Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus

A series of pneumonia cases caused by 2019 novel coronavirus (2019-nCoV, also named COVID-19) are being reported globally. Based on recent publications, the most common symptoms in patients infected by 2019-nCoV were fever and cough. However, the incidence of other clinical features differs in different reports. To address this issue, we collected the data from three reports and compared the incidence accordingly. We found that the incidence of leucopenia, fever and diarrhoea may be underestimated in previous investigations; (2) ACE2-expressing small intestinal epithelium cells might be more vulnerable to attack by 2019-nCoV.

In this study, we displayed that ACE2 was highly expressed in the small intestine, especially in proximal and distal enterocytes. Consistently, another group has recently reported a similar expression pattern in the human digestive system. Interestingly, other virus receptors like DPP4 displayed similar expression patterns as ACE2 in the small intestine. DPP4 is a known receptor for MERS-CoV through interacting with MERS-CoV spike protein.

Table 1 Intergroup comparison between three recent publications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Huang et al (41 cases)</th>
<th>Chan et al (6 cases)</th>
<th>Chen et al (99 cases)</th>
<th>Difference between groups (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.0 (17.0)</td>
<td>46.2 (28.3)</td>
<td>55.5 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>11/41 (27%)</td>
<td>3 (50%)</td>
<td>32 (32%)</td>
<td>0.4591</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>13/41 (32%)</td>
<td>4 (67%)</td>
<td>50 (51%)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Fever</td>
<td>40/41 (98%)</td>
<td>5 (83%)</td>
<td>82 (83%)</td>
<td>0.0345*</td>
</tr>
<tr>
<td>Cough</td>
<td>31/41 (76%)</td>
<td>4 (67%)</td>
<td>81 (82%)</td>
<td>0.3829</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1/38 (3%)</td>
<td>2 (33%)</td>
<td>2 (2%)</td>
<td>0.016†</td>
</tr>
<tr>
<td>Shortness of breath/ difficulty in breath</td>
<td>22/40 (55%)</td>
<td>NA</td>
<td>31 (31%)</td>
<td>–</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2/39 (5%)</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Sputum production</td>
<td>11/39 (28%)</td>
<td>2 (33%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Myalgia or fatigue</td>
<td>18/41 (44%)</td>
<td>3 (50%)†</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>3/38 (8%)</td>
<td>NA</td>
<td>8 (8%)</td>
<td>–</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>10/40 (25%)</td>
<td>0 (0%)</td>
<td>9 (9%)</td>
<td>0.0443§</td>
</tr>
<tr>
<td>Platelet count</td>
<td>2/40 (5%)</td>
<td>0 (0%)</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

Leucopenia: less white blood cell count (<4*10^9/L); platelet count: <100*10^9/L.

Difference between groups was calculated by Fisher’s exact test in R software.

* Huang vs Chan: 0.2414; Chan vs Chen: 1.00; Huang vs Chen: 0.0235.
† Symptom: generalised weakness.
§ Huang vs Chan: 0.3145; Chan vs Chen: 1.00; Huang vs Chen: 0.026.
NA, not available.
It is known that ACE2 controls intestinal inflammation and diarrhoea. Therefore, mutual interaction between 2019-nCoV and ACE2 might disrupt the function of ACE2 and results in diarrhoea. Here, we found that the incidence of diarrhoea significantly differed in different reports. As 2019-nCoV is highly homologous to SARS-CoV and around 20%–25% of SARS patients have diarrhoea, it is confusing to observe the relatively low incidence (2%–3%) of diarrhoea in two cohorts from hospitals in Wuhan. The underestimation may result from that we still do not have a precise criterion for diarrhoea. The definition of diarrhoea by the WHO is having three or more loose or liquid stools per day or having more stools than a person’s health condition. To a certain extent, this criterion is subjective. Besides, we still cannot exclude the effect of the small sample size (n=6) of the Hong Kong cohort, which affects the result of statistical analysis. Emerging evidence shows that 2019-nCoV RNA can be detected in stool samples as SARS. Based on the postulation from the epidemiological features of SARS, which is transmitted through fecal-oral, 2019-nCoV might use the same path for transmission. Thus, future efforts at prevention and control must take into consideration the potential for fecal-mediated spread of this virus.

Taken together, the symptoms of diarrhoea could be underestimated. The information on discharge frequencies and the Bristol stool scale should be carefully collected. When infected patients with diarrhoea visit the gastroenterology department, it may increase the risk of infection of healthcare workers. To reduce healthcare-associated infection, clinicians should be careful when their patients complain of diarrhoea.

**Contributors** Study concept was created by WL, QZ and WQ. Data collection was performed by WL, ZF, S and WQ. Bioinformatics analysis was conducted by ZF and S. Data interpretation was conducted by WL, ZF, S and WQ. Critical revision of the manuscript was done by WL, QZ and WQ. Final version was approved by all authors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Ethics approval** Not applicable.
PostScript

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