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ABOUT COVER

Peer reviewer of World Journal of Virology, Dr. Xie is an Assistant Researcher at the Clinical Medicine School of Inner Mongolia University for Nationalities (China). Dr. Xie's career efforts have been devoted to the study of development of new drugs and vaccines for human immunodeficiency virus. He also recently (2019) published an important report on the pathogenesis of respiratory syncytial virus and small cell lung cancer at the International Conference on Geological Research and Environmental Sciences. His clinical virus research has led to the publication of several academic papers, all of which are indexed in the Science Citation Index/Engineering Index. He currently serves as a member of the Inner Mongolia Autonomous Region STD and AIDS Prevention Association and of the Clausius Publishing Group (Canada). His ongoing research interests have expanded to include clinical medicine, cancer medicine, molecular biology, and viral microbiology. (L-Editor: Filipodia)

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The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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FRONTIER

Hypothesis of design of biological cell robot as human immunodeficiency virus vaccine

Yao-Ying Xie, Fan Yang, Xiao-Yu Liao

ORCID number: Yao-Ying Xie 0000-0001-9981-356X; Fan Yang 0000-0001-9982-356X; Xiao-Yu Liao 0000-0001-9985-356X.

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Yao-Ying Xie, Fan Yang, Xiao-Yu Liao, College of Clinical Medicine, Inner Mongolia University for Nationalities, Tongliao 028000, Inner Mongolia Autonomous Region, China

Corresponding author: Yao-Ying Xie, PhD, Research Fellow, College of Clinical Medicine, Inner Mongolia University for Nationalities, No. 536, Huolinhe Street (West), Tongliao 028000, Inner Mongolia Autonomous Region, China. xieyaoying@outlook.com

Abstract

High genetic variability of human immunodeficiency virus (HIV) has been a major intractable challenge to the practical design of vaccines. But a recent pioneer study published in PNAS Xenobots, is likely to revolutionize HIV prevention as it presented the world's first living robot made of cells. In the advent of this discovery, we herein discuss the possibility of using living biological cell robots to target HIV-infected T lymphocytes, and the prospects of this approach being a new HIV vaccine. We capture the current research status and trend of advances in biological cell robots' design as a new HIV vaccine. The key differences between this novel vaccine and other HIV vaccines are highlighted.

Key Words: Human immunodeficiency virus; New vaccine; Biologically inspired microrobots; Human immunodeficiency virus target cell surrogate; CD4

Core Tip: In February 2020, the birth of the world's first live-cell robot has brought hope for the artificial design of human live cells. Therefore, herein we propose a hypothesis: Can we artificially design a cell as an alternative target cell for human immunodeficiency virus (HIV) infection and use it as a new acquired immune deficiency syndrome vaccine to prevent HIV infection.

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INTRODUCTION

While preventive human immunodeficiency virus (HIV) vaccine development has been a constant goal since the discovery of HIV, interest in a therapeutic vaccine for HIV-infected people has fluctuated. Many people thought that therapeutic vaccines were impossible because until recently there were no examples of such vaccines being used for other diseases. With the emergence of more capable, simple, and relatively non-toxic combination drug therapies, there have been fewer calls for the development of a therapeutic acquired immune deficiency syndrome (AIDS) vaccine. However, the world's first living somatic cell robot has rekindled interest in a therapeutic vaccine. The vaccine can not only be used as a stand-in for HIV target cells, through alternative ways to protect the body's healthy immune cells, but can also enhance immune-mediated clearance of virus-producing cells and/or assist in the destruction of the reservoir of latently infected cells that drug therapy alone does not seem to be able to eliminate[1]. So, herein we propose a hypothesis that artificial design of the live-cell robot can be considered as a new AIDS vaccine.

CURRENT STATUS OF HIV VACCINES

Since the discovery of AIDS in 1981, massive resources have been directed at research aimed at developing preventive and curative agents for affected patients. Nearly 40 years later, AIDS has become a global public health threat claiming many lives. A few years ago, a meeting was held in Keystone Symposia (March 21 to 26, 2012) to focus on basic aspects of immunology and HIV-1 virology to highlight issues that challenge the field. The genetic diversity of circulating HIV-1 variants puts extreme demands on the quality of the response that a prophylactic vaccine will need to elicit. The recent trials of therapeutic HIV vaccines were introduced and the results of therapeutic vaccines in non-human primate models were discussed. It is clear that therapeutic vaccine development trials and studies follow a standard preventive vaccine development path. After conceptualizing the product, 10 to 15 years of animal model testing are performed prior to 4 to 6 years of GMP product development, allowing another 5 to 10 years of phase I, phase II, and then phase III clinical trials for licensing and distribution of specific vaccine candidate products before they occur. We can see that this path is frustratingly slow and may not be the best way to address several of the key issues to be discussed in the development of therapeutic vaccines. It is risky for researchers to try to design a vaccine that solves such a complex problem by reasoning through aspects of the final product before testing it. At the end of a long trial, however, it is likely to fail completely because it does not contain a necessary ingredient or contains unnecessary ingredients that undermine the overall efficacy. We have long believed that it is postulated that the HIV vaccine is the most effective approach to control the AIDS pandemic. Although much progress has been made to achieve this goal[1,2], no licensed HIV vaccine has been put on the market to prevent HIV infections. It was clear that therapeutic HIV vaccine development requires addressing several very different issues including: (1) How to correctly understand the mechanism of HIV infection? (2) How does the vaccine respond to HIV mutations? and (3) How to choose the optimal way to block HIV infection?

MECHANISM BY WHICH HIV INFECTS HOST CELLS

HIV selectively infects helper T lymphocytes, dendritic cells, and macrophages because these cells express CD4 molecules. The HIV infection process is complex, with several stages: Adsorption, entry, uncoating, reverse transcription, integration, replication, transcription, translation, assembly, and maturation (Figure 1). Current research provides evidence that HIV infection requires not only CD4 molecules and helper receptors (CXCR4 and CCR5), but also proteins encoded by HIV genes, such as gp120 and gp41. A detailed list of proteins encoded by genes associated with HIV infection in host cells is provided in Table 1[3]. When HIV enters the human bloodstream, it selectively invades host cells expressing CD4 molecules on their cell surface. HIV binds to the CD4 receptor on the surface of the host cell *via* its surface envelope protein gp120[4]. Upon binding, gp120 protein undergoes structural alterations exposing another envelope protein gp41. Meanwhile, the gp120-CD4 dimers formed to interact with the host's cell surface auxiliary receptor CXCR4/CCR5 to create three molecular complexes constituting gp120-CD4-CXCR4/CCR5. These

Table 1 Human immunodeficiency virus-related genes and their coding proteins, specific functions, and host-cell related proteins

Gene	Encoding protein	Protein function	Host cell-related proteins
Structural genes			
gag	MA	Matrix proteins	Karyopherins, HO3, Calmodulin, VAN/NAF1, TRIM5α, CyPA
	CA	Capsid protein	HP68/RNase L inhibitor, Actin
	NC	Nucleocapsid protein	ESCRT, Tsg-101, AIP-1, Nedd4, Ubiquitin
	p6	Nucleocapsid protein	-
pol	RT	A viral genome that can be transcribed and copied	-
	PR	Cut polymerized protein	-
	IN	Integrate viral DNA with cellular DNA	INI1/hSNF5, LEDGF/p75, BAF, HMGal, ATR, ATM, Karyopherins, XRCC5
env	gp120	Attach the virus to the surface of the cell	CD4, CCR5. CXCR4, DC-SIGN, DC-SIGNR, MR, CD207
	gp41	Fusion with host cells	-
Necessary regulatory genes			
tat	Tat	Trans-activated proteins that activate HIV gene transcription	NF-κB, cyclin T, CDK9, Med28
rev	Rev	A regulator of viral protein expression that regulates mRNA splicing and promotes mRNA transport to the cytoplasm	TNPO3, importin β, Crm1, Ran GTPase, Sam68, p32
Nonessential regulatory genes			
nef	Nef	Negative regulatory factors, which change cell signals, reduce the expression of CD4 and MHC-I molecules, and reduce the killing of HIV infected cells by CTL, representing essential factors in the development of infection into AIDS	PACS-l, ASK1, PAK, PI3-K, Lck, VAN/NAFl
vif	Vif	Viral infectious factors that promote viral assembly and maturation	APOBEC3G
vpr	Vpr	Viral protein regulatory, which transports viral DMA to the nucleus and inhibits cell growth	Karyopherins, Uracil-DNA glycosylase, Weel
vpu	Vpu	Viral protein U that promotes the release of the virus	CD317 (Tetherin, BST-2)

HO3: Heme oxygenase-3; TRIM5α: TRIpartite motif-5α; CyPA: Cyclophilin A; ESCRT: Endosomal sorting complex required for transport; Tsg-101: Tumor susceptibility gene-101; AIP-1: Apoptosis-linked gene-2-interacting protein 1; Nedd4: Neural precursor cell expressed, developmentally down-regulated 4; INI1: Integrase interactor 1; BAF: Barrier-to-autointegration factor; ATR: Ataxia telangiectasia and RAD3-associated kinase; ATM: Ataxia telangiectasia-mutated gene; SIGN: Specific intercellular adhesion molecule-3-grabbing nonintergrin; DC-SIGNR: Dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintergrin receptor; MR: Mannose receptor; HIV: Human immunodeficiency virus; NF-κB: Nuclear factor-κB; CDK9: Cyclin-dependent protein kinase 9; Med28: Mediator of RNA polymerase II transcription, subunit 28 homolog; TNPO3: Transportin-3; Crm1: Chromosome maintenance protein 1; Ran: Ras-related nuclear protein; Sam68: Src mitogen-associated protein 68 kDa; Nef: Negative regulate factor; CTL: Cytotoxic T lymphocytes; AIDS: Acquired immune deficiency syndrome; ASK1: Apoptotic signal-regulated kinase 1; PAK: p21 activated kinases; PI3-K: Phosphatidylinositol 3-kinases; Lck: Lymphocyte-specific protein-tyrosine kinase; VAN/NAF1: Virion associated nuclear shuttling protein/nef-associated factor 1; Vif: Viral infectivity factor; Vpr: Viral protein regulatory; Weel: Weel kinase is an important regulator to cell cycles; Vpu: Viral protein U.

complexes expose the host cell membrane and the envelope protein gp41, which is hydrophobic, enabling the HIV to be coated with the host cell membrane followed by HIV and host cell fusion. Finally, HIV nucleic acid is released into the host cell (Figure 2).

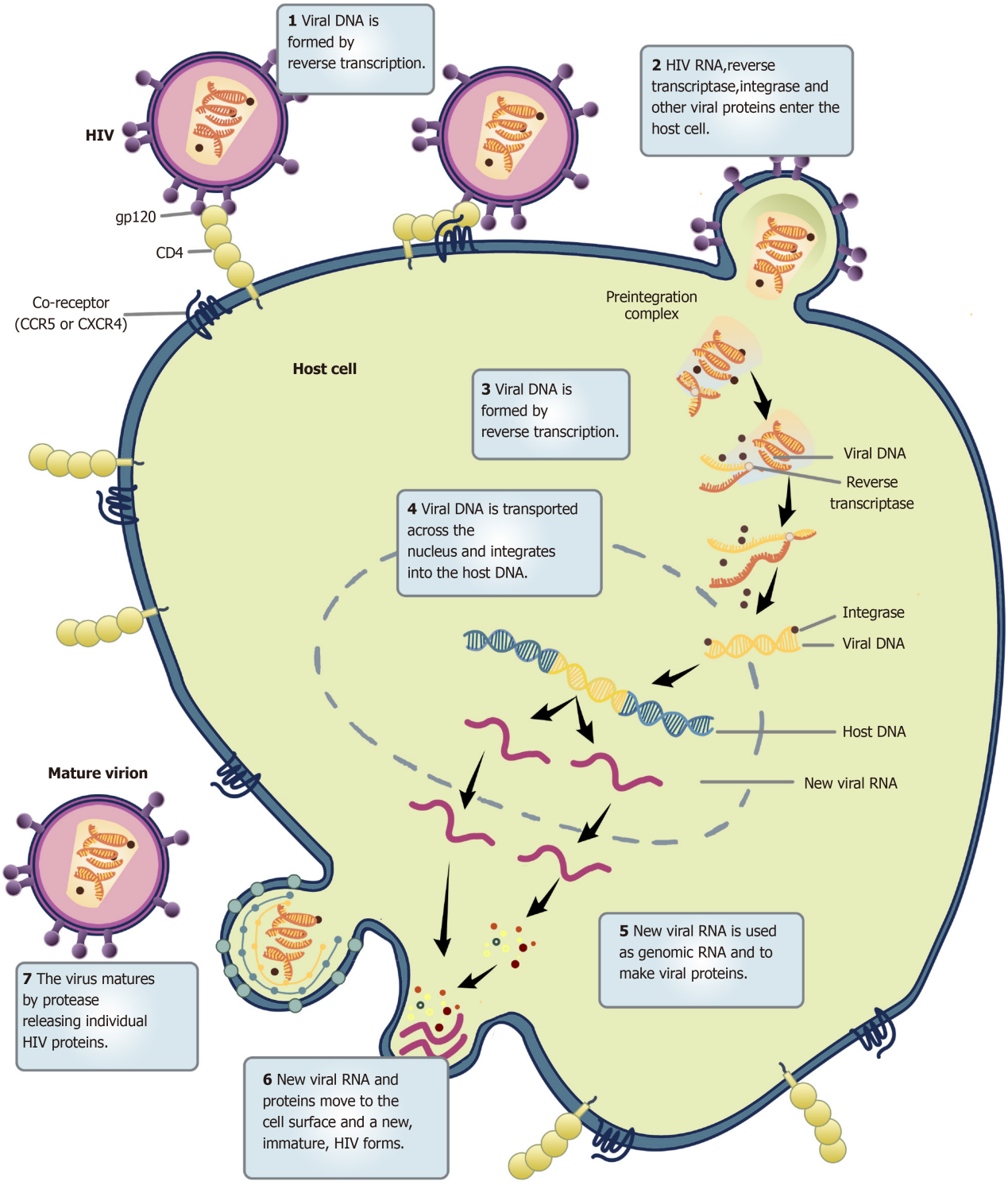

Figure 1 The mechanism by which human immunodeficiency virus attacks a target cell. HIV: Human immunodeficiency virus.

HIV IS HIGHLY VARIABLE

HIV is the most complex of all retroviruses. Its genetic material ranges between 9.2 and 9.8 kb of RNA. Structurally, it is not very stable and has a high mutation rate. Once HIV is coated and fused with the host cell membrane, it releases its capsid protein HIV p24, which is gradually degraded within the host cell to release HIV RNA and reverse transcriptase[5]. The reverse transcriptase uses the RNA as a template to synthesize viral DNA. The HIV DNA is integrated into the host cell nucleus chromosome by the integrase enzyme. Subsequently, the viral DNA uses existing host cell gene copies and protein replication machinery to synthesize its proteins.

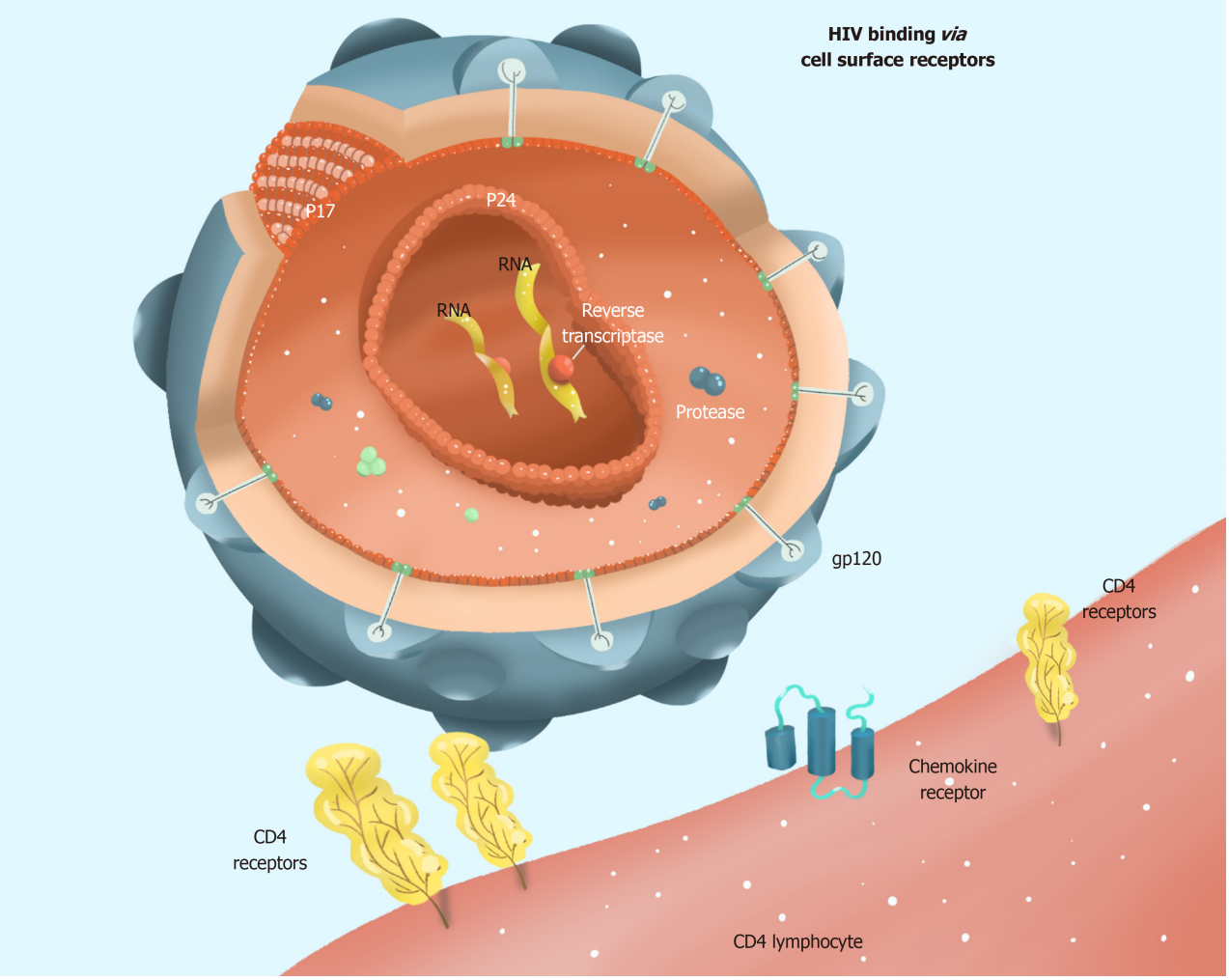

Figure 2 Human immunodeficiency virus recognizes and binds a CD4 lymphocyte. HIV: Human immunodeficiency virus.

Activation of HIV-infected cells triggers the transcription of pre-viral DNA into viral RNA, further translated into structural proteins of HIV. These proteins assemble in the cytoplasm, forming several new viral particles. Eventually, viral particles are exported to the cell surface in the form of buds, which recognize and attack other target cells. Currently, it is known that HIV exhibits high RNA variability. More importantly, the reverse transcriptase of HIV is prone to the problem of base mismatch in the reverse transcriptase synthesis of DNA using RNA as a template, because the reverse transcriptase lacks base proofreading. This leads to a failure to remove the mis-introduced nucleotides in time for replication. An error occurs about once in every replication cycle, causing the virus to replicate with random mutations that are high-frequency and non-directional. The high genetic variability translates to high variability in the encoded proteins. A comparison of antigens extracted from wild type strains of HIV with those from AIDS patients in which HIV has already undergone many replications reveals that the structure and amino acid sequence of proteins from these two groups are different. It has been observed that the injection of vaccines based on HIV antigen into AIDS patients fails to induce the formation of immune cells and antibodies to neutralize HIV. This is because HIV surface antigen molecules undergo rapid mutations that help HIV-infected cells to escape immune recognition due to decreased affinity of produced antibodies for the mutant HIV antigens.

ALTERNATIVE TARGET CELLS FOR HIV INFECTION

We analyzed the recently reported world's first living bio-robot, which we believe could be a new HIV vaccine. This vaccine differs significantly from conventional vaccines. We know that HIV has a high degree of antigenic variability. For this reason, HIV samples used for vaccine development contain mutated versions of HIV, hence

such vaccines are not sufficient for controlling AIDS. This has been the biggest challenge hindering HIV vaccine research and development. Notably, we have observed that despite its many variants, HIV always targets cells expressing CD4 molecules, and the expression of the vast majority of CD4 particles is conserved; variations are rare. This means that human CD4 units are the primary receptors for HIV infection. Based on the recent publication by Kriegman *et al*[6], we believe that a living biological cell robot can be designed to target CD4 molecules.

The surface molecules of this bio-bot are highly similar to the target cells, which not only express CD4 molecules but also other helper receptors needed for HIV infection (CXCR4/CCR5). We believe that this somatic cell robot can be an alternative target cell for HIV infection. This robot can be programmed using supercomputers and gene recombination technologies, to shorten its lifespan and make it undergo rapid apoptosis after HIV infection. Other cellular automata that are not infected with HIV will also degrade themselves within a short time, to avoid unnecessary immune responses. We can also enzymatically engineer the cell robot to synthesize HIV-RNase in the cell, degrade the HIV-RNA that enters the battery, or make the cell robot carry drugs that inhibit HIV replication (Figure 3). In this way, the reproduction of HIV in host cells can be immediately suppressed. To improve the binding rate of HIV to the cell robot, the target cells should be selectively and temporarily sealed with CD4 molecules in the original body using antibodies with radioactive isotopes. Blocking immune cells with CD4 molecules carrying the antibodies may reduce immunity in HIV-infected people, but only temporarily. A recent study showed that the use of live-cell robots as alternative target cells for HIV infection, combined with HIV fusion inhibitors, may reduce the use of CD4 blocking antibodies, which will indirectly enhance the new vaccine's effect without reducing the function of the patient's immune system. Besides, HIV fusion inhibitors can block the entry of HIV into human cells. This novel mechanism requires further research. Strategies that inhibit HIV fusion hold massive promise in solving the problem of HIV resistance. Such agents can be used as adjuvant treatments to the new vaccine, given after vaccination to reduce the adverse reactions of the new vaccine (Figure 4).

RESULTS AND DISCUSSION

The new live-cell robot vaccine is still in the developmental stage and may remain an idea that requires further research. However, we note that it is a better alternative to other HIV vaccines because it overcomes the high variability of HIV. Traditional HIV vaccines currently being studied are primarily based on subunit vaccines, live attenuated vaccines, and inactivated vaccines. But these approaches are proving difficult due to the high antigenic variability of HIV, which hinders the identification of crucial representative genotypes or specific protein antigens. Live attenuated vaccines are associated with safety concerns. In a rhesus monkey model, the simian immunodeficiency virus (SIV) mutant strain lacking the nef gene prevents attack by pathogenic SIV. It protects monkeys from developing AIDS, but it cannot safeguard vaccinated monkeys against the over-infection of wild-type virus. Moreover, SIV without the nef gene can still cause AIDS, especially when given orally to young monkeys. Of note, genetic mutations or deletions in HIV may attenuate viral reproduction, but at the cost of reducing the vaccine's effectiveness. For inactivated vaccines, physical or chemical methods are needed to kill the virus, which requires that the antigenic nature of HIV be changed. These inactivated HIV antigens cannot effectively activate the body's immune system to produce immune responses, and the produced antibody titers are also very low[7]. This calls for collaborative research between computer science and biological science. In natural sciences, cellular simulations based on the ability of HIV to recognize and bind to CD4 receptors in host cells should be developed. Such simulations should consider some conserved proteins such as gp120 and gp41 to design alternative target cells for HIV infection. In computer science, supercomputers with well-designed evolutionary algorithms, through trial and error approaches, should be employed to program cell robots[5]. The development of "surrogate target cells" for HIV infections will lead to "HIV suicide" because they cannot replicate and reproduce[8].

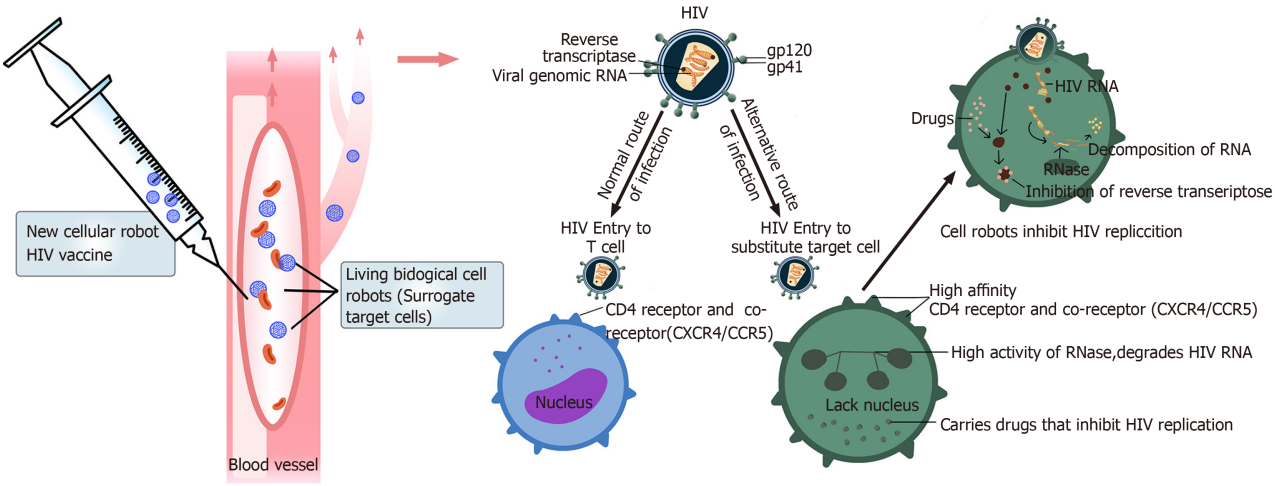

Figure 3 Functions of a living biological cell robot. After entering the body, the living cell robot mediates human immunodeficiency virus (HIV) infection by the high-affinity receptor expressed on the cell surface, and HIV is killed by drugs or RNase carried by the cell. HIV: Human immunodeficiency virus.

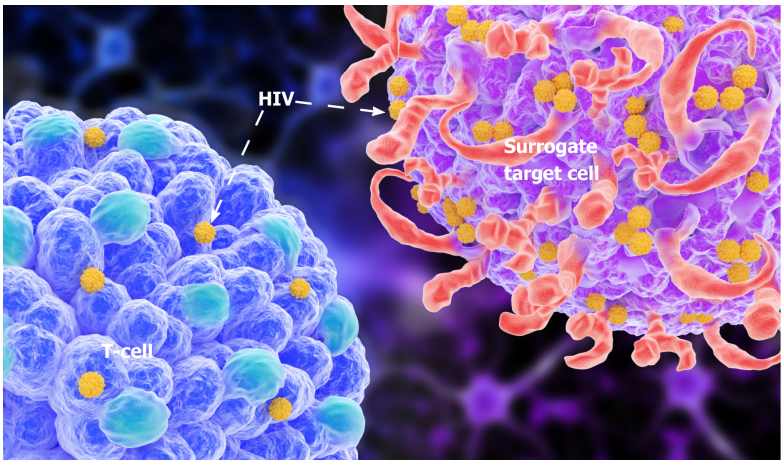

Figure 4 A simulation of human immunodeficiency virus infecting a surrogate target cell by the alternative infection. By blocking the receptor on the T cell surface with the blocking antibody, the probability of human immunodeficiency virus infection surrogate target cell will increase. HIV: Human immunodeficiency virus.

CONCLUSION

However, we note that the new cell robot vaccine is still in the early stages of development, and many fundamental questions need to be addressed before it can be put into practical use. If cell robots can be made from patients' cells, the technology could be used for drug delivery in humans. Otherwise, it may elicit problematic immune responses. The most successful HIV vaccine is still in early trial stages at the population level. Although the results are promising, further large-scale clinical trials are needed before it can be deemed suitable for clinical application. The HIV vaccine induces antibody response in the body, but it does not show that it can effectively fight HIV and prevent AIDS. HIV mainly attacks the body's immune system, and the production of antibodies in traditional vaccines is inseparable from the immune system, which often causes failure of vaccination. So far, there has not been a single HIV self-healing case, suggesting that our immune system alone cannot suppress or eliminate HIV. More importantly, the primary defense against HIV in humans relies on cytotoxic T lymphocytes (CTL), which secrete a variety of cytokines involved in immune function. In the fight against HIV, the central role of CTL is to kill cells that have been invaded by the virus, thereby halting the reproduction of HIV. However, none of the vaccines developed so far are effective at activating CTL. Another challenge in vaccine development is the long incubation period of HIV/AIDS, which can last for years or decades. As a result, highly active antiretroviral therapy remains by far the most popular treatment for HIV, and we are still a long way from a truly

widespread HIV vaccine.

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OPINION REVIEW

Current status of COVID-19 treatment: An opinion review

Sveva Di Franco, Aniello Alfieri, Stephen Petrou, Giovanni Damiani, Maria Beatrice Passavanti, Maria Caterina Pace, Sebastiano Leone, Marco Fiore

ORCID number: Sveva Di Franco 0000-0003-0399-2677; Aniello Alfieri 0000-0002-1330-5968; Stephen Petrou 0000-0001-9627-5444; Giovanni Damiani 0000-0002-2390-6505; Maria Beatrice Passavanti 0000-0002-9659-0847; Maria Caterina Pace 0000-0002-9352-4780; Sebastiano Leone 0000-0001-7852-4101; Marco Fiore 0000-0001-7263-0229.

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Sveva Di Franco, Aniello Alfieri, Maria Beatrice Passavanti, Maria Caterina Pace, Marco Fiore, Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples 80138, Italy

Stephen Petrou, Department of Emergency Medicine, Good Samaritan Hospital Medical Center, New York, NY 11795, United States

Giovanni Damiani, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan 20122, Italy

Giovanni Damiani, Clinical Dermatology, IRCCS Instituto Ortopedico Galeazzi, Milan 20122, Italy

Sebastiano Leone, Division of Infectious Diseases, "San Giuseppe Moscati" Hospital, Avellino 83100, Italy

Corresponding author: Marco Fiore, MD, Academic Fellow, Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Piazza Miraglia 2, Naples 80138, Italy. marco.fiore@unicampania.it

Abstract

The pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has garnered the attention of scientists worldwide in the search for an effective treatment while also focusing on vaccine development. Several drugs have been used for the management of coronavirus disease 2019 (COVID-19), which has affected many hospitals and health centers worldwide. Statistically significant results are lacking on the effectiveness of the experimented drugs in reducing COVID-19 morbidity or mortality, as there are very few published randomized clinical trials. Despite this, the literature offers some material for study and reflection. This opinion review attempts to address three burning questions on COVID-19 treatment options. (1) What kind of studies are currently published or ongoing in the treatment of patients with COVID-19? (2) What drugs are currently described in the literature as options of treatment for patients affected by the infection? And (3) Are there specific clinical manifestations related to COVID-19 that can be treated with a customized and targeted therapy? By answering these questions, we wish to create a summary of current COVID-19 treatments and the anti-COVID-19 treatments proposed in the recent clinical trials developed in the last 3 mo, and to describe examples of clinical manifestations of the SARS-CoV-2 infection with a cause-related treatment.

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Key Words: Antiviral drugs; Coronavirus; COVID-19; SARS-CoV-2; Tocilizumab; Eculizumab; Enoxaparin; Hydroxychloroquine; Pandemic; Treatment; Opinion review

Core Tip: The pandemic spread of coronavirus disease 2019 (COVID-19) has led to the need to standardize a therapeutic approach in order to offer the same indications for all patients admitted to the hospital admissions for severe acute respiratory syndrome coronavirus 2 infection. However, no specific drug or drug regimen has been approved for treatment. This opinion review describes the recent literature on this topic and summarizes the treatment strategies currently in use for COVID-19 related complications.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, defined as coronavirus disease 2019 (COVID-19), was originally discovered and identified as the cause of numerous viral pneumonia cases occurring in Wuhan (Hubei Province, China)[1]. It has now spread worldwide with recent epidemiological data reporting 18614177 infected and 702642 deaths[2]. In the context of a growing global health emergency, medical professionals demand a need for up-to-date guidelines for the management and treatment of this novel infection. Currently, there are multiple approved treatments (drugs, monoclonal antibodies, vaccines) for COVID-19. According to the WHO Interim Guidance on the 2019 coronavirus, early treatment is suggested if patients have confirmed diagnosis with mild symptoms associated with co-morbidities, increased risk of mortality, or moderate-severe clinical manifestations. Due to the swab time delay for confirmation of results, in the presence of a strong suggestive clinical presentation it is reasonable to start antiviral treatment as soon as possible[3]. Due to the severity of clinical symptoms and no statistically significant recommended treatment regimen, experimental use of a drug not yet approved may be necessary to improve patients' outcomes. To get more oriented among the numerous options of treatments proposed, this opinion review will summarize and clarify the role of each drug that has been used against COVID-19 in the clinical practice and those now under scientific examination.

WHAT KIND OF STUDIES ARE CURRENTLY PUBLISHED OR ONGOING IN THE TREATMENT OF PATIENTS WITH COVID-19?

The treatments proposed in the literature for COVID-19 are mainly based on the results of retrospective or observational studies, making it more difficult to hypothesize evidence-based therapies. Due to the need for more reliable data, the number of ongoing clinical trials are increasing. According to the International Clinical Trial Registry Platform database there are 1918 reported studies, with 1744 ongoing on COVID-19 patients[4]. Of these studies, 1661 are specific for the treatment of SARS-CoV-2 infection.

The most common classes of drugs used include antimalarial drugs, immunomodulators, convalescent plasma (CP), antiretrovirals, antibacterial drugs, lipid-lowering medications, anticoagulants and recently ivermectin. In this context, a large volume of data will soon be available and provide valuable novel recommendations regarding pathogenesis, treatment and prognosis[5].

WHAT DRUGS ARE CURRENTLY DESCRIBED IN THE LITERATURE AS OPTIONS OF TREATMENT FOR PATIENTS AFFECTED BY SARS-COV-2 INFECTION?

There is currently no therapy for COVID-19 infection whose efficacy has been proven. Nonetheless due to the current global crisis, it is crucial to be able to formulate an effective therapeutic strategy based on the evidence existing in the literature. From the analysis of all of the clinical trials designed on COVID-19 infection, we found a wide number of drugs employed in a multimodal treatment.

Hydroxychloroquine, an old anti-malaria drug, displayed the ability to inhibit coronavirus replication *in vitro*. Real-life data are currently discordant in recognizing its anti-SARS-CoV-2 claimed effect[6,7]. Since the virus was found to utilize the cell surface receptor angiotensin-converting enzyme 2 (ACE2) expressed in the lung, heart, kidney, and intestine[8], it has been hypothesized that hydroxychloroquine may also interfere with ACE2 receptor glycosylation, thus preventing SARS-CoV-2 binding to target cells[9]. In addition, hydroxychloroquine can inhibit the acidification of lysosomes and endosomes, interfering with the fusion process of the virus with the host[10]. The results of the Phase 3 clinical trial NCT: 04315948 may clarify the role of hydroxychloroquine in COVID-19 patients' prognosis.

Chloroquine alone or in combination with remdesivir and/or tocilizumab (under investigation by the clinical trial NCT: 04303507) may be effective against COVID-19 despite the more dangerous side effects than compared to hydroxychloroquine[11].

Among the drugs that seem to possess immunomodulatory benefits and reduce SARS-CoV-2 cell penetration, there are statins (the most prescribed ones are the atorvastatin 20 mg/d or an equivalent dose of rosuvastatin 40 mg/d). Statins act by reducing chemokine release, adhesion molecules, and modulating T-cell activity. Rosuvastatin, in particular, appears to have direct antiviral properties by binding and inhibiting the active site of the main protease enzyme (Mpro) of SARS-CoV-2. In a retrospective analysis Zhan *et al*[12] found that statin treatment among 13981 patients with COVID-19 was associated with a lower risk of all-cause mortality. Furthermore, the addition of ACE inhibitors or angiotensin II receptor blockers did not affect statin-associated outcomes in the studied cohort[12].

Remdesivir is a nucleoside analogue with a promising virus-inhibitory effect. It exhibits *in vitro* antiviral activity against coronaviruses[13] and *in vivo* has been shown to curb severe acute respiratory syndrome caused by coronavirus infection[14]. The drug can also inhibit viral replication interfering with the nascent viral-RNA chain resulting in its premature termination[15]. In a Phase 1 clinical trial the security and pharmacological effects of remdesivir were assessed[16]. Recently, in patients with severe COVID-19 receiving remdesivir clinical improvement was observed in 68% of cases (36 of 53 patients)[17]. However in a randomized, double-blind, placebo-controlled, multicenter trial, remdesivir was not associated with statistically significant clinical benefits[18]. Ongoing clinical trials (NCT: 04292899 and 04292730) should provide additional data on its effectiveness.

Azithromycin has shown *in vitro* antiviral activity against SARS-CoV-2, documented in literature at dosages similar to those used to treat bacterial pneumonia[19,20]. The mechanism of action is not well understood. It is believed to interfere with the acidification processes of lysosomes and endosomes[21] or amplification of the antiviral action of interferon in the host[22]. The use of azithromycin in combination with chloroquine/hydroxychloroquine has been described in the treatment of COVID-19 but the available clinical data is derived from retrospective, observational or uncontrolled studies[23,24]. The randomized telemedicine-based trial NCT: 04332107, now in Phase 3, may elicit further information.

Lopinavir and ritonavir are protease inhibitors used in HIV infections. Their use in combination allows the increase in half-life of lopinavir by enzymatic induction[25]. It has demonstrated *in vitro* antiviral activity for SARS-CoV[26] and MERS-CoV through inhibition of the 3-chymotrypsin-like protease[27]. Currently, there is no statistically significant evidence of its efficacy against SARS-CoV-2 *in vitro*. The studies available on the use of the lopinavir/ritonavir combination for the treatment of COVID-19 are mainly reports or retrospective studies, making it difficult to evaluate its effectiveness. In a randomized, controlled, open-label Chinese trial, no benefit was observed with lopinavir-ritonavir treatment[28]. There are several ongoing clinical trials. Among them NCT: 02735707 in its recruiting phase, is structured to compare the administration of lopinavir-ritonavir with no antiviral treatment.

Tocilizumab and sarilumab are monoclonal antibodies directed against the interleukin 6 (IL-6) receptor in which COVID-19 appears to target in the severe

inflammatory process and cytokine storm causing critical damage to the lungs and other organs[29,30]. Tocilizumab appears to be a viable treatment strategy in COVID-19 patients with risk of developing cytokine storm[30]. Studies supporting this thesis are mainly case-reports and retrospective analyses. There are a few randomized clinical trials (RCTs) in development (ChiCTR: 200002976, EuCTR: 2020-001110-38 NCT: 04320615) for the evaluation of the efficacy and safety of Tocilizumab, alone or in combination, in the treatment of severe pneumonia in COVID-19 hospitalized patients. Sarilumab is currently being studied in a multicenter Phase 2-3 study for the treatment of severe forms of COVID-19 (NCT: 04315298).

Anakinra is another monoclonal antibody used in the treatment of patients in critical condition. (NCT: 04330638). By blocking the IL-1 receptor, the drug could help reduce the cytokine storm triggered by the virus[31].

The monoclonal antibody eculizumab, which prevents the cleavage of the C5 fraction of the complement in the C5a and C5b, could also reduce this cytokine cascade. Currently, an encouraging case series has been published on the topic by Diurno *et al*[32] (2020) and we are looking forward to the results NCT: 04288713.

Among the immunomodulatory drugs with a possible action in reducing cytokine storm, colchicine has also been used. It is a non-selective inhibitor of NLRP3 inflammasome, and inhibitor of microtubule polymerization and leukocyte infiltration[33]. The COLCORONA trial is now ongoing in the recruiting phase (NCT: 04322682), while the GRECCO-19 study (NCT: 04326790) of 189 patients has recruited the necessary samples[34].

Several studies have analyzed the role of corticosteroids. Such drugs could theoretically act as immunomodulators. Wang *et al*[35] completed a randomized controlled trial, albeit with few patients, on the use of methylprednisolone highlighting that the short-term administration of the drug could be beneficial. In February 2020, Villar *et al*[36] published a randomized clinical study (NCT: 01731795) of 277 patients that defined the usefulness of the early administration of dexamethasone in reducing days of endotracheal intubation and overall mortality. Although these studies seem encouraging, further evidence of efficacy is needed[36].

In addition, CP has frequently been used as supplement therapy. It is a classic adaptive immunotherapy that was successfully and safely used in the treatment of infections caused by viruses similar to SARS-CoV-2[37], such as SARS, MERS, and in the 2009 H1N1 pandemic[38,39]. Data from the meta-analysis conducted By Mair-Jenkins *et al*[40] reported that this treatment can reduce the mortality of patients with COVID-19 especially if administered early to the onset of symptoms. The limitation of this treatment is the scarce availability of donor plasma considering that only recovered COVID-19 patients with neutralizing antibody titers above 1:640 are considered good plasma donors. Once the plasma is collected from donors, it is adequately treated and then infused into clinically symptomatic patients. A single 200 mL transfusion of CP is generally well tolerated and followed by improvement of the clinical symptoms. There is a subsequent increase of oxyhemoglobin saturation within 3 d and a rapid neutralization of the viremia[41]. The clinical trial NCT: 04321421 would clarify the usefulness of this treatment.

Among the integrative treatments, vitamin C infusion may produce an increase in the synthesis of norepinephrine and vasopressin[42], reduce cytokine levels[43], and prevent neutrophil activation and trap formation promoting vascular injury[44]. Its role is being investigated by the clinical trial NCT: 04264533.

Due to the increased incidence of thrombo-inflammation and hypercoagulability related to COVID-19, enoxaparin which inhibits factor Xa and thrombin is frequently present in almost all the clinical practice protocols of treatment[45]. The clinical trial identified as NCT: 04367831 is investigating the role of enoxaparin in COVID-19 and is currently ongoing.

There has also been an increase in tumor necrosis factor alpha (TNF-α) and IL-17 in peripheral blood samples of COVID-19 patients, but evidence in customized treatment is still lacking. Encouraging results arrived from real-life data in a large cohort of psoriatic patients on biologic agents. They demonstrated an increased risk of infection rates but without an increased risk of intensive care unit hospitalization or death[46]. Two trials were registered in the Chinese Clinical Trial Registry (ChiCTR2000030089, ChiCTR2000030703) that evaluate the potential use of adalimumab (anti-TNF-α) and ixekizumab (anti-IL-17) in the armamentarium to treat severe COVID-19 patients. Apremilast, a phosphodiesterase type 4 inhibitor, was a candidate treatment because it demonstrated inhibition of neutrophil, monocyte and lymphocyte migration during lung inflammation and decreased pro-inflammatory cytokine production[47].

A wide array of drugs used in current clinical practice but not yet approved and investigated by more than three ongoing clinical trials are presented in Table 1.

Table 1 Summary of the most investigated drugs for the treatment of coronavirus disease 2019

Therapeutic agent	Mechanism of action	Ongoing trials, *n*	Associations	Suggested dosage	Route of administration	Principal side effects	Ref.	NCT identifier
Hydroxychloroquine	Changes the pH of endosomes, prevents viral entry, transport and post-entry replication	224	Azithromycin, tocilizumab, lopinavir-ritonavir	200 mg BID or TID (10 d)	Oral-intravenous	Retinal toxicity, QT prolongation, nausea	[6-10]	NCT04315948
Chloroquine	Increases the endosomal pH interfering with the process of virus/cell fusion	225	Remdesivir, tocilizumab	2.5 g (3 d)	Oral-intravenous	Retinal toxicity, QT prolongation, nausea	[11]	NCT04303507
Convalescent plasma	Adaptive immunotherapy (neutralizing antibody tiers above 1:640)	129	Remdesivir, Interferon-alpha, oseltamivir, antibacterial and antifungal frugal drugs, methylprednisolone	200 ml single dose	Intravenous	Evanescent facial red spot	[37-41]	NCT04321421
Lopinavir/Ritonavir	Inhibition of the HIV protease/inhibition of CitP450-iso3A4 and augmented plasmatic concentration of lopinavir	67	Hydroxychloroquine, azithromycin, dexamethasone	200 mg/50 mg BID	Oral	Gastrointestinal upset, augmented plasmatic concentration of colchicine And HGAM-CoA reductase inhibitors	[25-28]	NCT02735707
Azithromycin	Prophylaxis of bacterial super-infection	59	Hydroxychloroquine, tocilizumab, atovaquone	500 mg	Oral-intravenous	QT prolongation	[19-24]	NCT04332107
Tocilizumab	Monoclonal antibody which targets the IL-6 receptor	50	lopinavir-ritonavir, remdesivir, chloroquine, hydroxychloroquine	Dosing according to weight range	Intravenous	Runny or stuffy nose, sinus pain, sore throat, headache, gastrointestinal upset, urinary tract infection	[30]	NCT04320615
Ivermectin	Suppression of SARS-CoV-2 viral replication in cell cultures (*in vitro*)	30	Hydroxychloroquine Dutasteride Azithromycin Proxalutamide	600 mcg/kg	Oral	Tiredness, loss of energy, stomach pain, loss of appetite, nausea, vomiting, diarrhea, dizziness	[48]	NCT04381884
Statin	Reduces chemokine release, adhesion molecules, and modulating T cell activity	23	Standard of care; colchicine + rosuvastatin	20 mg/d atorvastatin Rosuvastatin 40 mg/d or equivalent	Oral	rabdomiolisis	[12]	NCT04472611
Remdesivir	Nucleotide analogue that is incorporated into the nascent viral RNA chain resulting in its premature termination	20	Hydroxychloroquine, chloroquine, tocilizumab, convalescent plasma	200 mg 1st day – 100 mg (10 d)	Intravenous	Phlebitis, constipation, headache, ecchymosis, nausea, pain in extremities	[13-18]	NCT04292899
Methylprednisolone	Immunosuppression against cytokine storm	17	Siltuximab, tacrolimus	40 mg BID (5 d) - f 1-2 mg/kg/d (5-7 d)	Oral-intravenous	Headache, nausea, weight gain, excitement, infections	[35]	NCT04323592
Sarilumab	Monoclonal antibody which targets the IL-6 receptor	17	Not available	400 mg or 200mg single dose	Intravenous	Neutropenia, increased ALT, injection site redness, upper respiratory infections, nasal congestion, sore throat, urinary tract infections,	[29]	NCT04315298

						thrombocytopenia		
Colchicine	Non-selective inhibitor of NLRP3 inflammasome, inhibitor of microtubule polymerization and leukocyte infiltration	17	Not available	0.5 mg per os (BID) for 3 d - then once daily for the last 27 d	Oral-intravenous	Gastrointestinal upset, low blood cells count and rhabdomyolysis	[33-34]	NCT04322682
Heparin	Inhibition of Xa factor and thrombin	15	Methylprednisolone	Dosed to target activated partial thromboplastin time (aPTT) between 1.5-2.0 times the normal value	Subcutaneous injection	Reduced creatinine clearance	[45]	NCT04485429
Anakinra	Monoclonal antibody which targets the IL-1 receptor	11	Siltuximab or tocilizumab (single i.v. injection)	1 injection a day (max 28 d)	Subcutaneous injection	Gastrointestinal upset, headache, joint pain, flu symptoms, redness-bruising-pain in the injection site	[30,31]	NCT04330638
Dexamethasone	Immunosuppression against cytokine storm	10	Not available	20 mg/d (5 d) then 10 mg/d (5 d)	Intravenous	Headache, weight gain, excitement, infections	[36]	NCT04325061
Enoxaparin	Inhibition of Xa factor and thrombin	5	Not available	4000 UI/d or 100 UI/kg	Subcutaneous injection	Skin irritation in injection site, bleeding, heparin-induced thrombocytopenia, fatigue, fever	[45]	NCT04367831
Eculizumab	Monoclonal antibody which targets C5 inhibiting its cleavage in C5a and C5b	3	Hydroxychloroquine, lopinavir-ritonavir, ceftriaxone, vitamin C	3600 mg/wk (8-22 wk)	Intravenous	Fever, headache, nausea and vomiting, body aches, confusion, increased sensitivity to light, stiffness	[32]	NCT04288713
Vitamin C	Antioxidant, increases the synthesis of norepinephrine and vasopressin, attenuate increases in cytokine levels	3	All mentioned drugs	12 g/12 h (7 d) or 50 mg/kg/6 h (4 d)	Oral-intravenous	Gastrointestinal upset	[42-44]	NCT04264533

In this table are the most utilized and investigated drugs for the treatment of coronavirus disease 2019. It provides the name of the therapeutic agent, mechanism of action, number of ongoing trials, drug association if available, suggested dosage and maximum period of time the drug should be administered, route of administration, principal side effects, a reference on the drug, and an example of randomized clinical trial (RCT) identified by the national clinical trial number. Drugs investigated in less than three RCTs have been excluded. BID: Bis in die; IL-1: Interleukin 1; NCT: National clinical trial; RCT: Randomized clinical trial; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TID: Tris in die.

Among these drugs is Ivermectin, an FDA-approved anti-parasitic. This drug showed to have broad-spectrum anti-viral activity only *in vitro*[48], and results of a Phase 1 study are absolutely needed before using ivermectin. There are not enough data to support a recommendation for its use in a higher-than-approved dosage.

ARE THERE SPECIFIC CLINICAL MANIFESTATIONS RELATED TO COVID-19 THAT CAN BE TREATED WITH A CUSTOMIZED AND TARGETED THERAPY?

The pathogenesis of the damage induced by the SARS-CoV-2 virus is presently being analyzed. There are two clinical manifestations that are most frequently found in infected patients, namely respiratory failure and systemic coagulopathy. Currently it appears, according to a report by Magro *et al*[49], that the multiple district damage induced by the infection is caused by a hyper-activation of the complement system and exacerbation of the cytokine cascade. On histological samples of patients' lung and skin tissue who died from COVID-19, there was a discernable deposit of C5b9, C4d, and the mannose-binding lectin-associated serine protease 2. These proteins are the residual products of complement activation[49]. Once the host's barriers are overcome, the virus stimulates the innate immunity and enters the cell by binding to the ACE2 receptor. It goes on to destroy the endothelial cells of all organs whose cells express the ACE2 receptor widely. The same cell destruction increases tissue permeability and facilitates the systemic release of the virus. This results in hyperproduction of interleukins (cytokine storm and intracellular activation of the inflammasome) and hypercoagulability with diffuse thrombosis in the microcirculation.

Due to the unproven efficacy of antiviral drugs alone, there is strong reason to believe it useful to administer other drug treatments to facilitate meaningful recovery. Drugs such as eculizumab, which act by blocking the cleavage/activation of complement factor C5; tocilizumab, sarilumab, and anakinra which block the interleukin receptors by limiting the cytokine cascade; colchicine which acts by interfering with the inflammasome NLRP3; vitamin C which may reduce the activation of neutrophils and stimulate the endogenous production of vasopressors; and enoxaparin which assists in the prevention and treatment of hypercoagulation thrombosis. The mechanisms of drug action according to cell damage, complement activation and cytokine storm are described in Figure 1.

CONCLUSION

Although a short period of time has passed since the novel coronavirus was initially described, several treatment options have been introduced. To simplify the current therapeutic armamentarium, Table 1 summarizes the most investigated options for the treatment of COVID-19 in decreasing order by number of ongoing RCTs. Nonetheless there is still no proven evidence based therapeutic plan that can offer the best survival chance to patients infected. The inconsistent results presented in the literature on the treatment of SARS-CoV-2, is likely due to the lack of well-controlled studies with an adequate sample size. A meticulous understanding of the pathophysiology and immunological response of the host is also still necessary. Additional data are required to provide a proper risk stratification for patients and an adequate place in therapy of current investigational options.

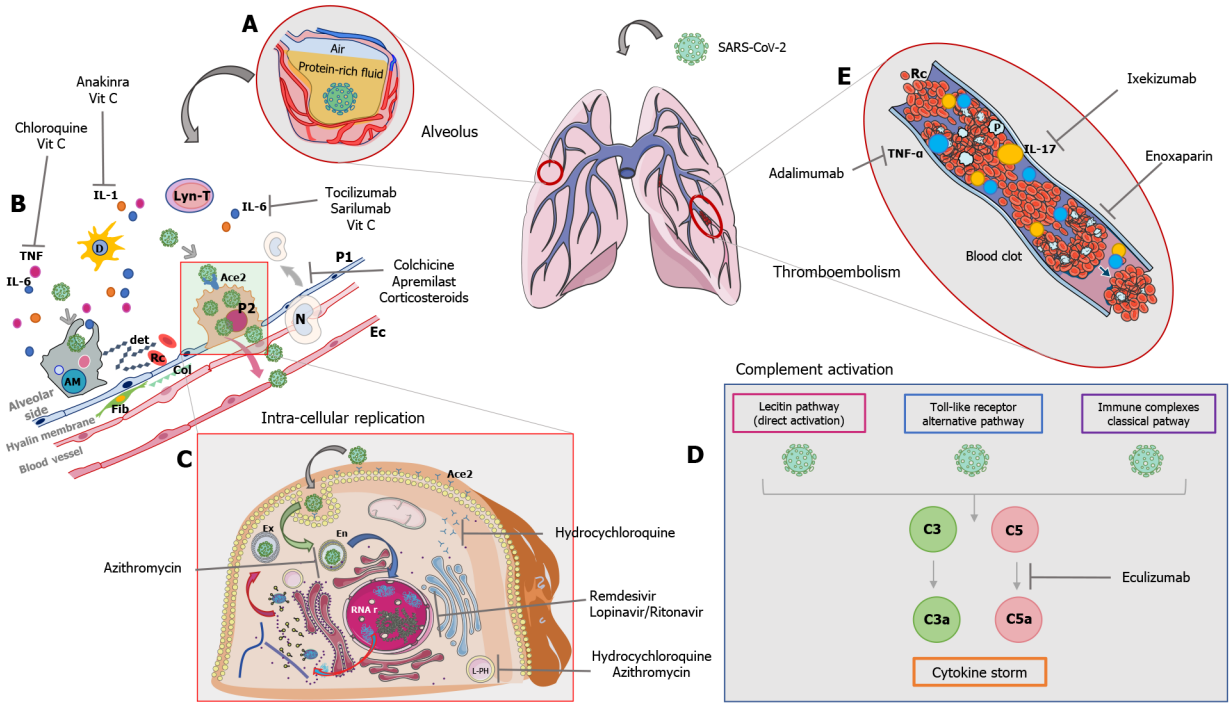

Figure 1 Severe acute respiratory syndrome coronavirus 2 infection, consequences and rationale of treatment. A: The virus in the alveolus induces the production of a protein rich fluid interfering with ventilation gas exchanges; B: Description of what happens in the alveolus after the infection and drugs involved in this phase. The virus binds the angiotensin-converting enzyme 2 (ACE2) receptor and replicates in the Type 2 pneumocyte (P2), leading to apoptosis (accumulation of cellular dendrites), activation of alveolar macrophages, dendritic cells, lymphocytes T, and neutrophils. There is an augmentation of cytokines levels, especially interleukin 6 (IL-6), IL-1, and tumor necrosis factor (TNF). The inflammatory process leads to damage of the alveolar barrier and to the formation of the hyaline membrane between the alveolar side and the blood vessels. In this phase, chloroquine reduces the levels of TNF; vitamin C reduces the levels of TNF, IL-1, and IL-6; anakinra inhibits IL-1 binding to its receptor; tocilizumab and sarilumab inhibit IL-6 binding to its receptor; and colchicine, apremilast, and corticosteroids reduce the migration of lymphoid cells into the alveolus; C: Synthesis of the intra-cellular replication of the virus. Hydroxychloroquine reduces the exposition of ACE2 receptors on the surface of P2, and as azithromycin reduces the pH in lysosomes and endosomes. Remdesivir and lopinavir/ritonavir interfere with viral replication; D: The virus is capable of activating the complement system that can be inhibited by eculizumab. E: Enoxaparin may be effective against the typical thromboembolism induced by the virus. Furthermore, in the plasmatic torrent, the high levels of TNF-alpha and IL-17 can be reduced by selective binders such as adalimumab and ixekizumab, respectively. Original picture by Di Franco S and Alfieri A (2020).

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ORIGINAL ARTICLE

Observational Study

Chinese medical students' interest in COVID-19 pandemic

Nan-Ze Yu, Zhi-Jin Li, Yu-Ming Chong, Yuan Xu, Jun-Ping Fan, Yang Yang, Yue Teng, Yu-Wei Zhang, Wen-Chao Zhang, Ming-Zi Zhang, Jiu-Zuo Huang, Xiao-Jun Wang, Shu-Yang Zhang, Xiao Long

ORCID number: Nan-Ze Yu 0000-0002-6296-6236; Zhi-Jin Li 0000-0002-7060-8797; Yu-Ming Chong 0000-0001-9307-3046; Yuan Xu 0000-0003-3500-6587; Jun-Ping Fan 0000-0002-6722-9278; Yang Yang 0000-0002-3971-6474; Yue Teng 0000-0002-6169-6780; Zhan-Qing Zhang 0000-0002-3971-6474cuo; Wen-Chao Zhang 0000-0003-1986-8662; Ming-Zi Zhang 0000-0003-0250-1872; Jiu-Zuo Huang 0000-0002-0458-9006; Xiao-Jun Wang 0000-0003-3043-0020; Shu-Yang Zhang 0000-0002-1532-0029; Xiao Long 0000-0003-0136-2508.

Author contributions: Yu NZ was the principal investigator; Yu NZ, Li ZJ, and Chong YM designed the study; Xuan Y, Fan JP, and Zhang MZ established the protocol used; Yang Y, Teng Y, and Zhang WC distributed the questionnaire and collected the data; Li ZJ, Chong YM, Zhang YW, and Hang JZ drafted the manuscript; Long X, Wang XJ, and Zhang SY performed critical revisions of the manuscript; all authors read and approved the final manuscript.

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Nan-Ze Yu, Zhi-Jin Li, Yu-Ming Chong, Yue Teng, Yu-Wei Zhang, Wen-Chao Zhang, Ming-Zi Zhang, Jiu-Zuo Huang, Xiao-Jun Wang, Xiao Long, Department of Plastic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Yuan Xu, Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Jun-Ping Fan, Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Yang Yang, Department of Orthopaedics, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Shu-Yang Zhang, Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: Xiao Long, MD, Surgeon, Professor of Medicine, Department of Plastic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. pumclongxiao@126.com

Abstract

BACKGROUND

The outbreak of coronavirus disease 2019 (COVID-19) happened in early December and it has affected China in more ways than one. The societal response to the pandemic restricted medical students to their homes. Although students cannot learn about COVID-19 through clinical practice, they can still pay attention to news of COVID-19 through various channels. Although, as suggested by previous studies, some medical students have already volunteered to serve during the COVID-19 pandemic, the overall willingness of Chinese medical students to volunteer for such has not been systematically examined.

AIM

To study Chinese medical students' interest in the relevant knowledge on COVID-19 and what roles they want to play in the pandemic.

METHODS

approval for this study (IRB No. S-K1173).

Informed consent statement: Our study has not involved the patients' consent because it is not a clinical study.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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Medical students at Peking Union Medical College were surveyed *via* a web-based questionnaire to obtain data on the extent of interest in the relevant knowledge on COVID-19, attitude towards volunteerism in the pandemic, and career preference. Logistic regression modeling was used to investigate possible factors that could encourage volunteerism among this group in a pandemic.

RESULTS

A total of 552 medical students responded. Most medical students showed a huge interest in COVID-19. The extent of students' interest in COVID-19 varied among different student-classes ($P < 0.05$). Senior students had higher scores than the other two classes. The number of people who were 'glad to volunteer' in COVID-19 represented 85.6% of the respondents. What these students expressed willingness to undertake involved direct, indirect, and administrative job activities. Logistic regression analysis identified two factors that negatively influenced volunteering in the pandemic: Student-class and hazards of the voluntary job. Factors that positively influenced volunteering were time to watch COVID-19 news, predictable impact on China, and moral responsibility.

CONCLUSION

More innovative methods can be explored to increase Chinese medical students' interest in reading about the relevant knowledge on COVID-19 and doing voluntary jobs during the pandemic.

Key Words: COVID-19; Chinese medical students; Volunteer; Medical education; Public health emergency of international concern

Core Tip: Our survey of Chinese medical students showed an overall strong initiative for volunteerism in the coronavirus disease 2019 (known as COVID-19) pandemic. These students were willing to play direct, indirect, or administrative roles. Student-class and hazards of the voluntary job were the negative influencing factors of volunteering in the pandemic; thus, reducing students' fear of being infected, such as by providing strong personal protection, can improve their willingness to volunteer. As for their future career preference, nearly half of the students expressed reluctance to engage in pandemic-related specialties, which could imply measures needed to attract potential practitioners in the future.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), broke out in Hubei Province, China in December 2019[1]. The World Health Organization later declared this outbreak a pandemic, due to its rapid spread across the world[2]. Wuhan, the capital of Hubei Province, was locked down on January 23, 2020. As of March 8, 2020 — according to data published by the National Health Commission of China — about 42000 medical staff had been dispatched to different regions of Hubei during the lock-down[3]. Among these was a multidisciplinary team of 186 doctors and nurses from Peking Union Medical College (PUMC) hospital, who managed an intensive care unit (referred to as ICU) from February 4 to April 12 in the Sino-French New City Branch of Tongji Hospital (Wuhan), a designated hospital for COVID-19. No medical student was included in this medical team.

Because the outbreak of COVID-19 coincided with the Chinese Spring Festival, most of the medical students in China were scattered across the country and consequently

self-quarantined in their hometowns. The global outbreak has affected medical students worldwide, in many different ways. In the Chinese medical education system, medical students learn basic sciences and clinical medical courses in their junior and middle class-years, respectively; each class has very limited access to clinical practice during this time. Senior class students, on the other hand, enter hospitals for clerkship, internship, or clinical rotation as residents. With the help of various Internet-based learning technologies, the coursework of junior and middle class-year medical students was hardly affected by the pandemic lock-down. However, the clinical practice of senior students had to be suspended.

This disruption in medical school training was not exclusive to China. Medical students at Oxford University Hospitals faced a similar situation[4]. While their medical training was nearly completely suspended, medical students embarked on laboratory jobs and administrative tasks to alleviate the general understaffing burden brought on by the pandemic. Some scholars have advocated such involvement of medical students in the pandemic[5,6]. Yet, there is little data to show medical students' willingness, particularly for those in China. Thus, we designed and carried out a survey to assess Chinese medical students' willingness to know more about COVID-19 and participate in the pandemic, and investigate whether COVID-19 had increased their interest in specialties related to the prevention and treatment of severe infectious diseases.

MATERIALS AND METHODS

Questionnaire design

An 18-item questionnaire was designed to evaluate Chinese medical students' involvement in reading the relevant knowledge of COVID-19, their willingness to volunteer in the pandemic, and whether the outbreak of COVID-19 had any impact on their career choice. The design was adapted from a questionnaire verified by Mortelmans *et al*[7], inspired by surveys of the influenza pandemic[8] and Middle East respiratory syndrome[9,10], and based on a psychological survey conducted in the early stage of the COVID-19 outbreak[11]. The majority of items — including willingness to learn about COVID-19, interest level in the relevant knowledge on COVID-19, perceived personal and nationwide impact of COVID-19, and preference of professional choices - were evaluated using a Likert 5-point scale, with 1 being strongly disagree/unwilling and 5 being strongly agree/willing. For other items, the 5-point qualitative scale was as follows: 1-2: "a little"; 3: "moderate"; and 4-5: "very much". Further, interviewees answered "Yes" or "No" to the question "Are you willing to be a volunteer in the COVID-19 pandemic?", and selected their access to pandemic information and the type of pandemic-relevant department that they were willing to join. Before distribution, the questionnaire was assessed by an internal consistency test, and the Cronbach-α coefficient was determined to be 0.802. All information was anonymous and informed consent was obtained from respondents. The study was approved by the Medical Ethics Committee of PUMC Hospital.

Participants

A total of 916 medical students at PUMC, distributed among eight student classes, were invited to fill out the web-based questionnaire. Respondents could submit only a single time and had to answer each question under the platform system settings. From April 10 to April 18, the invitation to fill out the questionnaire was delivered three times, to make sure that every student received the message and with the ultimate goal of maximizing the response rate. By that time, the pandemic crisis-level had been downgraded in China and the lock-down of Wuhan had been lifted (on April 8); the new semester had not yet started at PUMC and the students had been restricted to their homes for more than 2 mo.

Statistical analysis

All analyses were carried out with the SPSS statistical software package (v23; IBM Corp., Armonk, NY, United States). Quantitative data are expressed as the mean ± SD. Qualitative data are described as constituent ratios. Kruskal-Wallis test was applied for difference analysis between student-class and interest in the relevant knowledge on COVID-19. Logistic regression modeling was used for influencing-factor analysis of willingness to be a volunteer in the COVID-19 pandemic. A *P* value less than 0.05 was considered as the threshold for statistical significance.

RESULTS

A total of 552 questionnaires (response rate of 60.3%) were returned from 33 provincial administrative regions of China during the 8-d survey period (Figure 1). Among all the responders, 57.8% were female and 42.2% were male. The total respondent pool was divided into three groups according to their curriculum setups, as follows: Junior students, whose coursework involved basic sciences and little medical knowledge; middle-grade students, who received medical education but had no access to clinical practice; and senior students who were currently in clinical rotations. The respondent distribution and the response rate of each group are provided in Table 1.

Involvement in reading about COVID-19

Seventy-one percent of the respondents showed willingness to follow the progress of the COVID-19 pandemic and sixty-eight percent of them reported that they spent 15-60 min per day on it. The most popular way to access the relevant information was social media (90.9%), followed by news app (67.4%) and television (52.0%). The question "Which aspect of the relevant knowledge on COVID-19 do you know best?" is designated to determine students' involvement in reading about COVID-19 upon they were self-quarantined at home and to assess which aspect of COVID-19 they will be most interested in when they followed news. Table 2 shows that medical students were most interested in preventive measures in daily life (4.38 ± 0.65) but less interested in diagnostic criteria and treatment procedures (3.12 ± 0.95). The medical students' preference varied among the different classes. The senior students showed a greater interest in clinical knowledge, such as in-hospital prevention and diagnosis and treatment procedures of COVID-19, followed by middle-grade students ($P < 0.05$), while the junior students appeared to have the least interest to these aspects. There was no statistically significant difference between the different classes for interest in pathogenesis. As for prevention in daily life, there was a tendency for the seniors to be more into protecting themselves in daily routine than the junior students ($P = 0.05$) (Table 2).

Attitude towards volunteering in pandemic

The number of people who were willing to offer spontaneous support and help in COVID-19 accounted for 85.6% of the respondents. The questionnaire was set up with some items about the role that medical students would prefer to play as a volunteer in the pandemic. Students could arbitrarily choose the task that they wanted to undertake, without being restricted to choose only one item. One-half (50.2%) expressed willingness to provide direct medical services, mainly involving management of patients under the guidance of superior physicians; importantly, this service has a possibility of direct clinical exposure. Indirect medical activities were more popular (69.4%), including working on the clinical front-line but not directly treating the patient. The majority of students (80.4%) expressed willingness to assist in administrative work, such as managing paper files and designing community pamphlets; this work carries the lowest risk of infection.

The incentives cited by the respondent Chinese medical students to volunteer in a pandemic are summarized in Table 3. Binary logistic regression modeling was used to investigate possible factors that could affect medical students' willingness to volunteer. Female medical students were found to be more likely to volunteer than their male counterparts. Notably, willingness to volunteer decreased with seniority. Next, it was remarkable that students were more willing to be a volunteer with increasingly more time spent on watching news and stronger will to learn about COVID-19. Not surprisingly, students who held the opinion that COVID-19 exerted a huge impact on China and those who thought that doctors volunteer because of moral obligation were more inclined to volunteer. Sixty-three percent of the respondents agreed or strongly agreed that health care professionals have a moral obligation to voluntarily provide medical services in a pandemic such as COVID-19. These medical students were significantly more willing to volunteer as well.

COVID-19 pandemic and career preference

How the pandemic was affecting career preference of medical students is illustrated in Figure 2. When asked to rate their inclination to join pandemic-related specialties (more than one option was available), nearly half of the students expressed reluctance. Public health specialties were the most popular among all related specialties, followed by ICU. Among the students who were interested in COVID-19-related specialties, only 18% chose infectious disease, making it the least popular option.

Table 1 Chinese medical student respondents

Characteristic	Junior	Middle	Senior	Total
Study sample, *n*	268	173	475	916
Returned questionnaire, *n*	157	134	261	552
Response rate	58.6%	77.5%	54.9%	60.3%

Table 2 Interest level of Chinese medical student respondents in relevant knowledge on coronavirus disease 2019

Item	Junior		Middle		Senior		Total		*P* value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Pathogenesis	3.45	0.87	3.53	0.91	3.62	0.85	3.55	0.87	0.098
Prevention in life	4.29	0.68	4.37	0.61	4.44	0.65	4.38	0.65	0.05
In-hospital prevention	3.23	1.08	3.43	0.92	3.84	0.87	3.57	0.98	< 0.001
Diagnosis and treatment	2.85	0.97	2.99	0.95	3.34	0.87	3.12	0.95	< 0.001

SD: Standard deviation.

DISCUSSION

It has been debated whether medical students should serve in a pandemic such as COVID-19, owing to the possibility of their getting infected during the clinical practice activities and their lack in knowledge about severe infectious disease[6,11]. So far, the different countries affected by COVID-19 have reacted differently. Portugal declared the closure of medical schools after 31 cases were confirmed[12]. On March 17, 2020, the American College of Medicine Association (United States) recommended suspension of all direct patient contact responsibilities for medical students[13] but policies differed among districts. New York University offered voluntary opportunities for senior students who met all graduation requirements to graduate in advance of the pandemic, and planned to have them in internal medicine and emergency departments[14].

At the same time, some medical students were also enthusiastic to offer their help during the pandemic. Compared with clinical jobs, non-clinical jobs seemed to be more acceptable. Medical students at Columbia University (New York, NY, United States) initiated a virtual volunteer group to perform the necessary chores for hospital staff and to participate in a COVID-19 laboratory program[15]. More than 500 medical students at Harvard Medical School (Boston, MA, United States) spontaneously formed volunteer teams to fulfill their potential through community mobilization[16]. To our relief, the study conducted at PUMC showed that Chinese medical students were also likely to offer support and help in a pandemic. This trend was more obvious when students sensed the threat of COVID-19 to China.

The self-assessment of results from PUMC, presented herein, indicate that students showed preference to know COVID-19 daily life prevention than hospital settings. Not surprisingly, the senior medical students had higher scores than their junior class counterparts for interest in disease prevention. This suggests that younger volunteers, who still lacked sufficient working experience in hospital, have not been aware of the significance of disease prevention yet, thus indicating that more consciousness and knowledge about self-protection can be instilled into these younger students.

According to our survey, several factors influenced the Chinese medical student's willingness to serve in a pandemic. It seems that senior students are more reluctant to volunteer. This may be because most of the senior students have their specialty of choice already. Moreover, the possibility of getting infected may have deterred them. Other influencing factors have been seen in previous studies, in which several lines of evidence have been obtained to suggest that inefficiency, prior training, financial security, and access to protective equipment can affect medical students' enthusiasm to be volunteers[17]. Ultimately, focusing on these collective factors will not only improve medical students' volunteerism but their protection as well.

This study also indicated that medical students preferred to get information from social media and news apps. According to data published by the China Internet

Table 3 Odds ratios for willingness to volunteer in the coronavirus disease 2019 pandemic

Item		*n* (%)	OR (95%CI)
Sex	Male	233 (42.2)	1
	Female	319 (57.8)	1.52 (0.86-2.72)
Student class	Junior	157 (28.4)	1
	Middle	134 (24.3)	0.79 (0.36-1.73)
	Senior	261 (47.3)	0.59 (0.29-1.21)
Time to watch news	< 15 min	125 (22.6)	1
	15-30 min	265 (48.0)	1.4 (0.7-2.81)
	30-60 min	111 (20.1)	2.13 (0.86-5.26)
	> 60 min	51 (9.2)	2.13 (0.65-6.95)
Willingness to know	Little	160 (29.0)	1
	Moderate	242 (43.8)	1.65 (0.86-3.18)
	Very much	150 (27.2)	0.85 (0.38-1.88)
Impact on personal life	Little	85 (15.4)	1
	Moderate	155 (28.1)	0.49 (0.16-1.57)
	Very much	312 (56.5)	0.62 (0.18-2.08)
Impact on China	Little	97 (17.6)	1
	Moderate	163 (29.5)	1.55 (0.6-4.05)
	Very much	292 (52.9)	2.16 (0.81-5.76)
Doctors' obligation	Little	202 (36.6)	1
	Moderate	216 (39.1)	4.29 (2.25-8.16)
	Very much	134 (24.3)	28.22 (6.03-131.98)
Hazards of voluntary job	Little	236 (42.8)	1
	Moderate	256 (46.4)	0.43 (0.22-0.85)
	Very much	60 (10.9)	0.24 (0.1-0.58)

Odds ratio and 95% confidence interval in binary logistic regression modeling were used for assessing a "Yes" answer to the question "Are you willing to be a volunteer in the COVID-19 pandemic?" OR: Odds ratio; CI: Confidence interval.

Network Information Center at the end of March of this year, 265 million students turned to online education. The number of online education users in China reached 423 million, equating to an increase of 110.2% from the end of 2018[18]. After the pandemic, schools can still consider a combination of in-class learning and some online learning modalities[19]. Our findings also confirmed the popularity and feasibility of this way. It can be a good chance for schools to penetrate into students' social circles and raise their intention of being volunteers by means of, for instance, posting high-quality videos about COVID-19 on social media[20].

The outbreak of COVID-19 also exposes the potential understaffing. It is imperative to take measures to appeal more practitioners. Although preventive medical courses are provided to students, there is no curriculum about public principles in response to emerging infectious diseases, and gradually students are reluctant to become doctors related to epidemic control[21]. It is reassuring that even not in clinical practice, medical students take a vivid public health course through COVID-19, which may increase students' emphasis on epidemic-related specialties. Although it remains unclear to know what extent their plans to specialize in a specialty relevant to the pandemic was altered by the pandemic, nearly 80% of students believed that this outbreak improved their interest and understanding of public health, which can be a good sign. Thus far, previous studies have revealed a correlation between lack of incentive mechanisms, little perception of public health, and students' choice of community medicine[22]. This suggests that students should be made clear of the significance of epidemic-relevant

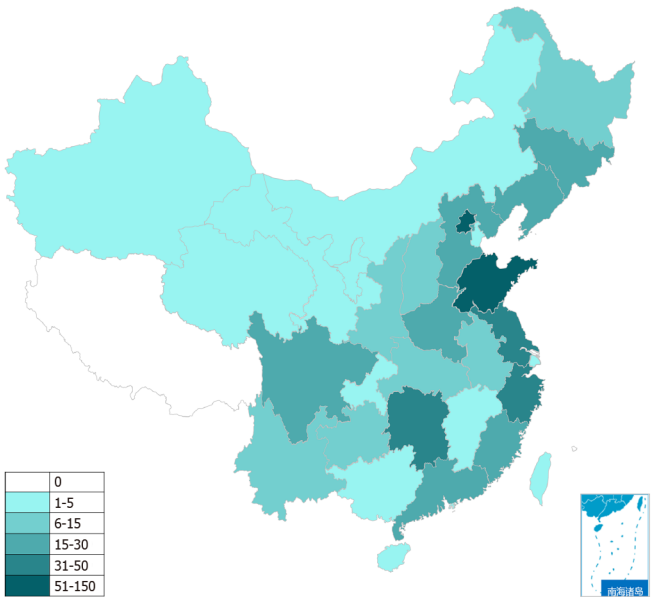

Figure 1 Distribution of medical students participating in this survey across China (*n* = 552).

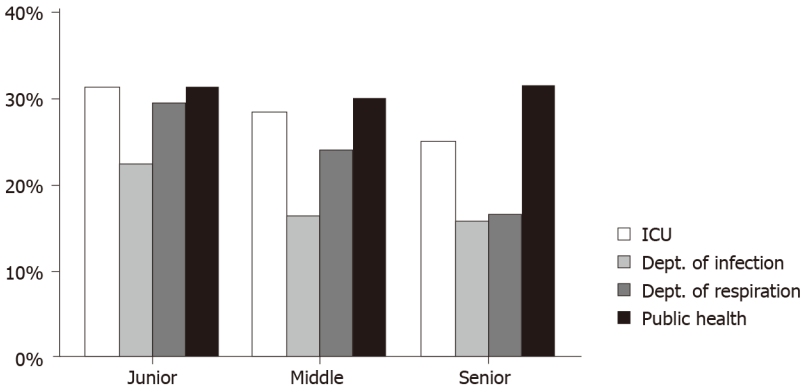

Figure 2 Career choice of medical students about pandemic-related specialties. ICU: Intensive care unit.

specialties, and encouraged by role models who have worked in epidemic areas.

This study has several limitations that must be considered when interpreting our findings. First, for the purpose of a higher response rate, only students at PUMC were surveyed; thus, the data collected might not be representative of the entire student population in China. However, despite studying at the same college (PUMC), the students involved in our study originated from across the entire country. Undoubtedly, our findings should be further confirmed by a multi-center study. A web-based questionnaire also has particular benefits for our study population, as it complements the geographic restriction caused by the pandemic. Second, the questionnaire was delivered in early April, when the pandemic in China had been basically controlled, and students were inherently more familiar with COVID-19. Hence, the results might be less optimistic if it had been conducted at an earlier stage of the pandemic.

CONCLUSION

In this study, a web-based questionnaire was used to reveal Chinese medical students' interest in the international public health event, COVID-19. We found that this emerging pandemic triggered students' curiosity and prompted their interest in reading about and responding to related events. Overall, students tended to read more about daily life prevention of COVID-19, and they expressed their passion to participate in volunteer activities in different ways.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) has raged across the world. The dramatically increasing numbers of infected cases consequently caused a heavy burden on medical staff worldwide. With the intent of helping ease the burden of medical systems, some medical students have been willing to volunteer in the pandemic but there is little systematic evidence to show that among Chinese medical students.

Research motivation

As medical students will emerge as the practitioners during future outbreaks and pandemics, it is essential to determine the profile of incentivizing factors for such volunteer work today. This knowledge will also help to construct strategies that will improve their enthusiasm for volunteerism.

Research objectives

A total of 552 medical students at Peking Union Medical College responded to the study questionnaire.

Research methods

This study was online-based and conducted through a questionnaire that explored students' interest in the relevant knowledge on COVID-19, attitude towards volunteerism in the pandemic, and career preference. Logistic regression modeling was used to investigate possible factors that could encourage medical students to volunteer in a pandemic.

Research results

Chinese medical students expressed a strong initiative to aid in COVID-19 by means of taking on direct, indirect, or administrative responsibilities. There were two negative influencing factors, namely, student-class and hazards associated with the voluntary job, which suggested that reducing students' fear of being infected and offering sufficient personal protection could help improve volunteerism in a pandemic. In terms of future career preference, nearly half of the students expressed reluctance to engage in pandemic-related specialties, which could imply more measures to attract potential practitioners in the future.

Research conclusions

Most Chinese medical students take initiatives to learn about COVID-19 and are glad to volunteer in a pandemic. However, hazards associated with the voluntary job can likely damp down students' enthusiasm for volunteerism, which means more innovative methods, such as Internet platforms, sufficient personal protection, specialized knowledge, and full training in advance, can be explored.

Research perspectives

Multi-center studies are needed, taking racial, geographic distribution, educational background, parental background, income and academic performance, *etc*. into consideration. In addition, more standard assessment questionnaires should be made and enacted to evaluate students' comprehensive understanding of COVID-19, in order to reduce the bias of different surveys conducted in different regions.

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