COVID-19 in Older People: A Rapid Clinical Review

Fiona E Lithander[1], Sandra Neumann[1], Emma Tenison[1], Katherine Lloyd[1], Tomas J Welsh[2,3,4], **Jonathan C. L. Rodrigues[3]**, Julian PT Higgins[1], Lily Scourfield[5], Hannah Christensen[1], Victoria J Haunton[6*], Emily J Henderson[1,3*]

*Joint last authors

[1]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK, [2]Research Institute for the Care of Older People (RICE), Bath, UK; [3]Royal United Hospital Bath NHS Foundation Trust, Bath, UK; [4]Institute of Clinical Neurosciences, University of Bristol, Bristol, UK; [5]Cardiff University School of Medicine, Cardiff, UK; [6]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

Corresponding author: Dr Fiona E Lithander, Population Health Sciences, Bristol Medical School, University of Bristol, 1-5 Whiteladies Road, Bristol, BS8 1NU, UK

fiona.lithander@bristol.ac.uk

Declaration of sources of funding: SN had salary support from the NIHR HTA. HC is supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions at the University of Bristol in partnership with Public Health England. HC is supported by a NIHR Career Development Fellowship (CDF-2018-11-ST2-015). FEL and ET had salary support from The Gatsby Foundation. EJH has received grants from Parkinson's UK, National Institute of Health Research (NIHR) and the Gatsby Foundation and has received travel consultancy and honoraria from Profile, Bial, Abbvie, Luye, Ever and Simbec Orion. JPTH is a National Institute for Health Research (NIHR) Senior Investigator (NF-SI-0617-10145). JPTH is supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions at the University of Bristol in partnership with Public Health England. JPTH is supported by NIHR Bristol Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. JPTH is supported by the NIHR Applied Research Collaboration West (ARC West) at University Hospitals Bristol NHS Foundation Trust. JPTH is a member of the MRC Integrative Epidemiology Unit at the University of Bristol. These funders played no role in the research or the article, and the views expressed in this article are those of the authors and do not necessarily represent those of the NHS, the NIHR, MRC, or the Department of Health and Social Care.

Declaration of conflicts of interest: None

Acknowledgements: We would like to express our appreciation and thanks to Professor Yoav Ben-Shlomo for his support and guidance.

KEYWORDS: COVID-19, Pandemic, Virology, Prognosis, Older adults, Non-pharmaceutical interventions

Abstract

Introduction

The COVID-19 pandemic poses a high risk to older people. The aim of this paper is to provide a rapid overview of the COVID-19 literature, with a specific focus on older adults. We frame our findings within an overview of the disease and have also evaluated the inclusion of older people within forthcoming clinical trials.

Methods

We searched PubMed and bioRxiv/medRxiv to identify English language papers describing the testing, treatment and prognosis of COVID-19. PubMed and bioRxiv/medRxiv searches took place on 20th and 24th March 2020, respectively.

Results

Screening of over 1,100 peer-reviewed and pre-print papers yielded n=22 on COVID-19 testing, n=15 on treatment and n=13 on prognosis. Viral-PCR and serology are the mainstays of testing but a positive diagnosis may be increasingly supported by radiological findings. The current evidence for the effectiveness of antiviral, corticosteroid and immunotherapies is inconclusive, although trial data are largely based on younger people. In addition to age, male gender and comorbidities, specific laboratory and radiology findings are important prognostic factors. Evidence suggests social distancing policies could have important negative consequences, particularly if in place for an extended period.

Conclusion

Given the established association between increasing age and poor prognosis in COVID-19, we anticipate that this rapid review of the current and emergent evidence might form a basis on which future work can be established. Exclusion of older people, particularly those with comorbidities, from clinical trials is well recognised and is potentially being perpetuated in the field of current COVID-19 research.

Key Points

- Older patients have a higher mortality and may present atypically with delirium, postural instability or diarrhoea, and without fever.
- Given the lack of sensitivity of individual tests, information from different testing modalities can be incorporated to support diagnosis.
- In addition to age, male gender and presence of comorbidities, specific laboratory and radiology findings are important prognostic factors.
- Social distancing and isolation may have negative consequences for older people, unrelated to COVID-19.
- Older patients are relatively excluded from clinical trials relating to COVID-19.

Introduction

In January 2020, a cluster of pneumonia cases in Wuhan City, Hubei province, China were identified as having been caused by the SARS-CoV-2 virus, leading to the disease now termed COVID-19. The subsequent global transmission led to the outbreak being classified as a pandemic by the World Health Organisation (WHO) on 11th March 2020. In the United Kingdom (UK), public health measures to control the spread of disease have, to date, included directives to self-isolate, socially distance, and so called 'lockdown' whereby activity and movement within a community is contained or limited.

Older adults, and those with comorbidities, are at particular risk of having severe infection [1] and are at higher risk of dying as a result of the disease [2-4]. In one of the largest case series so far published, of 72,314 cases reported by the Chinese Centre for Disease Control and Prevention, case fatality was 8.0% (312 of 3918) in patients 70-79 years old and 14.8% in patients aged ≥80 years (208 of 1408). Older adults appear to be more susceptible to the virus; 75% of known infections are in persons aged 50 and over.

In the UK and Europe, we are seeing an increasing number of cumulative cases and a rising trend in the daily number of confirmed COVID-19 cases. As such we have recognised an urgent need to provide clinicians, who may be less familiar with geriatric medicine, with a comprehensive overview of COVID-19 infection in older people. The overarching aim of this paper is to provide a rapid semi-systematic review of both peer-reviewed and pre-print evidence relating to COVID-19 testing, drug treatment and prognosis, as of late March 2020. We have presented these findings within a broader context discussing clinical presentation, supportive care strategies and social distancing in older people. Our findings, coupled with evaluation of the landscape of current and future clinical trials, have highlighted areas of priority for future research directed toward COVID-19 infection in older people.

Clinical overview of COVID-19

The current WHO suspected case definition is shown in Box 1 [5]. Clinical manifestations are summarised in Box 2. Cohort studies of patients with mild and moderate disease showed that fever was the most common symptom in 82-87% of cases, followed by cough in 36-66% [6]. This reflects findings from a meta-analysis of cases in China [7] where, of note, fever was more common during admission that at presentation [8]. In the RADAR COVID-19 study, in patients in a community setting with symptoms that warranted testing, anosmia was present in 59% who tested positive [9]. Other

clinical features include headache, rhinorrhoea, gastrointestinal symptoms, sore throat and fatigue. Cardiac complications are described including myocarditis [10], pericardial effusion on imaging [11] and arrhythmia [12] which is seen more commonly in those with greater disease severity [13]. Patients with severe infection can develop a pro-inflammatory cytokine release syndrome which can lead to rapid deterioration and death [14]. The majority of studies to date have notably reported symptoms occurring in patients with proven infection in hospitals.

Early reports substantiate that older people with COVID-19 will likely present atypically [15]; experience in France suggests that this group may initially present with delirium, postural instability or diarrhoea, rather than with typical respiratory symptoms and fever [16]. With COVID-19 being detected in older people who are in hospital for other illnesses, such as following a fall [16], it remains to be determined as to what extent these index events are precipitated by COVID-19 infection versus COVID-19 being found incidentally. Atypical presentations omitted from public health campaigns, such as diarrhoea, showed a pooled incidence rate of 9.2% [17]. Limited data are available on rates of delirium in COVID-19 infection, although the risk has been identified by the WHO and the British Geriatrics Society (BGS) who have produced specific guidelines to support delirium management in this context (Box 3) [18].

Typical findings on blood tests are lymphopenia and elevated C reactive protein (CRP) [19]. In moderate-to-severe cases increased procalcitonin levels have been observed [20]. Consistent with the aforementioned cardiac complications, severe cases often see raised levels of troponin I, D-dimer and lactate dehydrogenase [3, 12, 19, 21]. Chest radiograph (CXR) features are foci of ill-defined opacification with bibasal predilection, evolving to consolidation [17, 19]. On chest computerised tomography (CT), chest typical findings include lower lobe and peripheral predominance with multiple, bilateral foci of ground glass opacity [7, 17, 22] with or without crazy-paving, peripheral consolidation, air bronchograms and reverse halo or perilobular pattern [23]. Importantly, radiological changes may be absent in early disease (56% of 36 patients scanned between 0-2 days of symptom onset had a normal CT) [24] and minimal in mild disease (18% of 877 patients with non-severe disease clinically had no radiological abnormality. In severe cases, only 3% had no radiological signs. In light of this, COVID-19 cannot necessarily be ruled out on the basis of a normal CT whilst there is some evidence to suggest that the negative predictive value of CT is higher when symptom duration is >1 week [23, 25, 26].

The main complication of COVID-19 is acute respiratory distress syndrome (ARDS). This is reported to occur in between 15% [7] and 23% [17] of cases. Other complications include respiratory failure

[27], acute kidney injury [27, 28], and liver dysfunction [28]. Described causes of death include pneumonia, multi-organ failure, and severe acute respiratory syndrome [3, 19].

There is a striking paucity of peer reviewed evidence that examines the specific characteristics of COVID-19 in older people. Nonetheless, guidance relating to the care of older people is emerging from the international community. This guidance spans ethical considerations to the clinical management of COVID-19 in different settings [29] with a holistic assessment in their guidance on critical care in patients over 65 years old. The French Society of Geriatrics and Gerontology (SFGG) have highlighted the non-specific presentation of COVID-19 illness in older people. A joint consensus has been collated between the British Geriatrics Society, European Delirium Association, and the Faculty of Old Age Psychiatry at the Royal College of Psychiatrists on managing delirium in suspected and confirmed cases [18]. Specific guidelines from the United States have been published for Emergency Department providers [30] usefully outlining that immunosuppression in older adults, and or the presence of comorbidities, should prompt a lower threshold for COVID-19 testing. In addition, this guidance highlights the additional challenge of communicating with people with cognitive and sensory impairments whilst personal protective equipment (PPE) is being worn.

Systematic review methods

We searched PubMed and bioRxiv/medRxiv to identify all papers describing testing (including reverse transciption polymerase chain reaction assays/serology/radiology), treatment (including vaccines, at clinical phase only) or prognosis (predictors of clinical or viral outcomes) of COVID-19 (Figure 1). The search strategy for both databases is presented in Appendix 1. The PubMed search was run on 20th March 2020 and the bioRxiv/medRxiv search completed on 24th March 2020. Only articles published in English were considered for the purposes of the review. Further articles were identified through knowledge of the author team, reference and citation lists, and from any systematic reviews identified. Each article was screened by either FEL or ET on the basis of the title and abstract. Small workgroups focussing on testing, treatment and prognosis examined the full text articles within these topic areas and determined which studies provided relevant evidence. Any uncertainty about inclusion was resolved by discussion. Articles identified by this electronic search were combined with key clinical practice guidelines from expert groups and with relevant grey literature.

Testing

We included a total of 22 studies relating to testing: nineteen cohort studies of reverse-transcription polymerase chain reactions (RT-PCR) (9), serological testing (5) and combination testing (5) and three cross-sectional studies. Studies of the development and optimisation of current and novel laboratory techniques were excluded given the clinical focus of this review.

PCR

The World Health Organisation recommend testing of all suspected cases for COVID-19 (Box 1) [31]. The gold standard is RT-PCR to detect COVID-19 ribonucleic acid (RNA). Specimens can be upper respiratory (nasopharyngeal or oropharyngeal swab) or lower respiratory (sputum or endotracheal aspirate or broncho-alveolar lavage), although viral RNA has been detected in blood, anal swabs [32], stool [33-35], urine [36, 37] and in the conjunctival sac [38].

RT-PCR has good sensitivity (95%) and specificity (100%) at low numbers of COVID-19 RNA copies and against 297 samples of human respiratory and endemic human coronaviruses [39]. However, when applied clinically, a negative covid-19 PCR test may not be sufficient to rule out infection in suspected cases. There is discordance between negative respiratory swabs with detected viraemias, sputum samples and broncho-alveolar lavage [40, 41]. Initial PCR-negative suspected patients have subsequently become positive on repeat testing [42-45]. Poor specimen quality, specimens collected in very early or late disease or sample handling issues may explain these false negative results, and in clinical practice RT-PCR sensitivity is reported to be 60-70% [45, 46]. Therefore, a negative result in a suspected case does not rule out COVID-19 infection [31], and repeat testing may be advisable. The cohort and cross-sectional studies describing the sensitivity of PCR defined suspected cases as those presenting with fever, respiratory presentations, imaging findings consistent with COVID-19 or case contact [33, 34, 47]. The sensitivity of RT-PCR for diagnosing COVID-19 following alternative presentations in older people e.g. delirium or fall, is unknown. None of the studies commented on whether sensitivity of RT-PCR was affected by age and with the exception of one cohort study [41], the populations involved were younger hospitalised patients. The sensitivity of RT-PCR in older patients being cared for in different environments is unknown.

Understanding viral load dynamics throughout the COVID-19 disease course is important for interpreting RT-PCR results. PCR detects a higher viral load [33] and is more likely to be positive in earlier phases of the disease [48]. Although PCR tests become negative after viral clearance [19], the time frame of this remains unclear and positive RT-PCR has been shown to persist beyond symptom resolution [19, 48]. One study described 7 patients who were discharged following 2 negative RT-

PCR tests, but after 2 weeks follow up had positive results [50]. There remains controversy as to whether persistent positive RT-PCR detection of COVID-19 after symptom resolution represents ongoing infectivity. Woelfel et al readily isolated live virus from respiratory samples taken in the first week of symptoms but were not able to isolate live virus after 8 days despite detecting ongoing high viral RNA loads [49].

Serological testing

Serological tests of the immunological response to COVID-19 have also been developed and have demonstrated positive IgM and IgG in PCR-negative patients. This could represent better sensitivity than PCR, or lower specificity of serology [47, 50]. The utility of serological analysis as a diagnostic test for COVID-19 depends on the dynamics of the immunological response. Several large population studies have shown low sensitivity of serology in the first 5-7 days of the illness, with this increasing steadily as the disease progresses up to positive results of 90-100% between 12 and 20 days since following symptom onset [40, 43, 51, 52]. Although one study examined the use of serological testing in an outpatient setting in younger patients [54], there are currently no studies examining the sensitivity or dynamics of serological testing for COVID-19 in older populations in hospital or community settings.

Other testing

Characteristic radiological images have also been considered as diagnostic tools for COVID-19 given the lack of sensitivity of PCR and serological tests in early disease [53]. However, CT sensitivity is also dependent on the time course of symptoms. One study of hospitalised patients with a mean age of 51, found 97% positive CT chest findings in 1014 RT-PCR-positive COVID-19 patients, but also 75% positive CT chest findings in RT-PCR negative patients. The study reported a sensitivity of 97% with 68% accuracy and 25% specificity. Furthermore, they found that in a subgroup who tested negative and then positive with serial (repeated) RT-PCR, a large proportion (67%, 10/15) had positive initial chest CT although this only accounted for only 15.6% of those presenting with typical CT features at the time of the initial negative RT-PCR [45]. A retrospective study of 64 COVID-19 PCR-positive patients with a mean age of 56 in Hong Kong, showed that 69% of patients had CXR changes at presentation. They compared CXR at presentation with RT-PCR disease confirmation on serial testing. Presentation CXR changes had a sensitivity for detecting COVID-19 of 69% compared to 91% for presentation RT-PCR [53]. Multi-parameter screening tools are now being developed, which consider epidemiological factors, clinical features, radiological findings, and biochemical markers to

predict a diagnosis of COVID-19 [56]. No study has reported the diagnostic or prognostic role of imaging (CXR or CT) independent of the clinical parameters and/or biochemical parameters.

Rapid and accurate diagnosis of COVID-19 remains important to facilitate case isolation and, in older people, prognostication and advance care planning. The sensitivity of testing is dependent on disease stage, specimen site and quality. The clinical utility is further limited by test availability and delays in receiving results. In a health service faced with a rapidly increasing case load of patients with COVID-19, information from these different testing modalities can be incorporated to support diagnosis. We stongly advocate adopting a low threshold for testing older people with atypical symptoms where the result would alter management at an individual or population level. We recognise the lack of specific evidence on sensitivity of diagnostic tools in older people, testing in different care settings, and with varying symptom constellations e.g. dominance of lower or upper respiratory tract symptoms, as well as in those who are asymptomatic and / or contacts of positive cases.

Treatments

We identified two management guidelines [55, 56], four completed small-scale exploratory trials [57-60], four case series [12, 61-63], three retrospective reviews [64-66], and one rapid review of the effectiveness of antivirals [69]. Of the four trials, three reported experience with antivirals [58-60] and one with convalescent plasma [57]. The four case series reported experience with combination antivirals, corticosteroids, immunoglobulins and traditional Chinese medicine [12, 61-63]. Two of the retrospective reviews reported on the use of corticosteroids [64, 65] while one compared the treatment of older (>65 years) and younger patients. In addition, we were already aware of three rapid guidelines produced by NICE which covered critical care, dialysis and systemic anticancer treatment [NICE guidelines 159-161], [70-72] two WHO guidelines relating to the clinical care of people with COVID-19 infection and the Chinese COVID-19 guidance version 7 [71-73]. Since the search was completed further guidance on managing COVID-19 in care home settings has been produced and disseminated [76].

Antivirals

Gautret and colleagues conducted an open label non-randomised trial in France with 46 people (mean age 45 years, SD 22, (three >75 years)) using hydroxychloroquine and azithromycin and reported reduced viral loads at day 6 within the treatment group [61]. However, significant concerns have been raised about the methodological approach including the lack of control group and analysis whereby the results are likely to be confounded [77]. Chen and colleagues conducted an open label

randomised superiority trial in China comparing the efficacy of favipiravir and arbidol in 240 people (median age 46 years, IQR 34-59 (70 > 65 years)) with confirmed COVID-19 pneumonia [62]. At seven days, clinical recovery was higher in those on favipiravir but side effects of abnormal LFTs, psychiatric symptoms and GI upset were also more frequently reported [62]. Li and colleagues conducted an exploratory randomised controlled trial of lopinavir/ritonavir versus arbidol versus no antiviral medication in China in 44 people (mean age 52, SD 15 years, proportion >75 years not stated) with moderate COVID-19, and found no clear benefit and some potential harm of lopinavir/ritonavir [60].

Convalescent plasma

Duan and colleagues reported the feasibility of using pooled convalescent plasma on 10 people (median age 53 IQR 45-60, (one>75 years without comorbidity)) with severe COVID-19 already on maximal therapy [57]. Viral load became undetectable in 7 out of 10 patients following the infusion. No adverse events were reported. The authors felt the intervention was feasible and merited further study [57].

Corticosteroids

Wang and colleagues reported reduction in fever and improved oxygen saturations in a retrospective review of 46 people (median age 54 IQR 48-64) with severe COVID-19 pneumonia given methylprednisolone [67]. Zhou and colleagues reported findings from a retrospective review of the outcomes of 10 hospitalised people (mean age 52, SD 15) who received low dose corticosteroids and immunoglobulins with the majority also receiving anti-virals and antibiotics. A subsequent short course of methylprednisolone and further immunoglobulins were given when their condition deteriorated with observed improvement in oxygen requirements and inflammatory markers (CRP)[66].

Combination interventions

The four case series described the treatment and outcomes of 654 people (median ages 56, IQR 42-68; 55, IQR 39-67; 46, IQR 34-59; and 48, IQR 29-63) in China with confirmed COVID-19 infection. 609 (93%) participants received an antiviral including lopinavir/ritonavir (225 (34%)), arbidol (54 (8%)), oseltamavir (125 (19%)), and interferon (132 (20%). 244 (37%) received steroids. Use of the different antivirals or steroids did not appear to be associated with any change in outcome. Zhang and colleagues, however, reported a significantly higher positive fluid balance in those that died on ICU compared with those that were stepped down to wards. This finding has fed into clinical

guidance on using a cautious intravenous fluid strategy in those with confirmed or suspected COVID-19 [47].

The current evidence for the effectiveness of antiviral, corticosteroid and immunotherapies is inconclusive, and previous experience from the treatment of other viral pneumonias points to the risk of potentially significant side effects. This is particularly the case for corticosteroids where experience from RSV, influenza, and MERS-CoV shows no clear benefit while observational data point towards increased mortality and secondary infection rates [58]. On this basis, current guidance advocates using corticosteroids only to treat co-existing disease e.g. chronic obstructive pulmonary disease (COPD) and sepsis rather than COVID-19 infection / complications. The timings of therapy may be important such that anti-virals are utilised to reduce the viral load in early disease with corticosteroids or anti-inflammatory therapies having a role in reducing immunopathological damage that contributes to mortality as the disease progresses.

Limited data on the use of antivirals and corticosteroids in older age groups have been published. We identified one retrospective review which compared the treatments and escalation requirements of 136 older, defined as >60 years, (mean age 68, SD 7) and 652 younger (mean age 41, SD 11) patients with COVID-19 infections [66]. The older group were more likely to have a severe infection (24% vs 7% P<0.001), were more likely to need ICU admission (10% vs 1% P<0.001) and were more likely to require mechanical ventilation (7% vs 1% p=0.001). The difference in the proportions that received antiviral medications (86% vs 84% p=0.622) may have occurred by chance but corticosteroids were given more often in the older group (27% vs 9% p<0.001) reflecting their disease severity. More older people remained in hospital at the end of the review period than younger people (23% vs 45% p<0.001) [66]. Despite the urgency to identify effective treatments for COVID-19 it is imperative that this does not undermine the necessary rigor of therapy evaluation, and it is with some concern that we note the reports of the inclusion of unproven antiviral agents in national guidelines for the treatment of COVID-19 [78]. Of note, the majority of the studies identified in this review predominantly included younger people. Their applicability to older people, and populations in countries and healthcare systems outside China is therefore unclear. Future studies must prioritise the inclusion of older people to ensure that any findings are valid in the population most at risk of negative outcomes.

Prognosis

We identified 13 retrospective cohort studies of patients with COVID-19 that looked at prognosis. These studies examined the prognostic ability of one or more baseline factors to predict subsequent

COVID-19-related outcomes such as death, progression of disease severity, discharge from hospital or viral clearance studies (see Table 1, and Appendix). Information on such factors should help direct the most effective treatment to those for whom it has the potential to offer meaningful benefit. Eleven of the studies used traditional statistical epidemiology methods such as Cox regression and logistic regression, while two employed machine learning. Eight of the studies examined prognosis according to age. Not surprisingly, they all found that older patients had a worse prognosis: one large study observed the death rate to be more than double in the over 65s (hazard ratio 2.43, 95% confidence interval 1.66 to 3.56) [4]. Five studies reported prognosis by gender and all observed males to have a worse prognosis than females. Several specific comorbidities have been reported to predict poorer outcomes, including body mass index (BMI), hypertension, diabetes, COPD, coronary heart disease and malignant tumours. Furthermore, patients with two or more comorbidities have a poorer prognosis than patients with one [8].

Several symptoms were observed to predict outcomes. Higher levels of fever and higher respiratory rate in particular are associated with increased rates of progression or mortality, findings that have been replicated within or across studies. Numerous laboratory findings have also been observed to be prognostic, with higher white blood cell counts, lower lymphocyte counts, higher creatinine, higher creatine kinase, higher C-reactive protein, lower albumin, higher IL-6, higher myoglobin, higher lactate dehydrogenase, higher procalcitonin, higher high-sensitivity cardiac troponin I, higher total bilirubin, higher urea and presence of acute kidney injury, being characteristics consistently associated with worse prognosis across two or more studies. Future analysis of sequential measurements should help determine the trajectory of change and whether elevated levels in early disease are indicative of later deterioration.

The two studies using machine learning each identified a specific set of predictors. Bai et al identified age >55 years, hypertension, decreased albumin, decreased lymphocyte count, progressive consolidation on CT scan, elevated CRP and lack of fibrosis at initial CT scan as associated with higher risk of progression to severe COVID-19 [79] [80] Yan et al identified higher lactic dehydrogenase, lower lymphocytes and higher high-sensitivity CRP as associated with greater risk of mortality from a pool of more than 300 features [81].

Broader considerations

Supportive care

NICE recommend that the Clinical Frailty Scale (CFS) should be used to provide a functional evaluation of people presenting with COVID-19 in those aged 65 and over without long-term

disability such as cerebral palsy, learning disability or autism. They advise that in patients with a CFS between 1 to 4, who would like to be treated intensively, critical care referral would be appropriate [70]. Advanced care planning for those living with frailty, including sensitive consideration about the potential benefits of admission to hospital, is recommended. This is particularly relevant to people resident in care homes or with high clinical frailty scores where advanced care plans should be proactively revisited in the light of the current outbreak [76].

Guidelines advocate stratifying people by disease severity although older people, and those with comorbidity, despite presenting with mild symptoms are at higher risk of severe COVID-19 and of unpredictable, rapid, deterioration [73]. Features suggestive of severe COVID-19 include: respiratory rate >30 or oxygen saturations <93% on air [75] or CURB65 >1 and should prompt consideration of hospital admission [57]. However, the majority of prediction studies examining risk of hospitalisation, diagnosis of COVID-19 in those with symptoms and prognosis have been based on data from China. All have had a high risk of bias such that the prediction performance of tools in clinical practice is likely to be lower than initially reported [80].

In the absence of proven treatments for COVID-19, current management is essentially supportive. Older people living with frailty (clinical frailty score of 5 or more) presenting with COVID-19 should be managed through a comprehensive geriatric medicine framework with multidisciplinary working and a patient centred, goal driven approach [73]. Supplemental oxygen should be given to maintain oxygen saturations, and electrolyte and coagulation disturbances should be rectified. Where there is established bacterial infection or sepsis [73] or in mechanically ventilated patients [81] antibiotic therapy should be used. However, careful antibiotic stewardship is warranted and the diagnosis and management should be reviewed at 48-72 hours [84] given the established risk of antibiotic resistance, risk of drug toxicity and drug interactions. Use of antibacterials such as azithromycin with putative anti-inflammatory or antiviral activity should be given within the context of established randomised clinical trials. One such trial is the UK based RECOVERY trial which recently replaced the interferon beta arm with azithromycin 500mg for 10 days [85]. Co-morbidities should be managed as standard, being mindful of the non-specific presentation of disease in older patients to avoid attributing presenting symptoms solely to probable COVID-19 infection. Early medication review should occur to reduce the risks associated with polypharmacy in the context of COVID infection [73]. Early, sensitive, discussion around ceilings of care for older frailer people with COVID-19 should be carried out.

Non-pharmaceutical interventions: Social distancing and community containment

Comprehensive review of all non-drug interventions for COVID-19 infection were beyond the scope of this review. Recognising, however, that social distancing has a significant impact on older people we conducted a supplementary search to specifically consider the potential negative consequences of social distancing in older adults, using terms such as social distancing, social isolation, older adults and elderly.

In the current absence of preventative pharmaceutical interventions, such as vaccines and anti-virals, classic public health measures are required to reduce and prevent person-to-person transmission, namely: isolation and quarantine, social distancing and community containment [84]. Isolation and quarantine of ill, or possibly ill, individuals can be effective tools for preventing onwards transmission if early detection of cases is possible, as successfully implemented during the 2003 SARS epidemic [84]. Stricter measures of 'social distancing' and even more stringent 'community containment' may be deployed if community transmission, without obvious linkages between cases, is evident [84]. With evidence of widespread community transmission of COVID19, community containment ('lockdown') and social distancing has already been implemented in several countries. For older adults, the focus is on shielding such individuals from infection, because attack rates have been shown to be higher, and the disease more severe, in this age group [87]. Such measures, however, are highly disruptive for individuals and may have negative unintended consequences.

There is evidence that socially disconnected and isolated older adults are at increased risk of physical and mental health problems including cardiovascular disease, stroke, depression, anxiety, dementia and premature death, and as a result can require additional health and social care support [88-92]. For example, chronic loneliness has been associated with an increased number of doctor visits; in a study of 3530 older adults living in the community in the United States Gerst-Emerson et al found an increased number of doctor's visits for people reporting loneliness both in 2008 and 2012 (b=0.075, p=0.029), but not for each year alone [89]. There was limited evidence for an association with hospitalisations; being lonely in 2008 was associated with increased hospitalisations (b= 0.218, p=0.031), but not in 2012 or in both years. Low contact with friends in older adults, exclusion from social relationships and subjective feelings of exclusion have been negatively associated with well-being and associated with poor self-reported health [93, 94]. Loneliness caused by social isolation has been associated with impaired cognitive function in older adults. In a study of 7,410 Chinese older adults, Yang et al found an indirect effect of loneliness and cognitive function (b=−0.17, p<0.05), and after controlling for loneliness a direct effect of social isolation on cognitive functioning (b=−0.36,

p<0.05) [95]. Those experiencing a high degree of loneliness have been found to be at increased risk of becoming physically frail. Gale et al investigated the association between loneliness and pre-frailty and frailty in 2,346 English older adults and found multivariable adjusted relative risk ratios of 1.74 (95% CI 1.29, 2.34) for those living with pre-frailty and 1.85 (95% CI 1.14, 2.99) frailty among those with a high score for loneliness [96]. The same study considered social isolation and frailty, but found no evidence of association in the multivariable model aRRR 1.19 (CI 0.93, 1.53) and 1.12 (0.70, 1.78) for pre-frailty and frailty respectively) [96]. These data relate to social disconnection, isolation and loneliness more generally, as opposed to specifically in relation to social distancing in response to COVID-19 or other pandemics; therefore self-isolation during pandemics may result in different physical and psychosocial consequences from loneliness at other times. However, this evidence suggests the current social distancing policies could have important negative consequences, particularly if in place for an extended period.

Current and planned trials

Larger scale trials relating to COVID-19 are a priority and are now underway including the multi-arm trials SOLIDARITY run by the WHO [97] and Randomised Evaluation of COVID-19 Therapy (RECOVERY) [98]. These will examine some of the drugs identified as promising in early studies (lopinavir and ritonavir, chloroquine and hydroxychloroquine) and interferon-beta or dexamethasone. There are numerous planned and current clinical trials of adjuvant therapies aimed at improving survival in COVID-19.

As of the 16th March 2020 the WHO International Clinical Trials Registry Platform [99] listed 523 trials related to COVID-19, of which 258 were therapeutic interventional studies (excluding studies on prevention of COVID-19, and rehabilitation in survivors) (12). The majority of these trials are led by groups based in China and the United States. The trials can be broadly grouped into the aforementioned categories of antiviral (33), antibiotics (0), corticosteroids (4), immunoglobulin (15), other (199) or multi-arm combinations (7). The category 'other' was varied in terms of trialled drugs, including chloroquine (ChiCTR2000029868), interferon (ChiCTR2000030480), herbal compounds (ChiCTR2000030545), cytokines (ChiCTR2000030167), stem cell therapies (ChiCTR2000030138) and biologic agents (ChiCTR2000029765). In the majority of studies, the primary outcome is all-cause mortality, but others measured outcomes include improvement in oxygen saturation (ChiCTR2000029990) or time to fever reduction (ChiCTR2000029781). Notably, 10% of studies exclude patients over the age of 65. This figure rises to 17.4% excluding over-70s, and 37.2% excluding over-75s. Given the apparent increased risk of negative health outcomes in older people, it

is important that this vulnerable group is included in intervention trials with consideration given to age-related physiological, pharmacokinetic, pharmacodynamic changes and concurrent comorbidity.

Discussion and future directions

The emergence of COVID-19 represents a dynamic, specific and real threat to the health and well-being of older people. The scope of COVID-19 is such that ethical support is being proposed to aid in the decisions on critical care [98, 99], and the rapid NICE guidelines [70] suggest the use of the CFS in triage. These aspects combined with the compelling evidence that advanced age is a prognostic indicator for poorer outcome provides a clear basis on which guidance on the management of COVID-19 in older people is warranted [100, 101]. The research field is rapidly evolving as understanding of the clinical characteristics, transmission, and necessary public health and interventional measures becomes clearer. Recognising the real need for clinicians on the front lines to have reliable information, we have sought to rapidly synthesise and summarise the current evidence base of testing, treatments and prognostic factors, in addition to detailing the clinical and radiological features of the disease. Finally, we have provided a synopsis of the field of prospective clinical trials, with specific reference to the age-specific inclusion criteria.

One of the strengths of this paper has been the rapid screening of more than 1000 articles. In addition to the standard inclusion of published peer reviewed papers, the addition of pre-print articles is a particular strength that provides greater contemporary insight. We have set this literature review in the context of what is currently known about the clinical and radiological features of the disease, and we have systematically identified and summarised papers relating to prognosis. We anticipate that this may inform clinical practice in targeting treatment strategies accordingly. The limitations of this review include the fact that we have only identified papers published in English and have excluded editorials, correspondence, commentaries and single case reports. Evidence that has not been peer reviewed should be considered within that context and the findings interpreted with caution. Furthermore, the reported results may be subject to reporting biases, and particularly to selective presentation of findings in the investigations of prognosis. The degree to which prognostic data from China is more widely generalisable is unknown and these data are not specific for older adults.

Future research

Our review has highlighted areas with a paucity of evidence that may be tackled with future research (Box 4). This is a core component of the Department of Health and Social Care COVID-19 strategy to

Contain; Delay; Research; and Mitigate. These research objectives align with the approaches advocated by organisations including the BGS [104].

Testing

More research is needed to establish the sensitivity of diagnostic testing in older people, who are largely omitted from existing cohort studies of sensitivity. This further work should examine sensitivity in those with non-specific presentations and within different care settings e.g. care homes or patients own homes. Additionally, understanding of the dynamics of RT-PCR and serological testing throughout the COVID-19 disease course to guide interpretation of diagnostic tests will be valuable. Indications for testing patients in care homes to include non-specific presentation of COVID-19 illness would potentially facilitate containment and appropriate treatment

Presentation

Areas of focus may include evaluation of atypical and non-specific presentation of COVID-19 in older people, specific prognostic factors for those treated outside of intensive care settings, the impact of cognitive impairment and delirium on management, considerations about providing care in community settings, including nursing and residential homes, as well as optimal care for patients at the end of their lives.

Treatment and rehabilitation

We strongly advocate that upper age limits in interventional trials are justified, and that awareness, access and participation of older people in clinical trials is facilitated. Exclusion of older people, particularly those with comorbidities, from clinical trials is well recognised. Findings from trials that have enrolled younger participants are often extrapolated and applied in the management of older adults; a heterogeneous group of individuals. We have demonstrated a very real risk of 'ageism' occurring in the current portfolio of COVID-19 interventional trials whereby almost 40% of studies plan to exclude people over the age of 75. We are encouraged that this is not a feature of some of the larger trials including the 5 arm, SOLIDARITY trial [105] led by the WHO which includes a remdesivir treatment arm supporting promising in vitro findings. The 5 arm, UK RECOVERY trial [85], the 3 domain REMAP-CAP trial [106] all use adaptive design to tackle multiple hypotheses, providing rapid evidence on which to base care.

Development and evaluation of effective rehabilitation strategies and trajectories will be required for older people who have either experienced severe or critical COVID-19 infection and / or have mild or moderate disease but are living with frailty or comorbidity. The NHS Discharge to Assess model anticipates that 45% of patients will require support from health and social care on discharge from hospital with a further 4% requiring a bedded setting.[107] Identification of rehabilitation

settings to prevent the long-term adverse effects of COVID-19 may require specialist facilities or at least additional capacity to relieve pressure on acute services [108]. Data from survivors of acute respiratory distress syndrome (ARDS) and severe influenza A (H1N1) whom have been managed in intensive care settings suggests that the cognitive dysfunction and negative psychological sequalae including post-traumatic stress disorder, anxiety and depression in patients and families are common and should therefore provide a focus for intervention and evaluation.[109]

We wholly support the public health measures that support reduction in COVID-19 transmission. Effectiveness of future public health interventions such as vaccination, shielding and potential prophylactic treatments should include robust evaluation of unintended but potentially inevitable negative sequalae. Social distancing and isolation offer both protection and risk to some of the most vulnerable individuals in society. Future focus on aspects such as loneliness, deconditioning, progression of frailty and neglect of comorbidities are warranted as well as measures that might mitigate these harms.

Conclusion

The COVID-19 pandemic presents emergent and novel challenges as it evolves. Our review has highlighted areas within the domains of testing, treatment and prognostication that warrant future study. It will be imperative that research is proactively inclusive of older people so as to optimise prevention, treatment and rehabilitation strategies in this at-risk group.

Box 1 World Health Organisation suspected case definition ([5])
A suspected case is: A. a patient with acute respiratory illness (that is, fever and at least one sign or symptom of respiratory disease, for example, cough or shortness of breath) AND with no other aetiology that fully explains the clinical presentation AND a history of travel to or residence in a country, area or territory that has reported local transmission of COVID-19 disease during the 14 days prior to symptom onset OR B. a patient with any acute respiratory illness AND who has been a contact of a confirmed or probable case of COVID-19 disease during the 14 days prior to the onset of symptoms (see the definition of contact below) OR C. a patient with severe acute respiratory infection (that is, fever and at least one sign or symptom of respiratory disease, for example, cough or shortness breath) AND who requires hospitalization AND who has no other aetiology that fully explains the clinical presentation.

Box 2. Clinical Overview of COVID-19

Clinical Manifestations

- Fever [7]
- Dry Cough [7]
- Dyspnoea
- Myalgia
- Fatigue
- Diarrhoea [17]
- Asymptomatic [110]
- Acute Respiratory Distress Syndrome [7, 17]
- Atypical presentations (e.g. behavioural change, balance problems, falls), particularly in older adults
- Anosmia [9]

Typical biochemical Findings (not exhaustive) [17, 19]

- Lymphopenia
- Elevated C-reactive protein

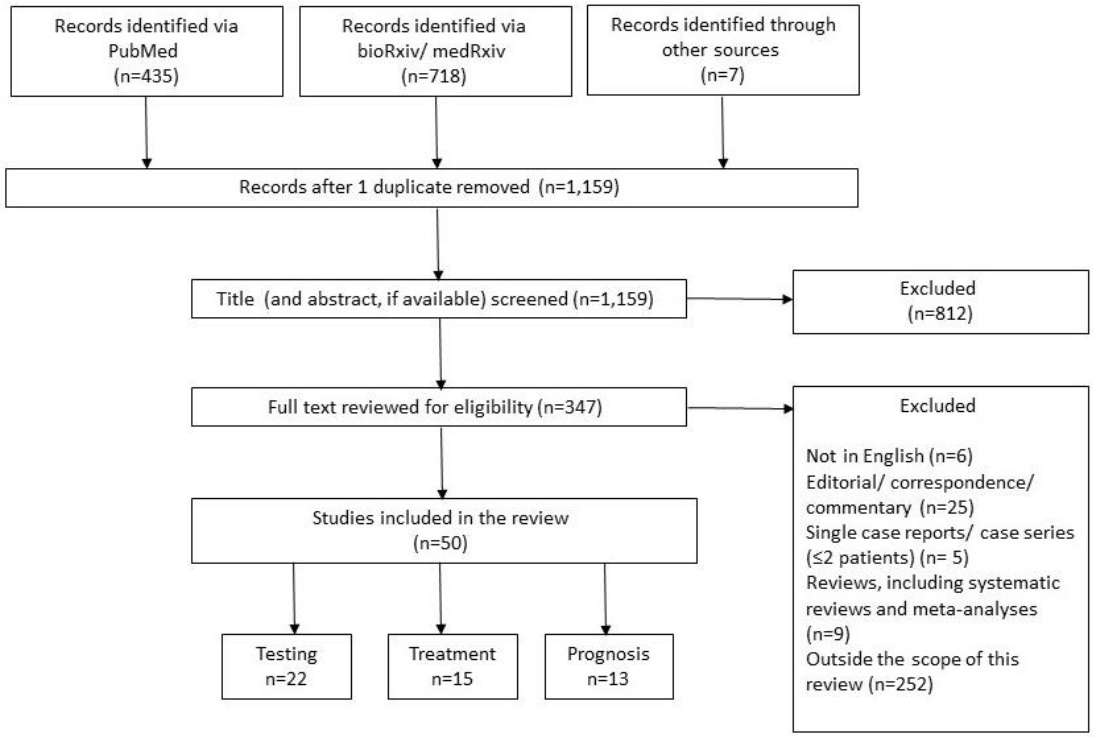
Radiological Findings [24]

- CXR [22]
    - bilateral, ground glass opacification which is ill-defined and more commonly seen in the periphery and the right-lower lobe
- CT Chest
    - Can be normal in the early stages of disease, but a normal CT after a week suggests COVID-19 much less likely
    - Lower lobe predominant, peripheral predominant, multiple, bilateral foci of ground glass opacity
    - ± Crazy-paving, Peripheral consolidation, Air bronchograms, Reverse halo/ perilobular pattern

Causes of Death [3, 19]

- Pneumonia
- Sepsis (viral or bacterial)
- Severe Acute Respiratory Syndrome

Figure 1. Systematic search results



Box 3. Useful resources

World Health Organisation
Case Management: outlines the management of people with COVID-19 infection in secondary care
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management

European Geriatric Medicine Society
EuGMS Task Force on COVID-19 collates topics on care of older people during the coronavirus pandemic from across Europe
https://www.eugms.org/news/read/article/490.html

The National Institute for Health and Care Excellence
UK Rapid guidelines and evidence reviews including critical care, patients on dialysis, risk of angiotensin converting enzyme (ACE) inhibitors and NSAIDS
https://www.nice.org.uk/covid-19

UK Government
Advice on people in residential care and supported living
https://www.gov.uk/government/publications/covid-19-residential-care-supported-living-and-home-care-guidance

Ethical framework for planning adult social care during the coronavirus outbreak
https://www.gov.uk/government/publications/covid-19-ethical-framework-for-adult-social-care

British Geriatrics Society
COVID-19: Managing the COVID-19 pandemic in care homes: good practice guide [76]
https://www.bgs.org.uk/resources/covid-19-managing-the-covid-19-pandemic-in-care-homes

Coronavirus: Managing delirium in confirmed and suspected cases [18]
https://www.bgs.org.uk/resources/coronavirus-managing-delirium-in-confirmed-and-suspected-cases

British Society of Thoracic Imaging
COVID-19 guidance for the reporting radiologist
https://www.bsti.org.uk/standards-clinical-guidelines/clinical-guidelines/bsti-covid-19-guidance-for-the-reporting-radiologist/

Table 1 Prognostic Studies – Study characteristics and outcomes

Reference	Sample Size	Population	Hospital	Admissions	Outcome
Fu L [111]	200	Hospital admissions confirmed by real-time RTPCR assay for SARS-CoV-2 RNA	Union Hospital of Huazhong University of Science and Technology, Wuhan, China	1 Jan – 30 Jan 2020	Mortality
Gao L [2]	54	Hospital admissions with Laboratory (RT-PCR) confirmed SARS-Cov-2 infection; CT of the lung conformed to the manifestation of viral pneumonia.	Hubei General hospital, Chongqinq, China	Not available	Mortality
Liu W [1]	78	Hospital admissions with positive test result for COVID-19 nucleic acids by real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) hospitalized for > 2 weeks, died while hospitalized, or had recovered and been discharged	1) The Central Hospital of Wuhan, 2) Tongji Hospital, 3) Wuhan Pulmonary Hospital, Wuhan, China	30 Dec 2019 – 15 Jan 2020	Disease progression to severe, critical or death
Zhou F [3]	191	Hospital admissions diagnosed with COVID-19 according to WHO interim guidance	Jinyintan Hospital and Wuhan pulmonary hospital, Wuhan, China	29 Dec 2019 – 31 Jan 2020	Mortality
Chen J [110]	249	Hospital admission diagnosed according to Chinese national guideline for COVID-19 diagnosis and treatment, as well as the World Health Organization interim guidance	Shanghai Public Health Clinical Center (SPHCC), Shanghai, China	20 Jan – 6 Feb 2020	ICU admission
Guan W [111]	1590	high-throughput sequencing or real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay findings for nasal and pharyngeal swab specimens were positive	575 Hospitals across China, nationwide	21 Nov 2019 – 31 Jan 2020	ICU admission, or invasive ventilation, or death
Liu J [80]	64	Medical staff following admission to isolation wards with RT-PCR positive nCoV-19 positive cf. WHO interim guidance	Wuhan Union Hospital, Wuhan, China	16 Jan – 15 Feb 2020	Hospital discharge
Cai Q [114]	298	Hospital admissions confirmed according to WHO interim guidance (RT-PCR)	Third people's Hospital of Shenzhen, Guangdong, China	11 Jan – 6 Feb 2020	Duration of positive viral test results. Virus clearance defined as 2 negative qPCR detection results at an interval of 24h

Reference	Sample Size	Population	Hospital	Admissions	Outcome
Cheng Y [115]	701 (of which 442 included in prognostic analysis)	Hospital admissions COVID-19–positive according to the guidance provided by the Chinese National Health Commission: ≥2 clinical diagnosis criteria and a positive result to high-throughput sequencing or RT-PCR assay. Patients with a history of maintenance dialysis or renal transplantation were also excluded	Tongji Hospital, Wuhan, China	28 Jan -11 Feb 2020	Mortality association between kidney disease and in-hospital death
Yang P [116]	55	Hospital admission with SARS-CoV-2 confirmed by qRT-PCR or sequencing	Fifth Medical Center of PLA General Hospital, Beijing, China	27 Dec 2019 – 18 Feb 2020	Disease progression
Liu R [117]	41	Staff of the central hospital of Wuhan admitted with COVID-19 confirmed by RT-PCR	Central Hospital of Wuhan, Wuhan, China	15 Jan – 24 Jan 2020	In-hospital adverse events (defined as respiratory failure or ARDS, transfer to ICU, invasive mechanic ventilation, acute cardiac injury, acute kidney injury, acute hepatic injury, acute myocyte injury, shock, secondary infection and death)
Bai X [79]	199	Hospital admission with positive viral nucleic acid test result on throat swab samples (n=80) or clinical parameters (n=53)	Wuhan Pulmonary Hospital, Wuhan, China	3 Jan – 13 Feb 2020	Progression of disease severity (using machine learning; results not in Appendix 2)
Yan L [81]	404	Hospital admissions with SARS-CoV-2 nucleic acid positive by RT-PCR; or 2) virus shares detected by high homology with the known sequence of SARS-CoV-2 in respiratory or blood samples	Tongji Hospital, Wuhan, China.	10 Jan – 18 Feb 2020	Critical illness (using machine learning with supervised XGBoost classifier, results not in Appendix 2)

Box 4. Suggested future research directions

Testing

Identification of the diagnostic accuracy, indication and optimal method(s) for testing in older people in the presence and absence of symptoms and in different settings e.g. primary versus secondary care, residential and nursing homes.

Clinical presentation

Evaluation of the extent to which frailty, comorbidity, and age and specific drugs (e.g. ACE inhibitors, non-steroidal anti-inflammatories (NSAIDs) and others e.g. immunosuppressants) influence the clinical presentation and disease trajectory of COVID-19 in older people. Ascertainment of the longer-term morbidity with evaluation of physical, cognitive and psychosocial outcomes.

Treatment and rehabilitation

Ongoing monitoring and advocacy to ensure that randomised clinical trials recruit older adults and that their enrolment is facilitated. Rapid implementation and evaluation of established and novel rehabilitation strategies are required to support post-acute care of older patients with COVID-19 infection. Evaluation of the advanced care planning discussion, documentation and communication along with optimal treatment strategies at the end of life.

Wider impact

Ascertainment of the impact of public health measures, particularly social isolation, on older people is warranted to determine the relative risks versus benefit of these strategies. Evaluation of multidisciplinary working across organisations to optimise acute care and rehabilitation.

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