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Commentary

A rapid and effective strategy for repurposing drugs for COVID-19

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Coronavirus disease 2019 (COVID-19) is an emerging condition that was first detected in December 2019 in Wuhan, China, and spread around the globe very quickly. The World Health Organization declared this as a public health emergency of international concern on 31st January 2020 and as a pandemic on 11th March 2020. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has a very similar RNA sequence identity to SARS-CoV[1] and Middle East respiratory syndrome (MERS) viruses.[2] As of 20th September 2020, the number of confirmed COVID-19 cases worldwide was 30,675,675 with 954,417 deaths in 216 countries.[3]

Health care authorities recommend certain preventive procedures to protect against the spread of the disease and control this pandemic, including quarantining infected patients, frequent handwashing with surfactants, wearing suitable masks, placing areas with high case load under lockdown, and maintaining physical distance. COVID-19 is diagnosed via several approaches, including clinical observations, radiographical assay, and aggressive nasopharyngeal swab sampling, which could potentially be replaced by the non-invasive sampling method of exhaled breath condensate[4] for rapid diagnosis of suspected victims based on laboratory testing. It is obvious that early detection is very important in controlling the transmission of this virus. Despite these general recommendations to control the spread of the virus, intense research activity globally is focused on developing a vaccine against SARS-CoV-2 and discovering new antiviral drugs. New treatments are urgently needed for patients infected by this virus, especially those suffering from other background diseases, such as diabetes mellitus, asthma, and heart diseases. At the moment, there is no vaccine available to immunize against SARS-CoV-2 and no suitable drugs for treating COVID-19. However, numerous clinical trials are underway around the world and COVID-19 is the top priority for health system research and development departments and also pharmaceutical/bioscience companies. The aims of this editorial are to propose an effective and short-term strategy to facilitate the discovery of new drugs to be used in the treating COVID-19 and other critical conditions. A brief discussion is also provided on mid-term and long-term approaches.

Strategies that are commonly used in drug discovery investigations include: 1) virtual screening, 2) high-throughput screening, 3) phenotype screening, 4) structure-based drug design, 5) fragment-based drug design, 6) ligand-based drug design, and 7) drug repurposing based on clinical data. However, most of these strategies are time-consuming and costly. Classical drug repurposing procedure can also be considered as a potentially quicker strategy that is based on the connection between basic and clinical sciences (bench to bedside). There are various examples of repurposing with US FDA-approved drugs that

are now used for treating conditions in addition to the intended applications from their discovery and development, such as sildenafil (repurposed from coronary artery disease for the treatment of erectile dysfunction), sulfonylureas (hypoglycemic sulfonamides to the antidiabetic effects of sulfonylureas), aspirin (NSAID to the prevention of thrombosis), and thalidomide (from tragedy to US FDA approval for the treatment of multiple myeloma). More examples have been summarized by Opera *et al.*, such as the use of NSAIDs for treating ovarian cancer, the use of astemizole, a second-generation antihistamine, for inducing cellular autophagy in prostate cancer, and the application of anti-retroviral drugs, such as raltegravir, for the treatment of neck squamous cell carcinoma.[5]

Beside classical drug repurposing procedures, in this communication and as a short-term solution, we propose the numerical analysis of available databases containing detailed records for COVID-19 patients. Statistical analysis of data for confirmed and suspected COVID-19 patients, particularly regarding their drug therapy profiles in the past months and careful follow-up of hospitalized COVID-19 patients, in an appropriate database could help to identify possible correlations between COVID-19 outcomes and preventive or curative action of drugs used before infection by the virus. Obviously, any candidate drugs proposed by these statistical analyses should be subjected to controlled clinical trials for final confirmation of their beneficial effects. Chloroquine (CQ) and hydroxychloroquine (HCQ) are among the potential candidates to be used in the treatment of COVID-19. CQ and HCQ have been shown to have antiviral activity *in vitro* and *in vivo*.[6-8] As an example to show the practical applicability of our proposed strategy, patients suffering from rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) may or may not receive CQ or HCQ in their pharmacotherapy regimens. In clinics with organized and well-documented patient registry systems, if the number of RA/SLE patients receiving CQ or HCQ that became infected with SARS-CoV-2 is lower than those patients not receiving CQ or HCQ, this difference suggests that CQ or HCQ did act against SARS-CoV-2 somehow. A schematic representation of the central idea proposed in this article is shown in Figure 1. Our proposed statistical analysis could

also be applied to hypertensive patients receiving drugs that affect the renin-angiotensin system (RAS group) and those receiving other antihypertensive drugs (non-RAS group) to investigate the possible *in vivo* effects of RAS drugs against SARS-CoV-2. Meng *et al.* [9] reported that RAS drugs improved the clinical outcome of COVID-19 patients with a history of hypertension; 23.5% of hospitalized COVID-19 patients in the RAS group had severe symptoms compared with 48.0% for hypertensive patients in the non-RAS group. More examples can be found in the literature. Obvious rules (e.g. the importance of building matched case/control groups) in such comparisons should be kept in mind. It is possible to conduct a large-scale multicenter study and reach a final decision within 3–4 days by employing the proposed strategy. A list of potential drugs for treating COVID-19 patients could be obtained from a literature search (*e.g.* references[10-13]) and from clinical observations. A very short study time (the most favorable characteristics for pandemic conditions), very low cost, and no further medical intervention are the main advantages of our proposal. Possible drug–drug interactions and the effects of any background illnesses on the outcomes of the proposed numerical analysis are the main disadvantages, which could be managed through the use of large databases and complementary statistical analyses.

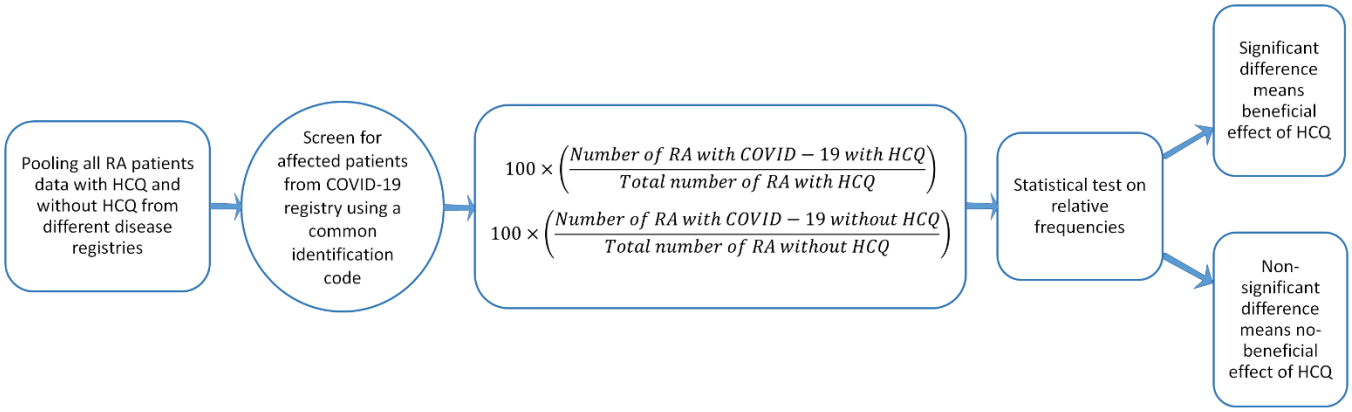

Figure 1. Schematic representation of the proposed strategy for numerical analysis of patient records. In this example, data from rheumatoid arthritis (RA) patients is analyzed to elucidate any possible effects of hydroxychloroquine (HCQ) on COVID-19.

As a mid-term solution, research and development departments in pharmaceutical companies and medical centers could focus on conducting systematic clinical trials with antiviral, anti-bacterial, and anti-fungal drugs, since we need new drugs in many therapeutic areas. At this time, there are no effective antiviral drugs for SARS-CoV-2. Most anti-bacterial drugs are not applicable today in infection control owing to drug resistance and drugs with novel mechanisms of actions are urgently needed.

Our long-term solution should attract the attention of health policy makers and researchers around the world. The COVID-19 pandemic is a real disaster and has negative effects on human life and global economics in both short- and long-term. However, the pandemic has highlighted a very simple fact to everyone, especially to governors and health policy makers, that a non-controlled communicable disease such as COVID-19 does not consider who it infects. Among those infected and killed by the virus, there are prime ministers, ministers, parliament speakers, members of parliament, scientists, rich people, and poor people of different ethnic/racial backgrounds. To prevent or better manage such disasters in the future, it is essential to increase healthcare, research and development budgets and provide the necessary facilities to support drug discovery and development investigations around the world in different disciplines. Human health is more valuable than anything else and we should focus our attention on improving it for the benefit of all. We believe that reforms are required to support novel drug discovery and development studies, especially in universities, biomedical research centers, and small business research units.

In conclusion, we suggest that research groups in countries with well-organized disease registry systems and detailed medical records conduct meta-analyses on the recorded data to identify patient groups receiving a drug (or drugs) with potential for prophylaxis or treatment of COVID-19. In addition to this short-term solution, mid- (further activation of new drug development studies) and long-term solutions relating to reforms in global policy surrounding the development of new drugs are briefly discussed in this commentary.

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