al., 2007).

Delirium in the COVID-19 cohort was more commonly hypoactive than hyperactive (70% vs 30% respectively). This is of particular interest as hypoactive delirium is often missed compared to hyperactive delirium (Fong et al., 2009), and this finding may explain why COVID-19 delirium is particularly underdiagnosed. Evidence from other studies investigating the subtyping of hypoactive vs. hyperactive delirium in COVID-19 patients is mixed (Hawkins et al., 2021).

Older age and increased diabetes prevalence in the COVID-19 positive group are best explained by evidence these risk factors lead to increased COVID-19 hospitalisation (Ioannou et al., 2020; Ko et al., 2021) with increased polypharmacy in the COVID-19 positive group likely being due to older age (Bjerrum et al., 1998). Many other risk factors for COVID-19 hospitalisation such as high BMI, hypertension, dyslipidaemia, heart, renal, kidney and lung disease (Ioannou et al., 2020; Ko et al., 2020) were not shown to be significant, perhaps due to small sample sizes and such comorbidities also being risk factors for non-COVID-19 hospitalisations.

Raised CRP in suspected COVID-19 delirium compared to non-COVID-19 delirium supports existing studies finding SARS-CoV-2 infection leads to an increase in systemic pro-inflammatory mediators; particularly IL-6 but also IL-1 and TNF-α amongst others in what has been referred to as a 'cytokine storm' in critical COVID-19 patients (Diao et al., 2020; Ragab et al., 2020). However, this term may lead to a poorly defined, homogeneous view of elevated cytokines compared to other inflammatory syndromes. Whilst markers such as IL-6 and CRP are increased in COVID-19 infection, they are less elevated than what is typically seen in other inflammatory syndromes such as cytokine release syndrome and acute respiratory distress syndrome (ARDS) without COVID-19 (Leisman et al., 2020; McGonagle et al., 2021).

Nonetheless, the raised CRP in suspected COVID-19 delirium is clinically significant; a previous large review established a 1% increased risk of delirium in COVID-19 patients per 1 mg/L increase in CRP (Pranata et al., 2021). CRP has also been previously implicated in having prognostic value in determining recovery from delirium, determined by repeated CAM assessments during hospitalisation (Macdonald et al., 2007). As our findings show elevated CRP is a characteristic of delirium in COVID-19, this marker may help distinguish if delirium is due to COVID-19 in infected patients, or other factors. It is not possible to establish causality in a cross-sectional study of this nature and delirium is generally multifactorial, but our findings also support the hypothesis that delirium in COVID-19 is to some extent driven by systemic inflammation.

WBC was significantly lower in the COVID-19 cohort across bivariate analysis, but not multivariable analysis. Investigating differences in lymphocyte, neutrophil counts and NLR between the cohorts found all these markers to be lower in the COVID-19 cohort; however, these differences were not statistically significant. COVID-19 infection is known to cause lymphopenia and an increased NLR; both of which are associated with severity of disease and mortality (Huang & Pranata, 2020; Li et al., 2020). These associations are weaker in older age, which may explain why no such findings were discovered in our small study of older patients. The lower neutrophil count in the COVID-19 positive cohort is unexpected, as COVID-19 infection typically leads to an increase in circulating neutrophils (Cavalcante-Silva et al., 2021; Li et al., 2020).

There is little evidence to suggest SARS-CoV-2 infects T lymphocytes causing lymphopenia. Whilst previous findings reported this, they were later retracted as testing was done on T cell lines rather than primary T cells (Wang et al., 2020). Lymphopenia has instead been hypothesised to be due to a bias in lymphocyte distribution from blood into tissues, because the fast restoration of lymphocytes seen over a short period of recovery is likely due to recirculation of existing lymphocytes rather than generation of new lymphocytes (Huang & Pranata, 2020; Lin et al., 2020). Elevated IL-6 correlating with disease severity does also partly contribute to lymphopenia as IL-6 antagonism rescues lymphocyte count in COVID-19 (Chen et al., 2020; Giamarellos-Bourboulis et al., 2020; Li et al., 2020). This may be due to IL-6 mediated suppression of lymphocyte production either by acting on hematopoietic progenitors, or by inhibiting double negative thymocyte differentiation which has previously been proposed to explain thymic atrophy seen in SARS-CoV (Carbajosa et al., 2017; He et al., 2005; Maeda et al., 2005, 2009). IL-6 may also directly promote lymphocyte necrosis (Feng et al., 2020). Elevated soluble IL-2R in COVID-19 infection may also limit the survival and growth of lymphocytes (Jafarzadeh et al., 2021). Finally, more generalised host changes may repress lymphocyte production. Liver and kidney failure markers correlate with lymphopenia in COVID-19 which raises the prospect of metabolic changes following infection inducing lymphopenia such as metabolic acidosis, which has been reported to inhibit CD8 T cell proliferation (Fei et al., 2020; Fischer et al., 2007). However, whilst many patients in our study had pre-existing liver and kidney disease, only one patient in the COVID-19 positive cohort suffered acute kidney failure.

The lack of significant differences across pO_2 and pCO_2 values between the two cohorts demonstrates it is unlikely hypoxia or hypercapnia were significant contributors to delirium in this study. This may have been because hospitalised COVID-19 patients were treated with non-invasive respiratory support based on contemporaneous guidelines (NHS, 2020), which could explain the lack of differences in respiratory markers between the two cohorts. Furthermore, none of the COVID-19 patients were admitted to ICU during their hospitalisation. It is possible that in more severe COVID-19 disease causing life-threatening ARDS when interventions cannot maintain healthy oxygen tension that hypoxia may contribute to delirium. This is supported by autopsy data showing hypoxic brain damage in deceased COVID-19 patients (Kantonen et al., 2020; Reichard et al., 2020; Solomon et al., 2020).

This study had several limitations. Most importantly, inclusion criteria were based on hospitalised patients referred to the liaison psychiatry service. Such patients are unlikely to be representative of typical COVID-19 patients. The use of the time period 7 days before to 7 days after the COVID-19 swab test to determine if delirium was present was based on most neurological symptoms typically presenting within 7 days of the first symptoms (Ellul et al., 2020), but this period does allow for the possibility that the delirium was due to something other than COVID-19 infection. Although the CHART-DEL has been validated, it is likely to be inferior to systematic prospective assessment for delirium, especially considering both the high prevalence of dementia in our population, which can be confused for delirium using the CHART-DEL, and the potential for CAM features to be poorly documented (Inouye et al., 2005). Similar reports of a lack of a standardised screening tests were found in other studies (Emmerton & Abdelhafiz, 2020). This is problematic given up to 75% of cases may be missed without such tools (Grossmann et al., 2014) and implies the incidence of delirium may be higher than reported across both cohorts. The heterogeneity of causes of delirium in the control cohort was an intrinsic limitation to this study: other infections may have also caused a rise in CRP, for example, which could have made differences between the cohorts harder to ascertain. The specific population studied alongside the limited size of each cohort (which also limited the number of covariates) means conclusions drawn from this retrospective study must be interpreted cautiously.

Future studies investigating risk factors for developing delirium within COVID-19 patients may help us further stratify patients based on their risk of developing delirium. Data from electronic health records, which may include inflammatory markers, have been of use in machine-learning models predicting COVID-19 delirium which provides more accurate predictions of delirium than relying on patient age, highlighting the potential prognostic value of such markers (Castro et al., 2021). Establishing an inflammatory aetiology of COVID-19 delirium from an observational standpoint would require the contemporaneous recording of both serum and CSF levels of inflammatory markers and DAMPs, alongside concordant use of neuroimaging and neuropathological investigations. If accomplished, this raises the prospect of using immunomodulatory therapies such as tocilizumab or dexamethasone, which are already used to treat severe and critical COVID-19 but not COVID-19 delirium specifically, despite having been previously found to reduce incidence of delirium and cognitive dysfunction after surgery (Dieleman et al., 2012; NICE, 2021; Valentin et al., 2016). DAMP signalling inhibition (which has been used in animal studies, and in conjunction with dexamethasone (Fonken et al., 2016; Masouris et al., 2017)) may also treat severe or critical COVID-19 by reducing inflammation (Andersson et al., 2020). Further research into the prevention, management, and comparison to delirium of other aetiologies is also needed to improve patient care.

In conclusion, this cross-sectional study suggests delirium in hospitalised COVID-19 patients is widely prevalent across liaison psychiatry services. Our study did not show a difference between WBC, pO_2 or pCO_2 between COVID-19 and non-COVID-19 delirium. However, we did find a difference in CRP levels, demonstrating the value of measuring CRP in COVID-19 patients to help to discriminate between delirium due to COVID-19 or other factors. Inflammation may be a contributing factor to COVID-19 delirium on a background of deliriogenic risk factors and predispositions. Further studies measuring serum and CSF levels of inflammatory markers and DAMPs, alongside neuroimaging and neuropathological findings may elucidate the best management of these patients once aetiology is further clarified.

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Authors' contributions

AS and JPR conceived the project. AS, CCSFL, SP, ASD and JPR planned the project. AS, MC, DA, TO extracted data. AS conducted the statistical analysis and wrote the first draft of the report under supervision of JPR. GL advised on statistical analysis. All authors had the opportunity to comment. All authors had final responsibility for the decision to submit for publication.

Disclosure statement

Funders had no role in the design, analysis, or decision to publish.

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