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Chronic pain following COVID-19: implications for rehabilitation

Harriet I Kemp[1*], Eve Corner[2], Lesley A Colvin[3]

[1]Pain Research Group, Imperial College London, London, UK

[2] Department of Clinical Sciences, Brunel University London, London, UK

[3] Division of Population Health & Genomics, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

* Corresponding author. Email:

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Managing the immediate demands of the current COVID-19 global pandemic has tested many healthcare systems across the world, to their limits. As we move forward, new challenges due the impact of this must be faced. In the months since the initial outbreak of COVID-19 in December 2019, worldwide there have been more than 4.2 millions cases of infection with the SARS-Cov-2 virus reported[1]. However, the rapidity of spread appears to be slowing, the curve is flattening in many countries, and attention is now turning towards how the international healthcare community will address the ongoing needs of those most significantly affected by the pandemic. Recent UK data (covering February-April 2020) suggests 17% of cases admitted to hospital require support in high dependency or critical care environments, and of those just over 50% require mechanical ventilation[2]. About 20% of those requiring mechanical ventilation will be discharged with a further 27% receiving ongoing care. Critical care survival in other countries including Italy, the US and China has been reported as 16-37%, although many cohorts include those receiving ongoing care in ICU[3–5]. Given the number of global infections, this suggests a cohort of critically ill survivors of unprecedented size.

The treatment needs of COVID-19 survivors are not yet fully appreciated. Although initially assumed to be a respiratory disease, it is now clear that it affects a variety of systems. Multi-organ failure can occur, with reports of cardiac, renal, haematological and neurological effects in the acute stages. It is likely therefore, that these survivors will have significant multi-domain impairment requiring ongoing support. There has been a recent 'call to action' amongst the rehabilitation community to act quickly to ensure adequate resources to provide early phase, multidisciplinary interventions to promote physical and psychological recovery[6].

We can perhaps learn from previous studies of critical care survivorship, which has been relatively neglected until recently. This complex challenge has been termed post-intensive care syndrome (PICS)[7]. It incorporates the cognitive, physical and psychological dysfunction reported following ICU discharge that can have profound effects on quality of life. Chronic pain is often part of this, but how this additional co-morbidity affects critical care survivors is poorly understood. Estimates of chronic pain prevalence following ICU vary from 14-77% depending on timescale, method of measurement and population[8]. Pain also appears to be an important factor affecting ability to return to work and quality of life up to 5 years following discharge[9]. It is likely that those surviving critical illness with COVID-19 will be at particular risk of developing chronic pain. There are a number of reasons why this may be the case (Figure 1).

As a consistent risk factor for chronic pain development is the occurrence of acute pain, it is worth considering how this is managed in ICU. Those recalling higher pain and distress during ICU admission appear to be at higher risk of developing chronic

pain after discharge[10]. Unfortunately, even in quiet periods on ICU, pain is an often neglected symptom receiving low priority and surprisingly poor assessment and management given the highly staffed, well-skilled environment[11]. Guidelines to improve pain assessment and management in ICU have been developed in the US and Europe, and initiatives such as the ICU Liberation ABCDEF bundles of care have been adopted in some centres. These are aimed at improving long-term outcomes through multidisciplinary management of symptoms, mobility and communication[12,13].

However, these processes, which often involve non-pharmacological strategies, are labour intensive and realistically may be unachievable in current pandemic conditions. Furthermore, during this outbreak, the ICU workforce has been stretched beyond its capacity with patients being treated, through necessity, by staff with rapidly scaled-up training in units with reduced staffing ratios[14]. There is therefore the potential that non-lifesaving symptomatic control may have been further neglected. The critically ill undergo a significant pain burden during everyday procedures in ICU, such as tracheal tube suctioning, turning, positioning and line insertion[15]. Due to the severity of COVID-19 critical illness it is likely that survivors will have undergone multiple pain-associated interventions.

COVID-19 survivors are likely to have sustained a prolonged period of immobilisation, sedation and ventilation[5], putting them at high risk of associated ICU-acquired weakness (ICUAW). Commonly manifesting as any combination of critical illness myopathy (CIM), critical illness polyneuropathy (CIN) and muscle atrophy, known risk factors include the use of neuromuscular blockade and corticosteroids,

the presence of sepsis and multiorgan dysfunction as well as prolonged mechanical ventilation[16]. Neuromuscular blockade is now highlighted in several guideline publications as a strategy to improve ventilation in those with ARDS associated with COVID-19[17,18]; although there is no consensus, some recommendations also include use of corticosteroids in certain populations[19]. The prevalence of ICUAW in the general ARDS population is estimated at 25-96%,[20] and although reported following the Middle East Respiratory Syndrome (MERS) epidemic[21] is yet to be determined in those critically ill with COVID-19. Whilst the focus of ICUAW is often the motor component, there is growing evidence for sensory disruption and associated pain. Weakness can lead to rapid deconditioning, joint related pain and contractures and, although mechanisms remain unclear, shoulder pain in particular has been highlighted as a significant problem in the post ICU population[22].

A mainstay of respiratory support through the COVID-19 pandemic has been use of repeated patient proning to improve ventilation[17–19]. Complications associated with proning sedated patients include brachial plexopathy, joint subluxation and soft tissue damage. These have the potential to result in persistent neuropathic and musculoskeletal pain[23].

Neuropathic symptoms including numbness, paraesthesia and pain are well documented following critical illness with abnormalities in nerve conduction studies demonstrated up to 5 years following ICU discharge[24]. Even in the absence of electrophysiological abnormalities, small nerve fibre impairment associated with neuropathic symptoms can persist for several months[25]. Reports of neurological sequelae of COVID-19 infection are emerging, indicating both central and peripheral

nervous system involvement; symptoms such as confusion, headache and dizziness, as well as anosmia, ageusia and nerve pain are now described in retrospective cohorts and case reports[26]. This has led to speculation of potential neurotropism, with both muscle and neural tissue expressing Angiotensin Converting Enzyme-2 (ACE2) receptor, the functional receptor for SARS-CoV-2[27]. The related SARS-CoV virus is also associated with neural injury, including axonopathic polyneuropathy[28], and has been detected in both the CSF and brain tissue[29]. There are ongoing efforts to determine which human cells are susceptible to SARS-CoV-2 infection, but direct neural invasion has not yet been demonstrated[30].

Regardless of direct neural entry, SARS-CoV-2, like SARS and MERS, appears to have the capacity to induce painful para-infectious neurological disease as shown by a number of case reports of Guillan-Barre syndrome[31] and polyneuritis[32]. Thrombotic, hypotensive and hypoxaemic consequences of infection can also contribute to longstanding, potentially painful neurological sequelae such as stroke. Renal dysfunction is also common and may be associated with a peripheral neuropathy, particularly if renal impairment persists after the acute injury. A further aspect to consider is neuropathic pain as a side effect of putative therapeutic agents currently under investigation for modifying disease severity, such as lopinavir/ritonavir and hydroxychloroquine.

It is now clear that COVID-19 itself is associated with painful symptoms, including myalgia, arthralgia, abdominal pain, headache and chest pain, and even those not admitted to critical care environments may have pain requiring opioids for symptom management[33].

An important area to recognise is the psychological impact of COVID-19, with the unique social restrictions likely to create an additional burden. Severe psychological sequelae have been reported in ICU survivors with up to 30% of ARDS survivors developing post-traumatic stress disorder (PTSD)[34]. In COVID-19 this may be augmented by separation from family, use of personal protective equipment (PPE) adding to the already alien environment, breakdown of social networks and fear of mortality; this increases the potential for development of PTSD, anxiety and depression, as observed in the SARS outbreak[35]. Pain is thought to have a bidirectional relationship with such psychological factors: in the acute phase it may be a risk factor contributing to the development of mental health co-morbidities, with chronic pain being a well-recognised co-morbidity. Even baseline patient characteristics, identified as factors associated with the development of severe COVID-19, overlap with those associated with chronic pain after critical illness, including multi-morbidity and increasing age[36]. It is also likely that those with pre-existing multi-morbidity were at higher risk of chronic pain prior to infection, which may predispose them to exacerbation of current or development of new pain conditions[37].

Emerging reports from Wuhan, which is now operating several rehabilitation institutions for COVID-19 survivors, and Italy indicate a significant symptom burden in COVID-19 survivors including anxiety, sleep disorders, fatigue, limited exercise tolerance as well as memory and executive function impairment[38]. Such symptoms are likely to be exacerbated or even attributed to pain although this is yet to be explored. What remains unclear is the level of rehabilitation that will be possible for

different countries in the early phase of recovery. Early intervention including adequate pain management, psychological and physical therapy has the potential to reduce the risk of long-term pain as well as other features of PICS[39]. However, currently resources are focused on frontline services which may leave limited support for such an unprecedented cohort of patients.

There is conflicting evidence on the beneficial effects of post-ICU rehabilitation strategies in general on exercise tolerance and health-related quality of life in the pre-COVID era.[40,41] Qualitative evaluation suggests increased patient satisfaction and reduced anxiety[42]. Although pain forms a component of health-related quality of life measures, specific research into the effect of post-ICU rehabilitation on pain has never been formally evaluated. The majority of studies on efficacy of pain management and post-critical illness rehabilitation have focused on face-to-face delivery, often in a group-based setting. Such traditional models of care may not be possible for some time, with ongoing social distancing and diversion of healthcare resources. We therefore must develop and assess innovative ways to deliver therapy that is accessible to those who need it. Telemedicine and promotion of self-management programmes are being explored for this cohort, and may become part of the 'new normal' for delivery of this type of service. Yet for some vulnerable patient groups (e.g. elderly, cognitively impaired, high deprivation) access may be problematic.

Stratifying patients to high intensity or speciality specific rehabilitation through a stepped care model may be required but is difficult given the lack of specific COVID-19 research and experience. Extrapolation of best practice evidence from other

cohorts will be required. Historically, rehabilitation for survivors of critical illness has been disease specific. For example, cardiac patients may get streamed to a cardiac rehabilitation pathway; those with chronic respiratory disease to pulmonary rehabilitation; those with a stroke to post-stroke resources. However this was problematic for two reasons: firstly, these classes and pathways were not designed to address the additional burden of PICS in addition to the patients underlying condition, and secondly, there was a large proportion of patients that did not fall into these categories, 'slipped through the net' and received suboptimal care.

Several models of more contemporary general ICU follow-up clinics currently exist,[43] but they are by no means universal. It is likely that these have not been subject to the number of patients that will need their services in the foreseeable future. The make-up of such services may also need to be adjusted to address COVID-19-specific sequelae, and this may represent an opportunity to develop better links between pain and ICU survivorship programmes, as well as improving dialogue with other specialties such as renal, respiratory and mental health to build existing collaborations and manage multi-morbidity. Pain services are traditionally multidisciplinary, incorporating physical and psychological expertise with the goal of improving function and quality of life, and could therefore have a great deal to offer overwhelmed critical care services. Such integrated follow up pathways also provide an opportunity to develop embedded research and registries to learn more about the features, aetiology, risk factors and therapeutic interventions for chronic pain following critical illness, an as yet neglected area of critical care survivorship.

In the rapidly changing clinical environment, flexibility and changes to health and social care delivery are required. Whilst the trajectory of this pandemic has not given us the luxury of developing a high-quality evidence base on which to base our management decisions, it is beholden on us to critically assess what we are doing. Perhaps now more than ever we need to work collaboratively to assess interventions used in rehabilitation of post-COVID-19 patients. There is the opportunity to use a similar approach to that of some clinical trials of acute interventions (such as RECOVERY (https://www.recoverytrial.net/)), where adaptive trial design allows rapid evaluation of a range of potential COVID-19 treatments. Although the acute challenges of managing COVID-19 have been significant, it may be the long-term effects, including pain, that will have the greatest impact on survivors and society, As an academic community, understanding post-COVID-19 effects and ensuring a strong evidence base for how to manage these is vital for patients, health and social care systems, and for policy makers.

Authors' contributions

LC and HK devised the topic of the manuscript; HK, LC, EC drafted sections for and finalised the manuscript.

Declaration of interests

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Figure Legends

Figure 1. Potential risk factors for development of chronic pain following COVID-19. (PTSD=post-traumatic stress disorder)