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REVIEW ARTICLE/BRIEF REVIEW

Outcomes of critically ill COVID-19 survivors and caregivers: a case study-centred narrative review

Devenir des survivants et des soignants gravement atteints par la COVID-19 : une revue narrative centrée sur une étude de cas

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Abstract

Purpose *Critical illness is a transformative experience for both patients and their family members. For COVID-19 patients admitted to the intensive care unit (ICU), survival may be the start of a long road to recovery. Our knowledge of the post-ICU long-term sequelae of acute respiratory distress syndrome (ARDS) and severe acute respiratory syndrome (SARS) may inform our understanding and management of the long-term effects of COVID-19.*

Source *We identified international and Canadian epidemiologic data on ICU admissions for COVID-19, COVID-19 pathophysiology, emerging ICU practice patterns, early reports of long-term outcomes, and federal support programs for survivors and their families. Centred around an illustrating case study, we applied relevant literature from ARDS and SARS to contextualize knowledge within emerging COVID-19 research and extrapolate findings to future long-term outcomes.*

Principal findings *COVID-19 is a multisystem disease with unknown long-term morbidity and mortality. Its pathophysiology is distinct and unique from ARDS, SARS, and critical illness. Nevertheless, based on initial reports of critical care management for COVID-19 and the varied injurious supportive practices employed in the ICU, patients and families are at risk for post-intensive care syndrome. The distinct incremental risk of COVID-19 multiple organ dysfunction is unknown. The risk of mood disorders in family members may be further exacerbated by imposed isolation and stigma.*

Conclusion *Emerging literature on COVID-19 outcomes suggests some similarities with those of ARDS/SARS and prolonged mechanical ventilation. The pathophysiology of COVID-19 is presented here in the context of early outcome data and to inform an agenda for longitudinal research for patients and families.*

Résumé

Objectif *Les maladies au stade critique constituent une expérience bouleversante tant pour les patients que pour leurs proches. Pour les patients atteints de la COVID-19 admis aux soins intensifs (USI), la survie peut être le début*

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d'un long parcours vers la guérison. Notre connaissance des séquelles à long terme post-USI d'un syndrome de détresse respiratoire aiguë (SDRA) ou d'un syndrome respiratoire aigu sévère (SRAS) pourrait éclairer notre compréhension et notre prise en charge des effets à long terme de la COVID-19.

Sources *Nous avons identifié des données épidémiologiques internationales et canadiennes sur les admissions aux soins intensifs pour la COVID-19, la physiopathologie de la COVID-19, les schémas de pratique émergents en soins intensifs, les premiers rapports sur les issues à long terme et les programmes de soutien fédéraux pour les survivants et leurs familles. En nous centrant autour d'une étude de cas pour illustrer notre propos, nous avons appliqué la littérature pertinente à propos du SDRA et du SRAS afin de contextualiser les connaissances de la recherche émergente sur la COVID-19 et extrapoler les conclusions aux futures issues à long terme.*

Constatations principales *La COVID-19 est une maladie multisystémique dont la morbidité et la mortalité à long terme sont inconnues. Sa physiopathologie est unique et distincte du SDRA, du SRAS et des maladies graves. Néanmoins, en nous fondant sur les rapports initiaux de prise en charge aux soins intensifs de la COVID-19 et sur les diverses pratiques de support préjudiciables utilisées aux soins intensifs, les patients et les familles sont à risque de syndrome post-soins intensifs. Le risque distinct supplémentaire de dysfonctionnement multiviscéral de la COVID-19 est inconnu. Le risque de troubles de l'humeur chez les proches peut être encore exacerbé par l'isolement imposé et la stigmatisation.*

Conclusion *La littérature émergente sur les issues de la COVID-19 suggère certaines similitudes avec celles du SDRA/SRAS et de la ventilation mécanique prolongée. La physiopathologie de la COVID-19 est présentée ici dans le contexte des premières données sur les issues et pour éclairer un programme de recherche longitudinale pour les patients et leurs familles.*

Keywords mechanical ventilation · acute respiratory distress syndrome · outcome · COVID-19 · post-intensive care syndrome

COVID-19 is a multisystem disease with unknown recovery and long-term outcomes. Early systematic reviews documented 42% mortality,[1] but more adult patients with COVID-19 are now surviving their intensive care unit (ICU) stay, with a pooled 36% mortality rate.[2] Survivors typically experience long hospital and ICU lengths of stay (LOS).[3] An early systematic review of 52 international studies of hospitalized patients admitted between December 2019 and April 2020 documented a median hospital LOS varying from five to 29 days. This is consistent with hospital data from seven sites in the Toronto and Mississauga areas in the GEMINI network.[4] Canadian ICU cohorts reported hospital LOS varying from 17[5] to 18[6] days, and ICU LOS from 9[6] to 11[5] days (Table 1). Longer ICU LOS increases the risk of disability after ICU and hospital discharge.[7]

Research from severe acute respiratory syndrome (SARS) and acute respiratory distress syndrome (ARDS) may help to anticipate short- and long-term challenges faced by COVID-19 survivors and their caregivers. ICU survivors of COVID-19 are at particular risk for complex multimorbidities, weakness and physical disability, cognitive dysfunction, and mood disorders for both patients and families. This narrative review presents a case study of a composite critically ill adult patient with COVID-19, from ICU admission through to recovery and return to the community. We identified peer-reviewed international and Canadian epidemiologic data and cohort studies from PubMed and Canadian government websites for data on ICU admissions for COVID-19, COVID-19 pathophysiology, emerging ICU practice patterns, and early reports of long-term outcomes. We summarize federal support programs for survivors and their families from government websites. Throughout the course of this case, we highlight key discussion points in ICU management and summarize the supportive evidence, relevant pathophysiology, and potential implications for outcome-based ICU survivorship research.

Case study: initial ICU management

*Ms. Z. is a 45-yr-old functionally independent woman who worked full-time in a senior government position. Her medical history includes hypertension and type II diabetes with mild renal impairment. Ten days after diagnosis at a walk-in COVID-19 centre, she presented to an emergency room with shortness of breath and progressive hypoxemic respiratory failure, requiring urgent intubation and admission to the ICU. She was given 6 mg dexamethasone daily, deeply sedated with propofol and fentanyl, and pharmacologically paralyzed. Despite optimized, lung-protective ventilation settings, she remained hypoxemic with an arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2;P/F ratio) of 60. She was proned with good effect and this continued intermittently for 1 week. She received broad-spectrum antimicrobials for documented ventilator-associated pneumonia (*Klebsiella pneumoniae*).*

Table 1 Canadian critical care cohorts of patients with COVID-19

Cohort	Vancouver[6]	Montreal[5]	CAN-SARI[85]
N	117	75	328 (ICU only)
Number of centres	6	1	33
ICU types	Medical-surgical; quaternary (*n* = 1), tertiary (*n* = 3), community (*n* = 2)	Medical-surgical; quaternary	Medical surgical; academic (*n* = 15); community (*n* = 15); pediatric (*n* = 3)
ICU admission dates	21 February–14 April 2020	20 March–13 May 2020	Before 7 July 2020
Follow-up date	5 May 2020	27 July 2020	7 July 2020
Demographics			
Female, *n*/total *N* (%)	38/117 (32%)	25/75 (33%)	105/328 (32%)
Age (yr), median [IQR]	69 [60–75]	62 [53–72]	65 [54–72]
Comorbidity, *n*/total *N* (%)			
Hypertension	54/117 (46%)	50/75 (67%)	149/328 (45%)
Dyslipidemia	43/117 (37%)	NR	NR
Diabetes mellitus	36/117 (31%)	27/75 (37%)	90/328 (27%)
Chronic kidney disease	15/117 (13%)	NR	67/328 (20%)
None	31/117 (26%)	11/75 (15%)	NR
Body mass index ($kg \cdot m^{-2}$), median [IQR]	28 [24–33]	29 [25–32]	NR
Health care worker, *n*/total *N* (%)	NR	9/75 (12%)	NR
Severity of illness – APACHE II	18 [10–28]	NR	NR
SOFA day 1	6 [2–11]	6 [3–7]	NR
Duration of symptoms at ICU admission (days), mean (SD) or median [IQR]	8 (5)	8 [6–11]	7 [3–10][a]
ICU interventions			
Invasive mechanical ventilation, *n*/total *N* (%)	74/117 (63%)	43/75 (57%)	291/328 (89%)
Duration (days), median [IQR]	13.5 [8–22]	11 [5–22]	NR
Duration (days), median [IQR], for survivors	11 [6–16]	13 [5–24]	NR
Noninvasive mechanical ventilation, *n*/total *N* (%)	15/117 (13%)	16/75 (75%)	35/328 (11%)
High-flow nasal cannula, *n*/total *N* (%)	43/117 (37%)	2/75 (3%)	40/328 (12%)
ECMO, *n*/total *N* (%)	3/117 (3%)	1/75 (2%)	13/328 (4%)
Nitric oxide, *n*/total *N* (%)	NR	15/43 (36%)	NR
Proning, *n*/total *N* (%)	21/117 (18%)	11/43 (26%)	55/328 (17%)
Tracheostomy, *n*/total *N* (%)	NR	10/43 (24%)	10/328 (3%)
Continuous renal replacement therapy, *n*/total *N* (%)	16/117 (14%)	7/75 (9%)	49/328 (15%)[b]
Vasopressors, *n*/total *N* (%)	65/117 (56%)	NR	274/328 (84%)
Neuromuscular blockers, *n*/total *N* (%)	50/117 (47%)	16/43 (38%)	NR
Corticosteroids, *n*/total *N* (%)	28/117 (24%)	35/75 (47%)	95/328 (29%)
Deep sedation, *n*/total *N* (%)	NR	NR	NR
Outcomes			
ICU LOS (days)	9 [5–21]	10 [4–19]	NR
Hospital LOS (days)	18 [11–30]	17 [10–42]	NR
ICU mortality, *n*/total *N* (%)	18/117 (15%)	17/75 (23%)	86/328 (26%)
Hospital mortality, *n*/total *N* (%)	18/89 (20%)	19/74 (25%)	NR
Still in ICU or hospital, *n*/total *N* (%)	28/117 (24%)	1/75 (1%)	NR
Discharge destination (survivors), *n*/total *N* (%)		NR	NR

Table 1 continued

Cohort	Vancouver[6]	Montreal[5]	CAN-SARI[85]
Home	71/71 (100%)		

[a] To hospital admission and median [IQR] 0 [0–1] days from hospital to ICU admission

[b] Renal replacement therapy

APACHE II = acute physiology and chronic health evaluation II, a severity of illness score where higher values (0 to 71) represent higher risk of hospital mortality; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; NR = not reported; SD = standard deviation; SOFA = sequential organ failure assessment score—a measure of organ dysfunction, where higher values (0 to 24) represent higher risk of mortality

Discussion and literature context

Approximately 80% of patients with COVID-19 develop mild to moderate symptoms, 15% require oxygen support, and 5% progress to ARDS and multiple organ dysfunction syndrome.[9] SARS-CoV-2 infects type I and II pneumocytes and capillary endothelial cells. Viral uptake is promoted by TMPRSS2 (serine protease) cleavage of angiotensin converting enzyme 2 and activation of the SARS-CoV-2 spike protein. Subsequent kinin release causes vascular leak, angioedema, and coagulation activation. Hypoxemia is the culmination of endotheliitis with diffuse injury of the microcirculation, complicating thrombotic events and increased dead space ventilation; alveolitis; pulmonary edema and shunt from consolidation, and atelectasis.[9]

Initial management of COVID-19 respiratory failure may necessitate deep coma with continuous administration of multiple sedative-hypnotic agents and use of neuromuscular blocking agents, corticosteroids, and proning. An international observational study of 2,088 ICU patients in 69 centres documented that 88% received invasive mechanical ventilation, 63% received benzodiazepines for a median [interquartile range (IQR)] of 7.0 [4.0–12.0] days, 71% received propofol for 7.0 [4.0–12.0] days, and 82% experienced deep coma for 10.0 [6.0–15.0] days.[10] Early multicentre ICU cohort studies that enrolled 547 patients with COVID-19 in France[11,12] and Belgium[12] documented a 15 [10–25] day ICU LOS, with a 13 [9–23] day duration of mechanical ventilation.[11] Sedation included 6 [3–12] days of midazolam and 10 [5–15] days of sufentanil;[11] 84% received a neuromuscular blocking agent (NMBA), for 5 [2–10] days, and 80% were proned.[12]

Proning is a proven intervention to reduce mortality in ARDS[13,14] and is a cornerstone of therapy in COVID-19.[15] The duration of daily proning in patients with COVID-19 ARDS is similar ($\sim$16 hr)[16] to randomized controlled trials (RCTs) identified in a systematic review of moderate-to severe ARDS (16–18 hr).[17] Nevertheless, recurrent, daily proning requires sustained deep coma and prolonged paralytic use, which may promote muscle unloading and further exacerbate ICU-acquired weakness. A systematic review of non-COVID-19 ARDS patients showed harm from proning, including an increased risk of pressure injuries (three RCTs; 1,109 patients; relative risk, 1.22; 95% confidence interval [CI], 1.06 to 1.41) and endotracheal tube obstruction (three studies; 1,594 patients; relative risk, 1.76; 95% CI, 1.06 to 1.41).[18] A small retrospective chart review identified that the most common upper limb nerve injuries in COVID-19 ICU survivors occurred in the ulnar nerve (40%) or brachial plexus (33%).[19] Given the rapid uptake of prone positioning for COVID-19 ARDS, short- and long-term evaluation of post-ICU outcomes and pragmatic trials evaluating efficacy are needed.

In summary, early studies highlight the complexities of respiratory failure in patients with COVID-19: approximately two weeks of invasive mechanical ventilation, ten days of deep coma, one week of sedation, and five days of NMBA administration. Proning is common. The adoption of sustained deep coma in COVID-19 patients is in sharp contrast to current critical care guidelines recommending judicious and intermittent use of sedation, usual care with light sedation targets (Richmond Agitation and Sedation Scale between -2 to $+1$),[20,21] and literature supporting only up to 48 hr of continuous paralytic to facilitate lung protective ventilation.[22] For COVID-19 patients with refractory hypoxemia requiring prolonged sedation and NMBAs, further research on management strategies and long-term outcomes is needed.

Intensive care unit convalescent phase and emergence of ICU-acquired morbidities

Ms. Z. was mechanically ventilated for more than seven days and developed anuric renal failure requiring renal replacement therapy (RRT). As her oxygenation improved, her pharmacologic paralysis was discontinued, and her sedative and opioid analgesic infusions were weaned. Nevertheless, she remained in a coma (Richmond Agitation Sedation Scale, −4 or −5) for four more days. As she wakened, she became increasingly distressed and agitated, and delirium with attendant disorganized thinking became apparent. She was serially trialled with different antipsychotics and was effectively managed with dexmedetomidine. Once her delirium settled, she could communicate with the team and obey simple commands but had profound global weakness and was functionally quadriplegic. Her renal failure improved and she no longer required RRT. On day 11 of her ICU stay, she was extubated, and 24 hr later was discharged to the general medical floor.

Discussion and literature context

Renal injury

Renal injury in COVID-19 is common (> 40% have proteinuria at hospital admission)[23] and acute kidney injury (AKI) affects 20–40% of critically ill patients.[24] The renal lesion in COVID-19 is multifactorial and contributors include endotheliitis, which has been implicated in proteinuria; direct infection of the tubular endothelium causing mitochondrial dysfunction and acute tubular necrosis; immune dysregulation; and multiple organ dysfunction.[25] There are no specific recommendations for managing AKI secondary to COVID-19. Content experts suggest implementation of the Kidney Disease: Improving Global Outcomes supportive care guideline.[26]

Development of delirium and signs of ICU-acquired weakness (ICUAW) often become apparent as patients emerge from coma. With long ICU and hospital stays, patients are at increased risk for infection, complex multimorbidities, pressure injuries,[27] contractures,[28] delirium,[29] and ICUAW. This section highlights key factors associated with delirium and ICUAW. Table 2 outlines the relationship between ICU exposure/interventions in COVID-19 patients, and reported outcomes in the ICU literature.

Delirium

Delirium is defined as an acute change in level of consciousness, characterized by impaired attention and disorganized thinking.[30] This patient experienced robust risk factors for ICU delirium including multiorgan dysfunction, mechanical ventilation, benzodiazepines, and prolonged sedation and narcotic use.[31] Delirium is morbid and associated with longer ICU and hospital LOS, ICU, hospital and one-year mortality, and long-term cognitive impairment.[32,33] The occurrence and duration of delirium are the most consistent factors associated with long-term cognitive impairment in critically ill patients.[34]

Brain injury is common in COVID-19; prevalent neurologic symptoms have been reported in cohorts from both China and France[35,36] and most commonly include headache, anosmia, and ageusia. Impaired consciousness, seizure, stroke, encephalopathy, and coma have also been described. The long-term sequelae of this injury are still emerging but commonly manifest as "brain fog" or dysexecutive syndrome and may be debilitating, limiting return to work or baseline function.

The pathophysiology of SARS-CoV-2 brain dysfunction is complex and multifactorial, including an initial extension to the central nervous system (CNS) via the transcribrial path via the olfactory epithelium to the olfactory nerve and bulb[37] via retrograde spread through endocytotic/exocytotic transfer and fast axonal transport. Other purported mechanisms include infection of CNS glial cells via infected endothelial cells, and by infected leukocytes that cross the blood–brain barrier to infect the CNS. The pervasive endotheliitis may also provide insight into further pathophysiologic mechanisms of brain injury. A recent research letter identified large cell nuclei morphologically consistent with megacakaryocytes in cortical capillaries of patients who died of COVID-19, an observation not previously documented in the literature.[38] From examination of *post mortem* brain samples from those who died from COVID-19, authors noted that these large cells may occlude capillary flow and result in a novel form of ischemic brain insult.[32] Brain injury in the critically ill patient is further potentiated by hypoxemia[39] and exposure to continuous infusions of sedation and opioid analgesics,[10,33] intercurrent sepsis,[40] immobility,[41] and all the factors that mitigate delirium, including isolation from family.[10]

A multicentre, multinational cohort study of 2,088 critically ill patients with COVID-19 represents the largest sample of the epidemiology of coma and delirium to date.[10]

Table 2 Overview of COVID treatment approaches, clinical observations, relationship to previous knowledge, and long-term outcome considerations

Issues	COVID-19 treatments/policy changes	COVID-19 clinical observations	Knowledge from similar ICU clinical populations	Implications for long-term outcomes
Treatment	Dexamethasone	Improved 28-day mortality: 22.9% *vs* 25.5%; age-adjusted rate ratio, 0.8; 95% CI, 0.75 to 0.93; for mechanically ventilated patients: 29.3% *vs* 41.4%; rate ratio, 0.6; 95% CI, 0.51 to 0.81[51]	Corticosteroids associated with weakness[86]	ICUAW
Respiratory failure	Mechanical ventilation	Incidence: 23%[87]	Risk factor for ICUAW[50]	ICUAW
		Duration, median [IQR]: 13 [9–23] days[11]	Barrier to mobilization[88]	Fatigue
	Sedation	Duration of benzodiazepine administration, median [IQR]: 7 [4–12] days	Delirium associated with poor cognition and physical function[33]	Cognitive impairment at hospital discharge
		Duration of propofol administration, median [IQR]: 7 [4–12] days	Barrier to mobilization[88]	ICUAW
		Delirium incidence: 55%[10]		
	Proning	Awake proning:[89] ongoing RCTs Incidence in patients with COVID-19 ARDS: 79.9%[12]	For intubated patients: requires deep sedation and use of neuromuscular blockers	Nerve compression injuries Skin ulcers
	Neuromuscular blocking agents	Incidence in mechanically ventilated patients with COVID-19 ARDS: 84%[12]	In patients with ARDS, associated with ICUAW[22]	Nerve compression injuries
		Duration, median [IQR]: 5 [2–10] days[12]	Risk factor for ICUAW[50]	Cognitive impairments
ICU admission	Restricted hospital visitation policies[90]	Family visitation (in-person or virtual): 27% reduction in risk of delirium[10]	Risk for PICS[7,55-57,91,92] Risk for PICS-F[81]	Patients: Physical and cognitive impairments, mood disorders Family members: mood disorders
Hospital outcomes		Return to work: 60% returned by 60 days[83]	Return to work: SARS: 35% at 3 months; 63% at 6 months; 74% at 1 year [58] ARDS: 49% at 1 year[57]	Return to work planning; financial assistance

ARDS = acute respiratory distress syndrome; CI = confidence interval; ICUAW = intensive care unit-acquired weakness; IQR = interquartile range; PICS = post-intensive care syndrome; PICS-F = post-intensive care syndrome, family; RCT = randomized controlled trial; SARS = severe acute respiratory syndrome

Investigators observed a high burden of acute brain dysfunction (> 80% of patients had coma and > 50% developed delirium) with a median duration of two weeks. Similar to prepandemic studies, the development of delirium was associated with mechanical ventilation, vasopressor infusions, and antipsychotics.[10] Important modifiable determinants of delirium were benzodiazepine infusion (59% higher risk of delirium) and family visitation (27% lower risk of delirium). Hyperactive (agitated) delirium appeared to be more common,[10] in contrast to non-COVID-19 patients who present more commonly with hypoactive delirium.[42] Little is currently understood about the long-term effects of delirium in patients with COVID-19 and whether delirium is a risk factor for or a manifestation of specific COVID-19-related brain injury.[37] For COVID-19 patients who develop delirium in the ICU, screening for post-ICU cognitive impairment(s) is warranted.

Intensive care unit-acquired weakness

Intensive care unit-acquired weakness may present as critical illness polyneuropathy (axonopathy), critical illness myopathy (myosin-depletion myopathy), or mixed critical illness neuromyopathy.[43-47] It is a diagnosis of exclusion, when there is no other plausible etiology other than critical illness, and is associated with myriad risks during the ICU stay.[47] Intensive care unit-acquired weakness may be identified by electrodiagnostic testing (e.g., nerve conduction studies, needle electromyography) or clinical exam. A clinical exam requires patient participation and is not practicable in those who are deeply sedated or unable to follow commands.

The Medical Research Council (MRC) Sum Score is a clinical examination for ICUAW. The MRC score assesses strength in six bilateral muscle groups (shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and ankle dorsiflexors) and is graded from 0 (no contraction) to 5 (full strength against resistance). A sum score of < 48/60 indicates ICUAW.[48] Muscles from patients with ICUAW show a shift from fast- to slow-twitch fibres, a 70% reduction in myosin, a reduction in the actin/myosin ratio, and disruption of sarcomeric architecture.[49] Some disability may be fixed as recovery of muscle bulk and contractile force may be incomplete and discordant, and may have a genetic basis.[49]

In the pre-COVID-19 era, the median incidence of ICUAW was 39% (95% CI, 35 to 55),[50] with baseline risk factors being female sex, severity of illness, and diagnosis (e.g., sepsis, multiorgan failure). Intensive care unit therapies associated with ICUAW included duration of mechanical ventilation, immobility, and receipt of NMBAs, aminoglycosides, norepinephrine, and corticosteroids.[50] The 6,425-patient RCT, RECOVERY, showed improved 28-day mortality in those receiving 6 mg dexamethasone daily for up to ten days *vs* standard care (22.9% *vs* 25.7%; age-adjusted rate ratio, 0.83; 95% CI, 0.75 to 0.93).[51] Effect sizes were larger for those receiving mechanical ventilation (29.3% *vs* 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81).[51] Given the efficacy of dexamethasone in critically ill patients with COVID-19,[51] the impact of corticosteroids on the development of ICUAW is potentially very important. A prepandemic systematic review of ICU patients documented ICUAW in 43% of those receiving corticosteroids *vs* 34% in controls (odds ratio [OR], 1.84; 95% CI, 1.26 to 2.67).[52] Patients receiving mechanical ventilation and corticosteroids had twofold higher odds of developing ICUAW than those who did not (OR, 2.0; 95% CI, 1.23 to 3.27). Many patients with COVID-19 managed in the ICU have multiple risk factors for ICUAW, including mechanical ventilation, immobility, NMBAs, and corticosteroids; nevertheless, the unique contribution of COVID-19 is still under investigation. We recommend initial screening for a patient's ability to follow simple commands[45] and a clinical evaluation for ICUAW as soon as practicable in the ICU.

Recovery from COVID-19 critical illness and long-term outcomes

On transfer to the medical ward, the patient was unable to stand or walk, had difficulty feeding herself, and required assistance for bathing and toileting. She commented that just sitting in a chair was exhausting. Ms. Z. was lonely and missing her family, especially her husband and ten-year-old daughter, but was not allowed visitors because of local public health policies enacted by the Canadian Quarantine Act. Two weeks later, Ms. Z. was transferred to an inpatient rehabilitation facility. Over four weeks, she had a gradual improvement in her activities of daily living and functional independence. She noted that her memory was impaired and was having difficulty processing new information and organizing her thoughts. She began to have nightmares of her ICU stay including concerns that the ICU staff were mocking/tormenting her and trying to harm her and her family members.

Ten weeks after her initial hospital admission, she was discharged home. She used a cane to assist with walking and balance and required a personal support worker for two hours each day to assist with bathing/toileting and meal preparation. At three months after ICU discharge, she continued to report muscle loss and ongoing weakness, most pronounced in the shoulder and hip girdle, and dependency with some activities of daily living. She noted it was still difficult to get in and out of a car, climb stairs, and bathe independently. Formal neurocognitive testing confirmed short-term memory impairment, diminished processing speed, and executive dysfunction. Her Functional Independence Measure (FIM) was 80 and her six-minute walk test (6MWT) distance was 73% of predicted. While she did not have any oxygen desaturation during exercise, her pulmonary function testing showed a mild restrictive pattern with normal diffusion capacity. She reported some days with low mood but denied symptoms of post-traumatic stress disorder (PTSD).

At six-month follow-up, she was negotiating a gradual return to work, beginning with one day per week. She requested support from a social worker to assist with her transition back to work and disability insurance paperwork. Her cognitive function was better but still impaired. Her physical function was improved but had not returned to baseline. Her FIM was 95 and her 6MWT was 82% of predicted. Her pulmonary function testing was now normal, with stable oxygenation during exercise. She reported moderate to severe depressive symptoms and agoraphobia and was seeking a psychiatry referral. Her husband was experiencing moderate anxiety and symptoms consistent with PTSD and had developed a new substance use disorder in that context. Follow-up is ongoing.

Discussion and literature context

Challenges with weakness, multimorbidities, impaired cognition, and altered mood may be ongoing and typical of the transformative impact of critical illness[53] as well as consistent with the construct of post-intensive care

syndrome (PICS).[8] The recent extension highlights additional conditions observed in ICU survivors, including frailty, chronic pain, endocrine and metabolic disorders (e.g., new onset diabetes), and residual fatigue.[54]

Physical disability

Outcomes from survivors of non-COVID-19 ARDS may help us anticipate what we might expect for survivors of COVID-19.[55-57] A young cohort (median age, 45 yr) of 117 survivors with severe four-quadrant ARDS (Lung Injury Severity Score, 3.7/4 and Berlin definition of moderate to severe disease) had a median [IQR] ICU LOS of 25 [15–45] days, duration of mechanical ventilation of 21 [12–40] days, and hospital LOS of 48 [27–77] days. While pulmonary function test results returned to normal or near normal by six months, patients experienced persistent physical impairment.[55-57] At follow-up, the 6MWT was 49% of predicted values at three months, 64% at six months, 66% at 12 months, 68% at two years,[57] and 76% at five years.[56] In a cohort of SARS survivors, the 6MWT was 81% of the predicted value at three and six months, and 83% at 12 months.[58] From a ten-centre, 391-patient cohort of non-COVID-19 survivors who were mechanically ventilated for seven or more days, the majority were unable to walk at seven days post ICU, despite being able to walk independently before their critical illness.[7] Based on initial reports of long periods of sedation, immobilization, and subsequent slower time to initiate rehabilitation in COVID-19 ARDS ICU patients, we believe the physical disability will be at least similar to, if not worse than, non-COVID-19 ARDS, emphasizing the importance of long-term follow-up studies in survivors.

The FIM is a valid and reliable instrument typically used in inpatient rehabilitation that measures motor and cognitive disability in 18 items, using a seven-point scale (1 = total assistance; 7 = complete independence).[59,60] The 13 motor items include self-care (n = 6), sphincter control (n = 2), transfers (n = 3), and locomotion (n = 2), and the five cognitive items include communication (n = 2) and social cognition (n = 3). The minimum score is 18 and the maximum score is 126, with scores $<$ 40 reflecting maximal to total assistance, 50 reflecting moderate assistance, and $>$ 60 reflecting modified assistance.[7] In critically ill patients, the FIM at seven days after ICU discharge predicted the FIM score at one year, highlighting the potential for ICU interventions to mitigate modifiable long-term outcomes.

Rehabilitation

Rehabilitation interventions started in the ICU are one approach to address weakness and disability post ICU. Rehabilitation with critically ill patients is safe and feasible, even while patients receive mechanical ventilation.[61-63] An early report from the UK in 110 mechanically ventilated ICU survivors of COVID-19 documented a mean time to sitting at the edge of the bed of 14 days within an ICU LOS of 22 days.[64] These observations are similar to those from reports over a decade ago, which reported a median time from ICU admission to receipt of initial rehabilitation assessment of ten days, therapy only occurring on 14% of all ICU days, and patients unable to participate in rehabilitation because of sedation.[65] COVID-19-related factors, including early concerns for preservation of personal protective equipment supplies, limited healthcare provider interactions with patients, delay to rehabilitation assessment and intervention, fear of healthcare worker infection, and restricted visitor policies could further increase the incidence of ICUAW and subsequent functional disability. Given the longer ICU stay and longer time to initiate ICU rehabilitation in patients with COVID-19 ARDS, preventive rehabilitation maneuvers such as careful positioning to avoid pressure injuries and joint contractures will be critical to optimize future recovery.

Long-term functional disability

Longer-term follow-up data in survivors of COVID-19 are emerging and these will inform the extent and duration of functional disability. Early research suggests important physical disability. Half of COVID-19 ICU survivors needed to learn to walk again after ICU discharge, increasing to 83% by hospital discharge.[64] In a cohort study of 1,655 hospitalized COVID-19 survivors in China, 63% reported muscle weakness or fatigue at six months. Survivors who required high-flow nasal cannula, noninvasive ventilation, or invasive mechanical ventilation were more likely to report muscle weakness or fatigue than those not requiring supplemental oxygen (81% [95/117] *vs* 66% [281/424]; OR, 2.69; 95% CI, 1.46 to 4.96).[66] At six and 12 months, the median [IQR] six-minute walk distances were 495.0 [430.0–526.0] m (82.4% predicted) and 496.5 [455.0–552.0] m (87.9% predicted), respectively,[67] which is better than in non-COVID-19 ARDS survivors (six months, 396 [244–500] m [64% predicted]; 12 months, 422 [277–510] m [66% predicted]).[55] Once patients are emerging from sedation and are clinically stable,[68] we recommend documenting pre-ICU function and initiating rehabilitation. Patients will likely need to relearn fundamental mobility activities (e.g., rolling in bed, sitting at the edge of the bed, standing, walking), activities of daily living (e.g., bathing, eating), and those with prolonged intubation may be at risk for

dysphagia.[69] We recommend engaging rehabilitation professionals (e.g., physiotherapy, occupational therapy, speech and language pathology) in the ICU and on the wards, depending on patients' needs and availability of hospital staff.

Mood disorders

In the late 1990s, clinical researchers began publishing on mood disturbances in post-ARDS patients including PTSD as well as depressive and nonspecific anxiety phenomena.[70-72] A systematic review on psychiatric morbidity in ARDS survivors showed a median study prevalence of 28% PTSD, 28% depression, and 24% nonspecific anxiety symptoms.[70] Prior psychiatric illness is a potent risk factor for psychiatric morbidity after ARDS. Huang *et al*. noted that six months after ICU discharge, survivors of COVID-19 were mainly troubled with sleep difficulties and symptoms of anxiety or depression.[66] These outcomes were very similar to those reported in a Canadian one-year SARS follow-up.[58] Severe acute respiratory syndrome may also be used as a case study to analyze the impact on patient recovery and mental health. Psychological impacts of SARS included "fear of infecting others, stigmatization, reduced quality of life, and posttraumatic stress."[73] Many of the same psychological stressors are apparent in current COVID-19 patients, survivors, and family members. Managing the mental health crisis exacerbated by COVID-19 will be a crucial step towards recovery. The COVID-19 pandemic has created novel challenges for treatment of mental illness, and many services quickly adapted to meet these needs. The Toronto Centre for Addiction and Mental Health reported an over 12-fold increase in online patient sessions from fewer than 400 in February 2020 to over 5,000 by May 2020.[74]

Development of frailty

Frailty is a "medical syndrome with multiple causes and contributors, and is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death".[75] A patient's frailty status may potentiate the proinflammatory response related to COVID-19 infection, predisposing to more severe infections, higher degrees of organ failure, and a poorer prognosis.[76] Very little is known about frailty development following critical illness. A prepandemic, 567-patient longitudinal study in medical and surgical ICUs at five US centres found that the incidence of frailty increased from 24% at ICU admission to 37% at 12 months.[77] Further, transition to a worse frailty status in those already frail occurred in 40% of patients at 12 months. Since SARS-CoV-2 infections typically require prolonged ICU stays, survivors are at higher risk for either new or worsened frailty status, and further studies are needed to understand the relationships and modifiable risk factors for frailty following COVID-19 infection. We recommend documenting the frailty status from before COVID-19 baseline and at hospital discharge to help track the patient's longitudinal trajectory after discharge from hospital.

Impact of COVID-19-associated critical illness on family

The engagement of family as partners in the critical care environment has been shown to have significant physical, psychological, and emotional benefits for the patient and also benefits for communication and trust between care providers, LOS, and family mental health.[78] Family presence (in person or virtual) has been shown to be the strongest predictor for reduced ICU delirium in COVID-19 patients.[10] These potential benefits have disintegrated with the introduction of widespread visitor restriction policies via the Quarantine Act[79] during the COVID-19 pandemic, exacerbating frustration, anxiety, and post-traumatic symptoms among patients and families.[80] Furthermore, healthcare providers now have not only the responsibility for providing optimal care for their patients but also the added stress of balancing visitor restriction enforcement and supporting the needs of family members.

COVID-19 critical illness can also affect family members of patients with critical illness. Family members report domains of PICS, including psychological symptoms such as depression and PTSD. The prepandemic Canadian RECOVER program revealed that at seven days post ICU, 67% of caregivers of critically ill adults were at risk for clinical depression.[81] While 84% of these caregivers showed improvement, 16% continued to have significant symptoms one year later. These data suggest that family members of patients with COVID-19 may perhaps be at even higher risk of the PICS family sequalae, and are currently an important focus of pandemic research. The second and third waves in Canada witnessed multiple patients from the same households concurrently admitted to the hospital or ICU, further amplifying the complexities of survivorship and potentially exacerbating recovery challenges. When ICU teams communicate with patients' families, we suggest careful attention to potential indicators of mood disorders in family members. Referral of family members for further mental health supports may be necessary.

Return to work, disability insurance, and financial support

Data on return to work after COVID-19 are still emerging (Table 2), and may be confounded by increased unemployment in Canada during the pandemic. A pre-COVID-19 systematic review documented that 36% of critical illness survivors returned to work between one to three months, 64% by six months, and 60% by one year.[82] In patients post SARS, 35% had returned to their pre-SARS level of work by three months, and 63% by six months.[58] A 38-centre prospective cohort study from Michigan documented 60% employed full- or part- time before COVID-19 hospitalization returned to work by 60 days; however, this study was limited by a 39% follow-up rate.[83]

For critically ill survivors and their families, disability insurance or other forms of financial support may be necessary. Canada's economic response plan offers benefits that in some cases may extend up to 26 weeks for workers who have either stopped working, had their income reduced by 50%, or are the caregiver for a family member who is sick or required to quarantine.[84] The Canadian government created new financial support programs specifically for those affected by COVID-19, such as the Canada Recovery Benefit (CRB), Canada Recovery Sickness Benefit (CRSB), and the Canada Recovery Caregiver Benefit (CRCB).[84] The CRB provides CAD 500 per week up to 38 weeks to those who are unemployed because of COVID-19, or had their income reduced by 50%, and do not qualify for Employment Insurance.[84] The CRCB provides CAD 500 per week up to 38 weeks for households who have to care for a child or family member because of closures, sickness, or is required to quarantine due to COVID-19.[84] The CRSB is a shorter-term support of up to four individual weeks to help workers infected with COVID-19 who are unable to work for at least 50% of the week.[84]

The medical, financial, and social implications of COVID-19 have yet to fully manifest in Canada, and this disease will be responsible for the largest critically ill cohort in Canadian history. Post ARDS, the mean Canadian direct healthcare costs per patient after index hospitalization were CAD 16,200 in the first year and CAD 12,100 in the second year, primarily driven by subsequent hospitalizations, and inpatient rehabilitation.[57] As of 19 November 2021, the Public Health Agency of Canada reported 17,574 patients admitted to ICUs during the COVID-19 pandemic, based on hospitalization data available for 72.8% of over 1.75 million cases.[A] If we consider data from Canadian ARDS survivors, assuming a 75% COVID-19 ICU survival rate for 13,180 patients, and conservative estimate of 50% disability rate post ICU, the *minimum* two-year post-ICU healthcare costs alone are over 186 million, posing an important policy implication for our Canadian healthcare system to manage post-intensive care sequelae of this group alone. While financial support is crucial to those affected by COVID-19, psychological and physical rehabilitation will play key roles in the recovery of critically ill COVID-19 patients.

How can we prepare for the future? Summary and conclusions

Surviving an ICU stay for COVID-19 is the start of a complex road to physical, cognitive, and psychological recovery. We summarize key messages in Table 3. The emerging practice patterns documented for critically ill mechanically ventilated patients with COVID-19, including prolonged sedation, delirium, and ICUAW, are associated with important long-term morbidity in non-COVID-19 patients. COVID-19 may amplify and exacerbate these negative sequelae and may introduce new challenges for survivors, their families, and healthcare providers. Future understanding of context-specific exceptions for visitors will inform future decisions on balancing the risk and benefits of family partners and patient-centred care.

COVID-19 will serve to encourage careful consideration of establishing longitudinal programs for survivors of critical illness and their families, and rigorous follow up is urgently needed. In the hospital setting and beyond, future research is needed for a post ICU continuum of care to improve care transitions and systematically address the physical and neuropsychological sequelae of severe illness, immediate rehabilitation needs, and the longer-term assistance with return to community. As patients and their families navigate their recovery from critical illness, research and support to help them return to their lives and communities will be critically important.

[A] *Government of Canada.* COVID-19 daily epidemiology update. Available from URL: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html#a7 (accessed 22 November 2021).

Table 3 Key messages

Issue	Key message
Delirium	For COVID-19 patients who develop delirium in the ICU, screening for post-ICU cognitive impairment(s) is warranted
ICU-acquired weakness	We recommend initial screening for a patient's ability to follow simple commands and a clinical evaluation for intensive care unit-acquired weakness as soon as practicable in the ICU
Physical disability	Once patients are emerging from sedation and are clinically stable, we recommend documentation of pre-ICU function and initiation of rehabilitation. Patients will likely need to relearn fundamental mobility activities, activities of daily living, and those with prolonged intubation may be at risk for dysphagia. We recommend engaging rehabilitation professionals in the ICU and on the wards, depending on patients' needs and availability of hospital staff
Frailty	We recommend documentation of frailty status at pre-COVID-19 baseline and at hospital discharge to help track the patient's longitudinal trajectory after hospital discharge
Family	When ICU teams communicate with patients' families, we suggest careful attention to potential indicators of mood disorders in family members. Referral of family members for further mental health support may be necessary

ICU = intensive care unit

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Commercial or noncommercial affiliations that are or may be perceived to be a conflict of interest with the work for each author Michelle Kho leads a research program of early in-bed cycling with critically ill patients and received the loan of four in-bed cycles from Restorative Therapies, Baltimore, MD. J Gordon Boyd receives a stipend from the Trillium Gift of Life Network to support his role as Regional Medical Lead.

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