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Early View

Research letter

# The impact of the first COVID-19 surge on Severe Asthma Patients in the UK. Which is worse: The virus or the lockdown?

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**Title: The impact of the first COVID-19 surge on Severe Asthma Patients in the UK. Which is worse: The virus or the lockdown?**

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*To the editor:*

Respiratory viral infections are a significant cause of morbidity in asthma (1). Patients with severe asthma were assumed to be at greater risk from novel coronavirus-2 (COVID-19) infection. In the global response to the COVID-19 pandemic, multiple countries enacted social containment policies.

In the UK a countrywide lockdown occurred in March 2020, with stringent self-isolation ('shielding') advice for high-risk patients, including people with severe asthma.

Subsequently; ISARIC reported 14% of UK patients hospitalised with COVID-19 had an underlying diagnosis of asthma, but they did not associate asthma with higher mortality(2). The OpenSAFELY study of COVID-19-related deaths identified severe asthma as a factor associated with mortality [HR 1.13 [1.01-1.26] (3). However, 'severe asthma' was defined as anyone with asthma and a course of oral corticosteroids (OCS) in their records in the past year (3). Their analysis of inhaled corticosteroid (ICS) use showed increased mortality risk from COVID-19 in asthma patients on high dose versus no ICS, attributed to unrecorded health differences between the two groups (4). The Italian Severe Asthma Registry reported infrequent incidence of COVID-19 infection, based on participating centres reporting cases of confirmed/highly suspected COVID-19 with severe asthma and, as 21/26 cases were on anti-IL5/IL-5R biologics, they speculated that asthma biologics may modulate the risk of COVID-19 (5). To our knowledge, there is no information on the burden of social isolation (shielding) in people with severe asthma. There is a need for information on the impact of COVID-19 on a well-characterised severe asthma population in the community, effects of shielding and any association between asthma medication and COVID-19.

The UK Severe Asthma Registry (UKSAR) performed an audit in June 2020 across 14 centres, of patient adherence with shielding advice, potential COVID-19 infection and outcomes and asthma control since 1$^{st}$ March 2020. UKSAR centres with >100 registry patients used randomly generated lists to reduce potential bias. Where available, electronic hospital records were checked to confirm hospital admissions and COVID-19 swab/serology results. Permission was obtained by centres as per local audit requirements and all patients had previously consented to use of their anonymised Registry data.

Confirmed COVID-19 was defined as those with a positive PCR/serology test. Suspected COVID-19 was defined as typical symptoms, managed clinically as COVID-19, without a negative test. Ambulatory and hospitalised patients were labelled as 'mild' and 'severe' COVID-19, respectively. Audit data were combined with clinical data from the UKSAR. We used data from the most recent visit, and imputed missing values with data collected at previous visits. Univariate analyses were conducted using independent t-tests, Mann-Whitney U tests or chi-square tests as appropriate. Multivariate analyses were undertaken using logistic regression adjusting for age, gender, ethnicity, BMI, site, cardiac disease, diabetes and hypertension.

1365 patients were included (Table 1). Shielding advice was sent to 1268 (93.0%) patients and followed by 1131 (89.2%). Males and members of a non-shielding household were less likely to follow shielding advice (OR 0.40 [0.26,0.62], p<0.001 and OR 0.27 [0.16,0.45], p<0.001) respectively. 44 (57%) patients with suspected and 8 (42%) patients with confirmed COVID-19 were infected before receiving shielding advice 14 (77%) confirmed COVID-19 cases occurred in non-shielding households. Of those that shielded, 582 (47.0%) reported worsening of mental health. Although those with a history of depression/anxiety were particularly susceptible (OR 2.12[1.35,3.33], p=0.001), 447 (76.8%) had no such pre-morbidity documented. Other characteristics associated with worsening mental health were female gender (OR 1.59 [1.19, 2.13], p=0.001) and an elevated asthma control score (ACQ-6) ≥1.5 (OR 1.80[1.23, 2.63], p=0.004). Younger patients (aged <40) were more affected than those >60 (OR 1.56 [1.08,2.33], p=0.020).

Of 1365 patients, 97 (7.1%) had a confirmed/suspected COVID-19 infection, 19 (1.39%) had PCR/serology confirmed infection. 13 (0.95%) were hospitalised with COVID-19; the median hospital stay was 11 days (5,22). A higher proportion of hospitalised versus ambulatory patients were non-Caucasian (25% vs 17.9%, p=0.053). Two patients died; both were Caucasian men aged over 65.

918 (67.5%) of patients were on a biologic; 735 (80%) of these on anti-IL-5/5R agents. No association was seen between biologics and risk of COVID-19 (OR 0.73 [0.46,1.14], p=0.165), but they were associated with better asthma control (OR 0.56 [0.41,0.77], p<0.001) and fewer exacerbations (OR 0.6 [0.44, 0.83], p=0.002). There was no difference in the proportion of patients on biologic therapy in the mild and hospitalised COVID-19 groups (67.9% vs 61.5%, p=0.652). No association was seen between the type of biologic therapy and COVID-19 infection. Maintenance OCS (mOCS) was not associated with COVID-19 (OR 1.18 [0.78,1.80], p=0.427); 35 (47.9%) ambulatory patients and 3 (23.0%) hospitalised patients were on mOCS (p=0.151).

High dose ICS (2000 mcg beclometasone[BDP]/ equivalent) was no different from lower dose ICS (<1000mcg BDP equivalent) in its association with developing COVID-19 infection (OR 0.64 [0.32,1.31] p=0.234). However, hospitalised patients were on lower doses of ICS than ambulatory patients [median(IQR) BDP-equivalent mcg 1000 (800,1600) vs 2000 (1600,2000), p=0.002]) and a greater proportion had a history of poor adherence (53.8% vs 24.7%, p=0.033).

In summary; the majority of patients reported receiving and following shielding advice, 47% of shielding patients reported worsening of mental health, higher than the Office of National Statistics analysis of shielding patients in England (35%), with similar higher incidence in female and younger patients (6).

We found that monoclonal antibodies for asthma were not associated with increased risk of mild or severe COVID-19 infection. This agrees with other emerging findings of low incidence of COVID-19 in the severe asthma population and biologics not affecting clinical outcome (7). Poor asthma control increases the risk of severe viral exacerbations, so disease stability from biologics may be protective in itself (8).

Although numbers were small, there was an association seen with high dose ICS and reduced hospitalisation from COVID-19. The RECOVERY trial demonstrated that dexamethasone reduced mortality and progression to ICU in hospitalised patients(9). In vitro studies have suggested ICS can reduce viral replication whilst pre-treatment with ICS has been shown to reduce the risk of ARDS in hospitalised patients (10, 11). Further studies are required, but our findings support continued use of ICS at an appropriate dose for asthma control.

The strength of this study is the multicentre inclusion of well-characterised severe asthma patients. In addition to studying the impact of COVID-19 and effect of asthma medications, we enquired about the burden of shielding; a consideration when planning for the second wave. Limitations are the small number of patients hospitalised with COVID-19 preventing detailed analyses for risk factors. We also note that this study cannot separate out the risk of COVID-19 in an unshielded severe asthma population and that adherence to shielding was self-reported. Unfortunately, COVID-19 testing was not widely available in the early months of the pandemic, hence, despite including only patients reporting symptoms distinct from their usual asthma, the natural symptom overlap between poor asthma control and mild COVID-19 limits robust conclusions in the 'suspected COVID-19' group.

In conclusion, hospitalisation and death occurred in small numbers of this UK severe asthma population. Adherence to shielding guidance may have contributed to this, but led to worsening of mental health in our patents. Within our limited numbers of cases, biologic agents for asthma were not associated with increased risk of COVID-19 infection or hospitalisation.

**Table 1: Characteristics of Severe Asthma Patients According to COVID-19 Status, Disease Severity and Confirmed COVID-19**

| Characteristic<br>N (%) unless otherwise stated | N | COVID-19 Status<br>No COVID-19<br>(N = 1268) | <br>Suspected or confirmed COVID-19<br>(N=97) | <br>P value | COVID-19 Disease Severity<br>Non hospitalised<br>(N=84) | <br>Hospitalised<br>(N=13) | <br>P value | Confirmed COVID-19<br>Confirmed COVID-19<br>N=19 | <br>P value** |
|---|---|---|---|---|---|---|---|---|---|
| **Age (years)** [mean (SD)] | 1365 | 52.8 (15.5) | 51.2 (13.8) | 0.313 | 50.5 (13.8) | 55.6 (13.7) | 0.215 | 49.8 (13.7) | 0.404 |
| **Male gender** | 1365 | 453 (35.7%) | 43 (44.3%) | 0.089 | 39 (46.4%) | 4 (30.8%) | 0.290 | 5 (26.3%) | 0.395 |
| **BMI (kg-m2)** | 1166 | 31.0 (7.2) | 31.3 (6.1) | 0.704 | 31.3 (6.3) | 31.3 (4.9) | 0.967 | 30.6 (6.3) | 0.849 |
| **Smoking status** | 1322 | - | - | 0.584 | - | - | 0.739 | - | 0.522 |
| Never smoked | 1322 | 838 (68.4%) | 69 (71.9%) | - | 59 (71.1%) | 10 (76.9%) | - | 15 (78.9%) | - |
| Ex-smoker | 1322 | 337 (27.5%) | 22 (22.9%) | - | 20 (24.1%) | 2 (15.4%) | - | 3 (15.8%) | - |
| Current smoker | 1322 | 51 (4.2%) | 5 (5.2%) | - | 4 (4.8%) | 1 (7.7%) | - | 1 (5.3%) | - |
| **Non-Caucasian ethnicity** | 1345 | 150 (12.0%) | 18 (18.8%) | 0.054 | 15 (17.9%) | 3 (25.0%) | 0.553 | 3 (16.7%) | 0.547 |
| **Resident in London area** | 1365 | 306 (24.1%) | 44 (45.4%) | **<0.001** | 39 46.4%) | 5 (38.5%) | 0.591 | 11 (57.9%) | **<0.001** |
| **Resident outside London area [Rest of UK]** | 1365 | 962 (75.9%) | 53 (54.5%) | - | 45 (53.6%) | 8 (61.8%) | - | 8 (42.1%) | - |
| **Atopic disease** | 1236 | 662 (57.8%) | 58 (64.4%) | 0.216 | 48 (62.3%) | 10 (76.9%) | 0.310 | 11 (57.9%) | 0.991 |
| **Depression or anxiety** | 1365 | 126 (9.9%) | 9 (9.3%) | 0.834 | 9 (10.7%) | 0 (0.0%) | 0.215 | 0 (0.0%) | 0.148 |
| **Clinic $FEV_1$ (% predicted)** [$] | 1113 | 68.1 (52.9,82.6) | 67.9 (59.9,83.4) | 0.343 | 67.9 (59.9,82.8) | 73.7 (60.1,84.8) | 0.555 | 80.8 (60.7,86.2) | 0.141 |
| **Clinic FVC (% predicted)** [$] | 1081 | 83.6 (71.8,95.4) | 82.8 (71.3,92.6) | 0.779 | 83.1 (71.3,91.7) | 81.2 (68.9,92.6) | 0.814 | 87.3 (76.7,93.9) | 0.558 |
| ***Asthma Medication and Control*** | | | | | | | | | |
| **ICS dose (BDP equivalent-ug)** [$] | 1174 | 2000 (1600,2000) | 2000 (1600,2000) | 0.433 | 2000 (1600,2000) | 1000 (800,1600) | **0.002** | 1600 (1000,2000) | 0.106 |
| **Maintenance OCS** | 1363 | 481 (38.0%) | 34 (35.4%) | 0.620 | 30 (35.7%) | 4 (33.3%) | 0.872 | 9 (47.4%) | 0.402 |
| **Maintenance macrolides** | 1200 | 153 (13.8%) | 9 (10.2%) | 0.351 | 7 (9.9%) | 2 (16.7%) | 0.428 | 3 (16.7%) | 0.723 |
| **Theophylline** | 1237 | 294 (25.7%) | 12 (13.2%) | **0.008** | 10 (12.8%) | 2 (15.4%) | 0.800 | 3 (15.8%) | 0.328 |
| **Evidence of poor adherence** | 1190 | 248 (22.5%) | 25 (29.1%) | 0.160 | 18 (24.7%) | 7 (53.8%) | **0.033** | 6 (31.6%) | 0.346 |
| **On asthma biologic** | 1361 | 853 (67.5%) | 65 (67.0%) | 0.924 | 57 (67.9%) | 8 (61.5%) | 0.652 | 13 (68.4%) | 0.931 |
| **Biologic type** | 917 | - | - | 0.349 | - | - | 0.986 | - | 0.841 |
| Anti-IL5 [*] | 917 | 680(79.7%) | 55 (85.9%) | - | 49 (86.0%) | 6 (85.7%) | - | 11 (84.6%) | - |
| Anti-IgE | 917 | 157 (18.4%) | 9 (14.1%) | - | 8 (14.0%) | 1 (14.3%) | - | 2 (15.4%) | - |
| Anti-IL4/13 | 917 | 16(1.9%) | 0 (0%) | - | 0 (0.0%) | 0 (0.0) | - | 0 (0.0%) | - |
| ***Co-morbidities*** | | | | | | | | | |
| **Cardiac disease** | 1299 | 64 (5.3%) | 6 (6.3%) | 0.678 | 5 (6.1%) | 1 (7.7%) | 0.826 | 1 (5.3%) | 0.992 |
| **Diabetes** | 1365 | 78 (6.2%) | 5 (5.2%) | 0.692 | 5 (6.0%) | 0 (0.0%) | 0.366 | 1 (5.3%) | 0.873 |
| **Hypertension** | 1365 | 121 (9.5%) | 9 (9.3%) | 0.932 | 7 (8.3%) | 2 (15.4%) | 0.415 | 2 (10.5%) | 0.885 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Malignancy** | 1365 | 13 (1.0%) | 1 (1.0%) | 0.996 | 1 (1.2%) | 0 (0.0%) | 0.693 | 0 (0.0%) | 0.657 |
| **Associated COPD** | 1365 | 38 (3.0%) | 5 (5.2%) | 0.241 | 4 (4.8%) | 1 (7.7%) | 0.657 | 1 (5.3%) | 0.567 |
| ***Shielding & asthma control during lockdown*** | | | | | | | | | |
| **Advised to shield** | 1363 | 1,182 (93.2%) | 86 (90.5%) | 0.320 | 76 (90.5%) | 10 (90.9%) | 0.963 | 16 (88.9%) | 0.470 |
| **Followed shielding advice** | 1268 | 1,058 (89.5%) | 73 (84.9%) | 0.182 | 64 (84.2%) | 9 (90.0%) | 0.631 | 13 (81.3%) | 0.286 |
| **Shielding affected mental health** | 1237 | 544 (47.1%) | 38 (46.9%) | 0.980 | 33 (46.5%) | 5 (50.0%) | 0.835 | 8 (53.3%) | 0.629 |
| **Contracted COVID-19 before shielding advice** | 76 | 0 (0.0%) | 44 (57.9%) | - | 40 (60.6%) | 4 (40.0%) | 0.219 | 8 (53.3%) | - |
| **Non-Shielding household** | 1338 | 715 (57.3%) | 50 (54.9%) | 0.656 | 41 (51.2%) | 9 (81.8%) | 0.056 | 14 (77.8%) | 0.081 |
| **Specialist asthma attendance** | 1359 | 432 (34.2%) | 31 (32.6%) | 0.759 | 27 (32.1%) | 4 (36.4%) | 0.779 | 4 (22.2%) | 0.288 |
| **Asthma control worse during lockdown** | 1358 | 463 (36.7%) | 50 (52.6%) | **0.002** | 41 (48.8%) | 9 (81.8%) | **0.039** | 11 (61.1%) | **0.033** |
| **Acute OCS course during lockdown** | 1363 | 433 (34.2%) | 48 (50.0%) | **0.002** | 40 (47.6%) | 8 (66.7%) | 0.217 | 13 (68.4%) | **0.002** |
| ***Hospital admission with COVID-19*** | | | | | | | | | |
| **Admitted to hospital for COVID-19** | 97 | 0 (0.0%) | 13 (1.4%) | - | 0 (0.0%) | 13 (100%) | <0.001 | 11 (57.9%) | - |
| **Oxygen therapy** | 12 | 0 (0.0%) | 7 (7.2%) | - | 0 (0.0%) | 7 (58.3%) | - | 7 (36.8%) | - |
| **ITU admission for COVID-19** | 12 | 0 (0.0%) | 2 (2.1%) | - | 0 (0.0%) | 2 (15.4%) | - | 1 (5.2%) | - |
| **Chest X-Ray suggestive of COVID-19** | 8 | 0 (0.0%) | 7 (87.5%) | - | 0 (0.0%) | 7 (87.5%) | - | 7 (87.5%) | - |
| **Days in hospital** [$] | 9 | - | 11 (5,22) | - | - | 11 (5,22) | - | 11 (5,22) | - |

- Significant p values displayed in **bold**
- ***** anti-IL5 biologic agents include – mepolizumab, benralizumab and reslizumab
- - no data to present
- ** p value for confirmed COVID-19 vs No COVID-19
- $ Data presented as median (IQR) and refers to data collected at registry entry.

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