Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care

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As of July 31, 2021, SARS-CoV-2 had infected almost 200 million people worldwide. The growing burden of survivorship is substantial in terms of the complexity of long-term health effects and the number of people affected. Persistent symptoms have been reported in patients with both mild and severe acute COVID-19, including those admitted to the intensive care unit (ICU). Early reports on the post-acute sequelae of SARS-CoV-2 infection (PASC) indicate that fatigue, dyspnoea, cough, headache, loss of taste or smell, and cognitive or mental health impairments are among the most common symptoms. These complex, multifactorial impairments across the domains of physical, cognitive, and mental health require a coordinated, multidisciplinary approach to management. Decades of research on the multifaceted needs of and models of care for patients with post-intensive care syndrome provide a framework for the development of PASC clinics to address the immediate needs of both hospitalised and non-hospitalised survivors of COVID-19. Such clinics could also provide a platform for rigorous research into the natural history of PASC and the potential benefits of therapeutic interventions.

Introduction

The burden of COVID-19 survivorship is enormous. More than 190 million people had survived COVID-19 by the end of July 2021.[1] Even among previously young, healthy people with COVID-19 who require only outpatient care, nearly 20% do not return to their usual state of health within 3 weeks of infection.[2] In a study from China, approximately 75% of survivors who had been hospitalised with COVID-19 had at least one persistent symptom 6 months after acute illness.[3] The most commonly reported post-acute symptoms include fatigue, dyspnoea, cough, headache, loss of taste or smell, and cognitive or mental health impairments (eg, anxiety or depression).[4–6] Moreover, non-hospitalised patients with COVID-19 have a higher risk of death and health-care utilisation beyond the first 30 days of illness than do patients without COVID-19.[7] In response to the rapidly growing population of survivors of COVID-19 who experience a wide array of complex, multifactorial symptoms—referred to collectively as the post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection (PASC), or long COVID—the World Health Organization has advocated a multidisciplinary approach to support patients in their recovery.[8]

PASC might be specific to SARS-CoV-2 infection or represent a spectrum of symptoms that can also occur within the context of recovery from other acute infections or chronic conditions. For some patients, post-acute sequelae might arise as part of the post-intensive care syndrome (PICS), a collection of health impairments that are common in patients who survive critical illness and management in the intensive care unit (ICU). Although a clear definition of the post-COVID-19 condition is lacking at present, models of care are in development to address the long-term needs of patients with PASC. The overall goal of this Health-care Development paper is to inform the development of these multidisciplinary pathways of care, adapted from the PICS framework. The target audience includes patients, clinicians, educators, researchers, and policy makers. We describe the existing framework of care established to address the multifaceted needs of patients with PICS, and discuss the extension of ICU survivor clinics to meet the needs of patients after

Key messages

- The burden of post-acute sequelae of SARS-CoV-2 infection (PASC) is substantial in terms of the clinical complexity of symptoms and the number of patients affected worldwide
- Rigorous data characterising symptomology are limited at present, but physical, psychological, cognitive, and respiratory domains are key among those affected
- Clinics developed for survivors of critical illness, who experience a wide array of multifactorial symptoms, offer a model to address PASC survivorship for both acute and non-hospitalised patients with COVID-19; understanding of the determinants, clustering, and course of PASC will help to refine care pathways
- A multidisciplinary programme of care should include access to rehabilitation services, social work and welfare support, pharmacy, subspecialty care via direct inclusion or targeted referrals, and structured peer support programmes with trained moderators; coordination with primary care is essential
- Ensuring equitable provision of care, including access to care for under-served populations and the development of care pathways in low-income and middle-income countries, will be integral to international pandemic management
- PASC clinics offer research opportunities that should be harnessed to inform knowledge of survivorship trajectories after SARS-CoV-2 infection, and to improve service innovation and delivery

SARS-CoV-2 infection. We review key elements of a multidisciplinary programme—including physical medicine and rehabilitation, pharmacy, social work and welfare support, and primary care—and emphasise the importance of achieving equitable provision of care, including implementation in low-income and middle-income countries (LMICs). Finally, we consider the contribution that PASC clinics could make to research on the origins and natural history of PASC and the potential benefits of therapeutic interventions.

Post-acute sequelae of SARS-CoV-2 infection

Decades of research conducted prior to 2020 described the physical, cognitive, and mental health impairments experienced by survivors of critical illness, collectively termed PICS.[9] Knowledge gained about PICS can be leveraged to understand, describe, diagnose, and treat PASC. Specifically, survivors of acute respiratory distress syndrome (ARDS) experience exercise intolerance (eg, achieve below the predicted distance on a 6-min walk test), and half will not have returned to work at a year after discharge from the ICU.[10] Anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms are common and persist for months to years after critical illness.[11–13] Among critical illness survivors of all ages, median cognition scores are consistent with mild cognitive impairment; more than a third will have cognitive testing comparable to moderate traumatic brain injury a year later.[14]

There are few rigorous, prospective studies on the natural history of PASC, including prevalence and duration, with most studies following patients for fewer than 7 months (tables 1 and 2).[4,15–25] However, existing reports indicate that the burden of impairments is relatively high. An analysis of the US Department of Veterans Affairs electronic health database used a high-dimensional approach to evaluate 6-month outcomes for patients surviving the initial 30 days after

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	Number of studies	Number of patients	Age of patients	Studies of hospitalised or non-hospitalised patients	Study locations	Follow-up period*	Proportion with ≥1 persistent symptom at follow-up	PRISMA guidelines[24] followed?
Lopez-Leon et al[4]	15	47 910	Range 17–87 years	11 hospitalised; 4 mixed	8 Europe; 4 North America; 1 Australia; 1 China; 1 Egypt	14–110 days	80% (95% CI 65–92)†	Yes
Michelen et al[15]‡	39	10 951	Range <1 to 93 years (4 studies included children)	26 hospitalised; 4 non-hospitalised; 9 mixed	24 Europe; 9 Asia; 3 Middle East; 3 North America	Longest follow-up mean 222 (SD 11) days	NR	Yes
Nasserie et al[17]	45	9751	30 with mean or median <60 years; 14 with mean or median <50 years; 1 NR	33 hospitalised; 2 non-hospitalised; 10 mixed	31 Europe; 8 Asia; 5 North America; 1 Middle East	≥2 months from symptom onset, diagnosis, or hospitalisation	Median 73% (IQR 55–80)	No§
Domingo et al[18]‡¶	27‖	7162	NR	15 hospitalised; 5 non-hospitalised; 5 mixed; 2 unspecified	16 Europe; 5 Asia; 3 North America; 3 others	4–12 weeks; >12 weeks	83% (95% CI 65–93)**; 56% (34–75)††	Yes
Fernández-de-las-Peñas et al[19]	33	24 255	Mean 48 (SD 17) years	15 244 hospitalised; 9011 non-hospitalised‡‡	17 Europe; 8 North America; 5 Asia; 1 Egypt; 1 Russia; 1 multicountry	Median 21 days to 36 weeks	63% (95% CI 44–79) at 30 days†; 72% (53–85) at 60 days**; 46% (28–65) at ≥90 days†	Yes
Iqbal et al[20]	43§§ (30 in meta-analysis)	12 974	NR	20 hospitalised; 10 non-hospitalised; 13 mixed; 2 unspecified	35 Europe; 4 Asia; 3 North America; 1 Australia; 1 Middle East; 1 South America	28 days to 6 months	NR	Yes
Malik et al[21]¶	21	54 730	Median 54 years	Mixed	10 Europe; 4 North America; 2 Africa; 2 China; 2 Middle East; 1 Australia	>1 month in most studies	68%	Yes
Cabrera Martimbianco et al[22]	25	5440	NR	18 hospitalised; 2 non-hospitalised; 4 mixed; 1 unspecified	15 Europe; 5 China; 3 North America; 2 Middle East	NR	5–80%	Yes
Sanchez-Ramirez et al[23]	24	5323	Mean 55 (SD 8) years	Mixed	11 Europe; 7 China; 5 North America; 1 Middle East	Mean 4 months	NR	Yes

Systematic reviews of studies evaluating general post-COVID-19 symptoms in adult patients. Studies were excluded if they focused exclusively on a subset of symptoms (eg, neurological) or if they did not provide pooled estimates of symptom prevalence. NR=not reported. PASC=post-acute sequelae of SARS-CoV-2 infection. *Time zero differed between studies (eg, time from positive test *vs* symptom onset *vs* hospital discharge). †Based on seven studies. ‡Living systematic review. §Reported using the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines.[25] ¶Preprint. ‖Studies including adults with laboratory-confirmed SARS-CoV-2 infection. **Based on three studies. ††Based on four studies. ‡‡Number of hospitalised and non-hospitalised patients. §§43 studies given in PRISMA diagram; 45 studies reported.

Table 1: **Systematic reviews of PASC studies**

COVID-19. Beyond the first 30 days, results showed a higher risk of death for non-hospitalised patients with COVID-19 compared with those without COVID-19 (hazard ratio 1·59, 95% CI 1·46–1·73), as well as for patients hospitalised with COVID-19 compared with seasonal influenza (1·51, 1·30–1·76).[7]

As in PICS, cognitive impairment (so-called brain fog), fatigue, muscle weakness, and shortness of breath are among the commonly reported symptoms after COVID-19.[3,7,26–31] Using the 6-min walk test as a measure of physical function, nearly a quarter of survivors of COVID-19 perform below the lower limit of normal functioning 6 months after acute illness.[3] In a large international survey of COVID-19 survivors,[27] 3203 of 3762 respondents (85%) self-reported cognitive impairment; both older and younger respondents reported that such

	Lopez-Leon et al;[4] pooled prevalence (95% CI)	Michelen et al;[15] proportion (95% CI)*	Nasserie et al;[17] median proportion (IQR)	Domingo et al;[18] proportion (95% CI)†	Fernández-de-las-Peñas et al;[19] pooled prevalence (95% CI)†	Iqbal et al;[20] proportion (95% CI)†	Malik et al;[21] proportion	Cabrera Martimbianco et al;[22] proportion, range	Sanchez-Ramirez et al;[23] pooled prevalence (95% CI)‡
Systemic									
Fatigue	58% (42–73)	31% (24–39)	40% (31–57)	47% (27–68)	35% (25–47)	48% (23–73)	54%	7–64%	38% (27–49)
Sweat or night sweats	17% (6–30)	24% (21–27)	..	..	..	..	..	..	..
Weight loss	12% (7–18)	21% (8–45)	..	..	..	..	8%	..	..
Fever	11% (8–15)	1% (0–5)	1% (0–3)	0% (0–1)	..	..	..	0–20%	..
Pain	11% (7–18)	..	..	..	..	..	..	19–66%	..
Decreased functional capacity	..	..	..	..	..	..	..	6–50%	36% (22–49)
Neurological									
Headache	44% (13–78)	5% (2–10)	..	4% (2–10)	6% (3–12)	12% (0–44)	<1%	2–39%	..
Concentration impairment	..	26% (21–32)	22–28%§	..	..	..	..	..	..
Cognitive impairment	..	18% (0–98)	18% (15–22)	..	..	..	..	18–57%¶	..
Memory loss	16% (0–55)	18% (5–46)	28% (19–36)	..	..	..	8%	..	..
Ageusia or taste disturbance	23% (14–33)	14% (9–20)	16% (10–24)	10% (7–15)	10% (7–15)	18% (10–28)	10%	1–22%	..
Anosmia or smell disturbance	21% (12–32)	15% (11–21)	24% (12–41)‖	14% (9–22)	11% (8–15)	17% (10–25)	13%	0–26%	..
Hearing loss or tinnitus	15% (10–20)	..	..	..	..	..	..	..	..
Dermatological									
Hair loss	25% (17–34)	14% (5–33)	..	..	..	..	23%	20–29%	..
Skin manifestations, including rash	12% (7–18)	3% (1–8)	..	3% (2–3)	3% (2–4)	..	4%	2–20%	..
Respiratory									
Dyspnoea or breathlessness	24% (14–36)	25% (18–34)	36% (28–50)	22% (12–35)	26% (9–35)	39% (16–64)	24%	6–61%	32% (24–40)
Cough	19% (7–34)	8% (5–14)	17% (14–25)	6% (4–8) dry cough; 5% (3–7) productive cough	9% (5–14)	11% (7–17)	17%	2–59%	13% (9–17)
Cardiac									
Chest pain or discomfort	16% (10–22)	6% (3–12)	13% (11–18)	..	9% (7–13)	17% (5–35)	10%	0–89%	16% (12–21)
Palpitations	..	10% (6–15)	..	..	10% (6–15)	..	9%	9–62%	..
Musculoskeletal									
Joint pain or arthralgia	19% (7–34)	9% (6–15)	..	9% (8–11)	10% (7–15)	..	16%	6–55%	..
Muscle pain or myalgia	..	11% (6–20)	..	5% (2–12)	11% (7–18)	..	6%	2–51%	..
Impaired mobility	..	14% (5–37)	..	..	..	..	..	7%	..
Gastroenterological									
Nausea or vomiting	..	7% (2–24)	..	..	5% (2–10) nausea; 1% (0–2) vomiting	..	..	..	..
Loss of appetite	..	18% (4–51)	..	..	..	..	..	6–8%	..
Digestive disorders	..	..	..	..	..	..	8%	1–33%	..
Sleep									
Sleep disorder	11% (3–24)	18% (10–32)	..	25% (24–29)	..	44% (8–85)	26%	22–53%	..

(Table 2 continues on next page)

	Lopez-Leon et al;[4] pooled prevalence (95% CI)	Michelen et al;[15] proportion (95% CI)*	Nasserie et al;[17] median proportion (IQR)	Domingo et al;[18] proportion (95% CI)†	Fernández-de-las-Peñas et al;[19] pooled prevalence (95% CI)†	Iqbal et al;[20] proportion (95% CI)†	Malik et al;[21] proportion	Cabrera Martimbianco et al;[22] proportion, range	Sanchez-Ramirez et al;[23] pooled prevalence (95% CI)‡
(Continued from previous page)									
Psychological									
Anxiety	13% (3–26)	19% (9–35)	22% (10–30)	..	..	..	17%	3–25%**	..
Depression	12% (3–23)	8% (4–15)	15% (11–18)	..	..	..	14%	3–25%**	..
Quality of life									
Reduced quality of life	..	37% (18–60)	..	..	..	..	..	..	52% (33–71)

Symptoms were included in the table if at least one systematic review reported a pooled proportion estimate of >10%. Estimates from systematic reviews were included if at least two studies in the review evaluated the symptom. PASC=post-acute sequelae of SARS-CoV-2 infection. *Michelen et al was the only systematic review to report on weakness (proportion 41%, 95% CI 25–59), malaise (33%, 15–57), and decreased sensation (11%, 7–17). †Includes estimates from studies reporting symptoms from approximately >12 weeks after acute illness. ‡Sanchez-Ramirez et al was the only systematic review to report pooled estimates for abnormal chest CT (59%, 44–73), impaired diffusing capacity (31%, 24–38), and lung restriction as measured by pulmonary function tests (12%, 8–17). §Median not reported; numbers represent range from four studies. ¶Includes composite of "cognitive/memory/concentration impairment". ||Proportion with persistent anosmia. **Anxiety and depression listed together.

Table 2: **Pooled estimates of proportion of patients with persistent symptoms from systematic reviews of PASC studies**

impairment affected their daily lives and ability to return to work. Nearly one in four patients hospitalised with COVID-19 reports substantial depression or anxiety symptoms lasting at least 6 months after acute illness.[3] In an observational study from Wuhan, China, patients also commonly self-reported symptoms of PTSD.[32] Among hospitalised patients, the most common pulmonary impairment at 6 months after acute COVID-19 is a decreased diffusing capacity of the lung for carbon monoxide (DLCO; about 33% of patients), followed by reduced total lung capacity (approximately 17%).[3] Persistent pulmonary impairments probably differ by initial disease severity. Patients with more severe initial COVID-19 pneumonia according to the WHO severity classification had significantly lower percentage of predicted DLCO at 4-month follow-up (mean 73% predicted [SD 18] *vs* 95% predicted [20]; p=0·003).[33]

Dyspnoea and fatigue are common among survivors of COVID-19.[16,30,31,33–36] Importantly, there is no consistent association between dyspnoea and abnormalities on chest imaging, pulmonary function test, or initial disease severity.[33–36] Dyspnoea, like fatigue, is a complex, multifactorial symptom.[34] Notably, fatigue is common in survivors of ARDS (approximately 70% of patients) at 1-year follow-up.[37] Fatigue after acute respiratory failure is not consistently associated with severity of illness or ICU length of stay, but frequently co-occurs with impairments in cognition, mental health, and physical function.[37] Addressing complex symptoms such as dyspnoea and fatigue, in both hospitalised and non-hospitalised COVID-19 survivors, requires multidisciplinary interventions, informed by an understanding of risk factors and co-occurring impairments.[35]

Infection prevention and control measures during the COVID-19 pandemic have the potential to further affect recovery after SARS-CoV-2 infection (figure 1). For example, visitor restrictions for hospitalised patients with COVID-19 might increase the risk of delirium and

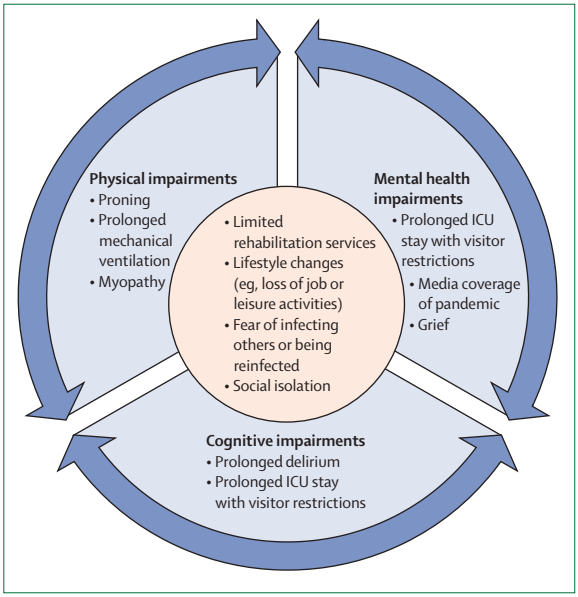

Figure 1: **COVID-19 pandemic-related factors that could exacerbate physical, cognitive, or mental health impairments**
The COVID-19 pandemic could further complicate recovery across key domains of mental, physical, and cognitive health, which are intimately linked and commonly impaired in the setting of critical illness. For example, rehabilitation services could be limited because of infection control and prevention measures, and social isolation in the community and due to restrictions on family presence in hospitals could affect the recovery of patients with post-acute sequelae of SARS-CoV-2 infection. Awareness of these factors could help in the provision of holistic post-acute care.

PTSD,[38] and social isolation in the outpatient setting can contribute to mental health disturbances among non-hospitalised patients as well. Essential rehabilitation and non-infection-related medical services might be limited or eliminated for patients with COVID-19, both during and after hospitalisation.[38,39]

Although cohort studies of people who become critically ill with COVID-19 will be important in

identifying any unique long-term sequelae of infection, outcomes are expected to mirror what we already know about ICU survivorship. Namely, survivors' experiences vary greatly, with many experiencing new and persistent impairments—including complex, multifactorial symptoms—for months to years. It remains unknown whether the experiences of patients with COVID-19 who require ICU care overlap substantially with those of hospitalised or non-hospitalised patients who are not admitted to the ICU, or whether these populations have distinct, multidisciplinary needs.

Survivorship clinics in the COVID-19 era

There are clinics in Europe, the Americas, and the Asia-Pacific that aim to address the multifaceted needs of survivors of critical illness and ICU care. These clinics offer key insights into potential barriers and facilitators in the establishment of PASC programmes, which have three key aims: (1) to meet survivors' immediate clinical needs; (2) to create a platform for research on the natural history of PASC; and (3) to expedite the rigorous evaluation of therapeutic options.[40] Challenges to creating ICU survivor or PASC programmes fall into two broad domains: patient engagement and organisation of care pathways.

Most patients who are discharged from the ICU will not have access to a post-ICU clinic, with fewer than half of eligible survivors cared for by an ICU survivor clinic in their region.[41,42] Reasons for lack of access to care include the following: the clinic is unable to contact the survivor; the survivor does not have transportation to access the clinic; the survivor lacks insurance or the means to access services; or the survivor is unaware of the potential benefit of attending follow-up services.[43] Similar barriers will affect access to PASC clinics for patients who have received community-based or hospital-based care for COVID-19. The COVID-19 pandemic is disproportionately affecting poorer communities of Black, Asian, and minority ethnic groups in high-income regions such as Europe and North America, and it is important that disparate provision of rehabilitation services does not exacerbate these inequalities further.[44,45] To overcome these challenges, clinicians should be flexible in their approach. While telemedicine, which was rapidly adopted during the pandemic, can overcome transportation barriers, digital poverty and illiteracy can hinder access to telemedicine appointments.[46] Hence, where possible, a hybrid model that incorporates both virtual and in-person clinic options is optimal.

Acute care teams need to proactively communicate with hospitalised patients and their primary care providers, ideally before discharge from hospital, to counsel about the recovery trajectory, convey the potential benefit of post-acute clinic attendance, ensure access, and foster patient engagement. This communication can be achieved through direct patient education at the bedside by acute care physicians, advanced practice providers, and nurses, as well as by members of essential therapy services. The electronic medical record can also be used to share discharge summaries and follow-up recommendations with primary care teams, and to facilitate referrals to multidisciplinary clinics.

In some health-care systems, billing infrastructure—including inconsistent insurance reimbursement and billing codes—presents a significant barrier to the creation of follow-up services.[43] Addressing this barrier requires changes in policy to reflect extension of support for acute COVID-19 care to cover PASC as well. A recent US Congressional hearing included advocacy for billing codes to capture PASC, allowing tracking of needs and services rendered, and incentivising the provision of services for this population.[47] For the time being, existing billing structures can capture the type of care provided in the USA. For example, transitional care codes are designed specifically to capture the complexity and high need of the post-hospital period. The value of survivorship clinics to both patients and institutions must be demonstrated to ensure consistent staffing and support. Given the increased risk of health-care utilisation among survivors of COVID-19,[7] programmes should prospectively evaluate the effect of multidisciplinary interventions on outcomes, including readmissions and health-care resource use.[40] Moreover, working in survivorship clinics might improve staff wellbeing and reduce burnout by allowing staff to reconnect with patients and families they cared for in the inpatient setting.[48] Importantly, the surge in COVID-19 survivors provides an opportunity to address gaps in knowledge regarding the management of frequently experienced symptoms after acute illness (panel). This includes identifying unmet needs, especially during transitions of care, and targeting interventions to meet such needs.[49]

The PASC clinic model

PASC have not yet been fully defined. Hence, the development of a clear case definition of the post-COVID-19 condition—and understanding of the origins, nature, and course of persistent symptoms—is the focus of ongoing research. Existing PASC clinics must base criteria for referral and ongoing care on capacity and the availability of local resources. Primary care practitioners can provide initial screening to identify patients with ongoing symptoms beyond the initial acute illness, and a number of post-acute COVID-19 services use a screen-and-refer model to identify which specialists are most urgently needed for each individual patient's problems. Current guidelines recommend that patients with PASC be referred to multidisciplinary programmes with expertise in evaluating and managing commonly reported symptoms after COVID-19, including fatigue, dyspnoea, mental health disturbances, and cognitive impairments.[50] Given overlapping symptoms and the need for multi-disciplinary care, ICU recovery clinics and the PICS framework provide a foundation for the management of

***Panel:* Research considerations to advance PASC knowledge and management**

Subjects for research

- Prevalence of long-term symptoms, including stratification by key variables (eg, demographic factors such as age and ethnicity, initial severity of COVID-19)
- Risk factors for development of persistent symptoms
- Trajectory, changes over time, and clustering
- Pathophysiological mechanisms of persistent symptoms
- Therapeutic interventions
- Economic, societal, and individual costs associated with persistent symptoms

Methodological considerations

- Rigorous prospective studies that aim to reduce bias through thoughtful recruitment and retention strategies, and careful consideration of control groups
- Development of core outcomes measurement sets to standardise assessments
- Randomised controlled trials of therapeutic interventions
- Epidemiological and interventional studies conducted in low-income and middle-income countries and areas with limited resources; participation of a diverse patient population in terms of factors such as age, sex, ethnicity, and socioeconomic status

PASC=post-acute sequelae of SARS-CoV-2 infection.

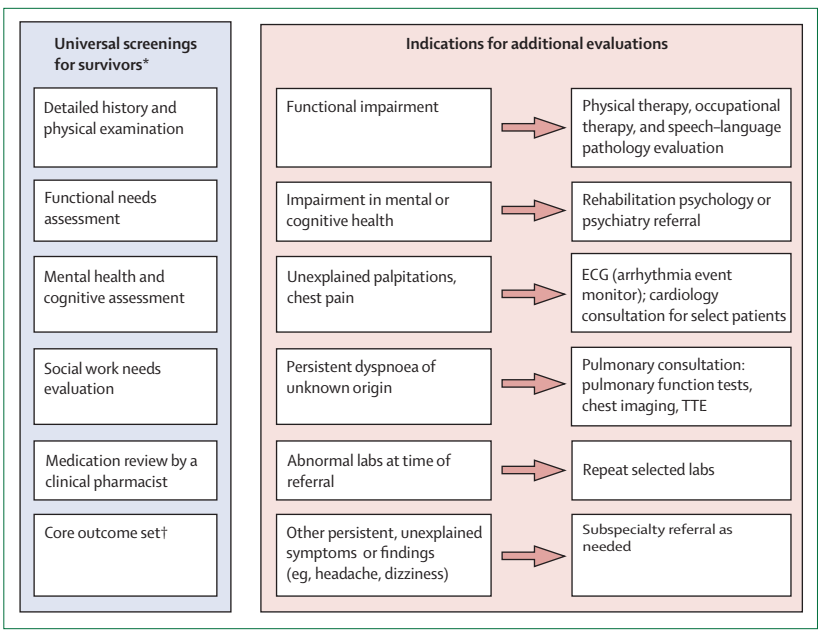

Figure 2: **Core services and evaluations for survivors of COVID-19 in a PASC clinic**
Elements of the initial screening evaluation, done in person or remotely, for survivors of COVID-19 are shown, based on current guidelines, with recommendations for additional evaluations. ECG=electrocardiogram. TTE=transthoracic echocardiogram. *Core services recommended by the UK National Institute for Health and Care Excellence guidelines.[50] †Core outcome set for acute respiratory failure[53] and COVID-19.[54,55]

PASC for both ICU and non-ICU populations. It is not essential that ICU practitioners lead such clinics. Existing PASC clinics have adopted different approaches to leadership, including both primary and cooperative leadership by internal medicine, respiratory medicine, physiatry, endocrinology, and infectious disease. More importantly, a multidisciplinary approach with integrated referral pathways[50] between PASC clinics, primary care practitioners, and core subspecialists is essential to success. Given the wide array of potential COVID-19 sequelae described over the weeks and months after acute infection,[4–7] a detailed history and physical examination is essential to identifying complications, evaluating contributing factors, and guiding referrals. Current guidelines recommend that follow-up begin 4–8 weeks after discharge, or from acute illness for those who were not hospitalised, and continue at 3-month intervals as needed.[51,52] Such guidelines might require adaptation both at the institution or site level based on available resources and to meet individual patient needs. Here, we describe the roles of specialists central to both ICU recovery services and comprehensive PASC programmes for all levels of acute illness (figures 2 and 3).[8,50,53–55]

Physical medicine and rehabilitation

Physiatrists, rehabilitation psychologists, physical therapists, occupational therapists, and speech and language pathologists have a fundamental role in evaluating functional, cognitive, and mental health needs, and provide essential rehabilitation services in the post-acute setting. Rehabilitation in the post-acute phase falls under five general categories: (1) acute or subacute inpatient rehabilitation; (2) rehabilitation in skilled nursing facilities; (3) rehabilitation at home with home therapy services; (4) rehabilitation at home with outpatient therapy services; and (5) rehabilitation at home without any services. Patients might engage with one or all three therapy pathways during their recovery, and the provision of such services hinges on evaluations by key members of the rehabilitation team.

Physiatry

Physiatrists are integral members of the multidisciplinary team and coordinate rehabilitation care in acute and all five post-acute phases, focusing on biopsychosocial functioning and return to life with a new functional baseline.[56,57] This care involves not only cardiopulmonary rehabilitation after ARDS, but also a comprehensive rehabilitation plan to address physical, cognitive, psychosocial, and vocational needs given the complex and long-lasting nature of PASC. Physiatrists diagnose neurological and musculoskeletal complications, including brachial plexopathy, critical illness neuropathy and myopathy, stroke, or limb ischaemia due to thrombotic events. Autonomic dysfunction occurs in patients with PASC, so the timely completion of autonomic function tests (eg, the tilt table test), when

Time from symptom onset	Patient X	Patient Y
0–6 days	Shortness of breath, cough, and fever	Loss of taste and smell, fever, cough, shortness of breath, body aches, fatigue, nausea, and vomiting
7–30 days	**Hospital presentation** • Admitted to ICU with ARDS due to severe COVID-19 pneumonia; interventions include sedation, paralysis, and prone positioning • Hospital stay of 23 days	**Hospital presentation** • Evaluated in the emergency room; chest x-ray normal, oxygen saturation 100% on room air • Discharged home with supportive care; symptoms persist
31–45 days	• Impairments in cognition, mobility, and ADLs • Acute inpatient rehabilitation, with physical therapy, occupational therapy, and speech–language pathology for 14 days • Discharged on supplemental oxygen at 2 L/min	• Loss of smell, shortness of breath, cough, and fatigue persist • New, persistent brain fog, dizziness on standing, palpitations
46 days	**PASC clinic evaluation** • Impairment in ADLs • 6MWT: 65% predicted • Need for supplemental oxygen confirmed • Pulmonary function tests: moderate restriction and moderate gas transfer defect • Neuropsychological evaluation: moderate cognitive impairment, anxiety and PTSD symptoms • Pharmacy: inappropriate continuation of several hospital medications • Not returned to work	**PASC clinic evaluation** • Tachycardia • 6MWT: 85% predicted • Cough partially responsive to short-acting bronchodilator and proton pump inhibitor (no postnasal drip reported) • Pulmonary function tests: normal • Neuropsychological evaluation: mild cognitive impairment, anxiety • Pharmacy: poor medication adherence due to memory impairment • Not returned to work
	Recommendations • Outpatient occupational therapy and physical therapy • Consideration of pulmonary rehabilitation • Speech–language pathology (cognitive impairment) • Rehabilitation psychology • Social work • Pulmonary follow-up (post-ARDS fibrosis) • Physiatry follow-up (impaired ADLs and mobility)	**Recommendations** • Outpatient physical therapy • Otolaryngology referral with consideration of speech–language pathology referral • ECG with consideration of cardiology referral pending results and clinical trajectory • Rehabilitation psychology • Social work • Pulmonary follow-up (persistent cough) • Physiatry follow-up (fatigue and impaired mobility)
Weeks to months	• Coordination with primary care for preventive health and management of chronic conditions	• Coordination with primary care for preventive health and management of chronic conditions

Figure 3: **Potential evaluation and management in a PASC clinic of patients with initial mild or severe COVID-19**
Details for patients X and Y, both about 50 years of age, represent common clinical manifestations and evaluations for patients presenting to a PASC clinic after COVID-19. Patients receiving care for PASC might have had acute COVID-19 ranging from mild (patient Y) to severe (patient X). 6MWT=6-min walk test. ADLs=activities of daily living. ARDS=acute respiratory distress syndrome. ECG=electrocardiogram. ICU=intensive care unit. PTSD=post-traumatic stress disorder.

indicated on the basis of initial screening, for proper diagnosis followed by appropriate medical and rehabilitation treatments is important to prevent further physical, mental, and cognitive impairments.[58] Standardised, routine evaluations can determine the need for essential rehabilitation services, including physical therapy, occupational therapy, speech–language pathology, and rehabilitation psychology.

Physical therapy

ICU-acquired weakness (ICUAW), including critical illness polyneuropathy or myopathy, is associated with decreased strength and physical function that can persist for years after acute illness.[49–61] Although the long-term effects of early intervention are uncertain, beginning early rehabilitation within 48 h of ICU admission is associated with improvement in strength and independent walking in the hospital.[62,63] Physical therapy services in the post-acute phase can be provided in the home as well as in the outpatient setting.[64] Some standardised assessments of muscle strength and activity limitations (eg, exercise capacity and gait speed) in the post-acute setting can be performed both via telemedicine and in person (eg, use of the Activity Measure for Post-Acute Care assessment or sit-to-stand tests), whereas others require in-person visits (eg, the 6-min walk test and manual muscle testing score for strength).[65] Early in the post-acute period, restorative interventions are of limited efficacy for patients recovering from critical illness. Therefore, physical therapy interventions in the post-acute setting initially focus on teaching both patients and caregivers compensatory strategies to adapt and improve functioning.[65] Once functioning has been optimised, restorative exercises (eg, aerobic strength and endurance training) titrated to overload can be implemented while assessing cardiorespiratory demand.[65]

Occupational therapy

In the post-acute phase, practice guidelines specific to occupational therapy for survivors of COVID-19 include the following: considering the effects of oxygen weaning on activities of daily living; providing energy conservation and work simplification strategies; addressing the impact of cognitive impairments on occupational performance; addressing mental health, stress, and coping related to

PTSD or anxiety disorders; and continuing the plan set in the early phases of the disease to return to participation in meaningful activities.[66] Occupational therapists assist survivors with returning to work by facilitating a graded return—part time versus full time, working from home, and adjusted work tasks and responsibilities—and by providing assistive technology and vocational rehabilitation.[67] Therapists also monitor for residual impairments in range of motion, sensation, fine motor coordination, or pain related to positioning such as prolonged proning. Occupational therapy interventions include remediation, such as strengthening or fine motor training, and compensation, such as writing aids or assistive technology.

Occupational therapists play an important part in the evaluation and management of cognitive impairment, encouraging active engagement in meaningful activities, resumption of a productive life, and a return to social participation and human connection.[68] Therapists help patients to focus on engagement in meaningful occupations, including activities they need to, want to, and are expected to do.[69] Cognitive rehabilitation includes retraining orientation, memory, attention, and executive functioning skills that are required to successfully complete tasks such as financial management and multitasking for return to work. In addition to retraining internal cognitive skills, occupational therapists also educate patients on the use of external strategies such as memory aids and assistive technology.[70]

Speech and language pathology

Speech–language pathologists are vital members of the multidisciplinary survivorship team.[9,71,72] They evaluate and treat impairments of speech, language, and cognition, disorders of the voice and airway, and swallowing disorders. In the ICU, speech–language pathologists focus on delirium prevention, communication options for mechanically ventilated patients, and swallowing assessments. As patients transition to the wards, rehabilitation facilities, outpatient clinics, and home care, focus shifts to a more traditional rehabilitative approach.[73] Patients who experienced delirium while critically ill appear to be particularly prone to cognitive-linguistic changes, including deficits of attention, memory, and other executive functions (eg, planning, organisation, and self-monitoring).[14,74,75] Because behavioural treatments by speech–language pathologists also occur after ICU discharge, they are essential members of outpatient survivorship clinics.

Patients who were intubated during the acute phase of critical illness are at high risk of voice and airway disorders after extubation.[76–79] Speech–language pathologists are often the first clinicians to identify the presence and nature of voice and airway disorders while evaluating laryngeal and upper airway anatomy.[80] Voice or breathing changes might reflect changes in vocal fold mobility and obstructions (eg, inflammation or tissue changes).[76,77] Intubation injuries extend from the voice and airway to dysphagia.[77,81,82] Speech–language pathologists evaluate patients for dysphagia, either after a failed swallow screening or as a result of clinical referral.[83] A videofluoroscopic swallow study or flexible endoscopic evaluation of swallowing is used to characterise disordered swallowing physiology and to plan treatment.[84,85] Although dysphagia can persist for many months after hospital discharge, most survivors will recover with proper care.[86]

Rehabilitation psychology and neuropsychology

Rehabilitation psychologists provide comprehensive evaluation, targeted psychotherapy, and health and behaviour interventions. Evaluations of current functioning follow a biopsychosocial model, which includes physical, emotional, cognitive, and social aspects of an individual's status in the context of medical and psychosocial history and current circumstances. A thorough assessment helps to identify barriers to optimal function as well as areas of strength and resilience. The following Patient-Reported Outcomes Measurement Information System (PROMIS)[87] health-related quality-of-life measures have been used to evaluate symptoms and gauge treatment progress: Pain Interference; Fatigue; Anxiety; Depression; Self-Efficacy for Managing Symptoms; and Ability to Participate in Social Roles and Activities. Since the start of the COVID-19 pandemic, most evaluations have been conducted using telehealth.

Psychotherapy or behavioural interventions focus on helping survivors to develop coping and compensatory strategies. Evidence-based therapeutic interventions for mental health difficulties include the following: cognitive behavioural therapy (CBT) for depression, anxiety, and pain; cognitive processing therapy for PTSD; interventions to improve sleep (eg, CBT for insomnia or CBT-I); fatigue management; and mindfulness-based interventions to improve awareness and distress tolerance. Patients with pre-existing psychiatric comorbidities or those requiring medication management are also evaluated by psychiatrists.

In many cases, persistent fatigue, sleep disturbance, and emotional distress further aggravate cognitive difficulties. Consistent with reported patterns of cognitive difficulties in PICS,[9,14,88] many patients with PASC present in the post-acute phase with generalised cognitive slowing and deficits in executive function, including impairments in divided and sustained attention, initiation, cognitive flexibility, and executive control over memory. Neuropsychological evaluation of cognitive function in the context of estimated optimal ability can help to identify current difficulties, aid in differential diagnosis, and develop treatment recommendations. A subset of survivors might benefit from referral to speech–language pathology services for cognitive rehabilitation. As a patient's disease process often is experienced closely by their family members, screening for psychological symptoms should be extended to this group.[89]

Neuropsychiatry

Neuropsychiatrists can provide specific input when the medical, biological, and psychological aspects of a patient's clinical presentation converge; for example, when knowledge about the antidepressant properties of anti-inflammatory treatments[90] and the anti-inflammatory aspects of antidepressant treatments can work synergistically.[91] Whereas rehabilitation psychologists approach a patient's problems from a mind-based perspective, with implications for brain function, neuropsychiatrists do the opposite, beginning with a brain-based perspective that has implications for psychological wellbeing. Together, rehabilitation psychologists and neuropsychiatrists can offer a complementary and collaborative approach to the care of patients, with the combined tools to address the many biopsychological manifestations of post-acute COVID-19.

Pharmacy

A comprehensive medication review is the core service provided by a pharmacist in a PASC clinic.[92,93] This multifaceted review encompasses medication de-prescribing, initiation or restarting of drug regimens, and therapy optimisation. Whereas stress ulcer prophylaxis in the ICU is classically associated with inappropriate continuation, any medication initiated for an inpatient indication has the potential to be inappropriately continued in the outpatient setting. In the post-COVID-19 phase, emphasis is placed on determining the duration of antithrombotic therapy, which might have been initiated in the setting of an unconfirmed diagnosis. A full understanding of the new and dynamic impairments facing ICU survivors is needed to properly adapt and adjust drug therapy regimens. Improving physical function can affect blood pressure or glucose levels and their associated medications. Close monitoring and frequent medication dose adjustments are particularly important for survivors experiencing recovery of kidney or liver function.

A pharmacist who understands the challenges of COVID-19 survivorship can also help to ensure that prescribed medications are accessible and taken at the right time. For example, new cognitive impairment could limit a survivor's understanding of newly prescribed medications and their side-effects. Memory impairments can decrease medication compliance. Restrictions on in-person primary care in 2020 might have resulted in missed immunisations, and changes in employment status or medication insurance coverage might affect the continuation of previous drug therapy.[92,93] A critical care clinical pharmacist is well positioned to address these challenges as part of an interdisciplinary clinic team.[94] Pharmacists work with a medication access team to ensure affordability and appropriate access to medications. They supply pillboxes or discuss strategies for medication reminders to improve medication adherence. Depending on local practice laws, pharmacists are often able to obtain a vaccination history and administer immunisations.

Social work and welfare support

Social workers address several important aspects of recovery after COVID-19. About one-third of patients in recovery report that persistent symptoms affect their ability to return to work up to 7 months after acute illness.[27] Social workers can connect patients with job resources and provide support to address financial needs. Social workers and community health workers can intervene to improve access to care for underserved populations, and enhance communication between patients, their families, and the health-care team.[95,96] They also conduct screening for mental health impairments in both patients and their family members or caregivers, and provide psycho-education and referrals as needed.[95] Addressing the needs of family caregivers is particularly important during large-scale disasters such as the COVID-19 pandemic, because social distancing and restricted family presence in hospitals threaten family integrity and make it difficult for family members to feel calm, connected, and useful.[97]

Primary care

In the long term, primary care practitioners will provide both aftercare and care coordination for the majority of survivors of COVID-19.[98,99] Their knowledge of patients' long-term medical history and expertise in care coordination mean that they are well placed to have a key role in the management of PASC, especially in regions where PASC clinics will not be available. However, the rapid growth of information relating to the diverse manifestations after SARS-CoV-2 infection is not yet readily available in a comprehensive format, making it challenging for primary care practitioners to stay up to date. Thus, effective information transfer from both hospital and the PASC clinic should be mandatory—regarding all dimensions, as detailed above, and including communication of evidence-based treatment recommendations. This process could occur through elaborated discharge letters handed to the patient directly with instruction to take to follow-up primary care appointments, direct communication between the hospital or PASC clinic and primary care providers, and further development of virtual services.[98]

Equitable provision of care

Under-served populations and implementation in LMICs

Ensuring equity of access to post-COVID-19 health-care services to optimise patient recovery is essential, and particular attention should be paid to under-served populations. Examples of under-served populations in Europe and North America include Black, Asian, and minority ethnic groups—which have an increased risk of SARS-CoV-2 infection and poorer outcomes, including higher mortality, from COVID-19[100,101]—those at educational or socioeconomic disadvantage, religious

minorities, people living in remote areas, those with caregiving responsibilities or in full-time employment, and those with factors associated with health status such as cognitive impairment, learning disability, or multiple comorbidities, among many others.[102,103] Strategies to help vulnerable communities to access health-care services have been reported, most notably the following four: (1) addressing the social determinants of health through screening and information provision, signposting health-care users to appropriate community services, and encouraging community stakeholders to support individualised service delivery according to the needs of patients; (2) adopting new and innovative virtual care strategies (eg, through various forms of telehealth); (3) designing global budget payments to support hospitals located in areas delivering services to vulnerable communities; and (4) using an inpatient–outpatient transformation strategy that more closely integrates hospital-based and community-based services, and adapts each, to meet the needs of individual communities.[103]

Implementation of multidisciplinary PASC clinics might be challenging in LMICs. Existing multidisciplinary models serve as a guide to addressing potential barriers.[104] Educational programmes that target health-care workers and community and public health staff, and focus on providing information on screening for commonly experienced symptoms, are essential.[104] Community health workers provide education and raise awareness in local communities.[105] A hub-and-spoke model, in which larger academic centres provide specialised care and consultation to surrounding providers and communities, is effective.[105] Finally, the provision of telehealth infrastructure to facilitate self-assessment and self-management can support patients in remote communities.[105]

Language services for non-native speakers

Language support services are vital for survivors of COVID-19 in immigrant communities that are experiencing disproportionately high rates of infection and severe disease (eg, Hispanic and Latino populations in the USA).[106,107] Multilingual staff are highly valued within PASC clinics, particularly when responding to phone calls from non-native speaking patients. Pre-translation of written informational documents is crucial to care delivery for these survivors. Interpreter services have adapted to telemedicine models, allowing interpreters to be present on both phone calls and video platforms, which can also be used during in-person clinic visits. In addition to being convenient to schedule, remote interpreter services reduce the need to accommodate additional people in the clinic space under infection control procedures.

Research collaboration

The chief goal of PASC clinics must be to support the recovery and wellbeing of people who survive infection. However, clinics can help to estimate the frequency of patient outcomes and identify survivor phenotypes without compromising their primary mission, by optimising the data they record in electronic health records.[108,109] Therefore, an international task force comprising 93 experts, including representatives of the European Respiratory Society (ERS) and the American Thoracic Society (ATS), that was convened in 2020 suggested that follow-up assessments of hospitalised COVID-19 survivors occur 6–8 weeks after discharge and include the core outcome set for survivors of acute respiratory failure.[54,55] The core outcome set comprises the EuroQol-5D (EQ-5D; a measure of health-related quality of life), the Hospital Anxiety and Depression Scale (designed to detect states of depression and anxiety in a general medical population of patients), and the Impact of Event Scale – Revised (a measure of PTSD symptoms), and can be administered entirely over the phone, making it feasible to implement in clinics using telehealth.[53] Importantly, the core outcome set represents a minimum number of assessments to facilitate research and comparisons, and most clinics will choose to incorporate additional assessments determined by resources and interest. In addition to assessment at 6–8 weeks post-discharge, a coordinated approach to COVID-19 care should plan for serial assessments triggered by life events. For example, assessment before hospital discharge will determine the need for post-acute care services, whereas the end of employment-based medical disability benefits, plateaus in recovery, or significant changes in symptoms or disability should prompt reassessment.[110]

PASC clinics provide a unique opportunity to advance the field of ICU survivorship clinics, given the unprecedented surge of critical illness survivors presenting for care. A Cochrane review in 2018 found insufficient evidence to conclude that ICU survivorship clinics

Search strategy and selection criteria

We searched PubMed and Embase for papers published in English between May 1, 2020, and Aug 1, 2021, using the terms "post-acute COVID-19 syndrome", "post-intensive care syndrome", "long COVID", "long haul" and "COVID", "post-acute sequelae" and "SARS-CoV-2 infection", "chronic COVID syndrome", and "post-COVID condition" or "post-COVID-19 condition". We selected peer-reviewed papers and high-quality preprints that pertained to the main aim of this Health-care Development paper: to inform the development of multidisciplinary pathways of care for the post-acute sequelae of SARS-CoV-2 infection. Details of preprints were updated with final publication details as this paper was prepared for publication. We referred to the reference lists of selected papers and to papers in our own files to provide the reader with a review of relevant evidence from before the COVID-19 pandemic.

improve outcomes by addressing unmet needs of patients after discharge from the ICU.[111] The review highlighted heterogeneity in the services delivered and in the design of studies evaluating efficacy as limitations. Prospective evaluation of the efficacy of PASC clinics, especially those including ICU survivors, and ideally with a randomised controlled design, could answer important questions about how such clinics might improve outcomes.

Conclusions

COVID-19 represents an unprecedented public health emergency. Multidisciplinary post-acute care programmes, established using a PICS framework, can deliver essential support for both hospitalised and non-hospitalised patients during their recovery. These programmes also provide an infrastructure for rigorous research, conducted alongside clinical care, to better understand the prevalence, natural history, and risk factors of PASC and to evaluate therapeutic interventions to improve outcomes. Given the disproportionate impact of COVID-19 on under-served populations, special attention should be given to ensuring the equitable delivery of care. The PICS–PASC model has the potential to endure beyond the COVID-19 pandemic as a means of providing essential multidisciplinary care for patients experiencing complex, multifactorial symptoms from a variety of acute and chronic illnesses. In parallel with clinical pathways of care, structured peer support groups, with trained moderators, provide an innovative opportunity for survivors of COVID-19 and their caregivers to support one another in their recovery.[112] The current paucity of data on the effectiveness of specific interventions to treat PASC means that PASC clinics will need to maintain the ability to adapt to evolving evidence (panel). Such evidence should be informed by the inclusion in follow-up and research of a diverse population of patients, and include evaluation of innovative approaches to care, such as telemedicine and new electronic applications.

Contributors

AMP and AET compiled the initial full draft of the manuscript, made essential content edits, and coordinated editing and revisions. Each co-author made direct contributions to key sections of the manuscript. All authors contributed to the literature search and review, and reviewed and edited the final draft of this Health-care Development paper.

Declaration of interests

JM reports payment from Springer for the book *Improving Critical Care Survivorship*. CMS also reports royalties from Springer for the book *Improving Critical Care Survivorship*. MBB reports payment for educational materials from MedBridge, outside of the submitted work. AET reports payment for consulting from Medical Science Affiliates, outside of the submitted work. AMP, EB, BC, AVA, MTK, KC, CR, KFRS, SYK, and AK declare no competing interests.

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