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# Comparisons of early and late presentation to hospital in COVID-19 patients

*To the Editors*:

Presentation, disease severity and outcomes of coronavirus disease 2019 (COVID-19) vary widely from asymptomatic carriage to death. Currently, there are little data on the relationship between the timing of symptom onset at presentation to hospital and disease outcome. Therefore, we aimed to identify the differences between 'early presenters' (patients presenting to hospital <7 days from symptom onset) and 'late presenters' (≥7 days from symptom onset).

This retrospective single-centre observational study collected demographic, clinical and radiological data from electronic patient healthcare records with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the University Hospital Southampton NHS Foundation Trust (Southampton, UK). Research ethics approval was gained as part of the REACT Study (Bromley REC 20/HRA/2986) and data were extracted from this study. There is no patient identifiable data included in this manuscript.

Chest radiograph (CXR) on admission was assessed for pulmonary infiltrates by an unblinded hospital clinician and radiological severity scores were assigned using an adapted Radiographic Assessment of Lung Oedema (RALE) score.[1] The composite end point was admission to the intensive care, the use of mechanical ventilation and/or death. Logistical regression models were used to explore the relationship between outcome and independent variables.

Between March and July 2020, data were collected for 574 SARS-CoV-2-positive patients. Early presenters were older ($P < 0.001$), more likely to have significant medical comorbidities (hypertension, thromboembolic and renal diseases; $P < 0.001$) and less likely to report cardinal symptoms of COVID-19: fever, cough and shortness of breath (SOB) ($P < 0.001$) (Table 1).

In the cohort overall, the presence of CXR infiltrates was not predictive of adverse outcome ($P = 0.214$). However, although early presenters were less likely to have infiltrates on their CXR ($P < 0.001$), the presence of infiltrates in this group revealed increased risk of adverse outcome (odds ratio (OR): 1.90, 95% CI: 1.11, 3.25). The presence or lack of infiltrates in late presenters was not predictive of outcome (OR: 0.58, 95% CI: 0.30, 1.16).

To our knowledge, we are the first to investigate radiological change in predicting outcome in the context of symptom duration at presentation to hospital. We demonstrate that heterogeneity in SARS-CoV-2 presentation varies with symptom duration, with early presenters being more likely to present atypically. This is notable in the context of national criteria for self-isolation and testing. Furthermore, late presentation is more likely to be associated with radiological change, reflective of current literature,[1,2] but is not predictive of outcome.

Most importantly, early presenters with radiological changes are at increased risk of adverse outcome, suggesting that symptom onset and detection of CXR infiltrates are important for clinical assessment at presentation to hospital. This may reflect a more

**Table 1** Symptoms at the time of presentation to hospital in 'early' and 'late' presenters

| Symptoms | Early presenters ($n = 388$) | Late presenters ($n = 238$) | *P*-value for difference |
|---|---|---|---|
| Fever | 225/352 (63.9%) | 152/182 (83.5%) | **<0.001** |
| Cough | 235/339 (69.3%) | 174/190 (91.6%) | **<0.001** |
| Shortness of breath | 211/328 (64.3%) | 165/190 (86.8%) | **<0.001** |
| Myalgia | 21/49 (42.9%) | 45/57 (79.0%) | **<0.001** |
| Arthralgia | 10/26 (38.5%) | 9/12 (75.0%) | **0.04** |
| Fatigue/malaise | 143/182 (78.6%) | 127/130 (97.7%) | **<0.001** |
| Headache | 26/80 (32.5%) | 36/59 (61.0%) | **0.001** |
| Confusion | 125/265 (47.2%) | 41/119 (34.5%) | **0.02** |
| Diarrhoea | 53/162 (32.7%) | 49/107 (45.8%) | **0.03** |
| Cold symptoms | 36/67 (53.7%) | 35/51 (68.6%) | 0.1 |
| Wheezing | 37/165 (22.4%) | 13/64 (20.3%) | 0.7 |
| Chest pain | 49/207 (23.7%) | 32/128 (25.0%) | 0.8 |
| Abdominal pain | 32/173 (18.5%) | 18/97 (18.6%) | 0.9 |
| Vomiting | 39/144 (27.1%) | 32/96 (33.3%) | 0.3 |

Chi-square statistical test was used to determine significance. Patient numbers vary as they were only included if there was a clear reference to presence or lack of symptom in clinical notes. $P < 0.05$ was considered statistically significant.

Early presenters, presentation to hospital <7 days of symptom onset; late presenters, presentation ≥7 days of symptom onset.




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aggressive inflammatory response, marking a worse clinical trajectory. The precise mechanisms of hyperinflammatory responses in COVID-19 are unknown but a theorized 'inflection point' between early infection and the respiratory phase with hyperinflammatory response occurs 5–7 days post-symptom onset,[3] which represents our 'early presenter' cohort. Therefore, this is a key group to identify, whereby accurate risk prediction could be crucial to improving outcomes. Given that CXR is part of the initial diagnostic algorithm and the primary imaging modality for COVID-19,[4] the identification of radiological infiltrates for predicting outcome in the context of symptom onset provides a useful tool for clinicians to identify patients who are most at risk of deterioration, which could be immediately translated to clinical practice as a second wave emerges.

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## REFERENCES

1 Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW *et al.* Frequency and distribution of chest radiographic findings in patients positive for COVID-19. *Radiology* 2020; **296**: E72–E8.

2 Vancheri SG, Savietto G, Ballati F, Maggi A, Canino C, Bortolotto C, Valentini A, Dore R, Stella GM, Corsico AG *et al.* Radiographic findings in 240 patients with COVID-19 pneumonia: time-dependence after the onset of symptoms. *Eur. Radiol.* 2020: **30:** 6161–6169.

3 Chatham WW, Cron RQ. Treating Covid-19 at the inflection point. *J. Rheumatol.* 2020; **47:** 1590–1591. https://doi.org/10.3899/jrheum.200679.

4 Nair A, Rodrigues JCL, Hare S, Edey A, Devaraj A, Jacob J, Johnstone A, McStay R, Denton E, Robinson G. A British Society of Thoracic Imaging statement: considerations in designing local imaging diagnostic algorithms for the COVID-19 pandemic. *Clin. Radiol.* 2020; **75**: 329–34.