Chest radiograph characteristics in COVID-19 infection and their association with survival

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ABSTRACT

Purpose: This study aims to systematically grade CXRs of COVID-19 patients to find associations between CXR (chest radiographs) characteristics and clinical outcomes.

Methods: A retrospective review and grading of CXRs in 161 COVID-19 positive patients was carried out in this single centre study. CXR changes primarily constituted that of presence or absence of ground glass opacification (GGO) or consolidation and their distribution across both lung fields. We used two grading systems normal/mild/moderate/severe grading and a numeric 0–8 grading system. We defined mild severity as up to 25 % lung involvement, moderate as 25–62.5 % and severe as 62.5–100% lung involvement.

Results: Peripheral GGO in lower/- mid zones of the lungs is the most common finding. Mid zone and perihilar GGO is associated with increased mortality. We additionally show that CXRs have a higher severity score in the non-survivor group and a CXR graded as severe has a relative risk ratio for mortality of 3.28. Finally, we describe the change in CXR severity with length of symptoms, finding 42.3 % of CXR were normal in the first 2 days of symptoms and 0% at 13 days.

Conclusion: Using a systematic approach to reviewing and grading CXRs in Covid-19 positive patients we clearly demonstrate that grading, location of airspace abnormalities and rate of CXR changes are related to clinical outcome.

1. Introduction

During the preparation of this document, infection from Coronavirus-19 (COVID-19) remains a global pandemic and has been accountable for over 2.1 million deaths world-wide [1]. The need for a quick diagnosis for isolation, along with reverse-transcription polymerase chain reaction (RT-PCR) testing taking several hours to days and reports of sensitivities of 60–70 % [2,3] has led to imaging being used for rapid risk stratification and diagnosis. Many articles have been published describing imaging features of COVID-19 infection, mostly focusing on CT. In CT thoracic imaging the predominant features are peripheral ground glass opacification (GGO) with or without consolidation in multiple lobes, with additional common findings later in the disease process being a ‘crazy paving’ appearance, the reverse halo sign and linear opacities [4]. Some studies have found CT thorax imaging is highly sensitive for detecting COVID-19 with one study finding the sensitivity to be as high as 98 % [3], however other studies have found the sensitivity to be lower with one study finding a normal CT 50 % of the time in the first few days of symptoms [4].

A small number of studies have focused on chest X-ray (CXR) characteristics of COVID-19 infection, mostly from countries worst effected early in the pandemic i.e. Italy and China. The predominant findings reported in CXRs are peripheral GGO or consolidation in the lower and mid zones [5,6]. CXRs have also been reported to have high sensitivity in some studies with one finding a sensitivity of 89 % [7]. Some articles have found CXR severity is significantly worse with age and in non-survivors [8–10], and other articles finding CXR severity was associated with increased likelihood of intubation and mechanical ventilation [11,12]. Additionally, as with CT one article found in the initial 2 days up to 50 % of CXRs are normal in COVID-19 and the severity worsens with time peaking around day 10–12, then improving [5].
In the UK the primary imaging modality to assist with diagnosis and risk stratification of COVID-19 infection is the CXR. The British society of Thoracic Imaging (BSTI) stance at this time is not to use thoracic CT outside of ‘routine clinical care’ [13]. The BSTI have additionally recommended the use of mild/moderate/severe grading of CXRs in suspected COVID-19 infection, although there is no clear guidance on what constitutes each severity grade on CXR [14].

Other CXR grading systems have been used in the literature a common example being the Radiographic Assessment of Lung Edema (RALE) score, where the lungs are split into quadrants, giving an involvement and density score, the quadrant scores are multiplied and then summed and is a 0–48 score [15], a simplified version of the RALE score has additionally been used, where each lung is given a score of 0–4 proportional to the amount of lung affected [5]. Another common score is the Brixia score [16,17], which is 0–18, where the left and right upper, middle and lower zones are each given a 0–3 score proportional to the amount of lung involvement, there is another similar score, but it is scored 0–4 in each zone and is therefore a 0–24 score [18].

In our group’s previous work, we looked at a number of laboratory and imaging results in 50 patients from our hospital, finding that CXR severity was a predictor of outcome and interestingly that shadowing in the mid zone of the lungs was associated with worse outcome [19]. In this retrospective patient review we assess a larger group of 161 patients with COVID-19 from our hospital from the first wave of the pandemic, performing a more detailed analysis of CXR findings. Our objectives were to:

1. Outline the CXR characteristics of COVID-19 infection and their association with mortality.
2. Describe a consistent CXR grading method for COVID-19 infection and its association with death.
3. Explore the relationship of CXR severity with length of COVID-19 infection symptoms.

2. Methods

2.1. Patient group and data collection

This is a continuation of our previous patient review and data collection methods are described in this paper [19]. In summary the review consisted of a retrospective review of 161 patients with positive SARS-CoV-2 RT-PCR assay of a nasopharyngeal swab (NPS) who were admitted to St Peter’s Hospital in Surrey, UK (part of Ashford and St Peter’s Hospitals NHS Foundation Trust and a medium sized district general hospital serving a population of approximately 400,000 people). Patients included in the retrospective review were all individuals aged >18 years old, admitted prior to 30/03/2020, had at least one CXR during this admission and had an eventual positive SARS-CoV-2 swab during admission. The cohort included the initial 50 patients analysed in our previous work [19].

The intranet archiving system was used to review the patients’ discharge summary or death certificate for clinical outcome. Clinical outcome was defined as a ‘non-survivor’ if the patient died within 30 days of admission, or ‘survivor’ if they were alive 30 days after admission. The emergency department clinical documentation was additionally reviewed to obtain the patients’ length of symptoms prior to admission.

Ethical approval was provided by the Ashford & St Peter’s Hospital Research and Development department as described in [19].

2.2. Radiographic assessment

All chest x-rays throughout the entire admission for each of the 161 patients were analysed. The CXR analysis involved a review of the initial admission CXR plus all subsequent CXRs performed during the hospital stay for each of the 161 patients. The CXRs were analysed independently by 1 Foundation Doctor (J.C.) and 2 Radiology Registrars (both with > 5 years postgraduate training, G.Z. and F.Seehan) using the hospital’s Intellispace Picture Archiving and Communication System (PACS), (Phillips, Netherlands). Findings and gradings were subsequently verified by a blinded Consultant Radiologist (with 7 years of experience, F. Saltissi). During radiographic assessment all investigators were blinded to other interpreters’ findings and the patients’ clinical outcome.

CXRIs were reviewed for the presence of consolidation or ground glass opacification (GGO). This was identified and defined in accordance with the Fleischner Society glossary of thoracic imaging terms [20]. Consolidation was defined as a homogenous increase in the air space that obscures lung markings. GGO was defined as a ‘hazy’ increase in air space density which does not obscure the lung markings. The changes were then noted to which lung zones it was in and whether the shadowing was peripheral or perihilar. The demarcation between peripheral and perihilar was halfway between the hilum and lung edge. Lung zones were defined as left or right, upper zone (above 2nd anterior ribs), mid zone (2nd to 4th anterior ribs) and lower zone (below 4th anterior ribs).

The presence of pleural effusions, atelectasis and other extraneous findings were noted (e.g. cardiomegaly, fibrosis, pleural plaques, lines and tubes etc.).

Two severity grading measures were then used to score each CXR, the previously described BSTI mild/moderate/severe grading, and a numeric scoring system used by Wong et al. (adapted from the Radiographic Assessment of Lung Edema (RALE) score) [5]. This constitutes a 0–4 score for each lung depending on the percentage involvement of each hemithorax with airspace GGO/consolidation (0 = no involvement; 1 = <25 %; 2 = 25–50 %; 3 = 50–75 %; 4 = 75–100 %). The scores for each lung were added together to give a total score out of 8. In this grading, mild was defined as a score of 1 or 2, moderate 3–5 and severe as >5; respectively However, unlike the 0–8 severity grading we graded any abnormalities thought to be due to COVID-19 e.g. atelectasis, and not just consolidation or GGO.

2.3. Statistics

Co-morbidities and CXR findings or grading were all categoric and therefore compared for significance using non-parametric testing. Age and blood tests markers while numeric were additionally found to not be normally distributed using the Anderson-darling test and therefore non-parametric significance testing was used. The non-parametric significance test used was a two tailed Mann–Whitney U test Inter-rater reliability of CXR grading and CXR findings was measured using Cohen’s kappa coefficient (κ), using the kappa library in Stata [21]. Where data is missing it is stated in the relevant table and the analysis performed with those subjects removed. All statistical analysis and graphs were produced in Microsoft Excel (Microsoft Corporation, 2019), Stata (version 16.0 for Windows) or prism GraphPad Prism (version 8.0.0 for Windows).

3. Results

3.1. Patient base line characteristics

In Table 1 we show the baseline characteristics of the 161 patients we analysed and the characteristic differences between the patients who were either alive (survivors) or died (non-survivors) at 30 days. The mean age was 66.7 (+/- 17.6) for the cohort and significantly higher in patients’ dead at 30 days (77.7 (+/- 10.4), P value = <0.0001). The male to female ratio was roughly equal (1:1.1), but lower in the non-survivors (0.8:1, P value = 0.107). Table 1 also depicts patient’s co-morbidities and laboratory results. We found that rates of heart failure and dementia were greater in the non-survivors, 18.6 % vs. 1.7 % (P = 0.0004) and 27.9 vs. 5.1 % (P = 0.0002) respectively. Amongst the laboratory test results, non-survivors had had a higher CRP (111.85 vs. 82.0, P = 0.0297) values and lower lymphocytes counts (0.85 vs. 1.03,
3.2. CXR characteristics on admission and with outcome

Table 2 demonstrates the proportion of different CXR findings in the admission CXRs of the entire cohort of patients (n = 161) and the differences between the survivor and non-survivor sub-groups. In the entire cohort of 161 patients, 16.8 % of the admission CXRs were either normal or unchanged from a previous CXR and the commonest abnormal CXR finding was ground-glass opacification (GGO). With regards to the overall distribution of abnormal findings (n = 161), peripheral shadowing was present in 71.9 %, lower zone and mid zone involvement were 66.8 % and 56.9 % respectively. Bilateral shadowing was a common finding at 50 % in the entire cohort. Uncommon findings were effusions (9.0 %), atelectasis (6.8 %) and upper zone shadowing (10.6 %). We additionally show the shadowing distribution of GGO and consolidation.

The reliability of each major finding was calculated by comparing the radiology consultant’s assessment to the other reviewers, to produce a kappa measurement with a 95 % confidence interval in brackets. These were as follows, GGO: κ = 0.604 (0.452–0.756), consolidation: κ = 0.714 (0.561–0.867), peripheral shadowing: κ = 0.520 (0.366–0.673), perihilar shadowing: κ = 0.460 (0.316–0.604), upper zone shadowing: κ = 0.584 (0.430–0.738), mid zone shadowing: κ = 0.764 (0.611–0.917), lower zone shadowing: κ = 0.659 (0.505–0.814), bilateral shadowing: κ = 0.825 (0.670–0.980).

The CXR characteristics on admission are additionally compared between survivors and non-survivors in Table 2. The presence of perihilar GGO and midzone GGO was significantly higher in the non-survivors compared with the survivor group, 37.2 % vs. 16.9 % (P = 0.0098) and 62.8 % vs. 42.4 % (P = 0.0318) respectively. Unusually, left sided consolidation was significantly more prevalent in the non-survivors (P = 0.0281). Additionally, significantly more patients in the non-survivor group had pleural effusions 16.3 % vs. 4.2 % (P = 0.0166).

3.3. CXR severity association with outcome

Inter-rater reliability of CXR grading between the radiology consultant (FS) and the other reviewers (JC, GZ, FS) on all subjects were κ = 0.787 (0.691–0.883) for the 0–8 grading and κ = 0.625 (0.521–0.729) for the normal/ mild/ moderate/ severe grading with 95 % confidence interval shown in brackets. The greater the score used either of the 2 CXR scoring methods, more severe or ‘worse’ are the CXR findings. Table 3 compares the highest or ‘worst’ CXR findings between survivors and non-survivors; taking into account all the CXRs performed on each patient during their entire in-patient hospital stay. The non-survivors (n = 43) had a marginally greater proportion of moderate or severe CXRs at admission. This difference is greater for the greatest CXR severity during in-patient stay shown in Table 3. The severity differences are displayed as a plot in Fig. 1 and in Fig. 2 as a 0–8 severity, the non-

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Table 1

| Patient Characteristics | All (n = 161) | Survivors (n = 118) | Non-Survivors (n = 43) | P value |
|-------------------------|--------------|---------------------|------------------------|---------|
| Demographics            |              |                     |                        |         |
| Male: Female ratio      | 1.1:1        | 1.2:1               | 0.8:1                  | 0.1075  |
| Age (years)             | 66.7 (17.6)  | 62.7 (18.0)         | 77.7 (10.4)            | <0.0001**|
| Comorbidities           |              |                     |                        |         |
| Diabetes (%)            | 17.4         | 14.4                | 25.6                   | 0.1057  |
| Hypertension (%)        | 35.4         | 32.2                | 44.2                   | 0.193   |
| Ischaemic Heart (%)     | 16.8         | 15.3                | 20.9                   | 0.4746  |
| Disease (%)             |              |                     |                        |         |
| Heart Failure (%)       | 6.2          | 1.7                 | 18.6                   | 0.0004**|
| Malignancy (%)          | 10.6         | 7.6                 | 18.6                   | 0.0773  |
| Atrial fibrillation (%) | 11.2         | 8.5                 | 18.6                   | 0.6319  |
| Chronic Kidney (%)      | 8.1          | 8.5                 | 7.0                    | 0.5621  |
| Respiratory Disease (%) | 26.7         | 25.4                | 30.2                   | 0.5754  |
| Dementia (%)            | 11.2         | 5.1                 | 27.9                   | 0.0002**|
| Admission Laboratory results (n = 158) | | | | |
| White cell count (mean +/-SD, 10^9/L) | 7.45 +/- | 7.33 +/- | 7.79 +/- | 0.0998 |
| Neutrophils (mean +/-SD, 10^9/L) | 5.88 +/- | 5.74 +/- | 6.27 +/- | 0.0590 |
| Lymphocytes (mean +/-SD, 10^9/L) | 0.98 +/- | 1.03 +/- | 0.85 +/- | 0.0191*|
| Neutrophil (mean +/-SD, 10^9/L) | 8.51 +/- | 7.63 +/- | 10.96 +/- | 0.0063*|
| Lympocyte ratio (mean +/-SD) | 7.80 | 6.80 | 9.76 | |
| C-reactive Protein (mean +/-SD, mg/ L) | 89.84 +/- | 82.00 +/- | 111.85 +/- | 0.0297*|
| Platelets (mean +/-SD, 10^9/L) | 80.83 | 82.73 | 71.99 | |

P = 0.0191. The Neutrophil: Lymphocyte ratio was noted to be greater in the non-survivors (10.96 +/- 9.76 vs. 7.63 +/- 6.80, P = 0.0063).

Table 2

| Radiology findings with or without presence of other findings | All (n = 161) | Survivors (n = 118) | Non-Survivors (n = 43) | P value |
|-------------------------------------------------------------|--------------|---------------------|------------------------|---------|
| All shadowing                                               |              |                     |                        |         |
| Normal admission CXR (%)                                    | 16.8         | 18.6                | 11.6                   | NS      |
| Peripheral (%)                                              | 71.9         | 70.3                | 74.4                   | NS      |
| Perihilar (%)                                               | 35.6         | 30.5                | 48.8                   | 0.0405* |
| Left (%)                                                    | 68.1         | 64.4                | 76.7                   | NS      |
| Right (%)                                                   | 66.3         | 64.4                | 69.8                   | NS      |
| Bilateral (%)                                               | 50           | 46.6                | 58.1                   | NS      |
| Upper zone (%)                                              | 10.6         | 10.2                | 11.6                   | NS      |
| Mid zone (%)                                                | 56.9         | 50.8                | 72.1                   | 0.0195* |
| Lower zone (%)                                              | 68.8         | 67.8                | 69.8                   | NS      |
| Other abnormalities                                         |              |                     |                        |         |
| Pleural effusion (%)                                        | 7.5          | 4.2                 | 16.3                   | 0.0166* |
| Atelectasis (%)                                             | 6.8          | 7.6                 | 4.7                    | NS      |
| Consolidation                                               |              |                     |                        |         |
| All (%)                                                     | 28.6         | 26.3                | 34.9                   | NS      |
| Peripheral (%)                                              | 24.2         | 22.9                | 27.9                   | NS      |
| Perihilar (%)                                               | 14.3         | 11                  | 23.3                   | NS      |
| Left (%)                                                    | 20.5         | 20.3                | 20.9                   | NS      |
| Right (%)                                                   | 20.5         | 16.1                | 32.6                   | 0.0281* |
| Upper zone (%)                                              | 5.6          | 5.9                 | 4.7                    | NS      |
| Mid zone (%)                                                | 20.5         | 16.9                | 30.2                   | NS      |
| Lower zone (%)                                              | 21.7         | 18.6                | 30.2                   | NS      |
| Ground glass opacification                                  |              |                     |                        |         |
| All (%)                                                     | 69.6         | 66.9                | 76.7                   | NS      |
| Peripheral (%)                                              | 58.4         | 58.5                | 58.1                   | NS      |
| Perihilar (%)                                               | 22.4         | 16.9                | 37.2                   | 0.0098* |
| Right (%)                                                   | 52.8         | 50                  | 60.5                   | NS      |
| Left (%)                                                    | 54           | 52.5                | 58.1                   | NS      |
| Upper zone (%)                                              | 5.6          | 5.9                 | 4.7                    | NS      |
| Mid zone (%)                                                | 47.8         | 42.4                | 62.8                   | 0.0318* |
| Lower zone (%)                                              | 55.3         | 54.2                | 58.1                   | NS      |
survivor group had significantly more severe CXRs.

Additionally, in Table 3 we display the Risk Ratio (RR) for death depending on the CXR severity. Those patients who had the ‘severe’ grade of CXR changes, were 3.28 (2.08–5.16) times more likely to die (P < 0.0001) in comparison to those who had ‘mild’ changes as their ‘worst’ CXR change during their entire in-patient hospital stay; a RR of 0.46 (0.25–0.84, P = 0.0122).

### 3.4. CXR severity over disease course

We explored CXR severity over the disease length, and a strong relationship with worsening CXRs over length of symptoms can be seen, with improvement later in the disease course. Of the 161 patient 6 patients were excluded due to missing data on symptom onset. Of the remaining 155 patients 61 had at least one repeat CXR, with 120 repeat
CXRs in total, giving 275 CXRs in total. Table 4 depicts the rates of normal CXRs and severities along with the mean 0–8 severity score. In 0–1 days of symptoms 42.3 % of CXR can be seen to be normal, 38.5 % mild, 11.5 % moderate, and 7.7 % severe. This is compared to 16–19 days of symptoms where 0% of CXRs are normal, 18.2 % mild, 27.3 % moderate, and 54.5 % severe. We show the 0–8 CXR severity over symptom length in a plot in Fig. 3 where a clear worsening trend over time can be seen with CXR improvement after 20 days.

4. Discussion

We performed a more detailed review of CXR findings in 161 patients at our hospital as a follow up to our initial 50 patient report with similar findings, further strengthening our previous claims [19].

We have described the typical characteristics of COVID-19 infection on CXR being GGO with or without consolidation and mid and/or lower zone peripheral shadowing with or without perihilar shadowing being key features. Bilateral changes are also prevalent, however only 50 % of the time. These findings agree with [5], although a key difference is, we found consolidation to be much less prevalent.

We have shown in our cohort that 82.3 % of admission CXR for patients with COVID-19 are abnormal. While this is in keeping with other studies, this is likely bias towards more unwell patients, as we only included patients needing admission. Moreover, the cohort of patients studies, this is likely bias towards more unwell patients, as we only included patients with COVID-19 are abnormal. While this is in keeping with other studies, this is likely bias towards more unwell patients, as we only included patients needing admission. Moreover, the cohort of patients who were included into the review were only those who were admitted to the hospital with suspected COVID-19 were offered a SARS-CoV-2 RT-PCR assay. We have also shown that symptom length is strongly related to CXRs being abnormal and its severity, with 42.3 % of patients in our review having normal CXRs in the first 2 days of symptoms, but 0% after 13 days, which is similar to the findings of other studies.

We additionally explored two different severity scores and clearly defined the mild/moderate/severe CXR grading, finding that CXR severity was strongly associated with death with a severe CXR having a risk ratio for death of 3.28. However, a large number of patients who were no longer alive at 30 days had normal or mild severity CXRs, 48.9 % on admission and 32.6 % as their worst CXR. This suggests a moderate or severe CXR may be a good predictor of poor outcome, however, a normal CXR is not necessarily reassuring as not significantly related to death. Analysing for the ‘worst’ or highest CXR changes amongst the entire cohort, we note that those who had normal CXR changes as their worst CXR had a marginal reduced risk of death (RR of versus), although this was not statistically significant. Perhaps this further reinforces the aforementioned point of moderate and severe CXR changes being a better predictor of outcome than normal or mild changes. The 0–8 numeric score was additionally significantly higher in non-survivors 4.1 vs. 2.5 on average (P = 0.0002), and likely can capture more subtle severity changes. These findings agree with many severity scores in the literature with the Brixia and RALE score being found to be significantly higher in non-survivors [15–17] and another study with a score similar to Brixia, but a 0–24 score, found it to be significantly higher in non-survivors (20.3 v.s 19.1, P = 0.038) [18]. Our Mild/Moderate/Severe and 0–8 score have the advantage of being more straightforward to calculate than other scores in the literate, and therefore easier to implement clinically, but may not be able to detect small differences in severity and does not take shadowing density into consideration (like the RALE score).

Additionally, we found mid zone GGO is strongly associated with death 37.2 % in non-survivors vs 16.9 % in survivors in keeping with our previous results [19]. We looked at the distribution of the GGO - peripheral or perihilar and we found perihilar GGO was significantly associated with non-survival, 30.2 % vs 16.9 %. The explanation for this will require larger studies perhaps involving histological examination of tissue. However, it is worth noting that recent studies have described that in early phase of COVID-19 illness, sub-segmental pulmonary vessels within the areas of the GGO enlarge and as there is progressive replacement of GGO by consolidation this enlargement returns to normal [22,23]. These changes may be related to hyperaemia or small vessel thrombosis. The worse prognosis may also suggest superimposed bacterial pneumonia, which has been recognised in several studies including some autopsy studies. One of the main limitations to this work is that at the time in the UK, patients were usually only tested for SARS-CoV-2 when admitted to hospital, along with the fact this patient review was performed in a single centre. Therefore, these results are not necessarily applicable to all patients with COVID-19 infection. Additionally, the CXRs were reviewed retrospectively and all observers knew the CXRs were of patients with proven COVID-19 infection, which may have biased the assessment to features know to be common in COVID-19 infection.

Another limitation of this work was that the timings of the CXRs were not uniform and may have some discrepancy especially in terms of monitoring the trajectory of severity in the groups compared, which would have been possible only in case of an experimental study rather than real world data from actual patients suffering the illness during this pandemic.

This patient review shows the promise and need for further work on CXR features, sensitivity and specificity for COVID-19 infection. Ideally a study will be done on CXRs with and without COVID-19 to evaluate the sensitivity and specificity of CXR in the disease. This work also shows the promise and limits of imaging for disease outcome prediction. Further work in a larger study is needed exploring the relationship of age and symptom length on CXR severity and its survival prediction accuracy and in the development of a prognostication score which may be crucial for risk stratification.

5. Conclusion

We clearly outline a consistent way of defining severity of COVID-19 on CXRs. We show that this grading is related to clinical outcome. We show the rates of different CXR findings and that more central shadowing (mid zone and perihilar) is associated with death. Finally, we show CXRs can be normal initially in the disease process and worsen in severity with time and then improve after around 20 days in our cohort.

Author contributions

Jordan Colman: Conceptualized the project, investigation, analysed data, created figures and wrote the original manuscript. Georgiana Zamir: investigation, reviewed and contributed to manuscript, Frances Sheehan: investigation, reviewed and contributed to the manuscript, Max Berrill: Conceptualized the project, aided data analysis, reviewed and contributed to manuscript, Sujoy Saikia: Conceptualized the project, reviewed and contributed to manuscript, Felicity Saltissi: supervision of investigators, investigation, reviewed and contributed to manuscript.
Fig. 3. Showing 0-8 severity over symptom length in days. The darker the orange colour the more cases at that point. Figure produced in Microsoft Excel (Microsoft Corporation, 2019).

Ethics statement

Ethical approval was provided by the Ashford & St Peter’s Hospital Research and Development department. All research was conducted in accordance with the declaration of Helsinki.

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Declaration of Competing Interest

The authors report no declarations of interest.

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