Identifying atypical presentations of COVID-19 in older adults to enhance screening and detection: a protocol

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Background

The COVID-19 pandemic is associated with high rates of hospitalization and mortality in older adults (age ≥65 years) [1–3]. Older adults with acute illness often present atypically with a geriatric syndrome or without classic disease symptoms [4]. Geriatric syndromes include delirium, functional decline, falls, weakness or anorexia [5]. Similarly, older adults with infections may present without fever or pain. Approximately 40% of older adults present without fever in seasonal influenza [6,7]. Surveillance data from a long-term care (LTC) outbreak in Washington, USA, showed that up to 56% of COVID-19 positive cases were asymptomatic or presymptomatic [8]. However, the dataset was small and the study did not investigate the breadth of atypical presentations in older adults. The current screening criteria for COVID-19 rely on the presence of symptoms of influenza-like Illness (ILI). ILI symptoms be blunted or absent in older adults. As a result, screening and diagnosis of COVID-19 in older adults may be delayed. This is a significant weakness in our ongoing containment strategy.

Delirium is an acute confusional state that is common in hospitalized older adults, with prevalence of up to 30-40% in medical wards and up to 75% in intensive care units [9]. The relevance of delirium to COVID-19 is two-fold: (i) delirium may be an atypical presentation of infections [4] and (ii) agitation and aggression in delirium may pose a risk to staff and other patients without management [10]. Timely detection and treatment of delirium can improve outcomes and mitigate risk [11]. The prevalence, characteristics and treatment strategies of delirium in COVID-19 are unknown, despite important safety and clinical considerations.

Several geriatric medicine organizations issued guidelines regarding management of older adults with COVID-19 based on expert consensus [12–15]. There are no published descriptive studies on the prevalence of atypical presentation and delirium in older adults with COVID-19. This data is crucial for screening, detection, and management of COVID-19 cases in hospital and LTC.

Objectives

1. To determine the prevalence of atypical presentations (e.g. delirium, falls, functional decline) of COVID-19 in older adults.
2. To determine the characteristics and management of delirium in older adults with COVID-19.
3. To determine the association of atypical presentations and delirium with clinical outcomes such as in-hospital mortality, intensive care unit (ICU) admission and other

complications (e.g. falls, secondary infection, aspiration pneumonia, myocardial infarction, venous thromboembolism).
4. To determine the management, outcomes, and predictors of survival in older adults with COVID-19 who were admitted to the intensive care unit (ICU).

Methods

Study design

This is a retrospective and prospective chart review of older adults (age ≥65) with confirmed COVID-19 in 5 academic hospitals networks in Ontario, Canada (Sunnybrook Health Sciences Centre, Baycrest Health Sciences, Unity Health Toronto, Sinai Health Systems, and University Health Network). The review will include cases in acute care, rehabilitation and LTC sites associated with the academic institutions (e.g. Providence, St. John's, Bridgepoint, Toronto Rehabilitation Institute). The chart review will assess cases from January 15, 2020 [16] until June 30, 2021, with ongoing analysis of data. Retrospective chart review will take place immediately on study start with a review of existing charts. Prospective chart review will happen by monthly retrieval of cases from decisions support.

Inclusion criteria

1. Patients with laboratory-confirmed COVID-19 by viral PCR swab available on hospital medical records.
2. Age ≥65 at the time of COVID-19 detection.
3. Admitted to one of the acute care hospitals, rehabilitation facilities, or LTC homes within the 5 academic health networks.

Exclusion criteria

1. Re-admission to hospital after index admission for COVID-19. Only charts from the initial admission will be assessed.

Data collection

Decision support services at each hospital network will identify COVID-19 cases in patients age ≥65 years. A research assistant (RA) will conduct a chart review of each identified case and complete the case report forms (CRFs) hosted on a secure REDCap server at Applied Health Research Centre in St. Michael's Hospital. The CRFs will capture basic demographic data (age, sex, hospital, place of residence), but patient data will be de-identified upon collection with a unique participant ID. We will include a linking log on separate spreadsheet located on a password-protected secure hospital server at St. Michael's Hospital (template in Appendix 4). Other identifiers will include date of admission, date of death, and discharge date. This data will be used to calculate length-of-stay.

The first CRF on atypical presentations, defined by geriatric syndromes reported in the literature [4,5,17], will be completed on every patient (Appendix 1). The second CRF on delirium (Appendix 2) will be completed in patients with identified delirium assessed by a validated chart review method [18]. The third CRF will assess clinical outcomes, such as in-hospital mortality, ICU admission, discharge destination and in-hospital complications (Appendix 3). A training exercise will be done on the first 5 records where one of the investigators (EW, JW) will extract

chart data in duplicate with the RA. Each of the 3 CRFs will be independently coded at least 5 times. If interrater agreement is less than 90%, we repeat the exercise.

COVID-19 variant and vaccination data collection

New variant strains of SARS-CoV-2 that increased transmissibility were discovered in late 2020 [19]. We amended our CRFs to collect data on COVID-19 variants in patients admitted in 2021. New two-dose vaccines were also developed and administered beginning in late 2020. Effectiveness after the second dose was high in observational studies [20], so we do not expect many vaccinated patients to be in our cohort. However, we added a data item to our CRFs to identify patients who had 1 or 2 doses of the vaccine and was admitted for COVID-19.

COVID-19 ICU substudy

The experience of older adults with COVID-19 admitted to intensive care units (ICU) was explored in the United States [21], but the Canadian experience is unknown. We will add a separate ICU CRF (Appendix 5) for patients who were admitted to ICU at Sinai Health, University Health Network, St. Michael's Hospital and Sunnybrook Health Sciences Centre. Respiratory parameters (e.g. PaO2/FiO2, tidal volume, arterial pH, time and mode of ventilation, duration of mechanical ventilation), ICU complications (e.g. acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), bacterial pneumonia), and ICU medication use will be collected. We will also collect relevant lab tests on admission to ICU and illness severity scores (e.g. daily SOFA score, APACHE II Score). ICU outcomes including ICU delirium duration, ICU length of stay, and ICU death will also be collected. A multivariable model will be created to determine predictors of ICU survival based on patient characteristics, illness severity, and physiologic parameters.

Sample size and analysis

Interim analyses will be done after the first 100 cases to provide timely data for healthcare workers during this pandemic. Given the surveillance data from Washington, 100 records will likely provide informative preliminary estimates for frontline staff [22]. We anticipate at least 1080 cases in the study based on 20,000 projected COVID-19 cases in Toronto by April 30, 2020 [23,24], of which 12% will require hospitalization [25] and 45% will be ≥65 years old [26].

Patient baseline characteristics will be analyzed descriptively with proportions, means (standard deviations), and medians (interquartile range), where appropriate. The prevalence of each atypical symptom including delirium (Appendix 1) will be calculated by a proportion of exhibiting patients compared with the whole group (primary outcome). The characteristics of delirium, including motor subtype, use of physical restraints, and treatment with antipsychotic medications, will be described by proportions. A multivariable model will identify independent risk factors for presenting with atypical symptoms. Co-variates of interest include age, place of residence (LTC vs. others), frailty (clinical frailty scale ≥5 vs. <5 [27]), dementia. Composite variables for any atypical symptom and geriatric-syndrome atypical symptoms will be created in the analysis. Multivariable models will be used to determine if atypical presentations are independently associated with mortality, ICU admission, and in-hospital complications. Co-variates of interest are same as above. The exported dataset from REDCap will be analysed using R version 4.0 [28].

COVID-19 wave 2

Given the differences in treatment in wave 2 of the pandemic (starting August 1, 2020), we will compare differences in patient characteristics, treatment and outcomes between waves 1 and 2. The analysis will investigate differences in mortality and delirium prevalence, and the effect of dexamethasone on delirium prevalence.

COVID-19 frailty study

At the completion of the data collection, we will analyze the impact of frailty on treatment and outcomes in the entire cohort. Areas of interest include the use of therapeutic agents on frail patients, provision of palliative care services, discharge destination, mortality and length of stay.

Research ethics approval

The main site will be Unity Health Toronto, where the initial research ethics board (REB) application will be submitted. We will contact the director of the REB to expedite approval given the importance of providing timely results for management of COVID-19. After REB approval at Unity Health, we will submit to the remaining sites. No patient identifiers will be stored in the database. Consent is not required as this is a chart review study.

Funding

Funding for this project will be obtained from COVID-19 contingency grants offered by the Academic Health Science Centre Alternate Funding Plans (AFP) at each hospital site. Funding will be required for a full-time research assistant, as well as database services, statistician support, and other administrative expenses. The results of the grant applications are pending.

Reporting standard

We will use the Consensus-based Clinical Case Reporting Guideline (CARE) for reporting this case series study [29].

Impact

This study will provide timely information for frontline healthcare providers screening and assessing older adults with suspected or diagnosed COVID-19. Knowledge about atypical presentations can identify older adults who require COVID-19 testing. Recognizing the characteristics and treatment requirements of delirium in COVID-19 will allow earlier detection and mitigation of risk. This data will be imperative for the management of this vulnerable population during the pandemic.

Appendix 1: Atypical presentation CRF

To be completed for all included cases of confirmed COVID-19 over age 65 years.

1. **Study ID** [unique sequential integer]
2. **Age** [number, integer, plus unknown option]
3. **Sex** [female, male, other]
4. **Hospital** [dropdown menu: Sunnybrook, St. Johns rehab, Sunnybrook LTC, St. Michaels, St. Joseph's Toronto, Providence rehab, Providence LTC, Mount Sinai, Toronto General Hospital, Toronto Western Hospital, Toronto Rehab, Baycrest rehab, Baycrest LTC, other]
5. **Place of residence prior to COVID-19 diagnosis** [home, rehab, retirement home, LTC, shelter, hospital, other institution, unknown]
6. **Was the patient transferred to acute care?** [dropdown: Yes – emergency department without admission, Yes – admitted to acute care, No, unsure]
7. **Date of admission** [date or not transferred to acute care]
8. **Date of diagnosis (first positive COVID-19 test)** [date]
9. **Did the patient have a SARS-CoV-2 variant detected? [yes/no]**
    a. **If yes, enter the variant detected. Enter the genetic mutation or geographic origin as indicated in the lab report.** [free text]
10. **Did the patient require ICU stay?** [Yes/no/unsure]
    a. **Did the patient require ventilator?** [yes/no/unsure]
    b. **Did the patient wean off the ventilator?** [Yes/no/unsure]
    c. **How many days was the patient in ICU?** [textbox]
11. **Admission diagnosis** [textbox]
12. **Why was the patient tested for COVID?** [checkbox matrix: Sick contact, residential home screening, symptoms, travel, unclear]
13. **What symptoms did the patient present with?** [checkbox matrix: fever (temp >37.8 [30]), cough, shortness of breath, malaise, nausea, sore throat, diarrhea, vomiting, rhinorrhea/congestion, myalgia, headache, chills, dizziness, tachycardia (heart rate >90), chest pain, abdominal pain, conjunctivitis, increased sputum production]
14. **What geriatric syndromes did the patient present with?** [checkbox matrix: delirium/confusion, anorexia, weakness, falls, weight loss, functional decline, incontinence]
15. **Describe symptoms if the options above do not capture patient presentation.** [free text]
16. **Onset of symptoms to COVID-19 testing** [text field]
17. **What was the maximum temperature measured in the emergency department or facility where COVID-19 was diagnosed?** (Use highest temperature within 2 days of positive swab) [textbox]
18. **Lymphocyte count, ferritin, lactate dehydrogenase, aminotransferase, C-reactive protein and D-dimer on COVID diagnosis** (Use labs within 5 days of first positive COVID swab) **[textbox]**
19. **Chest X-ray finding on COVID diagnosis** (Use CXR within 5 days of first positive COVID swab) [dropdown: no infiltrates, unilateral infiltrates, bilateral infiltrates, not done, uninterpretable]
20. **Was there a fracture on admission? [Yes/no]**

    a. Where was the fracture? [checkboxes: hip, vertebral, wrist, other femur/tibia, humerus, pelvic, skull, face, rib]
    b. Did the fracture require surgery? [yes/no]
21. **Did the patient have a history of the following?** [checkbox matrix: dementia, MCI, falls (at least 1 fall in past 12 months), heart failure, coronary heart disease (myocardial infarction), COPD, renal failure, dialysis, alcohol abuse, atrial fibrillation, diabetes, hypertension, stroke, active cancer]
22. **Baseline ADL:** needs help with [checkbox yes/no/unsure: bathing, dressing, toileting, transfers, walking, feeding]
23. **Baseline IADLs:** needs help with [checkbox yes/no/unsure: driving, banking, cooking, shopping, housekeeping, medications]
24. **Frailty:** clinical frailty scale (9-point scale) [integer]
25. **Baseline mobility:** [walks without gait aid, walks with walker, walks with cane, wheelchair, bedbound]
26. **Was the patient's goals of care known at time of COVID-19 diagnosis**? [yes/no/unsure]
    a. **What was the patient's code status (at time of COVID-19 diagnosis)?** [DNR, only for intubation, full code, not known]
    b. **Did the patient have a palliative care plan prior to COVID-19 diagnosis?** (includes keywords like 'palliative' or 'comfort care') [yes/no/unsure]

Appendix 2: Delirium CRF

To be completed for cases with identified delirium.

1. **Study ID** [unique sequential integer]
2. **Date of delirium onset** [date]
3. **Was there a geriatric consultation during this hospitalization?** [Yes/no/unsure]
4. **Hospital location when delirium first occurred** [emergency department, ward, long term care, rehab, ICU]
5. **How many times did the patient's room change during COVID infection?** [textbox] (We will batch inquiry for decision support because this has to extracted by them)
6. *Baseline risk factors*
    a. **Does the patient have pre-existing behaviours or agitation?** [Yes/no/unsure]
    b. **Is the patient on the following types of medications prior to admission?** [Yes/no checkboxes: Antipsychotics, benzodiazepines, trazodone, opioids, cholinesterase inhibitors]
7. *Characteristics of delirium*
    a. **Did delirium occur before or after classic COVID symptoms?** [Before, after, same time, unsure]
        i. **If delirium occurred after COVID symptoms, after how many days of COVID symptoms did delirium start?** [dropdown menu: <2 days, 2-5 days, >5 days, uncertain]
    b. **Motor subtype** [hyperactive, hypoactive, mixed, no subtype]
    c. **Agitation/aggression** present during hospitalization or COVID duration [yes/no/unsure]
    d. **Psychosis** (hallucinations/delusions) present during hospitalization or COVID duration [yes/no/unsure]
8. *Treatment of delirium*
    a. **Were physical restraints used at any point during hospitalization**? [yes, no, unsure]
    b. **Were antipsychotics used at any point during hospitalization**? [Yes – standing, yes – PRN, no, unsure]
        i. **Name the antipsychotic(s) used** [checkboxes for haloperidol, risperidone, quetiapine, loxapine, olanzapine, aripiprazole, ziprasidone, etc]
        ii. **What was the total daily dose of the antipsychotic medication(s)?** [textbox matrix]
    c. **Were other sedative medications used at any point during hospitalization**? [Checkbox matrix: benzodiazepine, gabapentin/pregabalin, trazodone, anticonvulsants, propofol, dexmedetomidine, Nozinan, other]
    d. **Were any of the following analgesics used at any point during hospitalization** (e.g. acetaminophen, opioids)? [checkbox yes/no/unsure: acetaminophen, oral NSAIDs, topical NSAIDs (Voltaren, Pennsaid), opioids, gabapentin/pregabalin, nabilone, tramadol]
    e. **Were any of the following nonpharmacologic interventions used?** [checkbox matrix: deprescribing offending medication, identify underlying cause, address oxygenation/toileting, others]

f. **Was family/caregivers present in person at any time during the hospitalization?** [Yes/no/unsure]
g. **Was family/caregivers present virtually (phone, video chat) at any time during the hospitalization?** [yes/no/unsure]
h. **Did delirium improve or resolve during the hospitalization?** [Yes/no/unsure]

Appendix 3: Outcomes CRF

1. **Study ID** [unique sequential integer]
2. **Did the patient die in hospital?** [yes/no/not applicable]
    a. **Date of death** [date or unknown]
    b. **How many days from admission to death?** [textbox, unsure, not applicable]
    c. **How many days from symptom onset to death?** [textbox, unsure, not applicable]
    d. **Cause of death** [textbox]
    e. **Did the patient die in ICU?** [yes/no/unsure]
    f. **Did the patient receive palliative care?** [yes/no/unsure]
3. **Where was the patient discharged?** [home, rehab, retirement home, LTC, shelter, hospital, other institution, death, unknown]
4. **Discharge date** [date or unknown]
5. **Did the patient have an in-hospital complication**? [checkbox matrix: falls, physical restraints, aspiration, infection, heart failure, MI, respiratory failure, VTE, medication side effect]
6. **Did the patient participate in a clinical trial**? [yes/no]
    a. **Which trials or trial drug was the patient on**? [textbox]
7. **Did the patient receive the following medications for treatment of COVID outside of a clinical trial**? [checkbox: hydroxychloroquine, azithromycin, tocilizumab, interferon, IVIG, Lopinavir-ritonavir, steroids, remdesivir]
8. **Was a surgical procedure(s) done in hospital**? [yes/no/unsure]
    a. **Which procedure(s)**? [textbox]

Appendix 4: Link log template (secure Excel file on hospital server)

1. Study ID [sequential integer]
2. MRN
3. Date acquired from decision support

Appendix 5: ICU CRF

1. **Study ID** [unique sequential integer]
2. **Date of ICU Admission** [date]
3. *Respiratory Parameters*
    a. **PaO2/FiO2 (lowest value)** [numeric]
    b. **Tidal volume (mL)** [numeric]
    c. **Arterial pH** [numeric]
    d. **Daily Positive End-Expiratory Pressure (PEEP; in cm of water; highest value)** [numeric]
    e. **Daily Highest Plateau Pressure (in cm of water; highest value)** [numeric]
    f. **Daily Highest Driving Pressure (in cm of water; highest value) [**numeric]
    g. **High Flow Nasal Cannula (HFNC; days)** [numeric, yes/no]
    h. **Proning (days)** [numeric, yes/no]
    i. **Inhaled Nitric Oxide (NO; days)** [numeric, yes/no]
    j. **High Frequency Oscillation (HFO; days)** [numeric, yes/no]
    k. **Extracorporeal Membrane Oxygenation (ECMO; days)** [numeric, yes/no]
    l. **Type of Ventilation** [checkbox: invasive, non-invasive, none]
    m. **Mode of Ventilation** [checkbox: pressure support, pressure control, volume control, other, none]
    n. **Timing of Invasive Mechanical Ventilation** [date, not applicable]
    o. **Duration of Invasive Mechanical Ventilation (days)** [numeric, not applicable]
4. *Complications*
    a. **Acute Respiratory Distress Syndrome (ARDS)** [yes/no]
    b. **Acute Kidney Injury (AKI)** [yes/no]
    c. **Need for Renal Replacement Therapy** [yes/no]
    d. **Prolonged Fever (>38.3C; beyond 7 days)** [yes/no]
    e. **Myocardial Infarction (MI)** [yes/no]
    f. **Stroke (Ischemic or Hemorrhagic)** [yes/no]
    g. **Bacterial Pneumonia** [yes/no]
    h. **Venous Thromboembolism (DVT)** [yes/no]
    i. **Venous Thromboembolism (PE)** [yes/no]
5. *ICU Medication Usage*
    a. **Propofol Infusion (days)** [numeric, yes/no]
    b. **Propofol Infusion Total Daily Dosage** [textbox, not applicable]
    c. **Midazolam Infusion (days)** [numeric, yes/no]
    d. **Midazolam Infusion Total Daily Dosage** [textbox, not applicable]
    e. **Dexmedetomidine Infusion (days)** [numeric, yes/no]
    f. **Dexmedetomidine Infusion Total Daily Dosage** [textbox, not applicable]
    g. Ketamine Infusion (days) [numeric, yes/no]
    h. **Ketamine Infusion Total Daily Dosage** [textbox, not applicable]
    i. **Timing Sedative Administration (days; 0 being on ICU admission)** [numeric, not applicable]
    j. **Dosage of Sedative Administration (varying units)** [textbox, not applicable]
    k. **Morphine Infusion (days)** [numeric, yes/no]
    l. **Morphine Total Daily Dosage** [textbox, not applicable]

m. **Fentanyl Infusion (days)** [numeric, yes/no]
n. **Fentanyl Total Daily Dosage** [textbox, not applicable]
o. **Hydromorphone Infusion**[yes/no]
p. **Hydromorphone Total Daily Dosage** [textbox, not applicable]
q. **Timing of Opioid Administration (days; 0 being on ICU admission)** [numeric, not applicable]
r. **Dosage of Opioid Administration** (**varying units)** [textbox, not applicable]
s. **Other Neuroleptics** [checkbox matrix: antipsychotic, clonidine, propranolol, benzodiazepine, other, none]
t. **Other Neuroleptics Dosage** [textbox, not applicable]
u. **Neuromuscular Blocker (days)** [numeric, yes/no]
v. **Neuromuscular Blocker Infusion (days)** [numeric, yes/no/not applicable]
w. **Neuromuscular Blocker Intermittent (days)** [numeric, yes/no/not applicable]
x. **COVID19-Specific Treatment** [checkbox matrix: dexamethasone, prednisone, solumedrol, solucortef, other steroids, remdesivir, tocilizumab, other, none]
y. **COVID19-Specific Treatment Dosage** (**varying units)** [textbox, not applicable]
z. **COVID19-Specific Treatment Number of Doses** [numeric, not applicable]

6. *ICU Lab Tests*
   a. **Hemoglobin, Neutrophil Count, Platelet Count, Creatinine, Urea Nitrogen, Albumin, ALT, Bilirubin, Interleukin-6** (**Use labs within 5 days before/after admission)** [textbox]
7. *Additional Characteristics*
   a. **Duration of ICU Delirium (days)** [numeric]
   b. **Physical restraint (ICU days)** [numeric, yes/no]
   c. **Accidental extubation (ICU days)** [numeric, yes/no]
   d. **Tracheostomy (ICU day)** [numeric, yes/no]
   e. **BMI (kg/m^2)** [numeric]
   f. **Obesity (BMI >= 30)** [yes/no]
   g. **Glasgow Coma Score** [numeric]
   h. **Mean Arterial Pressure (MAP)** [numeric]
   i. **Vasopressors** [yes/no]
   j. **Urine Output** (mL/day) [checkbox: <200, 200-500, >500]
   k. **Admission SOFA Score** [numeric]
   l. **Admission APACHE II Score** [numeric]
   m. **Metastatic disease (prognosis <1 year)** [yes/no]
   n. **Death in ICU** [checkbox matrix: during active treatment, following withdrawal of life support, no]

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