COVID-19

Delirium in Older People with COVID-19: Clinical Scenario and Literature Review

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Abstract

Delirium is a potentially fatal acute brain dysfunction that is characterised by inattention and fluctuating mental changes. It is indicative of an acute serious organ failure or acute infection. Delirium is also associated with undesirable health outcomes that include prolonged hospital stay, long-term cognitive decline and increased mortality. The new SARS-CoV-2 shows, not only pulmonary tropism but also, neurotropism which results in delirium in the acute phase illness particularly in the older age groups. The current assessment for COVID-19 in older people does not routinely include screening for delirium. Implementation of a rapid delirium screening tool is necessary because, without screening, up to 75% of cases can be missed. Delirium can also be exaggerated by health care policies that recommend social isolation and wearing personal protective equipment in addition to less interaction with patients. Non-pharmacological intervention for delirium prevention and management may be helpful if implemented as early and as often as possible in hospitalised older people with COVID-19. A holistic approach that includes psychological support in addition to medical care is needed for older people admitted to hospital with COVID-19.

Keywords Older people · Delirium · COVID-19 · Hospitalised · Management

Introduction

The respiratory disease COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was initially reported in Wuhan, Hubei province, China. [1] The disease has since spread across the continents to become a global pandemic. The SARS-CoV-2 is a zoonotic virus similar to the previous corona viruses that caused the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). The COVID-19 spreads rapidly by human-to-human transmission, primarily through respiratory droplets, physical contact and via fomites. [2] COVID-19 typically presents with fever, myalgia, fatigue and dyspnoea or with less common symptoms such as nausea, vomiting, diarrhoea, abdominal pain and headache. [2] It has a fatality rate of 2.3% across all age groups, with 14.8% in patients ≥ 80 years old and 8.0% in those 70–79 of age reported. [3] Mortality was found to be higher in

patients with pre-existing comorbidities such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease and cancer. [3] In addition to the typical presentation of COVID-19, acute brain dysfunction, symptomatically presenting as delirium, may be a feature of the neuro-invasive potential of the SARS-CoV-2 virus. Neuro-tropic properties of the corona viruses have been previously demonstrated. Older people affected by the SARS epidemic in 2003 presented not only with respiratory symptoms but also with general decline and delirium. [4] Because of the similarities in the pathogenicity of the SARS-CoV and SARS-CoV-2, it is plausible that SARS-CoV-2 has a similar ability to cause delirium. [5] This manuscript describes a clinical scenario of COVID-19 patients admitted to hospital with a main presentation of delirium compared with those without delirium symptoms and performs a literature review of the pathogenesis, prevention, diagnosis and treatment of delirium in older people affected by COVID-19.

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Clinical Scenario

We have previously reported a case series of a British cohort of 71 patients with COVID-19 infection consecutively admitted to a single UK centre over a 2-week period. [6] The

majority (75%) of patients were ≥ 65 years old and 58% were men. Most of the patients (85%) had pre-existing comorbidities, with hypertension (45%) most common, followed by cardiovascular disease (34%), chronic obstructive pulmonary disease (33%) and diabetes (23%). Respiratory symptoms were the most common presenting complaint such as fever (59% of patients), shortness of breath (56%) and cough (55%). However, a small group (16 patients) presented with delirium as the main presentation in addition to respiratory symptoms. Comparison of patients presenting with delirium and those without delirium is detailed in Table 1. Patients with delirium were significantly older (percent of patients aged ≥

75 years was 83% vs 41%, a difference of 42%, 95% confidence interval (CI) 17.3 to 66.7) compared with those with no delirium symptoms. All patients with delirium had a pre-existing comorbidity compared with 78% of non-delirium cases (difference of 22%, 95% CI 15.4 to 36.6). In addition, delirium presenting cases were more frail than those with no delirium (percent of patients scoring ≥ 5 on clinical frailty score (CFS) was 67% vs 36%, a difference of 31%, 95% CI 1.7 to 06.3). Mortality was significantly higher in the delirium-presenting cases (58% vs 27%, a difference of 31%, 95% CI 1.0 to 61.0) compared with those without delirium. Due to older age and frailty, none of the delirium-

Table 1 Comparison of patients with COVID-19 presenting with delirium and those without delirium

Parameter (%)	Delirium symptoms (%)	Non-delirium symptoms (%)	Difference (95% CI)
Number of patients	12 (17)	59 (83)	
Age (years)			
• Range	70–90	26–97	
• ≥ 75	10 (83)	24 (41)	42% (17.3 to 66.7)
Gender, male	7 (58.3)	34 (57.6)	0.7% (− 29.9 to 31.3)
Comorbidities (%)			
• Any comorbidity	12 (100)	48 (78)	22% (15.4 to 36.6)
• Hypertension	9 (75)	23 (39)	36% (8.8 to 53.2)
• DM	4 (33)	12 (17)	16% (− 11.7 to 44.3)
• COPD	6 (50)	18 (31)	19% (− 10.3 to 49.7)
• CVD	6 (50)	18 (31)	19% (− 10.3 to 49.7)
• CKD	3 (25)	6 (10)	15% (− 9.3 to 40.7)
• CLD	1 (8)	4 (7)	1% (− 8.7 to 11.3)
• Dementia	4 (33)	6 (10)	23% (− 3.3 to 50.7)
• CFS			
▪ Range	2–7	1–7	
▪ ≥ 5	8 (67)	21 (36)	31% (1.7 to 60.3)
Presentation (%)			
• Fever	5 (42)	37 (63)	− 21% (− 51.5 to 9.5)
• Hypoxia	10 (83)	37 (63)	20% (− 11.4 to 51.4)
• Tachypnoea	8 (67)	45 (76)	− 9% (− 38.0 to 20.0)
• Tachycardia	6 (50)	17 (30)	20% (− 9.4 to 50.6)
• AKI	6 (50)	16 (27)	23% (− 6.2 to 53.8)
• Acute hepatic impairment	5 (42)	21 (36)	6% (− 23.5 to 36.5)
• High CRP	10 (83)	47 (80)	3% (− 20.6 to 26.6)
• Leucocytosis	4 (33)	11 (19)	14% (− 14.4 to 42.4)
• Lymphopenia	10 (83)	42 (71)	12% (− 11.8 to 36.2)
• CXR opacification	6 (50)	28 (47)	3% (− 28.0 to 34.0)
Outcomes			
• Discharged home	5 (42)	43 (73)	− 31% (− 1.0% to − 61.0)
• ICU admission	0	9 (15)	− 9% (− 18.0 to 0.0)
• Died	7 (58)	16 (27)	31% (1.0 to 61.0)

CI confidence interval, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *CLD* chronic liver disease, *CFS* clinical frailty score, *AKI* acute kidney injury, *CRP* C-reactive protein, *CXR* chest X-ray, *ICU* intensive care unit

presenting cases was admitted to the intensive care unit (ICU) compared with 9 (15%) patients in the non-delirium group. Of clinical note, although delirium was diagnosed and documented in the medical records, diagnosis was largely based on clinical impression rather than the use of a universal and standardised delirium screening tool.

Literature Review

Delirium is not an infrequent presentation in older patients presenting with acute illness particularly infections. During the COVID-19 pandemic, older people presented atypically with delirium and in our clinical scenario, it appears to have affected the subgroup of the very old people with multiple comorbidities. Delirium seems to be less routinely screened for in clinical practice, although it has a serious negative impact on the outcome. In this literature review, we explore the pathogenesis, predisposing factors, clinical presentation, diagnosis and ways of prevention and management.

Pathogenesis

The possible causes of delirium in COVID-19 patients are likely multifactorial that include central nervous system (CNS) invasion by the virus. The SARS-CoV-2 enters human cells via the angiotensin-converting enzyme (ACE2) receptors which are expressed in various organs including the brain. [5] Entry route for the virus into the brain may be directly through intra-nasal access via olfactory nerves, with a possible anosmia as an early symptom, or indirectly by crossing the blood-brain barrier via haematogenous or lymphatic spread. [7] Cases of viral encephalitis and acute haemorrhagic necrotising encephalitis due to SARS-CoV-2 have been described. [8, 9] Secondary neurological effects include increased CNS inflammatory mediators, cerebral hypoxia, cerebrovascular involvement, multiple organ failure, pyrexia, neurotransmitter imbalance, dehydration and metabolic dysregulation. [10] Immunologic responses to SARS-CoV-2 virus are mediated by acute cytolytic T cell activation which may cause an autoimmune encephalopathy. [11] Environmental and iatrogenic factors such as prolonged mechanical ventilation, sedative use (especially hypnotics and anticholinergics), long hospital stay and immobility, urinary retention, constipation, sleep deprivation and social isolation can contribute to delirium development during acute COVID-19 infection especially in older people, who have no or limited support from carers. [12] Factors related to delirium are summarised in Table 2.

Table 2 Factors associated with delirium in older people with COVID-19

Patient-related
- Old age
- Comorbidity
- Frailty

Direct neurological
- Direct CNS invasion by the virus.
  - Intra-nasal access
  - Crossing blood-brain barrier
- Viral encephalitis
- Acute haemorrhagic necrotising encephalitis

Indirect neurological
- CNS inflammation
- Cerebral hypoxia
- Cerebrovascular involvement
- Multiple organ failure
- Persistent pyrexia
- Neurotransmitter imbalance
- Metabolic dysregulation
- Autoimmune encephalopathy

Environmental
- Isolation
- Limited interaction with family and hospital staff
- Use of personal protective equipment
- Prolonged mechanical ventilation
- Long hospital stay
- Sleep deprivation
- Immobility

Iatrogenic
- Use of sedatives
- Constipation
- Dehydration
- Urinary retention

Predisposing Factors

COVID-19 infection is more common in older people especially those with multiple comorbidities and frailty. The combination of increasing age, frailty and comorbidity appears to exert a negative effect on the immune system that leads to increased risk of infection. The ageing immune system is characterised by a low grade and chronic systemic inflammatory state or "inflammageing" marked by elevated inflammatory markers such as IL-6 and C-reactive protein. Frailty is characterised by multisystem dysregulation that leads to reduced physiologic reserve and increased risk of adverse health outcomes. Dysregulation in the innate and adaptive immunity also leads to chronic inflammation, with increase in inflammatory markers, and increased susceptibility to sever

infections. Comorbidity and frailty often overlap and lead to worse prognosis. It has been shown that 82% of community-dwelling older people who are frail also have comorbidities, 29% have disability in at least one activity of daily living and 93% have disability in at least one instrumental activity of daily living. [13] The synergistic effects of ageing, frailty and comorbidity not only increase the risk of severe illness but also lead to increased risk of delirium as a non-typical presentation of COVID-19. [14] Other factors that predispose to delirium include policies put in place to limit the spread of the virus. Hospitals have instituted very limited visitors policy, and limited interaction with hospital staff which may increase the sense of isolation and induce patients' disorientation and reduced awareness. In addition, the use of personal protective equipment (PPE) by staff members has some depersonalising and possibly frightening effect on older people especially those with cognitive impairment or dementia. Also, further isolation in intensive care units (ICU) and the need for mechanical ventilation may further increase the risk of delirium. Earlier epidemiological studies have shown that up to 75% of patients undergoing mechanical ventilation in intensive care units suffer from delirium at some point during their admission. [15]

Prevalence and Clinical Presentation

Impaired consciousness that ranges from somnolence, confusion, delirium, stupor and coma are the neurological manifestations that have been reported in patients with COVID-19. [14] In a retrospective Chinese case series, to explore the neurological manifestations of 214 hospitalised patients with ARS due to COVID-19, 41.1% of patients were severe and 58.9% were non-severe cases. Compared with non-severe patients, severe patients were older (mean (SD) age 58.7 (15.0) years vs 48.9 (14.7) years), had more underlying disorders (47.7% vs 32.5%), especially hypertension (36.4% vs 15.1%), and showed less typical symptoms such as fever 45.5% vs 73%) and cough (34.1% vs 61.1%). More severe patients were likely to have neurologic symptoms (45.5% vs 30.2%) such as acute cerebrovascular diseases (5.7% vs 0.8%), impaired consciousness (14.8% vs 2.4%) and skeletal muscle injury (19.3% vs 4.8%). [16] Other studies indicated that the rate of delirium in hospitalised patients with COVID-19 is around 30% but can reach up to 70% in severe cases. [17] Delirium has also been estimated to occur in up to 50% of hospitalised elderly patients and 80% of critically ill patients who receive mechanical ventilation. [18] Patients who are severely affected by COVID-19 are more likely to have neurological manifestation and less likely typical manifestation compared with those who are less severely affected. In the meta-analysis of SARS, MERS and COVID-19 studies, common neuropsychiatric symptoms leading to hospital admission were confusion (27·9%, 95% CI 20.5 to 36.0), depressed mood (32.6%, 24.7 to 40.9), anxiety (35.7%, 7.6 to 44.2), impaired memory (34.1%, 26.2 to 42.5) and insomnia (41.9%, 22.5 to 50.5). In the post-illness stage, the prevalence of post-traumatic stress disorder was 32.2% (95% CI 23.7 to 42.0), depression 14·9% (12.1 to 18.2) and anxiety 14.8% (11.1 to 19.4). When data for patients with COVID-19 was examined, common symptoms were delirium (65%), agitation (69%) and altered consciousness (21%). This analysis suggests that SARS-CoV-2 might cause delirium in a significant proportion of patients in the acute stage and clinicians should be aware of the possibility of depression, anxiety, fatigue and post-traumatic stress disorder in the longer term. [19] Recently, a British study has found that delirium is common in hospitalised patients with COVID-19, yet under-recognised and is associated with functional impairment in the medium term. Out of a total of 71 patients, 31 (42%) had delirium, of whom only 19 had been recognised by the clinical team. Physical function was substantially worse in people after delirium (− 39 points on functional scale/166, 95% CI − 92 to − 21, $p = 0.01$). [20]

Screening and Diagnosis

Older people with COVID-19 may not present typically with pyrexia or shortness of breath and about 40% of cases had no radiologic abnormalities. [21] Delirium may be a prodromal symptom of infection or hypoxia before respiratory failure occurs. The neuro-invasion by the SARS-CoV-2 may be associated with subsequent centrally mediated respiratory depression. Therefore, early identification of COVID-19 patients with delirium, which may be an early manifestation of CNS involvement, may be crucial as it may indicate impending respiratory failure. It has been shown that up to 75% of delirium episodes can be missed in patients unless an objective delirium screening tool is used. [22] Therefore, COVID-19 infection may be overlooked if delirium is not included as part of routine screening. This is of particular importance in care home residents as the mortality is reported to be high in these settings and the fact that delirium is associated with a high risk of subsequent long-term cognitive and functional decline. [23] As delirium can be the first manifestation of infection also, missing early diagnosis of delirium can lead to spread of the COVID-19 to other patients, families or members of staff and increased severity of the infection that may lead to increased mortality and other long term adverse effects such as cognitive and physical dysfunction. One of the most commonly used rapid screening tool is the 4AT which takes about 2 min to do. It was designed specifically to help practitioners for a quick and easy detection of delirium in routine clinical practice. The 4AT is a well-validated tool that shows good diagnostic accuracy with a pooled sensitivity of 0.

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88 (95% CI 0.80 to 0.93) and pooled specificity of 0.88 (95% CI 0.82 to 0.92) in older (≥ 65 years) people in various care settings that include emergency department, medical, stroke and surgical wards. [24] The 4AT has some advantages over other screening tools such as the Acute Confusion Method (CAM) as being shorter, simpler and not requiring special training for the operator. [24] The 4AT is designed to be used by any health care professional at the first contact with patient and at follow-up at any time when delirium is suspected (Table 3).

Management

In older people with COVID-19 infection, in whichever patient setting, health care professionals and carers should watch

Table 3 4AT delirium screening tool

Parameter	Score
1. Alertness	
Normal = fully alert	0
Mild sleepiness for < 10 s after waking then normal	0
Clearly abnormal	4
2. AMT4*	
No mistakes	0
1 mistake	1
≥ 2 mistakes	2
3. Attention**	
States 7 months correctly	0
Less than 7 months or refuses to start	1
Cannot start, drowsy or inattentive	2
4. Acute change***	
No	0
Yes	4

Score:

≥ 4: possible delirium ± cognitive impairment.

1–3: possible cognitive impairment.

0: unlikely delirium or severe cognitive impairment.

Features

• Takes <2 min to do

• No special training required

• Easy and simple

• Suitable for use in different settings of clinical practice

• Suitable for all patients including those unable to communicate (drowsy or agitated)

• Includes brief cognitive testing

AMT abbreviated mental test; *Ask about: age, date of birth, place and current year. **Ask about months of the year backwards. ***Significant change in alertness, cognition or mental function over last 2 weeks and still ongoing

for delirium and approach it as an urgent medical complication. Every effort should be made during the acute phase for early recognition and treatment and after recovery phase continuity of care and follow-up to help reduce long-term complications (Fig. 1).
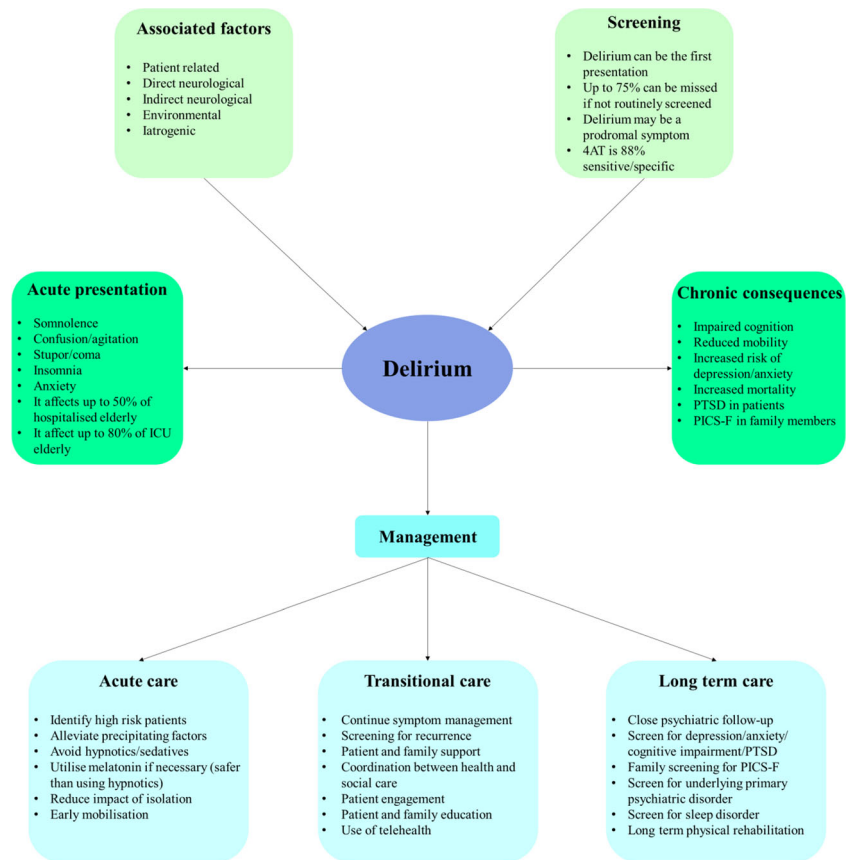
Acute Care

Non-pharmacological approaches for delirium prevention and management should be considered first, if possible, before pharmacological intervention. Clinicians should start with identification of high-risk group of patients with risk factors for delirium such as older age, multiple comorbidities, pre-existing cognitive dysfunction, depression and polypharmacy. [25] Alleviating precipitating factors for delirium as possible may help reduce the risk. For example, sleep deprivation can be a precipitating fact as well as a consequence of delirium. Although sedatives such as hypnotics and benzodiazepines can help sleep deprivation, they can exaggerate symptoms of delirium and also are associated with increased risk of respiratory depression in older people. It has recently been shown that melatonin or melatonin receptor agonists can reduce prevalence of delirium, length of ICU stay and improve quality of sleep. [26] Melatonin has also shown other anti-inflammatory, anti-oxidant and immune-enhancing properties that may help reduce the risk of infection-related progression to acute respiratory distress syndrome. [27] Other precipitating factors such as hypoxia, pain, constipation and urinary retention should be avoided or promptly treated as possible. Reduction of the impact of isolation by allowing face-to-face family contact through social media and the use of orientation cues may help. Frequent inquiry about patients' comfort and satisfaction and keeping them up to date with the progress of their condition and stage of treatment are important. The negative impact of the PPE can be minimised by using a name badge or a picture of the person looking after the patient. Early physiotherapy input and early mobilisation as able is vital in speeding up recovery.

Transitional Care

At hospital discharge, older people with COVID-19 are likely to be physically and emotionally vulnerable. The trajectories of healthcare needs of older people with COVID-19 in the weeks and months following hospital discharge are not yet clear and it may be a huge burden for recovering patients and their families. Transitional care is a management strategy to support patients and their carers and to improve the health and quality of life of older people after discharge from hospital to going home. This is to address the complex needs of older people affected by COVID-19 throughout their prolonged recovery period. [28] Transitional care includes building trusting relationships, improving patient engagement, coordinating collaboration across care teams of health and social

Fig. 1 Delirium in older people—risk factors, detection and management

Associated factors
- Patient related
- Direct neurological
- Indirect neurological
- Environmental
- Iatrogenic

Screening
- Delirium can be the first presentation
- Up to 75% can be missed if not routinely screened
- Delirium may be a prodromal symptom
- 4AT is 88% sensitive/specific

Acute presentation
- Somnolence
- Confusion/agitation
- Stupor/coma
- Insomnia
- Anxiety
- It affects up to 50% of hospitalised elderly
- It affect up to 80% of ICU elderly

Delirium

Chronic consequences
- Impaired cognition
- Reduced mobility
- Increased risk of depression/anxiety
- Increased mortality
- PTSD in patients
- PICS-F in family members

Management

Acute care
- Identify high risk patients
- Alleviate precipitating factors
- Avoid hypnotics/sedatives
- Utilise melatonin if necessary (safer than using hypnotics)
- Reduce impact of isolation
- Early mobilisation

Transitional care
- Continue symptom management
- Screening for recurrence
- Patient and family support
- Coordination between health and social care
- Patient engagement
- Patient and family education
- Use of telehealth

Long term care
- Close psychiatric follow-up
- Screen for depression/anxiety/cognitive impairment/PTSD
- Family screening for PICS-F
- Screen for underlying primary psychiatric disorder
- Screen for sleep disorder
- Long term physical rehabilitation

services, undertaking symptom management, enhancing family and carers' education and improving continuity of care. This approach will effectively address the holistic needs of the vulnerable older people with COVID-19 and cares for this population as they transition back from the hospital to the community. Care should include a comprehensive assessment of the recurrence of COVID-19 symptoms and also be aware that carers may develop COVID-19 themselves as well as their mental health responses to the crisis should be closely monitored. The use of digital telehealth may have a role in the transitional care and attention must be paid to ensure that effective, culturally sensitive strategies are considered in the development of these digital forms of communication such as engaging people from diverse racial and ethnic backgrounds to ensure that language competency and cultural values are addressed into care plans. [29]

Follow-up Care

Patients with COVID-19 and no previous psychiatric history have been presented with delirium in the form of psychotic symptoms characterised by thoughts of reference and structural delusional beliefs normally seen in primary psychotic disorders such as schizophrenia. Although these symptoms persisted after resolution of the acute delirium, it is not known whether these are primary psychosis (in patients who are genetically predisposed and triggered by acute illness) or secondary psychosis (purely related to COVID-19). [30] It was observed that those with subacute onset (less than a week), rapid recovery within 2 weeks and their symptoms were associated with hallucinations are likely to be COVID-19-related delirium. [30] However, patients with these symptoms will need a close psychiatric input and follow-up. In general, patients admitted to critical care will have increased risk of depression (29%), anxiety (34%) and post-traumatic stress (34%) respectively after 1 year of hospital discharge. [31–33] Similarly, patients who develop ARDS, which is recognised feature of COVID-19, will show post-discharge impairments of memory, attention and concentration or have slow mental processing speed. [34] Severe delirium that leads to ICU admission could be associated with severe adverse outcomes for patients as well as for their families. The general prevalence of delirium in ICU reaches up to 87% and is associated with post-discharge cognitive impairment, depression and post-traumatic stress disorder. [35, 36] Also relevant to older people is the post-discharge sleep disorders, muscle weakness and mobility disorders. [37, 38] Family members may develop post-intensive care syndrome in family (PICS-F) which includes symptoms of stress, anxiety or depression. [36]

Conclusion

The current assessment for COVID-19 in older people does not routinely include screening for delirium. Health care providers and carers should be aware about the atypical presentation of infections in older people and be educated about ways of prevention, detection and management of delirium to facilitate early intervention and improve long-term outcomes. Data on delirium caused by the SARS-CoV-2 is limited and future research is still required. Also, the provision of introducing digital health and telemedicine will need further exploration in the vulnerable older age groups.

Future Perspectives

Delirium appears to be more common in the short-term period during COVID-19 infection. However, it may unmask underlying primary psychiatric disorders or may leave a chronic unresolved effect. Therefore, there is a need for future prospective studies to explore the long-term impact of delirium on the mental health of affected older people. More training for health care professionals working in medical wards on delirium prevention and management will be required as part of a holistic medical-psychiatric care for older people. There will be also a need for novel ways for remote consultation and support for patients and their carers in the community.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflict of interest.

Ethical Approval   N/A

Informed Consent   N/A

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Key Points

- Delirium is a common presenting symptom in older people with COVID-19.
- Early routine screening along with non-pharmacologic intervention may delay the progression to delirium and improve the outcome.
- Future research on COVID-19-related delirium as well as exploration of the use of telehealth in the vulnerable older people is still required.