Chronic pain following COVID-19: Implications for rehabilitation

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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. The rapidity of spread appears to be slowing, the curve may be flattening, and cautiously, whilst alert to the risk of a 'second wave', the international healthcare community has started to acknowledge the need to develop strategies to address the ongoing needs of those most significantly affected by the pandemic. Globally critical care survival following COVID-19 infection is estimated at between 16-37%, although many cohorts include those receiving ongoing care in ICU. [1-4] The number of infections reported worldwide is in the many millions, and increases on a daily basis, [5] heralding a cohort of critically ill survivors of unprecedented size.

The treatment needs of COVID-19 survivors are not yet fully understood. 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] It is therefore timely to highlight the potential risk of chronic pain associated with COVID-19 infection, explore the challenges of pain management in this cohort and identify opportunities to improve clinical services, as well as the evidence base on the consequences of not only SARS-CoV-2 infection, but critical illness survivors more generally.

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 post discharge.[9] Therefore there is a real need to gain clarification on how to manage pain in these patients – perhaps those surviving critical illness with COVID-19, who may be at particular risk of developing chronic pain, present an opportunity for clinicians to understand more about the development and management of pain following critical illness and to initiate best practice that could continue as a positive legacy of the pandemic. There are a number of reasons why this may be the case, as outlined in Figure 1.

As one 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 'peace time' on ICU, pain management is problematic and evidence suggests a high proportion of those on critical care experience moderate to severe pain for prolonged periods.[11] Barriers to high quality pain management in ICU are multifactorial but appear to stem from a limited evidence base for best practice, the challenges of patient-clinician communication of symptoms, for example in those that are intubated, sedated or cognitively impaired,

pressures on staffing and workload, and from a lack of focus of education in the area. 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, in many countries the ICU workforce has been stretched to 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 detailed attention to non-lifesaving symptomatic control, that would be desirable in optimal circumstances, is not possible, with an increase in barriers to providing effective analgesia.. The critically ill undergo a significant pain burden during everyday procedures in ICU, such as endotracheal 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 during their admission.

COVID-19 survivors are likely to have sustained a prolonged period of immobilisation, sedation and ventilation,[4] putting them at high risk of associated ICU-acquired weakness. Commonly manifesting as any combination of critical illness myopathy, critical illness polyneuropathy 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 the use of corticosteroids in certain populations.[19] The prevalence of ICU acquired weakness in the general ARDS population is estimated at between 25-96% and although reported following the Middle East Respiratory Syndrome (MERS) epidemic, is yet to be determined in those critically ill with COVID-19.[20,21] Whilst the focus of ICU acquired weakness 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 pandemic has been the use of repeated patient proning to improve ventilation.[17-19] However, complications associated with proning sedated patients include brachial plexopathy, joint subluxation and soft tissue damage, that have the potential to result in persistent neuropathic and musculoskeletal pain.[23] The longer-term consequences of such strategies need to be carefully monitored.

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] Understanding more about sensory dysfunction could provide a great deal of insight into the pathophysiology of chronic pain after critical illness and allow for the development of strategies to both prevent and treat pain in a cohort where evidence is limited.

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 (ACE) 2 receptor, the implicated functional receptor for SARS-CoV-2.[27] The related SARS-CoV virus is also associated with neural injury, including axonopathic polyneuropathy, and has been detected in both the CSF and brain tissue.[28,29] There are ongoing efforts to determine which human cells are susceptible to SARS-CoV-2 infection but direct neural invasion has not yet been definitively established.[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 demonstrated by a growing number of case reports of Guillan Barre syndrome and polyneuritis).[31,32] Thrombotic, hypotensive and hypoxic 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 infection 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 require 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 demonstrated in ICU survivors with up to 30% of ARDS survivors developing 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 with the potential for development of PTSD, anxiety and depression, as was 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 illness, 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 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, however qualitative evaluation suggests increased patient satisfaction and reduced anxiety.[40,41] 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 need to 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 in the future may be 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, yet 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, whom ‘slipped through the net’ and received suboptimal care.

Several models of more contemporary general ICU follow-up clinics currently exist but they are by no means universal and it is likely that these have not been subject to the number of patients that will need their services in the foreseeable future.[42] 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. However, pain services in many countries are already under-resourced and overwhelmed by patient need therefore there is likely to be variation in the ability of services to respond to this need. Nonetheless, integrated follow up pathways which include pain could 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 we are working in now, 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 robustly 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 individuals and society, As an academic community, understanding post COVID effects and ensuring a strong evidence base for how to manage these is vital for patients, health and social care systems, and policy makers.

Author's Contributions

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

Declaration of interests

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Figure Legends

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