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Original article

Post-COVID-19 follow-up clinic: depicting chronicity of a new disease

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Abstract. *Background and aim of the work:* The coronavirus disease-19 (COVID-19) outbreak is posing considerable challenges to healthcare systems and societies worldwide. While the knowledge on the acute phase of the disease has rapidly expanded, little is known on the consequences of COVID-19 following clinical remission. We set up a multidisciplinary COVID-19 follow-up outpatient clinic to identify and address the clinical needs of COVID-19 survivors. Here we describe the features of our follow-up programme. *Methods:* The multidisciplinary assessment comprises a complete physical examination, respiratory evaluation (peripheral oxygen saturation, respiratory rate, dyspnoea assessment, lung ultrasound and pulmonary function), cardiovascular assessment (electrocardiography, echocardiography), nutritional assessment (anthropometrics, mini Nutritional Assessment screening tool), neurological examination including cognitive tests, and mental health assessment. All data are prospectively collected, and blood is sampled for biobanking. *Results:* Since 7 April to 5 June, 2020, 453 out of the 1388 COVID-19 survivors managed at our University Hospital have been evaluated at the Outpatient COVID-19 Follow-up Clinic. The characteristics of the follow-up cohort are similar to those of the whole cohort of COVID-19 in terms of demographics, comorbidities, and COVID-19 severity upon ED presentation, indicating that the follow-up cohort is representative of the whole cohort. *Conclusions:* Continuous patient monitoring might give an answer to the numerous unsolved questions about what comes next in this pandemic and beyond. This will help physicians and researchers establish strategies to face future pandemics and develop preventative and therapeutic strategies for similar hyperinflammatory conditions. (www.actabiomedica.it)

Key words: COVID-19, follow up, outpatient

Introduction

Coronavirus disease-2019 (COVID-19) is a novel disease caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). Since its first description in December 2019, COVID-19 soon progressed into a major public health concern, prompting the scientific society to join forces to respond consciously to this common challenge (1). Rapidly accumulating clinical experience on COVID-19 paved the way for an extensive and prompt characterization of the acute phase of the disease. However, we lag behind in the knowledge of COVID-19 evolution in survivors.

Available data on long-term sequelae of previous coronavirus diseases are scarce, and their reproducibility in SARS-CoV-2-infected patients is questionable (2,3). Besides pulmonary function, COVID-19 may

affect renal (4), cardiovascular (5), and neuropsychiatric (6) health, as well as nutritional status (7). The extent to which these alterations may persist remains obscure.

With the aim of identifying and addressing the clinical needs of COVID-19 survivors, we implemented a multidisciplinary COVID-19 follow-up outpatient clinic at our hospital. Patient data and blood samples are collected prospectively in an attempt to combine patient care and answer crucial questions about the pathophysiology of COVID-19 and the consequences of the disease.

Our multidisciplinary model

This follow-up programme is part of the COVID-BioB study, a large observational investigation performed at San Raffaele University Hospital, a tertiary health-care hospital in Milan, Italy. The study protocol was approved by the Hospital Ethics Committee (protocol no. 34/int/2020) and registered on ClinicalTrials.gov (NCT04318366). All patients enrolled in the follow-up programme provided a signed informed consent prior to any study procedures.

All hospitalized patients are offered to participate in the follow-up programme. For patients managed at home after discharge from the Emergency Department (ED), telephonic consultation by a trained physician discriminates patients for whom the follow-up visit is recommended. Outpatient visits are scheduled at 4 weeks, 3 months and 6 months after hospital discharge.

The Outpatient COVID-19 Follow-up Clinic's team comprises internists, neurologists, psychiatrists, cardiologists, nutritionists and nephrologists. Data about the initial presentation of COVID-19 and the disease course are retrospectively scrutinized from medical records in the presence of the patient and integrated with detailed medical history. Complete physical examination and vital sign assessment including measurement of peripheral oxygen saturation with a pulse oximeter are performed on all patients. Respiratory rate is measured by counting respiratory chest movements of over a period of 60 seconds. The modified Medical Research Council (mMRC) scale for dyspnoea is used to quantify residual shortness of breath. The respiratory assessment is complemented by lung ultrasound. Cardiovascular assessment includes electrocardiography and echocardiography. Patients are asked to self-rate their health status on a visuo-analogue scale (VAS)(8). The nutritional assessment includes measurement of height and body weight, as well as of waist circumference as an estimate of adiposity (9). The Mini Nutritional Assessment (MNA) screening tool is used to evaluate nutritional status, with an MNA value ≤7 defining malnutrition and a score between 8 and 11 identifying patients at risk of malnutrition(10). Complete neurological examination is performed to exclude neurological *sequelae*. Cognitive function is inspected through the Montreal Cognitive Assessment (MoCA) score(11), where a score <24 in the absence of known history of neurocognitive disease identifies cognitive impairment. Mental health counselling is an integral component of the follow-up evaluation. Quality of life assessment through the World Health Organization Quality of Life (WHO-QOL) –BREF questionnaire(1) and screening of insomnia, anxiety, and post-traumatic stress disorder (PTSD) through validated indicators (12-14) are performed in all patients.

Demographic, anthropometric, clinical and instrumental data are prospectively collected. Blood samples are centrifuged to separate plasma, serum, peripheral blood white cells, and supernatant, which are then aliquoted and frozen for subsequent use. Samples and data are available to the entire research community, upon reasonable request.

Our patients

Since the beginning of the Outpatient COVID-19 Follow-up Clinic on 7 April 2020, as of 5 June 2020 453 patients have been evaluated.

Patients admitted to our University Hospital as of 5 June were 1167, of whom 860 (73.8%) hospitalized. Of these, as of the same date, 187 (21.7%) had died, 628 (73%) had been discharged, and 45 (5.3%) were still hospitalised.

Of the 453 patients evaluated at the Outpatient Clinic, 363 (57.8% of the hospitalised cohort) had

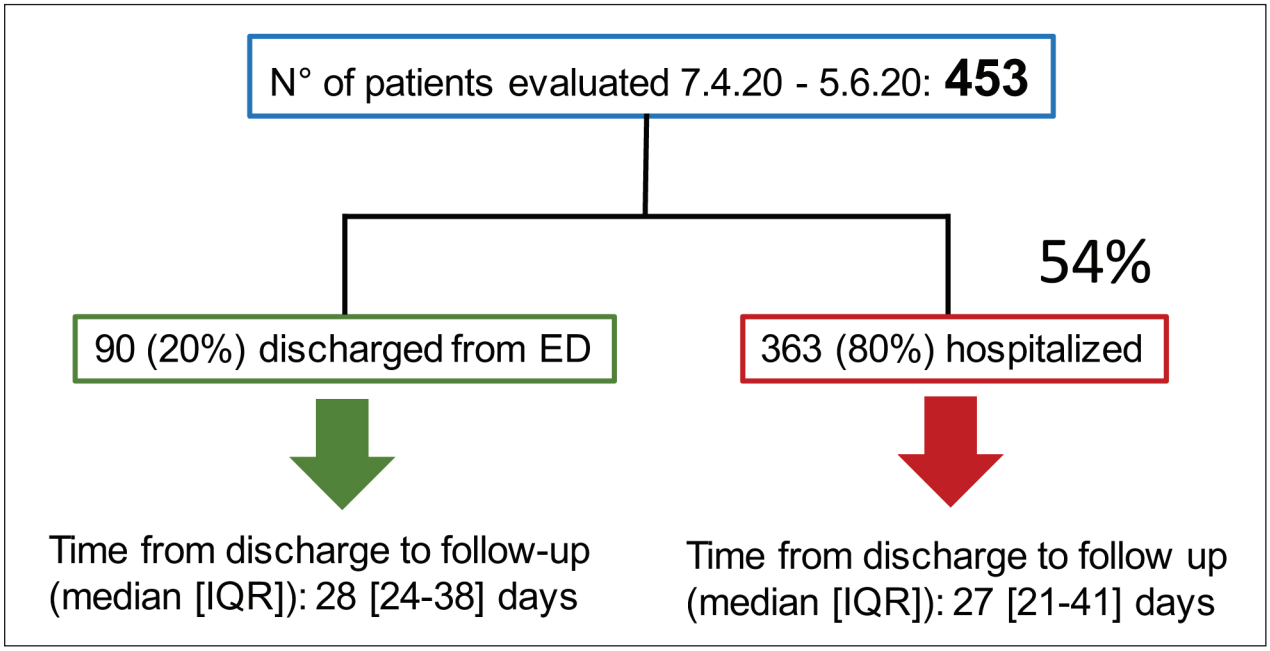

Figure 1. Study flow chart

been hospitalised and 90 discharged home from the ED (Figure 1). Reasons for patients' failure to follow-up included: *i)* missed phone calls (40%), *ii)* refusal to follow-up due to subjective recovery or work commitments (20%), *iii)* long distance of the hospital from home (15%), *iv)* stay in rehabilitation institutes (15%), and *v)* impossibility to physically reach the hospital due to transportation difficulties (10%).

Patients evaluated at the follow-up visit so far are representative of the whole cohort of COVID-19 survivors seen at our University Hospital, having comparable features in terms of demographics, comorbidities, and COVID-19 severity at ED presentation (Figures 2 and 3). Most patients were males in both groups of patients. Median (interquartile range, IQR) age in the entire COVID-19 population and in the follow-up cohort was 59 (49-70) and 59 (49-68) years, respectively ($p>0.05$).

The ratio of arterial oxygen partial pressure (PaO_2) in mmHg to fractional inspired oxygen (FiO_2) expressed as a fraction (PaO_2/FiO_2), serum levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH), and absolute lymphocyte count at ED presentation served as markers of disease severity. Median (IQR) PaO_2/FiO_2 was 304.8 (251.4-349) in the COVID-19 cohort and 309.5 (261.9-348.7) in the follow-up group ($p>0.05$). Median (IQR) absolute lymphocyte count was 1 (0.8-1.4) $x10^9$/L in both patient groups. Median serum levels of CRP and LDH in the entire COVID-19 population were 55.5 (19.1-109.2) mg/L and 325 (254-429) U/L, respectively. On the other hand, the follow-up cohort had median (IQR) levels of CRP and LDH of 54.6 (19-104.8) mg/L and 321 (256-415.2) U/L, respectively. No significant difference in serum CRP and LDH levels at ED presentation was found between the two patient cohorts ($p>0.05$) (Figure 4).

Questions that this project will allow us to answer

Awareness of what to expect from the second phase of this pandemic is crucial to minimise long-term morbidity and mortality associated with COVID-19. Following survivors over time might reveal unexpected COVID-19 *sequelae* and help guarantee prompt and informed medical care. Residual lung damage may be present after the resolution of the

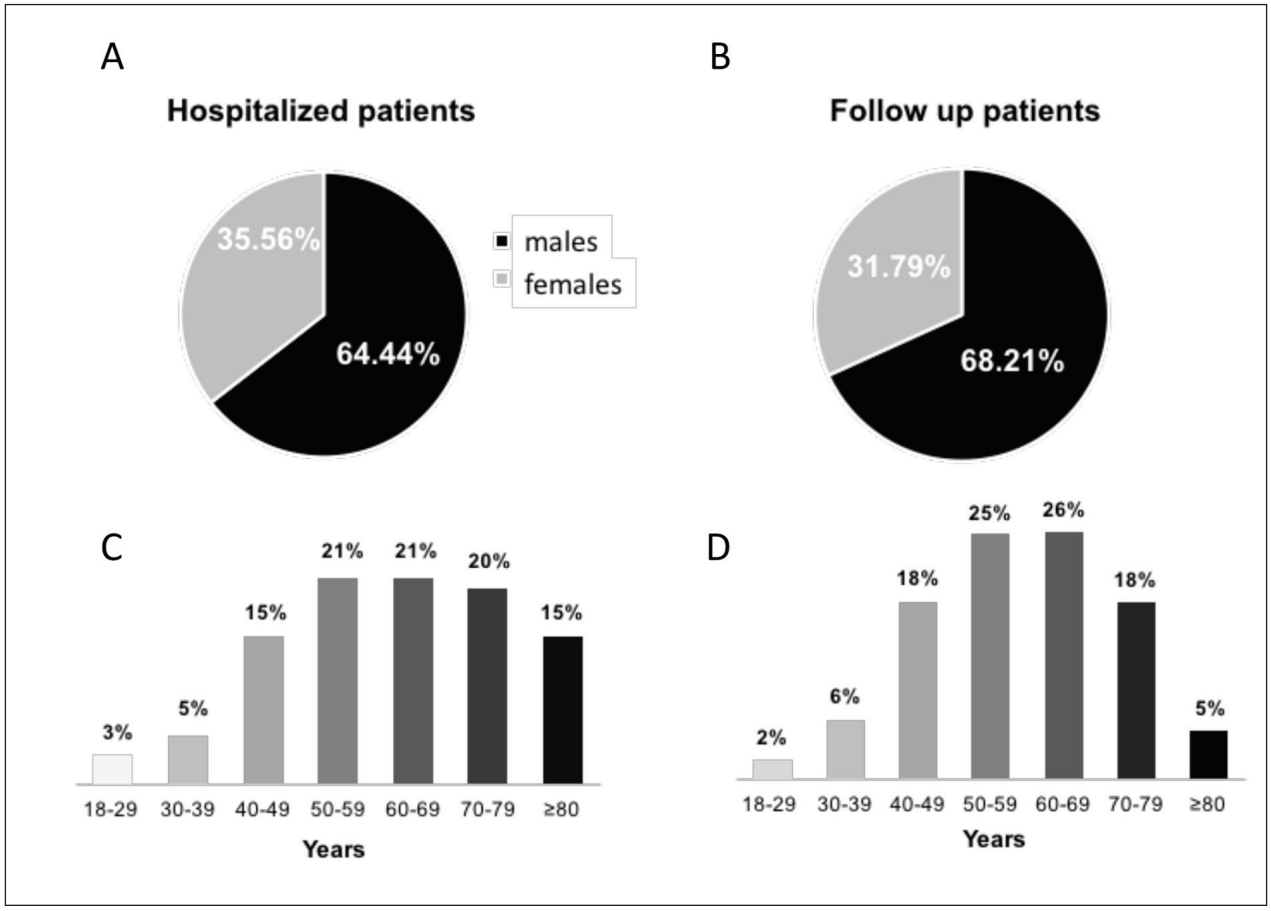

Figure 2. Comparison of demographics between hospitalized and follow-up COVID19 patients

acute phase of the disease (15). Indeed, fibrosis may supersede tissue inflammation independently of viral eradication (16). Besides clinical parameters and reported shortness of breath, PFT and lung ultrasound may provide an objective insight into pulmonary function and disclose persistent subclinical lung alterations. Chronic cardiovascular damage in COVID-19 has been hypothesised (17) . In this sense, periodic electrocardiographic and echocardiographic evaluations by an expert cardiologist may be needed to monitor both electric and mechanic heart function over time. Nutritional status is also a matter of concern in COVID-19 patients, systemic inflammation-related hypercatabolism representing a potential mechanism (18) . Patients surviving to acute respiratory distress syndrome tend to lose lean body mass during acute illness in favour of fat mass, which may be detrimental for functional recovery (19). In patients with a less severe pulmonary involvement, gastrointestinal symptoms (20). and smell and taste disturbances (21) associated with SARS-CoV-2 infection may play a role. Nutritional counselling is therefore crucial to COVID-19 patients. Cognitive function following COVID-19 should also be assessed, due to the potential impact of both direct viral pathogenicity and immune-mediated mechanisms on the development of cognitive *sequelae (22)*. Psychological health might be undoubtedly endangered by COVID-19. Fear of disease complications and restriction of human contact may generate anxiety, and in some cases post-

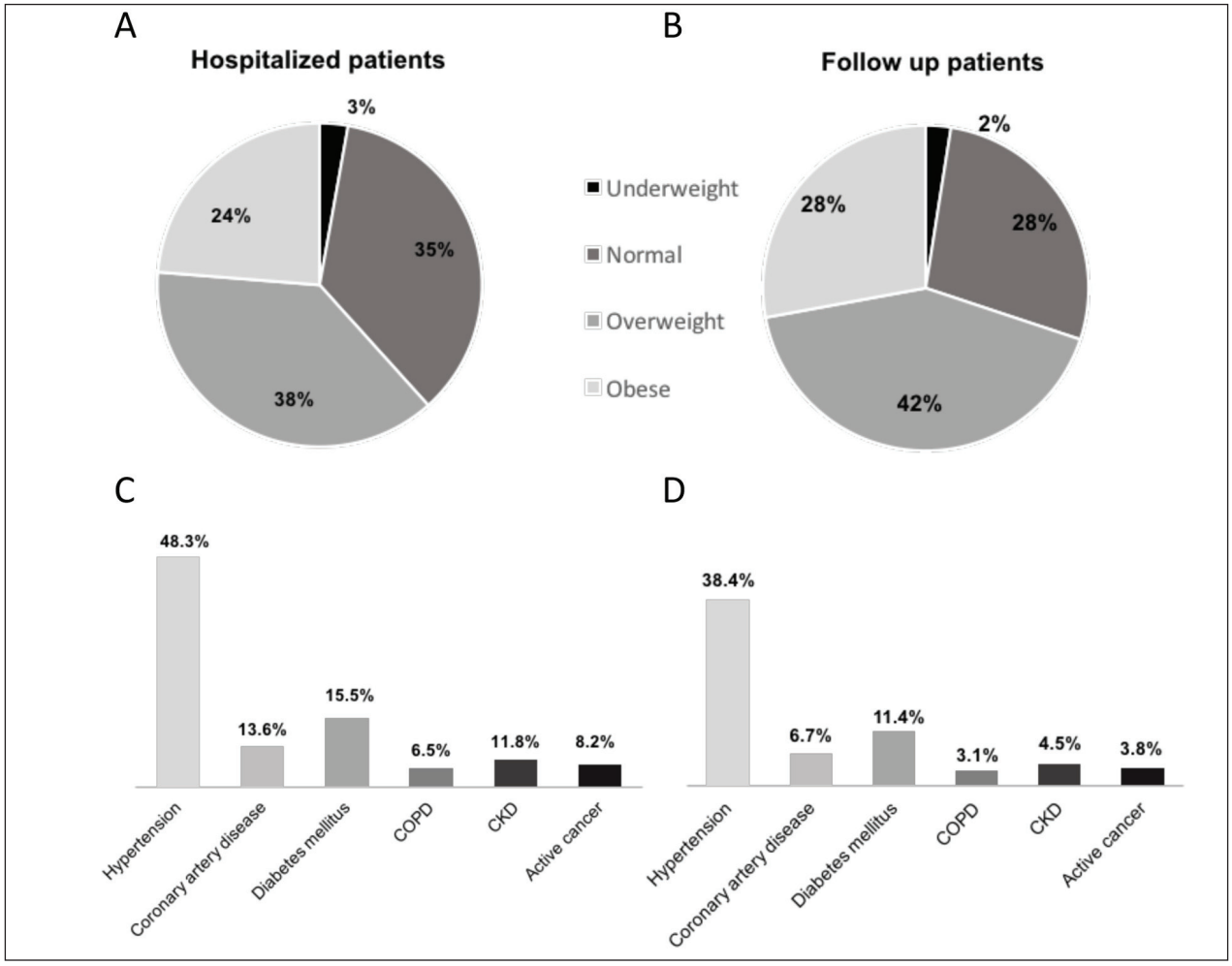

Figure 3. Comparison of comorbidities between hospitalized and follow-up COVID19 patients. COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease

traumatic stress disorder may develop (23). Adequate mental counselling is therefore critical to investigate neuropsychological *sequelae* of COVID-19 and to preserve mental well-being.

Besides the clear contribution to the advancement in the knowledge of COVID-19 *sequelae*, the prospective collection of blood samples implemented at our Outpatient COVID-19 Follow-up Clinic represents an invaluable source of biologic material to be used for research in COVID-19. Patients will be subsequently evaluated (internal medicine, neurological and psychiatric assessment) and biospecimens retrieved at 3 and 6 months post-discharge, which guarantees an attentive care-delivery system which may have important implications for both patient care and research. Patients who suffered from severe COVID-19 (those admitted to the Intensive Care Unit or requiring high-flow oxygen therapy or non-invasive ventilation) will undergo a specific pulmonary follow-up through pulmonary function tests (PFT), impulse oscillometry and lung CT scan.

In conclusion, continuous patient monitoring might give an answer to the numerous unsolved questions about what comes next in this pandemic and beyond. This will help physicians and researchers establish strategies to face future pandemics and develop

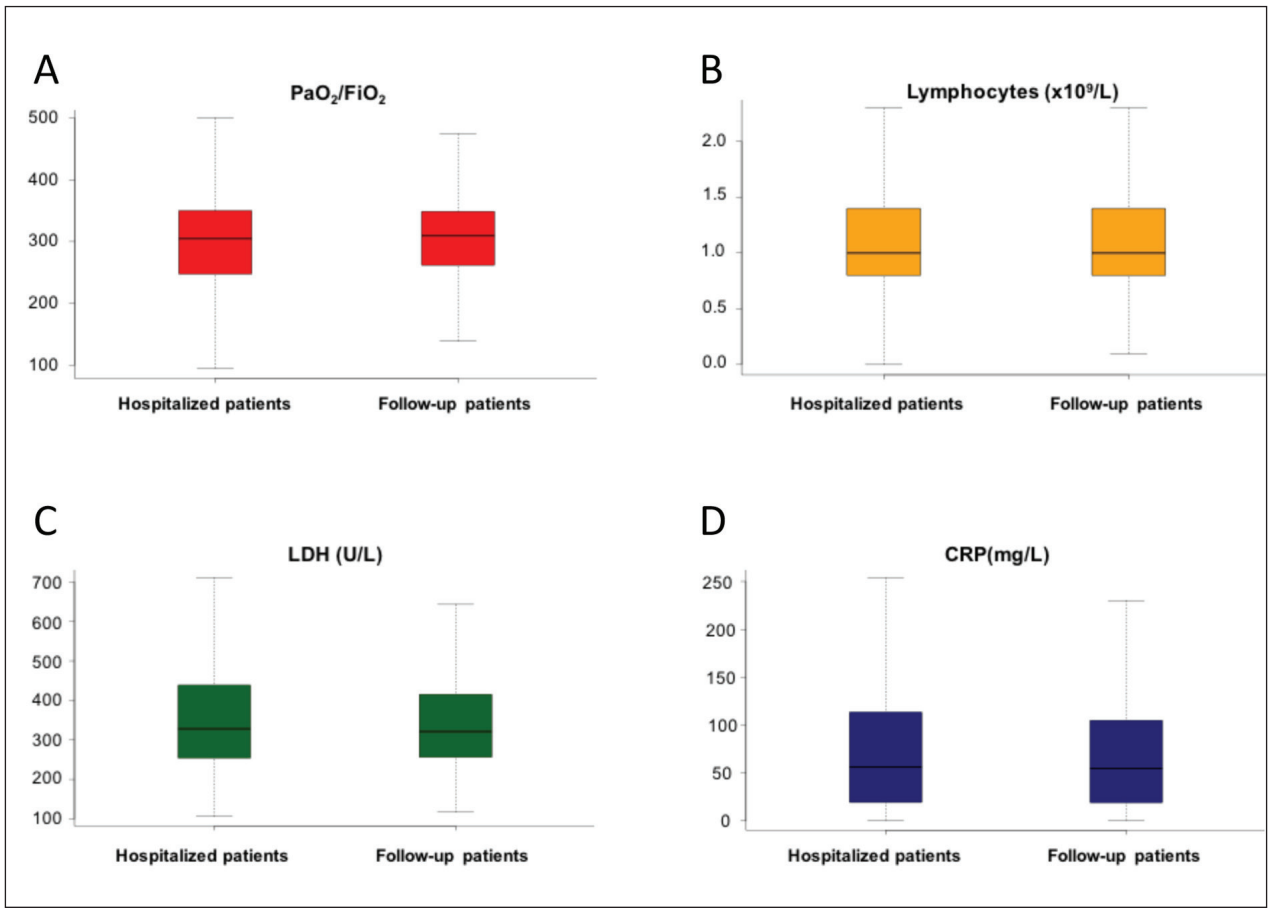

Figure 4. Comparison of markers of disease severity between hospitalized and follow-up COVID19 patients. PaO_2/FiO_2, ratio of arterial oxygen partial pressure (PaO_2) in mmHg to fractional inspired oxygen (FiO_2); CRP: C-reactive protein; LDH: lactate dehydrogenase

preventative and therapeutic strategies for similar hyperinflammatory conditions.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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