

# Evaluation of medication changes following severe COVID-19 infection: a multicentre evaluation

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## ABSTRACT

**Background** Critically ill patients often experience several transitions of care following critical illness. Research has explored the challenges which patients have with medication management across these transitions. It is unclear whether patients admitted to critical care due to COVID-19 will have similar challenges. The aim of this study was to explore medication management in critical care survivors following severe COVID-19.

**Methods** Between 3 and 7 months post hospital discharge, patients who had been admitted to critical care due to severe COVID-19 were invited to an established recovery service. During the clinic consultation a medication review was performed by a pharmacist. This included medicines reconciliation, assessing the appropriateness of each of the prescribed medications and identification of medication changes. We also assessed changes to pain management in the discharge period.

**Results** In total, 78 patients had a full medication review available. Over 70% of patients were taking an increased dose of medicine or a new medicine at clinic. There was a significant overall increase in new medication during the clinic consultation, across different British National Formulary classifications (OR: 1.73 (95% CI: 1.28 to 2.34),  $p < 0.001$ ). Compared with pre critical care admission, there was a significant increase in the number of patients taking regular analgesia following severe COVID-19 infection (23 (29.5%) vs 39 (50%),  $p < 0.001$ ).

**Conclusion** Following severe COVID-19, patients may require new or increasing doses of medicines. Ongoing review of these patients is crucial to ensure optimal outcomes.

## INTRODUCTION

Due to the pathophysiological progression of COVID-19, a proportion of hospitalised patients will require an admission to critical care.<sup>1</sup> Although critical care admission rates might be dependent on capacity and resource availability, most studies from Europe and North America report that between 10% and 20% of hospitalised patients undergo some form of advanced respiratory support either in the ward or in a critical care setting.<sup>2–4</sup> As such, the COVID-19 pandemic has resulted in

## Key messages

- There was a significant increase in the number of new medications prescribed and the number of patients taking regular analgesia following severe COVID-19 infection.
- Compared to pre critical care admission, there was a significant increase in the number of patients taking regular analgesia following severe COVID-19 infection

a significant rise in critical care use and critical care survivors.

It is well known that following discharge from critical care, patients can experience significant global challenges, which include new and worsening disability.<sup>5</sup> These challenges include physical disability such as muscle weakness, mobility issues and breathlessness.<sup>6</sup> Emotional and cognitive problems such as depression, anxiety and impaired memory are also encountered in up to two-thirds of survivors.<sup>7</sup> These issues are not benign and cause significant strain for the individual, such as an inability to return to employment and increased rates of suicide and self-harm.<sup>8,9</sup>

More recently, research has explored the challenges which patients have with medication management following discharge.<sup>10</sup> This includes unintentional continuation of acute medicines or discontinuation of long-term treatment across transitions of care.<sup>11</sup> It is unclear whether patients admitted to critical care due to COVID-19 will have similar challenges. The hospital environment was distinctly different during pandemic care. The lack of family visitation, which often scaffolds treatment plans across the recovery arc for critical care survivors, is one notable difference.<sup>12</sup> To improve rehabilitation pathways and ensure safe transitions of care during this challenging period, it is essential



that clinicians and policy-makers have evidence in this area.

The aim of this study was, therefore, to explore medication changes in critical care survivors, following severe COVID-19. We also assessed specific changes to analgesic prescribing following hospital discharge.

## METHODS

Patients admitted to one of the four critical care units, in three hospitals between March and May 2020 with a positive reverse transcriptase assay for SARS-CoV-2 (or a high clinical suspicion of SARS-CoV-2), were invited to the clinic. There were no specific exclusion criteria. We encouraged family members to attend alongside patients. Those with cognitive impairment were not excluded. A critical care unit delivered level two or three care, as defined by the UK Intensive Care Society.<sup>13</sup>

Patients were invited to a pre-existing critical care rehabilitation programme 3–7 months post hospital discharge. Details of this programme, Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE), have been published previously.<sup>14 15</sup> This programme provides a detailed patient assessment by the entire multiprofessional team, including nurses, medical staff, pharmacists and physiotherapists. Referral to mental health support and social and welfare services are available as needed. Due to hospital attendance restrictions, all consultations took place virtually or by telephone. Due to the anticipated long-term respiratory problems related to COVID-19, all patients were also part of an integrated respiratory pathway across the hospital sites.

During InS:PIRE, a medication review was performed by a pharmacist. This included medicines reconciliation, assessing the appropriateness of each of the prescribed medications and identification of medication changes. The pharmacist recorded the patient's prescribed medication prior to their critical care admission, at hospital discharge and current medication (at InS:PIRE). Data for the above were available from the electronic health record, primary care prescription information, patient, caregiver (if present) and community pharmacist, if appropriate. Critical care length of stay was taken for the first critical care admission.

We categorised medication changes within the British National Formulary (BNF) classification (online supplemental file 1).<sup>16</sup> Analgesia was categorised using the WHO analgesic ladder (online supplemental file 1).<sup>17</sup> This is a three-step approach for prescribing analgesia, with each step representing an increased potency of analgesia. Step 1 is non-opioid analgesia for mild pain (eg, paracetamol), step 2 is weak opioid analgesia for mild-to-moderate pain (eg, codeine) and step 3 is strong opioid analgesia for moderate-to-severe pain (eg, morphine).

The medicine changes were classified as either appropriate or inappropriate based on discussion with the clinical team, patient and ongoing clinical indication. For example, proton pump inhibitors still required

for ongoing gastrointestinal symptoms were deemed appropriate.

## STATISTICAL ANALYSIS

A McNemar's Test was used to compare the difference in prescribed analgesia before admission and at InS:PIRE. An unadjusted multilevel logistic regression determined whether there was a significant increase in new medications following severe COVID-19. The dependent variable examined which classification of medicine the patient was prescribed before and after admission. The independent variable of interest was time (prehospital admission and review at clinic). Additionally, the model adjusted for the repeated measures analysed. We opted for an unadjusted analysis, to ensure a balance between power and accuracy within our sample size. Analyses were undertaken in R (V.4.0.5).

## PATIENT AND PUBLIC INVOLVEMENT

The InS:PIRE Study was coproduced with survivors of critical illness and their family members. Using a patient and family forum, we designed the intervention and all outcome measures with these previous service users. After the initial feasibility work of the InS:PIRE programme, priority of the research question, choice of outcome measures and methods of recruitment were informed by further structured, service user feedback.

## RESULTS

Across the four critical care units, 122 patients attended the InS:PIRE programme. Of those patients who attended, 93 (76%) consented to inclusion and 78 (84%) had a pharmacy review documented. The median time to follow-up in those who consented was 135 (IQR: 85–181) days following hospital discharge.

Across those who had a pharmacy review, 64% of patients were male, the median age was 59 years (IQR: 53.9–67) and 60% were ventilated during admission. Half (50%) had two or more comorbidities, with hypertension the most frequently reported (table 1).

The median number of medications prescribed pre critical care was 5 (IQR: 1–8), at hospital discharge this was 5 (IQR: 2–7) and at the InS:PIRE clinic was 5 (IQR: 3–8). In total, 383 medicines were prescribed pre critical care and 444 prescribed across 70 patients at InS:PIRE (8 patients were not prescribed medicines). Of the drugs prescribed at InS:PIRE, 135 (30%) were either new drugs or increased doses of previously prescribed drugs (table 2). Over 70% of patients were taking an increased dose of medicine or a new medicine at clinic. There was a significant overall increase in new medication at InS:PIRE across different BNF classifications (OR: 1.73 (95% CI: 1.28 to 2.34),  $p < 0.001$ ).

After full clinical review, 94% of medication changes were deemed to be appropriate by the clinical team. Of the drugs deemed inappropriate, one-third were

**Table 1** Patient demographics and outcome summary

Demographic	n (n=78)
Gender, male (%)	58 (64.1)
Age, years, median (IQR)	59 (53.9–67)
Obesity (%)	23 (29.5)
Smoking (%)	7 (9.0)
Black and minority ethnic (%)	3 (3.8)
Acute Physiology and Chronic Health Evaluation II Score, median (IQR)	16 (11–19.3)
Critical care length of stay, days, median (IQR)	9.1 (4.9–25.1)
Hospital length of stay, days, median (IQR)	20 (12–45.3)
Ventilated (%)	47 (60.3)
Renal replacement therapy required (%)	14 (17.9)
<b>Comorbidities (%)</b>	
Respiratory	25 (32.1)
Endocrine	19 (24.4)
Hypertension	29 (37.2)
Cardiovascular	10 (12.8)
Liver	1 (1.3)
Gastrointestinal	9 (11.5)
Mental health	10 (12.8)
Other	18 (23.1)
Multimorbidity (two or more comorbidities)	39 (50)
<b>Scottish Index of Multiple Deprivation (SIMD) quintile (%)*</b>	
SIMD 1 (most deprived)	27 (34.6)
SIMD 2	13 (16.7)
SIMD 3	17 (21.8)
SIMD 4	8 (10.2)
SIMD 5 (least deprived)	12 (15.4)
SIMD missing	1 (1.3)
<b>Medication management</b>	
Median number of medications pre critical care (IQR)	5 (1–8)
Median number of medications at hospital discharge (IQR)	5 (2–7)
Median number of medications at clinic attendance (IQR)	5 (3–8)
Patients requiring new or increased medications (measured at clinic) following COVID-19 (%)	56 (71.8)
<b>Pain medication management (%)</b>	
Number of patients on pain medication pre critical care (steps 1–3 on WHO pain ladder)	23 (29.5)
Number of patients on pain medication at clinic attendance (steps 1–3 on WHO pain ladder)	39 (50)

\*The SIMD, produced by the Scottish Government as a measure of deprivation, defined socioeconomic status.

cardiovascular in nature. When reviewed at clinic, 10 patients were on reduced medication doses in comparison to pre admission. Additionally, 29.5% of patients had pre-existing medications discontinued during the hospitalisation that had not been restarted at the time of clinic review.

### BNF classifications

There were 32 new or increased doses of cardiovascular drugs across the 78 patients included in this analysis. Of these changes, 16 (50%) were related to anticoagulants, 5 (16%) were to antiarrhythmic medications and 9 (28%) were related to statins or antihypertensives. There were 37 new or increased doses of central nervous system (BNF category four) drugs across the 78 patients reviewed at InS:PIRE. Of these drug changes, 31 (84%) were related to analgesics and the remaining were related to mental health medication and the treatment of insomnia (16%).

### Analgesia management

Prior to the critical care admission, 23 (29.5%) of patients were taking regular analgesic (steps 1–3 on the WHO pain ladder). There was a significant increase in the number of patients taking regular analgesia following severe COVID-19 infection (23 (29.5%) vs 39 (50%),  $p < 0.001$ ). Of those patients who were receiving either no pain medication or non-opioid pain relief (WHO ladder step 1) before critical care, 8 (10%) were receiving weak or strong opioids (WHO ladder step 2 or 3) at the InS:PIRE review.

### DISCUSSION

In this evaluation, there was an increase in the number of patients prescribed new medicines and analgesia following severe COVID-19. In contrast to previous research, which has demonstrated unintentional continuation of medicines following critical illness, most of these medication changes appeared appropriate.<sup>18 19</sup>

There was an increase in new medicines prescribed for the management of respiratory, cardiovascular and gastrointestinal symptoms. Although we cannot confirm whether these changes represent new or worsening comorbidities, this patient cohort was experiencing symptoms which were either new or were not being managed before severe COVID-19 infection. There is a growing body of evidence which has demonstrated the impact of severe COVID-19 on chronic conditions; this small-scale work further highlights the need for future research in this field.<sup>20</sup>

Interestingly, in contrast to previous evidence, the majority of changes to medication (>90%) were deemed appropriate by the clinical team. This divergence from previous evidence may reflect a higher frequency of ongoing symptoms in the COVID-19 cohort, in comparison to previously studied cohorts. International research

**Table 2** Summary of changes to medicines following critical care discharge categorised by BNF category

BNF domains	Patients requiring increased dose of medication (in comparison to pre critical care) (n=78)*	Patients requiring new medication (in comparison to pre critical care) (n=78)	Total (n=78)
Respiratory	12 (15.4%)	9 (11.5%)	21 (26.9%)
Cardiovascular	6 (7.7%)	17 (21.8%)	23 (29.5%)
Gastrointestinal	1 (1.3%)	10 (12.8%)	11 (14.1%)
Central nervous system	4 (5.1%)	22 (28.2%)	26 (33.3%)
Other	1 (1.3%)	13 (16.7%)	14 (18%)

\*Patients could have one or more changes to medicines across each of the BNF domains.  
BNF, British National Formulary.

is ongoing to determine the prevalence and severity of 'long COVID-19', which will help delineate this issue.

The findings on new pain following discharge from hospital are consistent with previous research in this field.<sup>21</sup> This new pain, including anatomical region, severity and optimal modes of rehabilitation, requires urgent investigation to ensure optimal outcomes for this vulnerable group.

Strengths of this work include its detailed approach to generating data, with accurate accounts about individual medicine regimes directly from patients and family members. This contrasts with large-scale datasets which often use dispensing data only. There are also limitations to this research; it represents a small sample of those who were significantly unwell due to COVID-19. The data, therefore, may not represent all survivors across the severity spectrum. We did not control other services which patients attended outside of InS:PIRE. Finally, we do not have specific details about the clinical course of those patients who did not attend the programme. These patients could have a distinctly different recovery trajectory than those included in this study.

In conclusion, this multicentre study demonstrates following severe COVID-19, patients may require new or increasing doses of medicines, including analgesics. Ongoing review of these patients is crucial to ensure optimal outcomes.

**Contributors** JM and PM: conceptualisation of the study. JM, PM and MS: conducted the analysis (formal analysis) and contributed to the interpretation of the findings (validation). JM acts as guarantor. All authors critically revised the paper for intellectual content and approved the final version of the manuscript.

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**Supplementary File One**

BNF Category	Body System
1	Gastrointestinal
2	Cardiovascular
3	Respiratory
4	Central Nervous System
5	Infections
6	Endocrine
7	Obstetrics, Gynaecology and Urinary Tract Disorders
8	Malignancy and Immunosuppressants
9	Nutrition and Blood
10	Musculoskeletal and Joint Disorders
11	Eye
12	Ear, Nose and Oropharynx
13	Skin
14	Immunological Products and Vaccines
15	Anaesthesia

**Table 1:** Drug categories used in this analysis

Joint Formulary Committee. BNF 78: September 2019-March 2020. London: Pharmaceutical Press; 2019.

Step	Drug classification and example
Step 1	Non-Opioid ± Adjuvant <b>Example:</b> Paracetamol
Step 2	Weak Opioid ± Non-Opioid ± Adjuvant <b>Example:</b> Codeine
Step 3	Strong Opioid ± Non-Opioid ± Adjuvant <b>Example:</b> Morphine

**Table 2:** WHO Three step analgesic ladder