Improving the early identification of COVID-19 pneumonia

BMJ Open Respiratory Research

Improving the early identification of COVID-19 pneumonia: a narrative review

Daniel Goyal ,[1] Matthew Inada-Kim,[2,3] Fatam Mansab,[4] Amir Iqbal,[5] Brian McKinstry,[6] Adeeb P Naasan,[7] Colin Millar,[7] Stephen Thomas,[8] Sohail Bhatti,[4] Daniel Lasserson,[9,10] Derek Burke[11]

To cite: Goyal D, Inada-Kim M, Mansab F, *et al*. Improving the early identification of COVID-19 pneumonia: a narrative review. *BMJ Open Resp Res* 2021;**8**:e000911. doi:10.1136/bmjresp-2021-000911

Received 22 February 2021
Accepted 19 October 2021

For numbered affiliations see end of article.

Correspondence to
Dr Daniel Goyal;
daniel.goyal@gha.gi

ABSTRACT

Delayed presentation of COVID-19 pneumonia increases the risk of mortality and need for high-intensity healthcare. Conversely, early identification of COVID-19 pneumonia grants an opportunity to intervene early and thus prevent more complicated, protracted and less successful hospital admissions. To improve the earlier detection of COVID-19 pneumonia in the community we provide a narrative review of current evidence examining the clinical parameters associated with early disease progression. Through an evolving literature review, we examined: the symptoms that may suggest COVID-19 progression; the timing of deterioration; the utility of basic observations, clinical examination and chest X-ray; the value of postexertion oxygen saturations; and the use of CRP to monitor disease progression. We go on to discuss the challenges in monitoring the COVID-19 patient in the community and discuss thresholds for further assessment. Confusion, persistent fever and shortness of breath were identified as worrying symptoms suggestive of COVID-19 disease progression necessitating urgent clinical contact. Importantly, a significant proportion of COVID-19 pneumonia patients appear not to suffer dyspnoea despite severe disease. Patients with this asymptomatic hypoxia seem to have a poorer prognosis. Such patients may present with other signs of hypoxia: severe fatigue, exertional fatigue and/or altered mental status. We found duration of symptoms to be largely unhelpful in determining risk, with evidence of deterioration at any point in the disease. Basic clinical parameters (pulse, respiratory rate, blood pressure, temperature and oxygen saturations (SpO_2)) are likely of high value in detecting the deteriorating community COVID-19 patient and/or COVID-19 mimickers/complications (eg, sepsis, bacterial pneumonia and pulmonary embolism). Of these, SpO_2 carried the greatest utility in detecting COVID-19 progression. CRP is an early biochemical parameter predictive of disease progression and used appropriately is likely to contribute to the early identification of COVID-19 pneumonia. Identifying progressive COVID-19 in the community is feasible using basic clinical questions and measurements. As such, if we are to limit the mortality, morbidity and the need for complicated, protracted admissions, monitoring community COVID-19 cases for signs of deterioration to facilitate early intervention is a viable strategy.

INTRODUCTION

SARS-CoV-2 is the third respiratory betacoronavirus to infect humans. There have been over 100 million cases worldwide with over 2 million deaths.[1] Although it seems quite plausible that there will be a safe and effective vaccine strategy through 2021, given the expected lag time in achieving significant disruption to viral transmission, the high prevalence of SARS-CoV-2, and the potential difficulties posed by variant strains, the challenge of managing COVID-19 will remain with us for some time.[2] If we are to limit the direct and indirect impact, understanding the clinical aspects of SARS-CoV-2 remains pivotal.

Our ability to limit the progression of COVID-19 has improved with our growing knowledge and experience of the disease. Timely administration of optimally delivered oxygen reduces disease progression.[3 4] Steroids have been shown to be effective in reducing disease progression,[5] shortening hospital stays[6] and reducing mortality.[7] There are many other aspects of 'best supportive care' that impact disease progression.[8]

Here, we present the evidence supporting the role of a number of clinical parameters in detecting the deteriorating community COVID-19 patient earlier. We also discuss the challenges in early identification of the progressive COVID-19 patient and make suggestions on how to manage such challenges.

METHODS

We initially searched literature databases (such as Medline, medRxiv and Google Scholar) for studies reporting on clinical parameters relating to COVID-19. We focused on those clinical parameters that would be easily accessible within the community: symptoms, basic clinical observations (heart rate, blood pressure, oxygen saturations, respiratory rate (RR) and temperature) and clinical examination. An evolving literature search was permitted, and studies were included for review if they had relevant data pertinent to the underlying question of early identification of COVID-19 pneumonia.

We further searched for studies relating to clinical investigations that were accessible from the community and/or would be typically considered in other viral pneumonias: chest X-ray, postexertion oxygen saturations and serum C-Reactive Protein (CRP) levels. Again, an evolving literature search was permitted, and studies were included for review if they had relevant data pertinent to the underlying question.

Following identification of relevant studies, we sought to compare milder COVID-19 cohorts with more severe cohorts to extrapolate potential differences. Cohort severity was determined based initially on the overall cohort mortality rate or the rate of advanced respiratory support required (as described). The data pertaining to these clinical parameters and tests specific to community COVID-19 were insufficient to perform a systematic review or meta-regression analysis, and given the need to infer and extrapolate across studies, we deemed a narrative review as the most appropriate method for reporting such data during this phase of the pandemic.

Identifying disease progression

Symptoms

Sung and colleagues[9] provide a useful insight into the transition from mild to severe cases in their retrospective analysis of 3060 cases from South Korea. In the mild group (n=2585), symptoms included cough (40%), fever (30%) and dyspnoea (5%). Cough, history of fever and dyspnoea all increased in prevalence between groups, reaching 70.4%, 57.1% and 70.3% in the critical group, respectively.

While Sung *et al* provides a useful insight into early symptoms in mild COVID-19, other epidemiological studies provide larger datasets for mixed severity and severe COVID-19 cohorts. Two of these studies together with the South Korean mild cohort have been collated into a table for comparison of symptom trajectory (table 1).

Comparing the three different groups (mild, mixed and severe/inpatient), symptoms that may suggest COVID-19 progression include: shortness of breath, dry cough, fever, fatigue, chest tightness, confusion, diarrhoea, vomiting and abdominal pain. Of these, shortness of breath remains the most predictive of disease progression (summary box 1).

Duration of symptoms

There is an association between time from symptom onset to receiving clinical care and disease severity. Within a specified cohort, the longer the delay between symptom onset and admission, the greater the duration of stay and the higher the mortality.[10 11] Some patients however, can deteriorate rapidly, requiring intubation within 1 day of symptom onset.[12–14]

Table 1 Symptom prevalence across different COVID-19 severity levels

	Prevalence of symptoms (%)		
Symptom	**Mild cohort* (n=2585)**	**Mixed cohort† (n=55 924)**	**Inpatient cohort‡ (n=25 477)**
Breathlessness	4.8	18.6	65.2
Dry cough	40.8	67.7	68.0
Fever	25.9	87.9§	66.4
Fatigue	n/a	n/a	35.0
Confusion	0.0	n/a	23.3
Wet cough	25.3	33.4	20.1
Diarrhoea	6.9	3.7	16.4
Nausea and vomiting	2.4	5.0	16.3
Muscle and joint pain	18.6	14.8	14.6
Chest tightness	n/a	n/a	11.5
Headache	n/a	13.6	8.7
Abdominal pain	n/a	n/a	8.2
Wheeze	n/a	n/a	8.0
Sore throat	n/a	13.9	6.8
Haemoptysis	n/a	0.9	2.6
Runny nose	12.8	n/a	2.3
Conjunctival congestion	20.6	0.8	0.3

*Sung *et al* discussed previously.[9]
†55 924 PCR-confirmed positive cases from China were analysed in February 2020. Fever in this study was defined as temperature >37.2°C (WHO-China Joint Mission).[61]
‡A further inpatient cohort (n=25 477) examined symptoms at presentation to hospitals in the UK between February and May 2020. Overall mortality was 35%.[62]
§Fever was defined in this cohort as >37.2°C.

Box 1 Summary

Symptoms that may be associated with disease progression:
Dyspnoea.
Confusion.
Fatigue.
Dry cough.
Fever.
Chest tightness.
Abdominal pain.
Diarrhoea.
Vomiting.

This was highlighted well in a study from Mexico. Data were collected from 65 000 patients who had suspected COVID-19 between January and April 2020, with an overall Case Fatality Rate of 3.32%. The time from initial symptoms to actual clinical suspicion of COVID-19 was recorded and then analysed against medical disposition decision and mortality. Fourteen per cent of patients presented to healthcare within 24 hours of first symptoms and of those nearly half were admitted directly to hospital, with 2.8% being admitted to intensive care unit (ICU). The overall mortality for those presenting within 24 hours of symptom onset was 5.2%. Mortality fell to 2.5% if the patient presented to medical care when the symptom onset was between 1 and 3 days and rose significantly to 3.6% in the 4–7 days group. Where patients were admitted after 7 days of symptoms, mortality rose even further (4.1%). The delayed presentation group had a 59% higher chance of ICU admission if presenting after 7 days versus presentation between 1 and 3 days.[15]

While there have been reports of a 'second hit' deterioration in patients occurring between 5 and 10 days of symptom onset, the evidence for such a trajectory is limited. It remains feasible that such a 'second hit' merely relates to the delayed presentation of COVID-19 pneumonia and natural evolution of the disease. Regardless of what future research will show, there is clear evidence of sudden and rapid deterioration in a proportion of patients with COVID-19,[12–15] and as such, vigilance throughout the illness seems warranted.

Basic observations

Identifying disease progression in COVID-19 has been challenging in part due to the variable symptoms and in part due to the minimal changes that occur in basic observations (blood pressure (BP), temperature (Temp), oxygen saturations (SpO_2), heart rate (HR) and RR) despite severely progressive disease.

Even within a relatively severe cohort, the observation changes are modest. Data from the multicentre retrospective inpatient cohort study, International Severe Acute Respiratory and emerging Infection Consortium cohort (ISARIC) (n=122 361), yield an overall mortality rate of 31% (where outcomes are recorded) and mean CRP of ~90 mg/L. Despite this level of severity, the mean observations in the age bracket of 60–69 years at presentation were RR: 22, HR: 91, SpO_2: 95%, temp 37.3° and systolic BP: 130 mm Hg (table 2).[16]

Heart rate

Basic observations are of value in identifying COVID-19 complications (eg, pulmonary embolism, secondary bacterial pneumonia and cardiogenic shock) and in detecting an important group: COVID mimickers (sepsis, bacterial pneumonia, etc). As such, monitoring HR in patients under surveillance/evaluation for progressive COVID-19 is useful. Its use in detecting progressive

Table 2 The mean observations from the ISARIC inpatient cohort

	Median value of basic observations in ISARIC cohort (n=122 361) (IQR)					
Age range (years)	HR	SpO_2	RR	Systolic BP	Temp (°C)	Est. NEWS2
0–9	119 (32)	98 (3)	28 (12)	106 (24)	37.2 (1.6)	
10–19	106 (28)	98 (2)	20 (5)	119 (20)	37 (1.2)	
20–29	102 (27)	98 (3)	20 (5)	122 (22)	37 (1.3)	1
30–39	101 (24)	97 (3)	20 (7)	125 (23)	37.4 (1.5)	1
40–49	98 (24)	96 (4)	22 (8)	127 (25)	37.5 (1.5)	3
50–59	95 (23)	95 (4)	22 (7)	129 (28)	37.5 (1.5)	4
60–69	91 (24)	95 (5)	22 (7)	130 (30)	37.4 (1.5)	4
70–79	89 (25)	95 (5)	22 (8)	130 (32)	37.3 (1.5)	3
80–89	86 (26)	95 (4)	21 (8)	131 (35)	37.2 (1.5)	3
90+	85 (25)	96 (4)	21 (8)	132 (36)	37 (1.5)	2

Basic observations at presentation to hospital from an international inpatient cohort predominately made up of data from the UK and France (mortality 31%).(Raw data from the ISARIC cohort kindly provided by the ISARIC group).[16]
BP, blood pressure; HR, heart rate; NEWS2, National Early Warning Score 2; RR, respiratory rate.

COVID-19 in a timely manner however is likely quite limited.[16 17]

Blood pressure

In a New York cohort (n=3841, mortality 8%), BP at presentation was modestly predictive of disease progression to death. The mean diastolic BP was 71 mm Hg in the non-surviving group (mean age 73) versus 76 mm Hg in the surviving group (mean age 55).[17] These effects could however be age related. BP monitoring remains useful for COVID-19 mimickers and COVID-19 complications.

Respiratory rate

In a study evaluating outcomes following the disposition decisions of physicians in Detroit (n=463), RR (at baseline) was marginally predictive of the need for hospital admission in comparison with those who were discharged home (the overall cohort was severe with a mortality rate of 16%). Mean RR in those discharged home was 18 (IQR: 17–18) rising to 20 in those requiring admission (IQR: 18–22).[18] In very severe cohorts, RR seems to have value in predicting disease progression. In a London-based cohort (mortality 36%), mean RR was 26 (IQR: 21–32) on admission and was found to have predictive value for intubation or death (HR 1.53 (95% CI 1.38 to 1.71)).[19] Similar results were found in a moderately sized Madrid cohort (n=1549, mortality: 21.2%).[20] RR may have some value as a marker of severe disease, but the RR threshold for raising concern is probably lower than in other respiratory conditions (see section on 'Oxygen Saturations').

Temperature

A measured temperature is likely to be of use in capturing some deteriorating patients and certainly of use in monitoring for signs of time critical COVID-19 mimickers such as sepsis. In relation to COVID-19, the classification of an elevated temperature differs from nation to nation. In China, where much of the initial data came from, a fever is classed as anything >37.2°C,[21] whereas in the USA, a fever is classed as >38.0°C.[22]

Even in studies examining more severe cohorts, recorded temperature is not a reliable marker at presentation to hospital. In a New York cohort of 5700 hospital cases of COVID-19 (mortality=21%), the mean presenting temperature was 37.5°C, but only 30% of patients presented with confirmed fever (>38.0°C).[22]

While an isolated fever is likely of limited use in identifying disease progression, persistent fever—as in most infectious diseases—remains an ominous feature.

Oxygen saturations (SpO_2)

Oxygen saturations are the most consistent predictor for disease severity.[18 23 24] Oxygen saturations below 95% have been reported to be associated with twice the risk of death in comparison with normoxaemia at presentation.[25]

While SpO_2 seems to have a fairly clear relationship with disease progression, shortness of breath is more complicated. Silent hypoxia is the popular term used to describe patients who have limited sensation of feeling short of breath and/or no increased RR and yet when examined are found to be hypoxic.[26] This has been a feature of COVID-19 since the first cases were reported.[27] Imaging studies also demonstrate the disconnect between severity of lung pathology and the sensation of breathlessness. In a study from Marseilles, France, 757 (68%) of patients who did not complain of breathlessness had pneumonia on CT.[28]

The same study investigated the prevalence and consequences of hypoxia without the sensation of dyspnoea and reported 28.1% of patients who did not complain of dyspnoea were in fact hypoxic on blood gas analysis (n=96). The investigators also reported a dramatically increased rate of ICU admission in such patients of 42.6%, compared with 5.7% in dyspnoeic hypoxic patients, the mortality rate being 20.4% versus 5.7%, respectively. Such 'silent hypoxic' patients presented later than others in the group (half after day 5 of symptoms).[28]

Another useful study examined first responder observations of patients with COVID-19 throughout the first wave of infections in March 2020 in Paris (n=1201). There was a marked disconnect between level of hypoxia (mean SpO_2 of 90%) and RR (mean 20), comparing with the previous year where the mean SpO_2 was 96%, and RR was 22.[29]

The inability to rely on the self-reported symptom of breathlessness to identify progressive disease and hypoxia presents a substantive challenge.

Post-exertion oxygen saturations

Postexertion oxygen saturation measurement may help increase the sensitivity of our basic observations. In a recent literature review, the performance and safety of a number of specific exercise tests were analysed across a range of conditions. Both the 1 min sit to stand Test (1STST) and the 6 min walk test performed well in identifying disease severity in chronic lung disease.[30]

Perhaps the most apt proxy for COVID-19 in this context is interstitial lung disease (ILD), particularly in light of the infrequency of hypercapnoeic hypoxia in COVID-19 and ILD,[28] the CT similarities[31] and the presence of a more restrictive pattern in COVID-19 on spirometry.[32] In a prospective comparative trial, the 1STST performed well against the gold standard test (the 6 min walk test) (n=107). Over two-thirds of ILD patients (n=25) had a reduction in their baseline SpO_2 by >3% after the 1STST without adverse effect. The 1STST showed good predictive value for detecting patients with moderate and severe ILD.[33]

Exertional saturation testing is already in use within the acute medical setting, particularly when considering discharge. Goodacre *et al*[34] conducted a retrospective multicentre observational study of postexertion SpO_2 measurements where physicians chose to undertake the

test in patients with COVID-19 typically in the emergency department (ED). Out of 817 patients presenting to ED during the period of 26 March to 28 May 2020 who underwent postexertion oxygen saturation monitoring, COVID-19 related adverse events (death or level 2/3 organ support) occurred in only 30 patients (3.7%) with a mortality of 1.1%. This was from within a cohort where overall adverse events were high at 20.9% (mortality 14.8%). Unfortunately, Goodacre *et al* did not report on disposition outcomes, and no case–control comparison was attempted.

Nonetheless, more than half of patients who eventually suffered a COVID-19 related adverse event were positive on the postexertion test (dropping their SpO_2 by 3% or more). In the adverse group, 56% of patients who had a normal resting SpO_2 at admission (defined in this study as >93%), with a National Early Warning Score (NEWS) of <3, had a positive postexertion test. Indeed, 41% of those with an adverse outcome dropped their saturations by 5% or more, and almost 1 in 10 dropped their saturations by more than 10%. Goodacre *et al* reports a positive likelihood ratio of predicting adverse outcomes of 1.76 at the level of a drop in SpO_2 of 3% or more.[34] While further more controlled data are needed, postexertion SpO_2 may well help to detect more cases of progressive COVID-19 earlier. Within the current clinical climate, it seems reasonable to use postexertion oxygen saturations in patients with suspected/confirmed COVID-19 where they are normoxaemic at baseline and it is safe to do so at the discretion of the attending clinician.

Clinical examination

Very little has been published on clinical examination findings in COVID-19 pneumonia, beyond the value of basic observations as discussed previously. Reports have suggested certain characteristic features on auscultation (such as 'velcro' crackles, atypical bronchial breathing and basolateral distribution) that may denote underlying COVID-19 pneumonia and correlate with radiological changes. Such findings are subject to observer variation however, and the absence of such signs does not denote absence of disease.[35]

Inferentially, there is likely to be a demonstrable value in the 'eyeball' clinical assessment of patients with COVID-19. A Danish study compared an established triage system (based on observations and presenting complaint) versus an 'eyeball' assessment by a phlebotomist. The eyeball assessment was significantly superior, particularly in detecting those who may be incorrectly triaged low (green or yellow categories).[36] A further study examined physician and nurse predictions of mortality in ED at first assessment. Observations were to hand, but no test results. Both groups performed well, and performance improved with years of experience. When combined (ie, both physician and nurse were in agreement), the predictive value was excellent.[37]

While formal clinical examination is of unknown value, there is likely significant value in assessment by an experienced healthcare professional.

C reactive protein (CRP)

CRP has been reported as a reliable marker for disease severity and is routinely available including through point-of-care testing.[38–40] The optimum cut-off value to indicate significant risk of disease progression remains unknown. It has been previously established, however, that the majority of viral infections we are likely to encounter will *rarely* raise CRP >30 mg/L, and a CRP of >30 mg/L during a viral illness such as influenza would typically indicate progression of disease and risk of viral pneumonia.[41] Further elevations raise the possibility of severe inflammation, a bacterial or other invasive infection.[42] Additionally, imaging studies have consistently demonstrated that even a modest CRP rise is associated with infiltrative changes on CT prior to respiratory symptoms.[43] In this regard, CRP can be of use in identifying patients with disease progression.

CRP also has some reported use in the hyperacute COVID-19 phenotype. Manson *et al*[14] identified a significant subgroup of patients presenting to two tertiary hospitals in the UK in March 2020, where CRP >150 mg/L or doubling from 50 mg/L within 24 hours was strongly predictive of death or the need for intubation within the following 24 hours. A further analysis from South Korea reported that an admission CRP >80 mg/L had a higher sensitivity for predicting adverse outcome in COVID-19 than a NEWS score of 2 or more.[25]

There are several limitations with using CRP as a monitor for disease severity, or to detect those patients that require closer follow-up. Primarily, CRP has a lag time before rising. CRP results indicate the severity of inflammation from the previous day (with levels peaking 6–72 hours following an insult).[44] This makes the utility of an isolated CRP measurement taken at the point of symptom onset fairly limited. Furthermore, CRP rises in the elderly or those with multiple comorbidities are often blunted. In a multicentre study (although an inpatient high severity cohort), initial CRP measurement correlated with COVID-19 disease severity in all age groups except those in the >75-year-old age group.[45] Early changes in CRP in the elderly may still be predictive, although less so.

There are other biochemical parameters that have been associated with deterioration in the patient with COVID-19. Lymphocyte count, lactate dehydrogenase and D-dimer have been quite reliably reported as prognostic markers in the patient with COVID-19, although predominantly in inpatient cohorts. Whether there is clinical utility for monitoring these markers in the community setting remains unknown. Lymphocyte count may provide better prognostication in the elderly and offset the shortcomings of the CRP in this patient group.[38 39]

Table 3 Summary of recommendations for the early identification of progressive COVID-19 in the community

	Summary opinion on utility of specific symptoms and clinical parameters in identifying the progressive COVID-19 patient
Symptoms	Patients who present with or develop symptoms of shortness of breath, dry cough, persistent fever, fatigue, confusion, chest tightness, diarrhoea, vomiting or abdominal pain may be at higher risk of disease progression. Patients who present with shortness of breath, persistent fever and/or confusion require urgent clinical assessment. The absence of shortness of breath does not exclude the presence of severe and life-threatening COVID-19 pneumonia. Other symptoms of hypoxia may be present, for example, fatigue or altered mental status.
Duration of illness	Duration of illness is not reliable for predicting disease progression. Patients with COVID-19 can deteriorate at any time.
Observations	Oxygen saturations remain the most useful observation for detecting clinical deterioration in patients with COVID-19. Normal oxygen saturations or the absence of dyspnoea does not exclude disease progression. Consider postexertion SpO_2 measurements where resting SpO_2 is normal, and it is safe to do so. Increased respiratory rate (>20 BPM) is a later sign of disease progression. HR, BP, remp and confusion screen remain useful, particularly for detecting COVID-19 mimickers/complications.
Clinical examination	There was insufficient evidence to determine the utility of clinical examination as a tool for early identification of COVID-19 disease progression. Generally, a clinical 'eyeball' assessment is of use in detecting the deteriorating patient; however, such an assessment is insufficient to rule out disease progression.
CRP	CRP is of significant utility in monitoring disease progression over time. CRP is of less use at point of first contact, or with a single measurement. If available, it should still be undertaken as a baseline. CRP >30 mg/L should raise concern that a patient is deteriorating or at risk of deterioration (in elderly a CRP >20 mg/L).
Chest X-ray	The value of referring community COVID-19 patients for chest X-ray to determine disease progression is unknown.

BP, blood pressure; CRP, C reactive protein; HR, heart rate; SpO_2, oxygen saturations; Temp, temperature.

Chest X-ray (CXR)

In those cases where there are some concerns of progression but equivocal objective signs, there is a question as to the utility of CXR within the community setting.

Borakati *et al* produced a useful study exploring this, although in a high-severity cohort (n=763, mortality=24%). More than half of the patients had 'classic' CXR signs of COVID-19, and as such would have confirmed COVID-19 pneumonia (sensitivity 0.56 (95% CI 0.51 to 0.60)). Of considerable note, nearly one-third of PCR negative referrals with 'possible' COVID-19 also had 'classic' COVID-19 features on CXR.[46]

An urgent care cohort that was likely less severe (n=636) reported around 40% of confirmed cases had a positive CXR, although this was based on a consensus view of 12 radiologists and in the absence of objective disease severity markers.[47] A further milder cohort from Hong Kong (n=64, dyspnoea rate=6%) with a mean age of 56 years (SD: 19) reported 69% of chest X-rays were abnormal at baseline (but this also included all consolidations).[48]

DISCUSSION

SARS-CoV-2 causes a self-limiting viral infection in the majority of patients. Cough, sore throat, headache, myalgia, fever and other cold/influenza like symptoms are typical, and symptoms begin to resolve within a few days (although cough can persist longer). In some, the illness progresses to a Lower Respiratory Tract Infection, and this is typified as viral pneumonia.[49]

Time to hospital care in viral pneumonia is known to dictate outcome. Patients who present late have a longer hospital stay, increased ICU requirement and a higher mortality.[50 51] The same is true for other pneumonias.[9]

There are many reasons for an improved outcome with earlier inpatient care. Basic supportive care will include bed rest, appropriate hydration, venous thromboembolism (VTE) prophylaxis, medication review, early identification of complications (pulmonary embolism, acute kidney injury and secondary bacterial pneumonia and sepsis) and the commencement of oxygen at or soon after the onset of hypoxia.[52]

The early identification and correction of hypoxia is likely one of the key determinants of disease progression. A recent study (n=35 000) demonstrated a substantive mortality benefit when patients spent the majority of time in the optimal oxygen saturations of 94%–98%. Indeed, there was a 50% mortality saving when patients were in the optimum range for 80% of the time versus only 40% of the time.[53] One may potentially infer that patients

with COVID-19 left hypoxic at home carry a diminishing chance of survival.

Hypoxia (SpO_2 <95%) has numerous adverse health effects. In the acute setting, hypoxia increases the risk of fatal arrhythmia and end-organ damage.[54] In a subacute setting, hypoxia has been shown to drive pulmonary inflammation and the systemic inflammatory response[55 56] and to promote coagulation leading to an increase in thromboembolic events.[57 58] Long-term effects of hypoxia include ongoing cognitive impairment.[59]

Identifying hypoxia early is also important for identifying patients who may benefit from corticosteroids. In April 2020, an observational study reported significant benefit in hypoxic patients who received corticosteroids (equivalent dose of dexamethasone 12–24 mg once daily for 5–7 days) with a reduction in inpatient stay from 12 days to 8 days.[6] A further observational trial from New York demonstrated a dose equivalent of dexamethasone 12 mg once daily improved recovery of severely unwell patients (mean CRP >200 mg/L), conferring a substantial reduction in need for ICU admission (adjusted Hazards Ratio 0.16 (95% CI 0.07 to 0.34; p<0.001)).[5] While the full report from the randomised controlled Randomised Evalualtion of COVID-19 Therapy trial is still awaited, the preliminary report confirms a mortality benefit for dexamethasone 6 mg once daily in hypoxic patients with COVID-19 pneumonia.[7] The optimal dose, timing, patient selection and duration of use remain unknown, but certainly corticosteroids have an impact on COVID-19 pneumonia progression.

VTE prophylaxis is a cornerstone of acute medical management and is initiated in the majority of patients with pneumonia. Evidence is accruing that such an intervention may prevent disease progression and complications in COVID-19, providing yet another reason for identifying the progressive COVID-19 patient earlier.[60]

Our summary opinion as to the most useful clinical parameters in identifying the progressive COVID-19 patient earlier is presented at table 3.

CONCLUSION

COVID-19 pneumonia complicates a modest yet significant proportion of patients with SARS-CoV-2 infection. As with all pneumonias, time to intervention in COVID-19 pneumonia affects outcome. There is also the potential to reduce the consumption of healthcare resources and the need for high-intensity care through timely intervention. By doing so, we reduce the direct and indirect impact of the SARS-CoV-2 pandemic.

To achieve improved outcomes in COVID-19, we must understand its clinical features better. In line with this and pending more controlled studies in the community COVID-19 patient, we present the current relevant literature relating to the clinical parameters associated with disease progression. Dyspnoea, confusion, persistent fever, reduced SpO_2 (<95%) and later in the illness an elevated RR (>20 BPM) all seem reliable markers of COVID-19 progression. Fatigue and altered mental status may also be present and may be the only symptoms of hypoxia. While the evidence base for postexertion oxygen saturation measurement is lacking, the current evidence suggests it may be useful in detecting COVID-19 pneumonia earlier. CRP remains a useful marker for disease progression in the pneumonic COVID-19 illness.

Overall, it seems sensible and achievable to adopt a proactive clinical posture when monitoring patients with COVID-19 in the community. The presence of 'asymptomatic' hypoxia and the potential for rapid deterioration imposes a necessity for a more vigilant, rule-in approach, whereby patients may require repeated assessment prior to admission or disease resolution.

Author affiliations
[1]Department of Acute Internal Medicine, Gibraltar Health Authority, Gibraltar, Gibraltar
[2]Department of Infection, Antimicrobial Resistance and Deterioration, NHS England, Redditch, UK
[3]Department of Acute Medicine, Hampshire Hospitals NHS Foundation Trust, Winchester, UK
[4]Department of Public Health, Gibraltar Health Authority, Gibraltar, Gibraltar
[5]Department of Covid-19 Remote Monitoring of Patients During Response & Recovery, NHS Grampian, Aberdeen, UK
[6]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK
[7]Department of General Medicine, Islands Hospital, Oban, UK
[8]Department of Respiratory Medicine, Raigmore Hospital, Inverness, UK
[9]Hospital at Home, Oxford University Hospitals NHS Trust, Oxford, UK
[10]Department of Ambulatory Medicine, University of Warwick, Coventry, UK
[11]Department of Clinical Governance, Gibraltar Health Authority, Gibraltar, Gibraltar

Contributors All authors contributed to the conception and design of the review. All authors provided literature reviews on their relevant areas. DG, FM, AI, CM, BM and APN undertook the majority of the initial write-up. DL, MI-K, SB, ST and DB provided further input at the draft stage. All authors contributed to the discussion, conclusion and final review.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD
Daniel Goyal http://orcid.org/0000-0003-0418-8859

REFERENCES

1 WHO. COVID-19 weekly epidemiological update, 2021. Available: https://www.who.int/publications/m/item/weekly-epidemiological-update-9-february-2021
2 Koirala A, Joo YJ, Khatami A, *et al*. Vaccines for COVID-19: the current state of play. *Paediatr Respir Rev* 2020;35:43–9.
3 Sun Q, Qiu H, Huang M, *et al*. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care* 2020;10:33.

4 Somers VK, Kara T, Xie J. Progressive hypoxia: a pivotal pathophysiologic mechanism of COVID-19 pneumonia. *Mayo Clin Proc* 2020;95:2339–42.
5 Majmundar M, Kansara T, Lenik JM, *et al*. Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York metropolitan region. *PLoS One* 2020;15:e0238827.
6 Wang Y, Jiang W, He Q, *et al*. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. *Sig Transduct Target Ther* 2020;5:57.
7 RECOVERY Collaborative Group, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
8 Phua J, Dean NC, Guo Q, *et al*. Severe community-acquired pneumonia: timely management measures in the first 24 hours. *Crit Care* 2016;20:237.
9 Sung HK, Kim JY, Heo J, *et al*. Clinical course and outcomes of 3,060 patients with coronavirus disease 2019 in Korea, January-May 2020. *J Korean Med Sci* 2020;35:e280.
10 Faes C, Abrams S, Van Beckhoven D, *et al*. Time between symptom onset, hospitalisation and recovery or death: statistical analysis of Belgian COVID-19 patients. *Int J Environ Res Public Health* 2020;17:7560.
11 Pellaud C, Grandmaison G, Pham Huu Thien HP, *et al*. Characteristics, comorbidities, 30-day outcome and in-hospital mortality of patients hospitalised with COVID-19 in a Swiss area - a retrospective cohort study. *Swiss Med Wkly* 2020;150:w20314.
12 Bhatraju PK, Ghassemieh BJ, Nichols M, *et al*. Covid-19 in critically ill patients in the seattle region - case series. *N Engl J Med* 2020;382:2012–22.
13 Azoulay E, Fartoukh M, Darmon M, *et al*. Increased mortality in patients with severe SARS-CoV-2 infection admitted within seven days of disease onset. *Intensive Care Med* 2020;46:1714–22.
14 Manson JJ, Crooks C, Naja M, *et al*. COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study. *Lancet Rheumatol* 2020;2:e594–602.
15 Morgenstern-Kaplan D, Buitano-Tang B, Martínez-Gil M, *et al*. U-shaped-aggressiveness of SARS-CoV-2: period between initial symptoms and clinical progression to COVID-19 suspicion. A population-based cohort study. *PLoS One* 2020;15:e0243268.
16 Hall M, Pritchard M, Emmanuelle A. ISARIC clinical data report 20 November 2020. *medRxiv* 2020.
17 Yadaw AS, Li Y-C, Bose S, *et al*. Clinical features of COVID-19 mortality: development and validation of a clinical prediction model. *Lancet Digit Health* 2020;2:e516–25.
18 Suleyman G, Fadel RA, Malette KM, *et al*. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan detroit. *JAMA Netw Open* 2020;3:e2012270.
19 Goodall JW, Reed TAN, Ardissino M, *et al*. Risk factors for severe disease in patients admitted with COVID-19 to a hospital in London, England: a retrospective cohort study. *Epidemiol Infect* 2020;148:e251.
20 Jiménez E, Fontán-Vela M, Valencia J, *et al*. Characteristics, complications and outcomes among 1549 patients hospitalised with COVID-19 in a secondary hospital in Madrid, Spain: a retrospective case series study. *BMJ Open* 2020;10:e042398.
21 Guan W-J, Liang W-H, Zhao Y, *et al*. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;55:2000547.
22 Richardson S, Hirsch JS, Narasimhan M, *et al*. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the new York City area. *JAMA* 2020;323:2052–9.
23 Izcovich A, Ragusa MA, Tortosa F, *et al*. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. *PLoS One* 2020;15:e0241955.
24 Knight SR, Ho A, Pius R, *et al*. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC who clinical characterisation protocol: development and validation of the 4C mortality score. *BMJ* 2020;370:m3339.
25 Lee JY, Kim HA, Huh K, *et al*. Risk factors for mortality and respiratory support in elderly patients hospitalized with COVID-19 in Korea. *J Korean Med Sci* 2020;35:e223.
26 Couzin-Frankel J. The mystery of the pandemic's 'happy hypoxia'. *Science* 2020;368:455–6.
27 Xie J, Tong Z, Guan X, *et al*. Clinical characteristics of patients who died of coronavirus disease 2019 in China. *JAMA Netw Open* 2020;3:e205619.
28 Brouqui P, Amrane S, Million M, *et al*. Asymptomatic hypoxia in COVID-19 is associated with poor outcome. *Int J Infect Dis* 2021;102:233–8.
29 Jouffroy R, Jost D, Prunet B. Prehospital pulse oximetry: a red flag for early detection of silent hypoxemia in COVID-19 patients. *Crit Care* 2020;24:313.
30 Holland AE, Malaguti C, Hoffman M, *et al*. Home-based or remote exercise testing in chronic respiratory disease, during the COVID-19 pandemic and beyond: a rapid review. *Chron Respir Dis* 2020;17:1479973120952418.
31 Chang H-L, Chen Y-H, Taiwan H-C, *et al*. EGFR tyrosine kinase inhibitor-associated interstitial lung disease during the coronavirus disease 2019 pandemic. *J Thorac Oncol* 2020;15:e129–31.
32 Fumagalli A, Misuraca C, Bianchi A, *et al*. Pulmonary function in patients surviving to COVID-19 pneumonia. *Infection* 2021;49:153–7.
33 Briand J, Behal H, Chenivesse C, *et al*. The 1-minute sit-to-stand test to detect exercise-induced oxygen desaturation in patients with interstitial lung disease. *Ther Adv Respir Dis* 2018;12:1753466618793028.
34 Goodacre S, Thomas B, Lee E, *et al*. Post-exertion oxygen saturation as a prognostic factor for adverse outcome in patients attending the emergency department with suspected COVID-19: a substudy of the priest observational cohort study. *Emerg Med J* 2021;38:88–93.
35 Wang B, Liu Y, Wang Y, *et al*. Characteristics of pulmonary auscultation in patients with 2019 novel coronavirus in China. *Respiration* 2020;99:755–63. doi:10.1159/000509610
36 Iversen AKS, Kristensen M, Østervig RM, *et al*. A simple clinical assessment is superior to systematic triage in prediction of mortality in the emergency department. *Emerg Med J* 2019;36:66–71.
37 Brabrand M, Hallas J, Knudsen T. Nurses and physicians in a medical admission unit can accurately predict mortality of acutely admitted patients: a prospective cohort study. *PLoS One* 2014;9:e101739.
38 Yufei Y, Mingli L, Xuejiao L, *et al*. Utility of the neutrophil-to-lymphocyte ratio and C-reactive protein level for coronavirus disease 2019 (COVID-19). *Scand J Clin Lab Invest* 2020;80:536–40.
39 Zhang Z-L, Hou Y-L, Li D-T, *et al*. Laboratory findings of COVID-19: a systematic review and meta-analysis. *Scand J Clin Lab Invest* 2020;80:441–7.
40 Bannaga AS, Tabuso M, Farrugia A, *et al*. C-reactive protein and albumin association with mortality of hospitalised SARS-CoV-2 patients: a tertiary hospital experience. *Clin Med* 2020;20:463–7.
41 Rystedt K, Harbin NJ, Lindbaek M, *et al*. Is C-reactive protein associated with influenza A or B in primary care patients with influenza-like illness? A cross-sectional study. *Scand J Prim Health Care* 2020;38:447–53.
42 Haran JP, Beaudoin FL, Suner S, *et al*. C-reactive protein as predictor of bacterial infection among patients with an influenza-like illness. *Am J Emerg Med* 2013;31:137–44.
43 Varble N, Blain M, Kassin M. CT and clinical assessment in asymptomatic and pre-symptomatic patients with early SARS-CoV-2 in outbreak settings. *Eur Radiol* 2021;31:1–12.
44 Rajab IM, Hart PC, Potempa LA. How C-reactive protein structural isoforms with distinctive bioactivities affect disease progression. *Front Immunol* 2020;11:2126.
45 Jurado A, Martín MC, Abad-Molina C, *et al*. COVID-19: age, interleukin-6, C-reactive protein, and lymphocytes as key clues from a multicentre retrospective study. *Immun Ageing* 2020;17:22.
46 Borakati A, Perera A, Johnson J, *et al*. Diagnostic accuracy of X-ray versus CT in COVID-19: a propensity-matched database study. *BMJ Open* 2020;10:e042946.
47 Weinstock MB, Echenique A, Russell JW. Chest X-ray findings in 636 ambulatory patients with COVID-19 presenting to an urgent care center: a normal chest X-ray is no guarantee. *J Urgent Care Med* 2020 https://www.researchgate.net/publication/340608073_Chest_X-Ray_Findings_in_636_Ambulatory_Patients_with_COVID-19_Presenting_to_an_Urgent_Care_Center_A_Normal_Chest_X-Ray_Is_no_Guarantee
48 Wong HYF, Lam HYS, Fong AH-T, *et al*. Frequency and distribution of chest radiographic findings in patients positive for COVID-19. *Radiology* 2020;296:E72–8.
49 Ines S. A hundred days into the coronavirus disease (COVID-19) pandemic. *Euro Surveill* 2020;25:2000550.
50 Lee N, Chan PKS, Wong CK, *et al*. Viral clearance and inflammatory response patterns in adults hospitalized for pandemic 2009 influenza A(H1N1) virus pneumonia. *Antivir Ther* 2011;16:237–47.
51 Zarychanski R, Stuart TL, Kumar A, *et al*. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. *CMAJ* 2010;182:257–64.
52 Goyal DK, Mansab F, Iqbal A, *et al*. Early intervention likely improves mortality in COVID-19 infection. *Clin Med* 2020;20. doi:10.7861/clinmed.2020-0214. [Epub ahead of print: 01 May 2020].

53 van den Boom W, Hoy M, Sankaran J, *et al*. The search for optimal oxygen saturation targets in critically ill patients: observational data from large ICU databases. *Chest* 2020;157:566–73.
54 Roche F, Reynaud C, Pichot V, *et al*. Effect of acute hypoxia on QT rate dependence and corrected QT interval in healthy subjects. *Am J Cardiol* 2003;91:916–9.
55 Fröhlich S, Boylan J, McLoughlin P. Hypoxia-induced inflammation in the lung: a potential therapeutic target in acute lung injury? *Am J Respir Cell Mol Biol* 2013;48:271–9.
56 Gonzalez NC, Wood JG. Alveolar hypoxia-induced systemic inflammation: what low PO(2) does and does not do. *Adv Exp Med Biol* 2010;662:27–32.
57 Jha PK, Sahu A, Prabhakar A, *et al*. Genome-Wide expression analysis suggests hypoxia-triggered hyper-coagulation leading to venous thrombosis at high altitude. *Thromb Haemost* 2018;118:1279–95.
58 Børvik T, Evensen LH, Morelli VM, *et al*. Impact of respiratory symptoms and oxygen saturation on the risk of incident venous thromboembolism-the tromsø study. *Res Pract Thromb Haemost* 2020;4:255–62.
59 Michiels C. Physiological and pathological responses to hypoxia. *Am J Pathol* 2004;164:1875–82.
60 Helms J, Tacquard C, Severac F, *et al*. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020;46:1089–98.
61 WHO. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19), 2020. Available: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf [Accessed 24 Feb 2020].
62 Millar JE, Neyton L. Robust, reproducible clinical patterns in hospitalised patients with COVID-19. *medRxiv* 2020.