Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letters to the Editor

Comparing hospitalised, community and staff COVID-19 infection rates during the early phase of the evolving COVID-19 epidemic

Dear Editor,

We note with interest the study of Liu et al.[1] where they used routine laboratory test parameters to derive a potentially useful, independent measure (neutrophil – lymphocyte ratio – NLR) of hospital-based mortality for male patients with COVID-19.

Indeed, many routinely performed tests can offer useful insights into the status and evolving epidemiology of COVID-19 patients in local patient populations.[2] Here, we use our SARS-CoV-2 testing data to derive several useful epidemiological parameters, which can be applied simply by any team, to gain greater insight into the characteristics of their COVID-19-infected populations, which may help to target additional interventions and investigations, as appropriate.

Between 3 March 2020 and 29 April 2020, we performed a total of 8774 SARS-CoV-2 PCR tests (mostly from nose and throat swabs), either via the local Public Health England (PHE) Birmingham reference laboratory or in-house assays.[3,4] No asymptomatic testing was routinely performed during this period and those tested exhibited at least one or more of the following typical COVID-19 symptoms at the time of testing: fever, cough, myalgia, shortness of breath, sore throat, headache, chest tightness, fatigue, loss of taste and/or smell, abdominal discomfort and/or diarrhoea.

Hospital staff were mostly self-isolating at the time of testing or performing non-patient-facing duties. The community patient samples were collected by a mobile team consisting mostly of general practitioners, supported by East Midlands PHE team. This team travelled to the homes (during the day and out of hours) and took nose and throat swab samples of suspected COVID-19 cases who had called NHS 111, reporting COVID-19 compatible symptoms – including any recent relevant travel history to COVID-19 endemic areas. We decided to exclude children from the final analysis, as it is still uncertain what role they play in the transmission of SARS-CoV-2.[5] This meant that we excluded 658 test results from patients aged 0-17 years, of which only 30 were positive.

Thus, swab samples were obtained from symptomatic hospitalised and community–based patients, and hospital staff, with positivity rates as follows: 1674 positive cases (21.35%) out of 7840 hospitalised patients (**HOSP**) tested; 200 positive cases (48.70%) out of 411 community patients (**COMM**) tested; 152 positive cases (29.10%) out of 523 hospital staff (**STAF**) tested.

Our positivity rate for the cumulative total number of tests performed on hospitalised patients and hospital staff (21.35-29.10%) is slightly higher than that published by PHE on 5 May 2020 (under “Pillar 1: swab testing in PHE labs and NHS hospitals for those with a clinical need, and health and care workers”) of 18.5% (155,567/842,903).[6] The high positivity rate in our community patients is likely a result of a very targeted local COVID-19 testing program led by the NHS 111 and East Midlands PHE teams, where the COVID-19 case definition became relatively more sensitive and specific outside of our normal seasonal influenza period. The latter had ended earlier than usual this year in Leicester (effectively by the end of February 2020), making it more likely that any acute febrile influenza-like illness was due to COVID-19.

We can use these positivity rates obtained from these initially wholly suceptible populations,[7] during this exponential growth stage of the evolving COVID-19 epidemic (Fig. S1) to define the ‘attack rate’ (AR) as the proportion of infected individuals who develop symptoms during the early phase of an outbreak, in the absence of any intervention, by the formula:

$$R_0 = -\frac{\ln(1-AR)}{AR}$$

where R_0 is the basic reproductive number, which is the average number of secondary cases generated by a single index case in a wholly susceptible population, and ln is the natural logarithm.[8]

Thus, by solving the equation above for each of those populations we can derive a value for R_0 for each of these populations: R_0(HOSP) =1.13; R_0(COMM) =1.38; R_0(STAF)=1.21

During this early stage of the COVID-19 epidemic in this population, in the absence of any pre-existing immunity, we can equate R_0 to Rt, the effective reproductive number,[7,8] which describes the number of secondary cases in an evolving outbreak, taking into account various interventional factors, such as the use of handwashing, personal protective equipment, social distancing, as well as a non-uniformly distributed susceptible population.[9]

The data within each group (HOSP, COMM, STAF) was further age-stratified (18-49 years, 50-74 years, >75 years) and plotted with the changing value of Rt (Fig. 1).

From these plots we can see that the *Rt* value generally remains between 1-2 for all these populations, with wider fluctuations in the COMM population across all age groups, compared to the HOSP or STAF populations.

A value of $Rt>1$ indicates that the epidemic is still self-propagating, and further interventions are required to reduce the ongoing transmission of SARS-CoV-2 in that population, e.g. by increased social distancing measures (in the community patients), or more stringent adherence and/or additional infection control measures, such as improved ventilation (for hospital staff working within a hospital environment).

For the hospitalised patients, as for the hospital staff, *Rt* lies very close to 1, indicating that for these populations, the rate of new COVID-19 diagnoses – either from new COVID-19 patients being admitted or additional hospital staff getting infected – is still just around that required to maintain the ongoing COVID-19 epidemic, locally.

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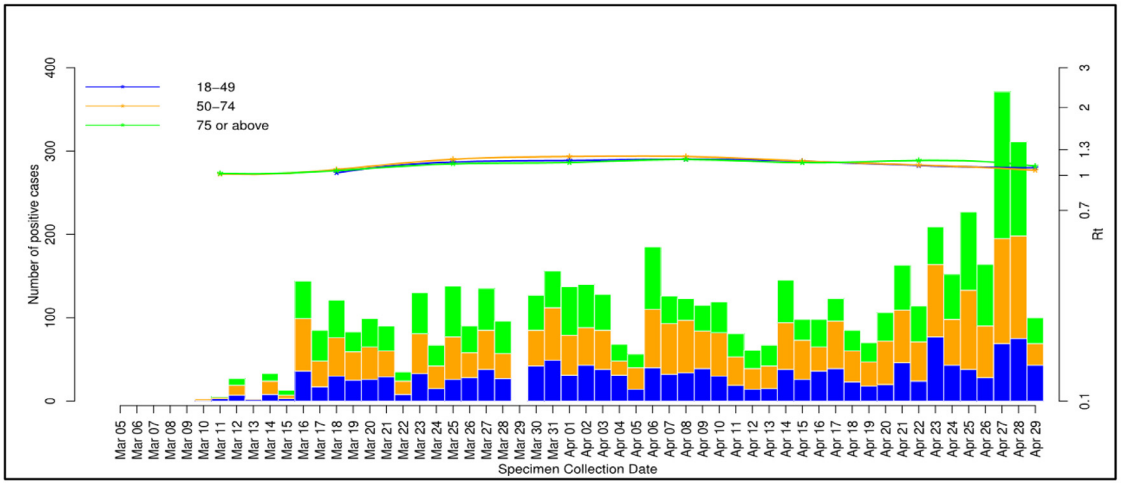
A.



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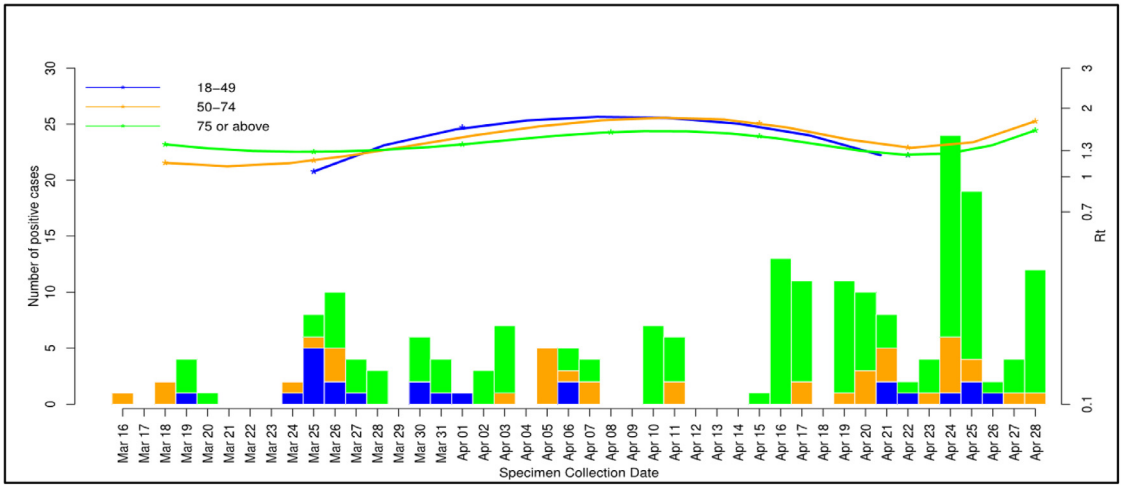

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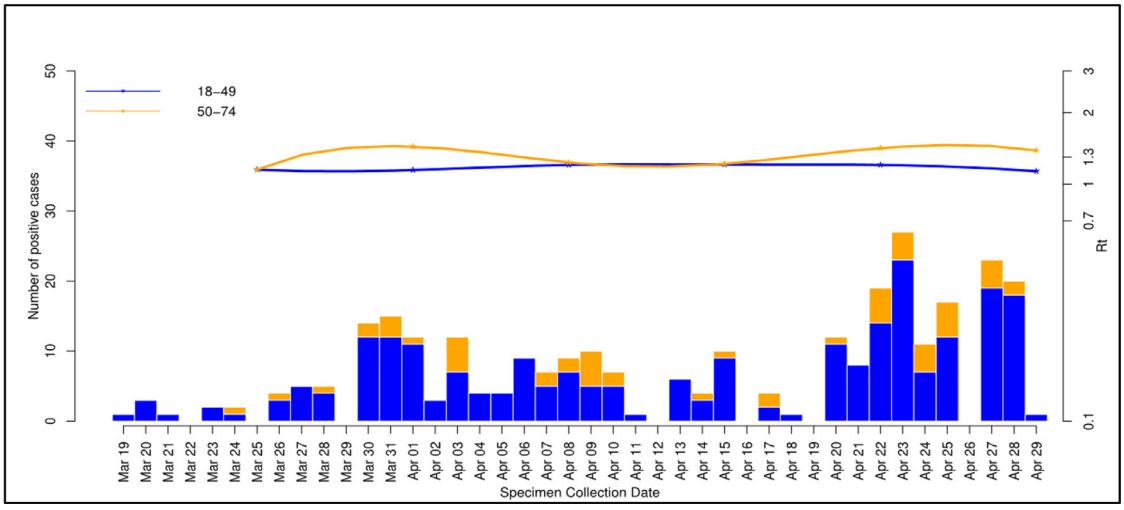

Fig. 1. Age-stratified (18-49 yrs, 50-74 yrs, >75 yrs) SARS-CoV-2 (COVID-19) positive cases (left vertical axis – linear scale) in hospitalised (**A** - HOSP) and community (**B** - COMM) patients, and staff (**C** - STAF) populations plotted over time. Effective reproductive number (*Rt* –right vertical axis – logarithmic scale) is plotted for each group with the same age-related colour code.

In summary, we have used our routinely collected diagnostic data on SARS-CoV-2 testing in suspected COVID-19 patients to derive some useful epidemiological parameters to understand better the characteristics of the evolving COVID-19 epidemic during its early exponential growth phase in our local population. These methods are easily applied by other teams where such SARS-CoV-2 testing data from the initial phase of the epidemic is available.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.05.029.

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Which cancer type has the highest risk of COVID-19 infection?

Dear Editor,

Zheng Z. et al. [1] showed their data of the risk factors of critical and mortal COVID-19 cases, but the malignancy was excluded, which is unsolid. Different cancer types have diverse risk of COVID-19 infection, maybe this is the reason they didn't get the positive result. Cancer patients are one of the susceptible people, and the mortality rate is high [2].

Carly G. K. Ziegle et al. [3] have shown that Angiotensin-Converting Enzyme 2 (ACE2) and Transmembrane Protease Serine 2 (TMPRSS2) are the receptors for SARS-CoV-2 to invade the human body, which are mainly located in the respiratory tract, lung, and intestines. But for cancer patients, not only are these organs at risk, but many tumor cells also express ACE2 and TMPRSS2.

Our pan-cancer analysis by using TIMER [4] showed that the expression levels of ACE2 in Esophageal carcinoma (ESCA), Kidney renal papillary cell carcinoma (KIRP), Lung adenocarcinoma (LUAD), Uterine Corpus Endometrial Carcinoma (UCEC) are high. Similarly, TMPRSS2 levels in Kidney Chromophobe (KICH), Prostate Adenocarcinoma (PRAD), Uterine Corpus Endometrial Carcinoma (UCEC) are also increased; hence the risk of COVID-19 infection in patients with these tumors is higher. We also found that only UCEC is co-expressing ACE2 and TMPRSS2 receptors; therefore, patients with UCEC carry the highest risk of COVID-19 infection (Fig. 1).

If the SARS-CoV-2 virus infects the tumor cells, it will be difficult to clear due to the inherent immune resistance in the tumor microenvironment. Numerous studies have shown that the longer the virus stays in the body, the more tissues and organs will be damaged directly or indirectly [5]. Though many tissues will not be invaded by the virus, inflammatory reactions such as cytokine storms can cause tissue damage. Also, the cytokine storm caused by COVID-19, such as IL-6, may promote the progression of the tumor, such as UCEC [6].

Currently, COVID-19 treatment is mainly supportive care even though there is a debate on the use of ACE inhibitors (ACEi) or Angiotensin Receptor Blocker (ARB) as a treatment option. Mortality rates for patients with hypertension not taking an ACEi or ARB, taking an ACEi, and taking an ARB were 26.7%, 32.7%, and 30.6%, respectively [5]. Studies have shown that Bruton Kinase (BTK) Inhibitors can reduce inflammation reaction by blocking the Toll-like receptors signaling pathways, which is a good choice for patients with lymphoma [7]. Cytokines can promote tumor progression, indicating cytokine inhibitors, such as anti-IL-6 (Tocilizumab), may bring more benefits to cancer patients.

This letter is, to our knowledge, the first to determine the risk of COVID-19 for patients with cancer by a pan-cancer analysis about the expression level of ACE2 and TMPRSS2, and want to provide some advices for clinical physicians.

In conclusion, patients with UCEC are at the highest risk of COVID-19 infection. ESCA, KIRP, LUAD, KICH, and PRAD are at high risk as well. At present, there is no guideline for the treatment of cancer patients with COVID-19 infection. Our findings indicate that in addition to the treatment of COVID-19 itself, the treatment of tumors may be necessary for cancer patients. Most importantly, close attention should be paid to patients with UCEC in determin-

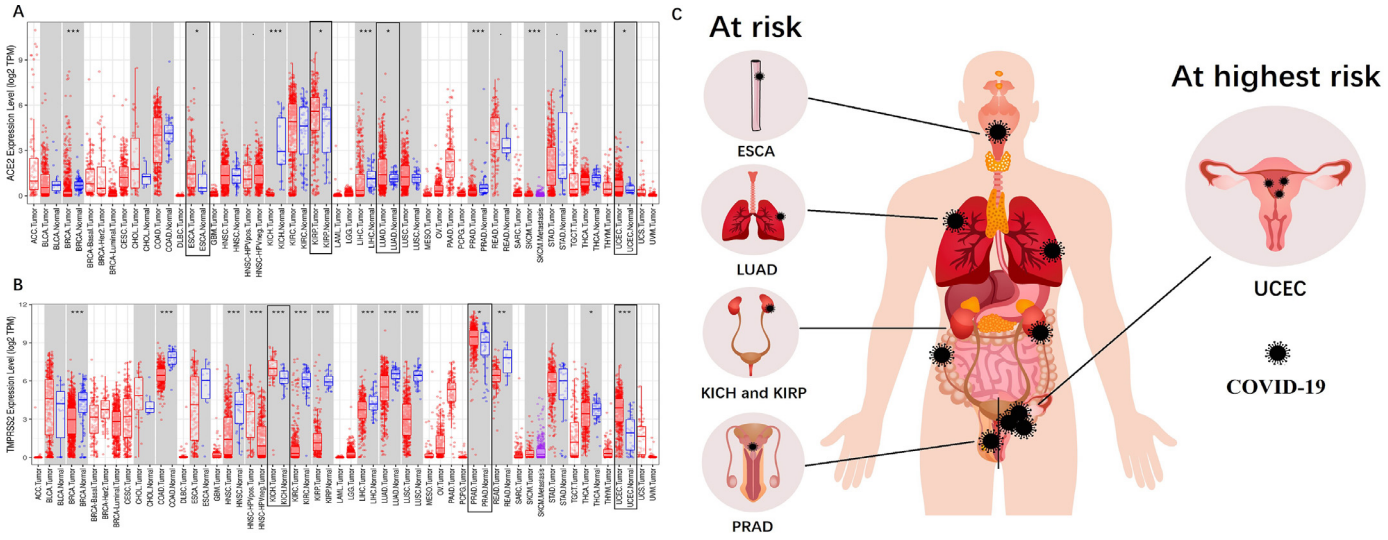

Fig. 1. Which cancer type has the highest risk of COVID-19 infection? (A) The expression level of ACE2 in pan-cancer analysis. (B) The expression level of TMPRSS2 in pan-cancer. (C) The body map of the risk of COVID-19 infection in cancer. (Esophageal carcinoma (ESCA), Kidney renal papillary cell carcinoma (KIRP), Lung adenocarcinoma (LUAD), Uterine Corpus Endometrial Carcinoma (UCEC), Kidney Chromophobe (KICH), Prostate adenocarcinoma (PRAD). P-value: $0 \leq$ *** $< 0.001 \leq$ ** $< 0.01 \leq$ * $< 0.05 \leq$. < 0.1)

ing whether they are cured of COVID-19. And to this effect, we suggest the use of a nucleic acid test of curettage specimens from the endometrium in addition to the nasal swab test.

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Nebulisers as a potential source of airborne virus

Dear Editor,

We were interested to read about environmental contamination by SARS-CoV-2 by Ye et al.[1] However, this study only investigated surface contamination and did not explore airborne contamination, which may also have led to surface contamination via settling.

Currently, in the context of COVID-19, nebuliser use is not considered as aerosol-generating procedure (AGP) by the World Health Organization (WHO)[2] or UK Public Health England (PHE),[3] though the US Centers for Disease Control and Prevention (CDC) does list nebulisation as an AGP.[4] Yet, when such masks are used, there are clearly visible 'smoke' plumes emanating from the mask side-vents during patient exhalations, which may act as a source of aerosols.[5]

We therefore tested this possibility, experimentally, using a licensed live-attenuated influenza vaccine (LAIV, Fluenz Tetra, AstraZeneca, Espoo, Finland) as a surrogate virus tracer.

We simulated a human patient using a heated manikin on a hospital bed in a full-scale mock isolation room with mixed ventilation at 12 air changes per hour (Fig. 1), wearing a home nebuliser mask (Titan Portable Home Nebuliser, 0.2 ml/min fluid, 6–8 L/min) nebulising distilled water.

The manikin was modified to continuously exhale at 10 L/min air, to simulate tidal breathing at a respiratory rate of ~14

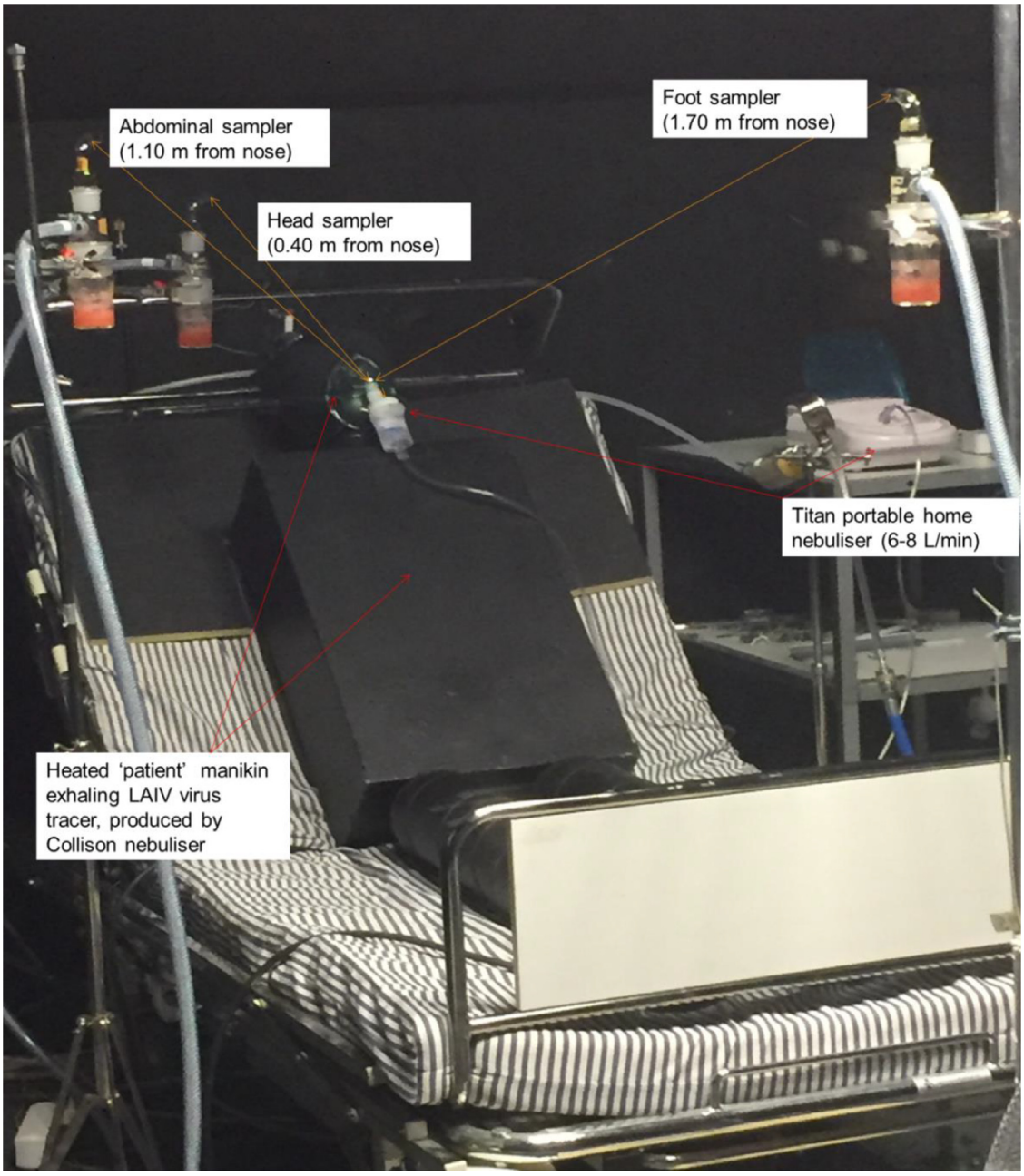

Fig. 1. Experimental layout of the heated 'patient' manikin, reclining on a bed. The positions of the three SKC biosamplers mimic healthcare worker positions during a typical ward round. LAIV – live-attenuated influenza virus.

breaths/min with a tidal volume of ~700 ml air. This exhalation flow was generated using a Collison nebuliser,[6] containing aerosols of the LAIV at a flow rate of 10 L/min.

Simultaneous air-sampling for 10 min, using three SKC biosamplers (SKC Ltd., Dorset, UK) running at 12 L/min, collected air samples into virus 20 ml transport medium (VTM) from three different locations around the bed. These positions were selected to simulate typical healthcare worker positions around a patient's bed during a clinical ward round, i.e. at distances of: 0.40 m (near the head), 1.10 m (near the abdomen) and 1.70 m (near the feet), from the manikin's nose and mouth (Fig. 1).

After sampling for 10 min (the duration of a typical nebuliser session) at 12 L/min (totalling 120 L air collected), the mean airborne viral load captured within the liquid VTM samples was detected and quantified using an influenza-specific digital polymerase chain reaction (PCR) assay (further details available upon request).

The experiment was run a total of 5 times over two days to give average viral loads at each of the SKC sampling locations: $7.34 \pm 0.28 \times 10^4$ copies/ml VTM (head), $2.09 \pm 0.41 \times 10^4$ copies/ml VTM (abdomen), and $1.41 \pm 0.23 \times 10^4$ copies/ml VTM (feet). Converting these averaged viral loads in copies/ml VTM to copies/L air (given that each air sample was obtained from a total air volume collection of 120 L), this gives approximately: 612 viruses/L (head), 174 viruses/L (abdomen), 118 viruses/L (feet).

These results show that aerosols from a nebulizer mask can spread throughout the room at a decreasing concentration with increasing distance from the source. This experiment was per-

formed within a ventilated experimental chamber with 12 ACH, which is typical of hospital, single-bedded isolation rooms.[7] However, in less well ventilated rooms, the airborne virus concentration may gradually increase over time,[8] potentially posing a hazard to healthcare workers entering the room to attend to the patient.

The use of nebulisers (and the very similar simple oxygen masks) is routine and widespread for patients presenting with respiratory problems on many general medical wards. The incoming oxygen airflow from these respiratory assist devices will periodically collide with the patient's outgoing virus-laden exhaled breath, causing plumes of mixed clean and contaminated air to be vented from the sides of these masks.

These findings indicate these respiratory assist devices, as per the US CDC guidelines,[4] should be considered as potential AGPs, as they can generate aerosols of airborne virus that can travel at least the length of a patient bed - further than those likely generated by normal breathing,[9] to potentially expose and infect others.

This is especially important during the current COVID-19 pandemic where large numbers of healthcare workers may be exposed to patients using these respiratory assist devices, and potentially become infected from aerosolised SARS-CoV-2.[5]

Acknowledgements

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Mesenchymal stem cell therapy in severe COVID-19: A retrospective study of short-term treatment efficacy and side effects

Dear Editor,

We read with interest the recent paper by Cantini et al., describing the safety and clinical impact of baricitinib therapy in Coronavirus disease 2019 (COVID-19).[1] COVID-19, caused by 2019 novel coronavirus (2019-nCoV), is increasing rapidly in an epidemic scale and has spread in over 200 countries, causing more than three million confirmed cases and two hundred thousand deaths as of May 5th, 2020. But currently, there is no vaccine against 2019-nCoV or effective treatment for COVID-19.[2]

The typical symptoms of COVID-19 are fever, cough and dyspnea, and the leading cause of mortality is acute respiratory distress syndrome (ARDS). As an immunopathologic event, ARDS is characterized by cytokine storm, which is an excessive systemic inflammatory response triggered by the release of proinflammatory cytokines.[3] Therefore, diminishing the cytokine storm may be an important part of treatment in patients with severe COVID-19.[4] Mesenchymal stem cells (MSCs) have been shown to possess powerful immunomodulatory properties and beneficial effects for preventing or reducing the cytokine storm.[5] Hence, MSCs therapy may be a promising option for the treatment of severe COVID-19. On this basis, we conducted a retrospective study to evaluate the treatment efficacy and side effects of MSCs therapy on severe COVID-19.

All hospitalized patients met the following criteria were consecutively recruited from February 20th, 2020 to March 30th, 2020: (1) definite diagnosis of severe COVID-19; (2) age≥18 years; (3) receiving MSCs therapy. All patients have signed written informed consent in line with the Declaration of Helsinki.

The diagnosis of severe COVID-19 was made according to the Guideline for Diagnosis and Treatment for COVID-19 of National Health Commission of China (version 5.0).[6] The detailed diagnostic criteria were one of the conditions 2 to 4 plus condition 1: (1) confirmation by real-time RT-PCR assay; (2) respiratory distress, RR≥30 beats/min; (3) oxygen saturation level≤93% in resting state; (4) arterial partial pressure of oxygen (PaO_2)/fraction of inspiration O_2 (FiO_2) ≤300 mmHg (1 mmHg=0.133 kPa).

Clinical grade MSCs were given at a dose of 1×10^6 mononuclear cells per kilogram of weight. Promethazine hydrochloride (intramuscular injection, 25 mg) was used before the injection of MSCs to prevent allergies. For patients received two or three times

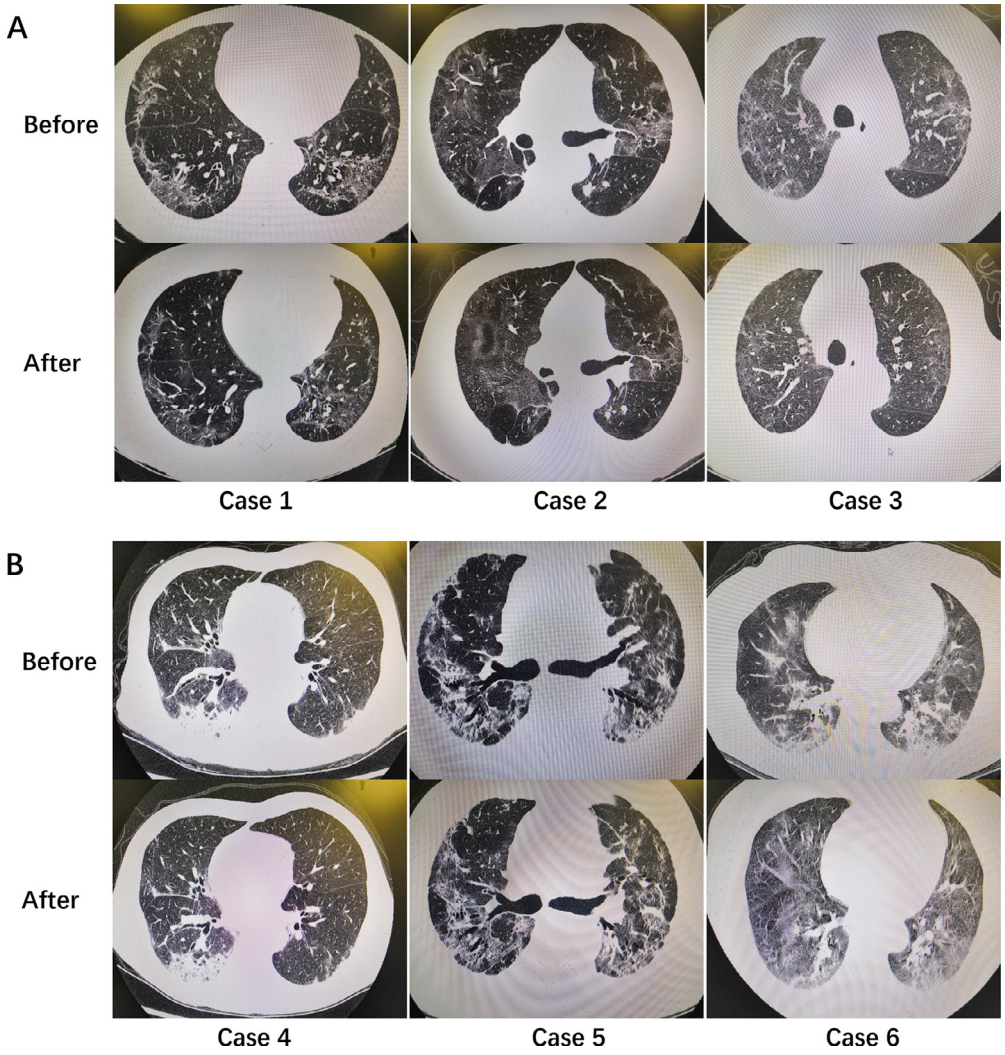

Fig. 1. Chest CT scans of severe COVID-19 cases before and after MSCs therapy. A, cases with apparently CT scan improvement; B, cases without apparently CT scan improvement.

MSCs therapy, the interval of injection was 5 days. Laboratory tests were conducted 2 to 3 h before the injection and 48 to 72 h after the injection.

Data were presented as mean±SD for continues variables with normal distribution, and median and interquartile range (IQRs) otherwise. Independent continuous variables were compared using the Student t-test or the Mann-Whitney test. Paired continuous variables were compared using the paired t-test or the Wilcoxon signed-rank test. Categorical variables were compared using the Chi-square test or the Fisher exact test (if any expected value <5). All of the analyses were conducted as 2-sided tests and $p<0.05$ was considered statistically significant.

Totally, 25 patients were enrolled according to the criteria. Among them, 20 cases (80%) were male and 5 cases (20%) were female. The median age was 70 (IQR: 59,71) years. Seven cases received MSCs therapy for one time, 7 cases received for two times and 11 cases received for three times. After MSCs therapy, 16 cases (64%) gained apparently CT scan improvement and all cases gained clinical improvement (Fig. 1). No fatalities occurred during hospitalization. However, 3 cases experienced treatment related side effects, specifically liver dysfunction, heart failure and allergic rash.

The laboratory findings before and after MSCs therapy were shown in Table 1. Inflammation indexes, including white blood cells (WBC) counts, C-reaction protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) did not change significantly after MSCs therapy. Similarly, significant changes of IgG and IgM were not found either. However, the serum levels of lactate (LAC), cardiac troponin T (cTnT) and creatine kinase-MB (CK-MB) elevated significantly after MSCs therapy ($p < 0.05$).

There are two main mechanisms of MSCs therapy for COVID-19. Firstly, MSCs could lodge in the pulmonary vascular bed after injection, release anti-inflammatory mediators and reduce the cytokine storm caused by viral infection.[7] Secondly, MSCs could secrete angiopoietin-1 and keratinocyte growth factor, which are pivotal in the restoration of alveolar capillary barriers disrupted by COVID-19.[8]

In our series, all the patients with severe COVID-19 survived and entered recovery after MSCs therapy, and only 3 patients experienced treatment side effects. This result indicated that MSCs therapy might be an effective therapeutic for severe COVID-19. However, none of the inflammation indexes changed significantly after MSCs therapy. The reason is unclear, may be related to three factors. Firstly, inflammation indexes, such as WBC counts and CRP were totally normal before MSCs therapy in most cases, which means that cytokine storm was mild to moderate and not serious in these cases. Secondly, relative studies have shown that MSCs will be cleared within 24 to 48 h after injection.[9] Nevertheless, in our study, laboratory tests were conducted 48 to 72 h after injection. As a result, we might miss the optimal time to track the changes of inflammation indexes. Thirdly, the inflammation in-

Table 1
Laboratory findings before and after MSCs therapy.

Variables	The 1th time			The 2th time			The 3th time		
	Before	After	*p*	Before	After	*p*	Before	After	*p*
WBC ($*10^9$/L)	6.3 ± 1.8	6.5 ± 2.0	0.475	7.1 ± 2.6	6.5 ± 1.6	0.315	6.0 ± 0.5	6.2 ± 0.7	0.186
CRP (mg/L)	1.8(0.5,8.9)	0.9(0.5,6.9)	0.287	0.6(0.5,6.8)	0.9(0.5,3.7)	0.678	0.8(0.5,1.1)	1.0(0.5,3.4)	0.484
PCT (ng/ml)	0.07(0.05,0.1)	0.07(0.05,0.09)	0.113	0.08±0.05	0.08(0.06,0.1)	0.221	0.07±0.02	0.07±0.02	0.108
IL-6 (pg/ml)	5.5(2.6,10.9)	5.2(2.8,9.1)	0.775	8.1 ± 6.1	6.9(3.9,15.0)	0.296	8.6 ± 6.0	7.1(3.0,13.6)	0.721
LAC (mmol/L)	1.8 ± 0.7	2.9 ± 1.2	**0.030**	2.1 ± 1.2	3.5 ± 1.5	**0.000**	3.0 ± 0.4	3.4 ± 1.2	0.782
ALT (U/L)	27.3(19.5,50.6)	30.0 ± 15.1	0.085	35.0 ± 17.1	31.7 ± 20.7	0.472	34.0 ± 16.4	32.4 ± 15.2	0.139
Cr (μmol/L)	54.6 ± 11.8	56.1 ± 12.0	0.293	55.8 ± 17.8	55.5 ± 19.5	0.867	65.6 ± 21.5	65.5 ± 18.2	0.923
cTnT (ng/ml)	12.7 ± 6.8	18.3 ± 13.4	**0.029**	9.6 ± 6.5	10.2 ± 9.2	0.686	2.3 ± 3.0	5.2 ± 2.1	0.132
CK-MB(μmol/L)	1.1(0.6,1.8)	0.9(0.8,1.9)	0.861	0.7 ± 0.2	0.8 ± 0.2	**0.031**	0.6 ± 0.2	0.3 ± 0.3	0.135
IgM (s/co)	0.8(0.5,1.7)	0.6(0.4,0.7)	0.343	0.8 ± 0.8	0.5(0.1,3.8)	0.715	0.5 ± 0.3	0.4 ± 0.2	0.424
IgG (s/co)	20.7(13.5,80.8)	32.4 ± 20.7	0.214	33.5 ± 28.3	27.2 ± 26.0	0.123	18.8 ± 15,3	13.2 ± 7.6	0.461

Values are presented as mean ± SD or median (P25, P75). WBC, White blood cells; CRP, C-reaction protein; PCT, procalcitonin; IL-6, interleukin-6; LAC, lactate; ALT, alanine aminotransferase; Cr, creatinine; cTnT, cardiac troponin T; CK-MB, creatine kinase-MB.

dexes tested and analyzed in this study were limited, and whether other cytokines like IL-2 and IL-7 would decrease after MSCs therapy is unknown.

Additionally, we found that the serum levels of LAC, cTnT and CK-MB were elevated significantly after MSCs therapy. The reason is unclear, but remind us that the use of MSCs therapy should be extremely cautious in patients with metabolic acidosis or coronary heart disease. Moreover, the infusion speed of MSCs must be slow enough. In this study, we injected MSCs saline solution at a speed of ~20 drops per minute, but there was still a patient experiencing heart failure while on treatment.

The major limitations of this study were small series, retrospective and no placebo. Therefore, additional prospective studies involving large cohort of patients are needed in order to confirm and supplement the present findings.

In conclusion, we suggested that MSCs therapy might be a promising option for the treatment of severe COVID-19, but should be used cautiously, especially in patients with metabolic acidosis or coronary heart disease.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Ethical standards

As a retrospective study and data analysis was conducted anonymously, written informed consent was not required in this study.

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High time for an efficient and effective internationally-supported Zoonosis Surveillance System?

Dear Editor,

Zhang et al's article[1] on the enormous importance of establishing the origin of the COVID-19 virus is timely, and prompts discussion of a broader issue around zoonotic illness which has appeared and re-appeared for many years without any satisfactory resolution.

Uncannily prophetically, while speaking at the 23rd Forum on Global Issues in 2009, Dr Margaret Chan of the World Health Organisation (WHO) said "Surveillance for emerging diseases contributes to global security. If basic surveillance and laboratory capacities are compromised, will health authorities catch the next SARS (severe acute respiratory syndrome), or spot the emergence of a pandemic virus in time to warn the world and mitigate the damage?"[2]

COVID-19 is of course a zoonosis, and the current desperate and damaging international situation makes it clear that a redoubling of international efforts on on-going surveillance for potential new emerging zoonoses remains vital. In fact since 1980 we have seen - among others – HIV-1, HIV-2, new variant Creutzfeld-Jacob Disease, avian influenza, swine influenza, SARS-1, Nipah virus, Sin Nombre virus, monkey pox, and MERS-CoV emerge out of animal populations and cause serious and even lethal human disease. COVID-19 arguably has already had more serious implications than all of its predecessors, - with 270,333 deaths recorded worldwide at the time of writing[3]- but what comes after it may be even worse. Put directly, we need to close the stable door before the horse has bolted.

In 2012, in a major report from the UK's DFID it was stated "the ability to detect and identify infection and disease is crucial for surveillance and as a prelude to intervention for controlling the disease."[4]

The massive worldwide medical and economic impacts of COVID-19 make it abundantly clear that the DFID report was correct, and what is badly needed is an efficient and effective worldwide integrated surveillance system for zoonotic disease which has the capability to identify the emergence of any serious new pathogens in human or animal populations anywhere in the world, and the power to act on the information, as early as is humanly possible and unimpeded by international borders.

The WHO certainly already has a vital role in this area,[5] but unfortunately the system is currently not as robust as it could be. A key further factor to take into account – and one that is increasingly widely appreciated – is that the WHO has long suffered from inadequate levels of funding to be able to deliver effectively on the massive remit it has to cover.[6]

To be able to achieve anything of genuine value going forward, this will not only require dedicated professional medical, veterinary, agricultural and scientific commitment but also serious domestic and international political and governmental support, with genuine inter-governmental cooperation at the highest levels. Furthermore, adequate and reliable financial support is a must.

However, it has - for a very long time - sadly been a truism that "political support for human development cannot be taken for granted."[7] Doctors and other healthcare workers are unlikely to be able to repair this problem themselves. Acquiring the necessary buy-in from the world of politics may well only be possible with people possessing the necessary expertise in how best to exert pressure (e.g. lobbying) at the highest levels of politics and international relations being brought in.[8]

However, the dire situation developing around the human race right now is sending out a powerful message that it would be worth it.

We all must start taking this seriously. In 2009, a National Research Council (US) report stated "An effective global, integrated zoonotic disease surveillance and response system currently does not exist."[2]

In 2020 it still doesn't. COVID-19 is telling us it should.

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Dyspnea rather than fever is a risk factor for predicting mortality in patients with COVID-19

Dear Editor,

Recently, the paper titled "Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis" was published in the Journal of Infection in April 2020. The results from Zheng et al. indicated that fever was negatively associated with the progression of COVID-19 such as severe illness and death (OR = 0.56, 95% CI [0.38–0.82], $P = 0.003$) and shortness

Table 1
Characteristics of the included studies.

Author	Location	Case	Non-survival patients					Survival patients				
			n	Age, years	Male	Fever	Dyspnea	n	Age, years	Male	Fever	Dyspnea
Yang X et al. P: 32105632	China	52	32	64.6 ± 11.2	21 (65.6)	31 (96.9)	21 (65.6)	20	51.9 ± 12.9	14 (70.0)	20 (100.0)	12 (60.0)
Zhou F et al. P: 32171076	China	191	54	69.0 (63.0–76.0)	38 (70.4)	51 (94.4)	NR	137	52.0 (45.0–58.0)	81 (59.1)	129 (94.2)	NR
Cao J et al. P: 32239127	China	102	17	72 (63–81)	13 (76.5)	12 (70.6)	NR	85	53 (47–66)	40 (47.1)	61 (71.8)	NR
Ruan Q et al. P: 32253449	China	150	68	67 (15–81)	49 (72.1)	59 (86.8)	59 (86.8)	82	50 (44–81)	53 (64.6)	68 (82.9)	51 (62.2)
Deng Y et al. P: 32209890	China	225	109	69 (62–74)	73 (67.0)	95 (87.2)	77 (70.6)	116	40 (33–57)	51 (44.0)	94 (81.0)	22 (19.0)
Zhang J et al. P: 32304745	China	663	25	67.1 (61–78)	15 (60.0)	19 (76.0)	11 (44.0)	638	59.1 (43–68)	306 (48.0)	508 (79.6)	150 (23.5)
Wu C et al. P: 32167524	China	84	44	68.5 (59.3–75.0)	29 (65.9)	39 (88.6)	29 (65.9)	40	50.0 (40.3–56.8)	31 (77.5)	39 (97.5)	21 (52.5)
Chen T et al. P: 32217556	China	274	113	68.0 (62.0–77.0)	83 (73.5)	104 (92.0)	70 (61.9)	161	51.0 (37.0–66.0)	88 (54.7)	145 (90.0)	50 (31.1)
Wang L et al. P: 32240670	China	339	65	76 (70–83)	39 (60.0)	56 (87.5)	38 (59.4)	274	68 (64–74)	127 (46.4)	255 (93.4)	100 (36.6)
Yuan M et al. P: 32191764	China	27	10	68 (63–73)	4 (40.0)	6 (60.0)	10 (100.0)	17	55 (35–60)	8 (47.1)	15 (88.2)	1 (5.9)
Leung C et al. P: 32353398	China	154	89	75 (67–81)	53 (59.6)	44 (67.7)*	25 (40.3)*	65	68 (66–74)	36 (55.4)	58 (90.6)*	4 (6.7)*
Wang D et al. P: 32354360	China	107	19	73.0 (64.0–81.0)	16 (84.2)	19 (100.0)	15 (78.9)	88	44.5 (35.0–58.8)	41 (46.6)	85 (96.6)	20 (22.7)
Yan Y et al. P: 32345579	China	48	39	70.5 ± 10.1	30 (76.9)	36 (92.3)	30 (76.9)	9	64.7 ± 7.3	3 (33.3)	7 (77.8)	3 (33.3)
Wang K et al. P: 32361723	China	296	19	65.6 ± 12.6	11 (57.9)	10 (52.6)	NR	277	46.0 ± 14.4	129 (46.6)	203 (74.9)*	NR
		44	14	69.0 ± 13.4	10 (71.4)	12 (100.0)*	NR	30	48.8 ± 14.2	14 (46.7)	27 (90.0)	NR
Tomlins J et al. P: 32353384	UK	95	20	77 (72–85)	12 (60.0)	12 (60.0)	NR	75	74 (56–82)	48 (64.0)	56 (74.7)	NR

All values are n (%), median (IQR), or mean±SD. P, PMID.
* data missing for patients; NR, not reported.

of breath/dyspnea was positively associated with the progression of COVID-19 such as severe illness and death (OR = 4.16, 95% CI [3.13–5.53], $P < 0.00001$),[1] which suggests that COVID-19 patients with fever may have a lower risk to develop to severe and critical disease outcomes and COVID-19 patients with dyspnea may have a higher risk to develop to severe and critical disease outcomes. However, Fu et al. observed that there was no statistically significant association between fever or shortness of breath and the severity of patients with COVID-19.[2] To unambiguously identify the risk factors for predicting mortality in patients with COVID-19, we carry out a meta-analysis to evaluate whether fever and dyspnea (not included shortness of breath) were associated with the risk of mortality in COVID-19 patients.

This meta-analysis was carried out based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. Li Shi and Ying Wang systematically searched the electronic databases, including Web of Science, Chinese National Knowledge Infrastructure (CNKI) and PubMed. These search engines were utilized to capture available literature by using the following three groups of keywords: “coronavirus 2019, 2019-nCoV, SARS-CoV-2, COVID-19″, “outcome, mortality” and “clinical”. The last search was conducted on May 4, 2020. Only articles reporting the number of COVID-19 patients with clinical symptoms of fever or dyspnea in the survival group and non-survival group were identified as eligible articles. All calculations were implemented with Stata 11.2 software. The pooled odds ratio (OR) with the corresponding 95% confidence interval (CI) was used to evaluate the risk of mortality in COVID-19 patients with fever or dyspnea. The robustness of the results was appraised by performing a sensitivity analysis. Both Begg’s test and Egger’s test were applied to evaluate publication bias.[3,4]

After selecting 1589 articles, 15 articles were finally obtained for this meta-analysis. As displayed in Table 1, data on 2851 COVID-19 patients (2114 survivors and 737 non-survivors) were available in these articles. The sample size ranged from 27 to 663. Most of the articles were performed in China, with the exception of one in the UK.

We found that dyspnea was significantly associated with higher mortality in COVID-19 patients on the basis of 11 studies with 2091 cases (OR = 4.34, 95% CI [2.68–7.05], $P < 0.001$; $I^2 = 69.2\%$, $P < 0.001$, random-effects model) (Fig. 1A). However, we did not observe a significant association between fever and the risk of mortality in patients with COVID-19 on the basis of 15 studies with 2818 cases (OR = 0.74, 95% CI [0.50–1.09], $P = 0.127$; $I^2 = 38.0\%$, $P = 0.062$, random-effects model) (Fig. 1B). As presented in sensitivity analysis, none of the individual studies significantly effected the overall OR, which proved the robustness of our results (Figs. 1C and D). No evidence of publication bias was provided by Begg’s test (dyspnea: $P = 0.350$ and fever: $P = 0.964$, respectively) and Egger’s test (dyspnea: $P = 0.294$ and fever: $P = 0.854$, respectively).

To our knowledge, the most common clinical symptoms were fever, cough, fatigue and dyspnea in COVID-19 patients.[5–7] Zheng et al. demonstrated that the proportion of fever was significantly lower in critical/mortal group compared with the non-critical group,[1] which suggests that fever may protect COVID-19 patients from developing to severe and critical disease outcomes. Fu et al. reported that the prevalence of fever in critical group was slightly higher than that in the non-severe group (80.8%, 95% CI [41.1–100.0]) vs. (71.2%, 95% CI [23.8–99.9]), but the difference was not statistically significant.[2] Our present study showed that fever was not significantly associated with the risk of mortality in COVID-19 patients. In addition, our study suggested that dyspnea was positively associated with the risk of mortality in COVID-19 patients. Taken together, dyspnea, rather than fever, is recommended as an indicator of poor outcome in COVID-19 patients, further well-designed studies with larger sample sizes are needed to validate the findings of our current study.

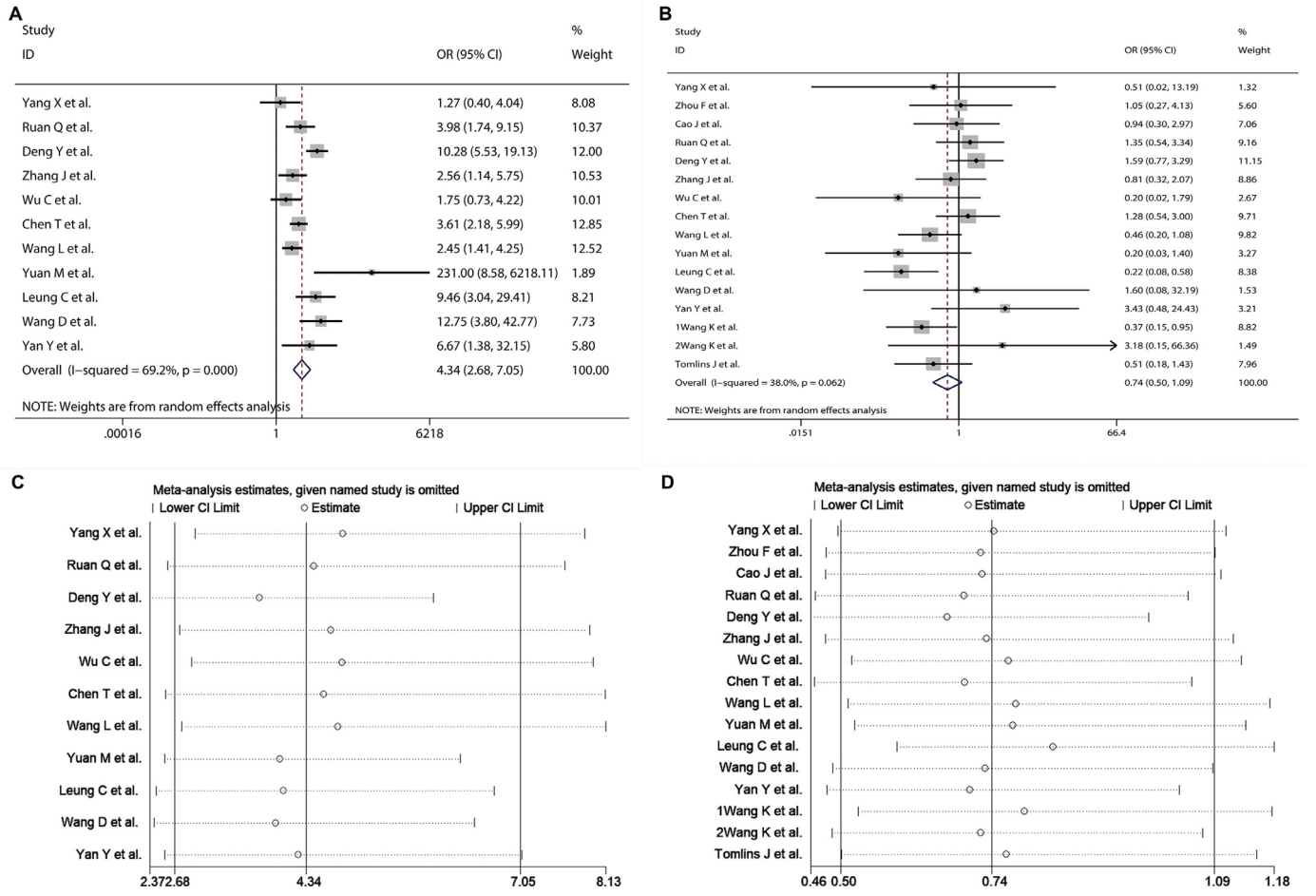

Fig. 1. The pooled odds ratio (OR) with the corresponding 95% confidence interval (CI) on the relationship between dyspnea (A) and fever (B) and the risk of mortality in COVID-19 patients. Sensitivity analysis for evaluating the relationship between dyspnea (C) and fever (D) and the risk of mortality in COVID-19 patients.

Contributors

LS, YDW, and HYY designed the study. LS and YW screened the literature and extracted the data. LS performed the meta-analysis and wrote the manuscript. HYY, YDW and GCD provided guidance and reviewed the manuscript. All authors have read and agreed the final manuscript.

Declaration of Competing Interest

All authors report that they have no potential conflict of interest.

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COVID-19 Follow up Testing ☆,☆☆,★

Dear Editor,

There is some uncertainty regarding the incubation period of the SARS-CoV-2 virus. There is also some uncertainly on the proportion of infected individuals who are asymptomatic carriers, and the timeframe from when a patient is infectious until becoming non-infectious.[1] We provide care for COVID-19 patients in the outpatient setting through a virtual clinic. Our patients have tested positive via nasopharyngeal swabs and RNA detection with RT-PCR. They are followed throughout their illness with visits at intervals based on the severity of their symptoms using telemedicine technology.

The CDC has two strategies to determine when a patient with COVID-19 can discontinue self-isolation. One is a "test-based" strategy, and the other is a "symptom-based" strategy. The symptom-based-strategy recommends that COVID-19 patients can discontinue self-isolation when they have been afebrile for 72 hours without anti-pyretic medications, have improvement in respiratory symptoms, and have at least 10 days elapse since symptoms started, recently increased from 7 days. The test-based strategy requires resolution of fever without the use of anti-pyretics, improvement of respiratory symptoms, and two consecutive negative COVID-19 nasopharyngeal swabs collected ≥24 hours apart.[2]

We decided as part of our COVID-19 Virtual Clinic to use the test-based strategy for all of our patients to better ensure that they were not contributing to the spread of disease. Our organization manufactures the test, so we had ample testing supplies and laboratory capacity. As this disease is a reportable condition, these patients were also followed by the respective county health departments. The county health departments were using the test-based strategy only for healthcare workers, or those with essential public service jobs.

As of April 17, 2020, we have enrolled 97 patients in our COVID Virtual Clinic. Of these, 72 have been tested after being afebrile for at least 72 hours, and had 7 days pass since symptoms started, along with symptom improvement. That is, 72 patients met criteria for the original release from self-isolation with the symptom-based-strategy, but were tested using the test-based strategy. Of these, twenty-two (30.1%) tested negative upon the first two tests, while the vast majority of patients (69.9%) tested positive at this interval. Of the 69.9% who failed, thirty-six (72%) were positive on the first test, while fourteen (28%) had a negative first test but were positive on the second test. In our patient population, the average time from the onset of symptoms to negative testing is 19 days.

This data shows that the CDC symptom-based-strategy may cause early release from isolation for COVID-19 patients and result in additional community transmission. Given this, it may be beneficial to prolong the self-isolation time to greater than 14 days after symptom onset.

Sincerely,
Amelita Woodruff, MD
Katherine Walsh PA-C, MPH
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Clinical and conceptual comments on "Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis"

Dear Editor,

Currently research on COVID-19 has been prioritised globally with a high frequency of the articles being published in the literature. The incidence of false-negative tests for 'happy hypoxia' in asymptomatic patients, evolving epidemiological characteristics, and the universal risk of infection in every single age group with unpredictable capricious outcomes, explains the need to explore the risk factors associated with the novel coronavirus. The systematic review and meta-analysis on COVID-19 by Zheng et al. contribute to this global research output, and attempts to inform clinical decision making during this crisis.[1] Nevertheless, there are a few recommendations that we would like to put forth in order to make the study robust enough to inform future decision making.

Few additional risk factors missing in the study

The epidemiology and clinical pattern of paediatric COVID 19 has a unique spectrum with infants and young children ≤ 5 years more likely to succumb to severe clinical symptoms of COVID19 than older children (i.e., ≥ 6 years). The immaturity of the immune system is cited as a plausible explanation.[1] Children can swiftly progress to acute respiratory distress syndrome (ARDS). They may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury.

The forgotten "Cancer"

The unprecedented outbreak of COVID-19 has caused a substantial risk for cancer patients who are immunocompromised due to the disease and its treatment.[2]

Fixed effect model of meta-analysis

We noted that the authors used the fixed-effect model to perform the meta-analysis. The fixed-effects model is practically

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applied when the studies across which the data is being pooled have, similar study parameters, and are devoid of any major heterogeneity. Hence, this model is often used to assess cohorts within a singular larger study. Nevertheless, the meta-analysis by Zhang et al., where multiple different studies are used, are inherently predisposed to heterogeneity due to the differential protocols and parameters of individual study. We propose the "random effects model" for this study.[3,4]

Analysis of heterogeneity

Furthermore, although the analysis of heterogeneity was conducted using the commonly used I^2 statistic, it may not have sufficient power by itself to determine between-study heterogeneity. The I^2 statistic has shown to be limited in its application; nonetheless we recommend the authors also asses heterogeneity via the Cochran's Q statistic and the Tau[2] statistic, which would add redundancy and robustness in the analysis of heterogeneity in this study.[5]

Publication bias

We also note that the authors fail to perform an analysis of publication bias as a mandatory application towards a mutable research subject where the bias of publication is likely to exist. Furthermore, systematic review and meta-analysis guidelines mandate the assessment of publication bias. Hence an analysis of publication bias also proposed for this study in order to achieve concrete results that can impact the clinical decision making.[6] We recommend the Eggers bias indicator test for lucid graphical assessment of publication bias.[7]

Competing Interest

The authors confirmed that they have no competing interests.

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Authors' contributions

RJ predominantly conceived this review and led the development of the letter to the editor. RJ, SSS and CK wrote the first draft of the letter, and GR, SSS, RRM, and PS critically revised and edited successive drafts of the manuscript. All authors read and approved the final version of the manuscript.

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Age but not sex may explain the negative effect of arterial hypertension and diabetes on COVID-19 prognosis

Dear Editor,

We read with great interest the article of Zheng and colleagues who summarized current evidence regarding risk factors for severe clinical forms of COVID-19.[1] The authors concluded that patients who are males, aged over 65 and smoking might face a higher risk of developing into the critical or mortal condition by COVID-19.[1] Besides, the authors highlighted that comorbidities such as hypertension, diabetes, cardiovascular and/or pre-existing respiratory diseases could also significantly affect the prognosis of the COVID-19.[1] Collectively, the authors confirmed the negative effect of comorbidities on the natural course of COVID-19. Nevertheless, there are some aspects that need to be carefully assessed, including the influence of essential demographic confounding variables such as age and sex, which are also strongly associated with the above mentioned comorbidities but unfortunately were not thoroughly included in the analysis.

Hence, to answer the question of whether age and sex may influence the effect size/s of pre-existing comorbidities on COVID-19 severe prognosis, we used the data of the Zheng and coworkers[1] as input to perform a meta-regression analysis. Of note, we found that the negative effect of underlying arterial hypertension on COVID-19 critical illness significantly and positively correlated with the age difference between critical/mortal and non-critical patients

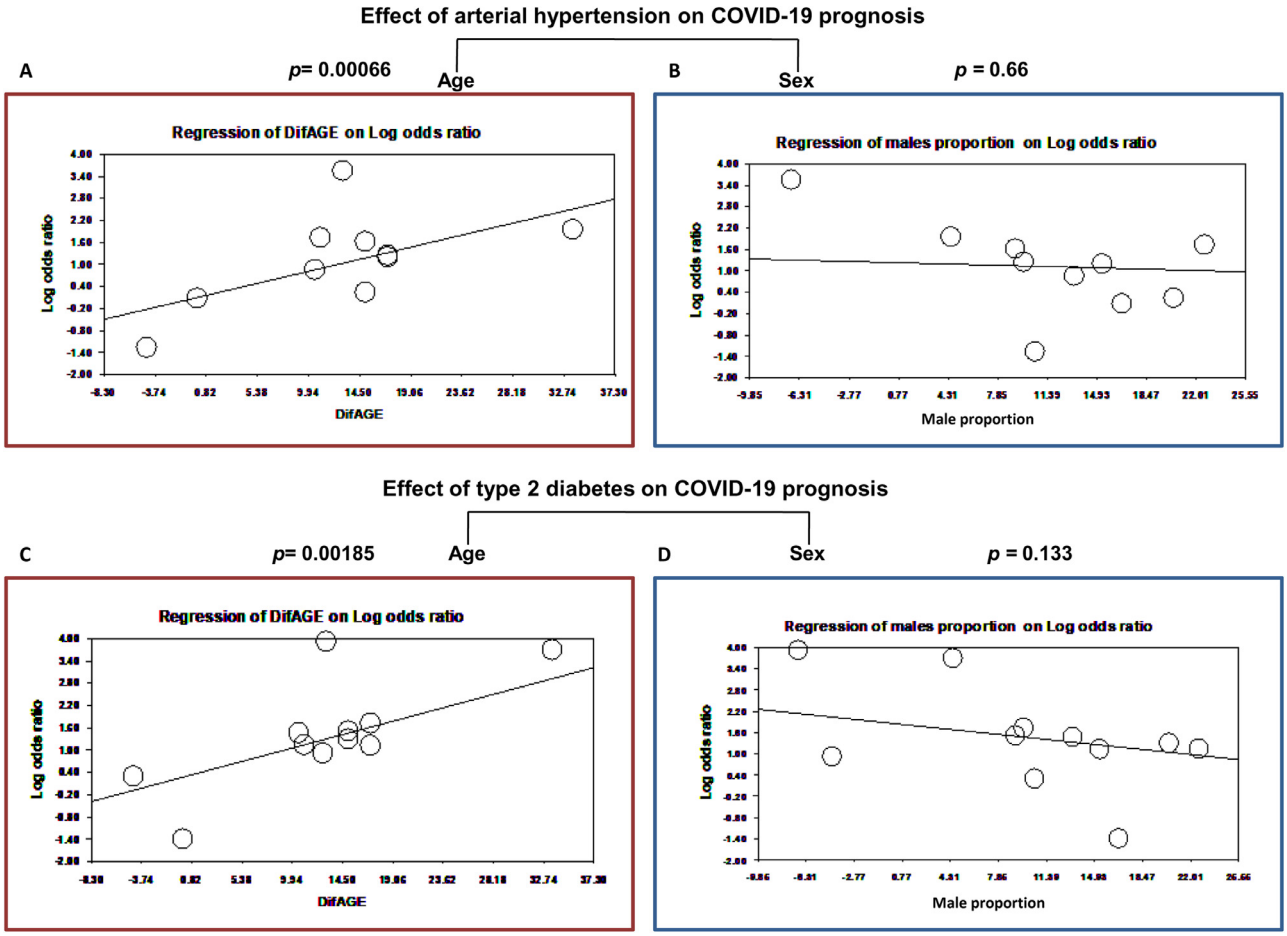

Fig. 1. Meta-regression analysis between the difference in age (DifAGE) and male proportion between the critical/mortal and non-critical groups of COVID-19 patients and the effect of comorbidities on COVID-19 critical illness among the studies.
Meta-regression was used to examine the impact of moderator variables (age and sex) on effect sizes using regression-based techniques. To determine the slope, we used meta-regression (methods of moments). Each circle represents a study according to the meta-analysis of Zheng et al.[1].

(slope±SE: 0.0718±0.021, p=0.00066) but not with the difference in male sex proportion (slope:-0.010±0.023, p=0.66) (Fig. 1, **A/B**). Likewise, the negative effect of type 2 diabetes on severe COVID-19 infection significantly and positively correlated with the age difference between the two groups (slope: 0.079±0.025, p=0.00185) but not with the difference in male proportion (slope: -0.040±0.027, p=0.133) (Fig. 1, **C**).

On the contrary, by meta-regression analysis, we found that the negative effect of pre-existing respiratory disease on COVID-19 critical illness significantly and positively correlated with the difference in male proportion (slope: 0.118±0.056, p= 0.034) but not with the age difference (slope: -0.030±0.048, p= 0.520).

Finally, we observed that the negative effect of pre-existing cardiovascular disease on severe COVID-19 clinical course is not influenced either by sex (slope: 0.0343±0.033, p= 0.300) or by age (slope: 0.048±0.033, p= 0.143).

In conclusion, there are three relevant messages to highlight. First, it is crucial to perform a meta-regression analysis to explain statistical heterogeneity in terms of study-level variables. Second, assessment of potential confounders, including essential demographic aspects, such as age and sex, are relevant to robustly demonstrate the putative association between variables, including assessment of disease risk and or severe prognosis. Most importantly, accurate assessment of confounding variables provides relevant information to stakeholders, including physicians and practitioners who need to take immediate action to reduce morbidity and mortality of COVID-19. Finally, assessment of the effect sizes of moderator variables on risk factors for severe COVID-19, including age and sex, may help to understand the biology of the disease in future larger studies.

Declaration of Competing Interest

We have no conflict of interest to declare.

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Acute kidney injury in hospitalized patients with coronavirus disease 2019 (COVID-19): A meta-analysis

Dear Editor,

We read with great interest the article by Zheng et al. published on 23 April 2020 in your esteemed journal. The authors conducted a meta-analysis to identify risk factors that could predict severe disease and mortality in patients with coronavirus disease 2019 (COVID-19). In their meta-analysis, using data from three studies, the authors reported that having a creatinine level of 133 µmol/L or more was associated with higher odds of having severe disease or mortality.[1] Some literature suggests that the risk of acute kidney injury (AKI) in patients with COVID-19 is low. However, when AKI develops, it is usually an indicator of more severe disease and multi-organ dysfunction.

Multiple observational studies have been published that have reported the clinical features of hospitalized COVID-19 patients such as acute respiratory distress syndrome. However, studies that have reported the incidence of AKI are scant. In our study, we take one step further to quantitatively synthesized available literature and performed a single-arm meta-analysis of proportions to report the pooled incidence rate of AKI and renal replacement therapy (RRT) use in hospitalized patients with COVID-19.

The meta-analysis was performed in accordance to the Meta-analysis of Observational Studies in Epidermiology (MOOSE) guidelines. A comprehensive literature search was performed on PubMed, Embase, Scopus and Web of Science to identify articles from 1 Jan 2020 till 20 April 2020. Backward reference searching was also performed. Various combinations and permutations of the following search terms “coronavirus”, “COVID-19″, “SARS-COV-2″, “2019-nCOV”, “acute kidney injury” and “acute renal failure” were used. Two authors (JJN and YL) independently screened the articles and any disagreements were resolved by consensus between all authors. We included observational studies that reported the pooled incidence rates of AKI and RRT use in hospitalized patients with proven COVID-19. We excluded studies that were not peer-reviewed or did not utilize the KDIGO definition for AKI. Relevant data from articles that were included after full-text review were extracted by a single author (KP) and verified by another (JJN). Data such as study design, sample size, patient demographics and incidence of AKI and RRT use were extracted. The Newcastle-Ottawa Scale was used to assess the quality of the included articles.

The primary outcomes in this study are the pooled incidence rates of AKI in an overall hospital and intensive care unit (ICU) setting. The secondary outcomes are the pooled incidence rates of RRT use in an overall hospital and ICU setting. Meta-analysis of proportions was performed using a random-effects model with Freeman-Tukey double arcsine transformation for variance stabilization. All analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA).

A total of nine studies were included (Table 1)[2–10]. Three studies were prospective in nature, while six were retrospective. Most studies originated from China, except for one study from the United States of America. Seven studies included all patients that were hospitalized, whilst two studies included only patients admitted to an intensive care unit.

Seven studies reported the incidence of AKI in an overall hospital setting, varying from 0% to 14.7%.[3–8,10] AKI occurred in 86 out of 2702 hospitalized patients. Meta-analysis of proportions revealed a pooled incidence rate of AKI of 3% (95% C.I. 1% - 7%, $I^2 = 93.8\%$) in all hospitalized patients (Fig. 1A). Four studies reported the incidence of AKI in an ICU setting, varying from 8.3% to 28.8%.[2,5,8,9] AKI occurred in 25 out of 122 ICU patients. Meta-analysis of proportions revealed a pooled incidence of AKI of 19% (95% C.I. 9% - 31%, $I^2 = 49.6\%$) in ICU patients (Fig. 1B).

Six studies reported the incidence of RRT use in an overall hospital setting, varying from 0.5% to 7.3%.[4–8,10] RRT was used in 31 out of 2001 hospitalized patients. Meta-analysis of proportions revealed a pooled incidence of RRT use of 2% (95% C.I. 1% - 4%, $I^2 = 80.8\%$) in hospitalized patients. Only three studies reported the incidence of RRT use in an ICU setting, varying from 5.6% to 23.1%.[5,8,9] RRT was used in 14 out of 101 ICU patients. Meta-analysis of proportions revealed a pooled incidence of RRT use of 13% (95% C.I. 4% - 25%, $I^2 = 47.5\%$).

We found that the overall risk of AKI in all hospitalized patients seemed to be low with a pooled incidence rate of 3%. This risk increases to 19% when patients are admitted to the ICU. Correspondingly, we found that the need for RRT in all hospitalized patients to be low with a pooled incidence of 2%. In ICU, the need for RRT increases to 13%. This is the first study that reported the pooled incidence rates of AKI and RRT use in an overall hospital and ICU specific setting. Although we cannot compare the pooled incidence rates of AKI and RRI between a general hospital and ICU setting, there is certainly an association between the development of AKI and ICU admission. Data from this study can potentially help in resource planning as the COVID-19 pandemic continues to affect multiple countries. This study also highlights the paucity of AKI data from the rest of the world as most studies are from mainland China.

There are, however, limitations to this study. A large majority of the included studies are from China and the results of this meta-analysis may not be applicable to other regions of the world. Second, some of the outcomes in this study had a high I^2 value signifying significant variability in the effect sizes of the included studies. This may be explained by variations in study design, study population, or even viral genotype. In conclusion, we report the pooled incidences of AKI and the need for RRT in an overall hospital and ICU setting for patients diagnosed with COVID-19. More high-quality data is needed to better understand the risk of AKI and its implication on prognosis and mortality in COVID-19 patients.

Table 1
Summary of characteristics of included studies.

	Location	Study design	Study Setting	N	Age	Male	DM[a]	HTN[b]	CKD[c]	ICU[d] Admission	Mortality	AKI[e], total	AKI, ICU	RRT[f], total	RRT, ICU
Arentz[2], 2020	USA	ROS[g]	ICU	21	70[i] (43–92)[l]	11 (52.4%)	7 (33.3%)	NR[i]	10 (47.6%)	NA[j]	11 (52.4%)[k]	NA	4 (19.1%)	NA	NR
Cheng[3], 2020	China	POS[h]	Hospital	701	63 (50–71)	367 (52.4%)	100 (14.3%)	233 (33.4%)	14 (2.0%)	73 (10.4%)	113 (16.1%)	36 (5.1%)	NR	NR	NR
Guan[4], 2020	China	ROS	Hospital	1099	47 (35–58)	637 (58.1%)	81 (7.4%)	165 (15.0%)	8 (0.7%)	55 (5.0%)	15 (1.4%)	6 (0.5%)	NR	9 (0.8%)	NR
Huang[5], 2020	China	ROS	Hospital	41	49 (41–58)	30 (73.2%)	8 (19.5%)	6 (14.6%)	NR	13 (31.7%)	6 (14.6%)	3 (7.3%)	3 (23.1%)	3 (7.3%)	3 (23.1%)
Shi[6], 2020	China	POS	Hospital	416	64 (21–95)[m]	205 (49.3%)	60 (14.4%)	127 (30.5%)	14 (3.4%)	NR	57 13.7%	8 (1.9%)	NR	2 (0.5%)	NR
Wang[7], 2020	China	POS	Hospital	116	54 (38–69)	67 (57.8%)	18 (15.5%)	43 (37.1%)	5 (4.3%)	11 (9.5%)	7 (6.0%)	0 (0%)	NR	5 (4.3%)	NR
Wang #2[8], 2020	China	ROS	Hospital	138	56 (42–68)	75 (54.3%)	14 (10.1%)	43 (31.2%)	4 (2.9%)	36 (26.1%)	6 (4.3%)	5 (3.6%)	3 (8.3%)	2 (1.4%)	2 (5.6%)
Yang[9], 2020	China	ROS	ICU	52	59.7[l] ±13.3[n]	35 (67.3%)	9 (17.3%)	NR	NR	NA	32 (61.5%)[k]	NA	15 (28.8%)	NA	9 (17.3%)
Zhou[10], 2020	China	ROS	Hospital	191	56 (46–67)	119 (62.3%)	36 (18.8%)	58 (30.4%)	2 (1.0%)	50 (26.2%)	54 (28.3%)	28 (14.7%)	NR	10 (5.2%)	NR
Pooled incidence rate after meta-analysis of proportions (95% confidence intervals)												3% (1% - 7%)	19% (9% to 31%)	2% (1% - 4%)	13% (4% - 25%)

Age is represented in median (interquartile range) unless otherwise specified
[a]Diabetes mellitus.
[b] Hypertension.
[c] Chronic kidney disease.
[d] Intensive care unit.
[e] Acute kidney injury.
[f] Renal replacement therapy.
[g] Retrospective observational study.
[h] Prospective observational study.
[i] Not reported.
[j] Not applicable.
[k] Intensive care unit specific mortality.
[l] Data represented as mean.
[m] Data represented as range.
[n] Data represented as standard deviations.

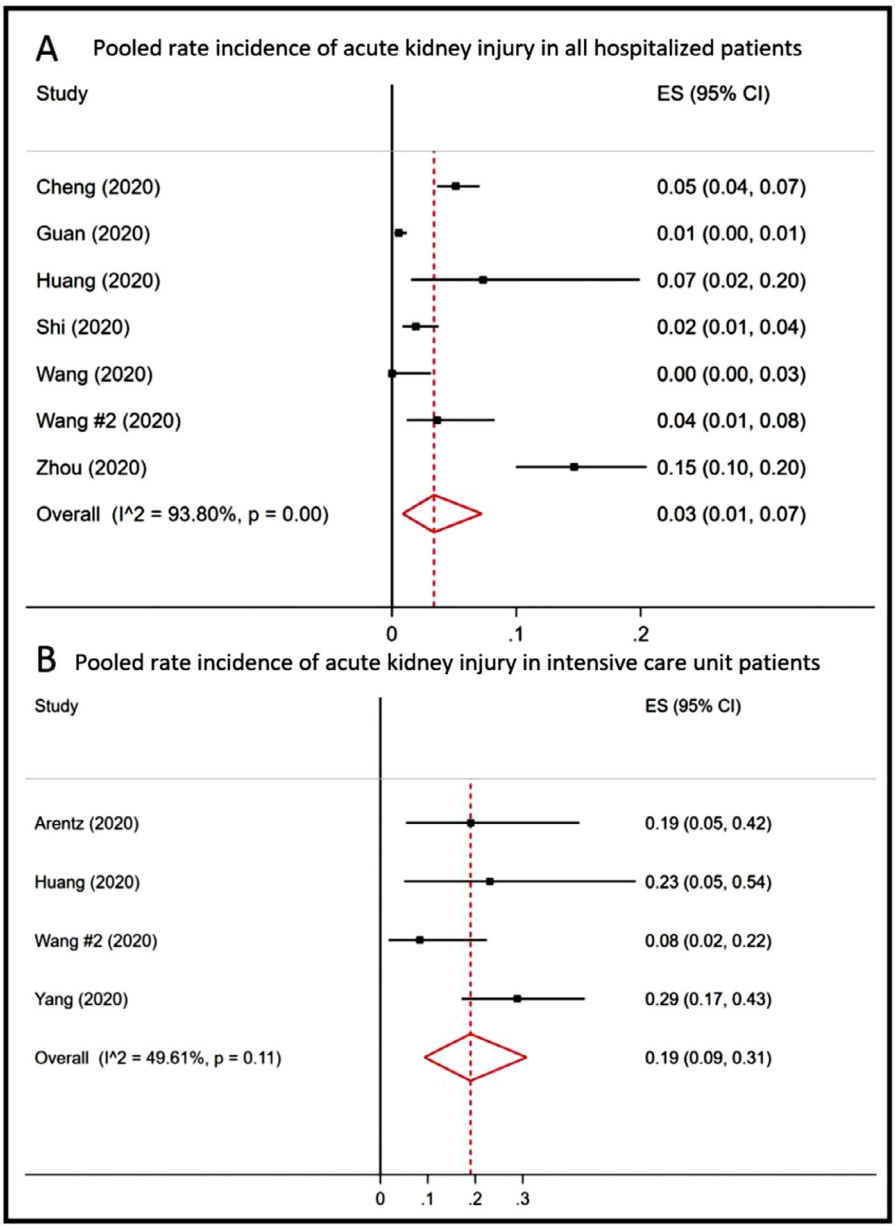

Fig. 1. Forest plot showing pooled rate incidences of acute kidney injury in (A) all hospitalized patients and (B) intensive care unit patients after meta-analysis of proportions.

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Declaration of Competing Interest

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Comparison of CRB-65 and quick sepsis-related organ failure assessment for predicting the need for intensive respiratory or vasopressor support in patients with COVID-19

Dear Editor,

We read the recent published paper by Chen and colleagues in journal of Infection with great interest, which described the clinical progression of patients with COVID-19 in Shanghai, China.[1] Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) emerged in Wuhan, China and spread globally to become a public health emergency of international concern.[2] Patients with COVID-19 tend to progress after onset of symptoms within 7 days[1] and severe type may rapidly progress to acute respiratory distress syndrome (ARDS) or end-organ failure.[3,4] Therefore, early and simple identification of patients who require intensive respiratory or vasopressor support (IRVS) would be of considerable value during the outbreak of the COVID-19 crisis. Thus far, there are no effective severity assessment tools for patients with COVID-19.

Here, we performed a retrospective single-center study to compare the performance of simple score systems such as quick sepsis-related organ failure assessment (qSOFA), the CURB-65 score adopted by the British Thoracic Society, and its simpler versions (CRB and CRB-65) to predict the need for IRVS in patients with COVID-2019. Patients with confirmed COVID-19 and age ≥18 years hospitalized between February 7, 2020 and February 17, 2020 in Renmin Hospital of Wuhan University were screened in this study. Patients were excluded if they died within 48 h of admission, were pregnant, or had a Do Not Resuscitate (DNR) order. Baseline demographics, co-morbidities, clinical symptoms or signs, vital signs, laboratory results on admission, and outcomes were collected. The CRB, CRB-65, CURB-65 and qSOFA scores were calculated on basis of demographic and clinical characteristics of each patient.

A total of 116 patients were eventually included for this study. The baseline characteristics are presented in Table 1. The median age of this cohort was 63[IQR 51 to 72] and 47.4% patients were males. The most common symptom was fever (86.2%), followed by fatigue (85.3%) and cough (69.0%). On admission, the median scores of CRB, CRB-65, CURB-65, and qSOFA were 0[0,1], [0,1], 1[0,2] and 1[0,1], respectively. A total of 25 (21.6%) patients needed IRVS during the period of hospital stay. Patients with IRVS had higher CRB (1[0,2] vs. 0[0,0], $P<0.001$), CRB-65 (2[1,3] vs. 1[0,1], $P<0.001$), CURB-65 (3[2,3] vs. 1[0,1], $P<0.001$), and qSOFA scores (1[1,2] vs. 1[0,1], $P=0.001$) than non-IRVS patients. The hospital mortality rate in this cohort was 7.8%. The median length of hospital stay was 29 [18,36] days.

ROC curve analyses were performed to evaluate the performance of four simple score systems to predict the need for IRVS. The AUC, optimal cut-off value, sensitivity, specificity, and positive and negative predictive values of each score system were shown in Table 2. The optimal cut-off score of CRB-65 for prediction of IRVS was 2, which provided sensitivity of 64% and specificity of 93.4%. The AUC values of the CRB-65 score in predicting the need for IRVS were much higher than those for the qSOFA score (0.81 ± 0.05 vs. 0.70 ± 0.06, $P=0.02$). The CRB-65 had higher AUC values than CRB score for IRVS prediction, however, the difference was not statistically significant (0.81 ± 0.05 vs. 0.77 ± 0.05, $P=0.22$). The AUC values were comparable between CRB-65 and CURB-65 for IRVS prediction (0.81 ± 0.05 vs. 0.85 ± 0.05, $P=0.08$).

To the best of our knowledge, the present study is the first to investigate the predictive performance of simple score systems in patients with COVID-19. In this study, the CRB-65 score could better identify patients with COVID-19 at risk for IRVS than the qSOFA score. The CRB score contains the same three clinical parameters used in qSOFA score (confusion, respiratory rate, and blood pressure). However, the thresholds for tachypnea and hypotension in CRB were stricter than the qSOFA score (respiratory rate ≥ 30/min in CRB vs. ≥ 22/min in qSOFA; blood pressure: systolic blood pressure ≤ 100 mmHg in qSOFA vs. < 90 $mmHg_{sys}$ or ≤ 60 $mmHg_{dias}$ in CRB). It seems that qSOFA is more accurate than the CRB score for predicting IRVS. However, in this study, the AUC values of CRB and qSOFA scores were comparable without statistically significant differences. After including the parameter of age, the CRB-65 score performed better than the qSOFA score in predicting requirement of IRVS. As age ≥ 65 years was included in the CRB-65 score, it provided additional predictive performance compared with the CRB score. This result was supported by previous reports, which showed that age was an independent risk factor for mortality in patients with COVID-19.[5,6]

The CRB-65 score has been reported to have a similar predictive performance to that of the CURB-65 and PSI scores in predicting the severity of CAP.[7–9] In our study, the CRB-65 and CURB-65 scores also had a similar prognostic value in predicting the receipt of IRVS. The CRB-65 score makes it easy to assess the severity of COVID-19 without the limit of laboratory data for blood urea nitrogen especially in the pandemic of COVID-19, thereby allowing earlier triage decisions.

In conclusion, the CRB-65 score could better identify patients with COVID-19 at risk for IRVS than the qSOFA score. The CRB-65 may be a useful score tool for COVID-19 because of its simplicity in application especially in emergent and complicated conditions.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Table 1
Clinical characteristics of COVID-19 patients.

	Entire cohort	No need for IRVS	Need for IRVS	*P* value
Number of patients	116	91	25	
Age (years)	63[51, 72]	61[48,69]	72[63,81]	<0.001
Gender (male), n (%)	55(47.4)	42(46.2)	13(52)	0.66
Smoking history, n (%)	10(8.6)	9(9.9)	1(4)	0.69
Comorbidities				
Hypertension, n (%)	38(32.8)	25(27.5)	13(52)	0.03
Diabetes mellitus, n (%)	20(17.2)	15(16.5)	5(20)	0.77
CAD, n (%)	12(10.3)	9(9.9)	3(12)	0.72
COPD, n (%)	2(1.7)	0(0)	2(8)	0.05
Cerebrovascular disease, n (%)	2(1.7)	1(1.1)	1(4)	0.39
Chronic renal disease, n (%)	4(3.4)	3(3.3)	1(4)	1.00
Signs and symptoms				
Fever, n (%)	100(86.2)	76(83.6)	24(96)	0.19
Cough, n (%)	80(69.0)	62(68.1)	18(72)	0.81
Sputum production, n (%)	15(12.9)	11(12.1)	4(16)	0.74
Fatigue, n (%)	99(85.3)	76(83.5)	23(92)	0.36
Headache, n (%)	6(5.2)	6(6.6)	0(0)	0.34
Dyspnea, n (%)	66(56.9)	44(48.4)	22(88)	<0.001
Nausea or vomiting, n (%)	25(21.6)	18(19.8)	7(28)	0.41
Diarrhea, n (%)	23(19.8)	18(19.8)	5(20)	1.00
Anorexia, n (%)	8(6.9)	2(2.2)	6(24)	0.001
Myalgia or arthralgia, n (%)	10(8.6)	8(8.8)	2(8)	1.00
Onset of symptom to hospital admission	12[9,16]	12[9,17]	10[7,16]	0.08
Vital signs at hospital admission				
Altered mental status, n (%)	6(5.2)	0(0)	6(24)	<0.001
Heart rate, beats/minute	90[79, 102]	86[78,100]	96[86,107]	0.02
Respiratory rate, breaths/minute	23[20,29]	22[20,25]	32[22,35]	<0.001
Systolic blood pressure, mm Hg	132[122,145]	131[122, 144]	137[121,152]	0.38
Diastolic blood pressure, mm Hg	78[68,84]	79[69,84]	74[66,91]	0.98
Severity of illness scores at hospital admission				
CRB	0[0,1]	0[0,0]	1[0,2]	<0.001
CRB-65	1[0,1]	1[0,1]	2[1,3]	<0.001
CURB-65	1[0,2]	1[0,1]	3[2,3]	<0.001
qSOFA	1[0,1]	1[0,1]	1[1,2]	0.001
Blood urea nitrogen, mmol/L	4.85[3.91, 6.30]	4.67[3.69,5.84]	7.35[4.85,9.28]	<0.001
Respiratory support				
High flow nasal cannula, n (%)	24(20.7)	0(0)	24(96)	<0.001
Non-invasive mechanical ventilation, n (%)	5(4.3)	0(0)	5(20)	<0.001
Invasive mechanical ventilation, n (%)	8(6.9)	0(0)	8(32)	<0.001
Renal replacement therapy, n (%)	3(2.6)	2(2.2)	1(4)	0.52
Extracorporeal membrane oxygenation, n (%)	1(0.9)	0(0)	1(4)	0.22
Need for vasopressor support, n (%)	9(7.8)	0(0)	9(36)	<0.001
Need for IRVS, n (%)	25(21.6)	0(0)	25(100)	<0.001
Hospital mortality, n (%)	9(7.8)	0(0)	9(36)	<0.001
Hospital length of stay, days	29[18,36]	28[18,33]	38[8,49]	0.18

Continuous variables are shown as the mean ± SD or median [IQR], as appropriate. Categorical variables are shown as number (%).
COVID-19, coronavirus disease 2019; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRB, confusion, respiratory rate, and blood pressure; CRB-65, confusion, respiratory rate, blood pressure and age ≥65 years; CURB-65, confusion, urea nitrogen, respiratory rate, blood pressure and age ≥65 years; SOFA, Sepsis-related Organ Failure Assessment; qSOFA, quick Sepsis-related Organ Failure Assessment; IRVS, intensive respiratory or vasopressor support.

Table 2
Performance of variables in predicting clinical outcomes.

Outcomes	Predictors	AU ROC	95% CI	P	Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV	LR+	LR-
Need for IRVS	**CRB**	**0.77 ± 0.05**	**0.69-0.85**	**<0.001**	**1**	**72**	**79.1**	**48.6**	**91.1**	**3.45**	**0.35**
	CRB				2	28	96.7	70	83	8.49	0.74
	CRB-65	0.81 ± 0.05	0.73-0.88	<0.001	1	88	45.1	30.6	93.2	1.6	0.27
	CRB-65				**2**	**64**	**93.4**	**72.7**	**90.4**	**9.71**	**0.39**
	CRB-65				3	24	97.8	75	82.4	10.92	0.78
	CURB-65	0.85 ± 0.05	0.77-0.91	<0.001	1	88	42.9	29.7	92.9	1.54	0.28
	CURB-65				**2**	**80**	**87.9**	**64.5**	**94.1**	**6.62**	**0.23**
	CURB-65				3	52	96.7	81.2	88	15.77	0.5
	CURB-65				4	12	98.9	75	80.4	10.92	0.89
	qSOFA	**0.70 ± 0.06**	**0.60-0.78**	**<0.001**	**1**	**80**	**47.3**	**29.4**	**89.6**	**1.52**	**0.42**
	qSOFA				2	24	98.9	85.7	82.6	21.84	0.77

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LR, likelihood ratio; PPV, positive predictive values; NPV, negative predictive value; CRB, confusion, respiratory rate, and blood pressure; CRB-65, confusion, respiratory rate, blood pressure and age ≥65 years; CURB-65, confusion, urea nitrogen, respiratory rate, blood pressure and age ≥65 years; qSOFA, quick Sepsis-related Organ Failure Assessment; IRVS, intensive respiratory or vasopressor support. Bold: the optimal cut-off values according to Youden index.

AUC comparisons

CRB-65 vs. qSOFA, *P*=0.02; CRB-65 vs. CRB, *P*=0.22; CRB-65 vs. CURB-65, *P*=0.08; CRB vs. qSOFA, *P*=0.09.

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Validity of the UK early access to medicines scheme criteria for Remdesivir use in patients with COVID-19 disease

Dear Editor,

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) released its Early Access to Medicines Scheme (EAMS) criteria for the use of Remdesivir in patients with COVID-19 on May 26th, 2020.[1] The MHRA Scientific Opinion supports the use of Remdesivir in patients with severe disease. However, given current limitations in drug supply, an interim risk score has been proposed to identify those patients thought most likely to benefit from the drug.

The score includes eight variables: radiographic severity score > 3, male gender, non-white ethnicity, diabetes, hypertension, neutrophils >8.0 10/L, age >40 and CRP >40.[1] It seems to have first been developed for a recently launched COVID-19 immune modulator therapy trial (TACTIC-R),[2] based on an initial unpublished cohort of 200 patients.[3] An adapted version of the risk score, with twelve variables, was used to predict clinical deterioration (i.e. death or admission to critical care) in a cohort of 1157 confirmed COVID-19 patients in one London NHS Trust.[4] This score showed good performance, with an area under the receiver operating curve (AUROC) of 71.2% (test data).[4] The findings were published in this journal, which we read with interest.

However, how the score proposed by EAMS performs in front-line settings and its implications for how many patients will likely receive Remdesivir for COVID-19 is currently unknown.

We evaluated the performance of the EAMS criteria in a cohort of 517 patients COVID-19 confirmed patients admitted to Imperial College Healthcare Trust between the start of the pandemic and 5th April 2020.[5] We found that 348 patients in our cohort would have met criteria to be considered for Remdesivir therapy (i.e. age > 12, weight > = 40 kg, creatinine clearance >50 ml/min and AST/ALT <5 x ULN or no history of Childs Pugh C liver cirrhosis).

According to the EAMS score, 262 (75.3%) of the eligible patients in our cohort would have been classified as high-risk and 86 (24.7%%) as low-risk. The composite risk of death or ITU admission was 2.58 times greater (95%CI 1.56–4.25, $p < 0.001$) for the high- compared to the low-risk group (Fig. 1a). The performance of the score was reasonable when considering the AUROC of 71.1% ($p < 0.001$) (Fig. 1b). However, the overall misclassification of outcome was of 45.7%, with 14 (4.0%) patients who deteriorated classified as low-risk and 145 (41.7%) who did not deteriorate as high-risk, which has potential implications for allocation of a scarce resource. Common characteristics of those classified as low-risk that subsequently deteriorated included being female, white and having a non-severe appearance by chest X-ray (Table 1). Additionally, of the eight individual covariates in the full predictive model proposed by EAMS, only RALE score and CRP levels were statistically significant in predicting the composite outcome in our cohort (Table 2).

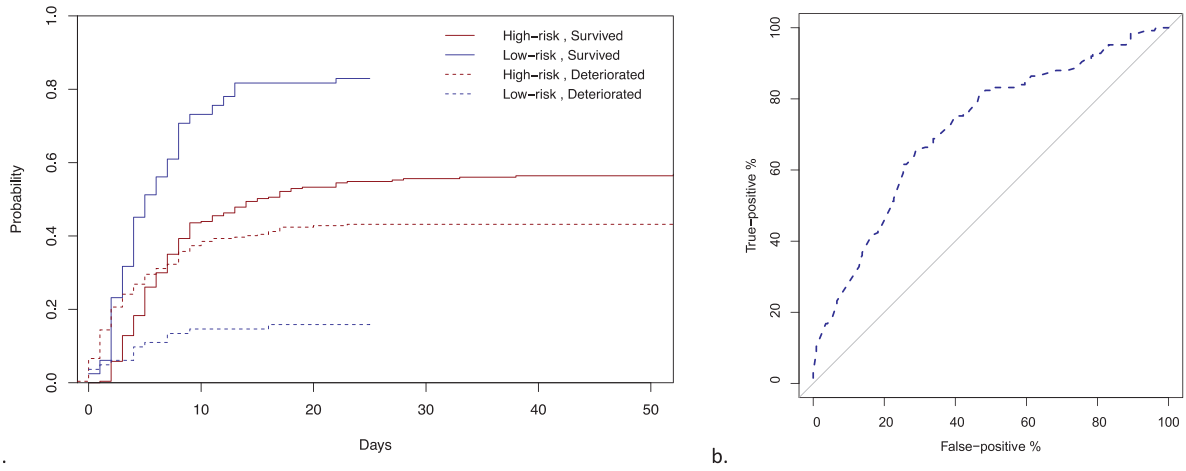

Fig. 1. EAMS criteria's performance amongst the ICHNT cohort of COVID-19 patients.
a) Cumulative incidence of discharge alive vs death by risk classification; b) receiver operating characteristic curve.

Table 1
Characteristics of patients who deteriorated by classification outcome by EAMS criteria.

	Patients scored as *'low-risk'* who deteriorated* $N = 14$ (4.02%)	Patients scored as *'high-risk'* who did not deteriorate* $N = 110$ (31.61%)
Age > 40	12 (85.71%)	103 (93.64%)
Male sex	4 (28.57%)	83 (75.45%)
Non-White ethnicity	4 (28.57%)	81 (73.64%)
Diabetes	1 (7.14%)	23 (20.91%)
Hypertension	0 (0.00%)	44 (40.00%)
Neutrophils > 8×10/L	4 (28.57%)	28 (25.45%)
CRP > 40 mg/L	10 (71.43%)	103 (93.64%)
RALE score > 3	1 (7.14%)	94 (85.45%)

* High- and low-risk as per EAMS criteria; deterioration defined as admission to ITU or death.

Also of note, 169 patients in our cohort did not meet initial EAMS eligibility criteria for Remdesivir. The majority ($n = 160$) would have been excluded due to a creatinine clearance <50 mL/min, 1 based on age, 1 for weight and 7 for known cirrhotic liver disease. The crude incidence rate of deterioration in this group was of 47.9% and, if the EAMS score would have been applied, it would not have differentiated the risk of deterioration between those classified as high or low-risk (RR 1.43, 95%CI 0.87–2.36, $p = 0.12$). Worryingly, their crude incidence rate of deterioration was similar to the high-risk group meeting inclusion criteria, at 42.0%. This highlights an important group of patients with renal impairment with poor COVID-19 outcomes who are often excluded from clinical trials.

We acknowledge the urgent need to be responsive to the rapidly changing context, given the enormous public health implications of treatment allocation decisions based on clinical criteria. Nevertheless, the release of the EAMS criteria based on a single cohort of patients seems premature. While reassuring that the scoring system seems to show reasonable performance in identifying most of those at high risk of adverse outcomes in our cohort, 11.3% of those who deteriorate and met inclusion criteria were missed by this score. Moreover, amongst those not meeting inclusion criteria, the score was not able to accurately predict outcome, highlighting the urgent need to identify safe treatments for use in those with renal and/or hepatic impairment. Importantly, in both the adapted risk criteria published previously in this journal and in that proposed by our group, hypalbuminaemia, reduced glomerular filtration and admission hypoxia (amongst other parameters) were also important predictors of worse hospitalisation outcomes.[4,5] None of these parameters are included in the EAMS criteria, which could improve the misclassification issues observed. However, rationalising the number of parameters included for a scoring system intended for front-line clinical use should be carefully assessed to maximise its utility and limit increasing workload for already overstretched clinical teams.

It has to be hoped that access to Remdesivir for all who may benefit from it will be achievable in coming months as manufacturing capacity expands. In the meantime, criteria for eligibility should be refined based on data from a wide range of clinical settings and shared as quickly as possible to ensure a finite resource is used as rationally as possible.

Declaration of Competing Interest

None to declare.

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Outbreak of COVID-19 in a nursing home in Madrid

Dear Editor,

We read with interest the study by Wang and colleagues recently reporting a high proportion of severe to critical cases associated to a high mortality in elderly hospitalized patients with COVID-19, what is in line with other reports.[1–7] In nursing homes it is of paramount importance to know the situation of the residents and staff members, which would allow health care workers and surviving residents to be presumed as "protected" or "exposed" to the disease. There are only a few COVID-19 outbreaks reported in nursing homes.[8–10] We evaluated the status against SARS-CoV-2 of people either residing or working at a privately run nursing home located at Madrid area (Spain) that was severely affected by an outbreak of COVID-19.

The 94 residents and staff members who consented to participate in the study were sampled on the 18th of April 2020 for nasopharynx PCR determination (GeneXpert®; Xpress SARS-CoV-2, Cepheid) and for finger stick whole blood and venepuncture IgG/IgM antibodies detection (All Test, Hangzhou All Test Biotech Co., LtD; Hangzhou, China). COVID-19 cases were proven (a patient with signs and symptoms and PCR-positive) or probable (a patient with signs and symptoms in the absence of PCR results). Clinical situation at the time of the study was active infection (PCR-positive), past infection (presence of antibodies in PCR-negative participants), and naïve "susceptible" population (no previous history of COVID-19 in both PCR- and antibody-negative participants). The qualitative variables are presented with their frequency distribution and the quantitative variables in mean and standard deviation or median and interquartile range in case of asymmetry. Categorical variables were compared using the Chi-square test or Fisher's test. In the case of quantitative variables, non-parametric methods were used (median test). The statistical significance was established at $p<0.05$. For the statistical analysis, the software SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY, USA) was used. The study was approved by the Hospital Ethics Committee (MICRO.HGUGM.2020–019).

The 84-available-bed facility had 79 beds occupied at the beginning of March 2020. The first case occurred on the 15th of March and preceded the additional 26 residents who died (34%) in the forthcoming 15 days what shrank the nursing home population to 52 survivors. All 27 (12 proven and 15 probable COVID-19 cases, respectively) residents presented with diarrhea and progressed to rapid deterioration with respiratory failure, shock, and death. Two residents died of other reasons. The clinical situation of the survivors in the prior month was no evidence of disease in 20 (40%), probable COVID-19 in 21 (42%), or proven COVID-19 in 9 (18%) who required hospital admission. Six staff members had proven COVID-19 (the PCR-positive result dated back on the 3rd of March in one of them) and 11 had probable disease. Twenty out of the 44 staff workers had been on sick leave due to COVID-19 in the last month.

On the day of the study, none of the 50 survivors was acutely ill (Table 1). Virtually all residents had at least one underlying condition and a median Charlson comorbidity index of 7 (IQR 5–8). Only one (2%) resident could be considered strictly immunocompromised. Functional self-sufficiency measured by the Barthel index was a median of 35 (IQR 10 and 75). Out of the 50 residents, 30 (60%) were still PCR-positive and had detectable antibodies in serum samples (Table 2). Sixteen out of the 20 (80%) PCR-negative residents were seropositive. Thus, 46/50 (92%) residents had data suggesting active or past disease. Accepting a potential universal exposure dated between the 15th and 22nd of March, all residents had a presumed time period of contact with the disease of more than three weeks. In the case of the 44 staff members, eight were men, and had ages ranging from 37 to 51 (median of 43); none of them had relevant underlying diseases. At the time of the study, five were PCR-positive (11.4%); 21 were found to be seropositive (45.4%) including the five PCR-positive cases. Of the 94 participants, 32 (34%) serum samples were IgM-positive and all but one were also IgG-positive; 14 patients (43.7%) were PCR-positive. In contrast, PCR was positive in 20 (32.25%) out of the 62 IgM-negative patients ($P=0.18$). In the 66 IgG-positive participants, 35 were PCR-positive (53%) while of the 28 IgG-negative participants all were PCR-negative ($P<0.001$). When the performance of the different serological techniques was compared to establish the criterion of seropositivity, the determination was positive in serum

Table 1
Comparison of PCR-positive and PCR-negative residents.

Residents	Total $N=50$	PCR + $N=30$	PCR - $N=20$	P
Median age in years (IQR)	87.0 (81.7–91.0)	88.0 (82.7–92.2)	86.5 (81.0–91.0)	0.34
Sex (%)				
Male	13 (26.0)	8 (26.7)	5 (25.0)	1.00
Female	37 (74.0)	22 (73.3)	15 (75.0)	
Underlying conditions (%)				
Myocardial infarction	2 (4.0)	0 (0.0)	2 (10.0)	0.15
Congestive heart failure	8 (16.0)	5 (16.6)	3 (15.0)	1.00
Central nervous system disease	15 (30.0)	8 (26.7)	7 (35.0)	0.54
Chronic obstructive pulmonary disease	7 (14.0)	3 (10.0)	4 (20.0)	0.41
Renal dysfunction	3 (6.0)	3 (10.0)	0 (0.0)	0.26
Diabetes mellitus	17 (34.0)	10 (33.3)	7 (35.0)	1.00
Peptic ulcer disease	14 (28.0)	8 (26.6)	6 (30.0)	1.00
Neoplastic disease	16 (32.0)	6 (20.0)	10 (50.0)	0.03
Dementia	34 (68.0)	21 (70.0)	13 (65.0)	0.76
Charlson, median (IQR)	7 (5.0–8.0)	6.0 (5.0–7.2)	7.0 (5.0–8.0)	0.30

Table 2
PCR and serum determination results of samples taken from residents and staff members of the nursing home.

People sampled	Positive PCR	Total positive antibodies IgG/IgM (serum)	Total positive antibodies IgG/IgM (Fingerstick)	IgG positive		IgM positive	
				Serum	Fingerstick	Serum	Fingerstick
Staff ($n=44$)	5	21	17	20	17	9	3
Residents ($n=50$)	30	46	43	46	43	23	7
Total	35	67	60	66	60	32	10

samples in 67/94 (71.3%) and in finger stick in 60/94 (63.8%). Concordance between finger stick and venepuncture samples was high though performance of the test was better when venepuncture samples were tested (Table 2).

We classified the residents in three groups: 30 (60%) residents who still had detectable viral RNA and, therefore, may be "potential" transmitters, 16 (32%) non-excreting but seropositive residents who could probably already lead freedom of movement, and four (8%) naïve susceptible residents at risk of acquiring COVID-19 who should be especially protected. In fact, the four naïve susceptible residents had unlimited mobility and two of them shared a room with PCR-positive patients. Our study highlights the extraordinary risk of lethal spread of SARS-CoV-2 infection in nursing homes, the very rapid transmission of the infection among residents and the high degree of infection in staff members. The presence of IgG antibodies with simultaneous PCR data determination poses a model of classification of residents and staff that allows for organizational decisions.

Disclaimer

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Serum ferritin as an independent risk factor for severity in COVID-19 patients

Dear Editor,

In this Journal, *Li* and colleagues recently reported that Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis[1]. Evidence shows that severe COVID-19 cases exhibit features of systemic inflammatory reactions, including hyperferritinemia. We conducted a retrospective study included 147 confirmed COVID-19 patients in Changsha, a non-epicenter city of China. The overall proportion of severe disease was 16.32% (24/147). **Table 1** shows the differences in the baseline characteristics between severe and nonsevere COVID-19 patients. The severe patients had higher levels of serum ferritin than the nonsevere patients (**Fig. 1A**). Multivariate logistic regression analysis indicated that the serum ferritin level on admission was an independent risk factor for disease severity in COVID-19 patients. CRP (OR=1.036; 95% CI 1.008 to 1.065; $P=0.012$) and lymphocyte counts (OR=0.284; 95% CI 0.08 to 1.005; $P=0.051$) were found to be two additional independent risk factors for disease severity through the multivariate logistic regression model. We found that higher serum ferritin was able to predict an increased risk of disease severity in patients with COVID-19 (**Fig. 1B**). The levels of serum ferritin positively correlate with levels of CRP ($r=0.4142$, $P<0.0001$) (**Fig. 1C**), and inversely correlate with lymphocytic counts ($r=-0.1841$, $P<0.03$) (**Fig. 1D**). These are two critical factors considered to be associated with the disease severity in patients with COVID-19. To our knowledge, this study is the first to study the epidemiologic impact of serum ferritin and to focus on the association between hyperferritinemia and disease severity in patients with COVID-19.

Wu et al. investigated 201 confirmed cases of COVID-19 to study the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died; their findings showed that higher serum ferritin was an independent risk factor associated with ARDS development.[2] Another meta-analysis also recommended serum ferritin as a candidate variable for risk stratification models that may serve as clinical predictors of severe and fatal COVID-19.[3] In our study, when patients were grouped according to the serum ferritin level with a cut off of 500 ng/ml derived from the HLH-2004 criterion, hyperferritinemia accounted for 29.93% (44/147) of patients. The hyperferritinemia group had a higher proportion of severe cases (31.82% vs. 9.71%, $P=0.0009$) and bilateral pulmonary infiltration rate (95.45% vs. 79.61%, $P=0.0297$) than patients without hyperferritinemia. Hyperferritinemic COVID-19 patients were older and more likely to be male. Moreover, these patients had significantly higher levels of serum creatine, ALT, AST and LDH, lower levels of lymphocytes, and significantly higher levels of inflammatory markers, such as CRP, PCT and D-dimer, than the patients in the nonhyperferritinemia group. All these indicators have been reported as warning parameters for severe or critical COVID-19 patients. In addition, these correlations may indicate that patients with hyperferritinemia tend to have more severe disease than those without hyperferritinemia. Multivariate logistic regression models were adjusted for several disease-related risk factors at admission, including age, neutrophil count, lymphocyte count, D-dimer, LDH, C-reactive protein, and procalcitonin, the analysis found that the serum ferritin level was an independent risk factor for disease severity in COVID-19 patients (OR = 3.302, 95% CI,

Table 1
Association between baseline variables and disease severity.

Variable	Severe ($n=24$)	Nonsevere ($n=123$)	P value
Age, years	52 (29–78)	40 (19~81)	**0.0011**
Sex			0.4772
Male	10 (41.67%)	61 (49.59%)	
Female	14 (58.33%)	62 (50.41%)	
Hypertension			0.4385
Yes	4 (16.67%)	11 (8.94%)	
No	20 (83.33%)	112 (91.06%)	
Diabetes			0.4385
Yes	2 (8.33%)	6 (4.88%)	
No	22 (91.67%)	117 (95.12%)	
White blood cells, 10^9/l	5.12 (1.48~8.27)	4.64 (1.75~13.43)	0.6702
Neutrophils, 10^9/l	3.455 (0.911~7.22)	2.84 (0.64~9.96)	**0.0373**
Lymphocytes, 10^9/l	0.8 (0.421~1.83)	1.35 (0.45~3.67)	**<0.0001**
Hemoglobin, G/L	123.5 (70~161)	130 (78~170)	0.3536
Platelets, 10^9/l	159.5 (58~423)	184 (31~429)	0.2971
ALT, U/L	23.22 (8.9~162.6)	20.13 (2.6~140.9)	0.2972
AST, U/L	25.31 (12.64~71.56)	22.88 (12.3~236.9)	0.0719
Creatinine, μmol/L	49.15 (21.92~255.7)	53.3 (20.58~160.3)	0.2311
PT, s	12.1 (9.9~19.6)	11.4 (9.1~13.7)	0.1028
APTT, s	31.75 (21.3~38.5)	32.4 (20.6~51.4)	0.1654
D-dimer, μg/L	0.575 (0.06~7.79)	0.2186 (0.01~4.15)	**0.0003**
LDH, U/L	209.6 (124.4~365.6)	150.8 (16.2~287.2)	**0.0002**
C-reactive protein, mg/L	38.05 (2.81~88.19)	12.25 (0.2~78.07)	**<0.0001**
Procalcitonin, ng/mL			**0.006**
<0.5	10 (41.67%)	87 (70.73%)	
≥ 0.5	14 (58.33%)	36 (29.27%)	
Serum ferritin, μg/L	733.1 (65.34~>2000)	296.4 (9.51~1568)	**<0.0001**

Data are median (range), or n (%). ALT: alanine aminotransferase, AST: aspartate aminotransferase,.
PT: prothrombintime, APTT: activated partial thromboplastin time, LDH: lactate dehydrogenase.

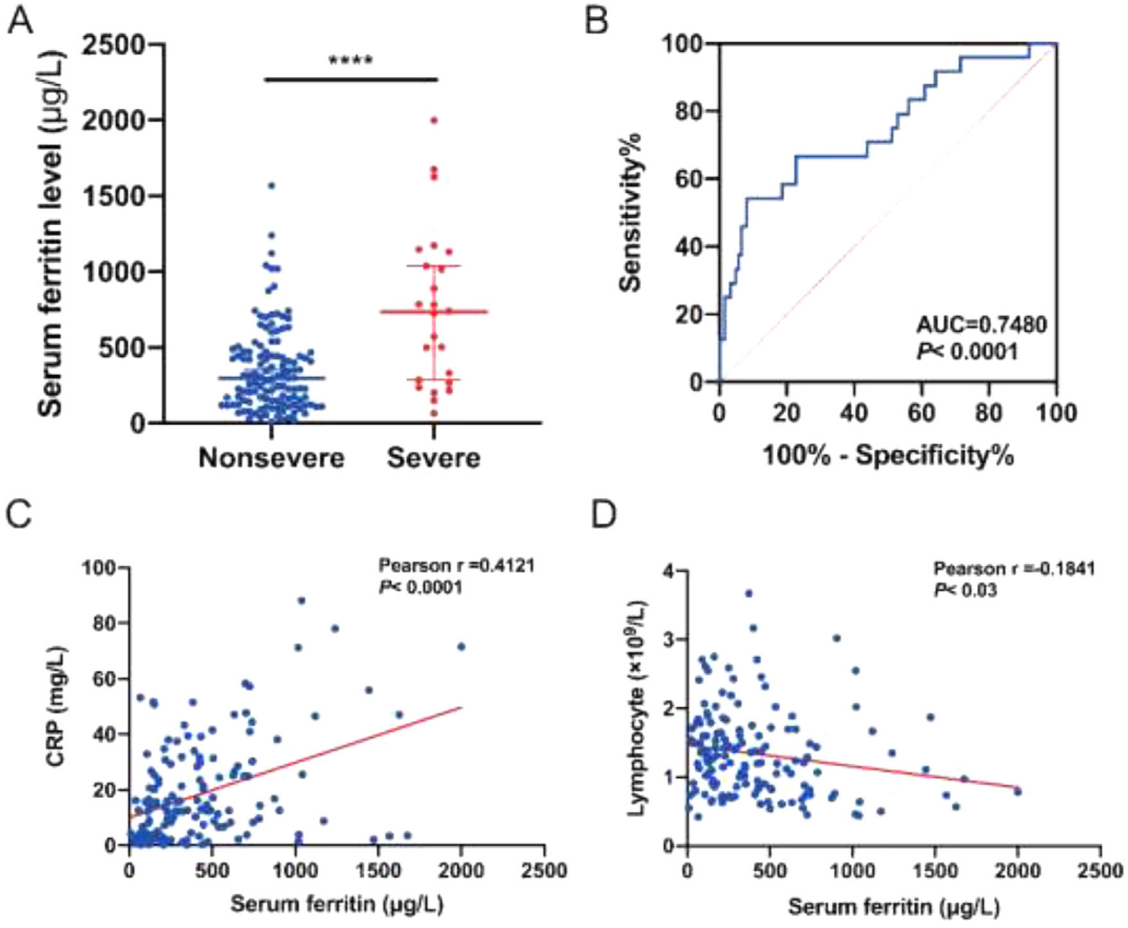

Fig. 1. Serum ferritin levels of COVID-19 patients and its correlation with the disease severity. A Serum ferritin levels on admission in severe and nonsevere COVID-19 patients ($P<$ 0.0001). B ROC curve of serum ferritin for the severity of COVID-19. Correlations between serum ferritin and C-reactive protein (**C**), lymphocyte (**D**).

1.141∼9.553, $P = 0.028$). And ROC curve study confirmed the predictive value of serum ferritin (AUC = 0.7480, $P < 0.001$).

Serum ferritin is an iron storage protein that is widely measured as an indicator of iron status, but it is also a well-known inflammatory marker. Serum ferritin levels can be increased significantly in response to inflammation and a variety of diseases. As early as 1997, Connelly et al. investigated serum ferritin levels in patients at risk for and with ARDS and found serum ferritin to be a predictor of ARDS.[4] Lagan et al. even found different genetic profiles of the genes involved in the processing and storage of cellular iron between patients with ARDS and healthy control subjects.[5] Garcia et al. found that ferritin >500 ug/L was associated with the most severe outcomes in children with severe sepsis and septic shock.[6] Consistent with these reports, our study also found that patients with hyperferritinemia (≥500 ug/L) were more likely to progress with bilateral pulmonary infiltration and a more severe disease course. In addition, there are a series of diseases whose presence or severity is known to be related to serum ferritin levels, i.e., amyotrophic lateral sclerosis (ALS), atherosclerosis (AS), systemic lupus erythematosus (SLE) and so on. Therefore, since the serum ferritin level is correlated with the degree of systemic and pulmonary inflammation, it is reasonable that hyperferritinemia is associated with disease severity in patients with COVID-19.

The mechanisms responsible for the association of hyperferritinemia and disease severity in patients with COVID-19 are unclear, but there are several possibilities for this phenomenon: 1) proinflammatory cytokines such as interleukin-Iβ (IL-lβ), tumor necrosis factor-a (TNF-α), and IL-6 may increase ferritin synthesis.[7] Hence, we speculated that SARS-CoV-2-induced production of proinflammatory cytokines (*i.e.*, IL-6, TNF-α), which are known to be elevated in COVID-19, might promote ferritin synthesis early in inflammation. 2) The cellular damage derived from inflammation can promote the leakage of intracellular ferritin, thus elevating serum ferritin.[8] 3) In acidosis, the microvascular environment and increased production of reactive oxygen species (ROS) might liberate iron from ferritin, and it is this unliganded iron that can participate in Haber-Weiss and Fenton reactions, creating hydroxyl radicals, causing further cellular damage,[8] and worsening tissue injury, thus causing a vicious cycle of inflammation. Similarly, one study found that the assembly of Middle East Respiratory Syndrome (MERS) coronavirus nanoparticles is related to chaperone-mediated ferritin.[9] However, further investigations are needed to confirm the role of serum ferritin levels in the pathogenesis of COVID-19.

In conclusion, this retrospective study performed in a Chinese population demonstrated that a high level of serum ferritin is an independent risk factor for the severity of COVID-19. Assessing serum ferritin levels during hospitalization may be important to recognize high-risk individuals with COVID-19.

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Declaration of Competing Interest

The authors state that they have no conflicts of interest to disclosure.

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Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study ★★,♆

Dear Editor,

As recently discussed in the Journal,[1] baricitinib was safe and improved the clinical conditions in 12 patients with mild-moderate Coronavirus Disease 2019 (COVID-19) pneumonia. It is known that severe symptoms of COVID-19 may develop after a median of 8-days from illness-onset, with a median time to Intensive Care Unit (ICU) admission of 5 days from the dyspnea occurrence.[2] Currently, no antiviral therapies or vaccines are available. An uncontrolled immune response[3] is observed and is likely involved in tissues injury.[4] Baricitinib is an anti-Janus kinase inhibitor-1 and −2, and has a dual action on COVID-19 therapy including the inhibition of cytokine release and SARS-CoV-2 endocytosis.[5] Based on this evidence, we conducted an observational, retrospective, longitudinal multicenter-study in consecutive-hospitalized patients with COVID-19 moderate pneumonia to evaluate the 2-week effectiveness and safety of baricitinib combined with antivirals (lopinavir/ritonavir) compared with the standard of care therapy which was hydroxychloroquine and lopinavir/ritonavir. Primary aim was to evaluate the mortality rate; secondary aims were to evaluate the rate of ICU transfer, hospital discharge, improvement of respiratory parameters, adverse events (AEs) occurrence. Moreover, associations between therapy and modification of respiratory parameters and C-Reactive Protein (CRP), interleukin-6 (IL-6), lymphocyte percentage were evaluated.

Clinical charts of patients with moderate COVID-19 pneumonia from 7 Italian hospitals (Hospital of Prato, Hospital of Pistoia, Hospital S.Maria Nuova, Florence, Hospital of Alessandria, Hospital of Fano, Hospital of Pesaro, Hospital of Ariano Irpino (Avellino) were reviewed.

Baricitinib-treated arm included consecutive-hospitalized patients,18 years-older, SARS-CoV-2 naso-pharingeal swab-positive, with a moderate pneumonia characterized by typical symptoms, radiological findings of pneumonia, SpO2 >92% on room air,and PaO2/FiO2 100–300 mmHg, admitted between March 15th-May 5th, 2020. Baricitinib 4 mg/day was provided orally associated with lopinavir/ritonavir tablets 250 mg/bid for 2 weeks.

Control-arm included all consecutive-hospitalized patients from February 20th-March 15th, 2020 with moderate COVID-19 pneumonia, 18 years-older, treated with hydroxychloroquine (HCLR) and lopinavir/ritonavir. Exclusion criteria were: history of thrombophlebitis, latent tuberculosis infection,[6,7] HBV or HCV infection, current varicella zoster or bacterial infection, pregnancy, lactation, contraceptive pills intake, previous (last 5 years) or current malignancy, neutrophil count$<1.0\times10^9$/L, lymphocyte count$<0.2\times10^9$/L, platelets count$<50\times10^9$/L, transaminases values 4-fold higher than the upper normal limit. Prophylactic anti-thrombotic therapy with low-weight molecular heparin was administered. Patients had supportive therapy (O_2 supply, rehydration, diuretics, anti-hypertensive, antibiotics) if needed. Corticosteroids were not allowed. If patients were discharged earlier than 2 weeks, they were requested to continue the ongoing therapy until the scheduled 14-days.

Temperature, respiratory and pulse rate, arterial blood gas analysis, blood pressure, blood cell count, liver and kidney tests function were daily assessed. IL-6 serum levels of (RayBio® Human IL-6 ELISA Kit, RayBiotech Co.,USA) were tested at baseline, week 1 and 2. Since low lymphocyte percentage can predict a poor prognosis[6], patients were stratified at baseline as: lymphocytes >20%, >5% to <20%, and <5%.

Patients provided a written-informed consent. The off-label use of baricitinib was approved by the Hospital-Committee and Ethical-Committee of Toscana-Region (Code: BARIC-off; 17,261; approval date: May 5th 2020).

Mann-Whitney U test was used to compare quantitative variables; Wilcoxon test for paired data; Chi-squared or Fisher's exact test for categorical variables. A two-tailed p-value <0.05 was considered significant.

At baseline, 113 patients were in the baricitinib-arm, and 78 in the control-arm (Table 1). The results indicate that the 2-week case fatality rate was significantly lower in the baricitinib-arm compared with controls [0% (0/113) vs 6.4% (5/78) (p-value: 0.010; 95%CI 0.0000–0.4569)] (Table 2). ICU admission was requested in 0.88% (1/113) vs 17.9% (14/78) patients in the baricitinib-arm compared to the control-arm (week 1, p-value: 0.019; 95%CI 0.0092–0.6818), (week 2, p-value: <0.0001; 95%CI 0.0038–0.2624). Discharge rate was significantly higher in the baricitinib-arm at week 1 [9.7% (11/113) vs 1.3% (1/78) (p-value: 0.039; 95%CI: 1.41–90.71)], and at week 2 [77.8% (88/113) vs 12.8% (10/78) (p:<0.0001; 95%CI 10.79–51.74)].

Except ageusia/anosmia, all clinical, laboratory and respiratory functions significantly improved at week 1. SpO_2 significantly improved at week 2 (p-value: 0.0018); $PaO2/FiO_2$ significantly improved at weeks 1 and 2 compared with baseline-values (p-value: 0.0016 and <0.0001, respectively). Significant differences resulted from the comparison between the baricitinib-arm and the control-group (SpO_2, week 1 p-value: <0.0001; week 2 p-value: <0.0001; PaO2/FiO2, week 1 p-value: 0.001; week 2 p-value: <0.0001). CRP and IL-6 levels significantly decreased in the baricitinib-arm (CRP at week 1, p-value: 0.003; at week 2, p-value: <0.0001; IL-6 at week 1, p-value: 0.001; at week 2, p-value: <0.0001). Lymphocytes significantly increased in the baricitinib-arm, with the exception of patients with a baseline proportions-value <5% (Table 2).

At discharge, the proportion of patients [positive to viral nasopharingeal swabs was significantly lower [12.5% (11/88)] in the baricitinib-arm compared to the control-arm [40% (4/10)] (p-value: 0.043; 95%CI 0.06044–0.7737).

Seven AEs, not requiring the therapy discontinuation, were recorded in the baricitinib-arm, including transaminase increase in 4 (3.5%) patients, epistaxis due to heparin overdose in 1 patient, urinary infection in 1 patient, and oral candidiasis in 1 patient.

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Table 1
Baseline demographic, clinical, and laboratory characteristics of COVID-19 patients treated with lopinavir/ritonavir and either baricitinib or with standard of care therapy.

Feature	Baricitinib Combined with lopinavir/ritonavir treated arm [a]	Hydroxychloroquine Combined with lopinavir/ritonavir treated arm (standard of care-treated arm) [b]	P value
Patient number, No (%)	113 (100)	78 (100)	
Male/female, No (%)	73/40 (64.6/35.4)	46/32 (59/41)	0.524
Age years, median (IQR)	68 (57–76)	63 (55.5–69.5)	0.602
Interval from symptoms onset and therapy starting, days, No	7 (5–10)	6.5 (4–9)	0.915
Cough, No (%)	75/113 (66.4)	53/78 (67.9)	0.943
Dyspnea, No (%)	84/113 (74.3)	58/78 (74.4)	0.869
Sputum production, No (%)	41/113 (36.2)	29/78 (37.2)	0.979
Headache, No (%)	56/113 (49.5)	31/78 (39.7)	0.234
Diarrhea, No (%)	26/113 (23)	11/78 (14.1)	0.179
Ageusia/anosmia, No (%)	44/113 (38.9)	29/78 (37.1)	0.925
Hypertension, No (%)	32/113 (28.3)	21/78 (26.9)	0.962
Diabetes, No (%)	18/113 (15.9)	13/78 (16.6)	0.949
COPD, No (%)	16/113 (14.1)	14/78 (17.9)	0.613
CVD, No (%)	10/113 (8.5)	5/78 (6.4)	0.732
Fever °C, median (IQR)	37.9 (36.7–38.3)	37.8 (37.7–38.7)	0.915
Breath rate n/min, median (IQR),	20 (17–22)	21 (19–24)	0.825
SpO2 (%),median (IQR)	95 (92–98)	93 (92–97)	0.234
PaO2/FiO2, median (IQR)	265.7 (202–330)	267.5 (263.1–301)	0.522
Pulse rate, median (IQR)	80 (70–90)	85 (79–92)	0.129
SBP mm/hg, median (IQR)	125 (112–135)	115 (105–130)	0.121
DBP mm/hg, median (IQR)	70 (65–80)	65 (60–72)	0.232
WBC ($x10^9$/l), median (IQR)	6.5 (4.9–8.3)	7.2 (5.8–8.6)	0.708
Neutrophils ($x10^9$/l), median (IQR)	4.7 (3.5–6.5)	4.9 (4.4–6.9)	0.911
Lymphocytes ($x10^9$/l), median (IQR)	0.93 (0.7–1.2)	0.88 (0.7–0.9)	0.728
Lymphocyte percentage			
>20 N (%)	39 (34.5)	24 (30.8)	0.701
>5-<20	70 (61.9)	51 (65.4)	0.740
<5	4 (3.6)	3 (3.8)	0.779
Hemoglobin (g/l), median (IQR)	118 (101–134)	125 (108–133)	0.426
Platelets ($x10^9$/l), median (IQR)	213 (167–308)	268 (156–392)	0.234
Alt (u/l), median (IQR)	29 (19–49)	34 (25–52)	0.168
Ast (u/l), median (IQR)	34 (25–51)	40 (34–47)	0.628
Creatinine (mg/dl), median (IQR)	0.9 (0.7–1.1)	1.00 (0.9–1.2)	0.925
Crp (mg/dl), median (IQR)	8.2 (4.1–14.5)	6.3 (2.8–13.6)	0.129
IL-6 (PG/ML), MEDIAN (IQR) [c]	29.4 (16–45)	32.6 (25–61)	0.225
Procalcitonin (ng/ml), median (IQR)	0.6 (0.3–1.2)	0.9 (0.8–2.1)	0.802
Mews, median (IQR)	1 (0–2)	2 (1–3)	0.225

Abbreviations and symbols: No= number;%= percentage; °C: grade Celsius; min= minute; SpO2= peripheral capillary oxygen saturation; PaO2/FiO2= ratio of arterial oxygen partial pressure to fractional inspired oxygen; SBP= systolic blood pressure; DBP= diastolic blood pressure; WBC= white blood cells; AST= serum glutamic oxaloacetic transaminase; ALT= serum alanine aminotransferase; MEWS= Modified Early Warning Score; IQR: Interquartile range.

[a] Baricitinib-treated arm: Baricitinib-therapy was given 4 mg/day orally combined with lopinavir/ritonavir tablets 250 mg/bid.

[b] Consecutive patients treated with standard of care therapy (hydroxychloroquine 200 mg/bid with lopinavir/ritonavir tablets 250 mg/bi) during the previous weeks before the first baricitnib-treated patient served as controls.

[c] IL-6 values were available in 58 patients of the baricitinib-treated group and in 36 controls.

The results of the present observational, retrospective, longitudinal, multicenter-study in 113 consecutive-hospitalized patients with moderate pneumonia confirm the effectiveness and safety of baricitinib in patients with moderate COVID-19 pneumonia previously reported.[1] Baricitinib-therapy was started in the early phase of COVID-19 disease (median: 7-days from symptoms onset), and the early treatment and the rapid action of the drug may explain the low number of ICU admissions and deaths. The importance of early starting COVID-19 therapies is highlighted in trials of tociluzimab showing a higher efficacy to reduce ICU admission if administered during the initial phase of pneumonia.[8,9]

Interestingly, a significant reduction of positive naso-pharingeal swabs was observed in the baricitinib-arm at discharge, with only 12.5% positive-swabs compared to 40% in the control-group, confirming the anti-inflammatory and anti-viral effects of the baricitinib recently described in 4 patients.[10]

The short-term administration of the drug compared to the long-term treatment in rheumatoid arthritis, may probably explain the absence of serious AEs.

In conclusion, baricitinib is a promising and safe therapy in patients with moderate COVID-19 pneumonia. A randomized clinical trial is needed to confirm our findings.

Table 2
Clinical, laboratory and respiratory parameters of COVID-19 patients after 1- or 2-week treatment in the baricitinib-treated group and in the standard-treated group: comparison within the same treatment group and between the 2 different treatment groups.

	Baricitinib combined with lopinavir/ritonavir treated arm 113 patients				Hydroxychloroquine combined with lopinavir/ritonavir treated arm (Standard of care-treated arm) 78 patients				Baricitinib-based therapy arm vs standard of care therapy arm
Clinical, laboratory, respiratory parameters	Baseline	Week 1	Week 2	P value Baseline values vs Week 1 [a] or vs Week 2 [b] values	Baseline	Week 1	Week 2	P value Baseline values vs Week 1 [a] or vs Week 2 [b] values	P value Week 1 [a] Week 2 [b]
Cough, No (%)	75 (66.4)	25 (22.1)	4 (3.5)	0.000 [a] 0.000 [b]	53 (67.9)	39 (50)	15 (19.2)	0.034 [a] 0.000 [b]	0.000 [a] 0.014 [b]
Dyspnea, No (%)	84 (74.3)	20 (1.7)	4 (3.5)	0.000 [a] 0.000 [b]	58 (74.4)	51 (65.3)	39 (50)	0.295 [a] 0.003 [b]	0.000 [a] 0.000 [b]
Sputum production, No (%)	41 (36.2)	15 (13.2)	10 (8.8)	0.000 [a] 0.000 [b]	29 (37.2)	18 (23)	12 (15.3)	0.081[a] 0.004 [b]	0.117 [a] 0.246 [b]
Headache, No (%)	56 (49.5)	12 (10.6)	2 (1.7)	0.000 [a] 0.000 [b]	31 (39.7)	24 (30.7)	10 (12.8)	0.315 [a] 0.002 [b]	0.000 [a] 0.005 [b]
Diarrhea, No (%)	26 (23)	2 (1.7)	0	0.000 [a] 0.000 [b]	11 (14.1)	1 (1.3)	0	0.007 [a] 0.002 [b]	0.745 [a] NA [b]
Ageusia/Anosmia, No (%)	44 (38.9)	32 (28.3)	24 (21.2)	0.121 [a] 0.006 [b]	29 (37.1)	25 (32)	19 (24.3)	0.614 [a] 0.118 [b]	0.694 [a] 0.740 [b]
Fever °C, median (IQR)	38 (37.4–38.2)	36.1 (36–36.4)	36 (36–36.1)	0.001 [a] 0.001 [b]	38 (37.7–38.7)	37.5 (36.5–38.1)	37 (36.3–37.4)	0.516 [a] 0.129 [b]	0.000 [a] 0.000 [b]
Breath, N/min, median (IQR)	20 (17–22)	18 (15–20)	16 (14–18)	0.003 [a] 0.002 [b]	21 (19–24)	19 (18–22)	17 (16–21.7)	0.083 [a] 0.058 [b]	0.724 [a] 0.225 [b]
SpO2%, median (IQR)	95 (92–98)	96 (95–98)	97 (96–98)	0.191 [a] 0.0018 [b]	93 (92–97)	93.8 (91.8–94.7)	93.6 (86.7–94.3)	0.678 [a] 0.715 [b]	0.000 [a] 0.000 [b]
PaO2/FiO2 value, median (IQR)	265.7 (202–330)	336.5 (245.5–452)	395 (320–452.3)	0.0016 [a] 0.0000 [b]	267.5 (263.1–301)	278.2 (258.3–302.4)	293.5 (244.2–315.1)	0.514 [a] 0.376 [b]	0.001 [a] 0.000 [b]
Pulse rate, No/min. median (IQR)	80 (70–90)	76 (68.5–81)	74.5 (68–80)	0.433 [a] 0.177 [b]	85 (79–92)	82.5 (76.5–91)	83 (77–96.4)	0.433 [a] 0.903 [b]	0.129 [a] 0.004 [b]
WBC, x10^9/L, median (IQR)	6.5 (4.9–8.3)	7.0 (5.7–9.2)	7.0 (5.8–8.6)	0.481 [a] 0.225 [b]	7.2 (5.8–8.6)	6.9 (6.5–7.4)	7.2 (6.4–8.6)	0.789 [a] 0.922 [b]	0.389 [a] 0.533 [b]
Neutrophils, x10^9/L, median (IQR)	4.7 (3.5–6.5)	5 (3.3–7)	4.4 (3.2–6.9)	0.720 [a] 0.876 [b]	4.9 (4.4–6.9)	5.4 (5.1–6.2)	6.7 (6.3–7.3)	0.054 [a] 0.002 [b]	0.136 [a] 0.068 [b]
Lymphocytes, x10^9/L, median (IQR) Lymphocytes, No (%)	0.93 (0.7–1.2)	1.11 (0.8–1.9)	1.3 (1–2.1)	0.0023 [a] 0.0017 [b]	0.88 (0.7–0.9)	0.86 (0.5–1)	0.9 (0.69–1.0)	0.524 [a] 0.836 [b]	0.023 * 0.004 †
>20	39 (34.5)	57 (50.4)	78 (69.0)	0.022 [a] 0.000 [b]	24 (30.8)	32 (41.0)	35 (44.9)	0.243 [a] 0.099 [b]	0.256 [a] 0.001 [b]
>5-<20	70 (61.9)	49 (43.4)	28 (24.8)	0.008 [a] 0.000 [b]	51 (65.4)	39 (50.0)	35 (44.9)	0.075 [a] 0.016 [b]	0.449 [a] 0.006 [b]
<5	4 (3.6)	7 (6.2)	7 (6.2)	0.536 [a] 0.536 [b]	3 (3.8)	7 (9.0)	8 (10.2)	0.327 [a] 0.211 [b]	0.658 [a] 0.452 [b]
Hb, g/L, median (IQR)	118 (101–134)	120 (106–112)	125 (118–131)	0.234 [a] 0.129 [b]	125 (108–133)	122 (112–125.2)	124 (114–128)	0.812 [a] 0.534 [b]	0.925 [a] 0.746 [b]
Platelets, Nox10^9/L, median (IQR)	213 (167–308)	347 (265–426)	284 (205–419)	0.121 [a] 0.189 [b]	268 (156–392)	328 (321–461)	359 (316–423)	0.268 [a] 0.189 [b]	0.786 [a] 0.144 [b]
ALT, U/L, median (IQR)	29 (19–49)	45 (29–68) (43.2–57.2)	45 (26.7–71 (43–83.7)	0.065 [a] 0.076 [b]	34 (25–52)	57.5 (38–69.4)	54.8 (39.5–54.5)	0.049 [a] 0.057 [b]	0.533 [a] 0.144 [b]
AST, U/L, median (IQR)	34 (25–51)	36 (25–49.2)	30 (23–43.5)	0.965 [a] 0.764 [b]	40 (34–47)	46.5 (41.7–52.5)	48.5 (42–55.8)	0.624 [a] 0.019 [b]	0.076 [a] 0.129 [b]
Creatinine, mg/dl, median (IQR)	0.9 (0.7–1.1)	0.86 (0.69–1.0)	0.88 (0.7–1.0)	0.969 [a] 0.934 [b]	1.00 (0.9–1.2)	1.0 (0.9–1.1)	1.1 (1–1.2)	0.956 [a] 0.783 [b]	0.433 [a] 0.246 [b]

(*continued on next page*)

Table 2 (*continued*)

	Baricitinib combined with lopinavir/ritonavir treated arm 113 patients				Hydroxychloroquine combined with lopinavir/ritonavir treated arm (Standard of care-treated arm) 78 patients				Baricitinib-based therapy arm vs standard of care therapy arm
Clinical, laboratory, respiratory parameters	Baseline	Week 1	Week 2	P value Baseline values vs Week 1 [a] or vs Week 2 [b] values	Baseline	Week 1	Week 2	P value Baseline values vs Week 1 [a] or vs Week 2 [b] values	P value Week 1 [a] Week 2 [b]
CRP, mg/dl median (IQR)	8.2 (4.1–14.5)	0.96 (0.51–2.28)	0.3 (0.13–0.88)	0.000 [a] 0.000 [b]	6.3 (2.8–13.6)	5.4 (2.8–8.9)	4.6 (2.3–6.4)	0.871 [a] 0.433 [b]	0.003 [a] 0.000 [b]
IL-6 (pg/ml), median (IQR) [c]	29.4 (16–45)	5 (2–9)	2.3 (0–4.2	0.0001 [a] 0.0001 [b]	32.6 (25–61)	29.3 (23–35.2)	16.3 (12–20.5)	0.189 [a] 0.087 [b]	0.001 [a] 0.000 [b]
Procalcitonin, ng/ml, median (IQR)	0.6 (0.3–1.2)	0.9 (0.6–1.4)	0.8 (0.6–1.8)	0.625 [a] 0.567 [b]	0.9 (0.8–2.1)	1.3 (0.7–1.9)	1.2 (0.8–1.4)	0.278 [a] 0.124 [b]	0.276 [a] 0.146 [b]
MEWS, median (IQR)	1 (0–2)	01 (0–0)	0 (0–0)	0.000 [a] 0.000 [b]	2 (1–3)	1 (1–2)	1 (0–2)	0.643 [a] 0.184 [b]	0.004 [a] 0.012 [b]
ICU transfer, No (%)	0	1 (0.88) [d]	0 (0)	0.000 [a] NA [b]	0	6 (7.7)	14 (17.9)	0.037 [a] 0.000 [b]	0.019 [a] 0.000 [b]
Discharged, No (%)	0	11 (9.7)	88 (77.8)	0.002 [a] 0.000 [b]	0	1 (1.3)	10 (12.8)	1.000 [a] 0.003 [b]	0.039 [a] 0.000 [b]
Positive RT-PCR swabs at discharge, No (%) [e]			11 (12.5)	NA			4 (40)	NA	0.043
Deaths, No (%)	0	0	0	NA	0	2 (2.6)	5 (6.4)	0.477 * 0.069 †	0.323 [a] 0.010 [b]

Abbreviations and symbols: No: number;%: percentage; °C: grade Celsius; min: minute; SpO2: peripheral capillary oxygen saturation; PaO2/FiO2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cells; AST: serum glutamic oxaloacetic transaminase; ALT: serum alanine aminotransferase; IU: international unit; MEWS: Modified Early Warning Score; IQR: Interquartile range. Statistical analysis was performed using the Wilcoxon test (for paired comparisons) or the Mann-Whitney test. P value was considered significant if <0.05.

[a] Differences between the values at baseline and after 1 week.

[b] Differences between the values at baseline and after 2 weeks. Standard of care therapy-treated group: COVID-19 patients under standard respiratory therapy and lopinavir/ritonavir and hydroxychloroquine treatment that were admitted in the hospital the week before starting the therapy with baricitinib and lopinavir/ritonavir.

[c] IL-6 values were available in 58 patients of the baricitinib-treated group and in 36 controls.

[d] This patient required intubation 2 days after baricitinib starting; she remained 2 day in ICU and then she prosecuted the drug. She was discharged 2 days after the treatment completion with baricitinib.

[e] RT-PCR= real time Reverse Transcription-Polymerase Chain Reaction.

Declaration of Competing Interest

All Authors have nothing to disclose.

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Investigation of a family outbreak of COVID-19 using systematic rapid diagnostic tests raises new questions about transmission ☆☆,†

Dear Editor,

We read with interest the letter by Jiang and colleagues who described the spread of SARS-CoV-2 in a family cluster in China.[1] Herein, we describe the epidemiological, clinical and biological characteristics of 30 households in close contact with SARS-CoV-2-infected members, living in a confined environment during the French national lockdown. This report highlights important issues about transmission.

Two families (26 and 4 members, respectively) were included in the study. During the 5 days before the French national lockdown, both families moved from their usual Parisian residence to a closed property in the countryside, composed by 3 neighboring houses (A, B and C) in a park. House A was inhabited by 8 persons from a single family, including 3 couples who shared their bed for at least 4 days after the onset of symptoms. In house B, there were 2 families composed of 9 persons. There were 2 married couples who shared their bed during all the time, even in presence of symptoms. In house C, there were 2 families composed of 13 persons. There were 4 married couples who shared the bed until the hospitalization of the 84-year-old subject for severe SARS-CoV-2 infection. With the exception of the elderly couple who already lived in House C, all the remaining people arrived there between March 12 and 16, before the beginning of the national lockdown (March 17, 2020). Thereafter, all residents were not allowed to quit until the end of lockdown (May 11, 2020). During the first week of cohabitation there were regular and close contacts among households from the 3 houses. Since the occurrence of the first 3 symptomatic cases, contacts among the 3 houses were reduced although they indirectly continued through children displacements.

Within their stay, all residents were clinically examined at least once. RT-PCR testing of SARS-CoV-2 was performed for symptomatic cases.[2] Serologic testing using the approved COVID-PRESTO® rapid diagnostic test[3] (AAZ, Boulogne-Billancourt, France), detecting both IgM and IgG, was performed on whole blood finger-stick more than 45 days after the onset of symptomatic cases on all the 30 subjects. Population characteristics are detailed in Table 1.

The first diagnosed case was a 67-year-old man (resident #1) living in the house A and referring to the Infectious Diseases outpatient clinic on March 17 for cough, fever and asthenia for 4 days. Investigation of the cluster began soon after resident #1 was formally diagnosed with COVID-19. This first recognized case was acquired before the arrival of resident #1, who probably transmitted the infection to resident #3 (his son-in-law) after arrival at home A. No transmission occurred between husbands and wives

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Table 1
Clinical characteristics of population, results of RT-PCR on nasopharyngeal swab specimen and rapid diagnostic tests.

Resident number, sex, age (years)	Kinship	Symptoms	Date of onset of symptoms	RT-PCR results	Ct positivity (for RdRP, N and E genes)	COVID-19 IgM	COVID-19 IgG	Smoking status
House A (one family)								
1. Male, 67	Husband case 2	Yes	March 13	**Positive**	20, 17, 16	**Positive**	**Positive**	No
2. Female, 65	Wife case 1	Mild	March 16	Negative		Negative	Negative	No
3. Male, 34	Husband case 4	Yes	March 20	**Positive**	22,19,18	**Positive**	Negative	Yes
4. Female, 33	Wife case 3	No	NA	Negative		Negative	Negative	No
5. Male, 33	Husband case 6	No	NA	Negative		Negative	Negative	Yes
6. Female, 33	Wife case 5	No	NA	ND		Negative	**Positive**	Yes
7. Female, 2	Daughter case 5	No	NA	ND		Negative	Negative	No
8. Male, 35	Son case 1 and 2	No	NA	ND		Negative	Negative	Yes
		No						
House B (two families)								
9. Male, 37	Husband case 10	Yes	March 12	ND		Negative	**Positive**	Yes
10. Female, 37	Wife case 9	No	NA	ND		Negative	Negative	Yes
11. Male, 6	Son case 9 and 10	No	NA	ND		Negative	Negative	No
12. Male, 4	Son case 9 and 10	No	NA	ND		Negative	Negative	No
13. Male, 2	Son case 9 and 10	Mild	NA	ND		Negative	Negative	No
14. Male, 49	Husband case 15	No	NA	ND		Negative	Negative	Yes
15. Female, 35	Wife case 14	No	NA	ND		Negative	Negative	Yes
16. Female, 6	Daughter case	No	NA	ND		Negative	Negative	No
17. Female, 4	14/15	No	NA	ND		Negative	Negative	No
	Daughter case 14/15							
House C (one family)								
18. Male, 84	Husband case 19	Yes, severe	March 21	**Positive**	27, 28, 26	**Positive**	**Positive**	No
19. Female, 75	Wife case 18	Yes	March 24	ND		Negative	**Positive**	No
20. Male, 48	Son case 18–19,	Yes	March 24	ND		Negative	**Positive**	No
21. Male, 27	Husband case 20	No	NA	ND		Negative	Negative	No
22. Female, 37	Daughter case	Yes	March 10	ND		Negative	**Positive**	Yes
23. Male, 38	19/20	Mild	March 14	ND		Negative	**Positive**	Yes
24. Male, 7	Husband case 22	No	NA	ND		Negative	Negative	No
25. Male, 3	Son case 22/23	No	NA	ND		Negative	Negative	No
26. Male, 47	Son case 22/23	No	NA	ND		Negative	Negative	Yes
27. Female, 46	Husband case 27	No	NA	ND		Negative	Negative	No
28. Male, 16	Wife case 26	No	NA	ND		Negative	Negative	No
29. Male, 14	Son case 26/27	No	NA	ND		Negative	Negative	No
30. Male, 8	Son case 26/27	No	NA	ND		Negative	Negative	No
	Son case 26/27							

Abbreviations: Ct = cycle threshold; NA = not applicable; ND = not done.

in house A although couples moved to separated rooms only 4 days after the onset of symptoms of the index case. As resident #6 was asymptomatic with IgG+/IgM-, it is not sure that she was infected prior or after her arrival at house A. In house B, a single resident (#9) was found to be infected with COVID-19. He probably acquired infection by the end of February after a close contact with a confirmed case in Paris. Symptoms occurred on March 12, four days before arriving at home B, with cough, asthenia, anosmia, cutaneous lesions lasting one week. As the COVID-19 cluster was unrecognized at this time, he was not separated from the rest of the residents, he continued to share the bedroom with his wife and he had remarkably close contacts with his children. Although he had close contacts with all his family and friends during all the symptomatic phase, no secondary cases occurred. In house C, resident #22 was the first (retrospectively) identified with COVID-19. She developed typical symptoms (cough, fever, headache and asthenia) on March 10 when she was in Paris. At her arrival in house C on March 13, she still had mild symptoms. She probably infected her husband, father and mother (residents #23, #18 and #19, respectively). Resident #18 developed a severe lower respiratory tract infection and was hospitalized for 2 weeks. Resident #23 developed a moderate cough for two days. Resident #20 may have been infected by resident #23, during a round trip by car on March 17, when resident #23 was already symptomatic. Resident #20 presented with diarrhea, cough and fever lasting four days. Fig. 1 shows distribution of residents in each house, kinship, confirmed COVID-19 cases and the temporal occurrence of each case.

Overall, 9 out of 30 residents (30%) were diagnosed with COVID-19. We identified 3 independent index cases (residents #1, #9, #22) that infected 6 secondary cases: 2 in house A, none in house B and 4 in house C. Therefore, the attack rate was 6 out of 27 (22.2%). Noteworthy, none of the 9 children present were infected, although they had very closed contacts with their infected parents. Among the 9 married couples who were present, all shared the same bed at least some days after the onset of symptoms or during all the time of disease. Nevertheless, partners were infected in only 3 couples, partners remained discordant in 5, and none of the partners were infected in 1. After careful questioning, discordant couples confirmed they had continued sexual activity during the period at risk of contagiousness of the infected partner.

This cluster investigation illustrates important facts concerning SARS-CoV-2 transmission. First, as no case occurred in children we are confident they did not participate in the viral transmission network, either within or between houses. This supports the hypothesis that, usually, children are not asymptomatic carriers who transmit the SARS-CoV-2.[4–6] Second, there was a limited transmission of SARS-CoV-2 among couples, even though discordant couples continued to be sexually active during the contagious period of the infected partner. To our knowledge, there are no similar reports published to date. If the determinants of such a “resis-

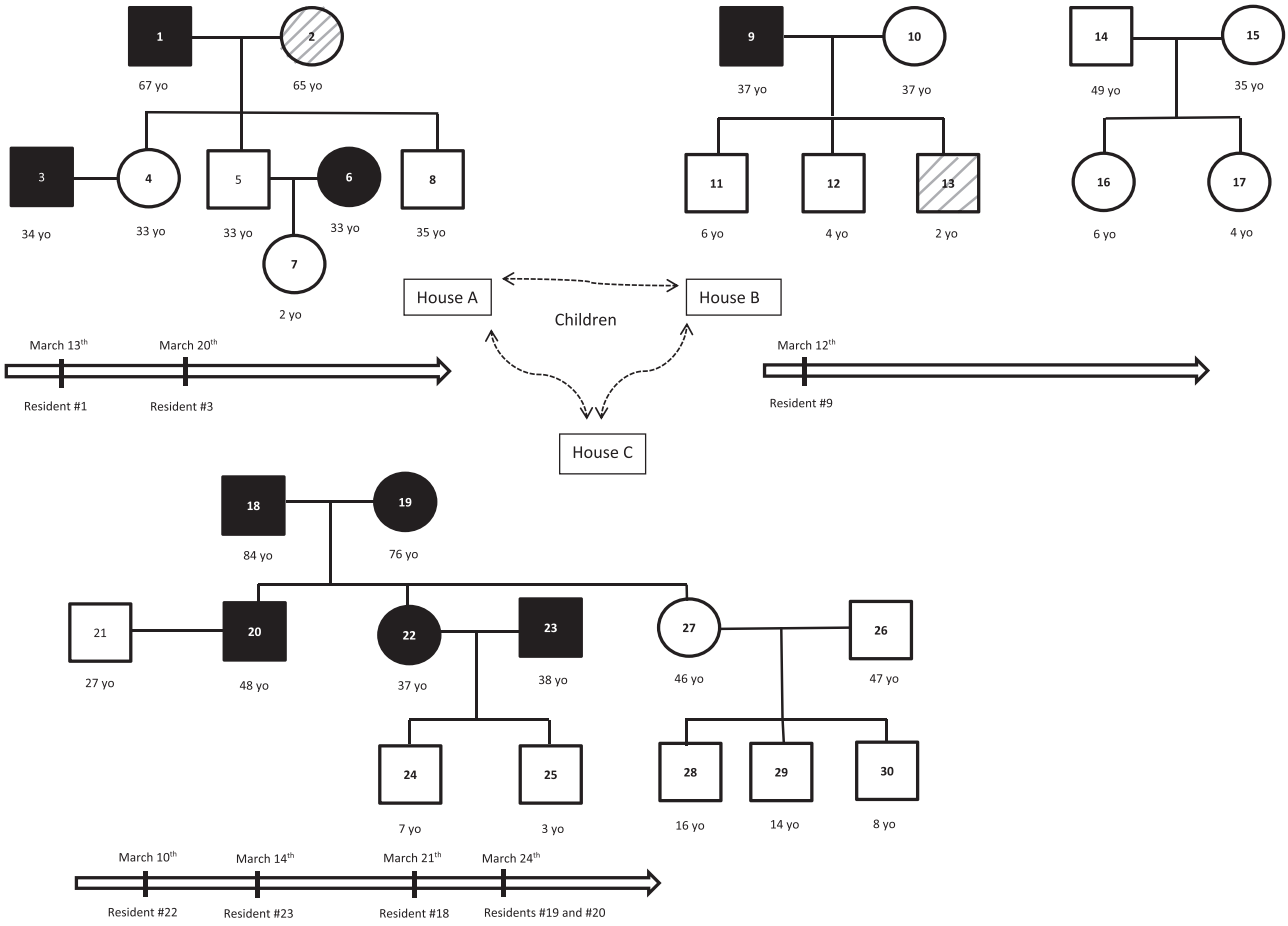

Fig. 1. Population's distribution in each house, kinship, confirmed COVID-19 cases and temporal occurrence of each case.
Legend: square = male; circle = female; horizontal bar = couples; vertical bar = parentage; black = confirmed COVID-19 case; white = excluded case; hatched grey = symptoms finally not related to COVID-19; vertical arrows = timelines of symptoms' onset in COVID-19 symptomatic residents.
Abbreviation: yo = year-old.

tance" to SARS-CoV-2 remain uncertain, some of our results (data not shown) allow us to speculate about a potential role of a genetic factor, currently under investigation.

Ethics

This study was approved by the local institutional review board. A written informed consent was obtained from all patients.

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